Oncologic Drugs Advisory Committee (ODAC) Meeting

[September 22, 2022]

NDA 214383

Drug name: PEPAXTO (melphalan flufenamide)

Applicant: Oncopeptides AB

Combined FDA and Applicant ODAC Briefing Document

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Applicant and the Food and Drug Administration (FDA) for the panel members of the advisory committee. We have brought the drug PEPAXTO (NDA 214383) to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Glossary

AE, adverse event

AESI, adverse event of special interest

ANC, absolute neutrophil count

ASCT, autologous stem cell transplant

BSA, body surface area

CAR T, chimeric antigen receptor T cell

CHMP, Committee for Medical Products for Human Use

CI, confidence interval

cilta-cel, ciltacabtagene autoleucel

CMA, conditional marketing authorization

CMQ, customized MedDRA query

CrCl, creatinine clearance

dex, dexamethasone

DOR, duration of response

ECOG, Eastern Cooperative Oncology Group

EHA, European Hematology Association

EMD, extramedullary disease

EMA, European Medicines Agency

ESMO, European Society for Medical Oncology

EU, European Union

evs, events

FAS, full analysis set

FDA, US Food and Drug Administration

FISH, fluorescence in situ hybridization

HR, hazard ratio

ide-cel, idecabtagene vicleucel

Ig, immunoglobulin

IMiD, immunomodulatory drug

ISS, Multiple Myeloma International Staging System

ISS, integrated summary of safety

KM, Kaplan-Maier

mAb, monoclonal antibody

MedDRA, Medical Dictionary for Regulatory Activities

mel, melflufen

melflufen, melphalan flufenamide

MM, multiple myeloma

NA, not available

NDA, new drug application

ODAC, Oncologic Drugs Advisory Committee

ORR, overall response rate

OS, overall survival

PD, progressive disease

PDC, peptide-drug conjugate

PFS, progression-free survival

PI, proteasome inhibitor

PS, performance status

PT, preferred term

pts, patients

R-ISS, Revised Multiple Myeloma International Staging System

ROW, rest of world

RRMM, relapsed/refractory multiple myeloma

SAE, serious adverse event

SAG-O, Scientific Advisory Group on Oncology

SFLC, serum free light-chain

SOC, system organ class

SPEP, serum protein electrophoresis

TCR, triple-class refractory

TTP, time to progression

UPEP, urine protein electrophoresis

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1 Introduction

1.1 Purpose of the Meeting

FDA Oncology has consistently evaluated products and indications approved under the accelerated approval regulations over the years. This has included the review of products that have outstanding confirmatory trials and those products in which the confirmatory trial has failed to confirm clinical benefit. Melphalan flufenamide received accelerated approval for the treatment of patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody in February 2021 based on the results of the single arm trial, Horizon. OP-103 (OCEAN) trial was the confirmatory trial selected to verify the clinical benefit. FDA is convening this Oncologic Drug Advisory Committee (ODAC) meeting to discuss efficacy and safety concerns arising from OCEAN, a randomized, Phase 3 trial, evaluating melphalan flufenamide with dexamethasone compared to pomalidomide and dexamethasone. The primary issues to be discussed include:

- Potential detriment in Overall Survival (OS),
- Failure to Demonstrate a PFS benefit and,
- Lack of an appropriate dose.

The purpose of this meeting is to obtain the advisory committee's input regarding the benefit-risk of melphalan flufenamide for the currently indicated patient population.

1.1.1 Context for the meeting

Melphalan flufenamide, a peptide conjugated alkylating drug was granted accelerated approval on February 26, 2021, in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor (PI), one immunomodulatory drug (IMiD), and one CD38-directed monoclonal antibody (a triple class refractory patient population).

The approval was based on the OP-106 (HORIZON; NCT02963493) trial, a single-arm trial that evaluated melphalan flufenamide in combination with dexamethasone. Efficacy was assessed in 97 patients in the HORIZON trial that had received 4 or more prior lines of therapy and were refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed antibody. The overall response rate (ORR) in this population was 23.7% (95% CI: 15.7, 33.4) with a median duration of response (DOR) of 4.2 months (95% CI: 3.2, 7.6). Myelosuppression was a significant safety issue identified. The risk of thrombocytopenia, neutropenia, anemia was included in the WARNINGS AND PRECAUTIONS section of the USPI.

For a product approved under accelerated approval, the FDA requires that the applicant conduct appropriate post-approval studies to verify and describe the clinical benefit of the product.

OCEAN, a randomized, phase 3 trial was conducted to serve as the confirmatory study to verify the clinical benefit of melphalan flufenamide.

OCEAN was a multicenter, open-label, randomized phase 3 trial comparing melphalan flufenamide and dexamethasone (MelDex) to pomalidomide and dexamethasone (PomDex) in patients with RRMM who had received 2-4 prior lines of therapy. The study randomized 495 patients 1:1 to MelDex versus PomDex. The primary endpoint was progression-free survival (PFS) superiority as assessed by an independent review committee (IRC). Overall survival (OS) and ORR were key secondary endpoints.

1.1.1.1 Issues

1. <u>Potential detriment in OS in the MelDex Arm</u>

There were higher rates of deaths in the MelDex arm (117/248; 47.6%) than in the PomDex arm (108/249; 43.4%) in the ITT population. The observed median OS was 5.3 months shorter in the MelDex arm compared to that of the PomDex arm (19.7 months vs. 25.0 months; HR 1.104 (95% CI: 0.846, 1.441). The updated OS results were consistent with the OS results from the primary analysis and continued to demonstrate higher rates of deaths in the MelDex arm with a HR>1.

The higher MelDex death rate was most notable in events that occurred beyond 60 days after the last dose; 31% of deaths in the MelDex arm versus 25% in the PomDex arm. There was a higher rate of Grade 3-4 TEAEs in the MelDex arm (90%) compared to the PomDex arm (74%). The increase in Grade 3-4 TEAEs were primarily due to higher rates of cytopenia.
OS is an efficacy and safety endpoint. A negative trend in OS, particularly in the context of drugs with substantial toxicity, is an important determinant of safety. Although not statistically significant, the OS results suggests an increased risk of death in patients receiving melphalan flufenamide compared to pomalidomide.

The assessment of overall survival in the ITT population based on all randomized patients is used for the FDA's evaluation of overall survival and benefit-risk.

The Sponsor conducted multiple post hoc exploratory subgroup analyses and initially proposed that the concerning OS HR result was primarily driven by patients who had received prior transplant and that there was benefit in patients who had not received a previous transplant. More recently, the Sponsor contends that the concerning OS results may be limited to patients who have had a transplant and have a time to progression (TTP) after transplant <36 months.

There are several limitations to the Sponsor's assertions. The subgroups identified by the Sponsor in the statistical analysis plan (SAP) were listed as exploratory analyses and were not powered prospectively to control for type I error. Subgroup analyses should only be used to confirm a consistent treatment effect across subgroups. Results from subgroup analyses cannot be used to conclude benefit in a subset of patients, when the overall patient population has shown a detrimental treatment effect.

The Sponsor has also hypothesized that the OS results in the OCEAN trial could be explained by the differential treatment effect of pomalidomide on overall survival based on age rather than

due to a safety signal with melphalan flufenamide. Specifically, that in the pomalidomide arm, older patients do poorly in terms of survival compared to younger patients.

Again, this a post hoc exploratory analysis that can only be hypothesis-generating. While our own analyses do not suggest significant interaction with age and IMiDs on OS, even if there were an interaction, this does not negate the overall results observed in the OCEAN trial and it does not provide substantial evidence of safety and effectiveness of melphalan flufenamide.

In fact, the preponderance of evidence from the prespecified analysis on the ITT population and in all other subgroups suggests an increased risk of death in patients and a potential for harm with melphalan flufenamide.

2. <u>Failure to Demonstrate a PFS benefit</u>

The original primary analysis submitted to the FDA on May 7, 2021, showed that OCEAN failed to meet the primary endpoint of a statistically significant improvement in PFS as assessed by IRC in the MelDex arm compared to the PomDex arm. After the FDA raised concerns regarding the lack of statistical significance, the Sponsor conducted a re-assessment of 29 patients (after the primary database lock) and contends that PFS superiority was met. Because the PFS definition for the primary analysis required confirmation of PD in two consecutive assessments, FDA informed the Sponsor that the primary analysis of PFS should be based on patients with confirmed PD as an event. The FDA's analysis considering only patients with confirmed PD as an event demonstrated that PFS was not statistically significant; HR 0.833 (95% CI: 0.665, 1.044; p-value = 0.1122). All sensitivity analyses confirmed the original primary analysis.

Regardless of the p-value and the statistical significance, the treatment effect estimates with respect to the difference in median PFS is only 2 months. Additionally, the 2-month difference in PFS improvement did not translate to a benefit in survival; rather, a detriment in survival is observed. The lower survival observed negates the clinical benefit of the observed PFS improvement. The FDA position paper referenced by the sponsor reinforces this. The paper states that "An anti-cancer therapy that prolongs PFS is not considered safe and effective if the therapy results in a detrimental effect on OS" [Amatya, et al 2021].

3. <u>Lack of an appropriate dose</u>

The safety concerns and the toxicity observed indicate that that the flat dose of 40 mg is not optimized to support a favorable benefit-risk profile. There was limited dose exploration and PK evaluation in early melphalan flufenamide studies prior to initiation of the Phase 2 HORIZON trial. There was limited efficacy, safety, and PK data available from the initial melphalan flufenamide Phase 1 and Phase 2 studies. Population Pharmacokinetics (PK), exposure-response (E-R), or dose-response analyses were not conducted in the early studies to support the 40 mg flat dose before moving to phase 3. At the time of accelerated approval, a PMR was issued for

exposure-response analyses and to evaluate the impact of dose in varying body sizes following the accelerated approval. In the confirmatory trial, OCEAN, high rates of adverse events and dose modifications were observed in the melphalan flufenamide arm compared to the control arm. Additionally, there was an association between higher melphalan (the active metabolite of melphalan flufenamide) exposure and increased risk of safety events such as Grade 3 and higher treatment emergent adverse events (TEAE) and rates of drug discontinuations, interruptions, and reductions, indicating that doses that result in lower exposures could be better tolerated. Importantly, melphalan exposures had no clear association with progression-free survival or overall survival. Additionally, patients with lower body weight tended to have higher melphalan exposure. The relationship was similar with body surface area (BSA) and melphalan exposure. Therefore, dosing by body size or BSA would decrease variability in exposure and may reduce the risk of safety events in patients with higher exposures, although the optimal target exposure remains to be identified.

Conclusion

Melphalan flufenamide was granted accelerated approval in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor (PI), one immunomodulatory agent (IMiD) and one CD38 directed monoclonal antibody. The approval was based on the results from a single-arm trial, HORIZON, that evaluated melphalan flufenamide in combination with dexamethasone at a flat dose of 40 mg. The results from the randomized confirmatory study OCEAN failed to confirm clinical benefit and suggests that the benefit-risk profile of melphalan flufenamide is unfavorable. Additional clinical study is needed to identify an appropriate dose optimized for a favorable benefit-risk profile.

The Applicant's Position:

The US Food and Drug Administration (FDA) and Oncopeptides agreed to collaborate in a joint briefing document supporting ODAC discussion of Pepaxto® (melphalan flufenamide; also known as melflufen) benefit/risk in patients with relapsed/refractory multiple myeloma (RRMM). The discussion should be held in light of the heterogeneity of outcomes first identified in the randomized, head-to-head, controlled Phase 3 study OCEAN (OP-103), based on patient age interaction for immunomodulatory drugs (IMiD®) and prior autologous stem cell transplant (ASCT) interaction for Pepaxto. These interactions overlap due to the correlation between patient age and ASCT eligibility, and although they make interpretation of the data complex, they clarify the results from OCEAN and support a positive benefit/risk profile for Pepaxto. Importantly, the patient age interaction for IMiDs has been confirmed in other studies, as discussed below and detailed in Appendix 1.

Pepaxto in combination with dexamethasone (dex), was first approved in February 2021 under accelerated approval based on promising data from the HORIZON study (OP-106). Additional data from the confirmatory OCEAN study, one of few randomized, head-to-head active

comparator oncology studies in the RRMM patient population, further supported the benefit/risk profile of Pepaxto. OCEAN compared Pepaxto/dex to pomalidomide/dex in patients with RRMM who had received 2 to 4 prior lines of therapy (an earlier line population than in HORIZON). The OCEAN study was completed in May 2021 and met the primary endpoint of superiority on progression-free survival (PFS) for Pepaxto/dex vs. pomalidomide/dex but showed numerically shorter overall survival (OS) vs. pomalidomide/dex. These data led to protracted interactions with the FDA and European Medicines Agency (EMA), which are presented in Appendix 2.

Pepaxto was briefly withdrawn from the US market on October 22, 2021, following FDA pressure. However, the emergence of historical registrational and non-registrational clinical data demonstrating heterogeneity of IMiD OS outcomes by age (i.e., better response in patients <65 years of age), prompted Oncopeptides to rescind this action on January 13, 2022.

Oncopeptides' actions to validate the heterogeneity of IMiD OS outcomes were supported by the Committee for Medicinal Products for Human Use (CHMP) as part of the EMA marketing authorization review of Pepaxto. There is a lack of existing IMiD subgroup data by age, and detailed OS data are generally not in the public domain, but Oncopeptides was able to receive data from IMiD registrational trials from European regulatory agencies.

As shown in Appendix 2, Oncopeptides initiated actions in June 2021 to investigate potential heterogeneity of age-related outcomes with IMiDs. The findings from these investigations (detailed in Appendix 1) supported CHMP's June 2022 positive opinion that will result in Pepaxto (brand name Pepaxti in the European Union [EU]) authorization and availability in the EU.

Although this age-dependent heterogeneity of IMiD OS outcomes in patients with RRMM was first identified in OCEAN, subsequent investigations of accessible registration studies consistently show a heterogenous treatment effect due to this interaction. Prior IMiD publications typically omitted OS discussions in patient subgroups. Given the prevalent use of IMiD therapy in RRMM over the last decade, Oncopeptides believes these data are important to communicate to patients and treating clinicians.

Applicant's Position on the Pepaxto Benefit/Risk Profile

Pepaxto/dex has meaningful clinical activity with a manageable safety profile in patients with heavily pretreated RRMM, as indicated by the HORIZON study. The randomized, comparative OCEAN study confirmed the safety of Pepaxto/dex and provides important new understanding of optimal Pepaxto use, as well as a previously unknown safety signal for IMiD use in elderly patients with RRMM.

Pepaxto/dex provides meaningful efficacy in adult patients with RRMM who have received at least 4 prior lines of therapy and whose disease is refractory to at least 1 proteasome inhibitor (PI), 1 immunomodulatory agent, and 1 CD38-directed monoclonal antibody (mAb), i.e., the currently approved US indication. Additionally, OCEAN data show that to benefit from Pepaxto, patients should either not have received a prior ASCT, or if a prior ASCT was received, patients should not have relapsed within 36 months of a prior ASCT.

Most MM patients receive high-dose melphalan as a myeloablative conditioning regimen before an ASCT. For patients with an early relapse (<36 months) following an ASCT, receiving further alkylator-based therapy is not recommended per the joint European Hematology Association (EHA) and European Society for Medical Oncology (ESMO) clinical practice guidelines. Based on OCEAN data, in patients whose disease relapsed within 36 months of a prior ASCT, potential harm cannot be excluded with Pepaxto compared with pomalidomide. Thus, the Applicant proposes that the label should include this information and advise against Pepaxto use in these patients. Future Pepaxto studies in patients with RRMM will omit these patients in order to eliminate confounding and better represent benefit/risk in the intended patient population. OCEAN and other studies show that pomalidomide and other IMiD products demonstrate age-related heterogeneity of outcomes when used to treat patients with RRMM. Patients <65 years of age obtain meaningful OS benefit with IMiDs, whereas patients ≥75 years of age do not (details are provided in Appendix 1). To what extent this is driven by toxicity and/or activity remains to be elucidated. Given the broad use of IMiDs in MM, clinicians should be informed of this heterogeneity, so they make informed decisions for patient therapy.

These 2 recently identified interactions confound interpretation of observed PFS and OS outcomes in the Full Analysis Set (FAS; i.e., intention-to-treat) population in OCEAN, given the overlap between age and eligibility for ASCT (i.e., younger age is generally associated with a higher rate of eligibility for ASCT).
The safety profile of Pepaxto/dex in OCEAN confirmed that observed in previous studies.

When accounting for these factors, Pepaxto provides a positive benefit/risk in adult patients with RRMM who have received at least 4 prior lines of therapy and whose disease is refractory to at least 1 PI, 1 immunomodulatory agent, and 1 CD38-directed mAb. However, physicians should be informed that potential harm cannot be excluded with Pepaxto/dex in patients with time to progression (TTP) <36 months after a previous ASCT.

Applicant's Regulatory Position

OCEAN met the primary endpoint of PFS with a positive hazard ratio (HR) of 0.79 favoring Pepaxto/dex vs pomalidomide/dex. When accounting for the identified heterogeneity of outcomes for Pepaxto/dex in patients who relapsed within 36 months of a prior ASCT and pomalidomide/dex by patient age in line with FDA precedence (Amatya et al. 2021), the OCEAN data fulfil the post-marketing requirements of a confirmatory study following the accelerated approval and confirm a positive benefit/risk profile for Pepaxto/dex. Thereby, the data support full new drug application (NDA) approval in adult patients with RRMM who have received at least 4 prior lines of therapy and whose disease is refractory to at least 1 PI, 1 immunomodulatory agent, and 1 CD38-directed mAb. However, physicians should be informed that potential harm cannot be excluded with Pepaxto/dex in patients with TTP <36 months after a previous ASCT.

The Applicant plans to update the label to appropriately communicate potential risk given the recent data.

1.2 Current Accelerated Approval Indication Based on the HORIZON Study

The Applicant's Position:

Pepaxto is an alkylating drug indicated in combination with dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody.

Limitations of Use

Pepaxto is not indicated and is not recommended for use as a conditioning regimen for transplant outside of controlled clinical trials.

The FDA's Position

FDA agrees this is the current accelerated approval indication and the limitation of use statement.

1.3 Background

The Applicant's Position:

1.3.1 Regulatory History

A detailed chronological description of key interactions with the FDA and EMA is included in Appendix 2.

Pepaxto NDA 214383 was approved on February 26, 2021 under 21 CFR 314 Subpart H accelerated approval based on response rate in HORIZON. The current approved indication is provided in Section 1.2.

In April 2021, Oncopeptides submitted a marketing authorization application to EMA, seeking conditional marketing authorization (CMA) based on data from HORIZON.

The top-line results from the intended confirmatory randomized, controlled, Phase 3 study, OCEAN, which became available in May 2021 (based on a February 3, 2021 data cutoff), showed that the study met the primary endpoint of PFS with a positive HR of 0.79 favoring Pepaxto/dex vs pomalidomide/dex. The study also showed a HR for OS of 1.104 for Pepaxto/dex vs pomalidomide/dex. Based on the OS result, the FDA issued a partial clinical hold on July 7, 2021 and publicly alerted patients and health care professionals on July 23, 2021 that the trial showed an increased risk of death for patients who received Pepaxto/dex.

In parallel, data from the Phase 3 OCEAN study was submitted to the EMA supporting a full Marketing Authorisation Application based on HORIZON and OCEAN data. On June 23, 2022, the CHMP issued a consensus positive opinion for a full approval of Pepaxto (brand name Pepaxti in the EU). In Europe, Pepaxti will be indicated in combination with dex for the treatment of adult patients with RRMM who have received at least 3 prior lines of therapy, whose disease is refractory to at least 1 PI, 1 immunomodulatory agent, and 1 anti-CD38 mAb, and who have

demonstrated disease progression on or after the last therapy. For patients with a prior ASCT, the TTP should be at least 3 years from transplantation.

A summary of key conclusions supporting authorization in the EU is provided in Appendix 3a. That information is taken from the verbatim 158-page EMA/CHMP assessment report provided in Appendix 3b.

The FDA's Position

The regulatory actions of other agencies are not relevant to the discussion at the ODAC and FDA regulatory decisions. The FDA must make regulatory decisions that are consistent with the U.S. legal and regulatory framework. That framework requires us to consider whether the OCEAN confirmatory study verifies that melphalan flufenamide is of clinical benefit to patients when used in accordance with its U.S.-approved indication. The information discussed at the ODAC should be viewed independently to inform decisions regarding benefits and risks of melphalan flufenamide for the indicated U.S. patient population.

The FDA disagrees with the Applicant's presentation of the regulatory history for the topline results of the OCEAN, confirmatory study, and the description of the events leading up to the NDA withdrawal as indicated below in Table 1.

The topline results shared with the Agency showed that the OCEAN trial failed to demonstrate PFS superiority, and the overall survival was worse in the melphalan flufenamide treatment arm compared to the control arm. The Sponsor initiated a re-analysis of the PFS results after the Agency conveyed their concerns and submitted revised results indicating PFS superiority on July 9, 2021.

Subsequently, the Sponsor also initiated and submitted several post hoc exploratory analysis in an effort to address the concerning OS results. However, these post hoc analyses did not adequately address the FDA concerns regarding the benefit-risk for melphalan flufenamide. An ODAC meeting was scheduled for October 28, 2021 to discuss the benefit-risk of melphalan flufenamide. Following receipt of the FDA's ODAC briefing document, an Oncopeptides board member contacted the FDA on October 18, 2021, requesting a meeting to discuss options regarding melphalan flufenamide and the ODAC. At a meeting on October 19th, the FDA reiterated their concerns outlined in the briefing document and the reason for the ODAC. At a follow-up meeting on October 20th, the Sponsor stated they planned to voluntarily withdraw the NDA for melphalan flufenamide and requested cancellation of the October 28, 2021 ODAC meeting and that the FDA ODAC briefing document not be made public.

The ODAC meeting, planned for October 28, 2021, was cancelled after receipt of a formal withdrawal letter on October 22, 2022. The FDA initiated the administrative processes to withdraw the NDA on the same day. During this time, there were no additional analyses conducted by the FDA and there was no communication from the Sponsor until the receipt of the notice from the Sponsor to rescind the withdrawal request. The Sponsor has not submitted new clinical data with melphalan flufenamide, but rather post hoc, exploratory, subgroup analyses from existing trials and analyses of IMiD trials external to the OCEAN trial.

The timeline for the several post hoc subgroup analysis of OS initiated and submitted by the Sponsor are displayed in Table 2.

Table 1 FDA Regulatory History

Date	Regulatory Event
Feb 8, 2013	IND initiated; Sponsor Oncopeptides
Aug 12, 2016	Special Protocol Assessment (SPA) Agreement Letter Issued for OCEAN. The primary endpoint as per the SPA was to demonstrate PFS superiority.
Feb 26, 2021	Accelerated Approval granted
May 24, 2021	Pre-sNDA meeting held to discuss the planned submission of the results of the randomized confirmatory study, OCEAN. Top line results were not included.
May 25, 2021	Press release of top line results of OCEAN; only non-inferiority results released; PFS superiority results and OS results were not included in the press release.
June 9, 2021	Topline results shared with the Agency following an information request (IR); OCEAN trial failed to demonstrate statistical significance for the primary PFS endpoint and demonstrated worse OS in the Melphalan flufenamide arm.
June 17, 2021	T-Con with Sponsor to discuss FDA's concerns regarding the results of OCEAN.
July 6, 2021	Sponsor submitted post hoc re-analysis of PFS indicating nominal superiority.
July 7, 2021	Trials evaluating melphalan flufenamide placed on hold under IND 116362.
July 28, 2021	CDER Safety Alert issued https://www.fda.gov/drugs/drug-safety-and-availability/fda-alerts-patients-and-health-care-professionals-about-clinical-trial-results-showing-increased
Sept 3, 2021	FR notice published announcing ODAC meeting to OCEAN results
Oct 7, 2021	FDA sent the FDA's ODAC briefing document to the Sponsor.
Oct 18, 2021	FDA was contacted by a designated board member of Oncopeptides.
Oct 19, 2021	FDA met with the designated board member and Sponsor to discuss options regarding melphalan flufenamide and ODAC.

Oct 20, 2021	Second meeting with designated board member and Sponsor. Oncopeptides stated that they planned to pursue formal withdrawal of approval.
Oct 22, 2021	NDA 214383 Withdrawal request received.
Oct 22, 2021	ODAC meeting scheduled for Oct 28, 2021 was cancelled.
Oct 22, 2021	OCE and Review division notified ORP that FR notice needed for melphalan flufenamide withdrawal, initiating withdrawal process.
Jan 13, 2022	Sponsor sent notification rescinding the previous NDA withdrawal request. Communication stated marketing in US was discontinued and no intention to market at this time.
Jan 21, 2022	T-con initiated by the FDA to discuss reasons for Sponsor rescinding withdrawal. The Sponsor stated that they would provide additional data/analyses by end of Feb 2022.
Mar 9, 2022	Additional analyses based on published data from IMiD trials received from the Sponsor. The Sponsor's analyses, based on post hoc subgroup exploratory analyses from external trials reported in the literature, did not address the Agency's clinical benefit and safety concerns.
Mar 18, 2022	T-con to discuss the additional analyses. The Agency reiterated their concerns.
June 14, 2022	FDA informed Sponsor of plans to reconvene an ODAC to discuss the benefit-risk of melphalan flufenamide.

Source: FDA Analysis

Table 2 Timeline of Post hoc Analyses Initiated by the Sponsor and Submitted to FDA

Date	Analysis submitted
July 2021	• OS subgroup analyses within treatment arm by age (<65, 65-75, ≥75)
August 2021	• OS subgroup analyses by prior ASCT (<5 years, ≥5 years since transplant, no transplant)
March 2022	• OS age subgroup analyses • OS gender subgroup analyses • OS multivariable analyses • OS modification by age in IMiD treatment effect (IMiD trials information from literature)

July 2022	• OS subgroup analyses by TTP following a prior ASCT (TTP < 36 months, TTP ≥ 36 months or no ASCT

Source: FDA Analysis

1.3.2 Identification of True Heterogeneity in OCEAN

The Applicant's Position:

Prior to completion of the OCEAN study, there was no publication mentioning age-related heterogeneity with pomalidomide or other IMiD products. During 2021, Oncopeptides analyzed the complex OS results from OCEAN. This led to pursuit of registrational data for pomalidomide and other IMiD products to investigate age-related heterogeneity. As a result, Oncopeptides was able to obtain data from several studies used to gain registration for lenalidomide and pomalidomide across global markets, and the data showed consistent signals for age-related OS heterogeneity for IMiDs.

Pomalidomide in combination with dex was chosen as the comparator in OCEAN because it is commonly used in patients with late-stage RRMM, regardless of patient age. Pomalidomide/dex was approved for treatment of RRMM based on compelling PFS and OS improvement compared to high-dose dex in the overall ITT population in study MM-003. PFS was significantly longer for pomalidomide/dex with an HR of 0.45 (95% CI: 0.35-0.59 p <0.001). OS was also significantly longer with an HR of 0.70 (95% CI: 0.54-0.92 p = 0.009). Given that the pomalidomide label has no information on differential efficacy or safety among patient age groups, it was unexpected to find that PFS results did not predict OS within the age subgroups for pomalidomide/dex in OCEAN. Pepaxto/dex resulted in shorter survival than pomalidomide/dex in younger patients but longer survival than pomalidomide/dex in older patients (median OS with Pepaxto/dex vs pomalidomide/dex: age <65 years, 16.2 months vs 31.7 months; age 65-74 years, 20.5 months vs 20.9 months; age ≥75 years, 26.5 months vs 17.5 months)[1]. This association between pomalidomide and age has been externally confirmed in an extensive review of large randomized clinical trials (e.g., MM007 and Myeloma XI) that isolate the treatment effect of pomalidomide and other IMiDs. The full description of this investigation is provided in Appendix 1. While age itself has a significant prognostic value for survival at the time of diagnosis of MM, the prognostic value of age in terms of survival is reduced by each subsequent line of treatment (Appendix 1). Large datasets demonstrate that after 2 prior lines of therapy, age is no longer a material prognostic factor for survival. Because OCEAN enrolled patients with at least 2 prior lines of treatment, no significant survival differences based on age within each treatment arm should have been expected in this trial.

Discussions with the EMA rapporteurs and a hearing with the EMA Scientific Advisory Group on Oncology (SAG-O) served to further refine the interpretation of the results. Post-hoc multivariable analyses of pre-specified subgroups revealed significant OS HR differences across age and previous ASCT (Section 2.3.3). These 2 subgroups are closely related since age and

[1] February 3, 2022 data cutoff date.

comorbidities are the main factors used to assess eligibility for an ASCT. Because older patients are generally frailer and have more comorbidities, they are generally less likely to be eligible for an ASCT. For Pepaxto, it has been concluded that potential harm compared with pomalidomide cannot be excluded in patients who received a prior ASCT (often younger patients) and progressed within 36 months after transplantation. The supporting data and a discussion around the biological rationale are provided in this document. Similarly, pomalidomide/dex demonstrated heterogeneity in survival outcomes along the age spectrum.

Due to the age effect on OS with pomalidomide/dex, the OS HR for the overall population in OCEAN is dependent on the actual age distribution, which significantly confounds the OS results and makes them challenging to interpret. This type of situation is discussed in ICH E9 guideline ("in the presence of true heterogeneity of treatment effects, the interpretation of the main treatment effect is controversial") and can conceptually be applied for the OCEAN study. It is therefore appropriate to interpret the OS results based on the relevant age and/or ASCT subgroups. This is also in line with EMA/CHMP/539146/2013; *Guideline on the investigation of subgroups in confirmatory clinical trials* as well as the FDA position paper "Subgroup analyses in oncology trials: regulatory considerations and case examples" (Amatya et al. 2021).

The FDA's Position

The Applicant makes several references to the actions of other regulatory agencies. The regulatory actions of other agencies are not relevant to the discussion at the ODAC and FDA regulatory decisions. The FDA must make regulatory decisions that adhere to U.S. laws and regulations. The information discussed at the ODAC should be viewed independently to inform decisions regarding the benefit-risk of melphalan flufenamide for the U.S. patient population. It is the Applicant's 's responsibility to provide substantial evidence of safety and effectiveness of melphalan flufenamide.

The FDA disagrees with multiple arguments put forth by the Applicant above; these are outlined below.

Caution on Post hoc and subgroup analyses

Because the Applicant's presentation relies heavily on post hoc subgroup analyses, FDA provides a brief cautionary note on their interpretation.

In evaluating data from a trial, a fundamental principle of statistical evaluation at the FDA is data should be analyzed as specified in the SAP. While age and transplant status were included in the protocol, these were listed as exploratory analyses and did not have a type I error control plan.

Subgroup analyses have an important role in clinical trials. Subgroup analyses are routinely used to check homogeneity of a treatment effect across patient groupings. Subgroup analyses are also commonly used for exploratory and hypothesis-generating purposes.

However, results from subgroup analyses cannot provide conclusive evidence of efficacy and safety, as such analyses can be misleading or biased and are subject to over-interpretation [Fleming 2010, Hemmings, 2014]. Even in a case where only one or two exploratory analyses are presented, if the analyses were not pre-specified in the protocol, type I error probability is difficult or impossible to control because many tests or other influences could have motivated the selection of the presented results [Cui, et al 2002].

FDA guidance for Industry E9 Statistical Principles for Clinical Trials [E9-fnl.PDF,1998] includes the following statements on exploratory subgroup analyses and pre-specifying analyses.

- Any conclusion of treatment efficacy (or lack thereof) or safety based solely on exploratory subgroup analyses is unlikely to be accepted.
- Only results from analyses envisaged in the protocol (including amendments) can be regarded as confirmatory.

The FDA guidance also describes how primary and secondary analyses should be specified in the protocol and statistical analysis plan. The guidance further states that type-I error probability should be strongly controlled when performing multiple statistical tests. Generally, pre-specified analyses are those analyses for which a type-I error control plan has been established.

See also FDA Appendix 10.1 for more discussion on statistical issues with post hoc analyses, subgroup analyses, and multiplicity.

Additionally, all post hoc models under discussion (FDA's and the sponsor's) are considered hypothesis-generating and not suitable for making conclusions. Further, it is well-known that using model selection algorithms to choose covariables tends to provide underestimates of the residual variance. This leads to overly optimistic (too narrow) confidence intervals for effect estimates. Therefore, any claim that an effect is statistically significant should be viewed with skepticism.

Acknowledging the limitations of the post hoc exploratory analysis, the available data does not support the conclusive Sponsor statements.

1. <u>True heterogeneity in OCEAN</u>

The FDA disagrees with Sponsor's statement "the shorter survival than pomalidomide/dex in younger patients but longer survival than pomalidomide/dex in older patients is due to the age effect on OS with pomalidomide/dex and makes the results difficult to interpret".

- The shorter survival in patients <65 years and 65-74 years in the MelDex arm compared to the PomDex arm are consistent with the results in the ITT population in the OCEAN Study.
- The number of subjects in the age group 75 and older is quite small, N=37 in the melphalan flufenamide arm and N=39 in the pomalidomide arm. In the OCEAN trial, this apparent benefit in the small subgroup of adults ≥75 years of age or is likely a random chance event.

- The OCEAN trial was not designed to evaluate the effect of PomDex treatment in the various age subgroups.

The preponderance of evidence from the prespecified analysis on the ITT population and in all age subgroups except the small subgroup of patients ≥75 years of age demonstrates a HR >1 in the melphalan flufenamide arm compared to the pomalidomide arm. A potential detrimental effect of melphalan flufenamide+ dexamethasone on survival in the overall population including patients ≥75 years cannot be ruled out.

2. <u>The association between age and pomalidomide has been externally confirmed.</u>

The FDA disagrees with this conclusion. Analysis based on cross trial comparisons are difficult to interrupt and biased. Differences in baseline characteristics, study design and difference in treatment regimens exist and confound interpretability of results. As an example, the Myeloma XI trial referenced by the Applicant compared lenalidomide to observation as maintenance following receipt of triplet induction regimens that included two different IMiD drugs in the combinations. Study MM007 evaluated pomalidomide bortezomib dexamethasone vs. bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma who had received 1-3 prior regimens.

As an exploratory analysis, FDA also evaluated the IMiD effect on survival and age using patient-level data from several trials of IMIDs submitted to the agency. The FDA's exploratory analysis did not find an interaction between IMiD, age and survival and does not support the Applicant's conclusions. See further details in FDA Appendix 10.2.

3. <u>The prognostic value of age as it relates to survival is reduced by each subsequent line of treatment, no effect expected after 2 prior lines.</u>

The prognostic value of age decreasing with each additional line of therapy is mentioned by the Applicant. This is based on a retrospective finding, rather than the result of a designed experiment. The statement that "large data sets demonstrate" tends to exaggerate the non-specific finding. After multiple lines of therapy, it appears plausible that patients' life expectancy may be so short as to make finding differences with respect to age groupings difficult. The fact that the observed data in OCEAN tend to deviate from an assumption that age is not prognostic for people having had >2 lines of treatment does not indicate that subgroup analyses based on age should be the basis for decision making.

4. <u>The Use of TTP with 36-months cut-off to define a population</u>

The Applicant is proposing a subgroup of patients who received a transplant and had a TTP after transplant of 36 months.

This subgroup is based on a recent post hoc exploratory analysis. The Applicant had previously proposed a different definition and time since transplant cut-off of 5 years.

Even if we consider the subgroup based on TTP of at least 36-months, the time cut off to define the patient population is arbitrary. There is no established cut-off for time to progression from transplant with biological rationale for risk of death.

While it is true that the EHA EMSO guidelines [Dimopoulos, et al 2021] state:

> Second-line ASCT is a logical approach for patients who received primary therapy that included an ASCT followed by lenalidomide maintenance and had an initial remission duration of ≥ 36 months.

The International Myeloma Working Group (IMWG) guidelines [Moreau, et al 2021] state the 36-month cut-off is arbitrary.

The IMWG recommendations state:

> The most important prognostic factor for progression-free survival after salvage ASCT is the duration of remission after the first ASCT procedure. Because front-line ASCT followed by lenalidomide maintenance is associated with a median duration of response of 50 months, salvage ASCT should not be recommended for patients with a response duration of less than 3 years after the first ASCT, but this cut-off is arbitrary and could be reduced to 2 years if the patient has not received maintenance therapy (grade 2A recommendation).

Even if we consider the 36 months cut-off, this cut-off is in reference to impact on progression free survival for patients receiving a salvage transplant with high dose melphan..

Additionally, the Applicant has analyzed TTP after transplant, which is defined as time from transplant to progression, irrespective of treatment initiation with melphalan flufenamide. If the analysis is done using time since transplant (using the definition initially proposed by the sponsor), which is defined as time from last transplant to randomization (when melphalan flufenamide would have been received if randomized to that arm), a different result is obtained (**Table 19**).This analysis demonstrates the variability of the results and risk of misinterpretation of results of post hoc exploratory analysis.

5. **Potential harm with melphalan flufenamide only exists for populations who received prior ASCT (often younger patients) and progressed within 36 months after transplant.**

FDA does not agree with this conclusion. Acknowledging the limitations of subgroup analysis, FDA notes that OS detriment was seen in multiple subgroups in the ITT population (Figure 6). Additionally, FDA constructed an exploratory model (FDA Appendix 10.3), which indicates that factors other than age or transplant also could explain the variability in OS.

6. <u>The Applicant's interpretation of FDA paper by Amatya et al.</u>

The FDA disagrees with the Applicant's interpretation of this paper. The paper by Amatya et al discusses different types of subgroups including inferential subgroups (with adequate power and alpha control), supportive subgroups (pre-specified but without prospective testing planned), or exploratory subgroups (to generate hypotheses). The paper discusses how regulatory decisions were based on subgroup analyses. In the first set of examples from the paper, the indication was granted to the ITT population despite a decreased treatment effect in a subgroup. This was done as the subgroups were not adequately powered to allow for meaningful conclusions. In the second set of examples in this paper, the overall ITT results were still positive, but the results were primarily driven by a subpopulation. The indication was then restricted to the subpopulation. It is important to note:

- In both sets of examples, the overall ITT results were positive.
- There are no examples where the overall population suggested harm and a subpopulation was carved out.
- The article states "An anti-cancer therapy that prolongs PFS is not considered safe and effective if the therapy results in a detrimental effect on OS".

2 Efficacy

2.1 Description of Clinical Setting

The Applicant's Position:

2.1.1 Overview of MM

MM is an incurable hematologic cancer. It is the second most common hematologic malignancy and accounts for 2% of all cancers and 10% of all hematologic malignancies (Rajkumar 2009; SEER 2022). In 2022, it is estimated that 34,470 new cases of MM and about 12,640 MM-related deaths will occur in the US (SEER 2022). MM predominantly affects older patients, with a median age at diagnosis of 69 years. The disease is more common in males and among individuals of African American descent (SEER 2022).

MM is characterized by a clonal proliferation of plasma cells in the bone marrow and the production of excessive amounts of a monoclonal immunoglobulin (Ig; usually of the IgG or IgA type or free light chain [paraprotein, monoclonal protein spike, or M component]).

Patients with MM often have significantly reduced quality of life due to bone pain, bone fractures, fatigue, anemia, infections, hypercalcemia, hyperviscosity of the blood, and decreased renal function (including renal failure). Patients with MM may have symptom-free periods, but the disease inevitably relapses. Although patients with relapsed disease can achieve responses to subsequent anti-myeloma regimens, the duration of response (DOR) typically shortens with successive relapses with associated increase in drug resistance. Patients with advanced disease often become refractory to all available treatment options. While the advent of novel treatment

regimens has translated to improvements in outcomes over the past 15 years (Sonneveld 2017), the disease is still ultimately fatal, with an estimated 5-year survival rate of 57.9% (SEER 2022).

2.1.2 Role of ASCT in MM

In MM, treatment with an alkylating agent, high-dose melphalan (200 mg/m^2), was established as a conditioning regimen before ASCT and remains the standard of care for younger, fit patients today (Dimopoulos 2021; Mikhael 2019). First-line therapy for patients with MM is chosen based on eligibility for an ASCT. Several factors are considered when assessing eligibility for ASCT, including age (<70 years), fitness, and comorbidities (Dimopoulos 2021; NCCN 2022).

The most recent joint EHA-ESMO clinical practice guidelines recommend salvage ASCT for eligible patients, but caution that salvage ASCT is not recommended in patients who have a remission duration of less than 36 months after the initial ASCT (Dimopoulos 2021). Real-world data indicate that the median progression-free interval is approximately 45 months after ASCT (Bergin 2021).

The FDA's Position:

FDA generally agrees with the Applicant's position regarding the disease and the role of ASCT in MM. The Agency agrees that the EHA-ESMO clinical practice guidelines caution salvage transplant with a remission duration of less than 36 months. However, the Agency does not agree that this applies to treatment with melphalan flufenamide or that there is a strong biologic rationale as discussed in Section 1.3.2.

2.1.3 Available Therapies and Unmet Medical Need in RRMM

The Applicant's Position:

Current treatment strategies in patients with RRMM include glucocorticoids (dex, prednisolone, methylprednisolone), chemotherapy (primarily alkylating agents), PIs (e.g., carfilzomib and ixazomib), immunomodulatory agents (e.g., pomalidomide), mAbs (e.g., daratumumab and isatuximab [anti-CD38 mAbs] and elotuzumab [anti-SLAMF7 mAb]), antibody-drug conjugates (belantamab mafodotin), selective inhibitors of nuclear export (e.g., selinexor), and chimeric antigen receptor T-cell (CAR T) therapies idecabtagene vicleucel [ide-cel] and ciltacabtagene autoleucel [cilta-cel]).

Patients who have disease that is refractory to all 3 major treatment classes (PIs, immunomodulatory agents, and anti-CD38 mAbs) are referred to as triple-class refractory (TCR) and have a poor prognosis with median OS of around 9.2 months (Gandhi 2019). Since the preferred first-line therapy options in patients with newly diagnosed MM include a combination of 2 of these treatment classes, patients often develop TCR disease as early as after second-line therapy. Treating patients with TCR disease is complex, and there remains no consensus on a clear treatment algorithm.

There are few approved agents available for patients with TCR RRMM who have received 4 or more prior lines of therapy. Belantamab mafodotin received FDA accelerated approval in a triple-class exposed population with at least 4 prior therapies (including at least 1 each: PI, immunomodulatory agent, anti-CD38 mAb) and selinexor is approved in combination with dex in a penta-refractory population that has received at least 4 prior therapies and whose disease is refractory to at least 2 PIs, 2 immunomodulatory agents, and 1 anti-CD38 mAb. Recently, anti-B-cell maturation antigen CAR-T cell therapies ide-cel and cilta-cel were also approved for triple-class exposed patients with at least 4 prior therapies (including at least 1 each: PI, immunomodulatory agent, anti-CD38 mAb) and may represent a treatment option for eligible patients.

Most patients with RRMM will relapse, and DOR with each subsequent therapy is generally shorter (Moreau 2021; Gandhi 2019; Rajkumar 2020). Furthermore, patients with RRMM may be frail due to age, disease symptoms, comorbidities, and adverse effects of prior treatment. To maximize outcomes, agents used in later lines of therapy must be safe, effective, and tolerable and must help maintain quality of life (Chim 2018; Mikhael 2019). Because of the severity of disease and high unmet need in patients with TCR RRMM, agents currently available to these patients were approved under accelerated approval and based on uncontrolled non-randomized trials. Additionally, not all patients may be eligible for these therapies due to the drugs' toxicity profile, cost, or other factors. For example, keratopathy, which is frequently observed with the use of monomethyl auristatin F-coupled antibody-drug conjugates and impacts quality of life (Farooq 2020; Neupane 2021), has been reported with belantamab mafodotin. Selinexor/dex has high rates of gastrointestinal events, confusional state, and insomnia, which may be burdensome for this severely frail patient population. In addition, ide-cel and cilta-cel, like other CAR T-cell therapies, require individualized production and treatment in specialized centers with transplant/cell therapy capabilities, which may result in high costs and limited availability for patients. In addition, monitoring and managing cytokine release syndrome and neurological toxicities, common adverse events (AEs) with ide-cel and cilta-cel, can be done only by specialized health care professionals and require prolonged stays (at least 4 weeks) nearby a certified facility.

Given the limitations of the available therapies, together with the complex disease biology and the heterogeneous patient population in RRMM, including a substantial number of elderly/frail patients, there is a clear unmet medical need for therapies with a different mechanism of action and a tolerable and manageable safety profile. Furthermore, access to therapy with straightforward administration and convenient dosing and without long waiting lists or burdensome procedures is important.

The FDA's Position

The FDA agrees that multiple new therapies have been approved for the treatment of MM. While evidence from literature indicates that patients who become refractory to the three major classes of myeloma therapy have poorer outcomes, new agents with novel mechanisms of action have been approved recently for those patients previously treated with 4 or more prior lines including an IMiD, PI, and anti-CD38, the current melphalan flufenamide indicated patient

population. These novel therapies include selinexor, belantamab mafodotin and CAR-T therapies. Additionally, while most patients in the United States with relapsed disease will have been exposed to an IMID, a PI, corticosteroids, and an anti-CD38 monoclonal antibody after one or two lines of treatment, retreatment with previously used agents or agents in the same class of drug can be effective. Current treatment options for RRMM are shown in Table 3. Although, not shown in the table, the oral drug, melphalan (the active metabolite of melphalan flufenamide), is available to patients with multiple myeloma as well.

The FDA disagrees with the Applicant's position regarding the recent approvals. The Applicant indicates that recent approvals for patients with TCR disease were accelerated approvals based on single arm trials and highlights limitations. FDA notes that accelerated approval still requires demonstration of substantial evidence of efficacy and safety and randomized clinical trials are required to confirm the clinical benefit of therapies granted accelerated approval. Selinexor was initially granted accelerated approval for a refractory late line population and subsequently converted to full approval following confirmation of clinical benefit in a randomized controlled trial. Accelerated approvals may be withdrawn if post marketing trials do not confirm clinical benefit or are not conducted with due diligence.

FDA also disagrees with the Applicant's promotional statements about ease of administration and tolerability in older frail populations. These statements are not substantiated by the current evidence. For example, insertion of a central line is required for the administration of melphalan flufenamide.

Table 3 Treatment Options for RRMM

Drug/Combination	Approval	Indication
Bortezomib	AA (2003)	RRMM/>2L,
Bortezomib	Regular (2005)	RRMM/, 1-3L
Liposomal doxorubicin HCl	Regular (2007)	RRMM/, ≥1L
Lenalidomide with dex	Regular (2005)	RRMM/≥1L
Carfilzomib	AA (2012)	RRMM/,≥1L
Carfilzomib with Rd	Regular (2015)	RRMM/≥1-3 prior lines
Carfilzomib with dex	Regular (2016)	MM, 1-3 prior lines
Pomalidomide with dex	AA (2013)	RRMM/≥2L, including lenalidomide and PI
Pomalidomide with dex	Regular (2015)	RRMM/≥2L, including lenalidomide and PI
Panobinostat with Vd ^	AA (2015)	RRMM/≥2L, including bortezomib and IMiD
Ixazomib with Rd	Regular (2015)	RRMM/≥1L
Daratumumab-IV	AA (2015)	RRMM/≥3L including PI and IMiD
Daratumumab-IV with Rd	Regular (2016)	RRMM/≥1L
Daratumumab-IV with Vd	Regular (2016)	RRMM/≥1L
Daratumumab-IV with Pd	Regular (2017)	RRMM/≥2L, including lenalidomide and PI
Elotuzumab with Rd	Regular (2015)	RRMM/1-3L
Elotuzumab with Pd	Regular (2018)	RRMM/≥2L, including lenalidomide and PI

Selinexor with dex	**AA (2019)***	**RRMM/≥4L, including 2 PIs, 2 IMiDs, and anti-CD38 mAb**
Selinexor with Vd	Regular (2020)	RRMM/≥1L
Daratumumab-IV with Kd	Regular (2020)	RRMM/1-3L
Daratumumab-SC	Regular (2020)	RRMM/≥3L, including PI and IMiD or PI/IMiD double-refractory
Daratumumab-SC with Rd	Regular (2020)	RRMM/≥1L
Belantamab mafodotin	**AA (2020)**	**RRMM/≥4L, including PI, IMiD, anti-CD38 mAb**
Isatuximab with Pd	Regular (2020)	RRMM/≥2L, including lenalidomide and PI
Isatuximab with Kd	Regular (2021)	RRMM/1-3L
Daratumumab-SC with Pd	Regular (2021)	RRMM/≥1L including lenalidomide and PI
Daratumumab-SC with Kd	Regular (2021)	RRMM/1-3L
Idecabtagene vicleucel (BCMA-CART)	**Regular (2021)**	**RRMM/≥4L, including PI, IMiD, anti-CD38 mAb**
Ciltacabtagene autoleucel (BCMA CAR-T)	**Regular (2022)**	**RRMM/≥4L, including PI, IMiD, anti-CD38 mAb**

*Accelerated approval converted to regular following verification of clinical benefit; ; ^ Accelerated approval of Panobinostat was withdrawn in 2021 due to lack of due diligence in verifying clinical benefit; **Red** text indicates approved regimens for patients with 4 or more prior lines of therapy including an IMiD, PI, and anti-CD38
Abbreviations: AA= accelerated approval, anti-CD38 mAb=anti CD38 monoclonal antibodies, dex= dexamethasone, IMiD=immunomodulatory drug, IV=intravenous, Kd=carfilzomib and dexamethasone, L=lines of therapy, Pd=pomalidomide and dexamethasone, PI=proteasome inhibitor, Rd=lenalidomide and dexamethasone, RRMM=relapsed refractory multiple myeloma, SC=subcutaneous, Vd=bortezomib and dexamethasone; not shown is melphalan flufenamide-accelerated approval granted February 26, 2021 but currently withdrawn from the US market.
Source: FDA Analysis

2.1.4 Scientific Rationale for Pepaxto in RRMM

The Applicant's Position:

Pepaxto is a lipophilic peptide-drug conjugate (PDC) with an alkylating payload. The peptide carrier functions as an enzymatic substrate, using the increased metabolic activity of cancer cells to hydrolyze the PDC into multiple active metabolites (primarily mediated by peptidases and esterases). The metabolites are more hydrophilic (compared to the PDC of origin), leading to intracellular enrichment in cancer cells. In cellular assays, Pepaxto inhibited proliferation and induced apoptosis of hematopoietic and solid tumor cells. Retained cytotoxic activity was demonstrated in MM cells with absent or impaired p53 functionality. Pepaxto showed synergistic cytotoxicity with dex in melphalan-resistant and non-resistant MM cell lines.

Pepaxto in combination with dex provides a valuable new treatment option that has demonstrated meaningful response durability coupled with a manageable safety profile in patients with RRMM who have few remaining treatment options. Even in patients with the most difficult-to-treat disease characteristics, such as extramedullary disease and high-risk cytogenetics, the benefit is clinically relevant. Although Pepaxto treatment is often characterized

by a relatively high incidence of hematologic AEs, most notably thrombocytopenia and neutropenia, these AEs can be monitored and managed by hematologists, with no need for additional medical expertise. Grade 3/4 nonhematologic AEs are relatively infrequent.

The FDA's Position

The Applicant's statements above are not supported by strong evidence.

Melphalan flufenamide is an alkylating drug that is processed into metabolites including melphalan. FDA cannot confirm the Sponsor's claims that melphalan flufenamide demonstrated increased activity in cancer cells relative to normal cells as the reports of studies conducted were not submitted to the NDA. The FDA generally agrees with the Applicant's characterization of the results of the in vitro studies conducted with melphalan flufenamide.

The Applicant also states, "Even in patients with the most difficult-to-treat disease characteristics, such as extramedullary disease and high-risk cytogenetics, the benefit is clinically relevant". The available evidence does not support this statement. Acknowledging the limitations of subgroup analysis, OS results from the OCEAN trial indicate that in Figure 6 the Hazard Ratio for overall survival in patents with high-risk cytogenetics is 1.02 (95% CI: 0.71-1.45) and in patients with extra medullary disease is 1.12 (95% CI: 0.59-2.11).

2.2 Summary of Clinical Trials Supporting Efficacy

2.2.1 HORIZON

The Applicant's Position:

HORIZON was a single-arm, open-label, Phase 2 multicenter study. Eligible patients were required to have RRMM. Patients received Pepaxto 40 mg intravenously on Day 1 and dex 40 mg orally (20 mg for patients ≥75 years of age) on Days 1, 8, 15, and 22 of each 28-day cycle until disease progression or unacceptable toxicity. All patients were followed for survival for up to 24 months following progression or start of subsequent anti-myeloma therapy.

In total, 157 patients were included in the US, Spain, Italy, and France.

2.2.1.1 Key Enrollment Criteria

Patients were eligible to be included in HORIZON if they met the following criteria:

Aged ≥18 years with RRMM
Measurable disease by either serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), or SFLC (serum free light-chain)
A minimum of 2 prior lines of therapy, including an IMiD (pomalidomide or lenalidomide) and a PI, and refractory to pomalidomide and/or an anti-CD38 mAb (refractory status included patients who relapsed while on therapy or within 60 days of last dose of pomalidomide and/or an anti-CD38 mAb in any line, regardless of response)

Absolute neutrophil count (ANC) ≥1000 cells/mm^3, platelet count ≥75 000 cells/mm^3, hemoglobin ≥8.0 g/dL, and estimated creatinine clearance (CrCl) ≥45 mL/min

Patients were excluded from study participation if they had had primary refractory disease (i.e., had never had at least a minimal response to any prior therapy).

2.2.1.2 Efficacy Endpoints

The primary endpoint was ORR. The key secondary endpoint was DOR. Other secondary endpoints included PFS and OS.

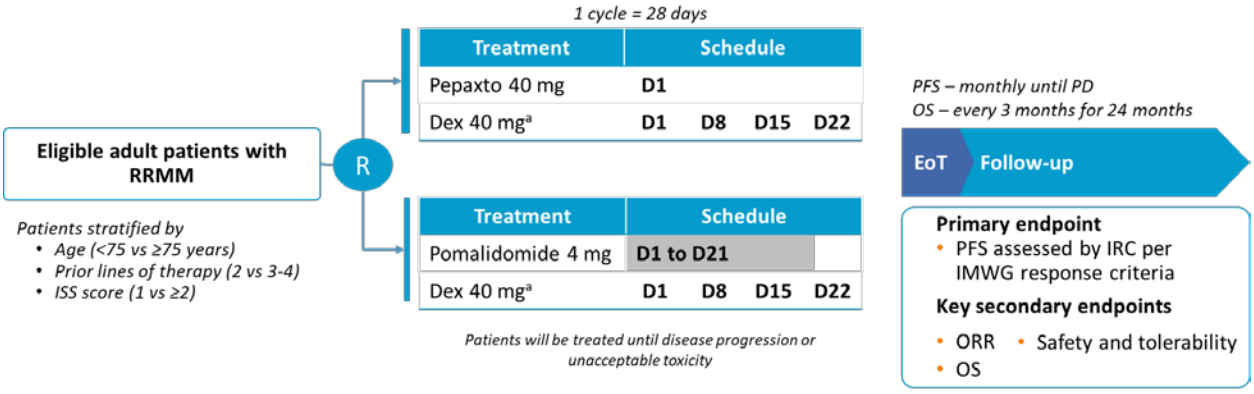
2.2.1.3 Statistical Analyses

ORR was analyzed as the percentage of patients reaching the primary endpoint with 95% exact confidence interval (CI). Time to event endpoints such as DOR, PFS, and OS were summarized as the median with 95% CI using the Kaplan-Meier (KM) method.

2.2.2 OCEAN

OCEAN, a randomized, controlled, open-label, Phase 3 multicenter study, enrolled patients with RRMM who had received at least 2 to 4 lines of prior therapy and had disease refractory to both last line of therapy and to lenalidomide (≥10 mg) administered within 18 months prior to randomization as demonstrated by progressive disease (PD) on or within 60 days of completion of the last dose of lenalidomide. Patients in OCEAN were randomized (1:1) to Pepaxto 40 mg on Day 1 or pomalidomide 4 mg on Days 1 to 21; patients in both treatment arms received dex 40 mg (20 mg if aged ≥75 years) on Days 1, 8, 15, and 22 (Figure 1). The treatment period consisted of 28-day cycles of Pepaxto/dex or pomalidomide/dex therapy.

Figure 1. OCEAN – Study Design



[a]Dex dose reduced to 20 mg in patients aged ≥75 years.
D, day; dex, dexamethasone; DOR, duration of response; EoT, end of treatment; IMWG, International Myeloma Working Group; IRC, independent review committee; ISS, International Staging System; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma.

A total of 495 patients were randomized at 144 sites in the US, Europe, and Asia.

2.2.2.1 Key Enrollment Criteria

Patients were eligible to be included in OCEAN if they met the following criteria:

Aged ≥18 years with RRMM
Measurable disease by either SPEP, UPEP, or SFLC
Received 2 to 4 prior lines of therapy, including lenalidomide and PI, either sequential or in the same line, and refractory (relapsed and refractory or refractory) to both the last line of therapy and to lenalidomide (≥10 mg) administered within 18 months prior to randomization
ANC ≥1000 cells/mm^3, platelet count ≥75 000 cells/mm^3, hemoglobin ≥8.0 g/dL, and an estimated CrCl of ≥45 mL/min

Patients were excluded from study participation if they had been exposed to pomalidomide previously or had known intolerance to either immunomodulatory agents or steroids. Patients who had primary refractory disease (i.e., had never had at least a minimal response to any prior therapy) were also excluded from study participation.

2.2.2.2 Efficacy Endpoints

The primary efficacy endpoint was PFS. Progression dates were assessed by an independent review committee. Key secondary endpoints included ORR, OS, and safety and tolerability.

2.2.2.3 Statistical Analyses

The FAS was defined as all patients who were randomized. Patients were analyzed according to the treatment assigned at randomization. The primary analyses of all efficacy endpoints were performed using the FAS.

The Safety Analysis Set was defined as all patients who received at least 1 dose of Pepaxto, pomalidomide, or dexamethasone. The Safety Analysis Set was used to analyze exposure and safety data. Patients were analyzed according to the treatment actually received.

The primary analysis of PFS was performed using a log rank test stratified by the randomization stratification factors to compare treatment group survival distributions. A stratified Cox proportional hazards model was performed to get an estimate of the relative difference between arms.
The differences in ORR between treatment groups were compared using the Cochran-Mantel-Haenszel chi square test. The 2-sided 95% exact binomial CI for ORR was calculated for each treatment arm. OS was analyzed using the same method as described to analyze PFS.

The *FDA's Position*

HORIZON

The FDA generally agrees with the description of the HORIZON trial a single arm multicenter trial that supported the accelerated approval of melphalan flufenamide. The efficacy population included 97 patients who received 4 or more lines of therapies and were refractory to at least 1

PI, 1 IMiD and a CD-38 directed monoclonal antibody. PFS and OS were included as additional, secondary endpoints in the HORIZON trial; however, time-to-event endpoints such as PFS and OS are not interpretable in the absence of a control arm and therefore did not contribute to FDA's assessment of efficacy.

OCEAN

FDA generally agrees with the high-level description of the eligibility criteria and statistical analysis plan. Additional information relevant to the ODAC discussion is noted below.

The OCEAN trial was conducted under a special protocol assessment (SPA). Briefly, a special protocol assessment (SPA) is a process in which Sponsors may meet with FDA to reach agreement on the design and size of certain clinical trials to determine if they adequately address scientific and regulatory requirements for a study that could support marketing approval [SPA-fnl.PDF, 2018]. A SPA agreement indicates concurrence by FDA with the adequacy and acceptability of specific critical elements of overall protocol design (e.g., eligibility criteria, endpoints, etc.) for a study intended to support a future marketing application. A SPA agreement does not indicate FDA concurrence on every protocol detail. Additionally, the existence of an SPA agreement does not guarantee that FDA will accept a biologic license application (BLA) or NDA or that the trial results will be adequate to support approval or satisfy the regulatory requirements.

The primary efficacy endpoint as agreed upon under a SPA was PFS superiority defined as the time (months) from date of randomization to the earlier of confirmed disease progression or death due to any cause. Progression dates were assessed by the IRC using the International Myeloma Working Group Uniform Response Criteria (IMWG-URC). Disease progression was defined by the standard IMWG criteria and required two consecutive assessments for confirmation.

FDA notes that PFS non-inferiority was the primary endpoint for other regulatory agencies outside of the United States. However, the FDA has significant concerns with the use of non-inferiority design for time-to-event endpoints and specifically, non-inferiority designs with PFS are discouraged.

Non-inferiority trials demonstrate effectiveness through indirect comparisons to placebo. Randomization date is often the defined starting point in time-to-event studies. Randomization balances start-time variability with respect to treatment arms and permits unbiased within-study comparisons. All non-inferiority designs using time-to-event analyses, particularly PFS, are challenging because it is difficult to determine a margin using historical data. Some issues include:

- There is no common starting point for time-to-event intervals in cross study analyses. This causes a problem similar to lead time bias (earlier diagnoses interpreted as longer survival, early study entry interpreted as longer survival).

- Meta-analyses of time-to-event studies will not detect lead-time-like biases due to cross study differences and are also likely to underestimate variability due to such differences. Cross study analyses of time-to-event data are likely to be unreliable.

Studies used in meta-analyses to estimate historical treatment effect may be non-comparable in ways that are not captured in publications and therefore impossible to address. Non-inferiority margins dependent on non-comparable studies are of dubious value. Examples of non-comparability:

- The definition of PFS can vary from study to study through changes in the definition (constancy), follow-up time, or study specific adaptations.
- Censoring rules vary from study to study.
- Reader/rater/laboratory variability can vary from study to study (increased cross-study variability) for an endpoint such as PFS.

FDA also notes that only ORR and OS were pre-specified as key secondary points in the SAP

Censoring rules for SAP

The Applicant's 's primary analysis was based on censoring rules which defined unconfirmed PD at last visit a progression event. Because the PFS definition for the primary analysis required confirmation of PD in two consecutive assessments, FDA informed the Applicant, that the primary analysis of PFS should be based on patients with confirmed PD as an event. Additionally, assessing unconfirmed PD at last visit as an event may lead to bias since patients who had one event of biochemical progression, but remained on the study and had labs value that did not confirm progression (i.e., the M protein subsequently went back down), were not deemed to have PD. Therefore, FDA's censoring rules considered an unconfirmed PD to be censored.

2.3 Efficacy Summary

2.3.1 Efficacy Results in HORIZON

The Applicant's Position:

A total of 157 patients were included in the FAS of HORIZON, of which 97 patients had received 4 or more prior lines of therapy and were refractory to at least 1 PI, at least 1 immunomodulatory agent, and 1 CD38-directed mAb, i.e., corresponding to the current indication population. The median age of the 97 patients was 65 years (range: 35 to 86 years); 58% were male, 87% were White, and 6% were Black or African American. Disease characteristics are summarized in Table 4.

Efficacy results in the 97 patients are provided in Table 5 for both the original data cutoff date (January 14, 2020) and a new data cutoff with longer follow-up (February 2, 2022). The ORR was higher, and DOR was prolonged with the longer follow-up time.

Table 4. HORIZON – Disease Characteristics, Patients with TCR and at Least 4 Prior Lines of Therapy

Parameter	Pepaxto/Dex (N=97)
Years from diagnosis to start of Pepaxto, median (range)	6.4 (2.1 to 24.6)
Prior treatment regimens, median (range)	6 (4 to 12)
Documented refractory status, n (%)	
Lenalidomide	91 (94)
Pomalidomide	89 (92)
Bortezomib	72 (74)
Carfilzomib	61 (63)
Daratumumab	90 (93)
Alkylator refractory, (%)	73 (75)
Previous stem cell transplant, (%)	68 (70)
International Staging System at baseline, (%)	
I	29 (30)
II	31 (32)
III	33 (34)
Missing/Unknown	4 (4)
High-risk cytogenetics[1], (%)	32 (33)
Extramedullary disease, (%)	40 (41)

[1]del(17p), t(4;14),t(14;16), gain (1q) and t(14;20) at study entry.
dex, dexamethasone; TCR, triple-class refractory.
Applicant internal analyses; source: ADSL.

Table 5. HORIZON – Efficacy Results, Patients with TCR and at Least 4 Prior Lines of Therapy

	Pepaxto/Dex (N=97)	
	Data cutoff: January 14, 2020	Data cutoff: February 2, 2022
ORR, n (% [95% CI])	23 (23.7 [15.7, 33.4])	26 (26.8 [18.3, 36.8])
Stringent complete response	0	0
Complete response	0	0
Very good partial response	9 (9.3)	9 (9)
Partial response	14 (14.4)	17 (18)
Median time to first response (range), months	2.1 (1.0, 6.1)	2.2 (1.0, 15.3)
Median DOR (95% CI), months	4.2 (3.2, 7.6)	5.4 (3.6, 9.8)
Median PFS (95% CI), months	3.8 (3.0, 4.6)	3.8 (3.0, 4.6)
Median OS (95% CI), months	9.1 (6.4, 11.5)	9.3 (6.4, 11.8)

CI, confidence interval; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TCR, triple-class refractory.
Applicant internal analyses; sources: ADRESP and ADTTE.

To evaluate whether prior exposure to alkylators reduced responses to Pepaxto, outcomes were evaluated in patients from HORIZON who were refractory to any previous alkylator therapy outside of the ASCT setting (i.e., any alkylator excluding high-dose melphalan). Among the 97 patients with TCR who had received at least 4 prior lines of therapy, 71 had disease refractory to

previous alkylators outside of the ASCT setting (i.e., excluding high-dose melphalan). Efficacy was maintained in patients with disease refractory to alkylators (independent from having a prior ASCT; Table 6.

Table 6. HORIZON – Efficacy in Patients with TCR and at Least 4 Prior Lines of Therapy Who Had Disease Refractory to Alkylator Therapy

	Refractory to Alkylator Therapy (n=71)
ORR, n (% [95% CI])	17 (23.9 [14.6, 35.5])
Stringent complete response	0
Complete response	0
Very good partial response	5 (7.0)
Partial response	12 (16.9)
Median (95% CI), months	
DOR	3.9 (3.2-7.5)
PFS	3.4 (2.6-4.4)
OS	8.4 (5.8-11.5)

CI, confidence interval; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TCR, triple-class refractory.
Data cutoff date: February 2, 2022.
Applicant internal analyses; sources: ADRESP and ADTTE.

The FDA's Position

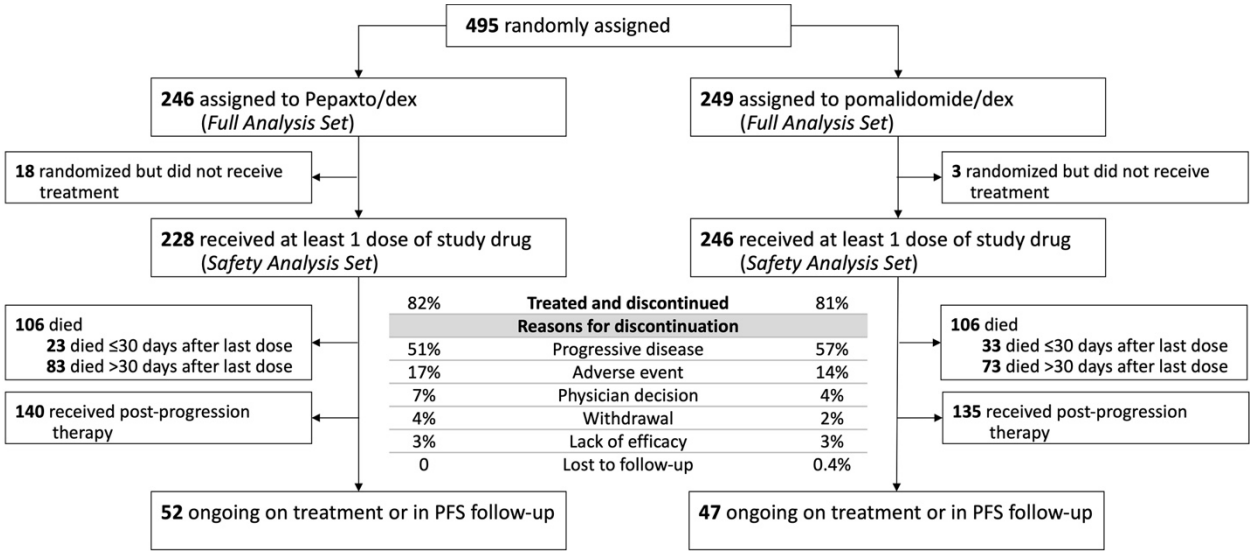
The HORIZON trial was the basis for accelerated approval of melphalan flufenamide. The updated results are consistent with the results that supported the accelerated approval. Single-arm trials do not adequately characterize time-to-event endpoints such as overall survival, DFS (and EFS), TTP, or PFS as the results cannot be attributed solely to the treatment vs the underlying disease and patient characteristics. Randomized clinical trials to verify clinical benefit have been required for therapies granted accelerated approval. The primary focus of the FDAs efficacy evaluation to support the benefit-risk assessment is the randomized, controlled trial, OCEAN, designed to verify the clinical benefit of melphalan flufenamide.

2.3.2 Efficacy Results in OCEAN

The Applicant's Position:

Baseline characteristics and prior myeloma therapy for the FAS (N=495) are summarized in Table 7, Table 8, and Table 9. Baseline characteristics were generally well balanced between treatment groups, including high light-chain combinations at study. Of 495 patients randomized, 474 received at least 1 dose of study medication (Figure 2).

Figure 2. OCEAN – Patient Disposition



dex, dexamethasone; PFS, progression-free survival.
Data cutoff date: February 3, 2021.
Source: CSR tables 14.1-1.1, 14.3.1-13.1, and 14.1-11.5.

Table 7. OCEAN – Demographics and Baseline Characteristics (FAS)

Characteristic	Pepaxto/Dex (N=246)	Pomalidomide/Dex (N=249)
Age, years[a]		
Median	68.0 (41-91)	68.0 (39, 87)
Age category, n (%)		
<65 years	96 (39)	85 (34)
65 to <75 years	113 (46)	125 (50)
<75 years, n (%)	209 (85)	210 (84)
≥75 years	37 (15)	39 (16)
Sex, n (%)		
Male	139 (57)	140 (56)
Female	107 (43)	109 (44)
Race, n (%)		
Asian	8 (3)	13 (5)
Black or African American	4 (2)	4 (2)
White	224 (91)	222 (89)
Other/Unknown or not reported	10 (4)	10 (4)
Ethnicity, n (%)		
Hispanic or Latino	8 (3)	5 (2)
Not Hispanic or Latino	232 (94)	237 (95)
Not reported	6 (2)	7 (3)
Baseline[b] ECOG performance status[c], n (%)		
0	90 (37)	92 (37)
1	130 (53)	136 (55)
2	26 (11)	21 (8)
Baseline[b] weight (kg)		
n	245	249
Median	75.0	74.0
Min, max	40, 125	47, 142

Dex, dexamethasone; ECOG Eastern Cooperative Oncology Group; FAS, full analysis set; max, maximum; min, minimum.
[a]Age is calculated as the integer duration from the date of birth to the date of informed consent.
[b]Baseline was defined as the most recent assessment prior to administration of the first dose of study drug.
[c]For ECOG performance status: 0 – Fully active, able to carry on all predisease performance without restriction; 1 – Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 – Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
Source: CSR table 14.1-6.1.

Table 8. OCEAN – Selected Myeloma Disease Characteristics at Study Entry and Baseline (FAS)

Characteristic	Pepaxto/Dex (N=246)	Pomalidomide/Dex (N=249)
Time since initial diagnosis, years		
Median (min, max)	4.0 (0.5, 26.3)	3.9 (0.4, 25.2)
ISS stage at study entry, n (%)		
I	119 (48)	124 (50)
II	94 (38)	94 (38)
III	33 (13)	31 (12)
R-ISS stage of disease at study entry, n (%)		
R-I	69 (28)	69 (28)
R-II	129 (52)	138 (55)
R-III	24 (10)	17 (7)
Missing	24	25
Extramedullary disease present at study entry		
Yes	31 (13)	31 (12)
No	215 (87)	218 (88)
Cytogenetic risk group based on FISH at study entry		
High	83 (34)	86 (35)
Standard	128 (52)	130 (52)
Unknown	35 (14)	33 (13)
Patients with deletion 17p, n (%)	33 (13)	37 (15)

Dex, dexamethasone; FAS, FULL ANALYSIS SET; FISH, fluorescence in situ hybridization; ISS, International Staging System; max, maximum; min, minimum.
Source: CSR table 14.1-8.

Table 9. OCEAN – Prior Treatment for MM (FAS)

Characteristic	Pepaxto/Dex (N=246)	Pomalidomide/Dex (N=249)
Patients with at least 1 prior ASCT, n (%)	125 (51)	120 (48)
Number of prior regimens per patient		
Median (min, max)	3.0 (2, 4)	3.0 (2, 4)
Total number of prior regimens per patient		
2	114 (46)	111 (45)
3	76 (31)	90 (36)
4	56 (23)	48 (19)
Patients exposed to standardized drug group/therapy in at least 1 prior regimen, n (%) [a]		
Alkylators	217 (88)	213 (86)
Monoclonal antibodies	54 (22)	50 (20)
IMiDs	246 (100)	249 (100)
PIs	246 (100)	249 (100)
Patients refractory to standardized drug group/therapy in at least 1 prior regimen, n (%) [a]		
Alkylators	78 (32)	75 (30)
Monoclonal antibodies	51 (21)	49 (20)

Characteristic	Pepaxto/Dex (N=246)	Pomalidomide/Dex (N=249)
IMiD	245 (100)	249 (100)
PI	163 (66)	163 (65)

ASCT, autologous stem cell transplant; dex, dexamethasone; IMiD, immunomodulatory drug; ISS, International Staging System; max, maximum; min, minimum; MM, multiple myeloma; PI, proteasome inhibitor.

[a]At each level of summarization (Standardized Drug Group, Therapy), patients reporting more than 1 medication are counted only once.

Source: CSR table 14.1-9.

The FDA's Position

FDA generally agrees with the Applicant's presentation of the patient disposition, demographic and disease characteristics from the OCEAN trial. There was a higher number of randomized not treated patients in the MelDex arm (n=18, 7.3%) compared to the PomDex arm (n=3, 1.2%). The reason for randomized not treated patients is listed in FDA Appendix 10.4. Similar numbers of patients received subsequent therapy in both the arms; MelDex (140/246, 57%); PomDex (135/249, 54%).

The demographics, including age and baseline disease characteristics, including receipt of prior transplant, were well balanced.

The patients in the OCEAN trial were less refractory than patients treated on the HORIZON trial (Table 4). The majority of patients in OCEAN had received 2 or 3 prior lines of therapies. Approximately 50% of patients had undergone prior transplant and 20% of patients had received 4 prior lines of therapy. Of note, 14% of patients were triple class refractory. Six percent of the population had received 4 prior lines of therapy and were TCR, the population currently approved to receive melphalan flufenamide.

The population enrolled in the OCEAN trial was not representative of the U.S. population with myeloma. Only 5.5% of the study patients were enrolled in the U.S; Black or African American patients only accounted for 8 patients or 1.6% of the study population. Additionally, only 21% of patients received a prior anti-CD38 monoclonal antibody prior to treatment on OCEAN. With today's current standard of care in the U.S, nearly all patients would be expected to have had treatment with an anti-CD38 in the first 1-2 lines of treatment.

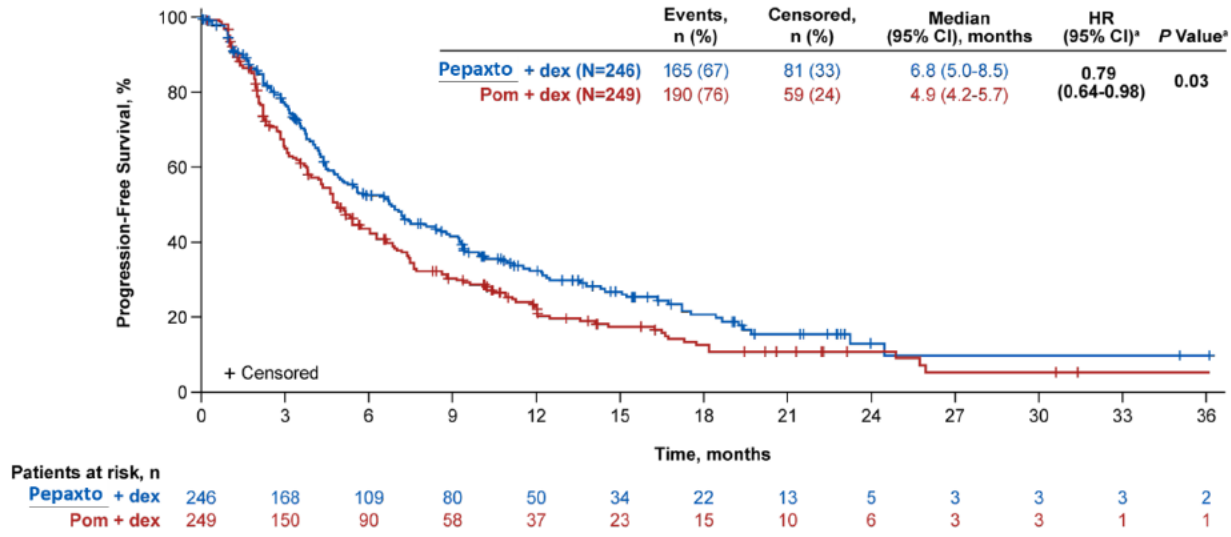
In addition to the lack of minority patients and the small percentage on patients previously exposed to monoclonal antibodies, there was a low percentage of older patients. The OCEAN trial enrolled only 15% of patients ≥ 75 years of age.

Primary Endpoint

The Applicant's Position:

The median PFS (primary endpoint) was 6.8 months in the Pepaxto/dex arm (N=246) and 4.9 months in the pomalidomide/dex arm (N=249) (HR: 0.79 [95% CI: 0.64, 0.98, 2-sided stratified log-rank p=0.03]; Figure 3), and thus the study met its primary endpoint.

Figure 3. OCEAN – Primary Endpoint - PFS by IRC (FAS)



CI, confidence interval; dex, dexamethasone; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; PFS, progression-free survival.
Data cutoff date: February 3, 2021.
Source: CSR Table 14.2-1.1.1 and Figure 14.4-3.1.

Several sensitivity analyses investigated the impact on the PFS results of, for example, an imbalance in randomized but not-treated patients between treatment arms. These sensitivity analyses confirmed internal validity of obtained PFS results (Appendix 4).

The FDA's Position

FDA does not agree with the Applicant's assertion that the OCEAN trial met the primary endpoint of PFS superiority.

The Applicant's original primary analysis of PFS results submitted on June 9, 2021 showed that the OCEAN trial failed the primary endpoint, demonstration of PFS superiority, HR 0.817 (95% CI: 0.659, 1.012), p = 0.0644. While the median PFS in the MelDex arm was 2 months longer than the PomDex arm (6.9 vs. 4.9 months, respectively), the results were not statistically significant (Table 10).

Table 10 PFS per IRC (Original Primary ITT Analysis)

	MelDex (N=246)	PomDex (N=249)
PFS Events, n (%)	163 (66.3)	185 (74.3)

Progression	148 (60.2)	163 (65.5)
Death	15 (6.1)	22 (8.8)
Median in months (95% CI)	6.9 (5.1, 8.5)	4.9 (4.2, 5.9)
HR (95% CI)	0.817 (0.659, 1.012)	
p-value	0.0644	

Source: FDA Analysis of the Applicant's Original Primary Analysis submitted June 9, 2021, data-cut-off Feb 3, 2021

As reported in the FDA's position in Section 2.2.2.3, the Applicant and FDA used different censoring approaches for analysis of PFS results. The Sponsor's primary analysis considered unconfirmed PD at last visit as a progression event. The FDA's PFS analysis considered an unconfirmed PD as censored. The FDA's analysis, considering only patients with confirmed PD as an event, also demonstrated that PFS was not statistically significant; HR 0.833 (95% CI: 0.665, 1.044; p-value = 0.1122)

FDA performed additional sensitivity analyses on PFS to determine if alternative censoring rules would impact the results. There were no alternative censoring rules considered that resulted in a significant treatment difference for PFS (FDA Appendix 10.5).

On July 6, 2021, the Applicant submitted revised PFS results. The Applicant's revised PFS results and HR are shown in Figure 3.

The Applicant noted that these revisions were a result of discrepancies noted in 29 patients by an independent audit initiated by the Applicant following the database lock and the top-line data readout on May 25, 2021 (FDA Appendix 10.6).

The Applicant has only chosen to present the revised PFS results and HR in Figure 3.

PFS from this updated data demonstrated nominally significant superiority, HR 0.793 (95% CI: 0.640, 0.981), nominal p = 0.0322.

FDA conducted their own analysis on the revised PFS results. As the original primary analysis of PFS results were not significant, all reported p-values except for the original primary analysis result are considered nominal and not suitable for inferring statistical significance.

The multiple PFS results based on different censoring approaches, post-hoc revision to the PFS results and FDA adjudication are presented in Table 11.

- FDA's assessment of the Applicant's re-assessment (revised 29 patients) confirmed the nominally significant p-value; however, the p-value was different from the Applicant's due to a difference in FDA adjudication of 4 patients.
- Censoring unconfirmed PD resulted in a non-significant p-value for the PFS analysis of 0.0837, indicating that there was no difference between treatment arms.

Regardless of the method used for the PFS analysis and the significance of the p-value, the median PFS (months) did not change and the PFS difference between the arms did not exceed 2 months.

Table 11 Original and Post hoc PFS Analysis Results

PFS Analyses	HR (95% CI)	Difference in medians	p-value
Applicant's Original ITT Analysis	0.817 (0.659, 1.012)	2.0	0.0644
FDA's Original ITT Analysis*	0.833 (0.665, 1.044)	1.7	0.1122
Applicant's Post hoc Reassessment	0.793 (0.640, 0.981)	1.9	0.0322
FDA Re-adjudicated Post hoc Analysis using Applicant's censoring rules**	0.796 (0.642, 0.985)	1.9	0.0359
FDA Re-adjudicated Post hoc Analysis using FDA's censoring rules*	0.820 (0.654, 1.027)	1.8	0.0837

Source: FDA analysis; *FDA's censoring rules- censor all unconfirmed PD;
Post hoc analyses do not have alpha allocation and p-values are considered to be nominal
** 3 patients from Applicant's updated results were not confirmed by FDA and reverted to the original analysis results, 1 patient had change in date (FDA Appendix 10.6);

The FDA does not agree with the Applicant's additional sensitivity analyses in the Applicant's Appendix 4. PFS Sensitivity Analysis.

The Applicant's analysis in which the PFS values were imputed (by the OS value) for patients who were randomized but not treated is not acceptable. Mixing values of one endpoint with another endpoint makes the results uninterpretable and subject to bias that is difficult to measure. Furthermore, since death happens later than progression, imputing PFS by OS artificially prolongs the progression free survival time. Since there were more patients who were randomized but not treated in the MelDex, this imputation distorts the results to show a better treatment effect. It is also possible that, if the PFS results were available for these 18 patients who were randomized and not treated, the PFS in the melphalan flufenamide arm could be worse than the pomalidomide arm.

The Applicant's tipping point analyses for randomized but not treated patients and for all prematurely censored patients are also not acceptable because PFS values for this subgroup of

patients were imputed based on arbitrary post hoc assumptions, therefore the results are difficult to interpret.

Conclusion

The original primary analysis submitted to FDA showed that OCEAN failed to meet the primary endpoint of statistically significant improvement in PFS as assessed by IRC in the MelDex arm compared to the PomDex arm. The Applicant contends that PFS superiority was met based on re-assessment of events for 29 patients after the primary database lock. Regardless of the revised analyses, the treatment effect estimates with respect to the difference in median PFS did not exceed 2 months and are significant only if we also assess patients with unconfirmed PD as having had an event. Additionally, the variability of the statistical significance raises concerns regarding the robustness of the PFS results.

The results of the primary endpoint of PFS from OCEAN indicate uncertainty about the clinical benefit of melphalan flufenamide.

Secondary Endpoints

The Applicant's Position:

The ORR and median DOR were consistent with the results for PFS, while the median OS was higher in the pomalidomide/dex group in the February 3, 2021 and February 3, 2022 data cutoffs, both with a HR >1, warranting further investigation (Table 12; see Section 2.3.3).

Table 12. OCEAN – Efficacy Results: ORR, DOR, and OS

	Pepaxto/Dex (N=246)	**Pomalidomide/Dex (N=249)**
ORR, n (% [95% CI])	80 (32.5 [26.7, 38.8])	67 (26.9 [21.5, 32.9])
P value	0.16	
Stringent complete response	0	0
Complete response	7 (3)	3 (1)
Very good partial response	23 (9)	18 (7)
Partial response	50 (20)	46 (18)
Median DOR (95% CI), months	11.2 (8.5, 17.5)	11.1 (7.6, 15.4)
Median OS (95% CI), months		
Primary data cutoff (February 3, 2021)	19.8 (15.1, 25.6)	25.0 (18.1, 31.9)
Hazard ratio (95% CI), *P* value	1.10 (0.85, 1.44), 0.47	
Updated data cutoff (February 3, 2022)	20.2 (15.8, 24.3)	24.0 (19.1, 28.7)
Hazard ratio (95% CI), *P* value	1.14 (0.91, 1.42), 0.24	

CI, confidence interval; dex, dexamethasone; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
Data cutoff dates: February 3, 2021 (ORR and primary overall survival); February 3, 2022 (updated overall survival).
CSR tables 14.2-2.1.1, 14.2-3.1.1, 14.2-4.1.1 and Applicant internal analyses; source: ADTTE.

To evaluate whether Pepaxto had reduced responses in patients with prior exposure to alkylators, outcomes were evaluated in patients from OCEAN who were refractory to any previous alkylator therapy outside of the ASCT setting (i.e., any alkylator excluding high-dose melphalan). In total, 153 patients in OCEAN had disease that was refractory to previous alkylator therapy (Pepaxto/dex, n=78; pomalidomide/dex, n=75) outside of the context of an ASCT. Both treatment arms showed similar efficacy in patients with disease refractory to alkylators (including low-dose melphalan) outside of the high-dose melphalan/ASCT setting (Table 13).

Table 13. OCEAN – Efficacy in Patients with Disease Refractory to Previous Alkylator Therapy (Outside of the ASCT Setting)

	Pepaxto/Dex (n=78)	Pomalidomide/Dexd (n=75)
ORR, n (% [95% CI])	19 (24.4 [15.3, 35.4])	21 (28.0 [18.2, 39.6])
Stringent complete response	0	0
Complete Response	2 (2.6)	2 (2.7)
Very good partial response	4 (5.1)	2 (2.7)
Partial response	13 (16.7)	17 (22.7)
Median (95% CI), months		
DOR	13.4 (5.3, NA)	15.4 (4.6, NA)
PFS	5.6 (4.2, 8.3)	4.7 (3.1, 7.3)
OS	23.4 (14.4, 31.7)	20.0 (12.0, 28.7)
OS HR (95% CI)	0.92 (0.62-1.38)	

CI, confidence interval; dex, dexamethasone; DOR, duration of response; NA, not available; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
Data cutoff dates: February 3, 2021 and February 3, 2022 (OS).
Applicant internal analyses; sources: ADRESP and ADTTE.

The FDA's Position

The FDA does not agree with the characterization of the results of the secondary endpoints of ORR and DOR. Because the trial failed to meet the primary endpoint of PFS superiority, the key secondary endpoints of ORR, and OS lacked alpha allocation for further testing. Additionally, subgroup analyses and data exploration were conducted in a post hoc manner without a prospectively defined scientific hypothesis and cannot support conclusion of safety or evidence of efficacy in a specific patient sub-population.

ORR and DOR

FDA notes that the 95% CI for the ORR difference between the two arms includes 0 (Table 12). This indicates that the ORR is not different between the two arms. Additionally, there was no

difference in the median duration of response (11.2 months vs. 11.1 months) between the two arms. The lack of a beneficial treatment effect for the secondary endpoints of ORR and DOR further substantiates the residual uncertainty regarding the clinical benefit of melphalan flufenamide raised with the PFS primary endpoint results.

OS Results

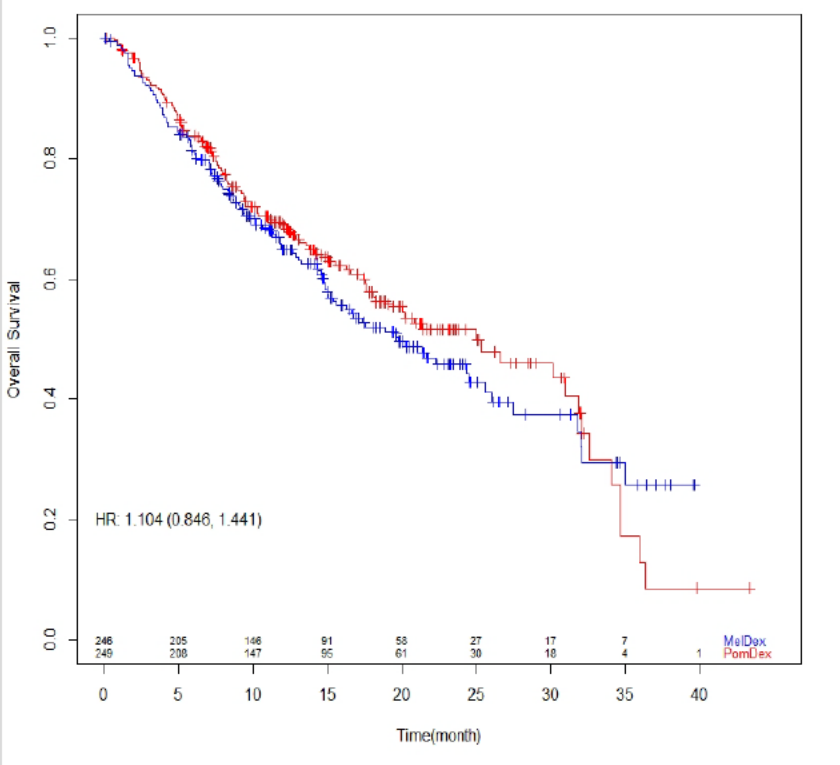
The FDA disagrees with the Applicant's description of the OS results from the OCEAN study

The overall survival results from the OCEAN trial from the primary cut-off data with a median follow-up time for OS of 19.1 months indicated a worse overall survival in patients treated in the MelDex arm compared to the PomDex arm. The median OS in the MelDex arm was 5.3 months less than the median OS in the PomDex arm. There were higher rates of deaths overall in the MelDex arm compared to the PomDex arm; 47.6% (117/246) and 43.4% (108/249) respectively.

The updated OS results with a median follow-up duration of nearly three years (31.8 months in MelDex and 29.8 months in PomDex) were consistent with the initial OS results. The rates of death in the ITT population with extended follow-up were also higher in the MelDex arm compared to the Pom Dex arm; 65.9% (162/246) and 59% (147/249) respectively.

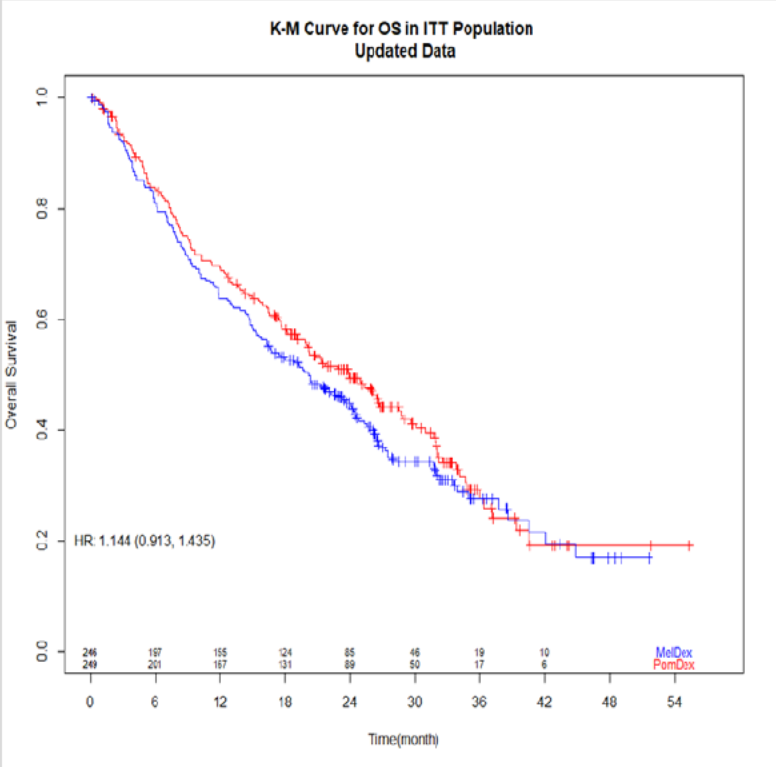
The K-M curves from the primary cut-off date of February 3, 2021 and the updated cut-off date of February 3, 2022 are shown in **Figure 4** and **Figure 5** respectively.

Figure 4. Kaplan-Meier Curve for OS (ITT Population) Data Cut-Off date February 3, 2021



Source: FDA Analysis

Figure 5. Kaplan Meier Curve for OS (ITT Population) Data Cut-Off date February 3, 2022



Source: FDA Analysis

While these results occurred in the context of evaluating OS with an active comparator and were not statistically significant, the OS results with HR>1 in the context of increased rates of deaths is a safety concern and indicate a potential for harm with melphalan flufenamide.

2.3.3 Analysis of Subgroups in OCEAN

The Applicant's Position:

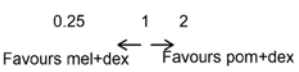
The OS results in OCEAN could be explained by either potential Pepaxto/dex toxicity (as discussed in Section 3), lack of efficacy, or different subgroups having significant interactions with OS (as discussed below).

An exploratory multivariable analysis comparing both treatment arms to explore factors related to diverging treatment effects (interaction) was conducted, where factors with treatment multiplied by factor interaction *P* value <0.2 were entered into a multivariable model. In the model, all factors were entered as was the treatment multiplied by factor interaction term. In a second step, the optimal model was selected using a stepwise approach based on Akaike information criteria. The interaction factor related to ASCT status and TTP after ASCT (cut-off 36 months) was selected because this is a clinically relevant definition based on EHA-ESMO clinical practice guidelines (Section 2.1.2). From the final model, the interaction terms remaining in the model were considered as relevant treatment modifiers.

In the univariable interaction tests, there were 6 factors with a *P* value <0.2: age (65+ vs <65), age (75+ vs <75), sex (male vs female), CrCl (≥90 vs <90), prior ASCT (yes vs no), and ASCT with TTP within 36 months vs no ASCT or TTP >36 months after prior ASCT (Figure 6).

Figure 6. OCEAN – Subgroup Analysis of OS

	Mel+dex		Pom+dex		Hazard ratio (95 % CI)	Log-rank p-value	Interaction p-value
	Evs/Pts	Median	Evs/Pts	Median			
Overall	162/246	20.2 (15.8-24.3)	147/249	24.0 (19.1-28.7)	1.13 (0.91-1.42)	0.2763	
Age							
<65	63/96	16.2 (11.9-24.5)	40/85	31.7 (21.3-NA)	1.68 (1.13-2.49)	0.0101	0.011
>=65	99/150	21.8 (16.6-26.0)	107/164	20.1 (16.4-25.9)	0.92 (0.70-1.21)	0.5322	
65-74	79/113	20.5 (16.3-24.8)	82/125	20.9 (17.0-26.5)	1.03 (0.76-1.41)	0.8356	
<75	142/209	19.6 (15.3-24.1)	122/210	25.0 (19.9-29.6)	1.26 (0.99-1.60)	0.0637	0.024
>=75	20/37	26.5 (14.6-NA)	25/39	17.5 (7.2-32.1)	0.62 (0.35-1.13)	0.1162	
Sex							
Male	91/139	20.5 (16.7-24.5)	86/140	20.9 (15.5-26.7)	1.00 (0.74-1.34)	0.9802	0.192
Female	71/107	16.4 (12.7-26.5)	61/109	25.0 (20.0-32.0)	1.34 (0.95-1.89)	0.0916	
Race							
White	152/224	19.6 (15.4-24.1)	134/222	24.0 (17.7-28.7)	1.17 (0.93-1.48)	0.1822	0.309
All other races	5/13	NA (10.0-NA)	6/17	NA (12.5-NA)	0.91 (0.28-2.99)	0.8752	
Region							
USA	4/11	NA (8.6-NA)	5/15	NA (17.4-NA)	1.13 (0.30-4.22)	0.8533	
Europe	130/180	16.7 (14.8-21.6)	110/176	20.2 (16.3-28.5)	1.20 (0.93-1.55)	0.1614	0.536
ROW	28/55	26.2 (14.3-NA)	32/58	24.9 (18.2-31.7)	0.88 (0.53-1.46)	0.6260	
ECOG							
0	51/90	26.5 (20.3-33.8)	44/92	28.7 (20.0-33.8)	0.99 (0.66-1.49)	0.9616	0.368
1-2	111/156	14.8 (11.4-18.9)	103/157	20.1 (15.0-26.5)	1.25 (0.96-1.64)	0.1040	
Prior lines							
2	77/114	20.3 (13.2-26.0)	70/111	20.9 (12.5-26.6)	1.00 (0.73-1.39)	0.9816	0.304
3-4	85/132	19.7 (15.4-25.3)	77/138	26.1 (19.8-33.8)	1.26 (0.93-1.72)	0.1383	
ISS							
I	68/119	26.0 (22.2-33.8)	64/124	30.1 (26.1-33.8)	1.13 (0.80-1.59)	0.4802	
II	67/94	16.3 (11.8-21.6)	60/94	19.1 (12.9-24.0)	1.07 (0.75-1.51)	0.7163	0.887
III	27/33	7.1 (4.3-9.0)	23/31	7.9 (5.3-9.3)	1.17 (0.67-2.06)	0.5857	
R-ISS							
I	30/69	38.6 (24.3-NA)	29/69	32.1 (26.6-NA)	1.00 (0.60-1.67)	0.9983	
II	89/129	19.2 (13.1-24.1)	89/138	19.9 (13.6-24.0)	1.03 (0.77-1.39)	0.8228	0.861
III	23/24	6.1 (2.6-7.7)	12/17	5.5 (3.5-7.5)	1.14 (0.56-2.32)	0.7228	
Cytogenetics							
High risk	62/83	15.3 (11.5-25.3)	61/86	17.6 (13.1-21.7)	1.02 (0.71-1.45)	0.9172	0.470
Not high risk	100/163	20.5 (16.7-26.0)	86/163	29.6 (20.9-32.6)	1.20 (0.90-1.60)	0.2159	
Creatinine clearance							
<60	33/50	16.3 (10.1-26.5)	46/68	16.4 (9.2-20.1)	0.92 (0.59-1.43)	0.7026	
60-90	76/119	20.3 (14.6-26.2)	66/112	24.9 (15.9-30.1)	1.04 (0.75-1.45)	0.8072	0.126
>=90	52/76	21.8 (16.6-27.2)	35/69	31.7 (25.9-34.7)	1.65 (1.07-2.53)	0.0215	
BSA							
Below median	74/116	18.9 (13.1-26.2)	73/128	26.1 (19.1-31.9)	1.24 (0.89-1.71)	0.1969	0.742
Above median	86/126	20.3 (16.3-25.3)	71/117	21.4 (17.0-28.7)	1.05 (0.77-1.44)	0.7379	
EMD							
Yes	21/30	9.7 (5.5-19.7)	18/26	12.4 (3.8-31.9)	1.12 (0.59-2.11)	0.7322	0.805
No	141/216	21.3 (16.7-25.3)	129/223	25.0 (20.0-28.7)	1.12 (0.88-1.42)	0.3537	
Stem cell transplant							
Yes	87/125	16.7 (13.8-24.1)	66/120	28.7 (21.3-33.8)	1.53 (1.11-2.11)	0.0088	0.010
No	75/121	22.2 (16.4-27.5)	81/129	17.5 (12.1-25.0)	0.84 (0.61-1.15)	0.2818	
ASCT progression wi 36m							
Yes	75/101	15.7 (11.9-20.5)	56/101	28.7 (20.2-34.1)	1.80 (1.27-2.55)	0.0007	0.001
No (includes no ASCT)	87/145	23.6 (18.9-28.0)	91/148	19.8 (12.6-26.5)	0.83 (0.62-1.12)	0.2249	



ASCT, autologous stem cell transplant; BSA, body surface area; dex, dexamethasone; ECOG, Eastern Cooperative Oncology Group; EMD, extramedullary disease; evs, events; ISS, International Staging System; mel, melflufen; NA, not available; OS, overall survival; pom, pomalidomide; pts, patients; ROW, rest of world; USA, United States of America.
Data cutoff date: February 3, 2022.
Applicant internal analyses; data sources: ADSL and ADTTE.

In the multivariable model, age 65+ vs <65 and the ASCT 36-month TTP variable were included, but not age 75+ vs <75 or ASCT yes/no. After the stepwise selection, 3 interaction terms remained: ASCT 36-month TTP, age, and sex (Table 14 and Table 15). That both age and ASCT 36-

month TTP remained as interaction terms is notable, since age and comorbidities are the main factors used to assess eligibility for an ASCT.

Analysis of the relative importance of these factors within each treatment arm showed that the only factor influencing the Pepaxto arm was ASCT with TTP <36 months. Patients with a progression within 36 months following a previous ASCT had a worse prognosis compared with patients without an ASCT or who progressed >36 months following a previous ASCT. As previously noted, the current EHA-ESMO guidelines state that patients with an unsuccessful ASCT (i.e., TTP <36 months post-ASCT) are not eligible for salvage ASCT (Dimopoulos et al. 2021). Within the pomalidomide/dex arm, age was the strongest predictor (older patients had a worse prognosis). Notably, younger patients are invariably more likely to be eligible for an ASCT.

Table 14. OCEAN – OS Multivariate Cox Model Within the Pepaxto Arm

	Hazard ratio	95% CI	*P* value
ASCT TTP (ASCT TTP <36 months vs No ASCT or ASCT TTP >36 months)	1.50	(1.09, 2.06)	0.013
Age (≥65 vs <65 years)	0.95	(0.69, 1.32)	0.766
Sex (male vs female)	0.90	(0.66, 1.23)	0.509

ASCT, autologous stem cell transplant; CI, confidence interval; OS, overall survival; TTP, time to progression.
Data cutoff date: February 3, 2022.
Applicant internal analyses; sources: ADSL and ADTTE.

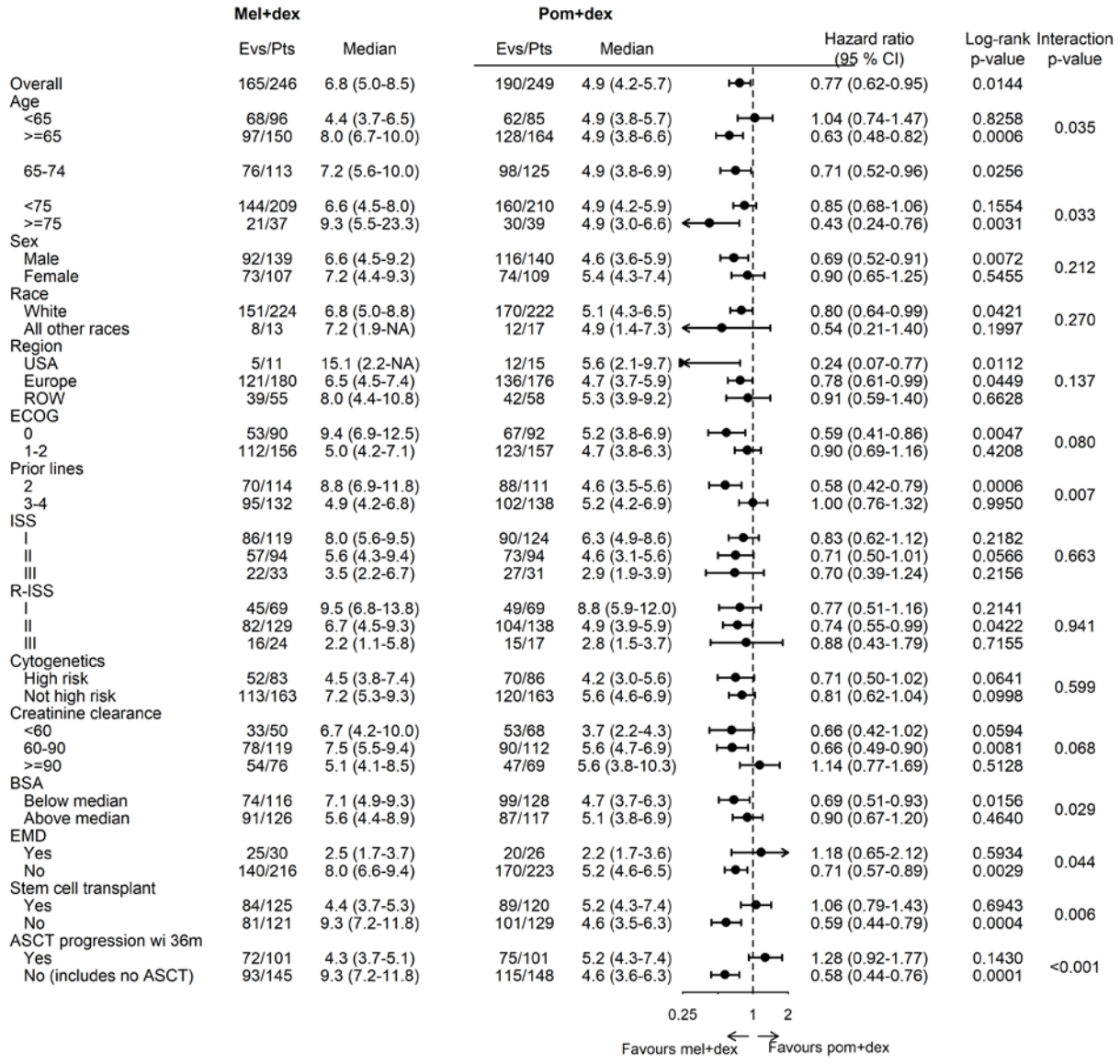
Table 15. OCEAN – OS Multivariate Cox Model Within the Pomalidomide Arm

	Hazard ratio	95% CI	*P* value
ASCT TTP (ASCT TTP <36 months vs No ASCT or ASCT TTP >36 months)	0.76	(0.54, 1.08)	0.121
Age (≥65 vs <65 years)	1.49	(1.02, 2.17)	0.039
Sex (male vs female)	1.28	(0.92, 1.78)	0.140

ASCT, autologous stem cell transplant; CI, confidence interval; OS, overall survival; TTP, time to progression.
Data cutoff date: February 3, 2022.
Applicant internal analyses; sources: ADSL and ADTTE.

Subgroup analysis of PFS data showed that PFS was also heterogeneous across subgroups when comparing Pepaxto vs. pomalidomide, although age was remarkably consistent in the pomalidomide arm with 4.9 months of PFS regardless of the age category (Figure 7). This is contrast to the observations on OS, where age had a major impact on the performance of pomalidomide.

Figure 7. OCEAN – Subgroup Analysis of PFS



ASCT, autologous stem cell transplant; CI, confidence interval; BSA, body surface area; dex, dexamethasone; ECOG, Eastern Cooperative Oncology Group; EMD, extramedullary disease; evs, events; ISS, International Staging System; mel, melflufen; NA, not available; OS, overall survival; pom, pomalidomide; pts, patients; ROW, rest of world; USA, United States of America.
Data cutoff date: February 3, 2021
Applicant internal analyses; sources: ADSL and ADTTE.

Based on these post-hoc analyses, TTP <36 months after ASCT was identified as a strong effect modifier by Pepaxto. As discussed in Section 1.3.2 and further detailed in Appendix 1, the pomalidomide interaction with age and the actual age distribution significantly confounds the

OS results and are major contributors to the OS HR >1, which makes the OS result in the FAS challenging to interpret and does not confirm definitive detriment in terms of OS.

2.3.4 Efficacy After Exclusion of Patients with Prior ASCT and Progression Within 3 Years After ASCT

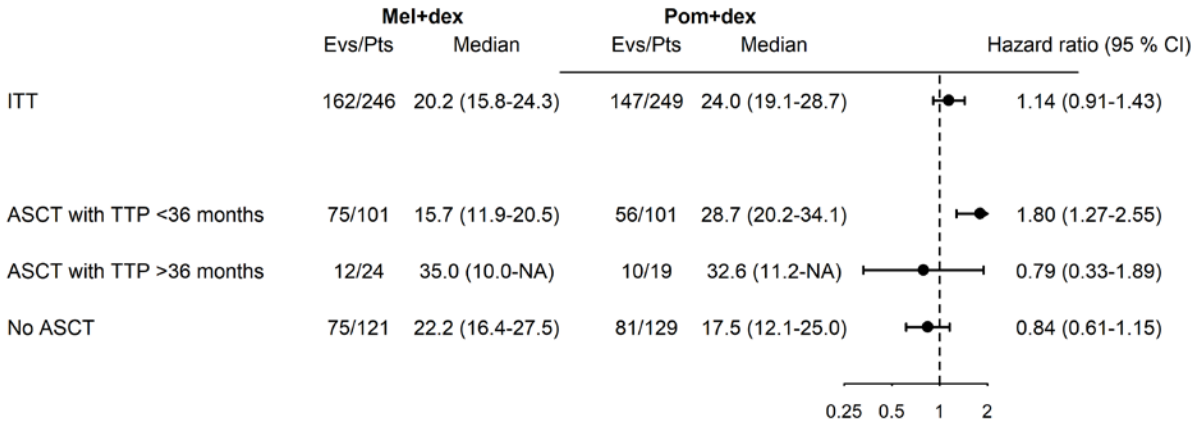
Analyses that compared PFS, ORR, and OS results by TTP after ASCT in OCEAN showed a consistent signal of reduced efficacy in patients with TTP <36 months, and results favored Pepaxto/dex in the subgroup that had not received a previous ASCT or who had a TTP >36 months after a previous ASCT (Table 16, Figure 8, and Figure 9)

Table 16. OCEAN – Efficacy Results by Subgroups According to TTP <36 Months After ASCT (Yes vs No or No ASCT)

	Pepaxto/Dex ASCT with TTP <36 Months		Pomalidomide/Dex ASCT with TTP <36 Months	
	Yes (n=101)	**No[a] (n=145)**	**Yes (n=101)**	**No[a] (n=148)**
Median PFS (95% CI), months	4.3 (3.7, 5.1)	9.3 (7.2, 11.8)	5.2 (4.3, 7.4)	4.6 (3.7, 6.3)
Median DOR (95% CI), months	9.3 (3.9, 11.2)	15.7 (9.2, NA)	10.2 (5.1, 24.9)	11.1 (7.4, 16.3)
ORR (95% CI), n (%)	19 (18.8) (11.7, 27.8)	61 (42.1) (33.9, 50.5)	28 (27.7) (19.3, 37.5)	39 (26.4) (19.5, 34.2)
Median OS (95% CI), months	15.7 (11.9, 20.5)	23.6 (18.9, 28.0)	28.7 (20.2, 34.1)	19.8 (12.6, 26.5)

Data cutoff dates: February 3, 2021, and February 3, 2022 (overall survival).
ASCT, autologous stem cell transplant; dex, dexamethasone; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.
[a]Includes no ASCT.
Applicant internal analyses; sources: ADSL, ADRESP, and ADTTE.

Figure 8. OCEAN – OS by Subgroups According to 36-Month TTP Post-ASCT or No ASCT

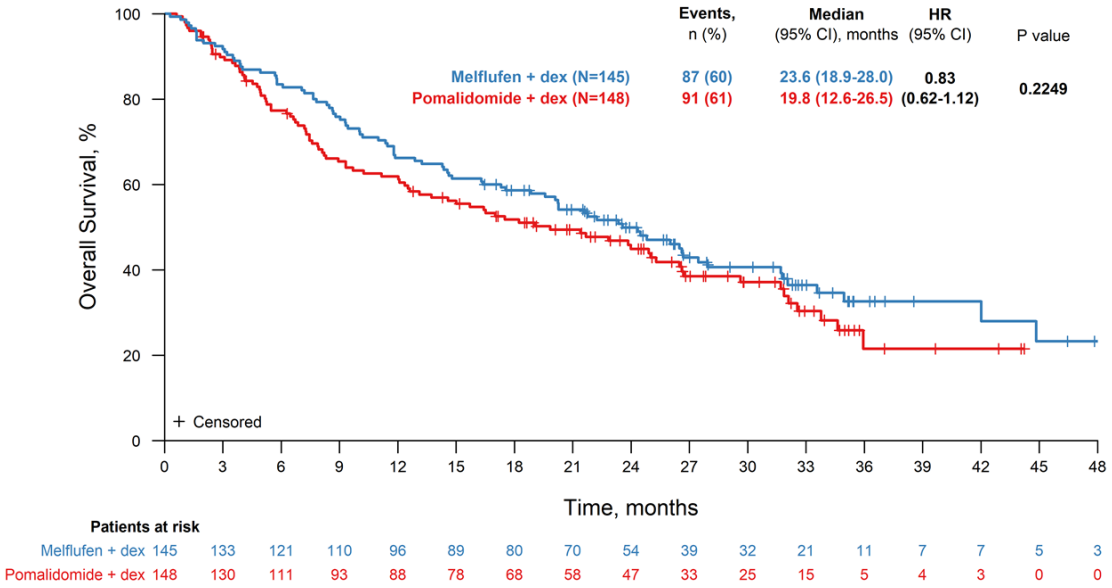


Data cutoff date: February 3, 2022.

ASCT, autologous stem cell transplant; CI, confidence interval; dex, dexamethasone; evs, events; ITT, Intention-to-Treat; mel, melflufen; pom, pomalidomide; TTP, time to progression.

Applicant internal analyses, source ADSL and ADTTE.

Figure 9. OCEAN – OS KM Curve When Patients With TTP <36 Months Post-ASCT Are Excluded



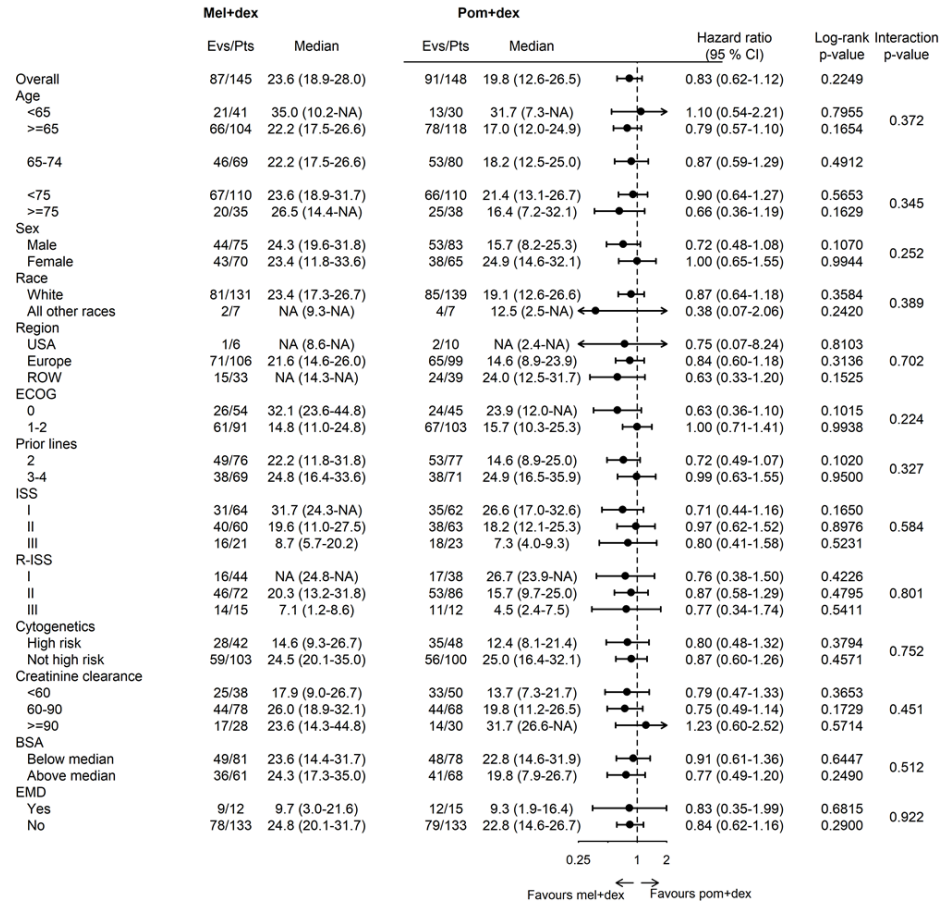
Data cutoff date: February 3, 2022.

ASCT, autologous stem cell transplant; CI, confidence interval; dex, dexamethasone; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; TTP, time to progression.

Applicant internal analyses, source: ADSL and ADTTE.

Figure 10 shows the OS forest plot once the patients with a TTP <36 months after ASCT have been excluded from the OCEAN study. No residual harm can be identified in any of the subgroups, supporting a positive benefit/risk in the non-transplanted and patients with a prior ASCT >36 months ago.

Figure 10. OCEAN – OS per Subgroup Excluding Patients with TTP <36 Months Post-ASCT



ASCT autologous stem cell transplant; BSA body surface area; CI confidence interval; ECOG Eastern Cooperative Oncology Group; EMD extramedullary disease; Evs events; ISS international staging system; mel melflufen; OS overall survival; pom pomalidomide; Pts patients; R-ISS revised international staging system; ROW rest of world.
Data cutoff date: February 3, 2022

Applicant internal analyses; data sources: ADSL and ADTTE.

Notably, Pepaxto treated patients below the age of 65, who were either not transplanted or had TTP more than 36 months following an ASCT, had an OS of 35.0 (95% CI 10.2, NA) months compared to 15.3 (95% CI 8.0, 19.2) months for patients progressing earlier than 36 months after an ASCT (Table 17). This difference is not seen for in patients treated with pomalidomide (31.0 vs 31.7 months), giving further support that the main patient characteristic driving the

observed OS findings in the Pepaxto arm is early progression after a prior ASCT. These analyses provide critical support for the statement that Pepaxto has a positive benefit/risk profile in both non-transplanted patients as well as those who progressed >36 months after an ASCT, regardless of age.

Table 17. OCEAN – OS Results for Patients <65 Years of Age Without a Prior ASCT or Progression >36 Months after ASCT Compared to Patients Progressing <36 Months of ASCT

	Pepaxto no ASCT or prog >36 months	Pepaxto prog <36 months	Pom no ASCT or prog >36 months	Pom prog <36 months
	n=41	n=55	n=30	n=55
Median OS (95 % CI), months	35.0 (10.2, NA)	15.3 (8.0, 19.2)	31.7 (7.3, NA)	31.0 (17.7, 39.3)

CI confidence interval; OS overall survival; pom pomalidomide; prog progression, NA not available
Data cutoff date: February 3, 2022
Applicant internal analyses; data sources: ADSL and ADTTE.

While these analyses were based on a post-hoc defined variable, there is a biological rationale for why patients who progress early after ASCT might be less responsive to another alkylator-based regimen. In MM, ASCT is preceded by conditioning with a myeloablative dose of an alkylating agent (typically high-dose melphalan 140-200 mg/m^2) with subsequent stem-cell support to recover hematopoiesis. In multiple studies, patients with TTP <36 months post-ASCT derived significantly less value from further alkylator-based therapies than those with TTP >36 months post-ASCT (Chow et al. 2012, Gonsalves et al. 2013, Michaelis et al. 2013). The current EHA-ESMO guidelines state that the PFS cutoff for a transplant to be considered successful enough to be eligible for a salvage ASCT is >36 months (Dimopoulos et al. 2021). The underlying reason is that if a tumor responds only briefly to a high-dose alkylator regimen, the likelihood of benefitting from additional alkylator-based treatment is low.

Studying the population in OCEAN with a prior ASCT (49.5% of the study population) revealed that 82% of these patients had progressed within 36 months of their ASCT (i.e., TTP <36 months post-ASCT), which is an unexpectedly high number. Real-world data indicate a median PFS (or TTP) of approximately 45 months after ASCT (Bergin 2021). As such, OCEAN appears to be enriched with patients less suitable for treatment with a potent alkylator like Pepaxto. In addition, the treatment effect observed in the subgroup is larger than the all-randomized study population, providing additional support for the subgroup (EMA/CHMP/539146/2013; *Guideline on the investigation of subgroups in confirmatory clinical trials*). Although results from subgroup analyses may have limitations, the FDA has acknowledged that these are important for interpreting pivotal trials in oncology. The post-hoc identification of subgroups with different treatment effects in OCEAN is in line with previous precedent for "Approval in subgroups" (PAOLA-1 olaparib/bevacizumab study) described in (Amatya et al. 2021). Subgroup analysis of HORIZON also suggest a larger effect on OS in patients with no ASCT or prior ASCT and TTP >36 months (Table 16); however, interpretation is hampered by the lack of a control arm.

At an EMA consultation with a SAG-O dated May 11, 2022, it was concluded that Pepaxto/dex is associated with clinically relevant efficacy, except for the subgroup of patients with a relapse within 36 months following high-dose melphalan and ASCT. In addition, the SAG-O considered that although the exact effect size cannot be determined due to differences in disease and treatment characteristics, the results of OCEAN obtained in patients of whom most had fewer lines of treatment than the patients in HORIZON, are relevant for the target population in HORIZON because: (1) results were consistent between the 2 studies; (2) the sample size was adequate; and (3) the biological rationale supported the findings.

Findings from the Phase 3 OCEAN study, which became available after the initial analysis of HORIZON results, indicated a lack of efficacy with Pepaxto/dex in patients with a TTP <36 months after a previous ASCT—that is, patients who relapsed within 36 months of having received a previous ASCT—(see Section 2.3.3). Thus, a post hoc analysis was performed on data from HORIZON comparing efficacy of Pepaxto/dex in patients with a TTP <36 months post-ASCT with patients with a TTP of >36 months or who had not received a previous ASCT. The results are provided in Table 18 and show a lower ORR, PFS, and OS in patients progressing <36 months after a transplant, as noted in OCEAN.

Table 18. HORIZON – Efficacy Results in Patients with TCR and at Least 4 Prior Lines of Therapy Stratified by ASCT Status

	No ASCT or ASCT with TTP ≥36 months (n=44)	ASCT with TTP <36 months (n=53)
ORR, n (% [95% CI])	14 (31.8 [18.6, 47.6])	12 (22.6 [12.3, 36.2])
Stringent complete response	0	0
Complete Response	0	0
Very good partial response	5 (11.4)	4 (7.5)
Partial response	9 (20.5)	8 (15.1)
Median (95% CI), months		
DOR	7.6 (3.5, 12.3)	3.8 (2.4, 7.4)
PFS	5.1 (2.3, 5.7)	3.4 (2.6, 4.0)
OS	11.2 (6.4, 13.6)	8.4 (5.4, 11.8)

ASCT, autologous stem cell transplant; CI, confidence interval; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TCR, triple-class refractory; TTP, time to progression.
Data cutoff date: February 2, 2022.
Applicant internal analyses; data sources: ADSL, ADRESP, and ADTTE.

2.3.5 Efficacy in Patients with Alkylator-Refractory Disease (Outside of the ASCT Setting)

In contrast to the potential harm of Pepaxto/dex in patients with TTP <36 months after high-dose melphalan in the context of ASCT (as discussed in Section 2.3.4), Pepaxto/dex performed well in patients with disease considered refractory to alkylators (normal dose alkylator therapy, including melphalan, bendamustine and cyclophosphamide), in both HORIZON and OCEAN (see Table 6. and Table 13). This indicates that Pepaxto has the ability to overcome normal dose alkylator refractoriness.

The FDA' Position

The FDA does not agree with the Applicant's position on the OS results in the OCEAN trial and conclusions based on post hoc subgroup analysis.

1. **The OS results in OCEAN are due to reasons other than toxicity**

FDA does not agree. The higher rates of deaths and shorter median survival noted in the melphalan flufenamide arm compared to pomalidomide arm suggests that melphalan flufenamide may be causing harm. Analysis of time-to-progression (TTP) indicates that the OS results cannot be clearly attributed to accelerated disease progression. The Safety results described in the FDA position in Section 3 indicate that the difference in death rates were most notable in events that occurred beyond 60 days after the last dose; 31% of deaths in the MelDex arm occurred beyond 60 days compared to 25% in the PomDex arm. This raises a concern that treatment with melphalan flufenamide may impact the ability to receive and tolerate subsequent lines of therapy. Additionally, there were higher rates of severe (Grade 3-4) adverse events overall (94% versus 74%) and higher rates of Grade 3-4 thrombocytopenia (81% versus 14%), and neutropenia (73% versus 59%) in the MelDex arm compared to the PomDex arm.

2. **ASCT with TTP <36 months is the strongest predictor of OS in the melphalan flufenamide arm and a different factor, age is the predictor in the pomalidomide arm**

FDA does not agree. We have previously outlined the limitations of post hoc exploratory analysis and our concerns with the Applicant 's rationale for using the TTP of least 36 months (Section 1.3.2).

Additional limitations are outlined below:

The multivariable analysis conducted to support that age and TTP<36 months are predictors of poor outcome are based on within treatment arm comparison. This is not an appropriate methodology to evaluate modification of treatment effect because there is not a randomized comparison and is unlikely to be balanced with respect to prognostic factors. These results only indicate there is interaction within the arm and cannot be used to make comparisons across arms. Furthermore, even if there may be an age interaction, it may be caused by either or both of the two treatments. In the OCEAN trial, the different HR of OS in age<65 and age>=75 could be due to melphalan flufenamide causing more harm to younger patients, or pomalidomide causing more harm to older patients, or both. It cannot be concluded that this age interaction is driven by the pomalidomide arm. Alternatively, the patterns observed past the main effects of the study could be the result of random variability of patients in the trial sample or other factors.

FDA reviewed the Applicant 's proposed post hoc modeling approaches and subgroup analyses. FDA conducted additional post hoc analyses, noting that there are other factors the Applicant did not consider such as ISS, subsequent therapy and time from diagnosis, which may better describe the variability in OS. In one exploratory model (FDA Appendix 10.3), FDA's results indicated that factors other than age or TTP <36 months from transplant could explain the variability in OS seen in the OCEAN trial.

In another exploratory analysis, FDA also evaluated the IMiD effect on survival and age using patient-level data from several trials that isolated the effect of IMIDs submitted to the agency. The FDA's exploratory analysis did not find an interaction between IMiD, age and survival and did not support the Applicant 's conclusions. See further details in FDA Appendix 10.2.

FDA does not endorse model-building for these purposes, but constructed the exploratory models to show that under different model selection approaches, there are also other models that may be considered for describing the variability. There is not one model that is most appropriate and varies depending on selection procedures. This multivariable analysis is exploratory and should be considered hypothesis-generating.

3. **Defining a patient population subgroup excluding patients with TTP<36 months**

Acknowledging the limitations with the post hoc exploratory nature of the analysis, FDA does not agree that potential harm is only restricted to patients with TTP<36 months.

When looking at the specific HR for OS for patients with TTP<36 months (Figure 8) we see a detriment in OS, HR 1.80 (95% CI: 1.27, 2.55). When looking at patients with TTP>36 months or the no transplant group the CI crosses 1. Any effect that the sponsor claims may be present in the non-transplant subgroup and TTP> 36-month subgroup is not detectable because the 95% CI crosses 1; therefore, a benefit is not inferred by the data, nor is a detriment ruled out in this subgroup.

Because the Applicant's 's definition for TTP of 36 months did not consider patients who received melphalan flufenamide at progression, FDA conducted an exploratory analysis utilizing a different definition (one that was initially proposed by the Applicant); time since transplant (defined as time from last transplant to randomization on OCEAN study). This definition was used by the Applicant for a previous post hoc analysis for time since transplant with a 5-year cut-off.

The results (**Table 19**) show that regardless of the time since transplant, ≥ 36 months or < 36 months, the HR are greater than 1 indicating potential harm. The upper limit of the confidence interval of the HR for the no transplant group is >1 indicating that potential harm cannot be ruled out. The FDA conducted this subgroup analysis to underscore the limitations of post hoc analysis and making conclusions based on these analyses. By simply varying definitions or the analysis method different results are obtained.

Table 19 Time Since Transplant

Transplant Status	Number of Patients			OS Hazard Ratio (95% CI)
	MelDex N=246	PomDex N=249	Total N=495	
Transplant	125	120	245	1.61 (1.09, 2.4)

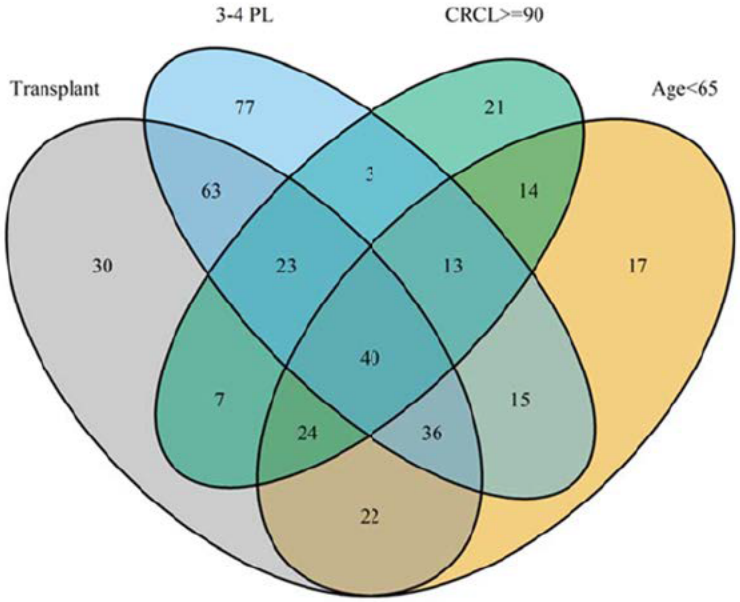
○ Time since transplant ≥ 36 months	71	73	144	1.19 (0.77, 1.82)
○ Time since transplant < 36 months of transplant	54	47	101	2.08 (1.28, 3.39)
No transplant	121	129	250	0.84 (0.61, 1.15)

Source: FDA Analysis, data cut-off Feb 3,2022

Within the OCEAN trial, the FDA notes that multiple subgroups had a worse OS providing credence to the primary OS detriment observed in the pre-specified randomized patient population. Specifically, those who received 3-4 prior lines of therapy, and those with a CrCl ≥90 ml/min, EMD among others (Figure 6). This suggests that transplant status or age are not the only variables impacting overall survival.

While there is some overlap between the patients who had transplant and the other subgroups with observed worse OS, these are distinct populations indicating that the transplant status is not driving the worse survival in these other subgroups (Figure 11).

Figure 11. Overlap in patient Subgroup Populations (OCEAN)



Source: FDA Analysis

Conclusion

The FDA does not agree that the Applicant's post hoc exploratory analysis and models provide conclusive evidence of a positive benefit-risk of melphalan flufenamide. The PFS and OS results in the ITT population indicate residual concerns with the benefit of melphalan flufenamide and indicate a potential for harm. The burden of proof is on the Applicant to show that the melphalan flufenamide is safe and effective based on data from adequate and well controlled trials. Post hoc subgroup exploratory analysis or post modelling cannot be used to support this conclusion or to support an indication in a subpopulation when the overall results show a detriment or unconfirmed benefit.

2.3.6 Summary

The Applicant's Position:

Given the poor prognosis of heavily pretreated patients with RRMM whose disease is TCR after 4 prior lines of therapy, the antitumor activity of Pepaxto/dex observed in HORIZON (ORR of 23.7%), together with the observed DOR of 4.2 months are clinically relevant and led to an accelerated approval in the US. A later data cutoff from this study shows a higher ORR and longer DOR. Response rates are in line with those observed for other agents in RRMM (25%-31%), although higher ORRs were reported for the recently approved CAR-T cell therapies ide-cel (72%) and cilta-cel (97.9%).

In OCEAN, superiority of Pepaxto/dex vs pomalidomide/dex was demonstrated for the primary endpoint of PFS, i.e., the primary objective of the study was met.

Despite the active comparator and the fact that OCEAN was not powered to demonstrate a difference in OS, the OS HR of >1 in this study warranted further investigation. The investigations revealed significant heterogeneity among subgroups in OCEAN, both within the Pepaxto arm and within the pomalidomide arm. The observed OS findings cannot exclude a potential harm in patients with TCR RRMM who received at least 4 prior lines of therapy and with a TTP <36 months after ASCT, as recognized in the EU label. Despite the post-hoc definition of this subgroup, the proposed recommendation to caution on the risks to these patients is justified based on the following:

- Identifying TTP <36 months post-ASCT as a highly significant interaction in multivariable analysis
- Repeated observations in both OCEAN and HORIZON
- A biological rationale for selection of this subgroup, based on resistance after prior use of high-dose melphalan and increased risk of myelotoxicity with loss of marrow reserve after recent transplantation
- Support for using TTP <36 months post-ASCT as a cutoff
- Support from external expertise (EMA SAG-O)
- Support from EMA guidance and FDA case examples on identifying subgroups with different treatment effects

The SAG-O concluded that Pepaxto/dex is associated with clinically relevant efficacy, except in the subgroup of patients with relapse within 36 months following high-dose melphalan and ASCT, and that the OCEAN results are relevant for the target population in HORIZON.

Overall, based on all available data, the Applicant considers that Pepaxto/dex has been shown to be efficacious in patients with TCR RRMM who received at least 4 prior lines of therapy. OCEAN data show that potential harm cannot be excluded with Pepaxto/dex in patients with TTP <36 months after a previous ASCT. Furthermore, in HORIZON, a risk for shorter survival cannot be excluded for patients with TCR who received at least 4 prior lines of therapy and had a TTP <36 months post-ASCT due to the absence of a control group. Thus, the current US label should contain language that adequately describes this for prescribing physicians. Importantly, patients who were never able to receive an ASCT due to old age, comorbidities, or lack of fitness, can be treated with Pepaxto because the benefit/risk profile is determined to be positive for these patients and for those who have a TTP > 36 months post-ASCT.

The FDA's Position

The FDA disagrees with the Applicant's position.

Melphalan flufenamide in combination with dexamethasone had modest efficacy in patients with RRMM who have received at least 4 prior lines of therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent and one CD38-directed monoclonal antibody. However, the intended population has limited treatment options and the benefit-risk assessment in the context of available therapies supported accelerated approval for this population based on an intermediate endpoint of ORR supported by DOR. The approval was contingent of the confirmation of a favorable risk benefit profile in the Phase 3 randomized confirmatory trial, OCEAN. The control arm PomDex represents a standard of care and is an FDA-approved regimen for this patient population.

The OCEAN trial failed to meet the primary endpoint. At the time of the original primary PFS analysis, the results did not demonstrate a statistically significant difference between the two arms on the primary efficacy endpoint, progression-free survival, HR 0.817 (95% CI: 0.659, 1.012), p = 0.0644. The Applicant's revised analysis demonstrated nominally significant superiority for PFS, HR 0.793 (95% CI: 0.640, 0.981), nominal p = 0.0322. FDA's assessment confirmed the significant p-value reported in the Applicant's revised PFS analysis; however, the FDA assessed p-value was different from the Applicant's, due to difference in FDA adjudication of 4 patients. Censoring unconfirmed progressive disease resulted in a non-significant p-value for the PFS analysis of 0.0837, indicating that there was no difference between the two arms on the PFS endpoint. Regardless of the PFS data and method of analysis, the median PFS did not change and the PFS difference between the arms remained at approximately 2 months. The results from other secondary endpoints such as ORR and DOR also did not demonstrate a significant treatment effect of melphalan flufenamide compared to the control arm.

Although not statistically significant, the original OS results and the updated OS results from the confirmatory trial, OCEAN, suggests a potential for harm in patients receiving melphalan flufenamide. At the time of the primary analysis, the observed median OS was 5.3 months shorter in the MelDex arm compared to that of the PomDex arm (19.7 months vs. 25.0 months; HR 1.104 (95% CI: 0.846, 1.441). There were higher rates of deaths in the MelDex arm (117/248; 47.6%) than in the PomDex arm (108/249; 43.4%). The updated OS results with a median follow-up duration of nearly three years (31.8 months in MelDex and 29.8 months in PomDex) were consistent with the initial OS results. OS is the ultimate clinical benefit endpoint. Any claim of clinical benefit based on PFS claimed by the Applicant is negated by the concerning OS results noted in the OCEAN trial.

We do not agree with the Applicant's position that outcomes in patients with TTP<36 months post-ASCT primarily influenced the detriment in OS in the melphalan flufenamide arm and patients who were never able to receive an ASCT due to old age, comorbidities, or lack of fitness, can be treated with melphalan flufenamide because the benefit/risk profile is determined to be positive for these patients and for those who have a TTP > 36 months post-ASCT. The available evidence does not support these conclusions.

- There are limitations with TTP and the 36-month cut-off definition as described in the FDA position in Section 1.3.2.
- The analyses used to support these assertions were not prospectively defined; therefore, these are hypothesis-generating and cannot be used as conclusive evidence of benefit or harm in a particular patient population. Subgroup analyses should only be used to confirm a consistent benefit-risk treatment effect across subgroups. Results from one subgroup cannot be used to identify a subset of patients who benefit when the overall patient population has shown a detrimental treatment effect.
- Even if we did consider the Applicant's post hoc analysis based on the TTP<36 months post-transplant, we note that while a detriment is noted in patients with TTP<36 months, a benefit or lack of harm cannot be inferred in the no transplant and TTP>36 months subgroups as the CI for HR crosses 1.
- Detriment in OS was noted in multiple subgroups evaluated, including patients 65-74 years of age, those with EMD, and those who received 3-4 lines of therapy. It is not possible to rule out potential harm in other subgroups.
- FDAs additional post hoc exploratory analyses indicate that there are other factors such as ISS, subsequent therapy and time from diagnosis that the Applicant did not consider that better describe the variability.
- Lastly, patients with comorbidities and frail patients were not the target population of the OCEAN trial, so there is no data to support benefit-risk of melphalan flufenamide in this patient population. A statement that benefit-risk positive is determined to be positive in these patients is promotional and misleading.

As the Applicant again references decisions of other regulatory Agencies, FDA notes that the regulatory actions of other agencies are not relevant to the discussion at the ODAC and FDA

regulatory decisions. The FDA must make regulatory decisions that are consistent with the U.S. legal and regulatory framework that mandate that a drug product is deemed safe and effective for marketing. The demonstration of effectiveness under this standard requires substantial evidence that the drug will have the effect it purports or is represented to have. It is the Applicant's responsibility to provide substantial evidence of safety and effectiveness.

The available evidence from OCEAN does not confirm the clinical benefit of melphalan flufenamide for the currently indicated patient population.

3 Safety

The Applicant's Position:

The safety profile of Pepaxto/dex has been consistent across all studies. It is characterized primarily by hematologic AEs that are clinically monitorable and manageable; severe non-hematologic events are infrequent.

The safety profile of Pepaxto/dex in the Phase 3 OCEAN study was consistent with that reported across studies, including the HORIZON study. Thus, the OCEAN study serves as a confirmatory trial for the safety of Pepaxto/dex and supports the current indication.

3.1 Analysis of Pooled Safety Data

The current safety profile for Pepaxto/dex is based on pooled safety data from 491 patients in 4 clinical studies in RRMM (O-12-M1[2], OCEAN[3], HORIZON[4], and BRIDGE[5]).

3.1.1 AEs

As expected, almost all patients (99.6%) reported treatment-emergent AEs, hereafter referred to as AEs (Table 20). The most commonly reported AEs were hematologic in nature, with thrombocytopenia (67.8%), anemia (65.4%), and neutropenia (57.2%) being the most commonly reported MedDRA Preferred Terms (PTs).

Some non-hematologic AEs were also common; fatigue, nausea, diarrhea, asthenia, and pyrexia all occurred in more than 15% of patients.

[2] Data cutoff date: November 9, 2017.
[3] Data cutoff date: February 3, 2021.
[4] Data cutoff date: March 31, 2020.
[5] Data cutoff date: April 5, 2021.

Table 20. AEs by MedDRA SOC and PT Occurring in >10% of Patients (Pooled Safety Data)

MedDRA SOC/PT	Total (N=491) n (%)
Blood and lymphatic system disorders	
Thrombocytopenia	333 (67.8)
Anemia	321 (65.4)
Neutropenia	281 (57.2)
Gastrointestinal disorders	
Nausea	105 (21.4)
Diarrhea	95 (19.3)
Constipation	52 (10.6)
General disorders and administration site conditions	
Fatigue	106 (21.6)
Asthenia	93 (18.9)
Pyrexia	92 (18.7)
Infections and infestations	
Upper respiratory tract infection	63 (12.8)
Pneumonia	55 (11.2)
Investigations	
Neutrophil count decreased	82 (16.7)
Platelet count decreased	81 (16.5)
White blood cell count decreased	79 (16.1)
Musculoskeletal and connective tissue disorders	
Back pain	51 (10.4)
Respiratory, thoracic, and mediastinal disorders	
Cough	54 (11.0)
Dyspnea	52 (10.6)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Affairs; PT, preferred term; SOC, system organ class.
Data cutoff date: Data as of February 3, 2021 are included for OCEAN; data as of April 5, 2021 are included for the OP-107 study; data as of March 31, 2020 are included for HORIZON; data as of November 9, 2017 are included for the O-12-M1 study.
Source: Updated ISS Table t-18-3-4-1-teae-soc-pt.

Hematologic events were also the most commonly reported grade 3/4 AEs. However, grade 3/4 non-hematologic events were relatively infrequent, with only pneumonia (7.5%) being reported in >5% of patients.[6]

Serious AEs (SAEs) were reported by 44.8% of patients (Table 21), with the most commonly reported MedDRA PT being pneumonia (7.9%).

Table 21. SAE Occurring in >2% of Patients (Pooled Safety Data)

	Total, n (%) (N=491)
Patients with at least 1 treatment-emergent SAE	220 (44.8)
MedDRA PT	
Pneumonia	39 (7.9)
Thrombocytopenia	16 (3.3)
Febrile neutropenia	15 (3.1)
Anemia	11 (2.2)
Neutropenia	11 (2.2)
COVID-19 pneumonia	11 (2.2)

COVID-19, coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SAE, serious adverse event.
Data cutoff date: Data as of February 3, 2021 are included for OCEAN; data as of April 5, 2021 are included for the OP-107 study; data as of March 31, 2020 are included for HORIZON; data as of November 9, 2017 are included for the O-12-M1 study.
Source: Updated ISS Table t-18-3-21-1-tesae-soc-pt.

Hematologic AEs are expected, based on the mechanism of action of alkylating drugs. Hematologic events can, however, be monitored and treated with supportive therapy, such as transfusions and granulocyte colony-stimulating factor.

3.1.2 AEs of Special Interest

AEs of special interest (AESI) are a subset of important AEs that usually cannot be fully described by single MedDRA PTs. Using AESIs therefore facilitates evaluation of specific types of events. Table 22 presents the most relevant AESIs identified for Pepaxto and their definitions.

[6] Source: ISS Table 18.3.7.1.

Table 22. Definition of AESIs

AESI	MedDRA Terms
Thrombocytopenia	SMQ: Hematopoietic thrombocytopenia
Bleeding events	SMQ: Hemorrhage terms (excluding laboratory terms)
Neutropenia[a]	CMQ[a]
Infections	SOC: Infections and infestations

AESI, adverse event of special interest; CMQ, customized MedDRA query; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SMQ, standardized MedDRA query; SOC, system organ class.
[a]PTs included in the Neutropenia CMQ: neutropenia, febrile neutropenia, neutrophil count decreased, neutropenic sepsis, neutropenic infection, cyclic neutropenia, band neutrophil count decreased, band neutrophil percentage decreased, neutrophil percentage decreased, agranulocytosis, granulocyte count decreased, and granulocytopenia.

A total of 408 (83.1%) patients reported AESIs of thrombocytopenia (Table 23), whereof 363 patients (73.9%) reported grade 3 or 4 events, but there was only 1 (0.2%) grade 4 bleeding event and 1 (0.2%) grade 5 bleeding event concomitant with a grade 3 or 4 thrombocytopenia.

In total there were 101 (20.6%) patients with bleeding events, whereof 71 (14.5%) reported bleeding starting in a cycle concomitant with a grade 3 or 4 thrombocytopenia. Of the 101 patients with bleeding events, 88 experienced bleedings with a maximum grade of only 1 or 2.

The results indicate that severe bleedings, both with and without severe thrombocytopenia, are infrequent.

Table 23. Summary of Thrombocytopenia and Bleeding AESI (Pooled Safety Data)

Parameter	Total, n (%) (N=491)
Patients with at least 1 thrombocytopenia event	408 (83.1)
Patients with at least 1 grade 3/4 thrombocytopenia event	363 (73.9)
Any action taken with study drug	265 (54.0)
Drug interrupted	202 (41.1)
Dose reduced	113 (23.0)
Drug withdrawn	57 (11.6)
Patients with at least 1 bleeding event	101 (20.6)
Bleeding events starting in a cycle concomitant with grade 3 or 4 thrombocytopenia	71 (14.5)
Grade 3	8 (1.6)
Grade 4	1 (0.2)
Grade 5	1 (0.2)

AESI, adverse event of special interest.
Notes: Percentages were based on the number of patients in the safety population (denominator).
"Concomitant with" was defined as a bleeding event that occurred between the start date of grade 3 or 4 thrombocytopenia – 7 days and the end date of that same grade 3 or 4 thrombocytopenia + 7 days.
Data cutoff date: Data as of February 3, 2021 are included for OCEAN; data as of April 5, 2021 are included for the OP-107 study; data as of March 31, 2020 are included for HORIZON; data as of November 9, 2017 are included for the O-12-M1 study.
Sources: ISS Table 18.3.37.1, 18.3.39.1, and ISS Table 18.3.53.1.

A total of 354 (72.1%) patients reported AESIs of neutropenia, whereof 325 (66.2%) patients reported grade 3/4 events (Table 24). More than half of infections were non-neutropenic, i.e., did not start in a cycle with a concomitant grade 3 or 4 neutropenia. In total, 254 (52%) patients reported at least 1 infection (any grade), including 104 (21%) patients who reported infections in connection with a grade 3 or 4 neutropenia. Of the 104 patients, grade 3, 4, and 5 infections concomitant with grade 3 or 4 neutropenia were reported in 37 (8%), 2 (0.4%), and 2 (0.4%) patients, respectively. The remaining 63 patients reported only grade 1 or 2 infections.

Table 24. Summary of Neutropenia and Infections AESI (Pooled Safety Data)

Parameter	Total, n (%) (N=491)
Patients with at least 1 neutropenia event	354 (72.1)
Patients with at least 1 grade 3/4 neutropenia event	325 (66.2)
Any action taken with study drug	154 (31.4)
Drug interrupted	125 (25.5)
Dose reduced	44 (9.0)
Drug withdrawn	18 (3.7)
Patients with at least 1 infection	254 (51.7)
Infections starting in a cycle concomitant with grade 3 or 4 neutropenia	104 (21.2)
Grade 3	37 (7.5)
Grade 4	2 (0.4)
Grade 5	2 (0.4)

AESI, adverse event of special interest.
Notes: Percentages were based on the number of patients in the safety population (denominator).
"Concomitant with" was defined as an infection that occurred between the start date of grade 3 or 4 neutropenia – 7 days and the end date of that same grade 3 or 4 neutropenia + 7 days.
Data cutoff date: Data as of February 3, 2021 are included for OCEAN; data as of April 5, 2021 are included for the OP-107 study; data as of March 31, 2020 are included for HORIZON; data as of November 9, 2017 are included for the O-12-M1 study.
Sources: ISS Table 18.3.37.1, ISS Table 18.3.41.1, and ISS Table 18.3.55.1.

There were more dose modifications of Pepaxto due to grade 3 or 4 AESIs of thrombocytopenia than neutropenia (Table 23and Table 24); dose interruption: 41.1% vs 25.5%, dose reduction: 23.0% vs 9.0%, and permanent discontinuation: 11.6% vs 3.7%, respectively.

Analyses of intrinsic factors indicated a relationship between a weight below 60 kg and a higher frequency of hematologic AESIs, including thrombocytopenia, neutropenia, and anemia[7]. A low BSA was also associated with a higher frequency of hematologic AESIs[8].

3.1.3 Fatal Events

PD was by far the most common cause of death (Table 25). A total of 260 (53%) patients died during the studies. Only 14 (3%) patients who died ≤30 days after last dose of Pepaxto/dex had

[7] Source: ISS Table 18.3.37.1i.
[8] Source: ISS Table 18.3.37.1d.

an AE stated as primary cause of death, while 24 (5%) patients who died >30 days after the last dose of Pepaxto/dex had an AE stated as primary cause of death.

Table 25. Overall Summary of Death (Safety Population)

Parameters	Total, n (%) (N=491)
Number of deaths	260 (53.0)
Death ≤30 days after last dose of Pepaxto	23 (4.7)
Death >30 days after last dose of Pepaxto	237 (48.3)
Primary cause of death (death ≤30 days after last dose of Pepaxto)	23 (4.7)
AE	14 (2.9)
Disease progression	8 (1.6)
Unknown	0
Other	0
Missing	1 (0.2)
Primary cause of death (death >30 days after last dose of Pepaxto)	237 (48.3)
AE	24 (4.9)
Disease progression	170 (34.6)
Unknown	15 (3.1)
Other	22 (4.5)
Missing	6 (1.2)

AE, adverse event.
Data cutoff date: Data as of February 3, 2021 are included for OCEAN; data as of April 5, 2021 are included for the OP-107 study; data as of March 31, 2020 are included for HORIZON; data as of November 9, 2017 are included for the O-12-M1 study.
Source: Updated ISS Table t-18-3-29-1-dth.

The most common fatal AEs were infections, reported in 20 (4%) patients, out of which COVID-19 pneumonia was the most common, occurring in 7 (1%) patients.[9]

In total there were 7 (1%) patients with 9 fatal treatment-related events. Five of these 7 patients experienced fatal infections.[10] In the overall late-stage MM population, infections are common causes of death.

The FDAs Position

FDA agrees that myelosuppression is the primary safety concern with melphalan flufenamide. However, FDA disagrees with the Applicant's conclusion regarding the safety profile of melphalan flufenamide based on primary safety evaluation in the pooled population. Evaluating safety in the pooled population is helpful for assessing safety signals that are rare and need a larger sample size to detect. However, in the absence of a comparator arm, it is challenging to

[9] Source: ISS Table 18.3.30.1.
[10] Source: ISS Table 18.3.32.1.

characterize safety. FDA's assessment of safety was based on the results in the randomized confirmatory trial, OCEAN. The act of randomization balances known and unknown factors between the treatment groups allowing differences in the study outcome to be attributed to the treatment being evaluated.

OCEAN-Safety

The Safety analysis was done on all subjects who received at least one dose of melphalan flufenamide, pomalidomide, or dexamethasone. The FDAs evaluation of hematologic adverse events in OCEAN is based on the laboratory data set (except SAEs) rather than hematologic adverse events as hematologic AEs are often underreported in the AE datasets.

Safety Overview

Nearly all patients had at least one treatment emergent adverse event (TEAE), Table 26. Higher rate of Grade 3-4 TEAEs is noted in the MelDex arm (90%) compared to the PomDex arm (74%). Additionally, there was a higher rate of dose interruptions due to TEAEs (60% vs. 44%) and dose reductions due to TEAEs (47% vs. 15%) in the MelDex arm compared to the PomDex arm.

Table 26 Overview of Safety (OCEAN)

	MelDex N= 228 n (%)	PomDex N= 246 n (%)
Any TEAE	226 (99)	241 (98)
Any Grade 3-4 TEAE	205 (90)	183 (74)
Grade 5 TEAE	27 (12)	32 (13)
Serious AEs	95 (42)	113 (46)
Dose* delayed due to TEAE	137 (60)	109 (44)
Dose* reduced due to TEAE	107 (47)	37 (15)
Drug* withdrawn due to TEAE	60 (26)	54 (22)

Source: FDA Analysis

*Dose and Drug = *melphalan flufenamide* or pomalidomide (does not include dose modifications made to dexamethasone) TEAE: treatment emergent adverse event

Deaths -Safety Population

Table 27 provides a summary of deaths that were reported on the OCEAN trial adjudicated by the FDA. There were more deaths in the MelDex arm (46%) than the PomDex arm (43%) in the safety population.

Overall, adverse events leading to death ≤30 days were similar between the two arms. Three patients in the MelDex arm were reported to have died due to hemorrhage. There were no deaths due to hemorrhage reported on the PomDex Arm.

The higher MelDex death rate was most notable in events that occurred beyond 60 days after the last dose; 31% of deaths in the MelDex arm occurring beyond 60 days compared to 25% in the PomDex arm. This raises a concern that treatment with MelDex may impact the ability to receive or tolerate subsequent lines of therapy.

Limited information was available for deaths occurring beyond 60 days. Hence, FDA was unable to confirm the cause of death reported, i.e., adverse event versus progression, for those patients with deaths beyond 60 days. The increased deaths in the melphalan flufenamide arm could be due to late toxicity or inability to tolerate next lines of therapy due to myelosuppression. However, since the death narratives had very limited information after patients stopped therapy, this could not fully be explored.

Table 27 Overview of Deaths (OCEAN)

	MelDex N = 228 n (%)	**PomDex N = 246 n (%)**
Total Deaths	106 (47)	106 (43)
Progressive Disease	60 (26)	54 (22)
Adverse Event	22 (10)	26 (11)
Other	11 (4.8)	11 (4.5)
Unknown	13 (6)	15 (6)
Death ≤30 Days After Last Dose*	23 (10)	33 (13)
Adverse Event	16 (7)	18** (7)
Progressive Disease	6 (2.6)	14 (6)
Unknown	1 (0.4)	1 (0.4)
30-60 Days After Last Dose	12 (5)	12 (5)
Adverse Event	4 (1.8)	3 (1.2)
Progressive Disease	6 (2.6)	7 (3)
Other	1 (0.4)	1 (0.4)
Unknown	1 (0.4)	1 (0.4)
Beyond 60 days after last dose	71 (31)	61 (25)
Progressive Disease	45 (20)	41 (17)
Other	10 (4.4)	7 (2.8)
Unknown	13 (6)	12 (5)
Adverse Event	3 (1.3)	1 (0.4)

Source: FDA Analysis

* The Grade 5 TEAE number represented in the overview of safety represents the total number of patients having a Grade 5 TEAEs as reported from the "AE Forms". Death due to AE in the overview of deaths reflects the number of fatal AEs listed as the primary cause of death on the "death form".

** FDA identified 5 patients in the PomDex arm originally listed as death due to AE within 30 days whose death narrative was consistent with death due to PD (AEs originally listed as renal failure, respiratory failure, general condition deterioration, multiorgan failure, cardiac arrest). FDA also disagreed on one "unknown" case which was consistent with PD.

Serious Adverse Events

Serious adverse events occurring in ≥2% in either treatment arm are presented in Table 28. There were more patients with serious adverse events in the PomDex arm (46%) compared to MelDex arm (42%). Thrombocytopenia and pneumonia were the most common SAEs reported in the MelDex arm. There was a higher rate of thrombocytopenia SAEs in the MelDex arm (6%) compared to PomDex arm (1.2%). There was a higher rate of pneumonia SAEs in the PomDex arm (11%) compared to MelDex arm (6%).

Table 28 Serious Adverse Events (≥ 2%, OCEAN)

	MelDex N = 228 n (%)	PomDex N = 246 n (%)
Total Patients with at least 1 SAE	95 (42)	113 (46)
Blood and Lymphatic System		
Thrombocytopenia (GT)	13 (6)	3 (1.2)
Anemia	7 (3.1)	5 (2.0)
Infections		
Sepsis (GT)	5 (2.2)	5 (2.0)
Pneumonia (GT)	13 (6)	26 (11)
Urinary Tract Infection (GT)	3 (1.3)	6 (2.4)
Influenza	0	5 (2.0)
Renal and Urinary Disorders		
Acute Kidney Injury	2 (0.9)	5 (2.0)
Cardiac Disorders		
Atrial Fibrillation	0	9 (3.7)

Source: FDA Analysis;
Thrombocytopenia (GT) includes thrombocytopenia and platelet count decreased.

Sepsis (GT) includes sepsis, septic shock, bacterial sepsis, bacteremia, E.coli sepsis, staphylococcal bacteremia, bacteremia, Pneumonia (GT) includes terms pneumonia, lower respiratory tract infection, pneumonia streptococcal, pneumocystis jirovecii pneumonia, pneumonia viral, COVID-19 pneumonia

Abbreviations: SAE: serious adverse events; GT: grouped term

Adverse Events of Special Interest

Adverse events of special interest are presented in Table 29. While the rate of Grade 3-4 neutropenia was higher in the MelDex arm (73%) compared to the PomDex arm (59%), the rate of infections (SOC) was not higher. There was a higher rate of Grade 3-4 thrombocytopenia in the MelDex arm (81%) compared to the PomDex arm (14%). These high rates of thrombocytopenia led to higher rates of all-grade (16% vs. 6.5%) and Grade 3-4 hemorrhage (2.2% vs. 0.4%) in the MelDex arm compared to the PomDex arm.

Table 29 Adverse Events of Special Interest (OCEAN)

	MelDex N = 228 n (%)		PomDex N = 246 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Thrombocytopenia*	220 (97)	184 (81)	152 (62)	35 (14)
Anemia*	205 (90)	99 (44)	160 (65)	46 (19)
Neutropenia*	211 (93)	166 (73)	213 (87)	144 (59)
Infections (SOC)	114 (50)	30 (13)	137 (56)	53 (22)
Hemorrhage (GT)	36 (16)	5 (2.2)	16 (6.5)	1 (0.4)

Source: FDA Analysis
SOC: system organ class; GT: grouped terms
Hemorrhage (GT) includes terms hematoma, hemorrhagic diathesis, hemorrhagic disorder, hematuria, cerebral hemorrhage, esophageal hemorrhage, epistaxis, catheter site hematoma, catheter site hemorrhage, conjunctival hemorrhage, contusion, ecchymosis, gingival bleeding, hematochezia, mouth hemorrhage, esophageal hemorrhage, hemorrhoidal hemorrhage, purpura, retinal hemorrhage, scleral hemorrhage, skin hemorrhage
*Blood and lymphatic system disorders change from baseline, ADLB (Laboratory Analysis) using safety population as denominator

Common TEAES

TEAEs which occurred in 10% or more of patients are listed in Table 30. Higher rates of anemia, neutropenia and thrombocytopenia were noted in the MelDex arm. Grade 3-4 thrombocytopenia lab abnormalities were substantially higher in the MelDex arm (81%) compared to the PomDex arm (14%). The rate of hemorrhage was two times higher in the MelDex arm (16%) compared to the PomDex arm (6.5%). However, the rates of Grade 3-4 hemorrhage occurred in less than 5% of patients in both treatment arms (MelDex 2.2%, PomDex 0.4%).

Table 30 Treatment Emergent Adverse Events including laboratory abnormalities (≥ 10%, OCEAN)

	MelDex (N=228) %		PomDex (N=246) %	
	All Grade	**Grade 3-4**	**All Grade**	**Grade 3-4**
Blood and lymphatic system disorders*				
Leukopenia	225 (99)	180 (79)	206 (84)	77 (31)
Lymphopenia	223 (98)	215 (94)	162 (67)	63 (26)
Thrombocytopenia	220 (97)	184 (81)	152 (62)	35 (14)
Neutropenia	211 (93)	166 (73)	213 (87)	144 (59)
Anemia	205 (90)	99 (44)	160 (65)	46 (19)
Gastrointestinal disorders				
Diarrhea (GT)	31 (14)	3 (1.3)	21 (9)	1 (0.4)
Nausea	30 (13)	1 (0.4)	17 (7)	1 (0.4)
Constipation	16 (7)	0	29 (12)	0
General disorders and administration site conditions				
Fatigue (GT)	61 (27)	4 (1.8)	66 (27)	9 (3.7)
Influenza Like Illness	2 (0.9)	0	27 (11)	4 (1.6)
Pyrexia	33 (14)	3 (1.3)	16 (7)	3 (1.2)
Edema (GT)	13 (6)	1 (0.4)	27 (11)	4 (1.6)
Infections and infestations				
Urinary Tract Infection (GT)	17 (7)	3 (1.3)	19 (8)	7 (2.8)
Pneumonia (GT)	27 (12)	15 (7)	46 (19)	30 (12)
Upper respiratory tract infection	29 (13)	3 (1.3)	25 (10)	1 (0.4)
Bronchitis	13 (6)	3 (1.3)	26 (11)	5 (2.0)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain (GT)	62 (27)	9 (3.9)	59 (24)	13 (5)
Respiratory, thoracic, and mediastinal disorders				
Dyspnea (GT)	22 (10)	2 (0.9)	27 (11)	2 (0.8)
Vascular				
Hemorrhage (GT)	36 (16)	5 (2.2)	16 (6.5)	1 (0.4)

Source: FDA Analysis, ADAE (Adverse Events Analysis) 6.25.2021,
Diarrhea (GT) includes terms diarrhea, enteritis, colitis Fatigue (GT) includes terms asthenia, fatigue,
Edema (GT) includes oedema, peripheral oedema, localized oedema, generalized oedema, oedema
Urinary Tract Infection (GT) includes terms urinary tract infection, cystitis, Escherichia urinary tract infection.
Pneumonia (GT) includes terms pneumonia, lower respiratory tract infection, pneumonia streptococcal, pneumocystis jirovecii pneumonia, pneumonia viral, COVID-19 pneumonia
Musculoskeletal Pain (GT) includes bone pain, spinal pain, back pain, pain in extremity, arthralgia, musculoskeletal chest pain, musculoskeletal pain, neck pain, myalgia, arthritis

Dyspnea (GT) includes terms dyspnea, dyspnea exertional
Hemorrhage (GT) includes terms hematoma, hemorrhagic diathesis, hemorrhagic disorder, hematuria, cerebral hemorrhage, esophageal hemorrhage, epistaxis, catheter site hematoma, catheter site hemorrhage, conjunctival hemorrhage, contusion, ecchymosis, gingival bleeding, hematochezia, mouth hemorrhage, esophageal hemorrhage, hemorrhoidal hemorrhage, purpura, retinal hemorrhage, scleral hemorrhage, skin hemorrhage,
*Blood and lymphatic system disorders change from baseline, ADLB (Laboratory Analysis) 6.25.21

3.2 Safety in HORIZON

The Applicant's Position:

The efficacy and safety of Pepaxto in combination with dex were evaluated in HORIZON, a multicenter, single-arm trial in 157 patients with RRMM (see Section 2.2.1). Cutoff for the data presented here is February 2, 2022.

As in the pooled safety data from 491 patients, hematologic events were the most frequently reported AEs in HORIZON, mainly MedDRA PTs thrombocytopenia, neutropenia, and anemia, which were reported in 60.5%, 55.4%, and 72.0%, respectively (Table 31). These events were also the most commonly reported grade 3 or 4 AEs.[11]

Table 31. AEs by MedDRA SOC and PT Occurring in >15% of Patients (Safety Analysis Set)

SOC PT	Overall, n (%) (N=157)
Number of patients with at least 1 AE	157 (100)
Blood and lymphatic system disorders	135 (86.0)
Anemia	113 (72.0)
Thrombocytopenia	95 (60.5)
Neutropenia	87 (55.4)
General disorders and administration site conditions	120 (76.4)
Fatigue	46 (29.3)
Asthenia	45 (28.7)
Pyrexia	41 (26.1)
Gastrointestinal disorders	99 (63.1)
Nausea	51 (32.5)
Diarrhea	43 (27.4)
Constipation	24 (15.3)
Infections and infestations	93 (59.2)
Upper respiratory tract infection	26 (16.6)
Investigations	69 (43.9)

[11] Source: Table 14.3.1-5.

SOC PT	Overall, n (%) (N=157)
White blood cell count decreased	45 (28.7)
Neutrophil count decreased	42 (26.8)
Platelet count decreased	41 (26.1)
Musculoskeletal and connective tissue disorders	81 (51.6)
Pain in extremity	24 (15.3)
Respiratory, thoracic, and mediastinal disorders	80 (51.0)
Cough	29 (18.5)
Dyspnea	24 (15.3)

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Affairs; MM, multiple myeloma; PT, preferred term; SOC, system organ class.

Notes: Adverse events are defined as AEs with onset date/time or increase in severity level after the initial dose of study drug and within 30 days (unless considered related to study drug) after the last dose of study drug or initiation of new MM therapy, whichever is sooner. At each level of summarization (any event, SOC, and PT), patients reporting more than 1 AE are counted only once.

Data cutoff date: February 2, 2022.

Source: Listing 16.2-7.1.

Thrombocytopenia was the most common AE leading to permanent discontinuation of Pepaxto (11.5%).[12] A total of 18.5% of patients in HORIZON had a grade 3 or 4 AESI of thrombocytopenia and a concomitant bleeding event; 3.2% were grade 3 or 4 bleedings. Most bleeding events were grade 1 or 2.

In HORIZON, 29.3% of patients had an infection and concomitant grade 3 or 4 AESI of neutropenia; 12.1% reported a grade 3 or 4 infection and concomitant grade 3 or 4 neutropenia. Overall, 59.2% of patients reported infections and 27.4% reported grade 3 or 4 infections.[13] Infections were in general manageable with anti-infective treatment and dose modifications.

Non-hematologic AEs frequently (>20%) reported with Pepaxto were asthenia, nausea, diarrhea, fatigue, and pyrexia.[14] These events were mostly grade 1 or 2. The frequencies of non-hematologic AEs is higher in HORIZON than in the pooled safety data, most likely because the patients in HORIZON had more advanced disease.

Overall, grade 3 or 4 AEs were reported in 95.5% of patients,[15] and SAEs were reported in 56.1% of patients. Pneumonia (10.2%) and febrile neutropenia (5.1%) were the most frequently reported SAEs.[16] In the overall population, 82.8% of patients died during the study and 9.6% died within 30 days after last dose of study drug. Most deaths were due to PD, and the fatal AE rate within 30 days after last dose of study drug was 5.1%.[17]

[12] Source: OP-106 CSR datacut 2 February 2022 Table 14.3.1-12.2.
[13] Source: Table 14.3.1-13.1.1.
[14] Source: Table 14.3.1-3.1.
[15] Source: Table 14.3.1-5.
[16] Source: Table 14.3.1-8.1.
[17] Source: Table 14.3.1-14.1.

Overall, 28.0% of patients reported an AE leading to discontinuation of Pepaxto[18] AEs leading to Pepaxto dose reductions were observed in 31.2% of patients,[19] and 65% had dose delays[20] of Pepaxto due to AEs.

The safety profile in the TCR population was comparable to that of the overall population in the study.

The data presented here, with cutoff February 2, 2022, are in line with the data presented in the current US prescribing information (data cutoff: January 14, 2020).

The overall safety profile in HORIZON is consistent with the pooled safety data from 491 patients. However, overall frequencies of AEs are slightly higher, likely reflecting that the OP-106 population is severely ill with a more advanced disease.

The FDA's Position

The safety of melphalan flufenamide from the single arm HORIZON trial was evaluated at the time of the accelerated approval.

The data presented by the Applicant differs from the USPI because of different data cut-off and due to the following additional differences:

- The use of grouped terms by the FDA to evaluate non-hematologic AEs
- The use of laboratory datasets to analyze hematologic AEs

For example, rates of thrombocytopenia based on laboratory data was 99% in the 157 patients who received melphalan flufenamide on the HORIZON trial. Grade 3 thrombocytopenia was reported in 26% and Grade 4 thrombocytopenia was reported in 54% of patients [PEPAXTO USPI]. Fatigue (fatigue and asthenia) was reported in 55% of the patients evaluated in HORIZON (n=157).

However, it is challenging to characterize safety in the absence of a comparator arm. The OCEAN trial was designed to verify the clinical benefit and assessment of risk of melphalan flufenamide following accelerated approval. FDA's assessment of the safety to support an assessment of benefit-risk of melphalan flufenamide is based on the OCEAN trial.

3.3 Supportive Safety Data from OCEAN

The Applicant's Position:

The Applicant has thoroughly analyzed the safety data in OCEAN and cannot identify a Pepaxto toxicity signal that could explain a potential detrimental effect on OS in the FAS population. Safety data in OCEAN are in line with the safety profile observed in pooled safety data.

OCEAN enrolled patients in earlier-stage RRMM (2-4 prior lines of treatment and refractory to both the last line and to lenalidomide) compared to HORIZON; 228 patients were treated with

[18] Source: Table 14.3.1-12.2.
[19] Source: Table 14.3.1-10.2.
[20] Source: Table 14.3.1-11.2.

Pepaxto/dex and 246 with pomalidomide/dex. Treatment duration with Pepaxto was longer in OCEAN than in HORIZON (median 25 weeks compared to 16 and median 5 cycles started compared to 3),[21] reflecting the patients' earlier disease stage. The safety findings in the Pepaxto/dex arm of OCEAN primarily consisted of hematologic AEs (mostly thrombocytopenia, anemia, and neutropenia).[22] These events were more frequent in the Pepaxto/dex arm than in the pomalidomide/dex arm. Non-hematologic AEs occurred at similar frequencies in both treatment groups.[23]

Both the total number and percentage of deaths were higher in the Pepaxto arm (117 patients [47.6%]) than in the pomalidomide arm (108 patients [43.4%]) when comparing the FAS population, which also includes randomized patients who did not receive study drug. When comparing the safety populations, i.e., only patients receiving the study drug, the difference is less pronounced (Table 32). Overall Pepaxto and pomalidomide display similar patterns in high-level safety parameters (Table 32).

Table 32. Summary of High-Level Safety Parameters in OCEAN

	Pepaxto/Dex (N=228)	Pomalidomide/Dex (N=246)
Total number of deaths – treated (safety population)	106 (46.5%)	106 (43.1%)
Deaths while on therapy or within 30 days of last dose	23 (10.1%)	33 (13.4%)
Patients with at least 1 AE	226 (99.1%)	241 (98.0%)
Patients with at least 1 treatment-related AE	216 (94.7%)	209 (85.0%)
Patients with at least 1 grade 5 AE	27 (11.8%)	32 (13.0%)
Patients with at least 1 serious AE	95 (41.7%)	113 (45.9%)
Patients with at least 1 treatment-related serious AE	42 (18.4%)	52 (21.1%)

AE. adverse event; dex, dexamethasone.
Data cutoff date: February 3, 2021.
Sources: Table 14.3.1-13.1; Table 14.3.1-13.1; Table 14.3.1-2.1; Table 14.3.1-5.1; Table 14.3.1-3.1; Table 14.3.1-7.1; and Table 14.3.1-7.3.

Fatal (grade 5) AEs were balanced between the Pepaxto and pomalidomide treatment arms; 27 patients (12%) in the Pepaxto arm and 32 (13%) patients in the pomalidomide arm had at least 1 grade 5 AE. In addition, the total number of deaths in the safety population was similar in both arms: 106 (46.5%) in the Pepaxto arm and 106 (43.1%) in the pomalidomide arm.

Severe (grade 3) bleeding events (AESI) in connection with AESIs of thrombocytopenia occurred only in the Pepaxto/dex arm but were uncommon and affected only 2 (0.9%) patients. There

[21] Source: OP-103 CSR data-cut 3 February 2021, Table 14.3.1-2.1 and OP-106 sCSR data-cut 2 February 2022, Table 14.3-1.2.
[22] Source: OP-103 CSR data-cut 3 February 2021, Table 14.3.1-2.1.
[23] Source: Table 14.3.1-2.1.

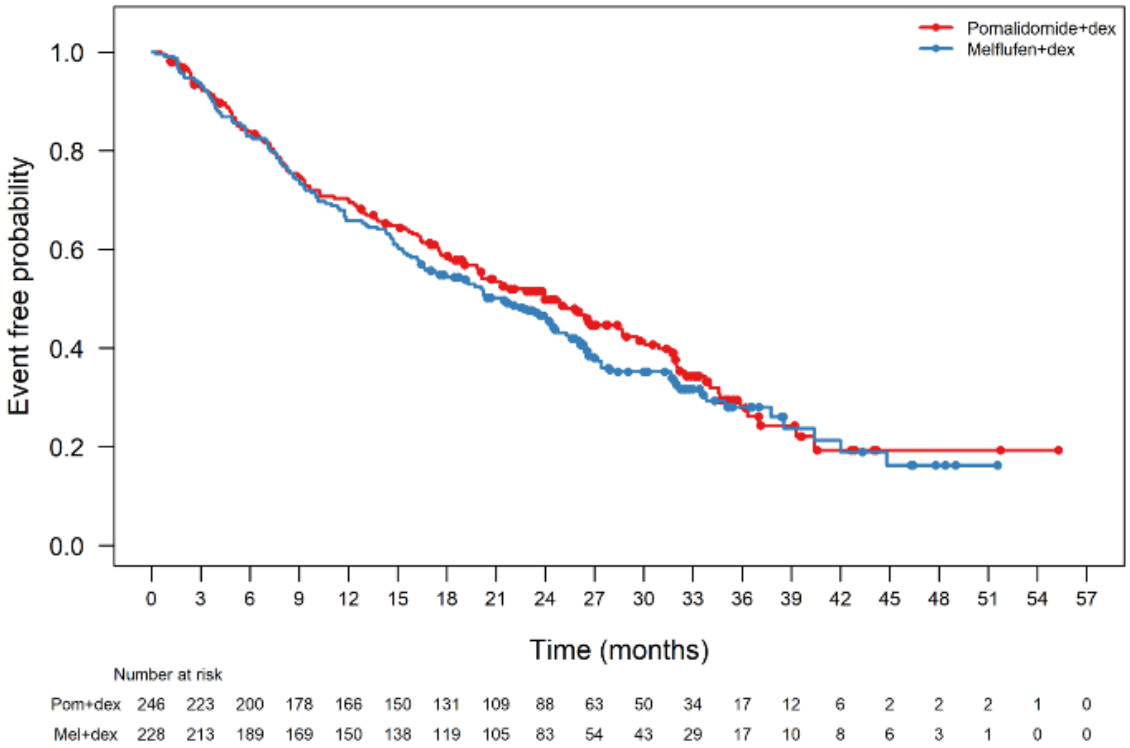
were no life-threatening (grade 4) or fatal (grade 5) bleedings in connection with thrombocytopenia.

The frequency of patients with AESIs of infection in connection with grade 3 or 4 AESIs of neutropenia was similar in the 2 treatment arms (12.7% vs 15.0%) despite grade 3 or 4 neutropenias being more frequent in the Pepaxto/dex arm (64.5% vs 49.2%).[24] Hematologic events were manageable with dose modifications and supportive care, which is consistent with results from other Pepaxto studies.

Results from OCEAN also indicated that patients who discontinued treatment with Pepaxto/dex due to AEs continued to subsequent therapy at least to the same degree as patients who discontinued treatment with pomalidomide/dex due to AEs. Notably, the TTP is longer in patients initially treated with Pepaxto/dex than in patients initially treated with pomalidomide/dex.

Furthermore, as can be seen in the KM plot of the safety population (Figure 12), the 2 treatment arms have a similar slope until approximately 10 months after start of treatment, which is well after reaching the median PFS. This, combined with the safety profile summarized above, suggests that the FAS OS difference is not driven by direct toxicity.

Figure 12. OCEAN – OS (Safety Analysis Set)



[24] Source: Table 14.3.1-12.1.1.

dex, dexamethasone; OS, overall survival; pom, pomalidomide.
Data cutoff date: February 3, 2022.
Applicant internal analyses; source: ADTTE.

The overall safety profile in OCEAN is consistent with the current safety profile for Pepaxto/dex, based on pooled safety data.

The FDA's position

The FDA does not agree with the Applicant's position that there is no toxicity signal with melphalan flufenamide and that melphalan flufenamide and pomalidomide displayed similar safety profiles.

The lack of a comparator arm in the pooled population and the HORIZON trial limits adequate characterization of the safety of melphalan flufenamide. The OCEAN trial results show a detriment in OS in the Mel/Dex arm compared to the control. The safety data from the OCEAN trial are indicative of significant safety concerns with melphalan flufenamide.

- Nearly all patients had at least one treatment emergent adverse event (TEAE).
- There was a higher rate of Grade 3-4 TEAEs in the MelDex arm (90%) compared to the PomDex arm (74%).
- Additionally, there was a higher rate of dose interruptions due to TEAEs (60% vs. 44%) and dose reductions due to TEAEs (47% vs. 15%) in the MelDex arm compared to the PomDex arm.
- There were more deaths in the MelDex arm (46%) than the PomDex arm (43%) in the safety population. While the deaths within 30 days were similar, there was a notable difference in deaths beyond 60 days of the last dose. The higher deaths in the melphalan flufenamide arm beyond 60 days after the last dose; 31% of deaths in the MelDex arm occurring beyond 60 days compared to 25% in the PomDex arm raises a concern that treatment with MelDex may impact the ability to receive and tolerate subsequent lines of therapy.

Similar to the HORIZON trial, myelosuppression was a major concern.

- There was a higher rate of Grade 3-4 thrombocytopenia in the MelDex arm (81%) compared to the PomDex arm (14%).
- The high rate of thrombocytopenia led to higher rates of all-grade (16% vs. 6.5%) and Grade 3-4 hemorrhage (2.2% vs. 0.4%) in the MelDex arm compared to the PomDex arm.
- The rate of Grade 3-4 neutropenia was higher in the MelDex arm (73%) compared to the PomDex arm (59%).

The myelosuppression with melphalan flufenamide may indicate late toxicity effects with a subsequent impact on the ability to receive subsequent therapy or increasing the risk of toxicity to subsequent therapies with an impact on the overall survival. The finding that the OS detriment is noted despite improved time to progression indicates toxicity concerns.

The FDA notes that the toxicity rates were higher in the HORIZON trial that enrolled a more refractory patient population. The impact of these toxicities on PFS and OS could not be evaluated in the single arm trial HORIZON. Given the detriment in OS seen in a less refractory patient population in OCEAN, it is possible that detriment in OS could be more severe in the patient population enrolled in the HORIZON trial, which aligns with the current indication.

3.4 Proposed Label Updates to Further Improve the Safety Profile

The Applicant's Position:

In addition to the proposed recommendation to inform prescribers that potential harm cannot be excluded in patients who have progressed within 36 months after an ASCT, the following changes to the current label, based on pharmacokinetic and pharmacokinetic/pharmacodynamic analyses (Appendix 5), are proposed to further reduce the risk for neutropenia and thrombocytopenia in connection with Pepaxto use:

- Patients with a body weight ≤60 kg should receive a dose of 30 mg instead of the currently recommended dose of 40 mg
- Patients who require a dose interruption due to neutropenia or thrombocytopenia should have an immediate dose reduction of Pepaxto in the next treatment cycle instead of only delaying the dosing without reducing the dose

The FDA's Position

The safety concerns and the toxicity observed indicate that that the flat dose of 40 mg is not optimized to support a favorable benefit-risk profile. The Applicant has proposed additional dose modifications for neutropenia and thrombocytopenia and a slightly lower flat dose of 30 mg for patients ≤60 kg in effort to address the risk. However, these proposals have not been evaluated in clinical trials. Additional FDA concerns are noted below.

Adequacy of the recommended starting dose of 40 mg

Prior to addressing the Applicant's proposed dose labeling updates, the FDA notes the inadequate dose selection leading to the 40 mg flat starting dose in the general population.

Dosing was initially explored in a traditional dose escalation study design in the Phase 1/2 study (O-12-M1) where 40 mg was identified as the maximum tolerated dose with very few patients evaluated at lower doses. At the time of accelerated approval, PK data were only available from 12 subjects, of which 8 subjects received the 40 mg starting dose (**Table 33**) and in the Phase 2 study, HORIZON, no PK data were collected and no population PK or exposure-response analyses were conducted. As such, the safety and efficacy of lower doses could not be adequately evaluated and the clinical efficacy and safety evaluations for doses lower than 40 mg or alternative dosing regimens were not fully explored.

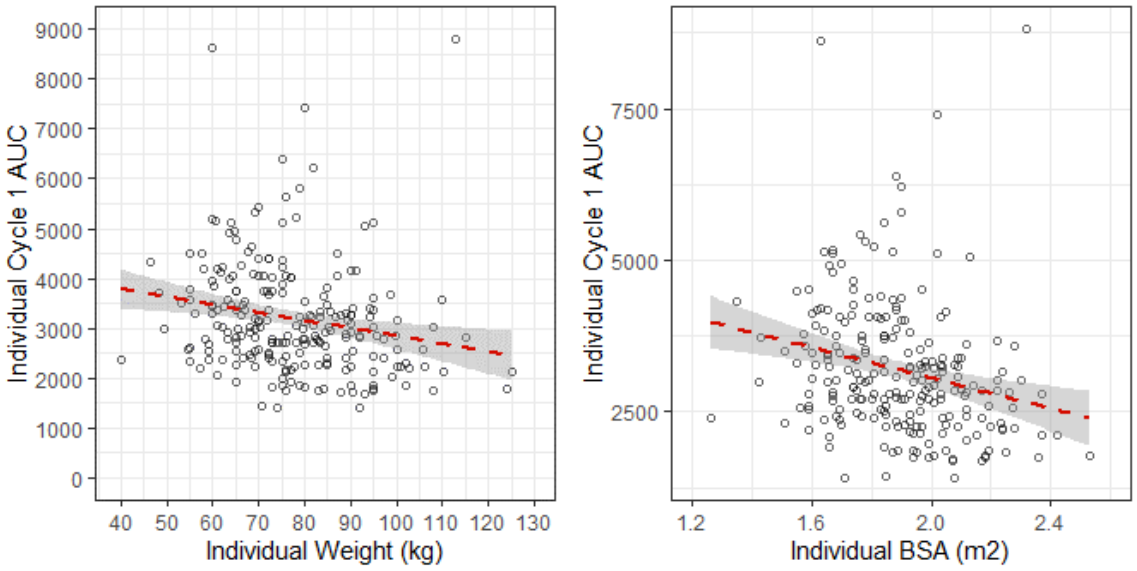
Table 33. Number of Subjects per Dose Level in Phase 1/2 Study O-12-M1

Melphalan Flufenamide Dose	Total patients	Patients with ≥1 measured melphalan concentration
15 mg	4	1
25 mg	7	2
40 mg	58	8
55 mg	6	1

Note: Melphalan is the active metabolite of melphalan flufenamide.
Source: FDA Analysis

Additionally, the Applicant did not collect sufficient PK data in the OCEAN study to allow for dose optimization evaluation. Only a few sparse PK samples were collected for Cycle 1 Day 1 and Cycle 2 Day 1. However, population PK analyses with the available data identified that individual drug exposure is significantly associated with BSA and body weight. Patients with lower body weight or lower BSA are predicted to have higher individual exposure, as shown in **Figure 13**.

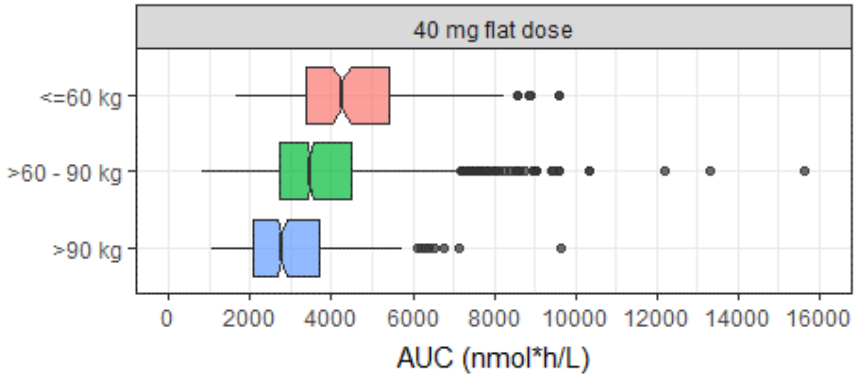
Figure 13. Individual Predicted Melphalan Exposure versus Individual Body Weight (left) and BSA (right) in OCEAN



AUC = Area under the concentration-versus-time curve; BSA = body surface area.
N=228 patients who received at least one dose of melphalan flufenamide in OCEAN trial.
Source: FDA Analysis

Following a flat dose of 40 mg, patients with lower body weight are expected to have higher exposure compared to patients with higher body weight (**Figure 14)**

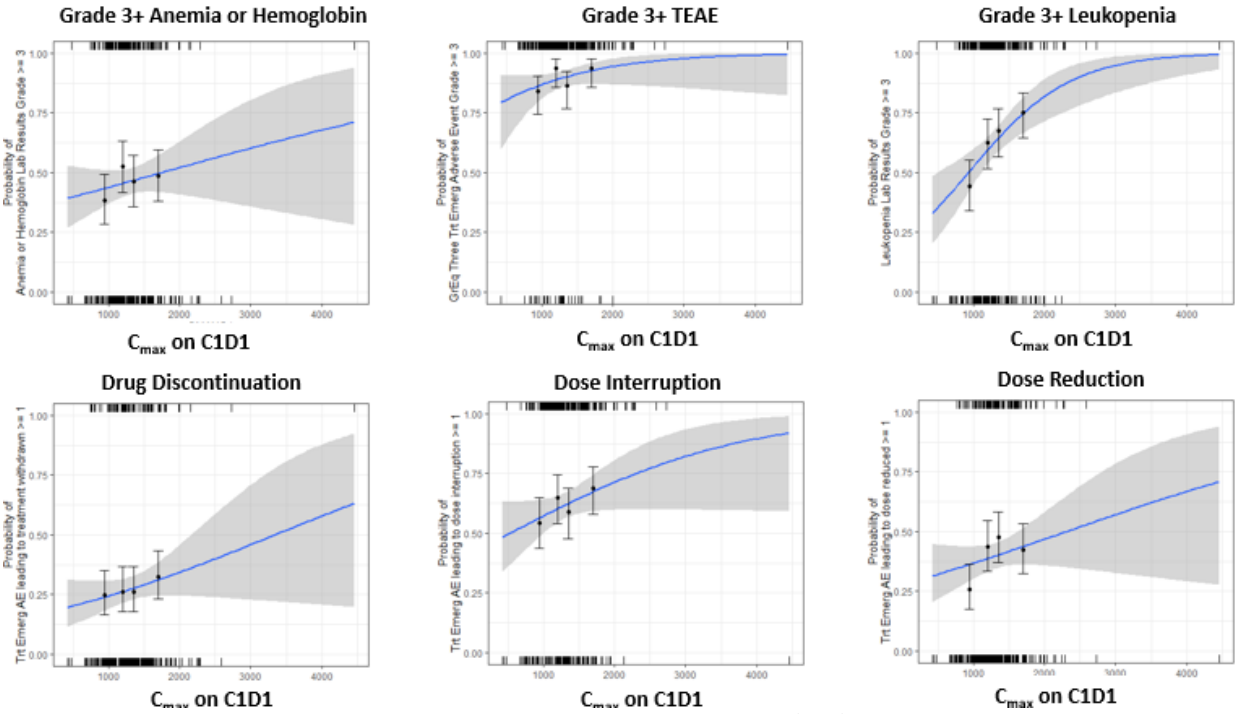
Figure 14. Predicted Melphalan Exposure after Melphalan Flufenamide 40 mg Flat Dosing



AUC = Area under the concentration-versus-time curve.
Source: FDA Analysis

The FDA identified some significant safety concerns when evaluating exposure-response relationships. Higher exposure was found to be associated with increased risk of TEAEs leading to dose modifications, Grade ≥3 TEAEs, Grade ≥3 anemia, and Grade ≥3 leukopenia (**Figure 15**). No associations between exposure and efficacy have been identified (FDA Appendix 10.7).

Figure 15. Melphalan Flufenamide Exposure-Response Relationships with Safety Events



C_{max} on C1D1 = Individual predicted peak concentration on Cycle 1 Day 1 (nM).
Data shown for E-R safety dataset containing 62 patients from OP-12-M1, 228 patients from OCEAN, and 31 patients from OP-107 who received melphalan flufenamide + dexamethasone (321 patients total).
Source: FDA Analysis

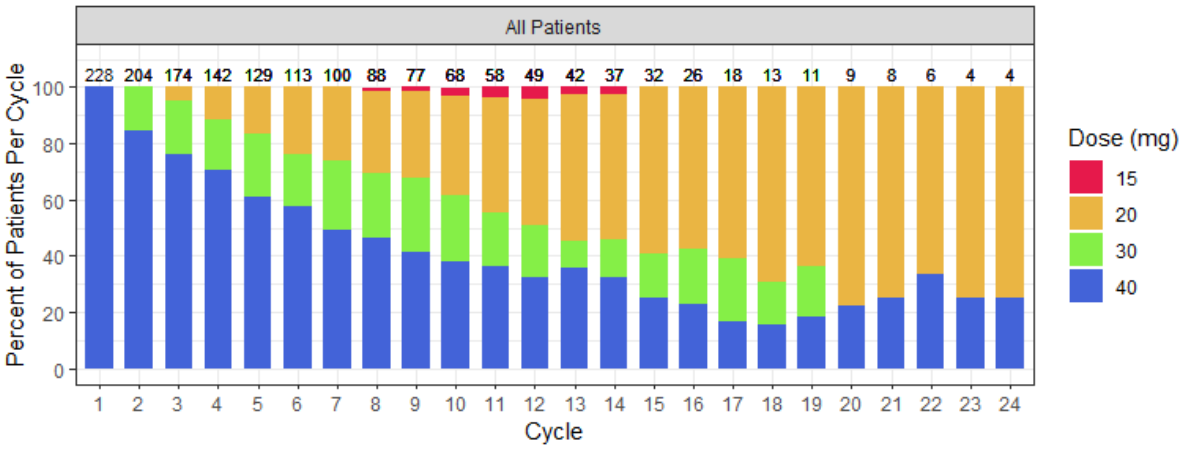
Overall, the toxicity of the 40 mg dose was high. In the OCEAN study, all patients who received a starting dose of 40 mg in the MelDex arm experienced higher rates of TEAEs (See FDA Position in Section 3.3) and TEAEs leading to dose modifications compared to the control arm (**Table 34**). In the MelDex arm, a large proportion of patients required one or more dose reductions in the overall population (**Figure 16**). Thus, the data suggest that the 40 mg dose is poorly tolerated in the general population.

Table 34. Treatment-Emergent Adverse Events Leading to Study Drug Dose Modification in OCEAN

	MelDex n=228 n (%)	**PomDex n=246 n (%)**
Patients with ≥1 TEAE leading to dose modification	178 (78.1%)	144 (58.5%)
Patients with ≥1 TEAE leading to dose delay	137 (60.1%)	109 (44.3%)
Patients with ≥1 TEAE leading to dose reduction	107 (46.9%)	37 (15.0%)
Patients with ≥1 TEAE leading to permanent discontinuation	60 (26.3%)	54 (22.0%)

Dose modification = dose delay, dose reduction, or permanent discontinuation of study drug; MelDex = melphalan flufenamide plus dexamethasone; PomDex = pomalidomide plus dexamethasone; Study drug = melphalan flufenamide or pomalidomide; TEAE = Treatment-emergent Adverse Event.
Source: FDA Analysis

Figure 16. Melphalan Flufenamide Dose Administration per Cycle in OCEAN for All Patients up to Cycle 24



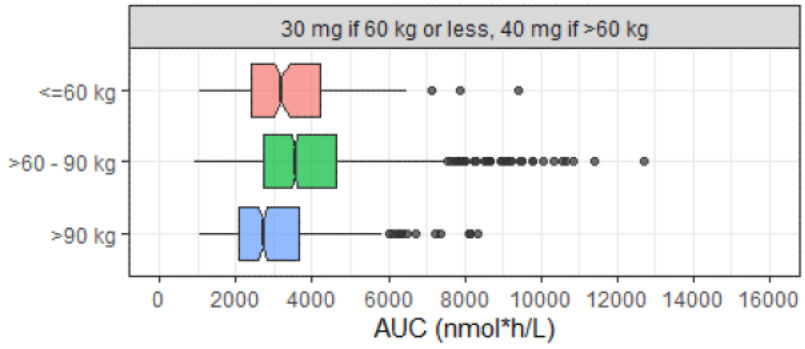
Number of subjects per cycle displayed at the top of each column.
Source: FDA Analysis

Proposed starting dose of 30 mg in patients weighing ≤ 60 kg

FDA does not agree with the proposed 30 mg starting dose in patients ≤60 kg. This reduced dose is intended to match the exposure following melphalan flufenamide administration in patients weighing >60 kg treated with 40 mg (**Figure 17**). However, as described above, the 40 mg dose was not adequately selected for the entire patient population. Based on population PK analysis

of all the available data, patients with lower body weight or body surface area (BSA) were more likely to experience higher exposure with the starting dose of 40 mg (**Figure 13**).

Figure 17. Predicted Melphalan Exposure after Melphalan Flufenamide Dosing of 30 mg in Patients Weighing 60 kg or Less and 40 mg in Patients Weighing Above 60 kg

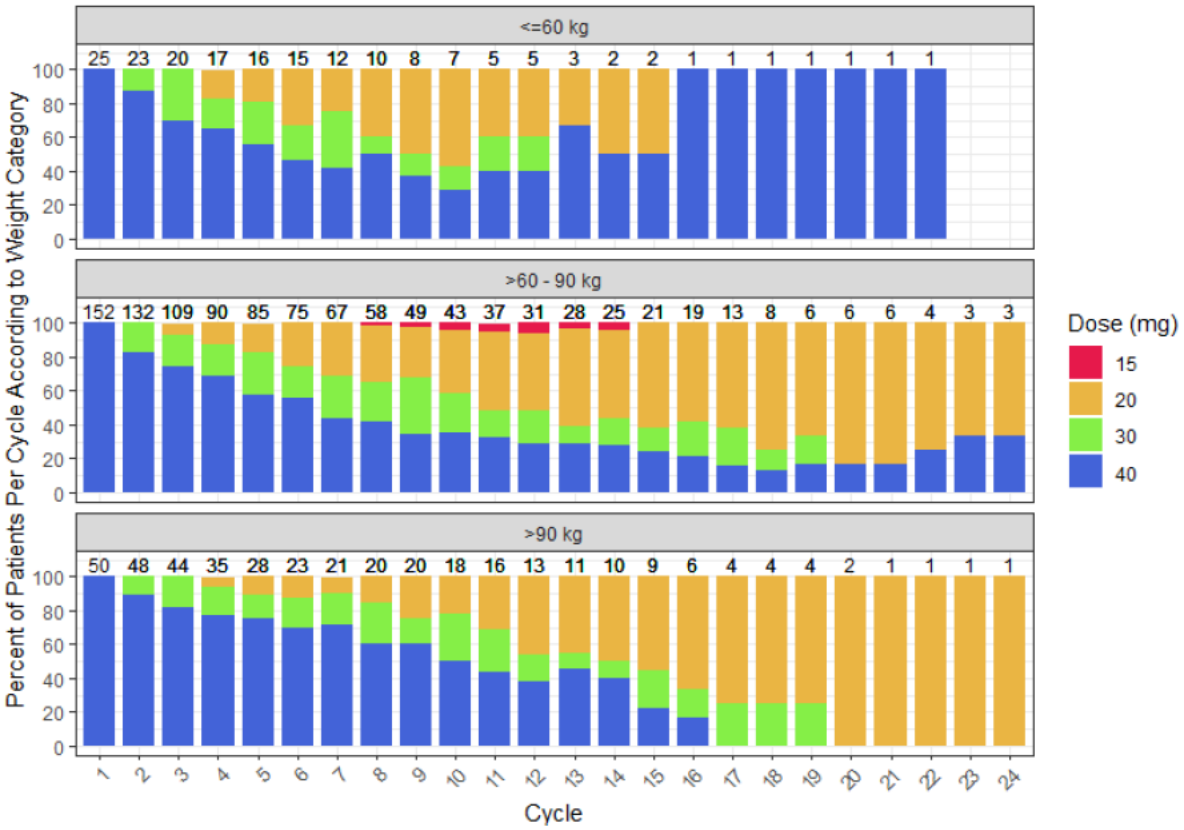


Source: FDA Analysis

Higher exposure is associated with higher risks of several TEAEs, including Grade ≥3 anemia, Grade ≥3 leukopenia, and TEAEs leading to dose modification (**Figure 15**). Although patients weighing ≤60 kg who receive the 30 mg starting dose would have exposures similar to patients weighing >60 kg treated with 40 mg (**Figure 17**), that exposure range is associated with unacceptably high TEAEs. Therefore, safety concerns for the general population and for the subgroup of patients weighing ≤60 kg would not be mitigated by lowering the starting dose to 30 mg in patients weighing ≤60 kg.

This conclusion is underscored in **Figure 18**, which depicts the percentage of patients across all body weight categories, including ≤60 kg, who required dose reductions from 40 mg and 30 mg to ≤20 mg. In the MelDex arm, a large proportion of patients required one or more melphalan flufenamide dose reductions in the overall population (**Figure 16**). High dose reduction rates were observed across different weight categories (**Figure 18**). More dose exploration is required before a dose or exposure range with favorable safety and efficacy can be determined.

Figure 18. Melphalan Flufenamide Dose Administration per Cycle in OCEAN for Patients Stratified by Weight Category up to Cycle 24



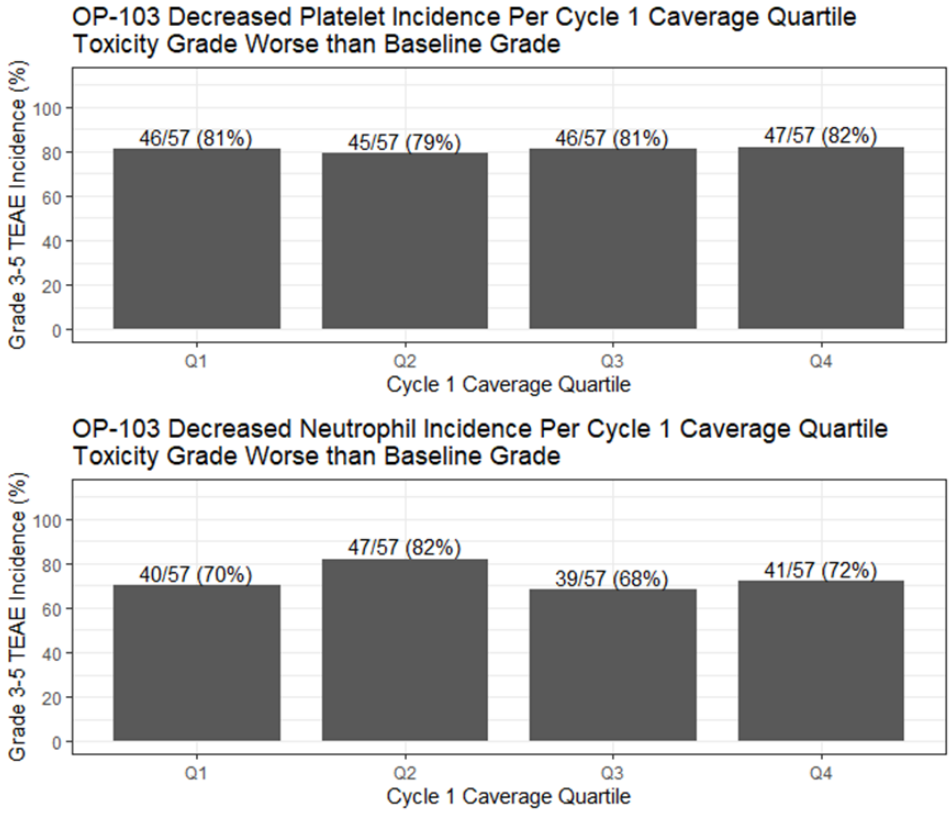
Number of subjects per cycle displayed at the top of each column.
Source: FDA Analysis

Proposed dose reduction following Grade ≥3 thrombocytopenia or Grade ≥3 neutropenia of any duration

The Applicant proposed to reduce the dose in the next cycle after incidence of Grade ≥3 neutropenia or thrombocytopenia of any duration in an effort to lower the rate of recurrent cytopenia. However, there is no clinical data provided to support this approach. In addition, this recommendation does not decrease the initial risk to patients based on the initially poorly selected dose and is unlikely to lower the overall incidence of cytopenia.

The FDA also notes that Grade ≥3 thrombocytopenia and Grade ≥3 neutropenia were not associated with individual predicted Cycle 1 melphalan average concentration (as shown in **Figure 19**) or clearance over the range of exposures studied but observed in all patients regardless of exposure. While this could be due to the limited range of exposures available at doses lower than 40 mg (Table 33), there is limited data to show that immediate dose reduction due to neutropenia or thrombocytopenia is likely to mitigate subsequent events or other adverse events associated with melphalan flufenamide.

Figure 19. Study OCEAN Grade ≥3 Thrombocytopenia and Grade ≥3 Neutropenia Incidence According to Melphalan Cycle 1 Average Concentration



Cycle 1 Caverage = Cycle 1 average melphalan concentration. TEAE = Treatment-emergent adverse event; Q = quartile.
Blood and lymphatic system disorders change from baseline, ADLB (Laboratory Analysis) 6.25.21
Source: FDA Analysis

Dosing Conclusion

The safety events and the extensive dose modifications indicate that the melphalan flufenamide flat dose of 40 mg does not favor an adequate benefit-risk profile, and further exploration of lower doses is warranted. Adjusting the dose in lower weight patients to match the exposure to the 40 mg dose is flawed because the 40 mg dose is not optimized for the general patient population. A body weight-based dosing or BSA-based dosing may be better tolerated and should be explored further in a clinical trial to support a favorable benefit-risk for melphalan flufenamide.

3.5 Summary

The Applicant's Position:

The safety profile of Pepaxto is consistent across clinical studies, populations, and treatment lines studied. In addition, post-marketing safety data from February 26, 2021 through May 27, 2022 has not raised any safety concerns. This confirms the appropriateness of using the pooled

safety data with 491 patients when evaluating the safety profile of Pepaxto, also in later-stage patients.

As expected of an alkylating drug such as Pepaxto, hematologic events, mainly thrombocytopenia, neutropenia, and anemia, are the most common AEs of clinical importance.

Some non-hematologic AEs are common, but non-hematologic grade 3/4 events are infrequent.

Thrombocytopenia and neutropenia are the most frequent grade 3 or 4 AEs, but there are few associated bleeding events or infections. Both thrombocytopenia and neutropenia are effectively managed with standard clinical treatment and dose modifications.

The introduction of a 30 mg dose in patients weighing ≤60 kg is expected to further reduce hematologic AEs and thereby improve the safety profile. In addition, dose reduction is recommended if a dose interruption is required due to thrombocytopenia or neutropenia.

The safety profiles both in HORIZON and OCEAN are consistent with the overall safety profile of Pepaxto, as seen in the pooled safety data.

In OCEAN, Pepaxto and pomalidomide display similar patterns in high-level safety parameters such as grade 5 and serious AEs, but hematologic AEs are more frequent in Pepaxto-treated patients. As in other Pepaxto studies, hematologic events were manageable with dose modifications and supportive care. Analysis of the safety data cannot identify a Pepaxto toxicity signal that can explain a potential detrimental effect on OS in the FAS population.

The safety profile of Pepaxto, including the effectiveness of dose modifications and supportive care, supports the current indication.

The FDA's Position

FDA does not agree with the conclusions on safety based on the pooled patient population and the single arm HORIZON trial. It is challenging to characterize safety in the absence of a control arm. FDA notes that all clinical trials for melphalan flufenamide were placed on hold on July 7, 2021, based on the safety concerns noted on the OCEAN trial. Additionally, marketing has been discontinued; melphalan flufenamide is currently not marketed in the US (Table 1).

The safety data from the OCEAN trial revealed higher rates of deaths, 46% in the MelDex arm and 43% in the PomDex arm. The higher MelDex death rate was most notable in events that occurred beyond 60 days after the last dose, raising a concern that treatment with melphalan flufenamide may impact the ability to receive or tolerate subsequent lines of therapy.

The higher rate of Grade 3-4 TEAEs in the MelDex arm (90%) compared to the PomDex arm (74%) were primarily due to myelosuppression. Neutropenia was higher in the MelDex arm (73%) compared to the PomDex arm (59%), and Grade 3-4 thrombocytopenia was higher in the MelDex arm (81%) compared to the PomDex arm (14%). These high rates of thrombocytopenia led to higher rates of all-grade (16% vs. 6.5%) and Grade 3-4 hemorrhage (2.2% vs. 0.4%) in the MelDex arm compared to the PomDex arm. These toxicities occurred despite high rates of dose modifications.

The toxicity noted in the OCEAN trial and the high rate of dose modifications indicate that the flat 40 mg dose is not tolerated. Doses lower than 40 mg or alternative dosing regimens have not been fully explored. While there was an association between higher melphalan exposure and increased risk of safety, there was no clear association with progression-free survival or overall survival, again suggested that the flat 40 mg dose is not optimized. The proposal to lower the dose to 30 mg for patients ≤60 kg and additional dose modifications for neutropenia and thrombocytopenia does not address the dosing concerns. FDA's position in Section 3.4 outlines limitations with the Applicant's proposal.

At this time, the overall available evidence indicates a potential for harm, uncertain clinical benefit and suggests that the overall benefit-risk profile of melphalan flufenamide is unfavorable. Additional dose exploration to identify a tolerable dose with dosing based on weight or body surface area is warranted.

4 Clinical Outcome Assessment Analyses

The Applicant's Position:

Not applicable

The FDAs position:

Patient-reported outcomes (PRO) in OCEAN were descriptive, exploratory, were not statistically tested, and were only collected in a subset of patients. In trial OCEAN, patient-reported outcomes were collected in only 32% of the trial population, as PRO measurement began after protocol amendment 4. No meaningful interpretation can be made from the PRO results because of these significant limitations.

5 Other Significant Issues Pertinent to Clinical Conclusions on Efficacy and Safety

5.1 [Issue for Discussion]

The Applicant's Position:

There are no non-clinical issues thought to impact the clinical conclusions.

The FDA's Position

1. <u>Evaluation of safety and efficacy of the patients who met the current indication on the OCEAN trial.</u>

Melphalan flufenamide is currently indicated for the treatment of patients with RRMM who have received at least 4 prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal

antibody. A total of 6.0 % of patients from OCEAN met the current indication of having both 4 prior lines of treatment and having triple class refractory disease shown in

Table 35.

Table 35 Baseline characteristics corresponding to the current indication

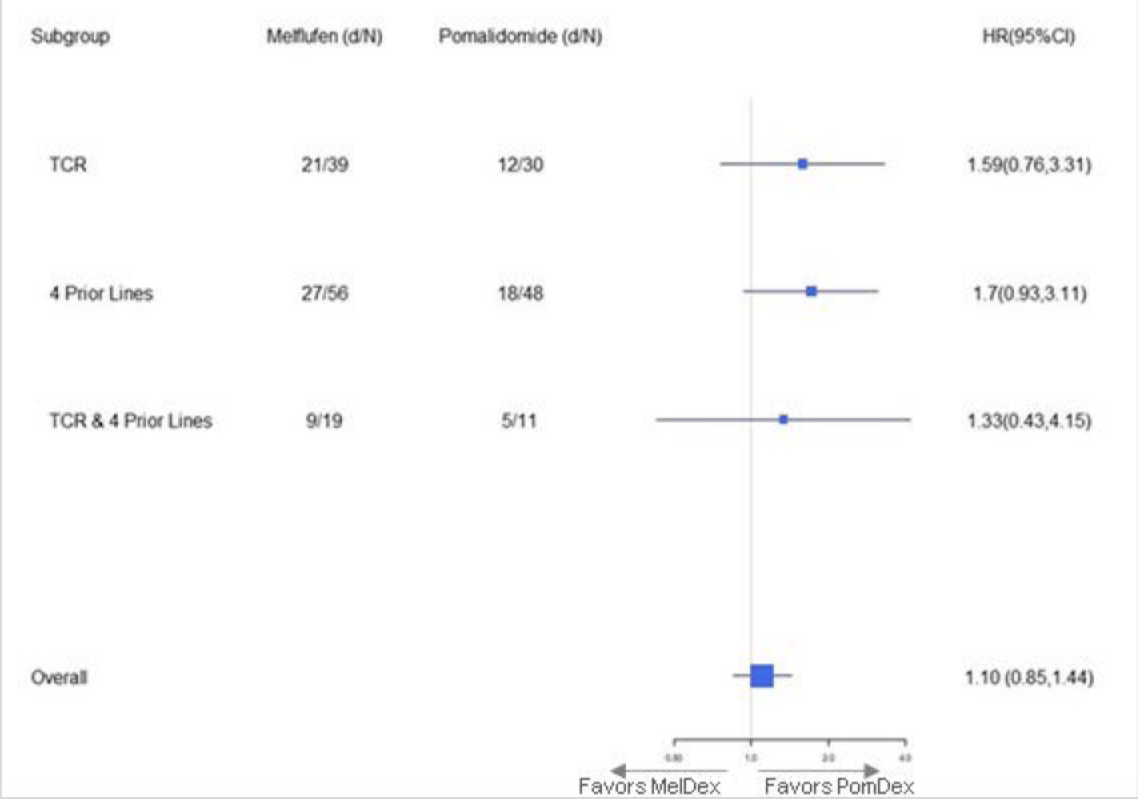
Disease Characteristics	MelDex N = 246 n (%)	PomDex N = 249 n(%)
4 Prior lines of treatment	56 (23)	48 (19)
Triple class refractory (TCR)*	39 (16)	30 (12)
4 prior lines + TCR	19 (8)	11 (4.4)
Lenalidomide refractory	246 (100)	249 (100)
Pomalidomide refractory	0	0
Proteasome inhibitor refractory	163 (66)	163 (65)
Anti-CD38 refractory	48 (20)	39 (16)

Triple class refractory = refractory to a proteasome inhibitor, immunomodulatory agent, and anti-CD38 and not intolerant
Source: FDA Analysis

Overall Survival

The OS results for patients who have received 4 prior lines of therapy and TCR is shown in the forest plot in Figure 20. While we cannot make definitive conclusions based on subgroup analysis, the OS results in this group of patients who have received 4 prior lines of therapies and are TCR are also consistent with the primary ITT population with an OS HR>1. The OS results in this subgroup suggests uncertain clinical benefit and raises questions regarding the safety of melphalan flufenamide in patients who have received 4 or more prior lines and are TCR. The updated OS result (February 3, 2022 data-cut-off) for the patients with 4 prior lines and TCR population was consistent with the OS results from the original analysis (HR 1.17 95% CI: 0.47, 2.96).

Figure 20. Forest Plot -4 Prior Lines of Therapy and TCR (OCEAN)



Source: FDA Analysis, Data cut-off Feb 3, 2021**Safety- 4 Prior Lines of Therapy and TCR**

The safety data in the patients who received 4 prior lines and are TCR was consistent with the overall safety population in OCEAN (FDA Appendix 10.8). However, due to the limited number of patients that met the criteria for the current indication in the safety population it is difficult to make definitive conclusions.

2. Lack of representation of the U.S. multiple myeloma patient population.

Racial and ethnic subgroups were also underrepresented in HORIZON trial, the pivotal trial that supported the accelerated approval for melphalan flufenamide (Section 2.3.2). Only 11 Blacks and 5 Hispanic or Latino patients were enrolled in the HORIZON trial. A higher incidence of dose modifications in association with Grade 3 or 4 thrombocytopenia and neutropenia was observed in minority patients than that in White patients. A PMR was issued to further characterize the exposure of melphalan flufenamide, the increased risk of serious adverse events including hematologic toxicities, and efficacy among U.S. racial and ethnic minorities with relapsed or refractory multiple myeloma.

The data from OCEAN adds to the uncertainty of safety and effectiveness of melphalan flufenamide to the U.S patient population.

6 Points for the Advisory Committee to Consider

The Applicant's Position:

The efficacy and safety of Pepaxto 40 mg/dex in HORIZON have been confirmed in OCEAN. OCEAN is a head-to-head comparison vs pomalidomide, a widely used drug in RRMM that was approved based on compelling PFS and OS improvement compared to high-dose dex in study MM-003.

The safety profile of Pepaxto is consistent across studies, pooled data sets, and subgroups and in post-marketing case reports. Hematologic events are the most common AEs of clinical importance, but they are effectively managed with standard clinical treatment and dose modifications. Severe non-hematologic events are infrequent.

There is no toxicity signal of Pepaxto that explains the observed OS detriment in the overall population in OCEAN. However, OCEAN identified a population where a detrimental effect on survival from Pepaxto treatment cannot be excluded, also backed by a strong biological rationale. In addition, the heterogeneous OS in age subgroups within the pomalidomide arm significantly contributed to the overall OS HR in the study.

Based on the available data, it is the Applicant's opinion that Pepaxto/dex has a clear positive benefit/risk profile in patients who either did not have a prior ASCT or who progressed more than 36 months after an ASCT. Given the potential harm of Pepaxto/dex in patients with prior ASCT and a TTP <36 months after ASCT in OCEAN and the fact that a risk for shorter survival cannot be excluded for these patients within the 4L+ TCR population in HORIZON due to the absence of a control group, special consideration may be warranted in this patient group. Although most patients will only receive Pepaxto/dex at a late stage within the current indication (and therefore may not have other treatment options available), the Applicant will advise prescribing physicians that a potential harm cannot be excluded in patients with a TTP <36 months after ASCT.

The Pepaxto/dex efficacy in the indication population in HORIZON is clinically relevant with an ORR of 27% and a DOR of 5.4 months, and HORIZON was the basis for the accelerated approval of Pepaxto. When implementing the effect of the recommendation to not use Pepaxto/dex in patients with TTP <36 months after prior ASCT treatment, the ORR improves to 32% and the DOR to 7.6 months. The results from the confirmatory OCEAN study support these results and demonstrate that Pepaxto/dex is superior to pomalidomide/dex in terms of the primary endpoint of PFS and has positive trend in terms of OS when limiting the population to patients who have not had a prior ASCT or progressed ≥36 months after an ASCT. Importantly, Pepaxto is also efficacious in patients who are refractory to standard-dose alkylator therapy, including melphalan, bendamustine, and cyclophosphamide.

The positive benefit/risk profile of Pepaxto in the indication population based on HORIZON results has now been confirmed by the results from OCEAN. Further, the results of OCEAN allowed for identification of a subgroup of patients where potential harm cannot be excluded, which can be used to inform prescribers appropriately in the label.

As a result, the Applicant is of the opinion that the safety alert, which was sent out by the agency on July 28, 2021, should be updated with focus on patients with prior ASCT and a TTP <36 months after ASCT.

In addition, the Applicant considers OCEAN a successful confirmatory study, having met its primary endpoint of superior PFS and having a positive benefit/risk in the patients who did not have a prior ASCT and in patients who progressed more than 36 months after their ASCT.

The FDA's Position

FDA does not agree with the Applicant's position that the results of the OCEAN trial confirm the clinical benefit of melphalan flufenamide.

The continued approval for the accelerated approval of melphalan flufenamide was contingent upon verification and description of clinical benefit in the Phase 3 randomized clinical trial, OCEAN. OCEAN was a randomized, phase 3 trial of melphalan flufenamide dexamethasone compared to pomalidomide dexamethasone in patients with relapsed refractory multiple myeloma who were refractory to lenalidomide. Pomalidomide-dexamethasone is a standard of care for patients with relapsed or refractory myeloma and is an FDA approved therapy. The confirmatory trial OCEAN did not meet the prespecified primary endpoint, PFS superiority of melphalan flufenamide compared to pomalidomide. The Applicant conducted a revised PFS analysis which indicated a marginal PFS significance, but only if we consider unconfirmed progression as events in the PFS analysis. Regardless of the sensitivity analysis, the difference in PFS was approximately 2 months. The results of analyses of other efficacy endpoints such as ORR and DOR were either not statistically significant or provided for a magnitude of effect that would not be considered clinically meaningful.

The results from the OCEAN trial demonstrated a detriment in overall survival for the melphalan flufenamide arm. The safety data indicate that the worse OS results are indicative of a safety concern and suggest a potential for harm with melphalan flufenamide. OS is an efficacy endpoint but is also a measure of product safety. As a safety measure, statistical significance is not required for assessing the risk of the product. A worrisome trend in OS, particularly in the context of drugs with substantial toxicity, is an important determinant of safety. Potential harm cannot be ruled out, whether from toxicities that occur due to melphalan flufenamide treatment or potentially from higher complication rates during subsequent anti-cancer therapy.

The Applicant has conducted several post hoc exploratory analyses and proposed that potential harm with melphalan flufenamide is restricted to a patient subpopulation with TTP <36 months and there is a potential survival interaction with age among the IMiDs. The FDA does not agree that the Applicant's post hoc exploratory analyses and models provide conclusive evidence of a positive benefit-risk of melphalan flufenamide. The PFS and OS results in the ITT population indicate residual concerns with the benefit of melphalan flufenamide and indicate a potential for harm. The burden of proof is on the Applicant to show that the melphalan flufenamide is safe

and effective based on data from adequate and well controlled trials. Post hoc subgroup exploratory analysis or modelling cannot be used to support this conclusion or to support an indication in a subpopulation when the overall results show a detriment or unconfirmed benefit.

Additionally, OS is an objective measure of clinical benefit. While PFS has been accepted as a measure of clinical benefit for myeloma, for randomized controlled trials with a PFS endpoint, OS results are evaluated to assess clinical benefit. OS provides an overall assessment of clinical benefit in the context of the toxicity observed with the drug. The decreased OS, and the higher rates of toxicities in the melphalan flufenamide arm negate the marginal treatment effect on PFS observed with melphalan flufenamide.

The concerning safety results noted in the OCEAN trial, the high rates of dose modification, and the inadequate dose exploration of the 40 mg flat dose prior to initiating the Phase 3 trial, indicate that the 40 mg flat dose is not optimized. This is also confirmed by the exposure-response and -safety analyses. Adjusting the dose in lower weight patients to match the exposure to the 40 mg dose does not address the dosing concerns because the 40 mg dose is not optimized for the general patient population. A lower target exposure and body weight-based dosing or BSA-based dosing may be better tolerated and should be explored further in a clinical trial to support a favorable benefit-risk for melphalan flufenamide.

At this time, the overall available evidence indicates a potential for harm, uncertain clinical benefit and suggests that the overall benefit-risk profile of melphalan flufenamide is unfavorable. Additional dose exploration to identify a tolerable dose with dosing based on weight or body surface area is warranted.

7 Draft Topics for Discussion by the Advisory Committee

Discuss whether the available data

- Confirms a positive benefit risk for melphalan flufenamide for the currently indicated patient population

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10 FDA Appendices

10.1 Statistical Issues with Post-hoc Analyses, Subgroup Analyses and Multiplicity

While subgroup analyses have an important role in clinical trials, results from such analyses can be misleading or biased and are subject to being over-interpreted [Fleming, 2010, Hemmings, 2014].

The risk of a false positive finding should be a major concern when interpreting subgroup analyses. Clinical trials can be designed to specifically consider subgroup findings, for example, when one is interested in results for a biomarker defined subgroup [Jiang, et al, 2007]. Typically, subgroup analyses are not included in the set of analyses for which multiple testing Type I error inflation is controlled, such as analyses of the primary and key secondary endpoints. It is not uncommon for clinical trial reports to present large tables or plots of subgroup analyses results. If we consider a setting where there is no treatment effect and the usual one-sided alpha of 0.025, there is greater than a 1 in 5 chance of seeing at least one false positive result when performing 10 hypothesis tests. If there is a barely detectable but significant treatment effect (p=0.05), the probability of observing a subgroup effect is markedly greater, approaching 1 when doing 10 tests [Buyse, et al 1989]. In the latter situation, one must consider whether there is a plausible biological reason for an observed effect in a subgroup or if it is simply due to chance grouping of the data.

Graphical representations can overlook inflation of Type I error probability. Forest plots of differences within subgroups and their 95% confidence intervals (CIs) make it possible to quickly assess homogeneity of treatment effect. Often forest plots include a boundary at either 1 or 0 demarking no relative or absolute difference, respectively. Because the CIs are generally not adjusted for multiplicity, one should consider them only as information about the variability of the estimate, not as a means for statistical testing. An unadjusted confidence interval excluding the point marking no difference should be viewed with caution and not automatically be taken as a statistically significant result.

Pre-specifying all analyses to be done using trial data in clinical trial protocols and statistical analysis plans helps prevent misinterpretation caused by post hoc, data driven, exploratory analyses [Hemmings, 2014]. Even in a case where only one or two exploratory analyses are presented, if the analyses were not pre-specified in the protocol, type I error probability is difficult or impossible to control because many tests or other influences could have motivated the selections of the presented results [Cui, et al 2002]. Finally, FDA guidance ICH E9 published in 1998 includes the following statements on exploratory subgroup analyses and pre-specifying analyses:

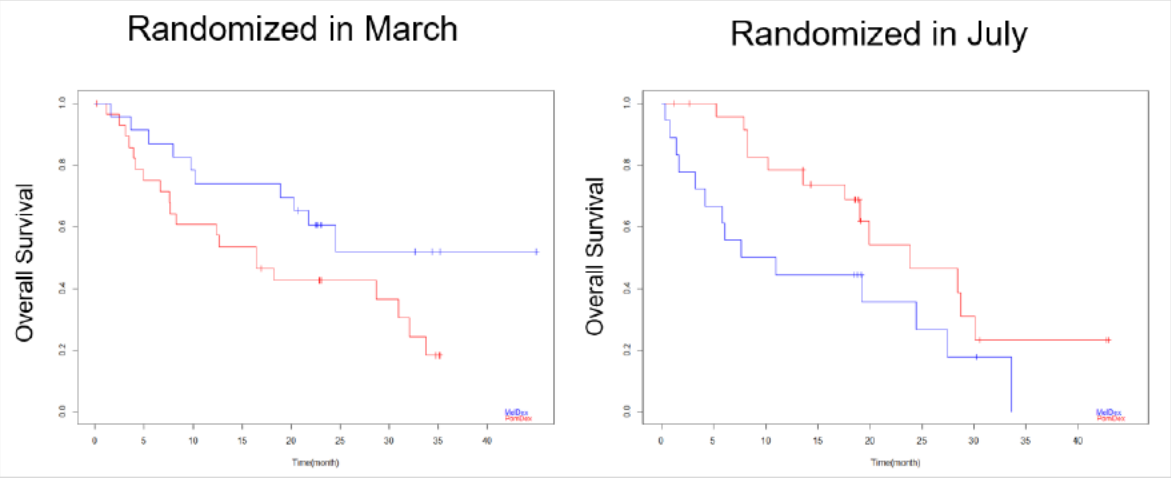
- *Any conclusion of treatment efficacy (or lack thereof) or safety based solely on exploratory subgroup analyses is unlikely to be accepted*."

- *"Only results from analyses envisaged in the protocol (including amendments) can be regarded as confirmatory.*

The patterns observed in the Applicant's subgroup forest plots and that of the transplant status partitioning may be caused by randomness, or they may be due to another mechanism. Because they were exploratory, for each analysis, it is difficult or impossible to rule out the possibility that the hazard ratio is one.

The literature is replete with examples of subgroup analysis risks and failures. To reinforce the point, we discuss two examples here. Using data from the STAMPEDE trial of androgen deprivation therapy to treat metastatic prostate cancer, [Spears, et al 2017] provide a subgroup analysis showing that men born on Thursdays do not benefit from the addition of abiraterone to a standard of care while the effect in the overall trial dataset was significantly positive for the addition of abiraterone. Additionally, the FDA observed in the 103 trial that patients randomized in March tended to have better survival if they were assigned MelDex and those randomized in July tended to have better survival if they were assigned to PomDex (Figure 21). These two examples show that although some observations and new hypotheses may be made based on a post hoc analysis, conclusions from these analyses are not scientifically valid.

Figure 21. KM plots for subgroup analyses of OS by randomization month (incorrect post hoc analysis example)



Source: FDA Analysis. Data Cut-off, 03FEB2022

10.2 FDA's Evaluation of IMiD Data

Age interaction model for OCEAN

Applicant conducted subgroup analyses of age for OS within the melphalan flufenamide arm and the pomalidomide arm separately (Table 15). Based on this the Applicant concluded that within patients who are <65 years old, the melphalan flufenamide arm showed a differential OS effect based on "early" progression after an ASCT. The subgroup analysis within a single treatment arm is NOT a valid approach to explore the modification of OS effect because it was not a randomized comparison and unlikely to be balanced with respect to prognostic factors. The estimates provided from such comparisons would be influenced by many factors for which the investigator did not control. Therefore, the survival difference cited by the Applicant is difficult to interpret and should be disregarded, along with other within treatment arm comparisons. Additionally, analyses within treatment arm do not provide information on treatment effect of the study drug and are not comparable across studies.

One exploratory analysis to evaluate the modification of OS effect by age is a model for the HR comparing treatment vs. control, with an interaction term of age*treatment. FDA conducted an interaction model treating age as a continuous variable with data from the OCEAN trial. This continuous age model resulted in a nominally significant p-value for the interaction term (nominal p-value = 0.0269), indicating that there may be a differential OS effect by age. However, this analysis is not prespecified and Type I error is not controlled due to multiple post hoc analyses. Only a prospectively designed and well controlled randomized clinical trial can serve as evidence for confirming this hypothesis.

Furthermore, even if there may be an age interaction, it may be caused by either or both of the two treatments. In the OCEAN trial, the different HR of OS in age<65 and age>=75 could be due to that melphalan flufenamide is more harmful to younger patients, or pomalidomide is more harmful to older patients, or both. It cannot be concluded that this age interaction is driven by the pomalidomide arm. The patterns observed past the main effects of the study could be the result of random variability of patients in the trial sample or other factors, including the possibility that older patients do not do well on pomalidomide.

Furthermore, this potential modification of OS effect by age is unstable and relies on the model being used. This is demonstrated by including other terms in the model. We ran a second model which includes treatment, age, transplant, interaction of treatment and age, and interaction of treatment and transplant.

$$OS\ HR = Treatment + Age + Transplant + Age{*}Treatment + Transplant{*}Treatment$$

In the second model, the interaction of treatment and age was not significant, however, the interaction of treatment and previous ASCT now had a nominally significant p-value of 0.0374. Therefore, age or transplant may differentially affect OS, and we cannot conclude which factor contributes to the modification of OS without a study designed to evaluate it.

Age interaction analyses in IMiD trials

The Applicant reported results of OS hazard ratios in age subgroups for lenalidomide and pomalidomide in MM based on published information (Applicant's Appendix 1, Figure 5). Based on published literature analysis of selected trials, the Applicant concluded that there is a modification of the OS effect by age. FDAs review of the selected trials indicated significant heterogeneity in the trials. Acknowledging the limitations with the heterogeneity of these studies, FDA notes that the only trial with the 95% CI of OS hazard ratios in the age subgroups excluding 1 is the OCEAN trial.

As the Applicant's analysis was based on published data, FDA conducted an exploratory analysis of trials submitted to the FDA that allowed for isolation of IMiD effect. The results of an exploratory analysis using age, treatment, and treatment*age in a model to evaluate the modification of OS effect by age in these IMiD trials are summarized in Table 36. The FDA's exploratory analyses did not indicate that there was an interaction term between age and IMiD treatment.

These analyses were not prespecified and Type I error rate was not controlled. Therefore, all p-values are nominal and statistical significance cannot be concluded. Another limitation of this exploratory analysis is that only age was evaluated, and there may be other factors that either have more important impact on the OS effect or associated with age. These post-hoc analyses can only be used for hypothesis generation. This modification of OS by age cannot be concluded without a well-controlled trial prospectively designed to evaluate OS by age.

Table 36 Age interaction model for OS in selected IMiD trials

Trial	Treatment	Variable	HR*	95% CI	Nominal p-value
CC-5013-MM-015	*A: N=152* *Melphalan+Lenalidomide* *B: N=153* *Melphalan + (Lenalidomide 9 cycles then Len Placebo)* *C: N=154* *Melphalan + Placebo*	Treatment *A vs. C*	0.07	(0, 6.24)	0.2505
		Treatment *B vs. C*	0.06	(0, 4.58)	0.2073
		Age	1.02	(0.98, 1.06)	0.3802
		Treatment A*Age	1.04	(0.97, 1.10)	0.2548
		Treatment B*Age	1.04	(0.98,1.10)	0.1914

CC-4047-MM-003	*Pom + LD Dex*: N=302 *High dose dex*: N=153	Treatment *PomDex vs. Dex*	1.58	(0.23,10.84)	0.6401
		Age	1.01	(0.99, 1.04)	0.2344
		*PomDex**Age	0.99	(0.96, 1.02)	0.4023
CC-5013-MM-009	*LEN+ High Dex*: N=177 *High dose dex*: N=176	Treatment *LenDex vs. Dex*	0.95	(0.15,5.95)	0.9594
		Age	1.02	(1.00, 1.04)	0.0958
		*LenDex**Age	1.00	(0.97, 1.03)	0.7973
CC-5013-MM-010	*LEN+ High Dex*: N=176 *High dose dex*: N=175	Treatment *LenDex vs. Dex*	0.40	(0.04, 4.27)	0.4501
		Age	1.01	(0.98, 1.03)	0.5963
		*LenDex**Age	1.01	(0.97, 1.05)	0.6022
CALGB100104	*Lenalidomide Maintenance*: N=231 *Placebo*: N=229	Treatment *Len vs. Placebo*	0.07	(0.01, 0.64)	0.0184
		Age	0.98	(0.96, 1.00)	0.1108
		*Len**Age	1.04	(1.00, 1.08)	0.0608

* Since interaction of age and treatment is included in the mode, HR for treatment refers to the HR when age=0; HR for age refers to the HR of 1 unit increase in age when treatment is the comparator arm; HR for age* treatment refers to the fold change in HR of treatment vs. control with 1 unit increase in age.
Source: FDA Analysis

10.3 FDA's Exploratory OS Model Building

FDA reviewed the Applicant's proposed post hoc modeling approaches and subgroup analyses. FDA conducted additional post hoc analyses, noting that there are other factors the Applicant did not consider which may better describe the variability in OS. Under different model selection approaches, there are other models that may be considered for describing the variability. There is not one model that is most appropriate and varies depending on selection procedures. This multivariable analysis is exploratory and should be considered hypothesis-generating.

All model building analyses were conducted in a post hoc manner without a prospectively defined scientific hypothesis. **Because this was a post hoc data driven approach, all models under discussion (the FDA's and the Applicant 's) may be considered hypothesis-generating, and not suitable for making conclusions.** Further, it is well-know that using model selection algorithms to choose covariables tends to provide underestimates of the residual variance. This leads to overly optimistic (too narrow) confidence intervals for effect estimates. Therefore, any claim that an effect is statistically significant should be viewed with skepticism. Additionally, note that lack of control for multiplicity may result in false-positive conclusions regarding subgroup effects. All p-values are considered to be "nominal" and not appropriate for making conclusions.

The list of **factors** considered for the OS model building included:

- Age (<65, 65-74, >75)
- Number of prior therapies (2,3,4)
- Previous alkylator exposure (Y,N)
- Creatine Clearance (<45, 45-90, >90)
- Subsequent therapy (Y,N)
    - Subsequent Proteasome inhibitor
    - Subsequent anti-CD38
    - Subsequent IMiD
- BSA (above median vs. below median)
- ISS (1,2,3)
- ECOG (0,1,2)
- Time from diagnosis (<2 years, 2-5, >5 years)
- TTP from ASCT (<36 months, >=36 months, No transplant)

FDA's model selection procedure used a nominal p-value boundary of 0.1 to select main effect and interaction terms. Then a backward selection procedure was used to include nominally significant terms; this resulted in a model including the following factors besides treatment:

- TTP from ASCT
- Age

- ISS score
- subsequent therapy
- ECOG
- time from diagnosis
- treatment*time from diagnosis (interaction)
- treatment*TTP from ASCT (interaction)
- transplant*age (interaction)

Figure 22. FDA's Exploratory Model -Forest Plot for OS HR (Post hoc model selection)

TTP from ASCT	Time from Diagnosis	Melflufen (d/N)	Pomalidomide (d/N)	HR(95%CI)
No	<2 years	14/28	24/34	0.5(0.27,0.9)
	2-5 years	46/64	39/66	1.06(0.72,1.57)
	>5 years	15/29	18/29	0.64(0.38,1.09)
<36 months	<2 years	6/7	4/7	1.26(0.63,2.53)
	2-5 years	40/51	30/54	2.71(1.77,4.13)
	>5 years	29/43	22/40	1.64(1.02,2.65)
>=36 months	<2 years	0/0	0/0	0.53(0.17,1.73)
	2-5 years	0/0	1/1	1.14(0.4,3.27)
	>5 years	12/24	9/18	0.69(0.28,1.71)

Covariates in the final exploratory model are treatment, TTP from ASCT, age, ISS score, subsequent therapy, ECOG, time from diagnosis, treatment*time from diagnosis, treatment*TTP from ASCT, and TTP from ASCT*age
Source: FDA analysis. DOC 03FEB2022

Results of the model selection method indicated that TTP from ASCT was not the most significant factor to explain variability of OS (Figure 22). Based on our exploratory model, age, ISS score, subsequent therapy and time from diagnosis could be other factors with a significant impact on OS. Multiple factors other than or in addition to TTP from ASCT can be found to explain the OS variability. However, because both the Applicant's post hoc analysis and FDA's analysis were data driven and post hoc, the results may be misleading and cannot be used to

conclude as evidence of benefit or lack thereof based on post hoc analyses. FDA does not agree with concluding that there are subgroups with OS benefit based on any post hoc analysis.

10.4 FDA Appendix Randomized Not Treated Patients Reason for Treatment Discontinuation

Melphalan flufenamide and Dexamethasone Arm: 18 patients randomized not treated

1. Overall Condition
2. Patient developed fever after randomization, antibiotic course was started, condition did not allow treatment start within 5 days of randomization
3. Platelet count <75,000 cells/mm^3 after randomization and prior to first dose
4. Patient withdrew consent
5. Creatinine clearance <45 ml/min
6. Withdrew consent
7. Did not meet required platelet level on C1D1
8. Thrombocytopenia on planned C1D1
9. Physician decision
10. Abnormal lab values
11. Infection event occurred after randomization
12. Due to Inclusion #10 (laboratory results must be met during screening and immediately before study drug administration) and exclusion #18 (prior major surgical procedure or radiation therapy within 4 weeks of randomization not including limited course of radiation used for management of bone pain within 7 days of randomization).
13. Hospitalized due to hypercalcemia, renal failure
14. Patient did not meet inclusion criteria
15. Not eligible
16. Due to kidney failure, exclusion criteria to obtain drug
17. Patient did not meet lab criteria for treatment administration
18. Withdrawal of consent

Pomalidomide and Dexamethasone Arm: 3 patients randomized not treated

1. Progressive disease
2. Treatment not given due to thrombocytopenia <75 in screen period.
3. C1D1 laboratory result (platelet count) of subject didn't meet eligibility criteria

Source: FDA Analysis ADSL, Database February 3, 2021

10.5 FDA PFS Sensitivity Analysis

Table 37 PFS Sensitivity Analysis (Original dataset, Data Cut-off February 3, 2021)

Additional PFS Censoring Rules	Hazard Ratio (95% CI)	Difference in medians (months)	p-value
Death or Progression Immediately After More than 1 Consecutively Missed Disease Assessment Visit Treated as a PFS Event	0.819 (0.662, 1.013)	1.9	0.0650
Censor for more than 2 missed assessments instead of 1	0.828 (0.669, 1.025)	1.9	0.0835
Censor for more than 3 missed assessments instead of 1	0.822 (0.664, 1.017)	1.9	0.0707
Initiation of subsequent therapy as an event	0.874 (0.714, 1.071)	1.0	0.1954
Initiation of Non-Protocol Anti-Cancer Therapy Treated as neither a PFS Event nor a Censoring Event	0.825 (0.666, 1.021)	1.9	0.0763
Analysis based on Scheduled Assessment Dates instead of Actual Assessment Dates	0.835 (0.673, 1.034)	1.8	0.0989
Censor at the date of pomalidomide home delivery if not progressed by that date	0.825 (0.665, 1.023)	2.0	0.0797
Unconfirmed progression at final visit not included as PFS event unless new plasmacytoma or lytic bone lesions	0.821 (0.659, 1.022)	1.9	0.0770

Source: FDA Analysis, Data cut-off Feb 3, 2021

10.6 FDA Analysis of PFS Revisions post database lock

As stated previously, the original primary analysis submitted to the FDA indicated that the OCEAN trial failed to meet the primary endpoint. The Applicant submitted revised PFS results indicating PFS superiority. The FDA requested clarification on the reason for the revised PFS results. In their response dated July 9, 2021, the Applicant stated that following the top-line data readout on May 25, 2021, the results were reviewed by the Applicant and the data indicated a technical issue in the IRC-based PFS results relating to imaging data for bone lesions and extramedullary disease. The contract research organization (CRO) holding the clinical database was requested to perform a data comparison of the 495 patients which identified 29 patients with discrepancies noted. The Applicant reported that the discrepancies were mainly found in two categories (1) data corrections made in the electronic data capture (EDC) between the last IRC meeting (4.19.2021) and the data snapshot (5.7.2021) and (2) ambiguous IRC assessments in relation to imaging data. The response data blinded to treatment arm for the 29 patients were compiled in a worksheet and re-reviewed by the IRC.

Based on the FDA's assessment, 9 patients did not have any change to their response assessment or date for the time-to-event and did not impact the PFS results. This was confirmed by the Applicant. Additionally, the Applicant clarified the measurable disease status for patients and noted the difference in assessments dates.

FDA notes the following limitations with these post hoc revisions:

- Lack of Agreement: FDA could not confirm the Applicant's revised response results for 3 patients and for one patient disagreed with the date (reference).
    1. Subject M we are unable to confirm that the plasmacytoma found on physical exam was new as the initial physical exam documented in the case report form did not comment on the involved area (breast) at baseline.
    2. Subject Z we disagree the hypermetabolic area found on PET/CT is clear evidence of progression as there was no underlying lytic area present on CT. There was no PET/CT at baseline to compare (baseline imaging was only a CT).
    3. Subject bb we are unable to confirm the lesion seen on MRI is new as the baseline PET/CT showed a lesion at that site at baseline.
    4. Subject cc, we do not agree with calling progression on March 3, 2020, as the date of imaging showing progression was performed on March 27, 2020.
- Revised results were primarily unconfirmed progression or related to imaging data submitted to the IRC. It is important to note that although the PFS was assessed IRC, the radiology/imaging results were not reviewed by blinded independent radiologists. Rather, the radiology report reviewed by individual radiologists in the respective countries were entered as line listings and a conclusion statement was included in the IRC file.

Table 38 FDA Readjudication of the 29 Patients with Revised PFS Results

Subject	Arm	Original Event	Time-to-event (months)	Revised Event	Revised Time-to-event (months)	FDA Assessment	PD Event (Confirmed, Unconfirmed or based on Imaging)	Additional FDA Comments
A	Pom	PD	1.3	PD	1.3	No Change*	Confirmed	
B	Pom	Alive, wo PD	6.5	Alive, wo PD	6.5	No Change*	None	
C	Mel	PD	3.7	PD	3.7	No Change*	Confirmed	
D	Pom	PD	11.1	PD	11.1	No Change*	Confirmed	
E	Pom	PD	4.7	PD	4.7	No Change*	Confirmed	
F	Mel	PD	5.1	PD	5.1	No Change*	Confirmed	
G	Mel	Other tx	3.3	Other tx	3.3	No Change*	None	
H	Mel	Death	9.3	Death	9.3	No Change*	None	
I	Mel	PD	1.1	PD	1.1	No Change*	None	
J	Mel	PD	3.4	PD	3.2	Agree	Confirmed	
K	Pom	PD	6.5	PD	7.4	Agree	Confirmed	
L	Pom	Alive, wo PD	1.1	Alive, wo PD	6.6	Agree	None	
M	Pom	PD	2.8	PD	2.0	Disagree	Imaging	Initially PD date of 9.14.18 due to an increase in an existing bone lesion seen on PET/CT. Readjudicated results changed PD date to 8.23.18 based on a

								plasmacytoma found on breast exam. This data was entered late in the CRF and initially missed. However, there was no information regarding baseline physical exam to confirm the plasmacytoma was new.
N	Pom	Death	2.4	PD	2.3	Agree	Unconfirmed PD	
O	Mel	Death	4.1	PD	3.5	Agree	Unconfirmed PD	
P	Mel	Death	3.5	PD	3.1	Agree	Confirmed	
Q	Pom	Death	2.3	PD	1.8	Agree	Unconfirmed PD	
R	Pom	Death	10.3	PD	8.6	Agree	Unconfirmed PD	
S	Mel	Other tx	4.4	PD	4.4	Agree	Confirmed	
T	Mel	Other tx	5.5	PD	5.5	Agree	Unconfirmed PD	
U	Mel	Other tx	3.3	PD	3.3	Agree	Unconfirmed PD	

V	Mel	PD	5.7	Alive, wo PD	9.3	Agree	None	
W	Pom	Other tx	5.3	PD	5.3	Agree	Unconfirmed PD	
X	Pom	Other tx	6.5	PD	6.5	Agree	Unconfirmed PD	
Y	Mel	PD	1.0	Alive, wo PD	21.5	Agree	Imaging	New plasmacytoma erroneously checked in system for C2D1 however the lesion was present at baseline
Z	Mel	Other tx	2.9	PD	3.2	Disagree	Imaging	PD based on "increased metabolic activity in right pelvis" Baseline imaging was a CT scan, not PET/CT. Follow-up CT shows partial response in most areas. Not enough informatio

								n to clearly state progression.
aa	Pom	Alive, wo PD	7.7	PD	7.7	Agree	Unconfirmed PD	PD based on a single UPEP increase. Tabular summary states response based on SPEP. However, we do agree the UPEP value is unconfirmed PD (despite the M protein being slightly decreased).
bb	Pom	Other tx	4.9	PD	4.9	Disagree	Imaging	PD based on MRI on 8.5.2020 describing a T5/T6 lesion. No MRI at baseline. Baseline PET/CT shows a "left posterior

								rib mass suggestive of myeloma involvement" This is likely the same location and without a baseline MRI it is difficult to call this progression. Of note, IRC member #2 said this patient was not evaluable because imaging was not Followed
cc	Pom	Alive, wo PD	21.3	PD	12.4	Disagree (on date)	Imaging	PD called based on a new 1 cm lesion on PET/CT dated on 3.27.20 however they listed the day of progression as

								3.3.2020 as that was the most recent clinic visit date. The date of progressi on should be the date of the imaging exam as no other signs of progressi on were identified on the date of visit. Initially recorded as No PD because "the IRC initially did not review imaging"

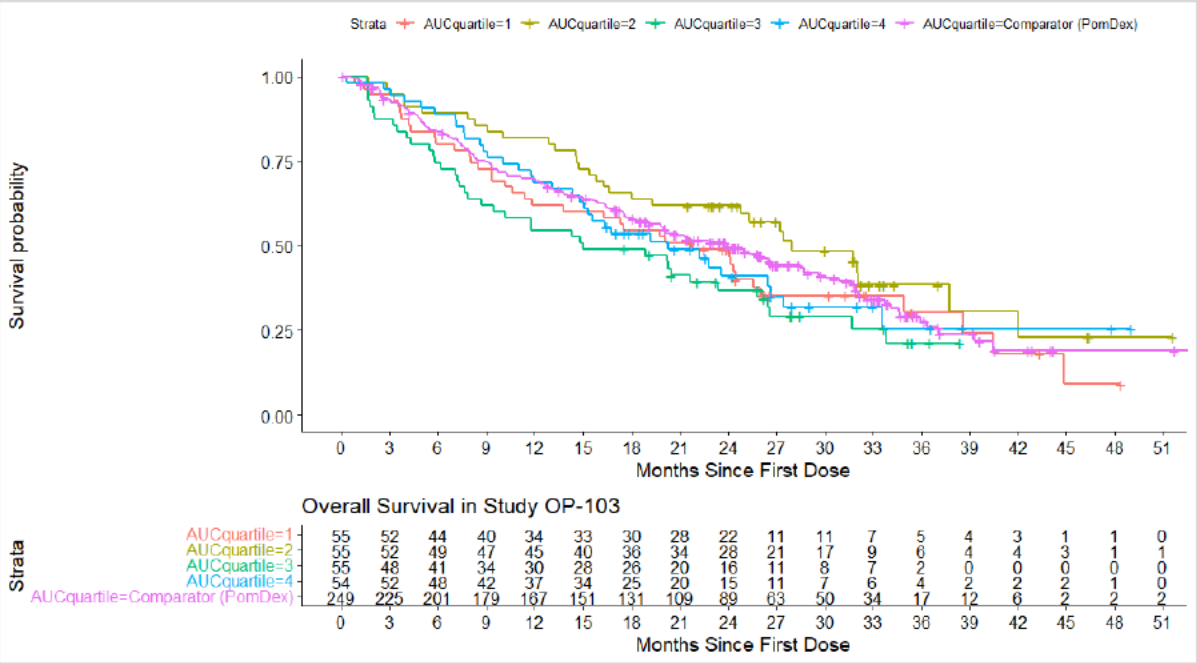
*The first 9 patients listed as "no change" were identified by the database comparison of the complete 495 patient data. However the IRC review did not find anything that warranted a change in response assessment. Therefore the original response and time-to-event remained the same. FDA review agreed. Abbreviations: tx: treatment
Source: FDA analysis

10.7 Additional FDA Clinical Pharmacology Analyses

Exposure-response efficacy relationships in OCEAN

No clear exposure-response relationships of efficacy have been identified for melphalan flufenamide. Cycle 1 melphalan exposure in OCEAN was not associated with any clear trends in overall survival (Figure 23) or progression-free survival.

Figure 23. Overall Survival According to Cycle 1 Exposure Quartile in Study OCEAN Subjects



AUC = area under the concentration-versus-time curve. Quartile 1 = lowest exposure. Quartile 4 = highest exposure. MelDex = melphalan flufenamide plus dexamethasone; PomDex = pomalidomide plus dexamethasone. Data shown for OCEAN subjects who received at least one dose of MelDex with Exposure Data (n=219) and OCEAN subjects who received at least one dose of PomDex (n=249)
Source: FDA Analysis of Study OP-103 (OCEAN) exposure data and OS with data cut-off 03Feb2022.

10.8 Safety in the Currently Indicated Patient Population -OCEAN

Table 39 Safety Overview - 4 Prior Lines of Therapy and TCR

	MelDex N=16 N (%)	PomDex N=10 N (%)
ANY TEAE	16 (100)	9 (90)
Any grade 3-4 TEAE	14 (87.5)	7 (70)
Grade 5 TEAE	3 (18.8)	2 (20)
Serious AEs	5 (31.2)	5 (50)
Dose delayed due to TEAE	8 (50.0)	3 (30.0)
Dose reduced due to TEAE	3 (18.8)	1 (10.0)
Drug withdrawn due to TEAE	4 (25.0)	4 (40.0)

Source: FDA Analysis

Table 40 AEs of Special Interest -TCR and 4 prior lines of therapy

	MelDex N = 16 n (%)		PomDex N = 10 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Thrombocytopenia*	16 (100)	12 (75)	6 (60)	0 (0)
Anemia*	15 (94)	9 (56)	8 (80)	1 (10)
Neutropenia*	16 (100)	14 (88)	9 (90)	4 (40)
Infections (SOC)	7 (43.8)	1 (6.2)	8 (80.0)	1 (10.0)
Hemorrhage (GT)	1 (6.2)	0 (0)	0 (0.0)	0 (0)

Source: FDA Analysis

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11 Sponsor Appendices

APPENDIX 1. OVERALL SURVIVAL HETEROGENEITY FOR IMMUNOMODULATORY DRUGS

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1. Background

OCEAN (OP-103) is a head-to-head randomized comparison between Pepaxto (melphalan flufenamide, also called melflufen) plus dexamethasone (dex) and pomalidomide/dex in patients with relapsed refractory multiple myeloma (RRMM) who have received two to four prior lines of therapy. The primary endpoint of superior progression free survival (PFS) according to the statistical analyses plan (SAP) was met, but the Full Analysis Set (FAS) overall survival (OS) hazard ratio (HR) of 1.10 (95% CI, 0.85-1.44) in the February 3, 2021 datacut (1.14 [95% CI, 0.91-1.43] in the February 3, 2022 datacut) raised questions regarding the internal validity of the primary endpoint of PFS and a potential detrimental effect on survival in the study.

The interpretation of the OS results in OCEAN, which on the FAS level showed a dissociation between PFS (Pepaxto/dex superior to pomalidomide/dex) and OS (Pepaxto/dex numerically worse than pomalidomide/dex), was complicated due to the highly heterogenous OS results in predefined subgroups. In the study, the full confidence intervals for OS HRs in key patient subgroups such as age were both >1 and <1 (Table 1).

Table 1. OS HRs With 95% CIs in FAS Pre-Specified Age Groups in OCEAN

Pre-Specified Age Group	Hazard Ratio	95% Confidence Interval
<65 years (N=181)	1.68	1.13-2.49
65-74 years (N=238)	1.03	0.76-1.41
≥75 years (N=76)	0.62	0.35-1.89

FAS, Full Analysis Set; HR, hazard ratio; OS, overall survival.
Data cutoff dates: Feb 3, 2022.
Sponsor internal analyses, Data source ADTTE.

The Applicant has thoroughly analysed the safety data in OCEAN and cannot find a Pepaxto toxicity signal that could explain a potentially detrimental effect on OS. Given the lack of a safety explanation, further analyses focused on identifying a heterogenic treatment effect with either one or both study drugs. These analyses revealed that there was a correlation between PFS and OS within the Pepaxto arm, but that PFS results did not predict OS outcome within the pomalidomide arm.

The Applicant has confirmed that, for the pomalidomide treatment effect, there appears to be a significant OS effect modification (i.e., the association between a predictor and an outcome is different depending on a third variable) based on primarily age in OCEAN. In order to investigate whether this was a random result unique to this study, the Applicant conducted a thorough analysis of other randomized controlled trials where the treatment effect of pomalidomide as well as other immunomodulatory agents can be isolated, both in multiple myeloma and in other malignancies. The results of this analysis are presented in this document as well as a discussion on the underlying prognostic value of age in late stage RRMM.

2. Analysis of Data

2.1 The Underlying Prognostic Value of Age for Survival in MM and Observations in OCEAN and Other RRMM Studies

Given the significantly heterogenous OS outcome by patient age in the pom/dex arm and similar OS outcome by patient age in the melflufen/dex arm in OCEAN (OP-103), the underlying prognostic value of age for survival at different stages of MM needs to be understood. At MM diagnosis, the underlying prognostic value of age is significant, with an OS HR of around 2 when comparing old and young MM patients. However, the FDA conducted a meta-analysis of the prognostic value of age in RRMM patients with 1+ prior line of therapy demonstrating an OS HR of only 1.21-1.25 (N=4,766) when comparing old and young patients (Table 2). The KM-plots also showed a decrease in the differences in risk of death as a function of age with each subsequent line of therapy (FDA analysis; Kanapuru et al, 2019).

Table 2. OS Hazard Ratio Per Age Group in MM Patients with 1+ Prior Line of Therapy

Age-Group Comparison	65-74 vs <65 N=1,816 vs 2,250	75-80 vs <65 N=531 vs 2,250	>80 vs <65 N=169 vs 2,250
OS HR (95% CI)	1.21 (1.07-1.36)	1.23 (1.02-1.48)	1.25 (0.93-1.67)

HR, hazard ratio; MM, multiple myeloma; OS, overall surival.
(FDA analysis; Kanapuru et al, 2019)

A comparison of 75+ and <65 patients within the pomalidomide arm in OCEAN exhibited an OS HR of 2.32 (p=0.003) (Table 3), which implies a clinically meaningful OS effect modification based on age since the magnitude of the increased risk of death is much larger than what could be explained only by age as a prognostic factor in MM. The PFS results in the pomalidomide arm were homogenous across subgroups, meaning that PFS does not predict the age-related effect on OS seen for pomalidomide (see Figure 5 in the main briefing document).

Table 3. OS and PFS HR Comparing 75+ and <65 Patients Within Each Treatment Arm of OCEAN

	PFS HR (95% CI) 75+ vs <65	OS HR (95% CI) 75+ vs <65
Pepaxto/Dex	0.62 (0.38-1.01)	0.63 (0.34-1.15)
Pomalidomide/Dex	1.42 (0.92-2.21)	2.32 (1.33-4.05)

HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
Data cutoff dates: Feb 3, 2022.
Sponsor internal analyses, Data source ADTTE.

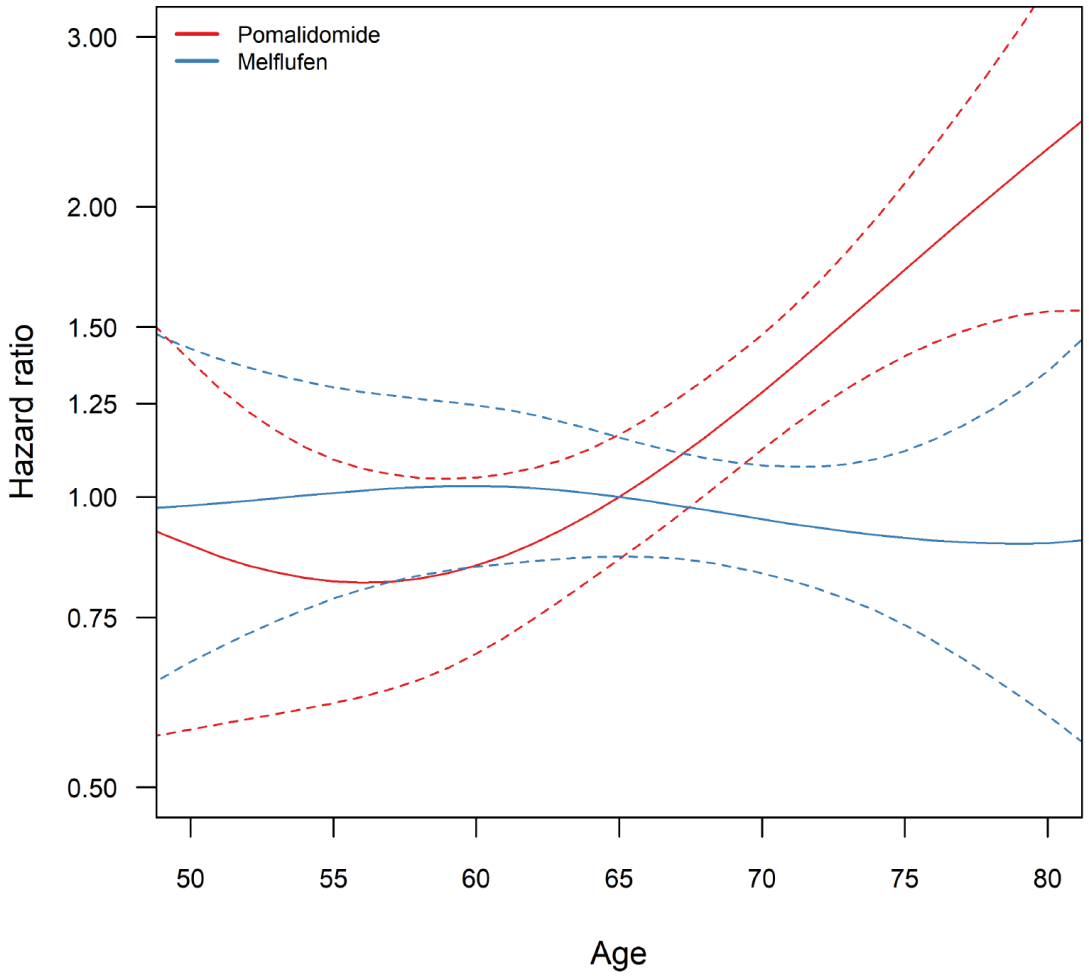
Table 4. OS and PFS HR Comparing 65-74 and <65 and Patients Within Each Treatment Arm of OCEAN

	PFS HR (95% CI) 65-74 vs <65	OS HR (95% CI) 65-74 vs <65
Pepaxto/Dex	0.84 (0.60-1.16)	0.83 (0.56-1.21)
Pomalidomide/Dex	1.17 (0.85-1.62)	1.45 (0.93-2.24)

HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
Data cutoff dates: Feb 3, 2022.
Sponsor internal analyses, Data source ADTTE.

The hazard ratios for OS and PFS results within the Pepaxto arm correlate when comparing 75+ and <65 age groups (Table 3). The largest contributor to the heterogenous OS HR result as a function of age in OCEAN is the variability in the pomalidomide treatment arm. A spline analysis of the OS HR within each arm in OCEAN as a function of age provides identification of the heterogeneity by age (Figure 1). As represented, the hazard of death in the pomalidomide arm rapidly accelerates in patients who are older than 65 years of age, and becomes 2-3x higher in elderly patients compared with younger patients. Given the underlying prognostic value of age at this stage of the disease, this is significantly different than expected in a late line MM patient population. This is unique, and not previously reported for pomalidomide. In comparison the hazard of death within the Pepaxto arm remains essentially level by patient age, in line with expectation for underlying patient population in OCEAN.

Figure 1. Spline Plot of OS HR by Age in OCEAN (Reference Age Set to 65)



HR, hazard ratio; OS, overall survival.
Data cutoff dates: Feb 3, 2022.

The high degree of variability in OS as a function of age seen in OCEAN is well replicated in other pomalidomide studies and also in studies with other immunomodulatory agents where OS data is available or was retrieved by Oncopeptides. In the pomalidomide/low dose dex arm of study MM002, a phase 2 study evaluating safety and efficacy of pomalidomide with/without low-dose dex in RRMM patients who had received at least 2 prior therapies, patients ≤65 had a mOS of 19.7 months compared with 11.8 months in patients >65 (Jagannath et al, 2012). In the ICARIA study, a phase 3 study in RRMM patients evaluating isatuximab, pomalidomide and low-dose dex (IsaPd) versus pomalidomide and low-dose dex (Pd) in patients who had received at least 2 prior lines of therapy, patients <65 had a mOS of 25.6 months compared with 10.3 months in patients 75+ (Richardson et al, 2022) in the Pd arm (Table 5). These analyses are collected from all studies that have reported IMiD efficacy by patient age. Those studies each

replicate this same age-dependent survival pattern. Unfortunately, the majority of pomalidomide or IMiD studies omit survival or PFS results by age. Yet, available studies support a consistent pattern as discussed in Section 2.3.

Table 5. Median OS in Months and OS HRs With 95% CIs by Age Group in ICARIA

	PFS HR Isa/Pd vs Pd	Median OS (months)		OS HR Isa/Pd vs Pd
		Isa/Pd	Pd	
FAS	0.60 (0.44-0.81)	24.6 (20.3-31.3)	17.7 (14.4-26.2)	0.76 (0.57-1.01)
<65	0.66 (0.40-1.07)	25.6 (16.3-36.1)	25.6 (13.4-36.2)	0.97 (0.61-1.53)
65-74	0.64 (0.39-1.06)	26.9 (20.3-NC)	19.8 (14.4-29.9)	0.70 (0.45-1.10)
75+	0.48 (0.24-0.95)	20.0 (14.2-NC)	10.3 (4.9-17.39	0.51 (0.28-0.92)

FAS, Full Analysis Set; HR, hazard ratio; isa, isatuximab; OS, overall survival; pd, pomalidomide; PFS, progression-free survival.
Source: Table C in Section 5 Appendices

2.2 Analysis of Effect Modification by Age in MM Trials That Isolate the Immunomodulatory Agent Treatment Effect

To further understand the pomalidomide OS effect modification by age observed in OCEAN, the Applicant collated all available phase 3 clinical data based on published information from other clinical trials that allow for the isolation of the immunomodulatory agent treatment effect in MM (Table A in Section 5 Appendices).

The search was conducted using the search terms “IMiD”, “thalidomide”, “lenalidomide” and/or “pomalidomide” with the filter “randomized controlled trial”. This resulted in 647 hits that were manually assessed. All trials that did not allow for the isolation of the immunomodulatory agent treatment effect or that were not powered for hypothesis testing were excluded from the final result. The trials that were included in the final analysis for lenalidomide or pomalidomide (total patient amount: 8,567 excluding thalidomide trials) are presented in Tables 6 and 7. It is noteworthy how consistently detailed OS data is missing in publications and even in CSRs and regulatory follow-up documents.

Table 6. Hypothesis Testing Trials That Allow for the Isolation of Lenalidomide or Pomalidomide in Multiple Myeloma

Indication	Study	Reporting Year	Isolated Drug	# Patients	OS Data comment
MM	MM009 (LenUS)	2006	Lenalidomide (add-on)	353	OS Subgroup data not published and not part of CSR

Indication	Study	Reporting Year	Isolated Drug	# Patients	OS Data comment
MM	MM010 (LenEU)	2006	Lenalidomide (add-on)	351	OS Subgroup data not published and not part of CSR
MM	MM009/MM010	2009	Lenalidomide (add-on)	704	LT OS follow-up. OS Subgroup data not part of regulatory file
MM	MM007	2018	Pomalidomide (add-on)	559	OS subgroup data not published. OS subgroup data part of CSR
MM	CALGB/ALLIANCE	2018	Lenalidomide (add-on)	460	OS subgroup data not published. Academic trial
MM	Myeloma XI	2019	Lenalidomide (add-on)	1,917	OS subgroup data published. Academic trial
MM	OCEAN	2021	Pomalidomide (head-to-head)	495	OS subgroup data published. OS subgroup data part of CSR

Source: Table A in Section 5 Appendices

Table 7. Hypothesis Testing Trials That Allow for the Isolation of Lenalidomide or Pomalidomide Outside Multiple Myeloma

Indication	Study	Reporting Year	Isolated Drug	# patients	OS Data comment
Prostate Cancer	MAINSAIL	2015	Lenalidomide (add-on)	1,059	Study stopped due to OS HR >1.5
Prostate Cancer	MAINSAIL II	2015	Pomalidomide (add-on)	Not reported but similar to MAINSAIL	Study stopped due to OS HR >1.5
CLL	CONTINUUM	2017	Lenalidomide (add-on)	314	OS subgroup data not published

Indication	Study	Reporting Year	Isolated Drug	# patients	OS Data comment
CLL	ORIGIN	2017	Lenalidomide (head-to-head)	450	OS subgroup data not published. Halted recruitment of pts >80 years of age due to OS HR of 3
DLBCL	REMARC	2017	Lenalidomide (add-on)	650	OS subgroup data not published
Lymphoma	RELEVANCE	2017	Lenalidomide (head-to-head)	1,030	OS subgroup data not published
Lymphoma	AUGMENT	2019	Lenalidomide (add-on)	358	OS subgroup data not published
DLBCL	ROBUST	2021	Lenalidomide (add-on)	570	OS subgroup data not published

Source: Table B in Section 5 Appendices

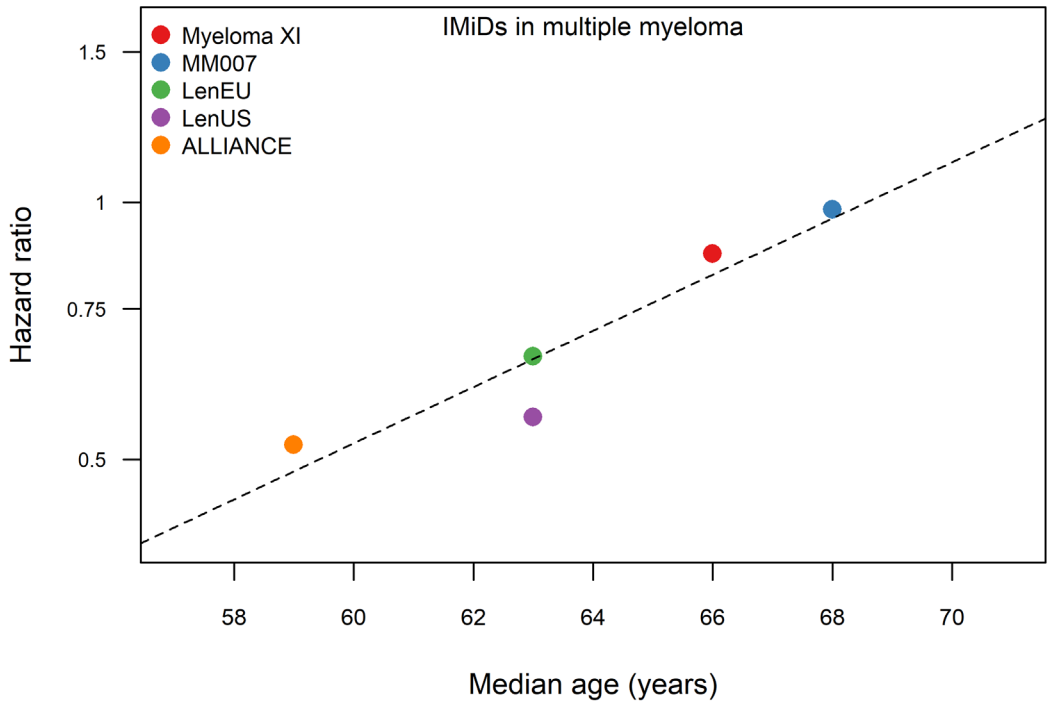
The Applicant has found only a few trials that allow for the isolation of the immunomodulatory agent treatment effect in MM and only some of the OS data from these trials are publicly available. To date, there are only 2 trials that allow for the isolation of the pomalidomide treatment effect: OCEAN (2021) with Pepaxto/dex vs pomalidomide/dex, and MM007 (2018) with pomalidomide/bortezomib/dex vs bortezomib/dex. For lenalidomide, there are 4 trials that allow for the isolation of the treatment effect: The original 2 lenalidomide registration trials LenEU (MM010) and LenUS (MM009) (2007) with lenalidomide/dex vs dex, the ALLIANCE trial (2018) with lenalidomide vs no lenalidomide and Myeloma XI (2019) with lenalidomide vs no lenalidomide. The ALLIANCE trial only included younger transplant-eligible patients making it unsuitable for studying effect modification by age. The complete study reports for the LenEU and LenUS were obtained via the MPA, Sweden in 2022 but were found not to contain any OS data for the prespecified subgroups. The Applicant has been collaborating with the National Cancer Research Institute in the UK to retrieve unpublished survival data regarding the potential OS effect modification by immunomodulatory agents from study Myeloma XI (NCRI UK) and received unpublished survival data from study MM007 from EMA in early 2022.

The data from OCEAN, MM007, and Myeloma XI have been analyzed by the Applicant to the extent possible based on publicly available data (a meta analysis was e.g. not possible). If the observations in OCEAN are correct there should be a relationship between the age of a patient population and the isolated immunomodulatory agent treatment effect as measured by OS. Head-to-head studies (such as ORIGIN, RELEVANCE and OCEAN) are included in the the tables in

Section 5 Appendices, but for correlation analysis they were excluded since the OS HR values in trials with active comparator have a different meaning than in trials with comparison to no treatment/placebo. The same principle was applied when analyzing non-immunomodulatory agents in Section 2.5.

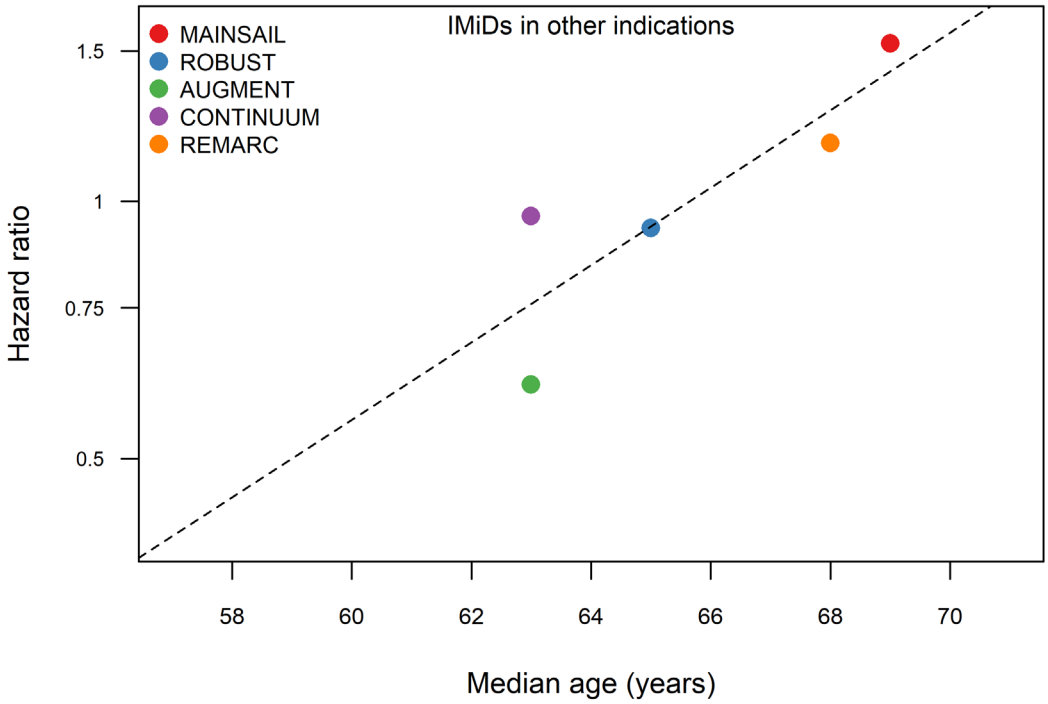
Despite the limitations in the underlying data, the correlation coefficient for the OS immunomodulatory agent treatment effect and median age in MM studies that allow for the isolation of the immunomodulatory agent treatment effect was found to be 0.94 (log OS HR and median age). Thus, there is a strong correlation between the immunomodulatory agent OS treatment effect and patient age. This is displayed in Figure 2.

Figure 2. Scatter Plot of OS Log HR by Median Age for IMiDs in MM, Correlation Coefficient: 0.94



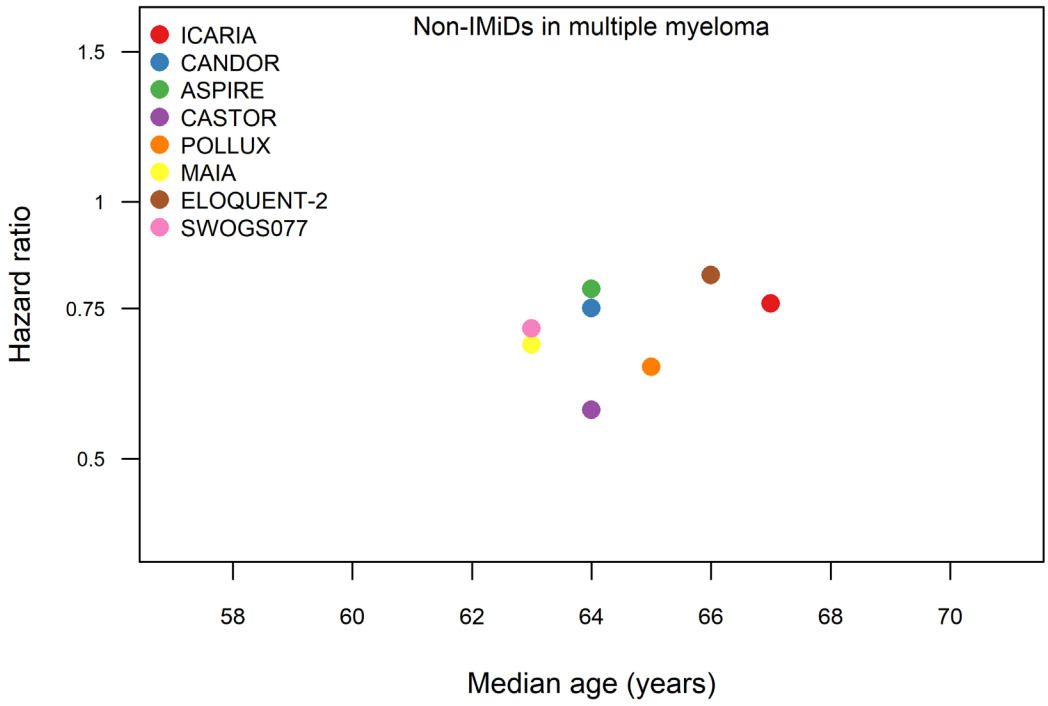
Source: Table A in Section 5 Appendices

Figure 3. Scatter Plot of OS Log HR by Median Age for IMiDs in Other Indications, Correlation Coefficient: 0.86



Source: Table B in Section 5 Appendices

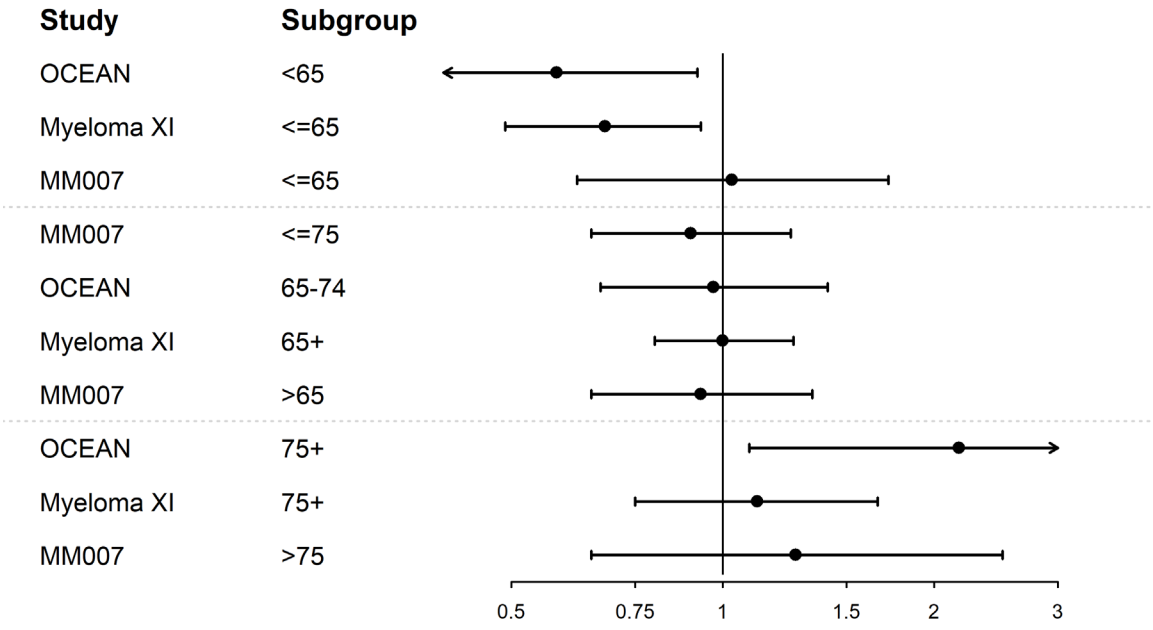
Figure 4. Scatter Plot of OS Log HR by Median Age for Non-IMiDs in MM, Correlation Coefficient: 0.36



Source: Table C in Section 5 Appendices

Figure 5 shows the age subgroup data as a forest plot in studies that allow for the isolation of the immunomodulatory agent treatment effect in multiple myeloma and where OS HR subgroup data by age is available including OCEAN. The data suggest that the immunomodulatory agent treatment effect is reduced as a function of age and may even become detrimental in patients 75+.

Figure 5. OS Hazard Ratios in Age Subgroups for Lenalidomide and Pomalidomide in MM



MM, multiple myeloma; OS, overall survival.
Source: Table A in Section 5 Appendices

2.3 Analysis of Effect Modification by Age in Trials in Other Indications Which Allow for the Treatment Isolation of Immunomodulatory Agents

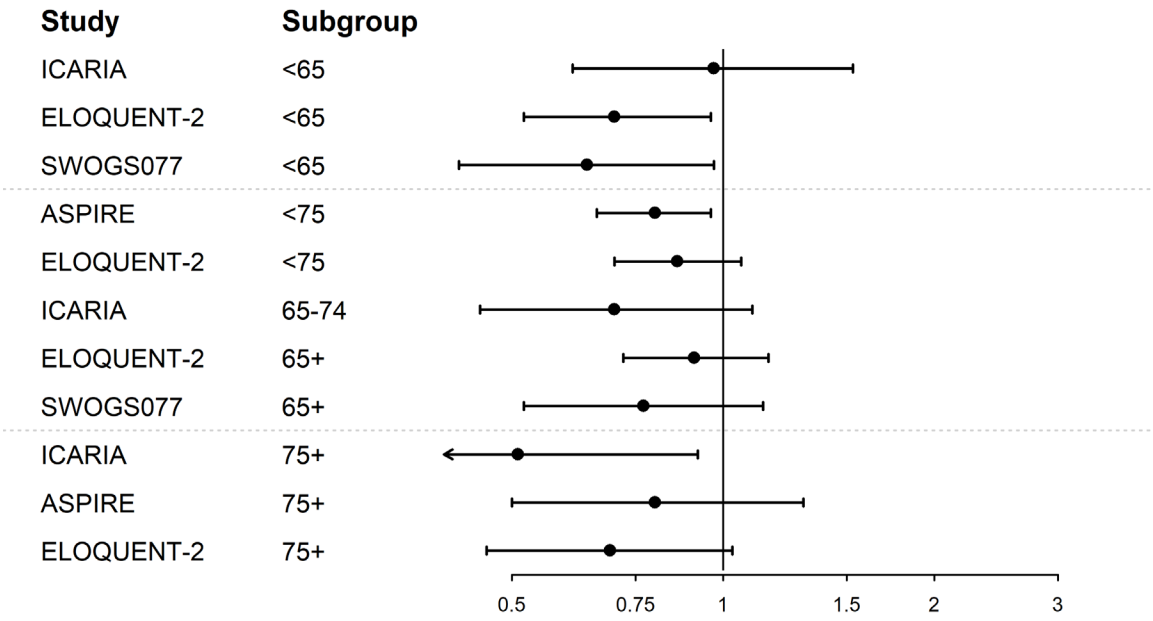
Data from studies isolating the immunomodulatory agent treatment effect in other indications have also been analyzed by the Applicant (Table B in Section 5 Appendices). The analysis was performed using the same methodology as in MM and despite the limitations in the underlying data showed a correlation coefficient of 0.86 between the log OS HR immunomodulatory agent treatment effect and median age across studies. There is a strong correlation between the immunomodulatory agent OS treatment effect and patient age also in indications other than MM, as seen in Figure 3. It can be noted that in the ORIGIN study (lenalidomide versus chlorambucil for older patients with chronic lymphocytic leukemia) the data monitoring committee observed an imbalance in deaths between the treatment arms favoring chlorambucil in the oldest patients and as a result, patients aged >80 years were discontinued from study treatment.

2.4 OS Data in MM Trials With Other Drug Classes by Age

To complete the analysis, the Applicant has also gathered OS data as a function of age from trials that isolate the treatment effect of other drug classes in MM (PIs, anti-CD38 and anti-CS1). The initial analysis was conducted using the same methodology as for immunomodulatory agents and showed a correlation between the drug OS treatment effect and median age of 0.36 (log OS HR and median age). Studies with available OS HR age subgroup data are shown in Figure 4and Figure 6. The list of studies is provided in Table C in Section 5 Appendices. There is

no correlation between patient age and the OS treatment effect of PIs, anti-CD38s and anti-CS1 based therapy with a consistent survival benefit across the age spectrum.

Figure 6. OS Hazard Ratio as a Function of Age for PIs, Anti-CD38s and Anti-CS1 in MM



MM, multiple myeloma; OS, overall survival; PI, proteasome inhibitor.
Source: Table C in Section 5 Appendices

3. Conclusion on Immunomodulatory Agent OS Effect Modification by Age

Based on the analyses presented in this document, the Applicant concludes that the pomalidomide treatment effect has a statistical interaction between age and OS. This conclusion is based on identical behavior for pomalidomide across all trials where the pomalidomide treatment effect can be isolated or where detailed survival data exists for an individual pomalidomide/dex treatment arm (in OCEAN, MM002, ICARIA, and MM007). The Applicant was unable to identify trial datasets supporting evidence to the contrary. The Applicant further concludes that the analyses show that immunomodulatory agents as a drug class have significant OS effect modification as a function of patient age (i.e., thalidomide, lenalidomide and pomalidomide). The Applicant conducted the same analyses for PFS (see data presented in Table A, B and C in Section 5 Appendices), but did not identify a material age differential for PFS outcomes. The homogenous PFS treatment effect and at the same time heterogenous OS treatment effect indicate that PFS as a surrogate endpoint does not accurately capture the benefit-risk profile of immunomodulatory agents. It is unclear to the applicant whether this phenomenon is driven by toxicity differences, activity differences or both. It is worth considering that the observed OS effect modification is in line with the characterized IMiD mode of action where the immunomodulatory effect is dependent on T-cell function. T-cell function is significantly reduced with increased age (the process of

immunosenescence). While the reason why surrogate endpoints do not capture the OS benefit-risk for IMiDs is unknown, the dissociation between surrogate endpoints and OS is also often observed with other T-cell dependent drug-classes such as check-point inhibitors. That immunosenescence might play a role for this phenomenon is further supported by observed gender differences in the younger patients where females have a larger OS benefit from immunomodulatory treatment than males – in line with a potential immunosenescence explanantion. However, that toxicity also plays a role seems likely based on the observation that OS HRs for the immunomodulatory treatment effect compared to placebo/ no treatment, consistently is >1 for elderly patients.

The observation that the OS IMiD treatment benefit differs significantly by patient age (with limited reflection by surrogate endpoints) is currently not part of immunomodulatory agent drug labels or peer-review articles.

4. List of References

Jagannath S et al. Pomalidomide (POM) with Low-Dose Dexamethasone (LoDex) in Patients (Pts) with Relapsed and Refractory Multiple Myeloma Who Have Received Prior Therapy with Lenalidomide (LEN) and Bortezomib (BORT): Updated Phase 2 Results and Age Subgroup Analysis. Blood (2012) 120 (21):450. https://doi.org/10.1182/blood.V120.21.450.450

Kanapuru B, Jin S, et al. FDA Analysis of Survival Outcomes in Older Adults with Relapsed-Refractory Multiple Myeloma (RRMM) Treated with Novel Drug Regimens. Blood 2019;134 (Supplement_1):3194.

Richardson P, Perrot A, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): follow-up analysis of a randomised, phase 3 study Lancet Oncol 2022;23(3):416-427.

5. Appendices

Table A – Summary of Data From Phase 3 Clinical Trials That Isolate the Immunomodulatory Agent Treatment Effect in MM (Including Available Age Subgroups), Sorted by Clinical Study.

Drug-class	Indication	Drug	Study	ITT/ Subgroup	Median Age	PFS HR	95% CI	OS HR	95% CI	Source
IMiD	MM	Lenalidomide	ALLIANCE	ITT	59	0,57	(0,46-0,71)	0,52	(0,26-1,02)	Holstein et al
IMiD	MM	Lenalidomide	LenEU	ITT	63	0,35	(0,27-0,46)	0,66	(0,45-0,96)	Dimopolous et al
IMiD	MM	Lenalidomide	LenUS	ITT	63	0,35	(0,27-0,47)	0,56	(0,34-0,95)	Weber et al
IMiD	MM	Pomalidomide	MM007	<=65	NA	0,58	(0,41-0,83)	1,03	(0,62-1,72)	Richardson et al; MM007 CSR
IMiD	MM	Pomalidomide	MM007	<=75	NA	0,59	(0,46-0,76)	0,90	(0,65-1,25)	Richardson et al; MM007 CSR
IMiD	MM	Pomalidomide	MM007	ITT	68	0,61	(0,49-0,77)	0,98	(0,73-1,32)	Richardson et al
IMiD	MM	Pomalidomide	MM007	>65	NA	0,64	(0,48-0,86)	0,93	(0,65-1,34)	Richardson et al; MM007 CSR
IMiD	MM	Pomalidomide	MM007	>75	NA	0,78	(0,46-1,32)	1,27	(0,65-2,50)	Richardson et al; MM007 CSR
IMiD	MM	Lenalidomide	Myeloma XI	<=65	NA	0,47	(0,39-0,58)	0,68	(0,49-0,93)	Jackson et al
IMiD	MM	Lenalidomide	Myeloma XI	ITT	66	0,46	(0,41-0,53)	0,87	(0,73-1,05)	Jackson et al
IMiD	MM	Lenalidomide	Myeloma XI	65+	NA	0,45	(0,39-0,53)	1,00	(0,80-1,26)	Jackson et al
IMiD	MM	Lenalidomide	Myeloma XI	75+	NA	NA	NA	1,12	(0,75-1,66)	Correspondence with study team
IMiD	MM	Pomalidomide	OCEAN	<65	NA	0,97	(0,68-1,37)	0,58	(0,37-0,92)	OCEAN CSR
IMiD	MM	Pomalidomide	OCEAN	ITT	68	1,27	(1,02-1,56)	0,91	(0,71-1,19)	OCEAN CSR
IMiD	MM	Pomalidomide	OCEAN	65-74	NA	1,35	(1,00-1,82)	0,97	(0,67-1,41)	OCEAN CSR
IMiD	MM	Pomalidomide	OCEAN	75+	NA	2,08	(1,16-3,85)	2,17	(1,09-4,35)	OCEAN CSR

IMiD, immunomodulatory agent; ITT, intent-to-treat; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival.

Table B – Summary of Data From Phase 3 Clinical Trials That Isolate the Immunomodulatory Agent Treatment Effect in Indications Outside of MM (Including Available Age Subgroups), Sorted by Median Patient Age.

Drug-class	Indication	Drug	Study	ITT/ Subgroup	Median Age	PFS HR	95% CI	OS HR	95% CI	Source
IMiD	Lymphoma	Lenalidomide	RELEVANCE	ITT	59	1,10	(0,85-1,43)	1,16	(0,72-1,86)	Morschhauser et al
IMiD	Lymphoma	Lenalidomide	AUGMENT	ITT	63	0,46	(0,34-0,62)	0,61	(0,33-1,13)	Leonard et al
IMiD	CLL	Lenalidomide	CONTINUUM	ITT	63	0,40	(0,29-0,55)	0,96	(0,63-1,48)	Chanan-Khan et al
IMiD	DLBCL	Lenalidomide	ROBUST	ITT	65	0,85	(0,63-1,14)	0,93	(0,65-1,32)	Nowakowski et al
IMiD	DLBCL	Lenalidomide	REMARC	ITT	68	0,73	(0,6-0,9)	1,17	(0,9-1,6)	Thieblemont et al
IMiD	Prostate Cancer	Lenalidomide	MAINSAIL	ITT	69	NA	NA	1,53	(1,17-2,00)	Petrylak et al
IMiD	CLL	Lenalidomide	ORIGIN	ITT	73	1,21	(0,88-1,66)	1,63	(1,06-2,67)	Chanan-Khan et al
IMiD	CLL	Lenalidomide	ORIGIN	>80	NA	NA	NA	3	NA	Safety Communication

IMiD, immunomodulatory agent; ITT, intent-to-treat; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival.

Table C – Summary of Data From Phase 3 Clinical Trials That Isolate the Treatment Effect of Non-Immunomodulatory Agents in MM (Including Available Age Subgroups), Sorted by Clinical Study.

Drug-class	Indication	Drug	Study	ITT/ Subgroup	Median Age	PFS HR	95% CI	OS HR	95% CI	Source
PI	MM	Carfilzomib	ASPIRE	<75	NA	NA	NA	0,8	(0,66-0,96)	Sigel et al
PI	MM	Carfilzomib	ASPIRE	75+	NA	NA	NA	0,8	(0,50-1,30)	Sigel et al
PI	MM	Carfilzomib	ASPIRE	<65	NA	0,6	(0,46-0,79)	NA	NA	Stewart et al
PI	MM	Carfilzomib	ASPIRE	65+	NA	0,85	(0,65-1,11)	NA	NA	Stewart et al
PI	MM	Carfilzomib	ASPIRE	ITT	64	0,69	(0,57-0,83)	0,79	(0,67-0,95)	Stewart et al
Anti-CD38	MM	Daratumumab	CANDOR	ITT	64	0,63	(0,46-0,85)	0,75	(0,49-1,13)	EPAR
Anti-CD38	MM	Daratumumab	CASTOR	ITT	64	0,39	(0,28-0,53)	0,57	(0,37-0,90)	Palumbo et al
Anti-CS1	MM	Elotuzumab	ELOQUENT-2	ITT	66	0,70	(0,57-0,85)	0,82	(0,68-1,00)	Lonial et al; Dimopolous et al
Anti-CS1	MM	Elotuzumab	ELOQUENT-2	<65	NA	0,75	(0,55-1,02)	0,70	(0,52-0,96)	Lonial et al; Dimopolous et al
Anti-CS1	MM	Elotuzumab	ELOQUENT-2	65+	NA	0,65	(0,50-0,85)	0,91	(0,72-1,16)	Lonial et al; Dimopolous et al
Anti-CS1	MM	Elotuzumab	ELOQUENT-2	<75	NA	NA	NA	0,86	(0,70-1,06)	Lonial et al; Dimopolous et al
Anti-CS1	MM	Elotuzumab	ELOQUENT-2	75+	NA	NA	NA	0,69	(0,46-1,03)	Lonial et al; Dimopolous et al
Anti-CD38	MM	Isatuximab	ICARIA	<65	NA	0,66	(0,40-1,07)	0,97	(0,61-1,53)	Richardson et al (incl. long-term FU)
Anti-CD38	MM	Isatuximab	ICARIA	65-74	NA	0,64	(0,39-1,06)	0,7	(0,45-1,10)	Richardson et al (incl. long-term FU)
Anti-CD38	MM	Isatuximab	ICARIA	75+	NA	0,48	(0,24-0,95)	0,51	(0,28-0,92)	Richardson et al (incl. long-term FU)
Anti-CD38	MM	Isatuximab	ICARIA	ITT	67	0,60	(0,44-0,81)	0,76	(0,57-1,01)	Richardson et al (incl. long-term FU)
Anti-CD38	MM	Daratumumab	MAIA	ITT	63	0,56	(0,43-0,73)	0,68	(0,53-0,86)	Facon et al
Anti-CD38	MM	Daratumumab	POLLUX	ITT	65	0,37	(0,27-0,52)	0,64	(0,40-1,01)	Dimopolous et al
PI	MM	Bortezomib	SWOGS077	ITT	63	0,71	(0,56-0,91)	0,71	(0,52-0,96)	Durie et al
PI	MM	Bortezomib	SWOGS077	<65	NA	NA	NA	0,64	(0,42-0,97)	Durie et al
PI	MM	Bortezomib	SWOGS077	65+	NA	NA	NA	0,77	(0,52-1,14)	Durie et al

IMiD, immunomodulatory agent; ITT, intent-to-treat; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival.

Appendix 2

Regulatory History – Key Interactions between Applicant and FDA or EMA Related to OCEAN Results and Pepaxto Benefit/Risk

Date	Type	Content/Topic
26 Feb 2021	FDA approval	Initial US accelerated approval of Pepaxto in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody based on pivotal HORIZON study (OP-106). The Phase 3 confirmatory study to fulfill accelerated approval requirements, OCEAN (OP-103), was fully enrolled at time of approval.
15 April 2021	Applicant to EMA	Application for conditional marketing authorization in Europe submitted to EMA, based on pivotal HORIZON study.
24 May 2021	FDA meeting	Discussed requirements for future submission of OCEAN study results and label updates. At the time of the meeting, Oncopeptides did not present the topline study results.
25 May 2021	Applicant to FDA	Press release on OCEAN results provided to FDA.
9 June 2021	Applicant to FDA	OCEAN top line data provided to FDA.
17 June 2021	FDA meeting	During the meeting, FDA expressed significant concerns on OCEAN top line results especially OS HR. Applicant informed FDA on planned blinded IRC review of complete PFS data from 29 patients (of the 495 total patients) who were identified as having missing information.
18 June 2021	FDA email	FDA requested timeline on new press release on OCEAN results with OS data.
23 June 2021	Applicant to FDA	Applicant provided written commentary on OCEAN results including • Assessment of safety data that failed to identify a safety signal contributing to the OS difference between treatment arms • Discussion of imbalances between treatment arm that may have contributed to OS • Discussion of ongoing analyses including observed variability in PFS HR and OS HR across pre-specified subgroups that appears to be primarily driven by both prior transplant and age. Transplant status seems to be an important prognostic factor for Pepaxto, whereas both transplant and age seem to be important prognostic factors for pomalidomide.

Date	Type	Content/Topic
6 July 2021	Applicant to FDA	Written notification provided to FDA that there appears to be a heterogeneous response in patients who received Pepaxto in OCEAN, which is dependent on whether they had previously received an autologous stem cell transplant (ASCT). Alerted the FDA about plans to inform investigators. Oncopeptides requested an urgent meeting with FDA to discuss this finding. Oncopeptides also provided updated OCEAN efficacy data that included blinded IRC review of PFS data from 29 patients for whom there was missing information. This reassessment resulted in the study result changing from non-inferiority to superiority of Pepaxto over pomalidomide based on the primary PFS endpoint. Oncopeptides provided new press release to FDA with updated PFS results and included OS results.
7 July 2021	FDA meeting	FDA informs Applicant that they are imposing a partial clinical hold (i.e., stop of enrollment of new patients in all clinical trials with Pepaxto). This is due to their safety concern related to potential detriment in OS compared to the pomalidomide arm, the rates of Grade 3 or 4 adverse events and serious adverse event of thrombocytopenia, adverse events of hemorrhage and dose modifications due to adverse events.
8 July 2021	Applicant to EMA	Oncopeptides provided EMA with information about OCEAN results and FDA's partial clinical hold.
20 July 2021	FDA meeting	FDA cited continued concerns with patient safety. The FDA proposed labelling changes and cited that further commercialization restrictions were likely. FDA recommended to the Applicant to pursue withdrawal of the product.
20 July 2021	FDA letter	FDA sent to applicant a Safety labeling change notification requesting changes to the Indication, the Warnings and Precautions, and Dosage and Administration.

Date	Type	Content/Topic
26 July 2021	Applicant email to the Acting Division Director at FDA	Oncopeptides sent written commentary on OCEAN results including discussions on • Imbalances in treatment arms impacting the OS HR result for the overall population. • Imbalances in subsequent treatments. • Overall population safety results showing comparable deaths and SAEs between treatment arms. • OS heterogeneity resulting in highly variable benefit-risk profiles for Pepaxto and pomalidomide across key prespecified subgroups, including age and prior ASCT. These analyses supported the conclusion that the OS in pomalidomide treated patients changes with age, showing significantly better survival in younger patients and poor survival in older patients, thereby influencing the OS HR. • An initial literature search identified some published reports of age-related heterogeneity with pomalidomide or other IMiDs. Of interest, most publications omit discussion of subgroups including age. • Multivariable analysis in stepwise regression models showing prior ASCT to be a negative prognostic factor for Pepaxto efficacy. Oncopeptides requested collaborative review with the FDA for analyses of available data. The applicant also requested that the FDA not take actions that may have a detrimental effect on patients currently benefiting from treatment with Pepaxto.
28 July 2021	FDA webpage	FDA alerts patients and health care professionals about clinical trial results showing an increased risk of death associated with Pepaxto.
30 July 2021	FDA email	FDA alerted Oncopeptides that an ODAC meeting would occur on 28 October 2021 to discuss the OCEAN OS results.
19 Aug 2021	Applicant to FDA	The applicant proposed modified labeling changes in response to FDA's safety labeling change notification dated 20 July 2021. This included adding information regarding worse OS in OCEAN (as requested by FDA), restricting use to only patients who have not received an ASCT within 5 years, lowering the dose in patient weighing ≤ 60 kg, and refined dose modification instructions for managing thrombocytopenia and neutropenia based on PK/PD analyses.
19 Aug 2021	FDA email	FDA requested information regarding the analysis of OS HR supporting pomalidomide heterogeneity by age, including data set used, variables included and the R code.
27 Aug 2021	Applicant to FDA	Response sent to FDA providing requested data from the 19 Aug 2021 information request.
17 Sep 2021	EMA procedure event	Day 120 list of questions on conditional marketing authorization application in Europe received from the CHMP, including a request for discussion of available data of the Phase 3 OCEAN study and any implications for the B/R in the currently proposed target population.
30 Sep 2021	Applicant to FDA	Applicant submitted response to FDA regarding clinical hold, suggesting restricting trial eligibility criteria to only enroll patients who have not received an ASCT within 5 years.

Date	Type	Content/Topic
7 Oct 2021	FDA briefing document for ODAC meeting	Oncopeptides received briefing document from the FDA for ODAC meeting.
7 Oct 2021	EMA meeting	Clarification meeting with CHMP rapporteur and co-rapporteur regarding Day 120 list of questions. Agreement that OCEAN clinical study report should be provided to allow the CHMP to perform an independent data analysis and assessment.
22 Oct 2021	Applicant to FDA	Oncopeptides acquiesces to FDA pressure and actions to influence clinical interpretation by other health authorities, including the EMA, requesting withdrawal of NDA 214383 and waiving the opportunity for a hearing. This action results in cancellation of scheduled 28 October 2021 ODAC meeting.
29 Oct 2021	FDA email	FDA notified Applicant of continued partial clinical hold since adequate justification for continued study of Pepaxto in clinical trials had not been provided.
16 Dec 2021	Applicant to EMA	Oncopeptides submitted response to Day 120 list of questions to EMA, the results of a multivariable analysis to explore the relative importance of the different subgroups in OCEAN, an examination of the subgroups of patients in study OCEAN who had no prior ASCT or had progressed ≥36 months after ASCT, and an updated integrated summary of safety. Applicant revised the application from conditional marketing application to full marketing authorization application.
11 Jan 2022	EMA meeting	Applicant informed EMA about the analysis showing interaction between pomalidomide and age and that the Day 120 response would be updated to include this information.
13 Jan 2022	Applicant to FDA	Oncopeptides sent written notification to the FDA rescinding the NDA withdrawal letter of 22 October 2021.
20 Jan 2022	EMA access-to-documents	Oncopeptides is informed that the final OS analysis in pomalidomide study MM007, with submission deadline Q3 2021, is not available since the submission deadline has been extended to Q4 2022.
21 Jan 2022	FDA meeting	Oncopeptides discussed that ongoing heterogeneity investigations and lack of survival detriment were reason for rescinding the NDA withdrawal with the FDA. The applicant clarified that Pepaxto will not be reintroduced to the market pending completion of investigations. FDA expressed continued significant concerns with the OCEAN OS results. [IF TRUE] Oncopeptides suggested that the FDA exam pomalidomide data to identify a signal for heterogeneity by age.
7 Feb 2022	EMA access-to-documents	Oncopeptides received subgroup analysis in pomalidomide study MM007.
28 Feb 2022	Applicant to FDA	Oncopeptides provided a written summary of the report to be submitted on the heterogeneity of OCEAN study data.

Date	Type	Content/Topic
1 Mar 2022	FDA email	Oncopeptides received information request from FDA requesting the data and/or analyses of results from several IMiD trials and a detailed summary of the Applicant's position based on the interpretation of the data/analyses
10 Mar 2022	Applicant to FDA	Oncopeptides provided a written summary of multi-study analysis showing interaction between pomalidomide and age. The accessible data sources spanned clinical studies over more than a decade. Studies as early as 2009 indicated potential heterogeneity by age for pomalidomide. This included registration data used to gain US approval.
13 and 16 May 2022	Swedish MPA public access to information	Oncopeptides received OS analysis including long-term survival follow-up in lenalidomide studies MM009 and MM010. Subgroup analysis of OS was not reported in the clinical study reports.
18 Mar 2022	FDA meeting	FDA informed Applicant that they had reviewed the information and analyses submitted and continue to have significant concerns with survival data and safety profile of Pepaxto. FDA did not mention the potential OS heterogeneity of pomalidomide, or considerations that the reporting of a safety signal may have been overlooked. FDA also stated that the Pepaxto NDA should be withdrawn expeditiously, and that FDA will pursue a Notice of Official Hearing if the Applicant does not voluntarily withdraw the NDA.
23 Mar 2022	EMA to Applicant	CHMP informed Oncopeptides of intent to hold Scientific Advisory Group – Oncology (SAG-O) meeting to discuss Pepaxto benefit-risk, interpretation of OS HR and feedback on OS heterogeneity in OCEAN.
25 Mar 2022	EMA procedure event	Day 180 final list of outstanding issues on marketing authorization application in Europe received from CHMP.
13 April 2022	Applicant to EMA	Submission of written responses to CHMP on Day 180 list of outstanding issues, including an updated summary of clinical safety.
11 May 2022	EMA SAG-O meeting	CHMP consultation with SAG-O regarding the marketing authorization application in Europe. Presentation by Applicant. Meeting was observed by FDA team.
16 May 2022	FDA email	FDA sent information request on data to support the information on pomalidomide submitted on 10 March 2022 and updated OS analyses in OCEAN.
19 May 2022	Applicant to FDA	Oncopeptides provided the first part of the requested data in response to 16 May information request
2 June 2022	Applicant to FDA	Response to 16 May information request finalized and submitted.

Date	Type	Content/Topic
14 June 2022	FDA meeting	FDA informed Oncopeptides that they have tentatively scheduled an ODAC meeting for 23 September 2022 to discuss Pepaxto benefit-risk Notification had no mention of pomalidomide heterogeneity findings or intention to hold inquiry regarding the lack of safety notification although the data supporting pomalidomide heterogeneity have been available for >10 year and were used for registrations in the US and globally.
23 June 2022	EMA procedure event	CHMP issued a positive opinion for Pepaxti (melphalan flufenamide) in combination with dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least three prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy. For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years from transplantation CHMP confirmed that the FDA observed CHMP discussion and decision.

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Appendix 3a. Summary of Pepaxti CHMP Assessment Report dated 23 June 2022

The CHMP Assessment Report for Pepaxti (Pepaxto in US) is a formal document that summarizes the comprehensive review by the Committee for Medicinal Products for Human Use (CHMP) of the Pepaxti marketing authorisation application (MAA) to the European Medicines Agency (EMA) in order to obtain authorization in the EU. The complete verbatim report is attached (Appendix 3b).

The table below contain key topics of interest within the 158-page document that relate to the ODAC discussion. The CHMP Rapporteur informed Oncopeptides that the FDA was actively informed during the procedure and that the FDA attended the May 11, 2022 meeting with the Scientific Advisory Group – Oncology (SAG-O) as well as final CHMP discussion and vote at the June 2022 meeting.

Section (page)	Relevance	Verbatim Paragraph from CHMP Assessment Report
2.6.6. Discussion on Clinical Efficacy (p.113)	Conclusions from the May 11, 2022 SAG-O, composed of independent EU clinical experts that was convened to discuss Pepaxto	Upon consultation, the SAG-O concluded that melflufen + low dose dex is associated with clinically relevant efficacy, with the exception of the subgroup of patients with relapse within 36 months following high-dose melphalan and autologous SCT. In addition, the SAG-O considered that although the exact effect size cannot be determined due to differences in disease and treatment characteristics, the results of study OP-103 obtained in patients of whom most had fewer lines of treatment than the OP-106 patients, are relevant for the target population in study OP-106 (see expert consultation below).
2.6.6. Discussion on Clinical Efficacy (p.113)	CHMP efficacy conclusion following SAG-O consultation	Overall, based on the available data and upon consultation of the SAG-O, it is considered that melflufen + low dose dex has been shown to be efficacious and from an efficacy perspective, the data can be considered comprehensive and support full approval. However, given the major concern on the benefit of melflufen + dex in patients with prior ASCT and TTP <36 months in study OP-103 and the fact that a risk for shorter survival cannot be excluded for these patients within the 3L+ TCR population in study OP-106 due to the absence of a control group, this patient group should be excluded from the applied indication.

Section (page)	Relevance	Verbatim Paragraph from CHMP Assessment Report
2.6.7. Conclusions on the clinical efficacy (p.115)	Overall conclusions regarding Pepaxto (melflufen) efficacy supporting marketing authorization.	Clinical data in the target population (Triple-class refractory patients with ≥3 prior treatment lines, excluding patients with recent prior ASCT) is derived from the single arm trial OP-106 + supportive data in an earlier line from a randomized controlled trial OP-103. The pivotal Study OP-106 updated ORR and DOR are considered clinically relevant for the target population. These results are confirmed in OP-103. Support from OP-103 is also derived for time-dependent endpoint PFS. OS data indicate a potential detriment with a HR of 1.14 in the overall study population, which seems mostly driven by a lack of efficacy/reduced efficacy in patients with progression within 3 years after ASCT. In line with the SAG-O conclusion, these patients should therefore be excluded from treatment by restricting the indication as follows: For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years.
2.6.10. Conclusions on the clinical safety (p.145)	Overall conclusions regarding Pepaxto (melflufen) safety supporting full marketing authorization	The safety profile of melflufen appears non-negligible, although generally manageable with adequate monitoring and dose adjustment or discontinuation. The most important safety concerns are the haematological toxicities and the possible serious clinical consequences of infections and bleeds. These are understood to be related to the mechanism of action and well known for the active substance melphalan. Relevant safety information and recommendations are presented in the SmPC. Also, the safety profile has been considered sufficiently characterized based on study OP-106 encompassing the target population and supported by comparative safety data from OP-103 in an earlier setting of RRMM. Safety data are therefore considered comprehensive potentially enabling a full MA. Additional safety data are expected on patients with severe renal impairment (see RMP).
4. Recommend-ations (p. 157)	Overall recommendation for marketing authorization in the EU	Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Pepaxti is favourable in the following indication: Pepaxti is indicated, in combination with dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least three prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy. For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years from transplantation.

23 June 2022
EMA/634000/2022
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Pepaxti

International non-proprietary name: melphalan flufenamide

Procedure No. EMEA/H/C/005681/0000

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AML	Acute myeloid leukaemia
AUC	Area under the curve
AUCinf	Area under the curve extrapolated to infinity
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
CL	Clearance
CBR	Clinical benefit rate
CMA	Conditional Marketing Authorization
Cmax	Maximum concentration
CR	Complete response
CrCl	Creatinine clearance
DOCB	Duration of clinical benefit
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EMD	Extramedullary disease
HRQoL	Health-related quality of life
IC50	Half maximal inhibitory concentration
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
IRC	Independent Review Committee
ISS	Integrated Summary of Safety or International Staging System
IV	Intravenous
M-protein	Monoclonal protein spike
MAA	Marketing Authorisation Application
mAb	Monoclonal antibody
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MR	Minimal response
NCCN	National Comprehensive Cancer Network
NE	Not estimable
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PI	Proteasome inhibitor
PK	Pharmacokinetics
PO	Oral (per os)
PR	Partial response
PT	Preferred term
QoL	Quality of life
RRMM	Relapsed-refractory multiple myeloma
SAE	Serious adverse event
sCR	Stringent complete response
SCS	Summary of Clinical safety

SD	Stable disease
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA query
SOC	System organ class
SPM	Second primary malignancy
TCR	Triple-class refractory
TEAE	Treatment-emergent adverse event
TFI	Treatment-free interval
TSP	Targeted Safety Population
TTP	Time to progression
TTR	Time to response
URC	Uniform Response Criteria
VGPR	Very good partial response
WBC	White blood cell
WRO	Written Response Only

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Oncopeptides AB submitted on 15 April 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Pepaxti, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 June 2020.

Pepaxti, was designated as an orphan medicinal product EMA/OD/293/14 on 19 March 2015 in the following condition: Treatment of plasma cell myeloma.

The applicant applied for the following indication:

Pepaxti is indicated, in combination with dexamethasone, for the treatment of adult patients with multiple myeloma whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody.

1.2. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/0001/2015 on the granting of a class waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request(s) for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation.

1.5.2. New active Substance status

The applicant requested the active substance melphalan flufenamide contained in the above medicinal product to be considered as a new active substance, as the applicant claimed that it was not a constituent of a medicinal product previously authorised within the European Union.

During the procedure, the applicant withdrew the new active substance claim.

1.6. Protocol assistance

The applicant did not seek Protocol assistance from the CHMP.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paula Boudewina van Hennik Co-Rapporteur: Elita Poplavska

The application was received by the EMA on	15 April 2021
The procedure started on	20 May 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	5 August 2021
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	23 August 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	23 August 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	16 September 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 December 2021
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	2 March 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 March 2022

The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	24 March 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	13 April 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	3 May 2022
SAG-Oncology experts were convened to address questions raised by the CHMP on The CHMP considered the views of the SAG-Oncology as presented in the minutes of this meeting.	11 May 2022
The CHMP agreed on a 2nd list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	19 May 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 May 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	8 June 2022
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Pepaxti on	23 June 2022
The CHMP adopted a report on similarity of Pepaxtiwith Blenrep, Darzalex, Farydak, Imnovid, Kyprolis, Ninlaro, Abecma and Carvykti on	23 June 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Multiple myeloma (MM) is an incurable malignant plasma cell disorder. It is characterised by clonal proliferation of plasma cells in the bone marrow and the production of excessive amounts of a monoclonal immunoglobulin protein (Ig; usually of the IgG or IgA type or free light chain [paraprotein, monoclonal protein spike (M-protein), or M-component]). MM predominantly affects the older patient, with a median age at onset of 72 years in Europe (Palumbo and Anderson 2011).

The most common criteria used in diagnosis of symptomatic MM are the presence of neoplastic plasma cells comprising greater than 10% of BM cells or presence of a plasmacytoma; paraprotein (M protein) in the serum and/or urine; and evidence of related organ or tissue impairment due to plasma cell disorder.

According to the International Myeloma Working Group (IMWG) criteria (Rajkumar et al. 2011), relapsed-refractory multiple myeloma (RRMM) is defined as disease that is nonresponsive while on salvage therapy, or progresses within 60 days of last therapy in patients who have achieved minimal response (MR) or better at some point previously, before then progressing in their disease course.

2.1.2. Epidemiology

MM is the second most common haematologic malignancy, and accounts for approximately 1-2% of all new cancer cases, with a global incidence rate of 1.7 per 100,000 and an age-standardised incidence rate of 2.1-3.4 per 100,000 in France, Germany, Italy, Spain and the UK. An estimated 35,842 patients were diagnosed in the EU27 during 2020, with an estimated 23,275 deaths due to the disease (ECIS 2020). Multiple myeloma is more common in men than women (ECIS 2020) and in the US, twice as common in African Americans than in other races and ethnicities (SEER 2019).

2.1.3. Aetiology and pathogenesis

The initiating event driving malignant development is either the acquisition of hyperdiploidy or a translocation involving the immunoglobulin heavy chain gene locus. Such clonal events can occur in almost all cells, and are present in the precursor conditions monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

Sometimes patients are asymptomatic and identified with routine blood testing, although most patients with MM experience symptoms leading to significant decrement to quality of life, including bone pain, bone fractures, fatigue, anaemia, infections, hypercalcemia, hyperviscosity of the blood, and renal insufficiency.

Patients with MM may have symptom-free periods, but the disease always relapses, and patients may become refractory to all available treatment options due to mutations and/or clonal evolution of the tumour cells.

Clinical outcomes for patients with multiple myeloma depend on several factors, including intrinsic tumour cell characteristics (cytogenetic abnormalities, gene expression profile, extramedullary growth, lactate dehydrogenase levels), tumour burden (β2- microglobulin [B2M], low platelet count), and patient features (age, comorbidities, frailty). Outcomes also depend on depth of response to therapy. Models combining patient and disease characteristics have been created, because individual prognostic factors do not capture the full heterogeneity in outcome. The original multiple myeloma International Staging System, based on serum albumin and B2M concentrations, reflects tumour burden and patient condition. This staging system has been updated as the Revised International Staging System, which includes information on the presence of high-risk genetic lesions—t(4;14), t(14;16), or del(17p), either alone or in combination—or increased lactate dehydrogenase concentration.

While the advent of novel treatment regimens has translated into improvements in outcomes over the past 15 years (Sonneveld 2017), the disease is ultimately fatal, with a 5-year survival around 50% (Seer 2019). Patients who develop disease refractory to immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and CD38- targeting monoclonal antibodies (mAbs), i.e., are triple-class refractory (TCR), have an overall survival of only a few months. Although patients with relapsed disease can achieve responses to subsequent anti-myeloma regimens, the duration of response typically decreases with successive relapses until resistant disease develops.

2.1.5. Management

The management of patients with relapsed/refractory disease represents a clinical challenge, as these patients suffer from continuing symptoms, complications of the disease (including renal failure, blood cytopenia or recurrent infections) and decreased quality of life. These patients typically receive salvage therapy until the next relapse, progression or the development of intolerable toxicity and then go onto the next salvage option. Current treatment strategies in pre-treated RRMM patients focus on controlling disease progression and prolonging survival. These strategies include glucocorticoids (dexamethasone, prednisolone, methylprednisolone), chemotherapy, PIs (e.g. bortezomib, carfilzomib and ixazomib), IMiDs (e.g. thalidomide, lenalidomide and pomalidomide), mAbs (e.g. daratumumab, isatuximab and elotuzumab) and the histone deacetylase inhibitor panobinostat. However, none of the newly approved medicinal products (mainly combinations) has provided a cure. Ultimately patients relapse and treatment options are exhausted.

With the approval of daratumumab and its wide use in combinations in earlier lines of MM treatment, a new population of patients is created who have become refractory to all available agents (including daratumumab). Triple class refractory (TCR) patients have generally been exposed to all 5 drugs that have demonstrated single-agent effect (with or without glucocorticoids), including bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab. Most of these patients have already received alkylating agent therapy, other anti-MM drugs, as well as multiple courses of glucocorticoids. Frequently, they also have numerous comorbidities and consequently receive multiple concomitant medications.

Recently, 3 new classes of products have received a conditional approval for use in patients with similar characteristics as the TCR subpopulation of pivotal clinical Study OP-106. Blenrep (belantamab mafodotin) is a BCMA-targeted mAb approved for the treatment of MM in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one PI, one IMiD, and an anti-CD38 mAb, and who

have demonstrated disease progression on the last therapy. It induced an overall response in approximately a third of the pivotal study population. Nexpovio (selinexor) is a Selective Inhibitor of Nuclear Export (SINE) compound, recently approved in combination with dexamethasone, for the treatment of MM in adult patients who have received at least four prior therapies and whose disease is refractory to at least two PIs, two IMiDs and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy. Selinexor has shown to be active in about a quarter of the pivotal study population. Abecma (idecabtagene vicleucel) is an anti-BCMA CAR-T cell therapy for the treatment of RRMM patients who have received at least three prior therapies, including an IMiD, a PI and an anti-CD38 mAb and have demonstrated disease progression on the last therapy. It induced an ORR in 67.1% of enrolled patients with a CR rate of 28.6% and median duration of response of 11 months.

Patients who have been heavily pretreated might also benefit from retreatment, which can be considered after long-lasting remission, because previously used drugs can be given in different combinations. Novel agents can also be combined with traditional cytotoxic agents, such as cyclophosphamide, anthracyclines, or bendamustine. Alternatively, patients with advanced disease can be enrolled in clinical studies evaluating new agents with novel mechanisms of action.

2.2. About the product

Melphalan flufenamide (melflufen) is a lipophilic peptide conjugated alkylating drug designed for targeted delivery of alkylating moieties to tumour cells. The drug is composed of a di-peptide and an alkylating moiety of the bischloroethylamine group. It shares the bis (2-chloroethyl)amino alkylating group with the marketed compounds cyclophosphamide, bendamustine, chloroambucil and melphalan. Although melphalan is one of the metabolites of melflufen, melflufen has the intrinsic capacity to act as an alkylator without any activating step. The lipophilic characteristics of melflufen allow for a faster cellular uptake whereas the peptide hydrolysis mediated by aminopeptidases (like aminopeptidase N (APN)), allows for a potentiated effect in APN-rich environments, resulting in accumulation of alkylating moieties in cancer cells. According to the applicant, this is expected to result in improved efficacy without an increase in toxicity compared to melphalan. Similar to other nitrogen mustard drugs, cross-linking of DNA is involved in the anti-tumour activity of melphalan flufenamide. In cellular assays, melphalan flufenamide inhibited proliferation and induced apoptosis of haematopoietic and solid tumour cells. Retained cytotoxic activity was demonstrated in multiple myeloma cells with absent or impaired p53 functionality. Melphalan flufenamide showed synergistic cytotoxicity with dexamethasone in melphalan resistant and non-resistant multiple myeloma cell lines.

2.3. Type of Application and aspects on development

At the time of submission, the applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive (according to the Applicant).
- It is likely that the applicant will be able to provide comprehensive data. The applicant states its intention to provide the following data as specific obligation:
    - Results from study OP-103 (OCEAN), an ongoing randomized, controlled trial, comparing melflufen and dexamethasone to pomalidomide and dexamethasone in relapsed-refractory MM. Although the patients can be enrolled to this study in an earlier stage of disease (2-4

prior lines of treatment and refractory to both the last line and to lenalidomide), there will be a substantial number of patients who are triple class refractory patients. This study will provide controlled efficacy and safety data in the indicated patient population.

- Unmet medical need will be addressed, as there are few available therapies for these patients and survival at this stage of the disease is limited. Melflufen offers a new treatment option with an alternative mechanism of action which shows efficacy and a different, manageable safety profile.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. Melflufen is intended for a subset of MM patients with a dismal prognosis and limited approved treatment options. Based on the positive benefit: risk demonstrated in study OP-106, immediate availability of melflufen would provide these patients with a novel therapeutic option with meaningful response durability and a manageable safety profile. Additional data are being generated to confirm safety and efficacy of melflufen in a randomised phase 3 study (OP-103).

During the procedure, in response to the List of Questions, the Applicant presented the full clinical study report of confirmatory Study OP-103, indicating that no additional results were planned to be submitted as confirmatory data. Hence, the Applicant applied for a Full Marketing Authorisation not subject to any specific obligations.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as powder for concentrate for solution for infusion containing 20 mg/vial of melphalan flufenamide (as hydrochloride) as active substance.

Other ingredients are sucrose. The product is available in 50 mL Type 1 glass vial sealed with chlorobutyl rubber stopper and aluminium overseal with a plastic removable cap containing 20 mg powder.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of melphalan flufenamide hydrochloride is 4-[Bis-(2-chloroethyl)amino]-L-phenylalanine-4-fluoro-L-phenylalanine ethyl ester hydrochloride corresponding to the molecular formula $C_{24}H_{31}Cl_3FN_3O_3$. It has a relative molecular mass of 534.9 g/mol and the following structure:

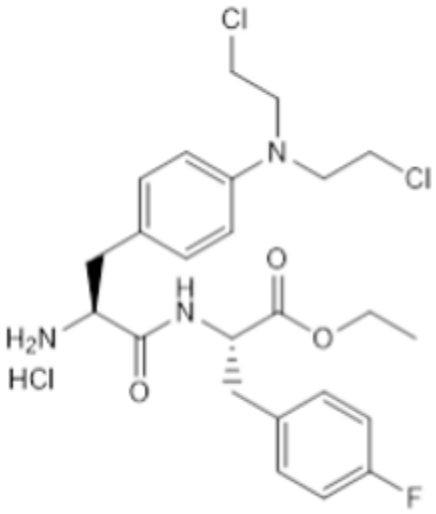


Figure 1 active substance structure

The active substance is a non hygroscopic, white to slightly yellowish powder. It is poorly soluble and susceptible to hydrolysis in water-based solutions. It is soluble in different solvents (e.g. ethanol, methanol).

The chemical structure of Melphalan flufenamide (also referred to as Melflufen) was elucidated by a combination of nuclear magnetic resonance spectroscopy (NMR), liquid chromatography-mass spectrometry (LC-MS and LC-MS/MS) and fourier transform infrared spectroscopy (FTIR).

The solid state properties of the active substance were measured by 2D-NMR studies for assignment of the 1H- and 13C-NMR spectra were performed as well as a polymorph screening study and determination of the absolute stereochemistry of melflufen hydrochloride by single crystal X-ray crystallographic methods. The active substance is highly crystalline and it consists of one crystalline modification.

The active substance includes two stereochemical centers in the S,S configuration. Stereoisomerism has been observed and is routinely control in the specifications.

2.4.2.2. Manufacture, characterisation and process controls

The active substance has been manufactured by one manufacturing site: Magle Chemoswed AB (Magle Chemoswed).

Melphalan flufenamide is synthesized in four main steps using well defined starting materials with acceptable specifications. A schematic flow chart of the active substance synthesis and a description of the manufacturing process including information on in-process controls for each step is provided.

The synthetic route for melflufen hydrochloride consists of four linear chemical steps, which are referred to as Reaction Step 1, 2, 3 and 4, respectively: amide coupling, catalytic hydrogenation, reductive bis-chloroethyl alkylation and Boc-deprotection/salt formation. No class 1 solvents are used. Pd is used as catalyst.

The reprocessing method is clearly described and the criteria for deciding when re-processing is performed is provided. Typical batch size is given with 3.4 kg.

The proposed starting materials are p-fluoro-L-phenylalanine ethyl ester hydrochloride and Boc-p-nitro-L-phenylalanine. Chloroacetic acid and sodium chloroacetate also contribute to the structure of melflufen hydrochloride. They are used to form a simple moiety (bis-ethyl chloride amine) of the structure of the intermediate Boc-melflufen and are not considered regulatory starting materials.

During the procedure a major objection was raised on the choice of p-fluoro-L-phenylalanine ethyl ester hydrochloride and Boc-p-nitro-L-phenylalanine as starting materials. The applicant provided additional scientific justification and data to support their choice and updated the active substance control strategy accordingly.

The synthetic routes from both starting materials and from the used starting material manufacturers are provided, including information on used solvents, reagents and potential catalysts. According to the information given no class 1 solvents and class 1 catalysts are used in the manufacture of both starting materials. The active substance includes two stereochemical centres in the S,S configuration which are derived from the two proposed starting materials. Batch data of the starting materials from all used SM manufacturers are given and comply with the proposed SM specifications. ICH Q7, Q11 and Q11 Q&A document has been followed by the applicant. Based on this the MO was satisfactorily resolved.

Materials used in the manufacture of the active substance (solvents, reagents, catalysts and auxiliary material) are listed including information where each material is used, which parameters are tested and which in-house acceptance criteria are set.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products (Melflufen aminodipeptide and melflufen nitrodipeptide), starting materials and reagents have been presented.

The manufacturing process of melflufen hydrochloride is a standard manufacturing process and does not involve aseptic processing or sterilization. The analysis results for the batches obtained in the process validation are presented and comply with the proposed acceptance criteria.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. An overview of the manufacturing process development, including information on used manufacturers, starting materials, intermediate formed in the penultimate reaction step and reagents used in the final reaction step was provided. Batch analysis data for active substance batches from the different synthetic routes are given. The batch data comply with the specification in place at time at the time of analysis. Purging of potential impurities is discussed. The used methods are described and suitable for their intended use. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process. Process parameter criticality has been assigned based on Design of Experiments (DoEs) which were carried out for process steps 1 - 4. Proven Acceptable Ranges (PARs) have been investigated as a part of the process understanding and development but are not included in the description of the manufacturing process in 3.2.S.2.2. Normal Operating Range (NOR) are stated and are considered acceptable. No design space is claimed.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Potential process impurities and drug-related impurities (this includes also reagents, solvents and catalysts) are discussed and summarized including information on control strategy and acceptance criteria. No discussion on potential genotoxic impurities is given. According to the given information from the applicant in the non-clinical overview melflufen is indicated for anticancer treatment in patients with few treatment options and the

molecule has identical alkylating functions as cyclophosphamide, bendamustine, chloroambucil and melphalan, compounds with documented carcinogenic and teratogenic activity. ICH M7 does not apply to active substances and finished products intended for advanced cancer indications as defined in the scope of ICH S9 (Ref. 4). This was considered acceptable.

The active substance is packaged in LDPE bags which complies with the EC directive 2002/72/EC and EC 10/2011 as amended and are commonly used for active substance packaging. The specification is appropriate and the suitability of the LDPE bags with respect to stability and compatibility with the active substance is confirmed by the results obtained from stability studies.

2.4.2.3. Specification

The active substance specification includes tests for appearance (for powder and solution in 1% methanol, visual), identification (by FTIR and HPLC by RT), assay (HPLC), total purity (HPLC), related substances (HPLC), chiral purity (HPLC), residual solvents (GC), water content (Ph. Eur.), sulphated ash (Ph. Eur.), chloride content (titration), microbial limits (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The performed tests and acceptance criteria are discussed and justified. Tests for identification, regioisomer, chiral purity, residual solvents, sulphated ash, chloride content and bacterial endotoxins are performed at release of active substance only which is accepted as these tests are not considered stability indicating.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data (n=5, full scale) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from three process validation batches stored at stored at long-term (5 °C) for up 36 months and accelerated storage conditions (25 °C) for up to 6 months according to the corresponding ICH guideline were provided. Furthermore, additional supportive stability data were submitted.

The following parameters were tested: appearance of powder, appearance of solution, assay, total purity, related substances, water content, microbial limits. The analytical methods used were the same as for release and were stability indicating.

No significant changes in any of the test results (stability indicating parameters) were observed in the long-term testing and accelerated testing.

Forced stress stability studies (including heat, artificial light, acidic and alkaline environment) were performed. The active substance is unstable under acidic and basic conditions. Results for forced degradation study and mass balance were provided. Photo-stability testing was performed according to ICH Q1B. Significant degradation is observed after exposure to light equivalent to 2 times the exposure level recommended in ICH Q1B.

The analytical procedures used are the same as the ones used for routine control and are stability indicating. Only stability indicating parameters have been tested, which is acceptable as outlined above.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months, when stored at 5 ± 3 °C in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is a powder for concentrate for solution for infusion. Lyophilised white to off-white powder. The qualitative and quantitative composition are outlined in Table 1.

Table 1 Composition of finished product

Name of Ingredient	Quality Standard	Function	Quantity (mg/vial)
Melflufen hydrochloride	In-house	Active ingredient	21.48 [a]
Sucrose	Ph. Eur.	Bulking agent	1,000
tert-Butanol	In-house	Co-solvent	N/A[b]
Water for Injections	Ph. Eur.	Solvent	N/A[b]
Nitrogen	Ph. Eur.	Inert gas	N/A[c]
Total			1,021.48

[a] Corresponding to 20 mg melflufen free base
[b] Removed during the lyophilisation process
[c] The exact amount of nitrogen per vial cannot be determined as the vials are backfilled with nitrogen at the end of the lyo process.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. In addition sucrose complies an in-house acceptance criterion for bacterial endotoxins NMT 0.07 EU/mg, thus with a stricter limit than Ph. Eur., which is acceptable. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report. Tert-butanol is used as a co-solvent which is removed during the lyophilization process (also WFI is removed). Tert-butanol is controlled according to in-house standards which is acceptable.

Melflufen is reconstituted with 40 ml 5% glucose solution and then further diluted with 0.9% sodium chloride – the amount of sodium chloride used to dilute o final volume is depending on the dose (40/30/20/15 mg active substance, resulting in final concentrations of 0.16/0.13/0.10/0.08 mg/ml respectively). Detailed instructions for reconstitution and dilution are presented in the SmPC section 6.6. The standard dose is 40 mg; the total amount of the reconstituted solution from two vials.

Formulation development is adequately described. Early development was based on a concentrate for solution for infusion (DMA formulation). Subsequently the development was aimed towards a new formulation replacing the DMA formulation with improved long-term stability, i.e. a powder for concentrate for solution for infusion (lyophilized formulation). Initially, ethanol/water mixtures were used, but after various tries, the final excipients have been found leading to a bulk solution for lyophilisation which is stable and a lyophilisate cake which is easy to reconstitute. Clinical formulations are described. Sugar concentration in the pharmaceutical form has been studied during the development of the production process. No overage is used. The proposed target fill weight is 18.8 g/vial.

Detailed information on manufacturing development history is presented. The dosage form is manufactured according to non-standard manufacturing processes according to Annex II of EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr.1 as the respective manufacturing processes include aseptic processing. Manufacturing of the powder additionally includes a lyophilisation step. The applicant states that compounding and filling procedures were established at an early stage, with only minor improvements implemented during the continued development. Separate data on compounding and filling process development are provided.

The selected sterilisation method (0.22 µm filtration) is in general justified. Further provided justification regarding thermal stability was provided. Selection of the container closure system is sufficiently justified. Primary packaging materials comply with respective Ph. Eur. requirements (i.e. Ph. Eur. 3.2.1 and Ph. Eur. 3.2.9).

The product is packaged in type 1 clear glass vials (50 ml vials, 20 mm) which comply with respective Ph. Eur. monograph 3.2.1, closed with chlorobutyl stoppers (20 mm grey), which comply with respective Ph. Eur. monograph 3.2.9 and closed with a flip-off cap (20 mm Alu unlined w/Flip-off; not in direct contact with the drug product). Technical drawings for all three parts of the immediate packaging are provided. Detailed descriptions and respective specifications are included (including appearance and dimensions). As secondary packaging, card boxes are used. The choice of the container closure is therefore regarded as justified.

Considering the dosage form (solid; reconstituted product has short contact time at moderate temperature) and compendial quality of primary packaging materials, it is acceptable that the intended CCS (container closure system) compatibility testing study is not included in the dossier. Extractables/leachables (E/L) deriving from the container closure system (vials and stoppers) were investigated. Toxicological assessment of the extractables detected above the AET level concluded that their estimated daily intakes are below the permitted daily exposure (PDE) values, thus E/L content is acceptable. The analytical principles of the applied analytical methods are appropriate for the intended use. Analytical methods are sufficiently discussed.

Container closure is confirmed to be verified applying compendial methods; accepted. Further, a container closure integrity test has been performed (and validated). CCIT is specified accordingly. Bulk solution compatibility with process materials have been investigated. E/L profile investigations are acceptable. Study design is appropriate and includes positive control (extraction with isopropanol).

The compatibility of melflufen finished product with the proposed reconstitution/dilution solution (5% glucose solution: 0.9% sodium chloride solution (8:17 v/v)) was investigated and confirmed, with acceptable assay results.

An extractables study has been performed regarding infusion components/materials. Study design is appropriate for in-use conditions and includes standard dose and lowest dose controls. Found amounts of extractables are toxicologically negligible. In conclusion, no significant difference is observed depending on which configuration of infusion materials were used, thus melflufen is compatible with commonly used infusion materials and no restrictions are required.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of seven main steps: preparation of excipient solutions, preparation of melflufen bulk solution, sterile filtration of bulk solution, vial filling, lyophilisation and stoppering, capping and sealing, and bulk packaging. The process is considered to be a non-standard manufacturing process.

Batch quantity is defined based on the theoretical amount of bulk solution and number of filled vials. Tert-butanol and water for injections are removed by freeze-drying.

The control strategy regarding critical manufacturing steps is accepted. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. Process parameters and details regarding sterile filtration and aseptic processing including filter integrity and control of bioburden are provided. The bulk solution is tested immediately prior to sterile filtration for microbiological purity with the acceptable IPC limit of NMT 10 CFU/100 ml.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Data on three production scale batches are submitted covering the batch size 112.8 kg. All process parameters were taken into account. Compliance of critical process parameters is demonstrated by means of batch data. Analytical data of IPCs and intermediate controls are provided. Out of Specifications (OOS) were found for manufacture overall yield (NLT 90%) however these were accepted as being due to high amount of sampling.

2.4.3.3. Product specification

The finished product specifications include appropriate tests for this kind of dosage form; appearance (visual), identification (HPLC), assay (HPLC), related substances (HPLC), water content (KF), residual solvents (GC), content uniformity(Ph. Eur.), particulate contamination (visible and subvisible particles) (Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), crystalline content (XRPD) and container closure integrity test (UV-blue dye).

The specification for the reconstituted solution (product reconstituted in 40 ml of 5% glucose) contains tests for: reconstitution time, completeness of solution, clarity and degree of opalescence (Ph. Eur.), degree of coloration (Ph. Eur.), pH (Ph. Eur.) and osmolality (Ph. Eur.).

Parameters included in specification complies with requirements of ICH Q6A and Ph. Eur. monograph for parenteral preparations. All set specification parameters and respective limits are justified by the Applicant. Regarding limit of TBA, following can be said from a nonclinical point of view: the calculated PDE for tert-butanol is 35 mg/day based upon the LOEL (lowest observed effect level) for nephropathy in females 333 from a 2-year rat carcinogenicity study. One vial of melflufen contains 1021.48 mg of which 3.5% would equate to 35.75 mg tert-butanol. This would be considered comparable to the proposed PDE from a non-clinical perspective, particularly so since a second scenario calculates a PDE of 42.5 mg/kg base on a mouse carcinogenicity study where follicular hyperplasia was observed in the thyroid of female animals.

Five degradation products are briefly discussed in respective dossier section: three actual (and specified) impurities, namely dechlorohydroxy melflufen, dechloroethyl melflufen and 5-hydroxymethyl furfural. All three actual degradants have been identified by a suitable reference standard. Further, two potential impurities, namely melflufen carboxylic acid and dechloroethyl-ethylcarboxy-melflufen are stated. Both have been found in early development batches below the ICH Q3B identification threshold. Thus, they are controlled as unspecified impurities which is acceptable.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The applicant investigated the risk of elemental impurities in three batches stored at 2-8°C for 11, 24 and 33 months respectively. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

Batch data from six batches (commercial batch size, 6000 vials) are provided. All results comply with respective specification limits except for one batch which had an OOS with parameter sterility, however the root cause has been identified and is not related to the process performance. Batch data for the same six batches are provided for the reconstituted drug product.

2.4.3.4. Stability of the product

Stability data from three, full scale batches of finished product stored for up to 24 months under long term conditions (5±3°C) and for up to 12 months under accelerated conditions (25±2°C) according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Supportive stability data from additional batches used for clinical supply were also provided.

Samples were tested for appearance, assay, related substances, water content, particulate contamination, sterility and bacterial endotoxins, crystalline content and container closure integrity. The analytical procedures used are stability indicating.

Forced degradation studies have been conducted (hydrolysis, acidic environment, alkali environment, oxidative environment, heat exposure and artificial light irradiation exposure). It is stated that degradation occurred (greater than 2.5%) at the hydrolysis, acidic, alkaline, oxidative and thermal forced degradation conditions. A decrease in assay of 8.4% could be found when the finished product was treated with light irradiation. Thus, melflufen is not regarded as stable under forced degradation conditions but the HPLC method is regarded as stability-indicating. Mass balance is regarded as acceptable.

Performed photostability study according to ICH Q1B (option 2) showed that the finished product is photolabile if not adequately protected from light. Thus, the finished product should be kept in the secondary packaging to avoid any degradation.

Since OOS are observed at accelerated storage conditions, storage in refrigerator is justified as well. In the SmPC it is stated that the finished product should not be frozen. This is acceptable as freeze-thaw studies have not been conducted and stability after freezing is thus unclear. Confirmation is given that the start of shelf-life is calculated according to CPMP/QWP/072/96.

In-use stability studies are performed with two batches. The in-use study was conducted using the proposed analytical procedures, with the exception of the HPLC methods that were adjusted with regards to sample

preparation and sample concentration to enable testing of the admixtures. An in-use stability specification is provided. The post-approval stability protocol and stability commitment is accepted.

Based on available stability data, the proposed shelf-life of 24 months and storage conditions (Store in a refrigerator (2°C to 8°C). Do not freeze. Store in the original package in order to protect from light.) as stated in the SmPC (section 6.3) are acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure a major objection was raised on the choice of active substance starting materials. The applicant provided additional scientific justification and data to support their choice and updated the active substance control strategy accordingly. The MO was satisfactorily resolved. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

2.5.2. Pharmacology

A range of in vitro and in vivo pharmacology studies have been performed to assess the efficacy of melflufen. These data have been published or are in manuscript form. The activity of melflufen has been examined using multiple myeloma (MM) cell lines and patient samples and in vivo using rodent xenograft or hollow fiber models.

Melflufen flufenamide (4-[Bis-(2-chloroethyl)amino]-L-phenylalanine-4-fluoro-L-phenylalanine ethyl ester hydrochloride), abbreviated melflufen and previously called J1, is an ethyl ester of a di-amino acid consisting of the amino acid derivative of melphalan (mustard-L-phenylalanine) and para-fluoro-L-phenylalanine.

Melphalan has been in clinical use as an antitumor agent for more than 60 years and has the classical bis-(2-chloroethyl) amino alkylating function identical to that in the other marketed cytotoxic compounds cyclophosphamide, chloroambucil and bendamustine. Melflufen has, due to the extra para-fluoro-L-phenylalanine group as compared to melphalan, an increased lipophilicity (logD 2.3), leading to an easier passage of the cell membrane.

2.5.2.1. Primary pharmacodynamic studies

Primary pharmacodynamics in vitro

Nitrogen-based alkylating agents like melphalan exert their cytotoxic action through covalent interaction with intracellular nucleophiles, especially DNA, as a result of the spontaneous formation of reactive cyclic aziridinium ion intermediates. Bifunctional agents (such as melphalan, cyclophosphamide, chlorambucil and bendamustine) are able to crosslink a DNA strand within a double helix (intrastrand), between two strands (interstrand) or between DNA and proteins and are more active than monofunctional agents. Cross-linking of DNA is probably the most important factor for the cytotoxic effect, resulting in inhibitory effects on DNA replication and transcription, which subsequently triggers cell death.

In vitro studies in multiple myeloma RPMI 8226 cells showed that melflufen (1 µM) easily crosses the cell membrane and was subsequently rapidly and extensively hydrolysed, forming desethyl-melflufen and, by peptidases, mainly melphalan. Intracellular concentration of melflufen was quantifiable for 30 min. In contrast, melphalan was detectable for up to 2 h having a 27-fold higher intracellular melphalan than melflufen exposure. When melflufen treatment of RPMI-8226 multiple myeloma cells was compared with melphalan, it was found that treatment with 5 µM of melflufen loads the cells with about 2.5-fold more melphalan than can be achieved with 100 µM of melphalan. In this case melflufen functions as a prodrug, loading the cell with a ~50-fold higher amount of intracellular melphalan than when exposing to melphalan.

Aminopeptidases such as LAP3, LTA4H, RNPEP and aminopeptidase N (APN) have shown similar capability to form melphalan out of melflufen. Moreover, cell lines with high hydrolytic activity also display a larger difference between melflufen and melphalan activity, suggesting a role of these enzymes in the activation of melflufen. If a peptidase inhibitor is added, the cytotoxic activity is decreased. Moreover, if the peptide bond in melflufen is chemically modified to be non-hydrolysable, the cytotoxic activity is significantly impaired.

The cytotoxic activity of melflufen has been examined in a range of Multiple Myeloma (MM) cell lines and in patient-derived MM samples and melflufen showed cytotoxicity in the MM cell line RPMI8226, and the melphalan-resistant 8226/LR5 and doxorubicin-resistant sublines. In the MM cell lines, the IC50 of melflufen varied from 0.4 – 1.7 µM and was 10-fold lower than of melphalan. Another in vitro study on the potency of melflufen in bortezomib-resistant MM cells showed that melflufen was significantly more potent in the bortezomib-adapted (to develop resistance) derivatives of AMO-1, RPMI-8226 and ARH-77 cell lines than in the corresponding unadapted cells. The ability of melflufen to exert activity in drug resistant MM cells was further documented in a study on carfilzomib-resistant subline of AMO-1 cells subjected to CRISPR/Cas knock-out of the ABCB1 gene.

When the cytotoxic effect was determined in primary cultures of 3 human myeloma cells, melflufen showed a mean IC50 that was approximately 0.2 µM. A similar cytotoxic activity of melflufen (IC50 ~0.5 µM) was observed when tested in MM patient tumour cells, purified by using CD138+ antibody enrichment. In a study investigating the cytotoxicity of melflufen in CD138+CD38+ bone marrow cells from MM patients (15 samples from 14 patients) a median IC50 of 0.9 nM was observed but with a high variability in response.

Additional in vitro studies to evaluate cytotoxicity were conducted with melflufen in a panel of different human tumour cell lines, including patient-derived tumour samples. The average half maximal inhibitory concentration (IC50) of melflufen in 23 cell lines derived from haematologic cells (acute leukaemia, lymphoma, and myeloma) was 0.20 µM compared to 6.9 µM for melphalan, a 35-fold difference. The average IC50 of melflufen in the 24 cell lines derived from solid tumour cells (neuroblastoma, lung cancer, ovarian cancer, and renal cell cancer) was 0.41 µM compared to 18 µM for melphalan, a 44-fold difference. Melflufen was shown to be more potent in haematologic malignancies than in solid tumours.

Combining melflufen with the commonly used myeloma drugs lenalidomide (immunomodulatory), bortezomib (proteasome inhibitor), or dexamethasone (glucocorticoid) triggered synergistic anti-myeloma activity in cell lines RPMI LR5 (melphalan resistant) and MM.1S.

In addition to the increased cytotoxicity of melflufen, as compared to melphalan, melflufen showed cytotoxic activity in cells with dysfunctional p53, suggesting that a functional p53 is not needed for melflufen-induced cytotoxicity. In line with this melflufen also showed cytotoxic activity in CD138+CD38+ plasma cells, isolated from primary bone marrow samples from MM patients with confirmed chromosome 17p deletion or TP53 mutations.

In vitro and in vivo studies found an anti-angiogenic effect, an inhibition of vessel formation, which is in line with highly expressed APN in vascular endothelial cells leading to a higher melphalan formation intracellularly. The relevance of different peptidase expression in other tissues on melflufen activity in humans is unclear. Melflufen showed a similar high sensitivity on immature human umbilical cord blood CD34+ progenitor cells (FMCA-GM7) and a more differentiated CD34+ derived cell population (FMCA-GM14) but melphalan was 68- and 23-fold less sensitive to GM7 and GM14 cells, respectively. In addition, cytotoxic effects were demonstrated on osteoclasts precursors and on osteoclastogenesis, possibly linked to lower tumour-induced bone resorption.

The mechanism of action for the cytotoxicity of melflufen is suggested to be the bis-(2-chloroethyl) amino alkylating function inducing cross-linking of DNA leading to inhibitory effects on DNA replication and transcription. In this respect melflufen was found to increase dose- and time-dependently γ-H2AX, a DNA damage response protein, and induces apoptosis (annexin V, caspase-3), which was found in vitro and in vivo. A flow cytometry study showed cell cycle arrest in the G2/M phase, which is in line with a higher sensitivity of rapidly dividing cells. Melflufen-induced DNA damage, as indicated by the proteins γ-H2AX, ATR and CHK1, was found to be more rapid and robust than with melphalan, and washout experiments showed that a 2 hour exposure of MM cells to melflufen was sufficient to initiate irreversible DNA damage and cytotoxicity.

In conclusion, from the presented in vitro PD data, it is not clear whether melflufen itself exhibits cytotoxicity as the ~50-fold increase in melphalan intracellularly with melflufen treatment is also in line with the increase in cytotoxicity, seen in most cell lines with melflufen as compared to melphalan. In addition, if a peptidase inhibitor is added, the cytotoxic activity is decreased. Moreover, if the peptide bond in melflufen is chemically modified to be non-hydrolysable, the cytotoxic activity is significantly impaired.

Primary pharmacodynamics in vivo

The in vivo efficacy of melflufen has been investigated in mice and in rats using the implanted hollow fiber method (fibers containing T-cell leukaemia, small cell lung cancer, renal adenocarcinoma ACHN and MM cells) as well as in subcutaneous tumour xenografts in nude rats and nude or SCID mice using tumour cells of different origin (neuroblastoma, ovarian carcinoma, B-cell lymphoma and MM).

The hollow fiber method consists of subcutaneously implanted fibers, in rodents and provides a robust model that reports modest sensitivity to several standard cytotoxic drugs. The read-out is a percentage net growth over 5 days of subcutaneous placement (SD or QD treatment). Three cell lines (T-cell leukaemia CCRF-CEM, small cell lung cancer NCI-H69, and renal adenocarcinoma ACHN) and two primary cultures of human tumour cells (from patients with CLL or ovarian carcinoma) were used as tumour models in the NMRI mouse. Both melflufen and an equal dose of melphalan inhibited growth of all three tumour cell lines and melflufen, but not melphalan, inhibited one (ovarian carcinoma) of the two primary tumour cells.

The effect of melflufen and of an equimolar dose of melphalan (4 µmol/kg) was also assessed in MM (MM.IS cell, sc) xenografts in SCID mice (2 mg/kg melflufen IV BIW for 3 weeks). At an equimolar dose, melflufen but not melphalan significantly inhibited tumour growth and time to survival. In addition to an effect on multiple myeloma, subcutaneous xenograft studies using other tumors types in nude (neuroblastoma SH-SY5Y) or SCID mice (ovarian carcinoma A2780) also showed significantly better antitumoral effects with melflufen than melphalan at equimolar doses.

In another SCID mouse xenograft leukaemia model, AML primary sample (AML-ps) tumour cells from bone marrow blasts of AML patient were used. Both melflufen and melphalan decreased the amount of circulating leukaemia cells by >99% and increased survival from 34 days to >104 days. Melflufen treatment (8 mg/kg) showed a higher proportion of leukemic free animals than that observed with equimolar melphalan treatment.

The Vk*MYC transgenic mouse with spontaneous occurring myeloma tumours has been suggested as an alternative model to predict single-agent drug activity. Both melflufen (4 mg/kg, IP, BIW) and melphalan were shown to be active in this model (>50% response).

Melflufen inhibited tumour growth in xenografted nude rats using the very resistant SK-N-BE(2) or sensitive SH-SY5Y neuroblastoma cell lines and also showed significant increase in caspase-3 positive cells and decrease in cell proliferation.

Using the hollow fiber method in the Sprague Dawley rat as tumour model, two cell lines (T-cell leukaemia CCRF-CEM and MM RPMI8226) were evaluated. Melflufen (IV, single dose 1.33 µmol/kg, i.e. 0.66 mg/kg) inhibited cell growth of the CCRF-CEM cell but not of the MM RPMI8226 cell line, while melphalan at an equimolar dose, was inactive in both models.

In conclusion, despite the, in contrast to human, instantaneous de-esterification of melflufen in rodent plasma upon administration, the xenograft and hollow fiber methods using nude/SCID mice or nude rats showed a higher efficacy on tumour cell growth inhibition with melflufen than with an equimolar melphalan dose in five of the seven xenograft models and three of the five hollow fiber models.

2.5.2.2. Secondary pharmacodynamic studies

Given the general cytotoxic, alkylating activity of melflufen, its rapid conversion to melphalan, the intended indication and the large clinical experience with melphalan, it is agreed that no secondary pharmacodynamic screening panel data have been provided.

2.5.2.3. Safety pharmacology programme

Safety pharmacology comprised of an in vitro study on the effect on hERG tail current amplitude and GLP-compliant studies in the rat and dog using a standardized observation battery study (rat),

respiratory/cardiovascular study (rat), a cardiovascular telemetry study (dog) and holter monitoring studies (dog). No stand-alone safety pharmacology studies have been performed concerning the potential effects of melflufen to affect renal function/urinary parameters, but this is evaluated in the general toxicity studies.

In a combined telemetry / plethysmography study, a single dose 30-min intravenous (IV) infusion of melflufen (9.17 mg/kg) to male Wistar rats (n=6), resulted in a short-lasting (<15 min) but statistically significant stimulatory action on respiration and heart rate. This might be explained as a stress response related to local irritation and pain, effects commonly associated with high dose chemotherapeutic regimens. There was no effect on tidal volume, blood pressure, temperature or locomotor activity.

In a GLP-compliant, 2-cycle IV infusion study in the rat, clinical signs were monitored using a standardized observation battery that included assessment of motor activity, mood/awareness, motor incoordination, and muscle tone. No signs of any CNS toxicity were observed at the low and mid doses of 3.3 and 6.6 mg/kg (Q3W), respectively, while high-dose animals (9.2 mg/kg) had mainly statistically significant incidences of piloerection, slowed body movements and occasional reduced spontaneous locomotor activity.

While melphalan did not show an inhibitory effect at 100 µM, melflufen showed a concentration-dependent inhibition of the human ether-a-go-go related gene (hERG) current in CHO cells yielding an IC50 of 1.6-3.1 µM (0.8 – 1.55 µg/mL), which is about 5.4 – 10.4 times higher than the anticipated Cmax of melflufen (148 ng/mL) at the proposed human dose of 40 mg. Therefore, hERG-related effects on QT interval cannot be completely excluded in humans. Although the in vitro hERG study was performed as non-GLP–compliant, the data of the study are considered adequate given the quality of the presented study data.

The multiple dose effect of melflufen on ventricular repolarization was investigated in vivo in two male and two female Beagle dogs upon IV administration (30 min infusion, 0.9 mg/kg, every three weeks for three cycles). No treatment related abnormalities in rhythm or in complex morphology were recorded in any animal at any time point. No relevant changes were observed in any measured or computed parameters, including repolarization parameters, i.e. QT or QTc interval corrected for heart rate. Using 24 hrs holter monitoring in male and female Beagle dogs, a single dose 30-minute IV melflufen infusion (2.5 mg/kg, n=6 and 8.75 mg/kg, n=1) revealed no evidence of any QT prolongation or other rhythm disorders. The ECG data from the 17.5 mg/kg study are not considered as, due to a human error, post dose ECG recordings up to 30 hrs are not available and two out of three animals died. The 2.5 mg/kg dose level is almost 4-fold the clinical dose but this corresponds to a 2-fold lower melflufen concentration than the clinical Cmax at 40 mg. These in vivo observations with high doses thus suggest that melflufen is devoid of significant effects on the heart but it should be noted that clinical Cmax concentrations were not reached and the melflufen plasma concentrations quickly declined to BLQ after the infusion. The effect of melflufen on ventricular polarization was also investigated in the clinic but, the available data are limited, may also raise a concern (see clinical AR).

In conclusion, in contrast to melphalan, melflufen induced a concentration-dependent inhibition of the hERG channel current, leading to an 30- to 60-fold lower IC50 than melphalan, which is about 5-10 times higher than the anticipated clinical melflufen Cmax. The in vivo studies did not reveal reasons of concern but it should be noted that clinical Cmax concentrations were not reached. Currently, the possible mechanism of this difference with melphalan and the clinical relevance of this finding is unclear.

2.5.2.4. Pharmacodynamic drug interactions

It is agreed that no pharmacodynamic drug interaction studies with melflufen are needed as it is quickly transformed into melphalan and there is ample clinical experience with melphalan.

2.5.3. Pharmacokinetics

Methods of analysis

Concentrations of melflufen, desethyl-melflufen and melphalan in plasma of rats, rabbits and dogs were measured with LC-MS/MS methods. Melphalan is a known antitumour agent. Melphalan flufenamide (melflufen) is a derivative of melphalan, which is hypothesised to lead to higher concentrations of melphalan in the tumour cells compared to melphalan treatment because melflufen is rapidly taken up into cells followed by a rapid enzymatic hydrolysis of the molecule to the active metabolite melphalan.

In toxicokinetic studies in dogs, validated methods were used. The validation was adequate regarding calibration, accuracy, precision, matrix effect and stability. Long-term stability was long enough to cover the maximum storage period of the samples. Dilution integrity in dogs was determined up to 3000 ng/mL.

In rats, no toxicokinetic studies were performed. Pharmacokinetic studies were performed in rats, separately from the toxicology studies but with similar doses as in the toxicology studies. In rat PK study 20050055TRB, a validated method was used. The method was validated for the measurement of melflufen and melphalan in rats, but not for desethyl-melflufen. In rat study 20050535TRB, it is not clear whether the method which was used, was the same as in study 20050055TRB. In rat PK study AB19-70-02, a method was used which was validated for use in dogs but not in rats.

The method used in rabbits was not validated for use in rabbit plasma. Rabbits were however not used in the toxicology studies.

Methods used in the other pharmacokinetic studies were fit for purpose.

Absorption

Studies were performed in rats, rabbits and dogs, with IV administration by 30-minute infusion.

After administration of melflufen to rats, melflufen was not detectable in plasma because it was degraded very quickly already in plasma (see further under “Metabolism”). Tmax of melphalan occurred at 0.58 h after the start of infusion (5 minutes after the end of infusion) and melphalan Cmax and AUClast increased approximately dose-proportionally at doses 3.3 to 9.2 mg/kg of meflufen. After comparing equimolar doses of melflufen and melphalan (9.2 mg/kg melflufen vs 4.9 mg/kg melphalan and 3.3 mg/kg melflufen vs 2.0 mg/kg melphalan), AUClast of melphalan was higher after administration of melflufen than after administration of melphalan. Cmax of melphalan after administration of melflufen was higher than after melphalan administration in one study, but slightly lower in another study. Elimination half-life of melphalan was 0.74 – 1.17 h. Volume of distribution of melphalan was 407 mL/kg (distribution slightly more than intracellular fluid) and clearance of melphalan was 379 mL/h/kg.

Also in rabbits, melflufen was degraded very quickly. Measurable concentrations of melflufen in plasma were only found during infusion, and also in one sample at 10 minutes after the end of infusion. Tmax of melphalan occurred at 0.42 h after the start of infusion. When equimolar doses of melflufen and melphalan were compared, Cmax and AUClast were lower (35% and 24% respectively) after administration of melflufen than after administration of melphalan. Elimination half-life of melphalan was 0.63 – 0.66 h. Volume of distribution of melphalan was 1024 mL/kg (approximately similar to total body water) and clearance of melphalan was 1131 mL/h/kg.

In dogs, low levels of melflufen were found, with Tmax at 0.28 – 0.50 h after the start of infusion. Tmax of melphalan occurred at 0.50 – 0.75 h after the start of infusion. Exposure to melphalan increased

approximately dose-proportionally after administration of melflufen (from 0.45 to 0.90 mg/kg and from 8.75 to 17.5 mg/kg). After comparing equimolar doses of melflufen and melphalan (0.9 mg/kg vs 0.55 mg/kg [day 1] and 17.5 mg/kg vs 10 mg/kg), Cmax and AUClast were lower (46-52% and 0.7-20%) after administration of melflufen than after administration of melphalan, although in study 2014-0252, there was only a minor difference in AUC. Elimination half-life was 0.04 – 0.07 h for melflufen and 0.61 – 0.79 h for melphalan. Volume of distribution was 780 – 2400 mL/kg for melflufen and 1310 – 1430 mL/kg for melphalan (both beyond total body water). Clearance was 15330 – 25020 mL/h/kg for melflufen and 1160 – 1460 mL/h/kg for melphalan. No consistent gender effect was observed. Only in study 0373-2012, at 0.90 mg/kg exposure was slightly higher in females, but the difference with males was less than two-fold and was therefore not clinically relevant.

In rabbits and dogs the administration of 0.9 mg/kg of melflufen or an equimolar dose of melphalan, showed that melflufen administration was associated with an approximately 25% lower AUCinf than that observed after melphalan administration. It was justified with more alkylator being retained in the tissues after melflufen administration.

Gender differences on melflufen absorption were investigated only in dogs and specific differences were not noted. Human and dog pharmacokinetic data were compared, and it was concluded that from a pharmacokinetic point of view dog can be considered as a suitable species for safety testing of melflufen, therefore it is considered sufficient to demonstrate gender differences only in this species.

In an experiment by Nygren (2009), melflufen was added to human blood. Melphalan peaked in the red blood cell compartment at 10 minutes, whereas in the plasma compartment it was still increasing at 45 minutes. Desethyl-melflufen was low in both compartments. This indicates that in human, melflufen is converted into melphalan faster in the blood cell compartment than in plasma.

Distribution

After in vitro incubation of melflufen in whole blood of rats, melflufen was mainly converted into desethyl-melflufen in the plasma fraction. Melphalan was low in both plasma and red blood cell fraction. In human blood, melflufen distributed quickly to blood cells (Tmax of melflufen in blood cell fraction 1 min) and melphalan in the blood cell fraction gradually increased with Tmax of 6 min. In human blood, melphalan formation was considerably higher in the red blood cell fraction than in plasma. In dog blood, the pattern was comparable to human blood, but the formation of melphalan was somewhat slower (Tmax of melphalan in blood cell fraction was 60 min). These results indicate preferential formation of melphalan in blood cells in dogs and humans. A comparable pattern was found in a human multiple myeloma cell line.

In a study in female CB17 SCID mice xenografted with MM.S1 cells (multiple myeloma cells), the highest concentrations of melflufen and melphalan at 15 min after injection were found in pancreas, kidneys, liver, heart and lung. At 4 hours post dose the concentrations were 4 to 10-fold lower than at 15 minutes. Melflufen and melphalan were also found in the tumours. The amounts in tumour appear limited.

In rats, covalent binding of melphalan-related radioactivity was found in all investigated tissues.

Protein binding of melphalan was 86% in plasma of rats at concentrations of 101 – 2747 ng/mL (0.33 – 9.0 nmol/mL). Protein binding of melphalan in plasma of healthy humans was 80 – 92% at concentrations of 92 – 10072 ng/mL (0.3 – 33 nmol/mL). Melphalan was primarily bound to albumin. In plasma from cancer patients, protein binding varied 54 – 94%.

Melanin binding was not studied.

Placental transfer and excretion into milk were not studied. As an alkylating anticancer agent, melphalan is expected to be teratogenic and because it is a genotoxic compound, women treated with melflufen should not breast-feed.

Metabolism

In vitro studies in mouse and rat blood showed that melflufen is degraded quickly, mainly into desethyl-melflufen by esterases (elimination half-life of melflufen 9 and 15 seconds in mouse and rat blood respectively). Subsequently, in rat plasma, desethyl-melflufen is slowly converted into melphalan. The amount of melphalan was low after incubation of melflufen in whole blood of rats. In an in vitro study in rat liver microsomes, the formation of monoglutathionyl and diglutathionyl melphalan derivatives has been observed. These conjugates have not been observed in vivo.

After incubation of melflufen in dog and human whole blood, melflufen was converted into melphalan in the red blood cell fraction (elimination half-life of melflufen 7.0 and 4.4 min in dog and human blood respectively). When melflufen was incubated in dog plasma, there was no appreciable formation of melphalan. Experiments in dog and human blood support a rapid inflow of melflufen to cells, formation of melphalan in the cells and then a slow out-transport of melphalan. The metabolism of melflufen is in humans more comparable to dogs than to rats.

Experiments in human multiple myeloma cell line RPMI 8226/S showed an intracellular rapid formation of melphalan, a short plateau and then a gradual decrease of intracellular melphalan. At 1 µM, intracellular melphalan could be quantified up to 120 min.

In vivo in rats, melflufen was metabolized so quickly into desethyl-melflufen that melflufen was not detected. High levels of desethyl-melflufen were observed during infusion, which decreased thereafter. In rabbits, melflufen was converted quickly into melphalan. In dogs, melflufen was detectable, but was quickly metabolized, mainly into melphalan.

Excretion

Melphalan-related radioactivity was excreted in both urine (44%) and faeces (25%) of dogs within 11 days after IV dosing. A total of 8% of melphalan-related radioactivity was excreted as intact melphalan in urine. In bile, 86% of melphalan-related radioactivity consisted of intact melphalan at 30 min after dosing and 72% at 4 hours after dosing.

Pharmacokinetic drug interactions

Pharmacokinetic drug interactions have not been studied for melflufen.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

The acute toxicity of a single dose of melflufen was evaluated in mice, rats, dogs and minipigs. Melflufen was administered intravenously (IV) via a bolus injection (rodents) or a 30-minute infusion (dogs and minipigs) followed by a follow-up period. In the non-GLP minipig study and in one non-GLP dog study (2014-0252), melflufen was compared with melphalan. In the other studies described, only the safety of melflufen was evaluated.

In GLP rodent studies, mortality was evident at the high dose of melflufen (46.7 mg/kg in mice, 11.7 mg/kg in rats) and was associated with haemorrhagic intestinal tract and red lungs preceded by several clinical signs. Tonic seizures have been reported in mice shortly after administration at ≥ 23.3 mg/kg. These have not been observed in any other species tested or in repeated-dose mice studies administered doses up to 23.3 mg/kg.

In the non-GLP minipig study (1 animal per group), the animal given 2.4 mg/kg melflufen was terminated earlier (Day 5) due to severe clinical signs. An equimolar dose of melphalan was better tolerated based on clinical signs. In both animals, a severe decrease in WBC counts, with a more rapid decline in the melflufen-treated animal, was observed and marked histologic changes were seen in the gastro-intestinal tract, bone marrow, spleen, and testicular tubular epithelium. The melflufen-treated animal appeared to show slightly more severe histologic changes compared to the melphalan-treated animal.

Three single-dose studies were performed in Beagle dogs. In non-GLP dog study 2014-0252, melphalan was included at an equimolar dose of 17.5 mg/kg melflufen. In non-GLP studies 0253-2021 and 2014-0252, mortality occurred at the high doses (1.25 and 17.5 mg/kg). In GLP study 2018-0158, no mortality occurred, but the follow-up period was restricted to six days. Effects of melflufen and melphalan were observed on the gastro-intestinal tract and the haemolymphopoietic system as main target organs. The haemolymphopoietic system was mostly affected by lymphoid depletion and severe drops in WBC populations. The gastro-intestinal and haematological effects, as well as the damage to the testicular epithelium seen in study 2018-0158, are probably related to the mode of action of an alkylating compound on rapidly replicating cell populations.

2.5.4.2. Repeat dose toxicity

The safety of melflufen was evaluated in a pivotal two-cycle mouse study, a pivotal two-cycle rat study and a pivotal three-cycle dog study. Melphalan was not included in these studies. Animals were given a dose of melflufen once per cycle, and the cycle duration was three weeks. Melflufen was administered via intravenous (IV) infusion over 30 minutes via the caudal vein in rodents and via the jugular vein in dogs. The animals were followed for 14 days (rodents) or 11/12 days (dogs) following the final infusion. For comparing the toxicity of melflufen for the different species tested, it is important to note that based on the pharmacokinetics of melflufen, results from dogs are likely to be more relevant for humans than rodents.

Mice

Swiss mice were administered with 5.8 – 23.3 mg/kg/cycle melflufen. Main adverse effects regarding haematology included dose-related reductions in white blood cells (WBCs), lymphocytes, red blood cells (RBCs), starting from the low dose, and reductions in haemoglobin, haematocrit and thrombocytes at the high-dose. All these findings resolved in the recovery period. The main histopathological treatment-related findings included bone marrow toxicity, effects on secondary lymphoid tissues and testicular toxicity. These findings included hyperplastic myelopoiesis in the sternum bone marrow and extramedullary haemopoiesis in the spleen and liver, of which the latter are probably compensative effects for the loss of blood cells. Testicular toxicity was apparent as observed by germinal epithelium degeneration in the testicles accompanied by hypospermia in the epididymides. Correlating with the histopathological findings, there were weight reductions of the testes and increases in spleen weight. The No Observed Adverse Effect Level (NOAEL) was not determined, as effects on haematology were apparent at all dose levels. The lowest observed adverse effect level (LOAEL) was 5.8 mg/kg. No toxicokinetics evaluation was performed.

Rats

Sprague-Dawley rats were treated with melflufen at doses of 3.3 – 9.2 mg/kg/cycle. The peptidase cleavage product para-fluorophenylalanine ethyl ester was administered to a separate group of rats at a dose equimolar to the high dose of melflufen. No major treatment-related effects were observed in this group.

For melflufen-treated animals, the main dose-related haematological effects starting from the lowest dose included reductions in WBCs, consisting of neutrophils, lymphocytes and eosinophils. Levels of RBCs, haematocrit, haemoglobin and thrombocytes were dose-dependently reduced starting from the mid-dose. With exception of lymphocytes and RBCs, all findings (partially) resolved in the recovery period. The main histopathological treatment-related findings included lymphoid depletion of secondary lymphoid tissues and testicular toxicity. Secondary lymphoid tissue toxicity with dose-related incidence consisted of lymphoid atrophy in the mesenteric and submaxillary lymph nodes and spleen starting from the lowest dose. Peyer's patch lymphoid degeneration and lymphoid atrophy of the thymus occurred with dose-related incidence as well as severity starting from the low-dose. Similar as in mice, extramedullary haemopoiesis in the spleen and liver was observed from the low dose onwards. Testicular toxicity was apparent in the mid-dose groups and higher with dose-related incidence and severity of germinal epithelium degeneration in the testicles. Correlating with these histopathological findings, there were weight reductions of the testis and thymus and an increased spleen weight. Other treatment-related histopathological changes included siderophages in the mesenteric lymph nodes and plasma cell hyperplasia in the submaxillary lymph nodes. Perivascular mononuclear cell infiltration and alveolar macrophage aggregates were found in the lungs with a dose-related incidence and severity. The NOAEL was not reached, as effects on haematology and histopathology were apparent at all dose levels. The LOAEL is considered to be 3.3 mg/kg. No toxicokinetics evaluation was performed.

Dogs

Beagle dogs were treated with melflufen at doses of 0.45 or 0.9 mg/kg/cycle. The main haematological effects starting from the lowest dose included dose-related reductions in neutrophils, lymphocytes, platelets, monocytes and eosinophils. RBCs, haematocrit and haemoglobin levels were less affected in dogs compared to rodents. In dogs, the decreases were only observed after the final dose in high-dose animals. The levels of thrombocytes were not affected in dogs. With exception of eosinophil levels, all findings (partially) resolved in the recovery period. Treatment-related histopathological findings associated with bone marrow toxicity included reduced cellularity in two high-dose dogs, while one high-dose dog showed increased cellularity. A dose-related increase in severity and incidence of lymphoid depletion in the spleen was observed. In addition, treatment-related extramedullary haematopoiesis in the spleen was seen, which was, similar as the increased bone marrow cellularity, probably a compensatory effect. Treatment-related testicular toxicity was apparent in high-dose animals that consisted of germ cell depletion in the testes and oligospermia of the epididymides. Correlating with this finding, there was a weight reduction of the testes. The NOAEL was not established, as effects on haematology and histopathology were apparent at both dose levels. At both dose levels, the exposure to melflufen and its quickly formed metabolite melphalan were below the human therapeutic exposure. The exposure multiples based on AUC0-inf were ranging from 0.2 (for both melflufen and its metabolite melphalan at 0.45 mg/kg) to 0.3 – 0.9 (for melflufen 0.5 and 0.9 for males and females at and its metabolite melphalan 0.3 and 0.4 for males and females, at 0.9 mg/kg). All observed effects must therefore be considered as clinically relevant.

Overall, adverse histopathological findings that were common for both rodents and non-rodents were bone marrow toxicity, lymphoid depletion of secondary lymphoid tissues, and testicular toxicity. Significant effects were seen on the male reproductive organs in mice, rats and dogs. Degeneration of the testicular epithelium accompanied by hypospermia in epididymides were observed at the highest melfufen dose of 23 mg/kg in

mice and at the highest melflufen dose of 0.9 mg/kg in dogs. Dose-related weight reductions of the testis and epididymides in the mid- and high-dose groups were also observed. The effects on the male reproductive organs were not reversible. No abnormality in organ weights, in macroscopic and microscopic observation were seen in females' reproductive organs in the pivotal repeat-dose toxicity mice, rat and dog studies. Female fertility was not further investigated. In rats, it appeared that was slightly more toxicity of secondary lymphoid tissues compared to dogs, which might be related to the fact that melflufen remained longer in plasma before it was metabolised, allowing for more systemic distribution and toxicity. In dogs, which are pharmacokinetically a more translatable model for humans compared to rats, adverse effects occurred below clinical exposures. The main targets of toxicity, bone marrow, lymphoid organs and testes, are suggestive of the pharmacological mode of action of an alkylating compound on rapidly replicating cell populations. The changes in the repeated dose toxicity studies were consistent with what was reported in single dose studies except that less gastro-intestinal toxicity was observed. This might be related to the higher doses administered in the single dose studies or due to a longer follow-up period, allowing for recovery from potential damage.

Interspecies comparison

Melphalan increased approximately dose-proportionally in rats, dogs and humans. Effect of gender was investigated only in dogs and humans. No consistent gender effect was observed in dogs. In humans, no gender effect was observed for melphalan. For melflufen data were too limited to draw a conclusion on gender effect, this was however not a problem because it was cleared very quickly. Protein binding was 86% in rats, 80 – 92% in healthy humans and 54 – 94% in cancer patients. Volume of distribution of melphalan was 407 mL/kg in rats (slightly more than intracellular fluid), 1024 mL/kg in rabbits (approximately total body water), and 1310 – 1430 mL/kg in dogs (more than total body water). Volume of distribution of melflufen in dogs was 780 – 2400 mL/kg (could not be determined in rats and rabbits). A more extensive distribution of melphalan in dogs than in rats is consistent with formation of melphalan in cells in dogs, whereas in rats, melphalan is mostly formed in plasma. In humans, volume of distribution was 35 L for melflufen and 76 L for melphalan after a single dose (beyond total body water for melphalan). In mice and rats, melflufen remains primarily in plasma and is converted there primarily into desethyl-melflufen and for a minor part into melphalan. In dogs and humans, melflufen was distributed quickly into red blood cells and was converted there into melphalan and desethyl-melflufen. Desethyl-melflufen was also converted into melphalan and melphalan was then slowly transported out of the cells. The metabolism of melflufen in humans is more comparable to dogs than to rats. Elimination half-life of melphalan was 0.74 – 1.17 h in rats, 0.63 – 0.66 h in rabbits, and 0.61 – 0.79 h in dogs. For melflufen, elimination half-life could only be determined in dogs (0.04 – 0.07 h). In humans, elimination half-life was 2 min for melflufen and 70-80 min for melphalan. Melphalan-related radioactivity was excreted in both urine (44%) and faeces (25%) of dogs. No human data regarding excretion in urine and faeces were provided.

2.5.4.3. Genotoxicity

In line with ICH S9, no standard genotoxicity studies have been performed with melflufen. Melflufen is an alkylating agent is a genotoxic substance by definition. Furthermore, it has been reported in literature that mutagenicity is induced by melphalan.

2.5.4.4. Carcinogenicity

No carcinogenicity studies were conducted for melflufen, which is in line with ICH S1 and S9. The mechanism of action of melflufen suggests that, similarly with all alkylating agents including the hydrolysis product melphalan, there is a risk for genetic damage and potentially carcinogenicity.

2.5.4.5. Reproductive and developmental toxicity

No standard reproductive and developmental toxicity studies have been conducted with melflufen. Based on its mechanism of action as an alkylating anticancer agent and literature, melflufen is suspected to induce testicular suppression and suppression of ovarian function. In addition, melphalan caused foetal harm when administered to rats, including teratogenicity and/or embryo-foetal lethality, as shown in reproductive studies conducted for melphalan. This has been reflected in section 4.6 of the SmPC. In line with ICH S9, it is accepted that embryo-foetal toxicity studies are not considered essential for the purpose of marketing applications for pharmaceuticals that are genotoxic and target rapidly dividing cells in general toxicity studies, or belong to a class that has been well characterized as causing developmental toxicity. Melflufen is not intended for use in a pediatric population; juvenile toxicity studies in animals were not conducted. This position is consistent with the ICH S9 guidance document.

2.5.4.6. Toxicokinetic data

Concentrations in control samples were below the lower limit of quantification (LLOQ). No toxicokinetic data were collected in studies in mice and rats. Also no pharmacokinetic studies were performed in mice. In pharmacokinetic studies in male rats, AUClast of melphalan at 9.2 mg/kg melflufen (which was the maximal dose in the pivotal rat study 20040837TR) was 6400 ng.h/mL (study 20050055TRB) or 8720 ng.h/mL (study 20050535TRB), corresponding to exposure multiples of 5.9 – 8.1 compared to human AUCinf, indicating sufficient exposure in the rat.

In dog studies 0373-2012 and 2018-0158, exposure to melflufen and melphalan was below the human therapeutic exposure. In study 2014-0252, exposure was sufficiently high (up to 11x and 7.5x human exposure for melflufen and melphalan respectively, after IV administration of melflufen). No consistent gender effect was observed in dogs.

2.5.4.7. Local Tolerance

The applicant has provided information on the local tolerance of melflufen infusions based on repeated-dose toxicity studies in mice, rats and dogs as well as on a combined PK and local tolerability study in dogs and a comparative local tolerance study in mice.

Local irritancy has been observed at (in dogs) and above (rodents) clinical concentrations when melflufen was administered via peripheral vein injections. When administered via the intended central vein infusion, clinically relevant concentrations did not cause local tissue irritancy in dogs.

2.5.4.8. Other toxicity studies

No specific studies were conducted with melflufen to investigate antigenicity.

No data on immunotoxicity are discussed. Melflufen is indicated and intended for myelosuppression and non-clinical data clearly suggest bone marrow- and haematologic toxicity.

No specific studies were conducted with melflufen to investigate dependence as melflufen is not a CNS active drug.

No dedicated studies on metabolites were conducted because there are no major metabolites in humans which were not formed in the animal studies.

Studies on impurities

The applicant has indicated the presence of impurities in the drug substance (DS) and drug product (DP) that concern five drug-related substances and a sucrose degradation product, 5-hydroxymethylfurfural (HMF), with specification limits above the qualification thresholds. The applicant indicated that the related substances are likely either as genotoxic as melflufen as they have identical alkylating functions as melflufen or are considered less genotoxic since they have lost alkylating functions that are present in melflufen. Hence, the genotoxic potential of these impurities have been sufficiently addressed.

An assessment of toxicity that is not linked to the genotoxic activity of the related substances was provided since the DS specification limits and the DP specification limit for dechloro-hydroxy-melflufen are all above the ICH Q3A(R2) qualification threshold of 0.15%. The impurity levels in non-clinical and clinical batches are low or unknown. Hence, the applicant has provided justifications for each impurity to discuss that they have been toxicologically qualified.

From a non-clinical point of view, it is agreed that melflufen carboxylic acid (desethyl melflufen), dechloro-hydroxy-melflufen,, HMF, 3(N)-,4(F)-melflufen, dechloroethyl-melflufen and dechloroethyl-4-hydroxy-1-methylbutyl melflufen have been sufficiently toxicologically qualified. .

Phototoxicity

Potential phototoxic activity of melflufen or melphalan was evaluated in a GLP-compliant in vitro 3T3 Neutral Red Uptake phototoxicity assay according to the validated BALB 3T3-NRU method (OECD 432) and demonstrated that melflufen nor melphalan are phototoxic.

2.5.5. Ecotoxicity / environmental risk assessment

Melphalan flufenamide PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT

substance as log Kow does not exceed 4.5. The compound is not considered as PBT nor vPvB.

Therefore melphalan flufenamide is not expected to pose a risk to the environment.

Table 1. Summary of main study results

Substance (INN/Invented Name): melphalan flufenamide			
CAS-number (if available): 380449-51-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	non-guideline shake flask	Log K_{ow} = 4.36 at pH 10 Log D_{ow} = 1.78 at pH 1.5 Log D_{ow} = 1.91 at pH 5.0 Log D_{ow} = 2.29 at pH 6.5 Log D_{ow} = 2.29 at pH 7.4	Potential PBT (N)

2.5.6. Discussion on non-clinical aspects

Pharmacology

Melflufen, i.e. melphalan flufenamide, is hydrolysed by peptidases forming melphalan. Melphalan has been in clinical use as an antitumor agent for more than 60 years. Nitrogen-based alkylating agents like melphalan exert their cytotoxic action through covalent interaction with intracellular nucleophiles, in particular DNA. Bifunctional agents, like melphalan are able to crosslink a DNA strand within a double helix, between two strands or between DNA and proteins. Cross-linking of DNA is probably the most important factor for the cytotoxic effect.

In vitro studies to evaluate cytotoxicity were conducted with melflufen in a panel of different human tumour cell lines, including patient-derived tumour myeloma samples. The average half maximal inhibitory concentration (IC50) of melflufen in 23 cell lines from haematologic origin (acute leukaemia, lymphoma, and myeloma) was 0.20 µM compared to 6.9 µM for melphalan, a 35-fold difference. The average IC50 of melflufen in the 24 cell lines derived from solid tumour cells (neuroblastoma, lung cancer, ovarian cancer, and renal cell cancer) was 0.41 µM compared to 18 µM for melphalan, a 44-fold difference. Melflufen was thus shown to be more potent in haematologic malignancies than in solid tumours.

In vitro studies in human multiple myeloma RPMI 8226 cells showed that melflufen easily crosses the cell membrane and that it was subsequently rapidly and extensively hydrolysed to desethyl-melflufen and, by peptidases, mainly to melphalan. Intracellular concentration of melflufen was low and only quantifiable for 30 min, while melphalan was detectable for up to 2 h and having a 27-fold higher intracellular exposure. When melflufen treatment of RPMI-8226 multiple myeloma cells was compared with melphalan, it was found that treatment with melflufen loads the cells with about 50-fold more melphalan than can be achieved with melphalan treatment. In this case melflufen functions as a prodrug, the in vitro cytotoxic activity (IC50) of melflufen, however, was only 10-fold lower, as compared to melphalan. Therefore, from the presented in vitro PD data, it is not clear whether melflufen itself exhibits cytotoxicity as the increase in melphalan intracellularly with melflufen treatment is also in line with the increase in cytotoxicity, seen in most cell lines

with melflufen as compared to melphalan. In addition, if a peptidase inhibitor is added, the cytotoxic activity is decreased. Moreover, if the peptide bond in melflufen is chemically modified to be non-hydrolysable, the cytotoxic activity is significantly impaired.

As reviewed by the Applicant, aminopeptidase N (APN) has previously been shown to efficiently hydrolyse the peptide bond of melflufen (Wickstrom, Viktorsson et al. 2010) but recent experiments have demonstrated that other aminopeptidases such as LAP3, LTA4H and RNPEP have the same capability (Schepsky, Traustadottir et al. 2020; Miettinen, Kumari et al. 2021). The increased aminopeptidase expression in tumour cells has been suggested as one of the major drivers of the selectivity for the cytotoxic activity of melflufen. It was also demonstrated that melflufen exhibits anti-angiogenic properties due to the high expression of aminopeptidases in human vascular endothelial cells. In this context, the Applicant was invited to further elaborate the possible effect of melflufen considering the level of aminopeptidase expression/activity in various human tissues (supposedly in the form of metanalyses) to provide additional valuable information regarding the activity of melflufen in humans. This is important also considering the limited availability of data on melflufen distribution in vivo. The Applicant has provided the summary of different aminopeptidase expression in various human tissues in a scientifically sound way and shortly commented on the impact of it with regards to the melflufen activity in different normal tissues. It is acceptable to acknowledge that the aminopeptidase expression levels cannot be directly correlated with melflufen activity in human body.

By using MM cell lines, Chauhan, Ray et al. (2013) have demonstrated that melflufen shows synergistic cytotoxicity with dexamethasone in melphalan-resistant and non-resistant multiple myeloma (MM) cell lines. The Applicant, based on recent scientific literature, has provided a discussion on the mechanism of action with regards to the synergy especially because the medicinal product is designated as an orphan medicinal product for the indication: Treatment of multiple myeloma (MM) in combination with dexamethasone. Justification of pharmaceutical combinations is suggested by ICH guideline S9 on nonclinical evaluation for anticancer pharmaceuticals. The Applicant acknowledges that the exact mechanism (mode of action) of the synergism has not been confirmed so far; however, it is highly plausible that it relies on the convergence of several of the above-mentioned pathways.

In vivo, despite the, in contrast to human, instantaneous de-esterification of melflufen in rodent plasma upon administration, the xenograft and hollow fiber methods using nude- or SCID mice or nude rats showed a higher efficacy on tumour cell growth inhibition with melflufen than with an equimolar melphalan dose in five of the seven xenograft models and three of the five hollow fiber models.

In contrast to melphalan, melflufen induced a concentration-dependent inhibition of the hERG channel current, leading to an 30- to 60-fold lower IC50 than melphalan, which is about 5-10 times higher than the anticipated clinical melflufen Cmax. The in vivo studies did not reveal reasons of concern but it should be noted that clinical Cmax concentrations were not reached. However, no QTc signals have been seen with melphalan previously and in the clinical studies most QTc prolongation signals were not considered related to melflufen.

Pharmacokinetics

Dilution integrity in dog was determined up to 3000 ng/mL. For concentrations exceeding 3000 ng/mL, i.e. for the highest concentrations in study 2014-0252, formally it is not certain how reliable the data are. This is however not expected to have a relevant effect on the conclusions.

In rat PK study 20050055TRB, a validated method was used. The method was validated for the measurement of melflufen and melphalan in rats, but not for desethyl-melflufen. Regarding the measurement of desethyl-melflufen in rats, it is therefore not certain how reliable the values are. It is however clear that desethyl-

melflufen formation is high in rats and that this is not representative for humans, because in humans melflufen is mainly metabolised into melphalan, and only for a minor part into desethyl-melflufen. Furthermore, the validation of the method used in the rat was not complete (back calculated concentrations of the calibration standards are not given and carry-over and freeze/thaw stability were not investigated) and there was a substantial matrix effect for melphalan in rat plasma. The matrix effect is one of the reasons that measured concentrations in rats may be less reliable. Because dogs are the most relevant species and rats are less relevant based on the comparability of the metabolism of melflufen with humans, this issue is not further pursued. In the method used in rat study 20050535TRB, changes were introduced in plasma handling, extraction and storage compared to the validated method used in study 20050055TRB, in order to investigate whether melflufen could be detected in plasma of rats. The method was not validated after these changes. This is however not expected to have influenced conclusions to a relevant extent, considering that dogs, and not rats were the most relevant species compared to humans. In rat PK study AB19-70-02, a method was used which was validated for use in dogs but not in rats. Overall, it is not clear how reliable the measured concentrations in rats are.

The hypothesis that melflufen is distributed to the cells quickly, after which it is converted to melphalan which then remains in the cells, would be supported by a lower melphalan exposure after melflufen administration than after melphalan administration. This is the case for the rabbit and the dog, though in dog the effect on AUC was only minor in one of the two comparative studies, while it was not the case in rat. In rats, melflufen is converted into melphalan so quickly, that most likely it is converted before melflufen reaches the cells. This is supported by results from an in vitro study described by Nygren (2009). In this study, the half-life of melflufen in blood of rats was 15 seconds and it was mainly converted into desethyl-melflufen, whereas it was 7 minutes in dog blood and 4.4 minutes in human blood. In dog and in humans melflufen was converted mainly into melphalan.

Both in dog and human red blood cells as in human multiple myeloma cells, it was observed that melphalan, after having been formed intracellularly, is gradually transported out of the cell into the plasma. Since melphalan is transported out of the cell following intracellular formation, the amount of time that melphalan is available for its action inside the cell appears limited. In an in vitro study in human myeloma cells, melphalan was detectable intracellularly up to 2 h after the start of incubation of melflufen (at 1 µM), with a peak at around 20 minutes.

In a study in female CB17 SCID mice xenografted with MM.S1 cells (multiple myeloma cells), the highest concentrations of melflufen and melphalan at 15 min after injection were found in pancreas, kidneys, liver, heart and lung. At 4 hours post dose the concentrations were 4 to 10-fold lower than at 15 minutes. Melflufen and melphalan were also found in the tumours. The amounts in tumour appear limited. This can be explained by the angiogenesis in xenografted tumour tissue, which is less pronounced and takes several days to develop, in combination with the rapid degradation of melflufen by esterases in mice. Melflufen will be largely degraded before it is distributed to the tumour and converted into melphalan there. A distribution study in rabbits was provided. Melphalan- and melflufen-derived radioactivity levels were high in kidneys, lungs and myocardium compared to plasma. In this study, the levels can however not be compared with levels in tumours.

It was noted that a statistically higher concentration of radioactivity was observed in the brain of melflufen-treated mice comparing to melphalan treated mice 4h post administration. Higher concentrations after melflufen treatment than after melphalan treatment were also found in a distribution study in rabbits (2.6 – 2.8 times higher). Absolute concentrations in brain were, however, low.

In a published melphalan distribution study in rats (Ahmed, Hsu et al. 1982) a slower rate of melphalan elimination has been reported from skin and eyes. Melanin binding of melflufen metabolites melphalan and desethyl-melflufen has not been studied nor discussed by the Applicant. Melflufen due to its rapid metabolism should not possess a risk. However the possible interaction of melfulfen metabolites with melanin remains questionable. The Applicant has conducted a QWB study in Dutch Belted rabbits to study melflufen and melphalan tissue distribution. Melflufen related radioactivity was equally distributed in pigmented and non-pigmented skin and radioactivity in the uveal tract/retina was similar to that observed in the brain indicating that melflufen does not specifically bind to melanin. The provided data in rabbits also suggest that melphalan, which is the main metabolite of melflufen, binds to melanin. Despite the fact that the provided data are very limited, strong binding of melphalan to melanin containing tissue was not observed and therefore should not be considered as a risk factor.

Applicant emphasizes that a dog from a pharmacokinetic point of view is considered to be the most relevant species for melflufen testing, however tissue distribution data in dogs have not been demonstrated nor discussed. Therefore, it is unclear how reliable the extrapolation of tissue distribution data from rodents to humans are, taking into consideration differences in the metabolism between species. Applicant was requested to provide literature data on the tissue distribution of melflufen and its metabolites in dogs or a justification that would support extrapolation of tissue distribution data from rodents to humans, taking into consideration that metabolism of melflufen in rodents differs from that observed in humans. Applicant claims that there are no literature data available on tissue distribution of melflufen in dogs but has performed a QWBA tissue distribution study in rabbits with radiolabelled melflufen and melphalan. Taking into consideration that melflufen has a higher lipophilicity, a more extensive tissue distribution than in melphalan dosed group was expected, and a higher concentration of radioactivity was found in 37 out of 52 investigated tissues of melflufen dosed animals. Differences between melflufen and melphalan covalently bound radioactivity in plasma, kidney cortex, kidney medulla, liver, lung and small intestinal wall was not observed. Rabbit, due to similarities in metabolism to humans and dogs, can be considered as a relevant species for tissue distribution studies.

The fate of melphalan was addressed only briefly and is not clearly described. It was described in an in vitro study in rat liver microsomes, that the formation of monoglutathionyl and diglutathionyl melphalan derivatives has been observed, but that these conjugates have not been observed in vivo. Also it was described that melphalan was found to be hydrolysed into mono- and dihydroxyderivatives in cancer patients. Overall it appears that in animals, additional metabolites may be formed besides mono- and dihydroxymelphalan, but that in humans melphalan is mainly converted into mono- and dihydroxymelpyhalan. It appears that monohydroxy-melphalan has cytotoxic activity and dihydroxy-melphalan has not.

The information provided regarding excretion of melphalan is very limited. Melphalan-related radioactivity was excreted in both urine (44%) and faeces (25%) of dogs within 11 days after IV dosing. Hence, in 11 days after dosing, only 69% of total radioactivity was excreted. This recovery is, however, in line with the recovery found in other mass balance studies with alkylating agents. According to Dubbelman et al (2013), incomplete recovery is not uncommon for an alkylating agent. Part of this may possibly be explained by irreversible binding to tissue components.

Pharmacokinetic drug interactions have not been studied for melflufen. The potential for pharmacokinetic drug-drug interactions is however expected to be low, since no metabolism by CYP enzymes is involved in the degradation of melflufen or melphalan, and no transporters are involved in the cellular uptake of melflufen.

Toxicology

The safety of melflufen was evaluated in three non-GLP single dose toxicity studies (dogs and minipigs), three non-GLP single dose toxicity studies (mice, rats and dogs) and in three GLP repeated dose toxicity studies (mice, rats and dogs). According to the ICH S9 guidance on nonclinical evaluation for anticancer pharmaceuticals (EMEA/CHMP/ICH/646107/2008), nonclinical studies of 3 months duration in both rodent and non-rodent species are required before marketing of anti-cancer pharmaceuticals. Melflufen has been tested for 35 days in mice and rats and 43 days in dogs. A rationale for not conducting appropriate duration toxicity studies for anticancer pharmaceutical is based on the toxicity profile of alkylating products. Furthermore, melflufen was used longer than 3 months in patients in clinical trials and haematological toxicity was the major and dose limiting toxicity for melflufen observed in these studies. Therefore, no new information was expected from the toxicity studies.

The observed melflufen-related findings in the pivotal repeated dose toxicity studies were likely related to its pharmacological action as an alkylating agent on rapidly dividing cells, and included severe effects on the bone marrow, lymphoid organs, testes and the haemolymphopoietic system.

In two single dose studies, in the non-GLP minipig study and in one non-GLP dog study, melphalan was included as comparator. It should be noted that acute single dose toxicity studies as currently performed using very high doses of a compound are not considered relevant to compare the toxicity of melflufen with melphalan (also see ‘Questions and answers on the withdrawal of the 'Note for guidance on single dose toxicity'' (EMA/CHMP/SWP/81714/2010)). In addition, there are several methodological issues: In the minipig study, the histologic comparison was performed on different days for each animal. Due to the lack of a recovery period for the earlier terminated minipig, the comparison of the histopathological findings between melflufen and melphalan is of limited relevance. In addition, the number of test subjects in the study was as low as one animal per group, which severely limits the interpretation of the study. In the comparative non-GLP dog study, the follow-up period was restricted to four days, due to expected severe effects of high doses. It should be noted that a limited number of animals per group were used, and that severe toxic effects, but also potential recovery, that could occur at a later timepoint, are most likely missed due to the short follow-up period. Together, the limitations of these studies prevent to conclude that the safety profile of melflufen is really different compared to that of melphalan.

Regarding the repeated-dose toxicity mice study, it should be noted that histopathology was only performed for animals in the high dose group. Possible treatment-related histopathological effects at lower doses were not reported. The NOAEL was not determined in this study. As no toxicokinetic data were available for mice, the safety margin compared to the clinical exposure is uncertain.

In the rat study, toxicokinetics were also not evaluated. Pharmacokinetics studies that used similar doses indicated a possible exposure multiple at the LOAEL of 2.4 based on an AUClast of 2570 ng.h/mL (study 20050055TRB) or 5.6 based on an AUClast of 6032 ng.h/mL (study AB19-70-02), indicating that the effects seen in rats are likely to be clinically relevant. However, it is not certain how reliable the measured concentrations are, as the used method was not validated in rats (study AB19-70-02) and a substantial matrix effect was observed in rat plasma (study 20050055TRB). In addition, it should be noted that based on the pharmacokinetics of melflufen, humans are more comparable to dogs than to rodents: in mice and rats, melflufen remained mainly in plasma where it was converted primarily into desethyl-melflufen and for a minor part into melphalan. In dogs and humans, melflufen was distributed quickly into red blood cells, where it was converted into melphalan and desethyl-melflufen. Desethyl-melflufen was also converted into melphalan and melphalan was then slowly transported out of the cells. Hence, the dog is considered the most relevant laboratory species for the human situation from a metabolic point of view.

Several impurities were reported in the drug substance (DS) and drug product (DP). These concern five drug-related substances and a sucrose degradation product, 5-hydroxymethylfurfural (HMF). For all of these impurities, specification limits are above the qualification thresholds. It is agreed that melflufen carboxylic acid (desethyl melflufen), dechloro-hydroxy-melflufen and HMF have been sufficiently toxicologically qualified. These substances have either been present in non-clinical/clinical studies due to being a major metabolite, a hydrolysis product of melflufen, or a sucrose degradation product with a known safety profile, respectively. The provided justifications for the toxicologically qualification of 3(N)-,4(F)-melflufen, dechloroethyl-melflufen and dechloroethyl-4-hydroxy-1-methylbutyl melflufen are also considered adequate. It should be noted that it would have been preferable if the Applicant had investigated the impurity levels in non-clinical batches which would enable comparison between batches. Stating that these substances should have been present to some degree in batches used for pivotal toxicity studies without providing data is wholly inadequate. However, based on the provided literature and the fact that these impurities have either lost one alkylating function (dechloroethyl-melflufen and dechloroethyl-4-hydroxy-1-methylbutyl melflufen) compared to melflufen or are of a similar structure as melflufen (3(N)-,4(F)-melflufen), it is presumable that these impurities are either less toxic or as toxic as melflufen itself. It can be agreed that ICH S9 should be taken into account (melflufen is a bifunctional alkylator with a distinct toxicity profile linked to this activity, indicated as last line treatment of multiple myeloma). Overall, there are no safety concerns expected from these impurities from a non-clinical point of view.

2.6. Clinical aspects

a marketing authorisation for melphalan flufenamide can be approvable from a non-clinical point of view.

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 1 Pharmacokinetic analyses in melflufen clinical studies

Study No.	Patient Population	Melflufen Dose Range (mg)	N with PK Data	Compound Analyzed	Sampling	Study Status
O-05-001	Solid tumor patients	25 to 130	29	Melflufen Melphalan	Rich	Completed
O-12-M1	RRMM	15 to 55	12	Melflufen Melphalan Desethyl-melflufen	Rich	Completed
OP-103	RRMM	30 to 40	96	Melphalan	Sparse	Ongoing
OP-104	RRMM	30 to 40	11	Melphalan	Sparse	Ongoing
OP-107	RRMM and renal failure	40	7	Melphalan	Sparse	Ongoing

Abbreviations: N=number of patients; No=number; PK=pharmacokinetics; RRMM=relapsed/refractory multiple myeloma

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Clinical pharmacokinetic (PK) and pharmacodynamic (PD) properties of melflufen and melphalan as well as exposure-response relationships of melphalan have been evaluated in studies in patients with solid tumours or multiple myeloma (**Error! Reference source not found.**).

Treatment with melflufen is hypothesised to lead to higher concentrations of melphalan in the tumour cells compared to melphalan treatment because melflufen is rapidly taken up into cells followed by a rapid enzymatic hydrolysis of the molecule to the active metabolite melphalan.

The recommended dose of melflufen is 40 mg administered intravenously over 30 minutes on Day 1 of each 28 day treatment cycle.

Specifically, PK information for melflufen is available from Study O-05-001 in patients with solid tumours and Study O-12-M1 in patients with multiple myeloma. Due to the very short disappearance half-life of melflufen from plasma, reflecting distribution, only the metabolite melphalan was measured in subsequent clinical studies. Melphalan PK parameters in patients with RRMM and impaired renal function are being assessed in the ongoing Study OP-107. In addition to the pharmacokinetics of melphalan studied in the melflufen clinical program, literature data have been used to complement pharmacokinetics of melphalan.

Bioanalytical methods

Samples with lithium or sodium heparin as anti-coagulant were centrifuged at +4°C in a pre-chilled centrifuge within 5 minutes after the sample was obtained. The tubes with plasma were frozen within 10 minutes to ensure that the degradation of the compounds was minimal.

Following protein precipitation, melflufen (or J1), desethyl-melflufen (or des-J1) and melphalan in human plasma were determined by UPLC-MS/MS. Melflufen-D8 hydrochloride and melphalan-D8 were used as internal standards. In general validation of bioanalytical method used in studies OP-103, OP-104, OP-107 have been performed in accordance with the requirements stated in the guideline EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**, however, approximately 20% of the plasma samples were analysed outside the long term stability period established. It was demonstrated by sensitivity analysis that this did not affect the popPK analysis to a relevant extent.

The bioanalytical method in study O-05-001 was suboptimal and does not meet current standards. Given these issues the PK data of study O-05-001 cannot be used for multi-study analyses. Since the in study performance of the quality controls and standards was acceptable and reproducible, the PK results of this study can be used for within study comparison but should be considered cautiously.

PopPK analysis

The population PK analysis was conducted via nonlinear mixed-effects modeling with a qualified installation of the NONMEM® software. The stochastic approximation expectation maximization (SAEM) method followed by Monte Carlo importance sampling (IMP) was employed for all model runs.

Data were pooled from studies O-12-M1, OP-103, OP107, and OP-109 for the development of the population PK model. The full PK analysis dataset included 294 patients, contributing a total of 2177 observations. Of these, 2155 samples had quantifiable melphalan concentrations, and 22 samples were BLQ (1.0%).

Approximately two-thirds (n=207, 70.4%) of patients had received less than four prior therapies when enrolled, 70 (23.8%) patients had received four to five and 17 (5.8%) patients had received 6 or more prior therapies. Patient's multiple myeloma was classed as triple class refractory if it was resistant to all three classes of standard myeloma therapies (i.e., proteasome inhibitors, immunomodulatory agents and monoclonal antibodies). This pooled population included 56 (19.0%) triple class refractory patients. The ISS classification and ECOG status are both measures of how a patient's disease is progressing. Most patients had an ISS disease classification of stage I or II (41.2 and 40.5%, respectively) and 17% of patients were classified as stage III. The ISS classification was missing for 4 patients (1.4%). Patients were similarly distributed among ECOG grades 0, 1 and 2 (37.4%, 52.7% and 9.9%, respectively). EMD is a rare but recognized manifestation of multiple myeloma in which the multiple myeloma cells form tumours outside of the bone marrow: 34 (11.6%) patients had EMD reported in this pooled population. There are multiple types of myelomas, here, patients were categorized according to whether they had an IgG or non-IgG myeloma: 180 (61.2%) patients had IgG myelomas and 114 (38.8%) had non-IgG myelomas.

The final model was a three-compartment model with melflufen dosing into a peripheral compartment and linear clearance. The final model included fixed effects of time-varying weight on clearance and volume terms. The effects of time-varying eGFR, baseline total protein, race (White versus Black/Asian/Other or Not Specified), baseline age, baseline AST and baseline BILI were estimated on CL. Additionally, the effects of baseline age, baseline AST and baseline BILI were estimated on V1.

Parameter estimates from the final SAEM-IMP run, and the median and 95% CIs of the bootstrap runs on sampled datasets are presented in Table 2 and Table 3. Compared to the base model, IIV on CL decreased from 42.8% to 33.4% and IIV on V1 decreased from 60.8% to 56.3%. Residual random effects were

described with a proportional (CV% = 23.2) error model. Fixed and random effects parameters were estimated with reasonable precision, but shrinkage was high for V1 and V3. Linear and log-linear pcVPC plots indicated that the pharmacokinetics of melphalan are reasonably well predicted by the popPK model. Melphalan exposure increased modestly with lower body weight and there was a clear increase in melphalan exposure with decreasing renal function with CrCL < 60 ml/min.

There were no obvious trends evident in the plots of NPDE or inter-individual random effects versus continuous or categorical covariates, may be some bias at early time points during the 30-minute infusion. Because of the high shrinkage on volume of distribution, PK metric parameters which are mostly influenced by clearance such as AUC (Cave) are preferred over Cmax values for exposure-response analyses.

Table 2 PK Final Model: Summary of population PK fixed effects parameter estimates.

			Final model	Non-parametric bootstrap	
			Estimate	Median	95% CI
Structural model parameters					
CL (L/h)	$\exp(\theta_1)$	Clearance	22.7	23.0	21.1, 25.0
V1 (L)	$\exp(\theta_2)$	Apparent central volume	2.94	2.74	2.00, 3.56
Q2 (L/h)	$\exp(\theta_3)$	Intercompartmental clearance to peripheral	0.227	0.239	0.142, 0.483
Q3 (L/h)	$\exp(\theta_4)$	Intercompartmental clearance to deep tissues	13.6	12.8	10.1, 18.7
V3 (L)	$\exp(\theta_5)$	Deep tissues volume	45.8	44.8	29.9, 67.4
V2/Q2 (/h)	θ_6	Proportional relationship between peripheral volume (V2) and Q2	1.16	1.19	0.927, 1.29
Covariate effect parameters					
CL_{eGFR}	θ_9	eGFR effect on CL	0.315	0.324	0.158, 0.502
CL_{PROT}	θ_{10}	Total protein effect on CL	0.710	0.749	0.481, 1.03
CL_{RACE}	θ_{11}	Race effect on CL	0.199	0.163	0.0493, 0.276
CL_{AGE}	θ_{12}	Age effect on CL	-0.000982	-0.0294	-0.311, 0.236
$V1_{AGE}$	θ_{13}	Age effect on V1	2.01	2.03	0.794, 3.68
CL_{AST}	θ_{14}	AST effect on CL	0.0181	0.0320	-0.0867, 0.152
$V1_{AST}$	θ_{15}	AST effect on V1	0.142	0.172	-0.452, 0.637
CL_{BILI}	θ_{16}	Bilirubin effect on CL	0.0681	0.0751	-0.0135, 0.161
$V1_{BILI}$	θ_{17}	Bilirubin effect on V1	-0.249	-0.328	-0.658, 0.0719

Parameters estimated in the log-domain were back-transformed for clarity
The confidence interval was determined from the 2.5th and 97.5th percentiles of the non-parametric bootstrap (n=500) estimates.
Abbreviations: CI = confidence interval; eGFR = estimated glomular filtration rate
Source code: pk-model-table-final.R
Source file: pk-param-boot-fixed.tex

Table 3 PK Final Model: Summary of population PK random effects parameter estimates.

		Final Model		Non-parametric bootstrap	
		Estimate	Shrinkage (%)	Median	95% CI
Interindividual variance parameters					
IIV-CL	$\Omega_{(1,1)}$	0.106 [CV%=33.4]	7.43	0.100	0.0707, 0.139
IIV-V1	$\Omega_{(2,2)}$	0.275 [CV%=56.3]	57.8	0.297	0.151, 0.775
IIV-Q2	$\Omega_{(3,3)}$	0.210 [CV%=48.4]	93.6	0.161	0.0100, 0.548
IIV-Q3	$\Omega_{(4,4)}$	0.230 [CV%=50.9]	25.4	0.237	0.0990, 0.381
IIV-V3	$\Omega_{(5,5)}$	0.0250 [CV%=15.9]	76.0	0.0250	FIXED
Residual variance					
Proportional	$\Sigma_{(1,1)}$	0.0537 [CV%=23.2]	11.6	0.0535	0.0438, 0.0631

Exposure-response analysis (report ONC0101F)

Data from studies O-12-M1 (N=76 with 12 PK), OP-103 (N=228 with 225 PK) and OP-107 (N=32 with 31 PK) were pooled for the development of the E-R efficacy models.

Logistic regression was used to develop an exposure-efficacy model of ORR using melphalan average concentration (Cavg) in Cycle 1 as the exposure. Cavg was calculated as the cumulative area under the concentration time curve (AUC) for Cycle 1 divided by the duration of Cycle 1. Since elimination half-life of melphalan is short 70 min, and the dosing interval is 28 days, the calculated Cavg is very low but Cavg, as used in exposure-response analysis, is actually a measure for AUC during the first cycle. Least absolute shrinkage and selection operator (LASSO) was implemented to identify predictive covariates of ORR. Patient data used in the covariate selection analysis were age, sex, race, body weight, body surface area, time since diagnosis, renal function, and hepatic function, triple refractory status, International Staging System (ISS) status, presence of extramedullary disease (EMD), Eastern Cooperative Oncology Group (ECOG) status, type of myeloma (IgG vs non-IgG), number of prior lines of therapy, prior autologous stem-cell transplantation (ASCT) transplant, time since prior ASCT transplant, and cytogenetic risk status. Main effects of these covariates as well as interactions with exposure were explored to develop a predictive model. Models were compared using model selection criteria, e.g., Akaike information criterion (AIC) and Bayesian information criterion (BIC), and were diagnosed and evaluated using randomized quantile residuals and visual predictive checks. The final predictive model was used to compute predictions of the probability of ORR at average exposures of different renal impairment populations (i.e., normal, mild, moderate, and severe).

Exposure-safety analysis were conducted for:

- multiple AEs, dose modifications etc. by logistic regression models or

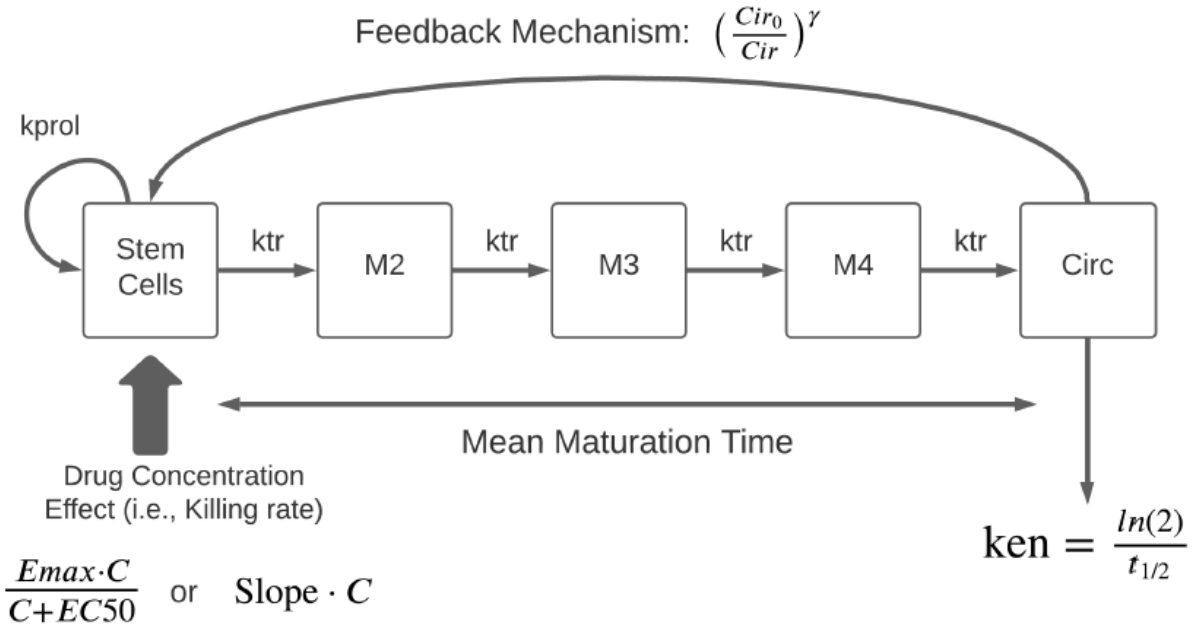
- exposure-myelosuppression AEs relationships by semi-mechanistic pharmacokinetic/pharmacodynamic (PK/PD) models for the time course of thrombocyte and neutrophil counts in relapsed refractory multiple myeloma (RRMM) patients receiving PEPAXTI and

- exploring the potential influence of ASCT on the pharmacodynamic (PD) parameters describing the time course of neutropenia and thrombocytopenia.

Pooled data from Studies O-12-M1, OP-103 and OP-107 were used.

The time-course of neutrophil and thrombocyte response to melphalan concentration were described using a semi-mechanistic PK/PD model of myelosuppression. The model was comprised of eight compartments (see Figure 2). The first 3 compartments represent the kinetics of melphalan; compartment 4 represents a proliferation compartment; compartments 5 to 7 are maturation compartments; and compartment 8 represents the blood stream with circulating neutrophils and thrombocytes from which PD samples were taken over time. All analyses were conducted via nonlinear mixed effects modeling with a qualified installation of NONMEM® version 7.4 (ICON Development Solutions, Dublin, Ireland).

Figure 2: PD model schematic.



The final thrombocytopenia model expanded the base model to include covariate effects. As with the base model, the final model included an estimated effect of TPO-RA treatment (i.e. romiplostim or eltrombopag with or without a blood or platelet infusion) if patients required treatment (and fixed it to 0 if they did not). Additionally, the effect of eGFR, EMD and hepatic impairment category (normal versus mild impairment) were estimated on EC50. The effect of ISS classification, EMD, and hepatic impairment category (normal versus mild impairment) were estimated on CIR.

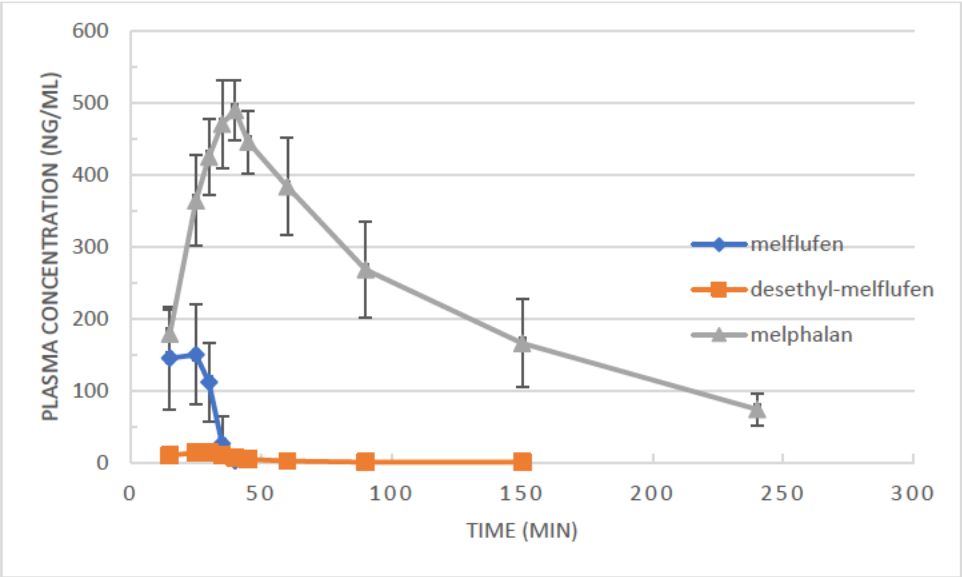
Absorption

Melflufen is administered intravenously and therefore, no bioavailability (BA) or bioequivalence (BE) studies have been performed.

In study O-12-M1, PK of melflufen and the metabolites desethyl-melflufen and melphalan were assessed in a subset of patients with relapsed/refractory multiple myeloma during the first treatment cycle. Melflufen PK is characterized by low plasma concentrations during the IV infusion and a very rapid disappearance after the end of infusion with a half-life of less than 5 minutes (Figure 3). Plasma concentrations of melphalan, the main active metabolite, increased rapidly and melphalan plasma concentrations exceed those of melflufen within 15 minutes after the start of the 30-minute melflufen infusion. Peak plasma concentrations of melphalan appear with a Tmax of 34-45 min, a delay by 5 to 15 minutes after the end of the melflufen infusion. Melphalan Cmax was approximately 3 to 4-fold higher than the Cmax of melfufen and AUC of melphalan was almost 20-fold higher than the AUC of melflufen (see *Table 4*).

Plasma concentrations of the metabolite desethyl-melflufen remained very low during and after melflufen administration. Because of the low plasma concentrations and hence low impact on the efficacy and safety, desethyl-melflufen was not measured in the other studies.

Figure 3 Mean plasma concentration-time profiles for melflufen, melphalan, and desethyl-melflufen after infusion of melflufen over 30 minutes at the 40 mg dose level (study O-12-M1, N=7)



PK parameters for melflufen and the metabolites desethyl-melflufen and melphalan following 40 mg melflufen IV dosing are summarised in *Table 4*.

Table 4 Descriptive statistics for PK parameters by compound in patients receiving the melfufen dose of 40 mg (study O-12-M1: N=8 melphalan and desethylmelflufen, N=7 for mellufen, updated Table D120 response).

PK parameter	Compound	Mean (SD)	Geometric mean (CV%)	Median	Min	Max
Tmax min	Melflufen	21.3 (4.82)	20.8 (24.8)	25	15	25
	Desethyl melflufen	27.8 (3.06)	27.6 (11.0)	27	25	32
	Melphalan	39.3 (3.92)	39.1 (9.95)	38.5	34	45
Cmax ng/mL	Melflufen	159 (63.4)	148 (42.6)	160	87	255
	Desethyl melflufen	16.8 (7.67)	15.4 (45.7)	13.5	9.1	30.7
	Melphalan	519 (71.6)	515 (13.8)	516	403	660
AUC0-t ng/mL*min	Melflufen	3406 (1501)	3124 (47.6)	2636	1772	5218
	Desethyl melflufen	315 (126)	293 (43.4)	283	166	508
	Melphalan	7034 (1266)	6930 (19.0)	6943	4745	9264
AUCinf ng/mL*min	Melflufen	3787 (1691)	3465 (48.4)	3009	1873	5983
	Desethyl melflufen	632 (354)	543 (66.3)	524	224	1125
	Melphalan	64,828 (14,416)	63,419 (22.8)	63,429	48,911	81,335
AUClast ng/mL*min	**Melflufen**	**3762 (1695)**	**3437 (49)**	**2966**	**1854**	**5959**
	Desethyl melflufen	**547 (311)**	**470 (65)**	**444**	**201**	**1048**
	Melphalan	**55,943 (12,101)**	**54,801 (22)**	**55,118**	**42,573**	**71,536**
T½ min	Melflufen	2.18 (0.604)	2.09 (34.3)	2.27	1.07	2.80
	Desethyl melflufen	13.2 (7.33)	11.2 (71.5)	12.0	3.82	24.3
	Melphalan	80.0 (9.55)	79.4 (12.0)	78.2	66.1	92.8
CL L/h	Melflufen	756 (334)	692 (48.5)	797	401	1282
	Desethyl melflufen	NC	NC	NC	NC	NC
	Melphalan	23.8 (5.26)	23.3 (22.7)	23.8	18.1	30.2

NC Not calculated

Melflufen and melphalan Cmax and AUC increased in approximate relation to dose over melflufen dose range 25-130 mg (study O-05-001). There is no accumulation with a monthly dosing interval. Intersubject variability of melflufen exposures is considerably higher than the intersubject variability of melphalan. Across studies, the intersubject variability of melphalan pharmacokinetics is modest 20-30% and the intrasubject variability is lower.

In most clinical studies, only pharmacokinetics of melphalan was evaluated. Descriptive statistics for melphalan PK parameters for cycle 1 for patients with RRMM from the ongoing studies OP-103, OP-104, and OP107 are shown in

Table 5.

Table 5 Melphalan PK parameters in patients with RRMM for Cycle 1 in studies OP-103, OP-104 and OP-107 at the melfufen dose of 40 mg (Interim PK report)

Variable (Unit)	N	Mean	Min-Max	Geometric Mean	Geometric Mean CV%
C_{max} (ng/mL)	104	461	158-988	441	30.3
AUC_{last} (ng/mL*min)	104	44,604	15,698 – 108,934	42,268	33.0
AUC_{0-inf} (ng/mL*min)	104	56,425	24,085 – 116,049	53,931	30.5
$t_{½}$ (min)	104	71.2	47.5 - 123	69.7	20.6

Distribution

In vitro studies were conducted to support that the formation of melphalan is not spontaneously but is formed in cells studies (Nygren 2009, Recipharm 2019). When melflufen was added to whole human blood at 37°C, the distribution to erythrocytes was very rapid with peak concentrations observed within one minute. The melflufen disappearance half-life from plasma and erythrocytes was approximately 4-5 minutes. However, when melflufen was added to human plasma, the disappearance half-life was 2-5 hours and there is no appreciable formation of melphalan.

In human plasma, protein binding of melphalan was 80 – 92% at concentrations from 0.3 – 33 nmol/mL (Greig, Sweeney et al. 1987). The plasma protein binding in cancer patients treated with melphalan has been reported to vary between 54–94% (Reece, Hill et al. 1988).

The mean (CV%) volume of distribution was 35 L (71%) for melphalan flufenamide (study O-12-M1) and the mean apparent volume of distribution is 76 L (32%) for the metabolite melphalan after a single dose of melphalan flufenamide (study OP-103).

Elimination

Total melflufen plasma CL in humans is very high with values ranging from 400 to 1280 L/h (study O-12-M1) with mean 692 L/h (CV 49%). Apparent clearance of melphalan was 23.3 L/h (CV=23%).

Elimination half-life of melflufen and melphalan is approximately 2 min and 60-80 min, respectively.

Excretion of melflufen in urine and faces was not evaluated.

Melflufen is readily metabolized by intracellular peptidases into melphalan or by esterases into hydrophilic desethyl-melflufen. Melphalan is eliminated primarily by spontaneous hydrolysis to monohydroxymelphalan and melphalan is to some extent excreted unchanged in the urine (Evans et al. 1982, Reece et al. 1988).

Special populations

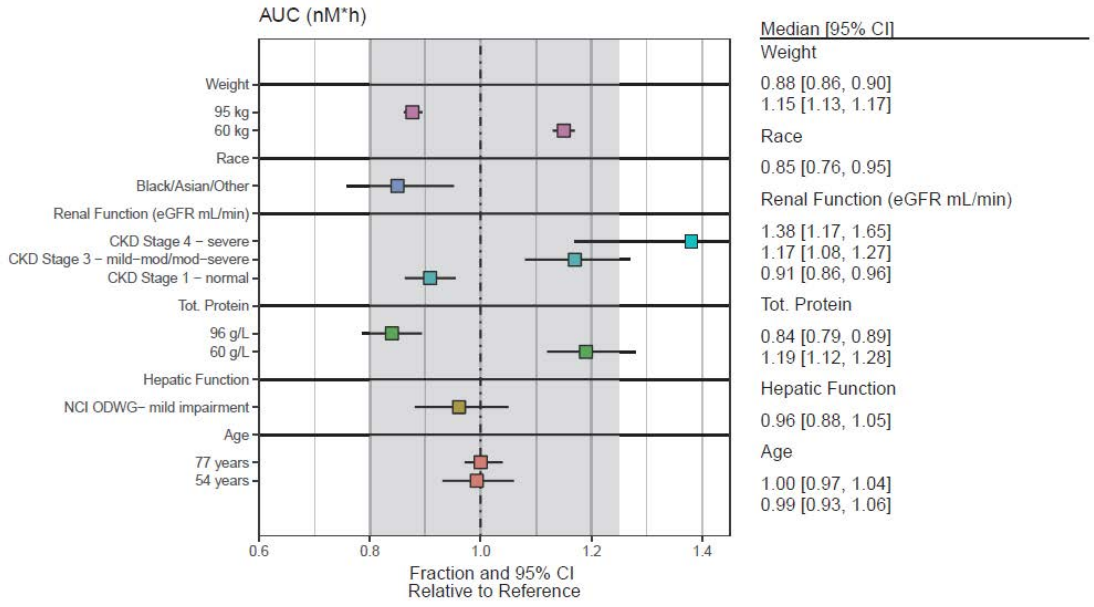
The relationship between demographic factors and the melphalan PK parameters Cmax and AUC for the melflufen dose 40 mg was evaluated by popPK analysis.

Patient race was predominantly reported as White (269 patients, 91.5%) with the other 8.5% of patients categorized as Black or African American, Asian and other or not specified (3.1%, 2%, and 3.4%, respectively). Patient age ranged from 41 to 91 years with a median of 68 years; 110 patients were <65 years, 129 patients were 65-74 years, 50 patients were 75-84 and 5 patients were ≥85 years. Body weight ranged from 40.0 to 140 kg with a median of 75.4 kg, and body surface area (BSA) ranged from 1.26 to 2.71 m^2 with a median of 1.88m^2. The pooled dataset included 65 patients (22.1%) with normal renal function, 139 patients (47.3%) with mild renal impairment, 84 patients (28.6%) with moderate renal impairment and six patients (2.0%) with severe renal impairment. Estimated glomerular filtration rate (eGFR) ranged from 27.2 to 121 with a median of 72.6 mL/min/1.73m^2. CRCL ranged from 29.2 to 160 mL/min with a median of 72.2 mL/min across all patients.

The Forest plot (Figure 4) shows the effects of the covariates on AUC and Cmax of melphalan following administration of 40 mg melfufen. Body weight and renal function were the demographic factors affecting melphalan exposure. Total protein, albumin, race, age, sex, aspartate transaminase, bilirubin, ECOG status, type of myeloma, presence of extramedullary disease, ISS disease classification, number of prior lines of therapy, and refractory status are not expected to result in clinically relevant differences (within 20% of mean) melphalan exposure.

Figure 4 PK Final Model: Effects of weight, race, renal function, chronic kidney disease (CKD), total protein, hepatic function and age on the melphalan maximum concentration in the 28 day dosing interval (AUC (top), Cmax (bottom)).

The grey shaded area is the reference range with a lower bound of 0.8 and an upper bound of 1.25. The reference subject was a 68 year old, 70 kg, White patient with mild renal impairment (eGFR=76 mL/min), normal hepatic function (AST=20.0 U/L, BILI=8.6 umol/L), and total protein level o 76 g/L. Mild hepatic impairment was simulated using AST=38.4 U/L and BILI=11.1 umol/L. Renal impairment for CKD stage 1, 3, and 4 was simulated using the median eGFR (102, 47.3 and 28.0 mL/min, respectively) for each of the renal impairment categories assigned based on eGFR (mL/min) in the observed dataset.



Source code: forest–plots.R
Source graphic: 64–forest–plot–cmax–auc.pdf page: 3

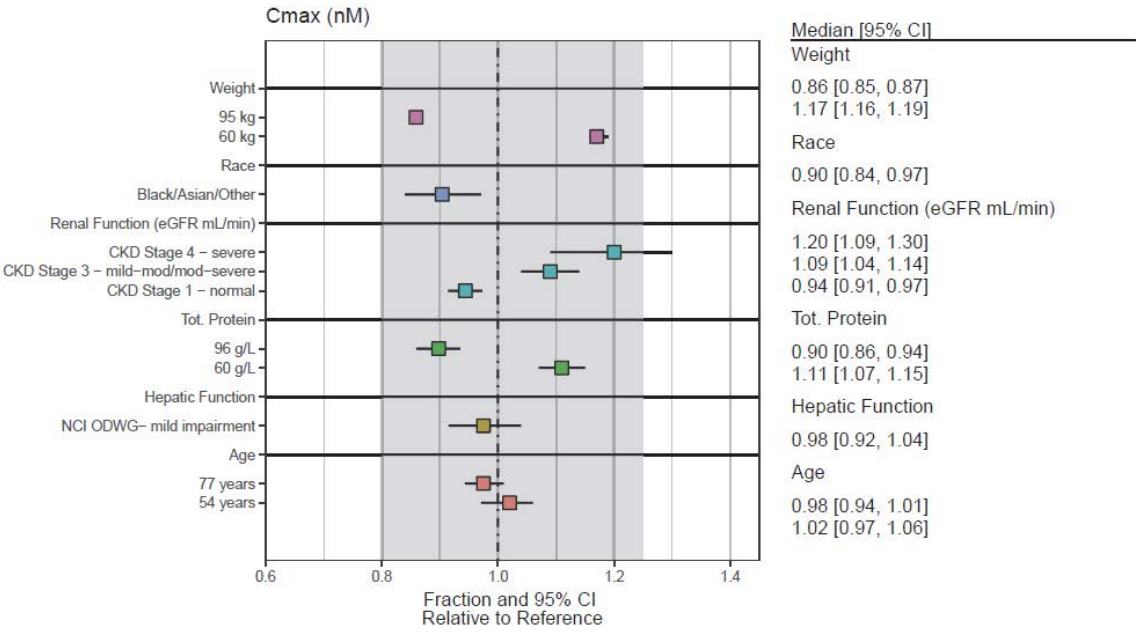


Table . Age distribution among patients included in PK analyses across studies

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	127/288	49/288	5/288

Pharmacokinetic interaction studies

Pharmacokinetic drug interactions have not been studied for melflufen.

Melflufen is rapidly metabolized intracellularly to melphalan. Systemic exposure to melflufen occurs only during the 30-minute infusion and for a few minutes after the end of infusion. Therefore, drug-drug interactions by competition for drug metabolic enzymes are highly unlikely for melflufen.

Melphalan is eliminated from plasma primarily by spontaneous hydrolysis to non-alkylating metabolites and with a contribution of direct renal elimination. There is no appreciable active metabolism of melphalan. Drug-drug interactions with melphalan caused by inhibition of drug metabolic enzymes are therefore unlikely.

2.6.2.2. Pharmacodynamics

Mechanism of action

Melphalan flufenamide (melflufen) is an optimized derivative of the classical nitrogen based alkylating agent melphalan. Owing to its high lipophilicity, melflufen freely and rapidly traverse the cell membrane. The rapid inflow of melflufen into cells is followed by rapid enzymatic hydrolysis of the ester/peptide bond leading to molecular trapping and high local concentration of primarily melphalan.

Nitrogen-based alkylating agents like melflufen exert their cytotoxic action through covalent interaction with intracellular nucleophiles, especially DNA, as a result of the spontaneous formation of reactive cyclic aziridinium ion intermediates. Cross-linking of DNA is probably the most important factor for the cytotoxic effect, resulting in inhibitory effects on DNA replication and transcription which subsequently triggers cell death.

Primary and Secondary pharmacology

Melphalan flufenamide (melflufen) is an optimized derivative of the classical nitrogen based alkylating agent melphalan. Melphalan has been in clinical use as an antitumor agent for more than 60 years. Owing to its high lipophilicity, melflufen freely and rapidly traverses the cell membrane. The rapid inflow of melflufen into cells is followed by rapid enzymatic hydrolysis of the ester/peptide bond leading to molecular trapping and high local concentration of primarily melphalan.

Nitrogen-based alkylating agents like melflufen exert their cytotoxic action through covalent interaction with intracellular nucleophiles, especially DNA, as a result of the spontaneous formation of reactive cyclic aziridinium ion intermediates. Cross-linking of DNA is probably the most important factor for the cytotoxic effect, resulting in inhibitory effects on DNA replication and transcription which subsequently triggers cell death. The proof of concept for efficacy of melflufen was shown through non-clinical *in vitro* and *in vivo* experiments, and thereby the mode of action is sufficiently demonstrated.

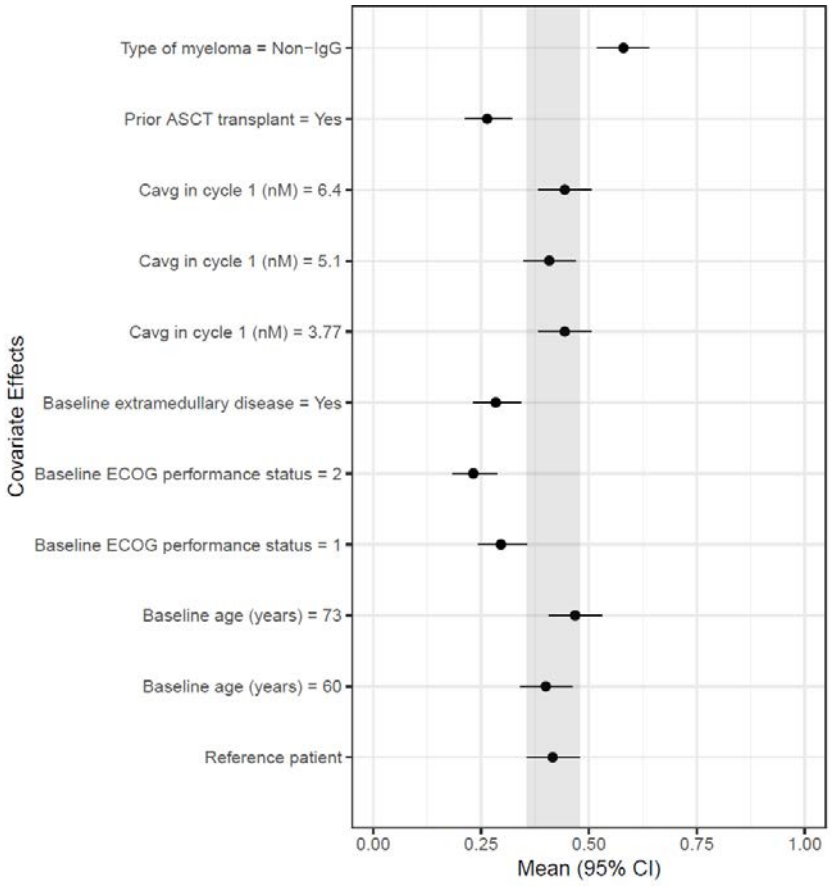
Effect on corrected QT interval (QTc)

The effect of melflufen on ventricular repolarization was studied in a phase I/IIa study in patients with relapsed and or relapsed-refractory multiple myeloma (study O-12-M1). The primary objective of the Phase 1 part of the study was to determine the maximum tolerated dose (MTD) of the combination of melflufen and dexamethasone (15 to 55 mg melflufen). Within phase II, additional patients were to be enrolled and treated at the MTD. Holter ECG data were collected in 23 patients, whereof 11 patients in the 40 mg melflufen plus dexamethasone cohort (i.e. the MTD in phase 1, selected as the clinical dose for phase 2), and from 2 to 4 patients in the remaining dose groups.
On Day 1 in Cycle 1, the mean change-from-baseline QTcF (DQTcF) was overall small and did not exceed 3.5 msec in the 40 mg melflufen+dexamethasone group. In the highest dose group (55 mg melflufen+dexamethasone) with only 2 observations on subsequent days, mean ΔQTcF was substantially higher on Day 1 in Cycle 2: mean ΔQTcF was 22.7 msec at the pre-dose time point and up to 35.7 msec post-start of dosing, representing a mean increase of 13 msec. In the 40 mg melflufen+dexamethasone group, mean ΔQTcF did not exceed 1.7 msec and 4.1 msec on Day 1 in Cycle 2 and Cycle 3, respectively. There were no subjects with QTcF > 480 msec and no subjects with ΔQTcF > 60 msec. Melflufen with dexamethasone at the studied dose did not show notable changes on cardiac conduction (the PR and QRS intervals) or heart rate.

Exposure-efficacy analyses

The ORR for Studies O-12-M1, OP-103 and OP-107 was 18.7%, 34.6%, and 54.8%, respectively, with an overall ORR estimate of 32.9% in the pooled relapsed refractory multiple myeloma (RRMM) population. Melphalan exposure did not affect ORR. Type of myeloma, prior autologous stem cell transplant, EMD status, and ECOG status were the main factors influencing ORR. Model predictions of overall response rate of melphalan Cavg in Cycle 1 at population average exposures of normal, mild, moderate, and severe renal function, showed comparable overall response rate after accounting for other factors (Figure 5). Sensitivity analyses using melphalan maximum concentration in the dosing interval (Cmax) in Cycle 1 exposure showed similar melphalan exposure effects on ORR.

Figure 5 ORR model: Predictions of ORR at typical Cavg in Cycle 1 values for different renal impairment function populations The shaded region represents the 95% CI for predicted ORR of the reference patient, who has melphalan Cavg in Cycle 1 of 4.31 (nanomoles (nM)), ECOG status 0, IgG myeloma, no prior autologous stem cell transplant, no extramedullary disease, and baseline age of 68 years. Melphalan Cavg in Cycle 1 exposures of 3.77, 4.31, 5.10, and 6.42 corresponded to average melphalan exposures for patients with normal, mild, moderate, and severe renal impairment.



Exposure-safety analyses

An interim analysis of the relationship between melphalan AUCinf and nadir levels of neutrophils and thrombocytes during the first melflufen treatment cycle for the completed Study O-12-M1 and the ongoing studies OP-103, OP-104, and OP-107, showed a clear increase in incidence of Grade 3 and Grade 4 neutropenia with increasing AUCinf values (Table 6).

Table 6 Incidence of Grade 3 and Grade 4 neutropenia and thrombocytopenia at Nadir in Cycle 1 by melphalan AUCinf Range (Interim analysis of studies OP-103, O-12-M1, OP-104, OP-107).

	Melphalan AUC_{inf} (ng/mL*min)		
	<45,000	45,000-65,000	>65,000
Neutrophils			
Grade 3	3/32 (9%)[a]	13/51 (25%)	15/33 (45%)
Grade 4	3/32 (9%)	7/51 (14%)	5/33 (15%)
Grade 3+4	6/32 (19%)	20/51 (39%)	20/33 (61%)
Thrombocytes			
Grade 3	7/32 (22%)	10/51 (20%)	4/33 (12%)
Grade 4	2/32 (6%)	5/51 (10%)	9/33 (27%)
Grade 3+4	9/32 (28%)	15/51 (29%)	13/33 (39%)

Neutropenia and Thrombocytopenia assessed by Laboratory Values

Abbreviations: AUC_{inf} = area under the concentration-time curve extrapolated to infinity.
a Incidence n/N (%)

Exposure-safety analysis were conducted for multiple AEs, dose modifications by logistic regression models (ONC0101F-BriefComm-AE-v1.0-Final, 2021-08-02) using pooled data from studies OP-103, O-12-M1, OP-104, OP-107. Cycle 1 exposure metrics were used because the use of cumulative metrics was hindered by the variable follow-up lengths and dose modification patterns. Since many AEs and dose modifications occurred soon after start of treatment, the use of cycle 1 exposures is acceptable to evaluate exposure-AEs relationships during the first two cycles. The strongest trends between melphalan exposure and dose modifications at least grade 3 AEs, and leukopenia events of at least grade 3.

Exposure-myelosuppression AEs relationships were evaluated further by semi-mechanistic pharmacokinetic/pharmacodynamic (PK/PD) models for the time course of thrombocyte and neutrophil counts in relapsed refractory multiple myeloma (RRMM) patients receiving PEPAXTO (ONC0101F-Report-v1.0-Draft 2021-08-10) and exploring the potential influence of ASCT on the pharmacodynamic (PD) parameters describing the time course of neutropenia and thrombocytopenia (ONC0101F-BriefComm-PKPD-ASCT-v1.0-Final 2021-10-08) using pooled data from studies OP-103, O-12-M1, OP-104, OP-107.

The PKPD models showed that thrombocyte and neutrophil count decreased with increasing melphalan exposures. Patients with moderate to severe renal impairment were less sensitive to thrombocytopenia and had higher baseline neutrophil counts than patients with normal or mild renal function. This may suggest that proliferation/maturation/circulation of neutrophils and thrombocytes may be different in patients with moderate and severe renal impairment.

EMD, mild hepatic impairment, and prior ASCT have an effect on the concentration resulting in 50% of the maximal effect relative to the reference patient, reducing EC50 value approximately 65%, 42%, and 60%, respectively. ISS and ASCT have an effect on the estimated baseline thrombocytes relative to the reference patient reducing the value approximately 30% and 34%, respectively. Including ASCT in the PKPD model for thrombocytopenia resulted in differences between the model parameter estimates for EMD and ASCT on EC50 and estimates from non-parametric bootstrap indicating that the model was less robust including ASCT. The other covariates were not influenced by inclusion of prior ASCT.

Higher melphalan concentrations caused more neutropenia in patients with an Eastern Cooperative Oncology Group (ECOG) status >0 relative to patients with an ECOG status of 0. The lower the patients' body weight, a higher incidence of thrombocytopenia and neutropenia could be observed, as seen in the safety data base (N=491).

Table 7 Neutropenia and Thrombocytopenia based on the safety data base (N=491)

Body weight	Neutropenia	Thrombocytopenia
<60kg n=57	71,9%	80,7%
60-75kg n=191	59,2%	70,2%
75-95kg n=177	53,7%	62,1%
>95kg n=64	46,9%	64,1%

Source: Table 18.3.4.

2.6.3. Discussion on clinical pharmacology

Clinical pharmacokinetic and pharmacodynamic properties of melflufen and its active metabolite melphalan as well as melphalan exposure-response relationships have been evaluated in 5 studies in patients with solid tumours or multiple myeloma. Pharmacokinetics were not evaluated in study OP-106, but were evaluated in study OP-103. Three of these studies are still ongoing and the data lock was May 2019. A population PK and exposure-response evaluation of melphalan plasma concentration data across melflufen studies will be performed when all data from the ongoing Study OP-103 are available. This analysis will further investigate the relationship between PK parameters and intrinsic and extrinsic factors, and the exposure-response relationship for safety and efficacy variables. With the response to the answers to the questions, the applicant has submitted the popPK report, an exposure-efficacy report and 3 reports on exposure-safety analyses.

Melflufen is a lipophilic peptide conjugated alkylating drug designed to increase cellular melphalan concentrations. Due to its high lipophilicity, the cellular uptake of melflufen is very rapid. Inside the cells the peptide bond is hydrolysed and melphalan is formed, resulting in a different disposition / higher cellular concentrations of melphalan. This is hypothesised to result in improved efficacy without increase in toxicity compared to melphalan.

Indeed, melflufen PK is characterized by a very rapid disappearance from plasma after the end of infusion with a half-life of less than 5 minutes. Melphalan, the main active metabolite, is rapidly formed with peak plasma concentrations of melphalan 5 to 15 minutes after the end of the melflufen infusion and melphalan plasma concentrations exceeded melflufen plasma concentrations halfway the infusion. Melphalan Cmax was approximately 3 to 4-fold higher than the Cmax of melfufen and AUC of melphalan was almost 20-fold higher than the AUC of melflufen. The plasma concentrations of the active metabolite desethyl-melflufen is in contrast to several animal species very low in humans.

No direct comparison of the pharmacokinetics of melphalan following equimolar doses of melflufen and melphalan in human were submitted to support the different disposition of melphalan following melflufen and

melphalan administration. In dogs, such a comparison was made (study OP-2019-002): melphalan mean Cmax was 40% lower and the mean AUC∞ 2% in melflufen administered dogs compared to in melphalan administered dogs (see non-clinical AR). The lower melphalan Cmax may support a different distribution of melphalan following infusion of melflufen compared to melphalan infusion.

Further, support for the hypothesis that melflufen is rapidly taken up into cells followed by a rapid enzymatic hydrolysis of the molecule, leading to high intracellular exposure to the more hydrophilic metabolites desethyl-melflufen and melphalan, is mainly supported by in vitro data. In vitro data showed that melflufen is stable in plasma at 37°C (half-life 2-5 hours) while melflufen was rapidly cleared form blood (half-life < 5min) and taken up by blood cells. These data indicate that melphalan is not spontaneously formed from melflufen in plasma but is formed in cells. This was further supported by a 50-fold higher accumulation of melphalan in cell lines when administered as melflufen compared to melphalan (see non-clinical part). It is doubtful that the increase in cellular melphalan concentrations is specific for tumour cells since melflulfen is rapidly widely distributed (animal tissue distribution) and enters cells by passive transport. Further, already 15 min after start of infusion melphalan plasma concentrations exceed melflufen plasma concentrations. This does not indicate a tumour specific response. In vitro data confirmed that melflufen, melphalan and desethyl melflufen exhibit alkylating activities and could contribute to the efficacy and toxicity in vivo. However, there are no data from MM patients treated with melflufen to indicate occurrence of similar distinct time profiles for cellular exposure to melflufen, desethyl-melflufen, and melphalan and their DNA adducts in vivo as was shown in vitro and it is not possible to estimate this contribution quantitatively in relation to the activity of melphalan without a direct comparison with melphalan. Therefore, the claim of an improved benefit-risk of melflufen treatment compared to melphalan treatment due to altered disposition of melphalan cannot be concluded without a direct comparison.

Pharmacokinetics of melflufen has only been evaluated in two studies. This is considered acceptable because melflufen can be considered a derivate of melphalan, designed to increase melphalan concentrations in the tumour cells. Melflufen and melphalan Cmax and AUC increased in approximate relation to dose over melflufen dose range 25-130 mg. No studies were conducted to evaluate the excretion of melflufen or melphalan, effect of hepatic impairment and no pharmacokinetics interaction studies have been performed. Melflufen is not metabolised by CYP enzymes but by cellular esterases and aminopeptidases to desethylmelflufen and melphalan, respectively. Given the short plasma elimination half-life of melfufen, and the much higher melphalan exposure compared to melflufen indicating that melphalan is the main moiety responsible for efficacy and safety, absence of excretion, hepatic impairment and drug interaction studies for melflufen is considered acceptable. Melphalan is eliminated primarily by spontaneous hydrolysis to monohydroxymelphalan and melphalan is partly excreted unchanged in the urine. Hence, the interaction potential of melphalan is low.

During the evaluation procedure, reports on popPK and melphalan exposure-response analyses were provided. The reporting and model evaluation of the popPK and exposure-response modelling was well described and in agreement with EMA guidelines (CHMP/EWP/185990/06). The popPK model seems to describe the pharmacokinetics of melphalan adequately, and seems fit for use in exposure-response analyses but some additional plots are requested for better evaluation. Body weight, renal function and total protein but not gender or age were co-variates on melphalan exposure. The applicant proposes a lower starting dose of 30 mg for subjects <60 kg and for subjects with renal function eGFR 30-45 mL/min/1.73 m2 (see dosing below).

Melphalan is partly excreted unchanged in the urine. At day 120 responses, the applicant has included results from study OP-107 in the popPK and the exposure-response analyses, this study included 24 subjects with

moderate and 6 subjects with severe renal impairment. The subjects were classified as having severe renal impairment the lowest eGFR was 27.2 ml/min/1.73m2 which is borderline severe renal impairment. Based on popPK modelling, melphalan exposure was 29% and 51% higher in subjects with moderate and severe renal impairment compared to subjects with normal renal function. A lower starting dose of 30 mg of Pepaxti has been proposed for patients with eGFR 30-45 mL/min/1.73 m2 because melphalan exposure was on average 30% higher in these subjects and melflufen was worse tolerated in the group started on 40 mg melflufen compared to the group started on 30 mg melflufen. Therefore, the reduced starting dose for subject with eGFR 30-45 mL/min/1.73 m2 is considered acceptable. Treatment of subjects with severe renal impairment is not recommended. This has sufficiently described in sections 4.2 and 5.2 of the SmPC. Data from 4 subjects with severe renal impairment enrolled in cohort 2a of study OP-107 and treated with 20 mg melflufen will be submitted when the study report is finalised (expected Q3-Q4 2022).

Logistic regression was used to develop an exposure-response model of ORR and a parametric time-to-event model was used to develop an exposure-response model of OS and PFS. For the exposure-efficacy relationships, melphalan Cave in the first cycle was used as exposure parameter. Use of AUC (Cave) over Cmax is supported because of the high shrinkage for volume of distribution. Since response is rather rapidly achieved for ORR, melphalan Cave in the first cycle is considered an acceptable exposure metric. Time to event exposure-PFS and exposure-OS analyses were hampered by the many dose reductions, which resulted in a decreasing melphalan exposure over time, and the lowest average exposures were associated with patients remaining under observation for the longest durations. This resulted in an inverse exposure-response relationship when KM curves were stratified by cumulative (and duration normalized) metrics of melphalan exposure. Therefore, for exposure-efficacy relationships, the exposure-ORR relationship is considered most informative.

There was no correlation between plasma melphalan exposure Cave and ORR. Since almost all patients started on 40 mg melflufen, the exposure range of melphalan in the first cycle is limited and this may hamper extrapolation to other dosing regimen. Disease related factors such as type of myeloma, prior autologous stem cell transplant, EMD status, and ECOG status were the main factors influencing ORR.

Exposure safety analyses focussed on thrombocytopenia and neutropenia. The choice of the thrombocyte and neutrophil nadir as the PD endpoint is in general considered acceptable for an alkylating agent. PKPD modelling showed that higher melphalan concentrations caused more thrombocytopenia and neutropenia ≥ grade 3. In addition to melphalan exposure, was ECOG status a covariate in the model: higher melphalan concentrations caused more neutropenia in patients with an ECOG status >0 relative to patients with an ECOG status of 0. EMD, mild hepatic impairment, and prior ASCT have an effect on the concentration resulting in 50% of the maximal effect relative to the reference patient, reducing EC50 value approximately 65%, 42%, and 60%, respectively. ISS and ASCT have an effect on the estimated baseline thrombocytes relative to the reference patient reducing the value approximately 30% and 34%, respectively.

The semi-mechanistic PKPD models for the time course of thrombocyte and neutrophil counts overestimated the variability, which renders simulations somewhat more uncertain. Nevertheless, simulations suggested that dose reduction after recovery from the first Grade 3 neutropenia event was likely to mitigate the overall risk of developing subsequent episodes of Grade 3 neutropenia. The recommended dosage modifications for adverse reactions of Pepaxti for haematologic adverse reaction accordingly. While this changed dosing recommendations may mitigate subsequent neutropenia grade 3 episodes, it is not estimated to reduce the risk of developing episodes grade 3 thrombocytopenia. The rate of Grade 3 thrombocytopenia events is more affected by a lower melflufen starting dose. Since the proposed dose modification may contribute to lower some AEs as simulated for neutropenia, the proposed change can be accepted.

Starting Dose

Sound rationale for the selected flat dosing regimen has not been provided. According to the pharmacokinetic data presented, melphalan exposure (Cmax and AUC) are ~50% higher in subjects with a BSA 1.6 m2 compared to subjects with a BSA of 2.2 m2. This does not support a flat dosing strategy. Melphalan is usually dosed based on body weight or based on body surface area. Higher melphalan exposures were associated with an increased incidence of grade 3+4 haematologic AEs. Thrombocytopenia was a major reason for premature discontinuation of melflufen treatment.

In response to request for justification of the flat dosing, the applicant proposes a lower melflufen starting dose of 30 mg instead of 40 mg for patients with bodyweight < 60 kg. The rationale is that there is a clear increase in thrombocytopenia and neutropenia with increasing melphalan exposure, while there was no correlation between melphalan exposure in the first cycle and ORR. The reduced starting dose for subjects with low body-weight was further substantiated by PK simulations indicating that the 30 mg starting dose in subjects weighing <60 kg is expected to result in a comparable melphalan exposure to subjects weighing 70-80 kg. In study OP-103, the overall incidence of AE leading to discontinuation was 32% in patients with a body weight <60 kg and 26% in patients with a body weight ≥60 kg, but the percentage of patients without dose reduction was 52% vs 47%, respectively. In the safety data base (N=491), a higher incidence of thrombocytopenia and neutropenia could be observed in subjects with lower body weight (Table 7). Therefore, the reduced starting dose for subjects with low body-weight is considered acceptable.

Though data are limited, melflufen in combination with dexamethasone did not result in a clinically relevant QTc prolongation in patients with MM. The absence of an effect on QTc prolongation is supported by what is known for melphalan.

2.6.4. Conclusions on clinical pharmacology

Pharmacology of melflufen has only been evaluated in two studies. This is considered acceptable because melflufen can be considered a derivate of melphalan, designed to increase melphalan concentrations in (the tumour) cells. Melphalan has been in clinical use as an antitumor agent for more than 60 years.

Overall, clinical pharmacology has been characterized.

2.6.5. Clinical efficacy

Main clinical efficacy data is derived from Phase 2 single arm trial OP-106 (HORIZON) investigating melflufen in combination with dexamethasone in relapsed refractory multiple myeloma (RRMM) patients (Table 7). Supportive data is derived from Phase 1/2 dose finding study O-12-M1. In response to the Day 120 List of Questions, results of recently conducted Phase 3 randomized controlled trial OP-103 (OCEAN) were submitted as confirmatory data.

Table 8. Overview of Clinical Studies Supporting Efficacy

Study No. / Study Sites (No.; Country) / Lead Investigator	Study Design / Population	Treatment Regimen: Total Daily Dose, Route of Administration	Study Enrollment	Efficacy Endpoints
Pivotal				
OP-106 (17 sites*; France, Italy, Spain, US) Global lead investigator: Richardson	A single-arm, open-label Phase 2 multicenter study to evaluate efficacy and safety of patients with RRMM who are refractory to pomalidomide and/or an anti-CD38 mAb Patients with progressive MM who have received at least 2 prior lines of therapy, including an IMiD and a PI, and are refractory to pomalidomide and/or an anti-CD38 mAb, demonstrating relapse while on therapy or within 60 days of completion of the last dose of pomalidomide and/or an anti-CD38 mAb in any line, regardless of response	40 mg Q4W melflufen + LD dexamethasone Patients received a 40-mg IV dose of melflufen on Day 1 of each 28-day cycle and 40 mg of PO dexamethasone on Days 1, 8, 15, and 22 of each cycle. Patients ≥ 75 years of age received a reduced starting dose of dexamethasone (20 mg) on the same schedule.	Overall: N=157 Triple-class refractory subpopulation: N=119	• ORR, DOR, PFS, OS, CBR, TTNT, TTNT or death, TTR, TTP, duration of SD, duration of disease stabilization, duration of clinical benefit, functional status and well-being Response was assessed according to IMWG criteria
O-12-M1 (7 sites; Denmark, Italy, Netherlands, Sweden, US) Global lead investigator: Richardson	An open-label Phase 1/2a multicenter study to identify the MTD, followed by efficacy, and safety of melflufen alone and in combination with dexamethasone Patients with RRMM who received at least 2 or more prior lines of therapy including lenalidomide and bortezomib	Phase 1: 15, 25, 40, or 55 mg Q3W melflufen + LD dexamethasone Phase 2: 40 mg Q3W→Q4W melflufen + LD dexamethasone Patients received an IV dose of melflufen on Day 1 of each cycle and PO dexamethasone on Days 1, 8, 15, and 22 of each 21/28-day cycle	Total: N=75 Melflufen + dexamethasone: Phase 1: N=23 Phase 2: N=45 (including 6 patients treated with 40 mg in Phase 1) Single-agent melflufen: Phase 2: N=13	• ORR, DOR, OS, PFS, TTP, TTR, time to first subsequent treatment Response was assessed according to IMWG criteria

Abbreviations: CSR = clinical study report; DOR = duration of response; IMiD = immunomodulatory drug; IMWG = International Myeloma Working Group; IRC = Independent Review Committee; IV = intravenous; LD = low dose; mAb = monoclonal antibody; MTD = maximum tolerated dose; NA = not applicable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PI = proteasome inhibitor; PO = by mouth; Q3W = every 3 weeks; Q4W = every 4 weeks; RP2D = recommended Phase 2 dose; RRMM = relapsed and refractory multiple myeloma; SD = stable disease; TTNT = time to next treatment; TTP = time to progression; TTR = time to response; US = United States.

* Twenty-two sites were open for enrollment, 20 sites screened patients, and 17 sites enrolled patients.

2.6.5.1. Dose response study(ies)

Study O-12-M1

Open-label, Phase 1/2a Study O-12-M1 was designed to determine the maximum tolerated dose (MTD) of melflufen + dexamethasone (dex) in patients with RRMM and subsequently the efficacy and safety in patients treated at the MTD.

The standard 3 + 3 Phase I design was followed, with 3 to 6 patients to be tested at each dose level, depending on the dose limiting toxicities (DLTs) observed. Meflufen dose levels tested were 15, 25, 40 or 55mg at Day 1 of each 21-day Cycle, all in combination with 40 mg dex at days 1, 8 and 15 of each 21 day Cycle.

Eligible patients were adults with RRMM that had at least 2 or more prior lines of therapy, including lenalidomide and bortezomib and had demonstrated disease progression on or within 60 days of completion of last therapy.

In Phase 1 of the study, the MTD was determined at 40 mg melflufen Day 1 of each cycle in combination with 40 mg dexamethasone weekly, based on a total of 4 (66.7%) patients that experienced at least one DLT in the 55 mg cohort.

An additional 45 patients received meflufen + dex at the MTD in Phase 2a of the study. The proportion of triple class refractory (TCR) patients was 6%. The treatment cycle was 21 days, until the cycle length was increased to 28 days due to delayed haematologic recovery. The overall ORR (>PR) was 31.1% (n=14) in the combination cohort. For an additional cohort of ≥ 20 patients that received single-agent melflufen, ORR was only 7.7% (n=1) and low dose dex was added back to the treatment regimen.

2.6.5.2. Main study

Study OP-106 - HORIZON

Single arm, open-label Phase 2 study of melflufen in combination with dexamethasone (dex) in patients with RRMM who are refractory to Pomalidomide and/or an anti-CD38 mAb.

Methods

- ***Study Participants***

Key inclusion criteria

- Male or female, age 18 years or older.
- A prior diagnosis of multiple myeloma with documented disease progression in need of treatment at time of screening.
- Measurable disease defined as any of the following:
    - Serum monoclonal protein ≥0.5 g/dL (≥5 g/L) by serum protein electrophoresis (SPEP);
    - ≥200 mg/24 hours of monoclonal protein in the urine on 24-hour urine protein electrophoresis (UPEP);
    - Serum immunoglobulin free light chain (FLC) ≥ 10 mg/dL (≥100 mg/L) AND abnormal serum immunoglobulin kappa to lambda FLC ratio.
- A minimum of 2 prior lines of therapy, including an IMiD and a PI, and was refractory to pomalidomide and/or an anti-CD38 mAb. (Refractory status included patients who relapsed while on therapy or within 60 days of last dose of pomalidomide and/or an anti-CD38 mAb in any line, regardless of response).
- Life expectancy of ≥6 months.
- ECOG performance status ≤2 (patients with worse performance status based solely on bone pain secondary to multiple myeloma may have been eligible following consultation and approval of the medical monitor).
- 12-lead electrocardiogram (ECG) with Fridericia's formula for the interval of time from the start of the Q wave to the end of the T wave, corrected for heart rate (QTcF) interval of ≤470 msec

- The following laboratory results must have been met during screening (within 21 days) and also prior to study drug administration on Cycle 1 Day 1:
    - Absolute neutrophil count (ANC) ≥1,000 cells/mm3 (1.0 x 109/L)
    - Platelet count ≥75,000 cells/mm3 (75 x 109/L)
    - Haemoglobin ≥8.0 g/dl
    - Total Bilirubin ≤1.5 x upper limit of normal (ULN); or higher value in patients diagnosed with Gilberts syndrome after review and approval by the medical monitor
    - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤3.0 x ULN
    - Renal function: Estimated creatinine clearance by Cockcroft-Gault formula ≥45 mL/min.

Key exclusion criteria

- Evidence of mucosal or internal bleeding and/or was platelet transfusion refractory.
- Any medical conditions that, in the Investigator's opinion, would have imposed excessive risk to the patient or would have adversely affected his/her participating in this study. Examples of such conditions are: a significant history of cardiovascular disease (e.g., myocardial infarction (MI), significant conduction system abnormalities, uncontrolled hypertension, ≥ Grade 3 thromboembolic event in the last 6 months).
- Active infection, treated with parenteral anti-infectives within 14 days, or oral anti-infectives within 7 days, prior to initiation of treatment
- Primary refractory (never responded (≥ minimal response [MR]) to any prior therapy).
- Other malignancy diagnosed or requiring treatment within the past 3 years with the exception of adequately treated basal cell carcinoma, squamous cell skin cancer, carcinoma in-situ of the cervix or breast, and very-low and low risk prostate cancer patients in active surveillance as defined in NCCN Version 3, 2016.
- Known human immunodeficiency virus (HIV) or active hepatitis B or C viral infection.
- Concurrent symptomatic amyloidosis or plasma cell leukaemia.
- POEMS syndrome [plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein (M-protein) and skin changes].
- Previous cytotoxic therapies, including cytotoxic investigational agents, for multiple myeloma within 3 weeks (6 weeks for nitrosoureas) prior to initiation of therapy. Immunomodulatory drugs, PIs, and/or corticosteroids within 2 weeks prior to initiation of therapy. Prednisone up to but no more than 10 mg orally q.d. or its equivalent for symptom management of comorbid conditions was permitted but dose should have been stable for at least 7 days prior to initiation of therapy. Other investigational therapies and monoclonal antibodies or live vaccines within 4 weeks prior to initiation of therapy (other washout times may have been considered following consultation with the medical monitor).
- Residual side effects to previous therapy > Grade 1 prior to initiation of therapy (Alopecia any grade and/or neuropathy Grade 2 without pain were permitted).
- Prior autologous or allogeneic stem cell transplant within 12 weeks of initiation of therapy.

- Prior allogeneic stem cell transplant with active graft-versus-host-disease (GVHD).
- Prior major surgical procedure or radiation therapy within 4 weeks of the initiation of therapy (this did not include limited course of radiation used for management of bone pain within 7 days of initiation of therapy).
- Known intolerance to steroid therapy.

- ***Treatments***

Melflufen 40 mg was administered as a 30-minute central IV infusion on Day 1 of every 28-day cycle.

Dexamethasone 40 mg was administered orally on Days 1, 8, 15 and 22 of each 28-day cycle (once weekly [q1w]). Patients ≥75 years of age received 20 mg of dexamethasone on the same schedule. Dexamethasone could be continued weekly at the Investigator's discretion in the event of a cycle prolongation with delayed administration of melflufen.

Treatment continued until disease progression (PD), unacceptable toxicity, or the patient/treating physician determined it was not in the patient's best interest to continue.

- ***Objectives***

The primary objective of this Phase 2 study was to evaluate the efficacy of melflufen treatment in RRMM patients.

The key secondary objectives of this study were to evaluate safety and tolerability of melflufen as well as duration of response (DOR).

- ***Outcomes/endpoints***

The primary endpoint was overall response rate (ORR), defined as the proportion of patients for whom the best overall confirmed response is stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR).

The key secondary efficacy endpoint was DoR defined for patients who achieved a PR or better as the duration in months from first documentation of a confirmed response to first evidence of confirmed disease progression or death due to any cause.

Main other secondary endpoints were:

- Progression free survival (PFS), defined as the duration in months from start of treatment until first evidence of confirmed disease progression. Disease progression was defined according to IMWG-URC as PD or death due to any cause, whichever occurred first.
- Overall survival (OS), defined as the time in months from the date of the first dose of study drug to date of death due to any cause.
- Clinical benefit rate (CBR), defined as the proportion of patients with the best overall confirmed response of minimal response (MR) or better.
- Time to response (TTR), defined for patients with confirmed responses of PR or better as the duration in months from the study treatment start to the first occurrence of a confirmed response of PR or better.

- Time to next treatment (TTNT), time (months) from the study treatment start to the start of first post study myeloma therapy (excluding radiotherapy). A second definition was used including death.
- Patient reported outcomes (PRO) change from baseline in QLQ-C30 and Eq-5D-3L.

- ***Randomisation and Blinding (masking)***

No randomisation or blinding was performed considering the single arm trial design. An independent review committee (IRC) sensitivity analyses was included for response assessment.

- ***Statistical methods***

The Full analysis set (FAS) was defined as all patients who fulfil all eligibility criteria at screening and prior to initiation of therapy and according to intention-to-treat principle as per ICH E9.

Patients that are triple-class refractory, defined as refractory to at least one PI, at least one IMiD, and at least one Anti-CD38 mAb, were specified as the primary subgroup of interest. This subgroup constitutes the majority of patients and will be used for all analyses of efficacy and safety.

Efficacy analysis - The primary endpoint, ORR, was to be considered met if the lower bound of the 95% confidence interval for actual ORR among triple-class refractory patients is higher than 15%.

Multiplicity control - No inferential statistical comparisons using p-values are planned as part of the statistical analysis plan (SAP). Confidence intervals will be provided for descriptive purposes, and the increasing probability of type I error by number of statistical conclusions should be considered when interpreting the results. The efficacy endpoints are listed by order of relevance.

Sample size - For the initial sample size estimation, inclusion of ~39 pomalidomide refractory patients and ~39 daratumumab refractory patients were to be enrolled. The sample size was adjusted during the study to ~150 patients. The updated sample size was precision-based, with an assumed observed ORR of 30%, and an exact 95% confidence interval from 22.3% to 38.7%, given a sample size of 130 patients. Sample size calculation has been based on the overall study population rather than the currently proposed target population of TCR MM patients.

Interim analysis - An interim analysis for futility was conducted after 19 patients had been enrolled in each (original) group and were evaluable for response. The response rates were 5/19 in the pomalidomide refractory group and 3/19 in the daratumumab refractory group based on which it was recommended to proceed the study without changes or limitations.

Handling of missing values/censoring/discontinuations - Secondary endpoint PFS was right-censored according to the conventions described in Table 9.

Table 9. Conventions for Censoring of PFS

Situation	Date of Progression or Censoring	Outcome
No post baseline response assessments	Date of first dose	Censored
Non-protocol systemic anticancer therapy started before documentation of PD or death	Date of last response assessment prior to start of new anticancer therapy	Censored
Death or PD after more than 1 consecutively missed response assessment	Date of last response assessment without documentation of PD that is before the first missed visit	Censored
Unconfirmed PD as the final response assessment	Date of latest PD assessment	Progressed
Alive and without PD documentation	Date of last response assessment	Censored
Death or PD between scheduled response assessments	Date of death or preceding response assessment showing PD, whichever occurs first	Progressed
Death before first response assessment	Date of death	Progressed

For secondary endpoints DOR and duration of clinical benefit the SAP defined that disease progression, and dates of progression and censoring, were to be determined as described for the analysis of PFS. For OS, patients who are alive will be censored at the last follow up visit or data cut-off date for patients still on-study.

Results

- ***Participant flow***

Out of 215 patients that signed the Informed Consent Form, 58 never received any study treatment. Out of the 58 patients, 50 failed to meet one of the study specific eligibility criteria; 36 failed one of the criteria set forth in inclusion criterion #10 related to laboratory values and another 14 failed various eligibility criteria. Eight patients met all eligibility criteria but were never treated due to various reasons.

A total of 119 patients (75.8%) were TCR, with generally consistent disposition compared to the overall FAS.

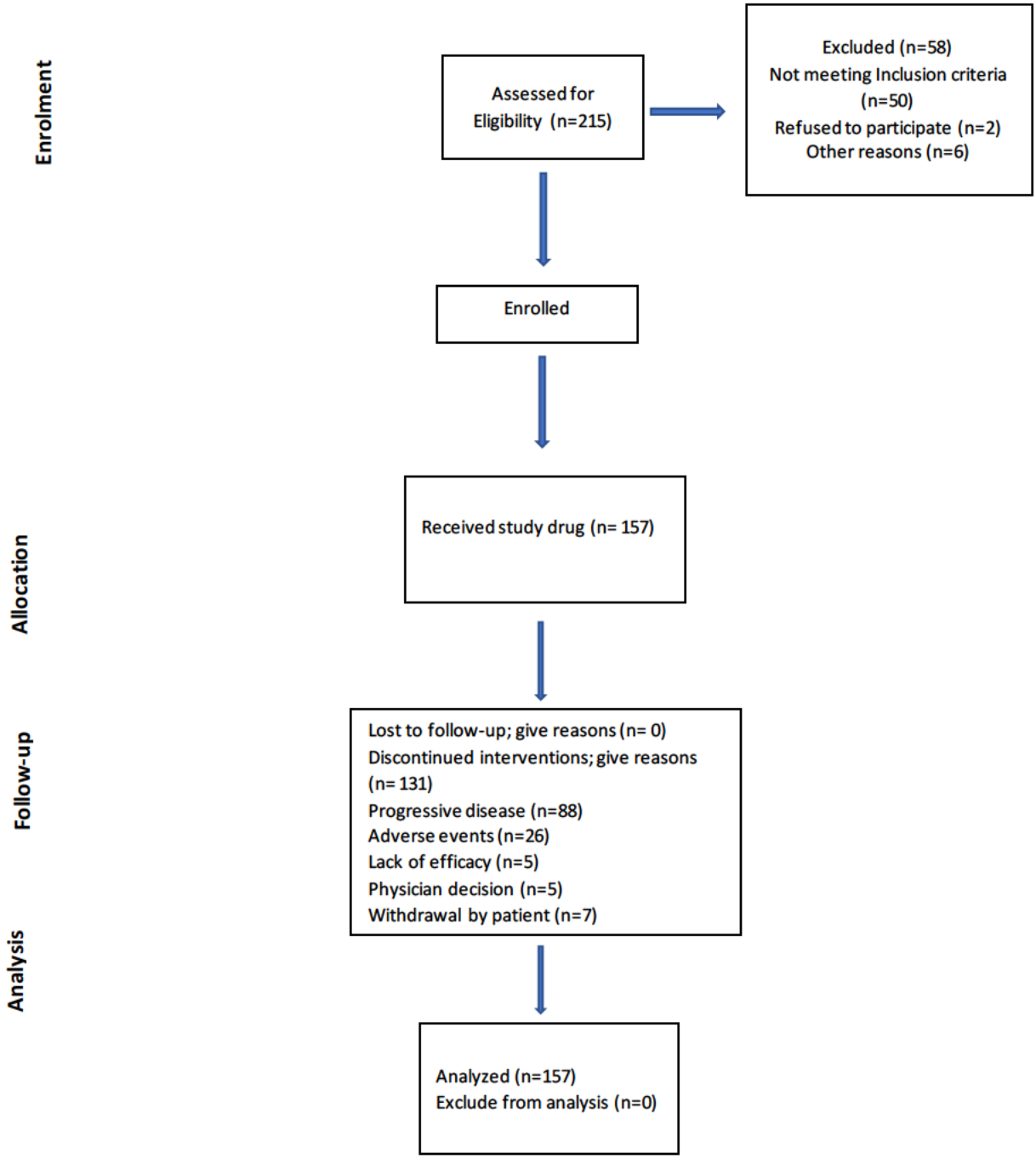

Enrolment
Assessed for Eligibility (n=215)
Excluded (n=58)
Not meeting Inclusion criteria (n=50)
Refused to participate (n=2)
Other reasons (n=6)
Enrolled
Allocation
Received study drug (n= 157)
Follow-up
Lost to follow-up; give reasons (n= 0)
Discontinued interventions; give reasons (n= 131)
Progressive disease (n=88)
Adverse events (n=26)
Lack of efficacy (n=5)
Physician decision (n=5)
Withdrawal by patient (n=7)
Analysis
Analyzed (n=157)
Exclude from analysis (n=0)

Table 10. Patient disposition (FAS)

Variable, n (%)	Triple-class Refractory	All
Number of enrolled/treated patients	119	157
Completed treatment		
Yes	102 (85.7)	131 (83.4)
Ongoing	17 (14.3)	26 (16.6)
Primary reason for discontinuation of treatment		
Progressive disease	71 (59.7)	88 (56.1)
Adverse event	16 (13.4)	26 (16.6)
Lack of efficacy	5 (4.2)	5 (3.2)
Physician decision	4 (3.4)	5 (3.2)
Withdrawal by patient	6 (5.0)	7 (4.5)
Patients in PFS follow-up	2 (1.7)	5 (3.2)
Patients in OS follow-up	26 (21.8)	35 (22.3)
Completed study		
Yes	74 (62.2)	91 (58.0)
Ongoing	45 (37.8)	66 (42.0)
Primary reason for study discontinuation		
Death	71 (59.7)	87 (55.4)
Lost to follow-up	1 (0.8)	2 (1.3)
Withdrawal of patient	1 (0.8)	1 (0.6)

Abbreviations: n = number of patients in each category; OS = overall survival; PFS = progression-free survival.

- ***Conduct of the study***

The original protocol was approved on 04 May 2016. There were 6 protocol amendments. Key changes to the protocol and SAP pertain to the population of interest (eventually TCR patients), related increase in sample size as well as the introduction of an independent review committee (IRC) and quality of life endpoints. A total of 27 protocol deviations were observed in 20 patients. Most deviations were related to study drug administration (15 deviations out of a total of 669 cycles) and missed laboratory assessments (6 deviations). Eleven patients did not meet eligibility criteria and were granted waivers.

- ***Baseline data***

Median age at enrolment was 65 years in the overall population and TCR subpopulation (Table 11). Almost 60% of patients were male and most patients were Caucasian (~85%) in both study populations.

Table 11. Baseline Demographic Characteristics (FAS)

Variable	Triple-class Refractory N=119	All N=157
Age (years), n	119	157
Mean (SD)	64.7 (9.46)	64.7 (9.36)
Median	65.0	65.0
Min, max	35, 86	35, 86
Age category (years), n (%)		
< 65	59 (49.6)	78 (49.7)
≥ 65 to ≤ 75	41 (34.5)	54 (34.4)
> 75	19 (16.0)	25 (15.9)
Sex, n (%)		
Male	70 (58.8)	89 (56.7)
Female	49 (41.2)	68 (43.3)
Race, n (%)		
Asian	1 (0.8)	1 (0.6)
Black or African American	8 (6.8)	11 (7.1)
Caucasian	100 (84.7)	135 (86.5)
Native Hawaiian/Other Pacific Islander	1 (0.8)	1 (0.6)
Other	8 (6.8)	8 (5.1)
Not reported	1	1
Ethnicity, n (%)		
Hispanic or Latino	4 (3.7)	5 (3.5)
Not Hispanic or Latino	103 (96.3)	139 (96.5)
Not reported	12	13

Abbreviations: max = maximum; min = minimum; n = number of patients in each category; N = total number of patients in the relevant analysis set; SD = standard deviation.

MM disease characteristics at baseline are summarized in Table 12. Median time since initial diagnosis was 6.2 years among TCR patients, and similar for the overall study population. As expected in this advanced patient population, patients with ISS stage III disease, extramedullary disease, and high-risk cytogenetic features were well represented.

Table 12. Baseline disease characteristics (FAS)

Category	Triple-class Refractory N=119	All N=157
Time since initial diagnosis[a] (years), n	119	157
Mean (SD)	6.7 (3.38)	7.0 (3.46)
Median	6.2	6.5
Min, max	0.7, 24.6	0.7, 24.6
ISS category, n (%)		
Stage I	41 (35.0)	63 (40.6)
Stage II	36 (30.8)	49 (31.6)
Stage III	36 (30.8)	39 (25.2)
Unknown	4 (3.4)	4 (2.6)
Missing	2	2
ECOG performance status, n (%)		
Grade 0	26 (21.8)	39 (24.8)
Grade 1	75 (63.0)	93 (59.2)
Grade 2	18 (15.1)	25 (15.9)
Serum β2-microglobulin (mg/L)[b], n	113	151
Mean (SD)	5.0 (5.63)	4.6 (4.98)
Median	3.8	3.5
Min, max	0.0, 57.0	0.0, 57.0
Heavy chain at study entry, n (%)		
IgA	26 (21.8)	30 (19.1)
IgD	2 (1.7)	2 (1.3)
IgG	65 (52.9)	88 (56.1)
IgM	2 (1.7)	2 (1.3)
Multiple	2 (1.7)	2 (1.3)
None	23 (19.3)	32 (20.4)
Unknown	1 (0.8)	1 (0.6)
Light chain at study entry, n (%)		
Kappa	75 (63.0)	100 (63.7)
Lamda	44 (37.0)	57 (36.3)
Heavy-light chain combination at study entry, n (%)		
IgA kappa	17 (14.3)	18 (11.5)
IgA lambda	9 (7.6)	12 (7.6)
IgD kappa	1 (0.8)	1 (0.6)
IgD lambda	1 (0.8)	1 (0.6)
IgG kappa	39 (32.8)	57 (36.3)
IgG lambda	24 (20.2)	31 (19.7)
IgM kappa	2 (1.7)	2 (1.3)
Multiple kappa	2 (1.7)	2 (1.3)
None kappa	13 (10.9)	19 (12.1)
None lambda	10 (8.4)	13 (8.3)
Unknown kappa	1 (0.8)	1 (0.6)
Maximum baseline plasma cell involvement in bone marrow[b,c] (%), n	103	137
Mean (SD)	29.0 (30.81)	29.6 (29.14)
Median	18.0	20.0
Min, max	0.0, 97.0	0.0, 97.0
Extramedullary disease, n (%)		
Yes	50 (42.0)	55 (35.0)
No	69 (58.0)	102 (65.0)
Baseline disease risk status category[c], n (%)		
High[d]	41 (34.5)	59 (37.6)
Standard	52 (43.7)	67 (42.7)
Unknown	26 (21.8)	31 (19.7)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; Ig = Immunoglobulin; ISS = International Staging System; n = number of patients in each category; N = total number of patients in the relevant analysis set; SD = standard deviation; .

a Time since initial diagnosis was calculated relative to first dose of study drug.

b Baseline laboratory tests were defined as the most recent assessment before administration of the first dose of study drug.

c Bone marrow aspirate or biopsy.

d Patients who had the genetic subtype t(4; 14), t(14:16), deletion 17p, gain 1q (+1q), t(14,20) were high risk.

Patients had received a median of 5 (range 2-12) prior therapies, and 119 (~76%) were TCR (

Table 13; Table 14). Approximately 16% of the TCR population was Melphalan refractory. The majority of patients (n=97/119, 81.5%) was also at least quad-refractory and 47% of patients was penta-refractory (n=56/119). In total 117/119 TCR patients had received 3 prior lines of therapy, in line with the newly proposed target population.

Table 13. Lines of Prior Therapy (FAS)

Variable	Triple-class Refractory N=119	All N=157
Number of lines of prior therapy, n	119	157
Mean (SD)	5.5 (1.87)	5.2 (1.84)
Median	5.0	5.0
Min, max	2, 12	2, 12
Number of prior regimens, n (%)		
2	2 (1.7)	5 (3.2)
3	15 (12.6)	24 (15.3)
4	14 (11.8)	23 (14.6)
5	36 (30.3)	46 (29.3)
6	23 (19.3)	28 (17.8)
7	14 (11.8)	15 (9.6)
8	5 (4.2)	6 (3.8)
9	6 (5.0)	6 (3.8)
10	2 (1.7)	2 (1.3)
11	1 (0.8)	1 (0.6)
12	1 (0.8)	1 (0.6)
Patients with a prior autologous transplant, n (%)		
Yes	81 (68.1)	108 (68.8)
No	38 (31.9)	49 (31.2)
Best disease response to most recent prior regimen, n (%)		
Stringent complete response (sCR)	0	1 (0.6)
Complete response (CR)	0	2 (1.3)
Very good partial response (VGPR)	7 (5.9)	13 (8.3)
Partial response (PR)	29 (24.4)	35 (22.3)
Minimal response (MR)	8 (6.7)	9 (5.7)
Stable disease (SD)	23 (19.3)	33 (21.0)
Progressive disease (PD)	22 (18.5)	30 (19.1)
Unknown	30 (25.2)	34 (21.7)
Refractory to at least 1 component of most recent prior regimen, n (%)		
Yes	117 (98.3)	154 (98.1)
No	2 (1.7)	3 (1.9)
Refractory to most recent prior regimen, n (%)		
Alkylator class	29 (24.4)	35 (22.3)
Cyclophosphamide	22 (18.5)	28 (17.8)
Bendamustine	5 (4.2)	5 (3.2)

Table continued next page

Variable	Triple-class Refractory N=119	All N=157
Melphalan	2 (1.7)	2 (1.3)
Anti-CD38 mAb class	59 (49.6)	63 (40.1)
Daratumumab	56 (47.1)	59 (37.6)
Isatuximab	3 (2.5)	4 (2.5)
IMiD class	49 (41.2)	74 (47.1)
Pomalidomide	37 (31.1)	60 (38.2)
Thalidomide	7 (5.9)	7 (4.5)
Lenalidomide	3 (2.5)	4 (2.5)
Miscellaneous IMiD	2 (1.7)	3 (1.9)
Other mAb class	12 (10.1)	16 (10.2)
Miscellaneous other monoclonal antibodies	8 (6.7)	12 (7.6)
Elotuzumab	4 (3.4)	5 (3.2)
PI class	44 (37.0)	57 (36.3)
Carfilzomib	23 (19.3)	27 (17.2)
Bortezomib	18 (15.1)	25 (15.9)
Ixazomib	3 (2.5)	5 (3.2)
Refractory to at least 1 prior regimen, n (%)		
Alkylator class	76 (63.9)	92 (58.6)
Alkylators miscellaneous	1 (0.8)	1 (0.6)
Bendamustine	13 (10.9)	14 (8.9)
Carmustine	6 (5.0)	6 (3.8)
Cyclophosphamide	65 (54.6)	80 (51.0)
High-dose melphalan	2 (1.7)	3 (1.9)
Melphalan	19 (16.0)	21 (13.4)
Anti-CD38 mAb class	119 (100)	125 (79.6)
Daratumumab	112 (94.1)	117 (74.5)
Isatuximab	9 (7.6)	10 (6.4)
IMiD class	116 (97.5)	153 (97.5)
IMiD miscellaneous	4 (3.4)	5 (3.2)
Lenalidomide	108 (90.8)	140 (89.2)
Pomalidomide	104 (87.4)	140 (89.2)
Thalidomide	25 (21.0)	34 (21.7)
Other class	119 (100)	155 (98.7)
Doxorubicin	19 (16.0)	22 (14.0)
Other miscellaneous[a]	119 (100)	155 (98.7)
Other mAb class	27 (22.7)	33 (21.0)
Elotuzumab	13 (10.9)	15 (9.6)
Other mAb miscellaneous	15 (12.6)	21 (13.4)
PI class	115 (96.6)	145 (92.4)
Bortezomib	80 (67.2)	101 (64.3)
Carfilzomib	72 (60.5)	86 (54.8)
Ixazomib	19 (16.0)	22 (14.0)
Oprozomib	1 (0.8)	1 (0.6)
PI miscellaneous	1 (0.8)	1 (0.6)
Received an IMiD, PI, and anti-CD38 mAb (triple-class exposed), n (%)		
Yes	119 (100)	125 (79.6)
No	0	32 (20.4)
Double-class refractory only, n (%)		
Yes	0	30 (19.1)
No	119 (100)	127 (80.9)

Abbreviations: IMiD = immunomodulatory drug; mAb = monoclonal antibody; n = number of patients in each category; N = total number of patients in the relevant analysis set; PI = proteasome inhibitor; SD = standard deviation.

a "Other miscellaneous" includes dexamethasone.

Table 14. Refractory status

Refractory Status	Triple-class Refractory * (N=119) n (%)	Overall (N=157) n (%)
Refractory to most recent prior regimen	117 (98.3%)	154 (98.1%)
Refractory to prior alkylator	76 (63.9%)	92 (58.6%)
Refractory to prior daratumumab	112 (94.1%)	117 (74.5%)
Refractory to prior pomalidomide	104 (87.4%)	140 (89.2%)
Refractory to prior daratumumab and pomalidomide	97 (81.5%)	100 (63.7%)
Refractory and/or intolerant to prior IMiD	119 (100%)	156 (99.4%)
Refractory to prior IMiD	116 (97.5%)	153 (97.5%)
Intolerant to prior IMiD	9 (7.6%)	10 (6.4%)
Refractory and/or intolerant to prior PI	119 (100%)	149 (94.9%)
Refractory to prior PI	115 (96.6%)	145 (92.4%)
Intolerant to prior PI	9 (7.6%)	10 (6.4%)
Refractory and/or intolerant to prior anti-CD38 mAb	119 (100%)	125 (79.6%)
Refractory to prior anti-CD38 mAb	119 (100%)	125 (79.6%)
Intolerant to prior anti-CD38 mAb	2 (1.7%)	2 (1.3%)
Received an IMiD and PI only but not anti-CD38 mAb (double-class exposed)	0	32 (20.4%)
Refractory to prior PI and IMiD only, and not anti-CD38 mAb (double-class refractory)	0	30 (19.1%)
Received an IMiD, PI, and Anti-CD38 mAb (triple-class exposed)	119 (100%)	125 (79.6%)
Patients refractory to at least 1 component of most recent prior regimen	117 (98.3%)	154 (98.1%)

FAS = Full Analysis Set; IMiD = immunomodulatory drug; mAb = monoclonal antibody; PI = proteasome inhibitor
* Triple-class refractory was defined as refractory or intolerant to at least one proteasome inhibitor, at least one immunomodulatory drug, and at least one anti-CD38 monoclonal antibody.

- ***Numbers analysed***

A total of 157 patients overall were treated in the study and included in the FAS. The TCR subpopulation consisted of 119 patients. The HRQoL analysis set comprised 64 of the 72 patients who enrolled on or after protocol version 5.0, and was used for analysis of PROs of the functional status and well-being endpoints.

- ***Outcomes and estimation***

Primary endpoint – ORR

Based on Investigator assessment, a total of 46 patients out of 157 had a best response of PR or better for an overall confirmed response rate of 29.3% (95% CI: 22.32%, 37.08%) in the overall study population (Table 15; data cut-off 14 Jan 2020). One sCR was reported and no complete responses. A sensitivity analysis based on IRC assessment indicated similar results for the ORR (29.9% [95% CI: 22.9, 37.8]).

The overall confirmed response rate was 26.1% (95% CI: 18.44%, 34.89%) for the triple-class refractory subpopulation based on Investigator and IRC assessment.

Exploratory updated results with 1.5 years additional follow up (data cut-off 12 Aug 2021) suggest an ORR of 33.8% (95% CI: 26.4%, 41.7%) for the overall population and 29.1% (95% CI: 21.0%, 38.2%) for the applicant's proposed indication population (N=117).

Table 15. ORR based on Investigator and IRC Assessment (FAS)

Variable	Investigator Assessment		IRC Assessment	
	Triple-class Refractory N=119 n (%)	All N=157 n (%)	Triple-class Refractory N=119 n (%)	All N=157 n (%)
ORR: sCR + CR + VGPR + PR, %	26.1	29.3	26.1	29.9
(95% CI)	(18.4, 34.9)	(22.3, 37.1)	(18.4, 34.9)	(22.9, 37.8)
CBR: sCR + CR + VGPR + PR + MR, %	39.5	45.2	37.8	43.9
(95% CI)	(30.7, 48.9)	(37.3, 53.4)	(29.1, 47.2)	(36.1, 52.1)
DSR: sCR + CR + VGPR + PR + MR + SD, %	64.7	68.8	63.9	68.2
(95% CI)	(55.4, 73.2)	(60.9, 75.9)	(54.6, 72.5)	(60.3, 75.4)
Best overall response, n (%)				
Stringent complete response (sCR)	0	1 (0.6)	0	1 (0.6)
Complete response (CR)	0	0	0	0
Very good partial response (VGPR)	13 (10.9)	17 (10.8)	14 (11.8)	19 (12.1)
Partial response (PR)	18 (15.1)	28 (17.8)	17 (14.3)	27 (17.2)
Minimal response (MR)	16 (13.4)	25 (15.9)	14 (11.8)	22 (14.0)
Stable disease (SD)	30 (25.2)	37 (23.6)	31 (26.1)	38 (24.2)
Progressive disease (PD)	35 (29.4)	42 (26.8)	30 (25.2)	36 (22.9)
Not evaluable[a]	7 (5.9)	7 (4.5)	13 (10.9)	14 (8.9)

Abbreviations: CBR = clinical benefit rate; DSR = disease stabilization rate; IRC = Independent Review Committee; n = number of patients in each category; N = total number of patients in the relevant analysis set; ORR = overall response rate.
a Not evaluable due to no postbaseline or only 1 postbaseline assessment before data cutoff, or no postbaseline assessment due to other reasons.

Key secondary endpoint – Duration of Response

At the time of the data cutoff (14 Jan 2020), 46 patients (30 patients with events and 16 censored patients) achieved PR or better; the median DOR in the overall study population was 5.5 months (95% CI: 3.9, 7.6) based on investigator assessment (Table 16). Of the 30 patients with events, 27 patients (17.2%) progressed and 3 patients died (1.9%). The reason for censoring was patients without documented progression at the time of the data cut-off (16 patients [10.2%]).

By Investigator assessment, median DOR in the TCR subgroup was 4.4 months (95% CI: 3.4, 7.6). DOR was measured for 31/119 (26.1%) of patients in this subgroup; 20 patients (16.8%) had an event and 11 were censored patients (patients without documented disease progression at the time of the data cut-off: 9.2%).

Assessment by the IRC yielded slightly longer median DORs compared with Investigator-assessed DORs in both the overall study population (6.7 months) and TCR subgroup (5.5 months).

The DOR at the updated data-cut of 12 Aug 2021 was 6.70 months (95% CI: 4.40, 8.11) for the overall population and 6.97 months (95% CI: 3.88, 9.79) for the applicant's proposed indication population (N=117).

Table 16. Duration of Response (PR or better) Based on Investigator and IRC Assessment (FAS)

	Investigator Assessment		IRC Assessment	
Variable	**Triple-class Refractory N=119**	**All N=157**	**Triple-class Refractory N=119**	**All N=157**
OR (≥ PR), n (%)	31 (26.1)	46 (29.3)	31 (26.1)	47 (29.9)
Patients with events, n (%)	20 (16.8)	30 (19.1)	21 (17.6)	31 (19.7)
Patients censored, n (%)	11 (9.2)	16 (10.2)	10 (8.4)	16 (10.2)
Response duration (months) Quartiles (95% CI)[a]				
P25	3.1 (2.4, 3.9)	3.7 (3.0, 4.0)	3.4 (2.4, 4.6)	3.8 (3.0, 4.4)
Median	4.4 (3.4, 7.6)	5.5 (3.9, 7.6)	5.5 (4.2, 8.1)	6.7 (4.2, 8.1)
P75	8.1 (7.4, NE)	11.2 (7.4, NE)	9.4 (7.5, NE)	12.2 (7.5, NE)

Abbreviations: BOR = best overall response; n = number of patients in each category; N = total number of patients in the relevant analysis set; NE = not evaluable; P25 = 25th percentile; P75 = 75th percentile; PR = partial response.
Notes: Only patients whose BOR of PR or better, as determined by the Investigator, are included.
a Kaplan-Meier product-limit estimates.

Other secondary endpoints

PFS

Median PFS in the overall study population was 4.24 months (95% CI: 3.42, 4.86;

Table 17; Figure 6) based on Investigator assessment and after a median follow up of 10.18 months. Based on IRC assessment, median PFS was similar: 4.37 months (95% CI: 3.42, 4.83).

Median PFS in the TCR subpopulation was 3.94 months (95% CI: 3.02, 4.63) based on Investigator assessment and 3.98 months (95% CI: 3.02, 4.53) based on IRC.

Table 17. PFS Based on Investigator and IRC Assessment (FAS)

	Investigator Assessment		IRC Assessment	
Variable	**Triple-class Refractory N=119**	**All N=157**	**Triple-class Refractory N=119**	**All N=157**
Patients with events, n (%)	94 (79.0)	121 (77.1)	93 (78.2)	118 (75.2)
Patients censored, n (%)	25 (21.0)	36 (22.9)	26 (21.8)	39 (24.8)
PFS Duration (months) Quartiles (95% CI)[a]				
P25	1.9 (1.6, 2.3)	2.0 (1.8, 2.5)	2.1 (1.8, 2.4)	2.3 (1.9, 2.8)
Median	3.9 (3.0, 4.6)	4.2 (3.4, 4.9)	4.0 (3.0, 4.5)	4.4 (3.4, 4.8)
P75	6.5 (5.3, 9.3)	7.8 (6.4, 10.5)	6.3 (5.2, 9.4)	7.8 (5.8, 10.3)

Abbreviation: CI = confidence interval; IRC = independent review committee; n = number of patients in each category; N = total number of patients in the relevant analysis set; P25 = 25th percentile; P75 = 75th percentile.
a Kaplan-Meier product-limit estimates.

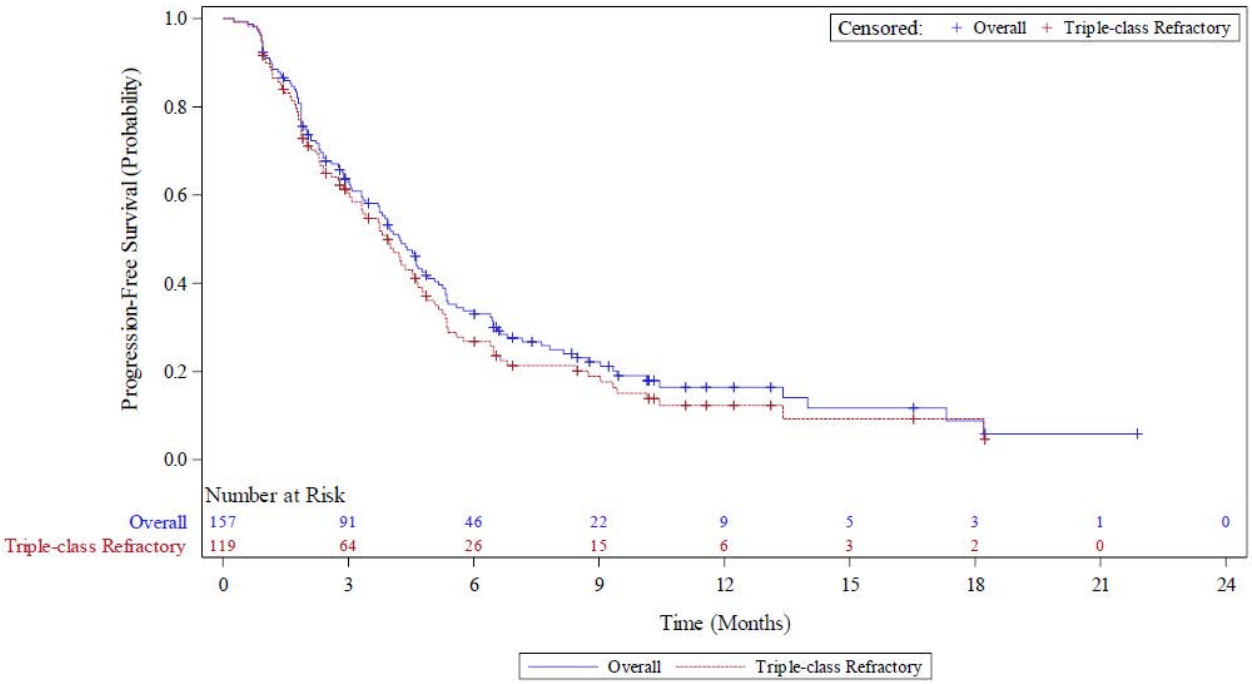


Figure 6. PFS Based on Investigator Assessment in overall study population and TCR subgroup (FAS)

OS

The median OS was 11.63 months (95% CI: 9.30, 15.41) for the overall study population after a median OS follow-up of 14.00 months (95% CI: 10.78, 18.69; Table 18, Figure 7).

In the TCR population, median OS was 11.24 months (95% CI: 7.66, 13.17).

Table 18. Overall Survival (FAS)

	EMD [a] (N=55)	Triple-class refractory [b] (N=119)	Overall (N=157)
Number (%) of patients with events	40 (72.7%)	72 (60.5%)	88 (56.1%)
Number (%) of patients censored	15 (27.3%)	47 (39.5%)	69 (43.9%)
Alive: Study discontinuation	0	2 (1.7%)	3 (1.9%)
Alive: Ongoing	15 (27.3%)	45 (37.8%)	66 (42.0%)
Survival duration (months) potential follow-up [c]	16.76 (9.72, 29.27)	14.00 (10.81, 17.41)	14.00 (10.78, 18.69)
Survival duration (months) quartiles (95% CI) [d]			
25th Percentile	3.42 (2.10, 5.13)	5.06 (3.88, 5.82)	5.26 (4.24, 6.41)
Median	6.47 (5.13, 9.66)	11.24 (7.66, 13.17)	11.63 (9.30, 15.41)
75th Percentile	18.46 (9.30, 24.44)	18.46 (14.49, 28.85)	21.13 (17.64, NE)

CI = confidence interval; EMD = extramedullary disease; FAS = Full Analysis Set; NE = not estimable

[a] Extramedullary disease was defined as myeloma disease either originating in, but extending beyond, the cortical bone or as a separate soft tissue mass.

[b] Triple-class refractory was defined as refractory or intolerant to at least one proteasome inhibitor, at least one immunomodulatory drug, and at least one anti-CD38 monoclonal antibody.

[c] Calculated using the reverse Kaplan-Meier method where the censoring variable is inverted.

[d] Kaplan-Meier product limit estimates.

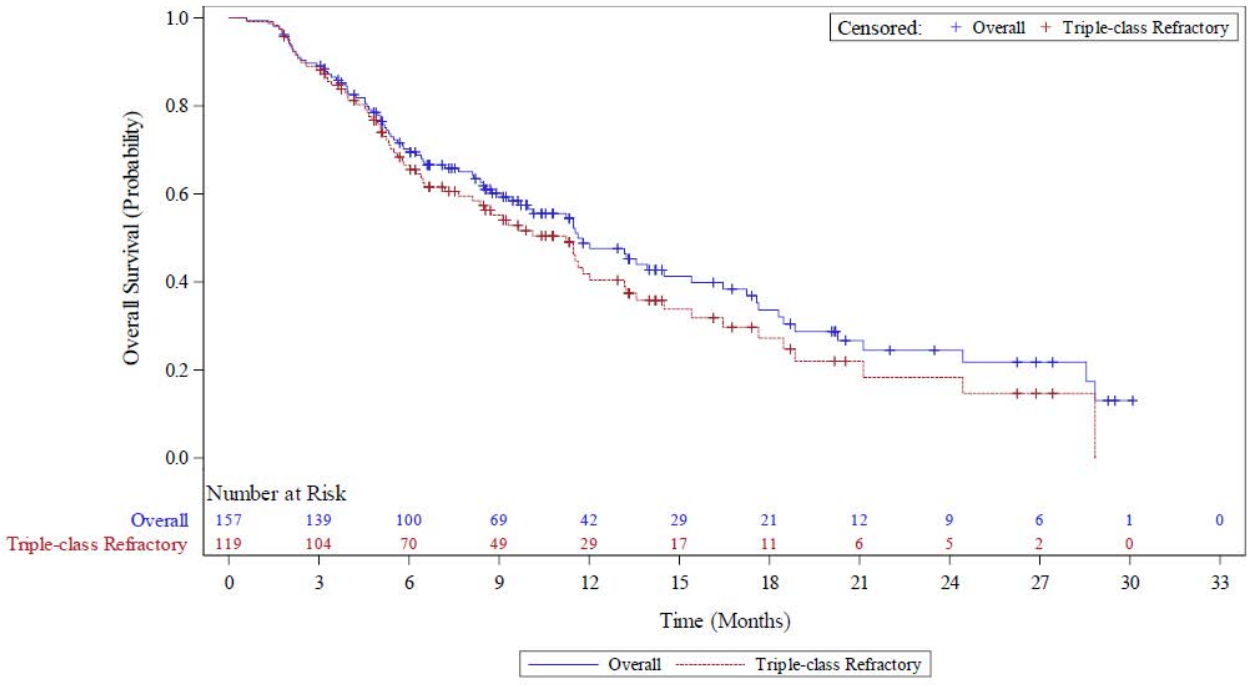


Figure 7. Overall Survival in overall study population and TCR subgroup(FAS)

CBR

The clinical benefit rate (MR or higher) was 45.2% (95% CI: 37.3, 53.4) based on investigator assessment in the overall study population and 39.5% (95% CI: 30.7, 48.9) in the TCR subpopulation. Similar results were obtained based on IRC assessment.

Time to response

In the overall and TCR study population, the median time to response was 1.9 months (Inv based). Based on IRC assessment, the TTR was 1.2 months and 1.5 months, respectively.

TTP

By Investigator assessment, median TTP in the overall study population was 4.4 months (95% CI: 3.8, 5.3) and among TCR patients 4.1 months (95% CI: 3.1, 4.9).

TTNT

Median time to next treatment or death was 5.8 months in the overall study population (95% CI: 4.8, 7.1) and 5.3 months (95% CI: 4.5, 6.3) in the TCR population. Median time to next treatment (without death as event) was 8.21 months (7.16, 10.84) in the overall study population, and 7.89 months (6.93, 10.87) in the TCR population.

Duration of stable disease

The median duration of SD was 3.8 months (95% CI: 3, 4.6) in both the overall study population as well as the TCR subgroup.

Duration of disease stabilization

For the overall study population, median duration of disease stabilization was 5.6 months (95% CI: 4.9, 6.8) and in the TCR subgroup 5.3 months (95% CI: 4.6, 6.5).

Duration of clinical benefit

Of the 71 patients with investigator-assessed response of MR or better in the overall study population, median duration of clinical benefit was 6.7 months (95% CI: 4.3, 7.5). Median duration of clinical benefit was 4.6 months (95% CI: 3.9, 7.5) in the 47 patients of the TCR subgroup with an Investigator-assessed response of MR or better.

Change from Baseline in levels of serum and urine M-protein spike

The majority of patients (118, 81.4%) achieved a decrease of M-protein levels.

Change from Baseline in QLQ-C30 assessment

A total of 36 patients of the HRQoL Analysis set met the criteria for having evaluable PROs at Cycle 4. In the EORTC-QLQ-C30, the mean change from baseline of the Global Health Status/QoL score to Cycle 4 was 2.8 (95% CI: -4.8, 10.4), the mean change from baseline in symptom score for Fatigue was 3.7 (95% CI: -3.0, 10.4), and the mean change from baseline in symptom score for Pain was 0.9 (95% CI: -7.8, 9.7). (Of note: For GHS/QoL positive values indicate improvement while for Pain and Fatigue negative values indicate improvement.) For the 27 evaluable TCR patients, similar results were presented.

Change from Baseline in EQ-5D-3L assessment

While small mean changes were observed, the EQ-5D-3L health utility index and VAS mean scores were generally stable over time by cycle for the overall and TCR study population.

Change from Baseline in levels of serum and urine M-protein spike

The median relative reduction from baseline to best response was -36.8% in 108 TCR patients evaluable for response. Greater reductions were seen in patients achieving responses (PR or VGPR); median reduction was 78.9% and 98.6% in patients with PR and VGPR as best response, respectively.

- ***Ancillary analyses***

Subgroup analyses of efficacy endpoints of Study OP-106 and O-12-M1 were performed by demographic and disease characteristics. Responses seem to increase with age and were slightly higher in females vs. males. Responses were shorter with increasing ISS Stage at baseline and with higher cytogenetic risk status. In patients that received ≥6 prior lines of therapy, responses were lower (19.2%) vs patients with <4 (29.4%) or ≥4-≤5 prior lines (32%) in the TCR population. Patients refractory to an alkylator had lower response rates (18.4%) vs. patients not refractory to an alkylator (39.5%). Of note: there was no formal hypothesis testing set up in this single-arm, open-label study and relatively small numbers of patients were included per subgroup.

Efficacy results for patients previously exposed to melphalan in Study OP-106 are presented in Table 19.

Table 19. Efficacy results in melphalan exposed patients

Efficacy results within subpopulations in OP-106 - original CSR efficacy Jan- 2020

	N	ORR, evs (%) [95% CI]	DOR (95% CI)	PFS (95% CI)	OS (95% CI)
Melphalan (high or standard dose) exposed	88	21 (23.9) [15.4-34.1]	4.24 (3.22-8.11)	3.81 (3.09-4.53)	8.74 (6.05-11.53)
HD melphalan exposed	73	18 (24.7) [15.3-36.1]	4.24 (3.22-8.11)	4.01 (3.09-4.67)	10.12 (6.47-13.24)
Melphalan (standard dose only) exposed	15	3 (20.0) [4.3-48.1]	6.36 (3.02-NA)	2.40 (1.12-5.06)	5.06 (1.77-7.20)
HD melphalan refractory	8	1 (12.5) [0.3-52.7]	3.22 (NA-NA)	3.98 (1.31-NA)	4.24 (2.23-9.66)
Melphalan refractory (standard dose only)	12	1 (8.3) [0.2-38.5]	3.42 (NA-NA)	3.32 (1.77-5.26)	5.78 (2.00-24.44)

In response to D195 list of outstanding issues, the Applicant presented post-hoc subgroup results for the 3L+ TCR study population by time to progression since stem cell transplantation (Table 20). This is based on exploratory analyses in study OP-103 (see supportive study below). The response rate as well as median DoR was numerically higher in patients without prior autologous stem cell transplantation (ASCT) or time to progression (TTP) ≥3 years compared to patients with more recent transplantation with TTP <36 months.

Table 20. Efficacy results in TCR 3L+ patients and with no prior ASCT or who have progressed more than 36 months from an ASCT and patient who have progressed within 36 months from an ASCT in OP-106 HORIZON study

Population	*TCR 3L+ (n=110)*	*No ASCT or progressed >=36 months (n=52)*	*ASCT progressed <36 months (n=58)*
Overall response rate (ORR), 95% CI (%)	*28 (25.5) [17.6%, 34.6%]*	*15 (28.8) [17.1, 43.1]*	*13 (22.4) [12.5, 35.3]*
Median duration of response (DOR), 95% CI (months)	*5.4 (3.5-8.1)*	*7.6 (3.0-12.3)*	*3.9 (3.1-7.4)*
Median time to first response (range)	*2.1 (1.0-15.3)*	*2.3 (1.0-10.5)*	*1.9 (1.0-15.3)*
Median PFS, 95% CI (months)	*3.7 (2.8-4.4)*	*4.2 (2.1-5.4)*	*3.4 (2.8-4.2)*
Median OS, 95% CI (months)	*9.5 (6.4-12.0)*	*11.2 (6.4-12.7)*	*8.6 (5.6-13.2)*

- ***Summary of main efficacy results***

The following table summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 21 Summary of efficacy for trial OP-106 (HORIZON)

Title: A Single Arm, Open-Label, Phase 2 Study of Melflufen in Combination with Dexamethasone in Patients with Relapsed Refractory Multiple Myeloma who are Refractory Pomalidomide and/or an anti-CD38 Monoclonal Antibody			
Study identifier	Sponsor ID: OP-106 (HORIZON) EudraCT number: 2016-000865-21 NCT number: NCT02963493		
Design	Phase 2 single-arm, open-label, multi-centre study of melphalan flufenamide in combination with dexamethasone (DEX) in patients with RRMM who are refractory to pomalidomide (POM) and/or daratumumab (DARA)/anti-CD38 monoclonal antibody.		
	Duration of treatment phase as defined in protocol: until progressive disease (PD) or unacceptable toxicity. Duration of Run-in phase: N/A. Duration of Follow-up phase as defined in protocol: until death, or subsequent therapy, or for 24 months after PD.		
Hypothesis	An ORR of at least 15% would represent a clinically meaningful treatment effect, according to protocol.		
Treatments groups	Overall study population		N=157. All treated patients.
	Triple class refractory (TCR) subpopulation		N=119. Refractory or intolerant to at least one PI, at least one IMiD, and at least one anti-CD38 monoclonal antibody.
Endpoints and definitions	Primary endpoint	Overall Response Rate (ORR)	Proportion of patients for whom the best overall confirmed response is stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR).
	Key secondary endpoint	Duration of response (DOR)	For patients who achieved a PR or better; the duration in months from first documentation of a confirmed response to first evidence of confirmed disease progression or death due to any cause.
	Other secondary endpoint	Progression free survival (PFS)	The time in months from start of treatment until first evidence of confirmed disease progression or death due to any cause, whichever occurred first.

	Other secondary endpoint	Overall survival (OS)	The time in months from the date of the first dose of study drug to date of death due to any cause.
Database lock	2020-03-28 (data cut-off 2020-01-14)		

Results and Analysis*

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set (FAS), defined as all subjects who received at least one dose of melflufen. Best confirmed response measured during treatment until progressive disease (PD).		
Descriptive statistics and estimate variability	Treatment group	Overall study population	TCR subpopulation
	Number of subject	n=157	N=119
	ORR 95% CI	29.3% (22.32; 37.08)	26.1% (18.44; 34.89)
	Median DoR** 95% CI	5.49 months (3.88; 7.59)	4.40 months (3.42; 7.59)
	Median PFS 95% CI	4.24 months (3.42; 4.86)	3.94 months (3.02; 4.63)
	Median OS 95% CI	11.63 months (9.30; 15.41)	11.24 months (7.66; 13.17)
Notes	*Presented results are based on Investigator assessment. **For the calculation of DoR, patients who achieved a PR or better were included.		

2.6.5.3. Clinical studies in special populations

Clinical efficacy has not been investigated for special populations in separate clinical studies.

Subgroup analyses by age (<65, ≥65-≤75 and >75) have been presented for the pivotal trial, suggesting increasing efficacy with age.

No separate efficacy data were presented for included patients with mild to moderate renal- or mild hepatic impairment. Patients with an estimated GFR below 45 mL/min/1.73 m2 or moderate to severe hepatic impairment have not been studied.

Table 22: Age distribution among patients included in efficacy analyses

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	113/246	33/246	4/246
Non Controlled Trials	54/157	24/157	1/157

2.6.5.4. In vitro biomarker test for patient selection for efficacy

N/A

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

N/A

2.6.5.6. Supportive study

Study OP-103 – OCEAN

Randomized, controlled, open-label Phase 3 Study OP-103 investigated melflufen + dex with pomalidomide + dex in patients with relapsed refractory MM who were refractory to lenalidomide.

Methods

Study Participants

Key inclusion criteria

- Male or female, age 18 years or older
- Prior diagnosis of multiple myeloma with documented disease progression in need of treatment at time of screening
- Measurable disease defined as any of the following:
    - Serum monoclonal protein ≥ 0.5 g/dL by serum protein electrophoresis (SPEP)
    - ≥ 200 mg/24 hours of monoclonal protein in the urine on 24-hour urine electrophoresis (UPEP)
    - Serum free light chain (SFLC) ≥10 mg/dL AND abnormal serum kappa to lambda free light chain ratio
- Received 2 to 4 prior lines of therapy including lenalidomide and a PI, either sequential or in the same line, and was refractory (relapsed and refractory or refractory) to both the last line of therapy and to lenalidomide (≥ 10 mg) administered within 18 months prior to randomization (refractory to lenalidomide included patients who relapsed while on lenalidomide therapy or within 60 days of last dose following at least 2 cycles of lenalidomide with at least 14 doses of lenalidomide per cycle)
- Life expectancy of ≥ 6 months

- ECOG performance status ≤ 2
- Females of childbearing potential had a negative pregnancy test or pomalidomide pregnancy prevention plan completed within 10 to 14 days prior to planned start of treatment. All patients had to agree to either commit to continued abstinence from heterosexual intercourse or begin two acceptable methods of birth control.
- 12-lead electrocardiogram (ECG) with corrected QT (QTc) interval calculated by Fridericia Formula (QTcF) interval of ≤ 470 msec
- The following laboratory results must have been met during screening (within 21 days) and also immediately before study drug administration on C1D1 (**"inclusion criterion 10"**):
    - Absolute neutrophil count (ANC) ≥ 1,000 cells/mm3 (1.0 x 109/L) (growth factors could not be used within 10 days prior to first drug administration)
    - Platelet count ≥ 75,000 cells/mm3 (75 x 109/L) (without required transfusions during the 10 days prior to first drug administration)
    - Hemoglobin ≥ 8.0 g/dl (red blood cell [RBC] transfusions were permitted)
    - Total bilirubin ≤ 1.5 x upper limit of normal (ULN), or patients diagnosed with Gilberts syndrome, that were reviewed and approved by the medical monitor
    - Aspartate transaminase/serum glutamic oxaloacetic transaminase (AST/SGOT) and alanine transaminase/serum glutamic pyruvic transaminase (ALT/SGPT) ≤ 3.0 x ULN
    - Renal function: Estimated creatinine clearance by Cockcroft-Gault formula ≥ 45 mL/min (Appendix G of the protocol [Appendix 16.1.1])
- Must be able to take antithrombotic prophylaxis

<u>Key exclusion criteria</u>

- Primary refractory disease (i.e., never responded with ≥ MR) to any prior therapy)
- Evidence of mucosal or internal bleeding and/or were platelet transfusion refractory (i.e., platelet count failed to increase by > 10,000 cells/mm3 after transfusion of an appropriate dose of platelets)
- Any medical conditions that, in the Investigator's opinion, would have imposed excessive risk to the patient or would have adversely affected his/her participating in this study.
- Prior exposure to pomalidomide
- Known intolerance to IMiDs (≥ Grade 3 hypersensitivity reaction or at the Investigator's discretion)
- Known active infection requiring parenteral or oral anti-infective treatment within 14 days of randomization
- Other malignancy diagnosed or requiring treatment within the past three years with the exception of adequately treated basal cell carcinoma, squamous cell skin cancer, carcinoma in-situ of the cervix or breast or very low and low risk prostate cancer in active surveillance
- Pregnant or breast-feeding females

- Serious psychiatric illness, active alcoholism, or drug addiction that may have hindered or confused compliance or follow-up evaluation
- Known human immunodeficiency virus or active hepatitis C viral infection
- Active hepatitis B viral infection
- Concurrent symptomatic amyloidosis or plasma cell leukemia
- POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein [M-protein], and skin changes)
- Previous cytotoxic therapies, including cytotoxic investigational agents, for multiple myeloma within 3 weeks (6 weeks for nitrosoureas) prior to randomization. The use of live vaccines within 30 days before randomization. IMiDs, PIs, or corticosteroids within 2 weeks prior to randomization. Other investigational therapies and monoclonal antibodies within 4 weeks of randomization. Prednisone up to but no more than 10 mg orally once daily or its equivalent for symptom management of comorbid conditions was permitted but dose should have been stable for at least 7 days prior to randomization
- Residual side effects to previous therapy > Grade 1 prior to randomization (alopecia any grade and/or neuropathy Grade 2 without pain were permitted)
- Prior peripheral stem cell transplant within 12 weeks of randomization
- Prior allogeneic stem cell transplantation with active graft-versus-host-disease
- Prior major surgical procedure or radiation therapy within 4 weeks of randomization
- Known intolerance to steroid therapy

Treatments

Patients were randomized to receive:

- Melflufen 40 mg IV on Day 1 of every 28-Day cycle, or
- Pomalidomide (POM) 4 mg capsules orally on Days 1 to 21 in each 28-Day cycle.

Both treatment arms were administered 40 mg dex orally once weekly on Days 1, 8, 15 and 22 of each 28-Day cycle for patients <75 years of age or 20 mg for patients ≥75 years.

Dose modifications, including reductions, and delays for both melflufen and dexamethasone were implemented based on patient tolerance.

Patients received treatment until there was documented PD (confirmed on two consecutive assessments), unacceptable toxicity or the patient/treating physician determined it was not in the patient's best interest to continue.

Objectives

The primary objective of this Phase 3 trial was to compare PFS between both treatment arms as assessed by IRC according to IMWG-URC response criteria.

Key secondary objectives were to assess and compare ORR, OS, safety and tolerability in both treatment arms.

Outcomes / endpoints

The primary endpoint was PFS, defined as time (months) from date of randomization to the earlier of confirmed disease progression or death due to any cause. Progression dates were assessed by the IRC using the IMWG-URC.

The key secondary endpoints were:

- ORR, defined as the proportion of patients achieving a best confirmed response of sCR, CR, VGPR, or PR using local laboratory evaluation.
- OS, defined as time (months) from date of randomization to death due to any cause. Patients still alive at end of study, or lost to follow up, were censored at last day known alive.

Other secondary efficacy endpoints were:

Unless stated otherwise, response and progression status were to be assessed by the IRC using the IMWG-URC.

- DOR defined as the time from the first evidence of confirmed assessment of sCR, CR, VGPR, or PR to first confirmed disease progression, or to death due to any cause. Duration of response was defined only for patients with a confirmed PR or better.
- Clinical benefit rate (CBR), i.e., ≥ MR: is the rate of response evaluable patients that achieved a confirmed MR or better.
- TTR defined as the time from the date of randomization to the date of the first documented confirmed response in a patient that had responded with ≥ PR.
- TTP defined as the time from the date of randomization to the date of the first documented confirmed PD.
- Duration of clinical benefit (DOCB) defined as the time from the first evidence of confirmed assessment of sCR, CR, VGPR, PR, or MR to first confirmed disease progression, or to death due to any cause. DOCB was defined only for patients with a confirmed MR or better.
- Best response during the study (sCR, CR, VGPR, PR, MR, SD, or PD) using the IMWG-URC.
- Primary and secondary endpoints as assessed by investigators.

Randomisation and blinding (masking)

Patients were 1:1 randomized and stratified by age (≥ 75 years of age versus < 75 years of age), number of lines of prior therapy (2 versus 3 to 4 prior lines) and international staging system (ISS) Score (1 versus ≥ 2).

The study was unblinded.

Statistical methods

Analysis sets - The Full analysis set (FAS) was defined as all subjects who were randomized. The Per Protocol (PP) analysis set was defined as all patients who received at least one dose of melflufen, pomalidomide, or dexamethasone, and had a baseline assessment of disease status and at least 1 post-baseline assessment for disease response. Patients who had major protocol deviations, related to critical eligibility criteria, the assessment of efficacy or the safety of the patient that could have significantly impacted the interpretation of study results, were excluded from the Per Protocol analysis set.

Efficacy analysis - The primary analysis of PFS was performed using a log-rank test stratified by the randomization stratification factors to compare treatment group survival distributions based on the FAS. Superiority of melflufen+dex over pomalidomide+dex with respect to the primary endpoints was claimed if the 2-sided p-value was <0.05 favoring melflufen+dex. In addition to a significant p-value for the treatment comparison based on the log-rank test, the superiority of melflufen+dexamethasone versus pomalidomide+dexamethasone was demonstrated if the upper limit of the 95% CI for the hazard ratio was < 1.0.

Non-inferiority of melflufen+dex versus POM + dex was demonstrated if the upper limit of the 95% CI for the HR was < 1.2.

Multiplicity control - Superiority testing of melflufen+dex over pomalidomide+dex with respect to the key secondary endpoints performed using a gatekeeping procedure based on a closed fixed-sequence test, provided the primary efficacy endpoint comparison was statistically significant at an alpha level 0.05. In case of statistical superiority on the primary endpoint then ORR was tested for statistical superiority. In case of statistical superiority on ORR, then overall survival was tested for statistical superiority.

Sample size – The planned sample size was 450 patients based on 90% power with 0.05 two-sided significance level and HR of 0.70 (melflufen + dex/POM+dex), an accrual time of 24 months, ~15% early censor rate and a median PFS of POM+ dex of 3.6 months.

Interim analysis – No interim analysis were performed. Based on sample size assumptions, the final analysis was to take place when 339 patients had experienced PFS events.

Handling of missing values/censoring/discontinuations - Unconfirmed PD as the final response assessment for PFS was also assessed as confirmed PD and, therefore, an event. PFS was right-censored according to the conventions described in Table 22.

Table 22. Conventions for Censoring of PFS

Situation	Date of Progression or Censoring	Outcome
No post baseline response assessments	Date of randomization	Censored
Non-protocol systemic anticancer therapy started before documentation of PD or death	Date of last response assessment prior to start of new anticancer therapy	Censored
Death or PD after more than 1 consecutively missed response assessment	Date of last response assessment without documentation of PD that is before the first missed visit	Censored
Unconfirmed PD as the final response assessment	Date of latest PD assessment	Progressed
Alive and without PD documentation	Date of last response assessment	Censored
Death or PD between scheduled response assessments	Date of death or preceding response assessment showing PD, whichever occurs first	Progressed
Death before first response assessment	Date of death	Progressed

PD = disease progression; PFS = progression-free survival

Results

Participant flow

A total of 495 patients were randomized in the study. Of these, 21 patients were randomized, but not treated;18 patients randomized to melflufen+dex and 3 patients randomized to pom + dex. The most common reasons were low laboratory values in both treatment arms (Table 23, Figure 8).

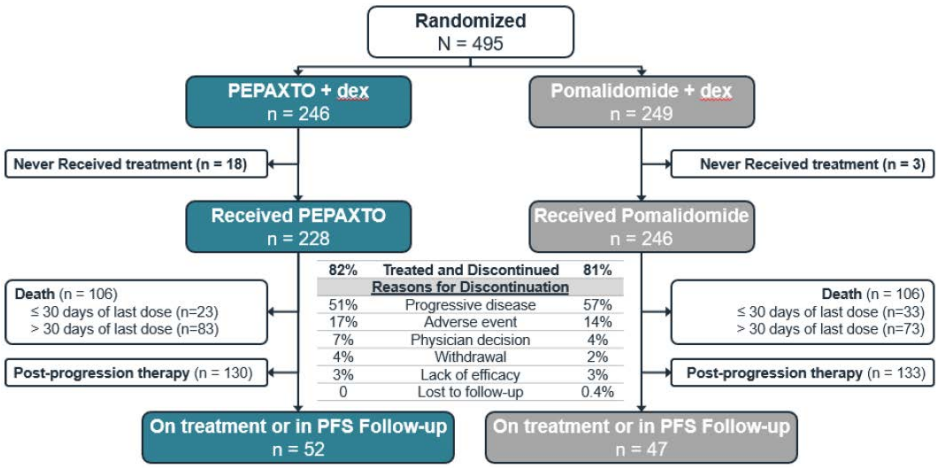
Approximately 18% of patients were still receiving treatment as of the data cut-off (3 Feb 2021).

The most common reason for treatment discontinuation was progressive disease (n=257, 54.2%), followed by adverse event (n=73, 15.4%).

Table 23. Summary of Patient Disposition

	Melflufen+Dexamethasone N=246 n (%)	Pomalidomide+Dexamethasone N=249 n (%)	Overall N=495 n (%)
Number of screened patients in the Enrolled Analysis Set [a]	—	—	644
Number of screen failures	—	—	149
Number of randomized patients in the Full Analysis Set [b]	246	249	495
Number of patients randomized not treated	18	3	21
Number of treated patients in the Safety Analysis Set [c]	228 (92.7%)	246 (98.8%)	474 (95.8%)
Number of treated patients in the Per Protocol Analysis Set [d]	218 (88.6%)	236 (94.8%)	454 (91.7%)
Number of treated patients in the PRO Analysis Set [e]	77 (31.3%)	81 (32.5%)	158 (31.9%)
Number of treated patients in the PK Analysis Set [f]	224 (91.1%)	—	224 (45.3%)
Treatment Status [g]			
Ongoing	42 (18.4%)	46 (18.7%)	88 (18.6%)
Discontinued	186 (81.6%)	200 (81.3%)	386 (81.4%)
Primary reason for treatment discontinuation			
Progressive disease	116 (50.9%)	141 (57.3%)	257 (54.2%)
Adverse event	38 (16.7%)	35 (14.2%)	73 (15.4%)
Lack of efficacy	6 (2.6%)	8 (3.3%)	14 (3.0%)
Physician decision	17 (7.5%)	9 (3.7%)	26 (5.5%)
Withdrawal by patient	9 (3.9%)	6 (2.4%)	15 (3.2%)
Lost to follow up	0	1 (0.4%)	1 (0.2%)
Number of treated patients in PFS follow-up [g]	10 (4.4%)	1 (0.4%)	11 (2.3%)
Number of treated patients in OS follow-up [g]	70 (30.7%)	82 (33.3%)	152 (32.1%)
Study Status			
Ongoing	126 (51.2%)	129 (51.8%)	255 (51.5%)
Discontinued	120 (48.8%)	120 (48.2%)	240 (48.5%)
Primary reason for study discontinuation [c]			
Death	116 (47.2%)	108 (43.4%)	224 (45.3%)
Lost to follow-up	1 (0.4%)	2 (0.8%)	3 (0.6%)
Withdrawal by patient	3 (1.2%)	10 (4.0%)	13 (2.6%)

OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PRO = patient-reported outcomes.
[a] The Enrolled Analysis Set was defined as all patients who were assigned a unique patient number by Interactive Response Technology system at the time of enrollment (signing of consent).
[b] The Full Analysis Set was defined as all randomized patients.
[c] The Safety Analysis Set was defined as all patients who received at least one dose of melflufen, pomalidomide, or dexamethasone.
[d] The Per Protocol Analysis Set was defined as all patients who received at least one dose of melflufen, pomalidomide, or dexamethasone, and had a baseline assessment of disease status and at least one post-baseline assessment for disease response. Patients with major protocol deviations, related to critical eligibility criteria, the assessment of efficacy or the safety that could significantly impact the interpretation of study results, were excluded from the Per Protocol Analysis Set.
[e] The PRO Analysis Set was defined as all patients who enrolled on or after protocol version 4.1 and had completed the same PRO questionnaire at baseline and post-baseline.
[f] The PK Analysis Set was defined as all patients in the Full Analysis Set who received at least 1 dose of melflufen and had 3 samples with measurable concentrations in at least one treatment cycle.
[g] Percentage calculations used the Safety Analysis Set as denominator.
[h] Patients reporting more than one screen failure reason were counted more than once.



Abbreviations: dex dexamethasone; PFS progression-free survival.
PEPAXTO=melflufen.

Figure 8. Study OP-103 – Patient Disposition

Conduct of study

The original protocol (version 1.1) was approved on 07 Dec 2016. There were 5 protocol amendments. Key changes pertained to a change of inclusion criteria 4 to allow patients that received lenalidomide and a proteasome inhibitor during the first line of therapy and were refractory to lenalidomide in the first line to potentially enroll in the study to improve accrual; addition of PRO as exploratory endpoint; and an increase in number of sites to ~100 as well as added Asia/Pacific region.

Changes to the planned analyses per the protocol were made in Apr and Jun 2021, following FDA feedback. Key changes pertained to: primary endpoint based on stratified log-rank test; DOR moved from key to other secondary endpoint removing it from multiplicity assessment; addition of 'time from prior ASCT to randomization subgroup analysis' for PFS, ORR and OS as well as imputation rules for this subgroup.

Protocol deviations

Overall, a total of 154 major protocol deviations were identified during the study as of the data cutoff: 61 deviations related to study procedure or assessment (Table 24).

Table 24. Major Protocol Deviations

Deviation Category	Melphalan Flufenamide + Dexamethasone (N=246)	Pomalidomide + Dexamethasone (N=249)	Overall (N=495)
Study Procedure or Assessment	38 (15.4%)	23 (9.2%)	61 (12.3%)
Study Medication	21 (8.5%)	14 (5.6%)	35 (7.1%)
Other: GCP	7 (2.8%)	12 (4.8%)	19 (3.8%)
Inclusion/Exclusion Criteria	6 (2.4%)	7 (2.8%)	13 (2.6%)
Randomization Procedure	7 (2.8%)	2 (0.8%)	9 (1.8%)
Excluded Concomitant Medication	2 (0.8%)	6 (2.4%)	8 (1.6%)
Withdrawal Criteria	3 (1.2%)	1 (0.4%)	4 (0.8%)
Other: Source Documentation	2 (0.8%)	1 (0.4%)	3 (0.6%)
Informed Consent	2 (0.8%)	0	2 (0.4%)

Baseline data

Demographics

Of the 495 patients in the FAS, the median age (years) was 68.0 years (Table 25). Approximately 36% of patients was <65 years of age. There were slightly more male than female patients (56.4% vs 43.6%) and 90.1% of patients was white. Around 90% of patients had ECOG 0 or 1.

Table 25. Demographics and Baseline Characteristics (FAS)

Characteristic	Melflufen + Dexamethasone N=246	Pomalidomide + Dexamethasone N=249	Overall N=495
Age (years) [a]			
n	246	249	495
Mean (SD)	66.1 (8.98)	66.5 (8.83)	66.3 (8.89)
Median	68.0	68.0	68.0
Min, max	41, 91	39, 87	39, 91
Age category (years), n (%)			
< 65 years	96 (39.0%)	85 (34.1%)	181 (36.6%)
65 to <75 years	113 (45.9%)	125 (50.2%)	238 (48.1%)
≥75 years	37 (15.0%)	39 (15.7%)	76 (15.4%)
Sex, n (%)			
Male	139 (56.5%)	140 (56.2%)	279 (56.4%)
Female	107 (43.5%)	109 (43.8%)	216 (43.6%)
Race, n (%)			
Asian	8 (3.3%)	13 (5.2%)	21 (4.2%)
Black or African American	4 (1.6%)	4 (1.6%)	8 (1.6%)
White	224 (91.1%)	222 (89.2%)	446 (90.1%)
Other	1 (0.4%)	0	1 (0.2%)
Unknown	9 (3.7%)	9 (3.6%)	18 (3.6%)
Not Reported	0	1 (0.4%)	1 (0.2%)
Ethnicity, n (%)			
Hispanic or Latino	8 (3.3%)	5 (2.0%)	13 (2.6%)
Not Hispanic or Latino	232 (94.3%)	237 (95.2%)	469 (94.7%)
Not reported	6 (2.4%)	7 (2.8%)	13 (2.6%)
Baseline [b] ECOG Performance Status [c], n (%)			
0	90 (36.6%)	92 (36.9%)	182 (36.8%)
1	130 (52.8%)	136 (54.6%)	266 (53.7%)
2	26 (10.6%)	21 (8.4%)	47 (9.5%)

ECOG = Eastern Cooperative Oncology Group; FAS = Full Analysis Set; Max = maximum; Min = minimum; SD = standard deviation

[a] Age was calculated relative to the date of informed consent.

[b] Baseline was defined as the most recent assessment prior to administration of the first dose of study drug.

[c] For ECOG Performance Status: 0 – Fully active, able to carry on all predisease performance without restriction; 1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work; 2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

Disease Characteristics

The median time since initial diagnosis was close to 4 months in both arms. At study entry, most patients had ISS stage I (49.1%) or II (38%) and extramedullary disease was present in 12.5%. Bone lesions were present in slightly fewer patients in the meflufen+ dex arm (74.8%) compared to the pom+dex arm (82.7%). Other disease characteristics at study entry were generally consistent between treatment arms.

Table 26 Selected Myeloma Disease Characteristics at Study Entry and Baseline (FAS)

Characteristic	Melflufen + Dexamethasone N=246	Pomalidomide +Dexamethasone N=249	Overall N=495
Time since initial diagnosis, years [a]			
N	246	249	495
Mean (SD)	4.88 (3.542)	4.82 (3.424)	4.85 (3.480)
Median (Min, Max)	3.98 (0.5, 26.3)	3.88 (0.4, 25.2)	3.93 (0.4, 26.3)
ISS stage at study entry, n (%)			
I	119 (48.4%)	124 (49.8%)	243 (49.1%)
II	94 (38.2%)	94 (37.8%)	188 (38.0%)
III	33 (13.4%)	31 (12.4%)	64 (12.9%)
R-ISS stage of disease at study entry, n (%)			
R-I	69 (28.0%)	69 (27.7%)	138 (27.9%)
R-II	129 (52.4%)	138 (55.4%)	267 (53.9%)
R-III	24 (9.8%)	17 (6.8%)	41 (8.3%)
Unknown/missing	24	25	49
Bone lesions present at study entry			
Yes	184 (74.8%)	206 (82.7%)	390 (78.8%)
No	62 (25.2%)	43 (17.3%)	105 (21.2%)
Extramedullary disease present at study entry			
Yes	31 (12.6%)	31 (12.4%)	62 (12.5%)
No	215 (87.4%)	218 (87.6%)	433 (87.5%)
Type of measurable disease at Baseline [b]			
SPEP and UPEP	48 (19.5%)	57 (22.9%)	105 (21.2%)
SPEP only	140 (56.9%)	128 (51.4%)	268 (54.1%)
UPEP only	37 (15.0%)	36 (14.5%)	73 (14.7%)
sFLC only	21 (8.5%)	28 (11.2%)	49 (9.9%)
Baseline SPEP M-Spike (g/dL) [b]			
n	245	248	493
Mean (SD)	18.35 (14.877)	19.07 (16.495)	18.71 (15.700)
Median (Min, Max)	17.00 (0.0, 71.0)	17.00 (0.0, 68.8)	17.00 (0.0, 71.0)

Characteristic	Melflufen + Dexamethasone N=246	Pomalidomide +Dexamethasone N=249	Overall N=495
Baseline UPEP M-Spike (mg/day) [b]			
n	241	247	488
Mean (SD)	588.3 (1604.36)	525.7 (1068.14)	556.6 (1358.60)
Median (Min, Max)	70.0 (0, 17016)	50.0 (0, 7991)	60.0 (0, 17016)
Cytogenetic risk group based on FISH at study entry			
High	83 (33.7%)	86 (34.5%)	169 (34.1%)
Standard	128 (52.0%)	130 (52.2%)	258 (52.1%)
Unknown	35 (14.2%)	33 (13.3%)	68 (13.7%)
Patients with two or more high-risk abnormalities, n (%)			
Yes	24 (9.8%)	25 (10.0%)	49 (9.9%)
No	201 (81.7%)	205 (82.3%)	406 (82.0%)
Missing	21	19	40
Patients with deletion 17p, n (%)	33 (13.4%)	37 (14.9%)	70 (14.1%)
Heavy-light chain combination at study entry			
IgA-Kappa	33 (13.4%)	29 (11.6%)	62 (12.5%)
IgA-Lambda	15 (6.1%)	18 (7.2%)	33 (6.7%)
IgA; IgG-Kappa	0	2 (0.8%)	2 (0.4%)
IgA; IgG; IgM-Kappa	1 (0.4%)	0	1 (0.2%)
IgA; IgG; IgM-Lambda	2 (0.8%)	0	2 (0.4%)
IgA; IgM-Kappa	1 (0.4%)	0	1 (0.2%)
IgA; IgM-Lambda	1 (0.4%)	0	1 (0.2%)
IgD-Kappa	1 (0.4%)	1 (0.4%)	2 (0.4%)
IgD-Lambda	1 (0.4%)	1 (0.4%)	2 (0.4%)
IgG-Biclonal	1 (0.4%)	0	1 (0.2%)
IgG-Kappa	99 (40.2%)	98 (39.4%)	197 (39.8%)
IgG-Lambda	48 (19.5%)	53 (21.3%)	101 (20.4%)
IgG; IgE-Kappa	0	1 (0.4%)	1 (0.2%)
IgG; IgM-Kappa	1 (0.4%)	0	1 (0.2%)
IgM-Kappa	4 (1.6%)	1 (0.4%)	5 (1.0%)
IgM-Lambda	1 (0.4%)	0	1 (0.2%)
None-Kappa	22 (8.9%)	25 (10.0%)	47 (9.5%)
None-Lambda	15 (6.1%)	20 (8.0%)	35 (7.1%)

Characteristic	Melflufen + Dexamethasone N=246	Pomalidomide +Dexamethasone N=249	Overall N=495
Baseline Kappa/Lambda FLC ratio [b]			
N	245	249	494
Mean (SD)	270.804 (1186.2441)	185.769 (554.5585)	227.942 (923.5617)
Median (Min, Max)	9.833 (0.00, 14222.22)	6.02 (0.00, 5430.23)	8.03 (0.00, 14222.22)

FAS = Full Analysis Set; FISH = fluorescence in situ hybridization; FLC = free light chain; Ig = immunoglobulin; Max = maximum; Min = minimum; (R-)ISS = (Revised-) International Staging System; SD = standard deviation; sFLC = serum free light chain; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

Note: The Multiple Myeloma History CRF at Diagnosis CRF and the Multiple Myeloma History CRF at Study Entry CRF were used where "at Diagnosis" and "at Study Entry" were indicated, respectively.

[a] Time since initial diagnosis was calculated relative to first dose of study drug.

[b] Baseline labs were defined as the most recent assessment prior to administration of the first dose of study drug.

Source: Table 14.1-8

Prior treatment

The median number of prior regimens was 3.0 (Table 27). The most common prior regimens contained PIs and IMiDs (100%, each), alkylators (86.9%), mAbs (21.0%), and other (99.8%). Dexamethasone was counted as 'other' therapy and represents the majority of this category.

Table 27. Prior treatment for MM (FAS)

Characteristic	Melflufen + Dexamethasone N=246	Pomalidomide + Dexamethasone N=249	Overall N=495
Patients with at least 1 prior radiotherapy, n (%)	60 (24.4%)	71 (28.5%)	131 (26.5%)
Patients with at least 1 prior autologous transplant, n (%)	125 (50.8%)	120 (48.2%)	245 (49.5%)
Mean (SD)	1.3 (0.46)	1.3 (0.47)	1.3 (0.47)
Median (Min, Max)	1.0 (1, 2)	1.0 (1, 3)	1.0 (1, 3)
Total number of prior autologous transplants per patient			
1	88 (35.8%)	86 (34.5%)	174 (35.2%)
2	37 (15.0%)	33 (13.3%)	70 (14.1%)
3	0	1 (0.4%)	1 (0.2%)
Time from autologous transplant to randomization, n			
<5 years	91	86	177
<2.5 years	43	35	78
2.5 to 5 years	48	51	99
>5 years	34	34	68
No autologous transplant	121	129	250
Time from front line transplant to relapse (years) [a]			
n	63	64	127
Mean (SD)	2.69 (2.660)	2.33 (1.815)	2.51 (2.272)
Median (Min, Max)	1.89 (0.1, 15.0)	1.82 (0.1, 9.0)	1.85 (0.1, 15.0)
<1 year	13 (20.6%)	15 (23.4%)	28 (22.0%)
1 to <1.5 years	8 (12.7%)	12 (18.8%)	20 (15.7%)
1.5 to 2 years	14 (22.2%)	10 (15.6%)	24 (18.9%)
>2 years	28 (44.4%)	27 (42.2%)	55 (43.3%)
Patients with at least 1 prior allogeneic transplant, n (%)	3 (1.2%)	0	3 (0.6%)
Number of prior regimens			
Mean (SD) number of prior regimens per patient	2.8 (0.80)	2.7 (0.76)	2.8 (0.78)
Median (Min, Max) number of prior regimens per patient	3.0 (2, 4)	3.0 (2, 4)	3.0 (2, 4)
Total number of prior regimens per patient			
2	114 (46.3%)	111 (44.6%)	225 (45.5%)
3	76 (30.9%)	90 (36.1%)	166 (33.5%)
4	56 (22.8%)	48 (19.3%)	104 (21.0%)
Patients exposed to standardized drug group/therapy in at least one prior regimen, n (%) [b]			
Alkylators	217 (88.2%)	213 (85.5%)	430 (86.9%)
Monoclonal antibodies	54 (22.0%)	50 (20.1%)	104 (21.0%)

Characteristic	Melflufen + Dexamethasone N=246	Pomalidomide + Dexamethasone N=249	Overall N=495
IMiD	246 (100%)	249 (100%)	495 (100%)
PI	246 (100%)	249 (100%)	495 (100%)
Other [c]	246 (100%)	248 (99.6%)	494 (99.8%)
Dexamethasone	243 (98.8%)	245 (98.4%)	488 (98.6%)
Patients exposed to standardized drug group/therapy in most recent prior regimen, n (%) [b]			
Alkylators	27 (11.0%)	30 (12.0%)	57 (11.5%)
Monoclonal antibodies	42 (17.1%)	39 (15.7%)	81 (16.4%)
IMiD	215 (87.4%)	218 (87.6%)	433 (87.5%)
PI	95 (38.6%)	91 (36.5%)	186 (37.6%)
Other [c]	230 (93.5%)	231 (92.8%)	461 (93.1%)
Dexamethasone	216 (87.8%)	220 (88.4%)	436 (88.1%)
Patients refractory to standardized drug group/therapy in at least 1 prior regimen, n (%) [b]			
Alkylators	78 (31.7%)	75 (30.1%)	153 (30.9%)
Monoclonal antibodies	51 (20.7%)	49 (19.7%)	100 (20.2%)
IMiD	245 (99.6%)	249 (100%)	494 (99.8%)
PI	163 (66.3%)	163 (65.5%)	326 (65.9%)
Other [c]	237 (96.3%)	233 (93.6%)	470 (94.9%)
Dexamethasone	226 (91.9%)	225 (90.4%)	451 (91.1%)
Patients refractory to standardized drug group/therapy in most recent prior regimen, n (%) [b]			
Alkylators	10 (4.1%)	13 (5.2%)	23 (4.6%)
Monoclonal antibodies	41 (16.7%)	39 (15.7%)	80 (16.2%)
IMiD	214 (87.0%)	218 (87.6%)	432 (87.3%)
PI	76 (30.9%)	72 (28.9%)	148 (29.9%)
Other [c]	216 (87.8%)	214 (85.9%)	430 (86.9%)
Dexamethasone	203 (82.5%)	206 (82.7%)	409 (82.6%)
Best response for most recent prior regimen			
Stringent Complete Response	1 (0.4%)	1 (0.4%)	2 (0.4%)
Complete Response	19 (7.7%)	17 (6.8%)	36 (7.3%)
Very Good Partial Response	50 (20.3%)	54 (21.7%)	104 (21.0%)
Partial Response	91 (37.0%)	89 (35.7%)	180 (36.4%)
Minimal Response	18 (7.3%)	19 (7.6%)	37 (7.5%)
Stable Disease	35 (14.2%)	39 (15.7%)	74 (14.9%)
Progressive Disease	27 (11.0%)	21 (8.4%)	48 (9.7%)

Characteristic	Melflufen + Dexamethasone N=246	Pomalidomide + Dexamethasone N=249	Overall N=495
Unknown	4 (1.6%)	7 (2.8%)	11 (2.2%)
Best response for second most recent prior regimen			
Stringent Complete Response	2 (0.8%)	4 (1.6%)	6 (1.2%)
Complete Response	32 (13.0%)	36 (14.5%)	68 (13.7%)
Very Good Partial Response	71 (28.9%)	76 (30.5%)	147 (29.7%)
Partial Response	83 (33.7%)	80 (32.1%)	163 (32.9%)
Minimal Response	13 (5.3%)	11 (4.4%)	24 (4.8%)
Stable Disease	30 (12.2%)	24 (9.6%)	54 (10.9%)
Progressive Disease	8 (3.3%)	10 (4.0%)	18 (3.6%)
Unknown	6 (2.4%)	7 (2.8%)	13 (2.6%)

FAS = Full Analysis Set; IMiD = immunomodulatory drug; Max = maximum; Min = minimum; PI = proteasome inhibitor; SD = standard deviation.

[a] Front-line transplant occurred within the first regimen of therapy from start of first dose of antimyeloma therapy prior to, or on the date of last dose of therapy within the first regimen.

[b] At each level of summarization (Standardized Drug Group, Therapy), patients reporting more than one medication were counted only once.

[c] Dexamethasone was counted as an 'other' therapy and represents the majority of this category.

Refractory status

All 495 patients (100%) in the FAS were double-class exposed, defined as patients who had received an IMiD and PI, and 89 patients (18.0%) were triple-class exposed, defined as patients who had received an IMiD, a PI, and an anti-CD38 mAb (Table 28). Of the 89 patients who were triple class exposed, 69 patients (14%) were triple class refractory.

Table 28. Refractory Status (FAS)

Refractory Status	Melflufen + Dexamethasone N=246 n (%)	Pomalidomide + Dexamethasone N=249 n (%)	Overall N=495 n (%)
Refractory to most recent prior regimen	245 (99.6%)	247 (99.2%)	492 (99.4%)
Refractory to lenalidomide in last line	213 (86.6%)	217 (87.1%)	430 (86.9%)
Refractory to lenalidomide within 18 months of randomization by dose [a]	245 (99.6%)	248 (99.6%)	493 (99.6%)
Refractory to 25 mg	159 (64.6%)	165 (66.3%)	324 (65.5%)
Refractory to <25 mg	81 (32.9%)	77 (30.9%)	158 (31.9%)
Refractory to dose unknown	5 (2.0%)	6 (2.4%)	11 (2.2%)
Refractory to prior alkylator	78 (31.7%)	75 (30.1%)	153 (30.9%)
Refractory or intolerant to prior IMiD	245 (99.6%)	249 (100%)	494 (99.8%)
Refractory to prior IMiD	245 (99.6%)	249 (100%)	494 (99.8%)
Refractory or intolerant to prior PI	177 (72.0%)	172 (69.1%)	349 (70.5%)
Refractory to prior PI	163 (66.3%)	163 (65.5%)	326 (65.9%)
Refractory and/or intolerant to prior anti-CD38 mAb	48 (19.5%)	39 (15.7%)	87 (17.6%)
Refractory to prior anti-CD38 mAb	48 (19.5%)	39 (15.7%)	87 (17.6%)
Received an IMiD and PI (double-class exposed)	246 (100%)	249 (100%)	495 (100%)
Number of patients with double-class refractory disease	162 (65.9%)	163 (65.5%)	325 (65.7%)
Received an IMiD, PI, and anti-CD38 mAb (triple-class exposed)	49 (19.9%)	40 (16.1%)	89 (18.0%)
Number of patients with triple-class refractory disease	39 (15.9%)	30 (12.0%)	69 (13.9%)
Patients refractory to at least 1 component of most recent prior regimen	245 (99.6%)	247 (99.2%)	492 (99.4%)

FAS = Full Analysis Set; IMiD = immunomodulatory drug; mAb = monoclonal antibody; PI = proteasome inhibitor.
[a] Number (%) of subjects who are refractory to lenalidomide 25 mg vs. lenalidomide < 25 mg (10 mg or 15 mg) during last (most recent) line of prior therapy or administered within 18 months prior to randomization.

Subsequent therapy

A total of 140 patients (56.9%) in the melflufen+dex group and 135 patients (54.2%) in the pom+dex group received subsequent therapy. In the melflufen+dex group, the most commonly received subsequent therapies were IMiDs (26.4%) and PIs (23.2%) followed by anti-CD38s (16.3%) and alkylators (8.1%; Table 29). In the pom+dex group, the most commonly received subsequent therapies were anti-CD38s (26.9%]) and PIs (26.1%) followed by alkylators (12.0%) and IMiDs (9.6%).

Table 29. Subsequent therapy (FAS)

	Melflufen+Dexamethasone N=246 n (%)	Pomalidomide+Dexamethasone N=249 n (%)
Any subsequent therapy	140 (56.9%)	135 (54.2%)
Alkylator	20 (8.1%)	30 (12.0%)
Cyclophosphamide	17 (6.9%)	15 (6.0%)
Melphalan	0	10 (4.0%)
Melflufen	0	1 (0.4%)
Anti-CD38	40 (16.3%)	67 (26.9%)
Daratumumab	40 (16.3%)	65 (26.1%)
Isatuximab	0	2 (0.8%)
IMiD	65 (26.4%)	24 (9.6%)
Pomalidomide	50 (20.3%)	4 (1.6%)
Lenalidomide	12 (4.9%)	15 (6.0%)
Thalidomide	3 (1.2%)	3 (1.2%)
PI	57 (23.2%)	65 (26.1%)
Bortezomib	30 (12.2%)	38 (15.3%)
Carfilzomib	21 (8.5%)	24 (9.6%)
Ixazomib	6 (2.4%)	3 (1.2%)

FAS = Full Analysis Set; IMiD = immunomodulatory drug; PI = protease inhibitor.

Numbers analysed

The first patient initiated study treatment in Jun 2017. Due to a slower than expected enrolment rate, the event rate in the study was lower than projected and, therefore, enrolment was extended and more patients were randomized to the study than originally planned.

In total of 495 patients were included in the FAS: 246 patients were randomized to the melflufen+dex group and 249 patients to pom + dex.

In total 454 patients were included in the PP analysis set.

In total 30 patients represented a post-hoc defined subgroup of patients aligning with the proposed target population of TCR patients after at least 3 prior lines of therapy.

Outcomes and estimation

Data cut-off 3 Feb 2021

Primary endpoint – PFS

The primary endpoint PFS was met for the overall study population (FAS). The median IRC assessed PFS was 6.83 (95% CI 4.96, 8.54) in the meflufen + dex arm vs. 4.93 (95% CI 4.24, 5.72) in the pom + dex arm. The stratified HR was 0.792 (95% CI: 0.640, 0.981; p=0.0319).

Subgroup analyses

A HR for PFS >1 was observed for the subgroups of patients with prior ASCT, refractory to anti-CD38 mAb, EMD at baseline, age <65, Creatinine clearance <45 ml/min or ≥90 ml/min and ≥1.5x ULN LDH (data not shown).

Sensitivity analyses

Key secondary endpoints

ORR

Based on IRC assessment for the FAS, key secondary endpoint ORR was not met. In total 80 patients out of 246 in the melflufen+dex group had a best response of PR or better for an overall confirmed response rate of 32.5% (95% CI: 26.71%, 38.76%) and 67 out of 249 patients in the pomalidomide+dex group had an overall confirmed response rate of 26.9% (95% CI: 21.50%, 32.87%). This difference was not significant (stratified p=0.1422).

OS

The other key secondary endpoint OS was also not met for the FAS and suggested a detriment for the melflufen arm. The results of the OS analysis in the FAS as assessed by the Investigator at the time of the data cutoff (03 Feb 2021) indicated that melflufen+dex did not lead to longer OS, as would have been expected by the superior PFS, as shown by the HRs and p-values for the comparison between the melflufen+dex group and pom+dex group (stratified log-rank p-value: p=0.4667 and HR of 1.104 [95% CI: 0.846, 1.441]). Median OS was 19.75 months (15.08, 25.56) for melflufen + dex vs. 25.00 months (18.14, 31.87) for pom + dex.

OS subgroup analysis – For multiple subgroups HR is above 1 suggesting a worse overall survival, including age <65, 3 or 4 prior lines of therapy, creatinine clearance ≥90 mL/min, low BSA, presence of EMD, prior ASCT, not refractory to alkylator, refractory to anti-CD38 mAb, females, BSA ≤ median, white race, ISS stage II or III, and standard or unknown risk status (Figure 9). For age<65 and prior ASCT, the 95% CI excludes 1.

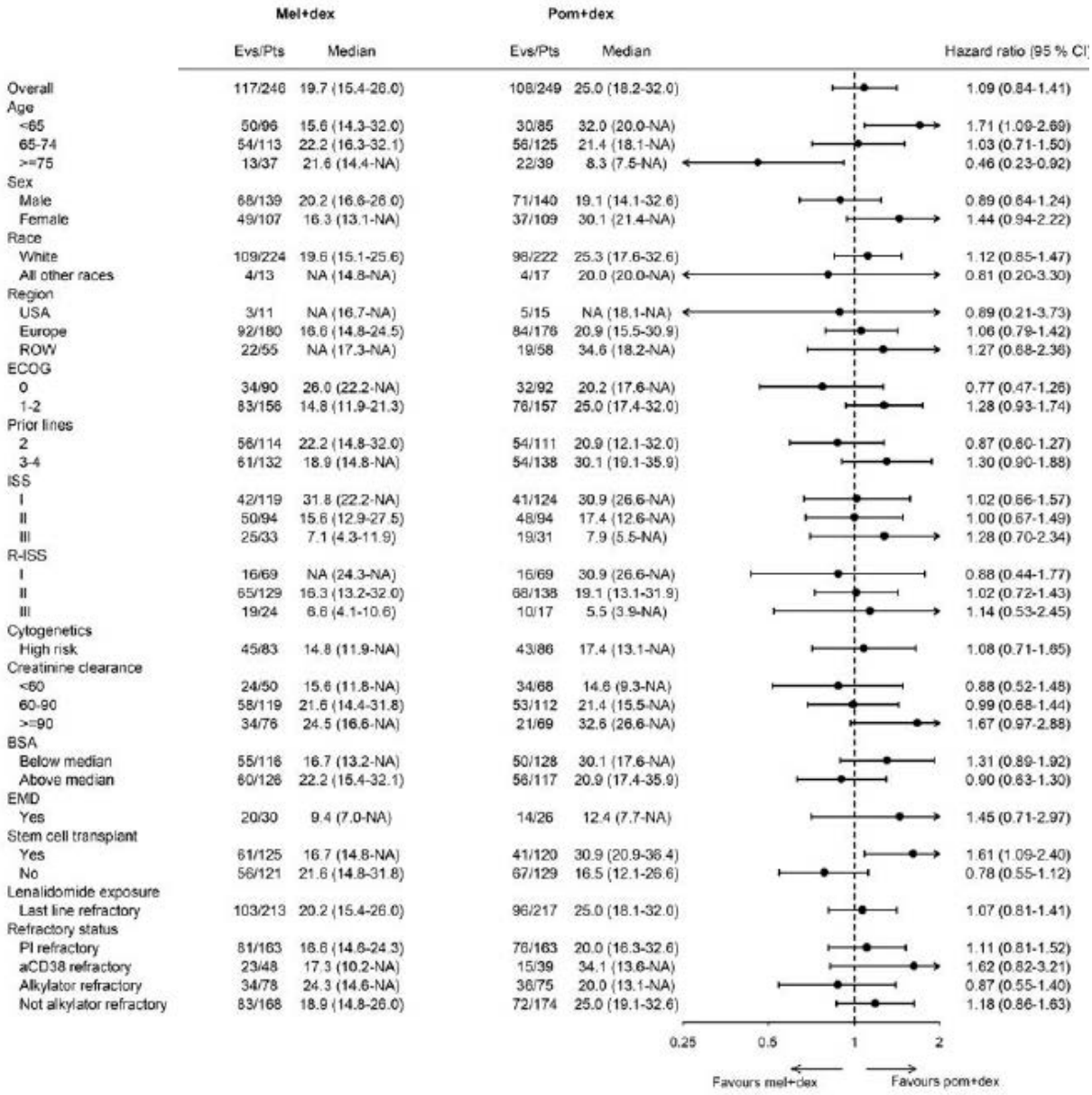


Figure 9. OS Subgroup Analysis

Main other secondary endpoints (*meflufen+dex vs. pom+dex*)

DOR – The IRC based median DOR for the FAS was 11.17 months (95% CI: 8.48, 17.48) in the melflufen+dex group and 11.07 months (95% CI: 7.62, 15.44) in the pom+dex group with a stratified HR of 1.061 (95% CI: 0.651, 1.728).

CBR - The CBR (i.e., proportion of patients with best response of MR or better) based on IRC assessment was 49.6% (95% CI: 43.18%, 56.02%) vs. 41.0% (95% CI: 34.80%, 47.35%), respectively.

TTR – The IRC based median TTR was 2.1 (min, max 0.9, 14.6) vs. 2.0 months (0.8, 9.4).

TTP – The median TTP based on IRC assessment in the FAS was 7.16 months (95% CI: 5.59, 9.23) vs. 5.32 months (95% CI: 4.63, 6.67) with a stratified HR 0.800 (95% CI: 0.640, 1.000; p=0.0498).

DOCB - The median DOCB was 9.23 months (95% CI: 7.46, 12.68) vs. 8.31 months (95% CI: 6.44, 10.38) with a stratified HR 0.895 [95% CI: 0.635, 1.261.

Ancillary analyses

Based on a DCO 03 Feb 2022 efficacy results for the 31 patients in Study OP-103 aligning with the TCR 3L+ population, suggest an ORR of 35.5% (95% CI: 19.2, 54.6), CR, VGPR and no sCR in 6 patients (19.4%), PR in n=5 (16.1%) and median DoR of 9.5 months (95% CI: 2.2, NE). Median PFS was 6.6 months (95% CI: 3.2, 9.4) and median OS was 18.1 months (95% CI: 7.1, 26.6).

The discrepancy between the PFS and OS results and the divergent results of the subgroup OS analyses prompted further exploratory analyses. A multivariable analysis was performed to explore any signals of effect modification for different subgroups (age, ASCT, gender, creatinine clearance). A strong signal of effect modification was observed for the post-hoc defined subgroup of time-to-progression (TTP) post ASCT <36 months vs no ASCT or TTP post ASCT ≥36 months (HR: 2.02 (95% CI: 1.26-3.25); multivariable Cox-model after stepwise selection based on Akaike Information Criteria). In response to Day 180 list of outstanding issues, main efficacy results of Study OP-103 were presented by time to progression post ASCT (

Table 30). Results seem to improve with larger time since ASCT or with no prior ASCT vs. the ITT. Further, for the primary endpoint of PFS as well as for ORR and OS, the results for patients with a time-to-progression post ASCT of <36 months consistently demonstrated reduced efficacy in this group. On the contrary, consistent results on efficacy in favour of melflufen were seen for the subgroup with no ASCT or prior ASCT and TTP ≥36 months (Table 31).

Table 30. OS, PFS and ORR by time-to-progression post-ASCT in Study OP-103

Time-to-progression post-ASCT	OS (95% CI)			PFS (95% CI)			ORR (95% CI)		
	Mel OS	Pom OS	HR	Mel PFS	Pom PFS	HR	Mel%	Pom%	OR
<1 year n=31 (Mel) n=32 (Pom)	13.1 (5.9, NE)	20.9 (18.1, NE)	2.18 (1.01, 4.73)	4.4 (3.2, 6.9)	4.3 (3.3, 8.6)	1.21 (0.69, 2.12)	19.4 (7.5, 37.5)	25.0 (11.5, 43.4)	0.72 (0.22, 2.38)
1-2 years n=47 (Mel) n=51 (Pom)	14.8 (10.2, NE)	30.1 (19.1, NE)	2.07 (1.13, 3.79)	4.0 (3.5, 6.6)	5.6 (3.8, 8.5)	1.20 (0.74, 1.94)	17.0 /7.6, 30.8)	23.5 (12.8, 37.5)	0.67 (0.25, 1.81)
2-3 years n=23 (Mel) n=18 (Pom)	19.7 (15.1, NE)	32.0 (30.9, NE)	1.27 (0.46, 3.53)	4.9 (3.7, 12.4)	6.9 (4.7, NE)	1.49 (0.70, 3.16)	21.7 (7.5, 43.7)	44.4 (21.5, 69.2)	0.35 (0.09, 1.35)
<3 years n=101 (Mel) n=101 (Pom)	15.6 (13.1-NE)	30.9 (20.2-NE)	1.86 (1.21-2.85)	4.3 (3.7, 5.3)	5.2 (4.3, 7.5)	1.28 (0.92, 1.77)	18.8 (11.7, 27.8)	27.7 (19.3, 37.5)	0.60 (0.31, 1.17)
≥3 years n=24 (Mel) n=19 (Pom)	35.0 (20.2, NE)	32.6 (NE, NE)	0.95 (0.33, 2.76)	6.7 (4.2, NE)	6.0 (4.3, NE)	0.68 (0.31, 1.48)	41.7 (22.1, 63.4)	21.1 (6.1, 45.6)	2.68 (0.68, 10.53)
Non-ASCT n=121 (Mel) n=129 (Pom)	21.6 (14.8, 31.8)	16.5 (12.1, 26.6)	0.78 (0.55, 1.12)	9.3 (7.3, 12.2)	4.6 (3.5, 6.5)	0.59 (0.44, 0.79)	42.1 (33.2, 51.5)	27.1 (19.7, 35.7)	1.96 (1.15, 3.32)
ITT n=246 (Mel) n=249 (Pom)	19.7 (15.4, 26.0)	25.0 (18.2, 32.0)	1.09 (0.84, 1.41)	6.8 (5.1,8.6)	4.9 (4.3, 5.9)	0.77 (0.62, 0.95)	32.5 (26.7, 38.8)	26.9 (21.5, 32.9)	1.31 (0.89, 1.93)

Abbreviations: ASCT Autologous stem-cell transplant; CI Confidence interval; HR Hazard ratio; ITT intent-to-treat; Mel Melflufen; NE Not estimable; Pom Pomalidomide; OR Odds ratio; ORR Overall response rate; OS Overall survival; PFS Progression-free survival; TTP Time to progression. Median values are shown in months for OS and PFS.

Table 31. Efficacy results Study OP-103 based on time-to-progression < or ≥36 months post-ASCT (DCO 3 feb 2022)

	Melflufen	Pomalidomide	
ITT	N=246	N=249	
Median PFS (95% CI), months	6.83 (4.96, 8.54)	4.93 (4.24, 5.72)	HR: 0.792 (0.640, 0.981)* HR: 0.770 (0.625, 0.949)
Median OS (95% CI), months	20.24 (15.84, 24.34)	23.98 (19.06, 28.71)	HR: 1.144 (0.912, 1.434)* HR: 1.132 (0.905, 1.416)
ORR (95% CI), %	32.5 (26.7, 38.8)	26.9 (21.5, 32.9)	P=0.1722
No ASCT or TTP≥36 months	N=145	N=148	
Median PFS (95% CI), months	9.26 (7.16, 11.79)	4.63 (3.65, 6.28)	HR: 0.577 (9.438, 0.760)
Median OS (95% CI), months	23.56 (18.86, 27.96	19.84 (12.62, 26.48)	HR: 0.833 (0.620, 1.120)
ORR (95% CI), %	42.1 (33.9, 50.5)	26.4 (19.5, 34.2)	P=0046
ASCT and TTP<36 months	N=101	N=101	
PFS	4.27 (3.68, 5.06)	5.16 (4.27, 7.39)	HR: 1.277 (0.920, 1.772)
OS (95% CI)	15.72 (11.89, 20.47)	28.71 (20.17, 34.07)	HR: 1.803 (1.274, 2.551)
ORR (95% CI)	18.8 (11.7, 27.8)	27.7 (19.3, 37.5)	P=0.1349

* Stratified HR

Twelve patients in the melflufen arm of OP-103 were 3L+ TCR without recent ASCT target. ORR for this subgroup was 50%, median DOR 4.8 months, median PFS 5.4 months and median OS 18.1 months, but results should be interpreted with caution due to the very limited patient number.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The application has been changed from a conditional marketing authorization (CMA) to a full approval MAA for TCR patients with ≥3 prior treatment lines, as the clinical study report for confirmatory Study OP-103 has been presented in response to the LoQ. Clinical data in the newly proposed target population is derived from the single, pivotal trial OP-106 (HORIZON). This is a single arm study of melflufen in combination with dexamethasone (dex) in patients with RRMM who had received a minimum of 2 prior lines of therapy, including an IMiD and a PI, and were refractory to pomalidomide and/or an anti-CD38 mAb. Support is provided by data from the randomized controlled trial OP-103 that included patients (mostly) in an earlier line of treatment. According to the applicant, no additional confirmatory data is deemed necessary.

Patient population

The population of interest changed several times during the trial. Given the evolving MM treatment landscape during the study, it was recognized that triple class refractory patients (TCR) patients had a high unmet

medical need. With final protocol amendment 6 (after inclusion of 143 patients) the Applicant considered the TCR patients (~76% study population) the main population of interest for this CMA application. The higher unmet medical need in TCR RRMM patients as compared to the initially proposed primary efficacy population is acknowledged and reassuringly, the objective of the study was met for the overall study population as well. Still, there is a potential that study integrity was affected as the primary efficacy population was modified several times during the trial (see discussion regarding sample size increase).

Another subgroup of interest was defined based on preliminary signals of efficacy, i.e. patients with extramedullary disease (EMD). These patients have a significantly worse prognosis than patients without any extramedullary involvement. However, given controversies surrounding the precise definition of EMD, absence of a rationale as to why melflufen + dex would be specifically efficacious in this subgroup of patients in comparison to other treatments and the absence of a pre-planned hypothesis testing, the EMD analysis will be considered exploratory.

Eligible patients had to have documented disease progression in need of treatment at time of screening which is adequately reflected in the indication.

Moreover, patients had to have measurable disease at baseline that was defined according to standard International Myeloma Working Group (IMWG) criteria, except for the serum M-protein levels. Allowed serum protein electrophoresis (SPEP) levels were slightly lower than standard criteria (0.5 instead of 1.0 g/dL). The number of patients that had measurable disease based on SPEP between 0.5-<1 g/dL only were limited to ~5% (n=6/119). Hence the overall TCR study population is considered sufficiently representative of patients in need of treatment.

Efficacy in primary refractory patients is unknown, as these patients were excluded from the pivotal trial. This is reflected in section 5.1 of the SmPC.

Endpoints

The efficacy endpoints are well-established endpoints for RRMM. All tumour response and progression-dependent endpoints were based on IMWG Uniform Response Criteria (IMWG-URC; Rajkumar et al., 2011). The primary efficacy endpoint ORR supported with an IRC-based sensitivity analysis is acceptable in the context of an uncontrolled trial. The Applicant defined a minimal ORR threshold of 15% as clinically relevant treatment effect. Although the single arm design could be acceptable for the TCR population considering the initiation date of the study and absence of a standard of care at that time, recent approval of alternative treatment options emphasizes the need for contextualization of the efficacy data, in particular for patients that are TCR after relative few prior lines of therapy. Moreover, uncertainty remains with regard to the effect on time-dependent endpoints, PFS and OS, which cannot be reliably interpreted in an uncontrolled study.

PRO endpoints were added post-hoc after evaluation of the primary endpoint and considered exploratory only, also given the non-randomized study design and limited evaluable data (see below).

Response definition

All response categories (including MR and SD) required 2 consecutive assessments. No minimal time between the 2 assessments was defined in the protocol, but only few patients had consecutive response assessments on the same day.

For ORR and DoR analysis, it appears that the start time of a confirmed partial response has been based on data from both scheduled and unscheduled visits. Considering the single-arm trial design, sensitivity analyses for DoR and ORR were requested, for which (confirmed) responses are derived using only scheduled visits.

For the determination of a progression both scheduled and unscheduled visits should be used. Results of these additional analyses were generally consistent with the primary results.

When it was established that HORIZON study would be pivotal for this CMA, an Independent Review Committee (IRC) was included to perform an independent assessment of response, which is acknowledged.

Dose

The proposed 40 mg meflufen dose regimen with 28 day cycle length is in line with the regimen used in the pivotal trial and adequately selected based on dose finding study O-12-M1. Since melphalan exposures are higher in patients with low body weight and in patients with renal impairment, a lower starting dose of 30 mg is proposed for those patients. The once per week 40 mg low dose dex schedule is considered well established in MM treatment. The single arm design of the pivotal Phase 2 trial does not allow to isolate the contribution of the two components of the combination. However, melflufen monotherapy data is available from the supportive dose finding study and some information with regard to low dose dex monotherapy is available in literature. In the melflufen monotherapy cohort, ORR was only 7.7% and clinical benefit rate (CBR) 23.1%, compared to ORR 31.1% and CBR 48.1% for the melflufen + dex combination (study O-12-M1). A recent publication (APL-C-001-09 – ADMYRE) with low dose dex (40mg once weekly) as comparator in RRMM patients with a median of 4 lines of prior systemic therapy indicated an ORR of 1.2%. These data contribute to alleviate the concerns that the effect observed with melflufen in combination with low dose dex would mainly be driven by only one of the components.

Other protocol deviations

A sample size increase was made in connection to the change to the study population of interest. The method of estimating the sample size was also changed, with the new sample size calculation based on precision around the estimate rather than the original pre-specified hypothesis. Details with regard to DSMC correspondence indicate that the conduct of the study (sample size and study population of interest) was substantially influenced by interim analysis results and B/R evaluation by the DSMC which is far beyond the scope of the planned futility purpose of the interim analysis. The conduct of study may not have fully complied with GCP requirements, but a GCP inspection is unlikely to change regulatory decision-making. A sensitivity analysis that was performed based on patients recruited after the protocol amendment provided reassurance that the results from the first group of patients prior to the amendment were not overly optimistic and were not increasing the effect compared with the second group.

Supportive data

Confirmatory trial OP-103 investigated RRMM patients in an earlier treatment line, although some patients representative of the target population were included (see below). The comparator pomalidomide + dex is acceptable in this line of treatment, as is the primary endpoint PFS + key secondary endpoints ORR and OS.

Most patients in study O-12-M1 were in an earlier stage of treatment: 66.7% was double refractory (PI and IMiD) and ~15% was refractory to the mAb class. The proportion of TCR patients was only 6%. Although Study O-12-M1 confirms anti-tumour activity, it provides limited direct support for efficacy in the target population.

Other considerations

Efficacy of melflufen as part of a myeloablative conditioning regimen prior to a stem cell transplant (similar to established use of melphalan) has not been investigated. This is adequately addressed in section 4.4 of the product information.

The effect of moderate to severe hepatic impairment (total bilirubin >1.5 × ULN and any AST) on melphalan flufenamide and the metabolite melphalan PK is unknown. Based on PK and experience with melphalan it is agreed that no dose adjustment is necessary for patients with hepatic impairment, this is adequately reflected in the SmPC.

Efficacy data and additional analyses

In **Study OP-106**, approximately 50% of the overall study population was younger than 65 years and almost 85% had an ECOG performance score of 0 to 1, suggesting a younger, less frail population than could have been expected for heavily pre-treated RRMM patients. This brings some uncertainty to the true effect size in clinical practice, although it is acknowledged that the decision to start treatment and the selection of treatment regimen is multifactorial. The patient characteristics have been adequately reflected in section 5.1 of the SmPC.

Patients had received a median of 5 (range 2-12) prior therapies. In total 119 patients were TCR, of which the majority, i.e.117 patients, were TCR with at least 3 prior lines. Approximately 16% of the TCR population was melphalan refractory and 1.7% was considered refractory to melphalan following high-dose melphalan.

The primary endpoint overall confirmed response rate (ORR) of partial response (PR) or better was 29.3% (95% CI: 22.32%, 37.08%; data cut-off 14 Jan 2020) for the overall study population. Exploratory updated results (data cut-off 12 Aug 2021) suggest an ORR of 33.8% (95% CI: 26.4%, 41.7%) and median DoR of 6.70 months (95% CI: 4.40, 8.11) for the overall population. In the TCR population with at least 3 prior lines (n=117), the ORR was 29.1% (95% CI: 21.0, 38.2) with a DOR of 6.97 months (95% CI: 3.88, 9.79; data cut-off 12 Aug 2021).

Although presented PRO data in Study OP-106 do not suggest an apparent deterioration in quality of life, no conclusions can be drawn given the limited number of patients with evaluable PRO data at Cycle 4 (n=27 for the TCR subgroup), the post-hoc definition of these endpoints and the single arm design.

No firm conclusions can be drawn regarding the presented OP-106 subgroup analyses for ORR, PFS and OS due to the lack of formal hypothesis testing, the single-arm design and small numbers of patients in each subgroup. Even so, response rates in (high dose) melphalan refractory patients seem to be substantially lower (ORR 12.5-16.7%) with shorter duration (~3 months) compared to prior melphalan exposed patients or the overall study population, this is adequately reflected in the SmPC.

Updated response rate and duration of response from OP-106 are considered clinically relevant for the TCR population. Response rates were in line with those observed for other products in the (TCR) RRMM (23-32%). Higher response rates were reported for the CAR-T cell therapy idecabtagene vicleucel (ORR ~67%)), which may considered to have a highly selected target population.

For pivotal study OP-106, uncertainty remains with regard to effect on time-dependent secondary endpoints, PFS and OS, which cannot be reliably interpreted in an uncontrolled study. Support can in principle be derived from PFS (primary endpoint) results from Study OP-103. Indeed, the primary endpoint PFS of the study was met with a HR of 0.79 and median PFS of 6.83 months (95% CI: 4.96, 8.54) with melflufen + dex vs. 4.93 months (95% CI: 4.24, 5.72) with pom + dex in the overall study population. Several sensitivity analyses were presented in response to Day 180 and 195 LoI, in which impact was investigated on the PFS results of an unplanned PFS re-analyses of 29 patients, an imbalance in randomised but not-treated patients between treatment arms and concerns regarding handling of these patients in the analysis. These sensitivity analyses confirmed internal validity of obtained PFS results. The response rate in OP-103 (ORR: 32.5%) was

comparable to that observed in OP-106 whereas median DoR appeared somewhat longer (± 11 months vs 7 months) and comparable to the comparator arm pom + dex. Overall, the PFS results are considered reliable and clinically relevant.

In a press-release of 8 July 2021, the company presented top-line results from confirmatory Study OP-103 indicating a potential detriment in OS observed for melflufen + dex compared to pom + dex. The FDA had requested a partial hold of all clinical studies with melflufen pending further investigation. In response to the first LoQ, the full clinical study report of Study OP-103 was presented. Results showed an OS HR for the overall study population of 1.104 (p=0.47). Updated median OS with one additional year of follow up indicated similar results, with a median OS of 20.24 months (15.84, 24.34) in the melflufen +dex arm vs. 23.98 months (19.06, 28.71) in the pom + dex arm, and a HR of 1.14 (95% CI: 0.912-1.434, nominal p=0.2438). Despite that Study OP-103 was not powered to demonstrate a difference in overall survival and the presence of an active comparator, the OS HR of 1.1 and KM curves in the OP-103 ITT population warranted further investigation. This was further supported by the large heterogeneity observed for OS among subgroups, especially age and prior ASCT. Based on a post-hoc defined cut-off, the subgroup of patients who progressed within 3 years after ASCT seemed to be the major contributor to the OS HR >1 result and multivariable OS analysis also provided a strong signal that TTP after ASCT was an effect modifier. Stratified analyses that looked at PFS, ORR and OS results by time to progression after ASCT in years also showed a consistent signal of reduced efficacy in patients with TTP <36 months. Interestingly, consistent results on efficacy in favour of melflufen were seen for the subgroup with no ASCT or prior ASCT and TTP ≥36 months. While these analyses were based on a post-hoc defined variable, there is the biological rationale that patients who progress early after ASCT, which requires high dose melphalan, might be less responsive to another alkylator-based regimen. In addition, these patients may have an increased risk of myelotoxicity with loss of marrow reserve after recent transplantation. A clear toxicity signal was, however, not observed (see safety section and BR discussion). The cut-off of 36 months is based on the data in the trial and to some extent supported by expert data stating that the PFS cut-off for a transplant to be considered successful enough to consider a salvage ASCT is ≥36 months, although not the same situation as in the trial (EHA-ESMO guidelines, Dimopoulus et al. 2021). In addition, the treatment effect observed in the subgroup is larger than the all-randomised study population, providing additional support for the subgroup (EMA/CHMP/539146/2013; *Guideline on the investigation of subgroups in confirmatory clinical trials*). Subgroup analysis of OP-106 also suggest a larger effect in patients with no ASCT or prior ASCT and TTP ≥36 months, however interpretation is hampered by the lack of a control arm.

Upon consultation, the SAG-O concluded that melflufen + low dose dex is associated with clinically relevant efficacy, with the exception of the subgroup of patients with relapse within 36 months following high-dose melphalan and autologous SCT. In addition, the SAG-O considered that although the exact effect size cannot be determined due to differences in disease and treatment characteristics, the results of study OP-103 obtained in patients of whom most had fewer lines of treatment than the OP-106 patients, are relevant for the target population in study OP-106 (see expert consultation below).

Overall, based on the available data and upon consultation of the SAG-O, it is considered that melflufen + low dose dex has been shown to be efficacious and from an efficacy perspective, the data can be considered comprehensive and support full approval. However, given the major concern on the benefit of melflufen + dex in patients with prior ASCT and TTP <36 months in study OP-103 and the fact that a risk for shorter survival cannot be excluded for these patients within the 3L+ TCR population in study OP-106 due to the absence of a control group, this patient group should be excluded from the applied indication.

Additional expert consultation

A SAG-Oncology was held on the 11th of May 2022. The SAG was consulted to reflect on the OS results from OP-103 and their clinical relevance for the applied target population.

1. **On the interpretation of the OS results from the confirmatory OP-103 study:**
    a) **The MM-003 study, the registrational study for the pomalidomide + low dose dexamethasone combination (pom+dex; n=302) vs high dose dexamethasone (dex; n=153), was performed in patients with relapsed/refractory multiple myeloma, who had received at least two prior treatment regimens. The results showed an OS HR of 0.53 ([2-sided 95% CI 0.37, 0.74], p-value <0.001). Are the results of the MM-003 study relevant for the population studied in OP-103? Please elaborate.**

The SAG discussed the population of the two trials (OP-106 and OP-103), the only partial overlap in regard to pretreatment (e.g. exclusion of prior treatment with pomalidomide + dexamethasone in OP-103), prior lines of therapy etc., and the assumptions that are generally needed with any type of extrapolation between patients with different disease and treatment characteristics. It was also discussed that the type of sequence of development (single-arm trial in a more advanced population (OP-106) followed by a phase III trial in an earlier population (OP-103)) is not unusual in cancer drug development.

Notwithstanding these considerations, the SAG agreed that although extrapolations cannot be precise, the activity and efficacy observed in the randomized trial as well as in the single arm trial are of some relevance. The SAG assumed that the combination of melflufen + low-dose dexamethasone may have a superior efficacy to high dose dexamethasone alone, if a comparative study would have been performed similar to the MM003 trial. The efficacy observed in the OP-103 trial in terms of ORR and PFS is of relevance for the triple refractory target population in the OP-106 trial. However, there are some uncertainties regarding OS in the experimental arm, which was lower, but not statistically significantly lower, than in the comparative arm with pomalidomide + dexamethasone (pom + dex). There was also an imbalance in early exclusion of patients (18 vs 3). Furthermore, the SAG pointed out that patients with relapse within 36 months following high-dose melphalan and autologous SCT, do not benefit from melflufen + low-dose dexamethasone.

    b) **Are there indications for absolute OS harm by the melflufen + low dose dexamethasone combination given the impact of the pom +dex on OS as shown in the registrational study? Please elaborate.**

Given the active-controlled trial, and the considerable effect established for the control arm, the effect noted in terms of OS for melflufen + low dose dexamethasone versus pom +dex can still be considered of interest if compared to a hypothetical high dose dexamethasone arm, as done in the MM003 trial. Hence, efficacy also in terms of OS can reasonably be concluded for the melflufen + low dose dexamethasone, even if likely not to the same magnitude as for pom + dex. The possible magnitude for OS in the triple refractory target population (OP-106) as an end-stage treatment cannot finally be concluded in the lack of a randomized trial in this population. The estimated effect on OS for melflufen + low dose dexamethasone compared to pom+dex, and the lack of effect in the identified resistant subgroup, should be clearly communicated in order to allow informed benefit-risk decisions.

Concerning PFS, it should be noted that there are some doubts about the robustness of the estimates of treatment given the high number of early censoring and other considerations. The aspect of informative censoring should be further investigated. In any case, given the methodological weaknesses of the PFS

analysis, the extrapolation between the two trial populations, the relatively small incremental effect, and the lack of corroborative results in terms of OS, strong “superiority” claims in terms of PFS may be not be justified.

c) **Are there (biologically plausible) reasons that the harm (if any) could differ by age (e.g. upon ASCT or prior alkylating drug exposure) or would these concern the full age-range?**

The SAG agreed that the activity of melflufen + low dose dexamethasone is likely importantly reduced with prior exposure to alkylating agents and ASCT, based on pharmacodynamic considerations (resistance) and confirmation by data from the randomized trial (post-hoc subgroup analyses). These treatment characteristics are likely associated with age, but age in itself does not seem to be key factor. The likely lack of efficacy in this subgroup should be taken into account in benefit-risk considerations.

2. **To what extent are the PFS and OS results from the OP-103 study relevant for the partially overlapping triple class refractory 3L+ multiple myeloma patient population that is applied for? Please elaborate.**

The PFS and OS results from the OP-103 study are of some relevance for the applied indication in triple refractory patients based on extrapolations and reasonable assumptions that the effect is not expected to be qualitatively different between populations. Overall, it can be concluded that melflufen + low dose dexamethasone is associated with clinically relevant efficacy although likely at a magnitude that is not as high as for pom+dex, especially in patients with relapse within 36 months following high-dose melphalan and autologous SCT. Although efficacy is not disputed, the precise magnitude is difficult to assess also in view of the methodological limitations and uncertainties described above. One SAG member disagreed on the basis that the results in terms of PFS and OS are insufficient to establish efficacy.

The SAG agreed that although the landscape has changed in the target indication with multiple new agents having become available, resistance often develops eventually, and additional active agents and combinations are still useful to offer alternative treatment options during the course of the disease.

One SAG member also noted that from a clinical perspective, it is important to keep in mind that the safety data are not well documented in the target population (especially in the older population of >80 years of age, a substantial proportion of patients with triple-class refractory disease currently), and that patients in the melflufen group had more toxicity, mainly myelosuppression requiring dose modifications, compared to the pomalidomide group.

2.6.7. Conclusions on the clinical efficacy

Clinical data in the target population (Triple-class refractory patients with ⩾3 prior treatment lines, excluding patients with recent prior ASCT) is derived from the single arm trial OP-106 + supportive data in an earlier line from a randomized controlled trial OP-103. The pivotal Study OP-106 updated ORR and DOR are considered clinically relevant for the target population. These results are confirmed in OP-103. Support from OP-103 is also derived for time-dependent endpoint PFS. OS data indicate a potential detriment with a HR of 1.14 in the overall study population, which seems mostly driven by a lack of efficacy/reduced efficacy in patients with progression within 3 years after ASCT. In line with the SAG-O conclusion, these patients should therefore be excluded from treatment by restricting the indication as follows: For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Safety data were available for a total of 495 patients (Safety population) from 5 clinical studies within RRMM setting. Besides study OP-106 which is the pivotal trial for the current application, safety data are available from study O-12-M1 (Phase 1/2a single arm study in patients with relapsed and/or RRMM, completed), study OP-103 (Phase 3 RCT of melflufen in combination with dex compared with pom/dex in patients with RRMM after 2 to 4 lines of prior therapy, ongoing), study OP-104 (Phase 1/2a open label study to assess the safety and efficacy of melflufen and dex in combination with either bor or dara in patients with relapsed MM or RRMM, ongoing) and study OP-107 (Phase 2 multicenter PK study of melflufen in combination with dex in patients with RRMM and impaired renal function, ongoing). The Targeted Safety Population (TSP) includes all 422 patients who received a starting dose of melflufen 40 mg on Day 1 of all planned 28-day cycles in combination with dex, including patients who received this combination as part of a triplet regimen in Study OP-104 (Table 32).

Study OP-106 has a higher percentage of TCR patients (76%) than the ISS (6%, 16%, 0% and 24% for Studies O-12-M1, OP-103, OP-104 and OP-107 respectively), and of the 422 patients in the TSP 146 (34.6%) were classified as TCR. The data cutoff dates were 14 January 2020 for Study OP-106 and 31 Mar 2020 for the pooled safety analysis.

Table 32 Composition of the targeted safety population

Treatment	O-12-M1 (N=75)	OP-106 (N=157)	OP-103 (N=195)	OP-104 (N=43)	OP-107 (N=25)	Total (N=495)
Melflufen 40 mg + dex[a]	16	156	195	—	21	388
Melflufen 40 mg + dex + bor	—	—	—	7	—	7
Melflufen 40 mg + dex + dara	—	—	—	27	—	27
n patients included in TSP	16	156	195	34	21	422

Abbreviations: bor = bortezomib; dara = daratumumab; dex = dexamethasone.
Note: The number of patients listed in the column headings (N) is the total number of patients contributed from each study to the Safety Population.
Patients who received melflufen 40 mg + dex in 21-day cycles during Study O-12-M1 were not included in the Targeted Safety Population.
Data cutoff date: 31 March 2020.

Median duration of treatment at the time of data cutoff for the TSP was 17.9 weeks (range: 4-117 weeks), and the median number of completed treated cycles was 3.0 (range: 0-28). More than 50% of the patients (224 patients, 53.1%) received study drug in 4 cycles, nearly 25% of patients (102 patients, 24.2%) received study drug in 8 cycles, and approximately 10% of patients (44 patients, 10.4%) received study drug in 12 cycles. Overall, 144/422 (34.1%) of patients were on study drug for ≥6 months and 46/422 (10.9%) for ≥12 months at the time of DCO. Melflufen exposure was similar to that of overall study drug.

For study OP-106, the median duration of treatment was 16.71 weeks and the median number of cycles started was started was 3.0 (range 1-17). The majority of patients were dosed in Cycle 2 and Cycle 3 (84.1% and 64.3%, respectively). The number of patients dosed in each cycle decreased to less than half at Cycle 4 (47.8%); beginning at Cycle 11, <10% of patients overall were dosed. Melflufen and dexamethasone exposure is shown in (Table 33). The relative dose intensity of melflufen was 84%. A total of 3.1% (cycle 7) to 18.7% (cycle 4) of patients received 30 mg melflufen whereas 3.6% (cycle 8) to 9.6% (cycle 5) received 20 mg melflufen. Overall, 45/157 (28.7%) of patients were on study drug for ≥6 months and 9/157 (5.7%) for ≥12 months at the time of DCO.

A total of 26 (16.6%) and 118 (28.0%) of patients were still on treatment in study OP-106 (DCO: 14 January 2020) and in the TSP (DCO: 31 March 2020), respectively. Most patients discontinued treatment due to disease progression.

Table 33 Extent of exposure to study cycle in study OP-106 (Safety analysis set)

	Triple-class refractory[a] (N=119)		Overall (N=157)	
	Melflufen	**Dex**	**Melflufen**	**Dex**
Treatment duration (weeks)[b]				
n	119	119	157	157
Mean (SD)	19.88 (16.538)	18.70 (16.532)	21.03 (17.274)	19.95 (17.134)
Median (min, max)	14.71 (4.1, 75.9)	13.43 (1.1, 78.6)	16.14 (4.1, 99.1)	15.29 (1.1, 95.1)
Number of treatment cycles started				
n	119	119	157	157
Mean (SD)	4.3 (3.53)	4.3 (3.53)	4.5 (3.53)	4.3 (3.53)
Median (min, max)	3.0 (1, 17)	3.0 (1, 17)	3.0 (1, 17)	3.0 (1, 17)
Cumulative dose received (mg)				
n	119	119	157	157
Mean (SD)	156.8 (120.59)	592.5 (511.07)	161.8 (121.55)	610.7 (506.49)
Median (min, max)	120.0 (40, 680)	480.0 (80, 2640)	120.0 (40, 680)	480.0 (40, 2640)
Relative dose intensity (%)[c]				
n	119	119	157	157
Mean (SD)	85.55 (15.617)	98.21 (29.551)	83.73 (16.517)	97.61 (29.392)
Median (min, max)	93.72 (43.9, 101.8)	100.0 (47.3, 275.0)	90.07 (30.3, 105.0)	100.0 (43.8, 275.0)

[a] Triple-class refractory was defined as refractory or intolerant to at least one proteasome inhibitor, at least one immunomodulatory drug, and at least one anti-CD38 monoclonal antibody
[b] Defined as (date of last dose + 28 days – date of first dose + 1) divided by 7.
[c] Defined as the ratio of the average dose administered per week to the prescribed dose (40 mg per cycle = 10 mg per week for melflufen and 160 mg per cycle for patients <75, 80 mg per cycle for patients=75 for dexamethasone), expressed as a percent.

2.6.8.2. Adverse events

An overview of the treatment-emergent adverse events (TEAEs) in study OP-106 is shown in (Table 34). All patients had at least one TEAE and most patients had one melflufen treatment-related TEAE (94.9%). Grade 3 or 4 TEAEs occurred frequently (93.6%) and were mostly melflufen-related (89.8%). The number of fatal TEAEs was low (6.4%) and not considered treatment-related. Serious TEAEs occurred in almost half of the patients (49.0%) and half of these were considered treatment-related (23.6%). Most patients had dose modifications (80.9%) and 73.9% of melflufen.
Overall, 23.6% of patients had at least one TEAE leading to discontinuation of study drug, and 21.7% with at least one TEAE leading to discontinuation of melflufen and 15.9% leading to discontinuation of

dexamethasone. Dose modifications and discontinuation rates for dexamethasone were 57.3% and 15.9%, respectively. Results for the TCR population were comparable to the FAS.

Table 34 Overview of treatment-emergent adverse events (Safety analysis set study OP-106)

Number of patients with:	Triple-class Refractory [a] (N=119) n (%)	Overall (N=157) n (%)
At least one TEAE	119 (100%)	157 (100%)
At least one treatment-related TEAE	112 (94.1%)	150 (95.5%)
At least one melflufen-related TEAE	111 (93.3%)	149 (94.9%)
TEAEs of CTCAE Grade 3:		
At least one Grade 3 TEAE	108 (90.8%)	145 (92.4%)
At least one treatment-related Grade 3 TEAE	102 (85.7%)	139 (88.5%)
At least one melflufen-related Grade 3 TEAE	102 (85.7%)	139 (88.5%)
TEAEs of CTCAE Grade 4:		
At least one Grade 4 TEAE	74 (62.2%)	105 (66.9%)
At least one treatment-related Grade 4 TEAE	72 (60.5%)	103 (65.6%)
At least one melflufen-related Grade 4 TEAE	72 (60.5%)	103 (65.6%)
TEAEs of CTCAE Grade 3 or 4		
At least one Grade 3 or 4 TEAE	110 (92.4%)	147 (93.6%)
At least one treatment-related Grade 3 or 4 TEAE	104 (87.4%)	141 (89.8%)
At least one melflufen-related Grade 3 or 4 TEAE	104 (87.4%)	141 (89.8%)
Fatal TEAEs (CTCAE Grade 5):		
At least one fatal (Grade 5) TEAE	8 (6.7%)	10 (6.4%)
At least one treatment-related fatal (Grade 5) TEAE	0	0
At least one serious TEAE	61 (51.3%)	77 (49.0%)
At least one treatment-related serious TEAE	29 (24.4%)	37 (23.6%)
At least one TEAE leading to dose modification of study drug	95 (79.8%)	127 (80.9%)
At least one TEAE leading to dose modification of melflufen	86 (72.3%)	116 (73.9%)
At least one TEAE leading to dose modification of dexamethasone	69 (58.0%)	90 (57.3%)
At least one TEAE leading to dose reduction of study drug	40 (33.6%)	60 (38.2%)
At least one TEAE leading to dose reduction of melflufen	28 (23.5%)	42 (26.8%)
At least one TEAE leading to dose reduction of dexamethasone	16 (13.4%)	23 (14.6%)
At least one TEAE leading to dose delay of study drug	76 (63.9%)	103 (65.6%)
At least one TEAE leading to dose delay of melflufen	72 (60.5%)	97 (61.8%)
At least one TEAE leading to dose delay of dexamethasone	49 (41.2%)	64 (40.8%)
At least one TEAE leading to discontinuation of study drug	27 (22.7%)	37 (23.6%)
At least one TEAE leading to discontinuation of melflufen	26 (21.8%)	34 (21.7%)
At least one TEAE leading to discontinuation of dexamethasone	19 (16.0%)	25 (15.9%)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; TEAE = treatment-emergent adverse event

Notes:

- Treatment-emergent AEs were defined as AEs with onset date/time or increase in severity level after the initial dose of study drug and within 30 days after the last dose of study drug or initiation of new multiple myeloma therapy, whichever was sooner.
- Treatment-related was defined as related to either melflufen or dexamethasone. Similarly, study drug refers to either melflufen or dexamethasone.

[a] Triple-class refractory was defined as refractory or intolerant to at least one proteasome inhibitor, at least one immunomodulatory drug, and at least one anti-CD38 monoclonal antibody.

Common AEs

A summary of TEAEs occurring in ≥ 5% of patients overall by PT for study OP-106 and the TSP are presented in Table 35. For study OP-106, overall 85.4% of patients had a TEAEs in the SOC Blood and lymphatic system

disorders, followed by General disorders and administration site conditions (74.5%), Gastrointestinal disorders (61.8%), Infections and infestations (58.0%), Musculoskeletal and connective tissue disorders (50.3%), and Respiratory, thoracic and mediastinal disorders (50.3%).

Table 35 Treatment-emergent adverse events by preferred term reported in ≥ 5% of patients overall in study OP-106 (OP-106 safety analysis set and ISS TSP)

	Study OP-106		Pooled ISS Analysis
Preferred Term	**Triple-Class Refractory (N=119) n (%)**	**Overall (N=157) n (%)**	**Total TSP (N=422) n (%)**
Patients with at least 1 TEAE	119 (100)	157 (100)	396 (93.8)
Anaemia[a]	77 (64.7)	111 (70.7)	261 (61.8)
Thrombocytopenia[a]	65 (54.6)	94 (59.9)	257 (60.9)
Neutropenia[a]	61 (51.3)	87 (55.4)	241 (57.1)
Fatigue	35 (29.4)	46 (29.3)	88 (20.9)
Nausea	38 (31.9)	50 (31.8)	87 (20.6)
Asthenia	28 (23.5)	42 (26.8)	80 (19.0)
Diarrhoea	27 (22.7)	42 (26.8)	79 (18.7)
Platelet count decreased[a]	31 (26.1)	36 (22.9)	73 (17.3)

Neutrophil count decreased[a]	33 (27.7)	41 (26.1)	67 (15.9)
White blood cell count decreased[a]	35 (29.4)	44 (28.0)	65 (15.4)
Pyrexia	29 (24.4)	38 (24.2)	64 (15.2)
Upper respiratory tract infection[a]	18 (15.1)	25 (15.9)	63 (14.9)
Cough	19 (16.0)	26 (16.6)	50 (11.8)
Constipation	19 (16.0)	23 (14.6)	38 (9.0)
Back pain	11 (9.2)	19 (12.1)	38 (9.0)
Insomnia	12 (10.1)	18 (11.5)	37 (8.8)
Pneumonia[a]	14 (11.8)	20 (12.7)	37 (8.8)
Dyspnoea	13 (10.9)	17 (10.8)	35 (8.3)
Leukopenia[a]	9 (7.6)	12 (7.6)	35 (8.3)
Hypokalaemia	15 (12.6)	22 (14.0)	33 (7.8)
Decreased appetite	13 (10.9)	22 (14.0)	33 (7.8)
Arthralgia	11 (9.2)	16 (10.2)	32 (7.6)
Oedema peripheral	11 (9.2)	22 (14.0)	31 (7.3)
Vomiting	19 (16.0)	21 (13.4)	31 (7.3)
Bone pain	16 (13.4)	20 (12.7)	29 (6.9)
Headache	17 (14.3)	21 (13.4)	29 (6.9)
Pain in extremity	17 (14.3)	20 (12.7)	27 (6.4)
Dizziness	8 (6.7)	17 (10.8)	26 (6.2)
Hypocalcaemia	10 (8.4)	16 (10.2)	25 (5.9)
Hypomagnesaemia	11 (9.2)	15 (9.6)	22 (5.2)
Contusion[b]	10 (8.4%)	15 (9.6%)	21 (5.0%)
Epistaxis[a]	12 (10.1)	14 (8.9)	21 (5.0)
Bronchitis	6 (5.0)	8 (5.1)	21 (5.0)
Lymphopenia	6 (5.0)	8 (5.1)	19 (4.5)
Respiratory tract infection	8 (6.7)	10 (6.4)	18 (4.3)
Blood creatinine increased	7 (5.9)	9 (5.7)	18 (4.3)
Dyspnoea exertional	11 (9.2)	16 (10.2)	18 (4.3)
Hyperglycaemia	4 (3.4)	8 (5.1)	17 (4.0)
Abdominal pain	5 (4.2)	8 (5.1)	16 (3.8)
Musculoskeletal chest pain	6 (5.0)	10 (6.4)	15 (3.6)

Table 30 Continued - Treatment-emergent adverse events by preferred term reported in ≥ 5% of patients overall in study OP-106 (OP-106 safety analysis set and ISS TSP)

Preferred Term	Study OP-106		Pooled ISS Analysis
	Triple-Class Refractory (N=119) n (%)	Overall (N=157) n (%)	Total TSP (N=422) n (%)
Myalgia	8 (6.7)	9 (5.7)	15 (3.6)
Hypophosphataemia	9 (7.6)	13 (8.3)	15 (3.6)
Febrile neutropenia	7 (5.9)	10 (6.4)	14 (3.3)
Musculoskeletal pain	7 (5.9)	8 (5.1)	12 (2.8)
Tachycardia	7 (5.9)	8 (5.1)	11 (2.6)
Hypotension	7 (5.9)	8 (5.1)	9 (2.1)

Abbreviations: ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event; TSP = Targeted Safety Population.
Notes: Percentages were based on the number of patients in the specified population in each column (denominator).
A TEAE was defined as an AE with an onset date/time or increase in severity level after the initial dose of study drug and within 28 days after the last dose of study drug or initiation of new multiple myeloma therapy, whichever was sooner.
Adverse events were coded to preferred term using MedDRA, version 19.0 or later.
Preferred terms are sorted by descending frequency in the Pooled ISS Analysis column.
[a] The indicated terms are included in the discussion of adverse events of special interest (Section 2.5.5.2.9), grouped under standardized, customized, or modified MedDRA queries as described in Module 2.7.4.1.1.3.4.2.
[b] The PT of contusion was coded under 2 system organ classes:Injury, poisoning and procedural complications and Skin and subcutaneous tissue disorders.
Source: OP-106 CSR Table 14.3.1-3.1 and ISS Table 18.3.2.1.2.3 and Table 18.3.2.2.3; data cutoff dates: 14 January 2020 for Study OP-106 and 31 March 2020 for the pooled ISS analysis.

The most commonly reported TEAEs were haematologic in nature, including anaemia (70.7%), thrombocytopenia (59.9%), and neutropenia (55.4%) in study OP-106. Other commonly reported haematologic TEAEs by PT included platelet count decreased (22.9%), neutrophil count decreased (26.1%), and white blood cell (WBC) count decreased (28.0%). The most common non-haematologic TEAEs were asthenia (26.8%), nausea (31.8%), diarrhoea (26.8%), fatigue (29.3%), pyrexia (24.2%), and upper respiratory tract infection (15.9%). Results for the TCR population were comparable to that of the FAS.

The overall profile of TEAEs was similar between patients in Study OP-106 and the TSP, the frequencies of AEs were generally higher in Study OP-106.

AE with toxicity Grade 3 or 4

The most frequently reported (≥20% of patients overall) Grade 3 or 4 TEAEs by PT were of haematological nature: thrombocytopenia (56.7%) and neutropenia (52.9%), followed by anaemia (42.7%), white blood cell count decreased (26.1%), neutrophil count decreased (23.6%), and platelet count decreased (21.0%) (Table 36). The most common Grade 3 or 4 non-haematological TEAEs were pneumonia (10.2%) and hypophosphatemia (5.1%) for the overall population in study OP-106. Results of the TCR population were comparable to the FAS. In addition, comparable results were seen for the TSP with slightly lower frequencies reported.

Table 36 Grade 3 or 4 Treatment-Emergent Adverse Events by Preferred Term Reported by at Least 5% of Patients Overall in Study OP-106 (OP-106 Safety Analysis Set and ISS Targeted Safety Population)

	Study OP-106						Pooled ISS Analysis		
	Triple-Class Refractory (N=119) n (%)			Overall (N=157) n (%)			Total TSP (N=422) n (%)		
Preferred Term	Grade 3	Grade 4	Grade 3/4[a]	Grade 3	Grade 4	Grade 3/4[a]	Grade 3	Grade 4	Grade 3/4
Patients with at least 1 Grade 3/4 TEAE	34 (28.6)	71 (59.7)	110 (92.4)	40 (25.5)	100 (63.7)	147 (93.6)	125 (29.6)	223 (52.8)	348 (82.5)
Thrombocytopenia[b]	22 (18.5)	40 (33.6)	62 (52.1)	28 (17.8)	61 (38.9)	89 (56.7)	103 (24.4)	127 (30. 1)	230 (54.5)
Neutropenia[b]	26 (21.8)	32 (26.9)	58 (48.7)	35 (22.3)	48 (30.6)	83 (52.9)	110 (26.1)	110 (26.1)	220 (52.1)
Anaemia[b]	54 (45.4)	1 (0.8)	55 (46.2)	66 (42.0)	1 (0.6)	67 (42.7)	162 (38.4)	3 (0.7)	165 (39.1)
Platelet count decreased[b]	11 (9.2)	18 (15.1)	29 (24.4)	12 (7.6)	21 (13.4)	33 (21.0)	25 (5.9)	40 (9.5)	65 (15.4)
Neutrophil count decreased[b]	17 (14.3)	12 (10.1)	29 (24.4)	22 (14.0)	15 (9.6)	37 (23.6)	38 (9.0)	22 (5.2)	60 (14.2)
White blood cell count decreased[b]	18 (15.1)	14 (11.8)	32 (26.9)	21 (13.4)	20 (12.7)	41 (26.1)	26 (6.2)	25 (5.9)	51 (12.1)
Pneumonia[b]	11 (9.2)	0	11 (9.2)	14 (8.9)	2 (1.3)	16 (10.2)	25 (5.9)	3 (0.7)	28 (6.6)
Leukopenia[b]	3 (2.5)	5 (4.2)	8 (6.7)	4 (2.5)	6 (3.8)	10 (6.4)	16 (3.8)	9 (2.1)	25 (5.9)
Lymphopenia[b]	4 (3.4)	2 (1.7)	6 (5.0)	6 (3.8)	2 (1.3)	8 (5.1)	10 (2.4)	7 (1.7)	17 (4.0)
Febrile neutropenia[b]	5 (4.2)	2 (1.7)	7 (5.9)	7 (4.5)	3 (1.9)	10 (6.4)	9 (2.1)	4 (0.9)	13 (3.1)
Hypophosphataemia	6 (5.0)	0	6 (5.0)	8 (5.1)	0	8 (5.1)	9 (2.1)	0	9 (2.1)

Abbreviations: AE = adverse event; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event; TSP = Targeted Safety Population.

Notes: Percentages were based on the number of patients in the specified population in each column (denominator).

A TEAE was defined as an AE with an onset date/time or increase in severity level after the initial dose of study drug and within 28 days after the last dose of study drug or initiation of new multiple myeloma therapy, whichever was sooner.

Adverse events were coded to preferred term using MedDRA, version 19.0 or later.

Preferred terms are sorted by descending frequency in the Pooled ISS Analysis column.

[a] Grade 3 or 4 may include patients with Grade 5 events if they also had Grade 3 or 4 events.

[b] The indicated terms are included in the discussion of adverse events of special interest (Section 2.5.5.2.9), grouped under standardized, customized, or modified MedDRA

Treatment-related AEs

Overall in study OP-106, 150 patients (95.5%) reported events that were considered by the Investigator to be treatment-related (i.e. related to any study drug) and 141 (89.8%) reported treatment-related AEs that were Grade 3 or Grade 4. A total of 149 patients (94.9%) reported events that were considered to be melflufen-related, 24.2% and 65.6% were Grade 3 or Grade 4, respectively (Table 37).

Most frequently reported melflufen-related AEs by PT were haematologic in nature and these were also the most frequently reported grade 3 or grade 4 events. Other frequently non-haematological treatment-related TEAEs were nausea, fatigue and diarrhoea. Few of these TEAEs were grade 3 and no grade 4 events occurred. Results for the TCR population were comparable to the FAS.

Dexamethasone-related adverse events

Overall, 110 patients (70.1%) reported events that were considered by the Investigator to be dexamethasone-related; 31.8% and 9.6% reported dexamethasone-related TEAEs that were Grade 3 and Grade 4, respectively. Dexamethasone-related TEAEs were most often reported in the SOCs of General disorders and administration site conditions and Gastrointestinal disorders.

The results of the TSP were supportive to that of the FAS and did not reveal new events.

Table 37 Treatment-emergent adverse events reported as melflufen-related in ≥3% of patients overall by any grade and by maximum severity (Safety analysis set study OP-106)

System Organ Class	Triple-class Refractory [b] (N=119) n (%)			Overall (N=157) n (%)		
Preferred Term [a]	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Patients with at least 1 melflufen-related TEAE	111 (93.3%)	32 (26.9%)	72 (60.5%)	149 (94.9%)	38 (24.2%)	103 (65.6%)
Blood and lymphatic system disorders	**96 (80.7%)**	**38 (31.9%)**	**47 (39.5%)**	**131 (83.4%)**	**44 (28.0%)**	**70 (44.6%)**
Anaemia	72 (60.5%)	51 (42.9%)	1 (0.8%)	104 (66.2%)	63 (40.1%)	1 (0.6%)
Thrombocytopenia	63 (52.9%)	22 (18.5%)	38 (31.9%)	92 (58.6%)	28 (17.8%)	59 (37.6%)
Neutropenia	59 (49.6%)	24 (20.2%)	32 (26.9%)	85 (54.1%)	33 (21.0%)	48 (30.6%)
Febrile neutropenia	7 (5.9%)	5 (4.2%)	2 (1.7%)	10 (6.4%)	7 (4.5%)	3 (1.9%)
Leukopenia	7 (5.9%)	1 (0.8%)	5 (4.2%)	9 (5.7%)	1 (0.6%)	6 (3.8%)
Lymphopenia	5 (4.2%)	3 (2.5%)	2 (1.7%)	7 (4.5%)	5 (3.2%)	2 (1.3%)
Gastrointestinal disorders	**45 (37.8%)**	**3 (2.5%)**	**0**	**62 (39.5%)**	**3 (1.9%)**	**0**
Nausea	29 (24.4%)	1 (0.8%)	0	39 (24.8%)	1 (0.6%)	0
Diarrhoea	13 (10.9%)	0	0	20 (12.7%)	0	0
Vomiting	13 (10.9%)	0	0	14 (8.9%)	0	0
Constipation	8 (6.7%)	0	0	8 (5.1%)	0	0
General disorders and administration site conditions	**41 (34.5%)**	**5 (4.2%)**	**1 (0.8%)**	**54 (34.4%)**	**6 (3.8%)**	**1 (0.6%)**
Fatigue	22 (18.5%)	3 (2.5%)	0	27 (17.2%)	3 (1.9%)	0
Asthenia	11 (9.2%)	0	1 (0.8%)	14 (8.9%)	0	1 (0.6%)
Pyrexia	6 (5.0%)	1 (0.8%)	0	10 (6.4%)	2 (1.3%)	0
Investigations	**43 (36.1%)**	**11 (9.2%)**	**27 (22.7%)**	**54 (34.4%)**	**13 (8.3%)**	**35 (22.3%)**
White blood cell count decreased	35 (29.4%)	18 (15.1%)	14 (11.8%)	44 (28.0%)	21 (13.4%)	20 (12.7%)
Neutrophil count decreased	33 (27.7%)	17 (14.3%)	12 (10.1%)	41 (26.1%)	22 (14.0%)	15 (9.6%)
Platelet count decreased	30 (25.2%)	11 (9.2%)	18 (15.1%)	34 (21.7%)	12 (7.6%)	21 (13.4%)
Infections and infestations	**25 (21.0%)**	**13 (10.9%)**	**0**	**31 (19.7%)**	**14 (8.9%)**	**0**
Pneumonia	7 (5.9%)	7 (5.9%)	0	9 (5.7%)	8 (5.1%)	0
Upper respiratory tract infection	6 (5.0%)	1 (0.8%)	0	8 (5.1%)	2 (1.3%)	0
Metabolism and nutrition disorders	**18 (15.1%)**	**2 (1.7%)**	**0**	**27 (17.2%)**	**5 (3.2%)**	**0**
Decreased appetite	6 (5.0%)	0	0	10 (6.4%)	0	0
Hypokalaemia	6 (5.0%)	0	0	8 (5.1%)	0	0
Hypophosphataemia	3 (2.5%)	2 (1.7%)	0	6 (3.8%)	4 (2.5%)	0
Respiratory, thoracic and mediastinal disorders	**17 (14.3%)**	**0**	**1 (0.8%)**	**21 (13.4%)**	**0**	**1 (0.6%)**
Cough	4 (3.4%)	0	0	6 (3.8%)	0	0
Epistaxis	4 (3.4%)	0	1 (0.8%)	5 (3.2%)	0	1 (0.6%)
Nervous system disorders	**12 (10.1%)**	**0**	**0**	**18 (11.5%)**	**0**	**0**
Dizziness	4 (3.4%)	0	0	8 (5.1%)	0	0
Headache	5 (4.2%)	0	0	6 (3.8%)	0	0
Skin and subcutaneous tissue disorders	**5 (4.2%)**	**0**	**0**	**9 (5.7%)**	**0**	**0**
Contusion	3 (2.5%)	0	0	5 (3.2%)	0	0

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event

Notes:

- Treatment-emergent AEs with onset date/time or increase in severity level after the initial dose of study drug and within 30 days after the last dose of study drug or initiation of new multiple myeloma therapy, whichever was sooner.
- At each level of summarization (any event, Grade 3 or 4, SOC, and PT), patients reporting more than one incidence of each adverse event were counted only once regardless of whether the TEAE was Grade 3 or 4.

[a] Adverse events were coded to preferred term using MedDRA, version 19.1.

[b] Triple-class refractory was defined as refractory or intolerant to at least one proteasome inhibitor, at least one immunomodulatory drug, and at least one anti-CD38 monoclonal antibody.

2.6.8.3. Serious adverse event / deaths / other significant events

Deaths

A total of 176 patients (41.7%) died during the studies within the TSP; 12 patients (2.8%) died ≤30 days after the last dose of melflufen. Most deaths occurred >30 days after the last dose of melflufen (38.9%) and for 122 of these 164 patients, the primary cause of death was reported as PD. A total of 23 patients (5.4%) had adverse event recorded as the primary cause of death, including 9 patients (2.1%) who died ≤30 days and 14 patients (3.3%) who died >30 days after the last dose of melflufen. Twenty patients (11.4%) experienced at least 1 TEAE with an outcome reported as fatal (*Table 38*). Six events were considered related to melflufen. These events included: Escherichia sepsis (related to melflufen and dex) and neutropenia (related to melflufen) in one patient, pneumonia (n=2; n=1 related to melflufen and dex, and n=1 related to melflufen) in study O-12-M1; sepsis (n=1 related to melflufen) in study OP-104; pneumonia influenzal (n=1 related to melfufen and dex) in study OP-106, and bacteraemia (n=1 related to melflufen and dex) in study O-12-M1.

Within study OP-106, 88 patients (56.1%) died during the study; most patients (n=76) died >30 days after last dose and the primary cause of death for these patients was PD (n=68). Overall, 10 patients (6.4%) reported a TEAE with a fatal outcome. The TEAEs included cardiopulmonary failure, plasma cell myeloma, diffuse alveolar damage, acute kidney injury, general physical health deterioration, and plasma cell leukemia (1 patient each) and respiratory failure and general physical health deterioration (2 patients each); 1 patient with a fatal TEAE of general physical health deterioration also had fatal TEAEs of pneumonia, hypercalcemia, metabolic disorder, and pleural effusion. None of these were considered by the investigator to be related to melflufen.

Table 38 Treatment-emergent adverse events with a fatal outcome by preferred term by treatment regimen (Targeted safety population)

Preferred Term	Melflufen + Dex (N=168) n (%)	Melflufen + Bor + Dex (N=1) n (%)	Melflufen + Dara + Dex (N=7) n (%)	Total (N=176) n (%)
Patients with at least 1 TEAE with a fatal outcome	19 (11.3)	0	1 (14.3)	20 (11.4)
Escherichia sepsis	2 (1.2)	0	0	2 (1.1)
Neutropenia	2 (1.2)	0	0	2 (1.1)
Pneumonia	2 (1.2)	0	0	2 (1.1)
Asthenia	1 (0.6)	0	0	1 (0.6)
Cardiopulmonary failure	1 (0.6)	0	0	1 (0.6)
Diffuse alveolar damage	1 (0.6)	0	0	1 (0.6)
Disease progression	1 (0.6)	0	0	1 (0.6)
General physical health deterioration	1 (0.6)	0	0	1 (0.6)
Multiple organ dysfunction syndrome	1 (0.6)	0	0	1 (0.6)
Oesophageal carcinoma	1 (0.6)	0	0	1 (0.6)
Plasma cell leukaemia	1 (0.6)	0	0	1 (0.6)
Plasma cell myeloma	1 (0.6)	0	0	1 (0.6)
Pneumonia influenzal	1 (0.6)	0	0	1 (0.6)
Post procedural complication	1 (0.6)	0	0	1 (0.6)
Pulmonary embolism	1 (0.6)	0	0	1 (0.6)
Renal failure	1 (0.6)	0	0	1 (0.6)
Respiratory failure	1 (0.6)	0	0	1 (0.6)
Sepsis	0	0	1 (14.3)	1 (0.6)
Sudden cardiac death	1 (0.6)	0	0	1 (0.6)

Abbreviations: bor = bortezomib; dara = daratumumab; dex = dexamethasone; TEAE = treatment-emergent adverse event.
Notes: Percentages were based on the number of patients who died on study in the Targeted Safety Population in each column (denominator).
The Targeted Safety Population includes all patients who received a starting dose of melflufen 40 mg on Day 1 of every planned 28-day cycle in combination with dex, including patients who received this combination as part of a triplet regimen in Study OP-104.
If a patient experienced more than 1 episode of a TEAE, then the patient was counted only once within a preferred term. Preferred terms are reported using the Medical Dictionary for Regulatory Activities version 19.0 or later.

Serious adverse events

Overall, 77 (49.0%) reported at least one serious TEAE (*Table 39*). The most frequently reported events were pneumonia (8.9%), febrile neutropenia (5.1%), and thrombocytopenia, platelet count decreased, respiratory tract infection, acute kidney injury, general physical health deterioration, and hypercalcaemia (2.5% each). Pneumonia, febrile neutropenia, and thrombocytopenia and platelet count decreased were the most common treatment-related SAEs (any drug) as well as the most common melflufen-related SAEs. Overall, 20.4% of patients reported at least one serious melflufen-related TEAE. Overall, 18 patients (11%) reported a Grade 3 SAE that was considered by the Investigator to be melflufen-related, and 13 patients (8%) reported a melflufen-related Grade 4 SAE. Results for the TCR were comparable to the FAS. The TSP did not reveal new signals.

Table 39 Treatment-emergent serious adverse events by PT in ≥2 patients overall in study OP-106 (OP-106 Safety analysis set and ISS TSP)

	Study OP-106				Pooled ISS Analysis	
Preferred Term	Triple-Class Refractory (N=119) n (%)		Overall (N=157) n (%)		Total TSP (N=422) n (%)	
	All	Related	All	Related	All	Related
Patients with at least 1 treatment-emergent SAE	61 (51.3)	29 (24.4)	77 (49.0)	37 (23.6)	153 (36.3)	90 (21.3)
Pneumonia	8 (6.7)	7 (5.9)	14 (8.9)	11 (7.0)	28 (6.6)	20 (4.7)
Thrombocytopenia	4 (3.4)	4 (3.4)	4 (2.5)	4 (2.5)	13 (3.1)	13 (3.1)
Febrile neutropenia	6 (5.0)	6 (5.0)	8 (5.1)	8 (5.1)	12 (2.8)	12 (2.8)
Neutropenia	2 (1.7)	2 (1.7)	2 (1.3)	2 (1.3)	9 (2.1)	8 (1.9)
Platelet count decreased	4 (3.4)	4 (3.4)	4 (2.5)	4 (2.5)	9 (2.1)	9 (2.1)
Pyrexia	3 (2.5)	2 (1.7)	3 (1.9)	2 (1.3)	6 (1.4)	4 (0.9)
Upper respiratory tract infection	0	0	2 (1.3)	1 (0.6)	6 (1.4)	3 (0.7)
Respiratory tract infection	4 (3.4)	0	4 (2.5)	0	5 (1.2)	1 (0.2)
Acute kidney injury	4 (3.4)	0	4 (2.5)	0	5 (1.2)	0
Bronchitis	2 (1.7)	2 (1.7)	2 (1.3)	2 (1.3)	4 (0.9)	3 (0.7)
Sepsis	1 (0.8)	1 (0.8)	2 (1.3)	1 (0.6)	4 (0.9)	3 (0.7)
Bone pain	2 (1.7)	0	2 (1.3)	0	3 (0.7)	0
General physical health deterioration	4 (3.4)	0	4 (2.5)	0	3 (0.7)	1 (0.2)
Influenza	2 (1.7)	1 (0.8)	2 (1.3)	1 (0.6)	3 (0.7)	1 (0.2)
Clostridium difficile infection	2 (1.7)	1 (0.8)	2 (1.3)	1 (0.6)	2 (0.5)	1 (0.2)
Femur fracture	2 (1.7)	0	2 (1.3)	0	2 (0.5)	0
Viral upper respiratory tract infection	2 (1.7)	1 (0.8)	2 (1.3)	1 (0.6)	2 (0.5)	1 (0.2)
Respiratory Failure	0	0	2 (1.3)	0	2 (0.5)	0
Soft tissue infection	2 (1.7)	1 (0.8)	2 (1.3)	1 (0.6)	2 (0.5)	1 (0.2)
Hypercalcaemia	4 (3.4)	0	4 (2.5)	0	2 (0.5)	0
Lower gastrointestinal haemorrhage	1 (0.8)	1 (0.8)	2 (1.3)	1 (0.6)	2 (0.5)	1 (0.2)
Squamous cell carcinoma	1 (0.8)	0	2 (1.3)	0	2 (0.5)	0
Hypotension	2 (1.7)	0	2 (1.3)	0	1 (0.2)	0
Pleural effusion	2 (1.7)	0	2 (1.3)	0	1 (0.2)	0
Dyspnoea	2 (1.7)	0	2 (1.3)	0	0	0

Abbreviations: dex = dexamethasone; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; TSP = Targeted Safety Population.
Notes: Percentages were based on the number of patients in the specified population in each column (denominator).
Note: PTs with fewer TEAEs in Study OP-106 as compared to ISS is due to different definitions used for TEAEs in Study OP-106 and ISS, see Section 2.7.4.1.1.3.4.1.
At each level of summarization (any event, system organ class, and preferred term), patients reporting more than 1 adverse event were counted only once.
Treatment-related was defined as a treatment-emergent SAE assessed by the Investigator to be possibly, probably, or definitely related to study drug (melflufen and/or dex), or that had a missing causality on the case report form.
Adverse events were coded to preferred term using MedDRA, version 19.0 or later.
Preferred terms are sorted by descending frequency in the Pooled ISS Analysis "All" column.

Other AEs of special interest (AESI)

An overall summary of AESIs for patients in study OP-106 and the TSP is shown in *Table 40*.

- Thrombocytopenia and bleeding events

Overall, 81.5% of patients in study OP-106 experienced AESIs of thrombocytopenia (SMQ) during the study, and 76.4% had a Grade 3 or 4 event. Twenty-nine patients (18.5%) and 36 patients (22.9%) overall reported Grade 3 and Grade 4, respectively, thrombocytopenia at Cycle 1. SAEs of thrombocytopenia (PT) were reported in 2.5% of patients. Dose modifications of melflufen due to thrombocytopenia occurred in 42.0% of patients: 31.8% had a dose delay, 14.0% had a dose reduction, and 10.2% discontinued melflufen. Supportive therapy for thrombocytopenia (platelet transfusions) was administered in 43% of patients.

Overall, 28.0% of patients reported AESIs of bleeding events. Twenty-five patients (15.9%) reported a TEAE of Grade 3 or 4 thrombocytopenia and concomitant haemorrhage, and 2.5% reported Grade 3 or 4 thrombocytopenia and concomitant Grade 3 or 4 bleeding events which were resolved after appropriate treatment. Five patients reported serious TEAEs; 3 of these events (lower gastrointestinal haemorrhage, hemorrhoidal haemorrhage, and epistaxis) were considered to be melflufen-related. No patients reported PTs related to haemorrhage that resulted in dose modifications of melflufen.

Table 40 Overall summary of adverse events of special interest (OP-106 Safety population and ISS Targeted safety population)

	Study OP-106		Pooled ISS Analysis
AESI	Triple-Class Refractory (N=119) n (%)	Overall (N=157) n (%)	Total TSP (N=422) n (%)
Thrombocytopenia	94 (79.0)	128 (81.5)	326 (77.3)
Bleeding events	31 (26.1)	44 (28.0)	73 (17.3)
CNS bleedings	0	1 (0.6)	1 (0.2)
Neutropenia	94 (79.0)	129 (82.2)	323 (76.5)
Infections	69 (58.0)	91 (58.0)	205 (48.6)
Infective pneumonia[a]	36 (30.3)	48 (30.6)	90 (21.3)
Infective pneumonia narrow	15 (12.6)	21 (13.4)	42 (10.0)
Febrile neutropenia	7 (5.9)	10 (6.4)	14 (3.3)
Anaemia	77 (64.7)	111 (70.7)	262 (62.1)
Second primary malignancies	5 (4.2)	6 (3.8)	8 (1.9)
MDS/AML	2 (1.7)	2 (1.3)	3 (0.7)

Abbreviations: AESI = adverse event of special interest; AML = acute myeloid leukaemia; ISS = Integrated Summary of Safety; MDS = myelodysplastic syndrome; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = standardized MedDRA query; TSP = Targeted Safety Population.
Notes: Percentages were based on the number of patients in the specified population in each column (denominator).
AESIs were defined using Standardized or modified Standardized (broad scope) or Customized MedDRA queries or multiple preferred terms.
[a] Broad SMQ, which includes respiratory tract infections among other terms.

- Neutropenia, infections, infective pneumonia, and febrile neutropenia

Overall, 82.2% of patients experienced AESIs of neutropenia (SMQ) during the study, and 79.0% had a Grade 3 or 4 event. A total of 30.6% and 20.4% overall reported Grade 3 and Grade 4, respectively, neutropenia at Cycle 1. SAEs of neutropenia (PT) were reported in 1.3% of patients. Dose modifications of melflufen due to neutropenia occurred in 21.7% of patients, mainly dose delay (19.1%). Discontinuations occurred in 3.2% of patients. Supportive therapy for neutropenia (neutrophil growth factors such as filgrastim and analogues) was administered in 68% of patients.

Just over half (58.0%) of patients in Study OP-106 overall reported AESIs of infections; 21.7% reported AESIs of infections that were Grade 3 or 4 and one grade 5 event occurred. Infective pn

eumonia was reported in 30.6% of patients. Overall, 28 patients (17.8%) had infections resulting in dose modifications, mainly dose delays (n=22, 14%). A total of 29.9% of patients reported an AESI of infection and concomitant Grade 3 or 4 neutropenia; 11.5% reported a Grade 3 or 4 AESI of infection and concomitant Grade 3 or 4 neutropenia.

A total of 6.4% of patients experienced an AESI of febrile neutropenia; of these patients, 5.1% reported serious AESIs of febrile neutropenia that were all considered to be melflufen-related.

- Anaemia

Overall, 70.7% of patients in Study OP-106 experienced an AESI of anaemia; 17.2% and 0.6% reported Grade 3 and Grade 4, respectively, anaemia at Cycle 1. Only one patient reported a SAEs of anaemia (PT); the event was considered to be melflufen-related. Dose modifications due to anaemia were seen in 12.1% of patients: 9.6% had a dose delay, 1.3% had a dose reduction, and 1.3% discontinued melflufen. Supportive therapy for anaemia (red blood cell transfusion) was given in 61% of patients.

- MDS/AML and other second primary malignancies (SMP)

Within the full ISS Safety Population (n=495), 2.6% had SPMs; 9 patients (1.8%) had at least 1 AESI of SPMs, and 4 patients were reported to have SPMs during the overall survival follow-up, but these were not reported as AEs. Six patients (1.2%) had MDS/AML; 4 had at least 1 AESI of MDS/AML, and 2 patients were reported to have MDS/AML during the overall survival follow-up, but these were not reported as AEs. All four adverse events of MDS/AML were considered possibly/probably related to melflufen.

Other SMPs occurring in seven patients (1.4%) included: cutaneous basal cell carcinoma (3 patients), cutaneous squamous cell carcinoma (2 patients), and cutaneous malignant melanoma (1 patient) and plasma cell leukaemia (1 patient). Three of these events occurred in the same patient: 1 event of cutaneous basal cell carcinoma and the events of cutaneous malignant melanoma and cutaneous squamous cell carcinoma. Other SMPs included in one patient were colon adenocarcinoma during the overall survival follow-up that was not reported as AE and oesophageal carcinoma. None of the other SMPs reported as AE was considered related to melflufen.

Within study OP-106, 4.5% (n=7) patients had SPMs; 2 patients (1.3%) had MDS/AML and 5 patients (3.2%) had other SPMs.

- Other events

Extravasation and infusion reactions:

Within the full Safety population (n=495) one SAE of grade 2 extravasation was reported (2nd dose of melflufen 40 mg IV), and was considered not related to melflufen.

Infusion-related complications: A nonserious TEAE of Grade 1 catheter site extravasation was reported one week after the first dose of melflufen 40 mg IV and considered not-related. Overall, there were 4 TEAEs of peripheral swelling, 3 events of localized oedema, one serious event of administration site extravasation and one event of infusion site irritation. Three events (localized oedema and peripheral swelling (n=2)) were considered possibly related to melflufen. In addition, 25 patients experienced 31 TEAEs that potentially may have been considered infusion reactions. Five out of the 13 infusion related reactions were considered related to melflufen.

Cardiac disorders:

Overall, 22 patients (14.0%) reported TEAEs in the SOC of Cardiac disorders in study OP-106. Ten patients (6.4%) reported TEAEs that were considered by the Investigator to be treatment-related: tachycardia (n=5, 3.2%) and bradycardia, cardiac failure, cardiomyopathy, palpitations, and sinus tachycardia (n=1, 0.6% each). Based on the TSP, there were in total 49/491 (10.0%) patients with TEAEs belonging to the SOC Cardiac disorders. Three PTs occurred in more than 5 (1%) patients, tachycardia, palpitations, and sinus tachycardia, with the PT tachycardia being the most common (n=10, 2.0%). Twenty patients (4.1%) reported TEAEs that were considered by the Investigator to be treatment-related, mostly tachycardia (n=7, 1.4%). Most events were non-serious, five patients experienced fatal events of which two were considered treatment-related by the investigator.

Regarding AEs potentially related to QTc prolongation, 9 TEAEs in 9/149 (1.8%) patients were identified (standardised MedDRA Query Torsade de pointes/QT prolongation). The most common was syncope experienced by 4 patients. All events except 1 were considered not-related to melflufen.

2.6.8.4. Laboratory findings

Haematology

For most patients in study OP-106, baseline values for haematological parameters was grade 0 or 1. Overall, there were mean decreases from Baseline at EoT in most haematologic parameters. Shifts to worst post-baseline decreased platelet counts were grade 3 or 4 for 26.2% and 53.5%, respectively. Shifts to post-baseline decreased neutrophil counts were grade 3 and grade 4 for 41.4% and 40.1%, respectively. The median times to onset of first Grade 3 or 4 neutrophils and platelets were 16 days and 26 days in the overall population, respectively. Similar shifts were seen for lymphocyte and leukocyte (WBC) counts.

In keeping with the higher incidence of AESIs of thrombocytopenia, neutropenia, and anaemia, shifts from Grade 0 or 1 to Grade 3 or 4 in haematology test results for platelet and neutrophil counts and haemoglobin values were more frequent in the Study OP-106 overall population compared with the TSP. However, there were no new or unexpected laboratory signals (post-baseline haematology or serum chemistry abnormalities) observed in either population.

Serum chemistry

Shifts to Grade 4 were rare and shifts to Grade 3 were uncommon for most parameters for patients in study OP-106 or the TSP. The most frequently reported shift from Grade 0, 1, 2, or 3 at Baseline to worst post-Baseline Grade 3 or 4 overall (> 10% of all subjects) was a Grade 0 to 3 increase in urate (13.9%) in study OP-106. There were no clinically relevant shifts from Baseline to EoT in the serum chemistry parameters during the study.

Vital signs

There were no clinically significant vital sign abnormalities nor were there clinically meaningful trends identified in observed values or changes in mean values at each visit from Baseline.

Effect on ECG parameters

Except for a subset of patients in Study O-12-M1, ECG assessments were performed only at the Screening and End of Treatment visits. Therefore, no additional on treatment data are available. Within study OP-106,

there were 3 patients with abnormal CS ECG interpretations post-Baseline of sinus tachycardia, sinus bradycardia, and R wave progression. The abnormal CS ECG of sinus tachycardia was reported as a TEAE (PT: tachycardia) that was considered by the Investigator to be unrelated to study drug; the other abnormal CS ECG interpretations were not reported as TEAEs. No clinically relevant changes in mean values from Baseline to EoT were observed for the QTcF interval or any other parameters based on study O-12-M1 (see section 3.3.2.). The TSP did not reveal new findings.

2.6.8.5. Safety in special populations

Selected AESIs (thrombocytopenia, neutropenia, febrile neutropenia, infections, infective pneumonia, anaemia, bleeding events and MDS/AML) were summarised per subgroup (age, sex, race, BMI and baseline CrCl) for study OP-106 and the TSP.

An analysis of safety data by subgroup did not identified clinically meaningful differences, although there were some imbalances in the incidence of certain AEs. For the TSP, an increased frequency (≥10% difference) in thrombocytopenia was shown for patients <65 years old or ≥65 and ≤75 years old (76.7% and 81.6% respectively) compared to patients > 75 years old (64.9%, n=57). The frequency of neutropenia was increased in male patients compared to female patients (84.0% vs 71.3%). An increased frequency of infections (50.1% vs. 33.3%), infective pneumonia (22.3% vs 10.0%) and anaemia (63.8% vs 43.3%) was seen in white versus non-white patients (n=30). Due to the requirement for patients to have a baseline CrCl ≥45 mL/min, limited patients with a baseline CrCl of <45 mL/min (n=21) were treated with melflufen. Overall, more patients with a baseline CrCl of <45 mL/min (85.7%) experienced an AE than patients with a baseline CrCl of ≥45-60 mL/min (71.8%). In addition, more patients with a baseline CrCl of ≥45-60 mL/min (24.7%, n=85) and ≥60 mL/min (20.6%, n=310) experienced infective pneumonia than patients with a baseline CrCl <45 mL/min (14.3%).

The safety profile by age group and by specific MedDRA terms is shown below for study OP-106 (Table 41).

Table 41 AEs by age groups and MedDRA terms (Study OP-106)

MedDRA Terms	Age <65 (N=78)	Age 65 - 74 (N=54)	Age 75 - 84 (N=24)	Age 85+ (N=1)	Overall (N=157)
Total AEs	78 (100%)	54 (100%)	24 (100%)	1 (100%)	157 (100%)
Serious AEs - Total	47 (60.3%)	23 (42.6%)	10 (41.7%)	-	80 (51.0%)
Serious AEs - Fatal	5 (6.4%)	5 (9.3%)	-	-	10 (6.4%)
Serious AEs - Hospitalization/prolong existing hospitalization	39 (50.0%)	15 (27.8%)	10 (41.7%)	-	64 (40.8%)
Serious AEs - Life-threatening	5 (6.4%)	1 (1.9%)	-	-	6 (3.8%)
Serious AEs - Other (medically significant)	4 (5.1%)	4 (7.4%)	1 (4.2%)	-	9 (5.7%)
AE leading to drop-out[1]	23 (29.5%)	13 (24.1%)	6 (25.0%)	-	42 (26.8%)
SOC Psychiatric disorders	18 (23.1%)	13 (24.1%)	5 (20.8%)	-	36 (22.9%)
SOC Nervous system disorders	29 (37.2%)	18 (33.3%)	13 (54.2%)	1 (100%)	61 (38.9%)
SOC Injury, poisoning and procedural complications	10 (12.8%)	10 (18.5%)	7 (29.2%)	-	27 (17.2%)
SOC Cardiac disorders	15 (19.2%)	4 (7.4%)	4 (16.7%)	-	23 (14.6%)
SOC Vascular disorders	16 (20.5%)	8 (14.8%)	4 (16.7%)	1 (100%)	29 (18.5%)
SOC Infections and infestations	49 (62.8%)	27 (50.0%)	15 (62.5%)	-	91 (58.0%)
PT Anticholinergic syndrome					No patients
PT Quality of life decreased					No patients
Sum of postural hypotension, fall, black outs, syncope, dizziness, ataxia, fractures [2]	12 (15.4%)	11 (20.4%)	4 (16.7%)	1 (100%)	28 (17.8%)
Other AE appearing more frequently in older patients: Infective pneumonia (SMQ)[3]	10 (12.8%)	6 (11.1%)	5 (20.8%)	-	21 (13.4%)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SOC = System Organ Class; SMQ = Standardized MedDRA Query; CMQ =Customized MedDRA Query; PT = Preferred Term; HLGT = High Level Group Term; HLT = High Level Term
Within each grouped term, patients reporting more than one term are counted only once.
Adverse events were coded to preferred term using MedDRA, version 19.1.
[1] Action taken with study drug: DRUG WITHDRAWN'
[2] CMQ, PT {'Orthostatic hypotension' 'Fall' 'Loss of consciousness' 'Syncope' 'Dizziness' 'Dizziness postural' 'Vertigo' 'Ataxia'}, HLGT {'Fractures'}, or HLT {'Coordination and balance disturbances' 'Vertigos NEC'}.
[3] SMQ 'Infective pneumonia Narrow terms.
[Data as of January 14th, 2020.
Program: \\EMA 2021\prog\tfl\subprogs\tflpgm\Q165-T1-ae-agegrp.sas, 2021-11-17 17:35.

2.6.8.6. Immunological events

N/A

2.6.8.7. Safety related to drug-drug interactions and other interactions

No specific clinical studies assessing the effects of other drugs or extrinsic factors on melflufen were submitted.

Overdose

The highest dose of melflufen tested in clinical studies was 130 mg in Study O-05-001 in patients with solid tumours. In Study O-12-M1 in patients with RRMM, 55 mg exceeded the MTD associated with reversible haematologic toxicity, and 40 mg every 28 days in combination with weekly dexamethasone was determined to be the recommended dose in patients with RRMM. Because no overdose of melflufen has been reported as of the data cutoff date for this SCS (31 March 2020), there are no available data on overdose. However,

because melflufen is rapidly converted to melphalan, the label of melphalan is of interest also in the treatment with melflufen.

2.6.8.8. Discontinuation due to adverse events

Overall, 37 patients (23.6%) had at least one TEAE leading to permanent discontinuation of study drug and 34 patients (21.7%) had at least one TEAE leading to discontinuation of melflufen (**Error! Reference source not found.**).Treatment-emergent AEs leading to discontinuation of melflufen were most often reported in the SOC of Blood and lymphatic system disorders (12.1%). The most frequently reported TEAE leading to discontinuation of melflufen by PT was thrombocytopenia (10.2%). All other TEAEs leading to discontinuation of melflufen were reported by <5% of patients.

TEAEs leading to dose reduction

Overall, 38.2% of patients had a TEAE that led to dose reduction of study drug and 26.8% patients had a TEAE resulting in dose reduction of melflufen. By PT, the most commonly reported TEAEs resulting in dose reductions of melflufen were thrombocytopenia (14.0%) and platelet count decreased (8.3%).

TEAEs leading to dose interruption

Overall, 65.6% of patients had a TEAE that led to dose delay of study drug and 61.8% patients had a TEAE resulting in dose delay of melflufen. By PT, the most commonly reported TEAEs resulting in dose reductions of melflufen were thrombocytopenia (31.8%), neutropenia (19.1%), platelet count decreased (11.5%), anaemia (9.6%) and neutrophil count decreased (9.6%).

Study OP-103 - OCEAN

A total of 228 patients and 246 patients in the melflufen+dex and pomalidomide+dex groups, respectively, were dosed with study drug on Day 1 and were included in the Safety Analysis Set. The median duration of study drug treatment was longer for the melflufen+dex group compared with the pomalidomide+dex group (25.14 weeks vs 22.14 weeks). The median number of cycles started was 5.0 for both treatment groups.

A summary of TEAEs is shown in Table 42. All patients had at least one TEAE and most patients had one melflufen treatment-related TEAE (93.9%). Grade 3 or 4 TEAEs occurred frequently (89.5%) and were mostly melflufen-related (84.2%). The number of fatal TEAEs was 11.8% and only one event was not considered treatment-related. Serious TEAEs occurred in 41.7% of patients and half of these were considered treatment-related (18.4%). Most patients (78.1%) had events leading to dose modifications of melflufen. Overall, 26.3% of patients had at least one TEAE leading to discontinuation of melflufen and 15.9% leading to discontinuation of dexamethasone. Treatment-related grade 3 or 4 events as well as dose modifications, including discontinuations, were more common for melflufen than for pomalidomide. SAEs and fatal events were in the same order of magnitude.

Table 42 Overview of treatment-emergent adverse events (Safety Analysis Set Study OP-103)

Number of patients with:	Melflufen + Dexamethasone N=228 n (%)	Pomalidomide + Dexamethasone N=246 n (%)
At least one TEAE	226 (99.1%)	241 (98.0%)
At least one treatment-related TEAE	216 (94.7%)	209 (85.0%)
At least one melflufen- or pomalidomide-related TEAE	214 (93.9%)	193 (78.5%)
TEAEs of CTCAE Grade 3:		
At least one Grade 3 TEAE	204 (89.5%)	176 (71.5%)
At least one treatment-related Grade 3 TEAE	194 (85.1%)	148 (60.2%)
At least one melflufen- or pomalidomide-related Grade 3 TEAE	192 (84.2%)	138 (56.1%)
TEAEs of CTCAE Grade 4:		
At least one Grade 4 TEAE	125 (54.8%)	68 (27.6%)
At least one treatment-related Grade 4 TEAE	118 (51.8%)	58 (23.6%)
At least one melflufen- or pomalidomide-related Grade 4 TEAE	118 (51.8%)	56 (22.8%)
TEAEs of CTCAE Grade 3 or 4		
At least one Grade 3 or 4 TEAE	205 (89.9%)	183 (74.4%)
At least one treatment-related Grade 3 or 4 TEAE	195 (85.5%)	157 (63.8%)
At least one melflufen- or pomalidomide-related Grade 3 or 4 TEAE	193 (84.6%)	148 (60.2%)
Fatal TEAEs (CTCAE Grade 5):		
At least one fatal (Grade 5) TEAE	27 (11.8%)	32 (13.0%)
At least one treatment-related fatal (Grade 5) TEAE	1 (0.4%)	4 (1.6%)
At least one SAE	95 (41.7%)	113 (45.9%)
At least one treatment-related SAE	42 (18.4%)	52 (21.1%)
At least one TEAE leading to dose modification of study drug	183 (80.3%)	164 (66.7%)
At least one TEAE leading to dose modification of melflufen or pomalidomide	178 (78.1%)	144 (58.5%)
At least one TEAE leading to dose modification of dexamethasone	129 (56.6%)	135 (54.9%)
At least one TEAE leading to dose reduction of study drug	115 (50.4%)	66 (26.8%)
At least one TEAE leading to dose reduction of melflufen or pomalidomide	107 (46.9%)	37 (15.0%)
At least one TEAE leading to dose reduction of dexamethasone	28 (12.3%)	43 (17.5%)
At least one TEAE leading to dose delay of study drug	153 (67.1%)	112 (45.5%)
At least one TEAE leading to dose delay of melflufen or pomalidomide	137 (60.1%)	109 (44.3%)
At least one TEAE leading to dose delay of dexamethasone	96 (42.1%)	74 (30.1%)
At least one TEAE leading to permanent discontinuation of study drug	60 (26.3%)	56 (22.8%)
At least one TEAE leading to permanent discontinuation of melflufen or pomalidomide	60 (26.3%)	54 (22.0%)
At least one TEAE leading to permanent discontinuation of dexamethasone	46 (20.2%)	55 (22.4%)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute; TEAE = treatment-emergent adverse event.
Notes:
- TEAEs were defined as AEs with onset date/time or increase in severity level after the initial dose of study drug and within 30 days after the last dose of study drug or initiation of new multiple myeloma therapy, whichever was sooner. Adverse events were graded per NCI-CTCAE v4.03.
- Treatment-related was defined as related, possibly related, probably related, or missing relation to melflufen, pomalidomide, or dexamethasone. Similarly, study drug refers to melflufen, pomalidomide, or dexamethasone.
- Dose modifications were defined as an action taken value of dose reduced, dose held, or permanent discontinuation.

The most commonly reported TEAEs for melflufen+dexamethasone were haematologic in nature, including thrombocytopenia (70.2%), anaemia (66.7%), and neutropenia (60.1%) (Table 43). The most common non-haematologic TEAEs were pyrexia (14.5%), asthenia and fatigue (each 14.0%), diarrhoea (13.6%), nausea (13.2%), and upper respiratory tract infection (12.7%).

Table 43 Treatment-emergent adverse events in ≥5% of patients in the melflufen+dexamethasone or pomalidomide+dexamethasone group by PT (Safety Analysis Set Study OP-103)

System Organ Class Preferred Term [a]	Melflufen + Dexamethasone N=228 n (%)	Pomalidomide + Dexamethasone N=246 n (%)
Number of patients with at least 1 TEAE	**226 (99.1%)**	**241 (98.0%)**
Blood and lymphatic system disorders	**200 (87.7%)**	**159 (64.6%)**
Neutropenia	137 (60.1%)	113 (45.9%)
Anaemia	152 (66.7%)	92 (37.4%)
Thrombocytopenia	160 (70.2%)	48 (19.5%)
Leukopenia	24 (10.5%)	11 (4.5%)
Infections and infestations	**114 (50.0%)**	**137 (55.7%)**
Upper respiratory tract infection	29 (12.7%)	25 (10.2%)
Pneumonia	20 (8.8%)	32 (13.0%)
Bronchitis	13 (5.7%)	26 (10.6%)
Urinary tract infection	11 (4.8%)	16 (6.5%)
Respiratory tract infection	7 (3.1%)	14 (5.7%)
General disorders and administration site conditions	**94 (41.2%)**	**107 (43.5%)**
Fatigue	32 (14.0%)	41 (16.7%)
Asthenia	32 (14.0%)	28 (11.4%)
Pyrexia	33 (14.5%)	16 (6.5%)
Oedema peripheral	11 (4.8%)	21 (8.5%)
Investigations	**86 (37.7%)**	**74 (30.1%)**
Neutrophil count decreased	30 (13.2%)	27 (11.0%)
Platelet count decreased	40 (17.5%)	11 (4.5%)
White blood cell count decreased	22 (9.6%)	6 (2.4%)
SARS-CoV-2 test positive	13 (5.7%)	12 (4.9%)
Musculoskeletal and connective tissue disorders	**74 (32.5%)**	**73 (29.7%)**
Back pain	17 (7.5%)	24 (9.8%)
Bone pain	17 (7.5%)	12 (4.9%)
Arthralgia	14 (6.1%)	5 (2.0%)
Gastrointestinal disorders	**75 (32.9%)**	**70 (28.5%)**
Diarrhoea	31 (13.6%)	21 (8.5%)
Nausea	30 (13.2%)	17 (6.9%)
Constipation	16 (7.0%)	29 (11.8%)
Respiratory, thoracic and mediastinal disorders	**54 (23.7%)**	**53 (21.5%)**
Dyspnoea	21 (9.2%)	24 (9.8%)
Cough	18 (7.9%)	19 (7.7%)
Nervous system disorders	**41 (18.0%)**	**58 (23.6%)**
Dizziness	8 (3.5%)	16 (6.5%)
Psychiatric disorders	**37 (16.2%)**	**39 (15.9%)**
Insomnia	19 (8.3%)	21 (8.5%)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TEAE = treatment-emergent adverse event.
Notes:
- TEAEs were defined as adverse events with onset date/time or increase in severity level after the initial dose of study drug and within 30 days after the last dose of study drug or initiation of new multiple myeloma therapy, whichever was sooner.
- At each level of summarization (system organ class and preferred term), patients reporting more than one AE were counted only once.

[a] AEs were coded to a lower-level term and presented by the linked preferred term and primary system organ class using MedDRA, version 23.0.

Haematological events were also the most frequently reported ≥Grade 3 events in both treatment arms and higher for melflufen arm (79.4% vs 52.0% for melflufen + dexamethasone and pomalidomide + dexamethasone, respectively) (Table 44). The percentage of patients who had at least one Grade 3 non-hematological TEAE was similar for the melflufen+dex group compared with the pomalidomide+dex group (32.5% vs 32.9%) and the percentage of patients who had at least one Grade 4 non-hematological TEAE was slightly lower in the melflufen+dex group compared with the pomalidomide+dex group (2.2% vs 6.1%).

Table 44 Incidence of treatment-emergent adverse events by maximum severity (grade 3 or 4) in ≥5% of patients in the melflufen+dex or pomalidomide+dex arm by PT (Safety analysis set Study OP-103)

System Organ Class Preferred Term [a]	Melflufen+Dexamethasone (N=228) n (%)			Pomalidomide+Dexamethasone (N=246) n (%)		
	Grade 3	Grade 4	Grade 3 or 4[b]	Grade 3	Grade 4	Grade 3 or 4[b]
Patients with at least one Grade 3 or Grade 4 TEAE	71 (31.1%)	108 (47.4%)	205 (89.9%)	102 (41.5%)	55 (22.4%)	183 (74.4%)
Blood and lymphatic system disorders	**78 (34.2%)**	**101 (44.3%)**	**181 (79.4%)**	**83 (33.7%)**	**45 (18.3%)**	**128 (52.0%)**
Neutropenia	64 (28.1%)	59 (25.9%)	124 (54.4%)	65 (26.4%)	37 (15.0%)	102 (41.5%)
Anaemia	92 (40.4%)	5 (2.2%)	97 (42.5%)	42 (17.1%)	2 (0.8%)	44 (17.9%)
Thrombocytopenia	72 (31.6%)	71 (31.1%)	143 (62.7%)	15 (6.1%)	11 (4.5%)	26 (10.6%)
Leukopenia	13 (5.7%)	2 (0.9%)	15 (6.6%)	5 (2.0%)	2 (0.8%)	7 (2.8%)
Infections and infestations	**28 (12.3%)**	**1 (0.4%)**	**30 (13.2%)**	**44 (17.9%)**	**4 (1.6%)**	**53 (21.5%)**
Pneumonia	10 (4.4%)	0	10 (4.4%)	19 (7.7%)	1 (0.4%)	21 (8.5%)
Investigations	**22 (9.6%)**	**27 (11.8%)**	**49 (21.5%)**	**24 (9.8%)**	**9 (3.7%)**	**33 (13.4%)**
Neutrophil count decreased	18 (7.9%)	10 (4.4%)	28 (12.3%)	15 (6.1%)	7 (2.8%)	22 (8.9%)
Platelet count decreased	18 (7.9%)	15 (6.6%)	33 (14.5%)	5 (2.0%)	1 (0.4%)	6 (2.4%)
White blood cell count decreased	7 (3.1%)	7 (3.1%)	14 (6.1%)	2 (0.8%)	0	2 (0.8%)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; NCI = National Cancer Institute; PT = preferred term; TEAE = treatment-emergent adverse event.

Notes:

- TEAEs were defined as AEs with onset date/time or increase in severity level after the initial dose of study drug and within 30 days after the last dose of study drug or initiation of new multiple myeloma therapy, whichever was sooner.
- At each level of summarization (system organ class and preferred term), patients reporting more than one incidence of each AE were counted only once by maximum severity.
- Adverse events were graded per NCI-CTCAE v4.03.

[a] Adverse events were coded to a lower-level term and presented by the linked preferred term and primary system organ class using MedDRA, version 23.0.

[b] Of note, in Table 14.3.1-3.1, TEAEs were only counted once based on maximum severity, including Grade 3, Grade 4, or Grade 5 (fatal) TEAEs; however, in Table 14.3.1-4, TEAEs were only counted once based on maximum severity, including only Grade 3 or Grade 4. Therefore, the total number of Grade 3 or Grade 4 TEAEs is representative of all Grade 3 and Grade 4 TEAEs, irrespective of whether the event resulted in a Grade 5 TEAE.

Haematological events were also the most commonly treatment-related events (Table 45).

Table 45 Melflufen- or pomalidomide-related adverse events in ≥5% of patients by any grade and maximum severity of grade 3 or 4 (Safety Analysis Set Study OP-103).

System Organ Class Preferred Term [a]	Melflufen+Dexamethasone (N=228) n (%)			Pomalidomide+Dexamethasone (N=246) n (%)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Patients with at least 1 melflufen- or pomalidomide-related TEAE	214 (93.9%)	75 (32.9%)	117 (51.3%)	193 (78.5%)	91 (37.0%)	54 (22.0%)
Blood and lymphatic system disorders	**193 (84.6%)**	**78 (34.2%)**	**96 (42.1%)**	**138 (56.1%)**	**71 (28.9%)**	**42 (17.1%)**
Neutropenia	134 (58.8%)	65 (28.5%)	57 (25.0%)	106 (43.1%)	62 (25.2%)	34 (13.8%)
Thrombocytopenia	157 (68.9%)	70 (30.7%)	68 (29.8%)	39 (15.9%)	13 (5.3%)	9 (3.7%)
Anaemia	132 (57.9%)	82 (36.0%)	5 (2.2%)	58 (23.6%)	23 (9.3%)	2 (0.8%)
Leukopenia	23 (10.1%)	12 (5.3%)	2 (0.9%)	10 (4.1%)	5 (2.0%)	1 (0.4%)
Investigations	**62 (27.2%)**	**19 (8.3%)**	**26 (11.4%)**	**37 (15.0%)**	**21 (8.5%)**	**6 (2.4%)**
Neutrophil count decreased	28 (12.3%)	17 (7.5%)	9 (3.9%)	25 (10.2%)	16 (6.5%)	6 (2.4%)
Platelet count decreased	39 (17.1%)	17 (7.5%)	15 (6.6%)	9 (3.7%)	5 (2.0%)	0
White blood cell count decreased	21 (9.2%)	6 (2.6%)	7 (3.1%)	6 (2.4%)	2 (0.8%)	0
Infections and infestations	**40 (17.5%)**	**14 (6.1%)**	**1 (0.4%)**	**46 (18.7%)**	**17 (6.9%)**	**3 (1.2%)**
Pneumonia	8 (3.5%)	5 (2.2%)	0	13 (5.3%)	7 (2.8%)	0
General disorders and administration site conditions	**39 (17.1%)**	**4 (1.8%)**	**0**	**42 (17.1%)**	**8 (3.3%)**	**1 (0.4%)**
Fatigue	20 (8.8%)	0	0	22 (8.9%)	2 (0.8%)	1 (0.4%)
Asthenia	15 (6.6%)	2 (0.9%)	0	13 (5.3%)	5 (2.0%)	0
Gastrointestinal disorders	**38 (16.7%)**	**2 (0.9%)**	**0**	**26 (10.6%)**	**2 (0.8%)**	**1 (0.4%)**
Nausea	24 (10.5%)	1 (0.4%)	0	6 (2.4%)	0	0
Diarrhoea	12 (5.3%)	1 (0.4%)	0	10 (4.1%)	0	0
Constipation	4 (1.8%)	0	0	14 (5.7%)	0	0

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Notes:
- TEAEs were defined as AEs with onset date/time or increase in severity level after the initial dose of study drug and within 30 days after the last dose of study drug or initiation of new multiple myeloma therapy, whichever was sooner.
- At each level of summarization (Grade 3 or 4, SOC, and PT), patients reporting more than one incidence of each AE were counted only once by maximum severity regardless of whether the TEAE was Grade 3 or 4.
- [a] AEs were coded to a lower-level term and presented by the linked PT and primary SOC using MedDRA, version 23.0.

AEs by prior ASCT status

While the overall AE profile was similar in transplanted and non-transplanted melflufen+dex treated patients, hematologic AEs were reported more frequently in transplanted patients compared to patients with no prior ASCT, mostly due to thrombocytopenia (92.0% vs 81.9%) and anemia (71.4% vs 62.9%) (

Table 46). Further, there is a trend towards higher frequencies of AEs leading to dose modifications and discontinuations among patients with prior ASCT compared to patients without prior ASCT for melflufen+dex. This difference is driven by the SOC Blood and lymphatic system disorders, primarily the PT thrombocytopenia (59.8% vs 40.5% respectively, in patients with and without prior ASCT). On the other hand, fatal AEs and SAEs were comparable.

No major differences in frequencies of AESIs depending on transplant status were seen for patients treated with pomalidomide+dex, although fatal AEs were less frequently observed in patients with prior ASCT.

Table 46 Overview of AEs by ASCT status (Safety Analysis Set Study OP-103)

	Prior ASCT = Yes		Prior ASCT = No	
	Melflufen +Dex	Pomalidomide +Dex	Melflufen +Dex	Pomalidomide +Dex
Number of patients with	(N=112)	(N=118)	(N=116)	(N=128)
at least one AE	111 (99.1%)	115 (97.5%)	115 (99.1%)	126 (98.4%)
at least one serious AE	43 (38.4%)	57 (48.3%)	52 (44.8%)	56 (43.8%)
at least one fatal AE	14 (12.5%)	10 (8.5%)	13 (11.2%)	22 (17.2%)
at least one AE leading to dose modification of melflufen or pomalidomide	94 (83.9%)	70 (59.3%)	84 (72.4%)	74 (57.8%)
at least one AE leading to permanent discontinuation of study drug	34 (30.4%)	19 (16.1%)	26 (22.4%)	35 (27.3%)

Abbreviations: AE = adverse event; ASCT = autologous stem cell transplantation; Dex = dexamethasone.
Notes:
- AEs were defined as adverse events with onset date/time or increase in severity level after the initial dose of study drug and within 30 days after the last dose of study drug or initiation of new multiple myeloma therapy, whichever is sooner.
- Dose modifications included dose reduction, dose delay, or permanent discontinuation.
- Study drug includes melflufen, pomalidomide, and dexamethasone.

When comparing AESI for mel+dex arm in patients with ASCT and TTP<36 months (n=91) versus patients with no ASCT or TTP ≥36 months, the main difference was an increase in grade 3/4 thrombocytopenia (85.7% vs 70.1%), whereas median treatment duration was shorter (16 vs 35.1 weeks).

SAEs and deaths

A total of 106 patients (46.5%) in the melflufen+dex group and 106 patients (43.1%) in the pomalidomide+dex group died during the study. Most of these patients (83 patients [36.4%] in the melflufen+dex group and 73 patients [29.7%]) died >30 days after last dose. The primary cause of death for patients in both treatment groups who died >30 days after last dose was PD (53 patients [23.2%] in the melflufen+dex group and 46 patients [18.7%] in the pomalidomide+dex group). A total of 12 patients (5.3%) in the melflufen+dex group and 8 patients (3.3%) in the pomalidomide+dex group died within 60 days after the first dose. The primary causes of death within 60 days after the first dose for both treatment groups were PD (6 patients [2.6%] in the melflufen+dex group and 2 patients [0.8%] in the pomalidomide+dex group) and AE (6 patients [2.6%] in the melflufen+dex group and 5 patients [2.0%] in the pomalidomide+dex group); 1 additional patient (0.4%) in the pomalidomide+dex group died due to "other" (pulmonary edema).

A total of 27 patients (11.8%) in the melflufen+dex group and 32 patients (13.0%) had a TEAE reported with a fatal outcome (Table 47). All of the fatal TEAEs in the melflufen+dex group were considered by the Investigator to be unrelated to melflufen, with the exception of pancytopenia and cardiac failure acute in one patient, which were considered possibly related. All of the fatal TEAEs in the pomalidomide+dex group were considered by the Investigator to be unrelated to pomalidomide+dex, with the exception of COVID-19 pneumonia, myelodisplastic syndrome in one patient each, and pneumonia in two patients, which were considered possibly related. Most TEAEs with a fatal outcome occurred within 30 days of last dose of melflufen and pomalidomide, respectively.

Table 47 Fatal treatment-emergent adverse event, by system organ class and preferred term (Safety Analysis Set Study OP-103)

System Organ Class Preferred Term [a]	Melflufen+ Dexamethasone (N=228)			Pomalidomide+ Dexamethasone (N=246)		
	All n (%)	Events	Related n (%)	All n (%)	Events	Related n (%)
Number of patients with fatal (Grade 5) TEAEs	**27 (11.8%)**	**31**	**1 (0.4%)**	**32 (13.0%)**	**33**	**4 (1.6%)**
Infections and infestations	**12 (5.3%)**	**12**	**0**	**13 (5.3%)**	**13**	**3 (1.2%)**
COVID-19 pneumonia	7 (3.1%)	7	0	4 (1.6%)	4	1 (0.4%)
Pneumonia	3 (1.3%)	3	0	4 (1.6%)	4	2 (0.8%)
Septic shock	0	0	0	2 (0.8%)	2	0
Urinary tract infection	2 (0.9%)	2	0	0	0	0
Escherichia sepsis	0	0	0	1 (0.4%)	1	0
Lower respiratory tract infection	0	0	0	1 (0.4%)	1	0
Sepsis	0	0	0	1 (0.4%)	1	0
General disorders and administration site conditions	**3 (1.3%)**	**3**	**0**	**9 (3.7%)**	**9**	**0**
Multiple organ dysfunction syndrome	2 (0.9%)	2	0	2 (0.8%)	2	0
General physical health deterioration	0	0	0	3 (1.2%)	3	0
Sudden cardiac death	0	0	0	2 (0.8%)	2	0
Asthenia	1 (0.4%)	1	0	0	0	0
Death	0	0	0	1 (0.4%)	1	0
Sudden death	0	0	0	1 (0.4%)	1	0
Respiratory, thoracic and mediastinal disorders	**3 (1.3%)**	**3**	**0**	**4 (1.6%)**	**4**	**0**
Respiratory failure	2 (0.9%)	2	0	1 (0.4%)	1	0
Pleural effusion	0	0	0	1 (0.4%)	1	0
Pulmonary embolism	1 (0.4%)	1	0	0	0	0
Pulmonary oedema	0	0	0	1 (0.4%)	1	0
Respiratory arrest	0	0	0	1 (0.4%)	1	0
Cardiac disorders	**2 (0.9%)**	**2**	**1 (0.4%)**	**2 (0.8%)**	**2**	**0**
Cardiac arrest	1 (0.4%)	1	0	2 (0.8%)	2	0
Cardiac failure acute	1 (0.4%)	1	1 (0.4%)	0	0	0
Renal and urinary disorders	**2 (0.9%)**	**2**	**0**	**2 (0.8%)**	**2**	**0**
Renal failure	2 (0.9%)	2	0	2 (0.8%)	2	0
Injury, poisoning and procedural complications	**2 (0.9%)**	**2**	**0**	**1 (0.4%)**	**1**	**0**
Craniocerebral injury	0	0	0	1 (0.4%)	1	0
Post procedural complication	1 (0.4%)	1	0	0	0	0
Subdural haematoma	1 (0.4%)	1	0	0	0	0
Nervous system disorders	**2 (0.9%)**	**2**	**0**	**1 (0.4%)**	**1**	**0**
Brain oedema	1 (0.4%)	1	0	0	0	0
Cerebral haemorrhage	1 (0.4%)	1	0	0	0	0
Cerebrovascular insufficiency	0	0	0	1 (0.4%)	1	0
Blood and lymphatic system disorders	**2 (0.9%)**	**2**	**1 (0.4%)**	**0**	**0**	**0**
Neutropenia	1 (0.4%)	1	0	0	0	0
Pancytopenia	1 (0.4%)	1	1 (0.4%)	0	0	0
Gastrointestinal disorders	**2 (0.9%)**	**2**	**0**	**0**	**0**	**0**
Abdominal mass	2 (0.9%)	2	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.4%)**	**1**	**0**	**1 (0.4%)**	**1**	**1 (0.4%)**
Myelodysplastic syndrome	0	0	0	1 (0.4%)	1	1 (0.4%)
Oesophageal carcinoma	1 (0.4%)	1	0	0	0	0

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Notes:
- TEAEs were defined as AEs with onset date/time or increase in severity level after the initial dose of study drug and within 30 days after the last dose of study drug or initiation of new multiple myeloma therapy, whichever was sooner.
- Treatment-related was defined as related to melflufen, pomalidomide, or dexamethasone.

[a] AEs were coded to preferred term using MedDRA, version 23.0.

A summary of SAEs and related SAEs reported in ≥2 patients in either treatment group by all PTs is presented in Table 48. Frequencies of overall patients with one SAE or one treatment-related SAE were comparable between treatment arms. Infections were the most common SAEs in both treatment arms. In the melflufen+dex group, the most frequently reported SAEs by PT were pneumonia (5.7% vs 8.5% in pomalidomide+dex group), thrombocytopenia (3.9% vs. 1.2% in pomalidomide+dex arm), and anemia

(3.1% vs 2.0% in pomalidomide+dex group). SAEs in the MedDRA SOC Blood and lymphatic system disorders were more common in the melflufen + dexamethasone arm (9.2%) than in the pomalidomide + dexamethasone arm (4.5%).

Table 48 SAEs and related SAEs reported in ≥2 patients by PT either treatment group (Safety Analysis Set Study OP-103)

System Organ Class Preferred Term [a]	Melflufen+Dexamethasone (N=228) n (%)		Pomalidomide+Dexamethasone (N=246) n (%)	
	All	Related	All	Related
Number of patients with at least 1 serious TEAE	95 (41.7%)	42 (18.4%)	113 (45.9%)	52 (21.1%)
Infections and infestations	**41 (18.0%)**	**15 (6.6%)**	**61 (24.8%)**	**24 (9.8%)**
Pneumonia	13 (5.7%)	6 (2.6%)	21 (8.5%)	10 (4.1%)
COVID-19 pneumonia	11 (4.8%)	0	9 (3.7%)	1 (0.2%)
Sepsis	1 (0.4%)	1 (0.4%)	6 (2.4%)	4 (1.6%)
Bronchitis	3 (1.3%)	3 (1.3%)	3 (1.2%)	0
Urinary tract infection	2 (0.9%)	0	6 (2.4%)	3 (1.2%)
Influenza	0	0	5 (2.0%)	2 (0.8%)
Upper respiratory tract infection	3 (1.3%)	1 (0.4%)	1 (0.4%)	0
Viral infection	1 (0.4%)	1 (0.4%)	2 (0.8%)	1 (0.4%)
Lower respiratory tract infection	0	0	3 (1.2%)	1 (0.4%)
Respiratory tract infection	1 (0.4%)	0	2 (0.8%)	1 (0.4%)
Septic shock	0	0	3 (1.2%)	1 (0.4%)
Infection	2 (0.9%)	0	0	0
Blood and lymphatic system disorders	**21 (9.2%)**	**19 (8.3%)**	**11 (4.5%)**	**9 (3.7%)**
Thrombocytopenia	9 (3.9%)	9 (3.9%)	3 (1.2%)	3 (1.2%)
Anaemia	7 (3.1%)	6 (2.6%)	5 (2.0%)	3 (1.2%)
Febrile neutropenia	4 (1.8%)	3 (1.3%)	2 (0.8%)	2 (0.8%)
Neutropenia	4 (1.8%)	3 (1.3%)	3 (1.2%)	2 (0.8%)
Pancytopenia	2 (0.9%)	1 (0.4%)	0	0
Cardiac disorders	**8 (3.5%)**	**2 (0.9%)**	**15 (6.1%)**	**9 (3.7%)**
Atrial fibrillation	0	0	9 (3.7%)	4 (1.6%)
Cardiac arrest	1 (0.4%)	0	2 (0.8%)	0
General disorders and administration site conditions	**13 (5.7%)**	**3 (1.3%)**	**16 (6.5%)**	**1 (0.4%)**
General physical health deterioration	2 (0.9%)	1 (0.4%)	4 (1.6%)	0
Pyrexia	4 (1.8%)	1 (0.4%)	2 (0.8%)	0
Multiple organ dysfunction syndrome	2 (0.9%)	0	2 (0.8%)	0
Sudden cardiac death	0	0	2 (0.8%)	0
Respiratory, thoracic and mediastinal disorders	**11 (4.8%)**	**2 (0.9%)**	**13 (5.3%)**	**5 (2.0%)**
Pulmonary embolism	3 (1.3%)	0	3 (1.2%)	3 (1.2%)

Table 45 – Continued: SAEs and related SAEs reported in ≥2 patients by PT either treatment group (Safety Analysis Set Study OP-103)

System Organ Class Preferred Term [a]	Melflufen+Dexamethasone (N=228) n (%)		Pomalidomide+Dexamethasone (N=246) n (%)	
	All	Related	All	Related
Respiratory failure	4 (1.8%)	0	3 (1.2%)	1 (0.4%)
Chronic obstructive pulmonary disease	1 (0.4%)	0	3 (1.2%)	0
Injury, poisoning and procedural complications	**10 (4.4%)**	**1 (0.4%)**	**12 (4.9%)**	**0**
Femur fracture	1 (0.4%)	0	2 (0.8%)	0
Hip fracture	1 (0.4%)	0	2 (0.8%)	0
Humerus fracture	1 (0.4%)	0	2 (0.8%)	0
Femoral neck fracture	2 (0.9%)	0	0	0
Sternal fracture	2 (0.9%)	0	0	0
Gastrointestinal disorders	**9 (3.9%)**	**2 (0.9%)**	**7 (2.8%)**	**3 (1.2%)**
Diarrhoea	2 (0.9%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
Abdominal mass	2 (0.9%)	0	0	0
Renal and urinary disorders	**4 (1.8%)**	**1 (0.4%)**	**12 (4.9%)**	**0**
Renal failure	2 (0.9%)	0	6 (2.4%)	0
Acute kidney injury	2 (0.9%)	0	5 (2.0%)	0
Musculoskeletal and connective tissue disorders	**7 (3.1%)**	**0**	**8 (3.3%)**	**1 (0.4%)**
Bone pain	1 (0.4%)	0	2 (0.8%)	1 (0.4%)
Pathological fracture	2 (0.9%)	0	1 (0.4%)	0
Spinal pain	0	0	2 (0.8%)	0
Investigations	**5 (2.2%)**	**4 (1.8%)**	**3 (1.2%)**	**3 (1.2%)**
Platelet count decreased	4 (1.8%)	4 (1.8%)	0	0
Nervous system disorders	**6 (2.6%)**	**0**	**8 (3.3%)**	**0**
Spinal cord compression	0	0	3 (1.2%)	0
Transient ischaemic attack	2 (0.9%)	0	1 (0.4%)	0
Metabolism and nutrition disorders	**2 (0.9%)**	**1 (0.4%)**	**8 (3.3%)**	**1 (0.4%)**
Hypercalcaemia	0	0	4 (1.6%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2 (0.9%)**	**1 (0.4%)**	**5 (2.0%)**	**2 (0.8%)**
Basal cell carcinoma	0	0	2 (0.8%)	1 (0.4%)
Vascular disorders	**1 (0.4%)**	**1 (0.4%)**	**5 (2.0%)**	**2 (0.8%)**
Deep vein thrombosis	0	0	2 (0.8%)	2 (0.8%)

Abbreviations: AE adverse event; MedDRA Medical Dictionary for Regulatory Activities; PT preferred term; TEAE treatment-emergent adverse event.
Notes:
- TEAEs with onset date/time or increase in severity level after the initial dose of study drug and within 30 days after the last dose of study drug or initiation of new multiple myeloma therapy, whichever was sooner.
- Study drug refers to either melflufen, pomalidomide, or dexamethasone.

AEs of special interest

The AESIs thrombocytopenia, anaemia, and neutropenia frequently occurred in both treatment arms (Table 49). Overall, the frequencies of these AESIs were higher in the melflufen + dexamethasone arm, as were AESIs of haemorrhage although few patients experienced a grade 3 haemorrhage in combination with thrombocytopenia (any grade). AESIs of infection, especially grade 3 or 4, were less common in the melflufen + dexamethasone arm.

Table 49 Overview of treatment-emergent adverse events of special interest (Safety Analysis Set OP-103)

	Melflufen + Dexamethasone (N=228)		Pomalidomide + Dexamethasone (N=246)		Overall (N=474)	
	n (%)	Events	n (%)	Events	n (%)	Events
At least one TEAE of Anaemia	153 (67.1%)	474	93 (37.8%)	211	246 (51.9%)	685
At least one TEAE of Neutropenia	161 (70.6%)	928	135 (54.9%)	478	296 (62.4%)	1406
At least one TEAE of grade 3 or 4 Neutropenia	147 (64.5%)	663	121 (49.2%)	338	268 (56.5%)	1001
At least one TEAE of Infection	114 (50.0%)	231	137 (55.7%)	281	251 (53.0%)	512
At least one TEAE of grade 3 or 4 Infection	30 (13.2%)	45	53 (21.5%)	71	83 (17.5%)	116
At least one TEAE of Infection and concomitant grade 3 or 4 Neutropenia	29 (12.7%)	41	37 (15.0%)	50	66 (13.9%)	91
At least one TEAE of Infection and concomitant grade 4 Neutropenia	6 (2.6%)	8	12 (4.9%)	14	18 (3.8%)	22
At least one TEAE of grade 3 or 4 Infection and concomitant grade 3 or 4 Neutropenia	7 (3.1%)	8	16 (6.5%)	19	23 (4.9%)	27
At least one TEAE of Thrombocytopenia	198 (86.8%)	1056	58 (23.6%)	168	256 (54.0%)	1224
At least one TEAE of grade 3 or 4 Thrombocytopenia	174 (76.3%)	713	31 (12.6%)	64	205 (43.2%)	777
At least one TEAE of grade 3 or 4 Haemorrhage and concomitant Thrombocytopenia	2 (0.9%)	3	0	0	2 (0.4%)	3

Abbreviations: TEAE treatment-emergent adverse event.

- Second primary malignancies and myelodysplastic syndromes

Three and six patients in the melflufen+dex (1.3%) and pomalidomide+dex (2.4%) groups, respectively, reported an AESI of SPM and 1 patient in each treatment group (0.4%) reported a TEAE of MDS. 1 patient had an AESI of SPM leading to permanent discontinuation of melflufen and 1 patient each had an AESI of SPM and an AESI of MDS leading to permanent discontinuation of pomalidomide.

- Other AESIs: thromboembolism, hemorrhagic central nervous system vascular conditions, peripheral neuropathy, and tachyarrhythmias

Overall, 8.3% and 8.9% of patients reported at least 1 TEAE of thromboembolism (SMQ), 0.9% and 0.4% of patients reported at least 1 TEAE of Haemorrhagic central nervous system vascular conditions (SMQ), 3.1% and 3.3% of patients reported at least 1 TEAE of Peripheral neuropathy (SMQ) narrow, and 3.1% and 4.9% of patients reported at least 1 TEAE of Tachyarrhythmias (including supraventricular and ventricular tachyarrhythmias) (SMQ) narrow in the melflufen+dex and pomalidomide+dex groups, respectively.

2.6.8.9. Post marketing experience

Post-authorization safety information received by Oncopeptides for the period of 26 Feb 2021 to 27 August 2021 has been summarized in 2 Periodic Adverse Drug Experience Reports (PADERs) which have been submitted to the FDA. No new safety signals have been identified based on these data.

2.6.9. Discussion on clinical safety

Safety database

Safety data of melflufen were available for 495 patients (Safety population) from 5 clinical studies in the RRMM setting; 422 patients received the recommended starting dose of melflufen 40 mg on Day 1 of a 28-

day cycle in combination with dexamethasone (Targeted safety population (TSP), 34 patients received melflufen as part of a triple combination treatment). The updated safety database used for the SmPC excluded patients receiving melflufen as part of a triplet regimen and included patients using the single agent (15-55 mg). This resulted in a safety database of 491 patients from 4 clinical studies. Main data are derived from study OP-103 (n=228, 46%) and OP-106 (n=157, 32%). This safety population was used for description of the safety profile in the SmPC, which is acceptable. No new safety signals were identified. The safety discussion below is mainly based on study OP-106 and OP-103.

There are several important limitations to the safety database:

1) With a median treatment duration of 17 weeks and a median number of 3-4 treatment cycles in the pivotal study OP-106 and the TSP, long-term safety data is limited. Twenty-six (16.6%) and 118 (28.0%) patients were still on treatment in study OP-106 (DCO: 14 January 2020) and in the TSP (DCO: 31 March 2020), respectively. A total of 45/157 (28.7%) and 144/422 (34.1%) were on study drug for ≥6 months in study OP-106 and for the TSP, respectively. Based on the updated total safety database including all patients from study OP-103 in an earlier setting of RRMM, treatment duration was slightly higher with a median treatment duration of 20 weeks and median number of cycles of 4.

2) The pivotal study lacks a control arm, making it difficult to distinguish the events related to melflufen from those related to dexamethasone, the underlying disease and/or previous treatment received. Results from the phase 3 RCT OP-103 were submitted and provide some contextualization of the safety profile in this aspect (see further below).

Importantly, uncertainties on long-term safety, less frequently occurring AEs and attributability may be partly overcome by what is known for melphalan, which has been in clinical use as an antitumor agent for more than 60 years. All in all, the safety database is considered sufficient to assess the safety profile of melflufen in the heavily pretreated triple class refractory (TCR) target population with a dismal prognosis (estimated OS of a few months to less than 1 year) with support from the phase 3 RTC OP-103 in an earlier setting.

This safety evaluation focusses primarily on the pivotal study OP-106 (n=157) as this study population most accurately represents the applied TCR indication (76% of the study OP-106 population vs 35% of the TSP). All patients reported TEAEs and almost all patients reported adverse events understood to be related to melflufen. Most patients (93.6%) reported ≥ grade 3 TEAEs and 49.0% reported SAEs.

Haematological events and consequences

Haematological events were the most frequently reported TEAEs; anaemia, thrombocytopenia, and neutropenia were each reported in over half of the patients. These events were also the most commonly reported ≥ grade 3 events, but SAEs were limited and highest for thrombocytopenia (2.5% by PT). These adverse events are expected based on the mechanism of action of melphalan.

Dose modifications of melflufen were common and about one-fifth of patients (21.7%) discontinued melflufen treatment due to TEAEs, indicating a non-negligible safety profile. Most frequently occurring TEAEs leading to dose modifications were haematologic in nature and included thrombocytopenia, platelet count decreased, neutropenia, neutrophil count decreased, and anaemia. Thrombocytopenia was the most common TEAE leading to discontinuation of melflufen (10.2%).

Haematological events were manageable with dose modifications and supportive treatments and regular monitoring of blood counts is required (section 4.2 and 4.4 SmPC). Patients with platelet count $<50 \times 10^9$/L or baseline ANC count $<1 \times 10^9$/L were excluded from the study and treatment in these patients is not recommended. Adequate information is provided in section 4.2 and 4.4 of the SmPC. Anaemia mostly

resulted in dose delays. Treatment of anaemia is established clinical practice and it is agreed that no additional dose recommendations are included in section 4.2, in addition to the statement in section 4.4 on regular monitoring and treatment of anaemia.

Thrombocytopenia may lead to serious bleeding events. A total of 16% in study OP-106 had a grade 3 or 4 thrombocytopenia (including platelet count decreased) and concomitant haemorrhage, most of these bleedings were grade 1 or 2. Overall frequency of bleeding events was 28.0%. There were no melflufen dose modifications due to haemorrhages. An appropriate warning for the risk of bleeding is included in the SmPC (section 4.4). The most common bleedings (PT Epistaxis and PT Haematoma) have been added to the ADR table in section 4.8 of the SmPC.

Neutropenia can lead to infections and 29.9% of patients reported an AESI of infection and concomitant Grade 3 or 4 neutropenia; 11% reported a ≥ grade 3 infection and concomitant ≥ grade 3 neutropenia. Overall, over half of the patients reported AESIs of infections, and infective pneumonia was the most commonly reported event. Pneumonia was also the most commonly reported SAE (7.0%). Infections rarely resulted in discontinuation of melflufen (2.5%), and were managed by dose delays and antimicrobial treatment. The increased risk of infections is of relevance in the target population prone to infections due to the underlying disease and use of immunosuppressive treatments. Three patients in the TSP experienced infections with fatal outcome concomitantly with Grade 3 or 4 neutropenia and a statement on the risk of fatal infections has been added to SmPC 4.8. An appropriate warning for the risk of infections is included in the SmPC (section 4.4). In addition, a recommendation for prophylactic concomitant treatment with antimicrobials is included (section 4.2 and 4.4 SmPC).

Febrile neutropenia is another potentially serious consequence of neutropenia for the patient and a frequently occurring SAE (5.1%). Supportive treatment with haematopoietic growth factors was allowed in the study and is recommended in section 4.4. SmPC. Febrile neutropenia is included in section 4.8 SmPC. In addition, based on the myelosuppressive action of melphalan, leukopenia cannot be excluded as an ADR and is included in the ADR table in section 4.8 of the SmPC, as well as lymphopenia.

Non-haematological events

Non-haematological TEAEs frequently reported with melflufen were asthenia, nausea, diarrhoea, fatigue, pyrexia, and upper respiratory tract infection (range 15.9% to 31.8%). Gastrointestinal events were mostly grade 1 or 2 and well known for melphalan. A recommendation for prophylactic concomitant use of anti-emetics is included (section 4.2 SmPC). Asthenia and fatigue were mostly grade 1 or 2 and known adverse events for treatments of MM. A high percentage (40%-60%) was considered treatment-related and asthenia and fatigue are included in section 4.8. Other commonly reported adverse events included in section 4.8 are hypokalaemia, decreased appetite, headache, dizziness, cough, dyspnoe and dyspnoe exertional. This is acceptable. No ≥ grade 3 events were reported for these TEAEs. Although frequently reported, constipation (14.6%; melflufen-related 5.1%) is not included as ADR, as it may be a complication of the use of (prophylactic) anti-emetics. In addition, there is no plausible biologic mechanism and constipation is also a known side effect of dexamethasone.

Furthermore, the risk of secondary primary malignancies (SPMs) was identified as an AESI. Within the overall safety population, 6 patients reported AMD/MDS and 7 patients had at least one ASEI of other SPM. The risk of SPMs is a known risk of MM treatments. A warning is included in section 4.4; SPMs are also added to section 4.8 SmPC.

Melflufen was not associated with QTc prolongation, although limited data are available, and is not a known risk for melphalan. However, in vitro data showed an effect of melflufen on hERG channel. Cardiac events

were infrequent in study OP-106, but some were considered melflufen-related. Cardiac disorders, though rare, are included in the melphalan SmPC, though the mechanism of action is unknown. Data from the TSP confirm that event rates in the SOC Cardiac disorders were low and there were no signals for melflufen-related TEAEs associated with QTc prolongation. Some uncertainty remains as patients at high risk of cardiovascular disease were excluded and the number of elderly patients (>75 age) is limited. Nevertheless it is agreed that no information on cardiac toxicity needs to be included in the SmPC.

Melphalan in combination with amongst others dexamethasone has been associated with an increased risk of thromboembolic complications (see SmPC Melphalan). Pulmonary embolism and deep vein thrombosis have been added to section 4.8 and an appropriate warning is included in section 4.4 for melflufen. Thrombosis prophylaxis was not warranted in the melflufen studies and it is agreed that there is no need for a statement in section 4.2. In the safety population (N=491) used for the proposed SmPC, 142 (29%) patients received concomitant ATT for a median time of 431 days (range 1-6942). A statement on anti-thrombotic prophylaxis in high-risk patients has been added in section 4.4 and is acceptable.

Several TEAEs (such as hypocalcaemia, hypomagnesemia, epistaxis, hypophosphatemia, tachycardia, hypotension) were reported with higher frequencies in study OP-106 compared to the pooled safety analysis. Not all of them could be straightforward substantiated by the severity and progression of the disease. The applicant reasonably argued that there was no evidence that these events were related to melflufen/melphalan and/or were likely related to underlying conditions. The risk of bleedings, including epistaxis has been now included in the SmPC.

Deaths

A total of 88 patients (56.1%) died within study OP-106, mostly due to PD. Ten patients (6.4%) reported a TEAE with a fatal outcome and none was considered related to melflufen. Within the TSP, 176 (41.7%) died during the studies and 11.4% experienced at least 1 TEAE with an outcome reported as fatal. Six events were considered related to melflufen, all in the SOC Infections and Infestations. Four grade 5 events of infections in 3 patients occurred concomitantly with Grade 3 or 4 neutropenia. Though infections are not uncommon in this heavily treated population and the contribution of melflufen may be difficult to assess, septic shock is known for melphalan (SmPC) and has been added to the ADR table in section 4.8.

Laboratory findings

Laboratory findings were dominated by changes in haematological parameters, and shifts to worst post-baseline grade 3 or 4 in haematological parameters were common. Shifts to grade 3 or 4 in serum chemistry were uncommon, the most frequently reported shift was a Grade 0 to 3 increase in urate (13.9%) in study OP-106. Hyperuricaemia has been added as ADR to section 4.8 of the SmPC. There were no other new or unexpected laboratory signals.

Drug-drug interactions

No specific clinical studies assessing the effects of other drugs or extrinsic factors on melflufen were submitted which is acceptable. Given the mechanism of action of melflufen, drug-drug interactions by competition for drug metabolic enzymes or any other interactions are unlikely. There are also no relevant interactions known for melphalan that need to be included, except for a statement on the use attenuated live vaccines for which a warning is included in section 4.4.

Adverse events of special interest by intrinsic/extrinsic factors

An analysis of AESIs (thrombocytopenia, neutropenia, febrile neutropenia, infections, infective pneumonia, anaemia, bleeding events and MDS/AML) by age, sex, race, BMI, and baseline CrCl did not identify clinically meaningful interactions. Further, the small number of patients included in some of the subgroups makes it difficult to draw conclusions. In general, there were no specific concerns based on the summary of specific adverse events presented by age category. Though the frequency of AEs in the SOC Nervous system disorder was higher in patients 75-84 years (54% vs 33-37%), there were no signs for an increase in a specific AE. The number of patients aged >75 years was limited (n=57; 15.9%), but comparable to that in other clinical studies in the RRMM setting. Given a median time since diagnosis of 6 years and a median age of 65 years, these patients may not represent the general MM population, as the median age at diagnosis in the general population is around 72 years. In addition, 16% had ECOG score of 2, therefore, the current safety profile may be an underestimation of that in clinical practice. Few patients with a baseline CrCl of <45 mL/min (n=21) were treated with melflufen, making it difficult to draw conclusions. Nevertheless, current data indicate an increase in exposure and potential for increase in AEs with reduced renal clearance and a recommendation for close monitoring has been added to section 4.4. A renal impairment study is ongoing and part of the RMP, which will provide more information.

Overdose

There are no reports on overdose of melflufen, the highest dose used in combination with dexamethasone was 55 mg (study-O-12-M). It is reasonable to assume that melflufen is not associated with withdrawal or rebound effects, or a risk of drug abuse, in line with what is known for melphalan. No formal studies on the effects of melflufen on the ability to drive or operate machinery have been performed, which is acceptable. Overall, information included in section 4.7 and 4.9 of the SmPC is acceptable.

Pregnancy, breast feeding and embryo-foetal toxicity

There are no data of pregnant women exposed to melflufen, nor data regarding the secretion of melflufen in human milk or its effects on the breastfed infant or on milk production. As with any other alkylating anticancer agents, melflufen is expected to induce embryo-foetal toxicity including malformations and has an impact on fertility. Adequate statements are included in section 4.6 of the SmPC.

Post-marketing data

Post-marketing safety data from the USA did not raise new safety signals.

Supportive safety data from Study OP-103

Additional comparative safety data was submitted from study OP-103 which was the confirmatory study in the context of the initially proposed CMA. This study enrolled patients in an earlier stage of disease (2-4 prior lines of treatment and refractory to both the last line and to lenalidomide), of which 228 patients were treated with melflufen + dexamethasone at the proposed dosing regimen and 246 subjects were treated with pomalidomide + dexamethasone. Treatment duration with melflufen was somewhat longer than for study OP-106 (median 25 weeks and median 5 cycles started), whereas the comparison arm allows contextualization of the safety profile. Safety data, though observed in an earlier treatment setting, support the safety profile of the combination observed in study OP-106, being mainly characterized by haematological and GI events. For the subgroup in study OP-103 that met the criteria of the proposed indication (n=30), frequencies of AEs were somewhat lower than observed in study OP-106. However, the potential detrimental effect observed for OS remains of major concern. Data show that the overall tolerability of melflufen + dexamethasone is lower than for pomalidomide + dexamethasone, as shown by higher frequencies of treatment-related grade 3/4 events and dose modifications (including discontinuations). On the other hand, frequencies of SAEs and fatal

events were in the same order of magnitude, and it is considered unlikely that the OS detriment can be explained by a direct toxicological effect of melflufen. As OS subgroup analyses indicated a differential effect based on prior ASCT (detriment in patients with prior ACT), this was further explored as discussed in the efficacy section. Further, safety data were presented by prior ASCT. These data showed that patients with a prior ASCT more frequently reported haematological events compared to patients without a prior ASCT in the melflufen + dexamethasone arm. The explanation of the applicant that pretreatment with high dose of melphalan (200 mg/m^2) negatively affects a patient's hematopoietic reserve and therefore these patients may be less likely to tolerate subsequent treatments that induce cytopenia and are more prone to develop haematological toxicity, appears reasonable. This resulted in higher frequencies of drug discontinuations, though SAEs and fatal AEs were comparable for patients with and without prior ASCT. An analysis in the updated total safety data supports the finding that especially thrombocytopenia is observed more frequently in patients with prior ASCT with progression within 36 months whereas treatment duration was shorter. Although myelotoxicity is increased, it is unlikely that this entirely explains the lower survival rate also taking into that no increase in fatal AEs was observed. Given the signal of reduced efficacy throughout efficacy endpoints, the indication should exclude patients who have a TTP <36 months post-ASCT (see efficacy discussion).

Based on the final data from study OP-103 submitted as part of the list of questions, the applicant requested a full MA instead of a CMA. From a safety perspective, the data can be considered comprehensive and potentially enable a full MA. Study OP-103 did not identify new safety signals to be included in section 4.8. The proposal of the applicant to update frequencies in section 4.8 based on the updated total safety database of 491 patients, including study OP-103, is considered acceptable. Though frequencies of some AEs were classified into a lower category and study OP-103 largely reflects an earlier setting of RRMM, the safety profile may be considered more accurate based on a larger number of RRMM patients.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

The safety profile of melflufen appears non-negligible, although generally manageable with adequate monitoring and dose adjustment or discontinuation. The most important safety concerns are the haematological toxicities and the possible serious clinical consequences of infections and bleeds. These are understood to be related to the mechanism of action and well known for the active substance melphalan.

Relevant safety information and recommendations are presented in the SmPC. Also, the safety profile has been considered sufficiently characterized based on study OP-106 encompassing the target population and supported by comparative safety data from OP-103 in an earlier setting of RRMM. Safety data are therefore considered comprehensive potentially enabling a full MA. Additional safety data are expected on patients with severe renal impairment (see RMP).

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 50 Summary of safety concerns

Summary of safety concerns	
Missing information	Use in patients with severe renal impairment

2.7.2. Pharmacovigilance plan

Table 51: Summary table of additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
OP-107 (BRIDGE) A Phase 2 study of the pharmacokinetics of melphalan during treatment with melflufen and dexamethasone in patients with relapsed-refractory multiple myeloma and impaired renal function Terminated	- Evaluate the relationship between renal function and pharmacokinetic parameters for melphalan during treatment with melflufen - Assess the safety and tolerability of melflufen in patients with moderate and severe renal impairment	Use in patients with severe renal impairment (eGFR <45 mL/min)	Start of enrolment End of recruitment Last patient last visit Clinical study report Supplemental clinical study report	Link to protocol 17/09//2018 29/06/2021 22/12/2021 17/12/2021 Estimated Q2 2022

2.7.3. Risk minimisation measures

Table 52: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in patients with severe renal impairment	Routine risk minimisation measures: • SmPC section 4.2 stating that there are insufficient data in patients with eGFR <30 mL/min/1.73 m^2 to support a dose recommendation. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: Study OP-107 (BRIDGE) A Phase 2 study of the pharmacokinetics of melphalan during treatment with melflufen and dexamethasone in patients with relapsed-refractory multiple myeloma and impaired renal function Supplemental clinical study report estimated Q2 2022

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Treatment of adult patients with multiple myeloma who have received at least three prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy. For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years from transplantation

3.1.2. Available therapies and unmet medical need

Current treatment strategies in relapsed/refractory (RR) MM patients include glucocorticoids (dexamethasone, prednisolone, methylprednisolone), chemotherapy, proteasome inhibitors (PIs; e.g. bortezomib, carfilzomib and ixazomib), immunomodulatory drugs (IMiDs; e.g. thalidomide, lenalidomide and pomalidomide), monoclonal antibodies (mAbs; e.g. daratumumab, isatuximab and elotuzumab) and the histone deacetylase inhibitor panobinostat.

Patients who have become refractory to all 3 major treatment classes (PIs, IMiDs and anti-CD38 mAbs) are referred to as triple-class refractory (TCR). Since first line therapy in newly diagnosed MM patients often represents a combination of 2 of these treatment classes, patients could already be TCR after second line therapy.

Blenrep (belantamab mafodotin) received a CMA in a TCR population after at least four prior therapies and recently, anti-BCMA CAR-T cell therapy Abecma (idecabtagene vicleucel) is recently approved in the same target population. Nexpovio (selinexor), a Selective Inhibitor of Nuclear Export (SINE) compound, was recently approved in a penta-refractory population. Although patients with relapsed disease can achieve responses to subsequent anti-myeloma regimens, the duration of response typically decreases with successive relapses until resistant disease develops. While the advent of novel treatment regimens has translated into improvements in outcomes, the disease is ultimately fatal. Triple or higher class refractory patients have an estimated overall survival of a few months to less than one year. The impact of the recently approved products on OS is yet unknown due to the single arm trial design of registration studies. Therapies with new mechanisms of action to overcome drug resistance, also including patients pre-treated with daratumumab, remain an unmet medical need.

Melphalan flufenamide is a lipophilic derivative of melphalan designed/aimed to enhance cell penetration and thus obtain higher intracellular concentrations than melphalan. Melphalan is formed from melphalan flufenamide upon intracellular hydrolysis by peptidases and is considered the main active substance of melflufen. Cross-linking of DNA is probably the most important factor for the cytotoxic effect. Melphalan itself is licensed for the treatment of multiple myeloma. In theory, this would allow treatment in TCR patients as well. In clinical treatment guidelines, melphalan is recommended only in first line. In patients eligible for autologous stem cell transplantation (ASCT) it is used as part of the conditioning regimen, whereas in patients in-eligible for ASCT, melphalan could be used in combination with daratumumab, bortezomib and prednisone.

3.1.3. Main clinical studies

The proposed posology is 40 mg of intravenous (IV) melflufen on Day 1 of each 28-day cycle and 40 mg (or 20 mg in patients ≥ 75 years) of oral (PO) dexamethasone (dex) on Days 1, 8, 15, and 22. This regimen is supported by the dose-finding Phase 1/2a Study O-12-M1 in RRMM after 2 or more prior treatment lines (ORR 31.3%, n=45).

Main clinical data is derived from Phase 2 study OP-106 (HORIZON), a single arm study of melflufen in combination with dexamethason at the proposed dose in patients with RRMM who had received a minimum of 2 prior lines of therapy, including an IMiD and a PI, and who were refractory to pomalidomide and/or an anti-CD38 mAb. The TCR target population was defined as the study population of interest during the study after several protocol amendments.

In total 157 patients were included in Study OP-106 and treatment at the proposed dose continued until disease progression (PD), unacceptable toxicity, or the patient/treating physician decided that it was not in the patient's best interest to continue.

In the overall study population (n=157) and TCR study population (n=119, of which n=117 with at least 3 prior treatment lines, and n=52 3L+ with a TTP ≥36 months after ASCT, median age was 65 years. Patients had received a median of 5 (range 2-12) prior therapies, i.e. were penta-exposed. Median treatment duration was 17 weeks at the time of data cut-off (DCO).

The primary endpoint was ORR (sCR + CR + VGPR + PR) and key secondary endpoint duration of response (DOR). Main other secondary endpoints were progression free survival (PFS), overall survival (OS). The primary endpoint, ORR, was to be considered met if the lower bound of the 95% confidence interval for actual ORR among TCR patients was higher than 15%.

Supportive data is derived from Phase 3 Study OP-103 (OCEAN). This study with confirmatory intent compared the efficacy of melflufen + dexamethasone (dex) vs. pomalidomide (pom) + dex in patients with a (mostly) earlier line RRMM. Enrolled patients had documented disease progression with measurable disease, had received 2-4 prior lines of therapy, including lenalidomide and a PI, and were refractory to both the last line of therapy and to lenalidomide administered within 18 months prior to randomization. In total 31 patients were TCR patients with at least 3 prior lines. In total 145 patients had no prior ASCT or TTP ≥36 months after ASCT.

The primary endpoint was PFS and key secondary endpoints ORR and OS (both planned to be alpha-controlled).

3.2. Favourable effects

Study OP-106

The primary endpoint ORR based on Investigator (Inv) assessment in the overall study population was 29.3% (95% CI: 22.32%, 37.08%). Comparable results were obtained per Independent Review Committee (IRC). The median DoR was 5.5 months (95% CI: 3.9, 7.6) based on Inv and 6.7 months (95% CI: 4.2, 8.1) based on IRC assessment. Exploratory updated results (data cut-off 12 Aug 2021) suggest an ORR of 33.8% (95% CI: 26.4%, 41.7%) and median DoR of 6.70 months (95% CI: 4.40, 8.11) for the overall population.

Median Inv based PFS was 4.24 months (95% CI: 3.42, 4.86) and comparable results were seen per IRC. Median OS was 11.63 months (95% CI: 9.30, 15.41).

For the new proposed TCR target population with at least 3 prior lines (n=117), ORR was 29.1% (95% CI: 21.0, 38.2) and DOR of 6.97 months (95% CI: 3.88, 9.79; updated data cut-off 12 Aug 2021).

Median PFS was 3.94 months (95% CI: 3.02, 4.63) and comparable for Inv and IRC assessment. Median OS was 11.24 months (95% CI: 7.66, 13.17).

Median PFS remained unchanged in the updated analysis, median OS decreased to 10.12 months (7.20; 12.29).

OP-106 results for this 3L+ TCR population with TTP ≥36 months after ASCT or no ASCT (n=52) indicate an ORR of 28.8% (95% CI: 17.1, 43.1) with median DOR of 7.6 months (95% CI: 3.0, 12.3).

Study OP-103

The primary endpoint median IRC assessed PFS was 6.83 (95% CI 4.96, 8.54) in the meflufen + dex arm vs. 4.93 (95% CI 4.24, 5.72) in the pom + dex arm. The stratified HR was 0.792 (95% CI: 0.640, 0.981; p=0.0319). The sensitivity analyses were in line with results from the primary PFS analysis.

Efficacy results for the 31 3L+ TCR patients, suggest an ORR of 40% (95% CI: 22.7, 59.4) and median DoR of 14.3 months (95% CI: 4.1, NE).

In patients (independent of treatment line) with TTP ≥36 months after ASCT or no ASCT (n=145), ORR was 42.1% (95% CI: 33.9, 50.5) for melflufen + dex vs. 26.4% (19.5, 34.2) with pom+dex, median PFS was 9.26 months (95% CI: 7.16, 11.79) vs. 4.63 (3.65, 6.28) with pom + dex, and median OS was 23.56 months (95% CI: 18.86, 27.96) vs. 19.84 (12.62, 26.48) with pom+dex.

3.3. Uncertainties and limitations about favourable effects

- Both key secondary endpoints ORR and OS for confirmatory Study OP-103 were not met. Although ORR was numerically in favour of the melflufen arm (32.5% vs. 26.9%. stratified p=0.1422), an OS HR of 1.104 (nominal p-value = 0.47) was observed for melflufen + dex compared to pom + dex. Median OS was 19.75 months (15.08, 25.56) for the melflufen + dex arm vs. 25.00 months (18.14, 31.87) with pom + dex. This was maintained with an OS update after one additional year of follow-up: median OS 20.24 months (15.84, 24.34) vs. 23.98 months (19.06, 28.71), with a HR of 1.14 (95% CI: 0.912-1.434, nominal p=0.2438). OS subgroup analyses showed large heterogeneity among several subgroups, especially age and prior ASCT. The results from post-hoc analyses indicate that the subgroup of patients with disease progression within 36 months after ASCT showed reduced efficacy; median OS was 15.72 months (11.89, 20.47) in the mel + dex arm vs 28.71 months (20.17, 34.07) in the pom +dex arm. Lower efficacy was consistently observed for all efficacy endpoints.

- The single arm design of the pivotal Phase 2 trial OP-106 does not allow to isolate the contribution of the two components of the combination. Nevertheless, melflufen monotherapy data from Study O-12-M1 showed an ORR of only 7.7% and a recent publication (APL-C-001-09 – ADMYRE) with low dose dex (40mg once weekly) as comparator in RRMM patients with a median of 4 lines of prior systemic therapy indicated an ORR of 1.2%. These data contribute to alleviate the concerns that the effect observed with melflufen in combination with low dose dex would mainly be driven by only one of the components.

- There are no interpretable quality of life data. PRO endpoints were added post-hoc in this single arm trial and only a limited number of patients had evaluable data.

- The study population was younger and less frail than could have been expected for heavily pre-treated RRMM patients. This brings some uncertainty to the true effect size in clinical practice, although it is acknowledged that the decision to start treatment and the selection of treatment regimen is multifactorial. The age categories and ECOG PS are adequately reflected in section 5.1 of the SmPC.

- Efficacy in primary refractory patients is unknown, as these patients were excluded from the pivotal trial. This is reflected in section 5.1 of the SmPC.

3.4. Unfavourable effects

Haematological events were the most frequently reported TEAEs, mainly anaemia, thrombocytopenia and neutropenia which were reported in 55.4% (neutropenia) to 70.7% (anaemia) of the patients in study OP-106 (n=157). These were also the most commonly reported ≥grade 3 events, with incidences of roughly 50%. Haematological AEs are expected based on the mechanism of action of melphalan. The events were manageable with dose modifications and supportive treatment. Thrombocytopenia was the most common adverse event leading to discontinuation of melflufen (10.2%). A total of 16% in study OP-106 had a grade 3 or 4 thrombocytopenia (including platelet count decreased) and concomitant haemorrhage, most of these bleedings were grade 1 or 2. Overall frequency of bleeding events was 28.0%. About one third (29.9%) of patients had an infection and concomitant Grade 3 or 4 neutropenia (including neutrophil count decreased); 11% reported a ≥ grade 3 infection and concomitant ≥ grade 3 neutropenia. Overall, 58% of patients reported infections, mostly infective pneumonia, and frequently ≥grade 3 events. Infections were in general manageable with anti-infective treatment and dose modifications.

Non-haematological TEAEs frequently (> 15%) reported with melflufen were asthenia, nausea, diarrhoea, fatigue, pyrexia, and upper respiratory tract infection. These events were mostly grade 1 or 2. Gastrointestinal events are well known for melphalan.

Overall, grade 3/4 TEAEs were reported in 93.6% of patients and SAEs were reported in 49.0% of patients. Pneumonia (8.9%) and febrile neutropenia (5.1%) were the most frequently reported SAEs. In the overall population, 56.1% of patients died during the study OP-106 and 8% died within 30 days after last study drug. Most deaths were due to progressive disease, fatal TEAE rate was 6.4% in study OP-106. Within the targeted safety population (TSP, n=422 melflufen 40 mg in combination with dexamethasone), fatal TEAE rate was 11.4% and 6/20 patients reported fatal TEAEs in the SOC Infections and infestations. Four grade 5 events of infections in 3 patients occurred concomitantly with Grade 3 or 4 neutropenia.

MDS/AML was reported in six patients (1.2%) in the TSP, four of these were reported as TEAEs and considered possibly/probably related to melflufen. Other SMPs occurred in 7 patients.

Overall, 21.7% reported a TEAE leading to discontinuation of melflufen. Melflufen dose reductions were observed in 26.8% of patients and 61.8% had a dose delay of melflufen.

The safety profile in the TCR population was comparable to that of the overall population in study OP-106.

Supportive safety data were derived from the RCT OP-103 in an earlier treatment setting, with a median treatment duration of 25 weeks for melflufen +dexamethasone. Safety data support the safety profile of the combination as observed in study OP-106, being mainly characterized by haematological and GI events and no new safety events were identified. In addition, post-marketing safety data from the USA over the period of 26 Feb 2021 – 27 Aug 2021 did not raise new safety signals.

An updated safety database with a slightly different composition consisting of 491 patients treated with melflufen as single agent or in combination with dexamethasone was used for the safety profile in the SmPC. The safety profile is in line with the initial data and no new safety signals were identified.

3.5. Uncertainties and limitations about unfavourable effects

One of the main uncertainties in relation to the safety database is the lack of a control arm, making it difficult to distinguish the events attributable to melflufen, the underlying disease and concomitant/previous treatment received. It is of help that the safety profile of melphalan is well known, considering clinical use as an antitumor agent for more than 60 years. Nevertheless, presented frequencies for melflufen should be interpreted as rough estimates.

The risk of bleeding and infections is of particular importance in a patient population prone to these risks.

The median duration of exposure in the pivotal study and the TSP is 17 weeks, and slightly longer with updated data (20 weeks), therefore long term safety data is limited. This is of relevance for AEs that might occur after long-term exposure, like secondary primary malignances. This risk is, however, well known based on the long-standing use of melphalan and no additional risk minimization measures are needed. This is addressed in the RMP based on what is known for melphalan.

Overall, within the safety database 422 patients received the recommended dose in combination with dexamethasone. With the understanding that the selection of type of treatment regimen is multifactorial, the observed safety profile may not be fully representative for clinical practice given the inclusion of a less frail patient population and a limited number of patients >75 age.

Higher melphalan exposures were associated with an increased incidence of grade 3 and 4 haematologic AEs. Thrombocytopenia was a major reason for premature discontinuation of melflufen treatment. As patients with low body weight have higher melphalan exposure, a lower starting dose of 30 mg melfufen is proposed for subjects with body-weight < 60 kg. This is considered acceptable

The safety profile with regard to the selected AESIs appeared comparable within various subgroups studied to the overall safety profile and did not reveal major differences, however, the small numbers in some subgroups prevent firm conclusions.

Only few patients with renal impairment were included, a study in patients with renal impairment is ongoing (OP-107) and part of the RMP. Interim analysis for patients with moderate renal impairment with eGFR 30-45 mL/min/1.73 m2 showed on average 30% higher melphalan exposure compared to patiens with normal renal function. Discontinuation of melphalan treatment due to TEAE was lower in Cohort 1b (30 mg starting dose) 20% compared to 46.7% in Cohort 1a (40 mg starting dose). Therefore, the reduced starting dose for subject with eGFR 30-45 mL/min/1.73 m2 is considered acceptable. Treatment of subjects with severe renal impairment is not recommended. This has adequately described in the SmPC.

There appears to be no direct toxicological signal of melflufen that explains the observed OS detriment in study OP-103. Patients with a prior ASCT and TTP ≤36 months appear to have lower tolerability for melflufen resulting in higher frequencies of drug discontinuations. However, SAEs and fatal AEs were comparable for melflufen-treated patients with and without prior ASCT. It is unlikely that the difference in tolerability is the main cause of OS detriment/the lower survival rate in this subgroup.

3.6. Effects Table

patients with multiple myeloma whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody (Study OP-106, data cut-off: 14 Jan 2020).

Effect	Short Description	Unit	Melflufen + dex	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ORR (95% CI) Inv based	Proportion of patients for whom the best overall confirmed response is sCR, CR, VGPR or PR.	%	*Overall study population* 29.3% (22.3, 37.1) *3L+ TCR population with TTP ≥36 months after ASCT or no ASCT (n=52)* **28.8%** (17.1, 43.1)	N/A	No control arm Sensitivity analysis based on IRC assessment showed similar results. Supported by OP-103 results. In patients (independent of treatment line) with TTP ≥36 months after ASCT or no ASCT (n=145), ORR was 42.1% (95% CI: 33.9, 50.5) for melflufen + dex vs. 26.4% (19.5, 34.2) with pom+dex, median PFS was 9.26 months (95% CI: 7.16, 11.79) vs. 4.63 (3.65, 6.28) with pom + dex, and median OS was 23.56 months (95% CI: 18.86, 27.96) vs. 19.84 (12.62, 26.48) with pom+dex.	CSR
Median DoR (95% CI) Inv based	Time between first documentation of a confirmed response to first evidence of confirmed disease progression or death due to any cause defined for patients who achieved PR or better.	Months	*Overall study population* 5.5 months (3.9, 7.6) *3L+ TCR population with TTP ≥36 months after ASCT or no ASCT (n=52)* **7.6 months** (3.0, 12.3)	N/A	IRC based assessment: 6.7 months IRC based assessment: 5.5 months	CSR
Unfavourable Effects*						

Effect	Short Description	Unit	Melflufen + dex	Control	Uncertainties/ Strength of evidence	References
Thrombocytopenia	Incidence of thrombocytopenia Grade 3-4	%	59.9 56.7		Discontinuations: 10.1% Concomitant bleedings mostly grade 1 or 2 Uncertainties: role of disease progression, concomitant and previous treatments, and incidence of events leading to bleeds. Supported safety data from study OP-103; no new safety signals	
Neutropenia	Incidence of neutropenia Grade 3-4	%	55.4 52.9		Concomitant infections partly ≥grade 3 Uncertainties: role of disease progression, concomitant and previous treatments, and incidence of events leading to infections. Supported safety data from study OP-103; no new safety signals	
Anaemia	Incidence of anaemia Grade 3-4	%	70.7 42.7		Uncertainties: role of disease progression, concomitant and previous treatments. Supported safety data from study OP-103; no new safety signals	
Infections	Incidence of infections Grade 3-4	%	58.0 21.7		11.5% grade 3/4 AESI of infection and concomitant grade 3/4 neutropenia Supported safety data from study OP-103; no new safety signals	
GI events	Nausea Diarrhoea Vomiting	%	31.8 26.8 13.4		Mostly grade 1 or 2 Supported safety data from study OP-103; no new safety signals	
Deaths	Incidence of deaths Incidence of death <30 days last dose of study drug	%	56.1 8		Mostly due to PD; 6.4% TEAE with fatal outcome	

Effect	Short Description	Unit	Melflufen + dex	Control	Uncertainties/ Strength of evidence	References
Discontinuation due to AE	Incidence of discontinuation any drug	%	23.6			
	Discontinuation melflufen		21.7			

Abbreviations: CI= confidence interval, CR= complete response, CSR= clinical study report, DoR= duration of response, Inv= investigator, IRC= independent review committee, N/A= not applicable, ORR= overall response rate, OS= overall survival, PR= partial response, sCR= stringent complete response, TCR= triple class refractory, VGPR= very good partial response, AESI=adverse event of special interest
Notes:* Based on the overall study population OP-106

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A full approval is requested for TCR patients with ≥3 prior treatment lines, with a contra-indication for the subgroup of patients with TTP <36 months after ASCT. Clinical data in the target population is derived from single arm trial OP-106 + supportive data in an earlier line from randomized controlled trial OP-103.

Given the poor prognosis of heavily pre-treated RRMM patients whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent and one anti-CD38 mAb after 3 prior treatment lines, the antitumour activity of meflufen + dex (updated ORR of 29.1%) might be considered of clinical relevance, in combination with the observed DoR close to 7 months. Response rates are in line with those observed for other products in RRMM (23-32%). Higher response rates were reported for the recently approved CAR-T cell therapy idecabtagene vicleucel (ORR ~67%).

For pivotal study OP-106, uncertainty remains with regard to the effect on time-dependent endpoints, PFS and OS, which cannot be reliably interpreted in a single uncontrolled study.

Support can be derived from PFS (primary endpoint) results from Study OP-103. Indeed, the primary endpoint PFS of the study was met with a HR of 0.79 and median PFS of 6.83 months with melflufen + dex vs. 4.93 months with pom + dex in the overall study population. Several sensitivity analyses (a.o. due to concerns regarding handling of randomised but not-treated patients) confirmed internal validity of obtained PFS results.

Despite the active comparator and the fact that study OP-103 was not powered to demonstrate a difference in overall survival, the updated OS HR of 1.14 and KM curves in the OP-103 ITT population warranted further investigation. Based on a post-hoc defined cut-off, the subgroup of patients who progressed within 3 years after ASCT seemed to be the major contributor to the OS result and multivariable OS analysis also provided a strong signal that TTP after ASCT was an effect modifier. Interestingly, consistent results on efficacy in favour of melflufen were seen for the subgroup with no ASCT or prior ASCT and TTP ≥36 months. While these analyses were based on a post-hoc defined variable, there is the biological rationale that patients who progress early after ASCT, which requires high dose melphalan, might be less responsive to another alkylator based regimen. In addition, these patients may have an increased risk of myelotoxicity with loss of marrow

reserve after recent transplantation. The cut-off of 36 months is to some extent supported by expert data stating that the PFS cut-off for a transplant to be considered successful enough to consider a salvage ASCT is ≥36 months, although not the same situation as in the trial (EHA-ESMO guidelines, Dimopoulus et al. 2021). In addition, the treatment effect observed in the subgroup is larger than the all-randomised study population, providing additional support for the subgroup (EMA/CHMP/539146/2013; Guideline on the investigation of subgroups in confirmatory clinical trials). Subgroup analysis of OP-106 also suggest a larger effect in patients with no ASCT or prior ASCT and TTP ≥36 months, however interpretation is hampered by the lack of a control arm.

Upon consultation, the SAG-O concluded that melflufen + low dose dex is associated with clinically relevant efficacy, with the exception of the subgroup of patients with relapse within 36 months following high-dose melphalan and autologous SCT. In addition, the SAG-O considered that although the exact effect size cannot be determined due to differences in disease and treatment characteristics, the results of study OP-103 obtained in patients of whom most had fewer lines of treatment than the OP-106 patients, are relevant for the target population in study OP-106 (see expert consultation below).

Overall, based on the available data and upon consultation of the SAG-O, it is considered that melflufen + low dose dex has been shown to be efficacious and data can be considered comprehensive. However, given the major concern on the benefit of melflufen + dex in patients with prior ASCT and TTP <36 months in study OP-103 and the fact that a risk for shorter survival cannot be excluded for these patients within the 3L+ TCR population in study OP-106 due to the absence of a control group, this patient group should be excluded from the applied indication.

The safety profile is dominated by haematological adverse events of which thrombocytopenia and neutropenia are the most important as they carry potentially severe clinical consequences in patients prone to bleeding events and infections. Fatal events of infections concomitant with neutropenia have been reported. The relative contribution of melflufen to these events is difficult to detangle from concomitant treatment with dexamethasone, disease progression and previous treatments. Non-haematological adverse events were mostly grade 1 or 2. Most frequently occurring SAEs were pneumonia and febrile neutropenia. Although the toxicity of melflufen is in line with what may be expected from a drug product with melphalan as the active substance in a setting where patients are heavily pre-treated and can be considered generally manageable with adequate monitoring and dose adjustment or discontinuation, it is not negligible and relevant safety information and recommendations are presented in the SmPC. The overall impact of the safety profile on the quality of life could not be adequately assessed within this study. Melflufen offers a different mechanism of action compared to other products used in clinical practice in the TCR population and thus a somewhat different safety profile. The safety profile as observed in the OP-106 study is supported by the results from the phase 3 OP-103 and safety data are therefore considered comprehensive. Although there appears no indication of a direct toxicological effect of melflufen, it is less tolerated in patients with ACST ≤36 months.

3.7.2. Balance of benefits and risks

The benefit risk balance in the restricted indication is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Pepaxti is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Pepaxti is not similar to Blenrep, Darzalex, Farydak, Imnovid, Kyprolis, Ninlaro, Abecma and Carvykti within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Pepaxti is favourable in the following indication:

Pepaxti is indicated, in combination with dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least three prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy. For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years from transplantation.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

4.1.

OP-103 (OCEAN)

PFS sensitivity analyses

2022-07-06

1. Randomized Not Treated

1.1. PFS – Impute Overall Survival Value if Censored

Table 1. PFS. Patients Who Were Randomized and Not Treated Use the OS Value if Censored Unless Censoring is Due to Withdrawal of Consent at Which the Time is Still Censored.

	Pepaxto/Dex (N=246)	Pomalidomide/Dex (N=249)
Events (%)	175 (71.1 %)	191 (76.7 %)
Time to event		
25th percentile (95 % CI)	3.2 (2.5-3.7)	2.2 (2.0-2.8)
Median (95 % CI)	6.7 (5.1-8.1)	4.9 (4.2-6.0)
75th percentile (95 % CI)	16.4 (12.4-19.3)	11.1 (8.8-13.6)
Stratified Log-rank p-value	0.0216	
Stratified Hazard ratio	0.8 (0.6-1.0)	
Stratified Cox p-value	0.0219	
Log-rank p-value	0.0124	
Hazard ratio	0.8 (0.6-0.9)	
Cox p-value	0.0125	

Dex, dexamethasone.

Figure 1. PFS

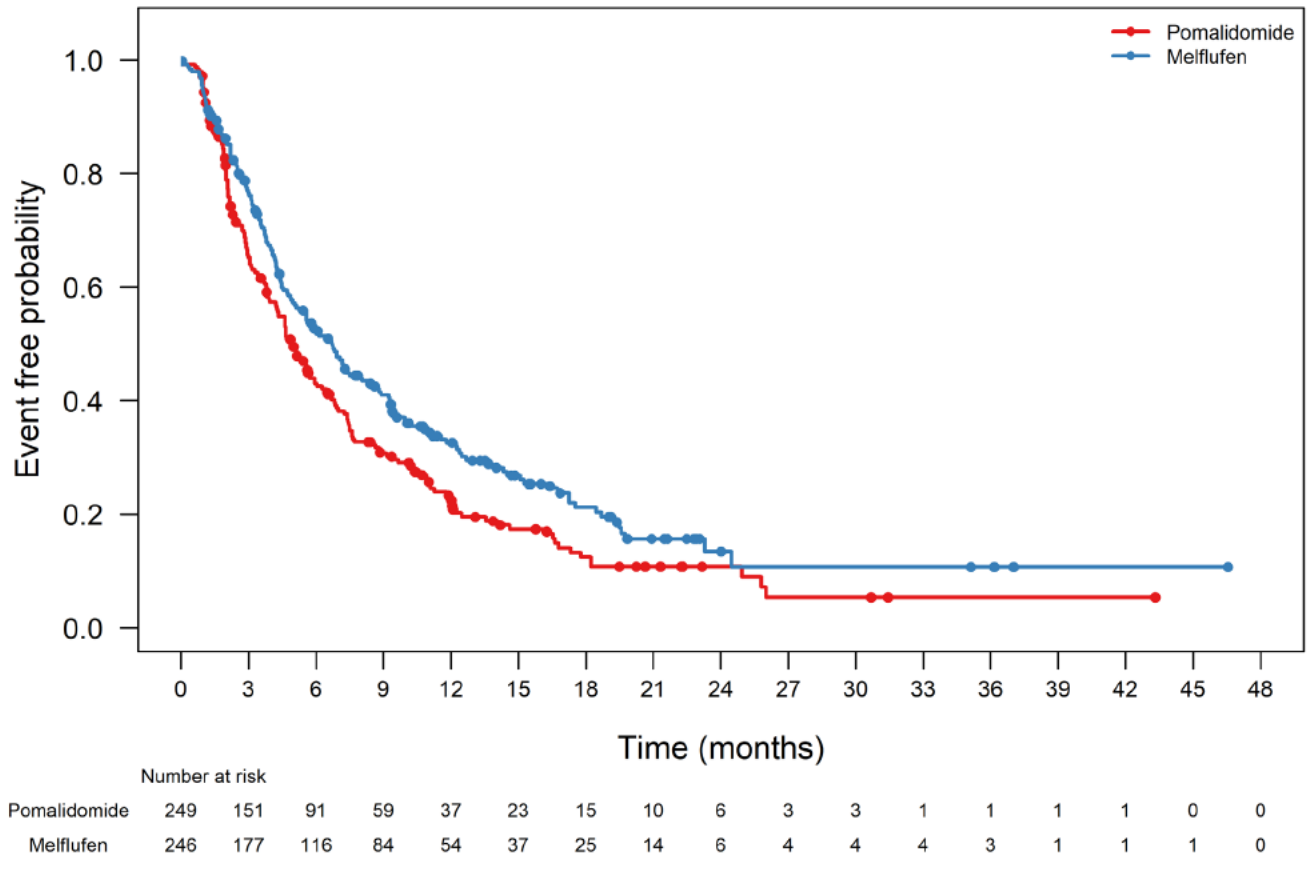


Figure 2. PFS Compared With FAS Analyses

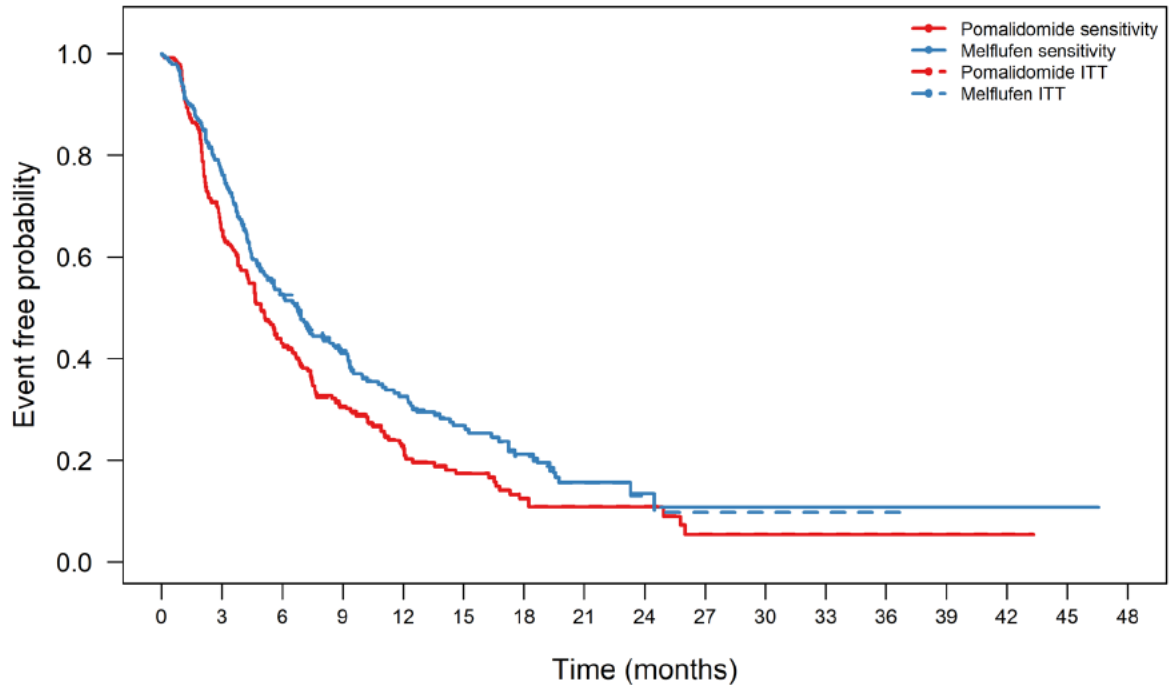
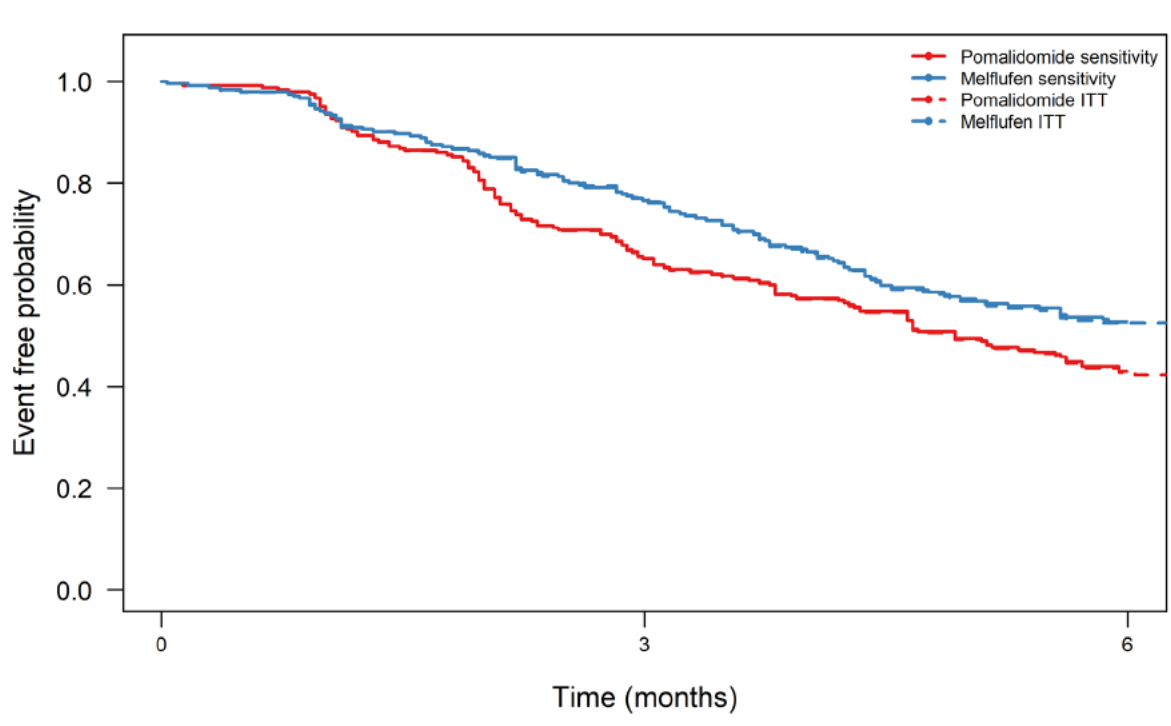


Figure 3. PFS Compared With FAS Analyses - Zooming in on First 6 Months



2. Effect of Excluding Patients Not Fulfilling Inclusion Criteria 10

Patients not fulfilling inclusion criteria 10 based on lab values, with a protocol violation indicating that inclusion criteria 10 is not fulfilled, or where the reason for not initiating treatment indicates that inclusion criteria 10 are not fulfilled are excluded

2.1. PFS – Independent Review Committee

Table 2. PFS

	Pepaxto/Dex (n=228)	**Pomalidomide/Dex (n=232)**
Events (%)	160 (70.2%)	179 (77.2%)
Time to event		
25th percentile (95 % CI)	3.22 (2.5-3.8)	2.23 (2.0-2.9)
Median (95 % CI)	6.93 (5.1-8.6)	5.09 (4.3-6.0)
75th percentile (95 % CI)	16.39 (12.3-19.3)	11.07 (8.8-13.6)
Stratified Log-rank p-value	0.0392	
Stratified Hazard ratio	0.8 (0.6-1.0)	
Stratified Cox p-value	0.0396	
Log-rank p-value	0.0201	
Hazard ratio	0.776 (0.6-1.0)	
Cox p-value	0.0202	

Dex, dexamethasone; PFS, progression-free survival.

2.2. OS

Table 3. OS

	Pepaxto/Dex (n=228)	**Pomalidomide/Dex (n=232)**
Events (%)	148 (64.9%)	135 (58.2%)
Time to event		
25th percentile (95 % CI)	8.7 (7.2-10.6)	9.3 (7.7-12.6)
Median (95 % CI)	21.3 (16.7-24.8)	25.3 (20.1-29.6)
75th percentile (95 % CI)	38.6 (32.1-NA)	39.3 (34.6-NA)
Stratified Log-rank p-value	0.2530	
Stratified Hazard ratio	1.148 (0.906-1.455)	
Stratified Cox p-value	0.2537	
Log-rank p-value	0.2596	
Hazard ratio	1.144 (0.905-1.444)	
Cox p-value	0.2599	

NA, not applicable.

Comment: Exclusion of patients not fulfilling inclusion criteria 10 did not change the results.

3. Tipping Point Analyses

3.1. Methods

The tipping point analysis aims to evaluate the effect of censored patients on the outcome of PFS. For the purpose of the analyses, all prematurely censored patients (i.e. censored prior to data cut date) will have an event date simulated according to various hazard ratio between pomalidomide and Pepaxto. The hazard ration that gives a p-value >0.05 is defined as the tipping point. For each hazard ratio 2000 simulations are performed, and the p-value is the mean of all of the simulations

3.2. Tipping Point for Randomized Not Treated

In the randomized not treated cohort, 5 patients had experienced an event, and 18 patients were prematurely censored, of which 17 in the Pepaxto arm. The reference median PFS is assumed to be 4.9 months for the pomalidomide arm

Table 4. Description of Patients

Hazard Ratio	*P* Value
0.80	0.032
0.81	0.033
0.82	0.034
0.83	0.034
0.84	0.034
0.85	0.035
0.86	0.036
0.87	0.036
0.88	0.036
0.89	0.037
0.90	0.038
0.91	0.039
0.92	0.039
0.93	0.039
0.94	0.040
0.95	0.040
0.96	0.041
0.97	0.042
0.98	0.042
0.99	0.043
1.00	0.044
1.01	0.044
1.02	0.044
1.03	0.045
1.04	0.045
1.05	0.045
1.06	0.046
1.07	0.047
1.08	0.047
1.09	0.049
1.10	0.049
1.11	0.049

Hazard Ratio	*P* Value
1.12	0.049
1.13	0.050
1.14	0.051
1.15	0.051
1.16	0.052
1.17	0.052
1.18	0.052
1.19	0.053
1.20	0.053

As can be seen in Table 4, the first hazard ratio that would give a p-value ≥0.05 is 1.13, which corresponds to a median PFS of 4.3 months in the Pepaxto arm

3.3. Tipping Point for All Prematurely Censored Patients

In the total cohort, a total of 51 patients where prematurely censored, of which 31 in the Pepaxto arm. The reference median PFS is assumed to be 4.9 months for the pomalidomide arm

Table 5. Description of Patients

Hazard Ratio	*P* Value
0.80	0.026
0.81	0.026
0.82	0.027
0.83	0.028
0.84	0.029
0.85	0.030
0.86	0.031
0.87	0.032
0.88	0.033
0.89	0.034
0.90	0.035
0.91	0.036
0.92	0.035
0.93	0.037
0.94	0.039
0.95	0.040
0.96	0.040
0.97	0.040
0.98	0.043
0.99	0.044
1.00	0.045
1.01	0.046
1.02	0.046
1.03	0.047
1.04	0.048
1.05	0.049
1.06	0.049
1.07	0.051

Hazard Ratio	*P* Value
1.08	0.052
1.09	0.053
1.10	0.054
1.11	0.056
1.12	0.057
1.13	0.057
1.14	0.060
1.15	0.060
1.16	0.061
1.17	0.063
1.18	0.063
1.19	0.065
1.20	0.065

As can be seen in Table 5, the first hazard ration that would give a p-value ≥0.05 is 1.07, which corresponds to a median PFS of 4.6 months in the Pepaxto arm

Appendix 5

Pharmacokinetics/Pharmacodynamics Analyses Supporting Label Updates

- Patients with a body weight ≤60 kg should receive a dose of 30 mg instead of the currently recommended dose of 40 mg
- Patients who require a dose interruption due to neutropenia or thrombocytopenia should have an immediate dose reduction of Pepaxto in the next treatment cycle instead of only delaying the dosing without dose reduction.

Background

The pharmacokinetics (PK) and pharmacodynamics (PD) of Pepaxto (melphalan flufenamide, also called melflufen) have been studied in RRMM patients.

Population PK
Plasma concentrations of melphalan, the main active metabolite of melflufen, have been measured to evaluate the PK, since melflufen disappears quickly with an elimination half-life of 2.1 minutes from plasma due to rapid distribution to cells and subsequent metabolism. The PK of melphalan following administration of Pepaxto was analysed in a population PK model based on pooled data from clinical studies O-12-M1, OP-103, OP-107 and OP-109[1].

Population PK/PD model on Pepaxto myelosuppressive effect
To evaluate the exposure response relationship of the effect of Pepaxto on thrombocyte and neutrophil counts, PK and PD data from the Pepaxto clinical studies O-12-M1, OP-103 and OP-107 were pooled and analyzed in a population PK/PD model.[2]

Proposed label update: Patients with a body weight ≤60 kg should receive a dose of 30 mg instead of the currently recommended dose of 40 mg.

Rationale:

Plasma exposure of melphalan was higher in patients with a lower body weight than in patients with higher body weight. Melphalan C_{max} was on average 36% higher and melphalan AUC was on average 31% higher at a body weight of 60 kg compared to a body weight of 95 kg based on the population PK analysis.[3]

Based on the PK/PD models demonstrating that neutrophil and thrombocyte counts decrease with increasing melphalan concentrations, a higher melphalan AUC is expected to translate to a higher incidence of grade ≥3 neutropenia and thrombocytopenia.[4] The findings in the PK/PD models were confirmed in the pooled safety population. When Adverse Events of Special Interest (AESIs) were evaluated based on body weight, there was an apparent relationship between lower weight and a higher percentage of neutropenia and

[1] Source: Population PK Report, Report Number: ONC0101F-Report-v4.0-Final, 2021-07-20.
[2] Source: Population PK/PD Myelosuppression Report, Report Number: ONC0101F-Report-v1.0-Date: 2021-08-10
[3] Source: Population PK Report, Report Number: ONC0101F-Report-v4.0-Final, 2021-07-20
[4] Source: Population PK/PD Myelosuppression Report, Report Number: ONC0101F-Report-v1.0-Date: 2021-08-10

febrile neutropenia events. Patient in the <60 kg group also had more thrombocytopenia and anemia events than patients with a higher weight (**Table 1**). Also grade 3/4 thrombocytopenia and anemia were most frequent in patients weighing <60 kg.[5]

Overall survival and progression-free survival were not affected by body weight in OP-103. A Pepaxto dose of 30 mg is therefore recommended in patients with a body weight ≤60 kg to compensate for higher melphalan concentrations in these patients and thereby reduce the incidence of thrombocytopenia and neutropenia.

Table 1. Pooled Safety Population: Number (%) of patients with at least one AESI of Neutropenia, Febrile Neutropenia, Thrombocytopenia, and Anemia.

Weight	N*	Thrombocytopenia n (%)	Neutropenia n (%)	Febrile Neutropenia n (%)	Anemia n (%)
<60 kg	57	54 (94.7)	48 (84.2)	4 (7.0)	47 (82.5)
≥60 to <75 kg	191	159 (83.2)	144 (75.4)	9 (4.7)	127 (66.5)
≥75 to <95 kg	177	141 (79.7)	123 (69.5)	5 (2.8)	108 (61.0)
≥95 kg	64	52 (81.3)	37 (57.8)	1 (1.6)	39 (60.9)

AESI, adverse event of special interest.

* N for Total Pooled Safety Population is 491, however information on body weight is missing in 2 patients.

Source: ISS Table 18.3.37.1i

Proposed label update: Patients who require a dose interruption due to neutropenia or thrombocytopenia should have an immediate dose reduction of Pepaxto in the next treatment cycle instead of only delaying the dosing without dose reduction.

Rationale: To further evaluate dose modifications, simulations using the PK/PD models were performed. They showed that decrease in thrombocyte counts was cumulative over the first 6 treatment cycles when administering the same dose with 28-day intervals. Dose interruptions due to cytopenias were frequent in the OP-106 and OP-103 studies, resulting in reduced dose intensity. The PK/PD analysis showed that with a more rapid dose reduction the need for dose interruptions would be lower, and dose intensity could be better maintained. The results thus indicated that a dose reduction is beneficial if a dose interruption is required due to thrombocytopenia and neutropenia.[6]

[5] Source: SS Table 18.3.51.1i
[6] Source: Population PK/PD Myelosuppression Report, Report Number: ONC0101F-Report-v1.0-Date: 2021-08-10