Polatuzumab vedotin in combination with immunochemotherapy in patients with previously untreated diffuse large B-cell lymphoma: an open-label, non-randomised, phase 1b–2 study

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Summary

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

Methods This was an open-label, non-randomised study composed of a phase 1b dose escalation and a phase 2 dose expansion at 11 hospitals and health centres in the USA and France. Patients aged 18 years or older with B-cell non-Hodgkin lymphoma were eligible. Exclusion criteria included peripheral neuropathy with grade greater than 1, major surgery within 4 weeks before enrolment, known CNS involvement of lymphoma, and uncontrolled heart disease. Phase 1b dose escalation had a three-plus-three design and established the recommended phase 2 dose. Phase 2 expansion evaluated the recommended phase 2 dose of polatuzumab vedotin in patients with newly diagnosed diffuse large B-cell lymphoma with an International Prognostic Index (IPI) of 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 1–5 of each 21-day cycle orally (CHP), plus either rituximab 375 mg/m² intravenously on day 1 of each cycle (R-CHP) or obinutuzumab 1000 mg intravenously on days 1, 8, and 15 of cycle 1 and on day 1 of the following cycles (G-CHP). Polatuzumab vedotin was administered on day 2 of cycles 1 and 2, and on day 1 of the following cycles at 1·0–2·4 mg/kg during the escalation phase and at the recommended phase 2 dose during the expansion phase. Treatment could last six or eight cycles, depending on investigator preference. The primary endpoints of the study were safety and tolerability, and determination of the maximum tolerated dose (or recommended phase 2 dose) of polatuzumab vedotin. All endpoints were analysed per protocol in the safety evaluable population, defined as all patients who received at least one dose of study treatment. This trial is registered with ClinicalTrials.gov, number NCT01992653.

Findings Between Dec 4, 2013, and July 26, 2016, 85 patients were enrolled. 82 patients were included in the safety and activity evaluable populations, 25 in phase 1b and 57 in phase 2. In light of information from other studies using polatuzumab vedotin reported during this study, in which the safety profile associated with exposure to polatuzumab vedotin at doses higher than 1·8 mg/kg every 3 weeks was not outweighed by any clinical benefit, the recommended phase 2 dose was set to 1·8 mg/kg in the R-CHP cohort and no higher doses were explored in this study. 66 patients with newly diagnosed diffuse large B-cell lymphoma received the polatuzumab vedotin recommended phase 2 dose (45 R-CHP; 21 G-CHP). In 66 patients with diffuse large B-cell lymphoma who received the recommended phase 2 dose, the most common adverse events of grade 3 or worse were neutropenia (20 [30%]), febrile neutropenia (12 [18%]), and thrombocytopenia (six [9%]). Among the 70 patients (any histology) who received the recommended phase 2 dose, 19 (27%) had grade 1 peripheral neuropathy, eight (11%) grade 2, and two (3%) grade 3. Four deaths were reported during follow-up: two treatment-related (one complication of atrial fibrillation and one septic shock) and two due to disease progression. As of the cutoff date of Dec 29, 2017, median follow-up time was 21·5 months (IQR 16·7–24·3) for the untreated diffuse large B-cell lymphoma cohort treated at the polatuzumab vedotin recommended phase 2 dose. 59 (89%) patients achieved an overall response at end of treatment (51 [77%] patients had a complete response, and eight [12%] patients had a partial response).

Interpretation The safety of incorporating polatuzumab vedotin to R-CHP or G-CHP was as expected and manageable. Preliminary clinical activity in newly diagnosed diffuse large B-cell lymphoma seems promising and encouraged a phase 3 trial comparing polatuzumab vedotin with R-CHP to R-CHOP.

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Introduction

Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) remain the standard treatment for previously untreated diffuse large B-cell lymphoma.[1] However, many patients are not cured by this therapy. Patients who have poor outcomes with R-CHOP include those with high-risk patient characteristics (eg, high International Prognostic Index [IPI]) or increased biological risk (eg, activated B-cell like subtype, double-expressor lymphoma, and double or triple-hit lymphoma).[2] Numerous strategies have been unsuccessful in improving upon R-CHOP in diffuse large B-cell lymphoma, including the addition of novel drugs, substitution of monoclonal antibodies, increase in dose, or addition of maintenance therapies.[3] Evolving strategies continue to match novel drugs to disease subtypes characterised on the basis of genetic and gene-expression profiling of patients.[4] Nonetheless, a successful strategy that applies broadly to diffuse large B-cell lymphoma has not been found thus far.

Antibody–drug conjugates have been useful in haematological malignancies, with approved indications for gemtuzumab ozogamicin, brentuximab vedotin, and inotuzumab ozogamicin.[5] The extent of their activity depends on the relevance of the antibody target and small molecule delivered by the antibody–drug conjugate. Polatuzumab vedotin is an antibody–drug conjugate targeting CD79b to deliver monomethyl auristatin E, 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[11] showed promising single-drug clinical activity of polatuzumab vedotin in a heavily pretreated patient population, including those with both activated B-cell-like and germinal centre B-cell-like subtypes of diffuse large B-cell lymphoma.[10] These data were used to support this study in previously untreated patients with diffuse large B-cell lymphoma.

We report the initial results of a study that evaluated the safety and activity of polatuzumab vedotin with cyclophosphamide, doxorubicin, and prednisone (CHP) chemotherapy and an anti-CD20 monoclonal antibody (rituximab or obinutuzumab). Since the mechanism of action and the neurotoxicity profile of polatuzumab vedotin overlap with those of vincristine, this regimen omits vincristine from standard CHOP-based therapy. A phase 1b dose escalation was done to establish the recommended phase 2 dose of polatuzumab vedotin in combination with rituximab-CHP (R-CHP) or obinutuzumab-CHP (G-CHP), and a phase 2 dose expansion study was done in previously untreated patients with diffuse large B-cell lymphoma to assess safety, tolerability, and activity at the recommended phase 2 dose.

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

Research in context

Evidence before this study

Effective first-line treatment of diffuse large B-cell lymphoma 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 diffuse large B-cell lymphoma. 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 diffuse large B-cell lymphoma. Because of 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 to vincristine, which has a known neurological toxicity, 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") from database inception 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 either rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) or obinutuzumab, cyclophosphamide, doxorubicin, and prednisone (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 diffuse large B-cell lymphoma. The safety profile was as expected and manageable, and preliminary activity was observed in a population of patients with high-risk characteristics.

Implications of all the available evidence

Results of this study suggest that combination of polatuzumab vedotin with R-CHP in first-line diffuse large B-cell lymphoma is safe with preliminary activity. Therefore, a phase 3 study comparing polatuzumab vedotin plus R-CHP to standard R-CHOP has been initiated in previously untreated patients with diffuse large B-cell lymphoma (POLARIX study, NCT03274492). The combination of brentuximab vedotin, another antibody–drug conjugate, and CHP in CD30-positive T-cell lymphoma has been shown to improve outcomes as compared with CHOP, reinforcing confidence in our approach.

dose expansion across 11 hospitals and health centres in the USA and France. Patients received polatuzumab vedotin (BSP Pharmaceuticals; Latina Scalo, Italy) in combination with CHP (all generic drugs that were supplied locally) chemotherapy and rituximab (F Hoffman-La-Roche; Basel, Switzerland; or Roche Diagnostics; Mannheim, Germany) or obinutuzumab (Roche Diagnostics). Separate dose-escalation and dose-expansion cohorts were formed on the basis of the anti-CD20 monoclonal antibody used.

Eligible patients were aged 18 years or older with locally histopathologically confirmed B-cell non-Hodgkin lymphoma. In the dose-escalation phase, patients with any B-cell non-Hodgkin lymphoma were enrolled. Patients who had previous lymphoma treatment were allowed in the dose-escalation part. In the expansion phase, only patients with previously untreated diffuse large B-cell lymphoma with an IPI of 2–5 were included. Other eligibility criteria were: Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; at least one measurable lesion larger than 1·5 cm; adequate bone marrow, liver, and renal function; and a life expectancy of at least 24 weeks. Key exclusion criteria included peripheral neuropathy worse than grade 1, major surgery within 4 weeks before enrolment, known CNS involvement of lymphoma, and uncontrolled heart disease (detailed eligibility and exclusion criteria are described in the appendix pp 2–3).

See Online for appendix

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 done according to the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the study was 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

Patients received cyclophosphamide 750 mg/m² on day 1 of each cycle intravenously, doxorubicin 50 mg/m² on day 1 of each cycle intravenously, prednisone 100 mg once daily on days 1–5 of each cycle orally, and either rituximab 375 mg/m² intravenously on day 1 of each cycle or obinutuzumab 1000 mg intravenously on days 1, 8, and 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 lasted 21 days and treatment could last six or eight cycles, depending on investigator preference.

Polatuzumab vedotin was administered to patients by intravenous infusion via a syringe pump with an infusion set containing a 0·22 µm in-line filter. Premedication (500–1000 mg of oral acetaminophen or paracetamol and 50–100 mg diphenhydramine; all generic drugs that were supplied locally) and prednisone or prednisolone (both generic drugs that were supplied locally) according to R-CHP or G-CHP dose (100 mg dose included in R-CHP or G-CHP; prednisolone was only given when prednisone was not available) were administered before polatuzumab vedotin. The initial dose was administered to a well hydrated patient over 90 min. The polatuzumab vedotin infusion could be slowed or interrupted for patients showing infusion-associated symptoms. If previous infusions had been well tolerated, subsequent doses of polatuzumab vedotin were administered over 30 min followed by a 30-min observation period.

During the dose-escalation phase, the standard three-plus-three design was applied. The observation period for dose-limiting toxicity was from cycle 1, day 1, to cycle 2, day 1 (the definition of dose-limiting toxicity is described in the appendix p 4). Decisions regarding the benefit–risk of dose escalations and establishment of the recommended phase 2 dose were made by the study team, which included the sponsor's medical monitor, a safety scientist, a biostatistician, and the participating investigators. The starting polatuzumab vedotin dose was 1·0 mg/kg, with planned dose escalations of less than 50% of the previous dose to a maximum of 2·4 mg/kg. However, information from other studies using polatuzumab vedotin emerged during the conduct of this study in which the safety profile associated with cumulative exposure to polatuzumab vedotin at doses higher than 1·8 mg/kg every 3 weeks was not outweighed by any clinical benefit, particularly in the case of diffuse large B-cell lymphoma being treated in a curative setting. Therefore, the recommended phase 2 dose was set to 1·8 mg/kg in the R-CHP cohort; no higher doses were explored in this study. Once the recommended phase 2 dose was established in the R-CHP cohort, the escalation recommended phase 2 dose immediately below (1·4 mg/kg) was used as the starting dose in the G-CHP cohort.

After the results of the GOYA study—which showed that G-CHOP did not improve progression-free survival compared with R-CHOP in patients with previously untreated diffuse large B-cell lymphoma—became available, a memo communicating the discontinuation of enrolment in the G-CHP expansion cohort was sent to investigators on July 25, 2016, with the protocol amendment finalised on Sept 23, 2016.

Pertinent dosing requirements stated that recovery of haematological parameters (absolute neutrophil count >1000 cells per uL, platelet count >75 000 platelets per uL) was necessary for the initiation of a treatment cycle and—for patients who experienced grade 2 or 3 peripheral neuropathy—regression of peripheral neuropathy to grade 1 or less within 14 days was required; failure to satisfy these requirements caused permanent discontinuation of polatuzumab vedotin. Patients who experienced grade 2 or 3 peripheral neuropathy with regression of peripheral neuropathy to grade 1 or less within 14 days would be required to reduce the polatuzumab vedotin dose by one 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.[13] In the expansion cohort, patients received the R-CHP or G-CHP regimen combined with polatuzumab vedotin at the recommended phase 2 dose.

The pharmacokinetics of polatuzumab vedotin, doxorubicin, cyclophosphamide, rituximab, or obinutuzumab were assessed by pharmacokinetic sampling at predetermined timepoints. Pre-treatment tumour samples were analysed for CD79b expression by immunohistochemistry using clone AT107–2 (Serotec; Oxford, UK) using the Ventana Benchmark XT platform (Ventana; Tucson, AZ, USA). A continuous variable of immunohistochemistry staining (H-score; range 0–300) that incorporates staining intensity (semiquantitative immunohistochemistry score from 0 to 3 marked 0, +1, +2, and +3) and the number of positively stained tumour cells was defined as: H-score=(% tumour cells stained at score 0)×0+(% tumour cells stained with score +1)×1+(% tumour cells stained with score +2)×2 + (% tumour cells stained with score +3)×3.[10] BCL2 and MYC immunohistochemistry was performed using the investigational-use-only BCL2 (clone 124) monoclonal antibody and MYC (clone Y69) monoclonal antibody on the Ventana BenchMark Ultra platform. The BCL2 immunohistochemistry was defined as positive when 50% or more of tumour cells stained with intermediate or high intensity on a semiquantitatve immunohistochemistry scale. The MYC clinical cutoff was defined as more than 40% of cells with MYC-positive nuclear staining above background level. Cell of origin was determined with the NanoString Lymphoma Subtyping Test (NanoString Technologies Inc, Seattle, WA, USA). In parallel, CD79b expression was quantified by measuring mRNA levels using the NanoString platform. Fluorescence in-situ hybridisation for MYC, BCL2, 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 medical history; physical examination; relevant laboratory tests (for a full list of laboratory tests see appendix pp 61–68); CT scan of the neck (if clinically indicated), chest, abdomen, and pelvis; ^{18}fluorodeoxyglucose PET; 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.[14] The response data after four cycles were collected at each site that participated in the study, but were not analysed. Bone marrow was sampled at treatment completion to confirm a complete response in patients who initially had bone-marrow involvement.

Safety was assessed by clinical physical examinations, measurements of protocol-specific haematological and chemistry laboratory parameters, measurement of protocol-specific vital signs, and assessments of electrocardiography and echocardiography multiple-gated acquisition scans. Adverse events were graded by the US National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Serious adverse events attributed to protocol-mandated interventions were recorded from the time of providing informed consent until the first dose of study treatment, and all adverse events were recorded 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 after the completion of study treatment.

Outcomes

The primary endpoints of the study were safety and tolerability, and determination of the maximum tolerated dose of polatuzumab vedotin. Secondary endpoints were response (overall response and complete response, according to the classification of the International Workshopto Standardize Response Criteria for Non-Hodgkin's Lymphomas 2007)[14] at the completion of the treatment as assessed by the investigators; preliminary activity (progression-free survival, event-free survival, response duration, and overall survival); neurological toxicity and pharmacokinetics of polatuzumab vedotin, cyclophosphamide, doxorubicin, and rituximab or obinutuzumab; and immunogenicity of polatuzumab vedotin and obinutuzumab. Progression-free survival was defined as the time from the first day of study treatment to disease progression, relapse, or death from any cause, as assessed by the investigator. Event-free survival was defined as the time from the first day of study treatment to disease progression or relapse (as assessed by the investigator), death from any cause, or initiation of any new anti-lymphoma therapy. Duration of response was defined, among patients with a response, as the time from documentation of the first complete response or partial response to the time of disease progression, relapse, or death from any cause, as assessed by the investigator. Overall survival was defined as time from the first day of study treatment to death from any cause.

Expanded pharmacokinetics and immunogenicity analyses will be reported in future publications.

Pre-planned exploratory endpoints included activity of therapy in different biological subgroups, including diffuse large B-cell lymphoma subtypes according to cell of origin (activated B-cell-like and germinal centre B-cell-like subtypes); double expression of MYC and BCL2 proteins (double-expressor lymphoma); and characterisation of tumour expression of CD79b (for a full list of pre-planned exploratory endpoints see the appendix p 36).

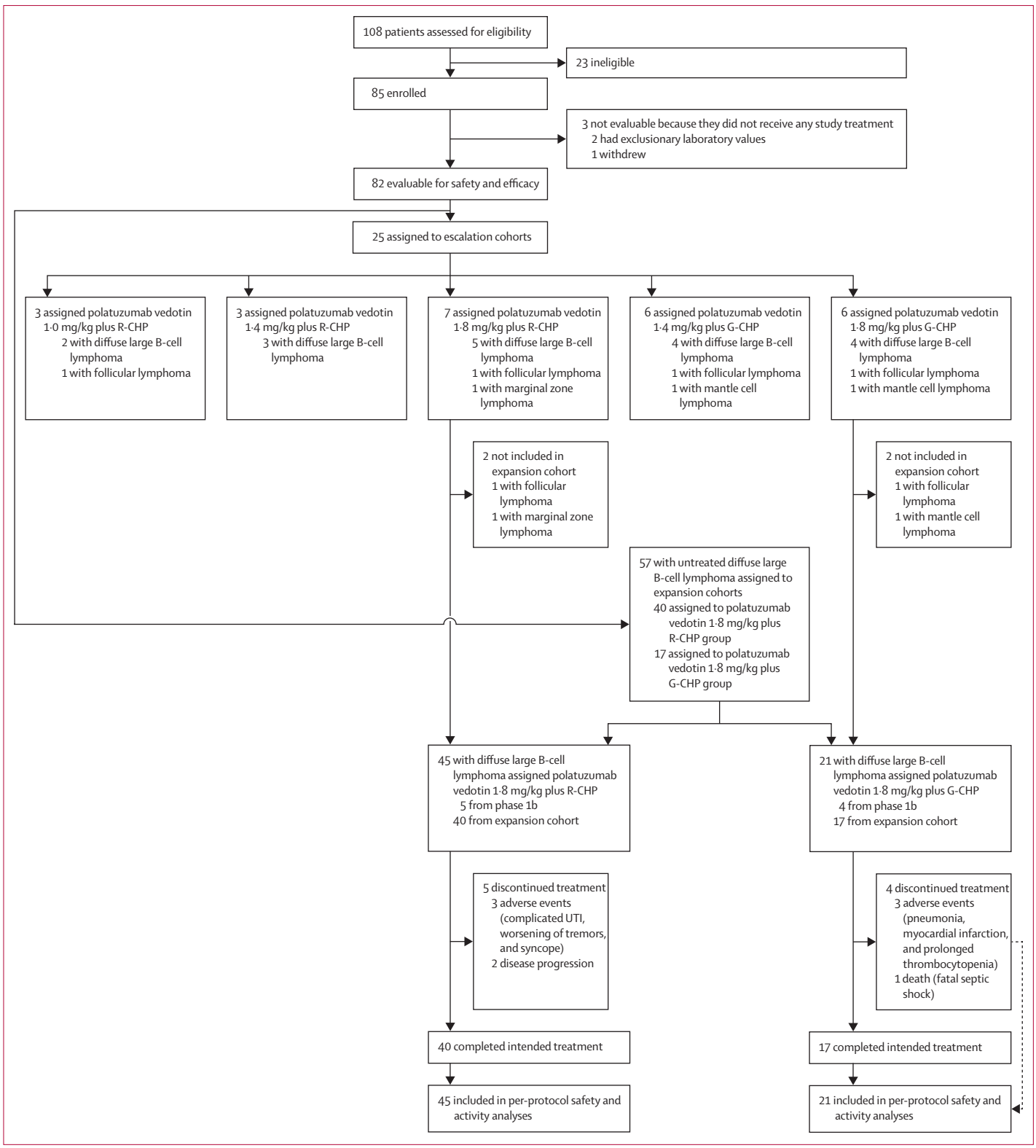

Figure 1: **Trial profile**
G-CHP=polatuzumab vedotin with cyclophosphamide, doxorubicin, prednisone, and obinutuzumab. R-CHP=polatuzumab vedotin with cyclophosphamide, doxorubicin, prednisone, and rituximab. UTI=urinary tract infection.

	Polatuzumab vedotin (<1·8 mg/kg) plus R-CHP or G-CHP group (n=12)	Polatuzumab vedotin (1·8 mg/kg) plus R-CHP group (n=47)	Polatuzumab vedotin (1·8 mg/kg) plus G-CHP group (n=23)	Polatuzumab vedotin (1·8 mg/kg) plus R-CHP or G-CHP group (n=66)
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
Median age, years (IQR)	70·0 (63·0–72·5)	69·0 (66·0–75·0)	65·0 (51·0–71·0)	67·5 (64·0–74·0)
Sex				
Male	7 (58%)	23 (49%)	13 (57%)	34 (52%)
ECOG performance status				
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 score				
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				
Diffuse large B-cell lymphoma	9 (75%)	45 (96%)	21 (91%)	66 (100%)
Follicular lymphoma	2 (17%)	1 (2%)	1 (4%)	..
Mantle-cell lymphoma	1 (8%)	..	1 (4%)	..
Marginal-zone lymphoma	..	1 (2%)	..	..
Biomarker for patients with DLBCL				
ABC subtype	..	12/36 (33%)	4/15 (27%)	16/51 (31%)
GCB subtype	6/6 (100%)	18/36 (50%)	10/15 (67%)	28/51 (54%)
Unclassified	..	6/36 (17%)	1/15 (7%)	7/51 (14%)
DEL	..	9/29 (31%)	4/12 (33%)	13/41 (32%)
Non-DEL	5/5 (100%)	20/29 (69%)	8/12 (67%)	28/41 (68%)

Data are n (%) or n/N (%), unless otherwise specified. R-CHP= rituximab, cyclophosphamide, doxorubicin, and prednisone. G-CHP=obinutuzumab, cyclophosphamide, doxorubicin, and prednisone. ECOG=Eastern Cooperative Oncology Group. IPI=International Prognostic Index. ABC=activated B-cell like. GCB=germinal centre B-cell like. DEL=double-expressor lymphoma.

Table 1: **Baseline characteristics by immunochemotherapy group**

Statistical analysis

The sample size for this study was based on the three-plus-three 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 (p 4). The results for all endpoints were reported descriptively. No statistical hypothesis testing or inferential analysis was done for this study. Categorical variables were reported as absolute count and percentage, and continuous variables were reported as median (range or IQR) or mean (SD), as appropriate.

Response at the end of treatment were reported as proportion (95% CI) calculated using the Clopper-Pearson method, with 40 patients enrolled into expansion cohorts such that the 95% exact Clopper-Pearson CIs for the true proportion of patients who achieved a complete response 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 done in the population of patients with previously untreated diffuse large B-cell lymphoma who were treated with the recommended phase 2 dose of polatuzumab vedotin. Progression-free survival was assessed at 12 months, 18 months, and 24 months using the Kaplan–Meier approach. We did post-hoc analyses of the occurrence of peripheral neuropathy according to the number of cycles of R-CHP or G-CHP plus polatuzumab vedotin, and progression-free survival according to number of cycles planned (six or eight), anti-CD20 antibody (rituximab or obinutuzumab), and IPI categories. Statistical analyses were performed using SAS (version 9.4) or R (version 3.4.4). This trial is registered with ClinicalTrials.gov, number NCT01992653.

Role of the funding source

The funder was involved in the study design; administration and 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, and 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

	Patients with mixed histology, treated with polatuzumab vedotin (<1·8 mg/kg) plus R-CHP or G-CHP group (n=12)*	Patients with mixed histology, treated with polatuzumab vedotin (1·8 mg/kg) plus R-CHP group (n=47)*†	Patients with mixed histology, treated with polatuzumab vedotin (1·8 mg/kg) plus G-CHP group (n=23)*	Patients with previously untreated DLBCL, treated with polatuzumab vedotin (1·8 mg/kg) plus R-CHP or G-CHP group (n=66)‡
Patients with adverse events	12 (100%)	47 (100%)	23 (100%)	66 (100%)
Patients with serious adverse events	3 (25%)	19 (40%)	9 (39%)	27 (41%)
Grade 3–4 adverse events	9 (75%)	29 (62%)	16 (70%)	43 (65%)
Grade 5 adverse events	0	1 (2%)	1 (4%)	2 (3%)
Adverse events leading to study withdrawal	0	2 (4%)	1 (4%)	3 (5%)

Data are n (%). A full table of adverse events by polatuzumab dose and anti-CD20 monoclonal antibody is provided in the appendix (pp 5-7). R-CHP=rituximab, cyclophosphamide, doxorubicin, and prednisone. G-CHP=obinutuzumab, cyclophosphamide, doxorubicin, and prednisone. *Mixed histology. †One patient with relapsed or refractory follicular lymphoma and previous vincristine treatment was dosed with polatuzumab vedotin at 2·4 mg/kg during the dose escalation due to medication error. ‡Only patients with previously untreated diffuse large B-cell lymphoma.

Table 2: **Summary of treatment-emergent adverse events**

data and statistical results. The corresponding author had access to all data in the study and final responsibility for the decision to submit for publication.

Results

Between Dec 4, 2013, and July 26, 2016, 85 patients were enrolled. 82 patients were included in the safety and activity evaluable populations, defined as patients having received any study treatment. Three (4%) of 85 patients did not receive any study treatment because of an exclusionary laboratory result (two [2%]) or patient withdrawal before starting study treatment (one [1%]; figure 1).

The evaluable population included 25 patients in phase 1b and 57 in phase 2 (figure 1), with 75 (91%) patients having previously untreated diffuse large B-cell lymphoma (table 1). 66 (88%) of 75 patients with previously untreated diffuse large B-cell lymphoma were treated with polatuzumab vedotin at the recommended phase 2 dose of 1·8 mg/kg. In this group, the median age was 67·5 years (IQR 64–74), with 46 (70%) patients aged 66 years or older; 19 (29%) had ECOG performance status of 2; and 43 (65%) had an IPI score of 3–5. At the clinical cutoff date for this study (Dec 29, 2017), median study duration for patients with diffuse large B-cell lymphoma treated at the recommended phase 2 dose of polatuzumab vedotin was 21·5 months (IQR 16·7–24·3).

Two events of dose-limiting toxicity were observed during dose escalation. One patient experienced a grade 4 pulmonary embolism at the 1·8 mg/kg polatuzumab vedotin dose in combination with R-CHP, and one patient had grade 4 febrile neutropenia and grade 3 thrombocytopenia at the 1·4 mg/kg polatuzumab vedotin dose in combination with G-CHP. The recommended phase 2 dose for each phase 2 expansion was determined to be 1·8 mg/kg on the basis of the safety and benefit–risk profile of the phase 1b cohorts with polatuzumab vedotin at this dose.

Seven (11%) of 66 patients with diffuse large B-cell lymphoma treated at the recommended phase 2 dose discontinued study treatment because of adverse events after receiving 1–5 cycles (figure 1): four (6%) who received G-CHP (pneumonia, myocardial infarction, prolonged thrombocytopenia, and fatal septic shock) and three (5%) who received R-CHP (complicated urinary tract infection, worsening of tremors, and syncope). Five (8%) patients with diffuse large B-cell lymphoma treated at the recommended phase 2 dose had a dose reduction of polatuzumab vedotin because of grade 1 peripheral neuropathy (one [2%] patient at cycle 2), weight loss (one [2%] at cycle 6), grade 2 peripheral neuropathy (one [2%] at cycle 5 and one [2%] at cycle 6), and recurrent neutropenia (one [2%] at cycle 5). One (2%) patient in the dose-expansion phase did not receive cycle 8 of polatuzumab vedotin because of grade 2 peripheral neuropathy but received R-CHP. Doxorubicin dose reductions in were reported in three (5%) patients (for weight loss, febrile neutropenia, and *Clostridioides difficile* infection) and cyclophosphamide dose reduction in one (2%) patient (for weight loss). Median relative dose intensity for cyclophosphamide and doxorubicin was 100% (IQR 98–100 for both drugs), with a relative dose intensity greater than 90% being achieved by 65 (98%) patients for cyclophosphamide and by 63 (95%) patients for doxorubicin.

Among the 12 patients who were assigned less than 1·8 mg/kg of polatuzumab vedotin, nine (75%) experienced a treatment-emergent adverse event of grade 3 or worse, and three (25%) experienced at least one serious adverse event. Among the 70 patients who were assigned polatuzumab vedotin at 1·8 mg/kg, 45 (64%) experienced a treatment-emergent adverse event of grade 3 or higher and 28 (40%) had at least one serious adverse event (table 2; appendix pp 5–7).

The adverse-event profile differed for different anti-CD20 monoclonal antibodies, with a greater prevalence of neutropenia and thrombocytopenia of grade 3 or higher observed in patients who received obinutuzumab than in patients who received rituximab (appendix pp 5–7); this observation is consistent with the known safety profile of the two antibodies.[12] Table 3 shows treatment-emergent adverse events in all evaluable patients and in those with diffuse large B-cell lymphoma treated at the recommended phase 2 dose. For patients with diffuse large B-cell lymphoma treated at the recommended phase 2 dose, the most common adverse events of grade 3 or worse were neutropenia (20 [30%] of 66 patients), febrile neutropenia (12 [18%]), and thrombocytopenia (six [9%]; table 3). Ten (15%) patients had an infection of grade 3 or higher. The most common serious adverse events were febrile

	All evaluable patients (all doses; n=82)				Patients with previously untreated DLBCL (polatuzumab vedotin 1·8 mg/kg; n=66)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	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 (48%)	1 (2%)	0	0
Peripheral neuropathy*	33 (40%)	2 (2%)	0	0	25 (38%)	2 (3%)	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 number of patients (%). Grade 1 and 2 adverse events occurring in at least 10% of patients, grade 3 and grade 4 adverse events occurring in at least 3% of patients, and all grade 5 adverse events are reported. DLBCL=diffuse large B-cell lymphoma. *Peripheral neuropathy includes preferred terms from the system organ class of peripheral neuropathy (including motor and sensory neuropathy).

Table 3. **Treatment-emergent adverse events**

neutropenia (nine [14%] patients), neutropenia (four [6%]), and pneumonia (four [6%]; data for other serious adverse events not shown).

Of the 12 patients who received polatuzumab vedotin at less than 1·8 mg/kg, six (50%) had grade 1–2 peripheral neuropathy (five [42%] of grade 1, one [8%] of grade 2; appendix p 5). Of the 70 patients assigned to the recommended phase 2 dose, 27 (39%) had grade 1–2 peripheral neuropathy (19 [27%] of grade 1, eight [11%] of grade 2) and two (3%) had grade 3 peripheral neuropathy, both treated with R-CHP (appendix p 5). One patient in the R-CHP cohort who had grade 2 peripheral neuropathy was assigned to the 1·8 mg/kg dose and received 2·4 mg/kg for four cycles because of medication error; this patient had also previously received vincristine in previous therapy for follicular lymphoma. At the data cutoff, seven (11%) of 66 patients with diffuse large B-cell lymphoma treated at the recommended phase 2 dose

	Overall DLBCL				DLBCL subtypes by cell of origin			DLBCL subtypes by BCL2+/MYC+ immunohistochemistry	
	Polatuzumab vedotin (<1·8 mg/kg) plus R-CHP or G-CHP group (n=9)	Polatuzumab vedotin (1·8 mg/kg) plus R-CHP group (n=45)	Polatuzumab vedotin (1·8 mg/kg) plus G-CHP group (n=21)	Polatuzumab vedotin (1·8 mg/kg) plus R-CHP or G-CHP group (n=66)	ABC subtype (n=16)	GCB subtype (n=28)	Unclassified (n=7)	DEL (n=13)	Non-DEL (n=28)
Overall response	8 (89%; 51–99)	40 (89%; 76–96)	19 (90%; 70–99)	59 (89%; 80–95)	14 (88%; 62–98)	28 (100%; 88–100)	5 (71%; 29–96)	12 (92%; 64–100)	26 (93%; 77–99)
Complete response	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	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	1 (11%; 0–48)	..	..	..	..	..	..	..	..
Progressive disease	..	3 (7%; 1–18)	..	3 (5%; 1–11)	..	..	2 (29%; 4–71)	..	1 (4%; 0–18)
Missing	..	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 (%; 95% CI). DLBCL=diffuse large B-cell lymphoma. R-CHP= rituximab, cyclophosphamide, doxorubicin, and prednisone. G-CHP= obinutuzumab, cyclophosphamide, doxorubicin, and prednisone. ABC=activated B-cell like. GCB=germinal centre B-cell like. DEL=double-expressor lymphoma.

Table 4: **Treatment response in patients with DLBCL**

continued to have peripheral neuropathy (six with grade 1, one with grade 2, table 3; appendix p 8). The median time to resolution of all grades of peripheral neuropathy from initial onset was 2·4 months (IQR 0·8–6·5) and the median time to resolution of grade 2 or 3 peripheral neuropathy was 4·9 months (1·0–9·1).

A post-hoc analysis was performed on the basis of the prevalence of peripheral neuropathy among patients with diffuse large B-cell lymphoma treated at the recommended phase 2 dose who received fewer than six cycles, six cycles, or more than six cycles of study treatment. Among the nine patients who received fewer than six cycles, two (22%) had grade 1 peripheral neuropathy and none had peripheral neuropathy of grade worse than 1; of the 36 patients who received six cycles, 11 (31%) had grade 1, two (6%) had grade 2, and one (3%) grade 3 peripheral neuropathy; of the 21 patients who received more than six cycles, six (29%) had grade 1, four (19%) had grade 2, and one (5%) grade 3 peripheral neuropathy (appendix p 8).

Pharmacokinetic parameters for analytes related to polatuzumab vedotin were similar for R-CHP and G-CHP administration (appendix pp 9, 10). Cyclophosphamide and doxorubicin plasma concentrations were similar in cycle 1 (before polatuzumab vedotin dosing) and cycle 3 (after polatuzumab vedotin dosing), suggesting that monomethyl auristatin E does not impact their pharmacokinetics when given in combination (appendix pp 9–10).

All seven patients who did not have diffuse large B-cell lymphoma—of whom three were treated with polatuzumab vedotin plus R-CHP and four with polatuzumab vedotin plus G-CHP—had a complete response as assessed by PET at end of study treatment. Response to treatment for patients with diffuse large B-cell lymphoma are summarised in table 4. As response to treatment and 12-month progression-free survival between patients were similar for those receiving either rituximab or obinutuzumab (table 4; appendix p 11), results are presented for previously untreated patients with diffuse large B-cell lymphoma who received the recommended phase 2 dose of polatuzumab vedotin. In this population, 59 (89%) of 66 patients achieved a response, and 51 (77%) achieved a complete response. 12-month progression-free survival was 91% (95% CI 84–98; figure 2A). and 24-month progression-free survival was 83% (73–93). In a post-hoc analysis, there was no difference in progression-free survival according to the number of cycles planned (six or eight), anti-CD20 antibody (rituximab or obinutuzumab), and IPI categories (0–2, 3, or 4–5; appendix pp 11, 12). Four (6%) of 66 patients with previously untreated diffuse large B-cell lymphoma treated with polatuzumab vedotin 1·8 mg/kg died (figure 2B); two (3%) as a consequence of grade 5 adverse events (complications of atrial fibrillation and septic shock) and two (3%) because of disease progression. 12-month overall survival (figure 2B) was 94% (88–100), 12-month event-free survival was 80% (71–90), and the proportion of responses ongoing at 12 months was 95% (95% CI 89–100; figure 2C).

Among 66 patients with previously untreated diffuse large B-cell lymphoma treated at the recommended phase 2 dose, 51 (77%) were assessable for cell of origin; 16 (31%) were found to have activated B-cell-like subtype, 28 (55%) to have germinal centre B-cell-like type, and seven (14%) to have unclassified cell of origin. Double expression of MYC and BCL2 was evaluable in 41 patients, of whom 13 (32%) were characterised as double-expressor lymphoma. 25 (89%) of 28 patients

with germinal centre B-cell-like subtype and 13 (81%) of 16 patients with activated B-cell-like subtype achieved a complete response at end of treatment (table 4) and progression-free survival was similar by cell of origin and by double expression of MYC and BCL2 proteins (appendix pp 12–13).

In prespecified exploratory analyses, biomarker-evaluable specimens were assessed for CD79b expression by immunohistochemistry relative to response measurements, including change in sum of the product diameters of target lesions and progression-free survival (figure 3A, B). 33 patients with CD79b immunohistochemistry (H-score median 180 [IQR 91–230], mean 167 [SD 78]) and corresponding decreases in the sum of the product diameters and 38 patients with CD79b immunohistochemistry (H-score median 171 [IQR 93–229], mean 163 [SD 77]) and corresponding progression-free survival were assessed. All tumour samples tested were positive for CD79b expression (H-score range 35–295). We observed no association between CD79b protein levels and response to treatment and progression-free survival (figure 3A, B). Similarly, parallel analysis of CD79b RNA expression showed no association with response and progression-free survival (figure 3C, D).

Discussion

Activity of polatuzumab vedotin has been shown[11,15] in patients with heavily pretreated, relapsed, and refractory diffuse large B-cell lymphoma. The findings from this study show that the combination of polatuzumab vedotin with an anti-CD20 antibody and CHP has a safety profile, similar to that of R-CHOP or G-CHOP, and preliminary clinical activity. Our findings suggest that polatuzumab vedotin could be incorporated into immunochemotherapy in the frontline treatment of diffuse large B-cell lymphoma.

Although the recommended phase 2 dose in an 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 established the recommended phase 2 dose for polatuzumab vedotin when combined with immunochemotherapy to be 1·8 mg/kg given every 21 days. Overall, the long half-life, small steady-state volume of distribution, low clearance for antibody-conjugated monomethyl auristatin E, and the low concentrations and delayed formation of unconjugated monomethyl auristatin E are largely consistent with the pharmacokinetic properties of polatuzumab vedotin as monotherapy in patients with B-cell non-Hodgkin lymphoma.[11] Population pharmacokinetic analysis confirmed that there is no clinically relevant effect of the combination with CHP or of the treatment-naive condition on the pharmacokinetics of antibody-conjugated or unconjugated monomethyl auristatin E (Lu D, unpublished). Moreover, plasma concentrations of cyclophosphamide and doxorubicin at cycle 3 were similar to those at cycle 1, suggesting a low risk of polatuzumab vedotin affecting the pharmacokinetics of these drugs when used in combination.

The safety profile observed in this study also suggests that the incorporation of polatuzumab vedotin at

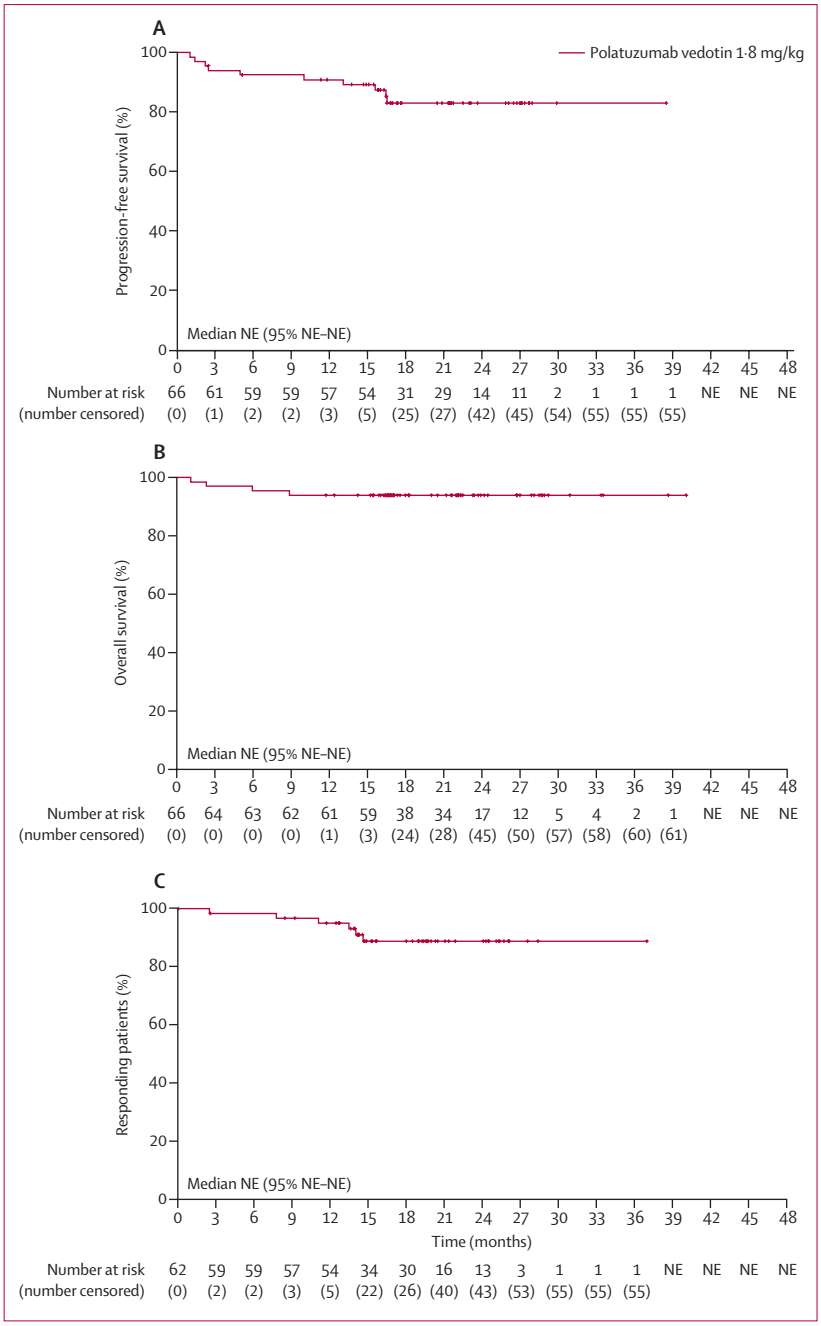

Figure 2: **Progression-free survival (A), overall survival (B), and response duration (C) in previously untreated patients with diffuse large B-cell lymphoma who received polatuzumab vedotin 1·8 mg/kg with immunochemotherapy (R-CHP or G-CHP)**

Progression-free survival (A) and overall survival (B) were assessed from study treatment initiation and response duration (C) from first documented response. Censoring occurred (A) at tumour assessment (by CT, MRI, or PET imaging) or (B) by telephone contact, clinical visits, or other assessments that document survival. n=66. R-CHP=rituximab, cyclophosphamide, doxorubicin, and prednisone. G-CHP=obinutuzumab, cyclophosphamide, doxorubicin, and prednisone. NE=not estimable.

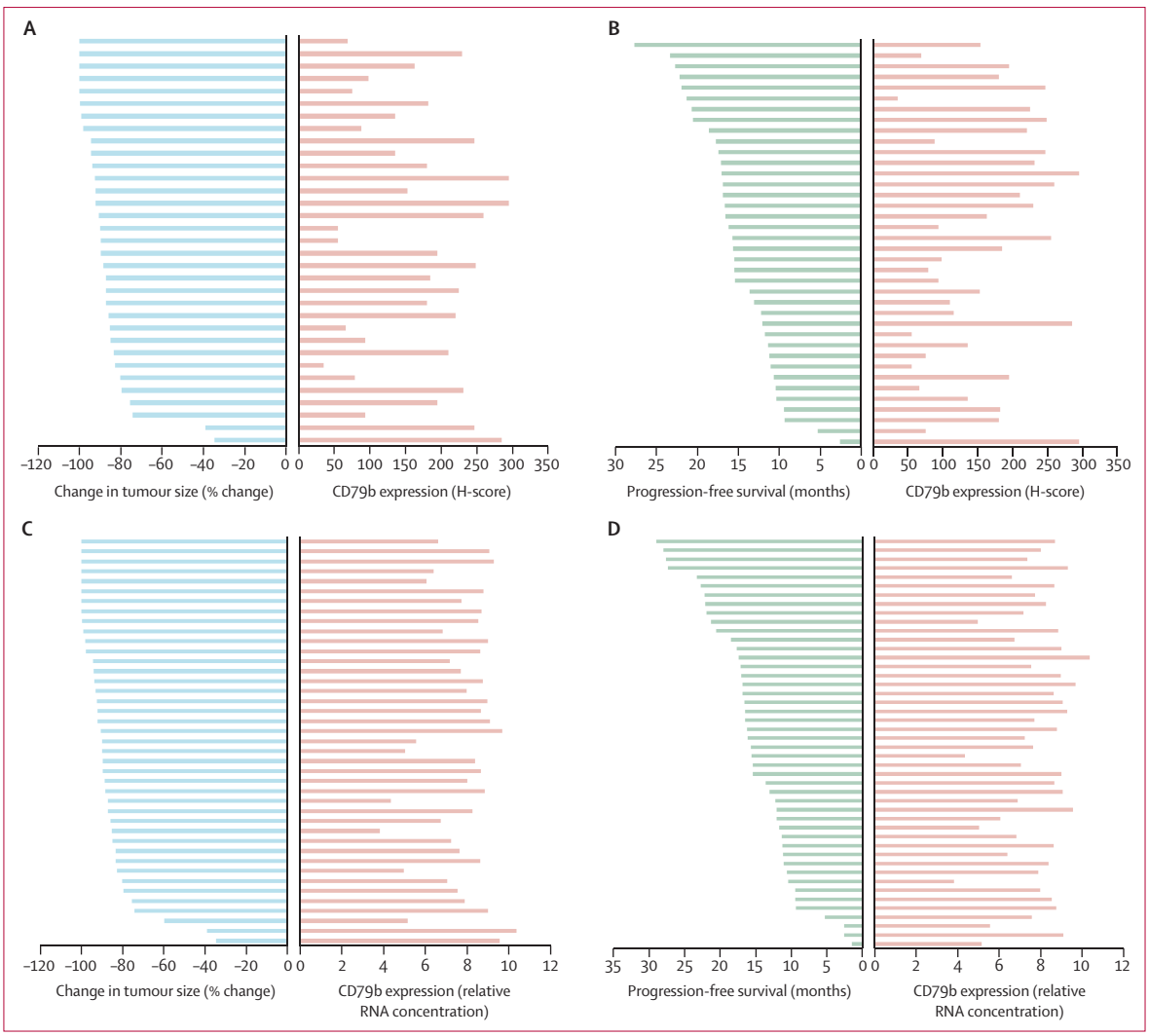

Figure 3: **CD79b expression by immunohistochemistry or RNA expression and responses to treatment**
CD79b expression (assessed by immunohistochemistry) and response assessed by tumour shrinkage by change in sum of the product diameters of target lesions (A), or progression-free survival (B). CD79b expression (assessed by RNA) and response assessed by tumour shrinkage by change in sum of the product diameters of target lesions (C), or progression-free survival (D).

1·8 mg/kg in the immunochemotherapy for diffuse large B-cell lymphoma does not alter the safety profile from that reported with R-CHOP or G-CHOP as described in the recent GOYA study.[12] Polatuzumab vedotin is known to cause myelosuppression and peripheral neuropathy when delivered as a single drug[11] in a heavily pretreated population; however, the combination of polatuzumab vedotin with immunochemotherapy did not seem to produce notable differences in key grade 3–5 adverse events relative to R-CHOP or G-CHOP as described in the GOYA study,[12] such as neutropenia (prevalence 46–55%), febrile neutropenia (15–18%), and infections (16–19%). A possible increase of grade 3–4 thrombocytopenia with polatuzumab vedotin plus R-CHP or 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 by the incorporation of polatuzumab vedotin in the treatment.

In view of its anti-tubulin mechanism of action, monomethyl auristatin E (polatuzumab vedotin's conjugate) is a rational replacement for vincristine in a CHOP-based regimen. As monomethyl auristatin E has a mode of action similar to that of vincristine, we monitored neurotoxicity closely during the study. Peripheral neuropathy was manageable with dose modifications and supportive care. The frequency of grade 3–4 peripheral neuropathy (3%) was in the range observed in large cohorts of patients treated with R-CHOP (5–7%).[16,17] The neuropathy experienced by patients was primarily dependent on dose and cumulative exposure of polatuzumab vedotin. Among

patients who received more than six cycles of study treatment, the prevalence of grade 2 or 3 peripheral neuropathy was higher than that observed among patients who received six or fewer cycles, supporting the exposure-based, cumulative nature of this treatment-emergent adverse event and also indicating the future use of six doses of polatuzumab vedotin at 1·8 mg/kg with immunochemotherapy. Moreover, of the 27 patients with diffuse large B-cell lymphoma treated at the recommended phase 2 dose who experienced any grade peripheral neuropathy, 20 (74%) patients had resolved peripheral neuropathy at data cutoff, with all patients having discontinued or completed study treatment.

We observed a high proportion of characteristics prognostic for poor outcomes in patients with previously untreated diffuse large B-cell lymphoma who received polatuzumab vedotin at 1·8 mg/kg and immunochemotherapy. These characteristics included a median age of 67·5 years (IQR 64–74), an ECOG performance status of 2 (in 29% of patients), and an IPI score of 3–5 (in 65%). These characteristics suggested that patients treated in this study would be likely to have increased prevalence of treatment-emergent adverse events, an outcome that was not observed in comparison with recent studies.[12]

The activity of polatuzumab vedotin at the recommended phase 2 dose could also be compared with that seen in the recent GOYA trial. Since the efficacy of the two anti-CD20 monoclonal antibodies used in this study—rituximab and obinutuzumab—were expected to be similar in previously untreated diffuse large B-cell lymphoma, our early activity results can mainly be attributed to the incorporation of polatuzumab vedotin in the immunochemotherapy. Patients in our study were older than those in the control group of the GOYA study[12] (67·5 years *vs* 62 years) and more of them had an IPI score of 4–5 (33% *vs* 16%). Additionally, a higher proportion of patients in this study achieved a complete response (77% *vs* 58%) and progression-free survival 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 diffuse large B-cell lymphoma subsets evaluated. Response to treatment and progression-free survival did not seem to be associated with CD79b expression. This observation is consistent with previous in-vitro studies and clinical trials, in which polatuzumab activity had a high cytotoxicity in B-cell non-Hodgkin lymphoma, independent of CD79b expression,[10] suggesting that identification of this marker might not be needed in subsequent studies of polatuzumab vedotin in diffuse large B-cell lymphoma. The percentage of patients with germinal centre B-cell-like subtype (55%) could be considered high in a population with a median age of 67·5 years. However, this proportion is broadly consistent with that found in 540 (58%) of 933 patients studied in the GOYA trial, which used the same gene-expression method.[12] The proportions of patients with a response and with progression-free survival were similar across the biological subsets of diffuse large B-cell lymphoma, which included the activated B-cell-like and germinal centre B-cell-like subtypes and those with or without double expression of BCL2 and MYC, although the small number of patients does not allow us to draw general conclusions. An ongoing phase 3 study aims to assess whether regimens including polatuzumab vedotin could overcome some of the prognostic implications across biological subsets of diffuse large B-cell lymphoma.

The current study has several limitations. First, although the study includes different regimens and different doses of polatuzumab vedotin, it is not a randomised study designed to enable comparisons. Second, 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 diffuse large B-cell lymphoma, necessitates a larger study. Finally, the duration of follow-up at the data cutoff date was short (in the context of a curative setting). However, the activity observed is promising, particularly in the context of high-risk patients, in terms of both patient risk and biological disease characteristics.

Contemporary clinical trials[18,19] are focusing on specific biological subtypes of diffuse large B-cell lymphoma, but the availability of a regimen that improves the outcomes for all patients with diffuse large B-cell lymphoma remains an unmet need. In this context, a phase 3 trial is being done to compare polatuzumab vedotin plus R-CHP with R-CHOP alone in previously untreated diffuse large B-cell lymphoma (POLARIX study, NCT03274492).

Contributors

All authors collected, analysed, and interpreted the data, and wrote the manuscript. HT, FM, GS, MY, and CL searched the literature. DL, EP, JH, and JPS designed the study. EP collected and analysed the data associated with biomarkers.

Declaration of interests

HT reports personal fees and non-financial support from F Hoffmann-La Roche, and personal fees from Karyopharm, AstraZeneca, and Bristol-Myers Squibb, outside the submitted work. FM reports personal fees from F Hoffmann-La Roche/Genentech, Celgene, Gilead, Janssen, and Bristol-Myers Squibb, outside the submitted work. NLB reports research funding from Affimed, Bristol-Myers Squibb, Celgene, Forty Seven, Genentech, Gilead, Janssen, KITE, Merck, Millennnium, Pharmacyclics, and Seattle Genetics, and advisory board fees from Pfizer and Acerta, outside the submitted work. AM reports grants from F Hoffmann-La Roche, Merck, Bristol-Myers Squibb, Epizyme, Incyte, Seattle Genetics, Takeda, Juno/Celegene, Forty Seven, Gilead, and personal fees from Bristol-Myers Squibb, Kite, Spectrum, AstraZeneca, Gilead, outside the submitted work. GS reports grants, personal fees, and non-financial support from F Hoffmann-La Roche during the conduct of the study; and personal fees from Amgen, Bristol-Myers Squibb, 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 during the conduct of the study, and 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, Pfizer, Juno/Celgene, Bristol-Myers Squibb, Genentech, and Kyowa, outside the

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Data sharing

Qualified researchers may request access to individual patient level data through the clinical study data request platform. Further details on Roche's criteria for eligible studies and on Roche's Global Policy on the Sharing of Clinical Information and on how to request access to related clinical study documents are available.

For the **data request platform** see www.clinicalstudydatarequest.com

For **Roche's criteria for eligible studies** see https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx

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