EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 March 2022
EMA/287823/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Polivy

International non-proprietary name: polatuzumab vedotin

Procedure No. EMEA/H/C/004870/II/0012

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Table of contents

List of abbreviations

Abbreviation	Description
ABC	Activated B-cell type
ADA	Anti-drug antibodies
ADC	antibody–drug conjugate
AE	Adverse event
AEGT	Adverse event grouped terms
AEPI	Adverse event of particular interest
AESI	AEs of special interest
ALT	Alanine aminotransferase
AST	Aspartate Aminotransferase
BAR	Bioanalytical report
BICR	Blinded independent central review
BLD	Below limit of detection
BOR	Best observed response
BSA	Body surface area
CCI	Commercially confidential information
CCOD	Clinical cutoff date
CCP	Confirmatory cut point
CDR	Complementarity determining region
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CHP	cyclophosphamide, doxorubicin, and prednisone
CIOMS	Council for International Organizations of Medical Sciences
CL	Confidence limits
CLL	Chronic lymphocytic leukemia
CMH	Cochran–Mantel–Haenszel
CMR	Complete Metabolic Response
CNS	Central nervous system
COA	Clinical outcome assessments
COO	Cell-of-origin
CR	Complete Response
CRF	Case report form
CSR	Clinical Study Report
CT	Computed tomography
ctDNA	Circulating tumor DNA

CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient variant
DAR	Drug-to-antibody ratio
DEL	Double-expressing lymphoma
DFS	Disease-free survival
DH	Double-hit
DHL	Double-hit lymphoma
DILI	Drug induced liver injury
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
ECG	Electrocardiogram
EFS	Event-free survival
ELISA	Enzyme-linked immunosorbent assay
EOT	End of treatment
ER	Exposure response
FFPE	Formalin Fixed Paraffin Embedded
FISH	Florescent in-situ hybridization
FL	Follicular lymphoma
GCB	Germinal center B-cell type
GCP	Good Clinical Practice
GCSF	Granulocyte colony-stimulating factor
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HGBL	High-grade B-cell lymphoma
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IDCC	Independent Data Coordinating Center
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IMP	Investigational medicinal products
INN	International Non-proprietary Name
INV	Investigator
IPI	International Prognostic Index

IRB	Institutional Review Boards
IRC	Independent Review Committee
IRF	Independent Review Facility
IRR	Infusion-related reactions
ITT	Intent-to-treat
IxRS	interactive voice or Web-based response system
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
LoPO	List of planned outputs
LST	Lymphoma Subtyping
LTR	less than reportable
LymS	Functional Assessment of Cancer Therapy–Lymphoma Lymphoma Subscale
MedDRA	Medical dictionary of regulatory activities
MMAE	mono-methyl auristatin E
MQC	Minimum quantifiable concentration
MRI	Magnetic resonance imaging
MUGA	Multiple-gated acquisition
NALT	New anti-lymphoma therapy
NCI	National Cancer Institute
ND	Not done
NHL	Non-Hodgkin lymphoma
NMR	No metabolic response
NOS	Not otherwise specified
OBD	Oncology Biomarker Development
ORR	Objective response rate
OS	Overall survival
PCL	Protocol Clarification Letter
PCR	Polymerase chain reaction
PD	Progression Disease
PDMS	Protocol Deviation Management System
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PMD	Progressive metabolic disease
PMR	Partial metabolic response
PN	Peripheral neuropathy
PO	Orally

pola	polatuzumab vedotin
PPD	Protected patient data
PR	Partial response
PRO	Patient-reported outcomes
PT	Preferred term
PV	Pharmacovigilance
QoL	Quality of life
RBC	Red blood cell
RDI	Relative Dose Intensity
RMST	Restricted mean survival time
RNA	Ribonucleic acid
SAE	Serious adverse events
SCP	Summary of Clinical Pharmacology
SD	Standard deviation
SE	Safety-evaluable
SMQ	Standardized MedDRA queries
SoC	Standard of care
SOC	System Organ Class
THL	Triple-hit lymphoma
TLS	Tumor lysis syndrome
TTD	Time to deterioration
ULN	Upper limit of normal
VHP	Voluntary Harmonization Procedure
WBC	White blood cell

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 5 November 2021 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of the indication to include: Polivy in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone, is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL) based on the efficacy and safety data from the Pivotal Phase III Study GO39942 (POLARIX). This submission fulfills SOB003 thus supporting the switch from CMA to full MA. Annexes I, II, IIIB are revised. The RMP is also updated.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Polivy, was designated as an orphan medicinal product EU/3/18/2013 on 16 April 2018. Polivy was designated as an orphan medicinal product in the following indication: Treatment of diffuse large B-cell lymphoma.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Polivy as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found here <insert link>.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMA/PDCO/818664/2017 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products. Assessment of these claims is appended.

Protocol assistance

The MAH received Protocol Assistance from the CHMP on 18 May 2017 (EMEA/H/SA/2809/3/2017/II). The Protocol Assistance pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	5 November 2021
Start of procedure:	27 November 2021
CHMP Co-Rapporteur Assessment Report	26 January 2022
CHMP Rapporteur Assessment Report	26 January 2022
PRAC Rapporteur Assessment Report	27 January 2022
PRAC members comments	2 February 2022
CHMP Co-Rapporteur Critique	3 February 2022
PRAC Outcome	10 February 2022
CHMP members comments	14 February 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	17 February 2022
Request for supplementary information (RSI)	24 February 2022
CHMP Rapporteur Assessment Report	09 March 2022
PRAC Rapporteur Assessment Report	10 March 2022
PRAC members comments	14 March 2022
CHMP members comments	14 March 2022
Updated PRAC Rapporteur Assessment Report	17 March 2022
Updated CHMP Rapporteur Assessment Report	17 March 2022
CHMP opinion:	24 March 2022
The CHMP adopted a report on similarity of Polivy with Minjuvi, Yescarta and Kymriah on	24 March 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Polatuzumab vedotin in the initial MA application was approved in combination with rituximab and bendamustin for treatment of relapsed/refractory (R/R) DLBCL. The present application is an extension of indication for first line treatment of DLBCL in combination with Rituximab, cyclophosphamide, doxorubicine, prednisone.

Epidemiology

DLBCL is the most common histologic subtype of non-Hodgkin's lymphoma (NHL), accounting for 30% of NHL cases (Armitage and Weisenburger 1998) and 80% of aggressive lymphomas. In 2020, 544,352 new NHL cases worldwide were estimated with over 163,000 patients estimated to be diagnosed with DLBCL (Global Cancer Observatory 2020). While DLBCL is mostly frequently diagnosed between ages of 65 and 74 years (with median age of 65 years at diagnosis [SEER]), it can also occur in the younger population, including children and young adults.

Biologic features, Aetiology and pathogenesis

DLBCL is a heterogeneous disease with a number of histologic, proteomic and molecular subsets with distinctive prognostic profiles, including cell of origin (activated Bcell-like [ABC], germinal center B-cell-like [GCB]), elevated protein expression of MYC and BCL2 seen in double-expressing lymphoma [DEL]), and gene rearrangements in MYC and BCL2 and/or BCL6 (double or triple-hit lymphoma [DHL/THL]) (Schmitz et al 2018; Scott et al 2015; Lenz et al 2008; Johnson et al 2009; Johnson et al 2012).

For the vast majority of patients, the etiology of DLBCL is unknown. Hereditary and acquired immunodeficiencies, occupational exposures, and pharmacological immunosuppression in the setting of transplantation or treatment of autoimmune diseases have been identified as factors thought to potentially confer increased risk of developing DLBCL.

Clinical presentation, diagnosis and stage/prognosis

Initially, DLBCL may be asymptomatic, but it may also be associated with constitutional symptoms such as fever, recurrent night sweats, weight loss, and/or local effects of lymph node enlargement, as well as those of bone marrow failure (Armitage and Weisenburger 1998). These disease symptoms, along with treatment-related side effects, often lead to impairments in aspects of health-related quality of life (HRQoL) including physical functioning and fatigue (Tholstrup et al 2011). Without treatment, DLBCL is fatal with a median survival of approximately 6 months (Armitage and Weisenburger 1998).

Although the biologic features of DLBCL are evaluated in clinical practice and clinical research, they do not clearly guide the choice of therapy, as no definitive studies have demonstrated superiority to R-CHOP in biomarker-selected populations. While molecular features help to define higher and lower risk subtypes, clinical features are also integrated into risk assessment and estimating prognosis. The International Prognostic Index (IPI) for aggressive NHL identifies five patient factors obtained at diagnosis used to stratify prognosis and overall survival (OS). The IPI factors reflect clinical features, each representing one point, and are a combination of patient characteristics (age >60, ECOG PS >2) and disease-related findings (Ann Arbor Stage III or IV, elevated LDH, and extranodal involvement in more than one site).

Management

The standard of care therapy for DLBCL involves frontline multi-agent chemotherapy with complementary mechanisms of action combined with immunotherapy. Up to 8 cycles of R-CHOP given in 21-day intervals (R-CHOP-21), or R-CHOP-like chemotherapy is considered to be the standard of care therapy for patients with previously untreated DLBCL. Analyses suggest that 6 cycles is not inferior to 8 cycles (Wästerlid et al 2018; Sehn et al 2018).

Since the introduction of R-CHOP there has been limited advancement in treatment options for previously untreated DLBCL patients for over 20 years as the majority of randomized studies in previously untreated DLBCL have failed to show a benefit. While R-CHOP may cure approximately 60% of patients with previously untreated DLBCL (Sehn and Salles 2021), alternative strategies have so far been unable to demonstrate meaningful benefit over R-CHOP. These include: increased dose density with R-CHOP given at 14 day intervals (Delarue et al 2013; Cunningham et al. 2013); dose intensification with dose-adjusted etoposide plus prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R), Bartlett et al 2019.

Thus there is a rationale for introducing novel therapeutic agents that can build upon R-CHOP and improve outcomes in patients with previously untreated DLBCL by preventing or delaying relapse.

2.1.2. About the product

Polatuzumab vedotin (pola) is an antibody-drug conjugate (ADC) that contains a humanized immunoglobulin G1 anti-CD79b monoclonal antibody (MCDS4409A) and a potent anti-mitotic agent, monomethyl auristatin E (MMAE). Pola binds CD79b, a surface antigen restricted to B-cells that is ubiquitously expressed across a majority of mature B-cell malignancies including diffuse large B-cell lymphoma (DLBCL). MMAE is a potent analog of dolastatin 10 that exerts its cytotoxicity by binding to microtubules and inhibiting microtubule polymerization, inhibiting cell division, inducing apoptosis. Upon binding to the CD79b, pola is rapidly internalized to enable targeted delivery of MMAE. This allows microtubule inhibition with greater potency and without additional toxicity.

In the EU, the initial MAA (procedure EMEA/H/C/004870/0000) for polatuzumab vedotin was granted Conditional Marketing Authorization (CMA) on 16 January 2020 for Polivy in combination with BR for the treatment of adult patients with relapsed/refractory DLBCL who are not candidates for haematopoietic stem cell transplant. The initial MAA for Polivy was based on data from one pivotal study GO29365, performed in a small number of patients and as comprehensive data on the product in the proposed indication were not available, the CHMP was of the view that a full marketing authorisation could not be

granted. Instead, a conditional marketing authorisation was proposed by the CHMP during the assessment, after having consulted the applicant.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease and is designated as an orphan medicinal product. In order to further confirm the safety and efficacy of polatuzumab vedotin in DLBCL the MAH will provide Study GO39942, a randomized, double-blind, placebocontrolled trial that evaluates polatuzumab vedotin in combination with R-CHP (rituximab, cyclophosphamide, doxorubicin, prednisone) versus R-CHOP in patients with previously untreated diffuse large B-cell lymphoma.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH received in the 2017 scientific advice (SA) (EMA/CHMP/SAWP/301908/2017) and was encouraged to increase the sample size to achieve higher power, particularly for the analysis of OS. Indeed, there was a concern that the lack of power may lead to immature OS results. However, the expected number of OS events at study termination was smaller in the study protocol than in the SA (estimated as 178 in protocol vs 209 in the SA request), leading to a smaller anticipated power of 52% (vs 62% in SA).

2.1.4. General comments on compliance with GCP

The MAH states that all studies included in this application were conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. The appropriate Ethics Committees and Institutional Review Boards reviewed and approved all studies. The studies also took guidelines into consideration regarding statistical principles (ICH E9), and EMA and FDA guidelines on clinical trial endpoints for the approval of cancer drugs (CPMP/EWP/205/95 Rev. 3 and the FDA Guidance to Industry, May 2007).

2.2. Non-clinical aspects

2.2.1. Introduction

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.2. Ecotoxicity/environmental risk assessment

No new data have been submitted in this application which was considered acceptable by the CHMP. As the original ERA included in the initial MAA was performed on the basis of a theoretical use of the product in the broad indication, a submission of an updated ERA on a potential increase in environmental exposure further to this extension of indication was not needed.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Protocol No.	Location of Synopsis Location of Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
GO39942 (POLARIX) [pivotal]	5.3.5.1 Primary CSR Report 1106275, Synopsis Primary CSR Report 1106275	Efficacy, safety, PK, immuno-genicity, PRO, biomarker, health status	Phase III, multicenter, randomized, double-blind, placebo-controlled	**Arm A:** pola 1.8 mg/kg + R-CHP + vincristine placebo q 21 days × 6 cycles followed by rituximab **Arm B:** R-CHOP + pola placebo q 21 days × 6 cycles followed by rituximab Rituximab 375 mg/m² as monotherapy in Cycles 7 and 8 in both arms	**Total 1L DLBCL=879[a]** **Arm A:** Pola + R-CHP=440 **Arm B:** R-CHOP=439	Previously untreated patients with CD20-positive DLBCL	6 cycles of pola+R-CHP or R-CHOP at 21-day intervals Both arms received two additional cycles (cycles 7 and 8) of single agent rituximab	Study ongoing Primary CSR Full report
GO29044 [supportive]	5.3.5.2 Final CSR Report 1109685, Synopsis Final CSR Report 1109685	Phase Ib: MTD of pola + R/G-CHP Phase II: safety, efficacy	Phase Ib/II, multicenter, open-label, single arm (pola + R/G-CHP)	**Dose escalation:** pola 1.0–1.8 mg/kg + R-CHP q 21 days × 6-8 cycles pola 1.4–1.8 mg/kg + G-CHP q 21 days × 6-8 cycles **Expansion:** pola 1.8 mg/kg + R-CHP q 21 days × 6–8 cycles pola 1.8 mg/kg + G-CHP q 21 days × 6–8 cycles	**Total n = 84** **Non-DLBCL** = 8 **1L DLBCL** (dose-escalation +expansion) = 75[b] Pola + R-CHP = 50 Dose-escalation = 10 Dose-expansion = 40 Pola + G-CHP = 25 Dose-escalation = 8 Dose-expansion = 17	**Dose escalation:** newly diagnosed or R/R B-NHL (≤1 prior line of systemic therapy) **Expansion:** Previously untreated DLBCL with IPI 2–5	6 or 8 cycles of pola+ R/G–CHP at 21-day intervals	Study completed Final CSR Full report

acMMAE = antibody-conjugated monomethyl auristatin E; ADA = anti-drug antibody; B-NHL=B-cell non-Hodgkin's lymphoma; DLBCL=diffuse large B-cell lymphoma; G=obinutuzumab; IPI=International Prognostic Index; IV=intravenous(ly); MMAE = monomethyl auristatin E; PK=pharmacokinetic; Pola=polatuzumab vedotin; popPK = population PK; PRO=patient reported outcomes; R=rituximab; R-CHP= rituximab, cyclophosphamide, doxorubicin, prednisone; R-CHOP= rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R/R=relapsed or refractory.

[a] The China extension cohort includes Chinese patients enrolled after the global study phase closed to enrollment and those patients are not included in the pivotal population analyses. The 121 Chinese patients enrolled in the China extension cohort followed the same study design as the global study.

[b] Safety and efficacy evaluable population in 1L DLBCL patients (n = 75). A total of 82 patients were safety evaluable, as n = 7 were other NHL histologies. Of the 75 DLBCL patient, 66 patients were treated with pola 1.8 mg/kg and 9 treated at doses < 1.8 mg/kg.

2.3.2. Pharmacokinetics

Polatuzumab vedotin clinical pharmacology has been described in the initial MA application where it was approved in combination with rituximab and bendamustin for treatment of relapsed/refractory (R/R)

DLBCL. The present application aims to characterize polatuzumab vedotin PK as a first line treatment for DLBCL in combination with Rituximab, cyclophosphamide, doxorubicine, prednisone.

The clinical PK has been investigated in two clinical studies. Study GO29044 was a phase 1/2 study with dose escalation phase followed by a dose expansion phase in patients with B-cell non-Hodgkin's lymphoma (NHL), including DLBCL previously untreated patients. This was the main study with frequent sampling to allow insight in polatuzumab vedotin PK, including the antibody- conjugated MMAE (acMMAE), the total antibody, and the unconjugated MMAE. The second study, a phase 3 study GO29042, was conducted in previously untreated DLBCL patients with sparse PK sampling for polatuzumab vedotin PK characterisation. These PK data were analysed in a pop PK model. The population PK model used was the model submitted in the initial application, so called "legacy model". The additional PK data were analysed by external validation using the latter data based on the legacy popPK model.

Bioanalytical methods: There have been no updates to the polatuzumab vedotin assay method (i.e., no additional studies conducted) since the initial MA procedure. It included the measurement of three key analytes (conjugate evaluated as antibody-conjugated monomethyl auristatin E [acMMAE], total antibody, and unconjugated MMAE) to assess the overall pharmacokinetics of polatuzumab vedotin. The acMMAE, total antibody, and unconjugated MMAE were quantitated by immunoaffinity HPLC MS/MS in human plasma, ELISA in human serum and LC/MS/MS in human plasma respectively. These three bioanalytical methods were used in the presented clinical studies: study GO29044 and GO39942 (POLARIX).

Immunogenicity: There have been no updates to the anti-polatuzumab vedotin antibody assay method (i.e., no additional studies conducted) since the initial MA procedure.

The potential for pola to induce an undesirable immune response was assessed in the available data from POLARIX and supportive Study GO29044. The ADA analysis strategy is based on a tiered approach designed to detect and characterize ADA responses to polatuzumab vedotin (as well as obinutuzumab in study GO29044).

Patient samples were screened to detect all antibody responses toward polatuzumab vedotin (and obinutuzumab in study GO29044). Samples that screened positive were analyzed in a confirmatory assay to assess the specificity of the positive response. Titers were determined for confirmed ADA positive samples. In study GO39942 (POLARIX), further characterization was assessed by competitive binding with the antibody component of pola to characterize whether the ADA responses were primarily to the antibody portion, the linker-drug regions, or neo-epitopes of the ADC.

ICDCBA 106 validation report describes the validation process of the qualitative assay designed to detect neutralizing antibodies against polatuzumab vedotin. Neutralizing antibodies are measured in human serum through the assessment of caspase 3/7 activity in Human Burkitt lymphoma B cells (BJAB), an Epstein-Barr virus (EBV) negative B lymphoma cell line transfected.

The method validation is summarized in the following *Table 1*.

Table 1 Bioanalytical method validation summary: NAb to polatuzumab vedotin in human serum

Species/Matrix:	Human serum
Matrix Population:	Non-Hodgkin's Lymphoma (NHL)
Analysis Method:	Luminescence
Data Capture of RLU:	Biotek Cytation 5 Multi-Mode Plate Reader
Additional Data Analysis and Calculations:	Microsoft® Excel Office 365, Gen 5 Version 2.09, and PPD Assist LIMS Version 6
Normalization Control (NC):	PNHS + polatuzumab vedotin (100 ng/mL) + cells
Maximum Control (Max):	PNHS + polatuzumab vedotin (40.0 µg/mL) + cells
Minimum Control (Min):	PNHS + assay medium + cells
Positive Controls (PC):	PNHS + polatuzumab vedotin (100 ng/mL) + anti-DCDS4501S + cells
Sample Volume (µL):	20.0 µL aliquot for screening
Sample Storage Temperature:	-80 °C
NC/LPC 2 Ratio:	1.09 to 1.89 (determined at the end of validation)
Max/Min:	3.34 to 7.32 (determined at the end of validation)
CPF:	0.911
PC Plate-Specific Cut Point:	Plate Mean NC x CPF, 0.911
Assay Cut Point:	Plate Mean NC x CPF
Relative Assay Sensitivity:	650 ng/mL
Matrix Interference/ Selectivity:	Unspiked: Acceptable, as ten out of ten individual donors with NHL screened negative. LPC 1: Ten out of ten individual donors with NHL screened positive (analyzed for informational purposes only). LPC 2: Acceptable, as ten out of ten individual donors with NHL screened positive.
Relative Drug Tolerance:	LPC 1: Neutralizing antibodies can be detected in PNHS samples in the presence of up to 14.6 µg/mL excess polatuzumab vedotin (analyzed for informational purposes only). LPC 2: Neutralizing antibodies can be detected in PNHS samples in the presence of up to 37.3 µg/mL excess polatuzumab vedotin. HPC: Neutralizing antibodies can be detected in PNHS samples in the presence of up to 80.0 µg/mL excess polatuzumab vedotin.

Intra-Assay Precision Across PCs:		**NC**		**LPC 1***		**LPC 2***	**HPC**	
	Conc. (ng/mL)	0		1000		1617	5000	
	Intra-Assay (%CV)	1.94		3.30		5.73	2.70	
Inter-Assay Precision Across PCs:		**NC**	**LPC 1***	**LPC 2***	**HPC**	**NC/LPC 2**	**NC/HPC**	**Max/Min**
	Conc. (ng/mL)	0	1000	1617	5000	N/A	N/A	N/A
	Inter-Assay (%CV)	21.3	22.1	24.2	25.9	11.7	21.7	16.0
Robustness/Ruggedness:		The minimum and maximum times for control sample incubation, control/sample/cell incubation, and substrate incubation were evaluated along with two different instruments. Data for all assay controls met the acceptance criteria, and robustness/ruggedness was demonstrated.						
Freeze/Thaw Stability:		Demonstrated for eleven cycles thawed at room temperature.						
Thawed Matrix Stability:		Demonstrated for 24 hours at room temperature and 24 hours at 2 to 8 °C.						
Cross Reactivity/Interference – Atezolizumab:		• No interference was observed at the LPC 2 (1617 ng/mL) and HPC (5000 ng/mL) levels in the presence of 1000 µg/mL atezolizumab. • No cross-reactivity was observed in samples without NAb in the presence of 1000 µg/mL atezolizumab.						
Cross Reactivity/Interference – Mosunetuzumab:		• No interference was observed at the LPC 2 (1617 ng/mL) and HPC (5000 ng/mL) levels in the presence of 5.00 µg/mL mosunetuzumab. • No cross-reactivity was observed in samples without NAb in the presence of 5.00 µg/mL mosunetuzumab.						
Cross Reactivity/Interference – Tocilizumab:		• No interference was observed at the LPC 2 (1617 ng/mL) and HPC (5000 ng/mL) levels in the presence of 200 µg/mL tocilizumab. • No cross-reactivity was observed in samples without NAb in the presence of 200 µg/mL tocilizumab.						
Cross Reactivity/Interference – Rituximab:		• No interference was observed at the LPC 2 (1617 ng/mL) and HPC (5000 ng/mL) levels in the presence of 600 µg/mL rituximab. • No cross-reactivity was observed in samples without NAb in the presence of 600 µg/mL rituximab.						
Cross Reactivity/Interference – Obinutuzumab:		• No interference was observed at the LPC 2 (1617 ng/mL) and HPC (5000 ng/mL) levels in the presence of 800 µg/mL obinutuzumab. • No cross-reactivity was observed in samples without NAb in the presence of 800 µg/mL obinutuzumab.						
Cross Reactivity/Interference – Hemolysis:		• No interference was observed at the LPC 2 (1617 ng/mL) and HPC (5000 ng/mL) levels in the presence of > 5% hemolyzed PNHS matrix. • No cross-reactivity was observed in samples without NAb in the presence of > 5% hemolyzed PNHS matrix.						
Cross Reactivity/Interference – Lipemia:		• No interference was observed at the LPC 2 (1617 ng/mL) and HPC (5000 ng/mL) levels in the presence of > 300 mg/dL triglycerides. • No cross-reactivity was observed in samples without NAb in the presence of > 300 mg/dL triglycerides.						
Prozone Effect:		No prozone (hook) effect was observed at concentrations up to 100 µg/mL anti-DCDS4501S antibody.						
Stability of Sera-Mag Streptavidin-Coated Magnetic Particles in BA003:		Sera-Mag Streptavidin-Coated Magnetic Particles in BA003 were stable for up to two weeks.						

Study GO29044

ADAs were assessed at pre-infusion of Cycles 1, 2, and 4, at treatment completion/early termination, and at the 3 month follow-up visit.

The relative sensitivities of the polatuzumab vedotin ADA screening assay were estimated to be 60.1 ng/mL using an anti-CD79b antibody complementarity determining region monoclonal antibody (positive control) and 1141 ng/mL using an anti-auristatin monoclonal antibody diluted in normal human serum. The screening assay was optimized to tolerate drug interference. In the presence of 20 µg/mL of polatuzumab vedotin, two levels of the positive control sample (90 and 500 ng/mL) tested positive.

The prevalence of ADA at baseline was calculated by dividing the total number of patients in all study groups that tested positive for ADA at baseline by the total number of patients with a valid ADA test result at baseline.

The incidence of ADAs post-baseline in each study group was calculated by dividing the number of patients that developed treatment-induced ADAs (i.e., patients with a negative or missing baseline ADA result(s) and at least one positive post-baseline ADA result) plus the number of patients that had treatment-enhanced ADAs (i.e. the ADA response had increased 0.6 titer units from baseline) in the study by the total number of patients with valid post-baseline results in that study group during the study period.

The overall treatment emergent ADA response rate in all polatuzumab vedotin and obinutuzumab treatment groups was 0.0%, because there were no observed ADA responses at either baseline or post-baseline timepoints.

False-negative ADA response results are unlikely regarding polatuzumab vedotin, as levels of circulating ADC were below levels expected to interfere in the assay based on the drug tolerance profile of the assay.

Table 2 Incidence of Anti-Drug Antibodies to Polatuzumab Vedotin in Study GO29044

	R-CHP+POV 1.8 mg/kg (N=1)	G-CHP+POV 1.4 mg/kg (N=6)	G-CHP+POV 1.8 mg/kg (N=6)	EXP R-CHP+POV 1.8 mg/kg (N=33)	EXP G-CHP+POV 1.8 mg/kg (N=17)	All Polatuzumab Vedotin Treated Patients (N=63)
Baseline Prevalence of ADAs						
Baseline evaluable patients	1	6	6	30	17	60
Patients with a positive sample at baseline	0	0	0	0	0	0
Patients with no positive samples at baseline	1	6	6	30	17	60
Post-Baseline Incidence of ADAs						
Post–baseline evaluable patients	1	6	6	33	17	63
Patients Positive for ADA	0	0	0	0	0	0
Patients negative for ADA	1	6	6	33	17	63
Treatment unaffected	0	0	0	0	0	0

Study GO39942 (POLARIX)

ADAs were assessed at pre-infusion of Cycles 1 and 4, at treatment completion/early termination, and at the 3 month follow-up visit.

The ADA screening and confirmatory assays were optimized to tolerate drug interference and were able to detect 100 ng/mL of the positive control sample in the presence of 50 µg/mL of pola. Pola total antibody concentrations were determined for each ADA sample. Out of a total of 1125 ADA samples that were measured for pola total antibody, 1124 samples had levels less than 50 µg/mL. Pola total antibody concentrations ranged from <0.05 µg/mL to 77.6 µg/mL with a median concentration of 1.3 µg/mL. Therefore, there is a low likelihood of false-negative ADA results.

The biological background signal can vary between the samples used to determine the cut points during assay validation and the patient population being analyzed. Therefore, in-study screening cut point factor (sCPF), confirmatory cut point (CCP), and titer offset were assessed using individual POLARIX baseline samples and compared to those determined during assay validation.

The sCPF, using 307 individuals and targeting a 5% untreated positive rate, was 0.854 with CI90% of 0.816 to 0.897. The validation sCPF (1.16) was outside the limits of the in-study sCPF; therefore, the in-study sCPF was implemented. The CCP, using 100 individuals and targeting a 1% untreated positive rate, was 40.3% with CI90% of 37.7% to 43.3%. Although the validation CCP (38%) was within the CI90%, it was decided to use the in-study cut points for both the sCPF and CCP for consistency. The in-study titer offset was also implemented. The titer offset value (0.0626) was based on 4 times the standard deviation of the assay signal from 307 individual baseline samples.

Using the in-study titer offset, the relative sensitivity of the screening assay was estimated to be 27.8 ng/mL. Using the CCP of 40.3%, relative sensitivity of the confirmatory assay was estimated to be 20.7 ng/mL. Both the screening and confirmatory assays were able to detect 100 ng/mL of the surrogate positive control in the presence of 50 µg/mL of pola.

For all patients, the baseline prevalence of ADAs was 2.4% (20 of 849 ADA evaluable patients). Post-baseline, ADAs were detected in 6 of 427 (1.4%) ADA evaluable patients treated with pola (Table 3). All 6 ADA-positive patients had treatment-induced responses. Out of the 6 patients with treatment-induced ADA, 0 patients had a transient response but all had persistent responses. The 8 patients from the pola+R-CHP treatment arm who tested positive for ADA at baseline were treatment-unaffected (ADA response was similar to, or lower than, that at baseline).

Table 3 Incidence of Anti-Drug Antibodies to Pola in POLARIX

	Arm A Pola+R-CHP (N=433)	Arm B R-CHOP (N=425)	All Patients (N=858)
Baseline Prevalence of ADAs			
Baseline evaluable patients	424	425	849
Patients with a positive sample at baseline	8 (1.9%)	12 (2.8%)	20 (2.4%)
Patients with no positive samples at baseline	416	413	829
Post-Baseline Incidence of ADAs			
Post–baseline evaluable patients	427		
Patients Positive for ADA	6 (1.4%)		
Treatment-Induced	6		
Treatment-Enhanced	0		
Patients negative for ADA	421		
Treatment unaffected	8		

Domain specificity assay indicated through competitive binding that the antibody responses were directed primarily against the linker, drug, or neo-epitopes. Furthermore, all 6 patients with treatment-induced ADA were negative for NAb.

No significant difference in pola PK exposure for acMMAE, total antibody, and unconjugated MMAE was observed between ADA positive and ADA-negative patients. Individual pola PK exposure for acMMAE, total antibody, and unconjugated MMAE for 6 ADA positive patients were within the range of ADA negative patients.

Absorption

The drug product is administered intravenously.

Distribution

Already characterized in initial MAA

Elimination

Already characterized in initial MAA

Dose proportionality and time dependencies

Already characterized in initial MAA

Pharmacokinetics in target population

Polatuzumab vedotin PK was characterized in Polivy initial application were the drug conjugate acMMAE, the unconjugated drug MMAE, and total antibody PK was characterized. Although the initial application target patients with relapsed/refractory DLBCL patients, clinical study GO29044 PK results also included DLBCL treatment naïve patients. The PK results, based on NCA analysis were presented in the initial application which included 1st line DLBCL PK data collected with the cut-off date of 29/12/2017. Polatuzumab vedotin PK in first line DLBCL treatment is thus considered characterised from the initial application. The PK results are reminded below in GO29044 study results.

Study GO29044 was an open-label, dose-escalation Phase Ib/II study with escalating dose phase of polatuzumab vedotin (1.0 mg/kg up to 2.4 mg/kg) in combination with a standard regimen of R-CHP or G-CHP in patients with B-cell NHL. An expansion phase was added which included newly diagnosed DLBCL patients receiving 1.8 mg/kg of polatuzumab vedotin with either R-CHP or G-CHP. PK parameters were estimated based on NCA analysis using Phoenix WinNonlin version 6.4.0.768 (Pharsight,Inc., Mountain View, CA). The estimated parameters were presented in the following table.

At cycle 1, following 1.8 mg/kg administered intravenously, acMMAE half-life is estimated to 5 days with a volume of distribution of 96.5 mL/kg (Vss). Cmax was estimated to 532 (±163) ng/mL and AUCinf to 1870 (±527) ng/mL*day. The unconjugated drug MMAE reached peak concentration of 2.60 ng/mL within 5.90 days ranging from 2.87 days to 6.99 days. The variability was low to moderate for acMMAE with CV% on Cmax of 30.6% and AUCinf of 28.1%; whereas, as expected, the variability on the unconjugated drug was moderate with CV% on Cmax of 39.2%, and AUClast of 46.9%. Overall based on cycle 1, polatuzumab vedotin PK in R/R NHL and newly diagnosed DLBCL appears to be comparable.

Table 4 Study GO29044: Mean (SD) summary of Cycle 1 PK parameters of polatuzumab vedotin in patients with B-NHL or DLBCL: dose escalation and expansion cohorts following 1.8 mg/kg Potuzumab vedotin co-administered with R-CHP or G-CHP in dose escalation and expansion cohort

Conjugate (evaluated as acMMAE)									
Dose (mg)	Treatment	Histology	Phase	No. of patients	Cmax (ng/mL)	AUCinf (ng/mL)*day	t1/2 (day)	Vss (mL/kg)	CL (mL/kg/day)
1.8	R-CHP+Pola	B-NHL	ESC	6	781 (72.6)	2600 (413)	4.79 (0.675)	57.7 (7.95)	12.8 (2.05)
1.8	G-CHP+Pola	B-NHL	ESC	6	557 (114)	1850 (491)	4.89 (0.526)	87.5 (19.3)	18.7 (5.30)
1.8	R-CHP+Pola	DLBCL	EXP	36	532 (163)	1870 (527) [b]	5.03 (0.621) [b]	96.5 (34.1) [b]	18.9 (5.27) [b]
1.8	G-CHP+Pola	DLBCL	EXP	17	530 (138)	1940 (482) [c]	5.50 (0.795) [c]	99.3 (27.4) [c]	17.7 (3.83) [c]
Unconjugated MMAE									
Dose (mg)	Treatment	Histology	Phase	No. of patients	C max (ng/mL)	AUClast (ng/mL)*day	Tmax (day)		
1.8	R-CHP+Pola	B-NHL	ESC	6	2.18 (0.653)	21.4 (11.1)	5.98 (5.87-		

1.8	G-CHP+Pola	B-NHL	ESC	6	3.48 (1.89)	27.0 (16.2) [e]	5.85 (0.0900-
1.8	R-CHP+Pola	DLBCL	EXP	35	2.60 (1.02)	24.5 (11.5) [f]	5.90 (2.87- 6.99)
1.8	G-CHP+Pola	DLBCL	EXP	14	2.88 (2.05)	23.9 (15.3) [g]	5.35 (0.0900- 6.02)

ac= antibody-conjugated; AUCinf = area under the concentration-time curve extrapolating to infinity; AUClast = area under the concentration-time curve from time zero to time of last measureable concentration; CHP=cyclophosphamide, dosorubicin, prednisone; CL = clearance; Cmax = peak serum/plasma concentration; DLBCL= diffuse large B-cell lymphoma; FL= follicular lymphoma; G=obinutuzumab; MMAE=monomethyl auristatin E; NHL=non-Hodgkin's lymphoma; R= rituximab; t1/2 = terminal half-life; tmax= time to reach maximum concentration; Vss = volume of distribution atsteady state. [a]n=2, [b]n=28, [c]n=11, [d]n=1, [e]n=5, [f]n=27, [g]n=10,

To further characterize polatuzumab vedotin PK, mainly acMMAE concentration and the unconjugated MMAE, pop PK approach (Pop PK report 1111192) was used to characterize PK in subpopulation and for exposure-response analyses purposes. Previous popPK model (PopPK Report 1090510) included treatment naïve DLBCL patients (study GO29044) developed in the initial application and should be applicable to characterize polatuzumab vedotin PK in this population. External validation was consequently performed using PK data from study GO39942 (POLARIX) in which only patients with treatment naïve patients with DLBCL administered intravenously 1.8 mg/kg Q3W pola for 6 cycles concomitant with R-CHP regimen (Pop PK report 1111192). This previously developed integrated acMMAE-MMAE model (Model 201) was re-run with all parameters fixed using the data of Study GO39942 as external evaluation of the formerly established population PK model, further refered to model 301.

Cross-study comparison of pola PK in R/R DLBCL and 1L DLBCL patients showed the observed acMMAE, total Ab and unconjugated MMAE concentrations at C1D1 and C1D4 pre-dose and/or post-dose at 1.8 mg/kg ,the PK of pola related analytes were found to be overall similar (Table 6).

Table 5 Observed Mean Pola PK Concentration Comparisons Across Three studies

					Ratio	
Analyte	**Visit**	**POLARIX Previously Untreated DLBCL**	**GO29365 (Combined Arm G and H)* R/R DLBCL**	**GO29044 R-CHP+Pola 1.8 mg/kg expansion Previously Untreated DLBCL***	**POLARIX/ GO29365**	**POLARIX/ GO29044**
acMMAE (ng/mL)	C1D1 30-min post dose	603; N=362	653; N=102	532; N=36	0.923	1.13
	C4D1 pre-dose	18.2; N=402	23.2; N=61	20.6; N=36	0.784	0.883
	C4D1 post-dose	657; N=360	659; N=60	561; N=36	0.997	1.17
Total antibody (µg/mL)	C1D1 30-min post dose	36.1; N=395	33.9; N=103	32.2; N=36	1.06	1.12
	C4D1 pre-dose	5.44; N=407	5.41; N=63	5.90; N=36	1.01	0.922
	C4D1 post-dose	44.4; N=398	39.2; N=61	38.1; N=35	1.13	1.17
unconjuagted MMAE (ng/mL)	C1D1 30-min post dose	0.424; N=403	0.590; N=103	0.509; N=36	0.719	0.833
	C4D1 pre-dose	0.144; N=406	0.186; N=61	0.133; N=36	0.774	1.08
	C4D1 post-dose	0.222; N=398	0.256; N=60	0.235; N=36	0.867	0.945

ac=antibody conjugated; DLBCL=diffuse large B-cell lymphoma; MMAE= monomethyl auristatin E ; PK= pharmacokinetic; R-CHP=rituximab plus cyclophosphamide, doxorubicin, and prednisone; R/R=relapsed or refractory.

*Polatuzumab vedotin 1.8 mg/kg IV on Day 2 of Cycle 1, then Day 1 of each subsequent cycle.

POLARIX/GO39942: A Phase III, multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of polatuzumab vedotin in combination with rituximab and CHP (R-CHP) versus rituximab and CHOP (R-CHOP) in previously untreated patients with diffuse large B-cell lymphoma.

GO29365: A Phase Ib/II, multicenter, open-label study evaluating the safety, tolerability, and anti-tumor activity of polatuzumab vedotin in combination with rituximab or obinutuzumab plus bendamustine in patients with R/R follicular lymphoma or R/R diffuse large B cell lymphoma.

GO29044: A Phase Ib/II multicenter, open-label, dose-escalation study evaluating the safety, tolerability and anti-tumor activity of polatuzumab vedotin (DCDS4501A) in combination with rituximab or obinutuzumab, cyclophosphamide, doxorubicin, and prednisone in patients with B cell non-Hodgkin's lymphoma.

Pop PK model (Pop PK report 1111192)

Methods

Dataset: study GO39942

Study GO39942 (POLARIX , Table 1, Figure 1) is an ongoing Phase III, multicenter, randomized, double-blind, placebo-controlled, trial comparing the efficacy and safety of pola plus R-CHP versus R-CHOP in previously untreated CD20-positive DLBCL. In the treatment arm, Pola 1.8 mg/kg, placebo for vincristine, rituximab 375 mg/m2 IV, cyclophosphamide 750 mg/m2 IV, and doxorubicin 50 mg/m2 IV each are given on Day 1 and prednisone 100 mg/day orally (PO) is given on Days 1-5 of every 21-day cycle for 6 cycles. Rituximab 375 mg/m2 IV is given as monotherapy in Cycles 7 and 8.

All patients who had at least one quantifiable acMMAE or unconjugated MMAE concentration value by the pharmacokinetic samples analysis data cut-off date (03/16/2021) were included in the analysis.

DLBCL=diffuse large B-cell lymphoma; ECOG PS=Eastern Cooperative Oncology Group Performance Status; IPI=International Prognostic Index; Q21D=every 21 days; R=randomization; R-CHOP=rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHP=rituximab plus cyclophosphamide, doxorubicin, and prednisone.

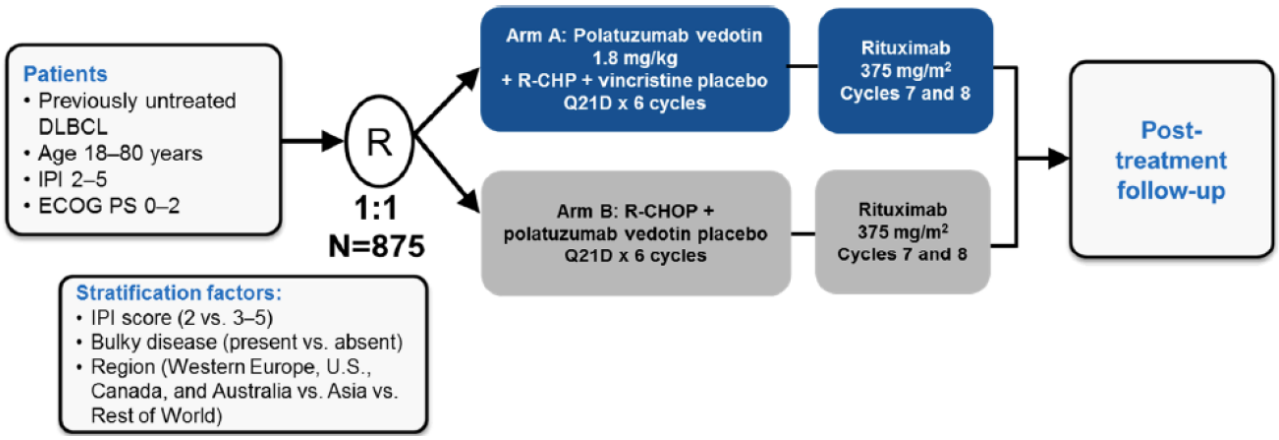


Figure 1 Study GO39942 overall design

A total of 429 patients from Study GO39942 (POLARIX) contributed to 1122 acMMAE and 1175 unconjugated MMAE concentration values that were used in the external evaluation of the formerly established population PK model.

At Cycle 1 Day 1 pre-dose, only a serum PK sample for total antibody was taken, while at Cycle 1 Day 1 30-minutes post-dose as well as Cycle 4 Day 1 pre-dose and 30 minutes post-dose, PK samples were taken for measuring all the three pola analytes: total antibody (serum, measured by ELISA minimal quantifiable concentration 50 ng/mL), antibody-conjugated Monomethyl Auristatin E (AacMMAE, plasma measured by immunoaffinity HPLCMS/MS LLOQ 0.359 ng/mL) and unconjugated MMAE (MMAE plasma, measured by LCMS/MS 0.0359 ng/mL). In addition, PK samples were taken at treatment completion or early treatment termination visit for the three analytes and at 3 month post-treatment follow-up visit for for the total antibody only. Summaries of plasma acMMAE, and unconjugated MMAE are presented respectively in Table 6 and Table 7.

Table 6 Summary table of plasma acMMAE concentration (ng/mL) by visit

Treatment Arm Study Visit	Sample Time Point	Number of Samples In the Analysis Including LTRs	Number Of LTRs	Mean (SD)	CV% Mean	Median	Range (Minimum – Maximum)	Geometric Mean	CV% Geometric Mean
Cycle 1 Day 1	30 minutes Post-Dose	362	0	603 (153)	25.3	594	16.6-1230	576	38.1
Cycle 4 Day 1	Pre-Dose	402	0	18.2 (12.0)	65.7	17.1	1.09-218	16.5	46.8
Cycle 4 Day 1	30 minutes Post-Dose	360	0	657 (175)	26.6	648	286-2520	639	23.8

acMMAE = antibody-conjugate Monomethyl Auristatin E; CV = coefficient of variation; LTR = less than reportable; SD = standard deviation

CV = coefficient of variation ; LTR=less than reportable; NE = Not Estimable; NR = Not Reportable; PK = pharmacokinetic; SD = standard deviation

Note: Number of LTRs = number of LTR concentration results, which are imputed as below.

Note: For post-dose pola samples if the sample is LTR, the value are replaced with 1/2(LLOQ=0.359 ng/mL) for calculating the summary statistics. If one-third or fewer values were LTR, then all summary statistics are reported, otherwise, only the n, median, minimum and maximum are reported.

Source: t_pkc_polaac

Table 7 Summary of plasma unconjugated MMAE concentration (ng/mL) by visit

Treatment Arm Study Visit	Sample Time Point	Number of Samples in the analysis including LTRs	Number of LTRs	Mean (SD)	CV% Mean	Median	Range (Minimum-Maximum)	Geometric Mean	CV% Geometric Mean
Cycle 1 Day 1	30 minutes Post-Dose	403	12	0.424 (0.335)	79.0	0.353	0.0180-3.07	0.327	93.4
Cycle 4 Day 1	Pre-Dose	406	19	0.144 (0.116)	80.4	0.112	0.0180-1.06	0.111	85.0
Cycle 4 Day 1	30 minutes Post-Dose	398	2	0.222 (0.142)	64.0	0.189	0.0180-1.37	0.189	63.3

CV = coefficient of variation ; LTR=less than reportable; MMAE; Monomethyl Auristatin E; PK = pharmacokinetic; SD = standard deviation

Note: LTRs = number of LTR concentration results, which are imputed as below.

Note: For post-dose pola samples if the sample is LTR, the value are replaced with 1/2(LLOQ=0.0359 ng/mL) for calculating the summary statistics. If one-third or fewer values were LTR, then all summary statistics are reported, otherwise, only the n, median, minimum and maximum are reported.

Source: t_pkc_polafree

Anti-drug antibodies to pola were detected in serum samples using a validated bridging enzyme-linked immunosorbent assay. The screening and confirmatory ADA assays were able to detect 100 ng/mL of a surrogate anti-pola antibody in the presence of 50 µg/mL of pola. All patients who had at least one quantifiable acMMAE or unconjugated MMAE concentration value by the pharmacokinetic samples analysis data cut-off date 16.03.2021 were included in the analysis.

Covariate definition

Baseline creatinine clearance (BCRCL) was calculated based on the widely used Cockcroft-Gault formula.

Renal function category was defined based on creatinine Clearance values, and hepatic function was based on The National Cancer Institute Organ Dysfunction Working Group Classification of Hepatic Dysfunction classification.

Summaries of the covariates from the study population are presented in Table 8 for continuous covariates and in Table 9 for categorical covariates

Table 8 Summary of continuous covariates of study POLARIX

Covariate	Description	Mean (SD)	Median [Range]
BAGE	Age (years)	62.9 (11.4)	65 [19-80]
BWT	Weight (kg)	75.9 (20)	74.4 [38.4-228]
BBSA	Body Surface Area (m^2)	1.86 (0.266)	1.85 [1.28-3.4]
BBMI	Body Mass Index(kg/m^2)	26.7 (6)	26.2 [16.4-68.1]
BLBWT	Lean Body Weight (kg)	53.5 (10.7)	51.9 [31.5-87.5]
BHT	Height (cm)	168 (10.2)	168 [144-200]
BALBUM	Albumin (g/L)	36.8 (6.14)	37 [17.1-54.2]
BTPROT	Total Protein (g/L)	66.6 (8.09)	67.3 [39.4-85]
BALP	Alkaline Phosphatase (u/L)	122 (139)	87 [1.52-1960]
BALT	Alanine Amino-transferase (u/L)	26.7 (21.2)	21 [0.3-149]
BAST	Aspartate Amino-transferase (u/L)	28.6 (23.9)	23 [0.35-288]
BBILI	Bilirubin (umol/L)	9.69 (7.09)	8 [1.71-79]
HGB	Hemoglobin (g/L)	121 (19)	123 [65-170]
BLDH	Lactate Dehydrogenase (u/L)	425 (422)	297 [4.2-4820]
BSCR	Serum Creatinine (umol/L)	75.1 (22.5)	71 [35-200]
BCRCL	Creatinine Clearance (ml/min)	94.8 (38)	88.1 [29.3-441]
BBCC	Absolute B Cell Count (10^6/L)	263 (1100)	90.5 [0-19100]
Log BBCC	Log of BBCC (10^6/L)	4.41 (1.42)	4.51 [0-9.86]
BTMBD	Tumor SPD (mm^2)	7420 (12900)	4690 [96-227000]

Source: ContCovMean.csv, ContCovMedian.csv (DLBCL_BLA_Report.R)

Table 9 Summary of categorical covariates of study POLARIX

Covariate	Level	Number (Percent)
Race (RACE)	White	228 (53.1%)
	Asian	84 (19.6%)
	Unknown or Other	117 (27.3%)
Gender (SEX)	Female	196 (45.7%)
	Male	233 (54.3%)
Region	West. Europe	159 (37.1%)
	Eeast. Europe	46 (10.7%)
	South and Central America	6 (1.4%)
	North America	117 (27.3%)
	Asia	80 (18.6%)
	Pacific	21 (4.9%)
ECOG Perfomance Status (BECOG)	0	169 (39.4%)
	1	196 (45.7%)
	2	64 (14.9%)
Bulky Disease (BBULKY)	Absent	242 (56.4%)
	Present	187 (43.6%)
Computed Hepatic Impairment (HEPA)	Missing	2 (0.5%)
	Normal	338 (78.8%)
	Mild	79 (18.4%)
	Moderate	9 (2.1%)
	Severe	1 (0.2%)
Renal Impairment (RENAL)	Missing	3 (0.7%)
	Normal	171 (39.9%)
	Mild	200 (46.6%)
	Moderate	54 (12.6%)
	Severe	1 (0.2%)
ADA Status (ATAP)	Missing	7 (1.6%)
	Present	6 (1.4%)
	Absent	416 (97%)
DLBCL Subgroup (ABCGCB)	ABC	99 (23.1%)
	GCB	180 (42%)
	Unclassified	44 (10.3%)
	Unknown	106 (24.7%)
Number of Risk Factors for IPI (BIPIN)	1	1 (0.2%)
	2	159 (37.1%)
	3	170 (39.6%)
	4	75 (17.5%)
	5	24 (5.6%)
NHL Subtype (NHL)	DLBCL NOS, ABC, GCB	363 (84.6%)
	HGBL, NOS, DHL/THL	42 (9.8%)
	Other Large B-cell	24 (5.6%)
LDH level (LDH)	>ULN	283 (66%)
	≤ ULN	143 (33.3%)
	missing	3 (0.7%)
Double Expressor by IHC (DEL)	DEL	135 (31.5%)
	No DEL	220 (51.3%)
	Unknown	74 (17.2%)
Covariate	**Level**	**Number (Percent)**
Ann Arbor Stage at Study Entry	1	2 (0.5%)
	2	43 (10%)
	3	120 (28%)
	4	264 (61.5%)

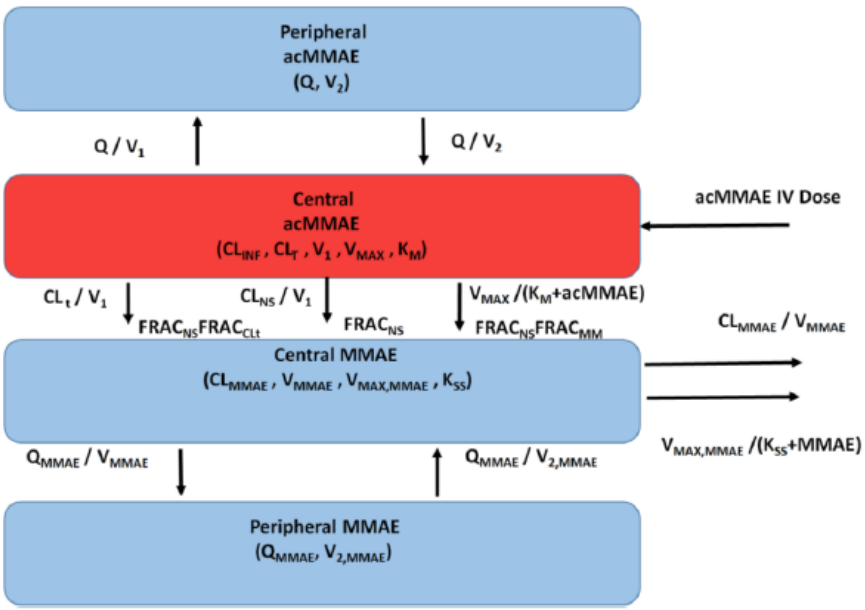
Source file: CatCov.csv (DLBCL_BLA_Report.R)

Structural model

The previously developed PK model of pola in patients with NHL (Model 201) was a complex four-compartment model that consisted of the acMMAE model and the unconjugated MMAE model. The unconjugated MMAE model had parallel linear and Michaelis-Menten elimination and time-dependent relative conversion fraction from acMMAE to unconjugated MMAE (Figure 2). Model 201 parameters estimates are reported in Table 9.

Figure 2 Schematic Representation of Structural acMMAE-MMAE Model (Report 1111192)

$CL_{NS} = CL_{INF} \cdot (1+CL_{INF,EMAX} \cdot T_{50}^{\gamma}/(T_{50}^{\gamma}+t^{\gamma}))$: acMMAE non-specific clearance (t in months); $CL_t=CL_T \cdot \exp(-k_{des} \cdot t)$ (t in hours); CL_{INF}: acMMAE non-specific linear clearance at time of infinity; Q: acMMAE inter-compartment clearance; V_1: acMMAE central volume; V_2: acMMAE peripheral volume; V_{max}: maximum acMMAE Michaelis-Menten elimination rate; K_M: Michaelis-Menten constant of acMMAE elimination.
$FRAC_{NS}$: acMMAE-unconjugated MMAE conversion fraction for non-specific elimination; $FRAC_{CLt}$: ratio of acMMAE-unconjugated MMAE conversion fractions for CL_t and CL_{NS} elimination pathways; $FRAC_{MM}$: ratio of acMMAE-unconjugated MMAE conversion fractions for MM and CL_{NS} elimination pathways; CL_{MMAE}: unconjugated MMAE apparent clearance; Q_{MMAE}: unconjugated MMAE apparent inter-compartment clearance; V_{MMAE}: unconjugated MMAE apparent central volume; $V_{2,MMAE}$: unconjugated MMAE peripheral volume; $V_{max,MMAE}$: maximum unconjugated MMAE Michaelis-Menten elimination rate; K_{SS}: Michaelis-Menten constant of unconjugated MMAE elimination.



This previously developed integrated acMMAE-MMAE model (Model 201) was re-run with all parameters fixed (Table 9) using the data of Study GO39942 as Model 301. The initial model (model 201) parameters were initially estimated from 4 studies: Studies DCS4968g in B-NHL patients, studies GO27834, GO29365 in R/R DLBCL and R/R FL patients (excluding Arm G and Arm H),, and study GO29044 in DLBCL 1st line patients. Covariates were investigated and the retained significant covariates were bodyweight, gender, race (Asian vs non-Asian) treatment naïve, combination therapy effect, B-cell count effect, tumor SPD, prior treatment, threshold B-cells hepatic impairment, ECOG score=0, albumin.

Table 10 Estimates of Structural Fixed-Effect Parameters from previous model, Integrated Model 201

The NONMEM combined control and output file of Model 201 can be found in [4].

Parameter		Description	Value	RSE%	95% CI
acMMAE parameters					
k_{des} (1/hr)	θ_1	rate constant of CL_t decrease	0.0046	7.95	0.00389-0.00532
CL_T (L/hr)	θ_2	initial time-dependent CL	0.00623	19.6	0.00383-0.00862
CL_{INF} (L/hr)	θ_3	non-specific linear clearance after repeated dosing	0.0344	3.6	0.032 - 0.0368
V_1 (L)	θ_4	central volume	3.15	1.58	3.05 - 3.25
V_2 (L)	θ_5	peripheral volume	3.98	2.92	3.75 - 4.2
Q (L/hr)	θ_6	inter-compartment rate	0.0145	2.53	0.0138-0.0153
V_{max} (ng/mL/hr)	θ_7	maximum MM elimination	0.0203	14.3	0.0146 - 0.026
K_M (ng/mL)	θ_8	MM constant	0.604	36.2	0.175 - 1.03
$CL_{INF,MAX}$	θ_9	maximum effect of time on CL_{NS}	0.223	8.6	0.185 - 0.261
T_{50} (month)	θ_{10}	time of the half-effect of $CL_{INF,MAX}$	3.53	6.77	3.07 - 4
γ	θ_{11}	Sigmoidicity of $CL_{NS}(t)$ function	2.27	12.5	1.71 - 2.82
Unconjugated MMAE parameters					
V_{MMAE} (L)	θ_{12}	unconjugated MMAE apparent central volume	82.2	8.15	69.1 - 95.4
CL_{MMAE} (L/hr)	θ_{13}	unconjugated MMAE apparent clearance	1.89	8.14	1.59 - 2.2
Q_{MMAE} (L/hr)	θ_{14}	unconjugated MMAE apparent inter-compartment clearance	36.3	12.3	27.5 - 45.1
$V_{2,MMAE}$ (L)	θ_{15}	unconjugated MMAE apparent peripheral volume	200	6.13	176 - 224
$V_{MAX,MMAE}$ (ng/mL/hr)	θ_{16}	maximum MM elimination	0.0307	9.17	0.0252 - 0.0362
K_{SS} (ng/mL)	θ_{17}	MM constant	0.581	10.5	0.461 - 0.701
$FRAC_{CLT}$	θ_{18}	factor for relative conversion fraction of CL_t pathway	3.70	3.11	3.48 - 3.93
$FRAC_{MM}$	θ_{19}	factor for relative conversion fraction of MM pathway	2.72	9.45	2.21 - 3.22
ALPH (1/month)	θ_{20}	rate constant of $FRAC_t$ decrease	0.167	38.5	0.0411 - 0.293
$FRAC_T$	θ_{21}	initial time-dependent part of FRAC	0.139	21.0	0.0816 - 0.196

SE: Standard Error; PE: Parameter Estimate; RSE%: Relative Standard Error = 100·SE/PE; 95% CI: 95% confidence interval

Parameter		Description	Value	RSE%	95% CI
Effects on acMMAE Model Parameters					
$CL_{INF, WT}$	θ_{22}	Weight effect on CL_{INF}	0.73	8.18	0.613 - 0.848
$V_{1,WT}$; $V_{2,WT}$; Q_{WT}	θ_{23}	Weight effect on V_1, V_2 and Q	0.50	6.24	0.439 - 0.561
$V_{1, males}$	θ_{24}	Male vs. female effect on V_1	1.20	1.83	1.16 - 1.24
$V_{1, ASIAN}$	θ_{25}	Asian race effect on V_1	0.929	4.18	0.852 - 1
$V_{1, NAIVE}$	θ_{26}	Treatment-naive effect on V_1	1.2	1.96	1.16 - 1.25
$CL_{INF, SEX}$	θ_{27}	Gender effect on CL_{INF}	1.1	2.66	1.04 - 1.15
$CL_{INF, ALBUM}$	θ_{28}	Albumin effect on CL_{INF}	-0.247	36.3	-0.423 - -0.0712
$CL_{INF, RTX,Ob}$	θ_{29}	Combination therapy effect on CL_{INF}	0.844	2.95	0.795 - 0.892
$CL_{INF, B-cells}$	θ_{30}	B-cell count effect on CL_{INF}	0.0212	17.9	0.0138 - 0.0286
$CL_{INF,TMBD}$	θ_{31}	Tumor SPD effect on CL_{INF}	0.0521	27.4	0.0241 - 0.0801
$k_{des,NAIVE}$	θ_{32}	Prior treatment effect on k_{des}	3.38	12.7	2.54 - 4.22
$K_{DES,RTX,Ob}$	θ_{33}	Combination therapy effect on k_{des}	0.932	11.2	0.727 - 1.14
$CL_{T,NAIVE}$	θ_{34}	Treatment-naive effect on CL_T	3.53	34.7	1.13 - 5.93
$CL_{T,TMBD}$	θ_{35}	Tumor SPD of 50% effect on CL_T	1150	46.0	114 - 2190
$CL_{T,Threshold}$	θ_{36}	Threshold of B-cells on CL_T	121	46.0	11.9 - 229
$CL_{T,B-cells}$	θ_{37}	B-cell count effect on CL_T	0.578	24.6	0.3 - 0.856
Effects on acMMAE-MMAE relative conversion fraction					
$FRAC_{WT}$	θ_{38}	Weight effect on FRAC	-0.467	23.1	-0.679 - -0.256
$FRAC_{SEX}$	θ_{39}	Gender effect on FRAC	0.911	4.72	0.827 - 0.995
$FRAC_{NAIVE}$	θ_{40}	Treatment-naive effect on FRAC	0.756	5.95	0.668 - 0.844
$FRAC_{RTX,Ob}$	θ_{41}	Combination therapy effect on FRAC	0.709	5.54	0.632 - 0.786
$FRAC_{HEPA}$	θ_{42}	Hepatic Impairment on FRAC	1.19	5.58	1.06 - 1.32
$FRAC_{ECOG}$	θ_{43}	ECOG (=0) effect on FRAC	0.905	4.34	0.828 - 0.982
$FRAC_{ALB}$	θ_{44}	Albumin effect on FRAC	-0.613	23.2	-0.892- -0.334

Missing data and BLQs

Missing continuous covariates were imputed by the median value of the covariate. There were no continuous covariates with more than 15% of missing values. Missing categorical covariates were not imputed and were identified as a separate "Missing" category. The imputation flags (1 or 0) were provided for the continuous covariates and for the categorical covariates that were derived from continuous covariates.

AcMMAE or unconjugated MMAE post-dose observation below the limit of quantification (BLQ) were excluded from the analysis (commented out in the analysis data file). It was not deemed necessary to apply a likelihood-based method for handling the BQL data.

Softwares

The population PK analysis was conducted via nonlinear mixed-effects modeling with the NONMEM software, Version 7.5.0 (ICON Development Solutions) [9]. The first-order conditional estimation method with interaction (FOCEI) was used for all NONMEM model runs.

Model validation

This model was then externally validated with study GO39942 (POLARIX) based on

- diagnostic plots (DV vs PRED, IPRED; CWRED vs TIME, nominal time, TAD and PRED; CWRES distribution; ETA distributions, …),
- shrinkage of the random effect distribution
- VPC
- NPDE
- Conditional VPCs

Model application

Simulation modalities

Model application included comparison of individual PK parameters and exposure measures. Simulations were utilized to compute individual exposures using the final population PK model. In the simulation procedure, individual values of random effects and individual values of covariates were used. The resulting exposures were used to compare exposures between groups of patients.

Individual empirical Bayes estimates of acMMAE PK parameters were used to estimate Cycle 6 terminal half-life (t1/2,term) of the linear part of the acMMAE PK model according to the equations of the two-compartment linear model, considering that the MM elimination only plays a minor role in the total clearance. The equations for estimating t1/2,term are listed below:

$$CL_{t6}=CL_T \exp(-k_{des}t_6)+C_{LINF}[1+CL_{INF,EMAX}T_{50}^{\gamma}/(T_{50}^{\gamma}+t_6^{\gamma})]; \quad t_6 = 3024 \text{ (hr)};$$

$$k_{10,t6} = CL_{t6}/V_1; \quad k_{12}=Q/V_1; \quad k_{21}=Q/V_2; \quad A_1 = k_{10,t6}k_{21}; \quad B_1=(k_{10,t6}+k_{12}+K_{21})/2;$$

$$\alpha=B_1+(B_1^2-A_1)^{0.5}; \quad \beta=B_1-(B_1^2-A_1)^{0.5}; \quad t_{1/2,\alpha}=\log(2)/\alpha; \quad t_{1/2,term}=t_{1/2,\alpha}=\log(2)/\beta$$

Simulations using individual parameter estimates were used to characterize changes in exposures with time from Cycle 1 to Cycle 6 (following six 1.8 mg/kg Q3W doses) and further to Cycle 30 in order to estimate time to steady state.

Impact of Key Variables on Pola PK Exposure Measures

To support key label claims and filing questions, simulations from the final model were conducted to assess the impact of covariates on model projected acMMAE and unconjugated MMAE exposure. The

proposed pola dosing regimen is 1.8 mg/kg Q3W for up to six cycles. Thus, a maximum (and the closest to steady-state) acMMAE exposure is expected to be observed at Cycle 6. The exposure at cycle 6 (AUC and Cmax), further called the steady state exposure, was used for all comparisons. While Ctrough was also computed, it was deemed irrelevant for safety and efficacy, and was not used for comparisons.

Individual exposure parameters were computed for all patients following simulated 1.8 mg/kg doses Q3W for 6 cycles.

The following covariate categories were compared: body weight (≥ 100 kg. vs. < 100 kg), sex (males vs. females), age (≥ 65 vs. <65 years old), race (Asian vs. non-Asian), country (Asia country vs. non-Asian country; Asian country vs. Western country; Asian countries vs. rest of the world except Asian and Western countries; Taiwan vs. not Taiwan; South Korea vs. not South Korea), hepatic impairment (mild, or moderate vs. normal), renal impairment (mild, moderate, or severe vs. normal), ECOG performance status (1 versus 0 and 2 versus 1), disease characteristics (bulky vs. not bulky; Ann Arbor stage at study entry 3-4-5 vs. 1-2; baseline IPI score 3 vs. 1-2 and 4-5 vs. 1-2; DLBCL subgroup GCB vs. ABC; NHL subtypes; Double Expressor by IHC DEL vs. not DEL, baseline LDH levels (above ULN vs. below ULN), ADA status (ADA positive versus negative).

Results

Comparison of the random effects of PK parameters shrinkage estimated from the initial model, model 201, and the present model based on study GO39942 PK results are presented in Table 10.

Bias was noticeable in the distribution of the random effects on the acMMAE to MMAE conversion fraction (η7), and the random effects on the residual error (η10 and η11). Shrinkage values are low (<30%) for inter-individual random effect on time-independent clearance (η2), central volume (η3), and acMMAE to MMAE conversion fraction (η7). Shrinkage of the random effect on time-dependent clearance (η1) was moderate (43.5%). For all other parameters, shrinkage of the random effects exceeded 50%. High shrinkage of the random effects is likely related to the sparse sampling.

Low shrinkage values (27.7% and 22.6% respectively) of the random effects on acMMAE time-independent clearance (η2) and central volume (η3) indicate that computation of the individual Cycle 6 acMMAE AUC and Cmax values is not shrinking toward the population mean and can be used for the exposure-response analysis.

Although shrinkage of the random effects on unconjugated MMAE model parameters is high, unconjugated MMAE exposure is mostly defined by the FRAC parameter, unconjugated MMAE central volume (for unconjugated MMAE Cmax value), and by the ratio of CLMMAE/FRAC (for unconjugated MMAE AUC value). Shrinkage of the FRAC parameter is low (19.3%), and unconjugated MMAE central volume does not have the random effect. The expected value of CLMMAE/FRAC variance is the sum of CLMMAE and FRAC variances estimated by the model (equal to 0.212) while the observed variance of the ratio is the variance of the difference η8-η7 (equal to 0.161). Due to the high correlation of the random effects on CLMMAE and FRAC, the resulting shrinkage of the ratio of CLMMAE/FRAC is low (13.0%). Thus, unconjugated MMAE AUC and Cmax values are not shrinking toward the population mean and can be used for the exposure response analysis.

Table 11 Shrinkage of Variance Parameters, Integrated Model 301

Parameter		Description	Value	Shrinkage of Model 201	Shrinkage of Model 301
ω^2_{CLT}	Ω_{11}	Random effect on CL_T	1.89	17.4%	43.5%
ω^2_{CLINF}	Ω_{22}	Random effect on CL_{INF}	0.0376	8.1%	27.7%
ω^2_{V1}	Ω_{33}	Random effect on V_1	0.0151	11.8%	22.6%
ω^2_{V2}	Ω_{44}	Random effect on V_2	0.107	21.6%	74.6%
ω^2_{Q}	Ω_{55}	Random effect on Q	0.0538	30.6%	79.8%
ω^2_{VMAX}	Ω_{66}	Random effect on V_{MAX}	0.462	33.4%	66.6%
ω^2_{FRAC}	Ω_{77}	Random effect on conversion fraction	0.0972	11.1%	19.3%
ω^2_{CLMMAE}	Ω_{88}	Random effect on CL_{MMAE}	0.115	21.5%	51.4%
$\omega^2_{V2,MMAE}$	Ω_{99}	Random effect on $V_{2,MMAE}$	0.0422	48.5%	83.8%
$\omega^2_{\sigma acMMAE}$	$\Omega_{10,10}$	Random effect on σ_{acMMAE}	0.0521	-2.7%	63.2%
R $\omega_{\sigma acMMAE}$ $\omega_{\sigma MMAE}$	$\Omega_{11,10}$	σ_{acMMAE} - σ_{MMAE} Correlation	0.038	-	-
$\omega^2_{\sigma MMAE}$	$\Omega_{11,11}$	Random effect on σ_{MMAE}	0.0427	0.1%	65.3%
σ^2_{acMMAE}	Σ_{11}	Residual error for acMMAE	0.0254	9.2%	26.8%
σ^2_{MMAE}	Σ_{22}	Residual error for unconjugated MMAE	0.0726	6.4%	43.6%

ω^2 and σ^2: variances of inter-individual and residual variability, respectively, R: correlation coefficient, SE: standard error; PE: parameter estimate; RSE (%): relative standard error = 100·SE/PE; 95% CI: 95%

The diagnostic plots are presented in Figure 4 for ac MMAE, and Figure 5 for unconjugated MMAE. The NPDE, and VPCs plots for both acMMAE, and unconjugated MMAE are presented in Figure 6, and Figure 7 respectively. The visual predictive check plots show an acceptable agreement between the simulated and observed acMMAE data. The visual predictive check plots for unconjugated MMAE show acceptable agreement between the simulated and observed data for the 10th percentile and the median, while the model over-estimated 90th percentile of observed data, especially at the first sampling point two hours after the first dose. A higher than observed variability of time-dependent acMMAE clearance estimated by the legacy model and higher than observed residual variability may explain the difference. The model was developed on a more diverse data set leading to higher than observed variability of predicted unconjugated MMAE concentrations following the first dose. As steady-state is approached (e.g., Cycle 4 Day 1 post-dose samples at nominal time of 1513 hours after the fisrt dose), differences of observed and simulated unconjugated MMAE concentrations are much smaller. A total of 96%, 60%, and 13% on NPDE values were above 10th, 50th, and 90th percentiles of the expected acMMAE NPDE distribution. A total of 93%, 44%, and 4% on NPDE values were above 10th, 50th, and 90th percentiles of the expected unconjugated MMAE NPDE distribution.

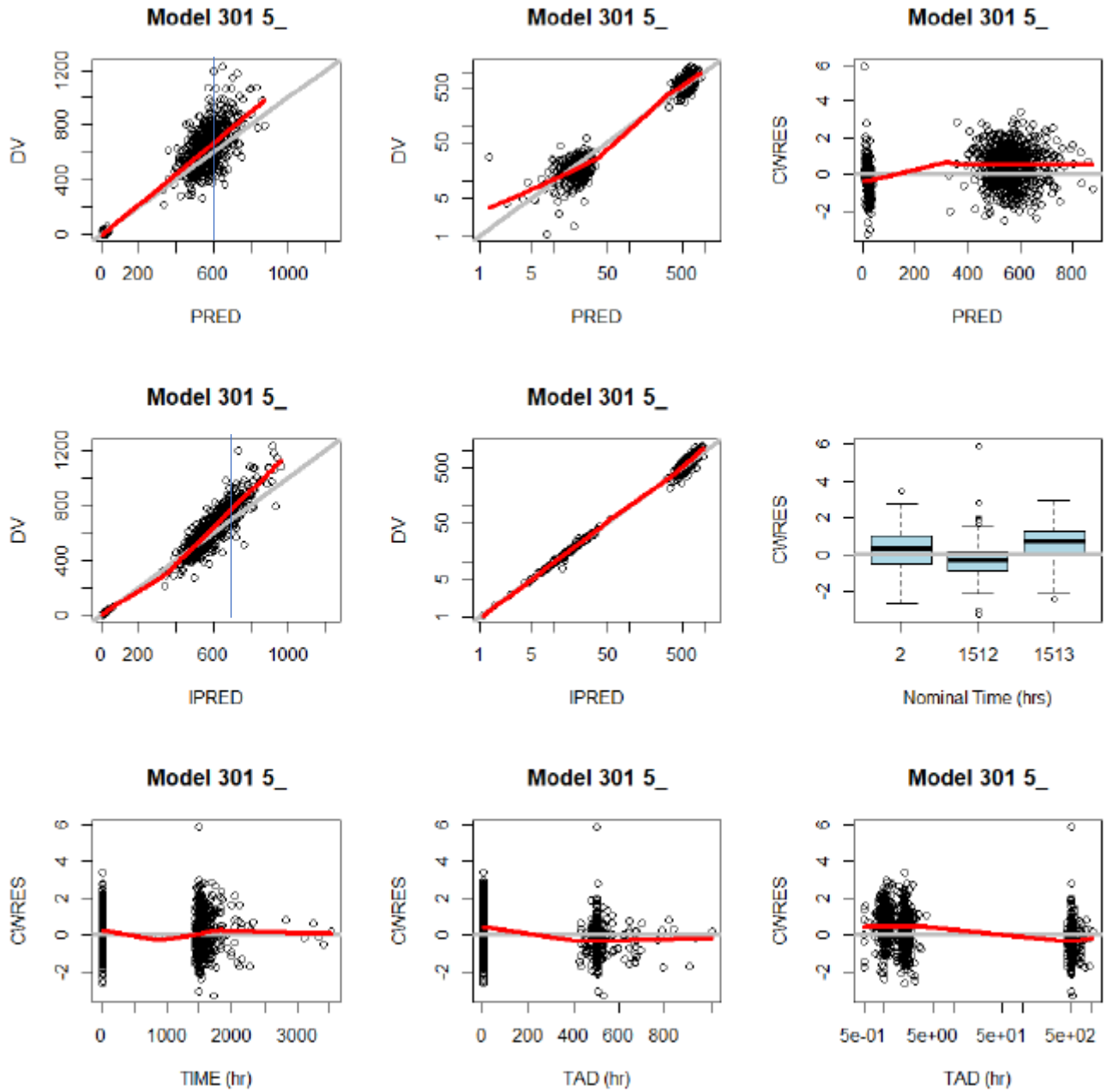


Figure 3 Goodness-of-Fit for Integrated Model 301: ***acMMAE***

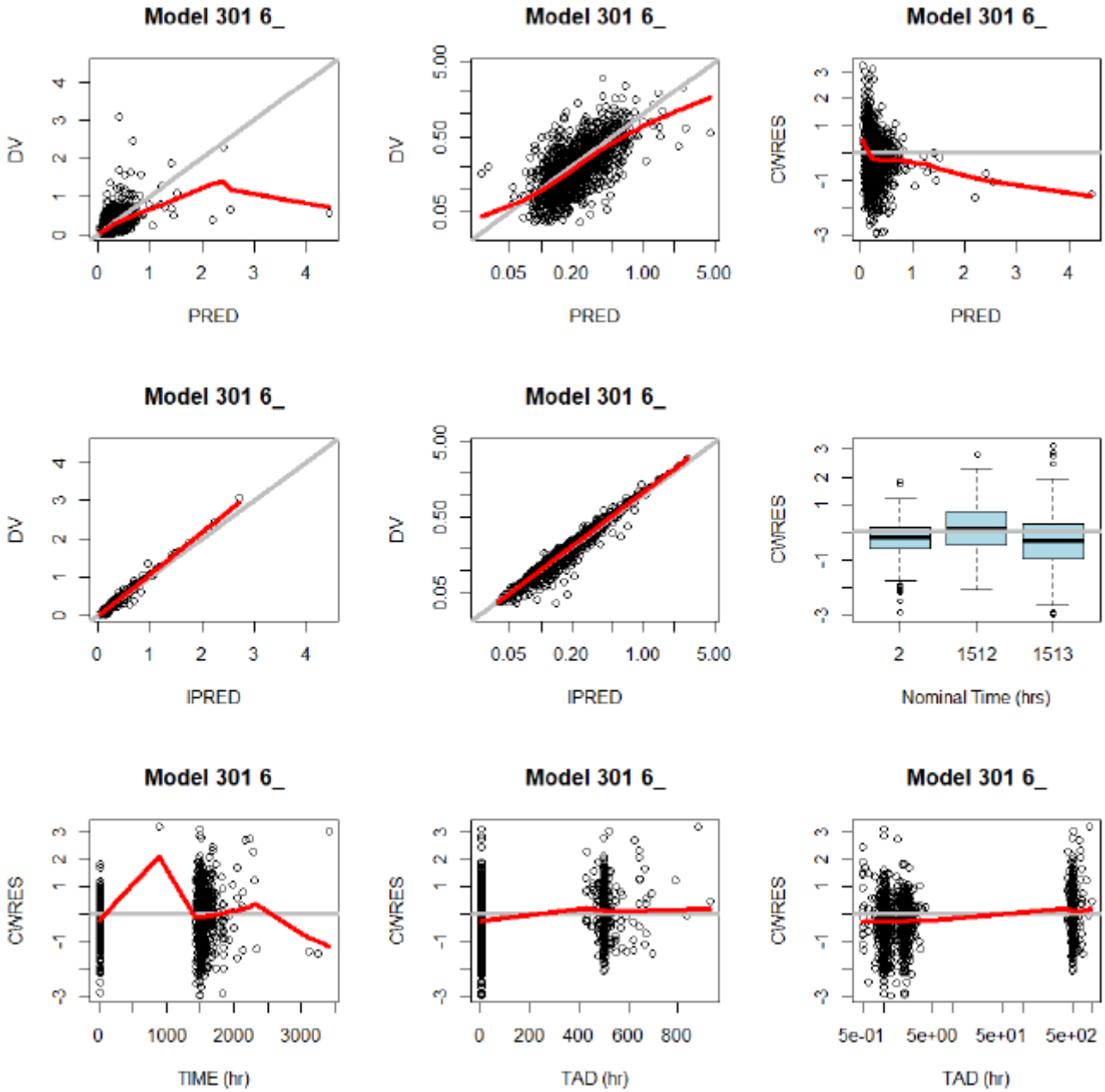


Figure 4 Goodness- of-Fit for Integrated Model 301: ***unconjugated MMAE***

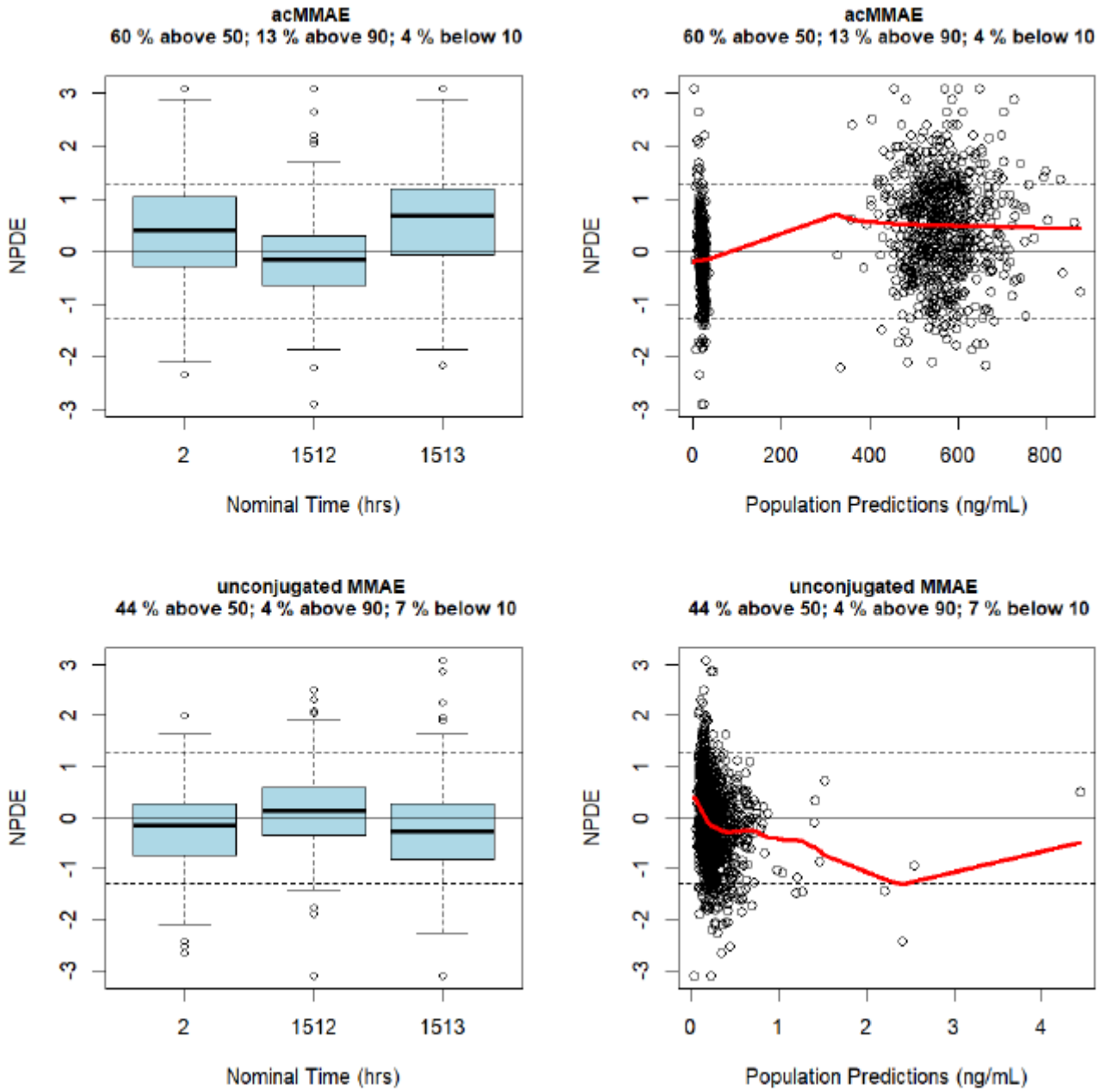


Figure 5 NPDE plots for integrated model 301. Circles correspond to NPDE of observations in the distribution of 500 simulated values. Lines at y=0 correspond to median, and dashed lines show the 10th and 90th percentiles. Percentages of points below 10th percentile and above 50th and 90th percentiles are reported. Red lines show the lowess trend lines.

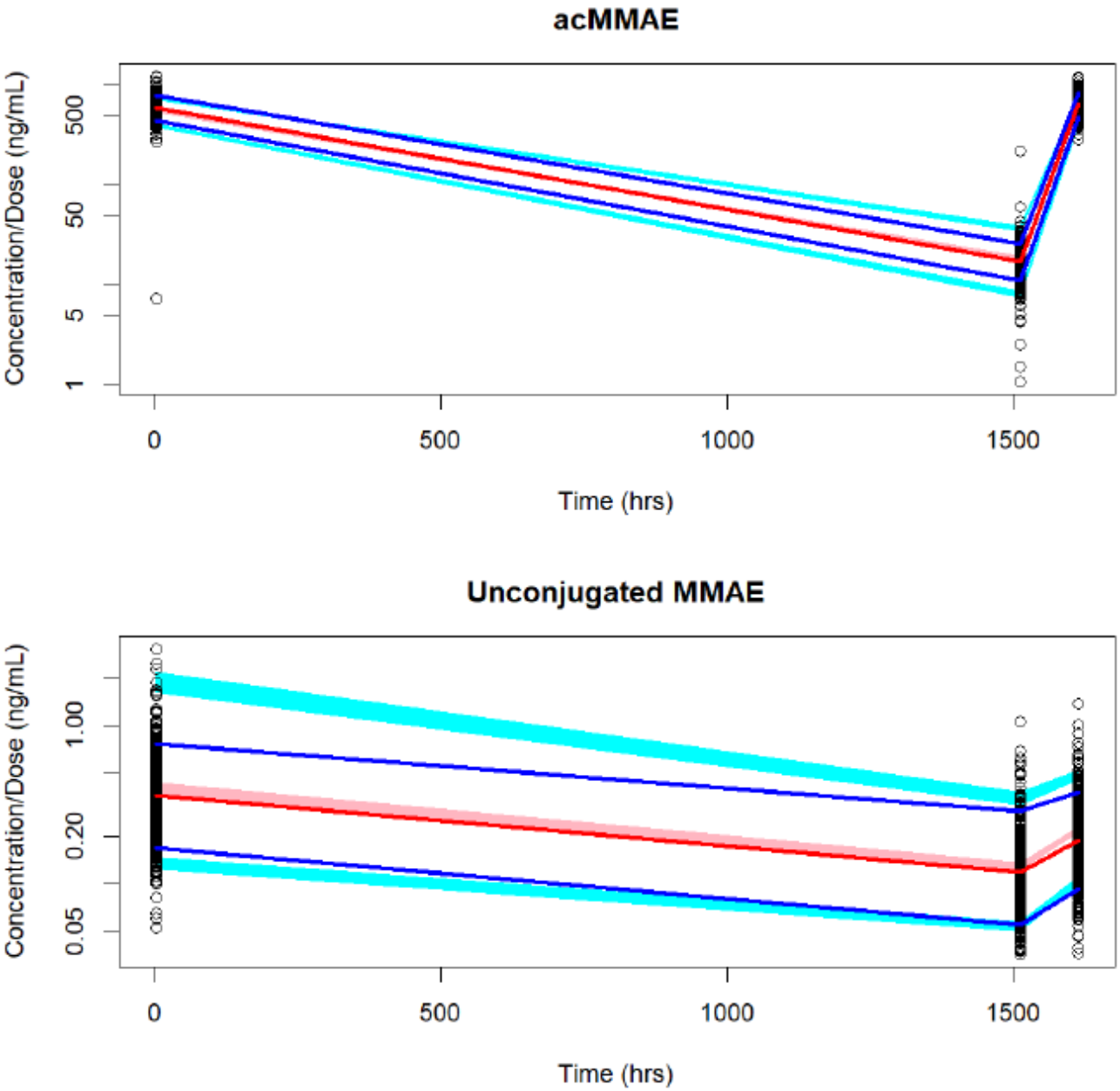


Figure 6 Visual Predictive Check for Integrated Model 301: Semi-log Scale Points are observed concentrations. The lines show median (red), and the 10th and 90th percentiles (blue) of observed concentrations. The shaded regions show the 80% confidence intervals on the respective predicted percentiles obtained by simulations. The simulated values were computed from 500 trials with dosing, sampling, and the covariate values of the analysis dataset. Nominal time point of 1513 hours was shifted for better visibility

Model application

<u>acMMAE PK properties</u>

- The median (2.5th-97.5th percentiles) terminal half-life of acMMAE in patients included in the analysis (estimated based on the values of the linear clearance at Cycle 6) was 11.8 (10.0-13.2) days.
- The acMMAE AUC and Ctrough increased mildly with repeated Q3W dosing, due to the decrease of acMMAE clearance with time. Based on the population PK simulations of exposures for each cycle up to 6 cycles of 1.8 mg/kg Q3W dose, the acMMAE Cycle 3 AUC and Ctrough (i.e., Cycle 4 day 1 pre-dose) were approximately 1.3 and 1.8 fold of the values at Cycle 1 AUC and Ctrough (i.e.,

Cycle 2 day 1 predose); the Cycle 6 values were approximately 1.4 and 2.2 fold of the values at Cycle 1. There were no apparent increase in Cmax values.

- Based on the population PK model simulation, the Cycle 3 acMMAE AUC, Cmax and Ctrough (i.e., Cycle 4 day 1 pre-dose) values were 92%, 99% and 82% of Cycle 6 AUC, Cmax and Ctrough (Cycle 6 day 21) values, which were the maximum acMMAE exposures for the proposed dosing regimen of up to 6 cycles of treatment. In turn, Cycle 6 acMMAE AUC, Cmax and Ctrough values are 90%, 99% and 80% of the model estimated steady-state AUC, Cmax and Ctrough values (represented by the simulated value for the exposure during hypothetical Cycle 30 after repeated Q3W dosing, at which time the CLNS approximated CLINF).

Unconjugated MMAE PK properties

- An integrated acMMAE-MMAE population PK model well described PK of unconjugated MMAE. Unconjugated MMAE demonstrated formation rate limited kinetics. Unconjugated MMAE exposures decreased after repeated dosing of pola, which is empirically fitted by a reduction of relative fraction of formation of unconjugated MMAE from acMMAE (FRAC) with time.
- Unconjugated MMAE AUC and Cmax decreased, potentially due to decrease of acMMAE clearance and decrease of relative fraction of formation of MMAE from acMMAE (FRAC) with time. Based on the population PK simulations of exposures for each cycle up to 6 cycles of 1.8 mg/kg Q3W dose, AUC and Cmax values were the highest in Cycle 1 after which they declined. The unconjugated MMAE AUC and Cmax at Cycle 3 are approximately 66% and 55% of the values at Cycle 1; the Cycle 6 values are approximately 64% and 51% of the values at Cycle 1. The Ctrough values are low (<0.5 ng/mL).

Special populations

Simulation of Cycle 6 exposures (AUC, Cmax) based on individual empirical Bayes estimates of PK parameters were performed. Heavy patients (body weight >= 100 kg) had mildly higher acMMAE exposures (14% for AUC, 18% for Cmax) and higher unconjugated MMAE exposures (54% for AUC and 48% for Cmax). Age, sex, race (Asian versus non-Asian), region (Asian country versus non-Asian country), renal function impairment (mild or moderate impairment), ECOG performace status, disease characteristics (bulky disease, Ann Arbor stage; IPI score, DLBCL subgroup, Double Expressor by IHC, LDH) were not associated with clinically relevant difference of acMMAE and unconjugated MMAE exposures.

Patients with mild hepatic impairment had similar acMMAE exposures to patients with normal hepatic function but moderately higher unconjugated MMAE exposures (46% higher for AUC and 35% for Cmax).

Pharmacokinetic interaction studies

Polatuzumab was evaluated as a potential victim and perpetrator of a PK drug–drug interaction with rituximab (R)/obinutuzumab (G)-CHP (GO29044 study). Prednisone was not assessed in this analysis given the wide therapeutic window of steroids and low risk for pola as a perpetrator of a PK DDI for prednisone.

Study GO29044 is a phase Ib/II, multicenter, open-label, and dose-escalation study (NCT01992653). Patients with B-NHL received six or eight cycles of pola 1.0–1.8 mg/kg + R/GCHP (21-day cycles; R/G-CHP was given as per the standard regimen). Patients were given either six or eight cycles of treatment based on the discretion of the investigator in accordance with local institutional practice.

Evaluation of the potential interaction of CHP as a perpetrator of a DDI with polatuzumab vedotin PK

Polatuzumab was assessed as a DDI 'victim' of CHP by comparing pola exposure with data from previous studies as a comparator, which included Study GO27834 where pola was administered with rituximab/obinutuzumab in the absence of CHP. Patients in Study GO27834 followed the same pola PK sampling scheme in comparison to GO29044 study.

Exposure comparisons included Cycle 1 Cmax and AUC of each polatuzumab vedotin analyte (acMMAE, total antibody, and unconjugated MMAE). The results are presented in both Table 11 & Table 12. The latter is taken from Shemesh et al. (2020) and provides data on variability as 90% confidence intervals associated with central values. Although taken from the same studies, the results presented in Table 11 & Table 12 are not based on the same number of patients.

Table 12 Comparison of mean (SD) PK parameters of polatuzumab vedotin (1.8 mg/kg) when given in combination with R/G-CHP in the expansion arm to historical data (Study GO27834)

Analyte	Parameter	GO29044 (Pola+R-CHP) DLBCL (N = 36)	GO27834 (Pola+R) FL (N = 20)	GO29044/GO27834 Comparative Ratio (%)
acMMAE	C_{max} (ng/mL)	532 (163)	787 (113) [a]	32.4% lower
	AUC_{inf} (ng*day/mL)	1870 (527) [b]	2600 (630) [c]	28.1% lower
Total Antibody	C_{max} (µg/mL)	32.2 (7.48)	42.2 (7.92) [d]	23.7% lower
	AUC_{inf} (µg*day/mL)	186 (52.9) [e]	258 (84.1) [f]	27.9% lower
Unconjugated MMAE	C_{max} (ng/mL)	2.60 (1.02) [g]	2.02 (1.34)	28.7% greater
	AUC_{last} (ng*day/mL)	24.5 (11.5) [h]	17.7 (9.39)	38.4% greater
Analyte	**Parameter**	**GO29044 (Pola+G-CHP) DLBCL (N=17)**	**GO27834 (Pola+G) DLBCL (N=40)**	**GO29044/GO27834 Comparative Ratio (%)**
acMMAE	C_{max} (ng/mL)	530 (138)	711 (155)[i]	25.5% lower
	AUC_{inf} (ng*day/mL)	1940 (482)[j]	2440 (665)[k]	20.5% lower
Total Antibody	C_{max} (µg/mL)	39.1 (12.0)[l]	35.0 (9.89)[m]	11.7% greater
	AUC_{inf} (µg*day/mL)	215 (45.9)[n]	218 (89.1)[h]	1.4% lower
Unconjugated MMAE	C_{max} (ng/mL)	2.88 (2.05)[o]	3.62 (3.73)	20.4% lower
	AUC_{last} (ng*day/mL)	23.9 (15.3)[p]	27.9 (21.3)	14.3% lower

DLBCL = diffuse large b-cell lymphoma; G-CHP+Pola = pola with obinutuzumab, cyclophosphamide, doxorubicin, and prednisone; Pola = polatuzumab vedotin; Comparative Ratio = exposure within GO29044 divided by exposure within GO27834 stratified by treatment and subtype and expressed as a percent.
[a]N=17, [b]N=28, [c]N=15, [d]N=19, [e]N=29, [f]N=17, [g]N=35, [h]N=27, [i]N=33, [j]N=11, [k]N=26, [l]N=16, [m]N=37, [n]N=9, [o]N=14, [p]N=10.
Source: t_pkpt_polaMmaeEXP; t_pkpt_polaTabEXP; t_pkpt_polaFreeEXP; Primary GO27834 CSR, Report No. 1081108

Table 13 Assessment of CHP as a perpetrator of a PK DDI with 1.8 mg/kg of pola as a victim based on C1 non-compartmental analysis results (Shemesh et al., 2020)

Analyte	Parameter	N	GO29044 (pola + R-CHP) DLBCL	N	GO27834 (pola + R) FL	GMR (90% CI)
acMMAE	C_{max} (ng/mL)	36	503 (36.4)	17	780 (14.4)	0.646 (0.576–0.724)
	AUC_{inf} (ng day/mL)	28	1800 (28.5)	15	2530 (25.9)	0.711 (0.616–0.820)
Unconjugated MMAE	C_{max} (ng/mL)	35	2.43 (37.9)	20	1.75 (54.3)	1.39 (1.11–1.73)
	AUC_{last} (ng day/mL)	27	22.6 (40.4)	20	15.8 (50.1)	1.43 (1.15–1.78)
Analyte	Parameter	N	GO29044 (pola + G-CHP) DLBCL	N	GO27834 (pola + G) DLBCL	GMR (90% CI)
acMMAE	C_{max} (ng/mL)	17	513 (26.6)	33	694 (22.7)	0.739 (0.651–0.839)
	AUC_{inf} (ng day/mL)	11	1890 (23.7)	26	2350 (28.4)	0.805 (0.691–0.938)
Unconjugated MMAE	C_{max} (ng/mL)	14	2.44 (60.0)	40	2.68 (81.1)	0.911 (0.664–1.25)
	AUC_{last} (ng day/mL)	10	20.4 (62.8)	40	22.5 (70.7)	0.907 (0.629–1.31)

All values are geometric mean (% geo CV), except for GMR

acMMAE antibody-conjugated MMAE, AUC_{inf} area under the concentration–time curve from 0 to infinity, AUC_{last} area under the concentration–time curve from 0 until the last measurable time point, *CHP* cyclophosphamide, doxorubicin, and prednisone, *CI* confidence interval, C_{max} maximum concentration, *CV* coefficient of variation, *DLBCL* diffuse large B-cell lymphoma, *FL* follicular lymphoma, *G* obinutuzumab, *G-CHP* obinutuzumab, cyclophosphamide, doxorubicin, and prednisone, *GMR* geometric mean ratio, *MMAE* monomethyl auristatin E, *PK* pharmacokinetic, *pola* polatuzumab vedotin, *R* rituximab, *R-CHP* rituximab, cyclophosphamide, doxorubicin, and prednisone

For exposure assessments of pola + R-CHP compared with pola combined with rituximab (without CHP), a direct comparison in patients of the same B-NHL type was not possible. However, given DLBCL and FL patients have generally similar PK for pola, a cross-study comparison of available data was conducted.

In both arms, Cycle 1 PK differences were within the PK variability of each analyte and could also be attributed to differences in patient characteristics (especially in the case of histological non-similarity). Furthermore, given the acceptable safety profiles of all treatment arms, the applicant considers that the observed PK differences were not considered as clinically meaningful after the first 1.8-mg/kg dose of pola + R/G-CHP vs. pola + R/G.

The applicant concludes that polatuzumab was not a victim of a drug–drug interaction with CHP.

PK of rituximab in combination with polatuzumab vedotin and CHP

To evaluate pola and CHP as 'perpetrators' for DDIs with rituximab, data were compared with those for rituximab exposure from historical studies, *e.g.* study BO22334 (NCT01200758).

According to the applicant, the mean serum concentrations of rituximab approximating steady-state conditions, (Cycle 4 pre-dose) in DLBCL patients within Study GO29044: 70.2 (23.5) µg/mL (N = 22) were generally comparable to those seen in Study BO22334 (R + CHOP): 66.2 (30.5) µg/mL (N = 197) in the absence of polatuzumab vedotin, and were also comparable to Study GO27834 (pola + R): 82.0 (29.4) µg/mL (N = 18) in the absence of CHP at the same time point, in similar patient populations. In conclusion, the applicant states that no significant impact of the combination on rituximab PK was observed either due to the administration of polatuzumab vedotin or CHP, based on the cross-study comparison of rituximab exposure.

Shemesh et al. (2020) presents mean rituximab serum C4 pre-dose concentration comparison between study GO29044 and study BO22334 (Table 13). Differences observed with cross-study comparison of rituximab exposure are within the variability of rituximab observed in study BO22334 (up to 111%). The authors drawn a similar conclusion to the applicant, *i.e.* no significant impact of the combination on rituximab PK was observed either due to the administration of polatuzumab vedotin or CHP.

Table 14 Assessment of 1.8 mg/kg of pola as a perpetrator of a PK drug–drug interaction with rituximab as a victim based on descriptive statistics of exposure comparisons (Shemesh et al., 2020)

DDI victim	Tx	Parameter	*n*	BO22334 R-CHOP	*n*	GO29044 Pola+R-CHP	GMR (90% CI)
Rituximab (µg/mL)	R-CHP	C4 pre-dose	189	45.0 (111)	28	66.3 (36.2)	1.47 (1.26–1.72)

PK of obinutuzumab in combination with polatuzumab vedotin and CHP

To evaluate pola and CHP as 'perpetrators' for DDIs with obinutuzumab, data were compared with those for obinutuzumab exposure from historical studies, *e.g.* study BO21003 (NCT00576758).

First, matching obinutuzumab dosing regimens for patients with DLBCL in Study GO29044 up to cycle 2 in patients with B-NHL in Study BO21003 allowed for a cross-study comparison of pola + G-CHP to single-agent obinutuzumab therapy based on cycle 2 pre-dose & cycle 1 mean Cmax concentrations. Therefore, comparison of Cycle 1 obinutuzumab Cmax and Cycle 2 pre-dose concentrations in patients with DLBCL in Study GO29044 receiving (pola + G-CHP) versus Study BO21003 (G) were evaluated.

In the study GO29044 body report, the applicant states that "*small numerical inter study differences in Cycle 2 pre-dose obinutuzumab PK between Study GO29044 and Study BO21003 were seen*" without further details. In the other hand, it is specified that the cycle 1 mean Cmax for DLBCL patients receiving pola + G-CHP in Study GO29044 was approximately 20% higher than the mean Cmax within NHL patients in Study BO21003 receiving G-monotherapy.

Furthermore, comparisons of serum obinutuzumab Cmax in Cycles 1 and 4 and pre-dose in Cycles 2 and 4 show generally comparable PK between the pola + G-CHP regimen in Study GO29044 and the pola + G regimen in Study GO27834 with mean maximal differences across all observations of less than 20% observed.

According to the applicant, the addition of CHP to the pola + G regimen does not appear to substantially impact obinutuzumab PK.

Shemesh et al. (2020) presents mean obinutuzumab serum C2 pre-dose concentration comparison between study GO29044 and study BO21003 (Table 14). The observed difference in GMR values was well within the variability of obinutuzumab (60% CV in Study BO21003), and may reflect variability in body weight, gender, and tumor burden due to differences in patient populations between the studies (e.g., DLBCL in GO29044 vs. R/R indolent B-cell NHL in BO21003).

Table 15 Assessment of 1.8 mg/kg of pola as a perpetrator of a PK drug–drug interaction with obinutuzumab as a victim based on descriptive statistics of exposure comparisons (Shemesh et al., 2020)

DDI victim	Tx	Parameter	*n*	BO21003 G	*n*	GO29044 Pola+G-CHP	GMR (90% CI)
Obinutuzumab (µg/mL)	G-CHP	C2 pre-dose	74	378 (60.5)	15	266 (71.0)	0.703 (0.517–0.955)

PK of cyclophosphamide in combination with rituximab (or obinutuzumab), polatuzumab vedotin, doxorubicin and prednisone

Polatuzumab was assessed as a 'perpetrator' of DDIs with cyclophosphamide by comparing cyclophosphamide between cycle 1, day 1 (prior to first pola dose on cycle 1, day 2) and cycle 3, day 1 (after pola dosing). Plasma PK concentrations of cyclophosphamide were evaluated at the end of infusion and at 3 and 23 hours after the first dose and after Cycle 3 in patients with DLBCL receiving 1.8 mg/kg of pola + R/G-CHP in the Phase II expansion portion of the study.

Comparisons of Cycle 1 exposures of cyclophosphamide (prior to polatuzumab vedotin administration) were similar to those in Cycle 3 (after polatuzumab vedotin administration). Cyclophosphamide was

administered on Day 1 of Cycle 1, with polatuzumab vedotin administered on Day 2 of Cycle 1; while on Day 1 of Cycle 3 both analytes were administered on Day 1. These results suggest that polatuzumab vedotin does not have a clinically relevant impact on the pharmacokinetics of cyclophosphamide when given in combination.

Shemesh et al. (2020) presents geometric mean C1D1 and C3D1 cyclophosphamide plasma 23h concentrations (Table 15).

Table 16 Assessment of 1.8 mg/kg of pola as a perpetrator of a PK drug–drug interaction with cyclophosphamide as a victim based on descriptive statistics of exposure comparisons (Shemesh et al., 2020)

DDI victim	Tx	Parameter	*N*	GO29044 (C1D1) Before pola dosing	*N*	GO29044 (C3D1) After pola dosing	GMR (90% CI)
Cyclophosphamide (µg/mL)	R-CHP	C_{23h}	25	2.64 (56.2)	19	2.67 (74.8)	1.01 (0.737–1.38)
	G-CHP	C_{23h}	14	3.00 (52.4)	14	2.83 (50.1)	0.943 (0.691–1.29)

PK of doxorubicin in combination with rituximab (or obinutuzumab), polatuzumab vedotin, cyclophosphamide and prednisone

Polatuzumab was assessed as a 'perpetrator' of DDIs with doxorubicin by comparing doxorubicin exposure between cycle 1, day 1 (prior to first pola dose on cycle 1, day 2) and cycle 3, day 1 (after pola dosing). Plasma PK concentrations of doxorubicin were evaluated at 2 and 24 hours after the end of infusion after the first dose and after Cycle 3 in patients with DLBCL receiving 1.8 mg/kg of pola + R/G-CHP in the Phase II expansion portion of the study.

Comparisons of Cycle 1 exposures of doxorubicin (prior to polatuzumab vedotin administration) were similar to those in Cycle 3 (after polatuzumab vedotin administration). Doxorubicin was administered on Day 1 of Cycle 1, with polatuzumab vedotin administered on Day 2 of Cycle 1; while on Day 1 of Cycle 3 both analytes were administered on Day 1. These results suggest that polatuzumab vedotin does not have a clinically relevant impact on the pharmacokinetics of doxorubicin when given in combination.

Shemesh et al. (2020) presents geometric mean C1D1 and C3D1 doxorubicin plasma 24h concentrations (Table 16).

Table 17 Assessment of 1.8 mg/kg of pola as a perpetrator of a PK drug–drug interaction with doxorubicin as a victim based on descriptive statistics of exposure comparisons (Shemesh et al., 2020)

DDI victim	Tx	Parameter	*N*	GO29044 (C1D1) Before pola dosing	*N*	GO29044 (C3D1) After pola dosing	GMR (90% CI)
Doxorubicin (ng/mL)	R-CHP	C_{24h}	25	8.79 (29.1)	20	8.43 (25.8)	0.959 (0.838–1.10)
	G-CHP	C_{24h}	12	9.44 (60.6)	14	8.94 (21.3)	0.947 (0.701–1.28)

2.3.3. Pharmacodynamics

Mechanism of action

Polatuzumab vedotin (pola) is an antibody-drug conjugate (ADC) that contains a humanized immunoglobulin G1 anti-CD79b monoclonal antibody (MCDS4409A) and a potent anti-mitotic agent, monomethyl auristatin E (MMAE). Pola binds CD79b, a surface antigen restricted to B-cells that is ubiquitously expressed across a majority of mature B-cell malignancies including diffuse large B-cell lymphoma (DLBCL). MMAE is a potent analog of dolastatin 10 that exerts its cytotoxicity by binding to microtubules and inhibiting microtubule polymerization, inhibiting cell division, inducing apoptosis. Upon binding to the CD79b, pola is rapidly internalized to enable targeted delivery of MMAE. This allows microtubule inhibition with greater potency and without additional toxicity.

Primary and secondary pharmacology

No additional pharmacology data has been provided by the MAH in this procedure.

2.3.4. PK/PD modelling

Based on study GO39942 POLARIX, , exposure response analyses following dose of 1.8 mg/kg Q3W of up to 6 cycles given in combination with R-CHP, were conducted to assess

- efficacy based on (Progression Free Survival) PFS, Event-Free Survival (EFSeff), Overall Survival (OS), and Complete response at end of treatment by FDG-PET as determined by blinded independent central review (CREOT)
- safety based on Grade ≥ 3 Neutropenia, Peripheral Neuropathy, Infections and Infestations; Anemia; Thrombocytopenia; AST increase (by lab); ALT increase (by lab); Bilirubin increase (by lab); Hepatic toxicity; Hyperglycemia; Cardiac Arrhythmia.

Methods

Pop PK model developed for polatuzumab vedotin was validated in patients newly diagnosed DLBCL in report 1111192. This model was subsequently used to simulate individual exposure for exposure-response analysis. The individual PK parameters estimated using the final population PK model and the relevant PK covariates for each subject were used to simulate individual concentration-time course following pola Q3W administration for a total of 6 cycles to compute individual exposure values in Cycle 6. Nominal (1.8 mg/kg) dose was used for each patient in the simulation. AUC and Cmax values of acMMAE and unconjugated MMAE in Cycle 6 were used as exposure measures for the exposure-response analyses as described in Table 17. AUC and Cmax were defined as AUC and Cmax over 21 day in Cycle 6 using nominal dose specified by the cohort assignment.

For some of the analyses (described in the following sections), categories of exposure (where patients were divided into 2 or 3 groups of equal size based on exposure) were evaluated in addition to continuous exposure measures.

Dataset:

Study GO39942 POLARIX; results were used in the exposure-response relationship.

Mathematical modeling

For safety and efficacy the modeling approach used, and the PK parameter used for exposure analyses are presented below:

Table 18 Model used for exposure response analyses

Analysis Type	Analyte	Exposure Measures[1]	Base Models[3]
Exposure-safety	acMMAE	AUC Cmax	Logistic regression models of AE probability versus exposure for each type of AEs with more that 5% frequency rate. KM plots and Cox proportional hazard models for time to the first dose modification due to AE. Summaries of dose intensity of pola, rituximab, doxorubicin, cyclophosphamide, and prednisone by tertiles of pola exposure; linear regression and box plots.
	unconjugated MMAE	AUC Cmax	
Exposure-efficacy	acMMAE	AUC	Logistic regression models of CREOT probability versus exposure. KM plots [2] and Cox proportional hazard models of PFS, EFSeff, and OS versus exposure.

1: AUC was defined as AUC over 21-day in Cycle 6 ($AUC=AUC_{Cycle6}$). Cmax was defined as Cmax over 21-day in Cycle 6 ($Cmax=Cmax_{Cycle6}$);

2: The R-CHOP control arm was included as a reference in the Kaplan Meier analysis of the survival endpoints;

3: Covariate analyses were performed for significant exposure-safety and exposure-efficacy relationships using AUC of acMMAE or unconjugated MMAE as exposure measure.

Exposure – Safety response

Endpoints with less than 5% incidence rate were excluded from the analysis. For each AE type, linear logistic regression models were implemented to assess the relationship between the probability of AE occurrence and pola exposure for acMMAE and unconjugated MMAE. The p-value as provided by the glm() function was used to evaluate whether or not the tested exposure metric was significant in the model at the significance level of α = 0.05. If a significant increase for probability of an AE with increasing exposure was detected, a covariate analysis was conducted using the relevant covariates described belowCovariates were added linearly in the logit scale:

$\text{logit}(p) = a0+a1\cdot COV + b0\cdot \text{exposure}$. (Eq.1)

To define the confidence interval for the model predicted probabilities, 1000 bootstrap samples were drawn with replacement from the analysis population, and the logistic regression models were fitted to each of these samples. For each value of exposure, 90% confidence intervals were defined as the 5th and 95th percentiles of the model predicted probabilities among 1000 bootstrap data sets. Distributions for time of the first AE occurrence were plotted and summarized to assess the acute or chronic feature of each AE.

The data sets for the exposure-safety analysis also included the following dose intensity related endpoints: occurrence status for the dose modification of pola due to AE (1 or 0), time for the first dose modification of pola due to AE (or censoring time if no event), dose intensity for pola, rituximab, doxorubicin, cyclophosphamide, and prednisone.

The dose modifications included reduction, delay, or discontinuation. The probability of dose modification due to AE was investigated using the logistic regression analysis, as described above. The time to first modification due to AE was investigated using the time-to-event analysis.

Dose intensity (%) accounted for dose delay and dose reduction. It was computed based on the actual doses administered to each patient up to the end-of-treatment assessment relative to the planned dose. The early discontinuation was not accounted in the dose intensity calculation. Only dose delays were allowed for rituximab. The impact of exposure on dose intensity of pola, rituximab, doxorubicin, cyclophosphamide, and prednisone was investigated by the linear regression, lowess regression, and by

comparison of distributions of intensity values between categories of exposure (tertiles) using box plots. Summary statistics (mean, standard deviation [SD], median, range, geometric mean [Geomean], coefficient of variation [CV]) stratified by categories of exposure were also provided. P-values of the linear regression models were used to assess significance of the exposure-dose intensity relationships at the significance level of α = 0.05.

Exposure – efficacy response

The logistic regression analysis (as described in Section 4.3.4) was implemented to assess the relationship of the probability of complete response with exposure. The covariate analysis was performed (using the covariates listed in Section 4.3.1) if a significant effect of exposure was detected at 0.05 level, using the strategy described in Section 4.3.4.

Two analyses were performed for each survival measure. In the first analysis, Kaplan- Meier plots were performed to compare the survival probability over time for patients with low and high exposure (categorized by the median value of acMMAE AUC) and also for patients in the control arm (R-CHOP). In the second analysis, the exposuresurvival relationships were described by semi-parametric Cox proportional hazards (CPH) models. The control arm was not used in these models.

The CPH relationships between exposure (acMMAE AUC) and EFSeff, PFS, or OS were first characterized using base models that described the marginal effect of exposure on survival without consideration of covariates. The hazard functions were expressed as:

$\lambda(t) = \lambda_0(t) \exp(\beta^T X_i)$, , (Eq.2)

where λ0(t) is the baseline hazard function and is a vector of predictor variables (covariates). For the base model, the vector of predictor variables consisted of a continuous exposure variable (acMMAE AUC). The parameters of vector were estimated by maximum partial-likelihood.

The P-value as provided by coxph() function was used for significance evaluation of exposure coefficients at the significance level of α = 0.05. Covariates were added linearly in the log hazard scale.

Covariate testing

Covariate selection.

The forward addition and backward elimination procedure was implemented for covariate screening. A significance level of α = 0.01 (the objective function change of 6.64 points for one parameter) was used for forward addition procedure while backward elimination steps used α = 0.001 significance level (the objective function change of 10.83 points for one parameter). The exposure was always kept in the model during the backward elimination steps.

The following covariates were tested

- Demographics: body weight, sex, age, race, region;
- Baseline Laboratory Measurements: lactate dehydrogenase (LDH), serum albumin, B-cell (CD19) count, neutrophil-to-lymphocyte ratio (NLR), neutrophil count, hemoglobin level (HGB), platelet count;
- Baseline disease characteristics and history: ECOG performance status, bulky disease, tumor SPD, Ann Arbor stage, NHL subtype, DLBCL cell origin, International prognostic index (IPI) score, double-expressor by IHC status, extra nodal involvement, active peripheral neuropathy status, baseline peripheral neuropathy active status;
- Anti-drug antibody (ADA) status for pola.

Missing continuous covariates were imputed by the median value of the covariate. Missing categorical covariates were set to a separate "Missing" category. The imputation flags (1 or 0) were also provided for the categorical covariates that were derived from continuous covariates and for the continuous covariates.

The following covariates were included only in the exposure-efficacy analyses as they were not expected to affect safety: B-cell (CD19) count, NLR, tumor SPD, Ann Arbor stage (stage 1-2 vs. stage 3 vs. stage 4-5), DLBCL cell origin (ABC vs. GCB vs. unclassified or unknown), double-expressor by IHC status (DEL vs. no DEL), IPI score (IPI 1-2 vs. 3 vs. 4-5), and bulky disease (yes versus no).

The following covariates were included only in the exposure-safety analyses: baseline neutrophil count for the analysis of neutropenia; baseline hemoglobin level for anemia; baseline platelet count for thrombocytopenia; peripheral neuropathy history and peripheral neuropathy status at baseline for peripheral neuropathy.

Results

Exposure-safety

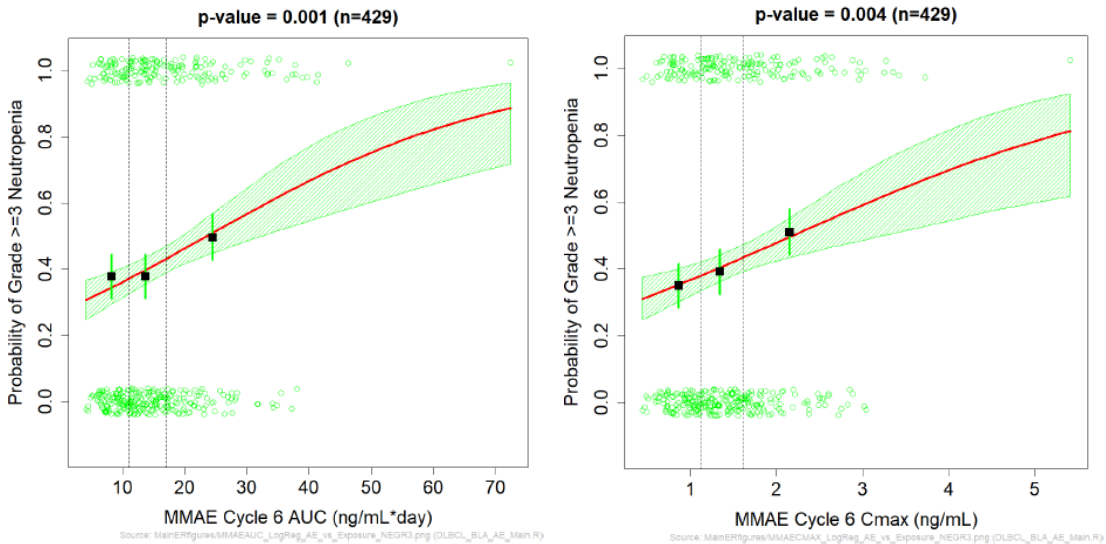


Figure 7 Logistic Regression for Grade ⩾ 3 Febrile Neutropenia, unconjugated MMAE AUC (left plot), a,d Cmax (right plot). The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions Dashed vertical lines show bounds of exposure groups.

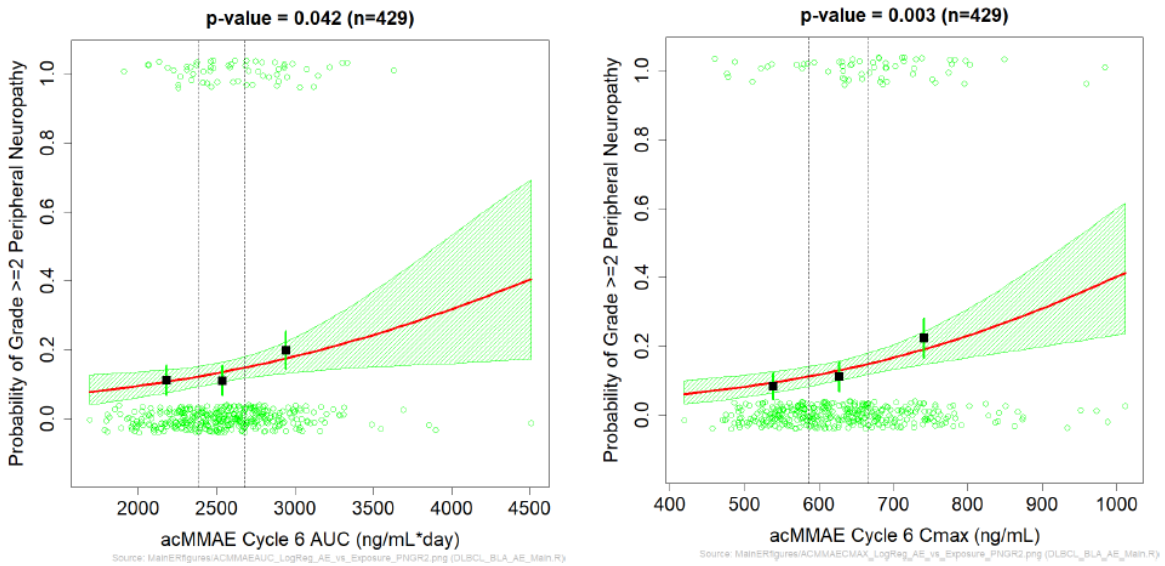


Figure 8 Logistic Regression for Grade ⩾ 2 Peripheral Neuropathy, acMMAE AUC (left plot) , and Cmax (right plot). The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions.Dashed vertical lines show bounds of exposure groups.

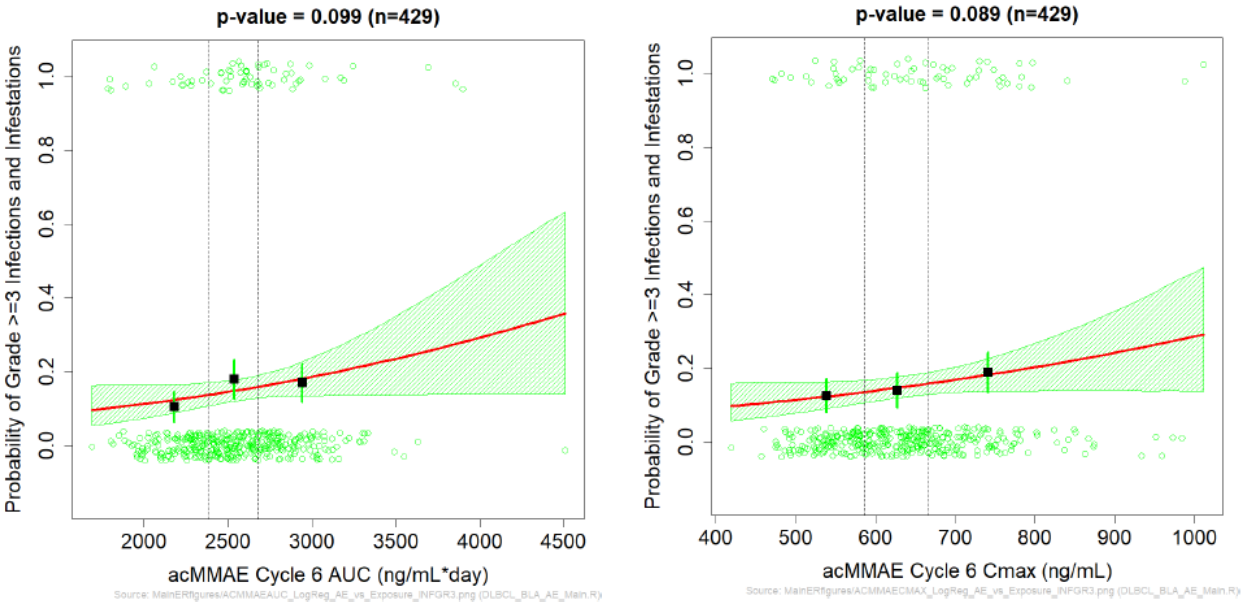


Figure 9 Logistic Regression for Grade ⩾ 3 Infections and Infestations, acMMAE AUC (left plot) and Cmax (right plot). The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups.

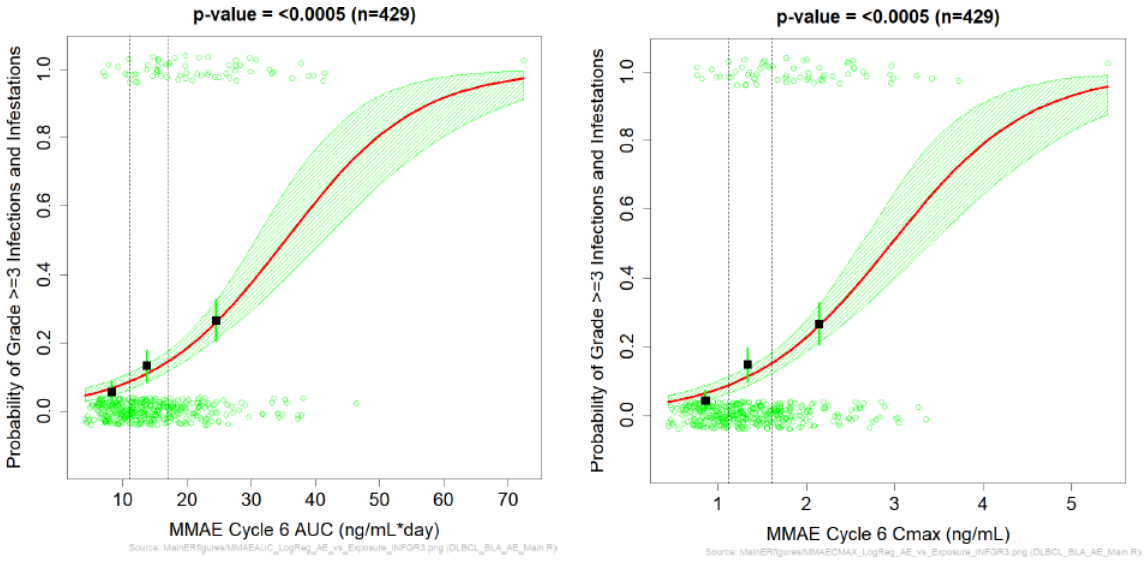


Figure 10 Logistic Regression for Grade ≥ 3 Infections and Infestations, unconjugated MMAE AUC (left plot), and Cmax (right plot). The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups.

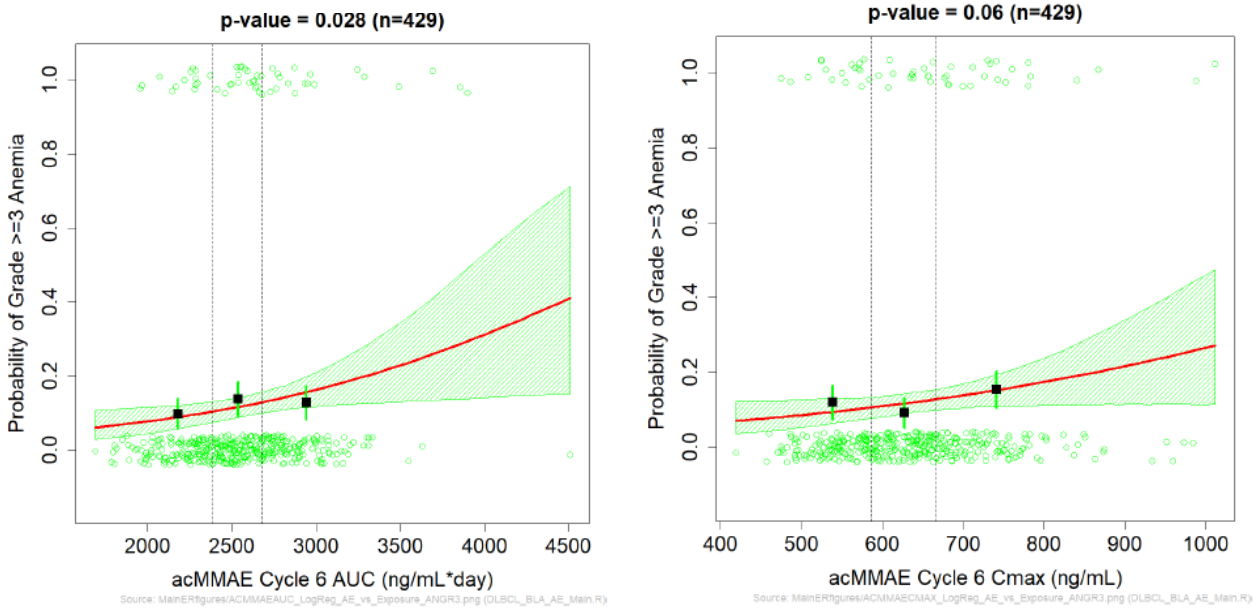


Figure 11 Logistic Regression for Grade ≥ 3 Anemia, acMMAE AUC (left plot), and Cmax (right plot) The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups.

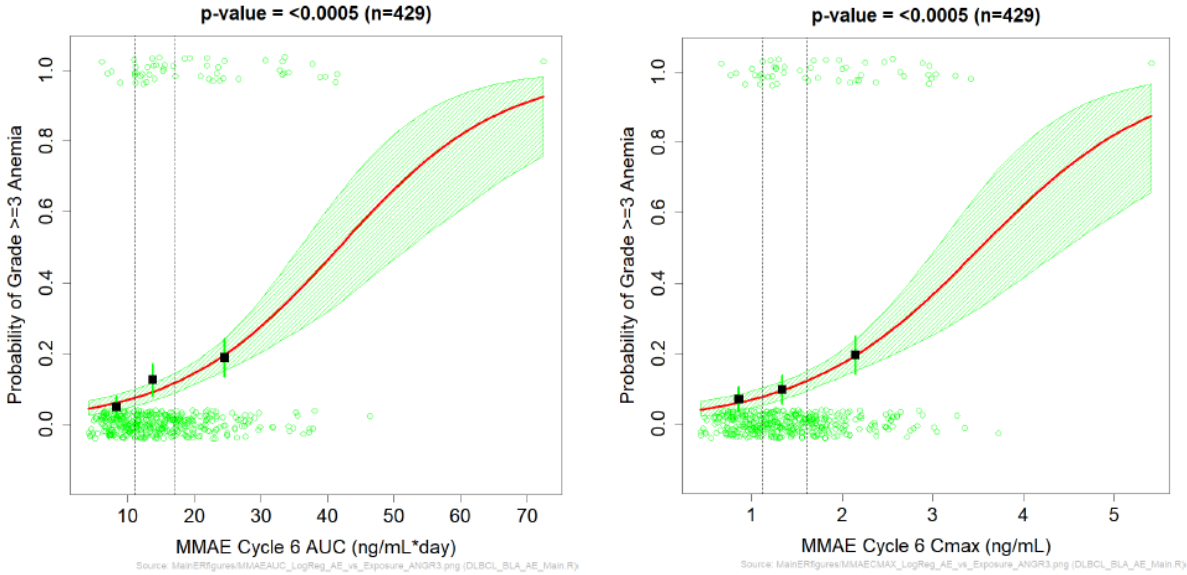


Figure 12Logistic Regression for Grade ⩾ 3 Anemia, unconjugated MMAE AUC (left plot), and Cmax (right plot). The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups.

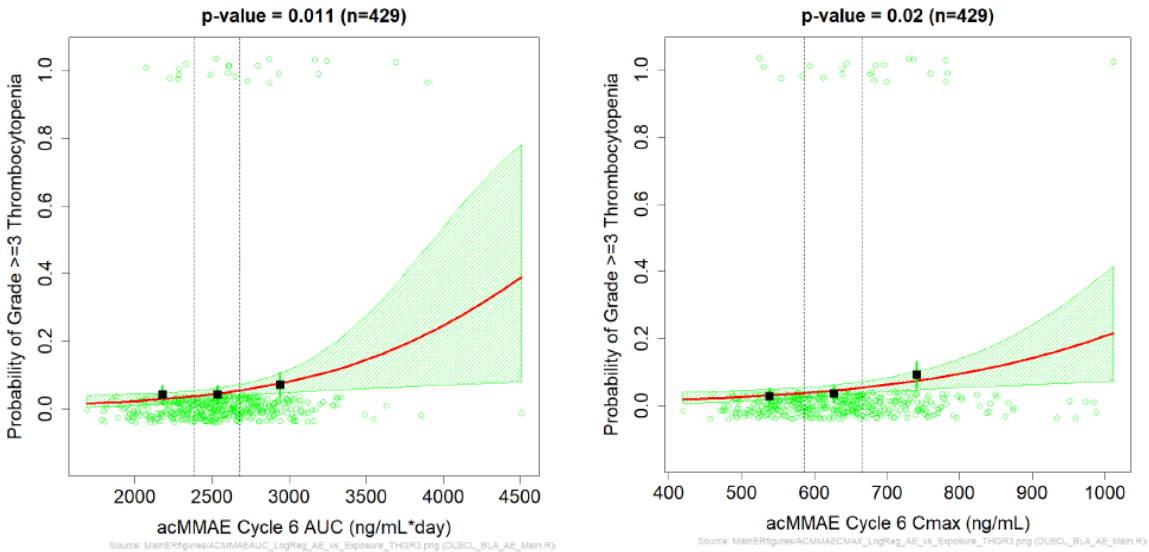


Figure 13 Logistic Regression for Grade ⩾ 3 Thrombocytopenia, acMMAE AUC (left plot), and Cmax (right plot).). The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups.

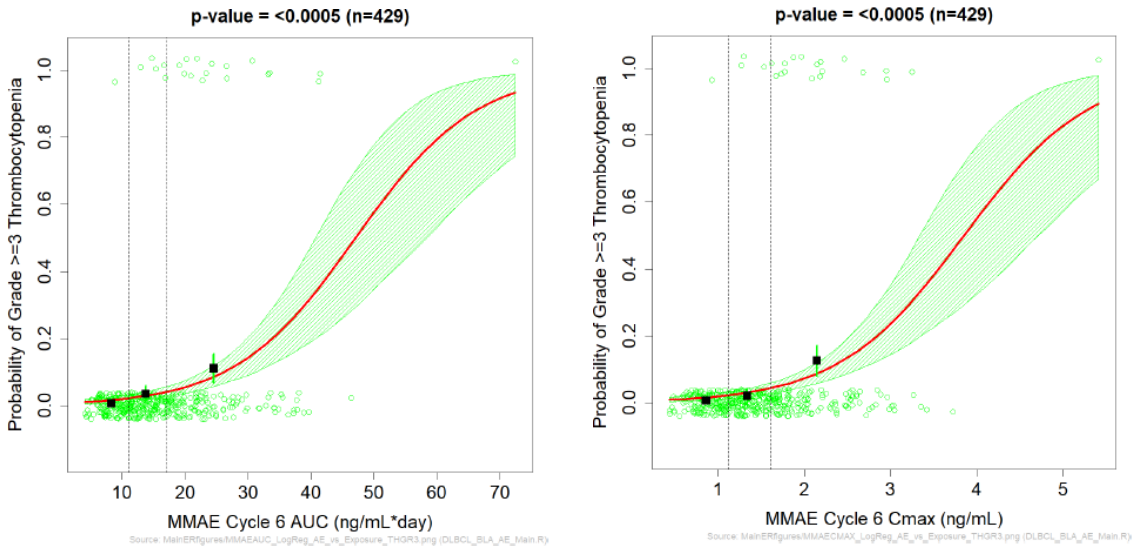


Figure 14 Logistic Regression for Grade ⩾ 3 Thrombocytopenia, unconjugated MMAE AUC (left plot), and Cmax (right plot).). The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups.

Exposure-Efficacy

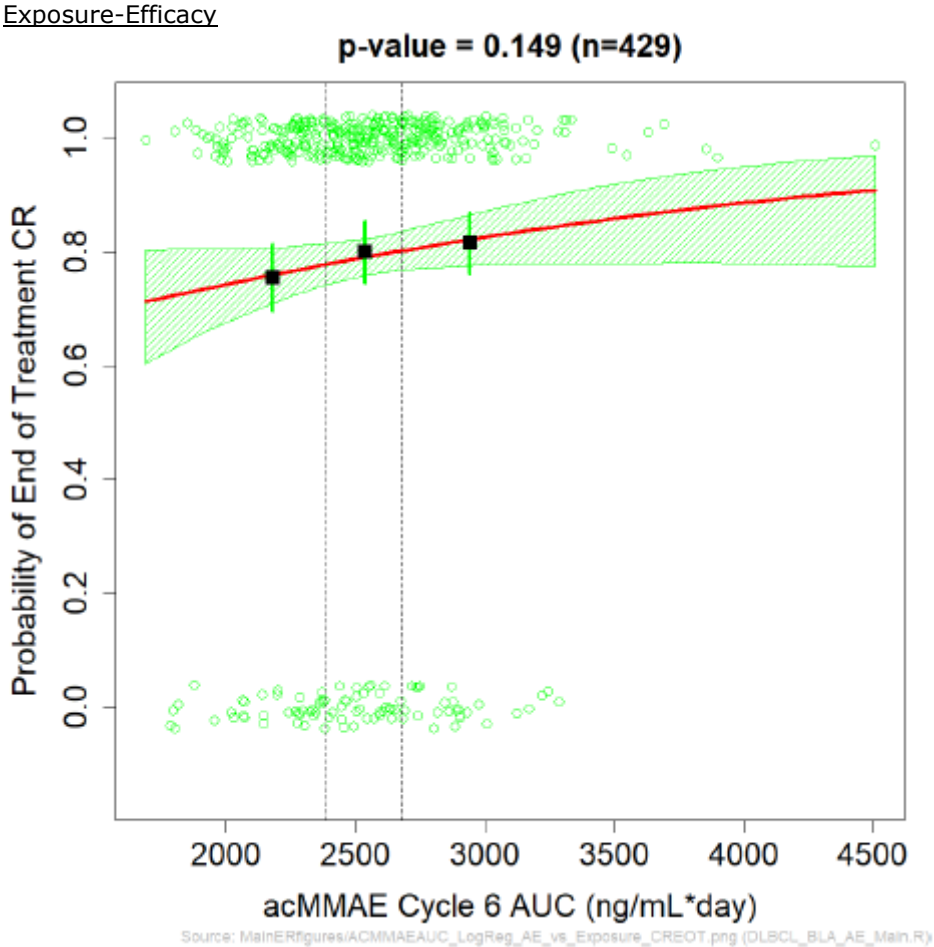


Figure 15 Logistic Regression for CR, acMMAE AUC The red solid line and green shaded area represent the logistic regression model prediction and 90% confidence interval of predictions. Points show exposure of individual patients with events (p=1) and without events (p=0). Black squares and vertical green lines

show observed fraction of subjects with events in each exposure group and 90% confidence interval for these fractions. Dashed vertical lines show bounds of exposure groups.

2.3.5. Discussion on clinical pharmacology

Overall, polatuzumab vedotin PK was characterized in newly diagnosed DLBCL patients in POLARIX study, and based on Pop PK analysis. Despite some clarification needed in the pop PK model validation, based on the provided study results, it is not expected that the PK of polatuzumab vedotin will be significantly different in DLBCL patients treated with polatuzumab vedotin in first-line.

Polatuzumab vedotin is indicated for first-line treatment of DLBCL in combination with R-CHP. The PK interaction between the administered drugs were assessed. In vivo DDI studies show that polatuzumab vedotin does not have a clinically relevant impact on the pharmacokinetics of doxorubicin nor cyclophosphamide when given in combination. However, given the confounding variabilities associated to the other DDI studies design, no clear conclusion can be drawn for polatuzumab vedotin potential interaction as perpetrator (i.e. on rituximab and obinutuzumab PKs) or victim (i.e. with –CHP as perpetrator). The applicant was invited to more soundly discuss the comparability of each study to study GO29044 in order to potentially manage DDI risks.

Among 435 previously untreated DLBCL patients treated with Polivy in combination with R-CHP in Study GO39942, 227 (52.2%) were ≥ 65 years of age. Patients aged ≥ 65 had an incidence of serious adverse reactions of 39.2% and 28.4% in patients aged < 65. A similar incidence of serious adverse reactions was seen in elderly patients in the R-CHOP treatment arm.

Exposure-safety analysis suggested that higher acMMAE exposures (AUC and Cmax) were significantly correlated with higher incidence of Grade ≥ 2 peripheral neuropathy, Grade ≥ 3 anemia (only AUC), and Grade ≥ 3 thrombocytopenia. The covariate analyses were performed only for the acMMAE AUC models. The forward-addition procedure identified HGB and LDH as the significant covariates for Grade ≥ 3 anemia at α = 0.01 level. Patients with higher baseline HGB had lower probability of Grade ≥ 3 anemia. Patients with higher baseline LDH had higher probability of Grade ≥ 3 anemia. The exposure-response relationship remained significant in the presence of these covariates. HGB was retained in the model at α = 0.001 level during the backward elimination.

Higher unconjugated MMAE exposures (AUC, Cmax) were significantly correlated with higher incidence of Grade ≥ 3 neutropenia, Grade ≥ 3 infections and infestations, Grade ≥ 3 anemia, Grade ≥ 3 thrombocytopenia, and Grade ≥ 3 febrile neutropenia. The covariate analyses were performed only for the unconjugated MMAE AUC models. The forward-addition procedure identified HGB as a significant covariate for Grade ≥ 3 anemia, and Asian race for Grade ≥ 3 neutropenia at α = 0.01 level. Patients with higher HGB had lower probability of Grade ≥ 3 anemia, and Asian patients had higher probability of Grade ≥ 3 neutropenia. The exposure response relationship remained significant in the presence of these covariates in the model; both covariates were retained in the final model at α = 0.001 level during backward elimination.

Exposure-Efficacy cox analysis suggested a significant correlation (p = 0.01 by Cox regression) between acMMAE AUC and EFSeff, with higher exposure leading to a longer EFSeff. The forward-addition procedure identified baseline bulky disease as a significant covariate at α = 0.01 level. The exposure-response relationship remained significant in the presence of this covariate in the model. Only bulky disease remained in the final model at α = 0.001 level during the backward elimination.

The Cox analysis suggested no significant correlation between acMMAE AUC and OS. Probability of complete response at the end of treatment did not correlate with acMMAE exposure (AUC).

In Studies GO39442 (POLARIX) and GO29365, 1.4% (6/427) and 5.2% (12/233) of patients tested positive for antibodies against polatuzumab vedotin, respectively, of which none were positive for neutralizing antibodies.

Sections 4.4 and 5.2 of the SmPC were updated accordingly.

2.3.6. Conclusions on clinical pharmacology

In general, the submitted clinical pharmacology studies are considered sufficient to characterize polatuzumab vedotin in the indication of first-line DLBCL treatment in combination with rituximab, cyclophosphamide, doxorubicine, and prednisone.

2.4. Clinical efficacy

2.4.1. Dose response study

Study GO29044: A Phase Ib/II Study Evaluating the Safety, Tolerability and Anti-Tumor Activity of Polatuzumab Vedotin (DCDS4501A) in Combination With Rituximab or Obinutuzumab, Cyclophosphamide, Doxorubicin, and Prednisone in Patients With B-Cell Non-Hodgkin's Lymphoma.

First Patient Enrolled: 29 November 2013 Last patient last visit: 20 December 2018

In the dose-finding portion of the study, the MTD of polatuzumab vedotin in combination with rituximab or obinutuzumab in combination with cyclophosphamide, doxorubicin, and prednisolone or prednisone [R-CHP or G-CHP] was determined. Following identification of the MTD, the dose-expansion portion of the study further evaluated the safety and tolerability and clinical activity of R-CHP or G-CHP plus polatuzumab vedotin in patients with newly diagnosed DLBCL.

The primary objectives of this study were to assess the safety and tolerability of the combination of pola+ R-CHP or G-CHP and to determine the MTD and schedule for pola+ R-CHP or G-CHP.

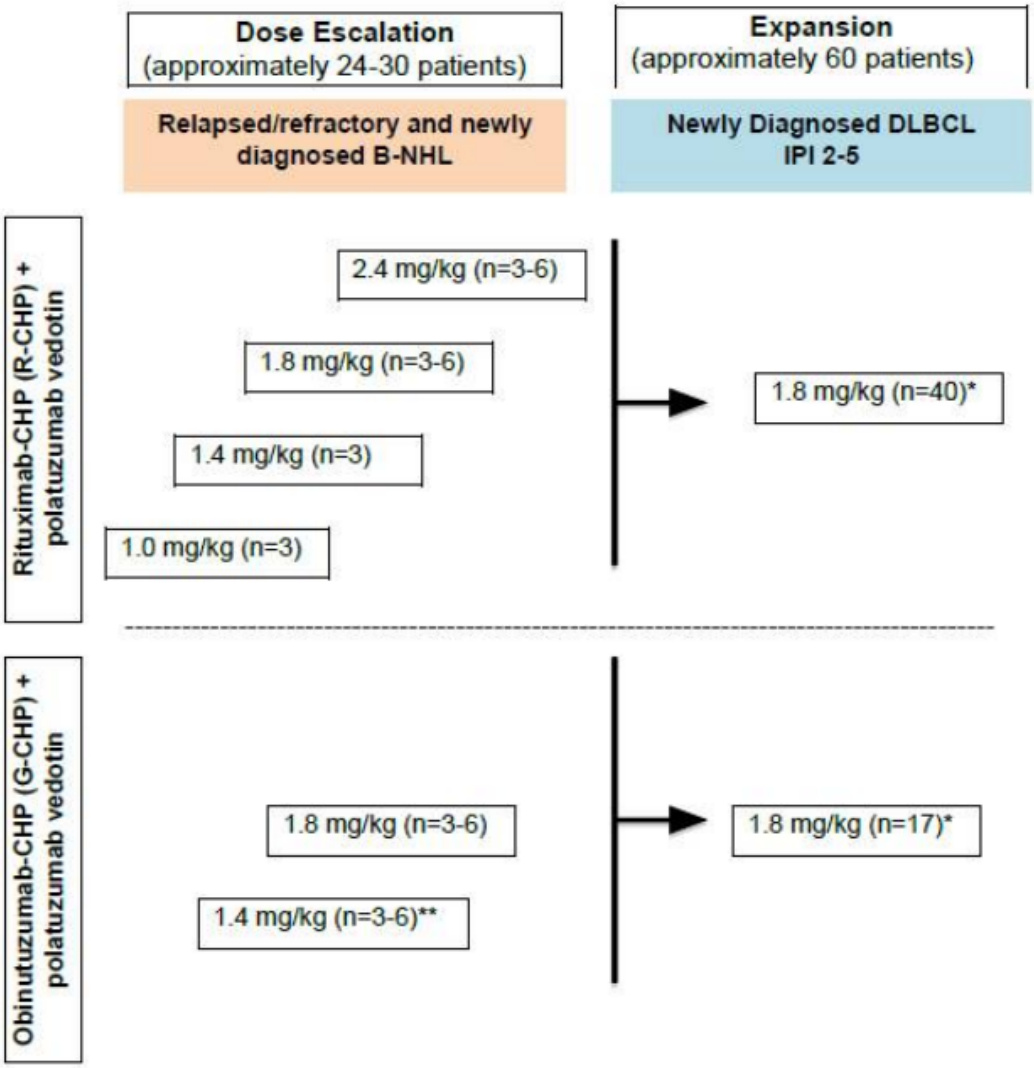
The secondary efficacy objectives of this study were the following: to make a preliminary assessment of efficacy as measured by CR rate determined by PET-CT scan, OR Rate, DOR, PFS, EFS and OS, to assess the potential relationships of such ADA formation with efficacy outcome measures

The exploratory efficacy objectives of this study were the following to assess the efficacy of therapy in different potential prognostic subgroups, including DLBCL genotypic subtypes (e.g. ABC, GCB) and high Bcl-2 expression, to assess tumor expression of CD79b, to assess prevalence and the correlation of lymphoma associated mutations with outcome, to assess MRD as quantified by measurements of lymphoma-specific markers in peripheral blood, to evaluate the prognostic significance of interim PET assessment, to evaluate response, by IRC, as determined through use of the PET-CT scans based on a modified version of the Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014), hereinafter referred to as Modified Lugano 2014 criteria (CR by PET at end of induction (EOI) by IRC, CR by CT at EOI by IRC, OR (defined as a CR or PR) at EOI, best response of CR or PR during the study, evaluate patients who have positive PET scans at EOI: CR at 12 months).

Design: Two parallel treatment arms explored doses of pola+R-CHP and G-CHP. The MTD or RP2D of polatuzumab vedotin in combination with R-CHP was identified before it was combined with G-CHP. This was an open-label study.

Study treatment was given in every-21-day cycles, with the first day of treatment constituting Day 1 of the cycles. Patients were treated for a total of six or eight cycles in accordance with local institutional practice.

Figure 16: Overview of Study Design



Once a dose was identified for the expansion stage, the study restricted enrollment to a group of patients with high medical need (newly diagnosed DLBCL patients who were aged ≥18 years and who had an IPI of 2-5) to further assess safety and efficacy of the combination.

The dose escalation of polatuzumab vedotin combined with R-CHP began at a dose level of 1.0 mg/kg, because this was the highest dose level at which no DLTs or clinically significant AEs were observed during the Phase I study (Palanca-Wessels et al. 2015). The MTD of polatuzumab vedotin in combination with R-CHP was identified before it was combined with G-CHP. Once the MTD was determined, polatuzumab vedotin was dosed at MTD-1 in combination with G-CHP to start the dose escalation of this combination.
Rituximab was administered after the prednisone/prednisolone dosing and before the cyclophosphamide, doxorubicin, and polatuzumab vedotin infusions. Six to eight cycles of rituximab at 375 mg/m2 were administered IV to patients every 21 days (or over 28 days for those patients who experienced toxicity that necessitated an extended cycle duration). No dose modifications of rituximab were allowed.

Cyclophosphamide 750 mg/m2 was administered IV on Day 1, Doxorubicin 50 mg/m2 IV on Day 1 and Prednisone 100 mg/day by PO on Days 1-5.

Main inclusion criteria

- *Dose-Escalation Portion of the Study:* Histologically confirmed B-cell NHL: Patients with newly diagnosed B-cell NHL or relapsed/refractory B-cell NHL were eligible, No more than one prior systemic treatment regimen for B-cell NHL (single agent anti-CD20 MAb therapy was not counted as a prior treatment regimen), No prior treatment with anthracyclines
- *Expansion Portion of the Study:* Previously untreated patients with DLBCL, IPI score of 2-5.

Statistical Hypothesis and Planned Sample Size

Since there was no pre-specified hypothesis, whether or not the efficacy endpoints were met could not be assessed using statistical tests. The sample size required for estimating the MTD was based on the dose-escalation rules. All dose-escalation cohorts will consist of at least 3 patients. If a DLT is observed in 1 patient at a given dose level during the DLT observation period before dose escalation, additional patients will be enrolled at that dose level for a total of at least 6 patients. Protocol version 8 discontinued enrollments in the pola +G-CHP arm at 17 patients and the total number of patients in the expansion arm was approximately 60, instead of 80. The decision to discontinue enrollment in the pola+G-CHP arm was made because of final results from Study BO21005 (GOYA) which showed no additional efficacy benefit of G-CHOP compared to R-CHOP as determined by the study's primary endpoint of investigator assessed PFS. Regarding efficacy data, CR rate was estimated by the number and percentage of responders with corresponding 90% CIs was presented. Estimates of the median PFS, DOR, OS and the corresponding two-sided 95% CI were presented along with the estimates for the 25th and 75th percentiles in all patients. The KM approach was used to estimate the distribution of DOR, PFS, EFS, and OS in all patients.

Results

A total of 85 patients were actually enrolled; however, due to a data transfer error from IXRS to RAVE, data for 1 patient was not captured. As this patient did not receive any study medication, only the intent-to-treat (ITT) analysis population was affected and data were captured for 84 patients.

There were 3 patients in the R-CHP treatment regimen non-DLBCL group, 51 patients in the R-CHP treatment regimen DLBCL group, 5 patients in the G-CHP treatment regimen non-DLBCL group, and 25 patients in the G-CHP treatment regimen DLBCL group.

<u>Only data of patients with DLCBL in the R-CHP treatment regimen are described below:</u>

A total of 50 patients in the R-CHP treatment regimen, DLBCL, were included in the efficacy analysis.

Study population was predominately White (43 [86.0%]) and female (26 [52.0%]), with a median age of 68.5 years (range: 45-80 years). The majority of patients (37 [74.0%]) were ≥65 years old. A total of 12 (24.0%) patients had an ECOG score of 0 at baseline, 23 (46.0%) patients had a baseline score of 1, and 15 patients (30.0%) had a baseline score of 2. A total of 14 patients (28.0%) had an IPI score of 0-2 and 36 patients (72.0%) had an IPI score of 3-5.

Pola dose cohorts were as follows: 2 patients, 1 mg/kg; 3 patients, 1.4 mg/kg; 5 patients, 1.8 mg/kg during dose-escalation phase and 40 patients, 1.8 mg/kg during dose-expansion phase.

At the last patient last visit, patients were on the study over a median period of 35.12 months (range 1.28 to 59.40 months).
8 were discontinued from the study. All these patients were from 1.8 mg/kg-dose expansion group (4 due to deaths and 4 due to diseases progressions).

The efficacy results are summarized below:

- The CR rate for all doses at the end of treatment window visit by CT/MRI with PET scan was 78.0% (39/50; 90% CI: 66.22, 87.14). In the 45 patients treated with 1.8 mg/kg pola, the CR rate was 100% (5/5; 90% CI: 54.93, 100.00) during the dose escalation phase and 75% (30/40; 90% CI: 61.29, 85.76) during the dose expansion phase

Table 1: Summary of Response at End of Treatment Window Visit by CT/MRI with PET Scan, Composite PD by Either Assessment Method, R-CHP Treatment Regimen – DLBCL

	R-CHP+POV (1.0) (N=2)	R-CHP+POV (1.4) (N=3)	R-CHP+POV (1.8) (N=5)	EXP R-CHP+POV (1.8) (N=40)	Total (N=50)
Responders	2 (100.0%)	3 (100.0%)	5 (100.0%)	36 (90.0%)	46 (92.0%)
Non-Responders	0	0	0	4 (10.0%)	4 (8.0%)
90% CI for Response Rates	(22.36, 100.00)	(36.84, 100.00)	(54.93, 100.00)	(78.56, 96.51)	(82.62, 97.22)
Complete Response (CR)	1 (50.0%)	3 (100.0%)	5 (100.0%)	30 (75.0%)	39 (78.0%)
90% CI	(2.53, 97.47)	(36.84, 100.00)	(54.93, 100.00)	(61.29, 85.76)	(66.22, 87.14)
Partial Response (PR)	1 (50.0%)	0	0	6 (15.0%)	7 (14.0%)
90% CI	(2.53, 97.47)	(0.00, 63.16)	(0.00, 45.07)	(6.74, 27.47)	(6.76, 24.69)
Stable Disease (SD)	0	0	0	0	0
90% CI	(0.00, 77.64)	(0.00, 63.16)	(0.00, 45.07)	(0.00, 7.22)	(0.00, 5.82)
Progressive Disease (PD)*	0	0	0	3 (7.5%)	3 (6.0%)
90% CI	(0.00, 77.64)	(0.00, 63.16)	(0.00, 45.07)	(2.08, 18.26)	(1.66, 14.78)
Missing or unevaluable	0	0	0	1 (2.5%)	1 (2.0%)
90% CI	(0.00, 77.64)	(0.00, 63.16)	(0.00, 45.07)	(0.13, 11.32)	(0.10, 9.14)

*Composite Progression of Disease is based on first PD for visit by either CT/MRI with PET or CT/MRI without PET
90% CI for rates were constructed using Clopper-Pearson method.
Database lock is March 28, 2019.

- Median PFS, DOR, and OS were not reached in any of the dose groups.

Table 2: Efficacy Results of Pola+R-CHP in DLBCL Patients from Study GO29044 (Efficacy Evaluable population)

Endpoint	Pola+R-CHP			
	Dose escalation			Dose-Expansion
	Pola 1.0 mg/kg N=2	Pola 1.4 mg/kg N=3	Pola 1.8 mg/kg* N=5	Pola 1.8 mg/kg* N=40
PFS24 95% CI	100.0% (100.00, 100.00)	100.0% (100.00, 100.00)	80.0% (44.94, 100.00)	77.50% (64.56, 90.44)
DOR24 95% CI	100.0% (100.00, 100.00)	100.0% (100.00, 100.00)	80.0% (44.94, 100.00)	83.60% (71.59, 95.61)
EFS24 95% CI	100.0% (100.00, 100.00)	100.0% (100.00, 100.00)	80.0% (44.94, 100.00)	65.0% (50.22, 79.78)
OS24 95% CI	100.0% (100.00, 100.00)	100.0% (100.00, 100.00)	100.0% (100.00, 100.00)	92.50% (84.34, 100.00)

- Due to the lack of ADA-positive results, no conclusions can be drawn concerning a potential effect of ADA on efficacy results.

Response by subgroups:

- Response by cell of origin subtype:

At the baseline, there were 12 patients with DLBCL subtype ABC. Response was observed in all 12 patients (100.0%); 11 patients had CR and 1 patient had PR.

A total of 22 patients had DLBCL subtype GCB. Response was observed in all 22 patients (100.0%); 19 patients had CR and 3 patients had PR.

- Response by BCL2 expressor status

BCL2 expression was negative in 18 patients. Of these, response was observed in 17 patients (94%); 15 patients had CR and 2 patient had PR. One patient had progressive disease.

BCL2 expression was positive in 15 patients. Response was observed in all 15 patients (100%); 11 patients had CR and 4 patients had PR.

- Response by MYC expressor status

MYC expression was negative in 13 patients. Response was observed in all 13 patients (100.0%); 12 patients had CR and 1 patient had PR.

MYC expression was positive in 19 patients. Of these, response was observed in 18 patients (94.7%); 13 patients had CR and 5 patients had PR. One patient had progressive disease.

- Response by BCL2/MYC double expressor

BCL2/MYC double expression was negative in 23 patients. Of these, response was observed in 22 patients (95.7%); 19 patients had CR and 3 patients had PR. One patient had progressive disease.

BCL2/MYC double expression was positive in 9 patients. Response was observed in all 9 patients (100.0%); 6 patients had CR and 3 patients had PR.

- Response by CD79b H-Score

No patients with DLBCL with H-score IHC of 0.

Eight patients had DLBCL with CD79b H-score IHC 1+. Response was observed in all 8 patients (100.0%); 7 patients had CR and 1 patient had PR.

Twelve patients had DLBCL CD79b H-score IHC 2+. Response was observed in all 12 patients (100.0%); 10 patients had CR and 2 patients had PR. Seven patients had DLBCL CD79b H-score IHC 3+. Response was observed in all 7 patients (100.0%); 5 patients had CR and 2 patients had PR.

- PFS by subgroups

There was no clinically meaningful difference noted in PFS results as assessed in the subgroups of biomarkers such as COO subtype, BCL2 expressor, MYC expressor, BCL2/MYC expresssor, and CD79b H score.

Pola+G-CHP

Of the 25 patients in the safety and efficacy evaluable populations in this cohort, 21 patients were treated with 1.8 mg/kg pola and are included in the 1L DLBCL safety analyses presented in this document.

Pola dose cohorts were as follows: 4 patients, 1.4 mg/kg, 4 patients, 1.8 mg/kg during dose-escalation phase, 17 patients, 1.8 mg/kg during dose-expansion phase. Patients were on the study over a median period of 29.8 months (range: 2.5–41.8 months). The majority of patients were male (60.0%); the ECOG score at baseline was 0 in 56.0% of patients, 1 in 28.0% patients, and 2 in 16% of patients. A total of 16 patients (64.0%) had an IPI score of 0–2 and 9 patients (36.0%) had an IPI score of 3–5.

A total of 25 patients (dose escalation + dose expansion) in the G-CHP treatment regimen, DLBCL were included in the interim efficacy analysis. The efficacy results are summarized below:

Table 27 Summary of Response at End of Treatment Window Visit by CT/MRI with PET Scan, Composite PD by Either Assessment Method, G-CHP Treatment Regimen – DLBCL (SE)

	G-CHP+POV (1.4) (N=4)	G-CHP+POV (1.8) (N=4)	EXP G-CHP+POV (1.8) (N=17)	Total (N=25)
Responders	3 (75.0%)	4 (100.0%)	15 (88.2%)	22 (88.0%)
Non-Responders	1 (25.0%)	0	2 (11.8%)	3 (12.0%)
90% CI for Response Rates	(24.86, 98.73)	(47.29, 100.00)	(67.38, 97.87)	(71.83, 96.65)
Complete Response (CR)	3 (75.0%)	4 (100.0%)	13 (76.5%)	20 (80.0%)
90% CI	(24.86, 98.73)	(47.29, 100.00)	(53.95, 91.54)	(62.46, 91.77)
Partial Response (PR)	0	0	2 (11.8%)	2 (8.0%)
90% CI	(0.00, 52.71)	(0.00, 52.71)	(2.13, 32.62)	(1.44, 23.10)
Stable Disease (SD)	1 (25.0%)	0	0	1 (4.0%)
90% CI	(1.27, 75.14)	(0.00, 52.71)	(0.00, 16.16)	(0.20, 17.61)
Progressive Disease (PD)*	0	0	0	0
90% CI	(0.00, 52.71)	(0.00, 52.71)	(0.00, 16.16)	(0.00, 11.29)
Missing or unevaluable	0	0	2 (11.8%)	2 (8.0%)
90% CI	(0.00, 52.71)	(0.00, 52.71)	(2.13, 32.62)	(1.44, 23.10)

*Composite Progression of Disease is based on first PD for visit by either CT/MRI with PET or CT/MRI without PET (example subject: GO29044-266060-30852 at "TREATMENT COMPLETION\EARLY DISCONTINUATION" Visit).
Data cutoff date is December 29, 2017. Extract date is March 12, 2018.

Program: /opt/BIOSTAT/prod/cdpt7884/go29044/t_resp_cmpv.sas / Output: /opt/BIOSTAT/prod/cdpt7884/i29044t/reports/t_resp_cmpv_GCHPDBS_CTMRIPET_BOTWIN_SE.out 01MAY2018 0:21

- The 12-month PFS was 91.64% (95% CI: 80.52, 100.00). Median PFS was not reached.
- Median DOR was not reached.
- The 12-month EFS was 84.0% (95% CI: 69.63, 98.37). Median EFS was not reached.
- The 12-month OS was 92.0% (95% CI: 81.37, 100.00). The median OS was not reached

Exposure-Response Analysis

The exposure-efficacy analysis was conducted for the 429 previously untreated patients with DLBCL from POLARIX Study GO39942 (pola + R-CHP arm), with an additional 439 previously untreated DLBCL patients from R-CHOP control arm for the Kaplan-Meier analysis only:

- To assess the relationships between pola exposure (Cycle 6 AUC for acMMAE) and progression-free survival (PFS) as determined by the investigator;
- To assess the relationships between pola exposure (Cycle 6 AUC for acMMAE) and probability of complete response at the end of treatment (CREOT) by FDGPET as determined by blinded independent central review.
- To assess the relationships between pola exposure (Cycle 6 AUC for acMMAE) and event-free survival for efficacy reasons as determined by the investigator (EFSeff);
- To assess the relationships between pola exposure (Cycle 6 AUC for acMMAE) and overall survival (OS).

Methodology:

The individual empirical Bayes estimates of pola PK parameters estimated by the population PK model were used to obtain the individual pola exposure measures, defined as Cycle 6 AUC and Cmax for acMMAE and unconjugated MMAE based on nominal dose (i.e., assuming that the subject received the planned 1.8 mg/kg Q3W doses during the entire study). Only AUC for acMMAE was used for the exposure-efficacy analysis.

Results:

- The Cox analysis suggested a significant correlation (p=0.01 by Cox regression) between acMMAE AUC and PFS, with higher exposure leading to a longer PFS. The forward inclusion identified baseline bulky disease and B cell count as significant covariates at α=0.01 level. The exposure-response relationship remained significant in the presence of those covariates in the model. Only bulky disease remained in the final model at α=0.001 level during the backward elimination.
- The Cox analysis suggested a significant correlation (p=0.01 by Cox regression) between acMMAE AUC and EFSeff, with higher exposure leading to a longer EFSeff. The forward inclusion identified baseline bulky disease as a significant covariate at α=0.01 level. The exposure-response relationship remained significant in the presence of this covariate in the model. Only bulky disease remained in the final model at α=0.001 level during the backward elimination.
- The Cox analysis suggested no significant correlation between acMMAE AUC and interim OS.
- Probability of CR at the end of treatment did not correlate with acMMAE exposure (AUC).

2.4.2. Main study

Study GO39942 (POLARIX)

A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing the Efficacy and Safety of Polatuzumab Vedotin in Combination with Rituximab and CHP (R-CHP) versus Rituximab and CHOP (R-CHOP) in Previously Untreated Patients with Diffuse Large B-Cell Lymphoma.

Methods

Approximately 875 patients were planned for enrollment in the global study; the population from which the primary analysis has been performed. After approximately 875 patients had been randomized into the study, enrollment outside of China (i.e., global enrollment) was closed and a China extension cohort opened.

Study participants

Main Inclusion Criteria

- Previously untreated patients with CD20-positive DLBCL, included one of the following diagnoses by 2016 WHO classification of lymphoid neoplasms:

    - DLBCL, not otherwise specified (NOS) included germinal center B-cell type, activated B-cell type
    - T-cell/histiocyte-rich large B-cell lymphoma
    - Epstein-Barr virus-positive DLBCL, NOS
    - ALK-positive large B-cell lymphoma
    - HHV8-positive DLBCL, NOS
    - High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements (double-hit or triple-hit lymphoma)
    - High-grade B-cell lymphoma, NOS
- Available, archived or freshly collected tumor tissue before study enrollment

The pathology report had to be available for review and a tissue block sent for retrospective central review of diagnosis.

- IPI score of 2-5
- Aged 18-80 years
- ECOG Performance Status of 0, 1, or 2
- Life expectancy ≥12 months
- At least one bi-dimensionally measurable lesion available, defined as >1.5 cm in its longest dimension as measured by CT or MRI
- Left ventricular ejection fraction (LVEF) ≥ 50% on cardiac multiple-gated acquisition (MUGA) scan or cardiac echocardiogram (ECHO)
- Adequate hematologic function (unless due to underlying disease, as established for example, by extensive bone marrow involvement or due to hypersplenism secondary to the involvement of the spleen by DLBCL per the investigator), defined as follows:
    - Hemoglobin ≥ 9.0 g/dL without packed RBC transfusion during 14 days before first treatment
    - ANC ≥ 1,000/μL
    - Platelet count ≥ 75,000/μL

Main Exclusion Criteria

- Contraindicated to any of the individual components of R-CHOP
- Prior organ transplantation
- Grade >1 peripheral neuropathy by clinical examination or demyelinating form of Charcot-Marie-Tooth disease
- History of indolent lymphoma
- Diagnosis of the following: follicular lymphoma grade 3B; B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma (grey-zone lymphoma); primary mediastinal (thymic) large B-cell lymphoma; Burkitt lymphoma; CNS lymphoma (primary or secondary involvement), primary effusion DLBCL, and primary cutaneous DLBCL
- Prior treatment with cytotoxic drugs within 5 years of screening for any condition (e.g., cancer, rheumatoid arthritis) or prior use of any anti-CD20 antibody
- Prior use of any monoclonal antibody within 3 months of the start of Cycle 1; any investigational therapy within 28 days prior to the start of Cycle 1; vaccination with live vaccines within 28 days prior the start of Cycle 1

- Prior radiotherapy to the mediastinal/pericardial region
- Prior therapy for DLBCL
- Corticosteroid use > 30 mg/day of prednisone or equivalent, for purposes other than lymphoma symptom control
    - Patients who received corticosteroid treatment with ≤ 30 mg/day of prednisone or equivalent for reasons other than lymphoma symptom control had to be documented to be on a stable dose of at least 4 weeks' duration prior to the start of Cycle 1.
    - Patients who required lymphoma symptom control during screening received steroids (up to 30 mg/day of prednisone or equivalent could be used for lymphoma symptom control during screening)
- History of other malignancy that could have affected compliance with the protocol or interpretation of results
- Evidence of significant, uncontrolled, concomitant diseases that could have affected compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm)
- Recent major surgery (within 4 weeks prior to the start of Cycle 1), other than for diagnosis
- History or presence of an abnormal ECG that was clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection at study enrollment or significant infections within 2 weeks before the start of Cycle 1
- Clinically significant liver disease, including active viral or other hepatitis, current alcohol abuse, or cirrhosis
- Any of the following abnormal laboratory values (unless any of these abnormalities were due to underlying lymphoma):
    - INR or PT > 1.5 ULN in the absence of therapeutic anticoagulation
    - PTT or aPTT > 1.5 ULN in the absence of a lupus anticoagulant
    - Serum AST and ALT ≥ 2.5 ULN
    - Total bilirubin ≥ 1.5 ULN
    - Serum creatinine clearance < 40 mL/min (using Cockcroft-Gault formula)
- Patients with suspected active or latent tuberculosis
- Positive test results for chronic hepatitis B infection
- Positive test results for hepatitis C
- Known history of HIV seropositive status
- Positive results for the human T-lymphotrophic 1 virus (HTLV-1)
- Patients with a history of progressive multifocal leukoencephalopathy
- Pregnancy or lactation

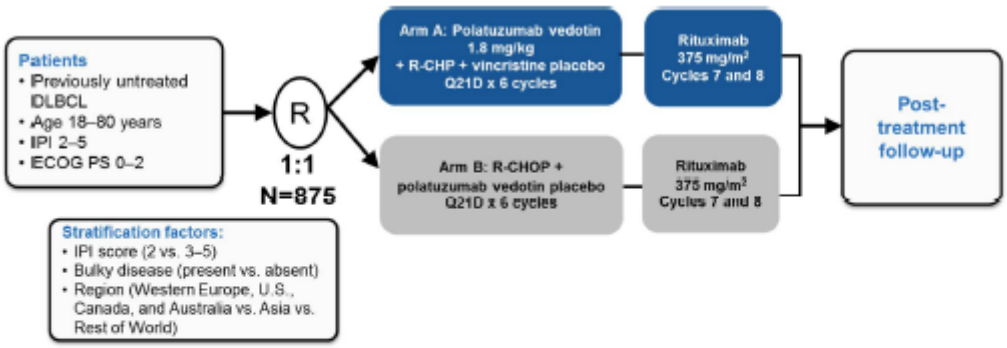
Treatments

Patients received six cycles of either pola+R-CHP or standard R-CHOP chemotherapy at 21-day intervals. Both arms then received two additional cycles of single agent rituximab. The study design and treatment regimens are respectively shown in Figure 2 and Figure 3.

Arm A; pola+R-CHP (investigational arm): pola 1.8 mg/kg IV, placebo for vincristine IV, rituximab 375 mg/m2 IV, cyclophosphamide 750 mg/m2 IV, and doxorubicin 50 mg/m2 IV each given on Day 1 and prednisone 100 mg/day orally (PO) given on Days 1-5 of every 21-day cycle for 6 cycles. Rituximab 375 mg/m2 IV was given as monotherapy in Cycles 7 and 8.

Arm B; R-CHOP (control arm): placebo for pola, rituximab 375 mg/m2 IV, cyclophosphamide 750 mg/m2 IV, doxorubicin 50 mg/m2 IV, and vincristine 1.4 mg/m2 IV (maximum 2 mg/dose) each given on Day 1 and prednisone 100 mg/day PO given on Days 1-5 of every 21-day cycle for 6 cycles. Rituximab 375 mg/m2 IV was given as monotherapy in Cycles 7 and 8.

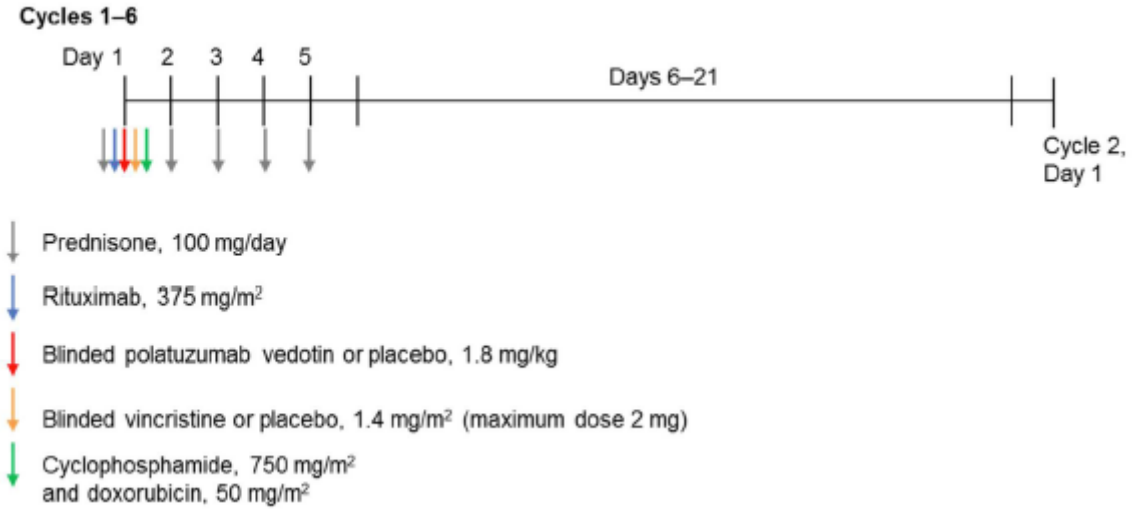
Figure 17: Study Design



DLBCL = diffuse large B-cell lymphoma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IPI = International Prognostic Index; Q21D = every 21 days; R = randomization; R-CHOP = rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHP = rituximab plus cyclophosphamide, doxorubicin, and prednisone.

No crossover to the experimental arm was allowed.

Figure 18: Schematic of Pola plus R-CHP and R-CHOP Regimens



Administration schedule

In Cycles 1-6, rituximab infusion was to be completed prior to starting any other agent administered by infusion. The order of administration for Cycles 1-6 were: first prednisone, second rituximab, and third blinded polatuzumab vedotin/placebo. Subsequent infusions of blinded vincristine/placebo, cyclophosphamide, and doxorubicin were to be administered according to institutional preference. Cycle 7 and Cycle 8 consisted of rituximab as monotherapy.

The infusion of rituximab may be split over 2 days if the patient is at increased risk for an IRR (high tumor burden or high peripheral lymphocyte count).

Blinded pola/placebo could be administered on Day 2 per investigator preference due to infusion times for rituximab and blinded pola/placebo. In this instance, blinded vincristine/placebo, cyclophosphamide, and doxorubicin could also be administered on Day 1 following the completion of rituximab, and blinded pola/placebo could be administered on Day 2 after prednisone. Alternative study drug administration regimens could be considered with consultation of the Medical Monitor.

Should infusion-related reactions or other adverse events occur (e.g., during rituximab infusion), treatment could be administered over more than 1 day.

Pre-Phase Steroids

Steroids prior to study treatment initiation were allowed according to guidelines described in Protocol. The pre-phase treatment was not considered part of study treatment. The purpose of the pre-phase treatment is to prevent tumor lysis syndrome (TLS) in patients with extensive disease and to reduce toxicity of the first cycle of study treatment (e.g., cytokine release syndrome). Staging study assessments (i.e., CT/MRI, PET-CT scan, tumor biopsy) were performed prior to initiation of pre-phase treatment.

Premedication

For Cycles 1-6, pola or its placebo were administered after the prednisone and rituximab components of R-CHP/R-CHOP were administered, as infusion reactions due to rituximab are typically more common than those for pola. The initial dose was administered to patients who are well hydrated over 90 (± 10) minutes. As required, premedication (e.g., 500-1000 mg of oral acetaminophen or paracetamol and 50-100 mg diphenhydramine as per institutional standard practice) was administered to an individual patient before administration of pola /placebo, unless already been administered as a premedication for rituximab). If infusion-related reactions (IRRs) were observed with the first infusion of pola in the absence of premedication, premedication must be administered before subsequent doses as described in *Table 3*.

Table 3: Premedication for Rituximab and Blinded Polatuzumab Vedotin/Placebo

Timepoint	Patients Who Require Premedication	Premedication	Administration
Cycle 1, Day 1	• All patients	• Corticosteroid [a]	Complete ≥ 1 hour prior to rituximab infusion and polatuzumab vedotin/placebo.
		• Antihistamine drug [b] • Analgesic/ anti-pyretic [c]	Administer ≥ 30 minutes prior to rituximab infusion; may be administered to patients prior to administration of any polatuzumab vedotin/placebo as well.
Cycles 2 and beyond, Day 1	• Patients with no IRR during the previous infusion	• Corticosteroid [a]	Complete ≥ 1 hour prior to rituximab and polatuzumab vedotin/placebo infusion.
		• Antihistamine drug [b] • Analgesic/ anti-pyretic [c]	Administer ≥ 30 minutes prior to infusion. These may be omitted or adapted at the investigator's discretion.
	• Patients with Grade 1 or 2 IRR during the previous infusion	• Corticosteroid [a]	Complete ≥ 1 hour prior to rituximab and polatuzumab vedotin/placebo infusion.
		• Antihistamine drug [b] • Analgesic/ anti-pyretic [c]	Administer ≥ 30 minutes prior to rituximab and/or polatuzumab vedotin/placebo infusion.
	• Patients with Grade 3 IRR, wheezing, urticaria, or other symptoms of anaphylaxis during the previous infusion • Patients with bulky disease	• Corticosteroid [a]	Complete ≥ 1 hour prior to rituximab and/or polatuzumab vedotin/placebo infusion.
		• Antihistamine drug [b] • Analgesic/ anti-pyretic [c]	Administer ≥ 30 minutes prior to rituximab and/or polatuzumab vedotin/placebo infusion.

IRR = infusion-related reaction.

[a] Part of study treatment: 100 mg of prednisone. May be substituted with 100 mg of prednisolone or 80 mg of methylprednisolone. Hydrocortisone should not be used, as it has not been effective in reducing rates of IRRs. In Cycle 7 and Cycle 8, corticosteroid used as premedication should be administered according to institutional standard.

[b] For example, 50–100 mg of diphenhydramine.

[c] For example, 650–1000 mg of acetaminophen/paracetamol.

The pola/placebo infusion could be slowed or interrupted for patients who experienced infusion-associated symptoms. Following the initial dose, patients were observed for 90 minutes for fever, chills, rigors, hypotension, nausea, or other infusion-associated symptoms. If prior infusions were well tolerated, subsequent doses of pola could be administered over 30 (± 10) minutes, followed by a 30-minute observation period after the infusion.

Dose modifications

The dose of blinded polatuzumab vedotin/placebo and blinded vincristine/placebo and chemotherapy (cyclophosphamide or doxorubicin) can be reduced stepwise to a maximum of two levels for management of drug-related toxicities. If further dose reduction is indicated after two dose reductions, the patient must discontinue the specific study drug but may continue treatment with the remaining study drugs at the investigator's discretion in consultation with the Medical Monitor.

If administration of R-CHP or R-CHOP is delayed, the administration of polatuzumab vedotin and R-CHP/R-CHOP should be delayed for the same time frame; that is, all study drugs should be delayed for the same time frame so that they are all given together beginning on Day 1 of the same cycle.

Guidelines on dose delays and dose modifications for R-CHP, blinded pola/placebo, and blinded vincristine/placebo are described in the tables below. No dose modifications of rituximab were allowed.

Table 4: Steps of Dose Reduction for Blinded Polatuzumab Vedotin/Placebo and Blinded Vincristine/Placebo

Dose Level	Blinded Polatuzumab Vedotin or Placebo [a]	Blinded Vincristine or Placebo [a]
Starting dose	1.8 mg/kg per cycle	100% of starting dose per cycle
First dose reduction	1.4 mg/kg per cycle	75% of starting dose per cycle
Second dose reduction	1.0 mg/kg per cycle	50% of starting dose per cycle
Third dose reduction	Discontinue drug	Discontinue drug

[a] Placebo contains no active medicinal product but due to the blinded nature of the study, dosing of placebo will be modified per protocol guidelines.

Table 5: Recommended Steps of Dose Reduction for Cyclophosphamide

Dose Level	Cyclophosphamide
Starting dose	100% of starting dose per cycle
First dose reduction [a]	75% of starting dose per cycle
Maximum dose reduction [a]	50% of starting dose per cycle or discontinue drug
Subsequent dose reduction	Discontinue drug

[a] Steps of dose reduction listed are suggested dose changes. Investigators may opt for alternative levels of dose reduction as clinically indicated.

Table 6: Recommended Steps of Dose Reduction for Doxorubicin

Dose Level	Doxorubicin
Starting dose	100% of starting dose per cycle
First dose reduction [a]	75% of starting dose per cycle
Maximum dose reduction [a]	50% of starting dose per cycle or discontinue drug
Subsequent dose reduction	Discontinue drug

[a] Steps of dose reduction listed are suggested dose changes. Investigators may opt for alternative levels of dose reduction as clinically indicated.

Objectives

This study evaluated the efficacy, safety, pharmacokinetics, and PROs of pola plus chemoimmunotherapy (pola+R-CHP) compared with SoC chemoimmunotherapy (RCHOP) in previously untreated patients with CD20-positive DLBCL. Efficacy objectives and corresponding endpoints for the study have been outlined in Table 7 below.

Table 7: Objectives and Endpoints

Objectives	Corresponding Endpoint/s
Primary	
• To evaluate the efficacy of pola+R-CHP compared with R-CHOP with respect to PFS	• PFS, defined as the time from randomization to the first occurrence of disease progression or relapse as assessed by the investigator, using the Lugano Response Criteria for Malignant Lymphoma, or death from any cause, whichever occurs earlier
Secondary	
• To evaluate the efficacy of pola+R-CHP compared with R-CHOP with respect to secondary efficacy endpoints	• Key secondary endpoints included in the hierarchical testing procedure: [a] – EFS_{eff} as determined by the investigator – CR rate at end of treatment [b] by FDG-PET [c] as determined by BICR – OS • Secondary endpoints that will not be adjusted for testing multiplicity: [a] – CR rate at end of treatment [b] by FDG-PET [c] as determined by the investigator – ORR at the end of treatment by FDG-PET[c] as determined by investigator [d] – ORR at the end of treatment by FDG-PET[c] as determined by BICR [d] – BOR rate as determined by investigator[d] – PFS24 as determined by the investigator – DFS – DOR – EFS_{all} – PRO endpoints: ○ Time to deterioration in EORTC QLQ-C30 physical functioning and fatigue and FACT-Lym LymS ○ Proportion of patients achieving meaningful improvement in EORTC QLQ-C30 physical functioning and fatigue, and FACT-Lym LymS • EORTC QLQ-C30 rate of treatment-related symptoms and FACT/GOG-NTX peripheral neuropathy rate

Objectives	Corresponding Endpoint/s
Exploratory Efficacy	
• To evaluate the efficacy of pola+R-CHP compared with R-CHOP with respect to exploratory endpoints	• PRO endpoints: All scales of the EORTC QLQ-C30, the FACT-Lym LymS, and FACT/GOG-NTX peripheral neuropathy [e]

Exploratory Biomarker Objective	
• To identify biomarkers that are predictive of response to pola (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to pola, are associated with susceptibility to developing adverse events, can provide evidence of pola activity, or can increase the knowledge and understanding of disease biology	• PFS, EFS_{eff}, PFS24, CR rate, OS, DFS, DOR, and PRO endpoints by exploratory biomarkers and molecular DLBCL prognostic subtypes such as cell-of-origin, DEL, and DHL/THL • ctDNA detectability in conjunction with FDG-PET response • ctDNA as a method of molecular disease detection • ctDNA identification of emerging resistance • Association of biomarkers (including molecular and proteomic subtypes and genomic profiles at baseline) with efficacy and/or adverse events associated with R-CHOP and pola+R-CHP treatment
Exploratory Health Status Utility Objective	
• To assess health status of patients treated with pola with R-CHP compared with R-CHOP	• Health status (EQ-5D-5L) [h]

ADA = anti-drug antibody; BICR = blinded independent central review; CR = complete response; ctDNA = circulating tumor DNA; DFS = disease-free survival; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EFS_{all} = event-free survival–all causes; EFS_{eff} = event-free survival–efficacy; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life–Core 30 questionnaire; EQ-5D-5L = EuroQol 5-Dimension, 5-Level questionnaire; FACT/GOG-NTX = Functional Assessment of Cancer Treatment/Gynecologic Oncology Group–Neurotoxicity; FACT-Lym LymS = Functional Assessment of Cancer Therapy–Lymphoma Lymphoma Subscale; FDG-PET = fluorodeoxyglucose positron emission tomography; IRF = Independent Review Facility; NCI = National Cancer Institute; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; PFS = progression-free survival; PFS24 = 2-year progression-free survival rate; PK = pharmacokinetic; PRO = patient-reported outcome; R-CHOP = rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHP = rituximab plus cyclophosphamide, doxorubicin, and prednisone.

[a] All analyses will be based on the investigator's assessment unless otherwise specified, using the Lugano Response Criteria for Malignant Lymphoma (Cheson et al. 2014).

[b] End of treatment is defined as all planned chemoimmunotherapy treatment only; should any radiotherapy be administered, end of treatment tumor assessment shall occur prior to initiating radiotherapy.

[c] Reffered to as PET-CT in results and outputs.

[d] These secondary endpoints are included in Protocol, Section 6.4.2 and are presented in detail in final SAP.

[e] Results of the exploratory PRO endpoint will not be presented in this Primary CSR.

[f] Safety and immunogenicity objectives will be non-key secondary endpoints.

[g] Exploratory analyses for pharmacokinetics are included in the PopPK and ER reports and will not be presented in this Primary CSR.

[h] Results of Health status (EQ-5D-5L) will not be presented in this Primary CSR.

Outcomes/endpoints

The primary and key secondary endpoints were tested in a hierarchical manner as detailed in the Statistical Methods section below. Endpoints for the study have been outlined in Table 7 above.

Assessment for disease response

The primary study endpoint was PFS as assessed by the investigator. Patients were assessed for disease response by the investigator using regular clinical and laboratory examinations and fluorodeoxyglucose positron emission tomography (FDG-PET; hereafter referred to as PET-CT) and dedicated computed tomography (CT) scans (magnetic resonance imaging [MRI] scan were performed if CT scans with contrast were contraindicated in the patient), according to the Lugano Response Criteria for Malignant Lymphoma.

PET-CT and dedicated CT scans were obtained at screening and 6-8 weeks after completion of study treatment. An interim assessment was obtained after Cycle 4 and including PET-CT and dedicated CT. If local practice prohibited obtaining both assessments after Cycle 4, PET-CT alone (preferred) or CT alone was obtained at this timepoint. During the follow-up period, CT scans (PET-CT also acceptable) were performed every 6 months (i.e., Months 6, 12, 18, and 24) until the end of Year 2 of follow-up (approximately 2.5 years after the first dose) in accordance with study (clinic) visits and included the neck (if involved at baseline), chest, abdomen, and pelvis. During Years 3, 4, and 5 of follow-up, CT scans (PET-CT acceptable) of sites of prior involvement were obtained every 12 months (at Months 36, 48, and 60). If disease in other areas were suspected, additional areas were imaged at all subsequent imaging assessments.

Response was evaluated at the end of study treatment, or sooner in the event a patient discontinued early. After completion of therapy, all patients were followed at clinic visits conducted every 3 months for 2 years, and then every 6 months until Month 60. At each visit up to the Year 5, Month 60 assessment (or until disease progression if it occurs before 5 years), assessments included but were not exhaustive to: physical examination, standard hematologic and biochemistry assessments, vital signs, and B-symptoms (i.e., weight loss, night sweats, or fever).

After 5 years, patients were followed only for survival and initiation of a new antilymphoma therapy (NALT) by telephone contact approximately every 6 months until study termination, patient withdrawal of consent or death. After disease progression, patients were followed by telephone contact for survival, applicable adverse event reporting, and initiation of a NALT.

While the primary efficacy endpoint was investigator-assessed PFS, tumor assessments were collected by an Independent Review Facility (IRF) for the key secondary endpoint of PET-CT CR rate at the end of treatment by the Lugano Response Criteria for Malignant Lymphoma.

Health status of patients

Information on health-related quality of life (HRQoL) and symptoms from self-reported questionnaires provided critical feedback about patients' well-being which were used to better understand the patient experience of treatment. These Patient-reported outcomes (PROs), important disease and treatment-related symptoms, as well as functioning, were assessed with the FACTLym LymS and EORTC QLQ-C30. In addition, peripheral neuropathy was assessed using the FACT/GOG-NTX, as it is a treatment-related effect common to both pola and vincristine. The FACT/GOG-NTX evaluated treatment-induced neurologic symptoms (including sensory, hearing, motor, and dysfunction) and consisted of 11 questions. The EQ-5D-5L was administered for the purpose of producing health utility scores for economic modeling.

Independent Data Monitoring Committee (iDMC)

An iDMC has been used to monitor patient safety and efficacy. Since protocol version 5, the rationale for iDMC was updated to reflect monitoring of only safety, no longer including efficacy.

Sample size

Sample Size of PFS in the Global Study

The planned enrolment for the global study was approximately 875 patients. Sample size considerations were based on the following assumptions:

- 1:1 randomization ratio in R-CHP + polatuzumab vedotin versus R-CHOP
- Planned enrolment for the global study was expected to complete in approximately 23 months
- A one-sided log-rank test
- 80% power at the 2.5% significance level
- A 31% reduction in the risk of disease progression, relapse, or death, i.e., the PFS hazard ratio of R-CHP + polatuzumab vedotin over R-CHOP is 0.69.
- PFS in the control arm follows a piece-wise exponential distribution, with the piece-wise hazard rate estimated using historical R-CHOP data

On the basis of this hazard rate assumption for the control arm and a hazard ratio of 0.69, the 3-year PFS rate was expected to improve from 62% (which was observed in the GOYA study among patients with IPI 2-5 who received R-CHOP) to 72%.

- An annual dropout rate of 5% assumed for both treatment arms

Based on these assumptions, approximately 228 investigator-assessed PFS events were needed to detect a hazard ratio of 0.69 in PFS (3-year PFS rate of 62% to 72%), with 80% power for the primary analysis of PFS. The minimal detectable difference (MDD) for the PFS hazard ratio at the primary PFS analysis was 0.771 (i.e., 22.9% reduction in the risk of disease progression, relapse, or death). The 3-year PFS was expected to improve from 62% to 70% under the MDD.

Sample Size of OS in the Global Study

Considerations of sample size for OS was also based on patients enrolled in the global study. A formal interim OS analysis was to be performed at the time of the primary PFS analysis only if the PFS efficacy boundary was crossed and the other secondary endpoints higher in the hierarchical order than OS had passed the corresponding significance levels. The sample size considerations were based on the following assumptions:

- 1:1 randomization ratio in R-CHP + polatuzumab vedotin versus R-CHOP
- A one-sided log-rank test
- A 27% reduction in the risk of death, i.e., the OS hazard ratio of R-CHP + polatuzumab vedotin over R-CHOP is 0.73
- OS in the control arm follows an exponential distribution with a hazard rate of 0.006923
- An annual dropout rate of 1.5% assumed for both treatment arms

Based on these assumptions, approximately 134 and 178 OS events was to be observed at the interim and the final OS analysis, respectively. The power for detecting a hazard ratio of 0.73 in OS at the final analysis was 52%, and the corresponding MDD for the OS hazard ratio was 0.74.

Sample Size for the Asia Subpopulation

After the global enrolment closes, additional Chinese patients are to be recruited into the China extension cohort for the purposes of registration in China. A total of approximately 150 Chinese patients are to be enrolled into the global study population and the China extension cohort combined.

Interim analysis

There were no planned interim analyses for PFS.

A formal OS interim analysis was to be performed at the time of the primary PFS analysis only if the PFS efficacy boundary was crossed and the other secondary endpoints higher in the hierarchical order than OS had passed the corresponding significance levels. OS was to be evaluated on the basis of the Haybittle-Peto boundary (Haybittle 1971) for statistical significance, with the alpha boundary at the interim specified as 0.001.

Randomisation

Patients will be randomised in a 1:1 ratio to receive either R-CHP + polatuzumab vedotin or R-CHOP. Both patients and the investigator will be blinded to the assigned active microtubule inhibitor (i.e., polatuzumab vedotin or vincristine) and placebo control.

During randomisation, permuted blocks will be employed using the following stratification factors:

- IPI score (IPI 2 versus IPI 3-5)
- Bulky disease, defined as one lesion ≥ 7.5 cm (present versus absent)
- Geographical region (Western Europe, United States, Canada, and Australia versus Asia versus Rest of World [remaining countries])

Blinding (masking)

This is a double-blind study.

Study site personnel (with the exception of unblinded pharmacists) and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, interactive voice or Web-based response system (IxRS) service provider, drug safety responsible, and iDMC members.

Because each patient will receive either polatuzumab vedotin or vincristine and the placebo form of the agent the patient is not assigned to, the IxRS will make the treatment assignment. The unblinded pharmacist will provide the active agent and the placebo agent according to the patient’s treatment assignment. The investigator will remain blinded to the treatment assignment.

While PK and anti-drug antibody (ADA) samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of this study. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patients' treatment assignments to identify appropriate samples to be analyzed. PK samples from patients assigned to the comparator arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline ADA samples will be analyzed for all patients. Post baseline ADA samples from patients assigned to the comparator arm will not be analyzed for ADAs except by request.

If unblinding is necessary for immediate patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in medical emergency situations.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any non-emergency unblinding. The investigator will be able to break the treatment code by contacting the IxRS.

As per health authority and applicable legislation reporting requirements, the Sponsor Drug Safety representative will break the treatment code for all serious, unexpected, suspected adverse reactions that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

Statistical methods

Analysis populations

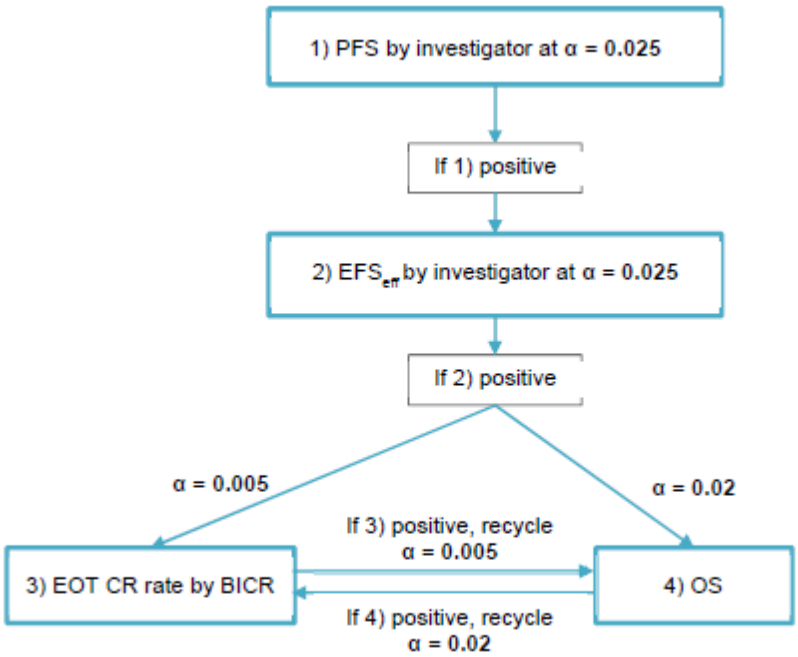
The ITT population is defined as all patients randomised during the global enrolment phase (including patients enrolled in mainland China during that phase), i.e., the global study, whether or not the patients received the assigned treatment. The global study is defined as the 879 patients randomised into the study on or before 27 June 2019. The ITT patients were analysed according to the treatment assigned at randomisation by the interactive voice/Web response system (IxRS). The ITT population was used for all efficacy analyses.

The China extension cohort is defined as patients from mainland China who were randomised after 27 June 2019. Patients randomised during the China extension phase are not be included in the ITT population; they are not included in the analyses in this report from the Primary CSR.

Multiplicity adjustment

To control the overall type I error rate at a one-sided 0.025 level of significance, a hierarchical testing procedure including possible α recycling was used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints. The test hierarchy and α spending plan for key secondary efficacy endpoints are described in the Figure 4 below:

Figure 19: Test hierarchy and alpha-spending plan for key secondary efficacy endpoints in POLARIX study



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

A formal OS interim analysis will be performed at the time of the primary PFS analysis only if the PFS efficacy boundary is crossed, and the other secondary endpoints higher in the hierarchical order than OS have passed the corresponding significance levels.

Given the low likelihood of OS crossing the boundary at the interim OS analysis, a Haybittle-Peto boundary (Haybittle 1971) is chosen with 0.001 at the interim as the nominal alpha value to control the type I error in the group sequential analysis of OS.

The remaining secondary endpoints were tested without adjusting for multiplicity.

Primary analysis

The primary efficacy endpoint is PFS, as determined by the investigator, defined as the time from the date of randomisation 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. For patients who have not progressed, relapsed, or died as of the clinical cutoff date for analysis, PFS is censored on the date of last disease assessment when the patient is known to be progression free. If no tumor assessments are performed after the baseline visit or all post-baseline tumor assessment results have overall responses of "not evaluable," PFS is censored on the date of randomisation. Censoring rules for PFS are also summarized in the Table 8 below.

Table 8: Censoring rules for PFS in the primary analysis (POLARIX study)

Scenario [1]	Date of Progression or Censoring	Status
No adequate[2] post-baseline assessment and no death	Randomization date	Censored
No death and no disease progression before data cutoff	Date of last adequate assessment before data cutoff	Censored
Withdrawal of treatment due to treatment toxicity, no death and no disease progression before data cutoff	Date of last adequate assessment before data cutoff	Censored
Withdrawal of treatment due to treatment toxicity, followed by disease progression or death	Date of earliest disease progression or death, before data cutoff	Event
New anti-cancer treatment[3] started due to efficacy reasons, followed by death or disease progression	Date of earliest disease progression or death, before data cutoff	Event[4,5]
New anti-cancer treatment[3] started due to efficacy reasons, no death or disease progression	Date of last adequate assessment before data cutoff	Censored[4,5]
New anti-cancer treatment[3] started due to non-efficacy reasons, followed by death or disease progression	Date of earliest disease progression or death, before data cutoff	Event[5]
New anticancer treatment[3] started due to non-efficacy reason, no death or disease progression	Date of last adequate assessment before data cutoff	Censored[5]
Death or disease progression following one or more consecutive missed assessments[6]	Date of earliest disease progression or death, before data cutoff	Event
One or more missed assessments followed by no adequate[2] assessments or death	Date of last adequate assessment before data cutoff	Censored

[1]Sensitivity analyses may be performed for other situations if significant imbalances between arms are observed.

[2]To be considered adequate, a tumor assessment not including PET should have CR, PR, SD and PD as outcome; and/or a tumor assessment including PET-CT should have CMR, PMR, NMR, or PMD using Lugano criteria. Assessments that are "unevaluable" and "not done" are considered not adequate.

[3]New anticancer treatment includes all non-protocol new anti-lymphoma treatment (NALT) for DLBCL. The protocol-permitted pre-planned radiotherapy will not be considered new anticancer treatment in any endpoint.

[4]In sensitivity analyses, the impact of NALT prior to PD due to efficacy reason will be assessed by discount method to investigate how the PFS results would have looked if the NALT was not available. More specifically, the time interval during which patients received NALT until the event or censoring time will be discounted at 10%, 30%, and 50% for both arms. Note that the primary analysis of PFS corresponds to a discount analysis with a discount rate of 0% on PFS time after NALT.

[5]As an additional sensitivity analysis to assess the overall impact of NALT, for patients who have taken NALT prior to or in the absence of subsequent death or disease progression, their PFS will be censored at the time of their last adequate tumor assessment before the first NALT.

[6]The impact of missing scheduled tumor assessments on PFS will be assessed by performing a sensitivity analysis based on the interval censoring analysis methods.

Treatment comparison were made using a one-sided level 0.025 stratified log-rank test.

The randomisation stratification factors to be used in the efficacy analyses were IPI score, bulky disease, and geographical region. They were obtained from the IxRS at the time of randomisation.

The Kaplan-Meier (KM) 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 were 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 1-year and 2-year rates were used to describe PFS in addition to the hazard ratio. Results from an unstratified analysis were also provided.

Key secondary analyses

Event-Free Survival - Efficacy Causes

EFS_{eff} is used to reflect EFS events that are primarily due to efficacy and will be defined as time from date of randomization to the earliest occurrence of any of the below listed events:

1. Disease progression/relapse

2. Death due to any cause

3. The primary efficacy reason determined by the investigator, other than disease progression/relapse, that leads to initiation of any non-protocol specified anti-lymphoma treatment (NALT)

4. If biopsy is obtained after treatment completion and is positive for residual disease regardless of whether NALT is initiated or not

For the third case above, the efficacy reason includes instances where a PET-CT scan, bone marrow test, CT/MRI, or physical finding is suggestive of residual disease; or instances where a biopsy confirms residual disease. EFS_{eff} event timing is at the time of the test or biopsy leading to NALT, rather than the date of NALT initiation.

For patients without the occurrence of any above cases (no EFS_{eff} event) at the time of analysis, EFS_{eff} was censored on the date of last tumour assessment when the patient was known to be progression-free. For patients who did not have post-baseline tumour assessments or all post-baseline tumour assessment results have overall responses of 'not evaluable', EFS_{eff} was censored on the date of randomization. Censoring rules for EFS_{eff} are also summarized in the Table 9 below.

Table 9: Censoring rules for EFS eff (POLARIX study)

Scenario	Date of Progression or Censoring	Status
No adequate[1] post-baseline assessment and no EFS_{eff} events[2] observed before data cutoff	Randomization date	Censored
No EFS_{eff} events observed before data cutoff	Date of last adequate assessment before data cutoff	Censored
Withdrawal of treatment due to treatment toxicity, no EFS_{eff} events observed before data cutoff	Date of last adequate assessment before data cutoff	Censored
Withdrawal of treatment due to treatment toxicity, followed by EFS_{eff} event	Date of earliest EFS_{eff} event before data cutoff	Event
New anticancer treatment[4] started due to non-efficacy reason[1], no EFS_{eff} event observed before data cutoff	Date of last adequate assessment before data cutoff	Censored
New anticancer treatment started due to non-efficacy reason[1], followed by EFS_{eff} event observed	Date of earliest EFS_{eff} event before data cutoff	Event
EFS_{eff} events observed following one or more consecutive missed INV assessments	Date of earliest EFS_{eff} event before data cutoff	Event
One or more missed assessments followed by no adequate INV assessments or EFS_{eff} events	Date of last adequate assessment before data cutoff	Censored

[1]To be considered adequate, a tumor assessment not including PET should have CR, PR, SD and PD as outcome; and/or a tumor assessment including PET-CT should have CMR, PMR, NMR, or PMD using Lugano criteria. Assessments that are "unevaluable" and "not done" are considered not adequate.

[2]EFS_{eff} events are defined above (Section 4.4.2.4).

[3]New anticancer treatment includes all non-protocol new anti-lymphoma treatment for DLBCL. The protocol-permitted pre-planned radiotherapy will not be considered new anticancer treatment in any endpoint.

[4]EFS_{all} considers this scenario as an event.

Treatment comparisons for EFS_{eff} were performed using the stratified log-rank test. KM methodology was used to estimate the EFS_{eff} distribution for each treatment arm and construct curves for the visual description of the difference between the treatment arms. Estimates of the treatment effect were expressed as hazard ratios using a stratified Cox proportional-hazards analysis, including 95% confidence intervals.

CR rate at end of treatment by PET-CT

CR rate at end of treatment by PET-CT by BICR or by the investigator is defined as the percentage of patients with CR at the end of treatment by PET-CT as determined by BICR or by investigator. Patients not meeting these criteria, including patients without the end-of-treatment tumor assessments or if their response at end of treatment is not evaluable, were considered non-CR patients.

An estimate of CR rate and its 95% CI were calculated with the Clopper-Pearson method for each treatment arm. The 95% CIs for the difference in CR rate between the two treatment arms was computed using the Wilson method (Wilson 1927). The CR rate was compared between the two arms using the CMH test stratified by the same factors used in the PFS primary analysis.

Overall Survival

OS is defined as the period from the date of randomization until the date of death from any cause. For patients who have not died at the clinical cutoff date for analysis, OS was censored on the last date when the patients were known to be alive, as documented by investigator. Patients who did not have post-baseline information were censored at the date of randomization. The duration of OS was analysed with the same methodologies as EFS_{eff}.

Sensitivity analyses

The ITT population was the primary population for all efficacy measures and was the only population examined for all sensitivity analyses.

1. Impact of missing scheduled tumour assessments on PFS

The impact of missing scheduled tumour assessments on PFS was assessed by performing a sensitivity analysis based on the interval censoring analysis methods. The PFS survival curves were estimated using the non-parametric maximum likelihood estimate (NPMLE) (Turnbull 1974) for each treatment arm. One-year and 2-year rates of each treatment arm will be reported and their 95% confidence intervals will be constructed based on the Greenwood method.

For descriptive purpose, hypothesis testing will be performed based on the log-rank test proposed by Sun (Sun 1996) to compare the PFS between the treatment arms. The treatment effect will be 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).

2. Impact of NALT prior to or in the absence of Progression on PFS

The impact of NALT prior to PD due to efficacy reason was assessed by discount method to investigate how the PFS results would have looked if the NALT was not available. More specifically, the time interval during which patients received NALT until the event or censoring time was discounted at 10%, 30%, and 50% for both arms. Note that the primary analysis of PFS corresponds to a discount analysis with a discount rate of 0% on PFS time after NALT.

An additional sensitivity analysis was also performed to assess the overall impact of NALT. For patients who have 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 tumour assessment before the first NALT.

3. Restricted Mean Survival Time Analysis on PFS and OS

The restricted mean survival time (RMST) (Royston and Parmar, 2011) method will be used as an additional sensitivity analysis to measure the difference in the average event-free survival time between treatment and control arm from the randomization through a pre-specified time point. Specifically, unstratified non-parametric KM estimate of RMST by arm as well as the difference of RMST between arms will be evaluated. The 95% confidence intervals (by Greenwood method) and p-values (by Z test) will be provided for descriptive purpose. The RMST of PFS and OS will be estimated at month 12, 24, and 36.

Subgroup analyses

To assess the consistency of the study results in subgroups defined by demographics (e.g., age, sex, and race/ethnicity), baseline prognostic characteristics (including but not limited to ECOG performance status, cell of origin determined by gene expression profiling, IPI, aaIPI, co-expression of BCL2 and MYC by immune histochemistry (IHC) [double-expressor lymphoma], and MYC and BCL2 and/or BCL6 translocations by FISH [high-grade B-cell lymphoma]), the duration of PFS in these subgroups was examined.

Changes to planned analyses

The study first patient enrolled was on 15 November 2017 and the data cut-off was on 28 June 2021.

There were 6 amendments to the study protocol. Protocol versions 5 and 6 included some changes to the planned analyses, as described below.

Table 10: Changes to planned analyses in protocol amendments

Protocol version	Changes to planned analyses
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. The rationale for iDMC was updated to reflect monitoring of only safety, no longer including efficacy.
Version 6 23 October 2020	Main changes involved updates to the timing of the primary analysis, the secondary efficacy analysis and the overall survival interim and final analyses The hierarchical testing procedure, including possible α recycling that will be used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints, was updated. The timing of the primary analysis was updated to occur when there are approximately 228 PFS events, and after all patients in the global study have been enrolled for at least 24 months, whichever comes later (vs when there are 236 PFS events in previous versions). The number of PFS events is 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 diffuse large B-cell lymphoma (DLBCL), most disease relapse occurs within this time frame. Other changes involve updates to the secondary efficacy analysis and the overall survival interim and final analyses. The timing of the Asian subpopulation analysis is clarified to occur no earlier than the primary analysis of the global cohort.

The first version of the statistical analysis plan (SAP) was finalised on 18 June 2020, with two subsequent revisions on 9 September 2020 (version 2) and 12 October 2020 (version 3). All three SAP version were therefore finalised while the study was ongoing but prior to data cut-off.

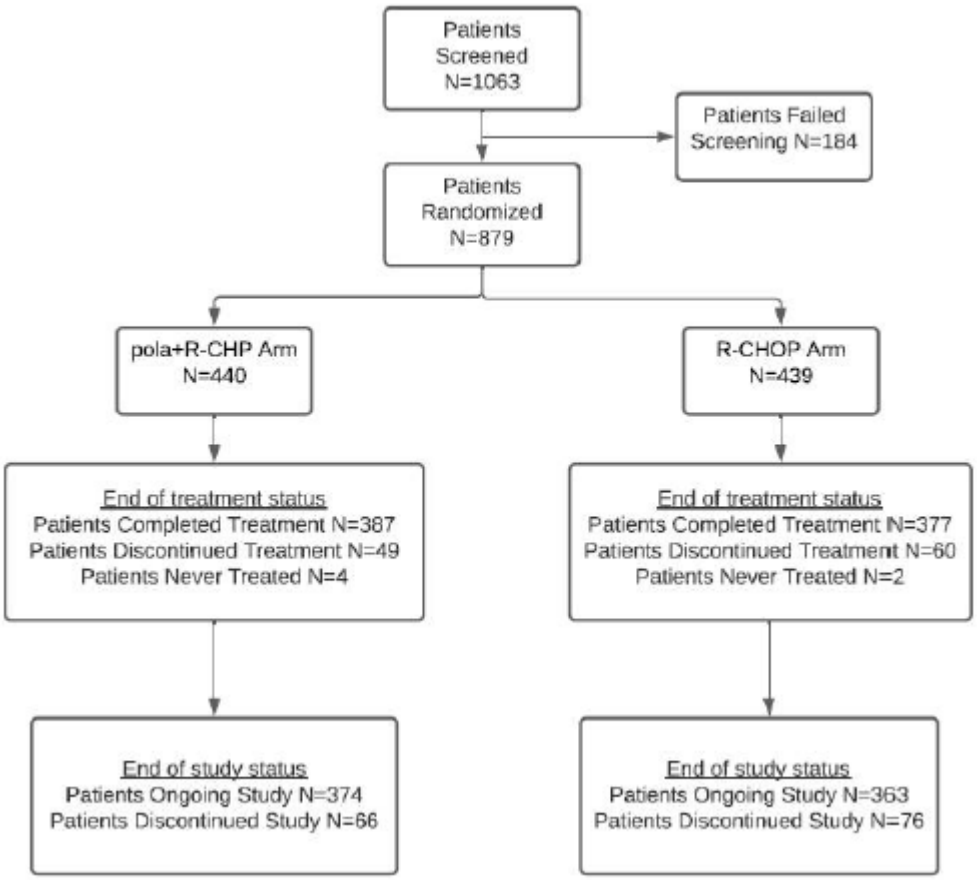
Updates to the SAP include:

- Censoring tables have been edited to clarify the efficacy analysis of PFS and event-free survival for efficacy causes (EFS_{eff}).
- EFS_{all} will be analyzed using the same methods as PFS because both endpoints will be evaluated in the ITT population.
- For time-to-event endpoints where the median survival time will not expect to be reached, 1-year and 2-year rates will be reported.

- The immunogenicity analysis population has been updated to be including all enrolled patients who have at least one serum ADA assessment.

Results

Participant flow



As of the CCOD (clinical cutoff date, 28-Jun-2021), 764 patients (86.9%) had completed treatment. A total of 737 patients (83.8%) were still on study, and 142 patients (16.2%) had discontinued the study. The most frequent reason for patients discontinuing the study was due to death (12.3%).

At the time of CCOD, 109 patients (12.4%) had discontinued from treatment (i.e. prior to completing all planned treatment cycles); 60 patients (13.7%) in the R-CHOP arm and 49 patients (11.1%) in the pola+R-CHP arm (Table 11):

Table 11: Summary of Study Drug Discontinuation (safety evaluable population)

Summary of Study Drug Discontinuation, Safety-Evaluable Patier
Protocol: GO39942

	R-CHOP (N=438)	Pola+R-CHP (N=435)	Total (N=873)
Discontinued polatuzumab vedotin/placebo			
n	49	35	84
Adverse event	19 (4.3%)	9 (2.1%)	28 (3.2%)
Death	3 (0.7%)	10 (2.3%)	13 (1.5%)
Other	4 (0.9%)	0	4 (0.5%)
Physician decision	5 (1.1%)	6 (1.4%)	11 (1.3%)
Progressive disease	10 (2.3%)	6 (1.4%)	16 (1.8%)
Withdrawal by subject	8 (1.8%)	4 (0.9%)	12 (1.4%)
Discontinued vincristine/placebo			
n	49	35	84
Adverse event	19 (4.3%)	9 (2.1%)	28 (3.2%)
Death	3 (0.7%)	10 (2.3%)	13 (1.5%)
Other	4 (0.9%)	0	4 (0.5%)
Physician decision	5 (1.1%)	6 (1.4%)	11 (1.3%)
Progressive disease	10 (2.3%)	6 (1.4%)	16 (1.8%)
Withdrawal by subject	8 (1.8%)	4 (0.9%)	12 (1.4%)
Discontinued rituximab			
n	61	48	109
Adverse event	16 (3.7%)	9 (2.1%)	25 (2.9%)
Death	4 (0.9%)	11 (2.5%)	15 (1.7%)
Other	3 (0.7%)	0	3 (0.3%)
Physician decision	13 (3.0%)	9 (2.1%)	22 (2.5%)
Progressive disease	16 (3.7%)	12 (2.8%)	28 (3.2%)
Withdrawal by subject	9 (2.1%)	7 (1.6%)	16 (1.8%)
Discontinued doxorubicin			
n	41	30	71
Adverse event	11 (2.5%)	4 (0.9%)	15 (1.7%)
Death	3 (0.7%)	10 (2.3%)	13 (1.5%)
Other	4 (0.9%)	0	4 (0.5%)
Physician decision	5 (1.1%)	6 (1.4%)	11 (1.3%)
Progressive disease	10 (2.3%)	6 (1.4%)	16 (1.8%)
Withdrawal by subject	8 (1.8%)	4 (0.9%)	12 (1.4%)
Discontinued cyclophosphamide			
n	41	30	71
Adverse event	11 (2.5%)	4 (0.9%)	15 (1.7%)
Death	3 (0.7%)	10 (2.3%)	13 (1.5%)
Other	4 (0.9%)	0	4 (0.5%)
Physician decision	5 (1.1%)	6 (1.4%)	11 (1.3%)
Progressive disease	10 (2.3%)	6 (1.4%)	16 (1.8%)
Withdrawal by subject	8 (1.8%)	4 (0.9%)	12 (1.4%)
Discontinued prednisone/prednisolone/methylprednisolone			
n	43	30	73
Adverse event	12 (2.7%)	4 (0.9%)	16 (1.8%)
Death	3 (0.7%)	10 (2.3%)	13 (1.5%)
Other	3 (0.7%)	0	3 (0.3%)
Physician decision	6 (1.4%)	6 (1.4%)	12 (1.4%)
Progressive disease	10 (2.3%)	6 (1.4%)	16 (1.8%)
Withdrawal by subject	9 (2.1%)	4 (0.9%)	13 (1.5%)

CCOD: 28JUN2021 Data Extract Date: 02AUG2021

Compliance with Treatment and Treatment Delays

A high proportion of patients (91.7% [399 patients] receiving pola as part of the pola+RCHP regimen and 88.5% [386 patients] receiving vincristine as part of the R-CHOP regimen) completed the planned 6 cycles of study treatment. The median number of cycles of pola or vincristine received was 6.0 and the median relative dose intensity was 99.8% for pola and 100.0% for vincristine. The median treatment duration for both pola and vincristine was as expected (3.5 months).

Overall, no differences between treatment arms were observed in regards to CHP treatment. The median duration of exposure to CHP (cyclophosphamide, doxorubicin, and prednisone) was balanced between treatment arms. Approximately 90% of patients in each treatment arm received 6 cycles of CHP treatment, corresponding to a median of 3.5 to 3.6 months of treatment

A total of 10.1% (44 patients) in the pola+R-CHP arm and 8.4% (37 patients) in the R-CHOP arm had a treatment delay of >7 days in at least one treatment cycle. The percentage of patients who had more than 1 treatment cycle delayed by >7 days was the same in each arm (0.9% [4 patients]).

Recruitment

Of the 1063 patients screened, 879 patients were randomized into the study and 184 patients failed screening based on information collected in the IxRS. The first patient was randomized on 15 November 2017. The last patient was randomized on 27 June 2019.

The main reasons for screen failure were patients not meeting the following inclusion criteria: IPI score of 2-5 (29 patients), availability of archival or freshly collected tumor tissue before study enrollment (28 patients) and provision of signed written ICF (21 patients).

A total of 879 patients were enrolled at 211 sites in 22 countries, in 3 regions. The top recruiting geographical region in descending order were:

- Western Europe/US/Canada/Australia (603 patients [Australia, Austria, Belgium, Canada, Switzerland, Germany, Spain, France, UK, Italy, US]).
- Asia (160 patients [China, Japan, South Korea and Taiwan]).
- Rest of the World (116 patients [Brazil, Czech Republic, New Zealand, Poland, Russian Federation, Turkey, Ukraine]).

Conduct of the study

Protocol Amendment

The original global protocol dated 18 July 2017 was amended six times.

The key changes to the protocol are summarized below in Table 12.

Table 12: Summary of Select Key Changes to the Protocol

Document Version, Protocol Amendment, 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.
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 α 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. Additonally, 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

Protocol deviations

Major protocol deviations were reported under the following four categories: inclusion criteria, exclusion criteria, procedural and medication. Protocol deviations of interest were chosen on the basis of being considered likely to have had a direct impact on data important for interpretation of the study results (including efficacy and patient safety).

Overall, 50/879 patients (5.7%) had at least one protocol deviation of interest. The most frequently reported major protocol deviations of interest were: exclusion criteria not met (1.9%), followed by non-compliance with study drug treatment modification (tx mod) or stoppage rules (either temporary or permanent) (0.9%), accidental unblinding of a subject or subjects (0.8%), and incorrect subject kit given/administered (0.7%).

Table 13: 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%)

CCOD: 28JUN2021 Data Extract Date: 02AUG2021

Baseline data

Table 14: Demographics and Baseline Characteristics (ITT Population)

		R-CHOP (N= 439)	Pola+R-CHP (N=440)	Total (N= 879)
Age (years)	n	439	440	879
	Mean (SD)	63.01 (11.87)	63.11 (11.36)	63.06 (11.61)
	Median	66.00	65.00	65.00
	25%, 75%	59.00, 71.00	58.00, 71.00	58.00, 71.00
	Min - Max	19.0 – 80.0	19.0 - 80.0	19.0 - 80.0
	18-64	203 (46.2%)	209 (47.5%)	412 (46.9%)
	≥65	236 (53.8%)	231 (52.5%)	467 (53.1%)
	18-60	131 (29.8%)	140 (31.8%)	271 (30.8%)
	>60	308 (70.2%)	300 (68.2%)	608 (69.2%)
Sex	n	439	440	879
	Female	205 (46.7%)	201 (45.7%)	406 (46.2%)
	Male	234 (53.3%)	239 (54.3%)	473 (53.8%)
Race	n	439	440	879
	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 America	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%)
	Unknown	100 (22.8%)	105 (23.9%)	205 (23.3%)
	Other	6 (1.4%)	6 (1.4%)	12 (1.4%)
Ethnicity	n	439	440	879
	Hispanic or Latino	30 (6.8%)	18 (4.1%)	48 (5.5%)
	Not Hispanic or Latino	306 (69.7%)	317 (72.0%)	623 (70.9%)
	Not Stated	49 (11.2%)	66 (15.0%)	115 (13.1%)
	Unknown	54 (12.3%)	39 (8.9%)	93 (10.6%)

Weight (kg) at Baseline	n	436	437	873
	Mean (SD)	76.12 (18.68)	75.92 (20.07)	76.02 (19.38)
	Median	75.0	74.4	74.5
	25%, 75%	63.0, 85.0	61.6, 87.0	62.5, 86.4
	Min, Max	39.8 – 191.1	38.4 – 227.9	38.4 – 227.9
Height (cm) at Baseline	n	436	438	874
	Mean (SD)	167.73 (10.34)	168.18 (10.16%)	167.95 (10.25)
	Median	168.0	167.8	168.0
	25%, 75%	160.0, 175.0	161.0, 175.0	160.0, 175.0
	Min, Max	141.3 – 200.0	144.3 – 200.0	141.3 – 200.0
ECOG Performance Status at Baseline	n	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	n	439	440	879
	I	9 (2.1%)	2 (0.5%)	11 (1.3%)
	II	43 (9.8%)	45 (10.2%)	88 (10.0%)
	III	108 (24.6%)	124 (28.2%)	232 (26.4%)
	IV	279 (63.6%)	269 (61.1%)	548 (62.3%)
Stratification - IPI Score (IxRS)	n	439	440	879
	IPI 2	167 (38.0%)	167 (38.0%)	334 (38.0%)
	IPI 3-5	272 (62.0%)	273 (62.0%)	545 (62.0%)
IPI at Screening (eCRF)	n	439	440	879
	1	0	1 (0.2%)	1 (0.1%)
	2	165 (37.6%)	164 (37.3%)	329 (37.4%)
	3	156 (35.5%)	174 (39.5%)	330 (37.5%)
	4	96 (21.9%)	76 (17.3%)	172 (19.6%)
	5	22 (5.0%)	25 (5.7%)	47 (5.3%)

Stratification - Bulky Disease (IxRS)	n	439	440	879
	Absent	247 (56.3%)	247 (56.1%)	494 (56.2%)
	Present	192 (43.7%)	193 (43.9%)	385 (43.8%)
Baseline Bulky Disease (eCRF)	n	439	440	879
	No	244 (55.6%)	247 (56.1%)	491 (55.9%)
	Yes	195 (44.4%)	193 (43.9%)	388 (44.1%)
Stratification - Geographic Region (IxRS)	n	439	440	879
	Asia	79 (18.0%)	81 (18.4%)	160 (18.2%)
	Rest of World	59 (13.4%)	57 (13.0%)	116 (13.2%)
	Western Europe/US/Canada/Australia	301 (68.6%)	302 (68.6%)	603 (68.6%)
Baseline LDH	n	438	437	875
	≤ 1xULN	154 (35.1%)	146 (33.2%)	300 (34.1%)
	.> 1x ULN	284 (64.7%)	291 (66.1%)	575 (65.4%)
Bone Marrow Involvement at Diagnosis	n	432	429	861
	Indeterminate	11 (2.5%)	11 (2.5%)	22 (2.5%)
	Positive	72 (16.4%)	76 (17.3%)	148 (16.8%)
	Negative	349 (79.5%)	342 (77.7%)	691 (78.6%)
No. of Extranodal Sites	n	439	440	879
	0-1	226 (51.5%)	227 (51.6%)	453 (51.5%)
	≥ 2	213 (48.5%)	213 (48.4%)	426 (48.5%)
Time from Diagnosis to Study Dose (days)	n	437	436	873
	Mean (SD)	33.02 (35.74)	29.99 (21.46)	31.51 (29.51)
	Median	27.00	26.00	27.00
	25th-75th	19.00 - 41.00	16.00 - 37.50	17.00 - 39.00
	Min - Max	1.0 - 621.0	1.0 - 195.0	1.0 - 621.0

NHL Histologic Diagnosis (eCRF)	n	439	440	879
	DLBCL, NOS, ABC, GCB	367 (83.6%)	373 (84.8%)	740 (84.2%)
	HGBL, NOS, DHL/THL	50 (11.4%)	43 (9.8%)	93 (10.6%)
	Other Large B-cell	22 (5.0%)	24 (5.5%)	46 (5.2%)
COO (Central Review)	n	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%)
Double-Expressor Lymphoma by IHC (Central Review)	n	366	362	728
	DEL	151 (41.3%)	139 (38.4%)	290 (39.8%)
	NON DEL	215 (58.7%)	223 (61.6%)	438 (60.2%)
Double/Triple-Hit Lymphoma (Central Review)	n	334	331	665
	DH/TH+	19 (5.7%)	26 (7.9%)	45 (6.8%)
	DH/TH-	315 (94.3%)	305 (92.1%)	620 (93.2%)

COO = cell-of-origin; DEL = double-expressor lymphoma; DH =double-hit; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; IHC = immunohistochemistry; IPI = International Prognostic Index; IxRS = interactive voice or Web-based response system; LDH = Lactate dehydrogenase; NHL = non-hodgkins lymphoma; TH = triple-hit; SD = standard deviation

Note: There was one patient in pola+R-CHOP recorded with IPI "1". This was a data entry error per eCRF and the patient was actually randomized as IPI "2".
Note: NHL Histologic Diagnosis (eCRF) are by local diagnosis/lab

By gene expression profiling, 25.1% of patients had ABC like DLBCL, 40.0% of patients had GCB like DLBCL, 10.8% were unclassified and 24.0% were unknown.

Prior Disease

All patients (100%) in the ITT population had at least one medical history condition (pola+R-CHP and R-CHOP arms). The most common medical history by SOC (≥30% in either arm) were: Metabolism and nutrition disorders (47.6% pola+R-CHP vs 51.1% R-CHOP), Vascular disorders (48.5% vs 48.9), Gastrointestinal disorders (47.4% vs 45.7%), Musculoskeletal and connective tissue disorders (37.9% vs 35.4%). Patient medical history reported in the ITT population was reflective of the expected medical comorbidities of this patient population, primarily associated with median age 65-66 years, and were generally well balanced between the arms with regard to system organ class (SOC) and individual medical history conditions.

Prior and concomitant therapy

Concomitant medication was defined as any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/discontinuation visit.

All patients (100%) in the ITT population received at least one concomitant medication (pola+R-CHP and R-CHOP arms).

The most frequently used types of concomitant medication (ATC level 1, ≥90% in either arm) were: Alimentary tract and metabolism (97.5% pola+R-CHP vs 97.5% R-CHOP), Dermatologicals (95.4% vs 95.9%), Antineoplastic and immunomodulating agents (94.0% vs 96.1%), Nervous system (93.1% vs 93.4%), Respiratory system (91.0% vs 92.5%).

The majority of patients in the ITT population received at least one prior concomitant medication (84.1%, pola+R-CHP vs 86.5% R-CHOP).

Pre-phase steroid treatment was received by 37.7% of patients in the pola+R-CHP arm and 38.6% of patients in the R-CHOP arm within 7 days prior to Cycle 1 Day 1 (C1D1).

Concomitant GCSF was received by 92.9% of patients in the pola+R-CHP arm and 95.2% of patients in the R-CHOP arm. Concomitant GCSF for prophylaxis use was received by 90.1% of patients in the pola+R-CHP arm and 93.2% of patients in the R-CHOP arm.

Concomitant medication for anti-infective prophylaxis use were received by 61.6% of patients in the pola+R-CHP arm and 57.1% of patients in the R-CHOP arm.

Concomitant medication related to AEs were received by 91.5% of patients in the pola+R-CHP arm and 87.2% of patients in the R-CHOP arm.

Numbers analysed

Table 15: Analysis Population

	R-CHOP (N)	Pola+R-CHP (N)	Total (N)
Intent-to-Treat	439	440	879
Safety-evaluable	438	435	873
Number of patients received any dose of pola	0	435	435
Number of patients received any dose of vincristine	436	0	436

For each biomarker analyzed, the biomarker-evaluable population was defined as all randomized patients in the global study who have a valid baseline assessment for that specific biomarker. The PRO-evaluable

population included all randomized patients in the global study who had a baseline and at least one post-baseline assessment.

Outcomes and estimation

Primary Efficacy Endpoint: Investigator-Assessed Progression-Free Survival

Table 16: Investigator-Assessed PFS (ITT Population)

	R-CHOP (N=439)		Pola+R-CHP (N=440)
Patients with event (%)	134 (30.5%)		107 (24.3%)
Earliest contributing event			
Death	20		19
Disease Progression	114		88
Patients without event (%)	305 (69.5%)		333 (75.7%)
Time to event (months)			
Median	NE		33.3
95% CI	NE		(33.3, NE)
25% and 75%-ile	15.8 - NE		25.4 - NE
Range	0* - 37*		0* - 34*
Stratified Analysis			
p-value (log-rank)		0.0177	
Hazard Ratio		0.73	
95% CI		(0.57, 0.95)	
Unstratified Analysis			
p-value (log-rank)		0.0326	
Hazard Ratio		0.76	
95% CI		(0.59, 0.98)	
6 months duration			
Patients remaining at risk	389		404
Event Free Rate (%)	92.73		93.76
95% CI	(90.27, 95.20)		(91.49, 96.04)
Difference in Event Free Rate		1.03	
95% CI		(-2.33, 4.38)	
12 months duration			
Patients remaining at risk	330		353
Event Free Rate (%)	79.77		83.91
95% CI	(75.92, 83.61)		(80.43, 87.39)
Difference in Event Free Rate		4.14	
95% CI		(-1.05, 9.32)	
18 months duration			
Patients remaining at risk	296		327
Event Free Rate (%)	73.45		79.84
95% CI	(69.21, 77.69)		(76.03, 83.65)
Difference in Event Free Rate		6.39	
95% CI		(0.69, 12.09)	
24 months duration			
Patients remaining at risk	220		246

	R-CHOP (N=439)		Pola+R-CHP (N=440)
Event Free Rate (%)	70.20		76.71
95% CI	(65.80, 74.61)		(72.65, 80.76)
Difference in Event Free Rate		6.50	
95% CI		(0.52, 12.49)	
30 months duration			
Patients remaining at risk	78		78
Event Free Rate (%)	65.92		72.39
95% CI	(60.81, 71.02)		(67.57, 77.22)
Difference in Event Free Rate		6.48	
95% CI		(-0.55, 13.50)	
36 months duration			
Patients remaining at risk	3		NE
Event Free Rate (%)	61.83		NE
95% CI	(54.52, 69.13)		NE
Difference in Event Free Rate		NE	
95% CI		NE	

* Censored observation.
Summaries of Progression Free Survival by Investigator (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Hazard ratios were estimated by Cox regression. Stratification Factors: Geographical Region, IPI Score, Bulky Disease Defined as One Lesion >= 7.5 cm.
CCOD: 28JUN2021 Data Extract Date: 02AUG2021

Figure 20: Kaplan-Meier Plot of Time to Investigator-Assessed PFS (ITT Population)

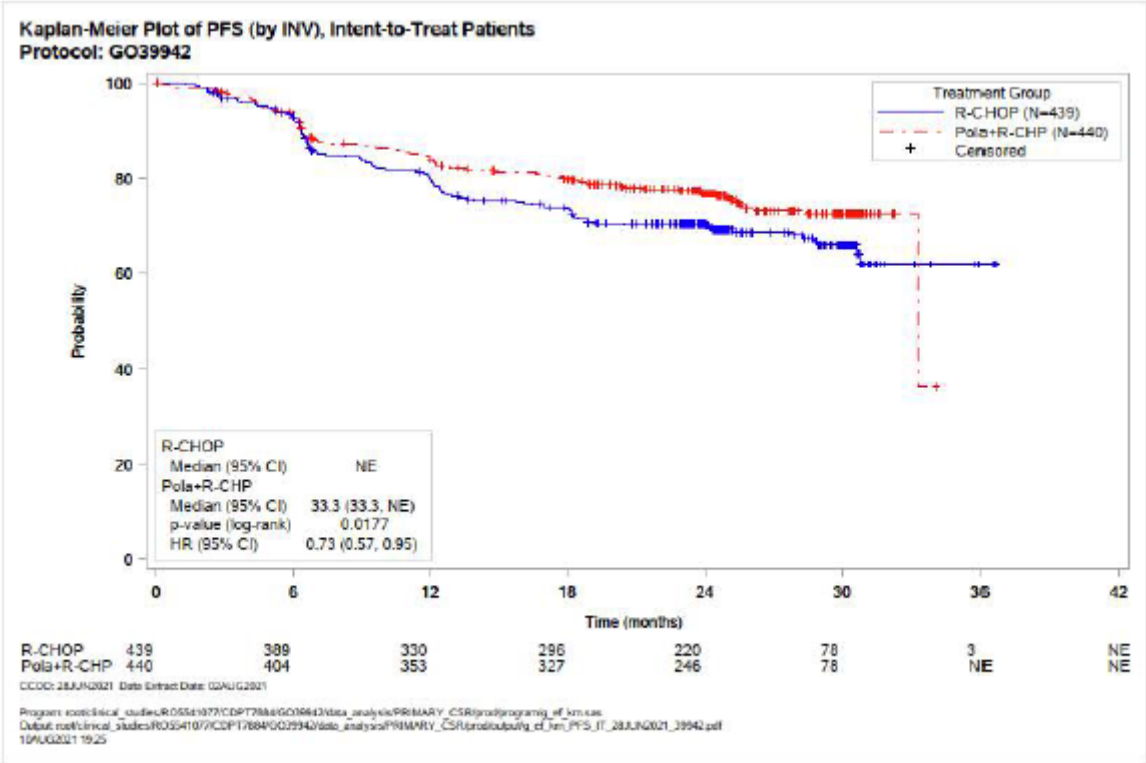


Table 17: Censoring Rules for Primary Analysis of Investigator-Assessed PFS: Patient Count (ITT Population)

Scenario[1]	Date of Progression or Censoring	Status	R-CHOP (N= 439)	Pola+R-CHP (N= 440)
Number of patients with:				
No adequate[2] post-baseline assessment and no death	Randomization date	Censored	7 (1.6%)	5 (1.1%)
No death and no disease progression before data cutoff	Date of last adequate assessment before data cutoff	Censored	298 (67.9%)	328 (74.5%)
Withdrawal of treatment due to nonefficacy reason, no death and no disease progression before data cutoff	Date of last adequate assessment before data cutoff	Censored	10 (2.3%)	4 (0.9%)
Withdrawal of treatment due to non-efficacy reason, followed by disease progression or death	Date of earliest disease progression or death, before data cutoff	Event	6 (1.4%)	4 (0.9%)
New anti-cancer treatment[3] started due to efficacy reasons, followed by death or disease progression	Date of earliest disease progression or death, before data cutoff	Event[4,5]	4 (0.9%)	3 (0.7%)
New anti-cancer treatment[3] started due to efficacy reasons, no death or disease progression	Date of last adequate assessment before data cutoff	Censored[4,5]	2 (0.5%)	5 (1.1%)
New anti-cancer treatment[3] started due to non-efficacy reasons, followed by death or disease progression	Date of earliest disease progression or death, before data cutoff	Event[5]	13 (3.0%)	6 (1.4%)
New anti-cancer treatment[3] started due to non-efficacy reason, no death or disease progression	Date of last adequate assessment before data cutoff	Censored[5]	29 (6.6%)	19 (4.3%)
Death or disease progression following one or more consecutive missed assessments[6]	Date of earliest disease progression or death, before data cutoff	Event	1 (0.2%)	4 (0.9%)
One or more missed assessments followed by no adequate[2] assessments or death	Date of last adequate assessment before data cutoff	Censored	20 (4.6%)	14 (3.2%)

1. Impact of missing scheduled tumour assessments on PFS

The impact of missing scheduled tumor assessments on PFS, and the fact that the actual timing of PFS events usually cannot be observed exactly was assessed by performing a sensitivity analysis based on interval censoring analysis method. The result of the analysis was consistent with the result of the primary

PFS analysis, and showed a higher reduction in the risk of PFS events for patients treated with pola+R-CHP compared with patients treated with R-CHOP. Stratified HR was 0.75 (95% CI: 0.58, 0.96) in favor of pola+R-CHP treatment.

2. Impact of NALT prior to or in the absence of Progression on PFS

The impact of initiation of NALT prior to or in the absence of subsequent death or disease progression was assessed by performing sensitivity analyses by discount method, and by censoring PFS at the last adequate tumor assessment before the initiation of NALT. Results from these analyses were consistent with the result of analysis of the primary endpoint indicating that there was minimal impact of NALT prior to PD on the PFS results.

Stratified HRs for PFS, after discounting time after the initiation of NALT by 10%, 30%, and 50% for both arms, were:

– 10% discount: 0.73 (95%CI: 0.57, 0.95) favoring pola+R-CHP treatment

– 30% discount: 0.73 (95% CI: 0.57, 0.95) favoring pola+R-CHP treatment

– 50% discount: 0.73 (95% CI: 0.57, 0.94) favoring pola+R-CHP treatment

Stratified HR for PFS censored at the last adequate tumor assessment before the initiation of NALT was 0.77 (95% CI: 0.59, 1.01) favoring pola+R-CHP treatment.

3. Restricted Mean Survival Time Analysis on PFS and OS

The difference in the average event-free survival time between treatment and control arm from randomization to 12, 24 and 36 months after randomization was assessed using restricted mean survival time (RMST) method to provide an alternative measure of treatment effect to the hazard ratio. RMST estimates suggested that patients treated with pola+R-CHP had longer mean PFS duration than patients treated with R-CHOP.

Mean survival time at various milestones (pola+R-CHP vs. R-CHOP) were:

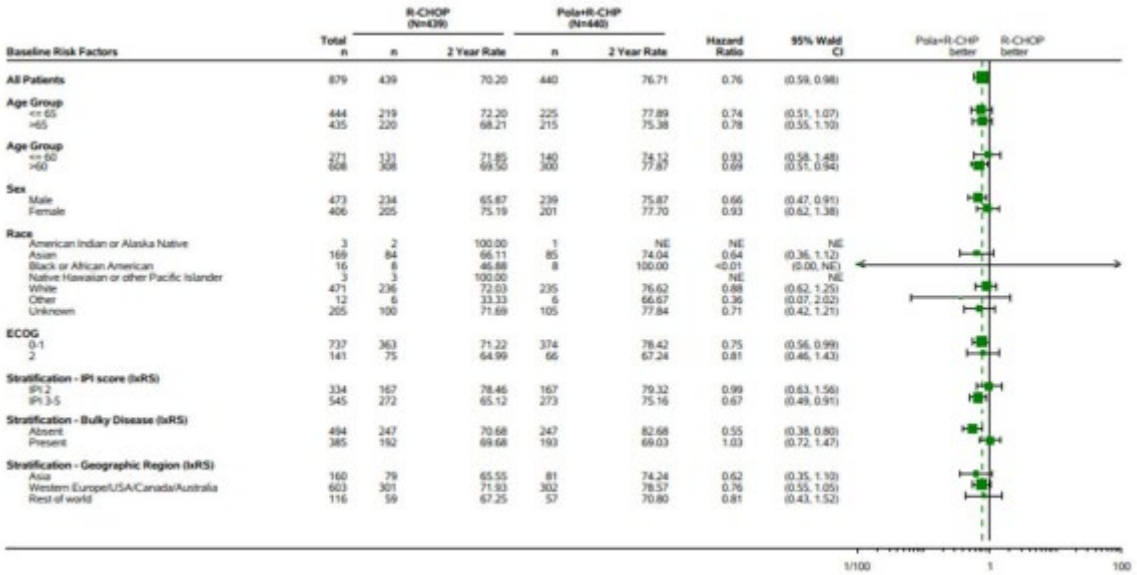
- 12 months: 11.1 months vs. 10.9 months (treatment difference= 0.2 [95% CI: -0.1, 0.5] favoring pola+R-CHP treatment)
- 24 months: 20.6 months vs. 19.6 months (treatment difference= 1.0 [95% CI: 0.1, 2.0] favoring pola+R-CHP treatment)
- 36 months: 28.4 months vs. 27.4 months (treatment difference= 1.0 [95% CI: -1.2, 3.1] favoring pola+R-CHP treatment. Please note that, since the median PFS follow-up was 24.7 months in both arms, the 36 month RMST estimates were not mature and is subject to change with longer follow-up.

<u>Subgroup Analyses of Investigator-Assessed Progression-Free Survival</u>

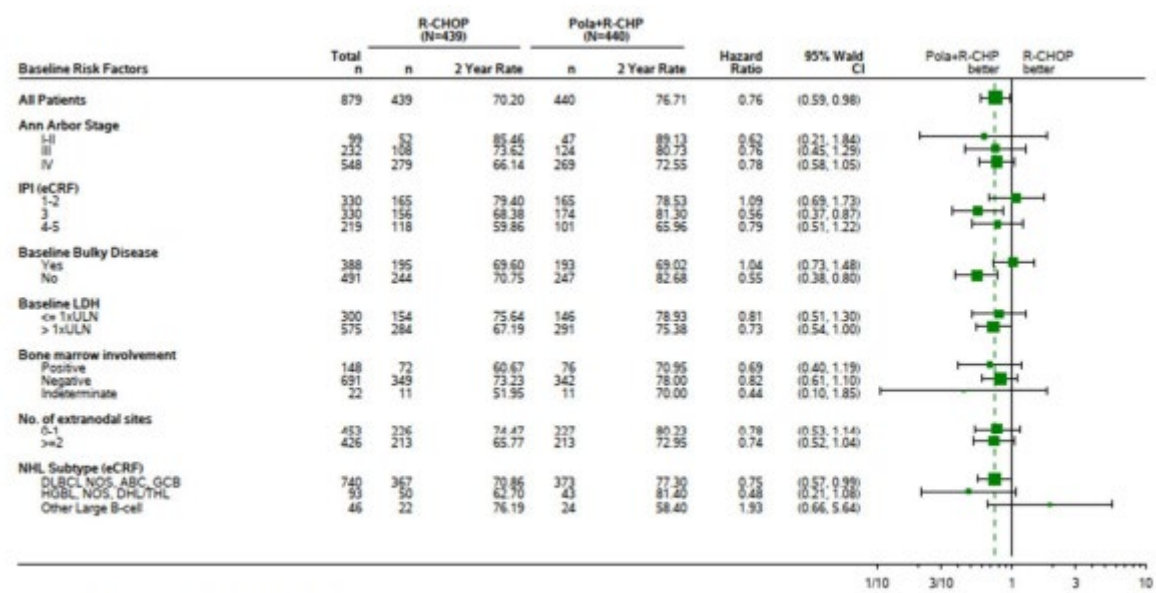
There was a directionally consistent treatment effect supporting the PFS benefit of pola+R-CHP in the majority of subgroups (HR <1), and all 95% CIs for HR in the major subgroups (with sample size > 100) include 0.73, i.e., the estimated stratified HR in the ITT population.

Given the known limitations of exploratory subgroup analyses (Wang et al, 2007; Alosh et al, 2016), results should not be over interpreted and there is no statistical evidence for heterogeneity of treatment effect in any of the subgroups.

Figure 21: Forest Plot of Hazard Ratio of Investigator-Assessed PFS by Baseline Risk Factors (ITT Population)



Unstratified hazard ratio is displayed.
CCOD: 28JUN2021 Data Extract Date: 02AUG2021



Unstratified hazard ratio is displayed.
CCOD: 28JUN2021 Data Extract Date: 02AUG2021

Secondary Efficacy Endpoint: Investigator-Assessed Event-Free Survival for Efficacy Reasons

EFSeff was defined as the time from the date of randomization to the earliest occurrence of disease progression/relapse, death, biopsy that is positive for residual disease after treatment completion, or start of a NALT due to efficacy reasons. A higher proportion of patients in the R-CHOP arm received NALT (30.3%) compared to pola+R-CHP arm (22.5%).

At the time of the CCOD, 112 patients (25.5%) in the pola+R-CHP arm, and 138 patients (31.4%) in the R-CHOP arm had an EFS event. Results of the secondary endpoint EFSeff, were statistically significant and highly consistent with results of the primary endpoint of investigator-assessed PFS and was supportive of the clinical benefit for pola+R-CHP compared with R-CHOP. A statistically significant reduction by 25% in the risk of an EFSeff event was observed in the pola+R-CHP arm compared with the R-CHOP arm (stratified HR: 0.75 [95% CI: 0.58, 0.96], two-sided p-value = 0.0244, two-sided α=0.05; Table 18). Median EFSeff estimates were not considered mature for either treatment arm as of the CCOD.

Table 18: EFSeff (ITT population)

Time to Event Summary for EFSeff (by INV), Intent-to-Treat Patients
Protocol: GO39942

	R-CHOP (N=439)		Pola+R-CHP (N=440)
Patients with event (%)	138 (31.4%)		112 (25.5%)
Earliest contributing event			
Death	20		18
Disease Progression	106		86
NALT due to efficacy reasons or positive biopsy	12		8
Patients without event (%)	301 (68.6%)		328 (74.5%)
Time to event (months)			
Median	NE		33.3
95% CI	NE		(33.3, NE)
25% and 75%-ile	13.2 - NE		24.9 - NE
Range	0* - 37*		0* - 34*
Stratified Analysis			
p-value (log-rank)		0.0244	
Hazard Ratio		0.75	
95% CI		(0.58, 0.96)	
6 months duration			
Patients remaining at risk	386		402
Event Free Rate (%)	91.57		93.30
95% CI	(88.94, 94.21)		(90.94, 95.66)
Difference in Event Free Rate		1.73	
95% CI		(-1.81, 5.26)	
12 months duration			
Patients remaining at risk	327		348
Event Free Rate (%)	78.67		82.52
95% CI	(74.76, 82.58)		(78.93, 86.12)
Difference in Event Free Rate		3.85	
95% CI		(-1.46, 9.17)	
18 months duration			
Patients remaining at risk	294		323
Event Free Rate (%)	72.62		78.70
95% CI	(68.35, 76.89)		(74.81, 82.58)
Difference in Event Free Rate		6.07	
95% CI		(0.30, 11.85)	
24 months duration			
Patients remaining at risk	218		243
Event Free Rate (%)	69.39		75.57

95% CI	(64.96, 73.81)		(71.46, 79.69)
Difference in Event Free Rate		6.19	
95% CI		(0.14, 12.23)	
30 months duration			
Patients remaining at risk	78		78
Event Free Rate (%)	65.14		71.31
95% CI	(60.03, 70.24)		(66.46, 76.16)
Difference in Event Free Rate		6.17	
95% CI		(-0.87, 13.21)	
36 months duration			
Patients remaining at risk	3		NE
Event Free Rate (%)	61.09		NE
95% CI	(53.84, 68.35)		NE
Difference in Event Free Rate		NE	
95% CI		NE	

* Censored observation.
Summaries of Event Free Survival (Efficacy) by Investigator (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratios were estimated by Cox regression. Stratification Factors: Geographical Region, IPI Score, Bulky Disease Defined as One Lesion >= 7.5 cm.
Event timing will be at the time of the test or biopsy leading to NALT, rather than the date of the NALT initiation.
CCOD: 28JUN2021 Data Extract Date: 02AUG2021

Secondary Efficacy Endpoint: New anti-lymphoma treatment

NALT could be administered after the patient had completed study treatment, and included both radiotherapy or systemically administered therapies. NALT was allowed to be administered with or without a disease progression documented in the patient. Follow-up anti-lymphoma treatments is described in Table 19.

Table 19: Follow-up Anti-Lymphoma Treatments (ITT Population)

	R-CHOP (N=439)	Pola+R-CHP (N=440)	Total (N=879)
Total number of patients with at least one NALT treatment	133 (30.3%)	99 (22.5%)	232 (26.4%)
Total number of NALT treatments	290	179	469
Total number of patients with at least one NALT treatment before PFS event	16 (3.6%)	7 (1.6%)	23 (2.6%)
Total number of patients with at least one NALT treatment after PFS event	93 (21.2%)	64 (14.5%)	157 (17.9%)
Total number of patients with at least one NALT treatment and without PFS event	31 (7.1%)	29 (6.6%)	60 (6.8%)
Radiotherapy			
Total number of patients with at least one treatment	57 (13.0%)	41 (9.3%)	98 (11.1%)
Total number of treatments	73	42	115
Total number of patients with pre-planned treatment	18 (4.1%)	11 (2.5%)	29 (3.3%)
Total number of patients with unplanned treatment	39 (8.9%)	30 (6.8%)	69 (7.8%)
Systemic therapy			
Total number of patients with at least one treatment	103 (23.5%)	75 (17.0%)	178 (20.3%)
Total number of treatments	217	137	354
Total number of patients received stem cell transplants	31 (7.1%)	17 (3.9%)	48 (5.5%)
Autologous transplant	30 (6.8%)	17 (3.9%)	47 (5.3%)
Allogeneic transplant	1 (0.2%)	0	1 (0.1%)
Total number of patients received CAR-T	16 (3.6%)	9 (2.0%)	25 (2.8%)

NALT includes pre-planned radiotherapy.
CCOD: 28JUN2021 Data Extract Date: 02AUG2021

In addition, 8 patients received pola as a NALT (either alone or in combination) in the R-CHOP arm, and no patients in the pola+R-CHP arm received pola as NALT.

Secondary Efficacy Endpoint: BICR-Assessed Complete Response Rate at End of Treatment (by PET-CT)

At the end of the treatment, BICR-assessed CR rate was high in both arms. A numerically higher proportion of patients treated with pola+R-CHP had complete response at the end of treatment compared to patients treated with R-CHOP (78.0% [95% CI: 73.79, 81.74] vs. 74.0% [95% CI: 69.66, 78.07]; Table 20). The treatment difference was 3.9% (95% CI: -1.9, 9.7) and was not statistically significant (two-sided p-value = 0.1557, two-sided α boundary of 0.01).

Table 20: Summary of BICR-Assessed CR Rate at EOT (ITT Population)

	R-CHOP (N=439)	Pola+R-CHP (N=440)
Complete Responders	325 (74.0%)	343 (78.0%)
95% CI	(69.66, 78.07)	(73.79, 81.74)
Stratified Analysis		
Difference in response rate (95% CI)	3.92 (-1.89, 9.70)	
p-value (Cochran-Mantel-Haenszel)	0.1557	

Stratification factors include IPI, bulky disease, and geographic region.
95% CI for rate are constructed using the Clopper-Pearson method. 95% CI for difference in response rates are constructed using Wilson method.
CCOD: 28JUN2021 Data Extract Date: 02AUG2021

In addition, concordance between BICR and Investigator assessments of CR was high (88.7%) and was balanced between treatment arms (88.9% vs. 88.6%; Table 21).

Table 21: Summary of Concordance Between BICR- and Investigator-Assessed CR Status at EOT by PET-CT (ITT Population)

	R-CHOP (N=439)	Pola+R-CHP (N=440)	Total (N=879)
Number of patients evaluable for concordance	422	422	844
CR Concordance			
Concordance	374 (88.6%)	375 (88.9%)	749 (88.7%)
CR per investigator and CR per BICR	297 (79.4%)	313 (83.5%)	610 (81.4%)
No CR per investigator and no CR per BICR	77 (20.6%)	62 (16.5%)	139 (18.6%)
CR Discordance			
Discordance	48 (11.4%)	47 (11.1%)	95 (11.3%)
CR per investigator and no CR per BICR	20 (41.7%)	17 (36.2%)	37 (38.9%)
No CR per investigator and CR per BICR	28 (58.3%)	30 (63.8%)	58 (61.1%)

CCOD: 28JUN2021 Data Extract Date: 02AUG2021

Secondary Efficacy Endpoint: Overall Survival

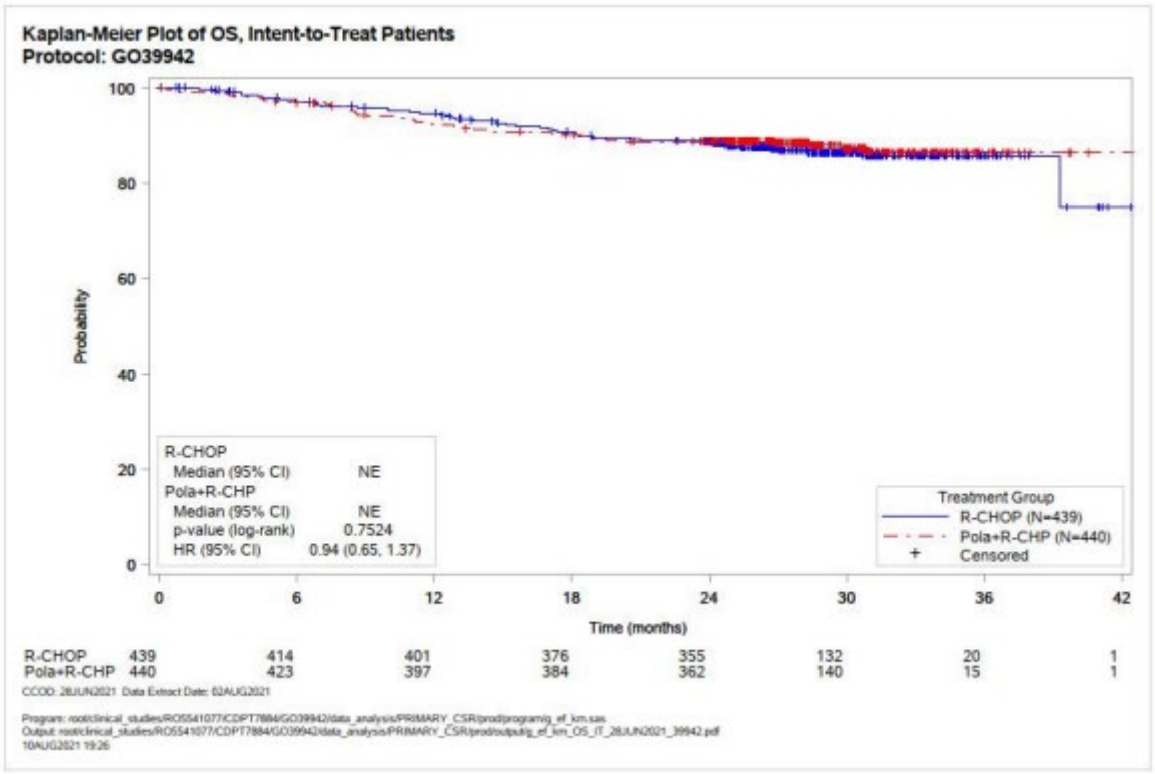
The frequency of OS events (deaths) were low in both arms (Table 22). A total of 53 deaths (12.0% patients) were reported in the pola+R-CHP arm, and 57 deaths (13.0% patients) were reported in the R-CHOP arm. With very few events in both arms, OS results were still immature at the time of the interim analysis of OS and did not meet the pre-specified threshold for statistical significance (stratified HR: 0.94 [95% CI: 0.65, 1.37]; two-sided log-rank p-value = 0.7524, two-sided α boundary= 0.002). The unstratified analysis of OS showed results similar to the stratified analysis. A KM curve is shown in Figure 7. Milestone OS results for the pola+R-CHP arm and the R-CHOP arm were 92.2% and 94.6% at 1 year, and 88.7% and 88.6% at 2 years, respectively.

Table 22: Summary of OS (ITT Population)

	R-CHOP (N=439)		Pola+R-CHP (N=440)
Patients with event (%)	57 (13.0%)		53 (12.0%)
Earliest contributing event			
Death	57		53
Patients without event (%)	382 (87.0%)		387 (88.0%)
Time to event (months)			
Median	NE		NE
95% CI	NE		NE
25% and 75%-ile	39.3 - NE		NE
Range	0* - 42*		0* - 43*
Stratified Analysis			
p-value (log-rank)		0.7524	
Hazard Ratio		0.94	
95% CI		(0.65, 1.37)	
Unstratified Analysis			
p-value (log-rank)		0.6720	
Hazard Ratio		0.92	
95% CI		(0.63, 1.34)	
6 months duration			
Patients remaining at risk	414		423
Event Free Rate (%)	96.97		96.80
95% CI	(95.35, 98.59)		(95.16, 98.45)
Difference in Event Free Rate		-0.17	
95% CI		(-2.48, 2.14)	
12 months duration			
Patients remaining at risk	401		397
Event Free Rate (%)	94.62		92.17
95% CI	(92.48, 96.76)		(89.64, 94.70)
Difference in Event Free Rate		-2.45	
95% CI		(-5.76, 0.86)	
18 months duration			
Patients remaining at risk	376		384
Event Free Rate (%)	90.79		90.07
95% CI	(88.03, 93.54)		(87.25, 92.89)
Difference in Event Free Rate		-0.72	
95% CI		(-4.66, 3.23)	
24 months duration			
Patients remaining at risk	355		362
Event Free Rate (%)	88.61		88.66
95% CI	(85.57, 91.64)		(85.67, 91.65)
Difference in Event Free Rate		0.05	
95% CI		(-4.21, 4.31)	
30 months duration			
Patients remaining at risk	132		140
Event Free Rate (%)	86.31		87.25
95% CI	(82.89, 89.73)		(83.89, 90.61)
Difference in Event Free Rate		0.94	
95% CI		(-3.86, 5.73)	
36 months duration			
Patients remaining at risk	20		15
Event Free Rate (%)	85.58		86.46
95% CI	(81.90, 89.26)		(82.79, 90.13)
Difference in Event Free Rate		0.88	
95% CI		(-4.32, 6.07)	

* Censored observation.
Summaries of Overall Survival (median, percentiles) are Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley.
Hazard ratios were estimated by Cox regression. Stratification Factors: Geographical Region, IPI Score, Bulky Disease Defined as One Lesion >= 7.5 cm.
CCOD: 28JUN2021 Data Extract Date: 02AUG2021

Figure 22: Kaplan-Meier Plot of Time to OS (ITT Population)



Others Secondary Efficacy Endpoints relative to response rates assessment:

Investigator-Assessed Complete Response Rate at End of Treatment (by PET-CT)

Investigator-assessed CR rates were high, and comparable to BICR-assessed CR rates (Section 5.1.3.2) in both arms. At the end of treatment, 75.0% (95% CI: 70.68, 78.98) patients in the pola+R-CHP arm, and 72.2% (95% CI: 67.76, 76.35) patients in the R-CHOP arm had complete response as assessed by the Investigator (Table 21). The difference in CR rate between the pola+R-CHP arm and the R-CHOP arm was 2.79 (95% CI: -3.20, 8.75). This analysis was not formally tested.

Investigator-Assessed Objective Response Rate at End of Treatment

At the end of treatment, a high proportion of patients achieved Investigator-assessed ORR (i.e. CR or PR) in both arms (84.5% [95% CI: 80.82, 87.79] vs. 80.9% [95% CI: 76.87, 84.44]), with patients in the pola+R-CHP arm achieving a better response in terms of ORR compared to patients in the R-CHOP arm (treatment difference=3.68% [95% CI: -1.49, 8.84]).

BICR-Assessed Objective Response Rate at End of Treatment

Similar to the Investigator-assessed ORR (Section 5.1.3.5), a high proportion of patients achieved BICR-assessed ORR (i.e. CR or PR) in both arms at the end of treatment (85.5% [95% CI: 81.81, 88.61] vs. 83.8% [95% CI: 80.04, 87.15]). Treatment difference between the pola+R-CHP arm and the R-CHOP arm was 1.63% (95% CI: -3.32, 6.57).

Investigator-Assessed Best Overall Response Rate

Investigator-assessed BOR revealed high response rates (i.e. best response of CR or PR while on study) in both the pola+R-CHP arm (95.9% [95% CI: 93.61, 97.56]) and the R-CHOP arm (94.1% [95% CI: 91.44,

96.10]). Best CR rate as of the CCOD was 86.6% (95% CI: 83.05, 89.63) in the pola+R-CHP arm and 82.7% (95% CI: 78.82, 86.11) in the R-CHOP arm.

Secondary Efficacy Endpoint: Investigator-Assessed Duration of Response

DOR was defined as the time from the date of the first occurrence of a documented clinical response (CR or PR) to the date of progression, relapse, or death from any cause for the subgroup of patients with a BOR of CR or PR, all assessed by the investigator.

Of the patients who achieved a best overall response of CR or PR, 94 patients (22.3%) in the pola+R-CHP arm, and 116 patients (28.1%) in the R-CHOP arm had subsequent disease progression or death. In patients who achieved CR or PR, treatment with pola+R-CHP reduced the risk of progression or death by 26% compared to R-CHOP treatment (stratified HR: 0.74 [95% CI: 0.56, 0.98]). The favorability of the pola+R-CHP treatment compared to R-CHOP treatment in DOR suggests that even though response rates are high in both treatment arms, response was more durable in the pola+R-CHP arm. KM curves for DOR started to separate at approximately 5 months after the first response in favor of the pola+R-CHP arm, and remained separated for the duration of the study (section 5.1.3.8 of the CSR). Milestone DOR results for the pola+R-CHP arm and the R-CHOP arm were 83.8% and 78.2% at 1 year, and 75.7% and 71.7% at 2 years, respectively, after first response.

Investigator-Assessed Disease-Free Survival

DFS was 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 with a BOR of CR, all assessed by the investigator.

A lower proportion of patients in the pola+R-CHP arm progressed or died subsequent to achieving a CR, compared to patients in the R-CHOP arm (62 patients [16.3%] vs. 79 patients [21.8%]). In patients who achieved CR, treatment with pola+R-CHP reduced the risk of progression or death by 30% compared to treatment with R-CHOP (stratified HR: 0.70 [95% CI: 0.50, 0.98]). The favorability of the

Pola+R-CHP arm compared to the R-CHOP arm in DFS suggests that even though CR was high in both treatment arms, remission status was more durable in the pola+R-CHP arm.

KM curves began to separate at approximately 6 months after randomization in favor of pola+R-CHP, and the separation was maintained for the duration of follow-up (section 5.1.3.9 of the CSR).

Milestone DFS results for the pola+R-CHP arm and the R-CHOP arm were 90.1% and 83.4% at 1 year, and 81.8% and 77.4% at 2 years after first CR, respectively.

Investigator-Assessed Progression-Free Survival Rate at 24 Months After Randomization

A higher proportion of patients in the pola+R-CHP arm remained alive and progression-free 24 months after randomization. The estimated 2-year investigator-assessed PFS was 76.7% in patients treated with pola+R-CHP compared to 70.2% in patients treated with R-CHOP (absolute difference of 6.5% [95% CI: 0.52, 12.5]). This analysis was not formally tested.

Investigator-Assessed Event-Free Survival-All Causes

EFSall differs from EFSeff, and was defined as the time from randomization to disease progression or relapse, as determined by the investigator, death from any cause, or initiation of any NALT. A higher proportion of patients in the R-CHOP arm received NALT (30.3%) compared to pola+R-CHP arm (22.5%).

The results for EFSall was consistent with the results for EFSeff. At the time of CCOD, 133 patients (30.2%) in the pola+R-CHP arm, and 165 patients (37.6%) in the R-CHOP arm had an EFSall event. The risk of an EFSall event was reduced by 27% following pola+R-CHP treatment compared to R-CHOP treatment (stratified HR: 0.73 [95% CI: 0.58, 0.92]). This analysis was not formally tested.

Secondary Efficacy Endpoint: Patient-Reported Outcomes

Completion rates of all questionnaires were high (≥95%) at baseline in both arms, and remained ≥80% at each subsequent timepoint.

Responder analysis

- Physical functioning

Patients in both arms showed high levels of physical functioning at baseline (mean: 80.04 vs. 80.55) with scores improving over time. As of the CCOD, a higher proportion of patients in the pola+R-CHP arm (42.4% [95% CI: 37.56, 47.30]) experienced clinically meaningful improvement in physical functioning, i.e. ≥7-point increase, as measured by EORTC QLQ-C30 physical functioning scale compared to the R-CHOP arm (39.6% [95% CI: 34.81, 44.47]). The difference in response rates between pola+R-CHP and R-CHOP treatments was 2.81 (95% CI: -4.06, 9.64).

- Fatigue

Patients in both arms reported fatigue at baseline (mean: 37.32 vs. 35.11). As of the CCOD, the proportion of patients experiencing a clinically meaningful improvement in fatigue (i.e. ≥9-point decrease, as measured by EORTC QLQ-C30 fatigue scale) was higher in the pola+R-CHP arm compared to the R-CHOP arm (74.8% [95% CI: 70.34, 78.93] vs. 68.2% [63.47, 72.68], treatment difference= 6.61 [95% CI: 0.28, 12.88]).

- Lymphoma symptoms

Patients in both arms reported lymphoma symptoms at baseline (mean: 44.7 vs. 45.3).

As of the CCOD, the proportion of patients experiencing a clinically meaningful improvement in lymphoma symptoms (i.e. a ≥3-point increase per FACT-Lym LymS) was high and comparable between treatment arms (82.3% [95% CI: 78.30, 85.88] vs. 81.3% [95% CI: 77.20, 84.96], treatment difference = 1.01 (95% CI: -4.43, 6.45)).

Time to Deterioration Analysis

- Physical functioning

A total of 183 patients (41.6%) in the pola+R-CHP arm, and 187 patients (42.6%) in the R-CHOP arm had a clinically meaningful deterioration (i.e. ≥10-point decrease) from baseline in physical functioning as of the CCOD. No difference in the risk of deterioration of physical functioning was observed between arms (stratified HR: 0.97 [95% CI: 0.79, 1.19]). The median time to clinically meaningful deterioration in physical functioning was not reached in the pola+R-CHP arm and was 25.5 months in the R-CHOP arm. Results of unstratified analysis was similar to the results of stratified analysis. Deterioration event-free rates in the pola+R-CHP arm and the R-CHOP arm were 57.0%, and 56.6%, respectively at 1 year and 54.9% and 53.3%, respectively at 2 years.

- Fatigue

Patients in the R-CHOP arm experienced clinically meaningful deterioration in fatigue (i.e. ≥ 10-point increase in fatigue scale from baseline) earlier (median TTD: 3.0 months) than patients in the pola+R-CHP arm (6.7 months). As of the CCOD, a total of 223 patients (50.7%) in the pola+R-CHP arm, and 230 patients (52.4%) in the R-CHOP arm had a clinically meaningful deterioration in fatigue scores (stratified HR: 0.94 [95% CI: 0.78, 1.13]). Results of unstratified analysis was similar to the results of stratified analysis. Deterioration event-free rates in the pola+R-CHP arm and the R-CHOP arm were 48.8%, and 44.1%, respectively at 1 year, and 45.2% and 41.8%, respectively at 2 years.

- Lymphoma symptoms

As of the CCOD, a total of 148 patients (33.6%) in the pola+R-CHP arm, and 138 patients (31.4%) in the R-CHOP arm had a clinically meaningful deterioration in lymphoma symptom (i.e. a ≥3-point decrease from baseline). No difference in the risk of deterioration of lymphoma scores was observed between arms (stratified HR: 1.03 [0.81, 1.30]). Results of unstratified analyses was similar to the results of stratified analysis.

Medians were not reached in either arm. Deterioration event-free rates in the pola+R-CHP arm and the R-CHOP arm were 66.4%, and 68.0%, respectively at 1 year, and 63.5% and 64.0%, respectively at 2 years.

- Fever

A total of 74 patients (16.8%) in the pola+R-CHP arm, and 73 patients (16.6%) in the R-CHOP arm had a clinically meaningful deterioration in fever score. No difference in the risk of deterioration of fever score was observed between arms (stratified HR: 0.94 [0.68, 1.30]). Results of unstratified analysis was similar to the results of stratified analysis. Medians were not achieved in either arm. Deterioration event-free rates in the pola+R-CHP arm and the R-CHOP arm were 84.1%, and 83.2%, respectively at 1 year, and 81.0% and 81.5%, respectively at 2 years.

- Weight loss

A total of 161 patients (36.6%) in the pola+R-CHP arm, and 161 patients (36.7%) in the R-CHOP arm had a clinically meaningful deterioration in weight loss score. No difference in the risk of deterioration of weight loss score was observed between arms (stratified HR: 0.97 [0.78, 1.20]). Results of unstratified analysis was similar to the results of stratified analysis. Medians were not achieved in either arm. Deterioration event-free rates in the pola+R-CHP arm and the R-CHOP arm were 60.8%, and 63.1%, respectively at 1 year, and 58.8% and 58.7%, respectively at 2 years.

- Night sweats

A total of 101 patients (23.0%) in the pola+R-CHP arm, and 119 patients (27.1%) in the R-CHOP arm had a clinically meaningful deterioration in night sweat score. Treatment with pola+R-CHP reduced the risk of deterioration of night sweat score by 22% compared to R-CHOP (stratified HR: 0.78 [0.60, 1.02]). Results of unstratified analysis was similar to the results of stratified analysis. Medians were not achieved in either arm, however KM plots separated approximately 4 months after randomization and the separation was maintained throughout the duration of follow-up. Deterioration event-free rates in the pola+R-CHP arm and the R-CHOP arm were 76.9%, and 74.2%, respectively at 1 year, and 74.8% and 68.9%, respectively at 2 years.

Secondary Efficacy Endpoint: Treatment-Related Symptoms and Peripheral Neuropathy

EORTC QLQ-C30 treatment-related symptom and the FACT/GOG-Ntx peripheral neuropathy scores between treatment arms were compared using mixed effects model for repeated measures.

- Treatment-Related Symptoms

While on treatment, a small improvement in scores for constipation was observed in the pola+R-CHP arm compared to the R-CHOP arm (range of mean change from baseline: -4.9 to -7.6 vs. -1.1 to -5.3). A small increase in diarrhea scores in the pola+R-CHP arm compared to the R-CHOP arm was observed at Cycle 2 (mean change from baseline: 6.3 vs. -0.02), however subsequent scores improved (range of mean change from baseline: 1.2 to 1.6 vs. -0.6 to 0.1). Scores for nausea and vomiting were very low at baseline (mean [SE]: 8.4 [0.916] vs. 6.2 [0.722]), and no difference was observed while on treatment (range of mean change from baseline: 1.7 to 1.7 vs. -0.1 to 1.2). Any increase observed was reversed by treatment completion.

- Peripheral Neuropathy

Both arms showed low levels of peripheral neuropathy at baseline (baseline mean [SE]: 39.8 [0.221] vs. 39.5 [0.248]). The possible range for the scores is 0–44 for this subscale, with higher scores representative of lower levels of peripheral neuropathy. Patients in the R-CHOP arm experienced increases in peripheral neuropathy earlier (Cycle 4; mean change from baseline: pola+R-CHP: -0.5 vs. R-CHOP: -1.5) than patients in the pola+R-CHP arm (Cycle 6; -2.0 vs. -2.9). In addition, timepoints subsequent Cycle 4 showed larger increases in peripheral neuropathy (i.e. larger decreases in the mean scores) for R-CHOP (range of mean change from baseline: -2.2 to -3.5) than for pola+R-CHP (-1.0 to -2.7) while on treatment.

Ancillary analyses

Biomarker Analyses

Methods

The cell-of-origin (COO) status of individual patients was determined by the Nanostring Lymphoma Subtyping (LST) (Scott et al. 2014; Scott et al. 2015) assay using RNA extracted from baseline formalin fixed paraffin embedded (FFPE) tissue samples/slides performed centrally at Expression Analysis.

Baseline protein expression of BCL2 and MYC in tumor cells was assessed centrally by immunohistochemistry (IHC) assays at Ventana (ex-China) or Roche Oncology Biomarker Development (OBD) China lab (for patients enrolled in mainland China only) using the analytically validated BCL2 (124) mAB and MYC (Y69) IHC assays on the Ventana Benchmark XT platform. BCL2+ was defined as ≥50% tumor cells with moderate (IHC 2+) or strong (IHC 3+) staining intensity. MYC+was defined as ≥ 40% tumor nuclei with positive MYC staining at any intensity above background staining (Punnoose et al 2020; Morschhauser et al 2021).

Gene translocations involving BCL2, BCL6, and MYC (dual translocations in BCL2 or BCL6 and MYC [DHL]; or triple translocations in BCL2, BCL6 and MYC [THL]) defined specific DLBCL subgroups with particularly poor outcomes using SoC therapies. In POLARIX, translocations involving these three genes were determined using baseline FFPE tissue slides by florescent in-situ hybridization (FISH) assay performed centrally at Histogenix (ex-China) or KingMed (for patients enrolled in mainland China only).

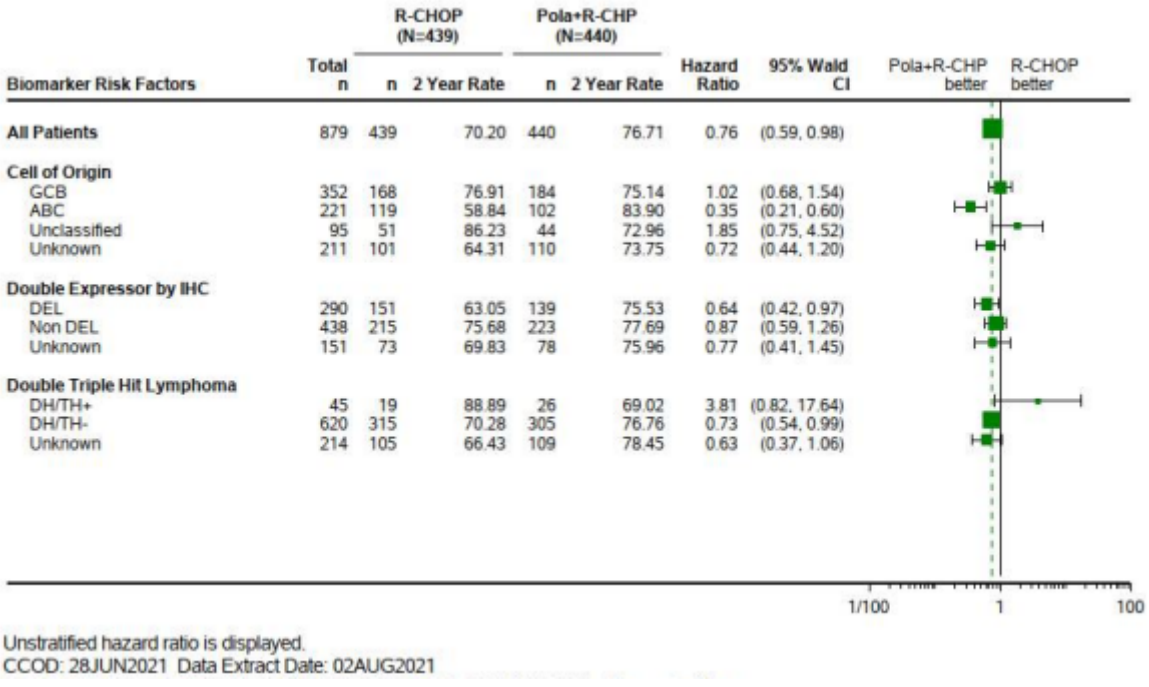
The translocation status of individual genes was evaluated for at least 50 tumor nuclei within the tumor region as annotated by a pathologist on the HE reference slide.

Negative cutoff values for individual FISH assay are determined by the vendors using tonsil samples from healthy donors. Given that BCL6 translocation mainly occurs concurrently with MYC translocation (Scott et al 2018), BCL6 FISH assay was performed only in patients with positive MYC translocation results (not performed in patients from mainland China).

Results

Exploratory analyses of unstratified Investigator-assessed PFS in subgroups by baseline molecular DLBCL subtypes (by centrally tested COO, centrally tested IHC for BCL2 and MYC [DEL], and centrally tested FISH for rearrangements in MYC, BCL2, and BCL6 [DHL/THL]) were performed (Figure 8). Treatment with pola+R-CHP resulted in numerically higher PFS over R-CHOP among patients in some of the more commonly represented high risk patient subgroups: • for the ABC-DLBCL subgroup, the 2-year investigator-assessed PFS rate was 83.9% in the pola+R-CHP arm vs. 58.8% in the R-CHOP arm (HR: 0.35 [95% CI: 0.21, 0.60]) • for the DEL subgroup, the 2-year investigator-assessed PFS rate was 75.5% in the pola+R-CHP arm vs. 63.1% in the R-CHOP arm (HR: 0.64 [95% CI: 0.42, 0.97]). The numbers of patients in the DH+/TH+ subgroup (pola+R-CHP: 26 patients, R-CHOP: 19 patients), and PFS events identified in the DH/TH+ subgroup are too small to make a meaningful assessment.

Figure 23: Forest Plot of Hazard Ratio of Investigator-Assessed PFS by Molecular DLBCL Subtypes (ITT Population)



The observed investigator-assessed progression free survival (PFS) hazard ratio was 0.48 [95% CI: 0.21-1.08] in patients with HGBL.

Summary of main study(ies)

The following table summarises the efficacy results from the main studies supporting the present

application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 23: Summary of Efficacy for trial POLARIX

Title: A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing the Efficacy and Safety of Polatuzumab Vedotin in Combination with Rituximab and CHP (R-CHP) versus Rituximab and CHOP (R-CHOP) in Previously Untreated Patients with Diffuse Large B-Cell Lymphoma.			
Study identifier	Study GO39942 (POLARIX)		
Design	Phase III, multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of polatuzumab vedotin in combination with R-CHP versus R-CHOP in previously untreated patients with diffuse large B-cell lymphoma		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		65 months after the first patient enrolled not applicable Chinese extension cohort (until a total of approximately 150 patients)
Hypothesis	Superiority		
Treatments groups	group descriptor		pola+R-CHP (n=440): pola was administered by IV infusion at 1.8 mg/kg on Day 1 of each 21-day cycle for 6 cycles; R-CHP and placebo for vincristine was administered concurrently every 21 days for each 21-day cycle. Rituximab was administered as monotherapy in Cycle 7 and Cycle 8.
	group descriptor		R-CHOP (n=439) was administered on Day 1 of each 21-day cycle for 6 cycles; placebo for pola was administered concurrently every 21 days for each 21-day cycle. Rituximab was administered as monotherapy in Cycle 7 and Cycle 8.
Endpoints and definitions	Primary endpoint	PFS	Progression free survival, defined as the time from randomization to the first occurrence of disease progression or relapse as assessed by the investigator, using the Lugano Response Criteria for Malignant Lymphoma, or death from any cause, whichever occurs earlier
	Secondary	EFSeff	Investigator-Assessed Event-Free Survival for Efficacy Reasons, defined as the time from the date of randomization to the earliest occurrence of disease progression/relapse, death, biopsy that is positive for residual disease after treatment completion, or start of a NALT due to efficacy reasons.
	Secondary	CR rate at end of treatment	BICR-Assessed Complete Response Rate at End of Treatment by PET-CT
	Secondary	OS	Overall Survival
Database lock	28 June 2021		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	R-CHOP	Pola +R-CHP
	Number of patients	440	439

	PFS Number of patients with event (%)	134 (30.5%)	107 (24.3%)
	EFSeff Number of patients with event (%)	138 (31.4%)	112 (25.5%)
	CR rate at end of treatment 95% CI	74% (69.66, 78.07)	78% (73.79, 81.74)
	OS Number of death (%)	57 (13.0%)	53 (12.0%)

Effect estimate per comparison	PFS	Comparison groups	Pola+R-CHP vs. R-CHOP
		Stratified HR	0.73
		95% CI	0.57, 0.95
		P-value	0.0177
	EFSeff	Comparison groups	Pola+R-CHP vs. R-CHOP
		Stratified HR	0.75
		95% CI	0.58, 0.96
		P-value	0.0244
	CR rate at EOT	Comparison groups	Pola+R-CHP vs. R-CHOP
		Difference in response rate	3.92
		variability statistic	-1.89, 9.70
		P-value	0.1557
	OS	Comparison groups	Pola+R-CHP vs. R-CHOP
		Stratified HR	0.94
		95% CI	0.65, 1.37
		P-value	0.6720
Notes	none		

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal study (Study GO39942: POLARIX) is a phase III, multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of polatuzumab vedotin in combination with R-CHP versus R-CHOP in previously untreated patients with diffuse large B-cell lymphoma.

Inclusion and exclusion criteria are acceptable and are in accordance with the claimed indication. The inclusion of IPI 2-5 allows to include higher risk populations who historically had poor outcomes with standard-of-care therapy, and also reflects the patient population included in the early GO29044 trial. Stratification factors (IPi score, bulky disease, geographical region) are deemed appropriate.

Patients received six cycles of either pola+R-CHP (and vincristine placebo) or standard R-CHOP chemotherapy (and polatuzumab vedotin placebo) at 21-day intervals. Both arms then received two additional cycles of single agent rituximab. The approach to withdraw vincristine from the pola-based regimen is acknowledged in order to exclude a risk of cumulative neurotoxicity. The polatuzumab vedotin

dose of 1.8 mg/kg given every 21 days in combination with R/G-CHP for 6 or 8 cycles was determined in the dose-finding study (Study GO29044) which is acceptable.

This design is acceptable as R-CHOP remains the standard of care therapy in previously untreated DLBCL. While R-CHOP may cure approximately 60% of patients with previously untreated DLBCL (Sehn and Salles 2021), alternative strategies have so far been unable to demonstrate meaningful benefit over R-CHOP. These include: increased dose density with R-CHOP given at 14 day intervals (Delarue et al 2013; Cunningham et al. 2013); dose intensification with dose-adjusted etoposide plus prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R), Bartlett et al 2019; substitution strategies such as the novel anti-CD20 monoclonal antibody obinutuzumab (Votolo et al 2017).

The efficacy analysis set, multiplicity adjustment procedure and statistical methods are generally acceptable.

The primary endpoint is the PFS, defined as the time from randomization to the first occurrence of disease progression or relapse as assessed by the investigator, using the Lugano Response Criteria for Malignant Lymphoma, or death from any cause, whichever occurs earlier. The PFS primary censoring rules follow the recommendations of the EMA guideline, with a set of sensitivity analyses to assess the potential impact of missing assessments or use of new anti-lymphoma therapy. It was agreed in the 2017 SA that a blinded independent central review of PFS was not required based on the study design.

Key secondary endpoints were included in the hierarchical testing procedure: EFSeff as determined by the investigator, CR rate at end of treatment by FDGPET as determined by BICR and OS.

Several important changes were made to the planned analyses, mostly as part of protocol amendments 5 and 6, including modifications to the hierarchical testing strategy and timing of the primary analysis. It is noted that the actual number of PFS events observed according to the updated rule is, in the end, relatively close to the original plan. For this reason, and given the double-blind nature of the study, these updates to planned analyses are not thought to have major impact on the overall interpretation of the study results. The difference in EFS only reached statistical significance because CR rate at end of treatment by PET-CT as determined by BICR was shifted to a lower position in hierarchy. This adds some uncertainty on the hypotheses and the confirmatory interpretation of EFS. However, since there is currently no reason to assume that the blind was compromised, this uncertainty is small.

Major protocol deviations were reported under the following four categories: inclusion criteria, exclusion criteria, procedural and medication. Number of major protocol deviations were low and balanced in both arms (29 in pola + R-CHP arm and 26 in R-CHOP arm). This should not impact efficacy data.

Efficacy data and additional analyses

A total of 879 patients were included in the intent-to-treat (ITT) population, 440 in pola+R-CHP arm and 439 in R-CHOP arm. Treatment arms were generally well-balanced with respect to demographic (age, sex, race, height, weight, geographic region) and baseline characteristics (ECOG performance status, Ann Arbor stage, IPI Score, presence of Bulky disease or not, bone marrow involvement, number of extranodal sites and NHL histologic diagnosis).

For both regimens, treatment exposure remained high. A high proportion of patients (91.7% receiving pola as part of the pola+RCHP regimen and 88.5% receiving vincristine as part of the R-CHOP regimen) completed the planned 6 cycles of study treatment. Approximately 90% of patients in each treatment arm received 6 cycles of CHP treatment.

At the CCOD, the median duration of PFS follow-up was 24.7 months in both arms with a minimum of 24 months from study enrolment in both arms. A statistically significant improvement in the primary endpoint of Investigator-assessed PFS is observed following treatment with pola+R-CHP compared to R-CHOP. A reduction in the risk of progression/relapse or death by 27% is observed in patients treated in pola+R-CHP arm (stratified HR: 0.73 [95% CI: 0.57, 0.95]; two-sided log-rank p-value=0.0177, two-sided α=0.05). Fewer patients in the pola+R-CHP arm had progressed or died compared to the R-CHOP arm (107 [24.3%] vs.134 [30.5%]).

Low maturity of PFS is reflected in relevant subgroups. Point estimates raise concern that there may be no benefit over R-CHOP in patients with IPI 2 as well as patients with bulky disease. It is currently unclear from the submitted data whether there were too few events in these patients to observe a treatment effect (confidence intervals are admittedly rather wide); of note IPI score and bulky disease were stratification factors. The study, however, is not powered to independently show effects in subgroups. Moreover, the substitution setting must be considered; there is a benefit of vincristine compared to which polatuzumab is overall superior. These analyses are neither type 1 error controlled nor powered for independent inferences; moreover there are no truly worrying outlying observations.

Results of all sensitivity analyses were consistent with results of the primary analysis of Investigator-assessed PFS in the ITT population. Of note, in some of these analyses, the significance threshold is crossed. These results confirm the slight improvement of PFS observed in the primary analysis.

Further, with a median of two years follow up, curves remain separated. The follow-up time of at least 24 months is considered sufficient as most relapses occur within the first 12-18 months. Patients with DLBCL without relapse at 24 months is considered to have a relapse risk of 8% and a survival similar to the normal population (Maurer et al. 2014).

Regarding the key secondary efficacy endpoints: EFSeff, a significant reduction in the risk of occurrence of disease by 25% was observed in patients treated in pola+R-CHP arm compared in patients treated in R-CHOP arm (stratified HR: 0.75 [95% CI: 0.58, 0.96]). Only a difference of 26 events was observed between both arms (2 due to death, 20 due to disease progression and 4 due to start of a NALT or a positive biopsy).

BICR-assessed CR rate was high (78.0% [95%CI: 73.79, 81.74] vs. 74.0% [95% CI: 69.66, 78.07]) but similar in both arms (treatment difference: 3.92 [95% CI: -1.89, 9.70]). In addition, concordance between BICR and Investigator assessments of CR was high (88.7%).

Notably, this is a curative setting. As stated in the introduction, "R-CHOP may cure approximately 60% of patients with previously untreated DLBCL". Moreover, the test regimen is a substitution of polatuzumab for vincristine. The treatment duration of test versus reference is limited to 6 cycles of 21 days, which is 18 weeks.

The OS results provided in this report come from the interim OS analysis performed at the time of the PFS analysis (stratified HR: 0.94 [95% CI: 0.65, 1.37]). The immaturity of OS data is expected to be a limitation to the interpretation of efficacy results. More generally, the study lacks power for OS, even for the final

analysis. This issue was discussed with the Applicant at the time of the 2017 scientific advice. It is noted that a total of 53 deaths (12.0% patients) were reported in the pola+R-CHP arm, and 57 deaths (13.0% patients) were reported in the R-CHOP arm. With very few events in both arms, OS results were still immature at the time of the interim analysis of OS and did not meet the pre-specified threshold for statistical significance (stratified HR: 0.94 [95% CI: 0.65, 1.37])". Finally, a 60% cure rate is anticipated in the control arm. Therefore, duration of follow-up rather than "maturity" of OS seems to be the key parameter here.

Follow-up anti-lymphoma treatments have been provided by the MAH. The number of patients each receiving radiotherapy, systemic therapy, chimeric antigen receptors cell therapy (CAR-T) were slighlty higher in the R-CHOP arm compared to the pola+R-CHP arm. It is interesting to note that in the pola+R-CHP arm, 3.9% of patients received stem cell transplants (n=30), compared with 7.1% in the R-CHOP arm (n=17). Also, in the pola+R-CHP arm 2.0% of patients received CAR-T (n=16), compared with 3.6% (n=9) in the R-CHOP arm.

Patient-reported outcomes analysis showed that impacts of pola+R-CHP and R-CHOP regimens on improvement in physical functioning, fatigue, lymphoma symptoms were similar. Also, no improvement in treatment-related symptoms and peripheral neuropathy were observed between both regimens.

Finally, for the HGBCL subgroup (N=93) the HR was 0.48 (0.21,1.08). Although HGBCL is a separate disease entity according to the WHO classification of 2016, a specific mention of HGBCL in the indication required extrapolation of efficacy and B/R from a DLBCL- to a HGBL population; these considerations were not possible on the current data. The initial indication as proposed by the MAH: *"Polivy in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL)"* is acceptable by the CHMP.

The recommended dose of Polivy is 1.8 mg/kg, given as an intravenous infusion every 21 days in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for 6 cycles. Polivy, rituximab, cyclophosphamide and doxorubicin can be administered in any order on Day 1 after the administration of prednisone. Prednisone is administered on Days 1-5 of each cycle. Cycles 7 and 8 consist of rituximab as monotherapy.

Per current Polivy SmPC Annex II.E, provision of efficacy and safety data by Q4 2021 is the last remaining specific obligation (SOB-CLIN-003) to the CMA of Polivy for the treatment of patients with relapsed/refractory DLBCL who are not candidates for haematopoietic stem cell transplant. The MAH believes that with the submission of this Type II variation, all specific obligations related to the conditional marketing authorization (CMA) are fulfilled. As a result, the MAH is requesting a full marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 (marketing authorisation not subject to specific obligations).

Interim OS results are still immature and could be considered as not sufficiently robust. However, OS interim results do not indicate detrimental effect of polatuzumab vedotin. The pivotal POLARIX study met its primary endpoint PFS and no meaningful differences in safety risks have been retrieved. Therefore, efficacy and safety data provided from untreated patients could be considered as confirmatory safety and efficacy data for treatment of patients with relapsed/refractory DLCBL. Therefore, obligations related to CMA are considered fulfilled.

The MAH have presented data based on a double blinded RCT where efficacy and safety of the substitution of vincristine with polatuzumab in the well-established 1L regimen R-CHOP have been assessed for 1L DLBCL. The study is statistically positive by acceptable standards. The MAH will provide the final OS results by Q4 2022 as a post approval measure. This is acceptable in order to obtain more long-term efficacy and safety data in this first line indication (see RMP). The CHMP also requested data

from an additional Chinese cohort. The MAH has requested approval for providing and opening access to Chinese Human Genetic Resources abroad from the Human Genetics Resources Administration of China (HGRAC) and would be able to provide the data from China extension cohort, in the form of Asia subpopulation CSR, if granted by HGRAC.

2.4.4. Conclusions on the clinical efficacy

A statistically significant improvement in the primary endpoint of Investigator-assessed PFS is observed following treatment with pola+R-CHP compared to R-CHOP. A reduction in the risk of progression/relapse or death by 27% is observed in patients treated in pola+R-CHP arm (HR: 0.73 [95% CI: 0.57, 0.95]. Results of secondary and sensitivity analyses were consistent with results of the primary analysis.

The PFS gain is sufficient to establish the efficacy and positive B/R of polatuzumab as substitute for vincristine. Further, as outlined above, given that treatment was 4-5 months and median time of follow-up is more than two years, it does not seem reasonable to anticipate any emerging detriment in OS of polatuzumab when substituted for vincristine.

Obligations related to CMA are considered fulfilled. The updated CSR at the time of final overall survival analysis containing final OS data -is expected to be submitted (see RMP).

Further, following the recommendation of the CHMP, the Applicant will submit the data from the China extension cohort of Study GO39942 (POLARIX) that are analyzed within an Asia subpopulation analysis and are reported in an Asia subpopulation CSR that includes all Chinese patients enrolled in the China extension and in the main global study, as well as patients from other Asian countries who were enrolled in the main global study Polarix.

2.5. Clinical safety

Introduction

As of 31 August 2021, polatuzumab in combination with bendamustine and rituximab (BR) is approved for the treatment of relapsed/refractory (R/R) DLBCL in >65 countries/regions including the European Union (EU) and United States (US).

The claimed indication in this application is in the first-line DLBCL setting for pola in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP). Safety data for pola 1.8 mg/kg in combination with R-CHP in patients with previously untreated DLBCL is based on the pivotal study POLARIX. At the time of the primary analysis (CCOD: 28 June 2021), the safety-evaluable population comprised of 873 patients who received at least one dose of study treatment with 435 patients in the pola+R-CHP arm and 438 patients in the R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) arm.

Additional supportive data are presented from a cohort of patients with previously untreated DLBCL (n=66) who received pola 1.8 mg/kg in combination with R-CHP (n=45) or G-CHP (n=21) in the GO29044 study.

The pooled population comprised all patients from POLARIX and GO29044 with previously untreated DLBCL receiving pola 1.8 mg/kg in combination with R-CHP/G-CHP (n=501).

Table 24. Summary of Studies Contributing to Safety Evaluation

Study Number	Overall Design	Patient Population	Dose and Schedule	Number of Patients (Safety Analysis Population)	Cutoff Date	Study Endpoints
Pivotal Phase III Study						
POLARIX (GO39942)	Phase III, multicenter, randomized, double-blind, placebo-controlled	Previously untreated patients with CD20-positive DLBCL	Pola 1.8 mg/kg+vincristine placebo+R-CHP q 21 days x 6 cycles Pola placebo+R-CHOP q 21 days x 6 cycles Rituximab 375 mg/m^2 as monotherapy in Cycles 7 and 8 in both arms All study treatments given IV except for prednisone, which was given orally	• Total 1L DLBCL: N=873 • Pola 1.8 mg/kg+R-CHP: N=435 • R-CHOP: N=438	28 June 2021	Safety, tolerability, anti-tumor activity
Supportive Phase Ib/II Study						
GO29044	Phase Ib/II, open-label, multicenter, single-arm (Pola+R/G-CHP)	Dose escalation: newly diagnosed or R/R B-cell NHL (≤1 prior line of systemic therapy)	Pola 1.0-1.8 mg/kg + R-CHP q 21 days x 6-8 cycles Pola 1.4-1.8 mg/kg + G-CHP q 21 days x 6-8 cycles	Other B-cell NHL [a] • Pola 1.8 mg/kg+R-CHP: N=1 • Pola 1.8 mg/kg+G-CHP: N=2 • Pola 1.0 mg/kg+R-CHP: N=1 • Pola 1.4 mg/kg+G-CHP: N=2 DLBCL [b] • Pola 1.8 mg/kg+R-CHP: N=45 • Pola 1.8 mg/kg+G-CHP: N=21 • Pola 1.0–1.4 mg/kg+R-CHP: N=5 • Pola 1.4 mg/kg+G-CHP: N=4	28 March 2019	PhIb: MTD of pola in combination with chemotherapy PhII: Safety and efficacy
		Expansion: Previously untreated DLBCL	Pola 1.8 mg/kg + R-CHP q 21 days x 6-8 cycles Pola 1.8 mg/kg + G-CHP q 21 days x 6-8 cycles All study treatments given IV except for prednisone, which was given orally			

CHP=cyclophosphamide, doxorubicin, and prednisone; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone; DLBCL=diffuse large B-cell lymphoma; G=obinutuzumab; MTD=maximum tolerated dose; NHL=non-Hodgkin's lymphoma; Pola=polatuzumab vedotin; q=every; R=rituximab; R/R=relapsed or refractory.

[a] One additional patient received pola at 2.4 mg/kg instead of the protocol-defined 1.8 mg/kg due to a medication error.

[b] Only data in 66 patients with previously untreated DLBCL who received pola 1.8 mg/kg+R-CHP (n=45) or pola 1.8 mg/kg+G-CHP (n=21) are presented in this SCS

Patient exposure

Study POLARIX

After initiation of study drug, all AEs regardless of relationship to study drug were reported until 90 days after the last dose of study drug, unless the patient begins a new anti-lymphoma therapy (NALT). This was defined as the treatment-emergent AE interval. All adverse events of special interest considered related to study drug by the investigator were reported until 12 months after the last dose of study drug.

The median Relative Dose Intensity (RDI) was >99.8% for all components of treatment in each arm. There was 93.6% (407/435) of patients in the pola+R-CHP arm and 90.6% (397/438) of patients the R-CHOP arm receiving at least 6 cycles of any study drug; 89.2% of patients in the pola+R-CHP arm and 86.3% of patients in the R-CHOP arm received 8 cycles of rituximab. A higher number of patients received all six planned doses of pola in the pola+R-CHP arm (91.7% among patients who received any dose of pola [n=435]) compared to the number of patients who received all six planned doses of vincristine in the R-CHOP arm (88.5% among patients who received any dose of vincristine [n=436]).

Patients in the pola+R-CHP arm received a median of 6 cycles of pola (range 1-6), corresponding to a median treatment duration of **3.5 months.** Mean (SD) cumulative dose of pola received by patients in the pola+R-CHP arm was 774.5 mg (228.9 mg).

Patients in the R-CHOP arm received a median of 6 cycles of vincristine (range 1-6), corresponding to a median treatment duration of **3.5 months**. Mean (SD) cumulative dose of vincristine received by patients in the R-CHOP arm was 11.2 mg (2.1 mg).

Patients in both the pola+R-CHP and R-CHOP arms also received a median of 8 cycles of rituximab (range 1-8). This corresponds to a median treatment duration of **4.9 months in both treatment arms**. A total of 89.2% of patients in the pola+R-CHP arm and 86.3% of patients in the R-CHOP arm completed 8 cycles of rituximab.

Table 25. Summary of Study Drug Exposure (SE Population, POLARIX)

	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

Supportive study GO29044

After initiation of study drug, all AEs regardless of relationship to study drug were reported until 90 days after the last dose of study drug. After this period, investigators reported any SAEs or deaths believed to be related to prior study drug treatment. Second malignancies were reported indefinitely for patients who received obinutuzumab, regardless of relationship to study treatment.

Median RDI was >99.8% for all treatment components. Patients received pola in combination with R-CHP or G-CHP over a median period of **3.5 months** (range: 0-6 months). The median number of cycles received was 6.0 (range: 1-8), and the mean (SD) cumulative dose was 857.8 (252.8) mg.

- *R-CHP Treatment Regimen – DLBCL*

Patients received polatuzumab vedotin over a median period of 3.49 months (range: 0.7-5.5 months). The median number of cycles received was 6.0 (range: 2.0-8.0), and the total cumulative dose was 864.00 mg (range: 212.0-1344.0 mg). The median missed doses were 0.0 doses (range: 0-1 doses).

Patients received rituximab over a median period of 3.50 months (range: 0.7-5.6 months). The median number of cycles received was 6.0 (range: 2.0-8.0). The total cumulative dose was 4625.00 mg (range: 1170.0-5920.0 mg). The median missed doses were 0.0 doses (range: 0-1 doses).

Patients received cyclophosphamide and doxorubicin over a median period of 3.51 months (range: 0.7-5.6 months). The median number of cycles received was 6.0 (range: 2.0-8.0). The total cumulative dose was 9270.00 mg (range: 2340.0-11800.0 mg) and 618.00 mg (range: 156.0-792.0 mg) for cyclophosphamide and doxorubicin, respectively. The median missed doses were 0.0 doses (range: 0-1 doses) for both cyclophosphamide and doxorubicin.

Patients received prednisone over a median period of 3.66 months (range: 0.9-5.7 months). The median number of cycles received for both drug was 6.0 (range: 2.0-8.0). The median total cumulative dose was 3000.00 mg (range: 1000.0-4000.0 mg). The median missed doses were 0.0 doses (range: 0-1 doses).

- *G-CHP Treatment Regimen – DLBCL*

Patients received polatuzumab vedotin over a median period of 3.43 months (range: 0.0-5.0 months). The median number of cycles received was 6.0 (range: 1.0-8.0), and the total cumulative dose was 828.00 mg (range: 126.0-1375.2 mg). There were no missed doses for polatuzumab vedotin.

Patients received obinutuzumab over a median period of 3.46 months (range: 0.7-5.1 months). The median number of cycles received was 6.0 (range: 1.0-8.0). The total cumulative dose was 8000.00 mg (range: 3000.0-10000.0 mg). The median missed doses were 0.0 doses (range: 0-1 doses).

Patients received cyclophosphamide and doxorubicin over a median period of 3.45 months (range: 0.0-5.1 months). The median number of cycles received was 6.0 (range: 1.0-8.0). The total cumulative dose was 8865.00 mg (range: 1329.0-11864.0 mg) and 576.00 mg (range: 89.0-792.0 mg) for cyclophosphamide and doxorubicin, respectively. There were no missed doses for both cyclophosphamide and doxorubicin.

Patients received prednisone over a median period of 3.61 months (range: 0.2-5.3 months). The median number of cycles received was 6.0 (range: 1.0-8.0). The total cumulative dose was 3000.00 mg (range: 500.0- 4000.0 mg). There were no missed doses for prednisone.

Pooled safety population

Relative dose intensity was high with a median RDI of >99.8% for all components of study treatment.

Patients received a median of 6.0 cycles of pola (range 1-8), corresponding to a median treatment duration of 3.5 months (Table 5). Mean (SD) cumulative dose of pola received by patients in the pooled safety population was 785.5 mg (233.6 mg).

Patients in the pooled safety population received a median of 8.0 cycles of rituximab (range 1-8) or 6.0 cycles of obinutuzumab (range 1-8). This corresponds to a median treatment duration of 4.9 months for rituximab and 3.5 months for obinutuzumab.

The median number of cycles of exposure to CHP (cyclophosphamide, doxorubicin, and prednisone) in the pooled safety population was 6.0 (range 1 – 8), corresponding to a median of 3.5 to 3.6 months of treatment.

Table 26. Extent of Exposure to Study Treatment, Safety-Evaluable Patients

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands An agency of the European Union
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands An agency of the European Union
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands An agency of the European Union
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands An agency of the European Union
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands An agency of the European Union
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Treatment	R-CHOP (POLARIX) N=438		Pola+R-CHP (POLARIX) N=435		Pola (1.8 mg/kg) + R-CHP/G-CHP (GO29044) N=66		All Pola (1.8 mg/kg) + R-CHP/G-CHP (POLARIX + GO29044) N=501	
	Median treatment duration, months (range)	Median number of cycles (range)	Median treatment duration, months (range)	Median number of cycles (range)	Median treatment duration, months (range)	Median number of cycles (range)	Median treatment duration, months (range)	Median number of cycles (range)
Pola	-	-	3.5 (0 – 5)	6.0 (1 – 6)	3.5 (0 – 6)	6.0 (1 – 8)	3.5 (0 – 6)	6.0 (1 – 8)
Vincristine	3.5 (0 – 8)	6.0 (1 – 6)	-	-	-	-	-	-
Rituximab	4.9 (0 – 11)	8.0 (1 – 8)	4.9 (0 – 8)	8.0 (1 – 8)	3.6 (1 – 6)	6.0 (2 – 8)	4.9 (0 – 8)	8.0 (1 – 8)
Obinutuzumab	-	-	-	-	3.5 (1 – 5)	6.0 (1 – 8)	3.5 (1 – 5)	6.0 (1 – 8)
Cyclophosphamide	3.5 (0 – 8)	6.0 (1 – 6)	3.5 (0 – 5)	6.0 (1 – 6)	3.5 (0 – 6)	6.0 (1 – 8)	3.5 (0 – 6)	6.0 (1 – 8)
Doxorubicin	3.5 (0 – 8)	6.0 (1 – 6)	3.5 (0 – 5)	6.0 (1 – 6)	3.5 (0 – 6)	6.0 (1 – 8)	3.5 (0 – 6)	6.0 (1 – 8)
Prednisone	3.6 (0 – 6)	6.0 (1 – 6)	3.6 (0 – 5)	6.0 (1 – 6)	3.6 (0 – 6)	6.0 (1 – 8)	3.6 (0 – 6)	6.0 (1 – 8)

G=obinutuzumab; Pola=polatuzumab vedotin; R-CHP=rituximab plus cyclophosphamide, doxorubicin and prednisone; R-CHOP=rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone.
Source: output t_ex_1LP_SE

Adverse events

Table 27. Overview of Adverse Event Profile in Previously Untreated DLBCL Patients, Safety-Evaluable Patients

Overall AE Profile, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Total number of patients with at least one AE	431 (98.4%)	426 (97.9%)	66 (100%)	492 (98.2%)
Total number of AEs	5189	5470	968	6438
Total number of patients with at least one				
Grade 5 AE	10 (2.3%)	13 (3.0%)	2 (3.0%)	15 (3.0%)
Grade 3-5 AE	262 (59.8%)	264 (60.7%)	44 (66.7%)	308 (61.5%)
Serious AE	134 (30.6%)	148 (34.0%)	27 (40.9%)	175 (34.9%)
Serious Related AE to any study drug	86 (19.6%)	112 (25.7%)	17 (25.8%)	129 (25.7%)
AE leading to study discontinuation	10 (2.3%)	13 (3.0%)	3 (4.5%)	16 (3.2%)
AE leading to any study treatment dose discontinuation	29 (6.6%)	27 (6.2%)	8 (12.1%)	35 (7.0%)
AE leading to any study treatment dose reduction	57 (13.0%)	40 (9.2%)	8 (12.1%)	48 (9.6%)
AE leading to any study treatment dose interruption	111 (25.3%)	103 (23.7%)	18 (27.3%)	121 (24.2%)
AE leading to polatuzumab vedotin/placebo discontinuation	22 (5.0%)	19 (4.4%)	8 (12.1%)	27 (5.4%)
AE leading to polatuzumab vedotin/placebo dose reduction	45 (10.3%)	24 (5.5%)	5 (7.6%)	29 (5.8%)
AE leading to polatuzumab vedotin/placebo dose interruption	62 (14.2%)	61 (14.0%)	6 (9.1%)	67 (13.4%)
AE leading to vincristine/placebo discontinuation	22 (5.0%)	19 (4.4%)	0	19 (3.8%)
AE leading to vincristine/placebo dose reduction	45 (10.3%)	24 (5.5%)	0	24 (4.8%)
AE leading to vincristine/placebo dose interruption	60 (13.7%)	60 (13.8%)	0	60 (12.0%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

Study POLARIX

The most common AEs (≥ 50% of patients in either arm) by System Organ Class (SOC) were (pola+R-CHP arm and R-CHOP arm, respectively):

- Gastrointestinal disorders (76.1% and 71.9%)

- Nervous system disorders (65.7% and 68.7%)

- General disorders and administration site conditions (65.7% and 68.7%)

- Blood and lymphatic system disorders (54.5% and 50.5%)

AEs reported by ≥ 20% of patients in either treatment arm (pola+R-CHP and R-CHOP) were: nausea (41.6% and 36.8%), neutropenia (30.8% and 32.6%), constipation (28.7% and 29.0%), anemia (28.7% and 26.0%), fatigue (25.7% and 26.5%), diarrhea (30.8% and 20.1%), alopecia (24.4% and 24.0%), peripheral neuropathy (24.1% and 22.6%), and peripheral sensory neuropathy (19.5% and 21.5%).

Grade 1-2 AEs (highest grade) were reported in 37.2% of patients in the pola+R-CHP arm and 38.6% of patients in the R-CHOP arm. The proportion of patients with Grade 3-4 AEs (highest grade) in the pola+R-CHP arm (57.7%) was comparable with the R-CHOP arm (57.5%).

The most common Grade 3-4 AEs by highest grade (≥ 5% of patients in either arm) and by SOC were (pola+R-CHP arm and R-CHOP arm, respectively):

– Blood and lymphatic disorders (42.1% and 39.7%)

– Infections and infestations (14.0% and 11.2%)

– Investigations (13.6% and 13.7%)

– Metabolism and nutrition disorders (9.2% and 7.8%)

– Gastrointestinal Disorders (9.4% and 8.2%)

– General Disorders and administration site conditions (5.5% and 5.3%)

– Nervous system disorders (3.9% and 5.3%)

A summary of the most common Grade 3-4 AEs by highest grade (≥ 2% of patients in either arm) and by PT is shown in Table 9. The majority of Grade 3-4 AEs were associated with myelosuppression.

Supportive study GO29044

All patients (66/66; 100%) in the pola+R-CHP/G-CHP population had at least one AE.

The most common AEs (≥ 50% of patients) by SOC were General disorders and administration site conditions (83.3%), Gastrointestinal disorders (80.3%), Nervous system disorders (66.7%), Blood and lymphatic system disorders (63.6%), and Infections and infestations (53.0%).

The most commonly reported AEs (≥20% of patients) by PT were diarrhea (50.0%), fatigue (48.5%), nausea (47.0%), neutropenia (40.9%), anemia (28.8%), constipation (25.8%), pyrexia (21.2%) and weight decreased (21.2%)

Pooled safety population

The proportion of patients with at least one AE in the pooled safety population (98.2% [492/501 patients]) was comparable to the R-CHOP arm from POLARIX (98.4% [431/438 patients]). The most frequently reported AEs of any grade in the pooled safety population were consistent with the pola+R-CHP arm in POLARIX and the majority of AEs were non-serious.

Table 28 Adverse Events by Preferred Term Occurring in ≥10% of Patients in either POLARIX Treatment Arm in Previously Untreated DLBCL Patients, Safety-Evaluable Patients

Summary of Adverse Events with an Incidence Rate of at Least 10% by Preferred Term, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

MedDRA Preferred Term	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Nausea	161 (36.8%)	181 (41.6%)	31 (47.0%)	212 (42.3%)
Neutropenia	143 (32.6%)	134 (30.8%)	27 (40.9%)	161 (32.1%)
Diarrhoea	88 (20.1%)	134 (30.8%)	33 (50.0%)	167 (33.3%)
Constipation	127 (29.0%)	125 (28.7%)	17 (25.8%)	142 (28.3%)
Fatigue	116 (26.5%)	112 (25.7%)	32 (48.5%)	144 (28.7%)
Anaemia	114 (26.0%)	125 (28.7%)	19 (28.8%)	144 (28.7%)
Alopecia	105 (24.0%)	106 (24.4%)	13 (19.7%)	119 (23.8%)
Neuropathy peripheral	99 (22.6%)	105 (24.1%)	10 (15.2%)	115 (23.0%)
Peripheral sensory neuropathy	94 (21.5%)	85 (19.5%)	10 (15.2%)	95 (19.0%)
Decreased appetite	62 (14.2%)	71 (16.3%)	10 (15.2%)	81 (16.2%)
Pyrexia	55 (12.6%)	68 (15.6%)	14 (21.2%)	82 (16.4%)
Vomiting	63 (14.4%)	65 (14.9%)	11 (16.7%)	76 (15.2%)
Weight decreased	52 (11.9%)	55 (12.6%)	14 (21.2%)	69 (13.8%)
Asthenia	53 (12.1%)	53 (12.2%)	12 (18.2%)	65 (13.0%)
Febrile neutropenia	35 (8.0%)	62 (14.3%)	12 (18.2%)	74 (14.8%)
Headache	57 (13.0%)	56 (12.9%)	7 (10.6%)	63 (12.6%)
Cough	53 (12.1%)	56 (12.9%)	8 (12.1%)	64 (12.8%)
Dysgeusia	57 (13.0%)	49 (11.3%)	6 (9.1%)	55 (11.0%)
Back pain	48 (11.0%)	41 (9.4%)	7 (10.6%)	48 (9.6%)
Dyspnoea	36 (8.2%)	48 (11.0%)	6 (9.1%)	54 (10.8%)

Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings. Incidence rate cutoff was only applied to R-CHOP (POLARIX) and Pola-R-CHP (POLARIX) columns. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. 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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

AEs by severity

Table 29 Grade 3-4 Adverse Events by Preferred Term Occurring in ≥ 2% of Patients in either POLARIX Treatment Arm in Previously Untreated DLBCL Patients, Safety-Evaluable Patients

MedDRA Preferred Term	R-CHOP (POLARIX) N=438	Pola-R-CHP (POLARIX) N=435	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) N=66	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) N=501
Neutropenia	135 (30.8%)	123 (28.3%)	20 (30.3%)	143 (28.5%)
Febrile neutropenia	35 (8.0%)	60 (13.8%)	12 (18.2%)	72 (14.4%)
Anaemia	37 (8.4%)	52 (12.0%)	3 (4.5%)	55 (11.0%)
Neutrophil count decreased	28 (6.4%)	30 (6.9%)	0	30 (6.0%)
Leukopenia	30 (6.8%)	25 (5.7%)	5 (7.6%)	30 (6.0%)
Thrombocytopenia	19 (4.3%)	14 (3.2%)	6 (9.1%)	20 (4.0%)
White blood cell count decreased	14 (3.2%)	18 (4.1%)	2 (3.0%)	20 (4.0%)
Pneumonia	17 (3.9%)	14 (3.2%)	5 (7.6%)	19 (3.8%)
Lymphocyte count decreased	15 (3.4%)	13 (3.0%)	0	13 (2.6%)
Diarrhoea	8 (1.8%)	17 (3.9%)	1 (1.5%)	18 (3.6%)
Lymphopenia	10 (2.3%)	7 (1.6%)	1 (1.5%)	8 (1.6%)
Syncope	9 (2.1%)	8 (1.8%)	3 (4.5%)	11 (2.2%)
Hypertension	10 (2.3%)	6 (1.4%)	2 (3.0%)	8 (1.6%)
Hyponatraemia	9 (2.1%)	6 (1.4%)	1 (1.5%)	7 (1.4%)
Fatigue	11 (2.5%)	4 (0.9%)	1 (1.5%)	5 (1.0%)
Platelet count decreased	3 (0.7%)	9 (2.1%)	0	9 (1.8%)

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. Includes treatment-emergent AE 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.

Adapted by PDRD from output t_ae_pt_ctc34_pi2_1LP_SE and output t_ae_soc_pt_grd_1LP_SE

Adverse drug reactions

The ADRs identified in previously untreated DLBCL patients treated with pola+R-CHP from POLARIX were pooled with ADRs in R/R DLBCL patients treated with pola in combination with BR from study GO29365 (N=151; data cut-off 02 January 2020) and represents a pooled safety population of 586 patients. Data outputs for Study GO29365 (N=151) were regenerated using the same CCOD of 02 January 2020 as used in the current EU SmPC in order to apply the updated MedDRA preferred terms grouping strategy as used for Study GO39942, to allow for alignment and pooling of ADRs.

Table 30 Summary of pola ADRs in pooled safety population of previously untreated DLBCL patients treated with pola+R-CHP and R/R DLBCL patients with pola+BR

Infections and Infestations	
Very common	pneumonia[a], upper respiratory tract infection
Common	sepsis[a], herpes virus infection[a], cytomegalovirus infection, urinary tract infection[c]
Blood and Lymphatic System Disorders	
Very common	febrile neutropenia, neutropenia, thrombocytopenia, anemia, leukopenia
Common	lymphopenia, pancytopenia
Metabolism and Nutrition Disorders	
Very common	hypokalaemia, decreased appetite
Common	hypocalcaemia, hypoalbuminaemia
Nervous System Disorders	
Very common	neuropathy peripheral
Common	dizziness
Eye disorders	
Uncommon	vision blurred[b]
Respiratory, Thoracic and Mediastinal Disorders	
Very common	cough
Common	pneumonitis, dyspnoea[c]
Gastrointestinal Disorders	
Very common	diarrhea, nausea, constipation, vomiting, mucositis[c], abdominal pain
Skin and Subcutaneous Tissue Disorders	
Very common	alopecia[c]
Common	pruritus, skin infections[c], rash[c], dry skin[c]
Musculoskeletal Disorders	
Common	arthralgia, myalgia[c]
General Disorders and Administration Site Conditions	
Very common	pyrexia, fatigue, asthenia
Common	peripheral edema[c], chills
Investigations	
Very Common	weight decreased
Common	transaminases increased, lipase increase[b], hypophosphataemia
Injury, Poisoning, and Procedural	
Very common	infusion related reaction

MedDRA version 24.0
The table includes a combination of grouped and ungrouped terms. ADR grouped terms are listed in Appendix Table 3. Events were graded using NCI CTCAE version 4.
[a] ADR associated with a fatal outcome
[b] ADRs for the R/R DLBCL safety population
[c] ADRs for the 1L DLBCL safety population
Rare and very rare ADRs: none
Source: Manual Table of Pooled ADRs.pdf

Analysis of safety data based on ≥2% difference in AE incidence between the pola+R-CHP arm versus the R-CHOP control arm and medical relevance from Study GO39942 (POLARIX) identified the following additional ADRs: mucositis, peripheral edema, rash, dyspnea, dry skin and skin infections.

Analysis of safety data based on a <2% difference in AE incidence identified the following additional medically relevant ADRs: alopecia, myalgia and urinary tract infection.

Adverse events of special interest

Events of neutropenia, peripheral neuropathy (PN), infections, hepatic toxicity, anemia, thrombocytopenia, tumor lysis syndrome (TLS), pulmonary toxicity and secondary malignancies of all grades have been observed in patients treated with pola as a single agent or in combination treatments, therefore, these events have been considered as adverse events of particular interest (AEPIs). Hyperglycemia, cardiac arrhythmia and infusion-related reactions (IRR) were also AEPIs.

- *Peripheral neuropathy*

Study POLARIX

Overall, the proportion of patients who experienced PN (52.9%) in the pola+R-CHP arm was comparable with the R-CHOP arm (53.9%) and the majority of patients experienced low grade PN.

Among patients in pola+R-CHP arm who developed PN events, 170/230 (73.9%) had Grade 1 PN and 53/230 (23.0%) had Grade 2 PN. This compares with 163/236 (69.1%) patients in the R-CHOP arm with Grade 1 PN and 68/236 (28.8%) patients with Grade 2 PN, indicating that a higher proportion of patients in the pola+R-CHP arm experienced low-grade PN compared with the R-CHOP arm.

The proportion of patients who experienced Grade 3 PN (highest grade) was 1.6% (7 patients) in the pola+R-CHP arm and 1.1% (5 patients) in the R-CHOP arm. No patients in either arm experienced Grade 4 or Grade 5 PN events.

The most commonly reported PN events by PT (≥ 2% of patients in either arm) were neuropathy peripheral (24.1% and 22.6%), peripheral sensory neuropathy (19.5% and 21.5%), paraesthesia (6.7% and 4.6%), hypoaesthesia (3.7% and 3.2%), polyneuropathy (1.4% and 2.5%), and peripheral motor neuropathy (0.7% and 2.3%) in the pola+R-CHP and R-CHOP arms, respectively.

The majority of patients (93.8% in the pola+R-CHP arm and 92.2% in the R-CHOP arm) had no prior history of PN. In the pola+R-CHP arm, of the 230 patients who experienced a PN event during treatment, 16 patients had a history of prior PN, and of these, 14 patients had ongoing PN at baseline. In the R-CHOP arm, of the 236 patients who experienced a PN event during treatment, 14 patients had a history of prior PN, and of these, 10 patients had ongoing PN at baseline. The proportion of patients who experienced a serious PN event was the same in each arm (0.2% [1 patient]).

Median time to onset of first PN was 2.27 months (range: 0.0 – 6.7 months) in the pola+R-CHP arm and 1.87 months (range: 0.0 – 8.1 months) in the R-CHOP arm.

Resolution of PN was reported in the majority of patients at the time of CCOD, with more patients having had resolution of PN in the R-CHOP arm (66.9% [158/236 patients with events]) compared with the pola+R-CHP arm (57.8% [133/230 patients with events]).

The later time to onset of PN events in the pola+R-CHP arm compared with the R-CHOP arm, in combination with similar median time to PN resolution (4.04 months [range: 0.0 – 36.0 months] in the pola+R-CHP arm and 4.60 months [range: 0.0 – 34.9 months] in the R-CHOP arm), likely contributed to more patients with unresolved PN in the Pola+RCHP arm at the time of CCOD.

Doses modifications to manage peripheral neuropathy are commented in section 5.4.2. of this report.

Supportive study GO29044

A total of 26/66 patients (39.4%) experienced 36 peripheral neuropathy events during the study (Table 15). Twenty-five (of 62) patients with no prior history of PN experienced treatment-emergent peripheral neuropathy and 1 of 4 patients with PN ongoing at baseline experienced a worsening of PN during the study.

Eighteen patients experienced Grade 1 PN (worst grade) and 6 patients experienced Grade 2 PN (worst grade). Two patients had Grade 3 events (1 during post-treatment follow up and 1 during treatment, dose not changed). Three patients had study treatment (pola) dose reduced due to a PN event (2 Grade 2 events, 1 Grade 1 event) and 1 patient discontinued study treatment (pola) due to Grade 2 peripheral neuropathy.

At the time of the CCOD for the final analysis for GO29044 all PN events were reported as resolved in 20 of the 26 patients with PN events. Median time to onset of first treatment-emergent peripheral neuropathy event was 2.51 months (range 0.1-8.0 months). Median time to resolution of first treatment-emergent peripheral neuropathy was 2.40 months (range: 0.1 – 25.0 months).

Pooled safety population

Overall, the proportion of patients who experienced PN in the pooled safety population (51.1% [256/501 patients]) was consistent with the pola+R-CHP arm from POLARIX and comparable with the R-CHOP arm (53.9% [236/438 patients]).

Table 31 Overview of AEPI Peripheral neuropathy in previously untreated DLBCL patients, safety-evaluable patients

Overall AE Profile - AEPI Peripheral Neuropathy, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Total number of patients with at least one AE	236 (53.9%)	230 (52.9%)	26 (39.4%)	256 (51.1%)
Total number of AEs	292	301	36	337
Total number of patients with at least one				
Grade 5 AE	0	0	0	0
Grade 3-5 AE	5 (1.1%)	7 (1.6%)	2 (3.0%)	9 (1.8%)
Serious AE	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
Serious Related AE to any study drug	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
AE leading to study discontinuation	0	0	0	0
AE leading to any study treatment dose discontinuation	10 (2.3%)	3 (0.7%)	1 (1.5%)	4 (0.8%)
AE leading to any study treatment dose reduction	36 (8.2%)	20 (4.6%)	3 (4.5%)	23 (4.6%)
AE leading to any study treatment dose interruption	5 (1.1%)	6 (1.4%)	0	6 (1.2%)
AE leading to polatuzumab vedotin/placebo discontinuation	9 (2.1%)	3 (0.7%)	1 (1.5%)	4 (0.8%)
AE leading to polatuzumab vedotin/placebo dose reduction	36 (8.2%)	17 (3.9%)	3 (4.5%)	20 (4.0%)
AE leading to polatuzumab vedotin/placebo dose interruption	3 (0.7%)	3 (0.7%)	0	3 (0.6%)
AE leading to vincristine/placebo discontinuation	9 (2.1%)	3 (0.7%)	0	3 (0.6%)
AE leading to vincristine/placebo dose reduction	35 (8.0%)	19 (4.4%)	0	19 (3.8%)
AE leading to vincristine/placebo dose interruption	3 (0.7%)	3 (0.7%)	0	3 (0.6%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

- *Neutropenia including Febrile Neutropenia*

Study POLARIX

Overall, the proportion of patients who experienced neutropenia (including febrile neutropenia) in the pola+R-CHP arm (46.0%) was generally comparable with the R-CHOP arm (42.7%).

The proportion of patients who experienced a serious neutropenia event in the pola+R-CHP arm (11.5%) was higher than in the R-CHOP arm (8.4%) and was mainly due to a higher incidence of serious febrile neutropenia in the pola+R-CHP arm (9.9%) than in the R-CHOP arm (6.4%).

Median time to onset of first neutropenia (all grades) was 0.49 months (range: 0.1 – 7.2 months) in the pola+R-CHP arm and 0.43 months (range: 0.1 – 6.4 months) in the R-CHOP arm. Neutropenia was reported as resolved in 98.0% (196/200 patients with events) in the pola+R-CHP arm and 97.9% (183/187 patients

with events) in the R-CHOP arm, as of the CCOD. Median time to resolution of neutropenia was 0.23 months (range: 0.0 – 16.5 months) in the pola+R-CHP arm and 0.26 months (range: 0.0 – 18.5 months) in the R-CHOP arm.

Supportive study GO29044

A total of 34/66 patients (51.5%) experienced 60 neutropenia events (including febrile neutropenia) with a median time to onset of 0.26 months (range: 0.0-6.7 months).

Twelve patients (18.2%) experienced 15 febrile neutropenia events; 7 patients had Grade 3 febrile neutropenia events and 5 patients had Grade 4 febrile neutropenia.

Eleven patients (16.7%) experienced an SAE of neutropenia and 9 patients (13.6%) had an SAE of febrile neutropenia.

One patient discontinued study treatment due to a serious event of Grade 4 febrile neutropenia, 2 patients had their study treatment interrupted (1 due to Grade 3 neutropenia; 1 due to Grade 4 febrile neutropenia), and 1 patient had their study treatment dose reduced due to Grade 3 neutropenia.

All events of neutropenia and all but one of the events of febrile neutropenia were reported as resolved at data cut-off. Median time to resolution of neutropenia was 0.23 months (range 0-9.2 months).

Pooled safety population

The proportion of patients who experienced neutropenia (including febrile neutropenia) in the pooled safety population (46.7% [234/501 patients]) was consistent with the pola+R-CHP arm from POLARIX and comparable with the R-CHOP arm (42.7% [187/438 patients])

Table 32 Overview of AEPI Neutropenia in Previously untreated DLBCL patients, Safety-evaluable patients

Overall AE Profile - AEPI Neutropenia, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Total number of patients with at least one AE	187 (42.7%)	200 (46.0%)	34 (51.5%)	234 (46.7%)
Total number of AEs	443	456	60	516
Total number of patients with at least one				
Grade 5 AE	0	0	0	0
Grade 3-5 AE	176 (40.2%)	182 (41.8%)	27 (40.9%)	209 (41.7%)
Serious AE	37 (8.4%)	50 (11.5%)	11 (16.7%)	61 (12.2%)
Serious Related AE to any study drug	34 (7.8%)	49 (11.3%)	9 (13.6%)	58 (11.6%)
AE leading to study discontinuation	0	0	0	0
AE leading to any study treatment dose discontinuation	0	2 (0.5%)	1 (1.5%)	3 (0.6%)
AE leading to any study treatment dose reduction	7 (1.6%)	7 (1.6%)	2 (3.0%)	9 (1.8%)
AE leading to any study treatment dose interruption	28 (6.4%)	23 (5.3%)	10 (15.2%)	33 (6.6%)
AE leading to polatuzumab vedotin/placebo discontinuation	0	0	1 (1.5%)	1 (0.2%)
AE leading to polatuzumab vedotin/placebo dose reduction	2 (0.5%)	2 (0.5%)	1 (1.5%)	3 (0.6%)
AE leading to polatuzumab vedotin/placebo dose interruption	13 (3.0%)	12 (2.8%)	2 (3.0%)	14 (2.8%)
AE leading to vincristine/placebo discontinuation	0	0	0	0
AE leading to vincristine/placebo dose reduction	2 (0.5%)	1 (0.2%)	0	1 (0.2%)
AE leading to vincristine/placebo dose interruption	13 (3.0%)	12 (2.8%)	0	12 (2.4%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

- *Anemia*

Study POLARIX

Overall, the proportion of patients who experienced anemia in the pola+R-CHP arm (28.7%) was comparable with the R-CHOP arm (26.9%).

Median time to onset of first anemia (all grades) was 1.12 months (range: 0.0 – 7.4 months) in the pola+R-CHP arm and 1.05 months (range: 0.0 – 4.6 months) in the R-CHOP arm. Anemia was reported as resolved in 84.8% (106/125 patients with events) in the pola+R-CHP arm and 86.4% (102/118 patients with events) in the R-CHOP arm, as of the CCOD. Median time to resolution of anemia was 0.69 months (range: 0.0 – 21.0 months) in the pola+R-CHP arm and 0.72 months (range: 0.0 – 17.7 months) in the R-CHOP arm.

Supportive study GO29044

A total of 19/66 patients (28.8%) experienced 36 anemia events with a median time to onset of 0.99 months (range: 0.2-3.1 months).

In all but two patients (1 patient with Grade 1 event, 1 patient with Grade 2 event) anemia was reported as resolved at data cut-off. Median time to resolution of anemia was 0.90 months (range 0-8.7 months).

Pooled safety population

The proportion of patients who experienced anemia in the pooled pola+R-CHP/G-CHP arm (28.7% [144/501 patients]) was consistent with the pola+R-CHP arm from POLARIX and comparable with the R-CHOP arm (26.9% [118/438 patients]).

Table 33 Overview of AEPI Anemia in previously untreated DLBCL patients, Safety-evaluable patients

Overall AE Profile - AEPI Anemia, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Total number of patients with at least one AE	118 (26.9%)	125 (28.7%)	19 (28.8%)	144 (28.7%)
Total number of AEs	178	190	36	226
Total number of patients with at least one				
Grade 5 AE	0	0	0	0
Grade 3-5 AE	38 (8.7%)	52 (12.0%)	3 (4.5%)	55 (11.0%)
Serious AE	6 (1.4%)	4 (0.9%)	0	4 (0.8%)
Serious Related AE to any study drug	4 (0.9%)	4 (0.9%)	0	4 (0.8%)
AE leading to study discontinuation	0	0	0	0
AE leading to any study treatment dose discontinuation	0	0	0	0
AE leading to any study treatment dose reduction	2 (0.5%)	0	0	0
AE leading to any study treatment dose interruption	1 (0.2%)	2 (0.5%)	0	2 (0.4%)
AE leading to polatuzumab vedotin/placebo discontinuation	0	0	0	0
AE leading to polatuzumab vedotin/placebo dose reduction	0	0	0	0
AE leading to polatuzumab vedotin/placebo dose interruption	1 (0.2%)	2 (0.5%)	0	2 (0.4%)
AE leading to vincristine/placebo discontinuation	0	0	0	0
AE leading to vincristine/placebo dose reduction	0	0	0	0
AE leading to vincristine/placebo dose interruption	1 (0.2%)	2 (0.5%)	0	2 (0.4%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

- *Thrombocytopenia*

Study POLARIX

Overall, the proportion of patients who experienced thrombocytopenia in the pola+R-CHP arm (13.3%) was comparable with the R-CHOP arm (13.2%).

Median time to onset of first thrombocytopenia (all grades) was 1.68 months (range: 0.2 – 7.2 months) in the pola+R-CHP arm and 0.41 months (range: 0.1 – 7.7 months) in the R-CHOP arm. Thrombocytopenia was reported as resolved in 94.8% (55/58 patients with events) in the pola+R-CHP arm and 86.2% (50/58 patients with events) in the R-CHOP arm, as of the CCOD. Median time to resolution of thrombocytopenia was 0.36 months (range: 0.1 – 13.2 months) in the pola+R-CHP arm and 0.36 months (range: 0.0 – 24.1 months) in the R-CHOP arm.

Supportive study GO29044

A total of 14/66 patients (21.2%) experienced 26 thrombocytopenia events (Table 18), with a median time to onset of 0.87 months (range: 0.1-5.1 months).

Thrombocytopenia was reported as resolved in all but one patient at data cut-off. Median time to resolution of thrombocytopenia was 0.46 months (range 0.1-12.6 months).

Pooled safety population

The proportion of patients who experienced thrombocytopenia in the pooled safety population (14.4% [72/501 patients]) was consistent with the pola+R-CHP arm from POLARIX and comparable with the R-CHOP arm (13.2% [58/438 patients]).

Table 34 Overview of AEPI Thrombocytopenia in Previously untreated DLBCL patients, Safety-evaluable Patients

Overall AE Profile - AEPI Thrombocytopenia, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Total number of patients with at least one AE	58 (13.2%)	58 (13.3%)	14 (21.2%)	72 (14.4%)
Total number of AEs	123	102	26	128
Total number of patients with at least one				
Grade 5 AE	0	0	0	0
Grade 3-5 AE	22 (5.0%)	23 (5.3%)	6 (9.1%)	29 (5.8%)
Serious AE	1 (0.2%)	2 (0.5%)	0	2 (0.4%)
Serious Related AE to any study drug	1 (0.2%)	2 (0.5%)	0	2 (0.4%)
AE leading to study discontinuation	0	0	0	0
AE leading to any study treatment dose discontinuation	0	1 (0.2%)	1 (1.5%)	2 (0.4%)
AE leading to any study treatment dose reduction	2 (0.5%)	2 (0.5%)	0	2 (0.4%)
AE leading to any study treatment dose interruption	0	0	2 (3.0%)	2 (0.4%)
AE leading to polatuzumab vedotin/placebo discontinuation	0	1 (0.2%)	1 (1.5%)	2 (0.4%)
AE leading to polatuzumab vedotin/placebo dose reduction	2 (0.5%)	0	0	0
AE leading to polatuzumab vedotin/placebo dose interruption	0	0	0	0
AE leading to vincristine/placebo discontinuation	0	1 (0.2%)	0	1 (0.2%)
AE leading to vincristine/placebo dose reduction	2 (0.5%)	0	0	0
AE leading to vincristine/placebo dose interruption	0	0	0	0

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

- *Infection*

Study POLARIX

Overall, the proportion of patients who experienced infections in the pola+R-CHP arm (49.7%) was higher than the R-CHOP arm (42.7%).

The proportion of patients who experienced Grade 3-4 infections (highest grade) was 14.0% in the pola+R-CHP arm and 11.2% in the R-CHOP arm. The proportion of patients who experienced Grade 5 infections (highest grade) was 1.1% (5 patients) in the pola+R-CHP arm and 1.4% (6 patients) in the R-CHOP arm. Grade 5 infections by PT occurring in the pola+R-CHP arm were pneumonia (4 patients) and sepsis (1 patient) and in the R-CHOP arm were pneumonia (3 patients), septic shock (2 patients) and sepsis (1 patient).

Median time to onset of first infection was 1.92 months (range: 0.0 – 8.3 months) in the pola+R-CHP arm and 1.58 months (range: 0.0 – 7.8 months) in the R-CHOP arm.

Infection was reported as resolved in 87.0% (188/216 patients with events) in the pola+R-CHP arm and 84.5% (158/187 patients with events) in the R-CHOP arm, as of the CCOD. Median time to resolution of infection was 0.39 months (range: 0.0 – 21.5 months) in the pola+R-CHP arm and 0.46 months (range: 0.0 – 17.8 months) in the R-CHOP arm.

A low number of opportunistic infections was reported in both treatment arms (1.6% [7 patients] in the pola+R-CHP arm and 0.7% [3 patients] in the R-CHOP arm).

No patients in the pola+R-CHP arm experienced an AE of hepatitis B virus (HBV) reactivation during the study; 1 patient in the R-CHOP arm experienced a Grade 2 AE of HBV reactivation.

Based on laboratory data, 44 patients (10.1%) in the pola+R-CHP arm and 50 patients (11.4%) in the R-CHOP arm had a previous history of HBV infection and were considered at risk of developing HBV reactivation. Of the patients at risk, 2/44 in the pola+R-CHP arm and 7/50 in the R-CHOP arm had evidence of HBV reactivation any time post-baseline. Both patients in the pola+R-CHP arm and 5/7 patients in the RCHOP arm had evidence of HBV reactivation during the follow up period.

Supportive study GO29044

A total of 35/66 patients (53.0%) experienced 58 events of infection, with a median time to onset of 1.58 months (range: 0.2-6.6 months).

Grade ≥3 infections were reported in 11 patients (16.7%); 8 patients had Grade 3 infections and 2 patients had a Grade 4 infection. One patient experienced a Grade 5 infection (septic shock, unrelated).

Nine patients (13.6%) experienced a serious infection. Two patients discontinued study treatment due to an infection (Escherichia urinary tract infection [Grade 2]; septic shock [Grade 5]), 3 patients had their study treatment interrupted (ophthalmic herpes zoster [Grade 3], bronchitis [Grade 2], and pneumonia [Grade 3]). One patient had their study treatment dose reduced due to an infection AE.

No opportunistic infections or hepatitis B reactivation events were reported in any patient.

All but one of the infections were reported as resolved at data cut-off with a median time to resolution of 0.49 months (range 0.1-1.5 months).

No patients had evidence of HBV reactivation during the study.

Pooled safety population

Table 35 Overview of AEPI Infections in Previously untreated DLBCL patients, Safety-evaluable Patients

Overall AE Profile - AEPI Infections and Infestations, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Total number of patients with at least one AE	187 (42.7%)	216 (49.7%)	35 (53.0%)	251 (50.1%)
Total number of AEs	343	409	58	467
Total number of patients with at least one				
Grade 5 AE	6 (1.4%)	5 (1.1%)	1 (1.5%)	6 (1.2%)
Grade 3-5 AE	55 (12.6%)	66 (15.2%)	11 (16.7%)	77 (15.4%)
Serious AE	45 (10.3%)	61 (14.0%)	9 (13.6%)	70 (14.0%)
Serious Related AE to any study drug	28 (6.4%)	45 (10.3%)	6 (9.1%)	51 (10.2%)
AE leading to study discontinuation	6 (1.4%)	5 (1.1%)	2 (3.0%)	7 (1.4%)
AE leading to any study treatment dose discontinuation	10 (2.3%)	7 (1.6%)	3 (4.5%)	10 (2.0%)
AE leading to any study treatment dose reduction	4 (0.9%)	1 (0.2%)	1 (1.5%)	2 (0.4%)
AE leading to any study treatment dose interruption	22 (5.0%)	27 (6.2%)	3 (4.5%)	30 (6.0%)
AE leading to polatuzumab vedotin/placebo discontinuation	7 (1.6%)	5 (1.1%)	2 (3.0%)	7 (1.4%)
AE leading to polatuzumab vedotin/placebo dose reduction	1 (0.2%)	0	0	0
AE leading to polatuzumab vedotin/placebo dose interruption	20 (4.6%)	21 (4.8%)	3 (4.5%)	24 (4.8%)
AE leading to vincristine/placebo discontinuation	7 (1.6%)	5 (1.1%)	0	5 (1.0%)
AE leading to vincristine/placebo dose reduction	2 (0.5%)	0	0	0
AE leading to vincristine/placebo dose interruption	19 (4.3%)	22 (5.1%)	0	22 (4.4%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

- *Hepatic toxicity*

Study POLARIX

Overall, the proportion of patients who experienced hepatic toxicity in the pola+R-CHP arm (10.6%) was slightly higher than the R-CHOP arm (7.3%). The majority of hepatic toxicity events were low-grade liver enzyme elevations in both the treatment arms. No patients experienced Grade 4 or Grade 5 hepatic toxicity events.

Median time to onset of first hepatic toxicity event was 0.85 months (range: 0.0 – 6.7 months) in the pola+R-CHP arm and 0.69 months (range: 0.0 – 5.2 months) in the R-CHOP arm.

Hepatic toxicity was reported as resolved in 87.0% (40/46 patients with events) in the pola+R-CHP arm and 84.4% (27/32 patients with events) in the R-CHOP arm, as of the CCOD. Median time to resolution of hepatic toxicity was 0.56 months (range: 0.1 – 9.1 months) in the pola+R-CHP arm and 0.54 months (range: 0.1 – 14.3 months) in the RCHOP arm.

Using an algorithm based on laboratory values of liver enzymes in combination with elevated bilirubin levels/clinical jaundice, potential cases of drug-induced liver injury (DILI) were identified in 1 patient in the pola+R-CHP arm and 2 patients in the R-CHOP arm. All cases were confounded by concomitant medical conditions and the underlying illness.

In the pola+R-CHP arm, 1 case of potential DILI was identified:

- Patient 10688 - This 55-year-old female patient presented Grade 4 cytopenia on Study Day 10. On Study Day 12, the patient experienced life-threatening sepsis with a blood culture positive for Staphylococcus aureus, and was treated with antibiotics. The events of cytopenia and sepsis resolved by Study Day 16. Elevated ALT and bilirubin were noted on Study Day 23; however, no AEs relating to the abnormal liver enzymes were reported. The patient received study treatment on Study Day 23 (Cycle 2, Day 1) as planned. This case is confounded by the event of sepsis in the period preceding the ALT and bilirubin increase.

In the R-CHOP arm, 2 cases of potential DILI were identified:

- Patient number 10762- The first was a 49-year-old male patient with a medical history of biliary tract infection. On Study Day 10, laboratory work-up showed Grade 4 neutropenia and Grade 1 abnormal hepatic function. On Study Day 11, the patient was hospitalized for fever and persistent neutropenia. A blood culture was positive for Escherichia coli and the patient was diagnosed with Escherichia sepsis. The abnormal hepatic function worsened to Grade 3. The patient was treated with antibiotics and the events of neutropenia, sepsis and abnormal hepatic function resolved by Study Day 22. This case is confounded by the event of E.coli sepsis and history of prior biliary tract infection.
- Patient number 10802 - The second patient, a 69-year-old male received study treatment (Cycle 5 Day 1) on Study Day 83. On Study Day 89, the patient was hospitalized with Grade 4 febrile neutropenia. On Study Day 90, the patient was diagnosed with Grade 3 pneumonia, and laboratory work-up showed elevated liver enzymes, total bilirubin, creatinine, urea, C-reactive protein, and decreased platelets, WBC count and hemoglobin. The patient was diagnosed with life-threatening Grade 4 multiple organ dysfunction syndrome and was discontinued from study treatment. The patient died due to multiple organ dysfunction syndrome on Study Day 157. No other AEs related to abnormal liver function were reported. This case is confounded by multiple organ dysfunction in the setting of febrile neutropenia.

<u>Supportive study GO29044</u>

Five of 66 patients (7.6%) experienced 8 hepatic toxicity events with a median time to onset of 2.00 months (range: 0.3-4.1 months). One patient experienced a Grade ≥3 hepatic toxicity AE (gamma-glutamyltransferase increased [Grade 3]). All other events were Grade ≤ 2.

No hepatic toxicity SAEs were reported and no patient had their study treatment dose changed as a result of a hepatic toxicity event. All hepatic toxicity events were reported as resolved at data cut-off. Median time to resolution of hepatic toxicity was 0.61 months (range 0.1-3.1 months).

Pooled safety population

The proportion of patients who experienced hepatic toxicity in the pooled safety population (10.2% [51/501 patients]) was consistent with the pola+R-CHP arm from POLARIX and slightly higher than that in the R-CHOP arm (7.3% [32/438 patients]).

Table 36 Overview of AEPI Hepatic toxicity in Previously untreated DLBCL patients, Safety-evaluable Patients

Overall AE Profile - AEPI Hepatic Toxicity, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Total number of patients with at least one AE	32 (7.3%)	46 (10.6%)	5 (7.6%)	51 (10.2%)
Total number of AEs	61	74	8	82
Total number of patients with at least one				
Grade 5 AE	0	0	0	0
Grade 3-5 AE	4 (0.9%)	8 (1.8%)	1 (1.5%)	9 (1.8%)
Serious AE	0	1 (0.2%)	0	1 (0.2%)
Serious Related AE to any study drug	0	0	0	0
AE leading to study discontinuation	0	0	0	0
AE leading to any study treatment dose discontinuation	0	0	0	0
AE leading to any study treatment dose reduction	1 (0.2%)	2 (0.5%)	0	2 (0.4%)
AE leading to any study treatment dose interruption	1 (0.2%)	4 (0.9%)	0	4 (0.8%)
AE leading to polatuzumab vedotin/placebo discontinuation	0	0	0	0
AE leading to polatuzumab vedotin/placebo dose reduction	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
AE leading to polatuzumab vedotin/placebo dose interruption	1 (0.2%)	4 (0.9%)	0	4 (0.8%)
AE leading to vincristine/placebo discontinuation	0	0	0	0
AE leading to vincristine/placebo dose reduction	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
AE leading to vincristine/placebo dose interruption	1 (0.2%)	4 (0.9%)	0	4 (0.8%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

- *Carcinogenicity / Secondary malignancies*

Study POLARIX

Overall, the proportion of patients who experienced a carcinogenicity/secondary malignancy during the treatment-emergent AE interval (90 days after last dose of study drug or prior to NALT, whichever is earlier) in the pola+R-CHP arm (0.9% [4 patients]) was comparable with the R-CHOP arm (1.1% [5 patients]).

Grade 3-4 carcinogenicity events (highest grade) were reported in 0.9% (4 patients) in the pola+R-CHP arm and 0.5% (2 patients) in the R-CHOP arm. No patients experienced a Grade 5 carcinogenicity event. The proportion of patients who experienced a serious carcinogenicity event in the pola+R-CHP arm (0.7% [3 patients]) was comparable with the R-CHOP arm (0.2% [1 patient]). No patients in either arm experienced a carcinogenicity event that led to study treatment discontinuation, dose reduction or treatment interruption.

Median time to onset of first carcinogenicity event was 5.86 months (range: 2.7 – 6.5 months) in the pola+R-CHP arm and 5.06 months (range: 3.4 – 6.8 months) in the R-CHOP arm. Carcinogenicity events were reported as resolved in 1 of 4 patients with events in the pola+R-CHP arm and 3 of 5 patients with events in the R-CHOP arm, as of the CCOD. Median time to resolution of the carcinogenicity event was 3.25 months in the patient in the pola+R-CHP arm and 5.06 months (range: 0.0 – 12.2 months) for the 3 patients in the R-CHOP arm.

Carcinogenicity events were distributed across a range of tumor types in individual patients. In the pola+R-CHP arm 1 patient had adenocarcinoma of colon, 1 patient had adenocarcinoma of the pancreas, 1 patient had colorectal cancer, and 1 patient had papillary renal cell carcinoma. In the R-CHOP arm, 1 patient had adenocarcinoma, 1 patient had basal cell carcinoma, 1 patient had Hodgkin's disease, 1 patient had a lung neoplasm and 1 patient had malignant melanoma in situ.

Carcinogenicity events reported over the entire study period (which included the treatment emergent AE interval and up until CCOD) were reported in an additional 1 patient in the pola□R-CHP arm (colorectal cancer) and 4 patients in the R-CHOP arm: One patient had acute myeloid leukemia, 1 patient had adenocarcinoma, 1 patient had lung neoplasm malignant, and 1 patient had prostate cancer.

Study GO29044

No carcinogenicity/secondary malignancy events were reported in any patient

Pooled safety population

Table 37 Overview of AEPI Secondary Malignancy / Carcinogenicity in Previously untreated DLBCL patients, Safety-evaluable Patients

Overall AE Profile - AEPI Carcinogenicity, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Total number of patients with at least one AE	5 (1.1%)	4 (0.9%)	0	4 (0.8%)
Total number of AEs	9	4	0	4
Total number of patients with at least one				
Grade 5 AE	0	0	0	0
Grade 3-5 AE	2 (0.5%)	4 (0.9%)	0	4 (0.8%)
Serious AE	1 (0.2%)	3 (0.7%)	0	3 (0.6%)
Serious Related AE to any study drug	0	1 (0.2%)	0	1 (0.2%)
AE leading to study discontinuation	0	0	0	0
AE leading to any study treatment dose discontinuation	0	0	0	0
AE leading to any study treatment dose reduction	0	0	0	0
AE leading to any study treatment dose interruption	0	0	0	0
AE leading to polatuzumab vedotin/placebo discontinuation	0	0	0	0
AE leading to polatuzumab vedotin/placebo dose reduction	0	0	0	0
AE leading to polatuzumab vedotin/placebo dose interruption	0	0	0	0
AE leading to vincristine/placebo discontinuation	0	0	0	0
AE leading to vincristine/placebo dose reduction	0	0	0	0
AE leading to vincristine/placebo dose interruption	0	0	0	0

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

- *Pulmonary toxicity*

Study POLARIX

The proportion of patients who experienced a pulmonary toxicity event was the same in both arms (1.6% [7 patients]).

Median time to onset of first pulmonary toxicity event was 2.14 months (range: 2.0 – 4.4 months) in the pola+R-CHP arm and 2.73 months (range: 0.0 – 6.0 months) in the R-CHOP arm. Pulmonary toxicity was reported as resolved in 7/7 patients with events in the pola+R-CHP arm and 5/7 patients with events in the R-CHOP arm, as of the CCOD.

Median time to resolution of pulmonary toxicity was 0.59 months (range: 0.1 – 3.8 months) in the pola+R-CHP arm and 0.72 months (range: 0.3 – 4.2 months) in the RCHOP arm.

Study GO29044

One of 66 patients (1.5%) experienced a pulmonary toxicity event with a time to onset of 3.78 months. The non-serious event of Grade 2 pneumonitis did not lead to a change in study treatment and was reported as resolved at data cut-off for the final analysis.

Pooled safety population

The proportion of patients who experienced a pulmonary toxicity event in the pooled safety population (1.6% [8/501 patients]) was consistent with the pola+R-CHP arm from POLARIX and comparable with the R-CHOP arm (1.6% [7/438 patients]).

Table 38 Overview of AEPI Pulmonary Toxicity in Previously untreated DLBCL patients, Safety-evaluable Patients

Overall AE Profile - AEPI Pulmonary Toxicity, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Total number of patients with at least one AE	7 (1.6%)	7 (1.6%)	1 (1.5%)	8 (1.6%)
Total number of AEs	7	8	1	9
Total number of patients with at least one				
Grade 5 AE	0	0	0	0
Grade 3-5 AE	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
Serious AE	2 (0.5%)	1 (0.2%)	0	1 (0.2%)
Serious Related AE to any study drug	0	1 (0.2%)	0	1 (0.2%)
AE leading to study discontinuation	0	0	0	0
AE leading to any study treatment dose discontinuation	0	3 (0.7%)	0	3 (0.6%)
AE leading to any study treatment dose reduction	0	0	0	0
AE leading to any study treatment dose interruption	4 (0.9%)	2 (0.5%)	0	2 (0.4%)
AE leading to polatuzumab vedotin/placebo discontinuation	0	2 (0.5%)	0	2 (0.4%)
AE leading to polatuzumab vedotin/placebo dose reduction	0	0	0	0
AE leading to polatuzumab vedotin/placebo dose interruption	4 (0.9%)	1 (0.2%)	0	1 (0.2%)
AE leading to vincristine/placebo discontinuation	0	2 (0.5%)	0	2 (0.4%)
AE leading to vincristine/placebo dose reduction	0	0	0	0
AE leading to vincristine/placebo dose interruption	4 (0.9%)	1 (0.2%)	0	1 (0.2%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

- *Infusion-related reactions*

As all components of the study treatment were administered on Day 1 of the first and subsequent treatment cycles, infusion-related reactions (IRRs) described in this section were identified based on entries in the Adverse Event page of the eCRF which met the following criteria:

– AEs suspected by the investigator to be caused by any study drug of the combination treatment (pola+R-CHP or R-CHOP) that occurred during infusion or within 24 hours after end of infusion.

– AE PT was one of the PTs identified as associated with Infusion-Related Reaction

Study POLARIX

Overall, the proportion of patients who experienced IRRs in the pola+R-CHP arm (13.3%) was comparable with the R-CHOP arm (16.0%). Most IRR events were low grade and non-serious.

No patient in the pola+R-CHP arm and 1 patient (0.2%) in the R-CHOP arm experienced an IRR that led to study treatment discontinuation.

No patient in either arm experienced an IRR that led to any study treatment dose reduction. The proportion of patients who experienced IRRs that led to study treatment interruption in the pola+R-CHP arm (4.1%) was comparable with the R-CHOP arm (5.7%).

IRRs were reported as resolved in 100% (58/58 patients with events) in the pola+R-CHP arm and 98.6% (69/70 patients with events) in the R-CHOP arm, as of the CCOD.

Doses modifications to manage infusion-related reactions and prophylaxis treatment are commented in section 5.4.2. of this report.

Study GO29044

A total of 30/66 patients (45.5%) experienced 51 IRR events (Table 23) occurring within 24 hours of the first dose of any study drug.

One patient experienced a Grade ≥ 3 IRR (Grade 3 hypertension). All other IRRs were Grade ≤ 2. No patient experienced a serious IRR event and no patients discontinued study treatment or had their dose reduced due to an IRR. Seven patients had their study treatment dose interrupted due to an IRR. IRRs in all but 2 patients were reported as resolved at data cut-off.

Pooled safety population

The proportion of patients who experienced IRRs in the pooled safety population (17.6% [88/501 patients]) was generally consistent with the pola+R-CHP arm from POLARIX and comparable with the R-CHOP arm (16.0% [70/438 patients]) from POLARIX.

Table 39 Overview of AEPI Infusion Related Reactions in Previously untreated DLBCL patients, Safety-evaluable Patients

Overall AE Profile - AEPI Infusion Related Reactions, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Total number of patients with at least one AE	70 (16.0%)	58 (13.3%)	30 (45.5%)	88 (17.6%)
Total number of AEs	106	83	51	134
Total number of patients with at least one				
Grade 5 AE	0	0	0	0
Grade 3-5 AE	7 (1.6%)	5 (1.1%)	1 (1.5%)	6 (1.2%)
Serious AE	3 (0.7%)	2 (0.5%)	0	2 (0.4%)
Serious Related AE to any study drug	3 (0.7%)	2 (0.5%)	0	2 (0.4%)
AE leading to study discontinuation	0	0	0	0
AE leading to any study treatment dose discontinuation	1 (0.2%)	0	0	0
AE leading to any study treatment dose reduction	0	0	0	0
AE leading to any study treatment dose interruption	25 (5.7%)	18 (4.1%)	7 (10.6%)	25 (5.0%)
AE leading to polatuzumab vedotin/placebo discontinuation	0	0	0	0
AE leading to polatuzumab vedotin/placebo dose reduction	0	0	0	0
AE leading to polatuzumab vedotin/placebo dose interruption	1 (0.2%)	0	0	0
AE leading to vincristine/placebo discontinuation	0	0	0	0
AE leading to vincristine/placebo dose reduction	0	0	0	0
AE leading to vincristine/placebo dose interruption	0	0	0	0

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

- *Tumor Lysis Syndrome*

Study POLARIX

Overall, the proportion of patients who experienced TLS in the pola+R-CHP arm (0.5% [2 patients]) was comparable with the R-CHOP arm (0.9% [4 patients]).

No patients in either treatment arm experienced TLS that led to study treatment discontinuation or study treatment dose reduction. No patient in the pola+R-CHP arm and 1 patient (0.2%) in the R-CHOP arm experienced TLS that led to interruption of study treatment.

Median time to onset of first TLS was 0.05 months (range: 0.0 – 0.1 months) in the pola+R-CHP arm and 0.26 months (range: 0.1 – 1.4 months) in the R-CHOP arm. TLS was reported as resolved in all patients in the pola+R-CHP and R-CHOP arms, as of the CCOD. Median time to resolution of TLS was 0.13 months (range: 0.1 – 0.2 months) in the pola+R-CHP arm and 0.20 months (range: 0.1 – 0.4 months) in the R-CHOP arm.

Study GO29044

No TLS events were reported in any patient.

Pooled safety population

The proportion of patients who experienced TLS in the pooled safety population (0.4% [2/501 patients]) was consistent with the pola+R-CHP arm from POLARIX and comparable with the R-CHOP arm (0.9% [4/438 patients]).

Table 40 Overview of AEPI Tumor lysis syndrome in Previously untreated DLBCL patients, Safety-evaluable Patients

Overall AE Profile - AEPI Tumor Lysis Syndrome, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Total number of patients with at least one AE	4 (0.9%)	2 (0.5%)	0	2 (0.4%)
Total number of AEs	5	2	0	2
Total number of patients with at least one				
Grade 5 AE	0	0	0	0
Grade 3-5 AE	3 (0.7%)	2 (0.5%)	0	2 (0.4%)
Serious AE	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
Serious Related AE to any study drug	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
AE leading to study discontinuation	0	0	0	0
AE leading to any study treatment dose discontinuation	0	0	0	0
AE leading to any study treatment dose reduction	0	0	0	0
AE leading to any study treatment dose interruption	1 (0.2%)	0	0	0
AE leading to polatuzumab vedotin/placebo discontinuation	0	0	0	0
AE leading to polatuzumab vedotin/placebo dose reduction	0	0	0	0
AE leading to polatuzumab vedotin/placebo dose interruption	1 (0.2%)	0	0	0
AE leading to vincristine/placebo discontinuation	0	0	0	0
AE leading to vincristine/placebo dose reduction	0	0	0	0
AE leading to vincristine/placebo dose interruption	1 (0.2%)	0	0	0

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

- *Cardiac Arrhythmia*

Study POLARIX

Overall, the proportion of patients who experienced a cardiac arrhythmia event in the pola+R-CHP arm (3.0%) was comparable with the R-CHOP arm (4.6%).

The proportion of patients who experienced a Grade 3-4 cardiac arrhythmia event (highest grade) was 0.5% (2 patients) in the pola+R-CHP arm and 0.7% (3 patients) in the R-CHOP arm. No patients in the pola+R-CHP arm experienced a Grade 5 cardiac arrhythmia event compared with 1 patient (0.2%) in the R-CHOP arm.

Median time to onset of first cardiac arrhythmia was 2.17 months (range: 0.0 – 4.8 months) in the pola+R-CHP arm and 3.45 months (range: 0.0 – 7.4 months) in the R-CHOP arm. Cardiac arrhythmia was reported as resolved in 61.5% (8/13 patients with events) in the pola+R-CHP arm and 55.0% (11/20 patients with events) in the R-CHOP arm, as of the CCOD. Median time to resolution of cardiac arrhythmia was 0.07 months (range: 0.0 – 3.1 months) in the pola+R-CHP arm and 0.07 months (range: 0.0 – 9.9 months) in the R-CHOP arm.

Study GO29044

Three of 66 patients (4.5%) experienced 5 cardiac arrhythmia events (Table 25) with a median time to onset of 2.60 months (range: 0.1-7.8 months). Two patients experienced a Grade ≥3 cardiac arrhythmia

event; 1 patient experienced Grade 3 supraventricular tachycardia and 1 patient experienced Grade 5 atrial fibrillation. Neither event was considered related to study treatment by the investigator.

All but one of the cardiac arrhythmia events were reported as resolved at data cut-off. Median time to resolution of cardiac arrhythmia was 0.07 months (range 0-3.5 months).

Pooled safety population

Table 41 Overview of AEPI Cardiac Arrhythmia in Previously untreated DLBCL patients, Safety-evaluable Patients

Overall AE Profile - AEPI Cardiac Arrhythmias, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Total number of patients with at least one AE	20 (4.6%)	13 (3.0%)	3 (4.5%)	16 (3.2%)
Total number of AEs	21	16	5	21
Total number of patients with at least one				
Grade 5 AE	1 (0.2%)	0	1 (1.5%)	1 (0.2%)
Grade 3-5 AE	4 (0.9%)	2 (0.5%)	2 (3.0%)	4 (0.8%)
Serious AE	4 (0.9%)	2 (0.5%)	3 (4.5%)	5 (1.0%)
Serious Related AE to any study drug	1 (0.2%)	1 (0.2%)	1 (1.5%)	2 (0.4%)
AE leading to study discontinuation	1 (0.2%)	0	1 (1.5%)	1 (0.2%)
AE leading to any study treatment dose discontinuation	0	0	0	0
AE leading to any study treatment dose reduction	0	0	0	0
AE leading to any study treatment dose interruption	1 (0.2%)	0	0	0
AE leading to polatuzumab vedotin/placebo discontinuation	0	0	0	0
AE leading to polatuzumab vedotin/placebo dose reduction	0	0	0	0
AE leading to polatuzumab vedotin/placebo dose interruption	0	0	0	0
AE leading to vincristine/placebo discontinuation	0	0	0	0
AE leading to vincristine/placebo dose reduction	0	0	0	0
AE leading to vincristine/placebo dose interruption	0	0	0	0

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

- *Hyperglycemia*

Study POLARIX

Overall, the proportion of patients who experienced hyperglycemia in the pola+R-CHP arm (6.0%) was comparable with the R-CHOP arm (6.2%).

Grade 3 hyperglycemia (highest grade) was reported in 1.8% (8 patients) in the pola+RCHP arm and 1.4% (6 patients) in the R-CHOP arm. No patients in either arm experienced Grade 4 or Grade 5 hyperglycemia.

Median time to onset of first hyperglycemia event was 0.79 months (range: 0.0 – 3.0 months) in the pola+R-CHP arm and 0.72 months (range: 0.0 – 3.5 months) in the R-CHOP arm. Hyperglycemia was reported as resolved in 53.8% (14/26 patients with events) in the pola+R-CHP arm and 48.1% (13/27 patients with events) in the R-CHOP arm, as of the CCOD. Median time to resolution of hyperglycemia was 2.28 months (range: 0.0 – 5.8 months) in the pola+R-CHP arm and 0.66 months (range: 0.1 – 8.8 months) in the R-CHOP arm.

Study GO29044

A total of 6/66 patients (9.1%) experienced 10 events of hyperglycemia with a median time to onset of 0.39 months (range: 0.3 - 2.9 months).

Four patients experienced Grade ≥3 hyperglycemia; all 4 patients experienced Grade 3 events. All other events were Grade ≤ 2.

One SAE was reported (Grade 3 hyperglycemia) which was considered related to prednisone. No patient experienced a hyperglycemia event leading to study treatment discontinuation or interruption. One patient had their study treatment dose reduced.

All hyperglycemia events were reported as resolved at data cut-off with a median time to resolution of 0.10 months (range 0.0-3.1 months).

Pooled safety population

Table 42 Overview of AEPI Hyperglycemia in Previously untreated DLBCL patients, Safety-evaluable Patients

Overall AE Profile - AEPI Hyperglycemia, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Total number of patients with at least one AE	27 (6.2%)	26 (6.0%)	6 (9.1%)	32 (6.4%)
Total number of AEs	36	34	10	44
Total number of patients with at least one				
Grade 5 AE	0	0	0	0
Grade 3-5 AE	6 (1.4%)	8 (1.8%)	4 (6.1%)	12 (2.4%)
Serious AE	0	0	1 (1.5%)	1 (0.2%)
Serious Related AE to any study drug	0	0	1 (1.5%)	1 (0.2%)
AE leading to study discontinuation	0	0	0	0
AE leading to any study treatment dose discontinuation	0	0	0	0
AE leading to any study treatment dose reduction	0	1 (0.2%)	1 (1.5%)	2 (0.4%)
AE leading to any study treatment dose interruption	0	0	0	0
AE leading to polatuzumab vedotin/placebo discontinuation	0	0	0	0
AE leading to polatuzumab vedotin/placebo dose reduction	0	0	0	0
AE leading to polatuzumab vedotin/placebo dose interruption	0	0	0	0
AE leading to vincristine/placebo discontinuation	0	0	0	0
AE leading to vincristine/placebo dose reduction	0	0	0	0
AE leading to vincristine/placebo dose interruption	0	0	0	0

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

Serious adverse event/deaths/other significant events

- *Deaths*

Study POLARIX

At the time of the clinical cut-off date (CCOD), a total of 111 patients (12.7%) had died due to any cause. The proportion of patients who died in the pola+R-CHP arm (12.0%) was comparable with the R-CHOP arm (13.5%). The most common cause of death during the entire study period in both treatment arms was disease progression (6.4% in the pola+R-CHP arm and 7.1% in the R-CHOP arm). Almost all deaths due to disease progression occurred during the follow-up period. Two patients (0.5%) in the R-CHOP arm died due to disease progression during the AE reporting period.

Fatal AEs were reported in 3.0% of patients in the pola+R-CHP arm and 2.5% of patients in the R-CHOP arm. Almost all deaths due to AEs occurred during the AE reporting period. One patient in the R-CHOP arm experienced a Grade 5 AE (acute myeloid leukemia) during the follow up period. Most of the fatal AEs in both arms were due to infections or complications of infection.

The most frequent Grade 5 AEs (by PT) were pneumonia (4 patients [0.9%] in the pola+R-CHP arm and 3 patients [0.7%] in the R-CHOP arm), death (4 patients [0.9%] in the pola+R-CHP arm and 1 patient [0.2%] in the R-CHOP arm) and septic shock (0 patients in the pola+R-CHP arm and 2 patients [0.5%] in the R-CHOP arm). The proportion of patients who died due to AEs that were considered related to the treatment by the investigator was 1.4% (6 patients) in the pola+R-CHP arm and 1.1% (5 patients) in the R-CHOP arm.

The treatment-related AEs that led to death in the pola+R-CHP arm were pneumonia (3 patients), cardiac death, acute kidney injury and death.

Treatment-related AEs that led to death in the R-CHOP arm were pneumonia (2 patients), multiple organ dysfunction syndrome, and sepsis. One additional patient had a Grade 5 AE (acute myeloid leukemia) during the follow-up period which the investigator assessed as related to study treatment.

Supportive study GO29044

A total of 6 deaths were reported in the pola+R-CHP/G-CHP population; 2 patients died due to an AE (atrial fibrillation, septic shock) during the AE reporting interval and 4 patients died due to disease progression in the follow-up period .

One patient with a history of mitral valve repair and concurrent conditions including mitral valve regurgitation and coronary artery disease, died due to atrial fibrillation. The investigator assessed this event as unrelated to any study drug and related to concurrent illness. The second patient died due to septic shock considered related to doxorubicin and cyclophosphamide treatment.

Pooled safety population

The proportion of patients who died in the pooled safety population (11.6% [58/501 patients]) was comparable with the R-CHOP arm from POLARIX (13.5% [59/438 patients]). The most common cause of death in both treatment arms was disease progression (6.4% in the pooled safety population and 7.1% in the R-CHOP arm from POLARIX).

Table 43 Summary of Deaths in Previously Untreated DLBCL Patients, Safety-Evaluable Patients

Summary of Deaths, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Total number of deaths	59 (13.5%)	52 (12.0%)	6 (9.1%)	58 (11.6%)
Primary Cause of Death				
Disease progression	31 (7.1%)	28 (6.4%)	4 (6.1%)	32 (6.4%)
Adverse event	11 (2.5%)	13 (3.0%)	2 (3.0%)	15 (3.0%)
Other	17 (3.9%)	11 (2.5%)	0	11 (2.2%)
DLBCL was a contributing factor	2 (0.5%)	3 (0.7%)	0	3 (0.6%)
DLBCL not known to be a contributing factor	15 (3.4%)	8 (1.8%)	0	8 (1.6%)
Deaths during AE reporting period	12 (2.7%)	13 (3.0%)	2 (3.0%)	15 (3.0%)
Primary Cause of Death				
Disease progression	2 (0.5%)	0	0	0
Adverse event	10 (2.3%)	13 (3.0%)	2 (3.0%)	15 (3.0%)
Deaths during follow-up	46 (10.5%)	39 (9.0%)	4 (6.1%)	43 (8.6%)
Primary Cause of Death				
Disease progression	29 (6.6%)	28 (6.4%)	4 (6.1%)	32 (6.4%)
Adverse event	1 (0.2%)	0	0	0
Other	16 (3.7%)	11 (2.5%)	0	11 (2.2%)
DLBCL was a contributing factor	2 (0.5%)	3 (0.7%)	0	3 (0.6%)
DLBCL not known to be a contributing factor	14 (3.2%)	8 (1.8%)	0	8 (1.6%)

AE reporting period is defined as time 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. Follow up period defined as time outside of the AE reporting period. Contributing factor includes treatment related death, or if the investigator considers DLBCL to be a contributing factor to the death.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

Program: root/clinical_studies/RO5541077/share/pool_1LDLBCL_SCS/prod/program/t_dd.sas
Output: root/clinical_studies/RO5541077/share/pool_1LDLBCL_SCS/prod/output/t_dd_1LP_SE.out
10AUG2021 23:29 Page 1 of 1

Note: One patient in the R-CHOP arm with a partially missing death date (unknown month, day) obtained from the public record was included in the 'Total number of deaths' row but excluded from the subtotal row of 'Deaths during AE reporting period' or 'Deaths during follow up' as the reporting period during which the death occurred could not be determined.

Table 44 Grade 5 AEs by SOC and Preferred Term in Previously Untreated DLBCL Patients, Safety-Evaluable Patients

MedDRA System Organ Class MedDRA Preferred Term	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Total number of patients with at least one adverse event	10 (2.3%)	13 (3.0%)	2 (3.0%)	15 (3.0%)
Overall total number of events	10	13	2	15
Infections and infestations				
Total number of patients with at least one adverse event	6 (1.4%)	5 (1.1%)	1 (1.5%)	6 (1.2%)
Total number of events	6	5	1	6
Pneumonia	3 (0.7%)	4 (0.9%)	0	4 (0.8%)
Septic shock	2 (0.5%)	0	1 (1.5%)	1 (0.2%)
Sepsis	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
General disorders and administration site conditions				
Total number of patients with at least one adverse event	2 (0.5%)	5 (1.1%)	0	5 (1.0%)
Total number of events	2	5	0	5
Death	1 (0.2%)	4 (0.9%)	0	4 (0.8%)
Cardiac death	0	1 (0.2%)	0	1 (0.2%)
Multiple organ dysfunction syndrome	1 (0.2%)	0	0	0
Cardiac disorders				
Total number of patients with at least one adverse event	1 (0.2%)	0	1 (1.5%)	1 (0.2%)
Total number of events	1	0	1	1
Atrial fibrillation	0	0	1 (1.5%)	1 (0.2%)
Atrioventricular block complete	1 (0.2%)	0	0	0
Gastrointestinal disorders				
Total number of patients with at least one adverse event	0	1 (0.2%)	0	1 (0.2%)
Total number of events	0	1	0	1
Intestinal perforation	0	1 (0.2%)	0	1 (0.2%)

MedDRA System Organ Class MedDRA Preferred Term	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Renal and urinary disorders				
Total number of patients with at least one adverse event	0	1 (0.2%)	0	1 (0.2%)
Total number of events	0	1	0	1
Acute kidney injury	0	1 (0.2%)	0	1 (0.2%)
Respiratory, thoracic and mediastinal disorders				
Total number of patients with at least one adverse event	0	1 (0.2%)	0	1 (0.2%)
Total number of events	0	1	0	1
Respiratory failure	0	1 (0.2%)	0	1 (0.2%)
Injury, poisoning and procedural complications				
Total number of patients with at least one adverse event	1 (0.2%)	0	0	0
Total number of events	1	0	0	0
Injury	1 (0.2%)	0	0	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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

- *Other serious adverse event*

Study POLARIX

The proportion of patients with at least one SAE in the pola+R-CHP arm (34.0%) was comparable with the R-CHOP arm (30.6%).

SAEs were most commonly reported (≥5% of patients in either arm) in the following SOCs (pola+R-CHP arm and R-CHOP arm, respectively):

– Infections and infestations (14.0% and 10.3%)

– Blood and lymphatic system disorders (11.5% and 9.1%)

– Gastrointestinal disorders (7.1% and 5.9%)

– General disorders and administration site conditions (6.0% and 4.6%)

The proportion of patients with at least one SAE considered related to treatment in the Pola+R-CHP arm (25.7%) was higher than in the R-CHOP arm (19.6%).

The most common related SAEs by PT (≥1% of patients in either arm) were (pola+RCHP arm and R-CHOP arm, respectively):

– Febrile neutropenia (9.7% and 5.7%)

– Pneumonia (3.7% and 3.0%)

– Diarrhea (2.3% and 0.2%)

– Neutropenia (0.9% and 1.4%)

– Sepsis (0.9% and 1.1%)

– Pyrexia (1.1% and 0.7%)

– Urinary tract infection (1.1% and 0.2%)

– Vomiting (1.1% and 0.5%).

No patients in either treatment arm discontinued study treatment due to the SAEs of febrile neutropenia, diarrhea or urinary tract infection.

Supportive study GO29044

The majority of SAEs in Study GO29044 were due to cytopenia and infections.

A total of 27/66 patients (40.9%) had SAEs. By SOC, SAEs reported in ≥5% of patients comprised of blood and lymphatic system disorders (16.7%), and infections and infestations (13.6%). By preferred term, febrile neutropenia, neutropenia, atrial fibrillation, influenza A virus test positive, syncope, pneumonia, and pulmonary embolism were the only SAEs reported in ≥1 patient.

SAEs considered related to treatment were reported in 17 patients (25.8%). The SAEs were febrile neutropenia (6 patients), neutropenia (4 patients), pneumonia (3 patients), atrial fibrillation, clostridium difficile infection, oral fungal infection, septic shock, diarrhea, vomiting, malnutrition, hyperglycemia, asthenia, arthritis, and pulmonary embolism. With the exception of vomiting and a fatal SAE of septic shock in one patient and a fatal SAE of atrial fibrillation in a second patient, all other related SAEs were resolved/resolved with sequelae.

Pooled safety population

The proportion of patients with at least one SAE in the pooled safety population (34.9% [175/501 patients]) was consistent with the pola+R-CHP arm from POLARIX and comparable with the R-CHOP arm (30.6% [134/438 patients]).

Table 45 Serious Adverse Events by SOC and Preferred Term Occurring in ≥ 1% of Patients in either POLARIX Treatment Arm in Previously Untreated DLBCL Patients, Safety-Evaluable Patients

Summary of Serious Adverse Events with an Incidence Rate of at Least 1% by System Organ Class and Preferred Term, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

MedDRA System Organ Class MedDRA Preferred Term	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Infections and infestations				
Pneumonia	17 (3.9%)	18 (4.1%)	5 (7.6%)	23 (4.6%)
Sepsis	7 (1.6%)	5 (1.1%)	1 (1.5%)	6 (1.2%)
Urinary tract infection	3 (0.7%)	8 (1.8%)	0	8 (1.6%)
Blood and lymphatic system disorders				
Febrile neutropenia	28 (6.4%)	43 (9.9%)	9 (13.6%)	52 (10.4%)
Neutropenia	6 (1.4%)	4 (0.9%)	4 (6.1%)	8 (1.6%)
Anaemia	6 (1.4%)	4 (0.9%)	0	4 (0.8%)
Gastrointestinal disorders				
Diarrhoea	2 (0.5%)	11 (2.5%)	1 (1.5%)	12 (2.4%)
Vomiting	2 (0.5%)	5 (1.1%)	1 (1.5%)	6 (1.2%)
Small intestinal obstruction	5 (1.1%)	0	0	0
General disorders and administration site conditions				
Pyrexia	8 (1.8%)	8 (1.8%)	0	8 (1.6%)

Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings. Incidence rate cutoff was only applied to R-CHOP (POLARIX) and Pola-R-CHP (POLARIX) columns. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. 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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

Laboratory findings

3-4 (Worst-Grade) Laboratory Test Parameters, Safety-Evaluable Patients

	R-CHOP (POLARIX) N=438	Pola-R-CHP (POLARIX) N=435	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) N=66	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) N=501
Hematology Laboratory Parameters				
↓ Lymphocytes (abs)	204/436 (46.8%)	205/431 (47.6%)	37/66 (56.1%)	242/497 (48.7%)
↓ Neutrophils (total, abs)	161/430 (37.4%)	152/427 (35.6%)	21/66 (31.8%)	173/493 (35.1%)
↓ Leukocytes (total)	132/436 (30.3%)	127/432 (29.4%)	23/66 (34.8%)	150/498 (30.1%)
↓ Hemoglobin	39/436 (8.9%)	45/432 (10.4%)	3/66 (4.5%)	48/498 (9.6%)
↓ Platelets	24/436 (5.5%)	30/432 (6.9%)	4/66 (6.1%)	34/498 (6.8%)
Biochemistry Laboratory Parameters				
↑ Uric acid	86/435 (19.8%)	95/430 (22.1%)	7/66 (10.6%)	102/496 (20.6%)
↑ Glucose	26/435 (6.0%)	28/431 (6.5%)	7/66 (10.6%)	35/497 (7.0%)

Source: t_lb_abn_1LP_SE

- *Immunogenicity*

In pivotal Study POLARIX, for all patients, the baseline prevalence of anti-drug antibodies (ADAs) was 2.4% (20/849 ADA evaluable patients). The 8 patients from the pola+R-CHP treatment arm who tested positive for ADA at baseline were treatment unaffected (ADA response was similar to, or lower than, that at baseline). Post-baseline, ADAs were detected in 6 of 427 (1.4%) ADA-evaluable patients treated with pola. All 6 ADA-positive patients had treatment-induced responses (ADA negative at baseline or missing a baseline sample for ADA analysis and at least one positive post−baseline ADA result). All 6 patients with treatment-induced ADA were negative for neutralizing antibody.

Table 46 Incidence of Anti-Drug Antibodies to Pola in POLARIX

	Arm A Pola+R-CHP (N=433)	Arm B R-CHOP (N=425)	All Patients (N=858)
Baseline Prevalence of ADAs			
Baseline evaluable patients	424	425	849
Patients with a positive sample at baseline	8 (1.9%)	12 (2.8%)	20 (2.4%)
Patients with no positive samples at baseline	416	413	829
Post-Baseline Incidence of ADAs			
Post−baseline evaluable patients	427		
Patients Positive for ADA	6 (1.4%)		
Treatment-Induced	6		
Treatment-Enhanced	0		
Patients negative for ADA	421		
Treatment unaffected	8		

ADA=anti−drug antibodies; Pola= polatuzumab vedotin; R-CHP= rituximab plus cyclophosphamide, doxorubicin, and prednisone; R-CHOP=rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.
Baseline evaluable patient = a patient with an ADA assay result from a baseline sample.
Post−baseline evaluable patient = a patient with an ADA assay result from at least one post−baseline sample.
Number of patients positive for ADA = the number (and percentage) of post−baseline evaluable patients determined to have treatment−induced ADA or treatment−enhanced ADA during the study period.
Treatment−induced ADA = a patient with negative or missing baseline ADA result(s) and at least one positive post−baseline ADA result.
Treatment−enhanced ADA = a patient with positive ADA result at baseline who has one or more post−baseline titer results that are at least 0.60 t.u. greater than the baseline titer result.
Number of patients negative for ADA = number of post−baseline evaluable patients with negative or missing baseline ADA result(s) and all negative post−baseline results, or a patient who is treatment unaffected.
Treatment unaffected = A post−baseline evaluable patient with a positive ADA result at baseline and (a) where all post−baseline titer results are less than 0.60 t.u. greater than the baseline titer result, OR (b) where all post−baseline results are negative or missing.
For any positive sample with titer result less than the minimum reportable titer or any positive sample where a titer cannot be obtained, titer value is imputed as equal to the minimum reportable titer.
Source: t_ada1

For supportive Study GO29044, there were no observed ADA responses at either baseline or post-baseline timepoints.

Table 47 Characterization of ADA Positive Samples in Study GO39942

Patient Number	Visit	Titer Units	Polatuzumab Vedotin Total Antibody µg/mL	Polatuzumab Antibody Immunodepletion	Patient Treatment-Emergent Status	Duration of ADA Response	Neutralizing Antibody
10000	Pre-dose Cycle 4 Day1	<1.7	7.97	–	Induced	persistent	negative
	TC/ED	<1.7	0.165	–			negative
10058	3MFU	<1.7	0.0568	–	Induced	persistent	negative
10082	TC/ED	<1.7	5.07	–	Induced	persistent	negative
10225	Pre-dose Cycle 4 Day1	<1.7	4.85	–	Induced	persistent	negative
	TC/ED	<1.7	0.617	–			negative
10267	Pre-dose Cycle 4 Day1	<1.7	5.98	–	Induced	persistent	negative
	3MFU	<1.7	<0.05	–			negative
	TC/ED	<1.7	0.934	–			negative
10728	Pre-dose Cycle 4 Day1	<1.7	9.37	–	Induced	persistent	negative
	TC/ED	<1.7	3.06	–			negative

ADA = anti-drug antibodies; Polatuzumab antibody=unconjugated humanized anti-CD79b antibody.
Minimum reportable titer = 1.70
Treatment-Emergent ADA = the number of post-baseline evaluable patients determined to have treatment-induced ADA or treatment-enhanced ADA during the study period.
Treatment-induced ADA = a patient with negative or missing baseline ADA result(s) and at least one positive post-baseline ADA result.
Treatment-enhanced ADA = a patient with positive ADA result at baseline who has one or more post-baseline titer results that are at least 0.60 t.u. greater than the baseline titer result.
3MFU=3-month follow-up visit; ADA=anti-drug antibody; TC/ED=treatment completion/early discontinuation
+=positive for immunodepletion; immune response directed mainly at antibody portion.
–=negative for immunodepletion; immune response directed mainly to linker, drug, or neo-epitopes.
Persistent ADA= ADA positive result detected (a) at the last post–baseline sampling time point, OR (b) at 2 or more time points during treatment where the first and last ADA positive samples are separated by a period >= 16 weeks, irrespective of any negative samples in between.
Transient ADA= ADA positive result detected (a) at only one post–baseline sampling time point (excluding last time point) OR (b) at 2 or more time points during treatment where the first and last ADA positive samples are separated by a period of < 16 weeks, irrespective of any negative samples in between.
Source: l_ada1, l_ada2

Table 48 Incidence of ADA to Pola in Study GO29044

	R-CHP+Pola 1.8 mg/kg (N=1)	G-CHP+Pola 1.4 mg/kg (N=6)	G-CHP+Pola 1.8 mg/kg (N=6)	EXP R-CHP+Pola 1.8 mg/kg (N=33)	EXP G-CHP+Pola 1.8 mg/kg (N=17)	All Pola Treated Patients (N=63)
Baseline Prevalence of ADAs						
Baseline evaluable patients	1	6	6	30	17	60
Patients with a positive sample at baseline	0	0	0	0	0	0
Patients with no positive samples at baseline	1	6	6	30	17	60
Post-Baseline Incidence of ADAs						
Post–baseline evaluable patients	1	6	6	33	17	63
Patients Positive for ADA	0	0	0	0	0	0
Patients negative for ADA	1	6	6	33	17	63
Treatment unaffected	0	0	0	0	0	0

ADA=anti–drug antibodies; EXP=expansion; G-CHP=obinutuzumab plus cyclophosphamide, doxorubicin, and prednisone; Pola= polatuzumab vedotin; R-CHP=rituximab plus cyclophosphamide, doxorubicin, and prednisone.
Baseline evaluable patient = a patient with an ADA assay result from a baseline sample.
Post–baseline evaluable patient = a patient with an ADA assay result from at least one post–baseline sample.
Number of patients positive for ADA = the number (and percentage) of post–baseline evaluable patients determined to have treatment–induced ADA or treatment–enhanced ADA during the study period.
Treatment–induced ADA = a patient with negative or missing baseline ADA result(s) and at least one positive post–baseline ADA result.
Treatment–enhanced ADA = a patient with positive ADA result at baseline who has one or more post–baseline titer results that are at least 0.60 t.u. greater than the baseline titer result.
Number of patients negative for ADA = number of post–baseline evaluable patients with negative or missing baseline ADA result(s) and all negative post–baseline results, or a patient who is treatment unaffected.
Treatment unaffected = A post–baseline evaluable patient with a positive ADA result at baseline and (a) where all post–baseline titer results are less than 0.60 t.u. greater than the baseline titer result, OR (b) where all post–baseline results are negative or missing.
For any positive sample with titer result less than the minimum reportable titer or any positive sample where a titer cannot be obtained, titer value is imputed as equal to the minimum reportable titer.
Source GO29044 Final CSR, Report 1109685, Section 8.2.

- *Vital sign, physical findings and other observations related to safety*
    - *Study POLARIX*

Vital signs parameters in both treatment arms were consistent throughout treatment and no clinically meaningful difference from baseline to any time post-baseline was observed between the pola+R-CHP and R-CHOP treatment arms in mean body surface area, mean diastolic blood pressure, mean systolic blood

pressure, mean pulse rate, mean respiratory rate, mean oxygen saturation (%), mean temperature, mean height or mean weight.

At screening, 5 patients (1.2%) in the pola+R-CHP arm and 3 patients (0.7%) in the R-CHOP arm had a clinically significant ECG abnormality.

Post-baseline, the proportion of patients with clinically significant ECG abnormalities was 1.3% (5 patients) in the pola+R-CHP arm and 1.0% (4 patients) in the R-CHOP arm.

Safety in special populations

- *Age*

Table 49 Overview of safety profile in patients <65 (N=428), safety-evaluable patients

Overall AE Profile by Age (< 65 vs. >=65 years), Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

Age Group: < 65 (N=428)

	R-CHOP (POLARIX) (N=203)	Pola-R-CHP (POLARIX) (N=208)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=17)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=225)
Total number of patients with at least one AE	199 (98.0%)	203 (97.6%)	17 (100%)	220 (97.8%)
Total number of AEs	2413	2537	221	2758
Total number of patients with at least one				
Grade 5 AE	1 (0.5%)	4 (1.9%)	0	4 (1.8%)
Grade 3-5 AE	108 (53.2%)	114 (54.8%)	10 (58.8%)	124 (55.1%)
Serious AE	53 (26.1%)	59 (28.4%)	5 (29.4%)	64 (28.4%)
Serious Related AE to any study drug	33 (16.3%)	46 (22.1%)	2 (11.8%)	48 (21.3%)
AE leading to study discontinuation	1 (0.5%)	4 (1.9%)	0	4 (1.8%)
AE leading to any study treatment dose discontinuation	11 (5.4%)	5 (2.4%)	0	5 (2.2%)
AE leading to any study treatment dose reduction	29 (14.3%)	16 (7.7%)	0	16 (7.1%)
AE leading to any study treatment dose interruption	48 (23.6%)	49 (23.6%)	6 (35.3%)	55 (24.4%)
AE leading to polatuzumab vedotin/placebo discontinuation	7 (3.4%)	4 (1.9%)	0	4 (1.8%)
AE leading to polatuzumab vedotin/placebo dose reduction	25 (12.3%)	13 (6.3%)	0	13 (5.8%)
AE leading to polatuzumab vedotin/placebo dose interruption	21 (10.3%)	26 (12.5%)	1 (5.9%)	27 (12.0%)
AE leading to vincristine/placebo discontinuation	7 (3.4%)	4 (1.9%)	0	4 (1.8%)
AE leading to vincristine/placebo dose reduction	24 (11.8%)	13 (6.3%)	0	13 (5.8%)
AE leading to vincristine/placebo dose interruption	21 (10.3%)	25 (12.0%)	0	25 (11.1%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

Table 50 Overview of safety profile in patients ≥65 (N=511), safety-evaluable patients

Overall AE Profile by Age (< 65 vs. >=65 years), Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

Age Group: >= 65 (N=511)

	R-CHOP (POLARIX) (N=235)	Pola-R-CHP (POLARIX) (N=227)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=49)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=276)
Total number of patients with at least one AE	232 (98.7%)	223 (98.2%)	49 (100%)	272 (98.6%)
Total number of AEs	2776	2933	747	3680
Total number of patients with at least one				
Grade 5 AE	9 (3.8%)	9 (4.0%)	2 (4.1%)	11 (4.0%)
Grade 3-5 AE	154 (65.5%)	150 (66.1%)	34 (69.4%)	184 (66.7%)
Serious AE	81 (34.5%)	89 (39.2%)	22 (44.9%)	111 (40.2%)
Serious Related AE to any study drug	53 (22.6%)	66 (29.1%)	15 (30.6%)	81 (29.3%)
AE leading to study discontinuation	9 (3.8%)	9 (4.0%)	3 (6.1%)	12 (4.3%)
AE leading to any study treatment dose discontinuation	18 (7.7%)	22 (9.7%)	8 (16.3%)	30 (10.9%)
AE leading to any study treatment dose reduction	28 (11.9%)	24 (10.6%)	8 (16.3%)	32 (11.6%)
AE leading to any study treatment dose interruption	63 (26.8%)	54 (23.8%)	12 (24.5%)	66 (23.9%)
AE leading to polatuzumab vedotin/placebo discontinuation	15 (6.4%)	15 (6.6%)	8 (16.3%)	23 (8.3%)
AE leading to polatuzumab vedotin/placebo dose reduction	20 (8.5%)	11 (4.8%)	5 (10.2%)	16 (5.8%)
AE leading to polatuzumab vedotin/placebo dose interruption	41 (17.4%)	35 (15.4%)	5 (10.2%)	40 (14.5%)
AE leading to vincristine/placebo discontinuation	15 (6.4%)	15 (6.6%)	0	15 (5.4%)
AE leading to vincristine/placebo dose reduction	21 (8.9%)	11 (4.8%)	0	11 (4.0%)
AE leading to vincristine/placebo dose interruption	39 (16.6%)	35 (15.4%)	0	35 (12.7%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

- *Gender*

Table 51 Overview of safety profile in male (N=504), safety-evaluable patients

Overall AE Profile by Sex (Male vs. Female), Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

Sex: Male (N=504)

	R-CHOP (POLARIX) (N=234)	Pola-R-CHP (POLARIX) (N=236)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=34)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=270)
Total number of patients with at least one AE	230 (98.3%)	230 (97.5%)	34 (100%)	264 (97.8%)
Total number of AEs	2560	2621	419	3040
Total number of patients with at least one				
Grade 5 AE	9 (3.8%)	6 (2.5%)	0	6 (2.2%)
Grade 3-5 AE	135 (57.7%)	140 (59.3%)	22 (64.7%)	162 (60.0%)
Serious AE	78 (33.3%)	81 (34.3%)	11 (32.4%)	92 (34.1%)
Serious Related AE to any study drug	52 (22.2%)	59 (25.0%)	7 (20.6%)	66 (24.4%)
AE leading to study discontinuation	9 (3.8%)	6 (2.5%)	2 (5.9%)	8 (3.0%)
AE leading to any study treatment dose discontinuation	13 (5.6%)	15 (6.4%)	3 (8.8%)	18 (6.7%)
AE leading to any study treatment dose reduction	23 (9.8%)	15 (6.4%)	5 (14.7%)	20 (7.4%)
AE leading to any study treatment dose interruption	52 (22.2%)	51 (21.6%)	9 (26.5%)	60 (22.2%)
AE leading to polatuzumab vedotin/placebo discontinuation	8 (3.4%)	11 (4.7%)	3 (8.8%)	14 (5.2%)
AE leading to polatuzumab vedotin/placebo dose reduction	18 (7.7%)	11 (4.7%)	3 (8.8%)	14 (5.2%)
AE leading to polatuzumab vedotin/placebo dose interruption	29 (12.4%)	32 (13.6%)	4 (11.8%)	36 (13.3%)
AE leading to vincristine/placebo discontinuation	8 (3.4%)	11 (4.7%)	0	11 (4.1%)
AE leading to vincristine/placebo dose reduction	17 (7.3%)	10 (4.2%)	0	10 (3.7%)
AE leading to vincristine/placebo dose interruption	29 (12.4%)	31 (13.1%)	0	31 (11.5%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

Table 52 Overview of safety profile in female (N=435), safety-devaluable patients

Overall AE Profile by Sex (Male vs. Female), Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

Sex: Female (N=435)

	R-CHOP (POLARIX) (N=204)	Pola-R-CHP (POLARIX) (N=199)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=32)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=231)
Total number of patients with at least one AE	201 (98.5%)	196 (98.5%)	32 (100%)	228 (98.7%)
Total number of AEs	2629	2849	549	3398
Total number of patients with at least one				
Grade 5 AE	1 (0.5%)	7 (3.5%)	2 (6.3%)	9 (3.9%)
Grade 3-5 AE	127 (62.3%)	124 (62.3%)	22 (68.8%)	146 (63.2%)
Serious AE	56 (27.5%)	67 (33.7%)	16 (50.0%)	83 (35.9%)
Serious Related AE to any study drug	34 (16.7%)	53 (26.6%)	10 (31.3%)	63 (27.3%)
AE leading to study discontinuation	1 (0.5%)	7 (3.5%)	1 (3.1%)	8 (3.5%)
AE leading to any study treatment dose discontinuation	16 (7.8%)	12 (6.0%)	5 (15.6%)	17 (7.4%)
AE leading to any study treatment dose reduction	34 (16.7%)	25 (12.6%)	3 (9.4%)	28 (12.1%)
AE leading to any study treatment dose interruption	59 (28.9%)	52 (26.1%)	9 (28.1%)	61 (26.4%)
AE leading to polatuzumab vedotin/placebo discontinuation	14 (6.9%)	8 (4.0%)	5 (15.6%)	13 (5.6%)
AE leading to polatuzumab vedotin/placebo dose reduction	27 (13.2%)	13 (6.5%)	2 (6.3%)	15 (6.5%)
AE leading to polatuzumab vedotin/placebo dose interruption	33 (16.2%)	29 (14.6%)	2 (6.3%)	31 (13.4%)
AE leading to vincristine/placebo discontinuation	14 (6.9%)	8 (4.0%)	0	8 (3.5%)
AE leading to vincristine/placebo dose reduction	28 (13.7%)	14 (7.0%)	0	14 (6.1%)
AE leading to vincristine/placebo dose interruption	31 (15.2%)	29 (14.6%)	0	29 (12.6%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

- *Race*

Study POLARIX

The majority of enrolled patients were of White (N=523) or Asian (N=168) ethnicity and assessment of differences between other race subgroups could not be performed due to the small sample sizes in these race subgroups (American Indian or Alaska Native [N=3], Black or African American [N=17], Native Hawaiian or Other Pacific Islander [N=3], Other [N=17]).

Overall, the safety profile was generally comparable between White and Asian subgroups with some numerical differences.

Grade ≥ 3 AEs were reported in a higher proportion of Asian patients (pola+R-CHP: 73.8% and R-CHOP: 67.9%) compared with White patients (pola+R-CHP: 58.9% and R-CHOP: 59.6%) in both treatment arms. The proportion of deaths due to AEs was numerically higher in the White race subgroup (pola+R-CHP: 10 deaths [4.3%] vs. R-CHOP: 8 deaths [3.4%]) compared with Asian race subgroup (pola+R-CHP: 1 death [1.2%] vs. RCHOP: 1 death [1.2%]).

Supportive study GO29044

The majority of patients enrolled in GO29044 were White (57/66 patients). Overall, no assessment of differences between race subgroups could be performed due to the small sample size in other race groups.

- *Body weight*

To investigate the incidence of AEs by weight, patients were categorized into two baseline weight categories; ≤100 kg (N=847) and >100 kg (N=86).

Table 53 Overview of safety profile in body weight ≤100 kg (N=847), safety-evaluable patients

Overall AE Profile by Baseline Weight (> 100 kg vs. <= 100 kg), Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

Baseline Weight: <= 100 (N=847)

	R-CHOP (POLARIX) (N=399)	Pola-R-CHP (POLARIX) (N=389)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=59)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=448)
Total number of patients with at least one AE	392 (98.2%)	380 (97.7%)	59 (100%)	439 (98.0%)
Total number of AEs	4715	4753	848	5601
Total number of patients with at least one				
Grade 5 AE	8 (2.0%)	11 (2.8%)	2 (3.4%)	13 (2.9%)
Grade 3-5 AE	241 (60.4%)	240 (61.7%)	38 (64.4%)	278 (62.1%)
Serious AE	120 (30.1%)	133 (34.2%)	23 (39.0%)	156 (34.8%)
Serious Related AE to any study drug	79 (19.8%)	103 (26.5%)	15 (25.4%)	118 (26.3%)
AE leading to study discontinuation	8 (2.0%)	11 (2.8%)	2 (3.4%)	13 (2.9%)
AE leading to any study treatment dose discontinuation	27 (6.8%)	26 (6.7%)	7 (11.9%)	33 (7.4%)
AE leading to any study treatment dose reduction	53 (13.3%)	34 (8.7%)	8 (13.6%)	42 (9.4%)
AE leading to any study treatment dose interruption	99 (24.8%)	92 (23.7%)	15 (25.4%)	107 (23.9%)
AE leading to polatuzumab vedotin/placebo discontinuation	20 (5.0%)	18 (4.6%)	7 (11.9%)	25 (5.6%)
AE leading to polatuzumab vedotin/placebo dose reduction	41 (10.3%)	19 (4.9%)	5 (8.5%)	24 (5.4%)
AE leading to polatuzumab vedotin/placebo dose interruption	56 (14.0%)	55 (14.1%)	4 (6.8%)	59 (13.2%)
AE leading to vincristine/placebo discontinuation	20 (5.0%)	18 (4.6%)	0	18 (4.0%)
AE leading to vincristine/placebo dose reduction	42 (10.5%)	20 (5.1%)	0	20 (4.5%)
AE leading to vincristine/placebo dose interruption	54 (13.5%)	54 (13.9%)	0	54 (12.1%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

Table 54 Overview of safety profile in body weight >100 kg (N=86), safety-evaluable patients

Overall AE Profile by Baseline Weight (> 100 kg vs. <= 100 kg), Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

Baseline Weight: > 100 (N=86)

	R-CHOP (POLARIX) (N=36)	Pola-R-CHP (POLARIX) (N=43)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=7)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=50)
Total number of patients with at least one AE	36 (100%)	43 (100%)	7 (100%)	50 (100%)
Total number of AEs	454	694	120	814
Total number of patients with at least one				
Grade 5 AE	2 (5.6%)	2 (4.7%)	0	2 (4.0%)
Grade 3-5 AE	20 (55.6%)	22 (51.2%)	6 (85.7%)	28 (56.0%)
Serious AE	13 (36.1%)	14 (32.6%)	4 (57.1%)	18 (36.0%)
Serious Related AE to any study drug	6 (16.7%)	9 (20.9%)	2 (28.6%)	11 (22.0%)
AE leading to study discontinuation	2 (5.6%)	2 (4.7%)	1 (14.3%)	3 (6.0%)
AE leading to any study treatment dose discontinuation	2 (5.6%)	1 (2.3%)	1 (14.3%)	2 (4.0%)
AE leading to any study treatment dose reduction	3 (8.3%)	6 (14.0%)	0	6 (12.0%)
AE leading to any study treatment dose interruption	11 (30.6%)	10 (23.3%)	3 (42.9%)	13 (26.0%)
AE leading to polatuzumab vedotin/placebo discontinuation	2 (5.6%)	1 (2.3%)	1 (14.3%)	2 (4.0%)
AE leading to polatuzumab vedotin/placebo dose reduction	3 (8.3%)	5 (11.6%)	0	5 (10.0%)
AE leading to polatuzumab vedotin/placebo dose interruption	5 (13.9%)	5 (11.6%)	2 (28.6%)	7 (14.0%)
AE leading to vincristine/placebo discontinuation	2 (5.6%)	1 (2.3%)	0	1 (2.0%)
AE leading to vincristine/placebo dose reduction	2 (5.6%)	4 (9.3%)	0	4 (8.0%)
AE leading to vincristine/placebo dose interruption	5 (13.9%)	5 (11.6%)	0	5 (10.0%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

- *Hepatic impairment*

To investigate the incidence of AEs by hepatic impairment, patients were categorized into four groups based on hepatic function at baseline:

- normal hepatic function (baseline bilirubin ≤ ULN and aspartate aminotransferase [AST] ≤ ULN); N=751
- mild hepatic impairment (baseline bilirubin ≤ ULN and AST > ULN); N=131 and/or (ULN < baseline bilirubin ≤ 1.5 x ULN); N=34
- moderate hepatic impairment (1.5 x ULN < baseline bilirubin ≤ 3 x ULN); N=14

- severe hepatic impairment (baseline bilirubin > 3 x ULN); N=2

Table 55 Overview of safety profile in normal hepatic function (N=751), safety-evaluable patients

Overall AE Profile by Hepatic Status, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

Baseline Hepatic Function Group: Normal (N=751)

	R-CHOP (POLARIX) (N=349)	Pola-R-CHP (POLARIX) (N=343)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=59)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=402)
Total number of patients with at least one AE	344 (98.6%)	335 (97.7%)	59 (100%)	394 (98.0%)
Total number of AEs	4101	4174	882	5056
Total number of patients with at least one				
Grade 5 AE	5 (1.4%)	7 (2.0%)	2 (3.4%)	9 (2.2%)
Grade 3-5 AE	201 (57.6%)	201 (58.6%)	38 (64.4%)	239 (59.5%)
Serious AE	102 (29.2%)	113 (32.9%)	22 (37.3%)	135 (33.6%)
Serious Related AE to any study drug	67 (19.2%)	85 (24.8%)	14 (23.7%)	99 (24.6%)
AE leading to study discontinuation	5 (1.4%)	7 (2.0%)	3 (5.1%)	10 (2.5%)
AE leading to any study treatment dose discontinuation	19 (5.4%)	19 (5.5%)	7 (11.9%)	26 (6.5%)
AE leading to any study treatment dose reduction	43 (12.3%)	34 (9.9%)	7 (11.9%)	41 (10.2%)
AE leading to any study treatment dose interruption	88 (25.2%)	79 (23.0%)	17 (28.8%)	96 (23.9%)
AE leading to polatuzumab vedotin/placebo discontinuation	14 (4.0%)	12 (3.5%)	7 (11.9%)	19 (4.7%)
AE leading to polatuzumab vedotin/placebo dose reduction	33 (9.5%)	19 (5.5%)	5 (8.5%)	24 (6.0%)
AE leading to polatuzumab vedotin/placebo dose interruption	49 (14.0%)	46 (13.4%)	5 (8.5%)	51 (12.7%)
AE leading to vincristine/placebo discontinuation	14 (4.0%)	12 (3.5%)	0	12 (3.0%)
AE leading to vincristine/placebo dose reduction	35 (10.0%)	19 (5.5%)	0	19 (4.7%)
AE leading to vincristine/placebo dose interruption	47 (13.5%)	45 (13.1%)	0	45 (11.2%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

Table 56 Overview of safety profile in mild hepatic impairment (N=131), safety-evaluable patients

Overall AE Profile by Hepatic Status, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

Baseline Hepatic Function Group: Mild 1 (N=131)

	R-CHOP (POLARIX) (N=68)	Pola-R-CHP (POLARIX) (N=59)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=4)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=63)
Total number of patients with at least one AE	66 (97.1%)	58 (98.3%)	4 (100%)	62 (98.4%)
Total number of AEs	845	802	39	841
Total number of patients with at least one				
Grade 5 AE	3 (4.4%)	1 (1.7%)	0	1 (1.6%)
Grade 3-5 AE	44 (64.7%)	40 (67.8%)	4 (100%)	44 (69.8%)
Serious AE	22 (32.4%)	19 (32.2%)	3 (75.0%)	22 (34.9%)
Serious Related AE to any study drug	14 (20.6%)	13 (22.0%)	2 (50.0%)	15 (23.8%)
AE leading to study discontinuation	3 (4.4%)	1 (1.7%)	0	1 (1.6%)
AE leading to any study treatment dose discontinuation	7 (10.3%)	2 (3.4%)	1 (25.0%)	3 (4.8%)
AE leading to any study treatment dose reduction	13 (19.1%)	4 (6.8%)	0	4 (6.3%)
AE leading to any study treatment dose interruption	18 (26.5%)	13 (22.0%)	1 (25.0%)	14 (22.2%)
AE leading to polatuzumab vedotin/placebo discontinuation	5 (7.4%)	2 (3.4%)	1 (25.0%)	3 (4.8%)
AE leading to polatuzumab vedotin/placebo dose reduction	11 (16.2%)	3 (5.1%)	0	3 (4.8%)
AE leading to polatuzumab vedotin/placebo dose interruption	10 (14.7%)	8 (13.6%)	1 (25.0%)	9 (14.3%)
AE leading to vincristine/placebo discontinuation	5 (7.4%)	2 (3.4%)	0	2 (3.2%)
AE leading to vincristine/placebo dose reduction	9 (13.2%)	3 (5.1%)	0	3 (4.8%)
AE leading to vincristine/placebo dose interruption	10 (14.7%)	8 (13.6%)	0	8 (12.7%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

Table 57 Overview of safety profile in mild hepatic impairment (N=34), safety-evaluable patients

Overall AE Profile by Hepatic Status, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

Baseline Hepatic Function Group: Mild 2 (N=34)

	R-CHOP (POLARIX) (N=12)	Pola-R-CHP (POLARIX) (N=20)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=2)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=22)
Total number of patients with at least one AE	12 (100%)	20 (100%)	2 (100%)	22 (100%)
Total number of AEs	128	308	19	327
Total number of patients with at least one				
Grade 5 AE	2 (16.7%)	3 (15.0%)	0	3 (13.6%)
Grade 3-5 AE	9 (75.0%)	13 (65.0%)	1 (50.0%)	14 (63.6%)
Serious AE	7 (58.3%)	9 (45.0%)	1 (50.0%)	10 (45.5%)
Serious Related AE to any study drug	4 (33.3%)	8 (40.0%)	1 (50.0%)	9 (40.9%)
AE leading to study discontinuation	2 (16.7%)	3 (15.0%)	0	3 (13.6%)
AE leading to any study treatment dose discontinuation	3 (25.0%)	5 (25.0%)	0	5 (22.7%)
AE leading to any study treatment dose reduction	0	2 (10.0%)	1 (50.0%)	3 (13.6%)
AE leading to any study treatment dose interruption	3 (25.0%)	6 (30.0%)	0	6 (27.3%)
AE leading to polatuzumab vedotin/placebo discontinuation	3 (25.0%)	4 (20.0%)	0	4 (18.2%)
AE leading to polatuzumab vedotin/placebo dose reduction	0	2 (10.0%)	0	2 (9.1%)
AE leading to polatuzumab vedotin/placebo dose interruption	2 (16.7%)	4 (20.0%)	0	4 (18.2%)
AE leading to vincristine/placebo discontinuation	3 (25.0%)	4 (20.0%)	0	4 (18.2%)
AE leading to vincristine/placebo dose reduction	0	2 (10.0%)	0	2 (9.1%)
AE leading to vincristine/placebo dose interruption	2 (16.7%)	4 (20.0%)	0	4 (18.2%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

Table 58 Overview of safety profile in moderate hepatic impairment (N=14), safety-evaluable patients

Overall AE Profile by Hepatic Status, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

Baseline Hepatic Function Group: Moderate (N=14)

	R-CHOP (POLARIX) (N=5)	Pola-R-CHP (POLARIX) (N=9)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=0)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=9)
Total number of patients with at least one AE	5 (100%)	9 (100%)	0	9 (100%)
Total number of AEs	70	161	0	161
Total number of patients with at least one				
Grade 3-5 AE	4 (80.0%)	7 (77.8%)	0	7 (77.8%)
Serious AE	1 (20.0%)	5 (55.6%)	0	5 (55.6%)
Serious Related AE to any study drug	1 (20.0%)	5 (55.6%)	0	5 (55.6%)
AE leading to any study treatment dose interruption	1 (20.0%)	3 (33.3%)	0	3 (33.3%)
AE leading to polatuzumab vedotin/placebo dose interruption	1 (20.0%)	2 (22.2%)	0	2 (22.2%)
AE leading to vincristine/placebo dose interruption	1 (20.0%)	2 (22.2%)	0	2 (22.2%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

Table 59 Overview of safety profile in severe hepatic impairment (N=2), safety-evaluable patients

Overall AE Profile by Hepatic Status, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

Baseline Hepatic Function Group: Severe (N=2)

	R-CHOP (POLARIX) (N=1)	Pola-R-CHP (POLARIX) (N=1)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=0)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=1)
Total number of patients with at least one AE	1 (100%)	1 (100%)	0	1 (100%)
Total number of AEs	4	10	0	10
Total number of patients with at least one				
Grade 5 AE	0	1 (100%)	0	1 (100%)
Grade 3-5 AE	1 (100%)	1 (100%)	0	1 (100%)
Serious AE	1 (100%)	1 (100%)	0	1 (100%)
AE leading to study discontinuation	0	1 (100%)	0	1 (100%)
AE leading to any study treatment dose discontinuation	0	1 (100%)	0	1 (100%)
AE leading to any study treatment dose reduction	1 (100%)	0	0	0
AE leading to polatuzumab vedotin/placebo discontinuation	0	1 (100%)	0	1 (100%)
AE leading to polatuzumab vedotin/placebo dose reduction	1 (100%)	0	0	0
AE leading to vincristine/placebo discontinuation	0	1 (100%)	0	1 (100%)
AE leading to vincristine/placebo dose reduction	1 (100%)	0	0	0

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

- *Renal impairment*

To investigate the incidence of AEs by renal impairment, patients were categorized into four groups based on GFR at baseline:

- normal renal function (creatinine clearance [CrCL] ≥90 mL/min); N=386
- mild renal impairment (CrCL ≥60 mL/min to <90 mL/min); N=428
- moderate renal impairment (CrCL ≥30 mL/min to <60 mL/min); N=116
- severe renal impairment (CrCL ≥15 mL/min to <30 mL/min); N=2

Table 60 Overview of safety profile in normal renalfunction (N=386), safety-evaluable patients

Overall AE Profile by Renal Impairment, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

Baseline Renal Impairment: Normal (N=386)

	R-CHOP (POLARIX) (N=184)	Pola-R-CHP (POLARIX) (N=172)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=30)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=202)
Total number of patients with at least one AE	179 (97.3%)	168 (97.7%)	30 (100%)	198 (98.0%)
Total number of AEs	2170	2025	395	2420
Total number of patients with at least one				
Grade 5 AE	2 (1.1%)	4 (2.3%)	0	4 (2.0%)
Grade 3-5 AE	100 (54.3%)	93 (54.1%)	17 (56.7%)	110 (54.5%)
Serious AE	52 (28.3%)	52 (30.2%)	11 (36.7%)	63 (31.2%)
Serious Related AE to any study drug	32 (17.4%)	40 (23.3%)	5 (16.7%)	45 (22.3%)
AE leading to study discontinuation	2 (1.1%)	4 (2.3%)	1 (3.3%)	5 (2.5%)
AE leading to any study treatment dose discontinuation	13 (7.1%)	4 (2.3%)	1 (3.3%)	5 (2.5%)
AE leading to any study treatment dose reduction	21 (11.4%)	14 (8.1%)	3 (10.0%)	17 (8.4%)
AE leading to any study treatment dose interruption	47 (25.5%)	37 (21.5%)	7 (23.3%)	44 (21.8%)
AE leading to polatuzumab vedotin/placebo discontinuation	9 (4.9%)	3 (1.7%)	1 (3.3%)	4 (2.0%)
AE leading to polatuzumab vedotin/placebo dose reduction	18 (9.8%)	8 (4.7%)	2 (6.7%)	10 (5.0%)
AE leading to polatuzumab vedotin/placebo dose interruption	20 (10.9%)	19 (11.0%)	2 (6.7%)	21 (10.4%)
AE leading to vincristine/placebo discontinuation	9 (4.9%)	3 (1.7%)	0	3 (1.5%)
AE leading to vincristine/placebo dose reduction	18 (9.8%)	8 (4.7%)	0	8 (4.0%)
AE leading to vincristine/placebo dose interruption	19 (10.3%)	19 (11.0%)	0	19 (9.4%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

Table 61 Overview of safety profile in mild renal impairment (N=428), safety-evaluable patients

Overall AE Profile by Renal Impairment, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

Baseline Renal Impairment: Mild (N=428)

	R-CHOP (POLARIX) (N=197)	Pola-R-CHP (POLARIX) (N=204)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=27)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=231)
Total number of patients with at least one AE	195 (99.0%)	200 (98.0%)	27 (100%)	227 (98.3%)
Total number of AEs	2245	2614	401	3015
Total number of patients with at least one				
Grade 5 AE	6 (3.0%)	9 (4.4%)	1 (3.7%)	10 (4.3%)
Grade 3-5 AE	120 (60.9%)	129 (63.2%)	20 (74.1%)	149 (64.5%)
Serious AE	61 (31.0%)	72 (35.3%)	13 (48.1%)	85 (36.8%)
Serious Related AE to any study drug	39 (19.8%)	52 (25.5%)	10 (37.0%)	62 (26.8%)
AE leading to study discontinuation	6 (3.0%)	9 (4.4%)	1 (3.7%)	10 (4.3%)
AE leading to any study treatment dose discontinuation	11 (5.6%)	15 (7.4%)	6 (22.2%)	21 (9.1%)
AE leading to any study treatment dose reduction	23 (11.7%)	22 (10.8%)	5 (18.5%)	27 (11.7%)
AE leading to any study treatment dose interruption	45 (22.8%)	47 (23.0%)	8 (29.6%)	55 (23.8%)
AE leading to polatuzumab vedotin/placebo discontinuation	11 (5.6%)	11 (5.4%)	6 (22.2%)	17 (7.4%)
AE leading to polatuzumab vedotin/placebo dose reduction	18 (9.1%)	13 (6.4%)	3 (11.1%)	16 (6.9%)
AE leading to polatuzumab vedotin/placebo dose interruption	28 (14.2%)	28 (13.7%)	4 (14.8%)	32 (13.9%)
AE leading to vincristine/placebo discontinuation	11 (5.6%)	11 (5.4%)	0	11 (4.8%)
AE leading to vincristine/placebo dose reduction	17 (8.6%)	14 (6.9%)	0	14 (6.1%)
AE leading to vincristine/placebo dose interruption	27 (13.7%)	28 (13.7%)	0	28 (12.1%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

Table 62 Overview of safety profile in moderate renal impairment (N=116), safety-evaluable patients

Overall AE Profile by Renal Impairment, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

Baseline Renal Impairment: Moderate (N=116)

	R-CHOP (POLARIX) (N=54)	Pola-R-CHP (POLARIX) (N=54)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=8)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=62)
Total number of patients with at least one AE	54 (100%)	54 (100%)	8 (100%)	62 (100%)
Total number of AEs	754	803	157	960
Total number of patients with at least one				
Grade 5 AE	2 (3.7%)	0	0	0
Grade 3-5 AE	41 (75.9%)	39 (72.2%)	6 (75.0%)	45 (72.6%)
Serious AE	20 (37.0%)	22 (40.7%)	2 (25.0%)	24 (38.7%)
Serious Related AE to any study drug	14 (25.9%)	19 (35.2%)	2 (25.0%)	21 (33.9%)
AE leading to study discontinuation	2 (3.7%)	0	0	0
AE leading to any study treatment dose discontinuation	5 (9.3%)	8 (14.8%)	0	8 (12.9%)
AE leading to any study treatment dose reduction	12 (22.2%)	4 (7.4%)	0	4 (6.5%)
AE leading to any study treatment dose interruption	18 (33.3%)	17 (31.5%)	3 (37.5%)	20 (32.3%)
AE leading to polatuzumab vedotin/placebo discontinuation	2 (3.7%)	5 (9.3%)	0	5 (8.1%)
AE leading to polatuzumab vedotin/placebo dose reduction	8 (14.8%)	3 (5.6%)	0	3 (4.8%)
AE leading to polatuzumab vedotin/placebo dose interruption	13 (24.1%)	12 (22.2%)	0	12 (19.4%)
AE leading to vincristine/placebo discontinuation	2 (3.7%)	5 (9.3%)	0	5 (8.1%)
AE leading to vincristine/placebo dose reduction	9 (16.7%)	2 (3.7%)	0	2 (3.2%)
AE leading to vincristine/placebo dose interruption	13 (24.1%)	11 (20.4%)	0	11 (17.7%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

Table 63 Overview of safety profile in severe renal impairment (N=2), safety-evaluable patients

Overall AE Profile by Renal Impairment, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

Baseline Renal Impairment: Severe (N=2)

	R-CHOP (POLARIX) (N=0)	Pola-R-CHP (POLARIX) (N=1)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=1)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=2)
Total number of patients with at least one AE	0	1 (100%)	1 (100%)	2 (100%)
Total number of AEs	0	5	15	20
Total number of patients with at least one				
Grade 5 AE	0	0	1 (100%)	1 (50.0%)
Grade 3-5 AE	0	1 (100%)	1 (100%)	2 (100%)
Serious AE	0	1 (100%)	1 (100%)	2 (100%)
Serious Related AE to any study drug	0	1 (100%)	0	1 (50.0%)
AE leading to study discontinuation	0	0	1 (100%)	1 (50.0%)
AE leading to any study treatment dose discontinuation	0	0	1 (100%)	1 (50.0%)
AE leading to any study treatment dose interruption	0	1 (100%)	0	1 (50.0%)
AE leading to polatuzumab vedotin/placebo discontinuation	0	0	1 (100%)	1 (50.0%)
AE leading to polatuzumab vedotin/placebo dose interruption	0	1 (100%)	0	1 (50.0%)
AE leading to vincristine/placebo dose interruption	0	1 (100%)	0	1 (50.0%)

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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

Safety related to drug-drug interactions and other interactions

R-CHP did not appear to have a clinically relevant impact on the PK of pola when given in combination based on observed data and population PK analysis. The PK of pola in the pivotal POLARIX study and supportive Study GO29044 are in line with the other studies of pola. Population PK analysis of POLARIX further supports the pola PK similarity among different studies. A two-analyte (acMMAE-MMAE) integrated pop-PK analysis (Report 1090510) based on PK data from 460 NHL patients from Studies DCS4968g, GO27834, GO29044, and GO29365 (excluding Arm G and Arm H) was previously established to characterize the PK properties of acMMAE and unconjugated MMAE. The previously developed population PK model

provides a good description of acMMAE and unconjugated MMAE concentrations following intravenous administration of pola+R-CHP in patients with previously untreated DLBCL.

In the supportive Study GO29044, pola did not appear to have a clinically relevant impact on the PK of cyclophosphamide or doxorubicin when given in combination based on observed data. No significant difference in cyclophosphamide or doxorubicin PK was observed for DLBCL patients receiving 1.8 mg/kg of pola+R/G-CHP based on similar cross-cycle exposure comparisons of each analyte both prior to and after administration of pola (Shemesh et al. 2020).

Discontinuation due to adverse events

- *AEs leading to study discontinuation*

Study POLARIX

The proportion of patients who experienced AEs leading to study discontinuation in the pola+R-CHP arm (3.0% [13 patients]) was comparable to the R-CHOP arm (2.3% [10 patients]). All AEs leading to study discontinuation were Grade 5 AEs.

Supportive study GO29044

The events that led to study withdrawal were events associated with underlying disease, with no apparent/clinically meaningful/relevant pattern among the other events leading to withdrawal.

A total of 3/66 patients (4.5%) had 5 AEs leading to study discontinuation. The AEs leading to study discontinuation by PT were Escherichia urinary tract infection, syncope and atrial fibrillation (both reported in the same patient), and pneumonia and coronary artery disease (both reported in the same patient).

Pooled safety population

The proportion of patients who experienced AEs leading to study discontinuation in the pooled safety population (3.2% [16/501 patients]) was consistent with the pola+R-CHP arm from POLARIX and comparable to the R-CHOP arm (2.3% [10/438 patients]). The majority of events that led to study withdrawal were events associated with underlying disease, with no apparent/clinically meaningful/relevant pattern among the other events leading to study withdrawal.

Table 64. Summary of Adverse Events Leading to Study Discontinuation

MedDRA System Organ Class MedDRA Preferred Term	Grade	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
- Any adverse events -	- Any Grade -	10 (2.3%)	13 (3.0%)	3 (4.5%)	16 (3.2%)
	Grade 1-2	0	0	1 (1.5%)	1 (0.2%)
	2	0	0	1 (1.5%)	1 (0.2%)
	Grade 3-4	0	0	1 (1.5%)	1 (0.2%)
	3	0	0	1 (1.5%)	1 (0.2%)
	Grade 5	10 (2.3%)	13 (3.0%)	1 (1.5%)	14 (2.8%)
Infections and infestations					
- Overall -	- Any Grade -	6 (1.4%)	5 (1.1%)	2 (3.0%)	7 (1.4%)
	Grade 1-2	0	0	1 (1.5%)	1 (0.2%)
	2	0	0	1 (1.5%)	1 (0.2%)
	Grade 3-4	0	0	1 (1.5%)	1 (0.2%)
	3	0	0	1 (1.5%)	1 (0.2%)
	Grade 5	6 (1.4%)	5 (1.1%)	0	5 (1.0%)
Pneumonia	- Any Grade -	3 (0.7%)	4 (0.9%)	1 (1.5%)	5 (1.0%)
	Grade 3-4	0	0	1 (1.5%)	1 (0.2%)
	3	0	0	1 (1.5%)	1 (0.2%)
	Grade 5	3 (0.7%)	4 (0.9%)	0	4 (0.8%)
Sepsis	- Any Grade -	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
	Grade 5	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
Escherichia urinary tract infection	- Any Grade -	0	0	1 (1.5%)	1 (0.2%)
	Grade 1-2	0	0	1 (1.5%)	1 (0.2%)
	2	0	0	1 (1.5%)	1 (0.2%)
Septic shock	- Any Grade -	2 (0.5%)	0	0	0
	Grade 5	2 (0.5%)	0	0	0

MedDRA System Organ Class MedDRA Preferred Term	Grade	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
General disorders and administration site conditions					
- Overall -	- Any Grade -	2 (0.5%)	5 (1.1%)	0	5 (1.0%)
	Grade 5	2 (0.5%)	5 (1.1%)	0	5 (1.0%)
Death	- Any Grade -	1 (0.2%)	4 (0.9%)	0	4 (0.8%)
	Grade 5	1 (0.2%)	4 (0.9%)	0	4 (0.8%)
Cardiac death	- Any Grade -	0	1 (0.2%)	0	1 (0.2%)
	Grade 5	0	1 (0.2%)	0	1 (0.2%)
Multiple organ dysfunction syndrome	- Any Grade -	1 (0.2%)	0	0	0
	Grade 5	1 (0.2%)	0	0	0
Cardiac disorders					
- Overall -	- Any Grade -	1 (0.2%)	0	2 (3.0%)	2 (0.4%)
	Grade 3-4	0	0	1 (1.5%)	1 (0.2%)
	3	0	0	1 (1.5%)	1 (0.2%)
	Grade 5	1 (0.2%)	0	1 (1.5%)	1 (0.2%)
Atrial fibrillation	- Any Grade -	0	0	1 (1.5%)	1 (0.2%)
	Grade 5	0	0	1 (1.5%)	1 (0.2%)
Coronary artery disease	- Any Grade -	0	0	1 (1.5%)	1 (0.2%)
	Grade 3-4	0	0	1 (1.5%)	1 (0.2%)
	3	0	0	1 (1.5%)	1 (0.2%)
Atrioventricular block complete	- Any Grade -	1 (0.2%)	0	0	0
	Grade 5	1 (0.2%)	0	0	0

MedDRA System Organ Class MedDRA Preferred Term	Grade	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Gastrointestinal disorders					
- Overall -	- Any Grade -	0	1 (0.2%)	0	1 (0.2%)
	Grade 5	0	1 (0.2%)	0	1 (0.2%)
Intestinal perforation	- Any Grade -	0	1 (0.2%)	0	1 (0.2%)
	Grade 5	0	1 (0.2%)	0	1 (0.2%)
Nervous system disorders					
- Overall -	- Any Grade -	0	0	1 (1.5%)	1 (0.2%)
	Grade 3-4	0	0	1 (1.5%)	1 (0.2%)
	3	0	0	1 (1.5%)	1 (0.2%)
Syncope	- Any Grade -	0	0	1 (1.5%)	1 (0.2%)
	Grade 3-4	0	0	1 (1.5%)	1 (0.2%)
	3	0	0	1 (1.5%)	1 (0.2%)
Renal and urinary disorders					
- Overall -	- Any Grade -	0	1 (0.2%)	0	1 (0.2%)
	Grade 5	0	1 (0.2%)	0	1 (0.2%)
Acute kidney injury	- Any Grade -	0	1 (0.2%)	0	1 (0.2%)
	Grade 5	0	1 (0.2%)	0	1 (0.2%)
Respiratory, thoracic and mediastinal disorders					
- Overall -	- Any Grade -	0	1 (0.2%)	0	1 (0.2%)
	Grade 5	0	1 (0.2%)	0	1 (0.2%)
Respiratory failure	- Any Grade -	0	1 (0.2%)	0	1 (0.2%)
	Grade 5	0	1 (0.2%)	0	1 (0.2%)

MedDRA System Organ Class MedDRA Preferred Term	Grade	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Injury, poisoning and procedural complications					
- Overall -	- Any Grade -	1 (0.2%)	0	0	0
	Grade 5	1 (0.2%)	0	0	0
Injury	- Any Grade -	1 (0.2%)	0	0	0
	Grade 5	1 (0.2%)	0	0	0

Investigator text for AEs encoded using MedDRA version 24.0. All counts represent patients. Multiple occurrences of the same AE in one individual are counted once at the highest grade for this patient. To the SOC Overall row counts, a patient contributes only with the AE occuring with the highest grade within the SOC. Percentages are based on N in the column headings. 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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

- *AEs leading to treatment discontinuation*

Study POLARIX

Overall, the proportion of patients who experienced at least one AE leading to discontinuation of any study treatment in the pola+R-CHP arm (6.2%) was comparable to the R-CHOP arm (6.6%).

In most SOCs, the proportion of patients discontinuing any study treatment due to an AE was comparable between the pola+R-CHP and R-CHOP arms. However, in the most common SOC with AEs leading to study treatment discontinuation for the R-CHOP arm (Nervous system disorders), a higher proportion of R-CHOP patients experienced an AE leading to discontinuation (2.5% [9 patients]) than the pola+R-CHP arm (0.7% [3 patients]). This difference was primarily driven by a higher incidence of AEs associated with peripheral neuropathy in the R-CHOP arm.

The proportion of patients who experienced AEs leading to discontinuation of pola study treatment in the pola+R-CHP arm (4.4%) was comparable to the proportion of patients who experienced AEs leading to discontinuation of vincristine study treatment in the R-CHOP arm (5.0%).

A numerically higher percentage of patients experienced an AE in the Nervous system disorders SOC which led to vincristine discontinuation (2.1% [9 patients]) than led to pola discontinuation (0.7% [3 patients]). This difference was primarily driven by a higher incidence of AEs related to peripheral neuropathy in the R-CHOP arm. In other SOCs, the proportion of patients discontinuing pola/vincristine in the pola+R-CHP and R-CHOP arms, respectively, was comparable.

The most common AEs by PT (≥ 2 patients each in the pola+R-CHP and R-CHOP arm, respectively), leading to pola/vincristine treatment discontinuation were pneumonia (4 patients [0.9%] in each arm), neuropathy peripheral (1 patient [0.2%] and 4 patients [0.9%]), peripheral motor neuropathy (0 patients and 2 patients [0.5%]) and death (2 patients [0.5%] and 1 patient [0.2%]).

The proportion of patients who experienced AEs leading to discontinuation of rituximab study treatment in the pola+R-CHP arm (4.6%) was comparable to the R-CHOP arm (4.8%).

The proportion of patients who experienced AEs leading to discontinuation of any of the components of the CHP regimen (cyclophosphamide, doxorubicin, prednisone) in the pola+R-CHP arm (3.4%) was comparable to the R-CHOP arm (3.7%).

Supportive study GO29044

The majority of events that led to withdrawal of study treatment were consistent with the known risks of each individual component.

A total of 8/66 patients (12.1%) in the pola+R-CHP/G-CHP population had AEs leading to discontinuation of pola. The AEs leading to pola discontinuation by PT were neuropathy peripheral, syncope, tremor, Escherichia urinary tract infection, septic shock, thrombocytopenia, febrile neutropenia, and coronary artery disease. In the majority of patients, these AEs led to discontinuation of all the study drugs.

A total of 7 patients (10.6%) had an AE leading to discontinuation of rituximab/obinutuzumab. AEs that led to discontinuation of rituximab/obinutuzumab were Escherichia urinary tract infection, syncope, tremor, febrile neutropenia, thrombocytopenia, pneumonia and septic shock.

A total of 7 patients (10.6%) had an AE leading to discontinuation of doxorubicin, cyclophosphamide, or prednisone (CHP). AEs that led to discontinuation of any of the CHP study treatments were Escherichia urinary tract infection, septic shock, febrile neutropenia, thrombocytopenia, syncope, tremor and coronary artery disease.

Pooled safety population

The incidence of AEs leading to withdrawal of any component of the study treatment was comparable between the pooled safety population (7.0% [35/501 patients]) and the R-CHOP arm from POLARIX (6.6% [29/438 patients]).

The proportion of patients who experienced AEs leading to discontinuation of pola study treatment in the pooled safety population (5.4% [27/501 patients]) was comparable to the proportion of patients who experienced AEs leading to discontinuation of vincristine study treatment in the R-CHOP arm from POLARIX (5.0% [22/438 patients]).

The proportion of patients who experienced AEs leading to discontinuation of rituximab/obinutuzumab study treatment in the pooled safety population (5.4% [27/501 patients]) was comparable to the proportion of patients who discontinued rituximab treatment in the R-CHOP arm from POLARIX (4.8% [21/438 patients]).

The proportion of patients who experienced AEs leading to discontinuation of any of the components of the CHP regimen (cyclophosphamide, doxorubicin, prednisone) in the pooled safety population (4.4% [22/501 patients]) was comparable to the R-CHOP arm from POLARIX (3.7% [16/438 patients]).

Table 65 Adverse Events by Preferred Term Leading to Discontinuation of Any Study Treatment in Previously Untreated DLBCL Patients, Safety-Evaluable Patients

Adverse Events Leading to Treatment Discontinuation for Any Study Drug by System Organ Class and Preferred Term, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

MedDRA System Organ Class MedDRA Preferred Term	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Total number of patients with at least one adverse event	29 (6.6%)	27 (6.2%)	8 (12.1%)	35 (7.0%)
Overall total number of events	30	27	9	36
Infections and infestations				
Total number of patients with at least one adverse event	10 (2.3%)	7 (1.6%)	3 (4.5%)	10 (2.0%)
Total number of events	10	7	3	10
Pneumonia	6 (1.4%)	5 (1.1%)	1 (1.5%)	6 (1.2%)
Sepsis	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
Escherichia urinary tract infection	0	0	1 (1.5%)	1 (0.2%)
Septic shock	0	0	1 (1.5%)	1 (0.2%)
Vulvovaginal mycotic infection	0	1 (0.2%)	0	1 (0.2%)
Intervertebral discitis	1 (0.2%)	0	0	0
Peritonitis	1 (0.2%)	0	0	0
Prostate infection	1 (0.2%)	0	0	0
Nervous system disorders				
Total number of patients with at least one adverse event	11 (2.5%)	3 (0.7%)	3 (4.5%)	6 (1.2%)
Total number of events	11	3	3	6
Neuropathy peripheral	4 (0.9%)	1 (0.2%)	1 (1.5%)	2 (0.4%)
Peripheral sensorimotor neuropathy	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
Peripheral motor neuropathy	2 (0.5%)	0	0	0
Peripheral sensory neuropathy	2 (0.5%)	0	0	0
Polyneuropathy	0	1 (0.2%)	0	1 (0.2%)
Syncope	0	0	1 (1.5%)	1 (0.2%)
Tremor	0	0	1 (1.5%)	1 (0.2%)
Cerebral infarction	1 (0.2%)	0	0	0
Hypoaesthesia	1 (0.2%)	0	0	0

MedDRA System Organ Class MedDRA Preferred Term	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Respiratory, thoracic and mediastinal disorders				
Total number of patients with at least one adverse event	1 (0.2%)	6 (1.4%)	0	6 (1.2%)
Total number of events	1	6	0	6
Pneumonitis	0	2 (0.5%)	0	2 (0.4%)
Dyspnoea	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
Interstitial lung disease	0	1 (0.2%)	0	1 (0.2%)
Pulmonary oedema	0	1 (0.2%)	0	1 (0.2%)
Respiratory failure	0	1 (0.2%)	0	1 (0.2%)
General disorders and administration site conditions				
Total number of patients with at least one adverse event	2 (0.5%)	5 (1.1%)	0	5 (1.0%)
Total number of events	2	5	0	5
Death	1 (0.2%)	3 (0.7%)	0	3 (0.6%)
Cardiac death	0	1 (0.2%)	0	1 (0.2%)
Fatigue	0	1 (0.2%)	0	1 (0.2%)
Chest pain	1 (0.2%)	0	0	0
Blood and lymphatic system disorders				
Total number of patients with at least one adverse event	0	3 (0.7%)	2 (3.0%)	5 (1.0%)
Total number of events	0	3	2	5
Neutropenia	0	2 (0.5%)	0	2 (0.4%)
Thrombocytopenia	0	1 (0.2%)	1 (1.5%)	2 (0.4%)
Febrile neutropenia	0	0	1 (1.5%)	1 (0.2%)
Gastrointestinal disorders				
Total number of patients with at least one adverse event	3 (0.7%)	2 (0.5%)	0	2 (0.4%)
Total number of events	3	2	0	2
Intestinal perforation	0	1 (0.2%)	0	1 (0.2%)
Necrotising colitis	0	1 (0.2%)	0	1 (0.2%)
Intestinal obstruction	1 (0.2%)	0	0	0
Intra-abdominal haemorrhage	1 (0.2%)	0	0	0
Nausea	1 (0.2%)	0	0	0

MedDRA System Organ Class MedDRA Preferred Term	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Cardiac disorders				
Total number of patients with at least one adverse event	1 (0.2%)	0	1 (1.5%)	1 (0.2%)
Total number of events	1	0	1	1
Coronary artery disease	0	0	1 (1.5%)	1 (0.2%)
Left ventricular dysfunction	1 (0.2%)	0	0	0
Renal and urinary disorders				
Total number of patients with at least one adverse event	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
Total number of events	1	1	0	1
Acute kidney injury	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
Investigations				
Total number of patients with at least one adverse event	1 (0.2%)	0	0	0
Total number of events	1	0	0	0
Ejection fraction decreased	1 (0.2%)	0	0	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.
GO39942 CCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

- *AEs leading to dose reduction*

Table 66 Adverse Events by Preferred Term Leading to Any Study Treatment Dose Reduction in Previously Untreated DLBCL Patients, Safety-Evaluable Patients

Adverse Events Leading to Dose Reduction for Any Study Drug by System Organ Class and Preferred Term, Patients with 1L DLBCL, Safety-Evaluable Patients
Protocols: GO39942, GO29044

MedDRA System Organ Class MedDRA Preferred Term	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Total number of patients with at least one adverse event	57 (13.0%)	40 (9.2%)	8 (12.1%)	48 (9.6%)
Overall total number of events	78	47	11	58
Nervous system disorders				
Total number of patients with at least one adverse event	36 (8.2%)	20 (4.6%)	3 (4.5%)	23 (4.6%)
Total number of events	38	20	3	23
Neuropathy peripheral	22 (5.0%)	9 (2.1%)	1 (1.5%)	10 (2.0%)
Peripheral sensory neuropathy	10 (2.3%)	8 (1.8%)	2 (3.0%)	10 (2.0%)
Polyneuropathy	2 (0.5%)	1 (0.2%)	0	1 (0.2%)
Paraesthesia	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
Dysaesthesia	0	1 (0.2%)	0	1 (0.2%)
Peripheral motor neuropathy	2 (0.5%)	0	0	0
Blood and lymphatic system disorders				
Total number of patients with at least one adverse event	6 (1.4%)	7 (1.6%)	2 (3.0%)	9 (1.8%)
Total number of events	14	7	2	9
Febrile neutropenia	2 (0.5%)	5 (1.1%)	1 (1.5%)	6 (1.2%)
Neutropenia	3 (0.7%)	1 (0.2%)	1 (1.5%)	2 (0.4%)
Thrombocytopenia	2 (0.5%)	1 (0.2%)	0	1 (0.2%)
Leukopenia	2 (0.5%)	0	0	0
Anaemia	1 (0.2%)	0	0	0
Erythropenia	1 (0.2%)	0	0	0

MedDRA System Organ Class MedDRA Preferred Term	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Investigations				
Total number of patients with at least one adverse event	6 (1.4%)	4 (0.9%)	2 (3.0%)	6 (1.2%)
Total number of events	7	7	2	9
Weight decreased	2 (0.5%)	1 (0.2%)	2 (3.0%)	3 (0.6%)
Neutrophil count decreased	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
Alanine aminotransferase increased	0	1 (0.2%)	0	1 (0.2%)
Aspartate aminotransferase increased	0	1 (0.2%)	0	1 (0.2%)
Blood alkaline phosphatase increased	0	1 (0.2%)	0	1 (0.2%)
Blood creatinine increased	0	1 (0.2%)	0	1 (0.2%)
Platelet count decreased	0	1 (0.2%)	0	1 (0.2%)
Blood bilirubin increased	1 (0.2%)	0	0	0
Haemoglobin decreased	1 (0.2%)	0	0	0
N-terminal prohormone brain natriuretic peptide increased	1 (0.2%)	0	0	0
Troponin t increased	1 (0.2%)	0	0	0
Gastrointestinal disorders				
Total number of patients with at least one adverse event	6 (1.4%)	3 (0.7%)	0	3 (0.6%)
Total number of events	6	3	0	3
Diarrhoea	2 (0.5%)	2 (0.5%)	0	2 (0.4%)
Constipation	0	1 (0.2%)	0	1 (0.2%)
Vomiting	2 (0.5%)	0	0	0
Abdominal distension	1 (0.2%)	0	0	0
Subileus	1 (0.2%)	0	0	0

MedDRA System Organ Class MedDRA Preferred Term	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
General disorders and administration site conditions				
Total number of patients with at least one adverse event	3 (0.7%)	2 (0.5%)	1 (1.5%)	3 (0.6%)
Total number of events	4	2	1	3
Fatigue	2 (0.5%)	1 (0.2%)	0	1 (0.2%)
Oedema peripheral	1 (0.2%)	0	1 (1.5%)	1 (0.2%)
Peripheral swelling	0	1 (0.2%)	0	1 (0.2%)
Malaise	1 (0.2%)	0	0	0
Infections and infestations				
Total number of patients with at least one adverse event	4 (0.9%)	1 (0.2%)	1 (1.5%)	2 (0.4%)
Total number of events	4	1	1	2
Clostridium difficile infection	0	0	1 (1.5%)	1 (0.2%)
Sepsis	2 (0.5%)	0	0	0
Staphylococcal infection	0	1 (0.2%)	0	1 (0.2%)
Neutropenic sepsis	1 (0.2%)	0	0	0
Pneumonia	1 (0.2%)	0	0	0
Metabolism and nutrition disorders				
Total number of patients with at least one adverse event	0	3 (0.7%)	1 (1.5%)	4 (0.8%)
Total number of events	0	4	1	5
Decreased appetite	0	2 (0.5%)	0	2 (0.4%)
Hyperglycaemia	0	1 (0.2%)	1 (1.5%)	2 (0.4%)
Hypocalcaemia	0	1 (0.2%)	0	1 (0.2%)
Psychiatric disorders				
Total number of patients with at least one adverse event	2 (0.5%)	0	1 (1.5%)	1 (0.2%)
Total number of events	2	0	1	1
Affect lability	0	0	1 (1.5%)	1 (0.2%)
Adjustment disorder	1 (0.2%)	0	0	0
Insomnia	1 (0.2%)	0	0	0

MedDRA System Organ Class MedDRA Preferred Term	R-CHOP (POLARIX) (N=438)	Pola-R-CHP (POLARIX) (N=435)	Pola (1.8 mg/kg) +R-CHP/G-CHP (GO29044) (N=66)	All Pola (1.8 mg/kg) +R-CHP/G-CHP (POLARIX + GO29044) (N=501)
Cardiac disorders				
Total number of patients with at least one adverse event	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
Total number of events	1	1	0	1
Palpitations	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
Ear and labyrinth disorders				
Total number of patients with at least one adverse event	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
Total number of events	1	1	0	1
Tinnitus	0	1 (0.2%)	0	1 (0.2%)
Hypoacusis	1 (0.2%)	0	0	0
Hepatobiliary disorders				
Total number of patients with at least one adverse event	0	1 (0.2%)	0	1 (0.2%)
Total number of events	0	1	0	1
Hyperbilirubinaemia	0	1 (0.2%)	0	1 (0.2%)
Vascular disorders				
Total number of patients with at least one adverse event	1 (0.2%)	0	0	0
Total number of events	1	0	0	0
Hypotension	1 (0.2%)	0	0	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.
GO39942 OCOD: 28JUN2021. Data extract date: 02AUG2021.
GO29044 Database lock date: 28MAR2019.

- *AEs leading to treatment interruption*

Study POLARIX

The proportion of patients who experienced AEs leading to interruption of any study treatment in the pola+R-CHP arm (23.7%) was comparable to the R-CHOP arm (25.3%) with the most commonly reported AEs leading to study treatment interruption in the pola+R-CHP arm being in the Infections and infestations SOC and the most commonly reported AEs leading to study treatment interruption in the R-CHOP arm being in the Blood and lymphatic system disorders SOC.

The proportion of patients who experienced AEs leading to pola treatment interruption in the pola+R-CHP arm (14.0%) was comparable to the proportion of patients who experienced AEs leading to vincristine treatment interruption in the R-CHOP arm (13.7%).

The proportion of patients who experienced AEs leading to rituximab dose interruptions in the pola+R-CHP arm (22.3%) was comparable with the R-CHOP arm (23.7%).

The proportion of patients who experienced AEs leading to CHP dose interruptions in the pola+R-CHP arm (14.0%) was comparable with the R-CHOP arm (13.7%).

Supportive study GO29044

A total of 6 patients (9.1%) had an AE leading to interruption of pola. AEs that led to interruption of pola were pulmonary embolism, ophthalmic herpes zoster, bronchitis, pneumonia, febrile neutropenia and neutropenia.

Seventeen patients (17/66; 25.6%) had AEs leading to interruption of rituximab or obinutuzumab. AEs that led to dose interruption in more than 1 patient each were neutropenia (8 patients), infusion related reaction (4 patients) and thrombocytopenia (2 patients).

Seven patients (7/66; 10.6%) had an AE leading to interruption of cyclophosphamide, doxorubicin or prednisone (CHP). AEs that led to interruption of any CHP study treatments were neutropenia, febrile neutropenia, pneumonia, bronchitis, ophthalmic herpes zoster, catheter site pain, and pulmonary embolism.

Pooled safety population

The proportion of patients who experienced AEs leading to interruption of any study treatment in the pooled safety population 24.2% [121/501 patients]) was consistent with the pola+R-CHP arm from POLARIX and comparable to the R-CHOP arm (25.3% [111/438 patients]).

The proportion of patients who experienced AEs leading to pola treatment interruption in the pooled safety population (13.4% [67/501 patients]) was comparable to the proportion of patients who experienced AEs leading to vincristine treatment interruption in the R-CHOP arm from POLARIX (13.7% [60/438 patients]).

The proportion of patients who experienced AEs leading to rituximab/obinutuzumab dose interruptions in the pooled safety population (22.8% [114/501 patients]) was comparable with the proportion of patients who had a rituximab treatment interruption in the R-CHOP arm from POLARIX (23.7% [104/438 patients]).

The proportion of patients who experienced AEs leading to CHP dose interruptions in the pooled safety population (13.6% [68/501 patients]) was comparable with the R-CHOP arm from POLARIX (13.7% [60/438 patients]).

Post marketing experience

POLIVY (polatuzumab vedotin) is approved in the EU, in combination with bendamustine and rituximab, for the treatment of adult patients with R/R DLBCL who are not candidates for hematopoietic stem cell transplant, and in the US, in combination with bendamustine and rituximab, for the treatment of adult patients with R/R DLBCL, not otherwise specified, after at least two prior therapies.

Since the International Birth Date (10 June 2019) through 09 June 2021, an estimated cumulative total of 10,529 patients have received polatuzumab from marketing experience (United States n=3,693 patients; European Union n=5,613 patients; Rest of the World n=1,223 patients). No new or unexpected safety findings have been identified in the post-marketing setting. The regimen of polatuzumab in combination with R-CHP administered in the POLARIX study is not yet approved.

2.5.1. Discussion on clinical safety

Safety data for polatuzumab vedotin 1.8 mg/kg in combination with R-CHP in patients with previously untreated DLBCL is based on the pivotal study POLARIX, N=873 (N=435 in the pola+R-CHP arm and N=438 in the R-CHOP arm). Additional supportive data from the GO29044 study are presented from a cohort of patients with previously untreated DLBCL (n=66) who received pola 1.8 mg/kg in combination with R-CHP

(n=45) or G-CHP (obinutuzumab, cyclophosphamide, doxorubicin and prednisone [n=21]). The pooled population comprised all patients from POLARIX and GO29044 with previously untreated DLBCL receiving pola 1.8 mg/kg in combination with R-CHP/G-CHP (N=501). Separate data for pola +R-CHP and pola+G-CHP in Study GO29044 would have allowed a direct comparison with the pola + R-CHP arm from POLARIX and a pooled population receiving similar treatment, therefore the MAH provided safety data from study GO29044 presented separately for pola +R-CHP and pola+G-CHP at least for all treatment-related AEs (all grades, grades 3-5 and SAEs). The nature and frequency of treatment-related AEs observed in the pola+R-CHP arm of GO29044 were generally consistent with that observed in the pola+R-CHP of POLARIX (within the limitation of the overall small number of patients in GO29044). It is noted that the schedule of treatments slightly differed across the two studies, i.e. 6 cycles for Pola + R-CHP in POLARIX with Rituximab as monotherapy in cycles 7 and 8 and 6-8 cycles for Pola + R-CHP and Pola + G-CHP in GO29044 study.

Extent of exposure

The period for AEs collection was similar across the two studies (90 days after the last dose of study drug). In POLARIX study, the extent of exposure to pola/vincristine, rituximab, cyclophosphamide, doxorubicin and prednisone were similar across the 2 treatment arms.

Overall the total duration of pola treatment and number of cycles of Pola were comparable across the 2 studies, i.e. median duration of 3.5 months and median number of cycles of 6 for both studies. The median total cumulative dose of pola was however higher in GO29044 study compared to POLARIX study, i.e. 864 mg in Pola+R-CHP arm in GO29044, 828 mg in Pola+G-CHP arm in GO29044 and 762.0 mg in Pola+R-CHP arm in POLARIX which is not considered unexpected based on the different schedule of treatments across the two studies.

The exposure to rituximab was lower in Study GO29044 compared to POLARIX. In POLARIX the median number of cycles was 8 and the median total cumulative dose was 5329 mg for the Pola+R-CHP arm and 5380 mg for R-CHOP arm; in study GO29044 the median number of cycles was 6 and median total cumulative dose was 4625.00 mg. The cumulative dose of cyclophosphamide and doxorubicin were higher in Study GO29044 compared to POLARIX, and similar for prednisone across the 2 studies. It cannot be ruled out that the differences observed in cumulative dose of pola, rituximab, cyclophosphamide and doxorubicin can have an impact on the safety profile in patients across the studies POLARIX and GO29044.

The median RDI was >99.8% for all components of study treatment in both studies reflecting a high treatment compliance.

Adverse events

Overall the AEs occurred at similar rates in the pooled pola-treated subjects and in the R-CHOP arm of POLARIX, 98.2% and 98.4% respectively. The majority of reported AEs in the safety population were Grade ≥3 AEs, i.e. 61.5% in all pola + R-CHP/G-CHP pooled population and 59.8% in R-CHOP. Serious AEs were slightly more reported with all pola + R-CHP/G-CHP pooled population than with R-CHOP, i.e. 34.9% and 30.6%. It is showed that grade 3-5 and serious AEs were more reported in the Pola+R-CHP/G-CHP group in GO29044 study than Pola+R-CHP arm in POLARIX.

The most frequently reported AEs in the pooled safety population were nausea (42.3%), neutropenia (32.1%), diarrhoea (33.3%), constipation (28.3%), fatigue (28.7%), anemia (28.7%), alopecia (23.8%) and neuropathy peripheral (23.0%). This remains coherent with the known safety profile of polatuzumab, except for alopecia considered as an additional ADR.

AEs with an incidence rate ≥10% that were reported in the pooled safety population (all pola + R-CHP/G-CHP) with a greater difference compared to R-CHOP arm of POLARIX were diarrhoea (33.3% and 20.1%, +13.2%), febrile neutropenia (14.8% and 8.0%, +6.8%), nausea (42.3% and 36.8%, +5.5%), pyrexia (16.4% and 12.6%, +3.8%), anemia (28.7% and 26.0%, +2.7%), fatigue (28.7% and 26.5%, +2.2%),

decreased appetite (16.2% and 14.2%, +2.0%), weight decrease (13.8% and 11.9%, +1.9%), asthenia (13.0% and 12.1%, +0.9%), vomiting (15.2% and 14.4%, +0.8%), cough (12.8% and 12.1%, +0.7%) and neuropathy peripheral (23.0% and 22.6%, +0.4%).

The most frequently (≥10%) reported Grade 3-4 AEs in the pooled safety population were neutropenia (28.5%), febrile neutropenia (14.4%) and anemia (11.0%). Febrile neutropenia and anemia were more reported in the pooled safety population than the R-CHOP arm of POLARIX study, i.e. +6.4% and +2.6% respectively.

The MAH provided the treatment-related AEs for the safety population. Overall the submitted analysis of treatment-related AE is consistent with the known safety profile of pola with no new safety concern identified.

The adverse drug reactions were based on the pooled data from POLARIX in previously untreated DLBCL patients treated with Pola+R-CHP and study GO29365 in R/R DLBCL patients treated with pola+BR. Since comparable safety profile of Polivy was observed in previously untreated DLBCL patients treated with Pola+R-CHP and in R/R DLBCL patients treated with pola+BR, the approach of ADRs in the pooled safety population is considered acceptable. However variability in the ADR frequencies was reported across the previously untreated DLBCL patients treated by pola+R-CHP and the R/R DLBCL patients treated by pola+BR such as peripheral neuropathy (52.9% in pola+R-CHP vs 30.5% in pola+BR), neutropenia (38.4% in pola+R-CHP vs 45.7% in pola+BR), nausea (41.6% in pola+R-CHP vs 33.1% in pola+BR), diarrhea (30.8% in pola+R-CHP and 35.8% in pola+BR). Therefore this ADR frequency variability in the two safety populations should be reflected in the section 4.8 of the SmPC, please refer to SmPC comments.

Adverse events of special interest

Peripheral neuropathy (PN): In POLARIX, the incidence of PN events was similar in both arms, i.e. 53.9% in R-CHOP and 52.9% in Pola+R-CHP. The majority of PN events reported with pola+R-CHP were Grade 1-2 and one serious PN occurred in each arm (0.2% each), related to the treatment in both cases. The majority of PN events occurring in POLARIX resolved with a higher rate of PN resolution in R-CHOP arm compared to pola+R-CHP arm (66.9% and 57.8% respectively) which may be partly explained by the difference in median time to onset (2.27 months in pola+R-CHP vs 1.87 months in R-CHOP) and the comparable median time to resolution across the two treatment arms. A higher rate of PN leading to any study treatment discontinuation and dose reduction was observed in R-CHOP arm compared to pola+R-CHP arm. Indeed there was a higher proportion of patients that had a vincristine dose reduction due to PN in the R-CHOP arm (8.0%) than PN leading to pola dose reduction in the pola+R-CHP arm (3.9%). There was a lower incidence of PN in Pola +R-CHP/G-CHP group of the supportive study GO29044 compared to the pola+R-CHP arm in POLARIX, i.e. 39.4% and 52.9% respectively.

Neutropenia including febrile neutropenia: In POLARIX, the incidence of neutropenia events was comparable in both treatment arms, i.e. 42.7% in R-CHOP and 46.0% in pola+R-CHP. The large majority of neutropenia were Grade 3-4 and occurred at similar rates in the two arms (40.2% in R-CHOP, 41.8% in pola+R-CHP). No Grade 5 events were reported. Neutropenia leading to any study treatment discontinuation, dose reduction or treatment interruption were also reported at similar rates across the two arms. Serious neutropenia were more reported in Pola+R-CHP arm compared to R-CHOP (11.5% vs 8.4%). Neutropenia events resolved in most of the cases (98.0% in the pola+R-CHP arm and 97.9% in the R-CHOP arm). A higher incidence of neutropenia was observed in study GO29044 compared to POLARIX (51.5%). Of note, G-CSF prophylaxis was required in POLARIX during Cycles 1-6 while it was strongly encouraged but not mandatory in study GO29044. An overview of AEPI Neutropenia allowing a direct comparison of the safety-evaluable patients receiving or not G-CSF prophylaxis was provided. The occurrence of AEPI neutropenia was comparable across subjects with and without G-CSF prophylaxis use but the imbalance between the 2 groups of subjects (n=800 in G-CSF prophylaxis use and n=73 in non-prophylaxis use) prevents a clear conclusion on the comparison of neutropenia events by G-CSF status.

Anemia: in POLARIX, the incidence of anemia events was comparable across the 2 treatment arms (26.9% in R-CHOP arm and 28.7% in Pola+R-CHP arm). Serious neutropenia were reported at similar rate in both arms, i.e. 1.4% in R-CHOP and 0.9% in Pola+R-CHP. It is noted a higher proportion of patients having Grade 3-4 neutropenia in Pola-R-CHP compared to R-CHOP (12.0% vs 8.7%) and no Grade 5 anemia in POLARIX. The majority of anemia events resolved in both arms, i.e. 84.8% in pola+R-CHP and 86.4% in R-CHOP. In study GO29044, the incidence of anemia was comparable to POLARIX (28.8%). The majority of anemia events were low grade with 4.5% of Grade 3-4 AEs and no Grade 5 anemia. No serious anemia event or anemia leading to treatment modification were observed in the supportive study

Thrombocytopenia: In POLARIX, the occurrence of thrombocytopenia was similar across pola+R-CHP arm and R-CHOP arms, i.e. 13.3% and 13.2% respectively. Grade 3-4 events were reported at comparable rate, i.e. 0.5% in pola+R-CHP and 0.2% in R-CHOP respectively, and serious thrombocytopenia occurred in two (0.5%) subjects in pola+R-CHP and one (0.2%) subject in R-CHOP. No Grade 5 thrombocytopenia was reported in POLARIX. One thrombocytopenia event led to study treatment discontinuation in pola+R-CHP arm and none in R-CHOP arm. Median time to onset was however longer in the pola+R-CHP arm compared to R-CHOP arm (1.68 months vs 0.41 months) but median time to resolution was similar across the two arms (0.36 months in both). More thrombocytopenia resolutions were observed in pola+R-CHP arm than R-CHOP arm, i.e. 94.8% and 86.2% respectively. Slightly more thrombocytopenia were reported in study GO29044 compared to POLARIX, i.e. 21.2% of patients experienced one thrombocytopenia event. Also more Grade 3-4 events were reported in GO29044 than in POLARIX (9.1%), but no SAE was observed. Most of the thrombocytopenia events resolved (92.9%).

Infection: In POLARIX the incidence of infection events, Grade 3-4 infections and serious infections was higher in pola+R-CHP arm compared to R-CHOP arm (49.7% vs 42.7%, 14.0% vs 11.2% and 14.0% vs 10.3%, respectively). The proportion of Grade 5 infections was comparable in both treatment arms (1.1% in pola+R-CHP and 1.4% in R-CHOP); pneumonia was the most reported AE among the Grade 5 Infections (4 patients in pola+R-CHP arm, 3 patients in R-CHOP arm) and the other Grade 5 Infection AEs were septic choc and sepsis. The incidence of opportunistic infections was higher in pola+R-CHP than R-CHOP. The majority of infections events resolved (87% in pola+R-CHP and 84.5% in R-CHOP) with a similar median time to resolution. Slightly more patients with an infection event were reported in study GO29044 compared to POLARIX (53.0%) but Grade 3-5 and serious infections occurred at comparable rates in Pola+R-CHP/G-CHP in study GO29044 and Pola+R-CHP in POLARIX.

Hepatic toxicity: hepatotoxicity events were more reported in the pooled safety population (all pola) than the R-CHOP arm in POLARIX, i.e. 10.2% and 7.3% respectively, and the majority of reported events were low grade. In POLARIX, the incidence of hepatotoxicity, Grade 3 events and serious events was higher in Pola+R-CHP arm than R-CHOP arm. The majority of hepatic toxicity reported in the study were ALAT and ASAT elevations. There was no Grade 4 or 5 hepatic toxicity event reported nor hepatotoxicity event leading to study treatment discontinuation in POLARIX. One SAE was observed in pola+R-CHP. Hepatic toxicity resolved in most of the cases in both arms, i.e. 87.0% in the pola+R-CHP arm and 84.4% in the R-CHOP arm. A total of 3 cases of potential DILI were reported in POLARIX: 1 in pola+R-CHP arm and 2 in R-CHOP arm. Two cases were confounded by events of sepsis and one was confounded by multiple organ dysfunction in the setting of febrile neutropenia. The incidence of hepatotoxicity in Pola+R-CHP/G-CHP in study GO29044 was comparable to R-CHOP arm in POLARIX. All events were low grade except one Grade 3 hepatic toxicity.

Carcinogenicity / secondary malignancies: Carcinogenicity has been identified as an important potential risk with Polivy. Overall, carcinogenicity events were reported at comparable rates across the two treatment arms in POLARIX, i.e. 0.9% in pola+R-CHP arm and 1.1% in R-CHOP arm, and no Grade 5 event

was reported. There were more serious events observed in pola+R-CHP arm than R-CHOP arm (3 [0.7%] vs 1 [0.2%] cases) but comparable median time to onset (5.86 and 5.06 months respectively). A higher proportion of carcinogenicity events resolved in R-CHOP arm compared to pola+R-CHP at the DCO (60% vs 25%).

Pulmonary toxicity: Overall similar incidence of pulmonary toxicity (1.6%) was observed across the two treatment arms in POLARIX. The majority of the events were low grade. There was one Grade 3 event in pola+R-CHP arm and one Grade 4 event in R-CHOP, and no Grade 5 pulmonary event was reported in POLARIX. Serious pulmonary toxicity events were reported in 2 subjects in R-CHOP arm and one subject in pola+R-CHP. One case (1.5%) of pulmonary toxicity was reported in study GO29044 (pola 1.8 mg/kg +R-CHP/G-CHP) and this event was Grade 2.

Infusion-related reactions (IRR): Overall the incidence of IRR in POLARIX was comparable across the treatment arms (16.0% in R-CHOP arm and 13.3% in pola+R-CHP arm). However the proportion of patients experiencing IRR observed in study GO29044 was inconsistent with POLARIX with a very higher IRR rate, i.e. 45.5%: this inconsistency in the incidence of IRR between POLARIX and GO29044 studieswas justified by the MAH by the IRR AEPI search strategy not aligned across the two studies. Proportion of patients who experienced IRRs from pola+R-CHP/G-CHP arms in study GO29044 was comparable with the pola+R-CHP arm in POLARIX (13.3% [58/435]) when the search strategy for IRR in GO29044 was aligned with that of POLARIX.
. The majority of IRR reported in the pooled safety population were low grade and no Grade 5 event was reported. The large majority of IRR cases resolved.

Tumor lysis syndrome: In POLARIX, slightly more TLS events were reported in R-CHOP arm compared to Pola+R-CHP (4 [0.9%] and 2 [0.5%] patients reported TLS, respectively). Grade 3-4 and serious TLS occurred at comparable rate, and no Grade 5 was reported in the study. All cases of TLS reported in POLARIX resolved. There was no case of TLS in study GO29044.

Cardiac arrhythmia: This AEPI is considered as adverse reaction with clinical consequences, even serious but occurring with a low frequency in the RMP but not mentioned in the SmPC. In POLARIX cardiac arrhythmia events were slightly more reported in R-CHOP compared to Pola+R-CHP arm, i.e. 4.6% vs 3.0%. The majority of the reported events were low grade. The proportion of patients who experienced a Grade 3-4 cardiac arrhythmia event was comparable across the two arms and one Grade 5 cardiac arrhythmia was reported in R-CHOP while none in pola+R-CHP. Serious AEs were reported at comparable rate in both arms.

Hyperglycemia: In POLARIX the proportion of patients reporting hyperglycemia was comparable across the treatment arms (6.2% in R-CHOP arm and 6.0% in pola+R-CHP arm). The majority of hyperglycemia events were low grade. No Grade 4, grade 5, serious events nor hyperglycemia leading to dose discontinuation or reduction were reported in POLARIX. One case of hyperglycemia led to treatment dose reduction in pola+R-CHP arm. The hyperglycemia events in POLARIX resolved in 53.8% of the cases in pola+R-CHP arm and 48.1% in R-CHOP arm.

Serious adverse event / deaths
The most common cause of death across the safety population was disease progression. Fatal AEs were more reported in the pola+R-CHP arm compared to R-CHOP arm in POLARIX (3.0% vs 2.5%). The most frequent Grade 5 AEs in the pooled safety group (all pola) were pneumonia (4 patients [0.8%]) and death (4 patients [0.8%]). The treatment-related AEs that led to death in the pola+R-CHP arm were pneumonia (3 patients), cardiac death, acute kidney injury and death. In the supportive study GO29044, 2 patients had a fatal AE: one case of fatal atrial fibrillation assessed by the investigator as unrelated to any study

drug and related to concurrent illness and one case of fatal septic shock considered related to doxorubicin and cyclophosphamide treatment. Pneumonitis and infections are known risks with polatuzumab. Infections and AV block were also reported as Grade 5 AEs in R-CHOP arm in POLARIX, i.e. 1.4% and 0.2% respectively.

Overall SAEs were more frequent in the pooled safety population (all pola) than the R-CHOP arm in POLARIX study, i.e. 34.9% and 30.6% respectively, driven by the incidence rate of SAEs in Pola + R-CHP/G-CHP group in study GO29044 (40.9%). In POLARIX, the proportion of patients with at least one SAE in the pola+R-CHP arm was comparable with the R-CHOP arm but more SAEs were treatment-related in pola+R-CHP than R-CHOP (25.7% and 19.6% respectively). The most common treatment-related SAEs reported with pola+R-CHP/G-CHP in both studies were febrile neutropenia (10.4%), neutropenia (1.6%) and infections (pneumonia [4.6%], sepsis [1.2%], urinary tract infection [1.6%], clostridium difficile infection, oral fungal infection, septic shock) and diarrhea (2.4%).The most frequent SAEs with R-CHOP were febrile neutropenia (6.4%) and pneumonia (3.9%).

Laboratory findings
Overall the Grade 3-4 laboratory findings were comparable across the treatment groups.

Immunogenicity
The post-baseline ADAs were reported at a low rate in ADA-evaluable patients treated with pola in POLARIX (1.4%, all treatment-induced) and none of them was neutralizing. There were no patients ADA positive at post-baseline in the supportive study GO29044. There was no data supporting a potential impact of ADAs to pola on safety and efficacy.

Vital sign, physical findings and other observations related to safety
In POLARIX, no new signal was detected regarding vital signs and the number of patients with a clinically significant ECG abnormality was low and comparable between the treatment arms at screening and post baseline.

Safety in special population
It is observed that the ≥65 group experienced more events than the <65 group with regard to the Grade 5 AEs (4.0% vs 1.8%), the Grade 3-5 AEs (66.7% vs 55.1%), the serious AEs (40.2% vs 28.4%), AEs leading to any study discontinuation (4.3% vs 1.8%), AEs leading to any study treatment dose discontinuation (10.9% vs 2.2%), AEs leading to any study treatment dose reduction (11.6% vs 7.1%) and AEs leading to pola/placebo discontinuation (8.3% vs 1.8%). The differences in safety profile between the <65 and the ≥65 years patients are reflected in section 4.4 of the SmPC.
There was an increase of the incidence of Grade 3-5 AEs, SAEs and AE leading to dose discontinuation/interruption in moderate and severe HI that should be interpreted with caution due to the small number of patients; furthermore the SmPC mentioned that the administration of Polivy in patients with moderate or severe hepatic impairment should be avoided.
With regard to the renal function, the proportion of patients who experienced all-grade AEs, Grade ≥ 3 AEs, SAEs and AEs leading to any study treatment discontinuation in both treatment arms increased with the severity of renal impairment, with very limited data on severe renal impairment (N=2).

Discontinuation due to adverse events

AEs leading to study discontinuation were more reported in the pola+R-CHP arm than the R-CHOP arm from POLARIX (3.0% vs 2.3%). In POLARIX all AEs leading to study discontinuation were the reported Grade 5 AEs. In study GO29044 only one of the two reported Grade 5 AEs led to study discontinuation (atrial fibrillation). The most reported AEs in the pooled safety population were pneumonia and death.

Overall the rate of AE leading to treatment discontinuation was comparable across the treatment arms in POLARIX (6.2% in pola+R-CHP arm and 6.6% in R-CHOP arm). However the incidence rate in study GO29044 was higher, i.e. 12.1%, with more reported AE leading to treatment discontinuation is SOCs Infections and infestations and Nervous system disorders. Pneumonia, pneumonitis, neutropenia and peripheral neuropathy were the most reported AEs leading to any treatment discontinuation in the pooled safety population.

AEs leading to dose reduction occurred more frequently in R-CHOP arm from POLARIX than all pola pooled safety population, i.e. 13.0% and 9.6%, mostly driven by the rate of AEs leading to vincristine dose reduction (10.3%) in R-CHOP arm which is higher than that leading to a pola dose reduction (5.8%) in the pooled population. The majority of AE leading to dose reduction in the pooled safety population were Nervous system disorders SOC.

In POLARIX, the incidence of AEs leading to interruption of any study treatment in the pola+R-CHP arm (23.7%) was comparable to the R-CHOP arm (25.3%). Infections and infestations were the most reported AEs leading to interruption of any study treatment in pola+R-CHP arm while it was Blood and lymphatic system disorders in R-CHOP arm.

Post-marketing experience
No new or unexpected safety findings have been identified in the post-marketing setting. The regimen of pola in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (R-CHP) administered in the POLARIX study is not yet approved.

2.5.2. Conclusions on clinical safety

Overall, no new safety concern arises from the safety data from polatuzumab vedotin 1.8 mg/kg in combination with R-CHP in patients with previously untreated DLBCL. The safety profile remained not negligible with a high incidence of Grade ≥3 AEs and SAEs (mainly myelosuppression and infections) to consider in the context of a life-threatening condition.

The following measures are considered necessary to address issues related to safety:

The updated CSR from study Polarix; A Phase III, multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of polatuzumab vedotin in combination with R-CHP versus in previously untreated patients with DLBCL aimed to study long term safety, will be submitted as category 3 measure (see RMP).

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 2.1 with the following content:

Safety concerns

Table 1. Summary of safety concerns

Important identified risks	Not applicable
Important potential risks	Carcinogenicity
Missing information	Long term safety Use in Severe Hepatic Impairment Use in Severe Renal Impairment Use in Pregnancy and Lactation

Pharmacovigilance plan

Table 2. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Date(s)
Category 1—Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorization				
There are no Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Category 2—Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances.				
There are no imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances.				
Category 3—Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA)—i.e. studies that investigate a safety concern or evaluate the effectiveness of risk-minimization activities				
Study GO29365 A Phase Ib/II, multicenter, open-label study evaluating the safety, tolerability, and anti-tumor activity of polatuzumab vedotin in combination with rituximab or obinutuzumab plus bendamustine in patients with R/R follicular lymphoma or R/R diffuse large B-cell lymphoma. **(Ongoing)**	To evaluate the risk of carcinogenicity in polatuzumab vedotin treated patients and provide all updated time-related endpoints for pooled Arm G+H.	Carcinogenicity	Final CSR	Q3 2022
A Phase III, multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of polatuzumab vedotin in combination with R-CHP versus in previously untreated patients with DLBCL. **(Ongoing)**	To evaluate the safety and efficacy of polatuzumab vedotin plus R-CHP compared with R-CHOP.	Long-term safety	Update CSR at the time of final overall survival analysis	Q4 2022

Risk minimisation measures

Table 3. Summary Table of Risk-Minimization Activities by Safety Concern

Safety Concern	Routine Risk-Minimization Activities
Important Potential Risk	
Carcinogenicity	*Proposed risk communication is described in*

	SmPC: • Section 5.3 Preclinical safety data *Routine risk-minimization activities recommending specific clinical measures to address the risk:* Information on carcinogenicity is provided in SmPC Section 5.3 *Other risk-minimization measures beyond the Product Information:* N/A
Missing Information	
Long-Term Safety	*Proposed risk communication is described in* *SmPC:* • None *Package Leaflet:* • None *Routine risk minimization activities recommending specific clinical measures to address the risk:* None *Other risk minimization measures beyond the Product Information:* N/A
Use in Patients with Severe Hepatic Impairment	*Proposed risk communication is described in* *SmPC:* • Section 4.2 Posology and method of administration: Special populations—Hepatic impairment • Section 5.2 Pharmacokinetic properties: Hepatic impairment *Routine risk-minimization activities recommending specific clinical measures to address the risk:* Information on posology for patients with severe hepatic impairment is provided in SmPC Section 4.2 *Other risk-minimization measures beyond the Product Information:* N/A

Use in Patients with Severe Renal Impairment	*Proposed risk communication is described in* *SmPC:* • Section 4.2 Posology and method of administration: Special populations—Renal impairment • Section 5.2 Pharmacokinetic properties: Renal impairment *Routine risk-minimization activities recommending specific clinical measures to address the risk:* Information on posology for patients with severe renal impairment is provided in SmPC Section 4.2 *Other risk-minimization measures beyond the Product Information:* N/A
Use in Pregnancy and Lactation	*Proposed risk communication is described in* *SmPC:* • Section 4.6 Fertility, pregnancy and lactation *Package Leaflet:* • Section 2 What you need to know before you use Polivy *Routine risk-minimization activities recommending specific clinical measures to address the risk:* Information on use of polatuzumab vedotin in pregnancy is provided in SmPC Section 4.6 *Other risk-minimization measures beyond the Product Information:* N/A
N/A=not applicable; SmPC=summary of product characteristics.	

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

The Annex II has been updated with the deletion of section E as all Specific Obligations have been fulfilled. Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) which were reviewed and accepted by the CHMP.

2.7.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

DLBCL is the most common histologic subtype of NHL, accounting for 30% of NHL cases (Armitage and Weisenburger 1998) and 80% of aggressive lymphomas. In 2020, 544,352 new NHL cases worldwide were estimated with over 163,000 patients estimated to be diagnosed with DLBCL (Global Cancer Observatory 2020). While DLBCL is mostly frequently diagnosed between ages of 65 and 74 years (with median age of 65 years at diagnosis [SEER]), it can also occur in the younger population, including children and young adults. Initially, DLBCL may be asymptomatic, but it may also be associated with constitutional symptoms such as fever, recurrent night sweats, weight loss, and/or local effects of lymph node enlargement, as well as those of bone marrow failure. Without treatment, DLBCL is fatal with a median survival of approximately 6 months (Armitage and Weisenburger 1998).

3.1.2. Available therapies and unmet medical need

The standard of care therapy for DLBCL involves frontline multi-agent chemotherapy with complementary mechanisms of action combined with immunotherapy. Up to 8 cycles of R-CHOP given in 21-day intervals (R-CHOP-21), or R-CHOP-like chemotherapy is considered to be the standard of care therapy for patients with previously untreated DLBCL. Although the biologic features of DLBCL are evaluated in clinical practice and clinical research, they do not clearly guide the choice of therapy, as no definitive studies have demonstrated superiority to R-CHOP in biomarker-selected populations. The fact that most patients who are not cured by R-CHOP or comparable immunochemotherapy will eventually die of lymphoma underscores the need for novel

approaches in upfront and subsequent lines of therapy for this aggressive disease.
There is therefore a high unmet medical need in the 1L setting and a strong rationale for introducing novel therapeutic agents that can build upon R-CHOP and improve outcomes in patients with previously untreated DLBCL by preventing or delaying relapse.

3.1.3. Main clinical studies

The main clinical study provided by the MAH in this application is a phase III pivotal study (Study GO39942: POLARIX) which is a multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of polatuzumab vedotin in combination with R-CHP versus R-CHOP in previously untreated patients with diffuse large B-cell lymphoma.

A total of 879 patients were included (ITT population) in the pivotal phase III, comparative randomized POLARIX study, 440 in pola+R-CHP arm and 439 in R-CHOP arm. Patients received six cycles of either pola+R-CHP (and vincristine placebo) or standard R-CHOP chemotherapy (and polatuzumab vedotin placebo) at 21-day intervals. Both arms then received two additional cycles of single agent rituximab. This design is acceptable as R-CHOP remains the standard of care therapy in previously untreated DLBCL. The

polatuzumab vedotin dose of 1.8 mg/kg given every 21 days in combination with R/G-CHP for 6 or 8 cycles was determined in the dose-finding study (Study GO29044). Inclusion and exclusion criteria are acceptable and are in accordance with the claimed indication. Treatment arms were generally well-balanced with respect to demographic and baseline characteristics. For both regimens, treatment exposure remained high. Approximately 90% of patients in each treatment arm received 6 cycles of CHP treatment.

3.2. Favourable effects

A statistically significant improvement in the primary endpoint of Investigator-assessed PFS is observed following treatment with pola+R-CHP compared to R-CHOP. A reduction in the risk of progression/relapse or death by 27% is observed in patients treated in pola+R-CHP arm (stratified HR: 0.73 [95% CI: 0.57, 0.95]; two-sided log-rank p-value=0.0177, two-sided α=0.05) with a minimum of 24 months from study enrollment in both arms. Results of all sensitivity analyses were consistent with results of the primary analysis of Investigator-assessed PFS in the ITT population.

Results of the primary endpoint are also supported by the EFSeff secondary endpoint. A significant reduction in the risk of occurrence of disease by 25% was observed in patients treated in pola+R-CHP arm compared in patients treated in R-CHOP arm (stratified HR: 0.75 [95% CI: 0.58, 0.96]). Also, the BICR-assessed CR rate was high (78.0% [95%CI: 73.79, 81.74] vs. 74.0% [95% CI: 69.66, 78.07]). In addition, concordance between BICR and Investigator assessments of CR was high (88.7%).

3.3. Uncertainties and limitations about favourable effects

A total of 53 deaths (12.0% patients) were reported in the pola+R-CHP arm, and 57 deaths (13.0% patients) were reported in the R-CHOP arm. With very few events in both arms, OS results were still immature at the time of the interim analysis of OS and did not meet the pre-specified threshold for statistical significance (stratified HR: 0.94 [95% CI: 0.65, 1.37])". Final OS data are expected in order to further document long term efficacy and safety provided by a pola+R-CHP regimen compared to a R-CHOP regimen in this population. Indeed, the OS results provided in this report come from the interim OS analysis performed at the time of the PFS analysis. Therefore, the MAH will provide an update of the CSR of study Polarix containing the final OS results by Q4 2022 as a post approval measure (see RMP) which is acceptable.

The CHMP requested data from an additional China extension cohort of Study GO39942 (POLARIX) that are analyzed within an Asia subpopulation analysis and are reported in an Asia subpopulation CSR that includes all Chinese patients enrolled in the China extension and in the main global study. For this purpose, the MAH has requested approval for providing and opening access to Chinese Human Genetic Resources abroad from the Human Genetics Resources Administration of China (HGRAC) and would be able to provide the data from China extension cohort, in the form of Asia subpopulation CSR, if granted by HGRAC. For the time being access is not granted and the data may be submitted later – as recommended by the CHMP - when available.

3.4. Unfavourable effects

Myelosupression was reported across all studies. Neutropenia, including febrile neutropenia, anemia and thrombocytopenia were all included in the AEs of particular interest. In the pivotal study, the incidence of neutropenia events was comparable in both treatment arms, i.e. 42.7% in R-CHOP and 46.0% in pola+R-CHP but higher serious neutropenia events were reported in the pola+R-CHP arm compared to the R-CHOP arm (11.5% vs 8.4%), mainly due to a higher incidence of serious febrile neutropenia in the pola+R-CHP arm (9.9%). The incidence of anemia events was comparable across the 2 treatment arms in POLARIX (26.9% in R-CHOP arm and 28.7% in Pola+R-CHP arm) but Grade 3-4 events were more reported with pola+R-CHP than R-CHOP (12.0% vs 8.7%). Incidence of thrombocytopenia was similar across pola+R-CHP arm and R-CHOP arms, i.e. 13.3% and 13.2% respectively. The majority of myelosuppression events resolved.

Infections are expected with polatuzumab vedotin. In the pivotal study, the incidence of infectious events, Grade 3-4 infections and serious infections was higher in pola+R-CHP arm compared to R-CHOP arm (49.7% vs 42.7%, 14.0% vs 11.2% and 14.0% vs 10.3%, respectively). Most of the fatal AEs in both arms were due to infections or complications of infection. The proportion of Grade 5 infections was comparable in both treatment arms (1.1% in pola+R-CHP and 1.4% in R-CHOP). Pneumonia was the most reported AE among the Grade 5 Infections (4 patients in pola+R-CHP arm, 3 patients in R-CHOP arm) and the other Grade 5 Infection AEs were septic shock and sepsis. The incidence of opportunistic infections was higher in pola+R-CHP than R-CHOP.

Peripheral neuropathy was reported across all studies. In the pivotal study, PN events occurred at comparable incidence in both treatment arms (53.9% in R-CHOP and 52.9% in Pola+R-CHP) and the majority of PN was low grade. None was fatal and 2 cases of PN were serious (one in each arm). The majority of PN events occurring in POLARIX resolved with a higher rate in R-CHOP arm compared to pola+R-CHP arm (66.9% and 57.8% respectively) which may be partly explained by the difference in median time to onset (2.27 months in pola+R-CHP vs 1.87 months in R-CHOP) and the comparable median time to resolution across the two treatment arms. The most commonly reported PN events were neuropathy peripheral (24.1% and 22.6%), peripheral sensory neuropathy (19.5% and 21.5%), paraesthesia (6.7% and 4.6%), hypoaesthesia (3.7% and 3.2%), polyneuropathy (1.4% and 2.5%), and peripheral motor neuropathy (0.7% and 2.3%) in the pola+R-CHP and R-CHOP arms, respectively.

3.5. Uncertainties and limitations about unfavourable effects

There are no new uncertainties about the unfavourable effects of Polivy.

3.6. Effects Table

Table 67: Effects Table for [polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone for the treatment of adult patients with previously untreated DLBCL] (data cut-off: 28 June 2021)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Primary endpoint	Nb patients	107 (24.3%)	134 (30.5%)	Stratified HR=0.73;	Study GO39942)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
		with events (%)			95%CI: 0.57, 0.95, p=0.0177	POLARIX study
EFSeff	Secondary endpoint	Nb patients with events (%)	112 (25.5%)	138 (31.4%)	Stratified HR=0.75; 95%CI: 0.58, 0.96, p=0.0244	Study GO39942) POLARIX study
CR rate	Secondary endpoint	% (95% CI)	78% (73.79, 81.74)	74% (69.66, 78.07)	P= 0.1557	Study GO39942) POLARIX study
OS	Secondary endpoint	Nb of deaths	53	57	interim results performed at the time of the PFS analysis	Study GO39942) POLARIX study
Unfavourable Effects						
Fatal AEs		%	3.0	2.3	In pola+R-CHP: pneumonia, sepsis, death, intestinal perforation, kidney injury, respiratory failure	Study GO39942 (POLARIX study)
Other SAEs		%	34.0	30.6	In pola+R-CHP (by SOC): Infections and infestations (14.0%), Blood and lymphatc system disorders (11.5%), GI disorders (7.1%)	Study GO39942 (POLARIX study)
Peripheral neuropathy	All grades	%	52.9	53.9	In pola+R-CHP (by PT): neuropathy peripheral (24.1%), peripheral sensory neuropathy (19.5%), paraesthesia (6.7%), hypoaesthesia (3.7%), polyneuropathy (1.4%), peripheral motor neuropathy (0.7%)	Study GO39942 (POLARIX study)
Serious infections	All grades	%	14.0	10.3	In pola+R-CHP: Serious pneumonia (4.1%), serious sepsis (1.1%), and serious urinary tract infection (1.8%)	Study GO39942 (POLARIX study)
Serious neutropenia	All grades	%	11.5	8.4	In pola+R-CHP: serious febrile neutropenia (9.9%)	Study GO39942 (POLARIX study)

Abbreviations: PFS: progression free survival, defined as the time from randomization to the first occurrence of disease progression or relapse as assessed by the investigator, using the Lugano Response Criteria for Malignant Lymphoma, or death from any cause, whichever occurs earlier, EFSeff: investigator-Assessed Event-Free Survival for Efficacy Reasons, defined as the time from the date of randomization to the earliest occurrence of disease progression/relapse, death, biopsy that is positive for residual disease after treatment completion, or start of a NALT due to efficacy reasons, CR rate: BICR-Assessed Complete Response Rate at End of Treatment by PET-CT, OS: overall survival, AE: adverse event, GI: gastrointestinal, PT: preferred term, SAE: serious adverse event, SOC: system organ class

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The primary efficacy endpoint of the pivotal phase III, comparative, POLARIX study defined as PFS was achieved. A statistically significant improvement in the primary endpoint of Investigator-assessed PFS is observed following treatment with pola+R-CHP compared to R-CHOP, the 1L DLCBL standard of treatment. One could question the clinical relevance of these results as only a difference of 27 events is observed between both arms of treatment. This slight improvement of PFS is supported by sensitivity analyses and secondary endpoints. The use of polatuzumab vedotin instead of vincristine did not lead to improvement in treatment-related symptoms and peripheral neuropathy in POLARIX study. The CHMP considers interim OS results are still immature and could be considered as not sufficiently robust. However, OS interim results do not indicate detrimental effect of polatuzumab vedotin.

The pivotal POLARIX study met its primary endpoint PFS and no large differences in safety risks, have been found. In this clinical situation, the presented median follow-up time is considered sufficient, and maturity of data is not relevant as a cure rate of 60% is anticipated in the control arm. No detriment in OS of polatuzumab vedotin is to be anticipated considering the results in combination with follow-up exceeding the time period in which most of the relapses would have occurred (i.e. 24 months).

The safety profile of pola+R-CHP does not raise new safety concern compared to pola+BR. Therefore, efficacy and safety data provided from untreated patient could be considered as confirmatory safety and efficacy data for treatment of patients with relapsed/refractory DLCBL.

The PFS gain, as primary endpoint in the pivotal study, and no detriment in OS is sufficient to establish clinical benefit of polatuzumab vedotin as a substitute for vincristine in the combination regimen.

3.7.2. Balance of benefits and risks

The balance of benefits and risks of polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone for the treatment of adult patients with previously untreated DLBCL is positive provided changes in SmPC and additional post-approval measures.

3.7.3. Additional considerations on the benefit-risk balance

Per current Polivy SmPC Annex II.E, provision of efficacy and safety data by Q4 2021 is the last remaining specific obligation (SOB-CLIN-003) to the CMA of Polivy for the treatment of patients with relapsed/refractory DLBCL who are not candidates for haematopoietic stem cell transplant. The pivotal POLARIX study met its primary endpoint PFS and no large differences in safety risks, have been found. Therefore, efficacy and safety data provided from untreated patient could be considered as confirmatory safety and efficacy data for treatment of patients with relapsed/refractory DLCBL. With the submission of this Type II variation, all specific obligations related to the CMA are fulfilled. As a result, the CHMP agreed on a full marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 (marketing authorisation not subject to specific obligations).

3.8. Conclusions

The overall B/R of polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone, for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL) is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of the indication to include: Polivy in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone, is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL) based on the efficacy and safety data from the Pivotal Phase III Study GO39942 (POLARIX). Annexes I, II, IIIB are revised. The RMP is also updated. This submission fulfills SOB003 thus supporting the switch from CMA to full MA.

In addition, the CHMP, having considered the application as set out in the appended assessment report and having reviewed the data submitted by the marketing authorisation holder including the evidence concerning compliance with specific obligations, is of the opinion that the risk-benefit balance of the above mentioned medicinal product remains favourable, that all specific obligations laid down in Annex II have been fulfilled and that comprehensive data supports a favourable benefit-risk balance of the above mentioned medicinal product. Therefore, pursuant to Article 14-a(8) of Regulation (EC) No 726/2004, the CHMP recommends by consensus the granting of a marketing authorisation in accordance with Article 14(1) of Regulation (EC) No 726/2004 for the above mentioned medicinal product for which the draft Summary of Product Characteristics is set out in Annex I.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Polivy is not similar to Minjuvi, Yescarta or Kymriah within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix X>

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Polivy-H-C-4870-II-0012'

Attachments

1. SmPC, Annex II, Package Leaflet (changes highlighted) of Polivy, 30 mg powder for concentrate for solution for infusion with changes highlighted as adopted by the CHMP on 24 March 2022.

Appendix

1. CHMP AR on similarity dated 24 March 2022

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 08 April 2022. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by 08 April 2022. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.