Oncologic Drugs Advisory Committee (ODAC) Meeting

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Drug name: Polatuzumab vedotin-piiq

Applicant: Genentech, Inc.

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 polatuzumab vedotin-piiq (BLA 761121/S008) 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.

Advisory Committee Briefing Materials: Available For Public Release

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Glossary

1L	first line
2L	second line
ABC	activated B-cell type
ADC	antibody-drug conjugate
AE	adverse event
ALK	anaplastic lymphoma kinase
AR	adverse reaction
AEPI	adverse events of particular interest
BICR	blinded independent central review
BLA	Biologics License Application
BOR	best overall response
BR	bendamustine and rituximab
BTD	Breakthrough Therapy Designation
CAR-T	chimeric antigen receptor T-cell
CCOD	clinical cut-off date
CHP	cyclophosphamide, doxorubicin, and prednisone
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free survival
DHL	double-hit lymphoma
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EFS_{eff}	event-free survival-efficacy
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 questionnaire
EOT	end of therapy
E-R	exposure-response
FACT/GOG-NTX	Functional Assessment of Cancer Treatment/Gynecologic Oncology Group-Neurotoxicity
FACT-Lym LymS	Functional Assessment of Cancer Therapy-Lymphoma Lymphoma Subscale
FCR	fear of cancer recurrence
FDG-PET	fluorodeoxyglucose positron emission tomography
GCB	germinal center B-cell type
G-CSF	granulocyte colony-stimulating factor
HGBL	high-grade B-cell lymphoma
HHV8	human herpesvirus 8

HR	hazard ratio
HRQoL	health-related quality of life
iDMC	independent Data Monitoring Committee
IND	Investigational New Drug Application
IPI	International Prognostic Index
IRC	Independent Review Committee
ITT	intent-to-treat
LBCL	large B-cell lymphoma
LYSA	The Lymphoma Study Association
LYSARC	The Lymphoma Academic Research Organisation
MedDRA	Medical dictionary of regulatory activities
MInT	MabThera International Trial
MMAE	monomethyl auristatin E
NALT	non-protocol anti-lymphoma therapy, new anti-lymphoma therapy
NCCN	National Comprehensive Cancer Network
NE	not estimable, not evaluable
NHL	Non-Hodgkin's Lymphoma
NOS	not otherwise specified
ODAC	Oncologic Drugs Advisory Committee
ORR	objective response rate
OS	overall survival
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
PMR	post marketing requirement
PN	peripheral neuropathy
Pola	polatuzumab vedotin-piiq
PRO	patient-reported outcomes
Q3W	every 3 weeks
R	rituximab
R-CHP	rituximab plus cyclophosphamide, doxorubicin, and prednisone
R-CHOP	rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	supplemental Biologics License Application
SCT	stem cell transplantation
SEER	Surveillance, Epidemiology, and End Results
TEAE	treatment-emergent adverse event
THL	triple-hit lymphoma
USPI	United States Package Insert, United States Prescribing Information

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1. Introduction

1.1 Purpose of the Meeting

The FDA's Position:
Polatuzumab vedotin-piiq in combination with bendamustine and rituximab (BR) received accelerated approval for the treatment of adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma, not otherwise specified (DLBCL NOS), after at least two prior therapies in June 2019. POLARIX (Study GO39942) is a confirmatory trial intended to verify the clinical benefit of polatuzumab vedotin. FDA is convening this Oncologic Drugs Advisory Committee (ODAC) meeting to discuss concerns arising from POLARIX, a randomized phase 3 trial evaluating the substitution of vincristine with polatuzumab vedotin in the R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen in patients with previously untreated large B-cell lymphoma (LBCL). The primary issues to be discussed include:

1. Modest progression-free survival benefit of polatuzumab vedotin + R-CHP (rituximab, cyclophosphamide, doxorubicin, and prednisone)
2. Overall survival results
3. Other efficacy endpoints
4. Heterogeneity of the study population.

The purpose of this meeting is to obtain the Advisory Committee's input regarding the benefit-risk of polatuzumab vedotin + R-CHP for patients with previously untreated LBCL, including DLBCL NOS, based on the POLARIX data.

1.1.1 Context for the Meeting

The FDA's Position:
Polatuzumab vedotin-piiq, a CD79b-directed antibody-drug conjugate, was granted accelerated approval on June 10, 2019, in combination with BR for the treatment of adult patients with R/R DLBCL NOS after at least two prior therapies. The approval was based on complete response (CR) rate and duration of response (DOR) in Study GO29365, a randomized, open-label trial that included a cohort of 80 patients with R/R DLBCL. Patients were randomized (1:1) to receive either polatuzumab vedotin in combination with BR (pola+BR) or BR for six cycles. At the end of therapy, the complete response (CR) rate was 40% (95% confidence interval [CI]: 25-57%) with pola+BR compared with 18% (95% CI: 7-33%) with BR alone.

POLARIX was intended to fulfill a post-marketing requirement (PMR), under accelerated approval regulations, to verify the clinical benefit of polatuzumab vedotin. POLARIX is a multicenter, randomized, double-blinded, placebo-controlled trial evaluating the substitution of vincristine with polatuzumab vedotin in the R-CHOP regimen as front-line therapy for LBCL, including DLBCL NOS. The study randomized 879 patients in a 1:1 ratio to receive polatuzumab

vedotin + R-CHP (pola+R-CHP) or R-CHOP. The primary endpoint was progression-free survival (PFS) superiority as assessed by investigators. The key secondary endpoints were modified event-free survival (also referred to as "EFS efficacy"), CR rate at the end of therapy by blinded independent central review (BICR), and overall survival (OS). POLARIX met its primary endpoint, with a statistically significant improvement in PFS with pola+R-CHP, but no improvement in CR rate or OS.

Newly diagnosed DLBCL is treated with curative intent, and standard first-line therapy cures approximately 60% of all cases. R-CHOP is the U.S. standard of care for DLBCL NOS and some other LBCLs.[1] This is based on the 2006 approval of rituximab in combination with CHOP for first-line therapy of DLBCL, which was supported by 3 randomized controlled trials, each demonstrating a statistically significant improvement in OS with the addition of rituximab (absolute improvement in 2-year OS, 9 to 11%).[2,3]

Based on the POLARIX results, a number of issues raise uncertainty about the benefit-risk of polatuzumab vedotin in this frontline, curative-intent setting. An overview of the major topics for discussion is next provided.

Major Topics

1. Modest PFS benefit of pola+R-CHP

Based on the Applicant's primary efficacy analysis, pola+R-CHP resulted in a modest PFS benefit over R-CHOP, with a hazard ratio (HR) of 0.73 (95% CI: 0.57, 0.95) and log-rank p-value of 0.0177 (two-sided α=0.05). The point estimates of 1-year and 2-year PFS rates differed by 4.1% and 6.5%, respectively. The difference in observed PFS rates is modest, and it is questionable whether this rate of difference is clinically meaningful. Although the modest PFS difference is in the setting of a substitution trial, these results must be considered along with the other efficacy results, OS results, and toxicity when considering the overall benefit-risk of polatuzumab in combination with R-CHP.

FDA conducted various sensitivity analyses to evaluate the robustness of the PFS result (Table 8). Regardless of the statistical approach, the upper bounds of the confidence intervals for the HR were near or greater than 1, and the largest calculated difference in 2-year PFS was 6.5%. Additionally, as mentioned in the sections below, the PFS benefit did not translate to a benefit in CR rate or OS.

2. Overall survival results

The final prespecified analysis of OS, with a median follow-up time of 39.7 months, did not demonstrate an improvement in OS for pola+R-CHP (HR 0.94; 95% CI: 0.67, 1.33). The Kaplan-Meier survival curves were similar for the pola+R-CHP and R-CHOP arms, but at some early timepoints, the OS rates were numerically lower in the pola+R-CHP arm (Figure 10). The HR for OS in the largest histological subgroup (DLBCL NOS) was 1.02 (Figure 28). While there is uncertainty associated with the point estimates due to low event rates, lack of improvement in

OS, particularly in the context of frontline therapy for LBCL, is a reflection of safety and efficacy and adds to the uncertainties in benefit-risk.

3. Other efficacy endpoints

Analyses of other efficacy endpoints, although supportive, have limitations.

- Modified EFS, an alpha-allocated secondary endpoint, was statistically significant in the pola+R-CHP arm, with a HR of 0.75 (95% CI: 0.58, 0.96; p-value = 0.0244). However, the treatment effect was modest, with the 2-year point estimate differing by 6.2%.
- The difference in CR rate by BICR was not statistically significant: 78.0% [95% CI: 73.8, 81.7] vs. 74% [95% CI: 69.7, 78.1] in the pola+R-CHP and R-CHOP arms respectively, with a p-value of 0.1557 (tested at 0.01 α allocation). The investigator-assessed ORRs were also similar (84.5% vs. 80.9%, respectively). The lack of improvement in CR rate raises further uncertainty about the treatment effect, particularly in the context of the modest PFS benefit with pola+R-CHP.
- Analyses of disease-free survival and duration of response suggested modest benefit with pola+R-CHP. These are not intention-to-treat (ITT) based analyses or controlled for Type I error, so are considered exploratory.

4. Heterogeneity of study population

Heterogeneity of the study population has the potential to impact the interpretability of the results. In total, 84% of the study population had DLBCL NOS, 11% had either HGBL NOS or HGBL with *MYC* and *BCL2* and/or *BCL6* translocations, and 5% had other LGBLs. More intensive regimens than R-CHOP are generally preferred in the U.S. for patients with HGBL (Table 29).

The treatment effect of pola+R-CHP appeared heterogeneous across non-Hodgkin lymphoma (NHL) subtypes. PFS HRs for DLBCL NOS, HGBL, and other LBCLs were 0.75, 0.48, and 1.93, respectively, and the OS HRs were 1.02, 0.42, and 1.89, respectively (Table 10).

Acknowledging that this is an exploratory post hoc evaluation with sample size limitations, the results tended to favor the pola+R-CHP for the HGBL subgroup, had variable results in DLBCL NOS, and favored the control arm for the other LBCL subgroup. When considering CR rates, pola+R-CHP appeared to benefit the HGBL subgroup (Table 10).

For DLBCL NOS, results across all of these endpoints were either marginal or not indicative of a positive treatment effect. In patients with DLBCL NOS (n=740, 84%), the OS HR was 1.02, with an estimated 1-year OS of 91.8% in the pola+R-CHP arm and 95.5% for the R-CHOP arm (Figure 11). However, for all of these results, there is high uncertainty in the point estimates as evidenced by the wide confidence intervals.

Conclusion

The results from the intended confirmatory study, POLARIX, require careful consideration to assess the benefit-risk profile of polatuzumab vedotin in the Applicant's proposed frontline setting, where patients are treated with curative intent.

The Applicant's Position:

Diffuse large B cell lymphoma (DLBCL) is one of the most common blood cancers among adults in the U.S. It is a fast-growing, aggressive disease with poor prognosis that results in death within months if left untreated. Based on advancements in clinical and pharmacological standard of care, today many patients can be cured of DLBCL. The highest likelihood of cure occurs with the first therapy and approximately 40% of those diagnosed are not cured with initial treatment and either have refractory disease or relapse. For lymphoma patients, disease progression and relapse are reported as their biggest concern and the burden of subsequent treatments adds risks and toxicities.

Over the last 20 years, there have been many unsuccessful efforts to try to build on the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as the only FDA-approved option for the first-line (1L) treatment of patients with DLBCL. Improving treatment options to cure more patients with 1L DLBCL remains a significant unmet medical need.

While there are potentially curative cellular therapies for treating refractory or recurring disease (autologous/allogenic stem cell transplant [SCT] or chimeric antigen receptor [CAR]-T cells), they offer lower chances of cure, are intensive, logistically challenging and cause significant morbidity and mortality. Patients who are ineligible for intensive cellular therapies are treated with non-curative palliative therapies. Ultimately for patients, increasing cure rates in the 1L setting, thereby sparing more patients from experiencing disease relapse and the burdens of additional therapies, is the most impactful way to address the unmet medical need in DLBCL.

The study GO39942 (referred to hereafter as POLARIX) assessed whether replacing vincristine in the R-CHOP regimen with polatuzumab vedotin could improve the outcome for patients in the 1L setting. POLARIX demonstrated that patients treated with polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (pola+R-CHP) have reduced risk of disease progression, disease relapse or death (PFS) by 27% relative to patients treated with R-CHOP (two sided p-value=0.0177). These results are statistically significant and clinically meaningful. Safety and tolerability were comparable between the regimens.

Based on the favorable benefit-risk observed in the POLARIX study, the Sponsor has applied for FDA approval in the 1L setting.

POLIVY® (polatuzumab vedotin-piiq; pola) is FDA-approved for the treatment of patients with relapsed/refractory DLBCL after at least two prior therapies when used in combination with bendamustine and rituximab (BR). Polatuzumab vedotin received Breakthrough Therapy

Designation (BTD) from FDA for the treatment of patients with relapsed/refractory DLBCL in 2017. Since receiving accelerated approval in 2019, over 12,000 patients have been treated with polatuzumab vedotin.

Polatuzumab vedotin in combination with BR is approved in over 80 countries for use in relapsed/refractory DLBCL. On the basis of POLARIX, pola+R-CHP is also currently approved for the 1L treatment of DLBCL in over 50 countries, including in countries in Europe, UK, Canada, and Japan, and is currently recognized in practice guidelines including various compendia and the Spanish and German guidelines (Clinical Pharmacology 2022; Lexicomp 2022; Micromedex 2022; Spanish Guidelines 2022; German Guidelines 2022).

Polatuzumab vedotin is an antibody-drug-conjugate (ADC) comprised of an anti-CD79b monoclonal antibody conjugated with monomethyl auristatin E (MMAE), a microtubule inhibitor that is approximately 10 times more potent than vincristine. In the POLARIX trial, pola+R-CHP substitutes polatuzumab vedotin for vincristine (brand name Oncovin = O) in the R-CHOP regimen to deliver more potent microtubule inhibition directly to malignant cells by binding to CD79b that is ubiquitously expressed on DLBCL cells.

POLARIX is a multiregional study, with the U.S. as the highest enrolling country. It is being conducted in collaboration with the Lymphoma Study Association (LYSA), an independent cooperative group for lymphoma research based in France, Belgium, Portugal, and the Lymphoma Academic Research Organisation (LYSARC), the LYSA's clinical research operational structure. The POLARIX trial also has a Steering Committee of prominent global lymphoma experts, including members from the U.S. The LYSA and the Steering Committee were involved in the design and execution of POLARIX. FDA feedback was incorporated into the study design prior to protocol finalization and into the statistical analysis plan (SAP) used to analyze the primary and key secondary endpoints.

The hierarchy of statistical testing was: progression-free survival (PFS) (primary endpoint), followed by event-free survival efficacy (EFS_{eff}; defined in collaboration with FDA to reflect EFS events that are primarily due to efficacy reasons), followed by alpha split between overall survival (OS) and complete response rate (CR) at end of treatment.

This trial met its primary endpoint by demonstrating that pola+R-CHP reduced the risk of disease progression, disease relapse or death by 27% compared to R-CHOP (PFS HR 0.73 [95% CI 0.57, 0.95]; two-sided log-rank p-value=0.0177). This finding is both statistically significant and clinically meaningful.

Sensitivity analyses censoring PFS for non-protocol anti-lymphoma therapies (NALT) administered prior to disease progression to study therapy yielded similar results (PFS HR 0.74 [95% CI 0.57, 0.96]).

OS was a key secondary endpoint in POLARIX. As approximately 60% of 1L DLBCL patients are

cured, most patients will ultimately experience deaths unrelated to DLBCL. Consequently, Phase III trials powered for OS as an endpoint can take approximately 10 years to complete (Shi et al. 2018; Stathis et al. 2018). Accordingly, POLARIX was designed to evaluate PFS with limited OS power at the time of PFS readout. With approximately 40 months median follow up in POLARIX, the OS analyses are still immature as only 15% of patients enrolled had died, and event accrual has decelerated as the survival curve has flattened in both arms. When compared to R-CHOP, pola+R-CHP was associated with an HR for overall mortality of 0.94 [95% CI 0.67, 1.33; p=0.7326] that was not statistically significant. There is no indication of OS detriment with pola+R-CHP.

Given the expected immaturity of POLARIX's OS results to assess the treatment effect of pola+R-CHP, other pre-specified secondary endpoints take on greater weight to supplement the PFS observation as evidence of meaningful clinical benefit.

EFS_{eff} ($EFS_{efficacy}$; defined in collaboration with FDA as disease progression or relapse, death from any cause, initiation of any non-protocol anti-lymphoma therapy administered for efficacy, or biopsy-confirmed residual disease after treatment completion) represents another clinically relevant endpoint. In the POLARIX trial, patients assigned to pola+R-CHP experienced a statistically significant and clinically meaningful improvement in EFS_{eff} (HR 0.75 [95% CI 0.58, 0.96]; two-sided p-value=0.0244) when compared to those treated with R-CHOP.

Achieving CR at the end of treatment is an important milestone for 1L DLBCL patients. For CR to translate into cure, remission must be sustained. Thus, cure in DLBCL is best manifested by sustained remission that can be assessed with time-to-event endpoints such as PFS, EFS_{eff}, disease-free survival (DFS) and duration of response (DOR).

While not statistically significant (two-sided p-value=0.1557), CR rates at end of treatment were numerically higher with pola+R-CHP at 78.0% (95% CI 73.8, 81.7) versus R-CHOP at 74.0% (95% CI 69.7, 78.1). Similarly, objective response rates (ORR) at end of treatment were also numerically higher, with pola+R-CHP at 84.5% (95% CI 80.8, 87.8) versus R-CHOP at 80.9% (95% CI 76.9, 84.4). Notably, remissions were more sustained in patients treated with pola+R-CHP as evidenced by longer DFS (HR 0.70 [95% CI 0.50, 0.98]) and DOR (HR 0.74 [95% CI 0.56, 0.98]). These observations are consistent with the prolonged PFS and EFS_{eff} observed with pola+R-CHP.

In POLARIX, the overall safety profile of pola+R-CHP was comparable to R-CHOP. The fixed treatment duration in both arms limits the time for adverse events to occur while on treatment, and enables adverse events to resolve upon treatment completion. The types and incidence of adverse events of any grade or of Grade 3 or 4 were similar in the two study arms. Febrile neutropenia is an adverse event associated with many therapies used to treat hematologic malignancies and is commonly managed by hematologists/oncologists. The incidence of febrile neutropenia, and infections, were higher in the pola+R-CHP arm. However, comparable rates of fatal infections (1.4% vs 1.1%), study treatment discontinuations, dose reductions, and study treatment interruptions were observed between the two arms. Therefore, febrile neutropenia

did not exacerbate patient morbidity and mortality.

Patients reported comparable global health-related quality of life, with similar treatment-related symptoms and no negative impact on physical and role functioning. These observations provide patient experience context to the comparability of pola+R-CHP's safety profile with that of R-CHOP.

POLARIX provides substantial evidence of effectiveness and safety by demonstrating that pola+R-CHP provides a clinically meaningful benefit with a comparable safety profile to R-CHOP.

The FDA's Position:
Refer to the FDA's position in Section 1.1.1 (Context for the Meeting) regarding the main issues for discussion. FDA analysis of patient-reported outcomes is provided in Section 4 (Clinical Outcome Assessment Analyses).

1.2 Proposed Indication

The Applicant's Position:
"POLIVY® in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL)."

The FDA's Position:
FDA acknowledges the proposed indication. However, the Applicant's use of the term "DLBCL" in the proposed indication and throughout the Applicant's sections in this document refers to large B-cell lymphoma (LBCL) and encompasses histologies distinct from DLBCL, including high grade B-cell lymphoma (HGBL) with *MYC* and *BCL2* and/or *BCL6* rearrangements (also referred to as double hit or triple hit lymphoma), HGBL NOS, T-cell/histiocyte-rich LBCL, and anaplastic lymphoma kinase (ALK) positive LBCL. The DLBCL subtypes eligible for POLARIX were DLBCL NOS, Epstein-Barr virus (EBV) positive DLBCL, and human herpesvirus 8 (HHV8) positive DLBCL.

1.3 Regulatory History

The Applicant's Position:

1.3.1 Polatuzumab Vedotin Accelerated Approval in R/R DLBCL

Polatuzumab vedotin received Breakthrough Therapy Designation (BTD) in 2017 and accelerated approval in 2019 based on the results of the Phase Ib/II Study GO29365 that compared polatuzumab vedotin in combination with bendamustine and rituximab (pola+BR) against BR alone in patients with relapsed/refractory DLBCL who were not candidates for hematopoietic stem cell transplant.

The observation of OS improvement with pola+BR over BR in the randomized Phase II part of Study GO29365 supported the BTD request in 2017. At the time of the study's primary analysis,

the OS hazard ratio (HR) was 0.42 [95% CI 0.24, 0.75] with median OS improvement from 4.7 months with BR to 12.4 months with pola+BR (Sehn et al. 2020). Accelerated approval was granted based on the increase in CR rate at end of treatment from 15 percent with BR to 40 percent with pola+BR (p=0.012) (POLIVY® USPI). The indication for polatuzumab vedotin in relapsed/refractory DLBCL is:

> *POLIVY® (polatuzumab vedotin-piiq) in combination with bendamustine and a rituximab product is indicated for the treatment of adult patients with relapsed/refractory DLBCL, not otherwise specified, after at least two prior therapies.*

At the time of the accelerated approval in 2019, the Sponsor was conducting two Phase III trials in DLBCL as part of polatuzumab vedotin's overall clinical development in multiple B-cell malignancies. POLARIX was designed to be the registrational study for the treatment of patients with 1L DLBCL and was initiated in 2017 after having incorporated FDA feedback into the study design. POLARIX was based on a scientific rationale of replacing vincristine in R-CHOP with polatuzumab vedotin, which was hypothesized to improve the regimen by increasing efficacy with comparable toxicity. Study MO40598 (hereafter referred to as POLARGO) initiated in 2019 to test adding polatuzumab vedotin to a different backbone than BR for relapsed/refractory patients. The POLARGO protocol was reviewed by FDA and the study evaluates the safety and efficacy of adding polatuzumab vedotin in combination with rituximab plus gemcitabine plus oxaliplatin (R-GemOx) versus R-GemOx alone in patients with relapsed/refractory DLBCL (Appendix 1).

As POLARIX and POLARGO were both ongoing at the time of POLIVY's accelerated approval, FDA designated either study to fulfill the post marketing requirement (PMR) to verify clinical benefit in DLBCL. POLARIX is the Sponsor's earliest opportunity to fulfill the PMR as it read out in 2021 whereas POLARGO is actively enrolling patients and is not anticipated to read out until 2024.

The FDA's Position:

FDA agrees that, under accelerated approval regulations, PMRs were issued for two confirmatory trials to verify the clinical benefit of polatuzumab vedotin and either could serve to verify the clinical benefit.

1.3.2 Supplemental BLA (Indication Extension: 1L DLBCL)

The Applicant's Position:

The regulatory history of key interactions with FDA regarding the development of polatuzumab vedotin in combination with R-CHP in 1L DLBCL is summarized in Table 1.

Table 1 Regulatory History of Key Interactions with FDA Regarding the Development of Polatuzumab Vedotin in Combination with R-CHP in 1L DLBCL

Date	Regulatory History
4 Feb 2011	• IND 109409 Study May Proceed for the development of polatuzumab vedotin for the treatment of B-cell malignancies.
12 Dec 2016	**Orphan Drug Designation** • Polatuzumab vedotin was granted orphan drug designation for the treatment of DLBCL.
3 Apr 2017	**Proposed POLARIX Study Design** • Type B meeting to discuss the proposed Phase III study in 1L DLBCL. The Sponsor obtained agreement on the design of the proposed study, including study endpoints, target patient population, safety monitoring plan, and the statistical analysis proposal. FDA agreed with PFS as the primary endpoint, as well as with the key secondary endpoints prior to the conduct of the study. FDA expressed concerns that dose was selected based on a relatively narrow exposure range.
19 Jul 2017	• The Sponsor received a FDA non-hold comment related to POLARIX regarding the primary PFS analysis to follow all patients for a minimum of 24 months. SAP v2 (9 September 2020) was amended to incorporate this requirement (see Appendix 5).
1 Oct 2020	**Proposed Content and Format of the sBLA for 1L DLBCL** • Type C written feedback regarding the proposed content and format of the sBLA to enable regular approval for the proposed indication in 1L DLBCL. FDA agreed with most of the proposed content and format in the official written responses, and additional topics were clarified via correspondence submitted on 23 October 2020 and 8 December 2020. On 6 January 2021 FDA confirmed their agreement with the Sponsor's final proposal for content and format of the sBLA.
12 Oct 2020	**POLARIX Statistical Analysis Plan (SAP)** • All versions of the SAP were submitted to IND 109409. The FDA confirmed that the proposed content of SAP v3 was reasonable. All statistical analyses performed for the primary analysis were conducted under SAP v3. • On 2 December 2021, SAP v4 to introduce a second interim analysis of OS to include in the initial sBLA submission was submitted for FDA review.
24 Sep 2021	**Pre-sBLA meeting for 1L DLBCL** • Type B Pre-sBLA meeting to discuss the clinical trial results from POLARIX and obtain feedback on the acceptability of the results to form the basis of an sBLA for POLIVY in the proposed indication. FDA advised the Sponsor to provide more mature OS data, during review of the application, to rule out an overall detriment. Following the discussion, the Sponsor aligned with the FDA on the submission timing such that final OS data would be provided during the review and a second interim OS analysis would be provided in the initial sBLA submission.

DLBCL=diffuse large B-cell lymphoma; IND=Investigational New Drug Application; FDA=Food and Drug Administration; PFS=progression-free survival; OS=overall survival; SAP=statistical analysis plan; sBLA=supplemental Biologics License Application.

2. Efficacy

2.1 Description of Clinical Setting

2.1.1 DLBCL Overview

The Applicant's Position:

DLBCL is the most common type of aggressive lymphoma, accounting for 30% of all non-Hodgkin's Lymphoma (NHL). Approximately 27,000 people in the U.S. are diagnosed with DLBCL each year (Teras et al. 2016). DLBCL most commonly presents in older adults with a median age of presentation around 65 years. The clinical course can be debilitating due to constitutional symptoms, local symptoms of lymphadenopathy, end-organ damage from disease involvement, and bone marrow failure that may lead to infections, anemia, and thrombocytopenia.

Without treatment nearly all patients would be expected to die within 1 year (Flowers et al. 2010). Similarly, patients with residual disease after completing treatment will require prompt salvage therapy for disease control due to the aggressiveness of the disease. Most patients who progress or relapse will do so within 24 months of starting treatment (Maurer et al. 2018). Relapsed/refractory disease and its treatment remain a major cause of morbidity and mortality (Friedberg 2011; Sehn and Salles 2021).

Definition of High Risk in the 1L Setting

High-risk DLBCL groups can be defined by molecular subtype (germinal center B-cell type [GCB] vs. activated B-cell type [ABC]), specific genetic aberrations (MYC and BCL2 translocations, P53 dysfunction), protein expression (MYC, BCL2, BCL6, KI-67), and/or clinical parameters. Importantly high-risk features in one category (e.g. MYC and BCL2 translocations) can be found concurrently with a lower risk disease feature from another category (e.g. GCB).

While molecular features help to define higher and lower risk subtypes, clinical features are also integrated into risk assessment and tools for estimating prognosis. The International Prognostic Index (IPI; comprised of age, lactate dehydrogenase [LDH], stage, more than one extranodal site, and performance status) has been a standard clinical method for risk stratification (International NHL Project 1993). IPI retains prognostic significance across R-CHOP-treated patients and is a useful predictor of outcomes (Ziepert et al. 2010; Nowakowski et al. 2016).

Based on data from historical 1L randomized trials, patients with IPI scores of 2-5 treated with R-CHOP or an R-CHOP-like regimen had an expected 5-year PFS and 5-year OS of 46-67% and 54-76% compared with 5-year PFS and 5-year OS of 81% and 88% for patients with IPI of 0-1 (low risk group) (Ruppert et al. 2020). Contemporary trials have shown improved outcomes in the R-CHOP arms, but the IPI 2-5 subgroups consistently have worse survival than IPI 0-1. While prognostic factors such as IPI and molecular subtypes are predictive of PFS and OS outcome, 1L patients with refractory DLBCL are very heterogeneous with both low risk and high risk features

and have a median survival of 6.3 months (Crump et al. 2017). Thus, 1L approaches that can reduce the likelihood of refractory DLBCL are of considerable clinical interest.

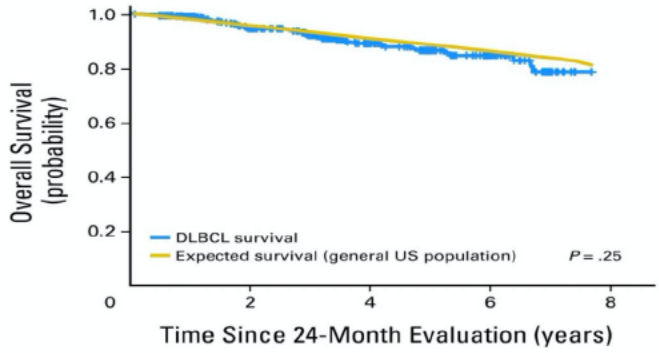
2.1.2 Current Treatment Options in 1L DLBCL

The Applicant's Position:

The primary goal of treatment in 1L DLBCL is to cure patients of their lymphoma. The most common initial treatment for DLBCL is R-CHOP, which has remained the standard of care for nearly 20 years (NCCN Guideline v5 2022; Appendix 2). The chemotherapy regimen and dosing for CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) was established in the 1970s (McKelvey et al. 1976) and the addition of rituximab (R) occurred in the early 2000s. There have not been any new FDA approved treatment options for 1L DLBCL since R-CHOP was approved.

Approximately 40% of patients have disease that does not adequately respond to R-CHOP (refractory disease) or will relapse after an initial response and will require subsequent treatment (Sehn and Salles 2021). The majority of patients who experience relapse will do so within 2 years of treatment (Maurer et al. 2018). Importantly, patients who are free of disease progression or relapse at 2 years after initial diagnosis are highly likely to have nearly the same life expectancy as that of a sex- and age matched general population (Maurer et al. 2014) (Figure 1). In discussions involving clinicians, epidemiologists, and patients at the Fifth European Conference on Survivors and Chronic Cancer Patients, the description of sex- and age-matched life expectancy was defined as 'cure' for cancer patients (Tralongo et al. 2015).

Figure 1 Overall Survival vs. Expected Survival in General U.S. Population After 24 Month Evaluation



Maurer et al. J Clin Oncol. 2014 Apr 1;32(10):1066-73.

2.1.3 Unmet Medical Need in DLBCL

The Applicant's Position:

Up to 40% of patients with 1L DLBCL are not cured with R-CHOP as their initial therapy. Since the greatest likelihood of cure occurs in 1L, this gap leaves an unmet clinical need. Relapse also is an important concern for patients. Fear of cancer recurrence (FCR) is reported in 88% of lymphoma patients (Latella et al. 2020). Improving the cure rate in 1L would reduce FCR, enable more patients to have a near normal life expectancy and avoid the impact of relapsed disease: low cure rates, very poor outcomes, and the higher toxicity burden of salvage therapies (Friedberg 2011).

Thirteen attempts to integrate a variety of new strategies and novel agents have failed to improve benefit-risk over R-CHOP (Sehn and Salles 2021). These attempts are described in Appendix 3.

For the patients who are not cured with R-CHOP, therapeutic approaches for relapsed or refractory disease depend on the disease response to salvage regimens, and a patient's fitness for intensive therapy that may be curative.

After first relapse of DLBCL, two second line (2L) therapies, autologous stem cell transplantation (SCT) and chimeric antigen receptor (CAR)-T products, may provide a second chance of cure but do so at a rate lower than 1L therapy (Westin and Sehn 2022). Moreover, a substantial proportion of 2L DLBCL patients are not eligible for SCT and/or CAR-T due to patient fitness, toxicities associated with these therapies, or disease that is not chemosensitive (Jagadeesh et al. 2022; Shah et al. 2021; CIBMTR 2020; Munshi et al. 2022). Taking into consideration patient fitness and chemosensitivity (factors that limit SCT and CAR-T usage in 2L DLBCL), and the effectiveness of SCT and CAR-T, these strategies provide cure for approximately 25% of all 2L DLBCL patients (Westin and Sehn 2022).

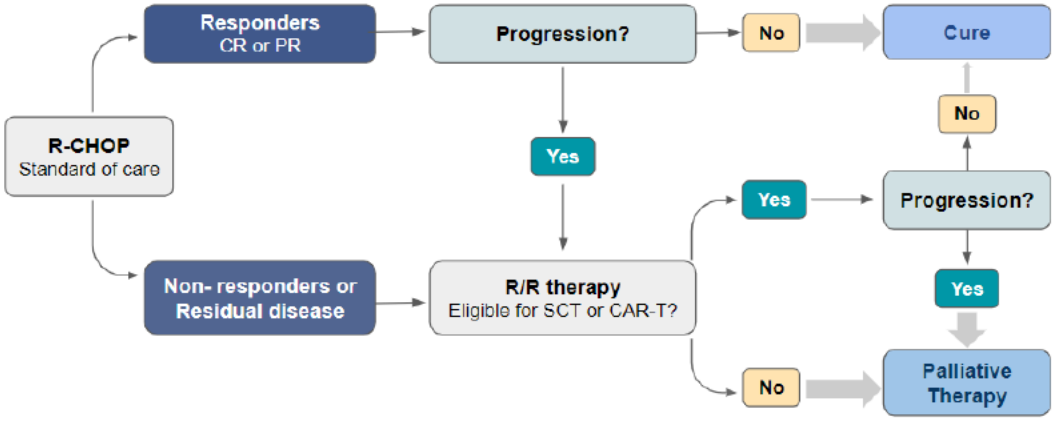
While CAR-T and SCT may cure a minority of patients, they are associated with fatal and severe (Grade 3-4) adverse events. The incidence of febrile neutropenia in these therapies may be as high as 36%. In addition, CAR-Ts are associated with unique, serious toxicities (cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome), which can be life-threatening and fatal. These therapies uniformly require inpatient hospitalization and are much more burdensome for both the patient and the healthcare system, with associated prolonged cytopenias, delayed immunologic reconstitution, and secondary malignancies.

For relapsed/refractory patients who are not eligible for SCT or CAR-T products (primarily because safety risks outweigh the potential benefit for these patients) and patients who progress despite SCT or CAR-T, palliative treatments include salvage chemotherapy regimens, polatuzumab vedotin with BR (Sehn et al. 2020), tafasitimab with lenalidomide (Salles et al. 2020), loncastuximab tesirine (Caimi et al. 2021), and selinexor (Kalakonda et al. 2020). These therapies have been shown to produce response rates up to 70%, with median PFS ranging from 2.6 to 12.1 months. This underscores the need for more efficacious 1L therapies that will

confer durable remissions because these therapies are unlikely to produce cure in the relapsed/refractory setting.

The treatment journey for patients with DLBCL is presented in Figure 2. Ultimately, the most effective and least toxic way to address the unmet need in DLBCL is to cure more patients in the 1L setting.

Figure 2 DLBCL Treatment Journey



The FDA's Position:

FDA agrees with the Applicant's presentation of the treatment landscape for untreated DLBCL NOS. However, there is no universal standard for previously untreated HGBL,[4] for which more intensive regimens are generally favored in the U.S. because of concerns with inferior outcomes with R-CHOP (Table 29).[1,5,6] Central nervous system (CNS) prophylaxis is routinely considered for HGBL because of the heightened risk of CNS dissemination. Although its role is not established, high-dose therapy with SCT can also be considered for HGBL in first remission, in contrast to most cases of DLBCL NOS.[1]

2.1.4 Assessing Novel Therapies to Address Unmet Need in 1L DLBCL

The Applicant's Position:

When assessing new therapeutics for the treatment of 1L DLBCL, long follow up, subsequent therapies and unrelated deaths confound overall survival (OS) analyses (Nowakowski et al. 2016). FDA recommends time-to-event endpoints based on tumor assessments "*where survival may be prolonged, making an overall survival endpoint impractical*" to support approval (FDA Guidance for Industry [2018]: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics). Prior studies have projected that phase III trials in 1L DLBCL using OS as an endpoint can take approximately 10 years to complete (Shi et al. 2018; Stathis et al. 2018) making this an impractical 1L endpoint.

Endpoints such as progression-free survival (PFS) and event-free survival (EFS) measure disease relapse and need for subsequent treatment. In the setting of 1L DLBCL where residual disease requires further therapy, and the vast majority of disease relapse and progression occurs within 2 years of diagnosis, these endpoints when evaluated with sufficient follow up (e.g. at least 24 months) have been deemed by the lymphoma community to be reflective of cure. This is further supported in studies that show that patients who remain event-free or progression-free at 24 months are highly likely to experience a life expectancy similar to age- and sex-matched general populations (Maurer et al. 2018; Shi et al. 2018). In addition, surrogacy of PFS and EFS for OS have been demonstrated at the trial level (Zhu et al. 2020). These analyses support PFS and EFS as earlier efficacy endpoints (Zhu et al. 2020), and PFS at 24 months as a surrogate for OS in DLBCL (Stathis et al. 2018). FDA lists PFS and EFS as surrogate endpoints acceptable to support traditional approval of drugs or biologics for the treatment of B cell lymphomas including DLBCL (Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure, FDA 2022).

Over the past decade, Phase III studies that were designed by the lymphoma community to demonstrate superiority to R-CHOP have targeted improvements translating to a 25% reduction in the risk of progression, relapse or death, or approximately 5-7% improvement in PFS at 24 months (Bartlett et al. 2019; Thieblemont et al. 2017; Vitolo et al. 2017; Davies et al. 2019; Nowakowski et al. 2016; Younes et al. 2019). An international collaboration of lymphoma clinical investigators and biostatisticians completed a systematic review of all published and unpublished 1L trials in DLBCL and performed a meta-analysis using individual-patient level data of 7507 patients from 13 trials (Shi et al. 2018). This group also substantiated PFS as a surrogate for OS and determined that future 1L trials for patients with DLBCL observing a PFS hazard ratio of ≤0.89 would meet the surrogate threshold effect and predict a significant treatment effect on OS. In line with this guidance, multiple 1L randomized clinical trials for DLBCL have targeted PFS HRs of 0.56-0.75 (Bartlett et al. 2019; Thieblemont et al. 2017; Vitolo et al. 2017; Davies et al. 2019; Nowakowski et al. 2016; Younes et al. 2019), establishing consensus targets for clinically meaningful improvements in PFS following 1L therapy for DLBCL.

The FDA's Position:

FDA does not agree that surrogacy of PFS for OS has been established in patients with previously untreated LBCL. There are many considerations when establishing surrogacy of an endpoint, in addition to the correlation measured in the Shi et al meta-analysis and other referenced studies.[7] While PFS has been used to support regular approval, FDA requires submission of OS data to support the regulatory decision.

2.1.5 Polatuzumab Vedotin Mechanism of Action

The Applicant's Position:

Polatuzumab Vedotin: Antibody-drug Conjugate (ADC)

Polatuzumab vedotin is a first-in-class ADC targeting CD79b. It contains:

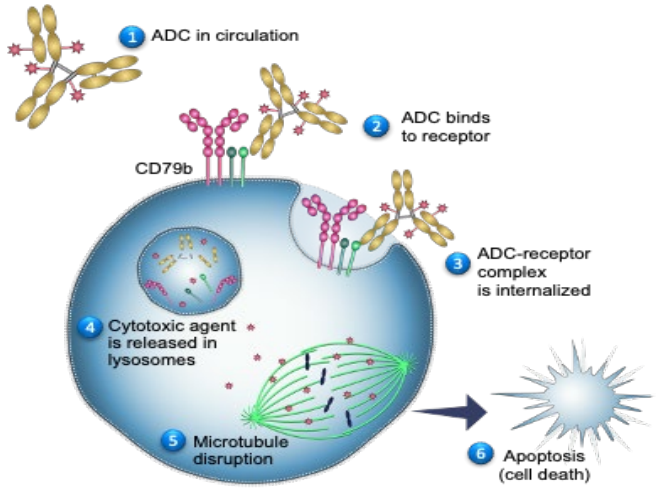
1) a humanized immunoglobulin G1 anti-human CD79b targeted monoclonal antibody (mAb) (MCDS4409A), and
2) monomethyl auristatin E (MMAE), an anti-mitotic microtubule inhibitor that inhibits cancer cell proliferation and induces apoptosis.

These two components are covalently linked through a protease cleavable linker, maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (mcvcP AB), with an average of 3.5 linked MMAE moieties per antibody. Upon binding CD79b, polatuzumab vedotin is internalized (Polson et al. 2007, 2009; Pfeifer et al. 2015) and the linker is cleaved by lysosomal proteases leading to intracellular release of MMAE (Sutherland et al. 2006), which results in delivery of a high level of MMAE to the tumor while limiting the systemic release of unconjugated MMAE. This linker and MMAE technology have been used in other FDA-approved products such as ADCETRIS® (brentuximab vedotin), PADCEV® (enfortumab vedotin-ejfv), and TIVDAK® (tisotumab vedotin-tftv).

CD79b is a signaling component of the B-cell antigen receptor complex on the surface of B-cells, and as such, is restricted to cells within the B-cell lineage. CD79b is ubiquitously expressed across the majority of B cell malignancies including DLBCL (Dornan et al. 2009).

Mechanism of Action
Polatuzumab vedotin targets the delivery of MMAE to CD79b expressing B cells. The mechanism of action is presented in Figure 3.

Figure 3 Polatuzumab Vedotin Mechanism of Action



2.1.6 Rationale for the Combination of Pola+R-CHP for 1L DLBCL

The Applicant's Position:

The ubiquitous expression of CD79b surface antigen across DLBCL subtypes supports the use of polatuzumab vedotin in this disease (Pfeifer et al. 2015). Polatuzumab vedotin is being

investigated in combination with chemotherapy and other targeted anticancer agents as a potential therapy for patients with B-cell malignancies expected to express CD79b.

Polatuzumab vedotin was evaluated in 1L DLBCL as a targeted replacement for the microtubule inhibitor vincristine (Tradename: Oncovin) in R-CHOP, given their overlapping mechanism of action and toxicities. Higher systemic administration of vincristine is not possible due to its cumulative toxicity. Polatuzumab vedotin's ADC technology enables MMAE to be delivered to the tumor via CD79b without substantial systemic exposure (Saber and Leighton 2015). By replacing vincristine with polatuzumab vedotin, there was potential to deliver MMAE, an ~10 times more potent microtubule inhibitor, directly to tumor cells to achieve greater effectiveness without additional toxicity.

The Phase Ib/II Study GO29044 evaluated the safety and preliminary efficacy of pola+R-CHP in patients with 1L DLBCL. Adverse events observed in patients who received pola+R-CHP were in line with what was described for R-CHOP. No new safety signals were identified. The ORR of 89% and CR rate of 77% of the pola+R-CHP regimen along with encouraging PFS and OS observations in Study GO29044 supported the further development of pola+R-CHP as a treatment in 1L DLBCL.

Based on the scientific rationale to replace vincristine ('O') in the R-CHOP regimen, and promising pola+R-CHP data from Study GO29044, the Sponsor initiated the Phase III POLARIX study to evaluate pola+R-CHP compared with R-CHOP in 1L DLBCL.

2.1.6.1 Rationale Supporting the Polatuzumab Vedotin Dose and Schedule

The Applicant's Position:

The 1.8 mg/kg every 3 weeks (Q3W) dose of polatuzumab vedotin for 6 cycles in POLARIX was chosen based on prior experience in patients with 1L DLBCL and relapsed/refractory DLBCL and exposure response (ER) analyses over a range of doses (0.1-2.4 mg/kg pola). 1.8 mg/kg Q3W is the approved dose of polatuzumab vedotin in combination with BR in relapsed/refractory DLBCL.

These ER analyses overall supported the 1.8 mg/kg Q3W polatuzumab vedotin for 6 cycles in combination with R-CHP in the POLARIX study. Polatuzumab vedotin pharmacokinetics was well characterized in patients with 1L DLBCL, with no clinically meaningful pharmacokinetic drug-drug interactions with R-CHP, and no clinically relevant impact of intrinsic or extrinsic factors on polatuzumab vedotin pharmacokinetics.

The FDA's Position:

FDA agrees with the Applicant's description of the mechanism of action and the rationale for evaluating pola+R-CHP. However, the current dose selection of polatuzumab vedotin at 1.8 mg/kg Q3W for the first-line treatment of DLBCL is based on limited dose-finding in a small number of patients. The activity and safety of polatuzumab vedotin in combination with R-CHP was evaluated in patients with previously untreated DLBCL as part of a dose-ranging study (GO29044) which evaluated doses of polatuzumab vedotin 1 mg/kg (n=2), 1.4 mg/kg (n=3), and 1.8 mg/kg (n=5) during dose escalation. All doses evaluated in dose escalation had ORRs of 100% with small differences in the safety profile. The 1.8 mg/kg dose was selected for expansion in previously untreated DLBCL (n=40). Given the limited dose exploration and the small number of patients, the evaluation of differences in the efficacy and safety profiles of the lower dose levels in combination with R-CHP is difficult, and the adequacy of a lower dose of polatuzumab vedotin in combination with R-CHP is unknown. In the April 3, 2017, end-of-phase 2 meeting (EOP2), FDA expressed concerns that adequate dose finding studies were not conducted and it was unclear if 1.8 mg/kg is the optimal dosage based on the relatively narrow exposure range and the majority of data being with 1.8 mg/kg.

While data from doses of 0.1 to 2.4 mg/kg polatuzumab vedotin in subjects with R/R DLBCL were included in an E-R efficacy analysis, the dose exploration data for monotherapy were limited, with 4 subjects given 1.8 mg/kg and 8 subjects given doses below 1.8 mg/kg.[8] There is no data is available for polatuzumab vedotin monotherapy in subjects with 1L DLBCL.

The E-R efficacy analysis in 1L DLBCL was limited to data from a single dose level (1.8 mg/kg) in combination with R-CHP. Associations between exposure and efficacy may differ between R/R DLBCL and 1L DLBCL due to disease characteristics and treatment regimens (single-agent polatuzumab vedotin versus polatuzumab vedotin in combination with rituximab, bendamustine, or R-CHP). In POLARIX, no associations between exposure and OS or CR rate were identified although subjects with higher exposure tended to have longer PFS. Additionally, higher polatuzumab exposure was associated with higher rates of multiple treatment-emergent adverse events (TEAEs) in patients with previously untreated DLBCL including Grade ≥3 neutropenia, Grade ≥3 febrile neutropenia, and Grade ≥2 peripheral neuropathy. Therefore, the benefit-risk profile of polatuzumab vedotin in 1L DLBCL for doses lower than 1.8 mg/kg is uncertain, and the proposed 1.8 mg/kg dosage in this setting may not be optimized in terms of efficacy and safety. The relationship between polatuzumab vedotin dose and clinical efficacy in previously untreated DLBCL is not well-characterized due to the limited dose-finding. Refer to FDA Appendix 1: Clinical Pharmacology for additional details regarding clinical pharmacology and E-R analyses.

2.2 Summary of Clinical Trials Supporting Efficacy

The Applicant's Position:

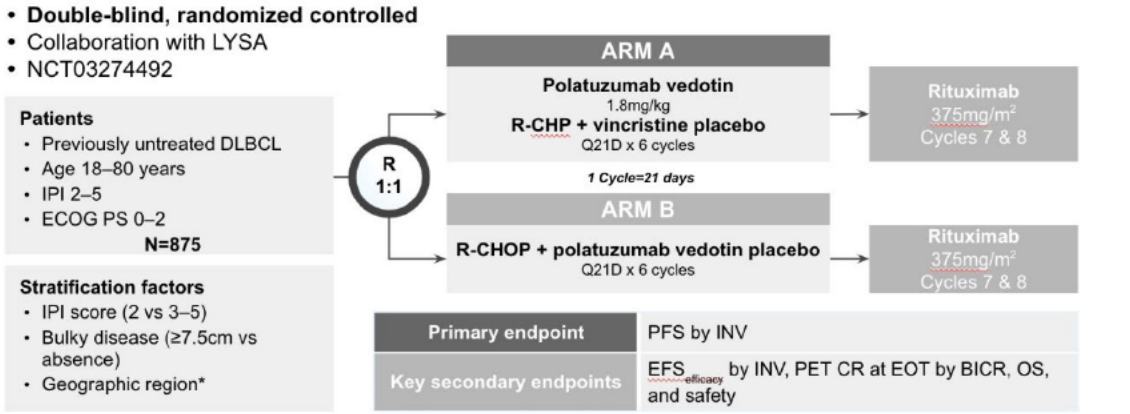
2.2.1 Study Design

POLARIX is an ongoing multicenter, randomized, double-blind, placebo-controlled Phase III

study comparing the efficacy, safety, pharmacokinetics and patient reported outcomes (PROs) of pola+R-CHP to those of R-CHOP in patients with 1L DLBCL (Figure 4). POLARIX enrolled 879 patients in 22 countries across North America, Europe, Asia-Pacific, and South America. It is being conducted in collaboration with LYSA (Lymphoma Study Association) and LYSARC (Lymphoma Study Academic Research Organization), both part of the Lymphoma Research Experts ecosystem based in France, Belgium, and Portugal. POLARIX's Steering Committee is comprised of LYSA members and includes leading U.S. lymphoma experts. FDA feedback including dose management, patient population, endpoint selection, primary and secondary efficacy analysis plan, and risk mitigation strategy were incorporated into the final study design.

An independent data and safety monitoring committee reviews safety data on a regular basis during the conduct of the trial. Blinded independent central review was used to determine CR rate at treatment completion. Major protocol amendments for POLARIX are summarized in Appendix 4.

Figure 4 Study Design for POLARIX



*Western Europe, United States, Canada and Australia vs Asia vs Rest of World.

BICR=blinded independent central review; CR=complete response; ECOG PS=Eastern Cooperative Oncology Group performance status; $EFS_{efficacy}$=event-free survival for efficacy; EOT=end of treatment; INV=investigator; IPI=International Prognostic Index; LYSA=Lymphoma Study Association; PET=positron emission tomography; Q21D=every 21 days; PFS = progression-free survival; R=randomization

Patients who required subsequent therapy were allowed to receive non-protocol anti-lymphoma therapy (NALT) including radiotherapy, systemic therapies, autologous stem cell transplantation (SCT) and chimeric antigen receptor (CAR)-T products.

2.2.2 Study Endpoints

Table 2 shows the primary and key secondary efficacy endpoints and their definitions in POLARIX study.

In addition, PRO measures, safety data in adverse event reporting, and NALT received such as radiotherapy, salvage therapies, and cellular therapies were collected.

Table 2 Primary and Key Secondary Efficacy Endpoints in POLARIX

Efficacy Endpoint	Definition	Rationale for the Choice of Endpoint
Primary Endpoint		
Progression-free Survival (PFS) PFS Observation/ Follow up Period of 24 months	Time from randomization to the first occurrence of disease progression or relapse, or death from any cause. In POLARIX, the primary analyses of PFS was planned to be performed after 228 events (disease progression, relapse, or death) had occurred and all patients had at least 24 months of follow up. *Set 1st in the statistical testing hierarchy (Appendix 5).*	• PFS measures direct clinical benefit in 1L DLBCL. ○ The absence of disease progression or relapse indicates that the patient may be cured. ○ Patients who are alive without progression or relapse at 24 months from the onset of initial therapy are highly likely to experience a near normal life expectancy similar to the age- and sex-matched general population (Maurer et al. 2018; Shi et al. 2018). ○ Avoiding disease progression or relapse is important because patients are less likely to be cured with later lines of therapy.
Key Secondary Efficacy Endpoints (included in the hierarchical testing procedure)		
Event-Free Survival for Efficacy Reasons (EFS_{eff})	Time from randomization to any of the following events: any progression of disease, death, non-protocol anti-lymphoma therapy (NALT) resulting from efficacy reason, or positive biopsy after treatment completion (if obtained). *Set 2nd in the statistical testing hierarchy (Appendix 5).*	• EFS_{eff} incorporates delay or absence of "initiation of next subsequent therapy for efficacy reasons" as assessed by the blinded investigator to contribute towards treatment benefit. • EFS_{eff} was defined in collaboration with FDA in order to reflect this as an efficacy endpoint, as opposed to reasons such as toxicity, or miscellaneous reasons.
Complete Response (CR) Rate at End of Treatment (by PET-CT)	The percentage of patients with CR at the end of treatment by PET-CT assessed by blinded independent review. *Split as 3rd in the statistical testing hierarchy with OS (Appendix 5).*	• CR is the optimal result of 1L DLBCL treatment as it means that all lymphoma detectable via PET-CT is absent at treatment completion.
Overall Survival (OS)	Time from randomization until the date of death from any cause. *Split as 3rd in the statistical testing hierarchy with CR at EOT (Appendix 5).*	• OS is a direct measure of clinical benefit, incorporating both efficacy and safety.

Note: Lugano classification response criteria for lymphoma (Cheson et al. 2014) were used by the investigators to perform tumor assessments, as well as by the independent central review committee to evaluate end-of-treatment response on the basis of PET-CT. CT and PET-CT were required at baseline and at treatment completion; CT, PET-CT, or both were planned after cycle 4 and during surveillance (i.e., every 6 months for the next 24 months, then every 12 months for the next 36 months).

The FDA's Position:
FDA agrees with the Applicant's summary of the study design and endpoints.

2.2.3 Statistical Methods

The Applicant's Position:

One primary (final) analysis of PFS and three analyses of OS (two interim and one final) were performed. Details of the pre-specified statistical testing hierarchy and major statistical analysis plan (SAP) amendments are summarized in Appendix 5.

The primary efficacy analysis was conducted on the intent-to-treat (ITT) population after the following conditions were met: approximately 228 PFS events were observed across both treatment arms and at least 24 months after the last patient was enrolled. This time frame allows for the robust assessment of PFS rate at 24 months. The clinical cutoff date (CCOD) was 28 June 2021.

FDA reviewed all versions of the SAP. All the recommendations made by FDA prior to unblinding, including analysis methodologies and all censoring rules for PFS and EFS, are specified in SAP version 3 that was used for the primary analysis.

The FDA's Position:
FDA reviews and re-analyzes data as appropriate to evaluate the robustness of the results across various sensitivity analyses, which may differ from what was specified in the protocol or SAP.

2.2.4 Patient Selection

The Applicant's Position:

Patients were eligible for inclusion if they were 18 to 80 years of age, had CD20-positive DLBCL, had not received previous treatment for lymphoma, had an Eastern Cooperative Oncology Group performance status score of 0 to 2, had a baseline IPI score between 2 and 5, and had adequate hematologic, renal, hepatic, and cardiac function, regardless of the cell of origin or the presence of rearrangements in *MYC*, *BCL2*, *BCL6*, or a combination of these.

Key exclusion criteria were a history of indolent lymphoma, a contraindication to any component of R-CHOP, previous receipt of anthracycline agents, and known central nervous system involvement.

The FDA's Position:

FDA agrees with the summary of eligibility criteria. However, as noted in Section 1.2 (Proposed Indication) the term "DLBCL" used by the Applicant refers broadly to the LBCL subtypes that were eligible for the trial, including HGBL (with *MYC* and *BCL2* and/or *BCL6* rearrangements and HGBL NOS) in addition to DLBCL NOS. The other eligible histologies were T-cell/histiocyte-rich LBCL, EBV+ DLBCL, ALK+ LBCL, and HHV8+ DLBCL; no patients with the latter two histologies were enrolled. The study excluded patients with primary mediastinal large B-cell lymphoma, transformed lymphoma, known CNS involvement by lymphoma, and Grade >1 peripheral neuropathy.

2.3 Efficacy Summary

2.3.1 Study Patients

The Applicant's Position:

2.3.1.1 Patient Disposition

A total of 879 patients were enrolled at 211 sites in 22 countries and comprised the ITT population. A total of 234 (26.6%) patients were enrolled at sites throughout the continental U.S. (Section 5).

Patients were randomized 1:1 (440 patients to the pola+R-CHP arm and 439 patients to the R-CHOP arm). 873 patients received at least one dose of study drug and were included in the safety-evaluable population (435 in pola+R-CHP and 438 in R-CHOP).

At the time of the primary analysis, 142 patients (16.2%) had discontinued the study: 66 (15.0%) patients in the pola+R-CHP arm and 76 (17.3%) in the R-CHOP arm. Patient discontinuations from the study were balanced between arms and a low number of discontinuations for reasons other than death were observed.

2.3.1.2 Protocol Violations/Deviations

Protocol deviations were balanced between arms and are unlikely to bias the study results. None of the major protocol deviations led to exclusion of data from the analyses, posed an increased safety risk to any patient continuing on study treatment, or were considered to have affected the integrity of the study findings (Appendix 6).

2.3.1.3 Demographic Characteristics

Patient demographics and baseline characteristics between the treatment arms were generally balanced and representative of patients with 1L DLBCL (see detailed breakdown in Appendix 7 and U.S.-specific demographics in Section 5).

The FDA's Position:
FDA's assessment of the representativeness of patients with DLBCL is discussed in Section 5.1 (Applicability of POLARIX Results to the U.S. Population).

2.3.2 Overview of Efficacy Results

The Applicant's Position:

2.3.2.1 Primary Efficacy Endpoint: Investigator-Assessed PFS

POLARIX met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement of PFS in the pola+R-CHP arm relative to the R-CHOP arm in patients with 1L DLBCL.

The observed PFS HR translated into a reduction of the risk of disease progression, relapse or death by 27% in the pola+R-CHP arm compared with the R-CHOP arm (stratified HR: 0.73 [95% CI 0.57, 0.95]; two-sided log-rank p=0.0177) (Table 3 and Figure 5). On the basis of Kaplan-Meier estimates, treatment with pola+R-CHP resulted in a higher proportion of patients who were progression-free at 2 years compared to R-CHOP (76.7% vs 70.2%) (Table 3).

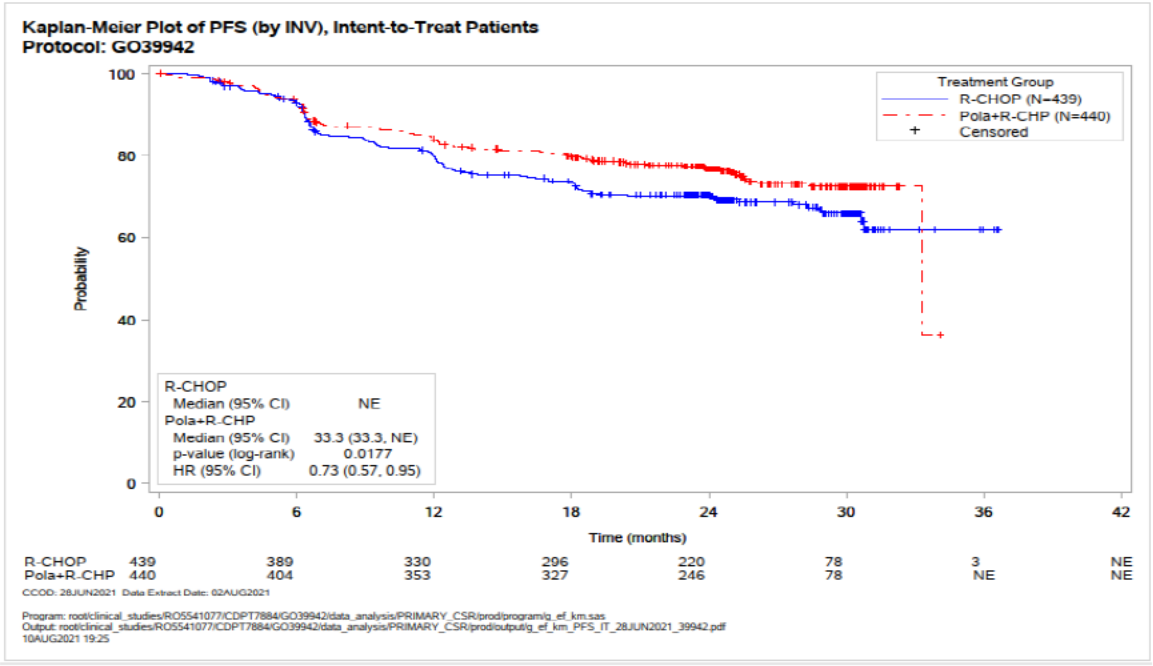
There was a directionally consistent PFS treatment effect in the majority of subgroups (HR <1), including for race, age, sex, and geographic region. All 95% CIs for HR in the subgroups with a reasonable sample size (e.g., > 100) included 0.73, i.e., the estimated stratified HR in the ITT population (Appendix 8).

Table 3 Results of the Primary Efficacy Endpoint PFS for POLARIX Study (ITT Population) (CCOD: 28 June 2021)

	R-CHOP	Pola+R-CHP
Progression-Free Survival (PFS)		
ITT population	439	440
Patients who died or had progression or relapse (%)	134 (30.5%)	107 (24.3%)
Stratified HR (95% CI)	0.73 (0.57, 0.95)	
p-value (two-sided log-rank)	0.0177	
2-year (24 months) INV-PFS estimate		
Patients remaining at risk	220	246
Event free rate (%) (95% CI)	70.2 (65.8, 74.6%)	76.7 (72.7, 80.8%)
Difference in event free rate (95% CI)	6.50 (0.52, 12.49)	

HR = hazard ratio; INV = investigator; ITT = intent-to-treat; PFS = progression-free survival.
Events of progression or relapse were assessed by the investigator.
Source: t_ef_tte_PFS_IT_28JUN2021_39942.

Figure 5 **Kaplan-Meier Plot of Time to PFS for POLARIX Study (ITT Population) (CCOD: 28 June 2021)**



INV = investigator; N = number of patients; PFS = progression-free survival.
Events of progression or relapse were assessed by the investigator.

The results of prespecified sensitivity analyses of PFS were consistent with results of the PFS primary analysis. PFS estimated using the interval censoring approach (Appendix 5) to account for missing tumor assessments (when timing of a PFS event is not observed precisely and instead, it is known to fall into a particular interval) resulted in a stratified HR: 0.75 (95% CI 0.58, 0.96).

Summary of Non-protocol Anti-Lymphoma Therapy (NALT) Received After Protocol Treatment: More patients in the R-CHOP arm received NALT, for either efficacy or safety reasons than in the pola+R-CHP arm (30.3% vs. 22.5%, respectively). Patients in both arms received the same types of NALT, defined as any non-protocol anti-lymphoma therapy comprising radiotherapy, systemic therapies, SCT, and CAR-T products. NALT was allowed to be administered with or without a disease progression. The majority of patients who received NALT received it after a PFS event.

To assess potential confounding of the treatment effect estimates by NALT administered without a disease progression, the Sponsor conducted a post-hoc sensitivity analysis, as requested by the FDA, to assess the impact of both ≥2 missing tumor assessments and initiation of NALT on PFS. In this analysis, the Sponsor aligned with the FDA to censor NALT that represents treatment beyond standard 1L therapy. Therapies that were not censored represent

either continuation of standard therapy or prophylactic therapies (e.g. methotrexate, radiation) that are not uniformly administered to patients (Table 4). This analysis yielded a stratified HR=0.75 (95% CI 0.57, 0.97). In addition, PFS censored for NALT alone (i.e., not combined with also censoring for ≥2 missing tumor assessments) yielded a stratified HR=0.74 (95% CI 0.57, 0.96). The results of both analyses were consistent with the primary PFS result.

Table 4 Scenarios for NALT Censoring Before a PFS Event as Agreed with the FDA

	Scenario	Censoring
NALT scenario, will not be censored		
1	IV or IT methotrexate administered in the absence of efficacy findings.	No
2	Standard of care R-CHOP or R-CHOP-like therapy in the absence of efficacy findings, including the presence of toxicity. Only includes dose modifications or discontinuations of R-CHOP components. May also include IV or IT methotrexate.	No
3	Preplanned radiation therapy, irrespective of any response at treatment completion.	No
4	Therapy that is given for a second malignancy unlikely to affect LBCL outcomes.	No
5	Therapy that is administered within 3 days of confirming disease progression.	No
NALT scenarios, will be censored		
6	Any unplanned radiation therapy.	Yes
7	Consolidation with chemotherapy and/or stem cell transplantation in the setting of a complete metabolic response.	Yes
8	Receipt of NALT therapy that is different from R-CHOP (e.g. R-ICE, R-GemOx) in the presence of efficacy reasons or not, including therapy that would be for an unrelated lymphoma that could impact LBCL outcome	Yes
NALT scenario, after event, not applicable in censoring		
9	Therapy after disease progression/disease relapse	N/A

IV=intravenous; IT=intrathecal; LBCL=large B-cell lymphoma; NALT=non-protocol anti-lymphoma therapy; R-CHOP rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-ICE=rituximab plus ifosfamide, carboplatin, and etoposide; R-GemOx=rituximab plus gemcitabine and oxaliplatin.

2.3.2.2 Secondary Efficacy Endpoints

The results of the key secondary endpoints (EFS_{eff} and CR at end of treatment) and additional secondary endpoints (BOR, DOR, DFS and ORR) are presented in Table 5.

Event Free Survival for Efficacy Reasons (EFS_{eff})

Additional therapy is indicated in the 1L treatment setting if the response is deemed suboptimal (e.g. residual disease, suggesting absence of cure). As such the delay or absence of any NALT for any reason in the setting of 1L therapy is a clinically meaningful outcome. In POLARIX, EFS_{eff} considers initiation of unplanned lymphoma therapy due to efficacy concerns as an EFS event. This endpoint was created with the FDA during the study design phase in 2017 to

account for the efficacy impact of NALT.

Under the Estimand framework in FDA's guidance (Statistical Principles for Clinical Trials: Addendum, 2021), EFS_{eff} accounts for the impact of NALT on efficacy when salvage therapies are available, as they do exist in the current DLBCL treatment landscape. By contrast, censoring PFS for NALT reflects a situation in which subsequent therapies such as salvage therapies would not exist.

Table 5 Secondary Efficacy Endpoints (CCOD: 28 June 2021)

	R-CHOP	Pola+R-CHP
Key Secondary Efficacy Endpoints (Hierarchically Tested)		
Event-Free Survival for Efficacy Reasons[1]		
ITT population, N	439	440
Patients with event, n (%)	138 (31.4%)	112 (25.5%)
Stratified HR (95% CI)	0.75 (0.58, 0.96)	
p-value (two-sided log-rank)	0.0244	
24 months duration		
Patients remaining at risk, N	218	243
Event Free Rate, % (95% CI)	69.4 (65.0, 73.8)	75.6 (71.5, 79.7)
Difference in Event Free Rate (95% CI)	6.2 (0.1, 12.2)	
Complete Response at End of Treatment (by PET-CT)[2]		
ITT population, N	439	440
Complete Responders, n (%)	325 (74.0%)	343 (78.0%)
(95% CI)	(69.7, 78.1)	(73.8, 81.7)
Stratified analysis		
Difference in response rate (95% CI)	3.9 (-1.9, 9.7)	
p-value (Cochran-Mantel-Haenszel)	0.1557	
Additional Secondary Endpoints (Not Formally Tested)		
Objective Response Rate at End of Treatment (by PET-CT)[1]		
ITT population, N	439	440
Responders, n (%)	355 (80.9%)	372 (84.5%)
95% CI	(76.9, 84.4)	(80.8, 87.8)
Stratified Analysis		
Difference in response rate (95% CI)	3.7 (-1.5, 8.8)	
Best Overall Response[1]		
ITT population, N	439	440
Responders, n (%)	413 (94.1%)	422 (95.9%)
95% CI	(91.4, 96.1)	(93.6, 97.6)
Stratified Analysis		
Difference in response rate (95% CI)	1.8 (-1.3, 5.0)	

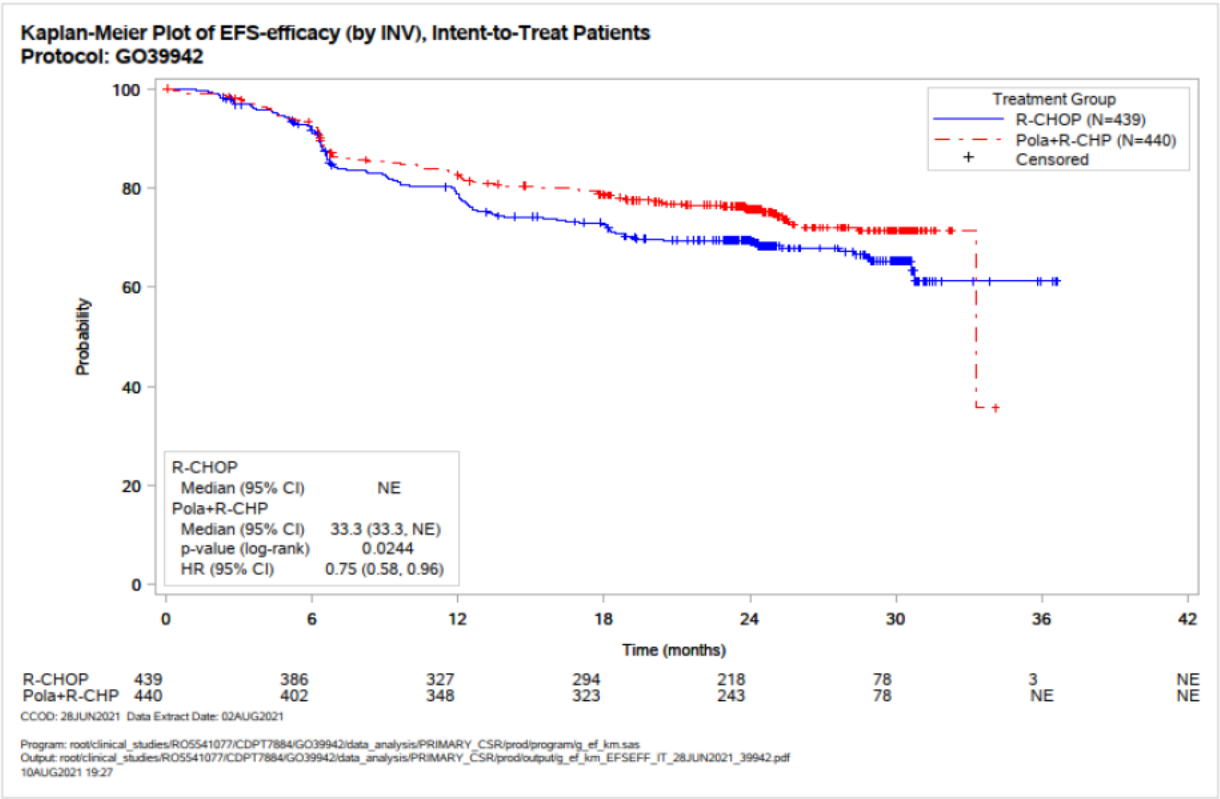
Complete Response as Best Overall Response[1]		
Complete response, n (%)	363 (82.7%)	381 (86.6%)
95% CI	(78.8, 86.1)	(83.1, 89.6)
	R-CHOP	**Pola+R-CHP**
Duration of Response[1]		
Responders, N	413	422
Patients with event (%)	116 (28.1%)	94 (22.3%)
Stratified HR (95% CI)	0.74 (0.56, 0.98)	
Disease-Free Survival[1]		
ITT population, N	363	381
Patients with event (%)	79 (21.8%)	62 (16.3%)
Stratified HR (95% CI)	0.70 (0.50, 0.98)	

[1]Assessed by the investigator.
[2]Response was assessed by blinded independent central review (BICR) committee.
CI=confidence interval; PET-CT=positron emission tomography-computed tomography; ITT=intent-to-treat.

Source: t_ef_tte_EFSEFF_IT_28JUN2021_39942, t_ef_rsp_EOTCRBICR_IT_28JUN2021_39942, t_ef_rsp_EOTOR_IT_28JUN2021_39942, t_ef_rsp_BOR_IT_28JUN2021_39942, t_ef_tte_DFS_IT_28JUN2021_39942, t_ef_tte_DOR_IT_28JUN2021_39942.

The Kaplan-Meier (KM) curve for EFS_{eff} is presented in Figure 6.

Figure 6 Kaplan-Meier Plot of EFS_{eff} (ITT Population)

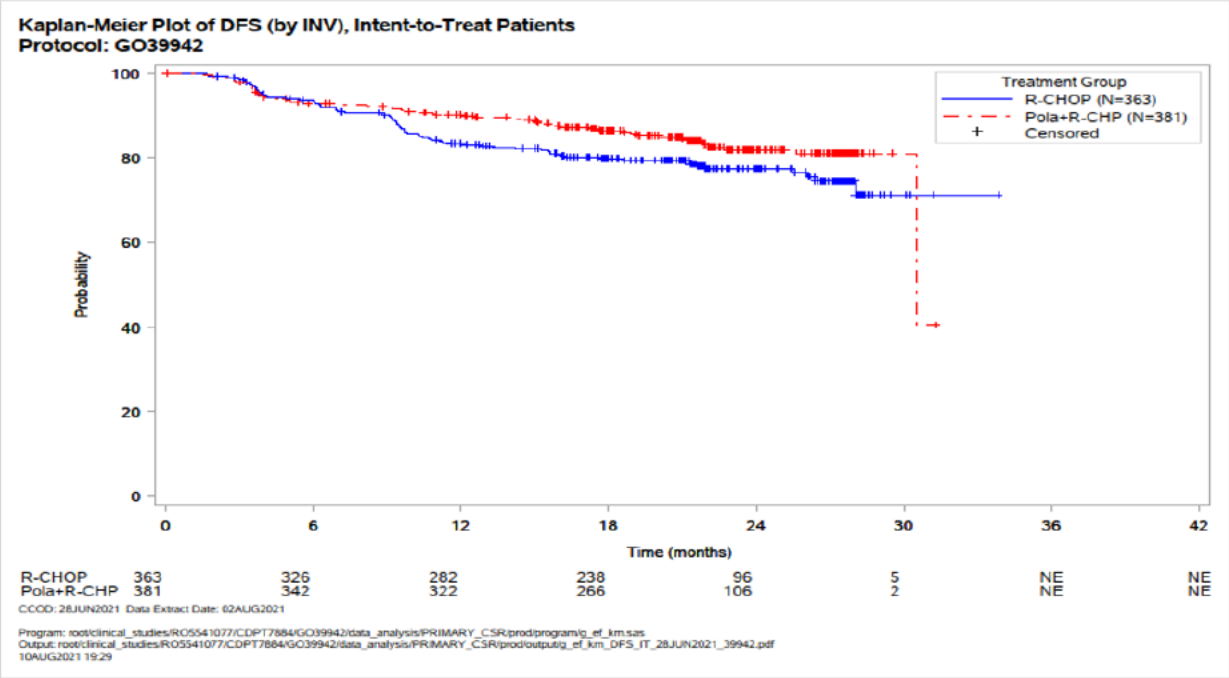


<u>Complete Response (CR)</u>, Objective Response Rate (ORR), Disease Free Survival (DFS) and Duration of Response (DOR)

While not statistically significant, complete response and objective response rates at treatment completion were numerically higher in the pola+R-CHP arms. Longer DFS (in patients who achieved complete response as best overall response) and DOR (in patients who achieved partial response or complete response as best overall response) demonstrated more durable remissions among patients treated with pola+R-CHP (**Table 4**).

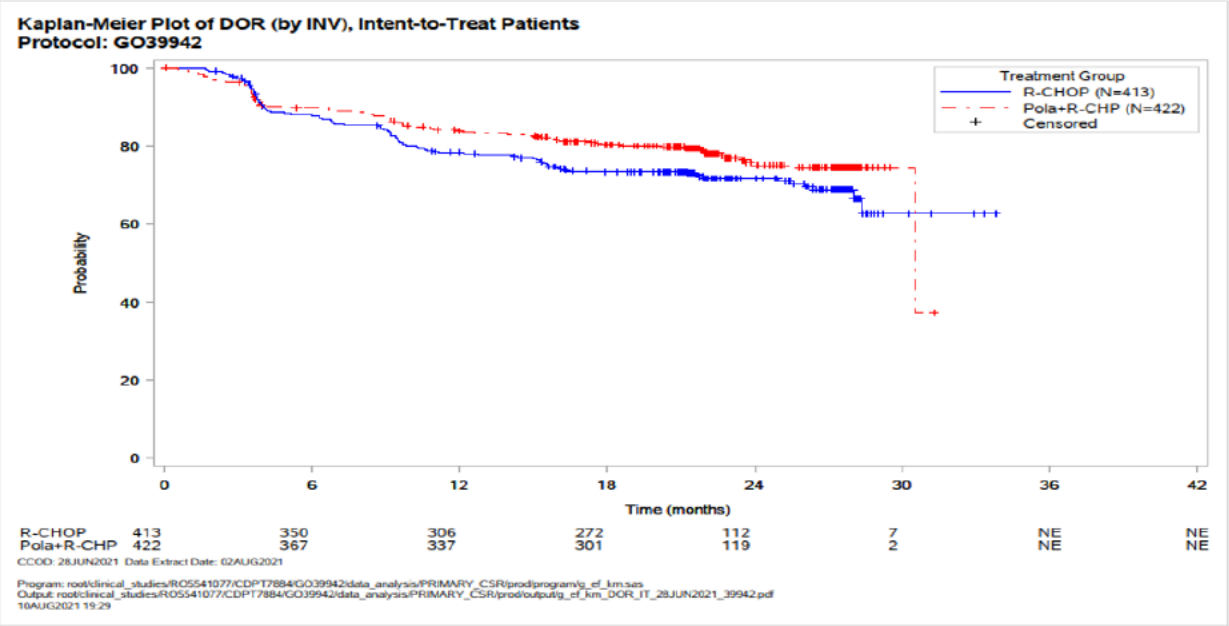
The Kaplan-Meier curve for DFS is presented in **Figure 7**.

Figure 7 Kaplan-Meier Plot of DFS (Patients Achieving Complete Response as Best Overall Response)



The Kaplan-Meier curve for DOR is presented in Figure 8.

Figure 8 **Kaplan-Meier Plot of DOR (Patients Achieved Complete Response or Partial Response as Best Overall Response)**



Overall Survival (OS)

The results of the key secondary endpoint OS at the two interim and final analyses are presented in Table 6 and Figure 9. The final OS analysis continued to have a low event-to-patient ratio (14.9% at the final OS, which was 2.4% more deaths compared to the primary analysis).

The Kaplan-Meier plots of the two interim analyses of OS are presented in Appendix 9.

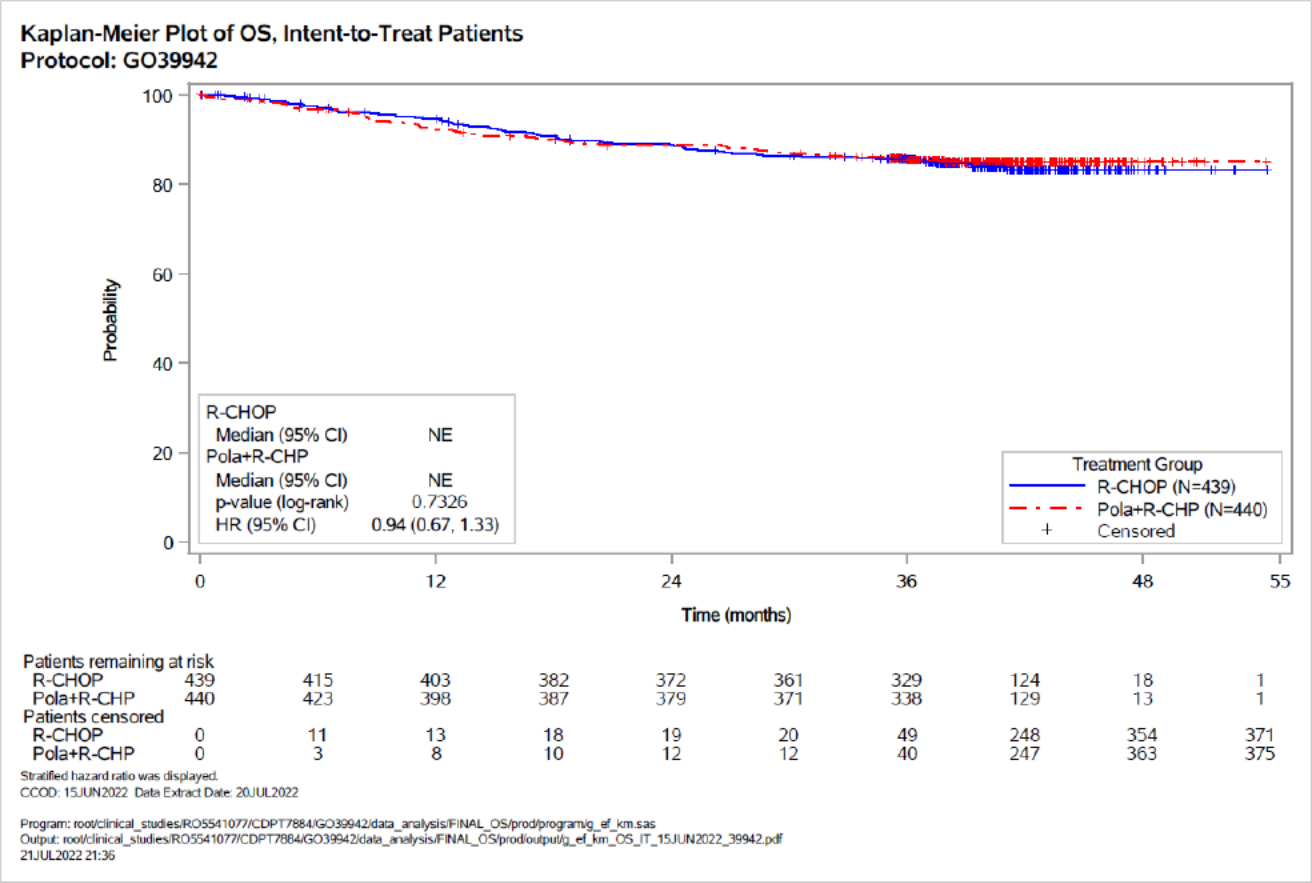
Table 6 Summary of Overall Survival at First and Second Interim and Final Analyses (ITT Population)

	First Interim Analysis of OS CCOD: 28 June 2021		Second Interim Analysis of OS CCOD: 25 February 2022		Final Analysis of OS CCOD: 15 June 2022	
	R-CHOP (N=439)	Pola+R-CHP (N=440)	R-CHOP (N=439)	Pola+R-CHP (N=440)	R-CHOP (N=439)	Pola+R-CHP (N=440)
Overall Survival						
Patients with event, n (%)	57 (13.0%)	53 (12.0%)	64 (14.6%)	61 (13.9%)	67 (15.3%)	64 (14.5%)
Stratified HR (95% CI)	0.94 (0.65, 1.37)		0.95 (0.67, 1.35)		0.94 (0.67, 1.33)	
p-value (log-rank)	0.7524		0.7696		0.7326	
OS rate (95% CI)						
12 months	94.6 (92.5, 96.8)	92.2 (89.6, 94.7)	94.6 (92.5, 96.8)	92.2 (89.6, 94.7)	94.6 (92.5, 96.8)	92.2 (89.7, 94.7)
18 months	90.8 (88.0, 93.5)	90.1 (87.3, 92.9)	90.9 (88.1, 93.6)	90.1 (87.3, 92.9)	90.8 (88.1, 93.6)	90.1 (87.3, 92.9)
24 months	88.6 (85.6, 91.6)	88.7 (85.7, 91.7)	88.7 (85.7, 91.7)	88.7 (85.7, 91.7)	88.7 (85.7, 91.7)	88.7 (85.7, 91.7)
30 months	86.3 (82.9, 89.7)	87.3 (83.9, 90.6)	86.3 (83.1, 89.6)	86.8 (83.6, 90.0)	86.3 (83.0, 89.6)	86.8 (83.6, 90.0)
36 months	85.6 (81.9, 89.3)	86.5 (82.8, 90.1)	85.8 (82.4, 89.1)	86.0 (82.8, 89.3)	85.6 (82.2, 88.9)	85.6 (82.3, 88.9)
42 months	NA	NA	82.4 (77.7, 87.1)	85.4 (81.9, 88.9)	83.3 (79.5, 87.0)	85.0 (81.7, 88.4)

CCOD=clinical cutoff date; HR=hazard ratio; NA=not applicable; OS=overall survival.

Source: t_ef_tte_OS_IT_28JUN2021_39942; t_ef_tte_OS_IT_25FEB2022_39942, t_ef_tte_OS_IT_15JUN2022_39942.

Figure 9 **Kaplan-Meier Plot of Time to Overall Survival (ITT Population; CCOD: 15 June 2022)**



Early Overall Survival (OS)

POLARIX evaluated fixed duration treatments administered over 3-4 months. Early OS may be an important indicator of efficacy and safety. When looking at deaths that occurred between 0-18 months on study, there were a similar number of patients who died during this time frame with no clear trend among reasons for death including adverse events, progressive disease, or other (Table 7).

Table 7 **Deaths Occurring Between 0-18 Months**

	R-CHOP N=439	Pola+R-CHP N=440	Total
Deaths, n	39	43	82
Median age (range)	70 (46-78)	67 (37-80)	69 (37-80)
Reason for Death, n			
Adverse event	10	13	23
Progressive disease	19	21	40
Other	10	9	19

Source: t_charac_LE18M_IT_28JUN2021_39942.

2.3.3 Overall Efficacy Conclusion for Polatuzumab Vedotin in 1L DLBCL

The Applicant's Position:

POLARIX met its primary endpoint of PFS by reducing the risk of disease progression, relapse, or death by 27% when treated with pola+R-CHP compared to R-CHOP. The PFS benefit in the pola+R-CHP arm compared with the R-CHOP arm was both statistically significant and clinically meaningful. This PFS difference meets the criteria for clinically meaningful benefit defined by experts and other trials.

Pola+R-CHP also offered a statistically significant improvement in the key secondary endpoint of EFS_{eff}, consistent with the PFS result.

While not statistically significant, the CR rate at the end of treatment was numerically higher in the pola+R-CHP arm. Importantly, CR achieved in patients who received pola+R-CHP were more durable as demonstrated by an improvement in DFS. Similarly, ORR at end of treatment was also numerically higher with pola+R-CHP, and complete or partial response as BOR achieved in the pola+R-CHP arm were also more durable as demonstrated by improved DOR compared to R-CHOP.

PFS, EFS_{eff}, CR, ORR, DFS, and DOR consistently show a lower proportion of patients experiencing disease relapse and a higher proportion experiencing sustained treatment effect with pola+R-CHP.

OS with approximately median 40 months of follow up remains immature and was not statistically different between the arms; however, it has consistently shown HR<1. The similar OS curves reflect a low frequency of accumulating events. This is not surprising in DLBCL where 1L treatment is expected to be curative for the majority of patients and, for patients who progress while on or after 1L therapy, multiple advances have been made in the relapsed/refractory setting during the course of the POLARIX trial that could confound OS analyses. As a result, the true underlying difference in OS between the two arms may be small, and even with longer follow-up, it is unlikely to observe a large improvement in OS with pola-R-CHP. While OS may remain similar, the burden of relapsing disease and salvage therapies can be detrimental to patients, which was better captured by endpoints such as PFS, EFS_{eff}, DFS, and DOR.

The FDA's Position:

FDA has a different interpretation than that presented by the Applicant. Several issues that require additional consideration are outlined below.

2.3.3.1 Magnitude of the PFS Benefit of Pola+R-CHP

Although the primary analysis of PFS was statistically significant, the effect size with pola+R-CHP was modest. The point estimates in 1-year and 2-year PFS rates differed by 4.1% and 6.5%,

respectively, and it is questionable whether this rate of difference is clinically meaningful. Additionally, there was heterogeneity in the observed treatment effect by lymphoma subgroups, as detailed in Section 2.3.3.4 (Heterogeneity of the Study Population and Treatment Effect). Although the modest PFS difference is in the setting of a substitution trial, these results must be considered along with the other efficacy results, OS results, and toxicity when considering the overall benefit risk of polatuzumab in combination with R-CHP.

Sensitivity analyses

FDA conducted various sensitivity analyses to evaluate the robustness of the PFS result (Table 8). The rationale for evaluating different censoring rules (or estimand strategies) is described in FDA Appendix 2: The Estimand Framework Applied to PFS and Comparison of Approaches. Regardless of the statistical approach, the upper bounds of the confidence intervals for the HR approached or exceeded 1, and the largest calculated difference in 2-year PFS was 6.5%, which is modest for a critical timepoint given that most DLBCL treatment failures occur within the first 2 years from diagnosis or treatment initiation.[9]

Table 8 PFS Results by Censoring Rules

PFS Analyses by Censoring Rules	Difference in 2-year PFS	HR (95% CI)	p-value
Original Data			
NALT: Not Censored ≥2 Missed Assessments: Not Censored	6.5%	0.73 (0.57, 0.95)	0.0177
Sensitivity Analyses on Original Data (nominal p-values)			
NALT: Censor ≥2 Missed Assessments: Not Censored	4.9%	0.77 (0.59, 1.01)	0.0567[a]
NALT: Censor ≥2 Missed Assessments: Censored	4.9%	0.77 (0.59, 1.01)	0.0541
Sensitivity Analyses on New Data (nominal p-values)			
NALT: Censored ≥2 Missed Assessments: Not Censored	6.1%	0.74 (0.57, 0.96)	0.0251
NALT: Censor ≥2 Missed Assessments: Censored	5.9%	0.75 (0.57, 0.97)	0.0308

[a] Prespecified by Applicant
Source: FDA analysis

The Applicant's prespecified sensitivity analysis, censoring for NALT, had a PFS HR of 0.77 with a nominal p-value of 0.0567. The Applicant's reported sensitivity analysis in Section 2.3.2.1 (Primary Efficacy Endpoint: Investigator-Assessed PFS), with a HR of 0.74 and nominal p-value < 0.05 when censoring for NALT, is based on new data incorporating post-hoc changes after FDA

noticed some discrepancies in the Applicant's NALT categorization and recategorized some NALT variables (Table 4). FDA considers assessment of the both the original and the new data to be important for sensitivity analyses to assess the robustness of the treatment effect. Additionally, in the original data, the number of PFS events when censoring for NALT was only 23 fewer. The fact that a small change in the number of events changed the statistical significance (nominal p-value = 0.0177 vs. 0.0567) suggests that the PFS benefit is modest and lacks robustness.

Note that clear alignment between a clinical question and the analysis approach (e.g., with respect to censoring for NALT) is described in the referenced ICH E9 (R1) guidance.[10] The clinical question of interest should inform the estimand strategy, but there is no recommendation provided in the guidance about a particular estimand strategy that should be used (see FDA Appendix 2: The Estimand Framework Applied to PFS and Comparison of Approaches).

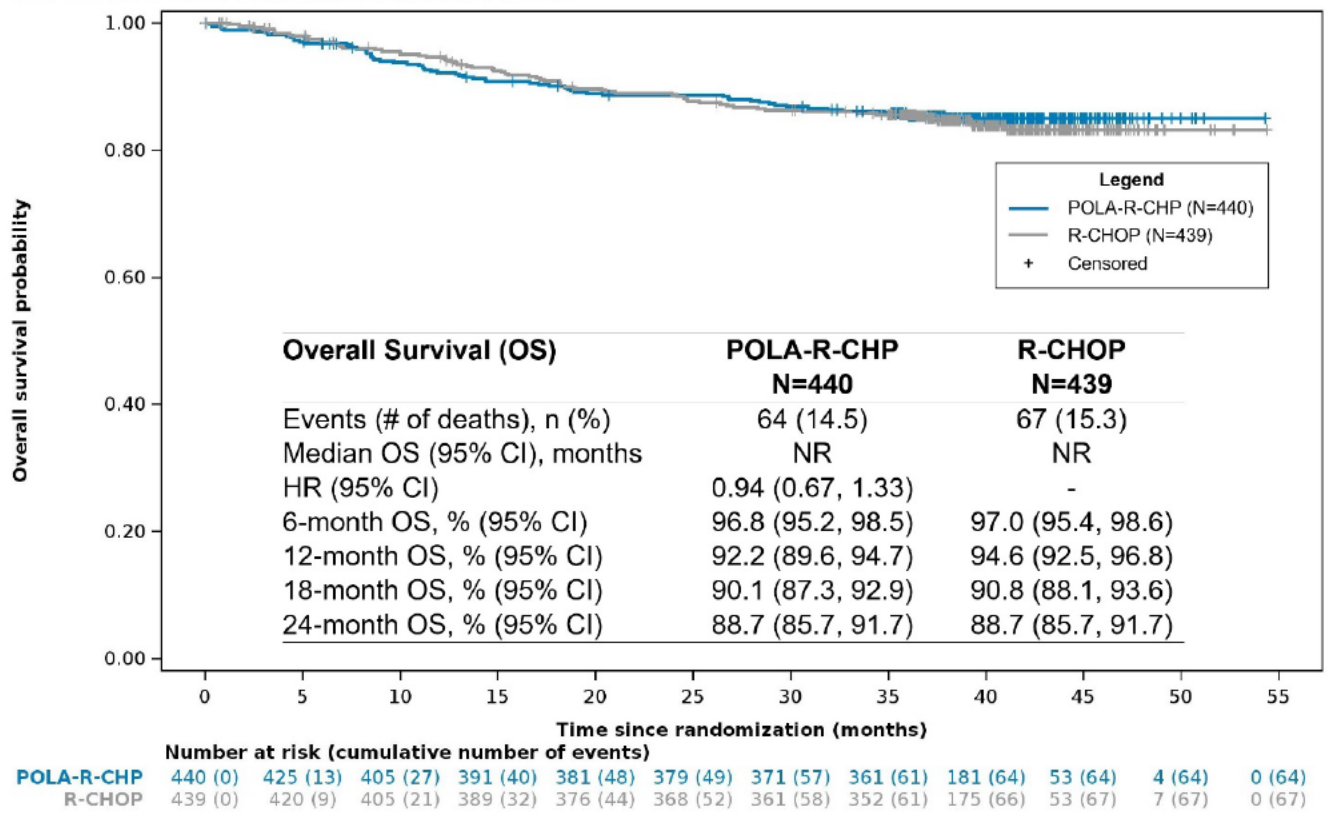
2.3.3.2 OS Results with Pola+R-CHP

As shown in the Kaplan-Meier plot of the final OS analysis (Figure 10), the PFS benefit of pola-R-CHP did not translate into an improvement in OS; the OS HR was 0.94 with an upper limit of the 95% confidence interval of 1.33. The OS curves appeared to be similar. The OS rates were numerically lower in the pola+R-CHP arm at some early time points (1-year estimate: 92.2% vs. 94.6% in the R-CHOP arm), but similar at the 2-year time point (Figure 10). As later detailed, the OS HR for DLBCL NOS, the largest lymphoma subgroup in POLARIX, exceeded 1 (Figure 11).

The FDA conducted additional interrogation of deaths to explore the uncertain OS results. Deaths within and beyond the safety reporting period are reviewed in Table 31 and Section 3.1 (Summary of Adverse Events). Additional investigation of OS with calculation of conditional probabilities under various assumptions is described in FDA Appendix 3: Additional Analyses of Overall Survival. While there is uncertainty based on the limited observed data and results are sensitive to the assumptions used, in many scenarios there was a substantial probability of the OS HR exceeding 1 (Table 26).

OS is an important metric of both efficacy and safety. POLARIX was not adequately powered to detect improvements in OS, and there is uncertainty due to the low event rates. However, a trial need not be powered for OS to provide important information, and FDA relies on the OS analysis, even if descriptive, to inform the benefit-risk determination.

Figure 10 Final OS Analysis and Estimated Early Survival Rates in the ITT Population



Overall Survival (OS)	POLA-R-CHP N=440	R-CHOP N=439
Events (# of deaths), n (%)	64 (14.5)	67 (15.3)
Median OS (95% CI), months	NR	NR
HR (95% CI)	0.94 (0.67, 1.33)	-
6-month OS, % (95% CI)	96.8 (95.2, 98.5)	97.0 (95.4, 98.6)
12-month OS, % (95% CI)	92.2 (89.6, 94.7)	94.6 (92.5, 96.8)
18-month OS, % (95% CI)	90.1 (87.3, 92.9)	90.8 (88.1, 93.6)
24-month OS, % (95% CI)	88.7 (85.7, 91.7)	88.7 (85.7, 91.7)

Source: FDA analysis. CCOD 6/15/2022.

2.3.3.3 Other Secondary Endpoints

Analyses of other efficacy endpoints, although supportive, have limitations.

Modified EFS (EFS eff)

Modified EFS, an alpha-allocated secondary endpoint, was statistically significant in the pola+R-CHP arm, with a HR of 0.75 (95% CI: 0.58, 0.96; p-value = 0.0244). However, the treatment effect on this endpoint was modest, with the 1-year point estimate differing by 3.8% and the 2-year point estimate differing by 6.2% (Table 9).

Table 9 Modified EFS, Duration of Response, and Disease-Free Survival

Secondary Endpoint	Outcome	Pola + R-CHP	R-CHOP
Modified EFS per investigator [a]	N	440	439
	Patients with event, n	112 (25.5%)	138 (31.4%)
	Death	18	20
	Progression	86	106
	NALT due to efficacy reasons[a]	8	12
	Positive biopsy	0	0
	HR (95% CI)	0.75 (0.58, 0.96)	
	Stratified log-rank p-value	0.0244[c]	
	1-year rate (95% CI)	82.5% (78.9, 86.1)	78.7% (74.8, 82.6)
	difference (95% CI)	3.8% (-1.5, 9.2)	
	2-year rate (95% CI)	75.6% (71.5, 79.7)	69.4% (65.0, 73.8)
	difference (95% CI)	6.2% (0.1, 12.2)	
DOR per investigator [b]	N	422	413
	2-year rate (95% CI)	75.7% (71.0, 80.3)	71.7% (67.1, 76.2)
	difference (95% CI)	4.0% (-2.5, 10.5)	
DFS per investigator [b]	N	381	363
	2-year rate (95% CI)	81.8% (77.4, 86.2)	77.4% (72.7, 82.0)
	difference (95% CI)	4.4% (-1.9, 10.8)	

[a] Modified EFS includes four events: disease progression, death, initiation of NALT due to an efficacy reason, and positive biopsy for residual disease after treatment completion. NALT initiated for safety reasons was not censored in this analysis.
[b] not censored for NALT
[c] two-sided $\alpha = 0.05$
Source: FDA analysis of originally submitted data

CR rate

FDA does not agree with the Applicant's efficacy claims based on a numerically, but not statistically significant, higher CR rate in the pola-R-CHP arm. The difference in BICR-assessed CR rate at the EOT, an alpha allocated endpoint, did not achieve statistical significance. Moreover, the observed difference was small (3.9%), with a 95% CI that crossed zero (95% CI: -1.9, 9.7). Thus, the PFS benefit observed with pola+R-CHP was not coupled by a significant improvement in the depth of response, raising further uncertainty about the treatment effect of polatuzumab vedotin. The ORRs were also similar (85.5% and 83.8% with pola+R-CHP and R-CHOP, respectively), with an observed difference of 1.7%.

Disease-free survival and duration of response

DFS and DOR are not validated, established regulatory endpoints for approval of a drug product. DFS is defined as the time from the date of the first occurrence of a documented CR to the date of relapse or death from any cause for the subgroup of patients achieving CR, and is

equivalent to duration of CR.

As shown in Table 9, the differences in DFS and DOR between treatment arms were modest. FDA considers results of these endpoints to be exploratory. Given that these endpoints are based on non-randomized subsets of patients and Type I error rate was not controlled, caution should be taken in comparing these outcomes between treatment arms (e.g., the comparison of the curves in the Applicant's Figure 7 and Figure 8 is not valid). No statistical significance or comparative efficacy claims should be inferred. Furthermore, the Applicant's analyses of these two endpoints do not censor for NALT, making it difficult to separate the effect of the investigational drug from the effect of NALT.

2.3.3.4 Heterogeneity of the Study Population and Treatment Effect

The heterogeneity of lymphoma subtypes has the potential to impact the interpretability and generalizability of the overall study findings.

In the ITT population, 84% of the study population had DLBCL NOS, 11% had either HGBL NOS (which itself is a heterogenous entity) or HGBL with *MYC* and *BCL2* and/or *BCL6* translocations, and 5% had other LGBLs. The treatment effect of pola+R-CHP appeared heterogeneous across lymphoma subtypes. As summarized in Table 10, PFS HRs for DLBCL NOS, HGBL, and other LBCLs were 0.75, 0.48, and 1.93, respectively, and the OS HRs were 1.02, 0.42, and 1.89, respectively. Additional results by lymphoma subgroup are provided in FDA Appendix 4: Efficacy Results by NHL Subgroup, including a tabular summary (Table 27) and forest plots of PFS (Figure 27) and OS (Figure 28).

Acknowledging that this is an exploratory post hoc evaluation with sample size limitations, the results tended to favor pola+R-CHP for the HGBL subgroup, had variable results in DLBCL NOS, and favored the control arm for the minority of other LBCLs combined. When considering CR rates and ORRs (Table 10 and FDA Appendix 4, Table 28), pola+R-CHP appeared to benefit the HGBL subgroup. For DLBCL NOS, the results were either marginal or not indicative of a positive treatment effect. Among those with DLBCL NOS (n=740, 84%), the OS HR was 1.02 as noted, with an estimated 1-year OS of 91.8% in the pola+R-CHP arm and 95.5% in the R-CHOP arm (Figure 11).

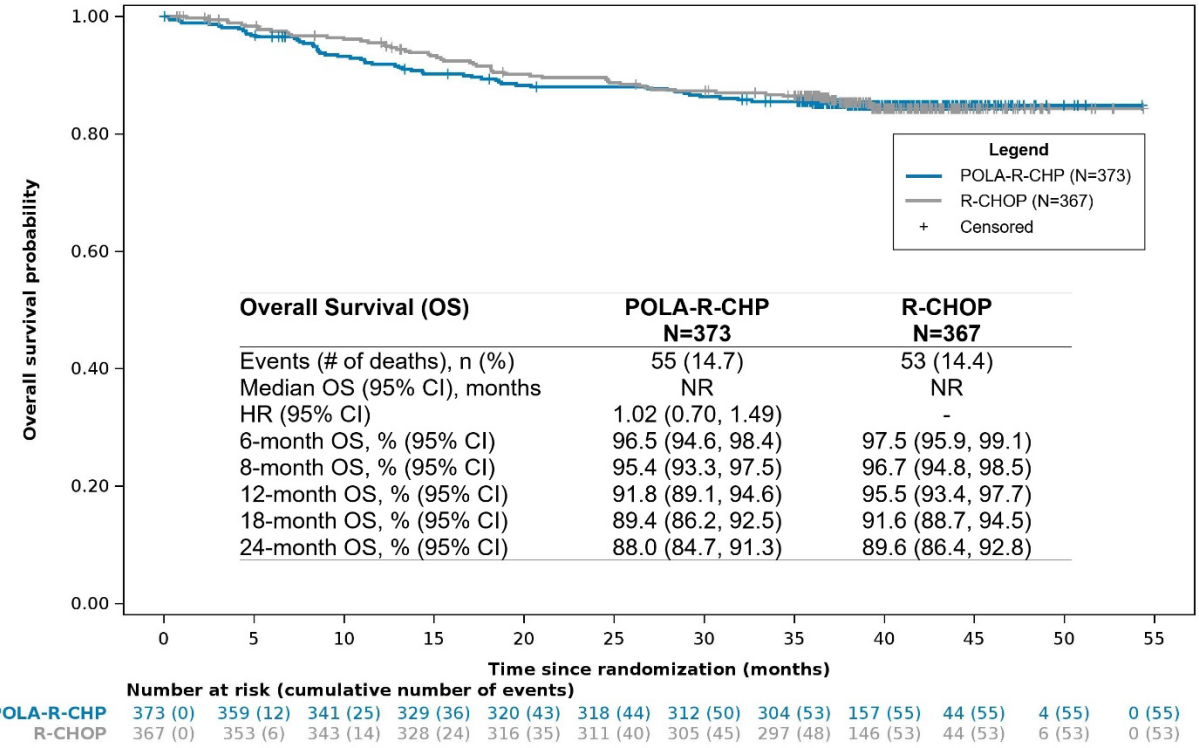
However, for all of these subgroup analyses, there is high uncertainty in the point estimates as evidenced by the wide confidence intervals, and the findings are hypothesis-generating.

Table 10 Summary of Outcomes by NHL Subgroup

	Pola+R-CHP	R-CHOP
ITT Population	n=440	n=439
PFS HR (95% CI)	0.73 (0.57, 0.95)	
OS HR (95% CI)	0.94 (0.67, 1.33)	
CR rate (95% CI)[a]	78.0% (73.8%, 81.7%)	74.0% (69.7, 78.1)
Difference (95% CI)	3.9% (-1.9, 9.7)	
DLBCL NOS	n= 373	n= 367
PFS HR (95% CI)	0.75 (0.57, 0.99)	
OS HR (95% CI)	1.02 (0.70, 1.49)	
CR rate (95% CI)	76.7% (72.0, 80.9)	74.9% (70.2, 79.3)
Difference (95% CI)	1.7% (-4.7, 8.2)	
HGBL NOS, DH/TH	n= 43	n= 50
PFS HR (95% CI)	0.48 (0.21, 1.08)	
OS HR (95% CI)	0.42 (0.15, 1.19)	
CR rate (95% CI)	88.4% (74.9, 96.1)	64.0% (49.2,77.1)
Difference (95% CI)	24.4% (5.8, 42.9)	
Other LBCL [b]	n= 24	n= 22
PFS HR (95% CI)	1.93 (0.66, 5.64)	
OS HR (95% CI)	1.89 (0.35, 10.33)	
CR rate (95% CI)	79.2% (57.8, 92.9)	81.8% (59.7,94.8)
Difference (95% CI)	-2.7% (-28.2, 22.9)	

[a] CR rate per BICR at the end of therapy
[b] T-cell/histiocyte-rich LBCL (n=28) and EBV+ DLBCL (n=18)
Source: FDA analysis. OS based on CCOD of 6/15/2022.

Figure 11 Kaplan-Meier Plot of OS in Patients with DLBCL NOS



Overall Survival (OS)	POLA-R-CHP N=373	R-CHOP N=367
Events (# of deaths), n (%)	55 (14.7)	53 (14.4)
Median OS (95% CI), months	NR	NR
HR (95% CI)	1.02 (0.70, 1.49)	-
6-month OS, % (95% CI)	96.5 (94.6, 98.4)	97.5 (95.9, 99.1)
8-month OS, % (95% CI)	95.4 (93.3, 97.5)	96.7 (94.8, 98.5)
12-month OS, % (95% CI)	91.8 (89.1, 94.6)	95.5 (93.4, 97.7)
18-month OS, % (95% CI)	89.4 (86.2, 92.5)	91.6 (88.7, 94.5)
24-month OS, % (95% CI)	88.0 (84.7, 91.3)	89.6 (86.4, 92.8)

Number at risk (cumulative number of events)

POLA-R-CHP	373 (0)	359 (12)	341 (25)	329 (36)	320 (43)	318 (44)	312 (50)	304 (53)	157 (55)	44 (55)	4 (55)	0 (55)
R-CHOP	367 (0)	353 (6)	343 (14)	328 (24)	316 (35)	311 (40)	305 (45)	297 (48)	146 (53)	44 (53)	6 (53)	0 (53)

Source: FDA analysis. CCOD 6/15/2022.

3. Safety

The Applicant's Position:

3.1 Summary of Adverse Events

In POLARIX, patients were randomized to receive one of two placebo-controlled blinded regimens:

- Pola+R-CHP: R-CHP combined with polatuzumab vedotin and placebo for vincristine for 6 cycles, followed by 2 additional cycles of rituximab as monotherapy
- R-CHOP: R-CHOP and placebo for polatuzumab vedotin for 6 cycles, followed by 2 additional cycles of rituximab as monotherapy.

Both regimens were administered for a fixed duration, and the adverse events predominantly accumulated during treatment. In addition, the study substituted vincristine, an anti-mitotic inhibitor, with polatuzumab vedotin, an antibody-drug conjugate that delivers a potent anti-mitotic inhibitor payload. Therefore, the adverse events (AEs) observed with pola+R-CHP were anticipated to be similar to what has been observed with R-CHOP, a well understood and well managed standard of care regimen for the past 20 years.

The safety results show that the overall safety profile of pola+R-CHP was comparable to R-CHOP (**Table 11**).

Table 11 Overview of Safety in POLARIX (Safety-Evaluable Population)

	R-CHOP (N=438)	Pola+R-CHP (N=435)
Total number of patients with at least one AE	431 (98.4%)	426 (97.9%)
Total number of AEs	5189	5470
Total number of patients with at least one		
Grade 5 AE	10 (2.3%)	13 (3.0%)
Grade 3-5 AE	262 (59.8%)	264 (60.7%)
Serious AE	134 (30.6%)	148 (34.0%)
AE leading to study discontinuation	10 (2.3%)	13 (3.0%)
AE leading to any study treatment dose discontinuation	29 (6.6%)	27 (6.2%)
AE leading to any study treatment dose reduction	57 (13.0%)	40 (9.2%)
AE leading to any study treatment dose interruption	111 (25.3%)	103 (23.7%)
AE leading to polatuzumab vedotin/placebo discontinuation	22 (5.0%)	19 (4.4%)
AE leading to polatuzumab vedotin/placebo dose reduction	45 (10.3%)	24 (5.5%)
AE leading to polatuzumab vedotin/placebo dose interruption	62 (14.2%)	61 (14.0%)
AE leading to vincristine/placebo discontinuation	22 (5.0%)	19 (4.4%)
AE leading to vincristine/placebo dose reduction	45 (10.3%)	24 (5.5%)
AE leading to vincristine/placebo dose interruption	60 (13.7%)	60 (13.8%)

Source: t_ae_profile_SE_28JUN2021_39942.

The pola+R-CHP arm had comparable incidence of treatment discontinuations and interruptions to the R-CHOP arm. In addition, there was a lower incidence of dose reductions in the pola+R-CHP arm (**Table 11**). This observation was driven by peripheral neuropathy (PN) adverse events leading to any study treatment dose reduction that were lower in the pola+R-CHP arm compared to the R-CHOP arm (Appendix 10). Relative dose intensity was high (median close to 100%) for both arms indicating that pola+R-CHP was as well tolerated as R-CHOP (Appendix 13).

The incidence of Grade 5 AEs observed in POLARIX were comparable between the two arms and similar to that observed in other randomized Phase III studies involving R-CHOP in 1L DLBCL (e.g. GOYA 4.3%, PHOENIX 2.9% and ROBUST 2% [Vitolo et al. 2017; Younes at al. 2019 and Nowakowski et al. 2021, respectively]).

Hematologic toxicities and peripheral neuropathy are well-recognized adverse events associated with R-CHOP therapy. The clinical management of these adverse events is well understood within the lymphoma community. The POLARIX protocol mandated G-CSF prophylaxis for all patients in both treatment arms, with 93.2% of R-CHOP patients receiving at least one G-CSF treatment for prophylaxis use compared to 90.1% in pola+R-CHP.

In POLARIX, hematologic toxicities (neutropenia, febrile neutropenia and anemia) graded by Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 were the most common Grade 3-4 adverse events in both arms (Appendix 14). Overall, the proportion of patients who experienced neutropenia (including febrile neutropenia) was generally comparable, R-CHOP (42.7%) compared to pola+R-CHP (46%) (Appendix 11). Neutropenia (including febrile neutropenia) and other hematologic adverse events were almost all resolved in both arms (R-CHOP: 97.9%; pola+R-CHP: 98.0%) (Appendix 15).

The proportion of patients who experienced serious neutropenia events was higher in the pola+R-CHP arm compared to R-CHOP and was mainly due to a higher incidence of serious febrile neutropenia in the pola+R-CHP arm (Table 12). The higher incidence of febrile neutropenia did not impact dose deliverability as study treatment discontinuations, dose reductions, and study treatment interruptions due to febrile neutropenia were comparable (Appendix 12).

Infections are a potential consequence of neutropenia. The proportion of patients who experienced infections in the pola+R-CHP arm was higher than in the R-CHOP arm. The incidence of Grade ≥3 infections was also numerically higher in the pola+R-CHP arm compared with the R-CHOP arm. There were no fatal neutropenia events, and fatal (Grade 5) infections were similar between arms (1.1% in pola+R-CHP and 1.4% in R-CHOP) (Table 12). The increased incidence of infections in the pola+R-CHP arm did not lead to an increase in study treatment discontinuations or dose reductions compared with the R CHOP arm. Treatment interruptions were comparable (Appendix 11). The majority of patients in both arms, pola+R-CHP (87.0%) and R-CHOP (84.5%), reported that all infections had resolved at the time of clinical cut off (Appendix 15).

FDA has expressed a concern that myelosuppression may be underestimated in the POLARIX laboratory dataset, as hematology labs were not mandated at the mid-cycle nadir. Midcycle nadir labs were not collected in POLARIX because this is not standard clinical practice for 1L DLBCL patients receiving R-CHOP. To address FDA's concern about potential underestimation of myelosuppression, an additional analysis of neutropenia was conducted. Taking a conservative approach of combining physician reported adverse events of neutropenia with reported laboratory data of neutropenia, the incidence of neutropenia was comparable (Table 12).

Table 12 Neutropenia (including Febrile Neutropenia) and Infections (Safety-Evaluable Population)

	R-CHOP (N=438)	Pola+R-CHP (N=435)
Neutropenia (including Febrile Neutropenia)		
All Grade[1]	264 (60.3%)	262 (60.2%)
Grade 3-4[1]	184 (42.0%)	171 (39.3%)
Grade 5[1]	0	0
Serious	37 (8.4%)	50 (11.5%)
Febrile Neutropenia	35 (8.0%)	62 (14.3%)
Serious Febrile Neutropenia	28 (6.4%)	43 (9.9%)
Infections		
All Grade	187 (42.7%)	216 (49.7%)
Grade 3-4	49 (11.2%)	61 (14.0%)
Grade 5	6 (1.4%)	5 (1.1%)
Serious	45 (10.3%)	61 (14.0%)

Source: t_lb_abn_v3_NTT_WORSEN_SE_28JUN2021_39942; t_ae_profile_INF_SE_28JUN2021_39942; t_ae_profile_FNEUT_SE_28JUN2021_39942; t_ae_aepi_pt_grd_SE_28JUN2021_39942.

[1]The incidence rate of the on-treatment laboratory abnormality includes lab data and the treatment-emergent adverse event data corresponding to the respective abnormal lab tests. For a patient with multiple worsened post-baseline lab abnormalities, the highest (worst) grade of these abnormalities for the given lab test is reported. "Any" is the number of patients with a worsened post-baseline abnormality of any grade for the specified lab test.

Microtubule inhibiting agents such as vincristine and polatuzumab vedotin are associated with peripheral neuropathy (PN) complications. The proportion of patients who experienced PN because of treatment was comparable between the two arms (Table 13). There were fewer dose reductions and discontinuations due to PN in patients treated with pola+R-CHP (Appendix 11). The majority of patients (R-CHOP: 66.9%; pola+R-CHP: 57.8%) reported that the PN events had resolved at the time of clinical cutoff (Appendix 15).

Table 13 Peripheral Neuropathy by Grade (Safety-Evaluable Population)

	R-CHOP (N=438)	Pola+R-CHP (N=435)
All Grade	236 (53.6%)	230 (52.9%)
Grade 1	163 (37.2%)	170 (39.1%)
Grade 2	68 (15.5%)	53 (12.2%)
Grade 3	5 (1.1%)	7 (1.6%)
Grade 4/5	0	0

Source: t_ae_aepi_pt_grd_SE_28JUN2021_39942.

Additional analyses were performed on other risks (anemia, thrombocytopenia, hepatotoxicity, TLS, pulmonary toxicity, hyperglycemia, cardiac arrhythmias, and infusion related reactions) with the potential to impact the benefit-risk assessment for pola+R-CHP. Rates were generally comparable between the pola+R-CHP and R-CHOP arms. Where there were differences, the impact on dose delivery was comparable, and therefore did not adversely impact the favorable benefit-risk profile of pola+R-CHP (Appendix 11). The incidence of secondary malignancies, a latent adverse event, was comparable between the R-CHOP and pola+R-CHP (Appendix 11).

The FDA's Position:

FDA agrees that the overall safety profile of pola+R-CHP was comparable to R-CHOP, and that the dose delivery of chemotherapy backbone was comparable. Selected safety analyses are shown in FDA Appendix 6: Selected Safety Analyses. Rates of SAEs, grade 3 or higher AEs, and fatal AEs were similar between treatment arms, and the incidences of these events were similar by histologic subgroup (Table 30). However, the incidences of infection, febrile neutropenia, nausea, and diarrhea were at least 5% higher in recipients of pola+R-CHP.

FDA generally agrees with the Applicant's assessment of infection rates and febrile neutropenia. However, myelosuppression is likely underestimated in the POLARIX trial, given that hematology labs were mandated only at the start of each cycle, thus not capturing the blood count nadir. Mandated prophylactic G-CSF was administered in 90% of patients in the pola+R-CHP arm and 93% in R-CHOP; 10% of patients in the pola+R-CHP arm and 6% of patients in the R-CHOP arm developed febrile neutropenia despite G-CSF prophylaxis.

The treatment arms had similar rates and grades of peripheral neuropathy, and similar rates of peripheral neuropathy- driven dose modifications and discontinuations. However, FDA notes that fewer patients in the pola+R-CHP arm had resolution of peripheral neuropathy, with or without sequelae, by the clinical cutoff date: 58%, versus 67% in the R-CHOP arm (Table 25).

Because the pola+R-CHP OS curve lies below that of the R-CHOP curve at some early time points (Figure 10), FDA conducted additional interrogation of deaths within and beyond the safety reporting period (FDA Appendix 6, Table 31). Limited information was available for some deaths occurring beyond 90 days, precluding confirmation of the cause of death (i.e., adverse event versus progression) in those cases. In summary, the number and patterns of deaths in the safety reporting period were similar between both arms with AEs, mostly infection, being the leading cause of death, followed by progressive disease. The FDA also interrogated deaths in the first 18 months from randomization in 6-month time periods, but did not identify a safety signal.

3.2 Overall Safety Conclusion for Polatuzumab Vedotin in 1L DLBCL

The Applicant's Position:

In POLARIX, pola+R-CHP was well tolerated and had a safety profile comparable to R-CHOP.

- Patients were randomized to one of two fixed duration regimens, R-CHOP and pola+R-CHP. The adverse events predominantly accumulated during treatment.
- Both arms had high relative dose intensity, with the pola+R-CHP arm having fewer dose reductions than the R-CHOP arm.
    - This observation is important because patients who do not receive the treatment at the prescribed doses and approximate 21-day cycle intervals tend to have poorer outcomes, indicating that maintaining intensity of therapy is predictive of positive curative outcome (Bataillard et al. 2021; Yamaguchi et al. 2011).
- The incidence of febrile neutropenia was higher in the pola+R-CHP arm. Almost all events resolved and study treatment discontinuations, dose reductions, study treatment interruptions, and fatal infections were comparable. There were no Grade 5 neutropenia events. The incidence of febrile neutropenia in pola+R-CHP treated patients is consistent with that observed with R-CHOP in other large studies in 1L DLBCL (Vitolo et al. 2017; Younes at al. 2019; Nowakowski et al. 2021).
- The incidence of PN was comparable between pola+R-CHP and R-CHOP arms.

The FDA's Position:

Refer to the FDA's position in Section 3.1 (Summary of Adverse Events). FDA agrees with the Applicant's position on the general comparable safety profile between pola-R-CHP and R-CHP arms but underscores the increased incidence of febrile neutropenia and infections in the pola-R-CHP arm. Patient-report outcomes are another important metric of tolerability and are discussed in the next section.

4. Clinical Outcome Assessment Analyses

The Applicant's Position:

Symptom presentation in DLBCL is variable and often dependent on the site of disease involvement. Patients may present as asymptomatic, while others will exhibit enlarged lymph nodes and experience B symptoms (e.g. fever, weight loss, and night sweats).

In POLARIX, patient reported outcome (PRO) measures were collected at treatment and follow up visits for patients who have not had progression. Because of this, the POLARIX PRO data measure treatment tolerability, disease symptoms, and global quality of life; they provide limited insight into disease relapse.

The PRO instruments Functional Assessment of Cancer Therapy-Lymphoma Lymphoma Subscale (FACT-Lym LymS), European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 questionnaire (EORTC QLQ-C30) and Functional Assessment of Cancer Treatment/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-NTX) were collected in

POLARIX. FACT-Lym LymS assesses symptoms common in patients with lymphoma; EORTC QLQ-C30 assesses global quality of life and common disease and treatment-related symptoms. The FACT/GOG-NTX assessed neuropathy symptoms, as it is a treatment-related effect common to both polatuzumab vedotin and vincristine. Completion rates were >90% in both arms in all PRO measures during treatment-to-treatment completion and were >80% at follow-up months 6 and 12.

Global quality of life (EORTC QLQ-C30), lymphoma subscale scores, and neuropathy symptom scores were similar over time between treatment arms, consistent with the similar safety profile of the treatment regimens. EORTC QLQ-C30 incorporates multiple functional scales and symptom scales. In both arms, POLARIX patients reported similar role and physical functioning as well as resolution to baseline of diarrhea, nausea, and loss of appetite symptoms after treatment was completed (Appendix 16).

The PRO data demonstrates that in a double-blinded manner, no detriment to global quality of life during treatment was observed with pola+R-CHP compared to R-CHOP.

The FDA's Position:

The Applicant included PROs as exploratory and descriptive endpoints without multiplicity adjustment. PROs were sparsely collected in the POLARIX trial using the EORTC-QLQ-C30, FACT-LYM and FACT-GOG-NTX measures. Although FACT subscales were included in the trial, the FACT GP5 item regarding "overall side effect bother" was not administered to patients, which could have allowed for improved tolerability assessment in POLARIX. Completion rate for PRO was high and symmetric up to follow up month 12, with completion rates greater than 80% for all measures throughout that time period.

FDA focused its PRO analysis on tolerability through the month 12 timepoint from the collected PRO data, FDA noted that there were more patients treated with Pola-R-CHP who reported diarrhea, nausea, and decreased appetite compared to R-CHOP during the treatment period but otherwise no major differences between arms (See Appendix 16). FDA disagrees with the Applicant statement that "no detriment to global quality of life during treatment was observed with Pola+R-CHP compared to R-CHOP." First, lack of superiority is not suitable evidence for claims of comparability or similarity between arms. A claim of non-inferiority or equivalence should be supported by evidence that the sensitivity of the measure is adequate and the trial should be adequately designed. Secondly, in POLARIX, the PRO assessment strategy, including the selected instruments, PRO assessment frequency, and PRO endpoints, were not designed to make this claim. Specifically, the Applicant should have assessed expected treatment-related side effects at a high frequency during the treatment period and included an overall side effect impact summary measure. Lastly, global health related quality of life is not an adequate measure of tolerability, and a symptom specific approach focusing on severity, frequency, duration and interference could have been used to characterize the tolerability of pola+R-CHP.

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

5.1 Applicability of POLARIX Results to the U.S. Population

The Applicant's Position:

POLARIX enrolled patients from 22 countries across North America, Europe, Asia Pacific, and South America. The large sample size (N=879) of the POLARIX study represents a generalizable 1L DLBCL population and includes a diverse population with poor prognostic factors (covered in multiple subgroups).

The U.S. contributed the highest enrollment. A total of 234 (26.6%) patients were enrolled at sites located in all regions of the continental U.S. Table 14 shows the racial and ethnic distribution of U.S. patients (Tilly et al. 2022). These patient distributions are similar to what was seen in estimates from American Cancer Society of the incidence of lymphoma in the U.S. (Teras et al. 2016), analyses of the U.S. Surveillance Epidemiology and End Results (SEER) cancer registry and the U.S. Lymphoma Epidemiology of Outcomes (LEO) cohort study funded by NCI U01CA195568 involving 8 academic medical centers (Flowers et al. 2018). Based on self-identified race/ethnicity, 85% of LEO participants were White, 7.4% were Black/African American, 2.6% were Asian, 3.5% other/more than one race, and 9.9% were Hispanic. Among people diagnosed with lymphoma in SEER, 83% were White, 7.5% were Black/African American, 7.1% were Asian, 0.5% other/more than one race, and 13.1% were Hispanic.

Table 14 Race and Ethnicity of POLARIX Patients Enrolled in the U.S.

	R-CHOP N=128	Pola+R-CHP N=106
American Indian or Alaska Native, n (%)	0	1 (1)
Asian, n (%)	3 (2)	3 (3)
Black or African American, n (%)	8 (6)	8 (8)
Native Hawaiian or other Pacific Islander, n (%)	0	0
White, n (%)	98 (77)	79 (75)
Other, n (%)	3 (2)	1 (1)
Unknown, n (%)	16 (13)	14 (13)
Hispanic or Latino, n (%)*	12 (9)	5 (5)

*Hispanic or Latino patients are also included in applicable race categories.
Source: Tilly et al. 2022 (supplementary appendix).

The FDA's Position:

Demographic information for the entire ITT population, including race and ethnicity, is provided in Table 19.

Racial and ethnic distribution is one of multiple determinants of applicability to the general U.S. population. The POLARIX study population may not be representative of the general population of patients with previously untreated LBCL given the eligibility requirements, such as the exclusion of patients with poor performance status, prohibitive comorbidities, end-organ dysfunction, or known CNS involvement by lymphoma. The latter may bias the HGBL outcomes

in particular, since HGBL is a highly aggressive lymphoma with a heightened risk of CNS dissemination. Accordingly, more intensive frontline regimens for HGBL include systemic agents that penetrate the blood-brain barrier, such as methotrexate and cytarabine.[1,4]

As noted previously, the Applicant's proposed indication for "DLBCL" includes a heterogeneous group of aggressive lymphomas, including HGBL which is itself heterogeneous. Importantly there is uncertainty to what extent use of R-CHOP is generalizable to the U.S. population with HGBL, given that other, generally more intensive frontline regimens tend to be preferred (Table 29).

6. Points for the Advisory Committee to Consider

The Applicant's Position:

The goal of DLBCL treatment is cure. The highest chance for cure is in the 1L setting and achieving cure without need for therapy beyond 1L treatment is meaningful to patients.

In the 1L DLBCL setting, PFS and EFS_{eff} best represent cure, as the vast majority of relapse or progression occurs within 2 years and patients who do not experience disease progression or relapse by 2 years are highly likely to have nearly the same life expectancy as that of a sex- and age matched general population (Maurer et al. 2014). CR and ORR are important milestones but require durability to reflect cure.

POLARIX met its primary endpoint by demonstrating that pola+R-CHP reduced the risk of disease progression, disease relapse or death by 27% compared to R-CHOP (PFS HR 0.73 [95% CI 0.57, 0.95]; two-sided log-rank p-value=0.0177). Given the importance of PFS at 2 years, the estimate for the pola-R-CHP arm was 6.5% higher than the R-CHOP arm (76.7% vs 70.2%). These results are statistically significant and clinically meaningful. The study design and statistical analysis plan complied with FDA feedback.

Results of pre-specified PFS sensitivity analyses as well as a post-hoc sensitivity analysis censoring PFS for missing tumor assessments and NALT were consistent with the primary PFS analysis, supporting the robustness of the treatment effect.

POLARIX also demonstrated a statistically significant and clinically meaningful improvement in the key secondary endpoint of EFS_{eff} (HR 0.75 [95% CI 0.58, 0.96]; p=0.0244), supportive of the PFS result.

With approximately median 40 months of follow up, OS remains immature and did not show a significant difference between groups (HR 0.94 95% CI 0.67, 1.33; p=0.7326). This was not surprising given that the median OS for patients receiving 1L treatment for DLBCL is >8 years (with the majority of deaths ultimately unrelated to DLBCL), and Phase III trials using OS as an endpoint can take approximately 10 years to complete (Shi et al. 2018; Stathis et al. 2018).

This was recapitulated in a simulation requested by the FDA in which the required number of OS events for a superiority comparison with at least 80% power in POLARIX was calculated, assuming a range of HRs from 0.73 to 0.81. A range of 317 to 708 deaths, respectively, would need to be observed to power for these HRs. In POLARIX, it would take approximately 8 years to observe 317 deaths or 40 years to observe 708 deaths. These illustrative timeframes, along with potentially small underlying difference in OS confounded by subsequent lymphoma therapies, underscore the challenges with designing a 1L DLBCL study to detect an improvement in OS with the aim of bringing safe and effective drugs to patients in a timely manner.

In FDA's guidance Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA 2018), when "*survival may be prolonged, making an overall survival endpoint impractical*", DFS is considered a direct measure of clinical benefit in specific disease settings and is important "*when a large percentage of patients achieve CRs with chemotherapy*". This is relevant to POLARIX as survival is prolonged in 1L DLBCL and CR as best response were 82.7% in the R-CHOP arm and 86.6% in the pola+R-CHP arm. Although DFS was not in the POLARIX testing hierarchy because it is assessed in the subset of patients who achieve CR rather than in the ITT population, DFS HR 0.74 (95% CI 0.56, 0.98) is consistent with PFS and EFS_{eff} and supports greater probability of cure with pola+R-CHP.

The overall safety profile of pola+R-CHP is comparable to R-CHOP. The comparable safety profile and median 99.8% relative dose intensity indicate that the 1.8 mg/kg dose of polatuzumab vedotin in combination with R-CHP used in POLARIX is as tolerable as R-CHOP and that pola+R-CHP is unlikely to compromise efficacy for patients who could derive benefit from R-CHOP.

Myelosuppression (including neutropenia, febrile neutropenia, thrombocytopenia, and anemia) is an identified risk associated with treatment with polatuzumab vedotin. In POLARIX, myelosuppression was generally comparable across arms except for febrile neutropenia that was higher with pola+R-CHP. The higher rate of febrile neutropenia with pola+R-CHP did not lead to an increase in fatal infections, the most severe long-term sequelae, nor impact dose deliverability. This is important because in the 1L DLBCL setting, maintaining intensity of therapy is predictive of positive curative outcome. Almost all neutropenia adverse events were reported as resolved (98%).

The clinical management of myelosuppression including febrile neutropenia is well understood by hematologists/oncologists. The POLIVY prescribing information will inform physicians about the risk of febrile neutropenia.

Fewer patients in the pola+R-CHP arm received salvage therapies (with their associated morbidity) compared to the R-CHOP arm. The reason for more salvage therapies in the R-CHOP arm is because more disease progression occurred in a higher proportion of these patients. Patients in both treatment arms did not have residual toxicities that would impact the ability to

receive the same types of non-protocol anti-lymphoma therapies (NALT).

Patients reported comparable quality of life across treatment arms, indicative of pola+R-CHP's similar tolerability with R-CHOP.

Deaths that occurred during the first 18 months on study did not demonstrate any short or intermediate term safety difference between the treatment arms. During this period, most deaths appeared to represent the highly heterogeneous refractory DLBCL population that remains unidentifiable prospectively.

FDA notes that under certain circumstances a single "*large multicenter trial can be considered, both scientifically and legally, to be, in effect, multiple trials and can be relied on to provide substantial evidence of effectiveness*" (FDA Guidance for Industry [2019]: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products). POLARIX meets FDA's criteria for a single study to demonstrate substantial evidence of safety and effectiveness as it is a large, multiregional, adequate, well-controlled, well-conducted trial with a statistically significant and clinically meaningful effect on PFS.

POLARIX is the first advance for 1L DLBCL patients in 20 years. DLBCL patients in the U.S. should have access to pola+R-CHP to increase their chance for cure in the 1L setting and avoid the need for salvage therapies.

The FDA's Position:

FDA does not agree with the Applicant's position that the results of POLARIX clearly demonstrate a positive benefit-risk with substituting polatuzumab vedotin-piiq for vincristine in the R-CHOP regimen.

In summary, the primary PFS analysis and various sensitivity analyses demonstrated a modest benefit for pola+R-CHP. The largest difference in the 2-year PFS rate was 6.5%. Additionally, the PFS benefit did not translate into a benefit in CR rate, and there was lack of an OS benefit and substantial uncertainty in the estimated OS. The utility of other secondary efficacy endpoints such as modified EFS, DFS, and DOR is limited and the results were modest. The latter two endpoints are not ITT-based analyses, and these endpoints can only serve as supportive evidence.

Additionally, the heterogeneity of the study population and outcomes with respect to histologic subgroups impacts the interpretability and generalizability of the study findings. Outcomes consistently favored pola+R-CHP in the minority of patients with HGBL, where the adequacy of R-CHOP is questionable and more intensive regimens are generally preferred. In the largest subgroup (DLBCL NOS, comprising 84% of the study population), the PFS effect was modest, there were similar CR and ORR rates and notably, the OS HR was 1.02 (95% CI: 0.70, 1.49) on the final prespecified analysis. Longer follow-up may be needed to inform the impact of pola+R-CHP on OS.

There was little dose exploration of polatuzumab vedotin in combination with R-CHP to determine whether the 1.8 mg/kg dose is optimized for efficacy and safety. FDA agrees with the Applicant that the overall safety profiles of pola+R-CHP and R-CHOP were comparable, and that delivery of the chemotherapy backbone was not compromised in the experimental arm. However, myelosuppression was incompletely characterized, and the incidences of febrile neutropenia, nausea, and diarrhea were at least 5% higher in the pola+R-CHP arm. Additionally, the PRO assessment strategy was inadequate to measure tolerability or to support that there no was detriment in the pola+R-CHP arm.

The only FDA approval for untreated DLBCL in the past two decades, rituximab, was based on 3 randomized trials, each demonstrating a statistically significant prolongation of OS as well as clear improvement in the primary efficacy endpoint. The Applicant seeks traditional approval of polatuzumab vedotin in the frontline, curative-intent setting based on the POLARIX trial results. Given the uncertainties with the PFS and OS results, the question arises whether, based on the totality of data, the benefit-risk for polatuzumab vedotin in patients with LBCL in the frontline setting, including patients with DLBCL NOS, is favorable.

7. Draft Topics for Discussion by the Advisory Committee

- Discuss the benefit-risk profile of pola+R-CHP for the proposed patient population with LBCL, including patients with DLBCL NOS, considering the results of the POLARIX trial.

- Based on the results of the POLARIX trial, specifically the OS results, discuss whether additional follow-up data from POLARIX should be required to inform the benefit-risk of polatuzumab vedotin-piiq in patients with LBCL in the frontline setting.

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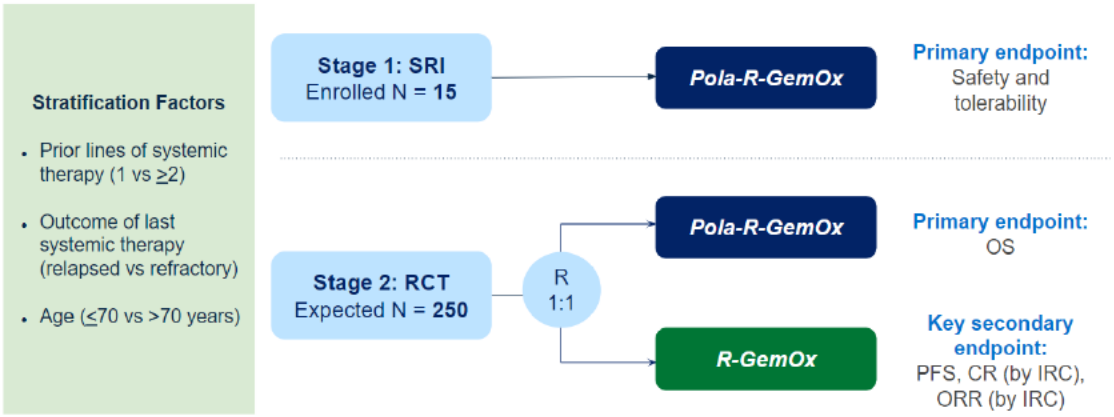
9. Appendices

9.1 Applicant's Appendices

Appendix 1: MO40598 (POLARGO) Study Design

Figure 12 MO40598 (POLARGO) Study Design



IRC=independent review committee; ORR=overall response rate; OS=overall survival; R-GemOx=rituximab plus gemcitabine and oxaliplatin; PFS=progression-free survival; RCT=randomized controlled trial; SRI=safety run-in.

Appendix 2: Summary of the Current Treatment Options in 1L DLBCL

Table 15 Summary of the Current Treatment Options in 1L DLBCL

	FDA Approved Treatments
Product Name **Relevant Indication** **Year/Type of Approval**	RITUXAN (rituximab) For the treatment of adult patients with previously untreated DLBCL, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens 2006/Full Approval
Efficacy Information	
NHL Study 7 (N=632)	**R-CHOP vs CHOP** Median PFS: 3.1 years vs 1.6 years HR: 0.69 OS at 2 years: 74% vs 63%
NHL Study 8 (N=399)	**R-CHOP vs CHOP** Median EFS: 2.9 years vs 1.1 years HR: 0.60 OS at 2 years: 69% vs 58%
NHL Study 9 (N=823)	**R-chemo vs chemo** Median time to treatment failure: NE years vs NE years HR: 0.45 OS at 2 years: 95% vs 86%
Important Safety and Tolerability Issues	Grade 3 or 4 ADRs occurring more frequently in the R-CHOP arm vs CHOP arm: thrombocytopenia (9% vs 7%) and lung disorder (6% vs 3%). Other Grade 3 or 4 ADRs occurring more frequently in the R-CHOP arm were viral infection (NHL Study 8), neutropenia (NHL Studies 8 and 9), and anemia (NHL Study 9).

Source: RITUXAN (rituximab) USPI.

Appendix 3: Randomized Clinical Trials in 1L DLBCL

Table 16 Randomized Clinical Trials in 1L DLBCL

Study	Accrual start	Treatment	N	Primary Endpoint	HR target	HR actual	Result Based on Primary Endpoint	Reference
LNH 03-2B	2003	R-CHOP21 vs R-ACVBP + methotrexate, rituximab, ifosfamide, etoposide, and cytarabine	380	EFS	@ 2yrs: 75%→85%	0.56	Positive (R-ACVBP toxic; vindesine, 'V', unavailable in the U.S.)	Recher (2011)
LNH 03-6B	2003	R-CHOP21 vs R-CHOP14	602	EFS	@ 2yrs: 55%→65%	@ 3yr: 56%→60% (HR 1.04)	Negative	Delarue (2013)
NHL-13	2004	R-CHOP→Observation vs rituximab (maintenance)	662	EFS	0.625	0.79	Negative	Jaeger (2015)
UK NCRI	2005	R-CHOP21 vs R-CHOP14	1080	OS	@2yrs: 70%→78%	@2yrs: 80.2%→82.7% (HR 0.90)	Negative	Cunningham (2013)
Alliance/CALGB 50303	2005	R-CHOP vs DA-EPOCH-R	524	**PFS**	**0.65**	0.93	Negative	Bartlett (2019)
PRELUDE	2006	R-CHOP→enzastaurin vs placebo (maintenance)	758	DFS	0.67	0.92	Negative	Crump (2016)
MAIN	2007	R-CHOP (14/21) vs RA-CHOP	787	**PFS**	**0.73**	1.09	Negative	Seymour (2014)

Table 13 Randomized Clinical Trials in 1L DLBCL (cont.)

Study	Accrual start	Treatment	N	Primary Endpoint	HR target	HR actual	Result Based on Primary Endpoint	Reference
HOVON-84	2007	R1: R-CHOP14 vs RR-CHOP14 R2: rituximab vs observation	574	CR	**CR: 77%→87%**	CR: 89%/86% HR 0.82	Negative	Lugtenburg (2020)
REMARC	2009	R-CHOP→lenalidomide vs placebo (maintenance)	650	**PFS**	**0.65**	0.71	Positive but OS HR, 1.218 (95% CI, 0.861 to 1.721)	Thieblemont (2017)
PILLAR-2	2009	R-CHOP/ R-EPOCH→everolimus vs placebo (maintenance)	742	DFS	0.70	0.92	Negative	Witzig (2018)
GOYA	2011	R-CHOP vs G-CHOP	1418	**PFS**	**0.75**	0.92	Negative	Vitolo (2017)
REMoDL-B	2011	R-CHOP vs bortezomib+R-CHOP	1128	**PFS**	**0.56**	0.86	Negative	Davies (2019)
PHOENIX	2013	R-CHOP vs ibrutinib+R-CHOP	838	EFS	0.75	0.93	Negative	Younes (2019)
ROBUST	2015	R-CHOP vs lenalidomide+R-CHOP	570	**PFS**	**0.625**	0.85	Negative	Nowakowski (2016)

Appendix 4: Major Protocol Amendments

The original global protocol dated 18 July 2017 was amended six times. The key changes to the protocol are summarized below in Table 17.

Table 17 Summary of Select Key Changes to the Protocol

Document Version, Protocol Amendement, Date	Summary of Key Changes
Protocol Amendment, Version 2, 18 October 2017	Amended according to Voluntary Harmonization Procedure (VHP) recommendations as summarized below: – Inclusion criterion for sexual abstinence for men updated per vincristine and cyclophosphamide SmPCs. – Clarification on the safety of immunization with live vaccines following rituximab therapy added. – Pregnancy testing for women of childbearing potential, 7 days of study treatment and on Day 1 of each cycle of therapy, added.
Protocol Amendment, Version 3, 3 August 2018	Inclusion and exclusion criteria revised as summarized below Inclusion criteria: – Text added stating receipt of tumor samples for central pathology review of diagnosis not required for patient enrollment. – Contraception inclusion criteria for women modified to specify when women must refrain from donating eggs. Exclusion criteria: – Some exclusion criteria were grouped for simplification. – Dose and duration of allowed corticosteroid use for lymphoma symptom control clarified. – Text added stating patients who had received curative treatment as well as patients with low-grade, early-stage prostate cancer were eligible to enroll in POLARIX. – Text added to clarify exclusion based on active infections was at the investigator's discretion. In addition, updates to align with common clinical practices were made. These changes can be found in more detail within the protocol.
Protocol Amendment, Version 4, 9 October 2018	Amended according to VHP recommendations as summarized below: – Pregnancy testing performed for women of childbearing potential, 7 days of study treatment and on Day 1 of each cycle of therapy; clarification Cycle 1 to 8 added. – Text stating exclusion based on active infections was at the investigator's discretion, added in Version 3, removed. – Typographical error in the product name corrected.
Protocol Amendment, Version 5, 3 December 2019	– Sample size and analysis plan of the Asia subpopulation analysis adjusted. – The planned futility analysis was removed. Given the timing of when the futility analysis was planned to occur, all patients would have been enrolled and completed study treatment in POLARIX. Performing the futility analysis would have not altered enrollment or exposure of study treatment to patients. Thus, it was removed. – The rationale for iDMC was updated to reflect monitoring of only safety, no longer including efficacy. Additional changes to the protocol, along with a rationale for each change, can be found in more detail in the protocol.

Table 14 Summary of Select Key Changes to the Protocol (cont.)

Document Version, Protocol Amendement, Date	Summary of Key Changes
Protocol Amendment, Version 6, 10 December 2020	Primarily statistical considerations and the analysis plan were updated as summarized below: Changes related to statistical analyses: – Main changes involved updates to the timing of the primary analysis, the secondary efficacy analysis and the overall survival interim and final analyses.
	– Timing of the primary analysis was updated to occur when there were approximately 228 PFS events, and after all patients in the global study were enrolled for at least 24 months, whichever comes later. The number of PFS events was selected to achieve statistical power of 80% for the target hazard ratio at the primary analysis and 24 months follow-up, given that in patients with previously untreated DLBCL, most disease relapse occurs within this time frame. – Hierarchical testing procedure, including possible a recycling that was used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints, was updated.
	Changes related to a Protocol Clarification Letter (PCL): – Details from a PCL dated 12 May 2020, included. This letter was sent to sites where patients were enrolled or actively received study treatment and updates the protocol where local lab sensitivity for hepatitis B DNA by PCR is above 10 IU/ml.
Protocol Amendment, Version 7, 18 December 2020	Primarily clarifications per VHP request were added regarding local lab sensitivity for hepatitis B DNA by PCR. It was clarified that the changes pertained to patients in China extension cohort. Additionally, further context to the statistical considerations and analysis plan were included. Additional changes made for increased clarity and consistency can be found in further detail within the protocol

BICR=blinded independent central review; DNA=deoxyribonucleic acid; CR=complete response EOT=End of treatment; PCL=protocol clarification letter; PCR=polymerase chain reaction; PFS=progression-free survival; OS=overall survival; VHP=voluntary harmonization procedure.

Appendix 5: Major SAP Amendments and Summary Hierarchical Statistical Testing Details

Major SAP Amendments

Major SAP amendments for POLARIX are summarized below.

SAP v1 was dated 18 June 2020. The summary of the SAP amendments is provided below:

SAP v2 (9 September 2020) was amended to incorporate the following major changes:

- The primary PFS analysis will be conducted after approximately 228 PFS events have occurred in the ITT population, and at least 24 months after the last patient is enrolled during the global enrollment phase, whichever occurs later.
- Censoring tables have been added to clarify the efficacy analysis of PFS, OS, and EFS.
- The boundary determination for the interim and final analysis of OS has been clarified.
- Additional sensitivity analyses for PFS and OS have been added.

SAP v3 (12 October 2020) amended the censoring tables to clarify the efficacy analysis of PFS and EFS_{eff}; updated the method for analyzing EFS_{all} to be consistent with the method for PFS; for time-to-event endpoints where median survival time will not expect to be reached, 1-year and 2-year rates will be reported; updated the immunogenicity analysis population to include all enrolled patients who have at least one serum anti-drug antibodies (ADA) assessment.

SAP v4 (1 December 2021) was amended to perform a 2^{nd} formal interim OS analysis in the global cohort approximately 32 months after last patient is enrolled.

Summary of Methodologies used for the Primary PFS Analysis and Selected Sensitivity Analyses

The primary efficacy endpoint is PFS, as determined by the investigator, defined as the time from the date of randomization until the first occurrence of disease progression or relapse as assessed by the investigator using the 2014 Lugano Classification for Malignant Lymphoma (Cheson et al. 2014), or death from any cause, whichever occurs first. The analysis population for this PFS analysis is the ITT population. For patients who had not progressed, relapsed, or died as of the clinical cutoff date for analysis, PFS was censored on the date of last disease assessment when the patient was known to be progression free. If no tumor assessments were performed after the baseline visit or all postbaseline tumor assessment results had overall responses of “not evaluable,” PFS was censored on the date of randomization.

The primary analysis of the study tested the equality of PFS distributions in RCHP + polatuzumab vedotin (pola) versus RCHOP:

H0: PFSR-CHP+pola=PFSR-CHOP versus H1: PFSR-CHP+pola>PFSR-CHOP

Treatment comparison was made using a one-sided level 0.025 (or equivalently, a two-sided level 0.05) stratified log-rank test. The randomization stratification factors used in the efficacy analyses are IPI score (IPI 2 vs. IPI 3-5), bulky disease (present versus absent), and geographical region (Western Europe, United States, Canada, and Australia versus Asia versus Rest of World [remaining countries]). The stratification factors were obtained from the IxRS at the time of randomization.

The Kaplan-Meier method was used to estimate the PFS distribution for each treatment arm and to construct curves for the visual description of the difference between the treatment arms. Estimates of the treatment effect was expressed as hazard ratios using a stratified Cox proportional-hazards analysis, including 95% confidence intervals. Median PFS was not expected to be reached in this study at the time of the primary PFS analysis clinical cutoff; hence, the 1year and 2year rates were used to describe PFS in addition to the hazard ratio. Results from an unstratified analysis were also provided.

As a sensitivity analysis to assess the overall impact of NALT, for patients who had taken NALT prior to or in the absence of subsequent death or disease progression, their PFS was censored at the time of their last adequate tumor assessment before the first NALT.

The impact of missing scheduled tumor assessments on PFS was assessed by performing a sensitivity analysis based on the interval censoring analysis methods. The PFS survival curves was estimated using the nonparametric maximum likelihood estimate (NPMLE) (Turnbull 1974) for each treatment arm. One-year and 2-year rates of each treatment arm were reported, and their 95% confidence intervals were constructed based on the Greenwood method. For descriptive purpose, hypothesis testing was performed based on the logrank test proposed by Sun (Sun 1996) to compare the PFS between the treatment arms. The treatment effect was estimated using a stratified proportional hazard regression model (Finkelstein 1986) with a parametric assumption of piecewise exponential distribution for the baseline hazard function (Friedman et al. 1982; Royston and Parmar 2002).

Summary Hierarchical Statistical Testing Details

Hierarchical Testing Procedure: To control the overall type I error rate at a one-sided 0.025 level of significance, the following hierarchical testing procedure including possible alpha recycling was used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints (Figure 13):

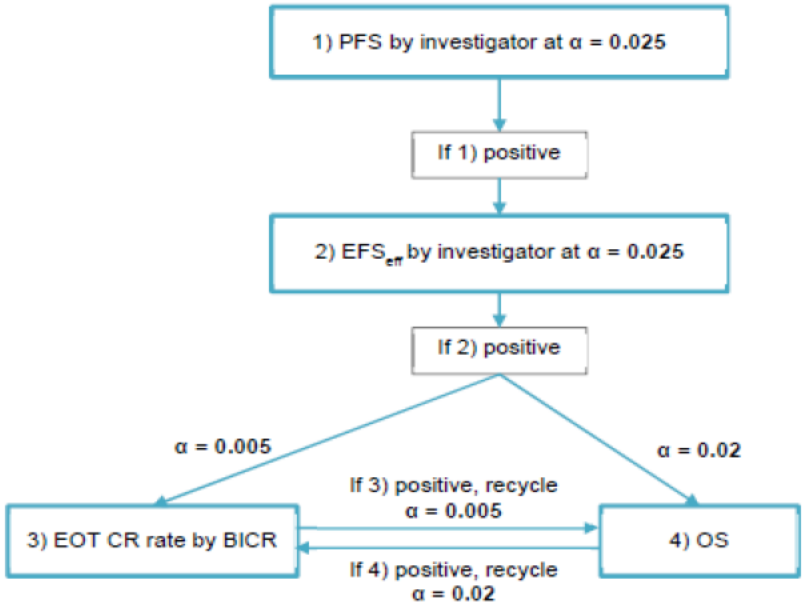
– **(1)** Test PFS assessed by investigator at a one-sided 0.025 level.

– **(2)** If **(1)** was significant, test EFS_{eff} by investigator at a one-sided 0.025 level

– If **(2)** was significant, the one-sided 0.025 alpha (α)was to be split between EOT CR rate by BICR (α = 0.005) and OS (α = 0.02). If either endpoint was significant at its corresponding α level, the corresponding α can then be recycled for the other endpoint so that the other endpoint can then be tested again at a one-sided 0.025 level.

Note that all p-values were reported as two-sided p-values, and were compared to corresponding two-sided alpha values. The overall type I error rate was strongly controlled at a one-sided significance level of 0.025 by a hierarchical testing procedure including possible α splitting and recycling (Bretz et al 2009).

Figure 13 PFS and Key Secondary Endpoints Analysis Hierarchy, Alpha Allocation, and Alpha Recycling (One-Sided)



BICR=blinded independent central review; EFS_{eff}=event-free survival for efficacy causes; OS=overall survival; PFS=progression-free survival.

Appendix 6: Major Protocol Deviations of Interest

Table 18 Major Protocol Deviations of Interest (ITT population)

Category Description	R-CHOP (N=439)	Pola+R-CHP (N=440)	Total (N=879)
Total number of patients with at least one major protocol deviation	23 (5.2%)	27 (6.1%)	50 (5.7%)
Total number of major protocol deviations	26	29	55
Exclusion criteria: Exclusion criteria not met	5 (1.1%)	12 (2.7%)	17 (1.9%)
Inclusion criteria: Inclusion criteria not met	1 (0.2%)	4 (0.9%)	5 (0.6%)
Medication:			
Incorrect subject kit given/administered	4 (0.9%)	2 (0.5%)	6 (0.7%)
Non-compliance with study drug tx mod or stoppage rules (either temporary or permanent)	5 (1.1%)	3 (0.7%)	8 (0.9%)
Procedural:			
>2 Tumor assessments not performed (during post-treatment phase)	2 (0.5%)	3 (0.7%)	5 (0.6%)
Accidental unblinding of a site staff team member or member(s)	2 (0.5%)	1 (0.2%)	3 (0.3%)
Accidental unblinding of a subject or subject(s)	4 (0.9%)	3 (0.7%)	7 (0.8%)
Any tumor assessments not performed (during treatment phase)	1 (0.2%)	0 (%)	1 (0.1%)

Source: t_dv_PDINT_IT_28JUN2021_39942.

Appendix 7: Demographics and Baseline Characteristics Tables

Table 19 Demographic and Baseline Characteristics

Parameters	ITT population R-CHOP (N=439)	Pola+R-CHP (N=440)	Total (N=879)
Demographics			
Age (years)			
mean (SD)	63.0 (11.87)	63.1 (11.36)	63.1 (11.61)
median (range)	66.00 (19.0-80.0)	65.00 (19.0-80.0)	65.00 (19.0-80.0)
< 65	203 (46.2%)	209 (47.5%)	412 (46.9%)
≥ 65	236 (53.8%)	231 (52.5%)	467 (53.1%)
Sex			
Male	234 (53.3%)	239 (54.3%)	473 (53.8%)
Female	205 (46.7%)	201 (45.7%)	406 (46.2%)
Geographic region (IxRS)			
Asia	79 (18.0%)	81 (18.4%)	160 (18.2%)
Rest of World	59 (13.4%)	57 (13.0%)	116 (13.2%)
Western Europe/ USA/Canada/Australia	301 (68.6%)	302 (68.6%)	603 (68.6%)
Race			
American Indian or Alaska Native	2 (0.5%)	1 (0.2%)	3 (0.3%)
Asian	84 (19.1%)	85 (19.3%)	169 (19.2%)
Black or African American	8 (1.8%)	8 (1.8%)	16 (1.8%)
Native Hawaiian or other Pacific Islander	3 (0.7%)	0	3 (0.3%)
White	236 (53.8%)	235 (53.4%)	471 (53.6%)
Other	6 (1.4%)	6 (1.4%)	12 (1.4%)
Unknown	100 (22.8%)	105 (23.9%)	205 (23.3%)
Baseline Disease Characteristics			
ECOG	438	440	878
0	173 (39.4%)	175 (39.8%)	348 (39.6%
1	190(43.3%)	199 (45.2%)	389 (44.3%)
2	75 (17.1%)	66 (15.0%)	141 (16.0%)
Ann Arbor Stage	439	440	879
I-II	52 (11.9%)	47 (10.7%)	99 (11.3%)
III-IV	387 (88.2%)	393 (89.3%)	780 (88.7%)
Stratification – IPI Score (IxRS)	439	440	879
2	167 (38.0%)	167 (38.0%)	334 (38.0%)
3-5	272 (62.0%)	273 (62.0%)	545 (62.0%)
Stratification – Bulky Disease (IxRS)	439	440	879
Present	192 (43.7%)	193 (43.9%)	385 (43.8%)
Baseline LDH	438	437	875
≤ 1xULN	154 (35.1%)	146 (33.2%)	300 (34.1%)
> 1x ULN	284 (64.7%)	291 (66.1%)	575 (65.4%)
	Biomarker-Evaluable population		
Parameters	**R-CHOP (N=439)**	**Pola+R-CHP (N=440)**	**Total (N=879)**
Double-Expressor evaluable (Central Review)	366	362	728
DEL	151 (41.3%)	139 (38.4%)	290 (39.8%)
Double/Triple-Hit evaluable (Central Review)	334	331	665
DH/TH+	19 (5.7%)	26 (7.9%)	45 (6.8%)
Cell of Origin (Central Review)	338	330	668
ABC	119 (35.2%)	102 (30.9%)	221 (33.1%)
GCB	168 (49.7%)	184 (55.8%)	352 (52.7%)
Unclassified	51 (15.1%)	44 (13.3%)	95 (14.2%)

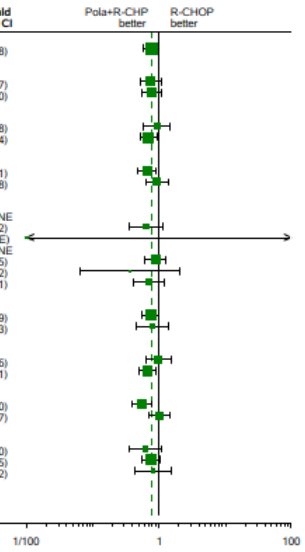
Source: t_dm_bsch_IT_28Jun2021_39942; t_bas_biom_IT.

Appendix 8: Subgroup Analyses of PFS

Figure 14 Forest Plot of Hazard Ratio of Investigator-Assessed PFS by Baseline Risk Factors (ITT Population)

Forest Plot of Hazard Ratio for PFS (by INV) by Baseline Characteristics Subgroup (part 1),
Intent-to-Treat Patients
Protocol: GO39942

Baseline Risk Factors	Total n	R-CHOP (N=439) n	R-CHOP (N=439) 2 Year Rate	Pola+R-CHP (N=440) n	Pola+R-CHP (N=440) 2 Year Rate	Hazard Ratio	95% Wald CI
All Patients	879	439	70.20	440	76.71	0.76	(0.59, 0.98)
Age Group							
<= 65	444	219	72.20	225	77.89	0.74	(0.51, 1.07)
>65	435	220	68.21	215	75.38	0.78	(0.55, 1.10)
Age Group							
<= 60	271	131	71.85	140	74.12	0.93	(0.58, 1.48)
>60	608	308	69.50	300	77.87	0.69	(0.51, 0.94)
Sex							
Male	473	234	65.87	239	75.87	0.66	(0.47, 0.91)
Female	406	205	75.19	201	77.70	0.93	(0.62, 1.38)
Race							
American Indian or Alaska Native	3	2	100.00	1	NE	NE	NE
Asian	169	84	66.11	85	74.04	0.64	(0.36, 1.12)
Black or African American	16	8	46.88	8	100.00	<0.01	(0.00, NE)
Native Hawaiian or other Pacific Islander	3	3	100.00			NE	NE
White	471	236	72.03	235	76.62	0.88	(0.62, 1.25)
Other	12	6	33.33	6	66.67	0.36	(0.07, 2.02)
Unknown	205	100	71.69	105	77.84	0.71	(0.42, 1.21)
ECOG							
0-1	737	363	71.22	374	78.42	0.75	(0.56, 0.99)
2	141	75	64.99	66	67.24	0.81	(0.46, 1.43)
Stratification - IPI score (IxRS)							
IPI 2	334	167	78.46	167	79.32	0.99	(0.63, 1.56)
IPI 3-5	545	272	65.12	273	75.16	0.67	(0.49, 0.91)
Stratification - Bulky Disease (IxRS)							
Absent	494	247	70.68	247	82.68	0.55	(0.38, 0.80)
Present	385	192	69.68	193	69.03	1.03	(0.72, 1.47)
Stratification - Geographic Region (IxRS)							
Asia	160	79	65.55	81	74.24	0.62	(0.35, 1.10)
Western Europe/USA/Canada/Australia	603	301	71.93	302	78.57	0.76	(0.55, 1.05)
Rest of world	116	59	67.25	57	70.80	0.81	(0.43, 1.52)



Unstratified hazard ratio is displayed.
CCOD: 28JUN2021 Data Extract Date: 02AUG2021
Program: root/clinical_studies/RO5541077/CDPT7884/GO39942/data_analysis/PRIMARY_CSR/prod/program/g_ef_fp.sas
Output: root/clinical_studies/RO5541077/CDPT7884/GO39942/data_analysis/PRIMARY_CSR/prod/output/g_ef_fp_PFS_PART1_IT_28JUN2021_39942.pdf 10AUG2021 19:41

Forest Plot of Hazard Ratio for PFS (by INV) by Baseline Characteristics Subgroup (part 2),
Intent-to-Treat Patients
Protocol: GO39942

Baseline Risk Factors	Total n	R-CHOP (N=439) n	R-CHOP (N=439) 2 Year Rate	Pola+R-CHP (N=440) n	Pola+R-CHP (N=440) 2 Year Rate	Hazard Ratio	95% Wald CI
All Patients	879	439	70.20	440	76.71	0.76	(0.59, 0.98)
Ann Arbor Stage							
I-II	99	52	85.46	47	89.13	0.62	(0.21, 1.84)
III	232	108	73.62	124	80.73	0.76	(0.45, 1.29)
IV	548	279	66.14	269	72.55	0.78	(0.58, 1.05)
IPI (eCRF)							
1-2	330	165	79.40	165	78.53	1.09	(0.69, 1.73)
3	330	156	68.38	174	81.30	0.56	(0.37, 0.87)
4-5	219	118	59.86	101	65.96	0.79	(0.51, 1.22)
Baseline Bulky Disease							
Yes	388	195	69.60	193	69.02	1.04	(0.73, 1.48)
No	491	244	70.75	247	82.68	0.55	(0.38, 0.80)
Baseline LDH							
<= 1xULN	300	154	75.64	146	78.93	0.81	(0.51, 1.30)
> 1xULN	575	284	67.19	291	75.38	0.73	(0.54, 1.00)
Bone marrow involvement							
Positive	148	72	60.67	76	70.95	0.69	(0.40, 1.19)
Negative	691	349	73.23	342	78.00	0.82	(0.61, 1.10)
Indeterminate	22	11	51.95	11	70.00	0.44	(0.10, 1.85)
No. of extranodal sites							
0-1	453	226	74.47	227	80.23	0.78	(0.53, 1.14)
>=2	426	213	65.77	213	72.95	0.74	(0.52, 1.04)
NHL Subtype (eCRF)							
DLBCL NOS, ABC, GCB	740	367	70.86	373	77.30	0.75	(0.57, 0.99)
HGBL, NOS, DHL/THL	93	50	62.70	43	81.40	0.48	(0.21, 1.08)
Other Large B-cell	46	22	76.19	24	58.40	1.93	(0.66, 5.64)

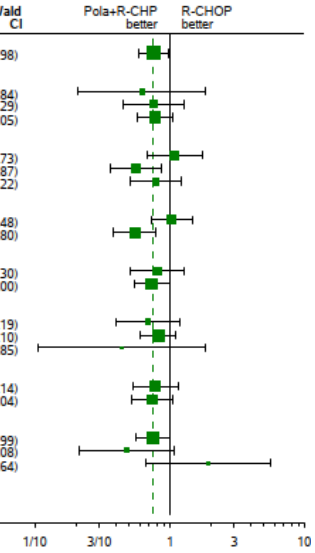


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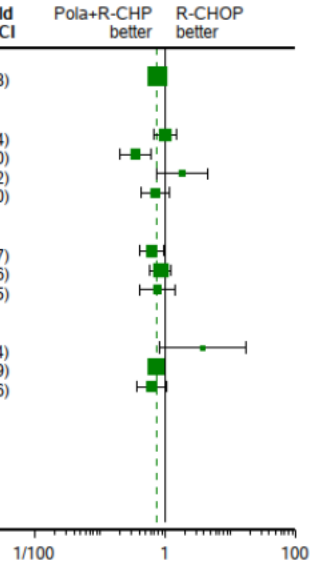
Figure 12 Forest Plot of Hazard Ratio of Investigator-Assessed PFS by Baseline Risk Factors (ITT Population) (cont.)

Note that there are two different data sources for IPI and Bulky Disease. "Stratification-IPI score (IxRS)" and "Stratification-Bulky Disease (IxRS)" in the first figure were stratification factors as collected in the Interactive Voice/Web Response System; "IPI (eCRF)" and "Baseline Bulky Disease" in the second plot were collected through the electronic case report forms.

Figure 15 Forest Plot of Hazard Ratio of Investigator-Assessed PFS by Molecular DLBCL Subtypes (ITT Population)

Forest Plot of Hazard Ratio for PFS (by INV) by Biomarker Subgroup, Intent-to-Treat Patients
Protocol: GO39942

Biomarker Risk Factors	Total n	R-CHOP (N=439) n	R-CHOP (N=439) 2 Year Rate	Pola+R-CHP (N=440) n	Pola+R-CHP (N=440) 2 Year Rate	Hazard Ratio	95% Wald CI
All Patients	879	439	70.20	440	76.71	0.76	(0.59, 0.98)
Cell of Origin							
GCB	352	168	76.91	184	75.14	1.02	(0.68, 1.54)
ABC	221	119	58.84	102	83.90	0.35	(0.21, 0.60)
Unclassified	95	51	86.23	44	72.96	1.85	(0.75, 4.52)
Unknown	211	101	64.31	110	73.75	0.72	(0.44, 1.20)
Double Expressor by IHC							
DEL	290	151	63.05	139	75.53	0.64	(0.42, 0.97)
Non DEL	438	215	75.68	223	77.69	0.87	(0.59, 1.26)
Unknown	151	73	69.83	78	75.96	0.77	(0.41, 1.45)
Double Triple Hit Lymphoma							
DH/TH+	45	19	88.89	26	69.02	3.81	(0.82, 17.64)
DH/TH-	620	315	70.28	305	76.76	0.73	(0.54, 0.99)
Unknown	214	105	66.43	109	78.45	0.63	(0.37, 1.06)



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Appendix 9: Kaplan-Meier Plots for First and Second Interim Analyses of OS

Figure 16 Kaplan-Meier Plot of Time to OS (ITT Population; CCOD: 28 June 2021)

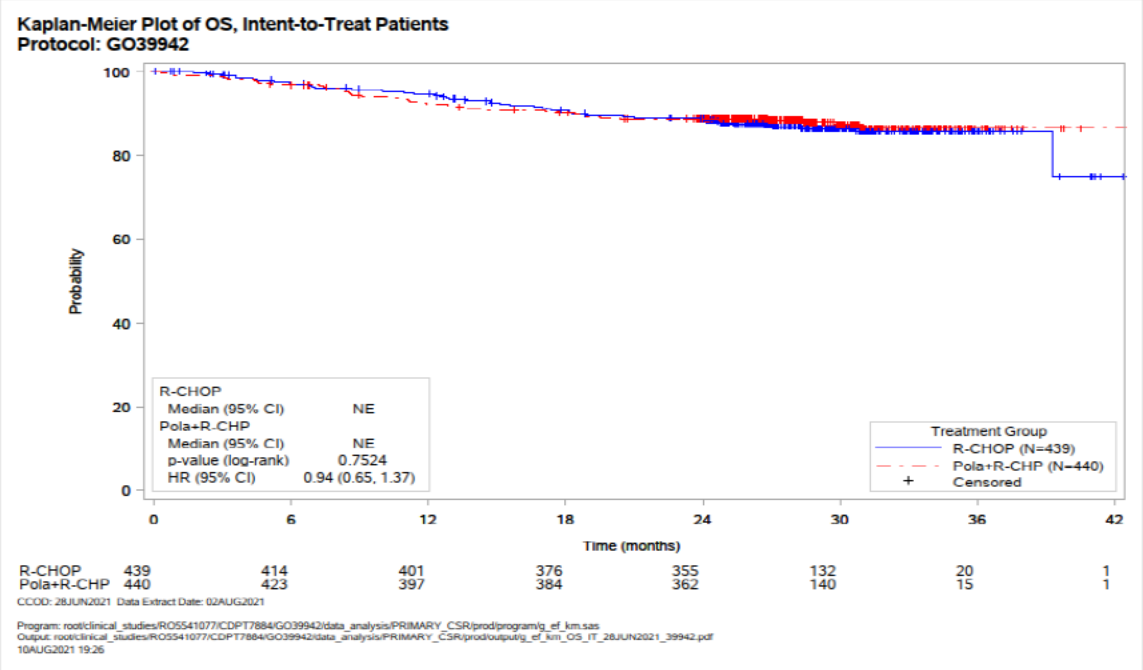
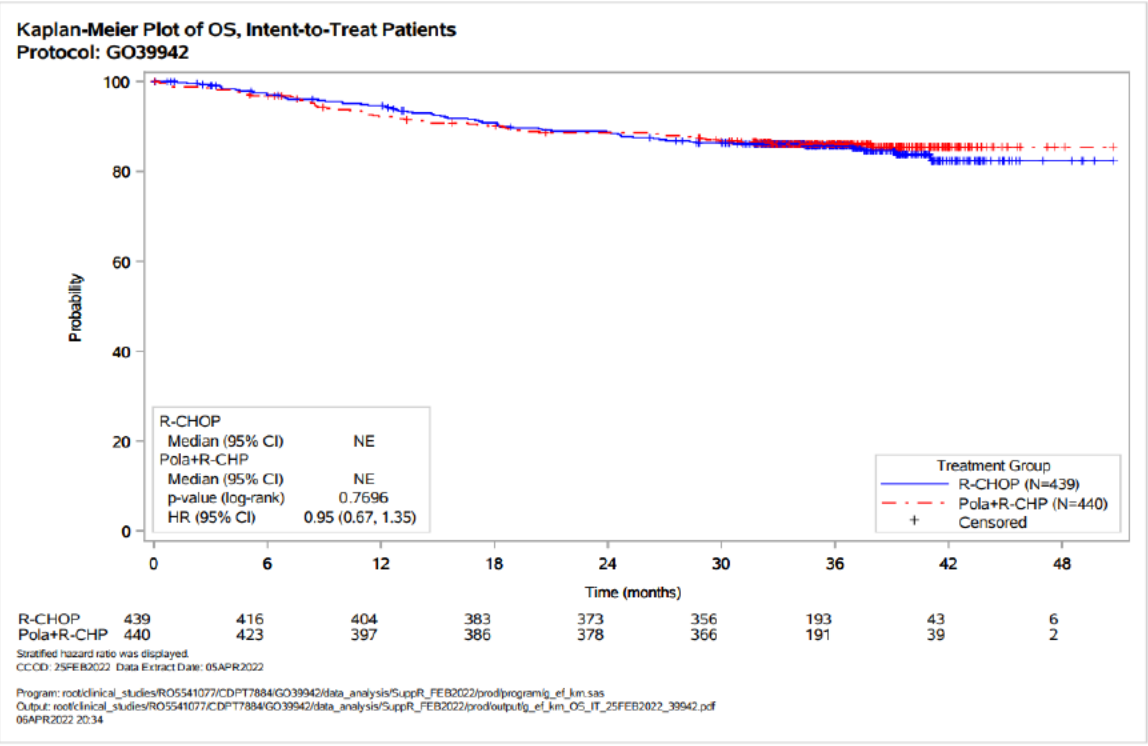


Figure 17 Kaplan-Meier Plot of Time to OS (ITT Population; CCOD: 25 February 2022)



Appendix 10: Summary of Adverse Events Leading to Dose Reduction

Table 20 Summary of Adverse Events Leading to Dose Reduction for Any Study Drug by System Organ Class (Safety Evaluable Patients)

Summary of Adverse Events Leading to Dose Reduction for Any Study Drug by System Organ Class,
Safety-Evaluable Patients, Protocol: GO39942

MedDRA System Organ Class	R-CHOP (N=438)	Pola+R-CHP (N=435)
Total number of patients with at least one adverse event	57 (13.0%)	40 (9.2%)
Overall total number of events	78	47
Nervous system disorders		
Total number of patients with at least one adverse event	36 (8.2%)	20 (4.6%)
Total number of events	38	20
Blood and lymphatic system disorders		
Total number of patients with at least one adverse event	6 (1.4%)	7 (1.6%)
Total number of events	14	7
Investigations		
Total number of patients with at least one adverse event	6 (1.4%)	4 (0.9%)
Total number of events	7	7
Gastrointestinal disorders		
Total number of patients with at least one adverse event	6 (1.4%)	3 (0.7%)
Total number of events	6	3
General disorders and administration site conditions		
Total number of patients with at least one adverse event	3 (0.7%)	2 (0.5%)
Total number of events	4	2
Infections and infestations		
Total number of patients with at least one adverse event	4 (0.9%)	1 (0.2%)
Total number of events	4	1
Metabolism and nutrition disorders		
Total number of patients with at least one adverse event	0	3 (0.7%)
Total number of events	0	4
Cardiac disorders		
Total number of patients with at least one adverse event	1 (0.2%)	1 (0.2%)
Total number of events	1	1
Ear and labyrinth disorders		
Total number of patients with at least one adverse event	1 (0.2%)	1 (0.2%)
Total number of events	1	1
Psychiatric disorders		
Total number of patients with at least one adverse event	2 (0.5%)	0
Total number of events	2	0
Hepatobiliary disorders		
Total number of patients with at least one adverse event	0	1 (0.2%)
Total number of events	0	1
Vascular disorders		
Total number of patients with at least one adverse event	1 (0.2%)	0
Total number of events	1	0

Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes treatment-emergent AEs during AE reporting period only, which is defined as new or worsening AE from the first dose of any study drug through 90 days after the last dose of any study drug or prior to NALT, whichever is earlier.
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Appendix 11: Overview of Adverse Events of Particular Interest (AEPIs)

Table 21 Overview of AEPIs (Safety-Evaluable Population)

AEPI	PN		Neutropenia including Febrile Neutropenia*		Anemia		Thrombocytopenia		Infections		Hepatotoxicity	
	R-CHOP N=438	Pola+ R-CHP N=435	R-CHOP N=438	Pola+ R-CHP N=435	R-CHOP N=438	Pola+ R-CHP N=435	R-CHOP N=438	Pola+ R-CHP N=435	R-CHOP N=438	Pola+ R-CHP N=435	R-CHOP N=438	Pola+ R-CHP N=435
Total number of patients with at least one AE	236 (53.9%)	230 (52.9%)	187 (42.7%)	200 (46.0%)	118 (26.9%)	125 (28.7%)	58 (13.2%)	58 (13.3%)	187 (42.7%)	216 (49.7%)	32 (7.3%)	46 (10.6%)
Total number of AEs	292	301	443	456	178	190	123	102	343	409	61	74
Total number of patients with at least one												
Grade 5 AE	0	0	0	0	0	0	0	0	6 (1.4%)	5 (1.1%)	0	0
Grade 3-5 AE	5 (1.1%)	7 (1.6%)	176 (40.2%)	182 (41.8%)	38 (8.7%)	52 (12.0%)	22 (5.0%)	23 (5.3%)	55 (12.6%)	66 (15.2%)	4 (0.9%)	8 (1.8%)
Serious AE	1 (0.2%)	1 (0.2%)	37 (8.4%)	50 (11.5%)	6 (1.4%)	4 (0.9%)	1 (0.2%)	2 (0.5%)	45 (10.3%)	61 (14.0%)	0	1 (0.2%)
Serious Related AE to any study drug	1 (0.2%)	1 (0.2%)	34 (7.8%)	49 (11.3%)	4 (0.9%)	4 (0.9%)	1 (0.2%)	2 (0.5%)	28 (6.4%)	45 (10.3%)	0	0
AE leading to study discontinuation	0	0	0	0	0	0	0	0	6 (1.4%)	5 (1.1%)	0	0
AE leading to any study treatment dose discontinuation	10 (2.3%)	3 (0.7%)	0	2 (0.5%)	0	0	0	1 (0.2%)	10 (2.3%)	7 (1.6%)	0	0
AE leading to any study treatment dose reduction	36 (8.2%)	20 (4.6%)	7 (1.6%)	7 (1.6%)	2 (0.5%)	0	2 (0.5%)	2 (0.5%)	4 (0.9%)	1 (0.2%)	1 (0.2%)	2 (0.5%)
AE leading to any study treatment dose interruption	5 (1.1%)	6 (1.4%)	28 (6.4%)	23 (5.3%)	1 (0.2%)	2 (0.5%)	0	0	22 (5.0%)	27 (6.2%)	1 (0.2%)	4 (0.9%)
AE leading to pola/placebo discontinuation	9 (2.1%)	3 (0.7%)	0	0	0	0	0	1 (0.2%)	7 (1.6%)	5 (1.1%)	0	0
AE leading to pola/placebo dose reduction	36 (8.2%)	17 (3.9%)	2 (0.5%	2 (0.5%)	0	0	2 (0.5%)	0	1 (0.2%)	0	1 (0.2%)	1 (0.2%)
AE leading to pola/placebo dose interruption	3 (0.7%)	3 (0.7%)	13 (3.0%)	12 (2.8%)	1 (0.2%)	2 (0.5%)	0	0	20 (4.6%)	21 (4.8%)	1 (0.2%)	4 (0.9%)
AE leading to vincristine/placebo discontinuation	9 (2.1%)	3 (0.7%)	0	0	0	0	0	1 (0.2%)	7 (1.6%)	5 (1.1%)	0	0
AE leading to vincristine/placebo dose reduction	35 (8.0%)	19 (4.4%)	2 (0.5%)	1 (0.2%)	0	0	2 (0.5%)	0	2 (0.5%)	0	1 (0.2%)	1 (0.2%)
AE leading to vincristine/placebo dose interruption	3 (0.7%)	3 (0.7%)	13 (3.0%)	12 (2.8%)	1 (0.2%)	2 (0.5%)	0	0	19 (4.3%)	22 (5.1%)	1 (0.2%)	4 (0.9%)

AE=adverse event; IRRs=infusion related reactions; PN=peripheral neuropathy; TLS=tumor lysis syndrome.
*The incidence of neutropenia including febrile neutropenia is based on physician reported adverse events for the followings PT: neutropenia, febrile neutropenia, neutrophil count decreased, neutropenic sepsis, agranulocytosis, and neutropenic colitis. It does not include laboratory data of neutropenia.

Table 18 Overview of AEPIs (Safety-Evaluable Population) (cont.)

AEPI	TLS		Pulmonary toxicity		Secondary malignancy/ carcinogenicity		Hyperglycemia		Cardiac arrhythmias		IRRs	
	R-CHOP N=438	Pola+ R-CHP N=435	R-CHOP N=438	Pola+ R-CHP N=435	R-CHOP N=438	Pola+ R-CHP N=435	R-CHOP N=438	Pola+ R-CHP N=435	R-CHOP N=438	Pola+ R-CHP N=435	R-CHOP N=438	Pola+ R-CHP N=435
Total number of patients with at least one AE	4 (0.9%)	2 (0.5%)	7 (1.6%)	7 (1.6%)	5 (1.1%)	4 (0.9%)	27 (6.2%)	26 (6.0%)	20 (4.6%)	13 (3.0%)	70 (16.0%)	58 (13.3%)
Total number of AEs	5	2	7	8	9	4	36	34	21	16	106	83
Total number of patients with at least one												
Grade 5 AE	0	0	0	0	0	0	0	0	1 (0.2%)	0	0	0
Grade 3-5 AE	3 (0.7%)	2 (0.5%)	1 (0.2%)	1 (0.2%)	2 (0.5%)	4 (0.9%)	6 (1.4%)	8 (1.8%)	4 (0.9%)	2 (0.5%)	7 (1.6%)	5 (1.1%)
Serious AE	1 (0.2%)	1 (0.2%)	2 (0.5%)	1 (0.2%)	1 (0.2%)	3 (0.7%)	0	0	4 (0.9%)	2 (0.5%)	3 (0.7%)	2 (0.5%)
Serious Related AE to any study drug	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	0	1 (0.2%)	0	0	1 (0.2%)	1 (0.2%)	3 (0.7%)	2 (0.5%)
AE leading to study discontinuation	0	0	0	0	0	0	0	0	1 (0.2%)	0	0	0
AE leading to any study treatment dose discontinuation	0	0	0	3 (0.7%)	0	0	0	0	0	0	1 (0.2%)	0
AE leading to any study treatment dose reduction	0	0	0	0	0	0	0	1 (0.2%)	0	0	0	0
AE leading to any study treatment dose interruption	1 (0.2%)	0	4 (0.9%)	2 (0.5%)	0	0		00	1 (0.2%)	0	25 (5.7%)	18 (4.1%)
AE leading to pola/placebo discontinuation	0	0	0	2 (0.5%)	0	0	0	0	0	0	0	0
AE leading to pola/placebo dose reduction	0	0	0	0	0	0	0	0	0	0	0	0
AE leading to pola/placebo dose interruption	1 (0.2%)	0	4 (0.9%)	1 (0.2%)	0	0	0	0	0	0	1 (0.2%)	0
AE leading to vincristine/placebo discontinuation	0	0	0	2 (0.5%)	0	0	0	0	0	0	0	0
AE leading to vincristine/placebo dose reduction	0	0	0	0	0	0	0	0	0	0	0	0
AE leading to vincristine/placebo dose interruption	1 (0.2%)	0	4 (0.9%)	1 (0.2%)	0	0	0	0	0	0	0	0

Source: t_ae_profile_ PN_SE_28JUN2021_39942; t_ae_profile_NEUT_SE_28JUN2021_39942; t_ae_profile_ANM_SE_28JUN2021_39942; t_ae_profile_TCP_SE_28JUN2021_39942; t_ae_profile_INF_SE_28JUN2021_39942; t_ae_profile_HTOX_SE_28JUN2021_39942; t_ae_profile_TLSN_SE_28JUN2021_39942; t_ae_profile_PTOX_SE_28JUN2021_39942; t_ae_profile_CARCG_SE_28JUN2021_39942; t_ae_profile_HGL_SE_28JUN2021_39942; t_ae_profile_CA_SE_28JUN2021_39942; t_ae_profile_IRR_SE_28JUN2021_39942

Appendix 12: Overall Adverse Event Profile - Febrile Neutropenia

Table 22 Overall Adverse Event Profile - Febrile Neutropenia (Safety Evaluable Patients)

Overall AE Profile - Febrile Neutropenia, Safety-Evaluable Patients
Protocol: GO39942

	R-CHOP (N=438)	Pola+R-CHP (N=435)
Total number of patients with at least one AE	35 (8.0%)	62 (14.3%)
Total number of AEs	41	84
Total number of patients with at least one		
Grade 5 AE	0	0
Grade 3-5 AE	35 (8.0%)	60 (13.8%)
Serious AE	28 (6.4%)	43 (9.9%)
Serious Related AE to any study drug	25 (5.7%)	42 (9.7%)
AE leading to study discontinuation	0	0
AE leading to any study treatment dose discontinuation	0	0
AE leading to any study treatment dose reduction	2 (0.5%)	5 (1.1%)
AE leading to any study treatment dose interruption	1 (0.2%)	3 (0.7%)
AE leading to polatuzumab vedotin/placebo discontinuation	0	0
AE leading to polatuzumab vedotin/placebo dose reduction	1 (0.2%)	2 (0.5%)
AE leading to polatuzumab vedotin/placebo dose interruption	0	3 (0.7%)
AE leading to vincristine/placebo discontinuation	0	0
AE leading to vincristine/placebo dose reduction	1 (0.2%)	1 (0.2%)
AE leading to vincristine/placebo dose interruption	0	3 (0.7%)

Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately. Includes treatment-emergent AEs during AE reporting period only, which is defined as new or worsening AE from the first dose of any study drug through 90 days after the last dose of any study drug or prior to NALT, whichever is earlier.
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10AUG2021 21:25 Page 1 of 1

Appendix 13: Summary of Exposure

Table 23 Summary of Study Drug Exposure (Safety Evaluable Population)

	R-CHOP (n=438)					Pola+R-CHP (n=435)				
	RTX	**CYC**	**DOX**	**VIN**	**PRED**	**Pola**	**RTX**	**CYC**	**DOX**	**PRED**
Treatment Duration (months)										
n	438	436	436	436	438	435	435	435	435	435
Mean (SD)	4.6 (1.2)	3.4 (0.7)	3.4 (0.7)	3.4 (0.7)	3.5 (0.7)	3.4 (0.6)	4.7 (0.9)	3.5 (0.6)	3.5 (0.6)	3.6 (0.6)
Median	4.9	3.5	3.5	3.5	3.6	3.5	4.9	3.5	3.5	3.6
Min-Max	0 - 11	0 – 8	0 - 8	0 - 8	0 - 6	0 - 5	0 - 8	0 - 5	0 - 5	0 - 5
Number of cycles										
n	438	436	436	436	438	435	435	435	435	435
Mean (SD)	7.4 (1.6)	5.7 (1.0)	5.7 (1.0)	5.7 (1.0)	5.7 (1.0)	5.8 (0.8)	7.6 (1.3)	5.8 (0.8)	5.8 (0.8)	5.8 (0.8)
Median	8.0	6.0	6.0	6.0	6.0	6.0	8.0	6.0	6.0	6.0
Min-Max	1 - 8	1 – 6	1 - 6	1 - 6	1 - 6	1 - 6	1 - 8	1 - 6	1 - 6	1 - 6
1-5	42 (9.6%)	39 (8.9%)	39 (8.9%)	50 (11.5%)	45 (10.3%)	36 (8.3%)	31 (7.1%)	29 (6.7%)	29 (6.7%)	29 (6.7%)
6	14 (3.2%)	397 (91.1%)	397 (91.1%)	386 (88.5%)	393 (89.7%)	399 (91.7%)	7 (1.6%)	406 (93.3%)	406 (93.3%)	406 (93.3%)
7	4 (0.9%)	-	-	-	-	-	9 (2.1%)	-	-	-
8	378 (86.3%)	-	-	-	-	-	388 (89.2%)	-	-	-
Relative Dose Intensity (%)										
n	435	433	433	436	438	432	431	431	431	435
Mean (SD)	99.1 (2.7)	98.6 (3.9)	98.7 (4.1)	98.5 (5.0)	98.4 (8.3)	98.1 (5.2)	99.0 (3.3)	98.5 (3.9)	98.5 (4.0)	98.4 (7.7)
Median	100.0	100.0	100.0	100.0	100.0	99.8	100.0	100.0	100.0	100.0
Min-Max	84 - 108	65 - 109	64 - 109	63 - 103	20 - 123	64 - 111	64 - 116	64 - 106	65 - 106	26 - 127
Total cumulative dose (mg)										
n	438	436	436	436	438	435	435	435	435	435
Mean (SD)	5128.1 (1284.7)	7864.6 (1717.9)	524.7 (115.2)	11.2 (2.1)	2817.4 (539.2)	774.5 (228.9)	5247.3 (1141.1)	7983.6 (1544.1)	532.4 (103.0)	2864.6 (447.7)
Median	5329.0	8042.1	540.0	12.0	3000.0	762.0	5380.0	8150.0	540.0	3000.0
Min-Max	570 - 9452	750 - 14185	66 - 948	2 - 12	100 - 3700	102 - 2125	600 - 9318	1200 - 14198	80 - 947	500 - 3800

CYC=cyclophosphamide; DOX=doxorubicin; Pola=Polatuzumab vedotin; PRED=prednisone; RTX=rituximab; VIN=vincristine.

Source: t_ex_SE_28JUN2021_39942

Appendix 14: Most Common Grade 3-4 AEs with an Incidence Rate of at least 2%

Table 24 Most Common Grade 3-4 AEs with an Incidence Rate of at least 2% (Safety Evaluable Population)

MedDRA Preferred Term	R-CHOP (N=438)	Pola+R-CHP (N=435)
Neutropenia	135 (30.8%)	123 (28.3%)
Febrile neutropenia	35 (8.0%)	60 (13.8%)
Anaemia	37 (8.4%)	52 (12.0%)
Neutrophil count decreased	28 (6.4%)	30 (6.9%)
Leukopenia	30 (6.8%)	25 (5.7%)
Thrombocytopenia	19 (4.3%)	14 (3.2%)
White blood cell count decreased	14 (3.2%)	18 (4.1%)
Pneumonia	17 (3.9%)	14 (3.2%)
Lymphocyte count decreased	15 (3.4%)	13 (3.0%)
Diarrhoea	8 (1.8%)	17 (3.9%)
Syncope	9 (2.1%)	8 (1.8%)
Lymphopenia	10 (2.3%)	7 (1.6%)
Hypertension	10 (2.3%)	6 (1.4%)
Hyponatraemia	9 (2.1%)	6 (1.4%)
Fatigue	11 (2.5%)	4 (0.9%)
Platelet count decreased	3 (0.7%)	9 (2.1%)

Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings. Includes treatment-emergent AE during AE reporting period only, which is defined as new or worsening AE from the first dose of any study drug through 90 days after the last dose of any study drug or prior to NALT, whichever is earlier.

CCOD: 28JUN2021 Data Extract Date: 02AUG2021.

Source: t_ae_pt_ctc34_pi2_SE_28JUN2021_39942; t_ae_soc_pt_grd_SE_28JUN2021_39942.

Appendix 15: Summary of Resolution Profile for Peripheral Neuropathy, Neutropenia, Thrombocytopenia, Anemia, and Infections

Table 25 Summary of Resolution Profile for Peripheral Neuropathy, Neutropenia, Thrombocytopenia, Anemia, and Infections (Safety Evaluable Population)

Summary of AEPI Resolution Profile, Safety-Evaluable Patients
Protocol: GO39942

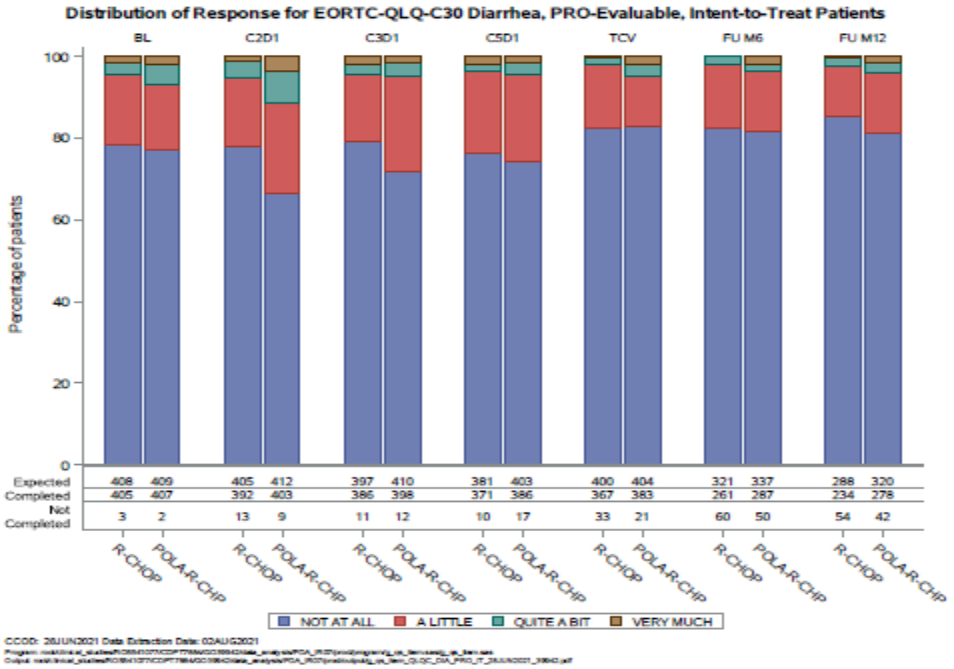
	R-CHOP (N=438)	Pola+R-CHP (N=435)
Peripheral Neuropathy		
Patients with at least one event	236 (53.9%)	230 (52.9%)
Patients with all AEs resolved	158 (66.9%)	133 (57.8%)
Patients with at least one event ongoing/unresolved	78 (33.1%)	97 (42.2%)
Total number of events	292	301
Number of events resolved	201 (68.8%)	195 (64.8%)
Neutropenia		
Patients with at least one event	187 (42.7%)	200 (46.0%)
Patients with all AEs resolved	183 (97.9%)	196 (98.0%)
Patients with at least one event ongoing/unresolved	4 (2.1%)	4 (2.0%)
Total number of events	443	456
Number of events resolved	439 (99.1%)	452 (99.1%)
Thrombocytopenia		
Patients with at least one event	58 (13.2%)	58 (13.3%)
Patients with all AEs resolved	50 (86.2%)	55 (94.8%)
Patients with at least one event ongoing/unresolved	8 (13.8%)	3 (5.2%)
Total number of events	123	102
Number of events resolved	115 (93.5%)	99 (97.1%)
Anemia		
Patients with at least one event	118 (26.9%)	125 (28.7%)
Patients with all AEs resolved	102 (86.4%)	106 (84.8%)
Patients with at least one event ongoing/unresolved	16 (13.6%)	19 (15.2%)
Total number of events	178	190
Number of events resolved	162 (91.0%)	171 (90.0%)
Infections and infestations		
Patients with at least one event	187 (42.7%)	216 (49.7%)
Patients with all AEs resolved	158 (84.5%)	188 (87.0%)
Patients with at least one event ongoing/unresolved	29 (15.5%)	28 (13.0%)
Total number of events	343	409
Number of events resolved	309 (90.1%)	380 (92.9%)

Investigator text for AEs encoded using MedDRA version 24.0.
Includes treatment-emergent AE during AE reporting period only, which is defined as new or worsening AE from the first dose of any study drug through 90 days after the last dose of any study drug or prior to NALT, whichever is earlier.
CCOD: 28JUN2021 Data Extract Date: 02AUG2021

Program: root/clinical_studies/RO5541077/CDPT7884/GO39942/data_analysis/PRIMARY_CSR/prod/program/t_ae_profile_res.sas
Output: root/clinical_studies/RO5541077/CDPT7884/GO39942/data_analysis/PRIMARY_CSR/prod/output/t_ae_profile_res_SE_28JUN2021_39942.out
10AUG2021 21:40

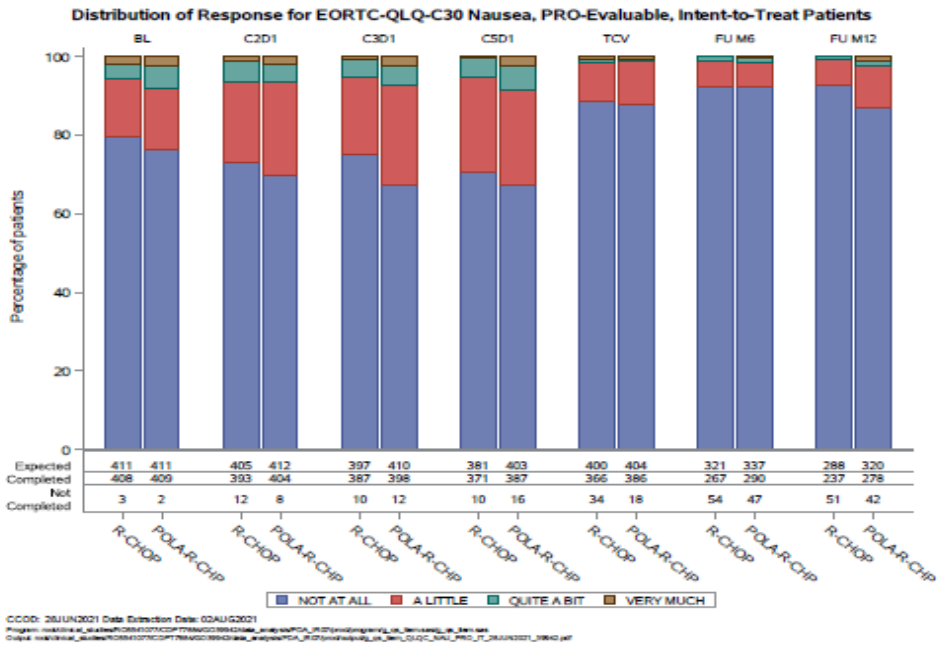
Appendix 16: Patient–Reported Outcome (PRO) Data

Figure 18 Distribution of Responses for EORTC-QLQ-C30 for Diarrhea (ITT Population where Denominator = PRO Evaluable)



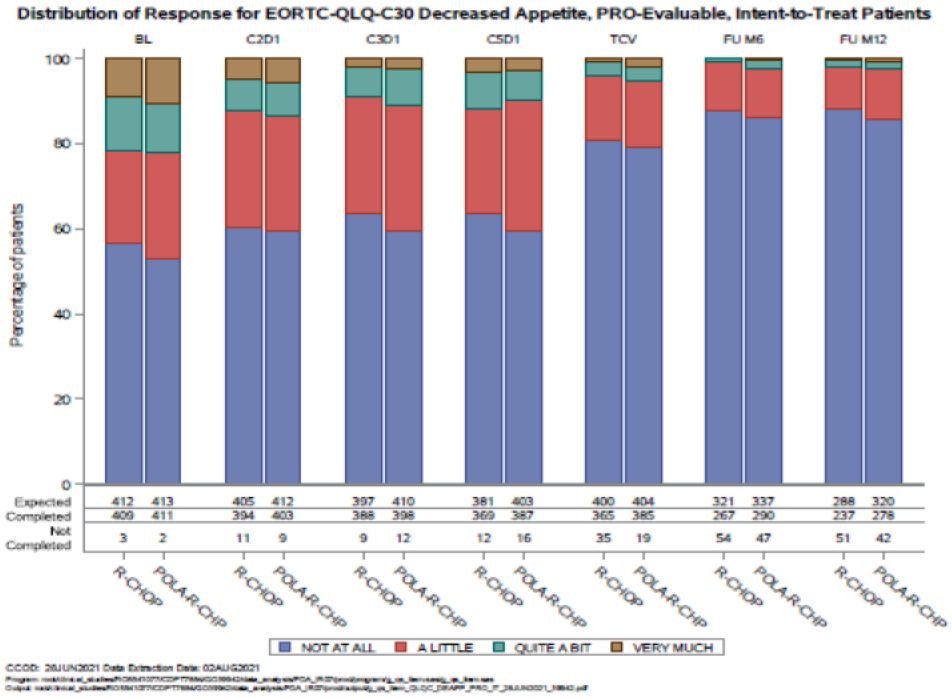
BL = baseline; C = cycle; D = day; TCV = treatment completion visit; FU = follow-up; M = month

Figure 19 Distribution of Responses for EORTC-QLQ-C30 for Nausea (ITT Population where Denominator = PRO Evaluable)



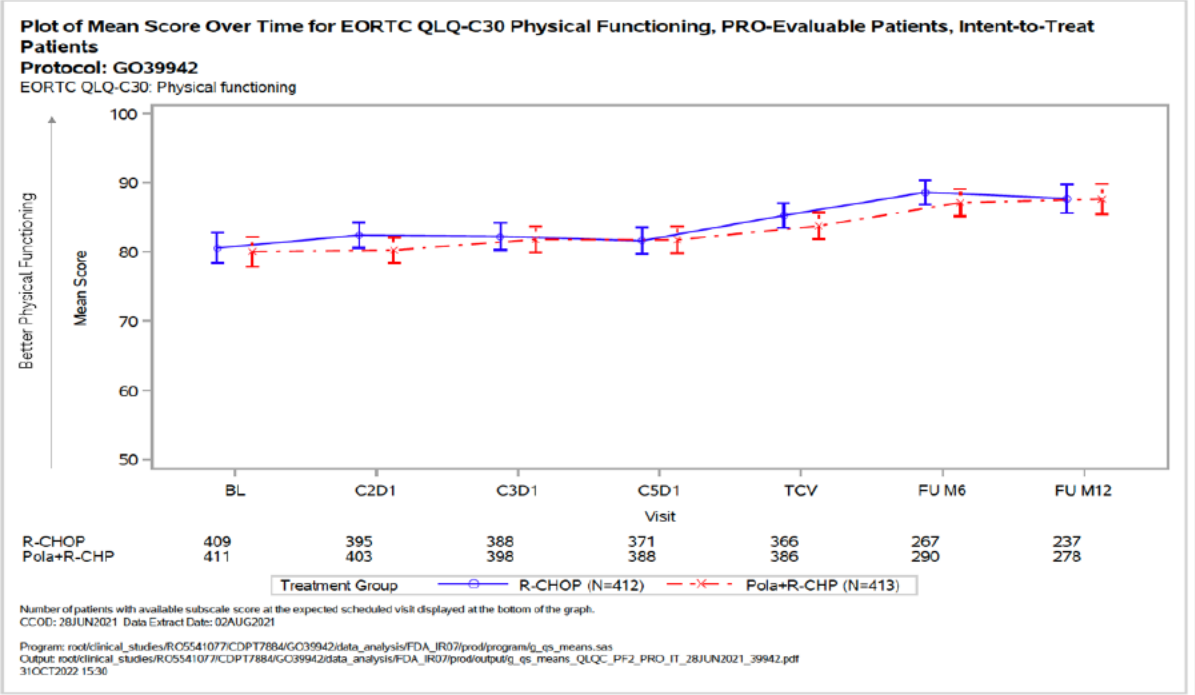
BL = baseline; C = cycle; D = day; TCV = treatment completion visit; FU = follow-up; M = month

Figure 20 Distribution of Responses for EORTC-QLQ-C30 for Decreased Appetite (ITT Population where Denominator = PRO Evaluable)



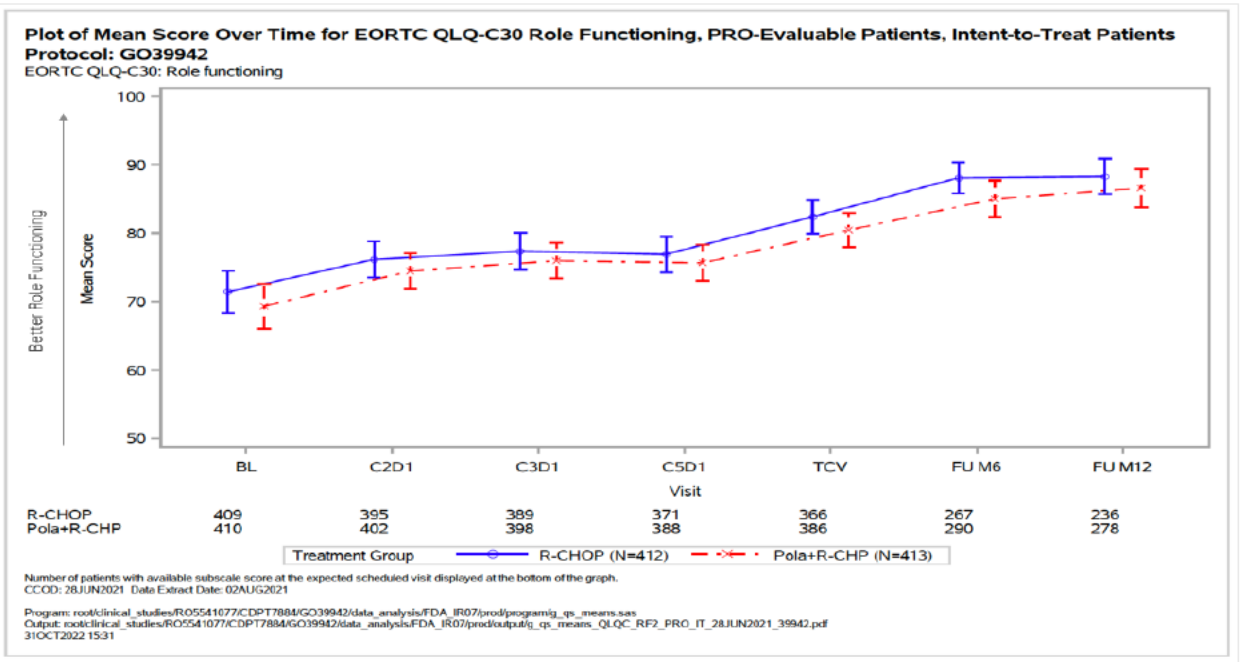
BL = baseline; C = cycle; D = day; TCV = treatment completion visit; FU = follow-up; M = month.

Figure 21 Plot of Mean Score Over Time for EORTC QLQ-C30 Physical Functioning, PRO-Evaluable Patients, ITT Patients



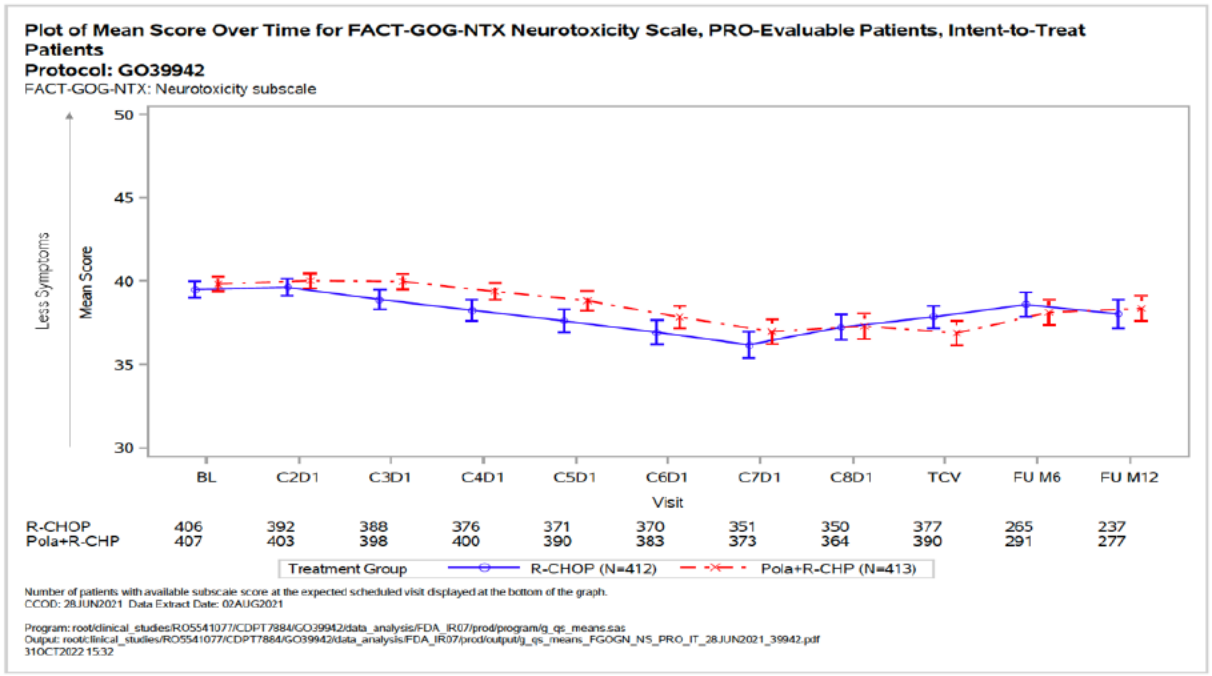
BL = baseline; C = cycle; D = day; TCV = treatment completion visit; FU = follow-up; M = month.

Figure 22 Plot of Mean Score Over Time for EORTC QLQ-C30 Role Functioning, PRO-Evaluable Patients, ITT Patients



BL = baseline; C = cycle; D = day; TCV = treatment completion visit; FU = follow-up; M = month.

Figure 23 Plot of Mean Score Over Time for FACT-GOG-NTX Neurotoxicity Scale, PRO-Evaluable Patients, ITT Patients



BL = baseline; C = cycle; D = day; TCV = treatment completion visit; FU = follow-up; M = month.

9.2. FDA's Appendices

FDA Appendix 1: Clinical Pharmacology

FDA identified the limited dose exploration and higher rates of select TEAEs with higher polatuzumab vedotin exposure as issues with the Applicant's submitted pharmacology data to support the first-line DLBCL indication in BLA 761121 S-008.

Limited Dose Exploration Data

Dose exploration of polatuzumab vedotin was limited by the small number of subjects with previously untreated DLBCL who received polatuzumab doses lower than 1.8 mg/kg. The Applicant's supportive study GO29044 tested the safety and efficacy of escalating body weight-based doses (1.0, 1.4, and 1.8 mg/kg) Q3W of polatuzumab vedotin in patients with R/R and newly diagnosed B-cell NHL. The study enrolled very few patients with untreated DLBCL for dosages lower than 1.8 mg/kg Q3W (2 subjects at 1 mg/kg and 3 subject at 1.4 mg/kg). The ORR for all doses in dose escalation were 100% (source: Study GO28944 clinical study report). Given the small number of patients, it is difficult to discern any preliminary efficacy or safety difference in lower dosages (e.g., 1.4 mg/kg) when compared to the selected polatuzumab vedotin RP2D at 1.8 mg/kg Q3W. Furthermore, polatuzumab vedotin monotherapy dose escalation study (DCS4968g) did not include any patients with untreated DLBCL and only included limited dose explorations in relapsed/refractory DLBCL with 4 subjects given 1.8 mg/kg and 8 subjects given doses below 1.8 mg/kg.[8]

Regarding pola+R-CHP, FDA expressed concerns regarding the inadequate dose finding in the end-of-phase 2 meeting on April 3, 2017. FDA communicated to the Applicant that "we are unable to determine if 1.8 mg/kg PV is the optimal dose for the phase 3 trial. We notice that exposure-response for efficacy and safety to justify the dose is based on a relatively narrow exposure range with the majority of data from 1.8 mg/kg PV." The relationships between polatuzumab vedotin dose and clinical efficacy are still not fully characterized in combination with R-CHP for previously untreated DLBCL or as monotherapy for R/R DLBCL.

Higher TEAE Rates with Higher Exposure

FDA notes that as described in Section 3 (Safety), patients who received pola+R-CHP had higher rates of febrile neutropenia and infection compared to patients who received R-CHOP in POLARIX. Higher rates of febrile neutropenia and infections were associated with higher acMMAE and MMAE exposure (AUC, Cmax) in plasma in the pola+R-CHP arm. Exposure-response (E-R) safety associations generally appeared stronger with MMAE exposure in plasma compared to acMMAE exposure, which is consistent with the mechanism of action of polatuzumab vedotin because MMAE is the toxic payload. These observed E-R trends support

the conclusion that rates of febrile neutropenia and infections were higher with pola+R-CHP compared to R-CHOP due to polatuzumab vedotin exposure.

Summary of E-R Analyses

The current E-R analysis of safety and efficacy includes data from 429 patients with previously untreated DLBCL in POLARIX who received 1.8 mg/kg polatuzumab vedotin Q3W in combination with R-CHP. The limited dose exploration and subsequent inclusion of only one dose level (i.e., 1.8 mg/kg) in the E-R analysis for the proposed patient population limits the ability to characterize polatuzumab vedotin dose-response safety and efficacy associations, as such, it is unclear what safety or efficacy outcomes to expect at dose levels lower than 1.8 mg/kg in patients with previously untreated DLBCL.

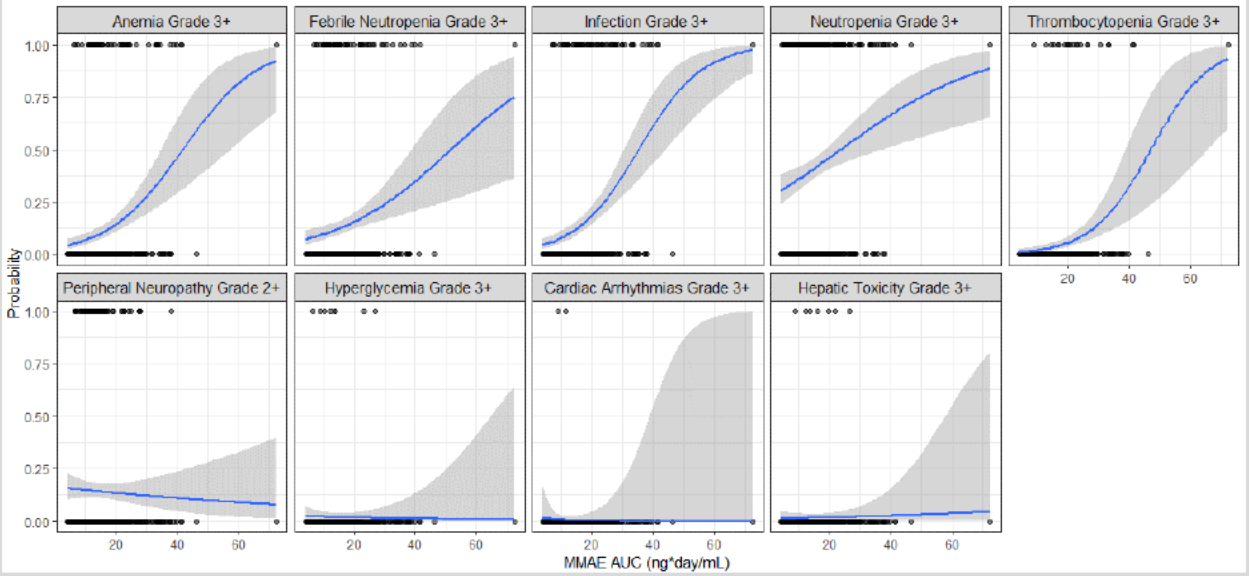
The E-R analysis for efficacy did not identify any clear associations between acMMAE AUC and overall survival or probability of complete response. Cox proportional hazard modeling identified that presence of bulky disease at baseline and acMMAE exposure had statistically significant associations with PFS.

For the E-R analysis for safety, both acMMAE and MMAE exposure in plasma (model-predicted Cycle 6 AUC) were associated with incidence of multiple safety events. Patients with higher MMAE exposure also tended to have higher acMMAE exposure. However, a greater number of E-R safety associations and generally stronger associations were observed with MMAE exposure compared to acMMAE. Associations between MMAE exposure and safety events are displayed in **Figure 24** and **Figure 25**.

Higher MMAE and acMMAE exposure were both associated with higher rates of Grade ≥3 anemia, Grade ≥3 febrile neutropenia, Grade ≥3 infection, and Grade ≥3 thrombocytopenia. Additionally, higher MMAE exposure was associated with higher rates of Grade ≥3 neutropenia, while higher acMMAE exposure was associated with higher rates of Grade ≥2 peripheral neuropathy as shown in **Figure 26.** No clear associations were identified between MMAE exposure and Grade ≥2 peripheral neuropathy, Grade ≥3 hyperglycemia, Grade ≥3 cardiac arrhythmias, and Grade ≥3 hepatic toxicity. However, the number of patients who experienced these safety events was relatively small.

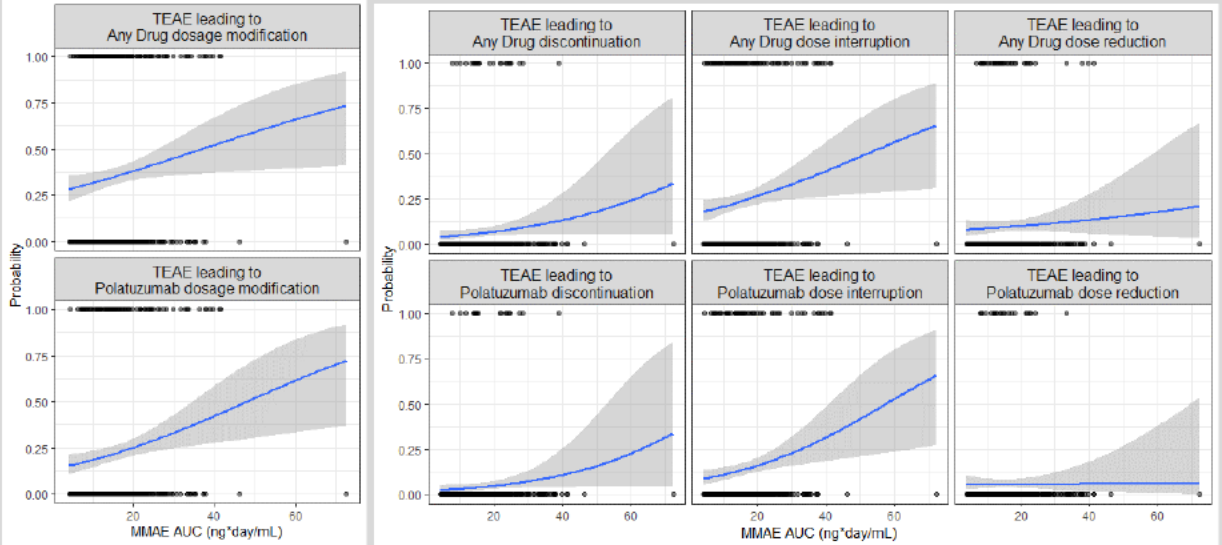
In regard to dose modifications, higher MMAE and acMMAE exposure were associated with higher rates of treatment-emergent adverse events (TEAEs) leading to dose modification (i.e., drug discontinuation, dose interruption, or dose reduction) of any drug, TEAEs leading to dose modification of polatuzumab vedotin, TEAEs leading to discontinuation of any drug, and TEAEs leading to discontinuation of polatuzumab vedotin. Higher MMAE exposure was also associated with higher rates of TEAEs leading to dose interruption of any drug and dose interruption of polatuzumab vedotin.

Figure 24 Logistic Regression for Unconjugated MMAE Exposure and Safety Endpoints



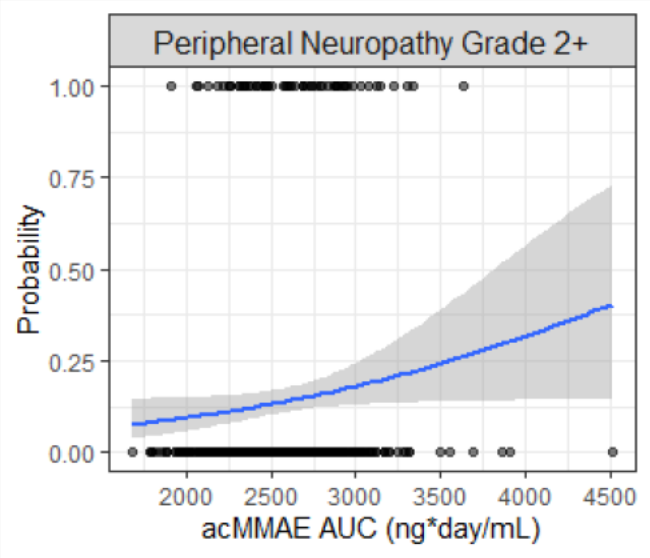
Grade 2+ refers to Grade 2 and above TEAEs. Grade 3+ refers to Grade 3 and above TEAEs. Data shown for pola+R-CHP arm (n=429) of POLARIX; TEAE data derived from adae.xpt dataset.
AUC = area under the concentration-versus-time curve; MMAE = monomethyl auristatin E; pola+R-CHP = polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; TEAE = treatment emergent adverse event.
Source: FDA analysis of Applicant's POLARIX adae.xpt dataset and exposure-response dataset.

Figure 25 Logistic Regression for Unconjugated MMAE Exposure and TEAEs Leading to Dose Modification



Any drug refers to polatuzumab vedotin/placebo, vincristine/placebo, rituximab, doxorubicin, cyclophosphamide, or prednisone. Data shown for pola+R-CHP arm (n=429) of POLARIX; TEAE data derived from adae.xpt dataset.
AUC = area under the concentration-versus-time curve; MMAE = monomethyl auristatin E; pola+R-CHP = polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; TEAE = treatment emergent adverse event.
Source: FDA analysis of Applicant's POLARIX adae.xpt dataset and exposure-response dataset.

Figure 26 Logistic Regression for acMMAE Exposure and Grade ≥ 2 Peripheral Neuropathy



Grade 2+ refers to Grade 2 and above TEAEs. Data shown for pola+R-CHP arm (n=429) of POLARIX; TEAE data derived from adae.xpt dataset.

acMMAE = antibody-conjugated monomethyl auristatin E; AUC = area under the concentration-versus-time curve; pola+R-CHP = polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, and prednisone; TEAE = treatment emergent adverse event.

Source: FDA analysis of Applicant's POLARIX adae.xpt dataset and exposure-response dataset.

FDA Appendix 2: The Estimand Framework Applied to PFS and Comparison of Approaches

Clear alignment between a clinical question and the analysis approach is described in ICH E9 (R1) guidance (Statistical Principles for Clinical Trials: Addendum, 2021).[10] The clinical question of interest should inform the estimand strategy.

A treatment policy estimand strategy (not censoring for NALT) assumes that whether or not NALT was given to patients is irrelevant. This addresses the clinical question: "What is the effect of treatment regardless of NALT being given to some patients?" FDA does not consider this analysis alone appropriate because use of NALT is relevant to understand patients' responses to treatment.

FDA also considered a hypothetical estimand strategy (censoring for NALT). Censoring for NALT is one approach to address a clinical question which FDA considers important to this application: "What is the effect of the treatment if NALT had not been administered?" The treatment policy estimand approach and the hypothetical approach answer different clinical questions and both approaches are important, but neither are explicitly recommended in ICH E9 (R1).

The Applicant's primary analysis of PFS did not censor NALT or ≥2 consecutive missed disease assessments, which is a treatment policy estimand approach. This approach evaluates the effect of the investigational drug incorporating the potential add-on effects of NALT and potentially poorly measured progression time during the missing intervals. For lymphoma products, the Division typically censors both for NALT and ≥2 consecutive missed disease assessments; this approach evaluates the sole effect of experimental treatment in absence of subsequent therapy, which is considered a hypothetical estimand strategy.

When comparing the treatment policy approach and the hypothetical approach, there are advantages and caveats to both. The treatment policy approach may avoid informative censoring, but it does not separate the treatment effect of the investigational drug from NALT. Neither does it censor poorly measured progression time when there was long interval of missing assessments. Therefore, neither approach is perfect and both strategies are important to characterize the effect of treatment. Ideally, they should be consistent and come to the same conclusion to demonstrate a robust PFS benefit.

FDA Appendix 3: Additional Analyses of Overall Survival

To further assess benefit-risk and OS, FDA requested additional analyses to assess the potential for harm based on potential additional follow-up time for OS. Associated analyses and calculations are listed below, as provided by the Applicant. Note that there are several assumptions associated with calculating the probability for observing different OS HRs in the future, and the results are sensitive to these assumptions. There is more uncertainty and variability as longer looks into future data were assumed.

Table 26 Probability of Point Estimate and Upper Bound of Confidence Interval Exceeding Thresholds with Additional Follow-Up, Assuming Different True HRs of OS

Estimated follow-up	**2 years after final OS analysis**	**5 years after final OS analysis**
Projected # of events* **(Estimated IF based on 631 deaths)**	196 (31%)	279 (44%)
Probability of Point Estimate / Upper Bound Exceeding 1		
HR=0.80	8.0% / 97.7%	4.6% / 84.2%
HR=0.90	17.7% / 99.3%	16.5% / 95.7%
HR=0.94 (observed at final OS analysis)	22.6% / 99.6%	23.9% / 97.6%
HR=1.00	30.7% / 99.8%	37.0% / 99.1%
HR=1.10	45.2% / 99.9%	59.7% / 99.8%

IF, information fraction.

* 131 events (21% IF) occurred at the final OS analysis (CCOD 6/15/2022).

Source: Conditional probabilities provided by Applicant; results dependent on parameter assumptions

Note that the HR of 0.73 assumed in the protocol is unrealistic to achieve 80% power. When assuming a HR of 0.8 and 80% power for OS evaluation, the projected information fraction was 44% with 5 years of additional follow up. Based on the information presented in Table 26 above, if additional deaths were observed at a HR=0.94 (the HR at the final OS analysis), at 2 years after the final OS analysis the probability of the point estimate for the OS HR exceeding 1 would be 22.6%. At 5 years after the final OS analysis the probability of the point estimate for the OS HR exceeding 1 would be 23.9%.

Due to the low rate of events accumulation, there is uncertainty in assessing and interpreting the effect on OS. However, under most scenarios, there is a substantial probability that the point estimate for the OS HR is greater than 1. While there is high variability due to limited observed survival information, lack of improvement in OS in many scenarios, particularly in the context of frontline therapy, reflects marginal safety and efficacy and adds to the uncertainties in the overall assessment of benefit-risk.

Additional considerations

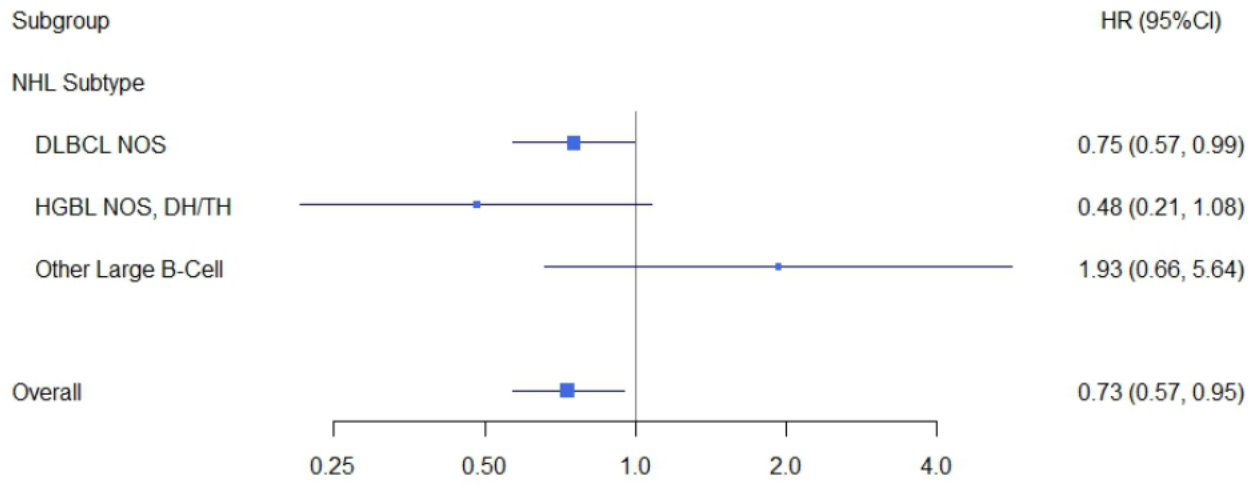
Varying the assumed HRs in the future and follow-up time may have a large effect on these calculated values, as described below.

- Power associated with the observed HR of 0.94: Given the 879 enrolled patients, a two-sided sided 5% level test, assuming a hazard rate of 0.006923 for the R-CHOP arm (protocol assumption), with 131 events observed at the final analysis of OS there is 15% power to detect the observed HR of 0.94.
- Power calculation for how many total OS events would be needed if a superiority comparison was to be performed with at least 80% power: For HRs range from 0.73 (protocol assumption) to 0.81, the number of events needed ranges from 317 to 708. For HRs exceeding 0.81, greater than 879 events would be required to achieve at least 80% power. This is infeasible because the number of events is greater than the number of enrolled patients.
- Conditional probabilities of the point estimate and the upper bound of 95% confidence intervals for the OS HR exceed 1 at different information fraction/follow-up times for potential future OS analyses: Assuming HR=0.8, to achieve 80% power 631 deaths were required. The information fraction in Table 26 is based on 631 deaths.

FDA Appendix 4: Efficacy Results by NHL Subgroup

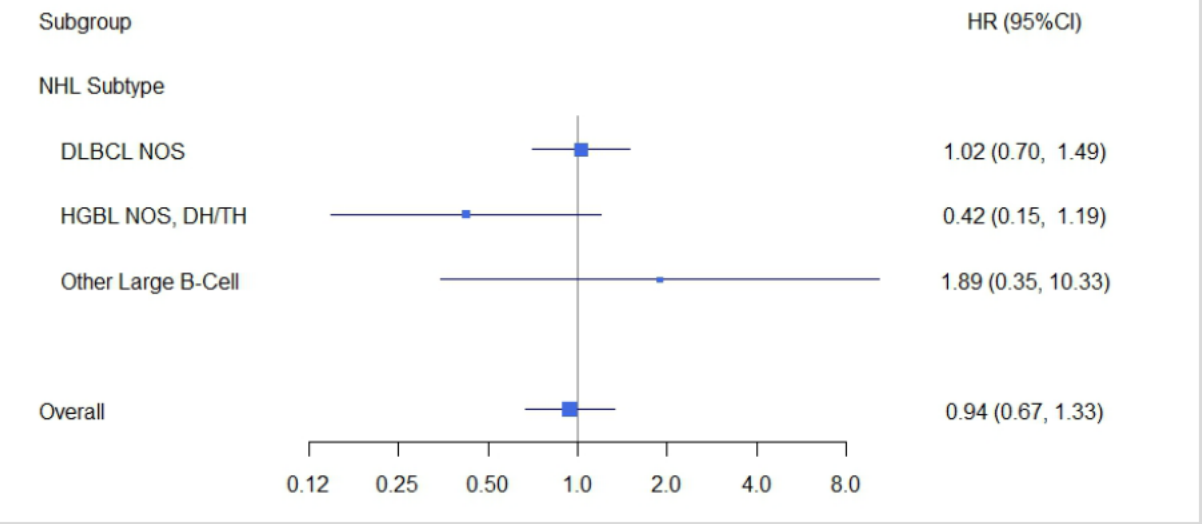
To assess the efficacy results in histology subtypes, FDA conducted analyses on PFS, OS, and response rate by three NHL subgroups: DLBCL NOS (n=740), HGBL (n=93), and other large B-cell lymphomas (n=46). The results suggest heterogeneity in the treatment effect.

Figure 27 Forest Plot of PFS by Histologic Subgroup



Source: FDA analysis

Figure 28 Forest Plot of OS by Histologic Subgroup



Source: FDA analysis. CCOD 6/15/2022.

Table 27 Results of PFS and OS by NHL Subgroups

NHL Subtype	Parameter	Pola + R-CHP	R-CHOP
Overall	**N**	440	439
	PFS		
	1-year rate (95% CI)	83.9% (80.1, 87.1)	79.8% (75.6, 83.3)
	diff	4.1% (-1.0, 9.3)	
	2-year rate (95% CI)	76.7% (72.3, 80.5)	70.2% (65.5, 74.4)
	diff	6.5% (-1.8, 10.1)	
	HR (95% CI)	**0.73 (0.57, 0.95)**	
	OS		
	1-year rate (95% CI)	92.2% (89.2, 94.3)	94.6% (92.0, 96.4)
	diff	-2.4% (-5.8, 0.9)	
	2-year rate (95% CI)	88.7% (85.3, 91.3)	88.6% (85.2, 91.3)
	diff	0.1% (-6.7, 1.8)	
	HR (95% CI)	**0.94 (0.65, 1.37)**	
DLBCL NOS	**N**	373	367
	PFS		
	1-year rate (95% CI)	84.0% (79.8, 87.4)	81.0% (76.5, 84.7)
	diff	3.0% (-2.6, 8.6)	
	2-year rate (95% CI)	77.3% (72.6, 81.3)	70.9% (65.8, 75.3)
	diff	6.4% (-3.5, 9.5)	
	HR (95% CI)	**0.75 (0.57, 0.99)**	
	OS		
	1-year rate (95% CI)	91.8% (88.5, 94.2)	95.5% (92.8, 97.2)
	diff	-3.7% (-7.2, -0.2)	
	2-year rate (95% CI)	88.0% (84.2, 90.9)	89.6% (85.9, 92.3)
	diff	-1.6% (-8.3, 0.9)	
	HR (95% CI)	**1.02 (0.70, 1.49)**	
HGBL (NOS or DH/TH)	**N**	43	50
	PFS		
	1-year rate (95% CI)	86.0% (71.6, 93.5)	67.4% (51.8, 79.0)
	diff	18.6% (1.5, 35.7)	
	2-year rate (95% CI)	81.4% (66.2, 90.2)	62.7% (46.9, 75.0)
	diff	18.7% (0.3, 36.9)	
	HR (95% CI)	**0.48 (0.21, 1.08)**	
	OS		
	1-year rate (95% CI)	95.2% (82.3, 98.8)	85.3% (71.6, 92.7)
	diff	9.9% (-2.0, 21.8)	
	2-year rate (95% CI)	95.2% (82.3, 98.8)	81.1% (66.8, 89.7)
	diff	14.2% (-3.0, 22.8)	

NHL Subtype	Parameter	Pola + R-CHP	R-CHOP
	HR (95% CI)	**0.42 (0.15, 1.19)**	
Other LBCL [a]	**N**	24	22
	PFS		
	1-year rate (95% CI)	78.4% (55.6, 90.4)	85.7% (62.0, 95.2)
	diff	-7.3% (-29.8, 15.2)	
	2-year rate (95% CI)	58.4% (34.8, 76.1)	76.2% (51.9, 89.3)
	diff	-17.8% (-35.3, 20.7)	
	HR (95% CI)	**1.93 (0.66, 5.64)**	
	OS		
	1-year rate (95% CI)	91.7% (70.6, 97.8)	100.0% (100.0, 100.0)
	diff	-8.3% (-19.4, 2.7)	
	2-year rate (95% CI)	87.5% (66.1, 95.8)	90.9% (68.3, 97.6)
	diff	-3.4% (-26.2, 9.5)	
	HR (95% CI)	**1.89 (0.35, 10.33)**	

[a] T-cell/histiocyte-rich LBCL (n=28) and EBV+ DLBCL (n=18)
Source: FDA analysis. OS based on the 6/15/2022 CCOD.

Table 28 Response Rates per BICR at the End of Therapy by NHL Subgroup

NHL Subtype	Parameter	Pola + R-CHP	R-CHOP
Overall	**N**	440	439
	CR rate (95% CI)	78.0% (73.8, 81.7)	74.0% (69.7, 78.1)
	diff (95%)	**3.9% (-1.9, 9.8)**	
	ORR (95% CI)	85.5% (81.8, 88.6)	83.8% (80.0, 87.1)
	diff (95%)	1.6% (-3.4, 6.6)	
DLBCL NOS	**N**	373	367
	CR rate (95% CI)	76.7% (72.0, 80.9)	74.9% (70.2, 79.3)
	diff (95%)	**1.7% (-4.7, 8.2)**	
	ORR (95% CI)	85.0% (81.0, 88.5)	85.0% (80.9, 88.5)
	diff (95%)	0.0% (-5.2, 5.1)	
HGBL NOS, DH/TH	**N**	43	50
	CR rate (95% CI)	88.4% (74.9, 96.1)	64.0% (49.2, 77.1)
	diff (95%)	**24.4% (5.8, 42.9)**	
	ORR (95% CI)	90.7% (77.9, 97.4)	74.0% (59.7, 85.4)
	diff (95%)	16.7% (-0.4, 33.8)	
Other LBCL[a]	**N**	24	22
	CR rate (95% CI)	79.2% (57.8, 92.9)	81.8% (59.7, 94.8)
	diff (95%)	**-2.7% (-28.2, 22.9)**	
	ORR (95% CI)	83.3% (62.6, 95.3)	86.4% (65.1, 97.1)
	diff (95%)	-3.0% (-26.7, 20.7)	

[a] T-cell/histiocyte-rich LBCL (n=28) and EBV+ DLBCL (n=18)

Source: FDA analysis

FDA Appendix 5: Treatment Guidelines for HGBL

Table 29 Treatment Guidelines for Newly Diagnosed HGBL with *MYC* and *BCL2* and/or *BCL6* Translocations

• Clinical trial is recommended
• **R-CHOP** may be associated with a sub-optimal outcome. Could be considered for low-risk IPI patients.
• **Dose-adjusted EPOCH-R**
• **R-HyperCVAD** alternating with **high-dose methotrexate** and **cytarabine** *
• **R-CODOX-M** alternating with **R-IVAC ***
• Additional considerations – Central nervous system prophylaxis – Consolidation with autologous SCT can be considered

* Potentially toxic regimens; performance status and comorbidities should be considered

EPOCH-R: etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab

R-HyperCVAD: rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone

R-CODOX-M: rituximab, cyclophosphamide, vincristine, doxorubicin, and methotrexate

R-IVAC: rituximab, ifosfamide, etoposide, and cytarabine

Source: Modified from NCCN Guidelines for B-Cell Lymphoma[1]

Table 30 Safety Overview by NHL Subgroup

	Pola+ R-CHP, %	R-CHOP, %
Total safety population	n=435	n=438
SAEs [a]	34	32
Grade ≥3 AE	61	60
Fatal TEAEs	2.8	2.3
DLBCL NOS	n= 368	n= 367
SAEs	33	32
Grade ≥3 AE	60	60
Fatal TEAEs	3.2	2.5
Completed treatment	89	86
HGBL	n= 43	n= 49
SAEs	44	35
Grade ≥3 AE	65	69
Fatal TEAEs	0	4
Completed treatment	88%	80%
Other LBCL	n= 24	n= 22
SAEs	25	23
Grade ≥3 AE	63	59
Fatal TEAEs	4.2	0
Completed treatment	96	95%

[a] SAEs in both arms were primarily driven by infections (14% and 10% with pola+R-CHP and R-CHOP, respectively) and blood system disorders (11% and 9%, respectively).
Source: FDA analysis

Table 31 Deaths Within and Beyond the Safety Reporting Period

Deaths by Time Period	Pola+R-CHP (N=435)	R-CHOP (N=438)
Death ≤ 90 days after last dose , n	16 (3.7%)	14 (3.2%)
Progressive disease	4 (0.9%)	4 (0.9%)
Adverse event	12 (2.8%) • infection (5) • kidney injury (1) • intestinal perforation (1) • sudden death (1) • unknown (4)	10 (2.3%) • infection 7) • cardiac (1) • unknown (1) • other (1)
Deaths 8 to 18 months from randomization, n	25 (6%)	22 (5%)
Progressive disease	16 (64%)	14 (64%)
Infections	5	3
Unknown	4	2
Cardiac arrest	0	1
Stroke	0	1
Second primary malignancy	0	1

Source: FDA analysis. CCOD 6/15/2022.