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Polatuzumab vedotin in combination with immunochemotherapy in patients with previously untreated diffuse large B-cell lymphoma: a phase 1b/2 study

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Abstract

Background Polatuzumab vedotin, an antibody-drug conjugate targeting the CD79b component of the B-cell receptor, has demonstrated activity in relapsed/refractory diffuse large B-cell lymphoma (DLBCL). In this study, we evaluated safety and activity of polatuzumab vedotin in combination with rituximab (R) or obinutuzumab (G) and cyclophosphamide, doxorubicin, and prednisone (CHP) in patients with previously untreated DLBCL.

Methods This is an open-label, non-randomised study composed of a phase 1b dose escalation and a phase 2 dose expansion performed at 11 sites in the USA and France. Patients aged 18 years of age or older, with B-cell non-Hodgkin lymphoma were enrolled to the study. The phase 1b dose escalation established the recommended phase 2 dose (RP2D). The phase 2 expansion evaluated the RP2D of polatuzumab vedotin in patients with newly diagnosed DLBCL with International Prognostic Index (IPI) from 2–5. Patients received cyclophosphamide 750 mg/m² on day 1 intravenously, doxorubicin 50 mg/m² on day 1 intravenously and prednisone 100 mg once daily on days 1 to 5 of each cycle orally (CHP) and either R 375 mg/m² intravenously on day 1 of each cycle or G 1000 mg intravenously on days 1, 8, 15 of cycle 1 and on day 1 of the following cycles. Polatuzumab vedotin was administered on day 2 of cycles 1 and 2 and on day 1 of the following cycles at 1.0 mg/kg to 2.4 mg/kg during the escalation phase and at RP2D during the expansion phase. Cycles were 21 days; treatment could be six or eight cycles, depending on investigator preference. The primary endpoints were safety, tolerability and determination of the RP2D for the phase 1b portion, and safety and response at the completion of treatment for the phase 2 portion. All endpoints were analysed per protocol in the safety evaluable population, defined as any patient who received at least one dose of study treatment. This trial is registered with ClinicalTrials.gov, (NCT01992653).

Findings Between Dec 4, 2013 and July 26, 2016, 85 patients were enrolled. The RP2D for polatuzumab vedotin was 1.8 mg/kg. Sixty-six patients with newly diagnosed DLBCL received the polatuzumab vedotin RP2D (45 R-CHP; 21 G-CHP). Median age was 67.5 (range 26–80) years and 43 patients (65%) were high intermediate or high risk IPI categories. The most common grade ≥ 3 adverse events were neutropenia (20 patients, 30%), febrile neutropenia (12 patients, 18%), and thrombocytopenia (six patients, 9%). Among patients who received the RP2D, 19 (29%) experienced grade 1 peripheral neuropathy, six (9%) grade 2, and two (3%) grade 3. Four deaths were reported during follow-up: two treatment-related (one complications of atrial fibrillation and one septic shock) and two due to disease progression. Fifty-nine patients (89%) achieved an overall response at end of treatment (complete response [CR]: 51 patients [77%], partial response: eight patients [12%]). As of the cutoff date of Dec 29, 2017, median observation was 21.5 months (IQR: 16.7–24.3 months) for

the untreated DLBCL cohort treated at the polatuzumab vedotin RP2D; 1-year PFS rate was 91% (95% confidence interval 84–98). In this population, 25/28 (89%) patients of the germinal centre B-cell subtype and 13/16 (81%) patients of the activated B-cell subtype obtained a CR at end of treatment.

Interpretation The safety of incorporating polatuzumab vedotin to R-CHP or G-CHP appears similar to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or G-CHOP. Response rates and early PFS in newly diagnosed DLBCL are promising and encouraged a phase 3 trial comparing polatuzumab vedotin with R-CHP to R-CHOP.

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Key words B-cell lymphoma, diffuse large B-cell lymphoma, polatuzumab vedotin, antibody-drug conjugate, ADC, R-CHOP, CD79b

Research in context

Evidence before this study

Effective first-line treatment of diffuse large B-cell lymphoma (DLBCL) is paramount in achieving a cure. For many years, the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) has been considered the standard first-line treatment for DLBCL. Many attempts have been made to increase the efficacy of this combination, but none have resulted in a decisive improvement. Polatuzumab vedotin is an antibody-drug conjugate that targets CD79b, which is present on B cells. Early studies have shown its high activity as a single agent in relapsing or refractory DLBCL. Due to the mechanism of action of the molecule coupled to the antibody, one possible side effect of polatuzumab vedotin is peripheral neuropathy. These findings suggest the rational use of polatuzumab vedotin as an alternative of vincristine to improve R-CHOP.

We searched PubMed, with no restrictions on language or publication date, using the search terms “polatuzumab vedotin” and (“CHOP” OR “CHP” OR “R-CHOP” OR “R-CHP”) up to Nov 1, 2018, and did not find any studies reporting on this combination.

Added value of this study

In this study, we explored the combination of polatuzumab vedotin with cyclophosphamide, doxorubicin, prednisone, and either rituximab or obinutuzumab (Pola-R-CHP or Pola-G-CHP). We first determined the optimal dose of polatuzumab vedotin and then explored the activity and safety of the combination in a cohort of patients with previously untreated DLBCL. The safety profile compared to standard treatment, and high activity in a population of patients with high proportion of high-risk factors, encourages further study of this combination in this population. Furthermore, the results suggest a similar activity of the combination across the subtypes of DLBCL, including cell of origin.

Implications of the available evidence

Results of this study support the comparison of Pola-R-CHP combination to the standard of care in first-line DLBCL. Therefore, a phase 3 study comparing Pola-R-CHP to standard R-CHOP has been initiated in previously untreated patients with DLBCL (POLARIX study, NCT03274492). Of note, in CD30 positive T-cell lymphomas, the combination of brentuximab vedotin, another antibody-drug conjugate, and CHP has been recently shown to improve the outcome as compared to CHOP, reinforcing confidence in our approach.

Introduction

R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) remains the standard treatment for previously untreated diffuse large B-cell lymphoma (DLBCL).¹ However, a substantial number of patients are not cured by this therapy. Patients who have poorer outcomes with R-CHOP include those that may be selected by patient characteristics (eg, higher International Prognostic Index [IPI]) or biological risk (eg, activated B-cell like [ABC], double-expressor lymphoma [DEL], double/triple-hit lymphoma [DHL]).² Numerous strategies have been unsuccessful in improving upon R-CHOP in DLBCL, including adding novel agents, substitution of monoclonal antibodies (mAbs), increasing dose intensity, or adding maintenance arms.³ Certainly, evolving strategies continue to match novel agents to biologically characterised subtypes based on genetic and gene expression profiling.⁴ Nonetheless, a novel strategy that applies broadly to DLBCL has yet to find success.

Antibody-drug conjugates (ADCs) have been impactful in haematological diseases with approved indications for gemtuzumab ozogamicin, brentuximab vedotin, and inotuzumab ozogamicin.⁵ The basis for their activity exists in the relevance of the antibody target and small molecule delivered by the ADC. Polatuzumab vedotin is an ADC targeting CD79b to deliver monomethyl auristatin E (MMAE), a small molecule with cytotoxic activity with an anti-tubulin mechanism of action.^{6,7} CD79b, a component of the B-cell receptor, is ubiquitously expressed in mature B-cell lymphomas.^{8–}¹⁰ A phase 1 study demonstrated promising single agent clinical activity of polatuzumab vedotin in a heavily pre-treated patient population, including those with both ABC and germinal centre B-cell like (GCB) subtypes of DLBCL.^{10,11} These data were used to support the current study in previously untreated patients with DLBCL.

We report the initial results of a study that evaluated the safety and activity of polatuzumab vedotin with cyclophosphamide, doxorubicin, prednisone (CHP) chemotherapy and an anti-CD20 monoclonal antibody (rituximab [R] or obinutuzumab [G]). Given the mechanism and neurotoxicity profile of polatuzumab vedotin overlaps with that of vincristine, this regimen omits vincristine from standard CHOP-based therapy. A phase 1b dose escalation was performed in order to determine the recommended phase 2 dose (RP2D) of polatuzumab vedotin in combination with R-CHP or G-CHP and phase 2 dose expansion cohorts were performed in previously untreated DLBCL patients to assess safety, tolerability, and activity at the RP2D.

Methods

Study design and participants

This is an ongoing, open-label, non-randomised study composed of a phase 1b dose escalation and a phase 2 dose expansion performed across 11 centres in the USA and France. Patients received polatuzumab vedotin in combination with CHP chemotherapy and R or G. Separate dose escalation and dose expansion cohorts were formed based on the anti-CD20 monoclonal antibody used.

Eligible patients were 18 years of age or older with local histopathologically confirmed B-cell non-Hodgkin lymphoma (B-NHL). In the dose escalation phase, patients with any B-NHL were enrolled. Patients with previous lymphoma treatment were allowed in the dose escalation portion. In the expansion phase, only patients with previously untreated DLBCL with IPI 2–5 were included. Other eligibility criteria included Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2, at least one measurable lesion >1.5 cm, and adequate bone marrow, liver, renal function and a life expectancy of at least 24 weeks. Key exclusion criteria included grade >1 peripheral neuropathy (PN), major surgery within 4 weeks before enrolment, known central nervous system (CNS) involvement of lymphoma, and uncontrolled heart disease (Detailed eligibility criteria are described in the appendix; pp 2-3).

All patients provided written informed consent before participation in the study. An institutional review board or ethics committee approved the protocol at each study site and the study was conducted according to the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the study is conducted, whichever affords the greater protection to the individual. The study complied with the International Conference of Harmonisation E6 guideline for Good Clinical Practice.

Procedures

Study treatment was administered according to figure 1. Patients received cyclophosphamide 750 mg/m² on day 1 intravenously, doxorubicin 50 mg/m² on day 1 intravenously and prednisone 100 mg once daily on days 1 to 5 of each cycle orally (CHP) and either R 375mg/m² intravenously on day 1 of each cycle or G 1000 mg intravenously on days 1, 8, 15 of cycle 1 and on day 1 of the following cycles. Polatuzumab vedotin was administered on day 2 of cycles 1 and 2 and on day 1 of the following cycles. Cycles were 21 days in length and treatment could be six or eight cycles, depending on investigator preference.

Polatuzumab vedotin was administered to patients by IV infusion via syringe pump with infusion set containing a 0.22 µm in-line filter. Premedication (500–1000 mg of oral acetaminophen or

paracetamol and 50–100 mg diphenhydramine) and prednisone/prednisolone according to R/G-CHP dose were administered before polatuzumab vedotin. The initial dose was administered to a well hydrated patient over 90 minutes. The polatuzumab vedotin infusion could be slowed or interrupted for patients experiencing infusion-associated symptoms. If prior infusions have been well tolerated, subsequent doses of polatuzumab vedotin could be administered over 30 minutes followed by a 30-minute observation period.

During the dose escalation phase, the standard 3 + 3 design was applied. The dose limiting toxicity (DLT) observation period occurred from cycle 1 day 1 to cycle 2 day 1 (DLT rules are described in the appendix; page 4). Decisions regarding the benefit-risk of dose escalations and determination of the RP2D were made by the study team including the sponsor medical monitor, safety scientist, biostatistician, and participating investigators. The polatuzumab vedotin dose started at 1.0 mg/kg with planned dose escalations to 2.4 mg/kg. However, information from other studies utilizing polatuzumab vedotin emerged during the conduct of this study in which the safety profile associated with cumulative exposure of polatuzumab vedotin at doses higher than 1.8 mg/kg every 3 weeks was not outweighed by any clinical benefit, particularly in the setting of DLBCL being treated in a curative setting. The RP2D was determined as 1.8 mg/kg in the R-containing arm; no higher doses were explored in this study. Once the RP2D was determined in the R-CHP cohort, the RP2D -1 dose (1.4 mg/kg) was used as the starting dose in the G-containing escalation arm. After the results of the GOYA study became available¹³, a memo communicating the discontinuation of enrolment in the G-containing expansion arm was sent to investigators on Jul 25, 2016 with the protocol amendment finalized on Sep 23, 2016.

Pertinent dosing requirements stated that the initiation of a treatment cycle required recovery of haematological parameters (absolute neutrophil count [ANC] >1000/uL, platelet >75 000/uL) and, for patients who experience grade 2 or 3 PN, for resolution to grade ≤1 PN within 14 days else the permanent discontinuation of polatuzumab vedotin. Patients who experienced grade 2 or 3 PN with recovery of PN to grade ≤1 within 14 days would be required to reduce PN by one dose level. Intrathecal CNS prophylaxis could be given per investigator judgement; high dose systemic therapies (eg, methotrexate) were not permitted. Supportive care, including growth factor support and anti-infective prophylaxis, were recommended according to American Society of Clinical Oncology guidelines. In the expansion cohort, patients received R-CHP or G-CHP regimen combined with polatuzumab vedotin at the RP2D.

The pharmacokinetics (PK) of polatuzumab vedotin, doxorubicin, cyclophosphamide, R, or G were assessed by PK sampling at pre-determined time points. Pre-treatment tumour samples were analysed for CD79b expression by immunohistochemistry (IHC) using clone AT107-2 (Serotec) using the

Ventana Benchmark XT platform. A continuous variable of IHC staining that incorporates staining intensity (ranging from 0 to 3+) and the number of positively stained tumour cells; H-Score (range 0-300) = (% at 0) x 0 + (% at 1+) x 1 + (% at 2+) x 2 + (% at 3+) x 3.¹⁰ BCL2 and MYC IHC was performed using the investigational use only BCL2 (clone 124) mAb; and MYC (clone Y69) mAb on the Ventana BenchMark Ultra platform. The BCL2 IHC was defined as positive when $\geq 50\%$ of tumour cells stain with intermediate or high intensity. The MYC clinical cut-off was defined as $>40\%$ cells with MYC positive nuclear staining above background. Cell of origin was determined using the NanoString Lymphoma Subtyping Test (LST) (NanoString Technologies, Inc., Seattle, WA, USA). In parallel, CD79b expression was measured by ribonucleic acid (RNA) using the NanoString platform. Fluorescence in situ hybridisation (FISH) for MYC, BCL2, and/or BCL6 translocations was not requested by the protocol, nor was this information collected from local testing.

The baseline status of the disease was evaluated by full history, physical examination, relevant laboratory tests, computed tomography (CT) scan of the neck (if clinically indicated), chest, abdomen, and pelvis, ¹⁸Fluorodeoxyglucose positron emission tomography (PET)-CT, and bone marrow sampling.

Tumour responses were assessed by local investigators after four cycles and at the end of treatment according to the classification of the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas 2007.¹² The response data following four cycles were provided for each site to conduct the study, however, the data were not analyzed. Bone marrow sampling was performed at treatment completion to confirm a complete response (CR) in patients who initially had bone marrow involvement.

Safety was assessed by clinical physical examinations, measurements of protocol-specific haematological and chemistry laboratory values, measurement of protocol-specific vital signs, assessments of electrocardiography and echocardiography (ECHO)/Multiple Gated Acquisition scans. Adverse events (AEs) were graded by US National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. Serious adverse events (SAEs) attributed to protocol-mandated interventions from the time of signing informed consent until the first dose of study treatment were collected, and all AEs were collected from cycle 1 day 1 until 90 days after the last dose of study treatment. Clinical assessments were performed every 3 months and CT scans were obtained every 6 months for 2 years following the completion of study treatment.

Outcomes

The primary endpoints of the phase 1b were safety, tolerability and determination of RP2D of polatuzumab vedotin. The primary endpoints of the phase 2 were safety and response (overall response and complete response) at the completion of the treatment as assessed by investigator. Other secondary endpoints related to polatuzumab vedotin activity were PFS, event-free survival, response duration, and overall survival. The other secondary endpoints were neurological toxicity and PK of polatuzumab vedotin, cyclophosphamide, doxorubicin, and R or G.

Exploratory endpoints, all pre-planned in the protocol, included activity of therapy in different biological subgroups, including DLBCL subtypes according to cell of origin (ABC and GCB), double expression of MYC and BCL2 proteins (DEL), and characterisation of tumour expression of CD79b. A post-hoc analysis studying the occurrence of peripheral neuropathy according to the number of cycles of R/G-CHP plus polatuzumab vedotin delivered was performed.

All endpoints were analysed per protocol in the population of patients who received at least one dose of study treatment.

Statistical analyses

The data cut-off date for the current analyses was Dec 29, 2017. The results for endpoints were reported descriptively. No statistical hypothesis testing or inferential analysis was conducted for this study. Categorical variables were reported as absolute count and percentage, and continuous variables were reported as median (range or quartiles) or mean (standard deviation) wherever they were appreciated. The sample size for this study was based on the 3+3 dose-escalation design. The planned enrolment for this study was approximately 40 patients, depending on the number and size of cohorts. The probability of observing adverse events in at least one patient, given varying actual adverse event rates, are listed in the appendix (page 4).

Response at the end of treatment were reported as proportion (95% confidence intervals [CIs]) calculated using the Clopper-Pearson method, with 40 patients enrolled into expansion cohorts such that the 95% exact Clopper-Pearson CIs for the true CR rate would have a margin of error not exceeding 17%. Safety analyses included all patients who received at least one dose of polatuzumab vedotin. Activity analyses were conducted in the population of patients with previously untreated DLBCL who were treated with the RP2D of polatuzumab vedotin. PFS was reported as progression free rate (95% CIs) assessed at 12, 18, and 24 months using the Kaplan–Meier approach. Statistical analyses were performed using SAS 9.4 or R version 3.4.4. This trial is registered with ClinicalTrials.gov, NCT01992653.

Role of the funding source

The funder (F. Hoffmann-La Roche Ltd.) was involved in the study design, administration/conduct of study procedures, coordination of data collection, data analysis and interpretation, and provision of polatuzumab vedotin. Authors who were employees of the sponsor (DL, MY, EP, JH, CL) contributed to the writing and approval of the manuscript. HT had full access to the raw data, and all authors had limited access to the data and statistical results. All authors have approved the final draft of the manuscript for submission. The corresponding author had access to requested data and the final responsibility to submit for publication.

Results

Between Dec 4, 2013 and July 26, 2016, 85 patients were enrolled. In total, 82 patients were included in the safety and activity evaluable population, defined as having received any study treatment. Three patients did not receive any study treatment because of an exclusionary laboratory result (n=2) or patient withdrawal prior to starting study treatment (n=1) (figure 1).

The evaluable population included 25 patients in the phase 1b portion and 57 in the phase 2 portion (figure 1). Histological distribution and patient characteristics are described in table 1, with 75 (91%) having previously untreated DLBCL. A total of 66 patients with previously untreated DLBCL were treated with polatuzumab vedotin at the RP2D of 1.8 mg/kg. Among this group, the median age was 67.5 years, with 70% of patients aged 66 years or older; 19 (29%) had ECOG PS 2; 43 (65%) were IPI 3–5. At the clinical cutoff date for this study, median study duration for patients with DLBCL treated at the RP2D of polatuzumab vedotin was 21.5 months (interquartile range [IQR:] 16.7–24.3).

Two dose limiting toxicities were observed. One patient experienced a grade 4 pulmonary embolism at the 1.8 mg/kg dose level in combination with R-CHP, and one patient experienced grade 4 febrile neutropenia and grade 3 thrombocytopenia at the 1.4 mg/kg dose level in combination with G-CHP. Based on the safety and benefit-risk profile of the phase 1b cohorts with polatuzumab vedotin at 1.8 mg/kg, the RP2D for each phase 2 expansion was determined to be this dose.

As shown in figure 1, seven patients (11%) with DLBCL treated at the RP2D discontinued study treatment due to AEs after receiving 1–5 cycles: four who received G-CHP (pneumonia, myocardial infarction, prolonged thrombocytopenia, and fatal septic shock) and three who received R-CHP (complicated urinary tract infection, worsening of tremors, and syncope). A total of five (8%) patients with DLBCL treated at the RP2D had the polatuzumab vedotin dose decreased due to: grade 1 PN (cycle 2), weight loss (cycle 6), two for grade 2 PN (one at cycle 5, one at cycle 6), and recurrent neutropenia (cycle 5). One patient omitted cycle 8 polatuzumab vedotin due to grade 2 PN but received R-CHP. Dose reductions in doxorubicin were reported in three patients (5%); weight loss

n=1; febrile neutropenia n=1; clostridium difficile infection n=1) and in one patient for cyclophosphamide (weight loss). Median relative dose intensity for cyclophosphamide and doxorubicin was 100%, with 65 patients (98%) and 63 patients (95%) achieving >90% relative dose intensity for cyclophosphamide and doxorubicin respectively.

Treatment emergent AEs are noted in tables 2 and 3, and in the appendix (pp 5–7). Among patients who were assigned <1.8 mg/kg of polatuzumab vedotin, nine (75%) experienced any grade ≥ 3 AE and three (25%) experienced at least one SAE. Among patients who were assigned polatuzumab vedotin at 1.8 mg/kg, 45 (64%) experienced a grade ≥ 3 AE and 28 (40%) experienced at least one SAE.

The AE profile was slightly different depending on the anti-CD20 monoclonal antibody with more grade ≥ 3 neutropenia and thrombocytopenia observed in patients who received obinutuzumab than in patients who received rituximab (appendix, page 5-7), consistent with the known safety profile of the two antibodies.¹³ For patients with DLBCL treated at the RP2D, the most common grade ≥ 3 AEs were neutropenia (30%; 20 patients), febrile neutropenia (18%; 12 patients), and thrombocytopenia (9%; six patients), respectively. Ten patients (15%) experienced a grade ≥ 3 infection. The most common SAEs were febrile neutropenia (14%; nine patients), neutropenia (6%; four patients), and pneumonia (6%; four patients), respectively.

Among the 12 patients who received polatuzumab vedotin at <1.8 mg/kg, six patients (50%) experienced grade 1–2 PN (five grade 1, one grade 2) (appendix page 5). In the 70 patients assigned to the RP2D, 27 (38%) experienced grade 1–2 PN (19 [27%] grade 1, eight [11%] grade 2) and two (4%) experienced grade 3 PN, both treated with R-CHP (table 3). One patient who experienced grade 2 PN was assigned to the 1.8 mg/kg dose and received 2.4 mg/kg due to medication error for four cycles; this patient had also previously received vincristine in prior therapy for follicular lymphoma. At the data cut, seven (11%) patients with DLBCL treated at the RP2D continued to experience PN (all grades; figure in appendix; page 8). The median time to resolution of all grades of PN from initial onset was 2.4 months (IQR, 0.8–6.5 months) and the median time to resolution of grade 2 or 3 PN was 4.9 months (IQR, 1.0–9.1 months).

A post-hoc analysis was performed based on the rate of PN among patients with DLBCL treated at the RP2D who received less than six cycles, six cycles, or more than six cycles of study treatment. Among the nine patients who received less than six cycles, two patients (22%) experienced grade 1 PN and none with grade >1 PN; for the 36 patients who received six cycles, 11 (31%) experienced grade 1 PN and two (6%) experienced grade 2 and one (3%) grade 3 PN; for the 21 patients who

received more than six cycles, six (29%) experienced grade 1, and four (19%) grade 2 and one (5%) grade 3 PN.

Largely similar PK parameters for polatuzumab vedotin related analytes were observed when combined with R-CHP or G-CHP (details on PK and drug-drug interactions are given in the appendix; pp 9-10). Cyclophosphamide and doxorubicin plasma concentrations were similar between cycle 1 (prior to polatuzumab vedotin dosing) and cycle 3 (after polatuzumab vedotin dosing), supporting that MMAE does not impact their PK when given in combination. Additional details are in the supplemental information.

All seven (100%) patients without DLBCL had a CR by PET-CT at end of study treatment (polatuzumab vedotin-R-CHP, n=3; polatuzumab vedotin-G-CHP, n=4). Response to treatment for patients with DLBCL are summarised in table 3. As response to treatment and the 12-month PFS estimates between patients were comparable for those receiving either rituximab or obinutuzumab, results are presented among previously untreated DLBCL patients who received the RP2D of polatuzumab vedotin. In this population, 59 (89%) responded, of which 51 (77%) achieved a CR. The 12-month PFS (figure 2A) was 91% (95% CI 84–98), with 57 patients remaining at risk, and the 24-month PFS estimate was 83% (95% CI 73–93) with 14 patients remaining at risk. There was no difference in PFS according to the number of cycles planned (six or eight), anti-CD20 antibody (R or G) and IPI categories (0-2, 3 or 4-5) as shown in the appendix (pp 11-12). Four patients (6%) with previously untreated DLBCL treated with polatuzumab vedotin 1.8 mg/kg died (figure 2B); two as a consequence of a grade 5 adverse event (one due to complications of atrial fibrillation, one due to septic shock) and two due to disease progression. The 12-month overall survival (figure 2B) was 94% (95% CI 88-100), 12-month event-free survival was 80% (95% CI 71-90), and 12-month response duration (figure 2C) was 95% (95% CI 89-100).

Among patients with previously untreated DLBCL treated at the RP2D, 51 patients were evaluable by NanoString LST: 16 (31%) with ABC, 28 (55%) with GCB, and seven (14%) with unclassified cell of origin. Double expression of MYC and BCL2 were evaluable in 41 patients with 13 (32%) characterised as DEL. Response rates at end of treatment and PFS among these subgroups are shown in table 4 and in the appendix; page 12-13.

Biomarker evaluable specimens were assessed for CD79b by IHC relative to response measurements including change in sum of product diameter (SPD) of target lesions and PFS (figure 3A, B). CD79b IHC considered positive if H-scores were >0 (range 0–300); all tumour samples tested expressed some level of CD79b (H-score range 35–295). CD79b levels were similar in the biomarker/response evaluable populations relative to overall DLBCL population treated at the RP2D. Among DLBCL

patients treated at the RP2D, CR rate was similar between evaluable patients with H-score above median (82%) and H-score below the median (81%). Thirty-three subjects with CD79b IHC (H-score median 180, mean 167) and corresponding measurements in decrease in the SPD and 38 subjects with CD79b IHC (H-score median 171, mean 163) and corresponding PFS were assessed. There was no relationship with CD79b protein levels and response, consistent with previous work in which lower CD79b H-score did not predict resistance to polatuzumab vedotin¹⁰. Similarly, parallel analysis of CD79b RNA expression showed no correlation with response (figure 3C, D).

Discussion

Polatuzumab vedotin has previously shown activity in patients with heavily pre-treated relapsed and refractory (R/R) DLBCL.^{11,14} The current study demonstrated that polatuzumab vedotin can be incorporated into immunochemotherapy in the frontline treatment of DLBCL, with a safety profile similar to those of the standard treatment and a high clinical activity.

While the RP2D in initial dose finding study was 2.4 mg/kg for polatuzumab vedotin as a single agent or in combination with rituximab,¹¹ the phase 1b dose escalation determined that the RP2D for polatuzumab vedotin when combined with immunochemotherapy was 1.8 mg/kg given every 21 days. Overall, the relatively long $t_{1/2}$, small steady state volume of distribution, low clearance for acMMAE (antibody-conjugated MMAE), and the low concentrations and delayed formation of unconjugated MMAE are largely consistent with the PK properties of polatuzumab vedotin in patients with B-NHL.¹¹ Population PK analysis further confirmed that there is no clinically relevant impact of CHP combination or the treatment-naïve condition on the PK of acMMAE and unconjugated MMAE (Genentech data on file). Moreover, plasma concentrations of cyclophosphamide and doxorubicin at cycle 3 are similar to cycle 1, supporting the low risk of polatuzumab vedotin to impact the PK of these agents.

The safety profile observed in this study also suggests that the incorporation of polatuzumab vedotin at 1.8 mg/kg into an immunochemotherapy backbone for DLBCL does not alter the safety profile relative to R-CHOP or G-CHOP described in the recent GOYA study.¹³ Polatuzumab vedotin is known to cause myelosuppression and PN as a single agent¹¹ in a heavily pretreated population; however, polatuzumab vedotin with immunochemotherapy did not appear to produce notable differences in key grade 3–5 AEs compared with R-CHOP or G-CHOP as a frontline therapy (as described in the GOYA study)¹³, such as neutropenia (ranging from 46.1% to 54.5%), febrile neutropenia (ranging from 15.2% to 17.5%), and infections (15.5% to 19.2%). A possible increase of grade 3–4 thrombocytopenia with pola-R/G-CHP will have to be evaluated in further trials. Furthermore, there were few instances in which there were dose reductions in doxorubicin and

cyclophosphamide, suggesting that delivery of R-CHP or G-CHP was not compromised with the incorporation of polatuzumab vedotin.

The anti-tubulin mechanism of action of the drug conjugate, MMAE, in polatuzumab vedotin makes it a rational replacement for vincristine in a CHOP-based regimen. As MMAE has a mode of action similar to that of vincristine, neurotoxicity was particularly monitored during the study. PN was manageable with dose modifications and supportive care. The frequency of grade 3–4 PN (4%) was in the range observed in large cohorts of patients treated with R-CHOP (5–7%).^{15,16} It was observed that the neuropathy experienced by patients was primarily dependent on dose and cumulative exposure of the agent. Among patients who received more than six cycles of study treatment, the incidence of grade 2 or 3 PN was higher than that observed among patients who received six or fewer cycles, supporting the exposure-based, cumulative nature of this treatment emergent AE and also supporting the future use of six doses of polatuzumab vedotin at 1.8 mg/kg with immunochemotherapy. Moreover, among the 27 patients with DLBCL treated at the RP2D who experienced any grade PN, 20 (74%) patients experienced resolution of PN at data cut-off, with all patients having discontinued or completed study treatment.

We observed a high proportion of poorer prognostic characteristics among patients with previously untreated DLBCL who received polatuzumab vedotin at 1.8 mg/kg and immunochemotherapy. These included a median age of 67.5 years, ECOG PS 2 (29%), and IPI 3–5 (65%). These characteristics suggest patients treated in this study would have higher rates of treatment emergent AEs, which was not observed when compared to recent studies.¹³

The activity of incorporating polatuzumab vedotin at the RP2D could also be compared with that seen in the recent GOYA trial. With comparable efficacy expected in previously untreated DLBCL between the two different anti-CD20 mAbs used in this study, the early activity results are most attributable to the incorporation of polatuzumab vedotin as part of an immunochemotherapy backbone. As compared with the control arm of the GOYA study,¹³ patients in the present study were older (67.5 vs 62 years) and more of them were IPI 4–5 (33% vs 16%). Additionally, patients in the present study had a higher CR rate (77% vs 58%) and higher PFS at 1 year (91% vs 81%). Further prospective studies comparing the new combination and the standard treatment are needed to establish a difference in safety and efficacy.

CD79b was detected across all tumour tissue and DLBCL subsets evaluated. Response to treatment does not appear to correlate to observed expression level, suggesting that identification of this marker may not be needed in subsequent studies of polatuzumab vedotin in DLBCL. The percentage of patients with GCB subtype (55%) could be considered quite high in a relatively old population.

However, this proportion is broadly consistent with that found in the 933 patients (58%) studied in the GOYA trial, which used the same gene-expression method.¹³ Response rates and PFS were comparable among different biological subsets, including the ABC and GCB subtypes and those with or without double expression of BCL2 and MYC, although small patient numbers limit conclusions. Whether polatuzumab vedotin containing regimens potentially overcome some of the prognostic implications across biological subsets will be evaluated in an ongoing phase 3 study.

The current study has several limitations. Firstly, while the study includes different regimens and different doses of polatuzumab vedotin, this is not a randomised study designed to enable comparisons. Secondly, the study was designed to evaluate the incorporation of polatuzumab vedotin into two regimens (R-CHP and G-CHP); the sample sizes within these regimens, particularly when accounting for different biological subtypes of DLBCL, necessitates a larger study. The length of the follow-up time at data cut-off date is relatively short (in the context of a curative setting). However, the activity observed is promising, particularly in the context of higher-risk patients, in terms of both patient risk and biological disease characteristics. As there are ongoing studies that are approaching specific biological subtypes of DLBCL, the availability of a regimen that improves outcomes for the entire DLBCL population remains an unmet need. In this context, a phase 3 trial is being performed to assess polatuzumab vedotin with R-CHP compared to R-CHOP in previously untreated DLBCL (POLARIX study, NCT03274492).

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Declaration of interests

The authors disclose the following potential conflicts of interest within the past three years:

HT reports personal fees and non-financial support from F. Hoffmann-La Roche Ltd., and personal fees from Karyopharm, Astra-Zeneca and BMS, outside the submitted work.

FM reports personal fees from F. Hoffmann-La Roche Ltd./Genentech Inc., Celgene, Gilead, Janssen, and BMS, outside the submitted work.

NLB reports research funding from Affimed, Bristol- Meyers Squibb, Celgene, Forty Seven, Genentech Inc., Gilead, Janssen, KITE, Merck, Millenium, Pharmacyclics and Seattle Genetics, and advisory boards from Pfizer and Acerta, outside the submitted work.

AM reports grants from F. Hoffmann-La Roche Ltd., Merck, BMS, Epizyme, Incyte, Seattle Genetics, Takeda, Juno/Celgene, Forty Seven Inc, Gilead, and personal fees from BMS, Kite, Spectrum, Astra-Zeneca, Gilead, outside the submitted work.

GS reports grants, personal fees and non-financial support from F. Hoffmann-La Roche Ltd. during the conduct of the study; personal fees from Amgen, BMS, Celgene, Acerta, Abbvie, Janssen, Merck, Novartis, Gilead, Epizyme, Morphosys, Pfizer and Servier, outside the submitted work.

CH reports personal fees from F. Hoffmann-La Roche Ltd. during the conduct of the study; personal fees from Amgen, Takeda, Janssen, Gilead, Novartis and Celgene, outside the submitted work.

JM reports personal fees from Gilead/Kite Pharma, Pharmacyclics/Janssen, Bayer, Alexion, Bayer, Pfizer, Pharmacyclics/Janssen, Juno/Celgene, Bristol-Myers Squibb, Genentech Inc. and Kyowa, outside the submitted work.

AC reports consultancy fees from Genentech Inc./F. Hoffmann-La Roche Ltd. during the conduct of the study; personal fees from Kite, research funding from Novartis and Asana, personal fees, research funding and consultancy fees from Seattle Genetics and Genentech Inc., and personal fees from Bayer, outside the submitted work.

KK reports no conflicts of interest

DL reports personal fees (employee) at F. Hoffmann-La Roche Ltd./Genentech Inc. outside the submitted work.

MY reports personal fees (employee) from F. Hoffmann-La Roche Ltd./Genentech Inc., outside the submitted work.

EP reports personal fees (employee) from F. Hoffmann-La Roche Ltd./Genentech Inc., outside the submitted work.

JH reports personal fees (employee) from F. Hoffmann-La Roche Ltd./Genentech Inc., outside the submitted work.

CL reports employment from Genentech Inc., outside the submitted work.

JPS reports consultancy fees from Genentech Inc. during the conduct of the study; personal fees from Abbvie, Pharmacyclics, Gilead, Acerta, Astra Zeneca, TG Therapeutics and Pfizer, outside the submitted work.

Contributors

HT, FM, NLB, AM, GS, CH, JM, AIC, KK, DL, MY, EP, JH, CL and JPS collected, analysed and interpreted the data, and wrote the manuscript. HT, FM, GS, MY, CL searched the literature. DL, EP, JH and JPS were involved in the study design. EP was involved in data collection and analysis associated with biomarkers.

Data sharing statement

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (<https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx>). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here(https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm)

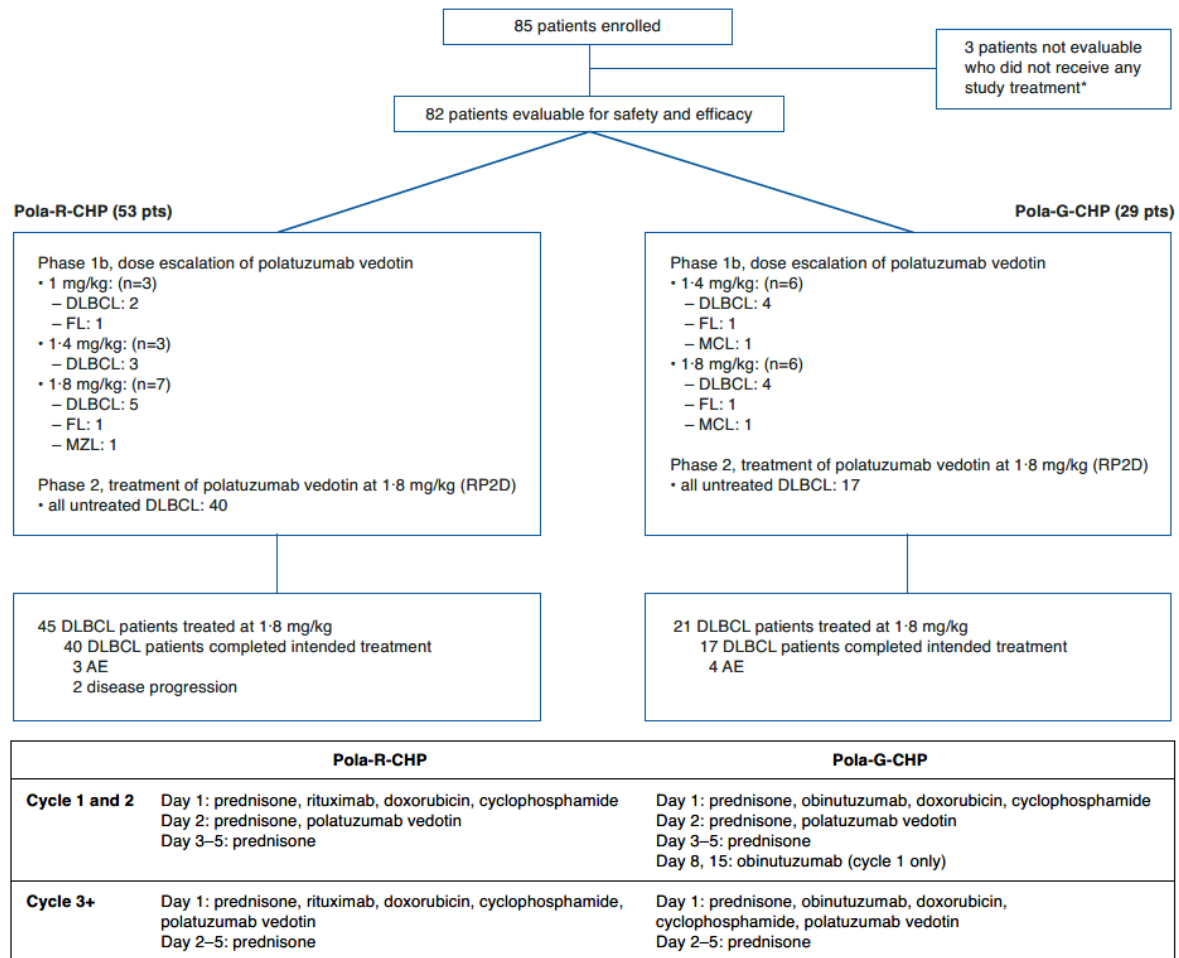
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FIGURES

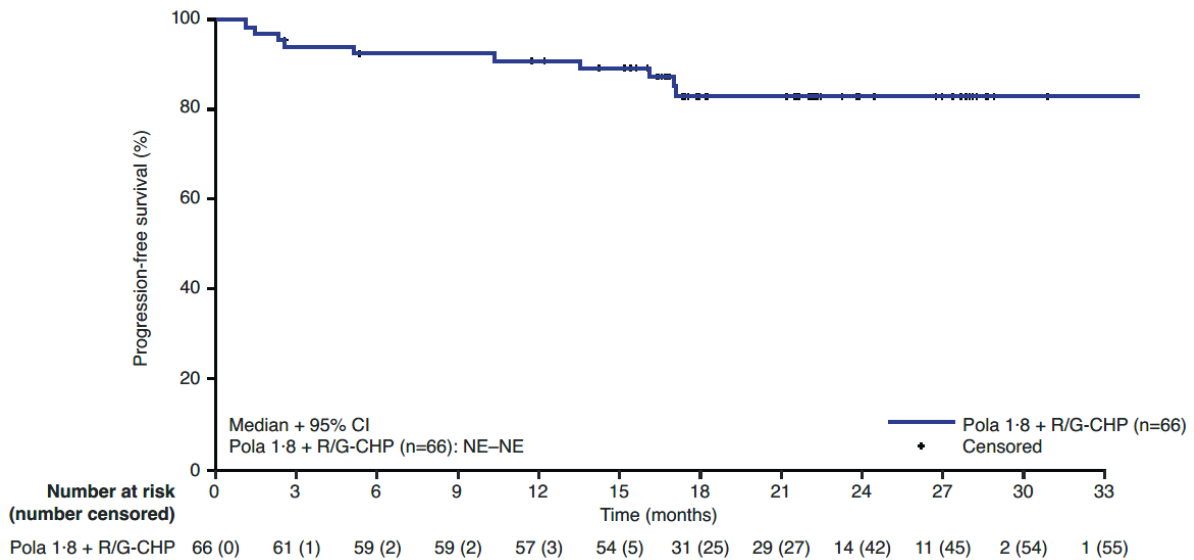
Figure 1: Patient disposition, study treatment, and administration



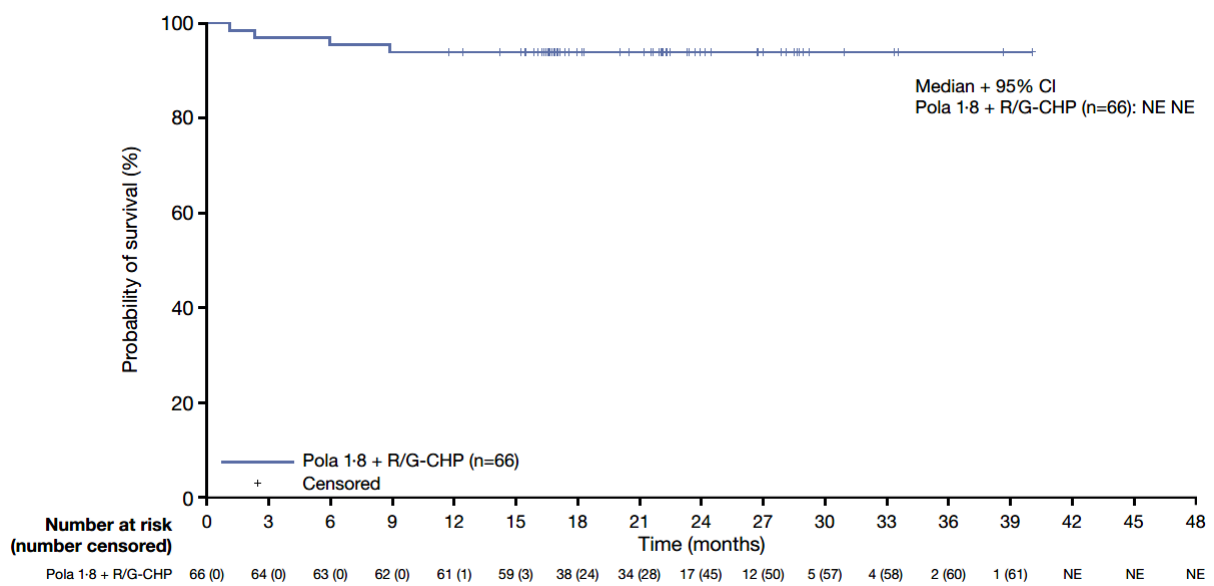
Treatment cycles were 21 days each, with investigator preference for six or eight cycles. Doses and administration were: Prednisone 100 mg/day po; Rituximab 375 mg/m² IV; Obinutuzumab 1000 mg IV; Cyclophosphamide 750 mg/m² IV; Doxorubicin 50 mg/m² IV; Polatuzumab vedotin 1.0–1.8 mg/kg IV. *Three patients did not receive any study treatment because of exclusionary lab values (n=2) and patient withdrawal from study prior to starting treatment (n=1). AE=adverse event. DLBCL=diffuse large B-cell lymphoma. FL=follicular lymphoma. MCL=mantle cell lymphoma. MZL=marginal zone lymphoma. Pola-G-CHP=polatuzumab vedotin with cyclophosphamide, doxorubicin, prednisone, and obinutuzumab. Pola-R-CHP=polatuzumab vedotin with cyclophosphamide, doxorubicin, prednisone, and rituximab. RP2D=recommended phase 2 dose.

Figure 2: A. Progression-free survival (PFS), B. Overall survival, and C. response duration in previously untreated patients with DLBCL who received polatuzumab vedotin 1.8 mg/kg with immunochemotherapy (R/G-CHP)

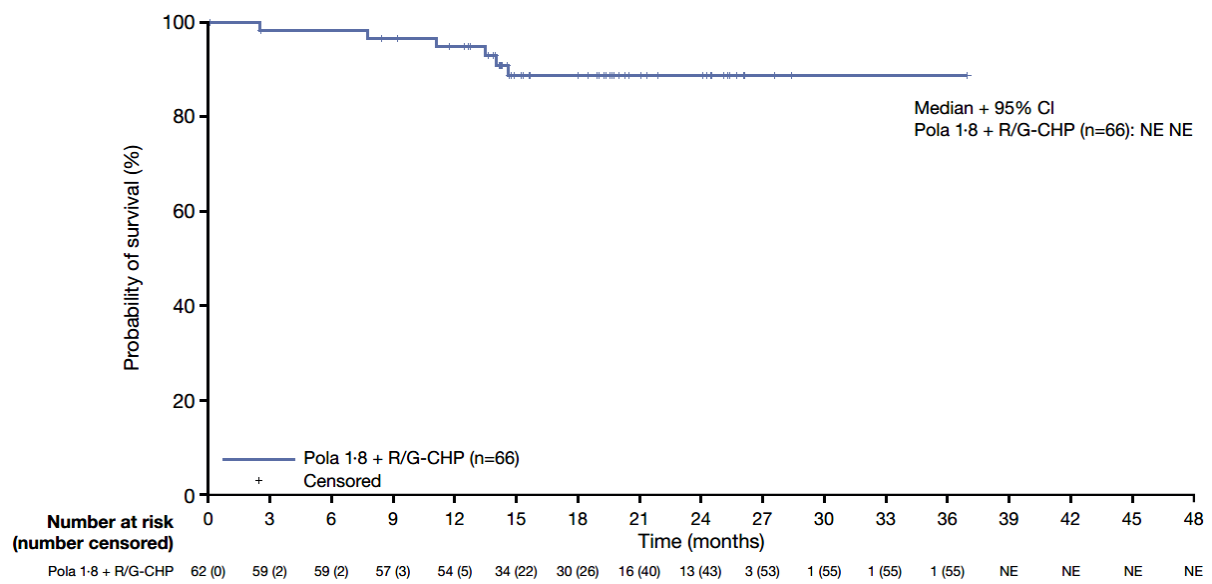
A



B

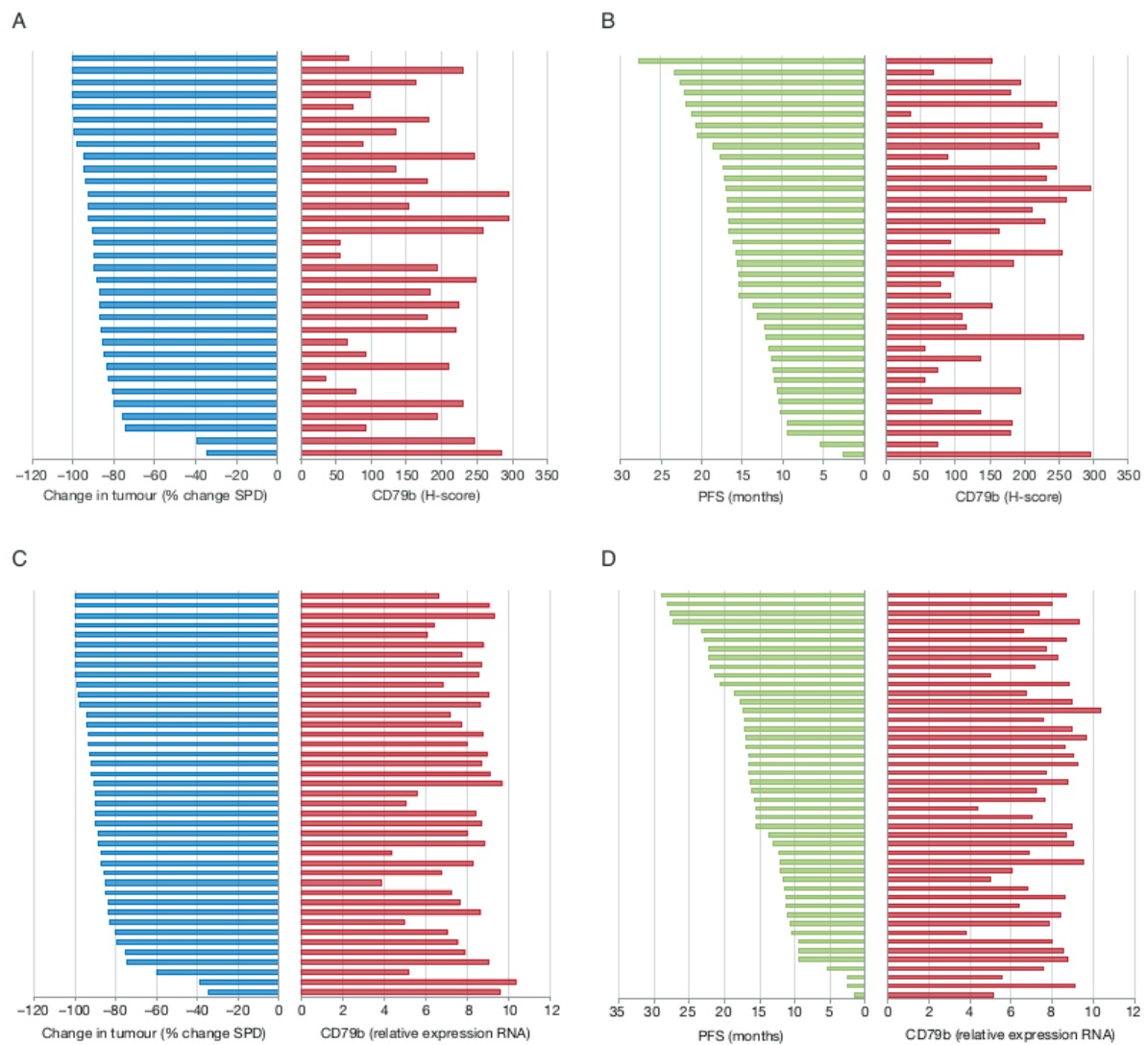


C



CI = confidence interval. NE, not estimable. Pola 1.8 = Polatuzumab vedotin 1.8 mg/kg. R/G-CHP=cyclophosphamide, doxorubicin, prednisone, and rituximab or obinutuzumab.

Figure 3: CD79b expression by IHC or RNA expression



CD79b expression (assessed by IHC) and response assessed by (A) tumour shrinkage by change in sum of the products of diameters, or (B) PFS. CD79b expression (assessed by RNA) and response assessed by (C) tumour shrinkage by change in sum percent diameter, or (D) PFS.

IHC=immunohistochemistry. PFS=progression-free survival. RNA=ribonucleic acid. SPD=sum of product diameter.

TABLES

Table 1: Patient characteristics

Histology	Mixed	Mixed	Mixed	Previously untreated DLBCL
Polatuzumab vedotin dose	<1.8 mg/kg	1.8 mg/kg	1.8 mg/kg	1.8 mg/kg
Immunotherapy	R/G-CHP (n=12)	R-CHP (n=47)	G-CHP (n=23)	R/G-CHP (n=66)
Median age, years (range)	70	69 (45–80)	65 (51–71)	67.5 (26–80)
Male	7 (58)	23 (49)	13 (57)	34 (52)
ECOG PS				
0–1	12 (100)	31 (66)	19 (83)	47 (71)
2	-	16 (34)	4 (17)	19 (29)
Stage III/IV disease	10 (83)	39 (83)	20 (87)	56 (85)
IPI				
0–1	3 (25)	2 (4)	3 (13)	4 (6)
2	4 (33)	9 (19)	11 (48)	19 (29)
3	5 (42)	17 (36)	5 (22)	21 (32)
4–5	-	19 (40)	4 (17)	22 (33)
Diagnosis				
1) DLBCL	9 (75)	45 (96)	21 (92)	66 (100)
2) FL	2 (17)	1 (2)	1 (4)	-
3) MCL	1 (8)	-	1 (4)	-
4) MZL	-	1 (2)	-	-
Biomarker for DLBCL patients	(n=6)	(n=36)	(n=15)	(n=51)
ABC	-	12 (33)	4 (27)	16
GCB	6 (100)	18 (50)	10 (67)	28
Unclassified	-	6 (17)	1 (7)	7
Biomarker for DLBCL patients	(n=5)	(n=29)	(n=12)	(n=41)
DEL	-	9 (31)	4 (33)	13 (32)
Non-DEL	5 (100)	20 (69)	8 (67)	28 (68)

Data are n(%). R/G-CHP=cyclophosphamide, doxorubicin, prednisone, and rituximab or obinutuzumab. ECOG PS=Eastern Cooperative Oncology Group performance status. DLBCL=diffuse large B-cell lymphoma. FL=follicular lymphoma. MCL=mantle cell lymphoma. MZL=marginal zone lymphoma. IPI=International Prognostic Index. ABC=activated B-cell like. GCB=germinal centre B-cell like. DEL=double-expressor lymphoma.

Table 2: Summary of adverse events in different cohorts

Histology	Mixed	Mixed	Mixed	Previously untreated DLBCL only
Polatuzumab vedotin dose Immunochemotherapy	<1·8 mg/kg R/G-CHP (n=12)	1·8 mg/kg R-CHP (n=47)*	1·8 mg/kg G-CHP (n=23)	1·8 mg/kg R/G-CHP (n=66)
Patients with AE, n (%)	12 (100)	47 (100)	23 (100)	66 (100)
SAE	3 (25)	19 (40)	9 (39)	27 (41)
Grade 3–4 AEs	9 (75)	29 (62)	16 (70)	43 (65)
Grade 5 AEs	0	1 (2)	1 (4)	2 (3)
AEs leading to study withdrawal	0	2 (4)	1 (4)	3 (5)

Data are n(%). AE=adverse event. SAE= severe AE. DLBCL=diffuse large B-cell lymphoma. G-CHP= cyclophosphamide, doxorubicin, prednisone, and obinutuzumab. R-CHP=cyclophosphamide, doxorubicin, prednisone, and rituximab. A full table of AEs by polatuzumab dose and anti-CD20 monoclonal antibody is provided in the appendix (pp 5-7).

*One patient with R/R FL and previous vincristine treatment was dosed with polatuzumab vedotin at 2·4 mg/kg during the dose escalation due to medication error.

Table 3. Treatment emergent adverse events

Patients		All evaluable patients (n=82)				Previously untreated DLBCL patients (n=66)			
Polatuzumab vedotin dose		All doses				1.8 mg/kg			
Preferred term		Worst grade 1–2	Worst grade 3	Worst grade 4	Worst grade 5	Worst grade 1-2	Worst grade 3	Worst grade 4	Worst grade 5
Nausea		40 (49)	0	0	0	30 (45)	0	0	0
Fatigue		40 (49)	0	1 (1)	0	31 (47)	0	1 (2)	0
Diarrhoea		38 (46)	1 (1)	0	0	32 (49)	1 (2)	0	0
Peripheral neuropathy‡		31 (38)	2 (2)	0	0	23 (35)	2 (4)	0	0
Alopecia		19 (23)	1 (1)	0	0	12 (18)	1 (2)	0	0
Constipation		20 (24)	0	0	0	17 (26)	0	0	0
Anaemia		17 (21)	3 (4)	1 (1)	0	15 (23)	2 (3)	1 (2)	0
Dizziness		14 (17)	0	0	0	7 (11)	0	0	0
Insomnia		14 (17)	0	0	0	10 (15)	0	0	0
Headache		12 (15)	0	0	0	7 (11)	0	0	0
Pyrexia		14 (17)	0	0	0	14 (21)	0	0	0
Weight decreased		14 (17)	1 (1)	0	0	13 (20)	1 (2)	0	0
Peripheral oedema		11 (13)	1 (1)	0	0	8 (12)	1 (2)	0	0
Dysgeusia		10 (12)	0	0	0	8 (12)	0	0	0
Anxiety		11 (13)	0	0	0	9 (14)	0	0	0
Vomiting		10 (12)	2 (2)	0	0	9 (14)	2 (3)	0	0
Cough		9 (11)	0	0	0	8 (12)	0	0	0
Asthenia		10 (12)	1 (1)	1 (1)	0	10 (15)	1 (2)	1 (2)	0
Chills		9 (11)	0	0	0	9 (14)	0	0	0
Back pain		7 (9)	2 (2)	0	0	5 (8)	2 (3)	0	0

Bronchitis	9 (11)	0	0	0	9 (14)	0	0	0
Thrombocytopenia	8 (10)	7 (9)	1 (1)	0	8 (12)	5 (8)	1 (2)	0
Bone pain	9 (11)	0	0	0	6 (9)	0	0	0
Decreased appetite	8 (10)	1 (1)	0	0	8 (12)	1 (2)	0	0
Neutropenia	7 (9)	5 (6)	21 (26)	0	7 (11)	4 (6)	16 (24)	0
Hypokalaemia	6 (7)	3 (4)	0	0	6 (9)	3 (5)	0	0
Hypertension	6 (7)	3 (4)	0	0	6 (9)	2 (3)	0	0
Leukopenia	4 (5)	1 (1)	4 (5)	0	4 (6)	1 (2)	4 (6)	0
Hyperglycaemia	3 (4)	4 (5)	0	0	2 (3)	4 (6)	0	0
Erythema	2 (2)	2 (2)	0	0	1 (2)	2 (3)	0	0
Pneumonia	2 (2)	3 (4)	1 (1)	0	1 (2)	3 (5)	1 (2)	0
Syncope	2 (2)	3 (4)	0	0	2 (3)	3 (5)	0	0
Pancytopenia	1 (1)	0	2 (2)	0	1 (2)	0	2 (3)	0
Atrial fibrillation	1 (1)	1 (1)	0	1 (1)	1 (2)	0	0	1 (2)
Leukocytosis	1 (1)	7 (9)	0	0	1 (2)	7 (11)	0	0
Febrile neutropenia	0	8 (10)	6 (7)	0	0	7 (11)	5 (8)	0
Septic shock	0	0	0	1 (1)	0	0	0	1 (2)

Data are n(%). Grade 1 and 2 AEs occurring in at least 10% of patients; grade 3 and grade 4 AEs occurring in at least 3% of patients and all grade 5 AEs are reported. AE=adverse event. DLBCL=diffuse large B-cell lymphoma. FL=follicular lymphoma. G-CHP= cyclophosphamide, doxorubicin, prednisone, and obinutuzumab. R-CHP=cyclophosphamide, doxorubicin, prednisone, and rituximab. ‡Peripheral neuropathy includes preferred terms from the system organ class of peripheral neuropathy (including motor and sensory neuropathy).

Table 4: Treatment completion response in DLBCL only, and in DLBCL biomarker subgroups.

Polatuzumab vedotin dose	<1·8 mg/kg	1·8 mg/kg				Cell of origin			BCL2+/MYC+ IHC	
Response	R/G-CHP, (n=9)	R-CHP, (n=45)	G-CHP, (n=21)	R/G-CHP, (n=66)		ABC (n=16)	GCB (n=28)	Unclassified (n=7)	DEL (n=13)	Non-DEL (n=28)
Overall response [95% CI]	8 (89) [51–99]	40 (89) [76–96]	19 (91) [70–99]	59 (89) [80–95]		14 (87) [62–98]	28 (100) [88–100]	5 (72) [29–96]	12 (92) [64–100]	26 (93) [77–99]
Complete response [95% CI]	7 (78) [40–97]	34 (76) [60–87]	17 (81) [58–95]	51 (77) [65–87]		13 (81) [54–96]	25 (89) [72–98]	4 (57) [18–90]	9 (69) [39–91]	23 (82) [63–94]
Partial response [95% CI]	1 (11) [0–48]	6 (13) [5–27]	2 (10) [1–30]	8 (12) [5–22]		1 (6) [0–30]	3 (11) [2–28]	1 (14) [0–58]	3 (23) [5–54]	3 (11) [2–28]
Stable disease [95% CI]	1 (11) [0–48]	-	-	-		-	-	-	-	-
Progressive disease [95% CI]	-	3 (7) [1–18]	-	3 (5) [1–11]		-	-	2 (28) [4–71]	-	1 (4) [0–18]
Missing [95% CI]	-	2 (4) [1–15]	2 (10) [1–30]	4 (6) [2–15]		2 (13) [2–38]	-	-	1 (8) [0–36]	1 (4) [0–18]

Data are n(%). DLBCL=diffuse large B-cell lymphoma. CI=confidence interval. ABC=activated B-cell like. GCB=germinal centre B-cell like. DEL=double-expressor lymphoma. R/G-CHP=cyclophosphamide, doxorubicin, prednisone, and rituximab or obinutuzumab.