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Polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed/refractory non-Hodgkin lymphoma: final results from a phase 2 randomised study (ROMULUS)

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Running header (65 characters, or fewer): R-pola or R-pina in relapsed/refractory non-
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Research into context

Evidence before this study

Despite the significantly improved survival with rituximab-based treatment regimens, a need remains for new agents to effectively manage non-Hodgkin lymphoma, particularly for high-risk or relapsed/refractory patients. Antibody–drug conjugates (ADCs) provide targeted drug delivery to tumours to broaden the therapeutic index of a cytotoxic agent, such as monomethyl auristatin E (MMAE). Therefore, ADCs have the potential to increase intracellular concentrations of the cytotoxic agent, while sparing tissues that do not express the target. A search for articles posted in PubMed from Jan 1, 2000, to Dec 31, 2016, with the terms “antibody–drug conjugate” or “conjugate” or “immunoconjugate” and “auristatin” identified a number of MMAE ADCs in development for non-Hodgkin lymphoma. Specifically, we identified 89 clinical trials posted in PubMed using the terms “immunoconjugate” or “antibody drug conjugate” and “lymphoma” (limited to clinical trials, randomised control trials and clinical studies), including trials with brentuximab vedotin (targeting CD30), coltuximab ravtansine (targeting CD19), inotuzumab ozogamicin (targeting CD22), polatuzumab vedotin (targeting CD79b), and SGN75 (targeting CD70). A further ADC, denintuzumab mafodotin, which targets CD19, is also in clinical development. All of these ADCs are currently in development for non-Hodgkin lymphoma, but with the exception of brentuximab vedotin, none are currently available for the treatment of non-Hodgkin lymphoma.

CD79b and CD22 are expressed on most B-cell haematological malignancies and are thus potential targets for ADCs, as demonstrated by the three preclinical publications identified on PubMed using the terms “antibody–drug conjugate” or “immunoconjugate” and “CD79B”

and “CD22”. Polatuzumab vedotin (pola) and pinatuzumab vedotin (pina) are ADCs consisting of the potent microtubule inhibitor MMAE conjugated to anti-CD79b and CD22 monoclonal antibodies, respectively, via a protease-cleavable peptide linker. In two phase 1 studies in patients with relapsed/refractory non-Hodgkin lymphoma, single-agent pina and pola demonstrated encouraging clinical activity with a generally acceptable safety and tolerability profile as single agents and, in a small number of patients, in combination with rituximab (R). The findings of these small and heterogeneous patient populations in separate phase 1 studies, which demonstrated the safety and tolerability of the ADCs with rituximab, together with evidence of an add on effect of R on the clinical activity of the anti-CD22 ADC inotuzumab ozogamicin in patients with non-Hodgkin lymphoma, led to development of the ROMULUS study. The study objective was to further expand on these initial findings in a way that addressed the patient heterogeneity characteristic of first-in-human phase 1 studies.

Added value of this study

Although the phase 1 studies suggested generally similar clinical activity between pina and pola, direct comparisons between the two ADCs were confounded by limited patient numbers and different baseline characteristics between the two trials. This randomised phase 2 clinical study, therefore, provides additional evidence of the clinical activity and safety profile of R-pola and R-pina in patients with relapsed/refractory diffuse large B-cell lymphoma and relapsed/refractory follicular lymphoma. Whereas the ADCs were associated with similar objective responses, patients treated with R-pola tended to have longer durations of response than those receiving R-pina. In patients with follicular lymphoma, these differences may be due to differing patient baseline characteristics rather than inherent differences in clinical activity. However, in patients with diffuse large B-cell lymphoma, age, number of prior therapies, and the proportion of refractory patients were similar in both arms. Furthermore,

apart from the imbalance in the number of patients with an Eastern Cooperative Oncology Group (ECOG) performance score of 2, the proportion of adverse factors such as bulky disease and activated B-cell-like (ABC) subtype was numerically higher in the pola arm, possibly indicating better disease control with this latter agent. The outcomes achieved with R-pola in the patients with treatment-refractory diffuse large B-cell lymphoma in particular, who constituted over two-thirds of the diffuse large B-cell lymphoma patient cohort in this study, compare favourably with those for other novel anti-lymphoma agents. This study confirmed that the ADCs have activity in patients with diffuse large B-cell lymphoma regardless of cell of origin (COO) subtype, a finding with clinical implications for the design of future phase 3 trials. Also of clinical importance is the finding that expression of CD79b and CD22 in the targeted lymphomas had no correlation with antitumour activity of R-pola and R-pina. The safety/tolerability profiles of R-pina and R-pola confirmed the data from the phase 1 trials, with neutropenia being the most common grade 3–4 adverse event. Consistent with the microtubule inhibitory action of MMAE, peripheral neuropathy was also a frequent adverse event, with the temporal evolution of peripheral neuropathy suggesting a cumulative effect of repeated administrations of pola or pina.

Implications of all the available evidence

These findings make pola one of the most promising novel candidates for further clinical evaluation in combination regimens in treatment-refractory patients and also in a first-line setting in B-cell non-Hodgkin lymphoma. Clinical development is continuing with pola, with studies investigating this ADC in combination with other anti-lymphoma agents in patients with non-Hodgkin lymphoma. Pola is currently being investigated in a randomised phase 3 study as first-line diffuse large B-cell lymphoma treatment in combination with ritximabi, cyclophosphamide, doxorubicin, and prednisone (R-CHP-Pola) and compared with the

standard R-CHOP regimen (POLARIX study, NCT03274492). The POLARIX study is one of the first clinical trials where the goal is to replace systemic chemotherapy agents with a novel agent, such as an ADC, with the potential of improving on the efficacy as well as safety and tolerability of treatment regimens for patients with non-Hodgkin lymphoma.

Given the apparent cumulative nature of peripheral neuropathy observed during this trial,²⁰ as well as exposure-response modelling data, these trials are employing a risk mitigation strategy with the treatment regimen limited to 1.8 mg/kg for a maximum of six to eight cycles.

Abstract (250 words)

Purpose Antibody–drug conjugates (ADCs), polatuzumab vedotin (pola) and pinatuzumab vedotin (pina), demonstrated clinical activity/tolerability in phase 1 trials. This multicentre, open-label phase 1b/2 study (ROMULUS; NCT01691898) evaluated rituximab (R)-pola/-pina in patients with relapsed/refractory diffuse large B-cell lymphoma and follicular lymphoma.

Patients and methods Patients were randomised 1:1 using a dynamic hierarchical randomisation scheme to R-pola or R-pina (R, 375 mg/m²; ADCs, 2·4 mg/kg) every 3 weeks until progressive disease/unacceptable toxicity up to 1 year. Primary objectives: safety/tolerability and antitumour response.

Results

Eighty-one patients with diffuse large B-cell lymphoma and 42 with follicular lymphoma were randomised (Sept 27, 2012–Oct 10, 2013), with 81 and 41 patients, respectively, eligible for analysis. Best objective response rates (ORRs) in the diffuse large B-cell lymphoma cohort (n=81) were 60% (n=25/42, 95% confidence interval [CI]: 43–74; complete response: 26% [n=11/42, 95% CI: 14–42]) for R-pina and 54% (n=21/39, 95% CI: 37–70; CR: 21% [n=8/39, 95% CI: 9–36]) for R-pola; respective ORRs (complete responses) in the follicular lymphoma cohort (n=41) were 62% (n=13/21, 95% CI: 38–82) (5%, n=1/21, 95% CI: 0·1–24) and 70% (n=14/20, 95% CI: 46–88) (45%, n=9/20, 95% CI: 23–68). In diffuse large B-cell lymphoma, grade 3–5 adverse events occurred in 79% (n=33/42) receiving R-pina, including nine (21·4%) grade 5 adverse events (five infection-related), and in 77% (n=30/39) receiving R-pola (no grade 5 adverse events). In follicular lymphoma,

grade 3–5 adverse events occurred in 62% (n=13/21) receiving R-pina and 50% (n=10/20) receiving R-pola (one grade 5 adverse event).

Conclusion R-pina/-pola are potential treatment options in this setting. Pola was selected for further development in non-Hodgkin lymphoma, partly due to higher complete response rates and longer durations of response than pina, and an overall benefit-risk favouring R-pola.

Funding F. Hoffmann-La Roche Ltd.

Introduction

Despite significantly improved survival with rituximab (R)-based treatment regimens, non-Hodgkin lymphoma remains an area of unmet medical need, particularly for high-risk patients and those with relapsed/refractory disease.^{1,2} Antibody–drug conjugates (ADCs), which provide targeted cytotoxic drug delivery to tumours with the goal of broadening their therapeutic index compared to systemic chemotherapy, are currently being evaluated in non-Hodgkin lymphoma.³ Polatuzumab vedotin (DCDS4501A; pola; F. Hoffmann La-Roche/Genentech Inc.) and pinatuzumab vedotin (DCDT2980S; pina; F. Hoffmann La-Roche/Genentech Inc.) comprise the microtubule inhibitor (monomethyl auristatin E; MMAE) conjugated via a protease-cleavable peptide linker to monoclonal antibodies targeting the B-cell lineage antigens CD79b and CD22, respectively.³⁻⁵ Pola and pina were manufactured by BSP Pharmaceuticals (address: S.r.l Via Appia Km 65.561 04013 Latina Scalo (LT) Italy).

Although both pola and pina have broad activity across non-Hodgkin lymphoma cell lines,^{4,5} some cell lines exhibited sensitivity to either pina or pola, but not both.⁶ Furthermore, expression levels of CD79b and CD22 are not strongly correlated with the cytotoxic activity of either ADC, suggesting that biological factors other than target expression confer ADC sensitivity.^{5,6}

In separate phase 1 studies in relapsed/refractory non-Hodgkin lymphoma patients, pina and pola each demonstrated single-agent clinical activity with acceptable safety/tolerability profiles; these studies also preliminarily demonstrated tolerability when pina or pola was combined with R.^{7,8} Because the addition of R to an ADC may increase clinical activity without a significant increase in toxicity,⁹ and to assess the clinical activity of pina and pola

in similarly selected patient populations, we conducted a randomised, phase 2 study evaluating the clinical activity and safety of pina and pola combined with R in patients with relapsed/refractory diffuse large B-cell lymphoma or relapsed/refractory follicular lymphoma. We additionally assessed the impact of relevant biomarkers on the clinical activity of R-ADC treatment.

Methods

Study design and participants

ROMULUS was a randomised, multicentre, open-label phase 2 study. The study design and sample size reflected the primary goal of signal seeking for clinical activity of the two treatments in similar patient populations; consequently, a comparative significance level between the treatment arms was not prospectively defined. Rituximab 375 mg/m² plus ADC (pina or pola, 2·4 mg/kg) was administered intravenously every 21 days until progressive disease or unacceptable toxicity, to a maximum of 1 year. Patients with progressive disease with sufficient recovery from any treatment-emergent toxicity with the initial ADC regimen were eligible to receive crossover treatment consisting of the alternative ADC alone or combined with R. Crossover patients were treated as per the intention-to-treat principle; safety and efficacy endpoints were reported for the treatment groups where the patients were originally assigned.

Eligible patients (figure 1) had histologically confirmed diagnosis of relapsed/refractory diffuse large B-cell lymphoma or relapsed/refractory grade 1–3a follicular lymphoma. Additional eligibility criteria included age ≥ 18 years, ≥ 1 bi-dimensionally measurable lesion (>1.5 cm in its largest dimension by computerised tomography scan or MRI), Eastern Cooperative Oncology Group (ECOG) performance status 0–2, life expectancy of ≥ 12 weeks,

and acceptable hepatic and haematological function. Patients were excluded if they had received prior monoclonal antibody-based or radioimmunoconjugate therapy within the previous 4 weeks, radiotherapy, chemotherapy, immunosuppressive therapy, or investigational anti-cancer agent within the previous 2 weeks, prior autologous stem cell transplant (Auto-SCT) within the previous 100 days, or eligibility for Auto-SCT, or any prior allogeneic stem cell transplant. Additional exclusion criteria included history of transformation of indolent diseases to DLBCL, current grade >1 peripheral neuropathy, uncontrolled concomitant diseases, active infection, or major surgery within the previous 6 weeks, ongoing corticosteroid use >30 mg/day prednisone, or equivalent, and pregnant or lactating women.

Patients with follicular lymphoma were stratified by R-refractory (defined as no response or relapse <6 months from last R treatment) versus relapsed disease (disease relapse after response \geq 6 months from last R treatment). Patients with diffuse large B-cell lymphoma were stratified by 1 versus >1 prior therapy. Patients who received 1 prior therapy were further stratified by no response or relapse <12 versus \geq 12 months from start of therapy; patients with >1 prior therapy were further stratified by refractory (defined as no response or progressive disease <6 months from start of most recent therapy) versus relapsed disease (disease relapse after initial response \geq 6 months from start of most recent therapy).

Stratification factors were implemented to ensure the balance of the pola and pina arms at randomisation and were not reflected in the analyses. Median survival of patients with relapsed/refractory diffuse large B-cell lymphoma is approximately 9–12 months with R-GemOx and R-Benda.¹⁰⁻¹² For relapsed/refractory follicular lymphoma, estimated progression-free survival (PFS) is heterogeneous depending on a number of clinicogenomic

factors, however, data from the PI3K delta inhibitor literature shows that median PFS is approximately 11 months.^{13,14}

Relevant institutional review boards and ethics committees of each participating centre approved the trial protocols. All patients provided written informed consent. The protocol is available at clinicaltrials.gov.

Randomisation and masking

Patients were assigned 1:1 to R combined with pina (R-pina) or pola (R-pola) using a dynamic hierarchical randomisation scheme with disease-specified stratification factors applied separately to each disease indication to minimise selection bias. A password protected interactive voice or web-based response system administered by an independent vendor was used to randomize patients. The treatment allocation was automatically assigned to a patient only when the patient was enrolled by the site. The sequence of the randomisation was not available to either the investigators or sponsor before the enrolled. Treatment allocations were not masked to the investigator, patients or sponsor after the patients were enrolled and randomized.

Procedures

Investigator-based antitumour response assessments were performed in accordance with revised International Working Group criteria for malignant lymphoma¹⁵ every 3 months, and within 30 days after the last study drug infusion.

Treatment-emergent adverse events were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Haematology and serum chemistries were assessed weekly during the first four treatment cycles and on days 1 and 15 of each cycle thereafter.

Pharmacokinetic profiles of R, pina, and pola, characterised after the cycle 1 dose, have been previously published.⁷

Targeted gene expression and immunohistochemistry (IHC) were performed on archival/baseline and on-treatment biopsy formalin-fixed paraffin-embedded specimens by quantitative RT-PCR (qtRT-PCR) using the Luminex Fluidigm platform and conventional IHC techniques, respectively.

Patients were discontinued from study if they experienced progressive disease as defined by the pre-specified response and progression criteria. Patients could continue crossover treatment following documentation of the first progressive disease event, but were discontinued from the study if they experienced a second progressive disease event on the crossover treatment. The investigator had the right to discontinue a patient from the study for any medical condition that the investigator determined may have jeopardised the patient's safety if they continued in the study, for reasons of non-compliance (e.g., missed doses, visits), pregnancy, or if it was in the best interest of the patient.

Outcomes

The primary objectives of the study were to assess the antitumour activity, safety, and tolerability of R-pina and R-pola in patients with relapsed/refractory diffuse large B-cell

lymphoma or relapsed/refractory follicular lymphoma. Pharmacokinetic and biomarker objectives included: assessing anti-drug antibody (ADA) formation against pina and pola; characterising the pharmacokinetics of pina, pola, and R; and preliminary assessment of potential prognostic and predictive biomarkers of R-ADC activity. The exploratory patient quality of life objective was to assess patient tolerability to study treatment and the impact of study treatment on patient-reported outcomes.

Statistical analysis

Planned target accrual was 120 patients in two separate cohorts (n=40 relapsed/refractory follicular lymphoma, n=80 relapsed/refractory diffuse large B-cell lymphoma). Target sample sizes were determined to provide sufficient precision in estimating separately the objective response rate (ORR) with R-pina or R-pola. An observed response rate of 40% would result in a 90% confidence interval (CI) of ~22–58% for the follicular lymphoma cohort, and ~27–53% for the diffuse large B-cell lymphoma cohort. For treatment-emergent adverse events, with 40 patients there was an 87% chance of observing ≥ 1 adverse event, with a true incidence of 5%.

ORRs in patients with baseline measurable disease and ≥ 1 post-treatment tumour assessment were calculated on the basis of best response at the data cutoff date. PFS, duration of response (DOR), and overall survival were analysed by the Kaplan-Meier method and defined as time from the day of enrolment/randomisation (PFS, overall survival) or response (DOR) to progressive disease or death; if these events were absent, PFS and DOR were censored on the day of the last tumour assessment. Safety analyses were based on the safety-evaluable population, which included all patients who received ≥ 1 dose of study treatment.

SAS® version 9.2 (SAS Institute, Cary, NC, USA) was used for statistical analyses, and Phoenix® WinNonlin® version 6.4 (Certara USA, Inc., Princeton, NJ, USA) for non-compartmental pharmacokinetic analysis.

The study is registered with ClinicalTrials.gov: NCT01691898.

Role of the funding source

This study was supported by F. Hoffmann-La Roche Ltd. It was designed by the funder (F. Hoffmann-La Roche Ltd.) and academic authors. Data were collected by the academic authors and their research teams, and were interpreted by the authors and funder. All authors had full access to the study data. The funder provided medical writing support. The corresponding author had full access to all the study data and final responsibility for the decision to submit for publication.

Results

Between Sept 27, 2012 and Oct 10, 2013, 81 patients with diffuse large B-cell lymphoma were randomised to treatment with R-pina (n=42) or R-pola (n=39); 42 patients with follicular lymphoma were randomised to receive R-pina (n=22) or R-pola (n=20), (figure 1; page 1 of the webappendix). However, one randomised patient with follicular lymphoma did not receive R-pina, leaving 41 patients with follicular lymphoma and 81 patients with diffuse large B-cell lymphoma eligible for analysis.

The data cutoff date for response, PFS, and DOR analyses was April 21, 2016; the data cutoff date for overall survival was April 10, 2017. Within each non-Hodgkin lymphoma cohort, patient stratification resulted in baseline patient demographics and clinical characteristics in the treatment arms being generally similar given the relatively small number of patients randomised to each cohort (table 1).

Among safety-evaluable patients, the median (range) numbers of cycles of R-pina and R-pola treatment were seven (1–17) and six (1–17), respectively, in the diffuse large B-cell lymphoma cohort, and seven (1–15) and ten (3–17), respectively, in the follicular lymphoma cohort. Pina and pola were discontinued in 79% (n=33/42) and 80% (n=31/39) of patients, respectively, with diffuse large B-cell lymphoma, and in 91% (n=19/21) and 85% (n=17/20), respectively, with follicular lymphoma. The most common reasons for treatment discontinuation were progressive disease (38%, n=31/81) in patients with diffuse large B-cell lymphoma and adverse events (62%, n=26/42) in those with follicular lymphoma (figure 1).

As summarised in table 2, objective and complete responses in relapsed/refractory diffuse large B-cell lymphoma were 60% (n=25/42, 95% CI: 43–74) and 26% (n=11/42, 95% CI: 14–42), and 54% (n=21/39, 95% CI: 37–70) and 21% (n=8/39, 95% CI: 9–36), for R-pina and R-pola, respectively. Individual antitumour responses according to disease, treatment arm, and R-refractory, non-refractory, or other treatment-refractory status are summarised in figure 2. Median PFS was 5.4 (95% CI: 3.9–10.6) and 5.6 (95% CI: 4.3–12.8) months for R-pina and R-pola, respectively (figure 3); median DOR was longer for R-pola (6.2 [95% CI: 3.6–12.4] and 13.4 [95% CI: 6.5–21.2] months for R-pina and R-pola, respectively; figure 4). Median overall survival among all patients was 16.5 (95% CI: 7.5–32.5) and 20.1 (95% CI: 10.4–38.6) months for R-pina and R-pola, respectively (figure 5); median overall

survival among treatment-refractory patients was 11.9 (95% CI: 6.3–25.0) and 11.7 (95% CI: 5.3–23.9) months for R-pina and R-pola, respectively.

Objective and complete responses in relapsed/refractory follicular lymphoma were 62% (n=13/21, 95% CI: 38–82) and 5% (n=1/21, 95% CI: 0.1–24), and 70% (n=14/20, 95% CI: 46–88) and 45% (n=9/20, 95% CI: 23–68), for R-pina and R-pola, respectively. Median PFS was 12.7 (95% CI: 8.9–27.5) and 15.3 (95% CI: 12.2–25.1) months for R-pina and R-pola; median DOR was 6.5 (95% CI: 6.0–11.1) and 9.4 (95% CI: 7.2–not estimable) months for R-pina and R-pola, respectively. Median overall survival was not reached in either follicular lymphoma population. Two-year overall survival among all patients was 90.5% (95% CI: 77.9–100) and 87.8% (95% CI: 72.0–100) for R-pina and R-pola, respectively.

Six patients who progressed on therapy with R-pola or R-pina received crossover treatment, including five patients with diffuse large B-cell lymphoma. Five of the six (83%) patients progressed following crossover. The sixth patient died after receiving only one cycle of crossover treatment prior to the first response assessment (table S2, page 2 of the webappendix). As of 21 April 2016, median duration of follow-up in diffuse large B-cell lymphoma was 10.9 months (95% CI: 5.9–22.6; range 0.46 to 41.4) for R-pina and 17.4 months (95% CI: 7.8–30.0; range 0.79 to 38.4) for R-pola. In follicular lymphoma, median duration of follow-up was NE (95% CI: 27.4–22.4; range 1.6 to 40.2) for R-pina and NE (95% CI: 22.4–NE; range 7.7 to 37.1) for R-pola.

The most common adverse events by grade with greater than 10% incidence are summarised on in tables S3 and S4 (pages 3 and 4 of the webappendix). Serious and grade 3–5 adverse events and the frequency of treatment discontinuation, dose reductions, or dose delays due to

adverse events are summarised in table 3; specific adverse events are further described in table S5 (page 5 of the webappendix).

Neutropenia was the most frequently observed grade 3–4 adverse event. Median times to first onset and duration of first grade ≥ 3 neutropenia were similar across groups (table S6, page 6 of the webappendix). Most patients with neutropenia received growth factor support. Febrile neutropenia was reported in one patient in the R-pina arm (grade 4) and in two patients in the R-pola arm (both grade 3) among the patients with diffuse large B-cell lymphoma, and in one patient (grade 3) in the R-pina group of the follicular lymphoma cohort. Twelve patients with diffuse large B-cell lymphoma treated with R-pina reported grade 3–5 infections, including two grade 5 infections; three had concomitant grade 3–4 neutropenia. No concomitant infections were reported in patients with diffuse large B-cell lymphoma who developed neutropenia with R-pola. Among patients with follicular lymphoma, one case of transient febrile neutropenia concurrent with a grade 3 skin infection was reported with R-pina, which did not require treatment and did not affect study treatment administration.

Similar to the phase 1 studies,^{7,8} peripheral neuropathy was a common treatment-emergent adverse events (table 4). The temporal evolution of peripheral neuropathy indicates a cumulative effect of repeated administrations of pina and pola, ultimately leading to treatment discontinuations in 21% (n=9/42) and 18% (n=7/39) of diffuse large B-cell lymphoma patients and 48% (n=10/21) and 55% (n=11/20) of follicular lymphoma patients.

A post-hoc subgroup analysis (not prespecified in the protocol) of efficacy endpoints by age was conducted for both diffuse large B-cell lymphoma and follicular lymphoma. No trends in

safety or efficacy by age, or between the two treatment regimens was observed (see tables S7–S10 on pages 7–10 of the webappendix).

A total of 52 patients died, 27 in the R-pina and 25 in the R-pola arms, with the majority (46 deaths, 24 in the R-pina and 22 in the R-pola cohorts) in patients with diffuse large B-cell lymphoma. Most deaths (19 of 27 in the R-pina and 24 of 25 in the R-pola cohorts) were due to progressive disease. There were ten grade 5 adverse events in nine patients (21.4%) in the R-pina diffuse large B-cell lymphoma cohort, and one grade 5 adverse event in one patient (5.0%) in the R-pola follicular lymphoma cohort (table 3).

Previously published⁷ pharmacokinetic profiles of R, pina, and pola, characterised after the cycle 1 dose, are provided in table S11 on page 11 of the webappendix.

Antitumour activity of both R-pina and R-pola was observed across diffuse large B-cell lymphoma cell-of-origin (COO) subtypes (see page 12 of the webappendix). Antitumour activity in patients with diffuse large B-cell lymphoma with high levels of BCL2 protein expression was observed with R-pina and R-pola; however, no association between BCL2 expression and tumour shrinkage for either treatment regimen was observed.

There was no observed difference in RNA expression between CD22, CD79b, or BCL2 in relapsed/refractory diffuse large B-cell lymphoma or follicular lymphoma (page 16 of the webappendix [figure S1A]). Median protein expression of BCL2, CD22, and CD79b was comparable between follicular lymphoma and diffuse large B-cell lymphoma, although the range of CD22, CD79b, and BCL2 protein expression levels was wider in diffuse large B-cell lymphoma than in follicular lymphoma (figure S1B). No correlation between CD22 and

CD79b expression and tumour shrinkage for either pina or pola was observed (figure S2, page 17 of the webappendix).

Results of the patient-reported outcomes, MDASI baselines scores and deterioration at cycle 8 are reported in the webappendix (table S13, page 14 and table S14, page 15).

Discussion

In this non-comparative, randomised study, which was designed to assess the clinical activity of R-pina and R-pola in patient populations with minimal selection bias, R-pina and R-pola had comparable antitumour activity in relapsed/refractory diffuse large B-cell lymphoma and follicular lymphoma. Notable numerical differences were observed in the complete response rate in relapsed/refractory follicular lymphoma, which was 5% (n=1/21, 95% CI: 0.1–24) for R-pina and 45% (n=9/20, 95% CI: 23–68) for R-pola, and the median DOR in relapsed/refractory diffuse large B-cell lymphoma, which was 6.2 (95% CI: 3.6–12.4) months for R-pina and 13.4 (95% CI: 6.5–21.2) months for R-pola. Despite the incorporation of stratification factors, some imbalances in baseline characteristics may have contributed to the observed differences in the rates and durability of objective response. Further adjustment for the imbalanced factors and multivariate modelling were not possible due to the small sample size. The higher complete response rate observed in follicular lymphoma patients treated with R-pola may reflect the more favourable baseline characteristics, eg, less refractory and/or bulky disease, and fewer prior therapies than in the R-pina arm. However, among enrolled diffuse large B-cell lymphoma patients, age, number of prior therapies, and proportion of refractory patients were similar in both arms. Furthermore, apart from the imbalance in the proportion of ECOG performance status 2 patients, the proportion of adverse factors such as bulky disease and activated B-cell-like (ABC) subtype was

numerically higher in the R-pola arm. The longer observed DOR with R-pola in light of these imbalances suggests better disease control with this regimen although this did not translate to striking differences in PFS or overall survival.

Specifically in relapsed/refractory diffuse large B-cell lymphoma, the clinical activities of R-pina and R-pola in aggregate is encouraging given the heavily pretreated non-Hodgkin lymphoma patient population, in which many patients were refractory to their last prior therapy. Among patients with refractory diffuse large B-cell lymphoma, complete response rates of 22% (n=7/32, 95% CI: 9–40) and 16% (n=5/31, 95% CI: 5–34), and median overall survival rates of 11·9 (95% CI: 6·3–25·0) and 11·7 (95% CI: 5·3–23·9) months, with R-pina and R-pola, respectively, compare favourably to immunochemotherapy regimens reported in the SCHOLAR-1 study, in which a complete response rate of 7% and a median overall survival of 6·3 months were observed, although it should be noted that definitions of refractoriness slightly differ (no objective response or relapse within 6 months of last prior treatment used in this study *vs* progressive disease or stable disease as best response at any point during chemotherapy [≥ 4 cycles of first-line or 2 cycles of later-line therapy] or relapse ≤ 12 months of Auto-SCT in SCHOLAR-1).¹ Response and survival outcomes with R-pina and R-pola also compare favourably with other R-ADC combinations evaluated in relapsed/refractory diffuse large B-cell lymphoma.^{10,16} Treatment with R-inotuzumab ozogamicin resulted in an ORR/complete response of 41%/13% and median overall survival of 9·5 months,¹⁰ R-coltuximab ravtansine (SAR3419) resulted in an ORR/complete response of 31%/9%, and a median overall survival of 9 months.¹⁶

The most common treatment-emergent adverse events for both R-pina and R-pola were fatigue, diarrhoea, peripheral neuropathy, nausea, and neutropenia. Neutropenia was

predominantly grade 3 or 4, similar to what was observed in the phase 1 studies,^{7,8} but led to treatment discontinuation in only a single patient treated with R-pina in each of the diffuse large B-cell lymphoma and follicular lymphoma cohorts, and no patients treated with R-pola, indicating that in most cases neutropenia was transient and reversible with growth factor support. On the other hand, two of five deaths due to infection-related adverse events among patients with diffuse large B-cell lymphoma treated with R-pina occurred with concomitant grade 3–4 neutropenia; no concomitant infections with neutropenia were reported among diffuse large B-cell lymphoma patients treated with R-pola.

Adverse events other than neutropenia were predominantly of grade 1 or 2. Peripheral neuropathy, consistent with phase 1 results,^{7,8} was a frequent adverse event, linked to the microtubule inhibitory action of MMAE.¹⁷ No grade 4 peripheral neuropathy was observed, and rates of grade 3 peripheral neuropathy were comparable with those reported with brentuximab vedotin, which has the same linker-MMAE construct as pina and pola,¹⁸ and with bortezomib plus rituximab in relapsed follicular lymphoma.¹⁹ Treatment discontinuations resulting from peripheral neuropathy were high, with approximately 30% and 20% of patients with diffuse large B-cell lymphoma in the R-pina and R-pola arms discontinuing treatment, respectively. Higher rates of discontinuations from peripheral neuropathy were observed in follicular lymphoma patients (~70% and 60% in the R-pina and R-pola arms, respectively); however, it is not possible to meaningfully compare the rates of polyneuropathy because of prior vinca alkaloid exposure. Approximately half of the patients had peripheral neuropathy prior to commencing study treatment, with approximately one-third having grade 1 peripheral neuropathy at study entry. Given the apparent cumulative nature of peripheral neuropathy leading to study treatment discontinuations, and supported by an exposure-response analysis based on logistical regression and time-to-event analysis,^{20,21}

ongoing and future studies are being conducted with a lower ADC dose of 1.8 mg/kg limited to six to eight cycles.²⁰

Biomarker analyses were conducted to evaluate potential differential activity based on ADC target expression, BCL2 expression as a potential mechanism of ADC resistance, and diffuse large B-cell lymphoma COO subtypes. CD79b gene expression was generally higher than CD22, with the percentage of tumours expressing high levels of CD79b (3+ by IHC) higher than those expressing high levels of CD22. This finding may, however, be due to differences in the IHC assays rather than real differences in levels of antigen expression, because no correlation was observed between target expression and tumour shrinkage for either R-pina or R-pola. Furthermore, no significant difference between CD22, CD79b, or BCL2 expression in diffuse large B-cell lymphoma and follicular lymphoma was observed, indicating that none constitutes a major determinant of ADC activity. That deep objective responses were observed in BCL2-high (2+/3+ by IHC) with both R-ADC combinations warrants further evaluation given recent data indicating that high levels of BCL2 expression were individually a negative prognostic factor in diffuse large B-cell lymphoma.²² Finally, R-pina and R-pola demonstrated activity across diffuse large B-cell lymphoma COO subtypes with no apparent association between diffuse large B-cell lymphoma COO subtype and CD22 and CD79b expression. Unfortunately, we were unable to conduct analysis of double expressors according to IHC, or evaluate MYC plus BCL2 and/or BCL6 rearrangements (i.e., double- or triple-hit lymphomas), which is a limitation of the study. Also, soluble CD22 was not measured in this study.

The availability of two ADCs targeting B cells raised the interesting question of whether ADC resistance was mediated by target modulation versus MMAE resistance and, relatedly,

whether there was clinical activity of crossover treatment. No evidence of any clinical benefit with ADC crossover treatment was observed in six patients, suggesting that resistance to MMAE rather than to the antibody target is the primary driver of progression. Similar findings have been reported in patients with Hodgkin lymphoma who developed resistance to brentuximab vedotin without loss of target CD30 expression, consistent with in vitro demonstration of MMAE resistance in CD30-expressing cell lines.²³ These results reinforce the need for novel strategies to reduce the development of resistance to the cytotoxic component of ADCs.

Data from the ROMULUS study support both R-pina and R-pola as potentially clinically meaningful treatment options for patients with B-cell non-Hodgkin lymphoma. In particular, observed outcomes in refractory diffuse large B-cell lymphoma appear promising given this difficult-to-treat population. We acknowledge the limitations of this randomised phase 2 study, and therefore the decision to select pola for continued development in non-Hodgkin lymphoma was based on a comprehensive assessment on an overall benefit:risk ratio qualitatively favouring R-pola and the numerically longer DOR observed with R-pola, including in patients with high-risk refractory diffuse large B-cell lymphoma. Furthermore, the fact that CD79b represents a novel target distinguishes it from CD22, for which therapies including other ADC and CAR-T are currently in development. This allows for multiple treatment options taking advantage of the diversity of B-cell directed therapies, e.g. combinations of pola with CD22-directed therapies, or preservation of treatment options with CD22-directed therapies in cases of disease progression on prior pola treatment. Consequently, studies investigating pola in combination with other antilymphoma agents in patients with non-Hodgkin lymphoma are currently in progress. Results from a phase 1b/2 study of pola in combination with bendamustine and R (pola + BR) versus BR in patients

with relapsed/refractory diffuse large B-cell lymphoma and follicular lymphoma showed a substantial benefit in the cohort receiving pola,²⁴ which resulted in the pola + BR combination being designated breakthrough therapy status by the US Food and Drug Administration and PRIME designation by the European Medicines Agency. Pola is also being investigated as first-line treatment in diffuse large B-cell lymphoma in combination with R, cyclophosphamide, doxorubicin, and prednisone (R-CHP) in the POLARIX study (NCT03274492).²⁵

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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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Declaration of interests

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Tables

Table 1: Patient baseline characteristics (safety population)

Characteristic	DLBCL		FL	
	R-pina (n=42)	R-pola (n=39)	R-pina (n=21)	R-pola (n=20)
Median age, years (range)	69 (35–85)	68 (28–89)	59 (45–82)	67 (46–87)
Sex, n (%)				
Male	26 (62)	25 (64)	10 (48)	10 (50)
Female	16 (38)	14 (36)	11 (52)	10 (50)
DLBCL cell of origin (%)*				
ABC	30	46	--	--
GCB	59	46	--	--
Unclassified	11	8	--	--
Baseline ECOG PS, n (%)				
0	9 (21)	12 (31)	12 (57)	13 (65)
1	24 (57)	25 (64)	9 (43)	6 (30)
2	9 (21)	2 (5)	0	1 (5)
Median IPI score†	3	2	--	--
Median FLIPI2 score†	--	--	2	2
Bulky disease, n (%)‡	8 (19)	12 (31)	2 (10)	0
Prior Auto-SCT (%)	7 (16.7)	7 (17.9)	1 (4.8)	2 (10.0)
Median number of prior systemic therapies (range)	3 (1–10)	3 (1–8)	3 (1–8)	2 (1–6)
Prior rituximab, n (%)	41 (98)	38 (97)	21 (100)	20 (100)
Rituximab-refractory, n (%)§	23 (55)	19 (49)	9 (43)	5 (25)
Median time from prior treatment, months (range)	2.8 (1.0–117.4)	2.0 (0.8–118.5)	9.2 (0.7–72.7)	10.1 (1.6–70.9)
Refractory to last prior treatment, n (%)#	32 (76)	31 (80)	11 (52)	7 (35)

DLBCL=diffuse large B-cell lymphoma. FL=follicular lymphoma. R=rituximab. pina=pinatuzumab vedotin. pola=polatuzumab vedotin. ABC=activated B-cell-like. GCB=germinal centre B-cell-like. ECOG PS=Eastern Cooperative Oncology Group performance status. Auto-SCT=autologous stem cell transplantation. *Targeted gene expression and immunohistochemistry: performed on archival/baseline biopsy formalin-fixed paraffin-embedded specimens by quantitative reverse transcription-polymerase chain reaction using the luminex fluidigm platform and conventional immunohistochemistry techniques as previously reported.⁶ †A total of 41 patients with diffuse large

B-cell lymphoma treated with R-pina, and 19 and 16 patients with follicular lymphoma treated with R-pina and R-pola, respectively, were evaluable for IPI and FLIPI2 scores. ‡Presence of baseline tumour >7.5 cm in largest dimension. §No objective response or disease relapse ≤6 months among patients whose last prior regimen contained rituximab. #No objective response or relapse within 6 months of last prior treatment.

Table 2: Investigator-assessed best responses, duration of response, PFS, and overall survival

	DLBCL		FL	
	R-pina	R-pola	R-pina	R-pola
Investigator-assessed best responses				
All patients	(n=42)	(n=39)	(n=21)	(n=20)
ORR, n (%) [95% CI]	25 (60) [43–74]	21 (54) [37–70]	13 (62) [38–82]	14 (70) [46–88]
CR, n (%) [95% CI]	11 (26) [14–42]	8 (21) [9–36]	1 (5) [0·1–24]	9 (45) [23–68]
PR, n (%) [95% CI]	14 (33) [20–50]	13 (33) [19–50]	12 (57) [34–78]	5 (25) [19–49]
Refractory to last prior therapy	(n=32)	(n=31)	(n=11)	(n=7)
ORR, n (%) [95% CI]	19 (59) [41–76]	14 (45) [27–64]	6 (55) [23–83]	4 (57) [18–90]
CR, n (%) [95% CI]	7 (22) [9–40]	5 (16) [5–34]	1 (9) [0·2–41]	2 (29) [4–71]
PR, n (%) [95% CI]	12 (38) [21–56]	9 (29) [14–48]	5 (46) [17–77]	2 (29) [4–71]
Not refractory to last prior therapy	(n=10)	(n=8)	(n=10)	(n=13)
ORR, n (%) [95% CI]	6 (60) [26–88]	7 (88) [47–100]	7 (70) [35–93]	10 (77) [46–95]
CR, n (%) [95% CI]	4 (40) [12–74]	3 (38) [9–76]	0 (0) [0–31]	7 (54) [25–81]
PR, n (%) [95% CI]	2 (20) [3–56]	4 (50) [16–84]	7 (70) [35–93]	3 (23) [5–54]
DOR, PFS, and OS				
All patients	(n=42)	(n=39)	(n=21)	(n=20)
Median DOR, months	6·2	13·4	6·5	9·4
(95% CI)	(3·6–12·4)	(6·5–21·2)	(6·0–11·1)	(7·2–NE)
Median PFS, months	5·4	5·6	12·7	15·3
(95% CI)	(3·9–10·6)	(4·3–12·8)	(8·9–27·5)	(12·2–25·1)
2-year OS (FL), %	N/A	N/A	90·5	87·8
(95% CI)			(77·9–100)	(72·0–100)
Median OS, months	16·5	20·1	NR	NR
(95% CI)	(7·5–32·5)	(10·4–38·6)	(44·0–NE)	NE
Refractory to last prior therapy	(n=32)	(n=31)	(n=11)	(n=7)
Median DOR, months	4·0	13·4	8·3	9·4
(95% CI)	(2·8–11·5)	(3·0–21·2)	(6·0–11·1)	(5·6–NE)
Median PFS, months	4·8	4·7	12·7	13·6
(95% CI)	(2·8–6·8)	(3·9–9·0)	(9·0–27·5)	(10·1–NE)
2-year OS (FL), %	N/A	N/A	81·8	71·4

(95% CI)			(59.0–100)	(38.0–100)
Median OS, months	11.9	11.7	NR	NR
(95% CI)	(6.3–25.0)	(5.3–23.9)	(27.5–NE)	(22.4–NE)

Safety evaluable population (all treated patients). PFS=progression-free survival. OS=overall survival. DLBCL=diffuse large B-cell lymphoma. FL=follicular lymphoma. R=rituximab. pina=pinatuzumab vedotin. pola=polatuzumab vedotin. ORR=objective response rate. CI=confidence interval. CR=complete response. PR=partial response. DOR=duration of response. NE=not estimable. N/A=not available. NR=not reached.

Table 3: Serious adverse events, grade 3–5 events, and adverse events leading to study drug discontinuation, reduction, or delay

	DLBCL		FL	
	R-pina 2·4 mg/kg (n=42)	R-pola 2·4 mg/kg (n=39)	R-pina 2·4 mg/kg (n=21)	R-pola 2·4 mg/kg (n=20)
Serious AE, n (%)	21 (50·0)	14 (35·9)	6 (28·6)	7 (35·0)
Grade 5 AE*, n (%)	9 (21·4)*	0	0	1 (5·0)†
Grade 3–5 AE, n (%)	33 (78·6)	30 (76·9)	13 (61·9)	10 (50·0)
Patients with ≥1 AE leading to:				
Discontinuation	18 (42·9)	12 (30·8)	16 (76·2)	11 (55·0)
Dose reduction	6 (14·3)	9 (23·1)	6 (28·6)	7 (35·0)
Dose delay	15 (35·7)	14 (35·9)	13 (61·9)	8 (40·0)

DLBCL=diffuse large B-cell lymphoma. FL=follicular lymphoma. R=rituximab. pina=pinatuzumab vedotin. pola=polatuzumab vedotin. AE=adverse event. *Sepsis (n=2); influenza and pneumonia (in the same patient); general physical health deterioration (n=2, including one death also attributed to disease progression); and one event each of *Clostridium difficile* sepsis, respiratory failure, urosepsis, and sudden death. †Pulmonary congestion 64 days after the last of 12 cycles of treatment in an 84-year-old patient with FL.

Table 4: Incidence of peripheral neuropathy (safety population)

	DLBCL		FL	
	R-pina (n=42)	R-pola (n=39)	R-pina (n=21)	R-pola (n=20)
Prior peripheral neuropathy, n (%)	19 (45)	18 (46)	10 (48)	9 (45)
Peripheral neuropathy at entry, n (%)*	15 (36)	15 (39)	7 (33)	5 (25)
All grades on study, n (%)	23 (55)	22 (56)	17 (81)	19 (95)
Grade 2, n (%)	13 (31)	10 (26)	8 (38)	15 (75)
Grade 3, n (%)	2 (5)	4 (10)	3 (14)	1 (5)
Grade \geq 4, n (%)	0	0	0	0
Median time to onset, months (IQR)				
First event	2.3 (0.9–3.6)	2.2 (1.1–4.3)	2.1 (1.2–2.7)	2.6 (1.4–4.9)
Grade \geq 2 event	4.3 (2.3–6.9)	4.9 (3.5–7.6)	4.6 (2.6–6.2)	5.5 (3.5–7.6)
Median duration, months (IQR)†				
First event	3.3 (1.1–14.6)	4.0 (2.0–12.0)	4.0 (3.5–6.3)	3.0 (0.7–29.5)
Grade \geq 2 event	13.1 (2.8–24.6)	14.2 (2.0–29.0)	25.6 (9.4–31.3)	16.7 (2.5–28.6)
Led to treatment discontinuation, n (%)	9 (21)	7 (18)	10 (48)	11 (55)
Median time to treatment discontinuation, months (IQR)	5.7 (4.3–6.9)	7.2 (3.7–8.3)	6.4 (1.4–9.0)	5.6 (2.4–8.3)

DLBCL=diffuse large B-cell lymphoma. FL=follicular lymphoma. R=rituximab. pina=pinatuzumab vedotin. pola=polatuzumab vedotin. IQR=interquartile range. *All grade 1 per protocol eligibility criteria. †From onset to resolution.

Figures

Figure 1: Patient disposition

R=rituximab. pina=pinatuzumab vedotin. pola=polatuzumab vedotin. DLBCL=diffuse large B-cell lymphoma. FL=follicular lymphoma. AE=adverse event. PD=progressive disease. ECOG PS=Eastern Cooperative Oncology Group performance status. R/R=relapsed/refractory. CT=computed tomography. MRI=magnetic resonance imaging.

Figure 2: Antitumour responses to R-pina or R-pola by refractory status in diffuse large B-cell lymphoma and follicular lymphoma (efficacy-evaluable population*)

R=rituximab. pina=pinatuzumab vedotin. DLBCL=diffuse large B-cell lymphoma. pola=polatuzumab vedotin. FL=follicular lymphoma. *Patients with post-baseline tumour measurement.

Figure 3: Progression-free survival

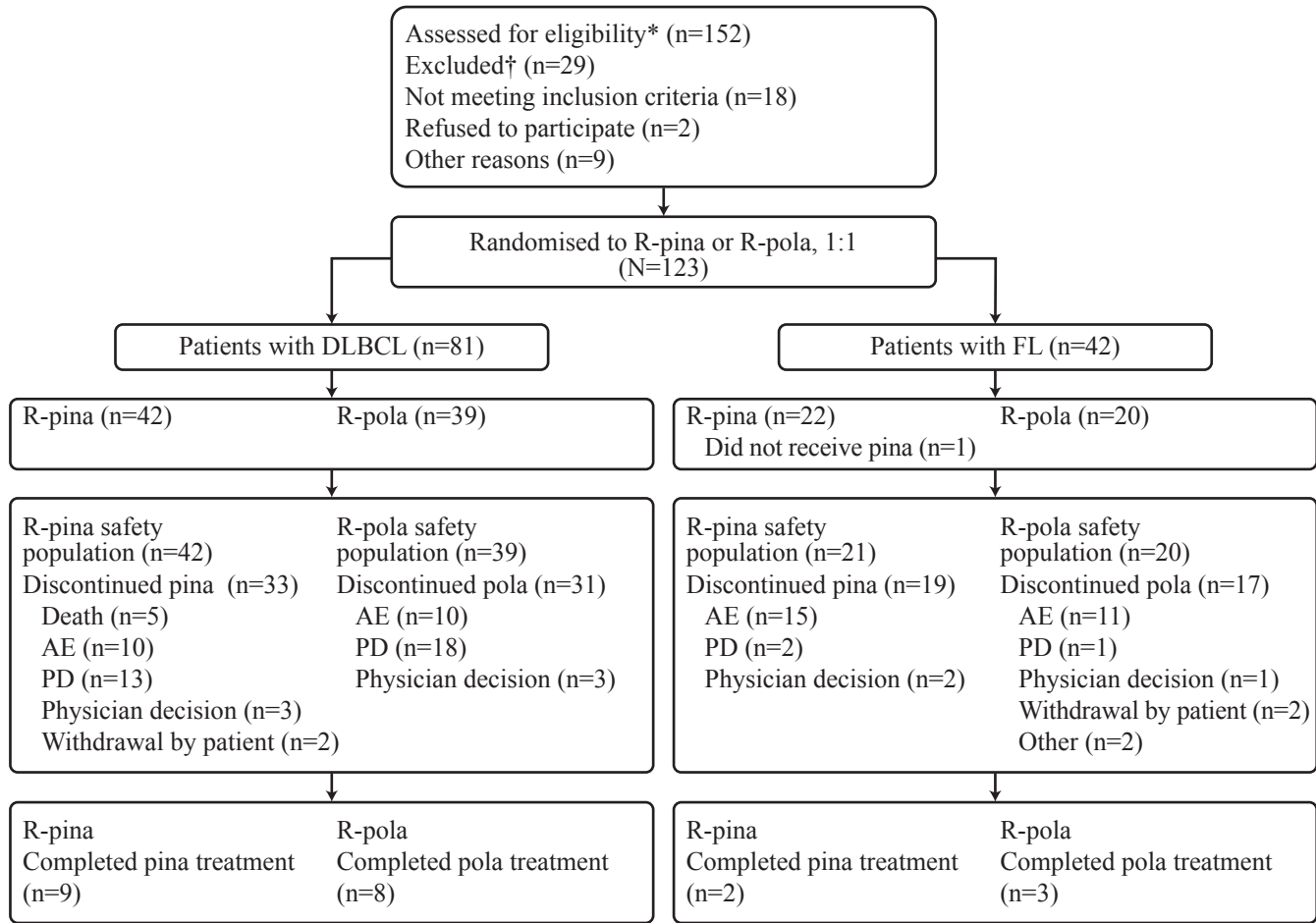
Figure shows Kaplan-Meier curves of progression-free survival as assessed by computed tomography/magnetic resonance imaging with or without positron emission tomography in patients with A) diffuse large B-cell lymphoma or B) follicular lymphoma, with number of subjects at risk and 95% Hall-Wellner bands. DLBCL=diffuse large B-cell lymphoma. R=rituximab. pina=pinatuzumab vedotin. pola=polatuzumab vedotin. CI=confidence interval. FL=follicular lymphoma.

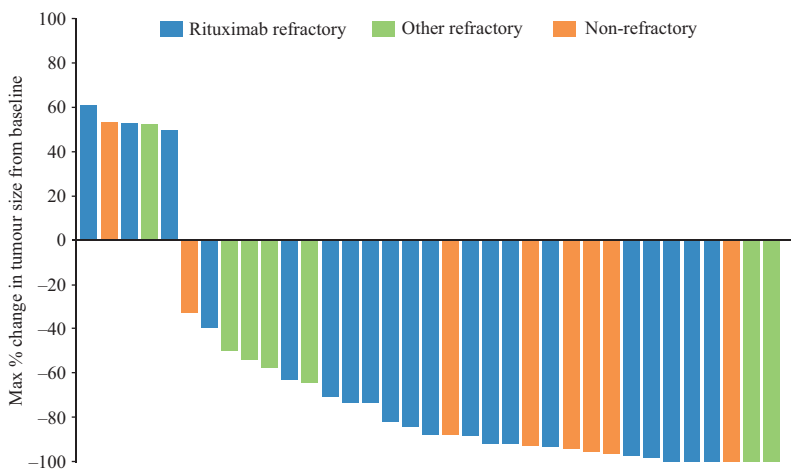
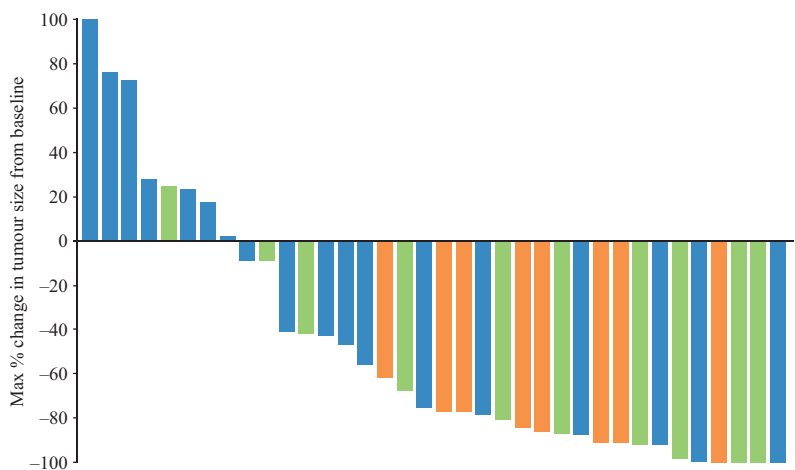
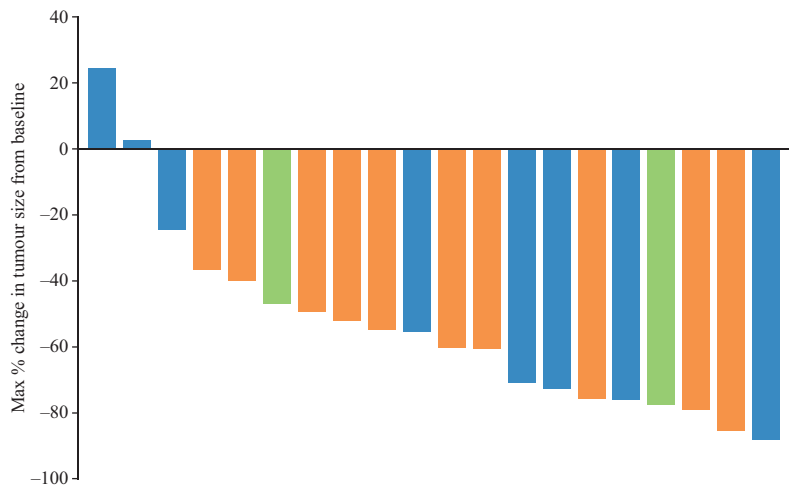
Figure 4: Duration of response

Figure shows Kaplan-Meier curves of duration of response as assessed by computed tomography/magnetic resonance imaging in patients with A) diffuse large B-cell lymphoma or B) follicular lymphoma, with number of subjects at risk and 95% Hall-Wellner bands. DLBCL=diffuse large B-cell lymphoma. R=rituximab. pina=pinatuzumab vedotin. pola=polatuzumab vedotin. CI=confidence interval. FL=follicular lymphoma.

Figure 5: Overall survival

Figure shows Kaplan-Meier curves of overall survival in patients with A) diffuse large B-cell lymphoma or B) follicular lymphoma, with number of subjects at risk and 95% Hall-Wellner bands. DLBCL=diffuse large B-cell lymphoma. R=rituximab. pina=pinatuzumab vedotin. pola=polatuzumab vedotin. CI=confidence interval. FL=follicular lymphoma.



A R-pina 2·4 mg/kg in DLBCL**B R-pola 2·4 mg/kg in DLBCL****C R-pina 2·4 mg/kg in FL****D R-pola 2·4 mg/kg in FL**