NDA 214383
Melphalan flufenamide (PEPAXTO)

Oncologic Drugs Advisory Committee Meeting
September 22, 2022

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Division of Hematologic Malignancies II
Office of Oncologic Diseases

Evidentiary Criteria for Approval

- Drugs granted accelerated approval or traditional approval must meet the same statutory standards for safety and effectiveness
- Safety
  - Sufficient information to determine that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling.
- Effectiveness
  - Substantial evidence of effectiveness
    - Based on adequate and well-controlled investigations
    - The drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling

Guidance for Industry: Expedited Programs for Serious Conditions- Drugs and Biologics.
FD&C Act Section 505(d) (21 U.S.C. § 355(d))

Regulatory Approval Pathways

- Regular Approval

- Accelerated Approval
  - Treatment of serious or life-threatening illness
  - Provides a meaningful benefit over available therapy
  - Approval is based on an endpoint reasonably likely to predict clinical benefit or an intermediate endpoint
  - Post-approval trials to verify anticipated clinical benefit

Abbreviations: AA: accelerated approval

21 CFR 314.510

FDA Approval Considerations

- Regulatory actions of other agencies are not relevant to the ODAC discussion or FDA regulatory decisions
- FDA decisions must adhere to U.S. laws and regulations
- Information discussed at the ODAC should be viewed independently

Abbreviations: ODAC: oncologic drugs advisory committee

Treatment Options for RRMM

Drug/Combination	Approval	Indication
Bortezomib	AA	RRMM/>2L,
Boretezomib	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	Regular (2015)	RRMM/≥2L, including lenalidomide and PI
Ixazomib with Rd	Regular (2015)	RRMM/≥1L
Daratumumab-IV	AA (2015)	RRMM/≥3L including PI and IMiD
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Daratumumab-IV with Vd	Regular (2016)	RRMM/≥1L
Daratumumab-IV with Pd	Regular (2017)	RRMM/≥2L, including lenalidomide and PI
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Selinexor with dex	**AA (2019)***	**RRMM/≥4L, including 2 PIs, 2 IMiDs, and anti-CD38**
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Idecabtagene vicleucel	**Regular (2021)**	**RRMM/≥4L, including PI, IMiD, anti-CD38 mAb**
Ciltacabtagene autoleucel	**Regular (2022)**	**RRMM/≥4L, including PI, IMiD, anti-CD38 mAb**

RRMM: relapsed/refractory multiple myeloma; Dex/d: dexamethasone; R: lenalidomide; V: bortezomib; IMiD: immunomodulatory agent; PI: proteasome inhibitor; P: pomalidomide; mAb: monoclonal antibody; RRMM relapsed refractory multiple myeloma; AA: Accelerated Approval; IV: intravenous; SC: subcutaneous; *Dara SC with Kd approved 2021.

Melphalan flufenamide

- Confirmatory trial failed to verify the clinical benefit

- Accelerated Approval
  - February 2021
  - Based on the results of the single-arm trial, HORIZON (OP-106)
  - Alkylating drug indicated in combination with dexamethasone
  - 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 CD-38 directed monoclonal antibody

- Confirmatory Trial
  - OCEAN (OP-103)
  - Randomized controlled trial of melphalan flufenamide-dexamethasone vs. pomalidomide-dexamethasone
  - RRMM who had received 2-4 prior lines of therapy, including a proteasome inhibitor and lenalidomide, must have been refractory to lenalidomide and their last line of therapy
  - Primary endpoint: PFS Superiority

Abbreviations: RRMM: relapsed/refractory multiple myeloma, PFS: Progression-free Survival

Melphalan flufenamide

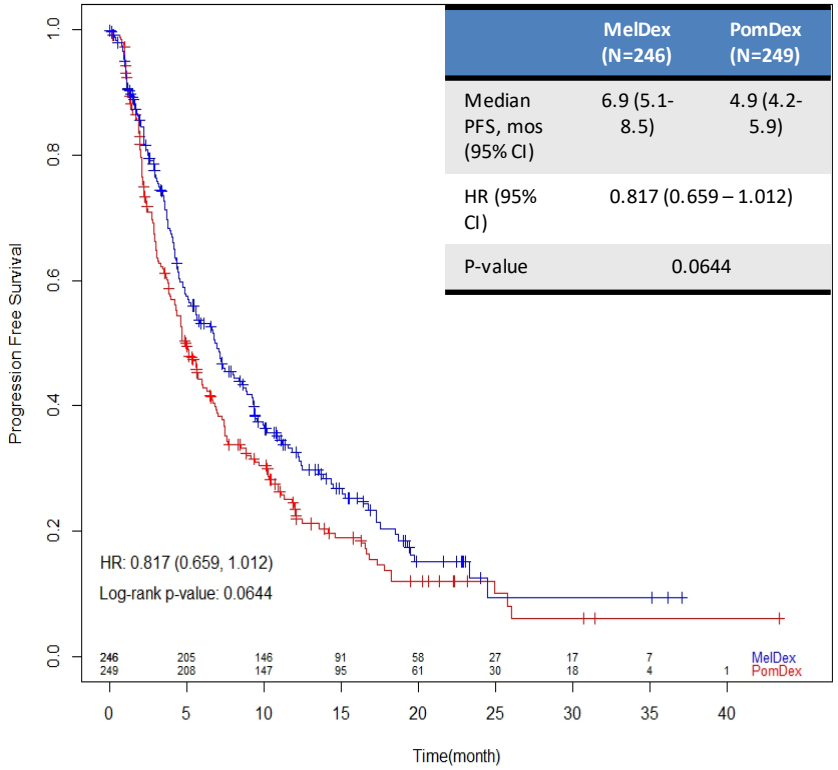
- June 9, 2021: Topline results from OCEAN trial shared with the FDA. Failed PFS superiority and worse survival.
- July 6, 2021: Sponsor submitted a post hoc re-analysis of PFS based on re-assessment of 29 patients
- July 7, 2021: IND placed on hold
- July 28, 2021: CDER Safety Alert was issued
- ODAC planned for October 28, 2021
- October 18, 2021: Oncopeptides board member requested a meeting with FDA
- October 19, 2021: Meeting held with Sponsor in which FDA expressed concerns with application
- October 20, 2021: Sponsor stated that they planned to voluntarily withdraw the NDA
- October 22, 2021: NDA withdrawal request was received and the ODAC was cancelled
- October 22, 2021: OCE and FDA Review Division initiated formal withdrawal process
- January 13, 2022: Sponsor sent notification rescinding the NDA withdrawal request
- March 9, 2022: Additional analyses based on published data submitted by the sponsor
- September 12, 2022: Sponsor proposed postponing ODAC to consider results of an ongoing trial with a different product

Abbreviations: PFS: Progression-free Survival

OCEAN (OP-103) Topline Results

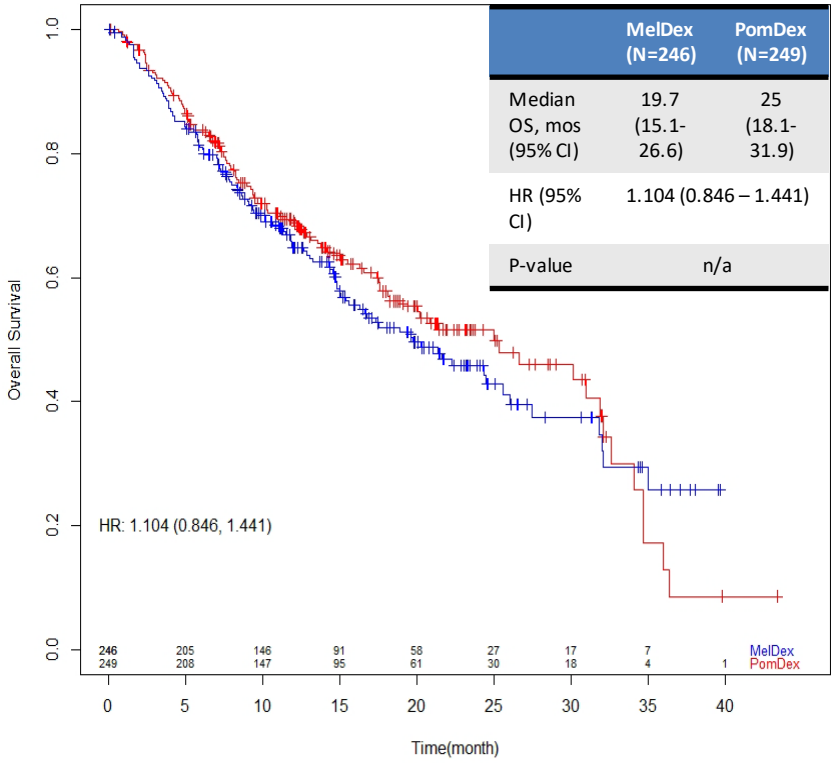
Progression-Free Survival

	MelDex (N=246)	PomDex (N=249)
Median PFS, mos (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	



Overall Survival

	MelDex (N=246)	PomDex (N=249)
Median OS, mos (95% CI)	19.7 (15.1-26.6)	25 (18.1-31.9)
HR (95% CI)	1.104 (0.846 – 1.441)	
P-value	n/a	

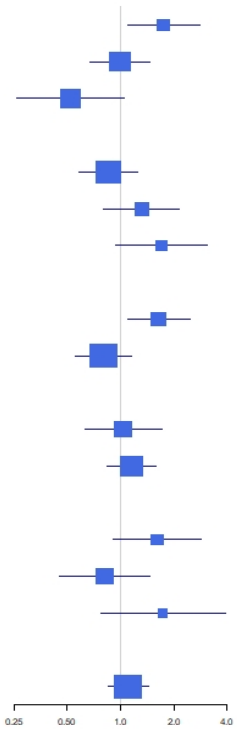


www.fda.gov

Abbreviations: PFS: Progression-free Survival, OS: Overall Survival, HR: Hazard Ratio, CI: confidence interval

Overall Survival: Subgroup Analysis

Subgroup	Melflufen (d/N)	Pomalidomide (d/N)	HR
Age			
<65	50/96	30/85	1.76
65-74	54/113	56/125	0.99
>=75	13/37	22/39	0.52
Prior line			
2	56/114	54/111	0.86
3	34/76	36/90	1.32
4	27/56	18/48	1.7
Previous autologous transplant			
Yes	61/125	41/120	1.64
No	56/121	67/129	0.8
Refractory to Alkylator Therapy			
Yes	34/78	36/75	1.04
No	83/168	72/174	1.16
Creatinine clearance			
>=90	34/76	21/69	1.61
<60	20/44	29/58	0.82
EMD at Baseline	20/30	14/26	1.74
Overall			1.10

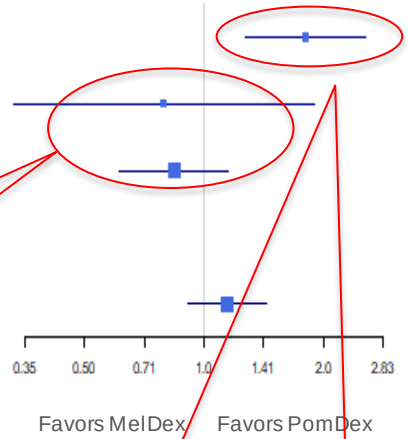


Favors Mel-dex Favors Pom-dex

Abbreviations: HR: Hazard Ratio, EMD: Extramedullary disease, Mel-dex: Melphalan flufenamide and dexamethasone, Pom-dex: pomalidomide and dexamethasone

Overall Survival: Subgroup Analysis

Subgroup	Melflufen (d/N)	Pomalidomide (d/N)	HR(95%CI)
ASCT TTP 36 months			
TTP<36 months	75/101	56/101	1.8(1.27,2.55)
TTP >=36 months	12/24	10/19	0.79(0.33,1.89)
No ASCT	75/121	81/129	0.84(0.61,1.15)
Overall			1.14 (0.91, 1.44)



No difference seen between treatments in patients without prior ASCT

OS with melphalan flufenamide inferior in patients with prior ASCT

Abbreviations: HR: Hazard Ratio; ASCT: autologous stem cell transplant, TTP: time-to-progression, Mel-dex: Melphalan flufenamide and dexamethasone, Pom-dex: pomalidomide and dexamethasone

Post-Hoc Subgroup Analyses

- Type I error probability
  - Chance of finding a difference when there is none (false positive)
  - Conventionally, Type I error is set at 5% or less

Ranganathan et al. Perspect Clin Res. 2016

Post-Hoc Subgroup Analyses

- Type I error probability
  - Chance of finding a difference when there is none (false positive)
  - Conventionally, Type I error is set at 5% or less
- Subgroup Analyses
  - Interest in comparing treatments among subsets of patients using recognized prognostic factors such as age, gender, stage, histology, etc.
  - If there were only 3 factors, 8 subsets could be formed ($2^3=8$)
  - If you compared the treatments among these 8 subsets, there would be a 33% probability to observe a statistically significant ($p \leq 0.05$) treatment effect.

Ranganathan et al. Perspect Clin Res. 2016

Post-Hoc Subgroup Analyses

- ISIS-2 Trial
  - Randomized 17, 187 patients post-MI to either streptokinase, Aspirin, both, or neither
  - Streptokinase alone, aspirin alone, and the combination significantly reduced death compared to the placebo arm

Abbreviations: MI: Myocardial Infarction

Schulz and Grimes Lancet 2005
ISIS-2 Collaborative Group. Lancet 1988

Post-Hoc Subgroup Analyses

- ISIS-2 Trial
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  - Astrological Sign Analyses
    - Geminis and Libras had an adverse effect from aspirin (9% increase), compared to patients in other astrological signs (28% reduction), p<0.00001

Abbreviations: MI: Myocardial Infarction

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Post-Hoc Subgroup Analyses

- **FDA Guidance E9 Statistical Principles for Clinical Trials (1998):**
  - *"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."*

Post hoc Analyses Submitted to FDA by Sponsor

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)

Abbreviations: OS: Overall Survival, TTP: Time-to-progression, ASCT: autologous stem cell transplant, IMiD: immunomodulatory agent

Age OS interaction with IMIDs

- The sponsor asserts that there is an age interaction with OS and the IMIDs
- The sponsor's analyses do not support this assertion
- The data from OCEAN trial do not support the safety and efficacy of melflufen

Abbreviations: OS: Overall Survival, IMiD: immunomodulatory agent

Lack of an Appropriate Dose

- Fixed 40 mg dose is poorly tolerated
- High rates of dose modification in the OCEAN trial
  - 78% of patients experienced at least one dose modification
  - 47% of patients experienced at least one adverse event leading to dose reduction
  - 26% of patients experienced at least one adverse event leading to drug discontinuation
- Weight or body-sized based dosing may be more appropriate
- A lower dose may be more tolerable

Issues

- Potential detriment in Overall Survival
- Failure to demonstrate a PFS benefit
- Lack of an appropriate dose

Regulatory Perspectives on the Issues

- Worse Overall Survival from a randomized trial against an active comparator
- Cannot assess survival from single arm trials
- With the data available unable to assess if melphalan flufenamide is causing harm in the currently indicated population
  - Toxicity, dose modifications and subgroup analyses suggestive of harm
- Accelerated Approval Requirement
  - Provide a meaningful advantage over available therapies

Discussion Topic

- Discuss the benefit-risk profile of melphalan flufenamide for the currently indicated patient population considering the results of the confirmatory OCEAN trial.

Voting Question

- Given the potential detriment in overall survival, failure to demonstrate a progression-free survival benefit, and lack of an appropriate dose, is the benefit-risk profile of melphalan flufenamide favorable for the currently indicated patient population?


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Melphalan flufenamide (PEPAXTO)
NDA 214383

Oncologic Drugs Advisory Committee Meeting
September 22, 2022

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Major Issues

- Potential detriment in OS
- Failure to demonstrate PFS benefit
- Lack of an appropriate dose

OS: overall survival, PFS: progression-free survival.

Treatment Options for RRMM

Drug/Combination	Approval	Indication
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RRMM: relapsed/refractory multiple myeloma; Dex/d: dexamethasone; R: lenalidomide; V: bortezomib; IMiD: immunomodulatory agent; PI: proteasome inhibitor; P: pomalidomide; mAb: monoclonal antibody; RRMM relapsed refractory multiple myeloma; AA: Accelerated Approval; IV: intravenous; SC: subcutaneous; *Dara SC with Kd approved 2021.

Melphalan Flufenamide

- A lipophilic peptide conjugated alkylator with the same alkylating moiety as melphalan
- Melphalan flufenamide is passively distributed into cells, then enzymatically hydrolyzed to melphalan
- DNA cross linking is involved in the antitumor activity

DNA: Deoxyribonucleic acid

Melphalan Flufenamide Regulatory History

- Granted Accelerated Approval on February 26th, 2021
- *Indication*: Melphalan flufenamide in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma 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**
- *Dosing*: **Flat** 40 mg intravenous day 1 of a 28-day cycle with weekly dexamethasone

Phase 2 Trial: OP-106 (HORIZON)

Design and Population

- Single arm, Phase 2 Trial
- N=97 TCR patients
- 70% of patients had a previous stem cell transplant

Efficacy Results

HORIZON	N = 97
ORR, % (95% CI)	23.7 (15.7, 33.4)
Median DOR, months (95% CI)	4.2 (3.2, 7.6)

Safety: High rate of Grade ≥3 neutropenia, thrombocytopenia, anemia

TCR: triple class refractory (disease refractory to at least 1 PI, 1 IMiD, 1 CD38 directed monoclonal antibody; PI: proteasome inhibitor, IMiD; immunomodulatory agent); ORR: overall response rate; CI: confidence interval, DOR: duration of response

Increased risk of mortality with PEPAXTO at dosages higher than recommended dosage

- Nonclinical safety study in dogs
- Melphalan flufenamide vs. equimolar dose of melphalan
- Increased mortality observed in dogs administered melflufen despite similar melphalan exposure

Limitation of Use: Melphalan flufenamide is not recommended for use as a conditioning regimen for transplant outside of clinical trials

PEPAXTO (melphalan flufenamide)[package insert] U.S Food and Drug Administration website. Oncopeptides, AB. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=321f455b-1de8-45bd-96f8-1bf14337f4e9#S13.2

Post Marketing Requirements

Accelerated Approval PMR

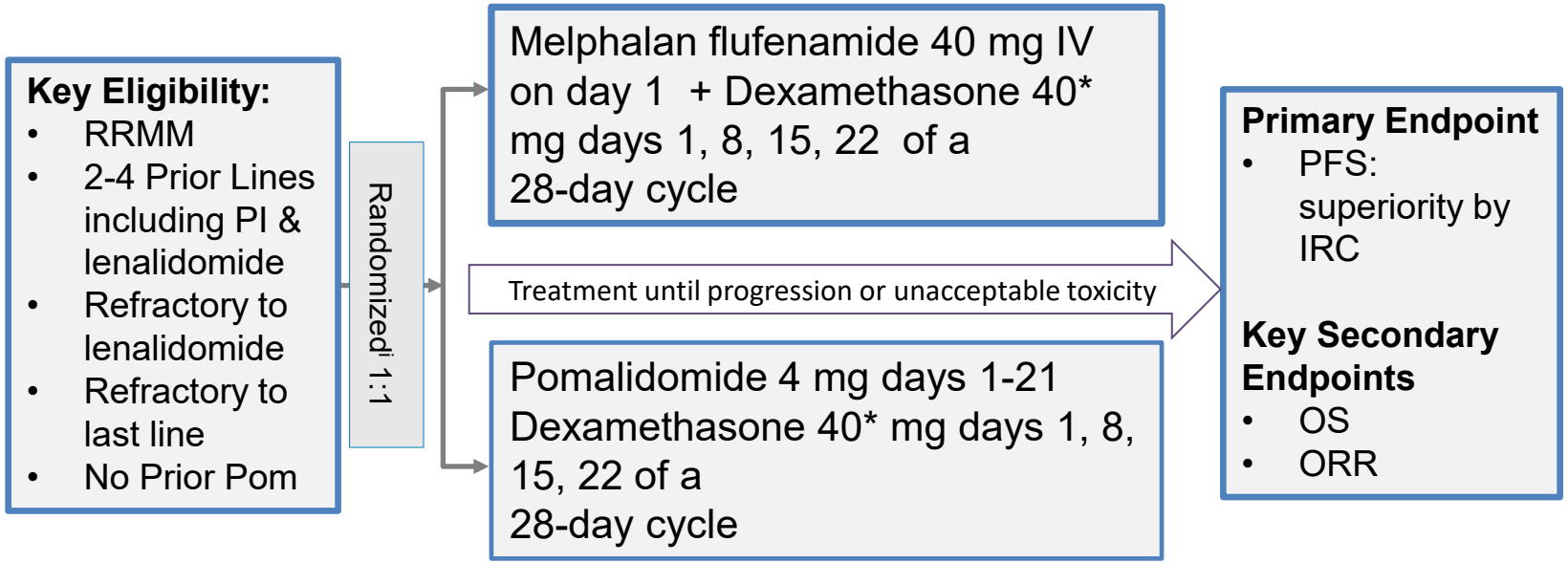
- Submit the final study report and datasets from the randomized phase 3 clinical trial of melphalan flufenamide compared to standard therapy control arm

Safety PMRs to Optimize Dosing

- Submit an integrated analysis evaluating the **fixed dose** of melphalan flufenamide in patients
- Conduct a **PK study** to determine the safe and appropriate dose in patients with CrCl $\leq$ 45 ml/min

PMR: Post Marketing Requirement; PK: pharmacokinetics, CrCl: creatinine clearance

OP-103 (OCEAN) Confirmatory Study



[i] Randomization stratified by age (<75 vs ≥75), number of previous lines (2 vs. 3-4), ISS Score (1 vs. ≥2)
* Patients aged ≥ 75 received Dexamethasone 20mg

RRMM: relapsed refractory multiple myeloma, PI: proteasome inhibitor, Pom: pomalidomide, IV: intravenous; PFS: progression-free survival, IRC: Independent Review Committee, OS: overall survival, ORR: overall response rate, ISS: International Staging System

Balanced Baseline Demographics

		MelDex (N=246)	PomDex (N=249)
Age	Median, years (range)	68 (41 - 91)	68 (39 - 87)
Age groups	< 65, %	39	34
	65 - < 75, %	46	50
	≥ 75, %	15	16
Race	Asian, %	3.3	5
	Black or African American, %	1.6	1.6
	White, %	91	89
Geographical Region	United States, %	4.8	6
	Rest of World, %	95	94
Creatinine Clearance	< 45 ml/min, %	2.4	4.0
	45-60 ml/min, %	18	23
	> 60 ml/min, %	79	73
Prior Lines of Therapy	2/3/4, %	46/31/23	45/36/19
Cytogenetics	High Risk*, %	34	35
ISS Score	I/II/III, %	48/38/13	50/38/12
Prior Therapies	Autologous Transplant, %	51	48
	CD38-monoclonal antibody, %	20	16
	Triple Class Refractory, %	16	12

MelDex: melphalan flufenamide and dexamethasone; PomDex: pomalidomide and dexamethasone; ISS: International Staging System; *High risk cytogenetics by FISH include t(4;14), t(14;16), deletion 17p, gain 1q (+1q), gain (1q21), t(14,20)

Major Issues

- **Potential detriment in OS**
  - Median OS 5.3 months shorter in melphalan flufenamide arm
  - Higher rates of deaths in the melphalan flufenamide arm
  - Higher rates of severe adverse events, hemorrhage and cytopenia
- Failure to demonstrate PFS benefit
- Lack of an appropriate dose

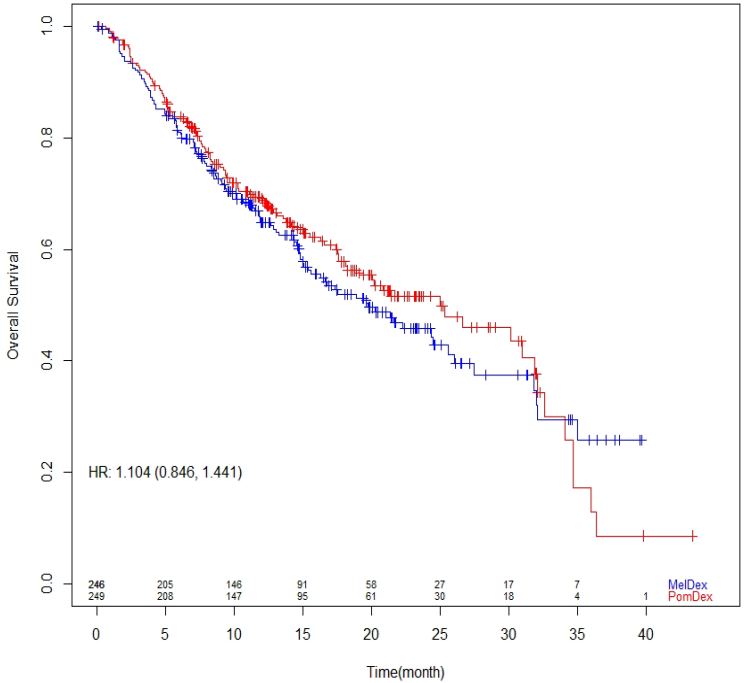
OS: overall survival; PFS: progression-free survival

OCEAN Overall Survival

	MelDex (N=246)	PomDex (N=249)
Death Events	117 (47.6%)	108 (43.4%)
Median OS, months (95% CI)	19.7 (15.1-26.6)	25 (18.1-31.9)
HR (95% CI)	1.104 (0.846 – 1.441)	

Median OS 5.3 months shorter in melphalan flufenamide arm

Data cut-off Feb 3, 2021



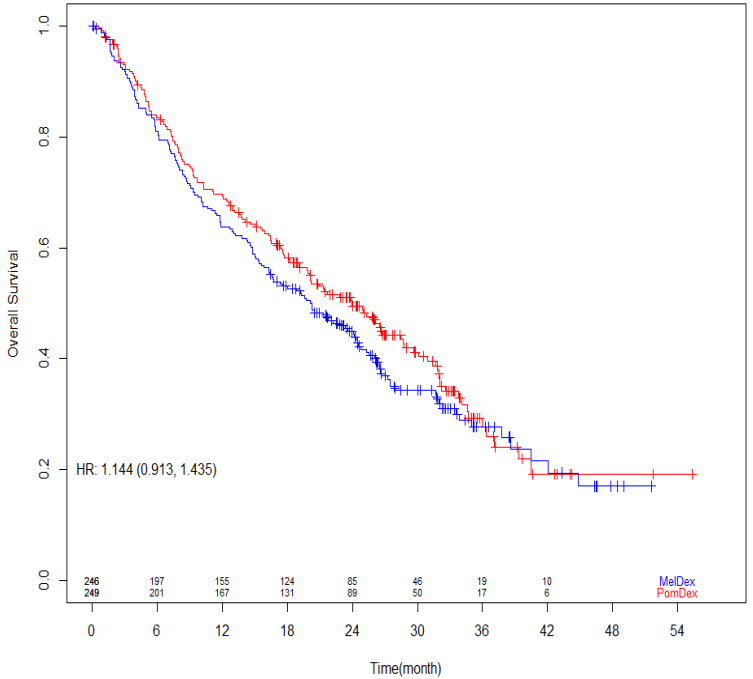
OS: overall survival; HR: hazard ratio; CI: confidence interval

OCEAN Overall Survival Updated

Data cut-off Feb 3, 2022

	MelDex (N=246)	PomDex (N=249)
Death Events	162 (65.9%)	147 (59%)
Median OS, months (95% CI)	20.2 (15.8-24.3)	24.0 (19.1-28.7)
HR (95% CI)	1.144 (0.913 – 1.435)	

Detriment in OS with longer follow-up



OS: overall survival; HR: hazard ratio; CI: confidence interval

Sponsor's Contention

- OS results are not indicative of a specific toxicity signal
- OS results driven primarily by results in the transplant subgroup, mostly patients with a TTP within 36 months of transplant
- For pomalidomide (and IMiDs) there is an OS effect modification based on age

OS: overall survival; TTP: time to progression; IMiDs: immunomodulatory drugs

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Deaths- OCEAN Safety Population

	MelDex N = 228 %	PomDex N = 246 %
Total Deaths	47	43
Progressive Disease	26	22
Adverse Event	10	11
Other	4.8	4.5
Unknown	6	6
Deaths within 30 days after last dose	10	13
Adverse event	7	7
Deaths beyond 60 days after last dose	31	25
Progressive Disease	20	17
Other	4.4	2.8
Unknown	6	5
Adverse Event	1.3	0.4

OCEAN Safety

	MelDex N= 228 %	PomDex N= 246 %
Any Treatment-Emergent Adverse Event (TEAE)	99	98
Grade 3-4 TEAEs	90	74
Grade 5 TEAEs	12	13
Serious TEAEs	42	46
Dose Modifications		
Drug discontinued due to TEAEs	26	22
Dose reduced due to TEAEs	47	15
Drug interrupted due to TEAEs	60	44

Treatment-Emergent Adverse Events

TEAEs >10% with >5% difference between groups	MelDex N = 228 N (%)		PomDex N = 246 N (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Blood and Lymphatic System				
Thrombocytopenia*	97	81	62	14
Anemia*	90	44	65	19
Neutropenia*	94	74	91	61
Gastrointestinal Disorders				
Diarrhea	14	1.3	9	0.8
Nausea	13	0.4	7	0.4
Infections and Infestations				
Pneumonia	16	7	24	13
Vascular Disorders				
Hemorrhage	16	2.2	6.5	0.4

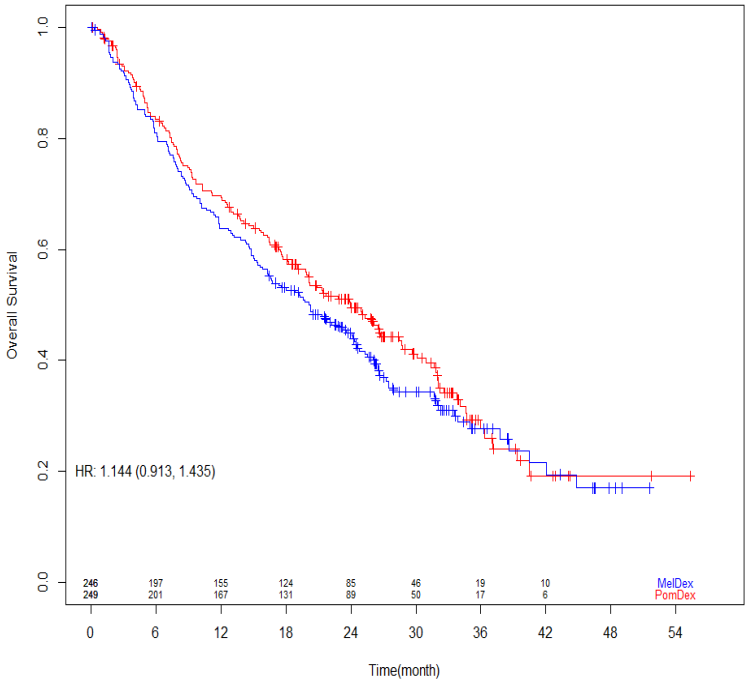
TEAE: treatment emergent adverse events
* ADLB dataset

Decreased Overall Survival in MelDex Arm

	MelDex (N=246)	PomDex (N=249)
Death Events	162 (65.9%)	147 (59%)
Median OS, months (95% CI)	20.2 (15.8-24.3)	24.0 (19.1-28.7)
HR (95% CI)	1.144 (0.913 – 1.435)	

OS is both an efficacy and safety endpoint

Data Cut-Off :03Feb2022



OS: overall survival; HR: hazard ratio; CI: confidence interval

Sponsor's Contention

- OS results are not indicative of a specific toxicity signal

- **OS results driven primarily by results in the transplant subgroup, TTP <36 months**

- For pomalidomide (and IMiD) there is an OS effect based on age

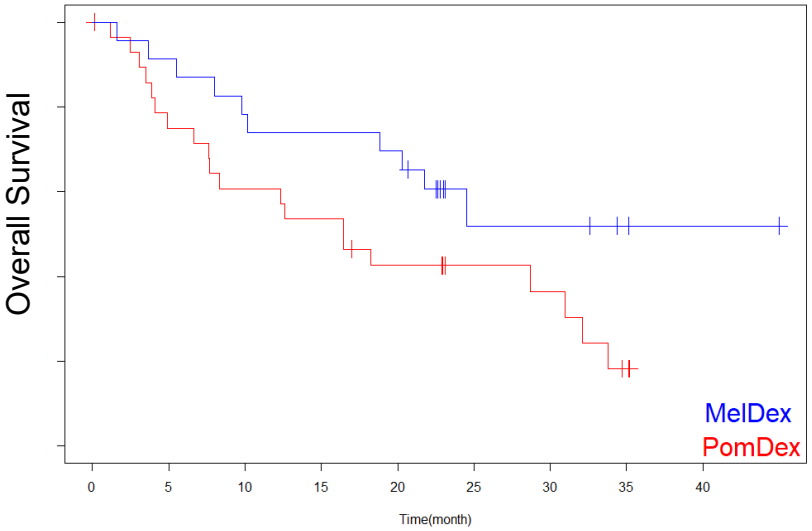
OS: overall survival; TTP: time to progression; IMiD: immunomodulatory drug

Subgroup Limitations

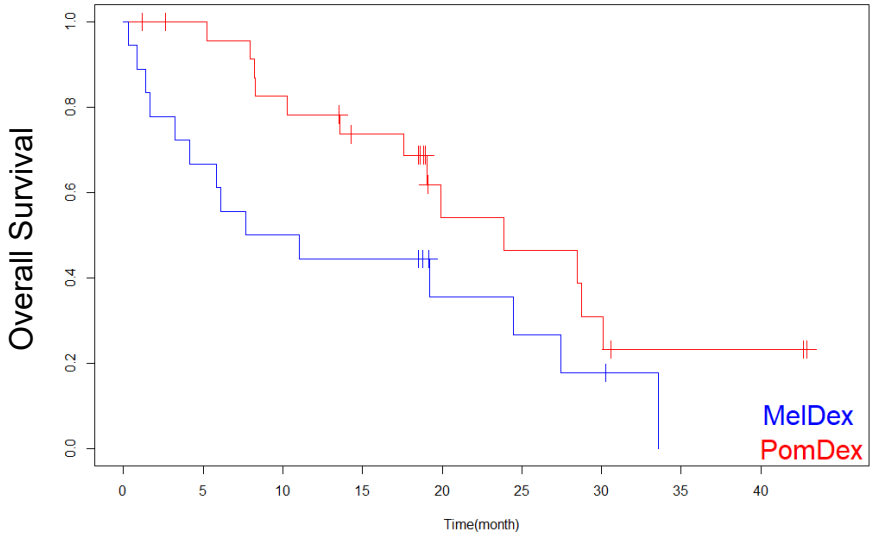
- Subgroups were not prospectively included in the statistical analysis plan with control of Type I error
- Subgroup analyses can be used to assess consistency of the treatment effect
- Cannot be used to conclude a treatment benefit in a subgroup

Limitation of Subgroup Analyses

Randomized in March



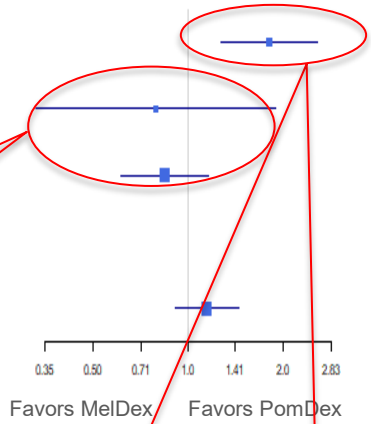
Randomized in July



A post hoc example leading to false conclusions

Overall Survival: Subgroup Analysis

Subgroup	Melflufen (death/N)	Pomalidomide (death/N)	HR(95%CI)
ASCT TTP 36 months			
TTP<36 months	75/101	56/101	1.8(1.27,2.55)
TTP >=36 months	12/24	10/19	0.79(0.33,1.89)
No ASCT	75/121	81/129	0.84(0.61,1.15)
Overall			1.14 (0.91, 1.44)



No difference seen between treatments in patients without prior ASCT and TTP ≥ 36 months

OS with melphalan flufenamide inferior in patients with TTP < 36 months

Abbreviations: HR: hazard ratio; ASCT: autologous stem cell transplant, TTP: time to progression, MelDex: Melphalan flufenamide and dexamethasone, PomDex: pomalidomide and dexamethasone

TTP vs Time Since Transplant

- TTP
  - Defined as the time from transplant date to progression date after the transplantation
- Time Since Transplant
  - Defined as time since transplant date to randomization on the OCEAN trial

TTP: time to progression

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 of transplant	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)

OS: overall survival; CI: confidence interval; Data Cut-Off Date: 03FEB2022

Time To Progression vs Time Since Transplant

Time to progression

	MelDex N=246 n	PomDex N=249 n	OS HR 95% CI
< 36 months	101	101	1.28 (0.92-1.77)
≥ 36 months	24	19	0.79 (0.33-1.89)

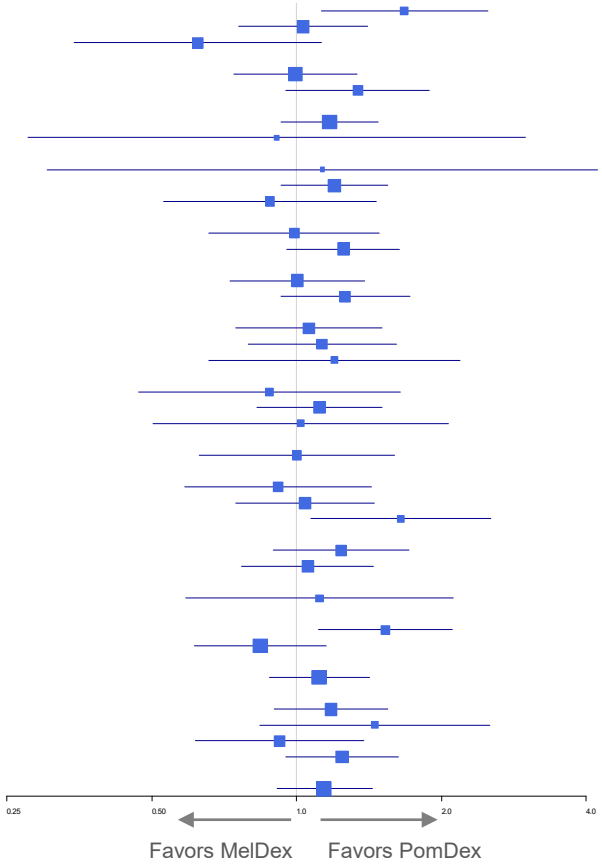
Time since transplant

	MelDex N=246 n	PomDex N=249 n	OS HR 95% CI
< 36 months	54	47	2.07 (1.16, 3.69)
≥ 36 months	71	73	1.28 (0.74, 2.22)

OS: overall survival; CI: confidence interval; Data Cut-Off Date: 03FEB2022

Subgroups Consistent with OS in ITT Population

Subgroup	Melflufen (d/N)	Pomalidomide (d/N)	HR(95%CI
Age			
<65	63/96	40/85	1.68(1.13,2
65-74	79/113	82/125	1.03(0.76,1
>=75	20/37	25/39	0.62(0.35,1
Sex			
Male	91/139	86/140	1(0.74,1.34
Female	71/107	61/109	1.34(0.95,1
Race			
White	152/224	134/222	1.17(0.93,1
All Other Races	5/13	6/17	0.91(0.28,2
Region			
USA	4/11	5/15	1.13(0.3,4.2
Europe	130/180	110/176	1.2(0.93,1.5
ROW	28/55	32/58	0.88(0.53,1
ECOG			
0	51/90	44/92	0.99(0.66,1
1-2	111/156	103/157	1.25(0.96,1
Prior lines			
2	77/114	70/111	1(0.73,1.39
3-4	85/132	77/138	1.26(0.93,1
ISS			
I	63/112	62/119	1.06(0.75,1
II	64/88	58/95	1.13(0.79,1
III	23/28	22/29	1.2(0.66,2.1
R-ISS			
I	19/50	22/58	0.88(0.47,1
II	90/130	82/134	1.12(0.83,1
III	16/17	16/18	1.02(0.5,2.(
Cytogenetics			
High Risk	37/54	34/51	1(0.63,1.6)
Creatinine clearance			
<60	33/50	46/68	0.92(0.59,1
60 - 90	76/119	66/112	1.04(0.75,1
>=90	52/76	35/69	1.65(1.07,2
BSA			
Below Median	74/116	73/128	1.24(0.89,1
Above Median	86/126	71/117	1.05(0.77,1
EMD			
Yes	21/30	18/26	1.12(0.59,2
Stem cell transplant			
Yes	87/125	66/120	1.53(1.11,2
No	75/121	81/129	0.84(0.61,1
Lenalidomide exposure			
Last line refractor	141/213	129/217	1.11(0.88,1
Refractory status			
PI refractory	111/163	98/163	1.18(0.9,1.5
aCD38 refractory	34/48	21/39	1.46(0.84,2
Alkylator refractory	48/78	48/75	0.92(0.62,1
Not alkylator refractory	114/168	99/174	1.24(0.95,1
Overall			1.14 (0.91,



OS; overall survival; ITT: intent to treat; d: deaths; N: number; ROW: rest of the world; ECOG: Eastern Cooperative oncology group; ISS: International staging system; HR: hazard ratio; CI: confidence interval; Data Cut-Off Date: 03FEB2022

Sponsor's Contention

- OS results are not indicative of a specific toxicity signal
- OS results driven primarily by results in the transplant subgroup, TTP <36 months
- **For pomalidomide (and IMiDs) there is an OS effect modification based on age**

OS: overall survival; IMiD: immunomodulatory drug

OS Effect Modification

- The OCEAN trial was not designed to compare or evaluate the effect of pomalidomide treatment in the various age subgroups evaluated by the sponsor.

- The Sponsor's within treatment arm comparisons of age groups are inappropriate and do not provide information on treatment effect of the study drug.

FDA does not agree with the sponsor’s claim of an IMiD age interaction

OS: overall survival; IMiD: immunomodulatory drug

FDA Exploratory Analysis on OS

OCEAN study

- Multiple factors other than those suggested by the sponsor can be found to explain the variability in OS.
- The post-hoc models are **unstable** and results rely on the model being used.
- Exploratory analyses indicated that **different modeling approaches yielded different results.**
- However, this is considered hypothesis generation and not suitable for making conclusions.

Modification of OS Effect by Age in IMiD Trials

- The age cutoff used for the sponsor's analysis is arbitrary and post hoc

- FDA conducted an analysis of age interaction with treatment in IMiD trials
  - The FDA exploratory analysis did not indicate that there was a significant interaction term between age and IMiD treatment

- Even if this post hoc evaluation of age was valid, **it does not support a determination that melphalan flufenamide is safe and effective.**

OS: overall survival; IMiD: immunomodulatory drug

Evaluation of OS Effect Modification Summary

- The sponsor's claim of "heterogeneity" in OS cannot be adequately evaluated without a prospectively designed trial

- The findings are based on exploratory post hoc analyses that do not address the finding of potential OS detriment in the prospectively defined ITT population

- The OCEAN study does not provide evidence that melphalan flufenamide is safe and effective in the ITT population under study

OS: overall survival; ITT: intent to treat population

Overall Survival Concerns

- Detriment in overall survival indicating potential harm
- The survival detriment is seen across multiple subgroups
- Post hoc subgroup analyses can be hypothesis generating, not confirmatory

Major Issues

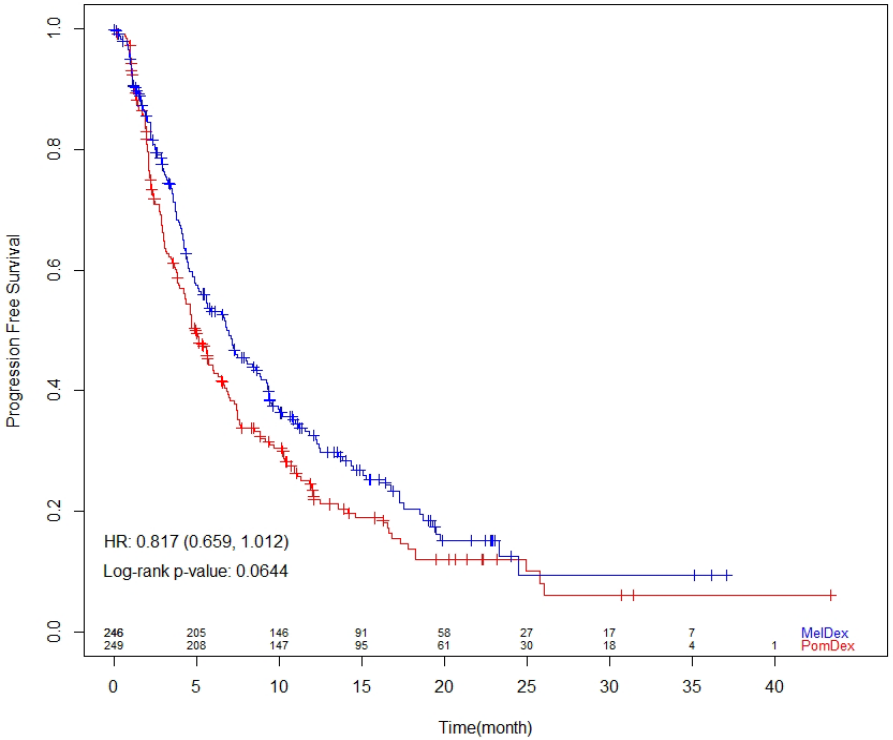
- Potential detriment in OS
- **Failure to demonstrate PFS benefit**
  - Primary PFS results did not meet prespecified statistical superiority
  - Worse OS negates any observed PFS improvement
- Lack of an appropriate dose

PFS: progression-free survival; OS: overall survival

Original PFS Results

	MelDex (N=246)	PomDex (N=249)
Median PFS, 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	

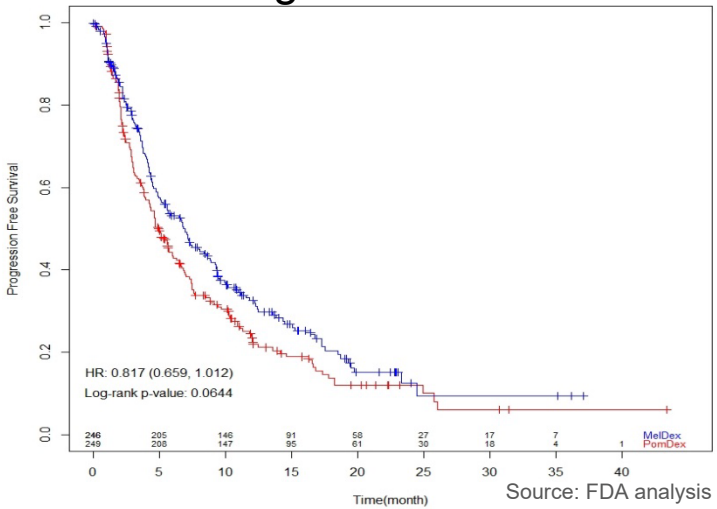
No statistical difference in PFS



PFS: progression-free survival; HR: hazard ratio; CI: confidence interval

OCEAN Revised PFS Results

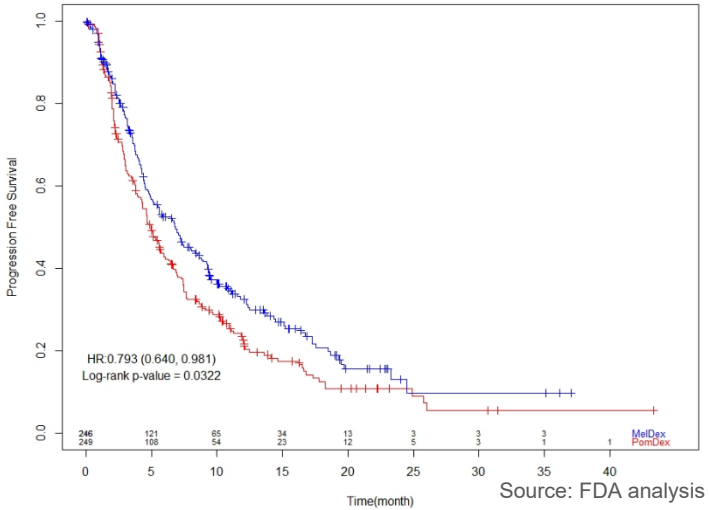
Original Results



On June 9th, 2021 the Sponsor submitted initial topline data including non-significant PFS results

HR 0.817 (95% CI: 0.659, 1.012), p =0.0644

Revised Results



On July 6th, 2021, the Sponsor submitted revised PFS results

HR 0.793 (95% CI: 0.640, 0.981), p = 0.0322

PFS: progression-free survival; HR: hazard ratio; CI: confidence interval

OCEAN Revised PFS Results

Assessment	Difference in Median PFS	HR (95% CI)	p-value
Sponsor's Original Results	2.0 months	0.817 (0.659, 1.012)	0.0644
FDA's Assessment of Original Using FDA's Censoring Rules*	1.7 months	0.833 (0.665, 1.044)	0.1122
Sponsor's Revised Assessment	1.9 months	0.793 (0.640, 0.981)	0.0322
FDA's Reassessment Using Sponsor's Censoring Rules	1.9 months	0.796 (0.642, 0.985)	0.0359
FDA's Reassessment Using FDA's censoring Rules*	1.8 months	0.820 (0.654, 1.027)	0.0837

* FDA's censoring rules censor all unconfirmed PD

PFS: progression-free survival; HR: hazard ratio; CI: confidence interval

Overall Response Rate and Durability

	MelDex (N=246)	PomDex (N=249)
ORR (95% CI)	32.1% (26.3 – 38.2)	26.5% (21.1 – 32.4)
Responses, n (%)	79 (32.1%)	69 (26.5%)
CR	5 (2.0%)	3 (1.2%)
sCR	2 (0.8%)	-
VGPR	25 (10.2%)	19 (7.6%)
PR	47 (19.1%)	47 (18.9%)
Median DOR, months, (95%CI)	11.2 (8.5-17.5)	11.1 (8.4-16.3)
Difference of ORR	5.6% (-2.8, 14.1)	

No difference in ORR or DOR

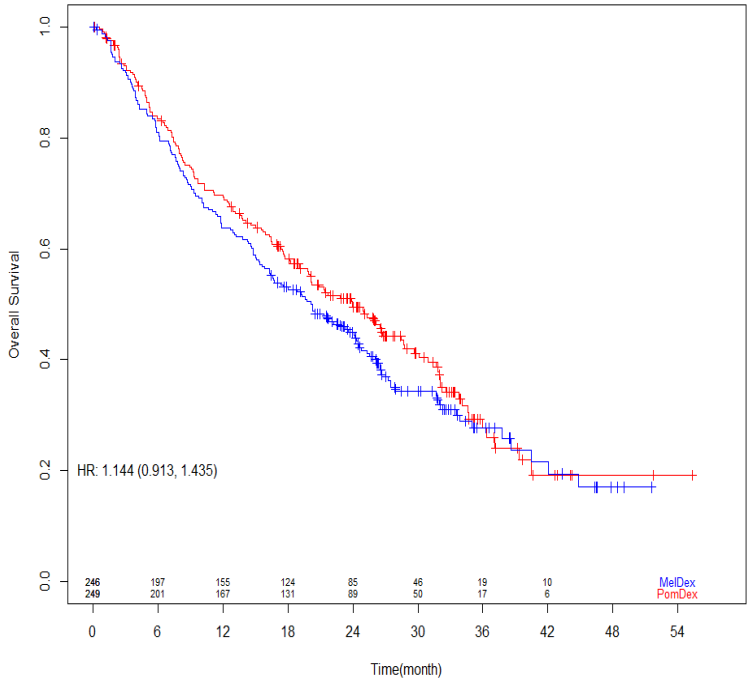
ORR: overall response rate, CI: confidence interval, CR: complete response, sCR: stringent complete response, VGPR: very good partial response, PR: partial response

Conclusion

	MelDex (N=246)	PomDex (N=249)
Death Events	162 (65.9%)	147 (59%)
Median OS, months (95% CI)	20.2 (15.8-24.3)	24.0 (19.1-28.7)
HR (95% CI)	1.144 (0.913 – 1.435)	

Potential detriment in OS

Data Cut-Off Date:03Feb2022



OS: overall survival; HR: hazard ratio; CI: confidence interval

Major Issues

- Potential detriment in OS
- Failure to demonstrate PFS benefit
- **Lack of an appropriate dose**
  - Flat 40 mg dose is poorly tolerated
  - Limited dose exploration in early clinical trials
  - Significant safety concerns with high melphalan exposure

Limited Dose Exploration

- Phase 1/2 study (O-12-M1)
  - 40 mg identified as Maximum Tolerated Dose
  - Lower doses/alternative dosing regimens not explored
- Pivotal Phase 2 Study (OP-106)
  - No PK or exposure-response analyses conducted to support the proposed 40 mg dose

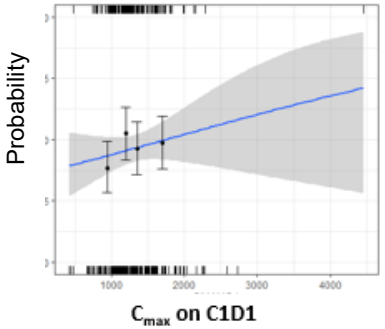
Study O-12-M1

Starting Dose	Total Patients	Patients with PK
15 mg	4	1
25 mg	7	2
40 mg	58	8
55 mg	6	1

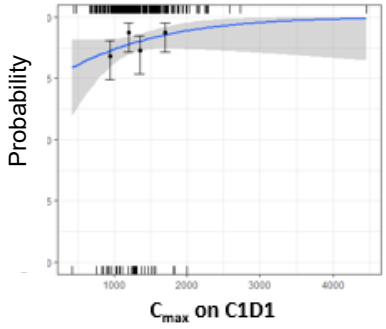
PK = Pharmacokinetic.

Exposure-Response Relationships for Safety

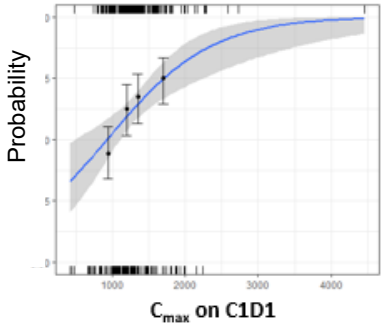
Grade ≥3 Anemia



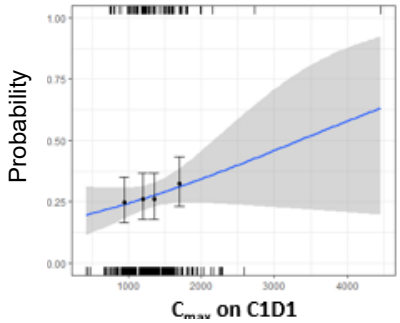
Grade ≥3 TEAE



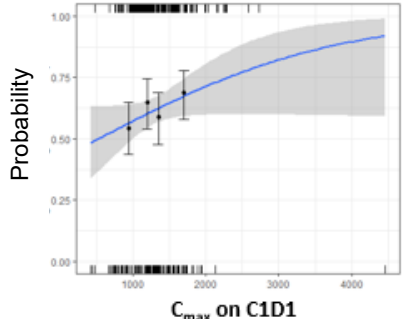
Grade ≥3 Leukopenia



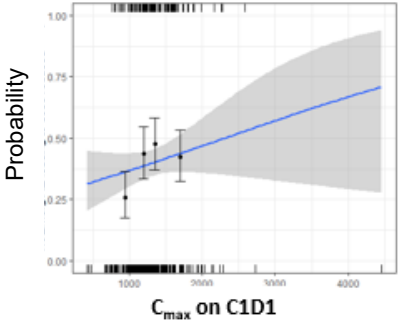
Drug discontinuation



Dose interruption



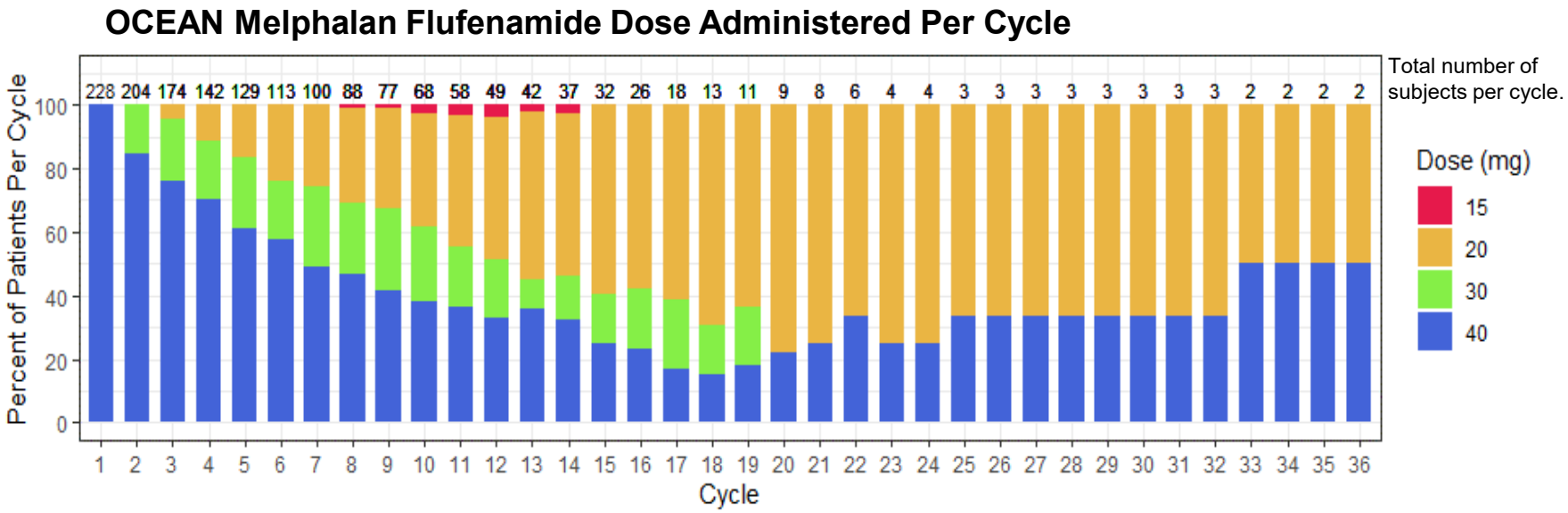
Dose reduction



No exposure-response relationships for efficacy observed.

www.fda.gov Exposure-Response safety conducted in all patients with safety data (n=321) from O-12-M1, OP-107, and OP-103 (OCEAN).
C1D1 = Cycle 1 Day 1; C_{max} = maximum concentration of melphalan; TEAE= treatment emergent adverse event.

Flat 40 mg Dose is Poorly Tolerated



Higher Exposure at Lower Body Weights

- Exposure has significant association with BSA and body weight
- High PK variability

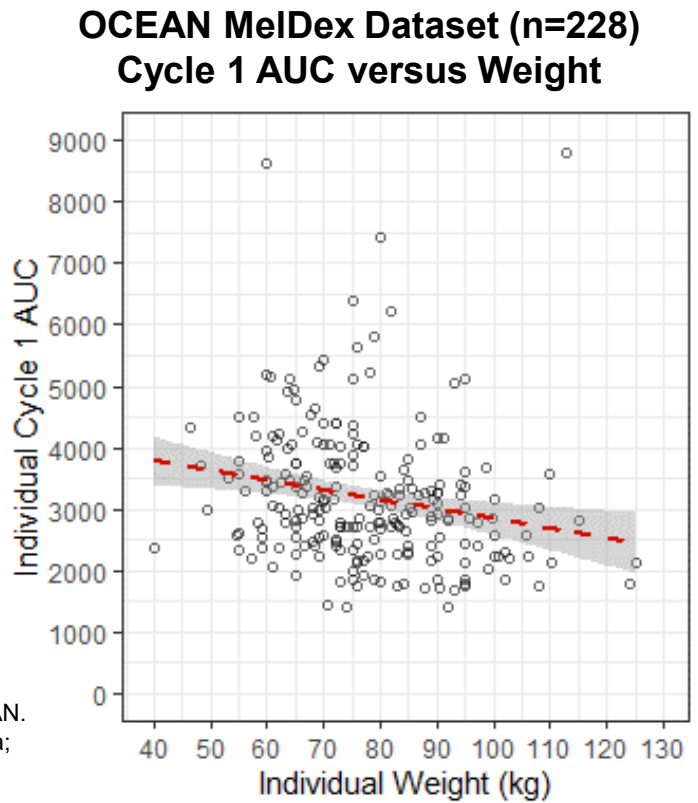
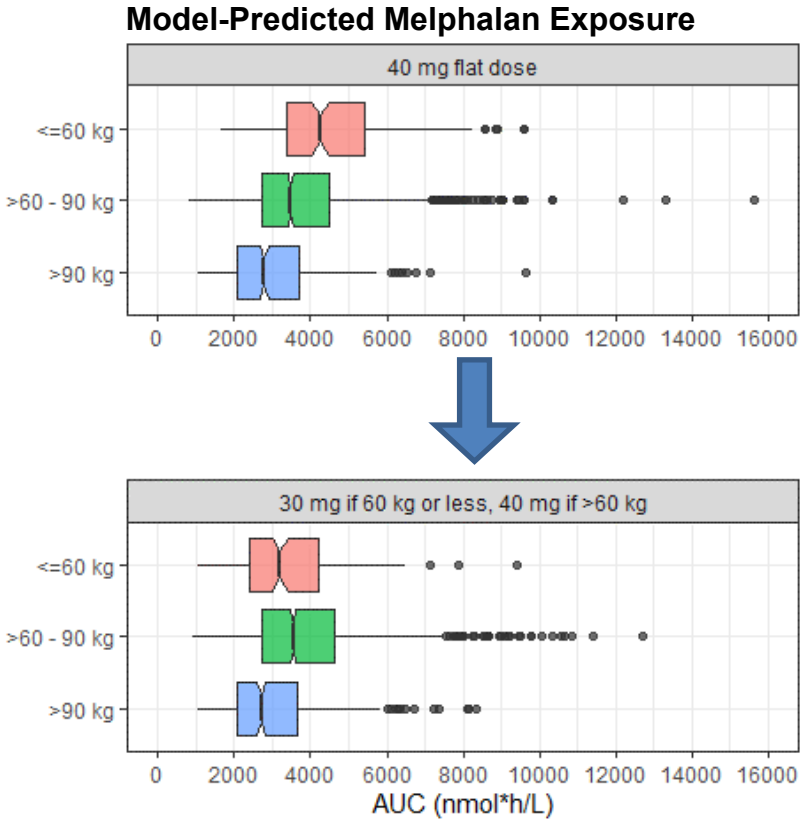


Figure displays melphalan exposure following 40 mg melphalan flufenamide dosing in OCEAN.
AUC = Melphalan area-under-the-concentration-versus-time curve; BSA = body surface area; MelDex = melphalan flufenamide plus dexamethasone; PK = pharmacokinetic.

Exposure-Matching to 40 mg

30 mg in ≤60 kg patients attempts to match exposure with 40 mg in 60 to 90 kg patients.

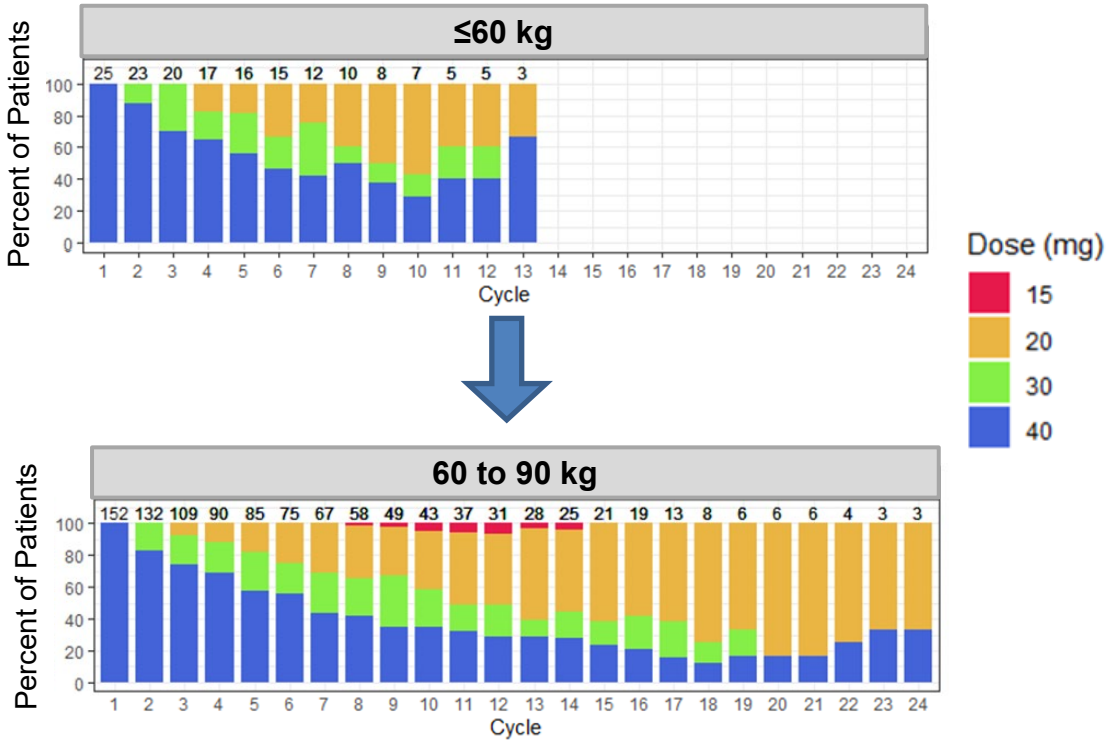


AUC = Melphalan area-under-the-concentration-versus-time curve.

30 mg starting dose for ≤60 kg is not justified

- <u>All weights</u> had tolerability issues with 40 mg
- 30 mg for ≤60 kg expected to match >60 kg patients at 40 mg
- Does not address issue with overall population
  - 40 mg is poorly tolerated

Melphalan Flufenamide Doses in OCEAN Per Cycle by Weight Category



Number of subjects per weight category per cycle displayed at top of each column.

Conclusions for Dosing

- Fixed 40 mg dose is poorly tolerated and exposure is too high
- High exposure (Cmax, AUC) correlates to high rates of grade ≥3 toxicities
  - No relationship between exposure and efficacy
- 30 mg dose for ≤60 kg to match exposure of 40 mg dose in >60 kg
  - Proposed dosing not justified
  - Does not address poorly selected 40 mg dose
- Lower doses and dosing by body size or weight warrants further study

AUC = Melphalan area-under-the-concentration-versus-time curve; Cmax = maximum concentration of melphalan.

Additional Issues

- Interpreting the results to the currently indicated population

- Inadequate representation of U.S. multiple myeloma population

Patients Meeting Current Indication

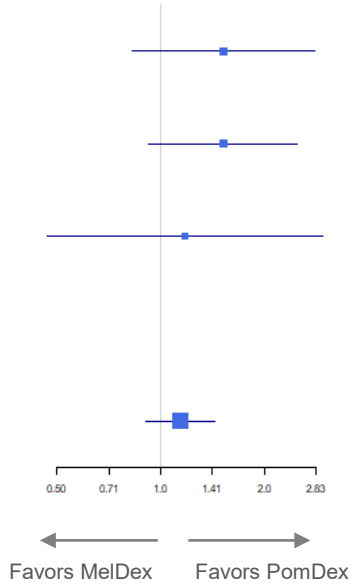
Indication: Melphalan flufenamide in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received **at least 4 prior lines** of therapy and whose disease is **refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody.**

OCEAN Disease Characteristics	MelDex N = 246 %	PomDex N = 249 %	
4 Prior lines of treatment	23	19	
Triple class refractory (TCR)*	16	12	
4 prior lines + TCR	8	4.4	= 6%
Lenalidomide refractory	100	100	
Pomalidomide refractory	0	0	
Proteasome inhibitor refractory	66	65	
Anti-CD38 refractory	20	16	

Triple class refractory = refractory to a proteasome inhibitor, immunomodulatory agent, and anti-CD38

Interpretation of OS Results to the Indicated Population

Subgroup	Melflufen (death/N)	Pomalidomide (death/N)	HR(95%CI)
TCR	30/39	16/30	1.52(0.83,2.81)
4 Prior Lines	39/56	26/48	1.52(0.92,2.5)
TCR & 4 Prior Lines	14/19	7/11	1.17(0.47,2.96)
Overall	162/246	147/249	1.14 (0.91, 1.44)



OS: overall survival; TCR: triple class refractory; Data Cut off: 03FEB2022

Inadequate Representation of U.S. Multiple Myeloma Population

OCEAN	MelDex (N=246)	PomDex (N=249)	Total (N=495)
Age, median (range)	68 (41 - 91)	68 (39 - 87)	66.4 (39 – 91)
Age groups, %			
< 65	39	34	37
65 - < 75	46	50	48
≥ 75	15	16	15
Race, %			
Asian	3.3	5.2	4.2
Black	1.6	1.6	1.6
White	91	89	90
Ethnicity, %			
Hispanic or Latino	3.3	2	2.6
Geographical Region, %			
Europe	73	71	71
Rest of World	22	23	23
United States	4.8	6.1	5.5
Prior Therapy, %			
anti-CD38	20	16	18

Conclusions

- Available evidence suggests an unfavorable benefit/risk of melphalan flufenamide
  - OS results indicate a safety concern
  - PFS results indicate lack of confirmed clinical benefit
  - Flat 40 mg dose is poorly tolerated

- Further studies are required to define the benefit/risk of melphalan flufenamide

OS: overall survival; PFS: progression-free survival

Discussion Topic

Discuss the benefit-risk profile of melphalan flufenamide for the currently indicated patient population considering the results of the confirmatory OCEAN trial

Voting Question

Given the potential detriment in overall survival, failure to demonstrate a progression-free survival benefit, and lack of an appropriate dose, is the benefit risk profile of melphalan flufenamide favorable for the currently indicated patient population?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ADMINISTRATION

Back Up Slides

Active comparator trials for multiple myeloma

Trial	Median PFS	PFS HR (95% CI) p value	OS HR (95% CI) P value
ENDEAVOR trial Kd vs Vd	Kd 18.7 mo Vd 9.4 months	0.533 (0.437, 0.651) P (1-sided) < .0001	0.79 (0.65, 0.96) P=0.01
FIRST trial Rd Continuous# vs Rd18^ vs MPT	Rd Continuous 25.5 mo Rd18 20.7 mo MPT 21.2 mo	Rd Continuous vs MPT 0.72 (0.61, 0.85); <0.0001* Rd Continuous vs Rd18 0.70 (0.60, 0.82) Rd18 vs MPT 1.03 (0.89, 1.2)	Rd Continuous vs MPT 0.75 (0.62, 0.90) Rd Continuous vs Rd18 0.91 (0.75, 1.09) Rd18 vs MPT 0.83 (0.69, 0.99)

*For the efficacy analysis of all endpoints, the primary comparison was between Rd Continuous and MPT arms
Rd Continuous given until documentation of progressive disease
^ Rd given for ≤ 18 cycles
K: carfilzomib; d: dexamethasone, V: bortezomib; PFS: progression-free survival; HR: hazard ratio; CI: confidence interval; R: lenalidomide, d:dexamethasone, M: melphalan; P: prednisone; T: thalidomide.

Statistical Analysis Plan (Version 3.0, 29 April 2021)

Analyses by Subgroups (Section 9.5.6)

Exploratory analyses of subgroups are planned to evaluate the robustness of results. PFS, ORR, DOR, OS, CBR, duration of clinical benefit, best confirmed response, TTR, and TTP will also be summarized for the following bulleted subgroups. In addition, forest plots presenting the hazard ratio and 95% confidence interval for efficacy endpoints PFS, DOR, OS, TTR, TTP, and DOCB will be provided for the following subgroups. The summaries will be based on the Full analysis set.

- Age
  - <65, ≥65 years
  - <75, ≥75 years
- Sex (male, female)
- BSA (below or above median BSA for FAS)
- Race (White, All Other Races)
- Geographic region (United States of America, Europe, Rest of World)
- Number of prior regimens (2, 3-4)
- ISS at baseline (I, II or III)
- R-ISS at baseline (R-I, R-II or R-III)
- Refractory to lenalidomide in last line versus refractory in earlier line
- Refractory status:
  - Refractory to an alkylator (yes, no)
  - Refractory to an anti CD38 mAb (yes, no)
  - Refractory to a PI and IMiD but not to an anti CD38 mAb (yes, no)
- Presence of Extramedullary Disease at Baseline (yes, no)
- Prior autologous stem cell transplant (yes, no)
- Maximum plasma cell involvement (%) at baseline, as assessed with bone marrow assessment (<30, 30 - <60, ≥60)

PFS: progression-free survival; ORR: overall response rate; DOR: duration of response; OS overall survival; CBR: clinical benefit rate; TTR: time to response; TTP: time to progression; DOCB: duration of clinical benefit; BSA: body surface area; FAS: full analysis set; ISS: International Staging System; PI: proteasome inhibitor; IMiD: immunomodulatory drug

Statistical Analysis Plan (Version 4.0, 25 October 2021)

In addition to the above subgroup analyses, PFS, OS, and ORR will be summarized by time from prior autologous stem cell transplant to randomization at the following levels:

- <2.5 years
- 2.5 – 5 years
- <5 years
- >5 years
- No transplant