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Safety and efficacy of polatuzumab vedotin + obinutuzumab for relapsed/refractory NHL: A phase IB/II study

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DATA SHARING STATEMENT

Qualified researchers may request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). 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)

ETHICS APPROVAL

Institutional review boards/ethics committees approved the protocol. The study was conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation guidelines for Good Clinical Practice, and country-specific laws and regulations.

PATIENT CONSENT

All participating patients provided written informed consent.

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CONFLICT OF INTEREST

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Genentech, Inc./F. Hoffmann-La Roche Ltd, and Seattle Genetics, and has received research support from Seattle Genetics, Bristol-Myers Squibb, Merck, Genentech, Inc., Incyte, LAM Therapeutics, Millennium/Takeda, MEI Pharma, and Trillium. J.C. is an employee of F. Hoffmann-La Roche Ltd. D.R. was a consultant to Genentech, Inc. at the time the study was carried out. J.H. is an employee of Genentech, Inc. F.M. has participated in advisory boards for Celgene, F. Hoffmann-La Roche Ltd, Gilead, Bristol-Myers Squibb, Epizyme, and Bayer, and reports receiving lecture fees from Celgene, Janssen, F. Hoffmann-La Roche Ltd, and Novartis, and research support from AbbVie, Pharmacyclics, and advisory board fees from Genentech, Inc., Bayer, Gilead, Pharmacyclics, Incyte, and Seattle Genetics. I.W.F. has acted as a consultant for AbbVie, Seattle Genetics, TG Therapeutics, and Verastem Oncology, and has received research funding from Acerta Pharma, Agios, Calithera Biosciences, Celgene, Constellation Pharmaceuticals, Genentech, Inc., Gilead Sciences, Incyte, Infinity Pharmaceuticals, Janssen, Karo Pharma, Kite Pharma, Novartis, Pharmacyclics, Portola Pharmaceuticals, F. Hoffmann-La Roche Ltd, TG Therapeutics, Trillium Therapeutics, AbbVie, ArQule, BeiGene, Curis Inc., FORMA Therapeutics, Forty Seven, Merck, Pfizer, Takeda, Teva, Verastem Oncology, Gilead Sciences, AstraZeneca, Juno Therapeutics, Unum Therapeutics, and MorphoSys AG.

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To the Editor:

Rituximab (R)-based therapies have greatly improved survival in B-cell non-Hodgkin lymphomas (B-NHL). However, approximately 40% of patients with diffuse large B-cell lymphoma (DLBCL) experience progression or relapse following an initial response[1] and the indolent disease follicular lymphoma (FL) is characterized by chronic relapses that become resistant to chemotherapy.[2] There is, therefore, a need to identify novel therapies and treatment combinations to improve outcomes and tolerability for patients with B-NHL.

Polatuzumab vedotin (pola) is an antibody-drug conjugate (ADC) comprising the microtubule inhibitor, monomethyl auristatin E (MMAE), conjugated to a monoclonal antibody (mAb) targeting the B-cell specific antigen, CD79b.[3] Pola (1.8 mg/kg) combined with bendamustine (B) and R (pola-BR) is approved for relapsed/refractory (R/R) DLBCL after ≥2 prior therapies.[3,4] Obinutuzumab (G) is a type II anti-CD20 mAb. In a phase III study, G-based immunochemotherapy resulted in longer progression-free survival (PFS) than R-based treatment in patients with previously untreated FL.[5]

The phase IB/II study, ROMULUS (NCT01691898), compared safety and activity of pola or pinatuzumab vedotin (pina; MMAE conjugated to anti-CD22 mAb), combined with R (pola-R or pina-R) in patients with R/R DLBCL and R/R FL.[6] Pola was selected for further development due to a longer duration of response (DOR) and overall benefit-risk profile vs pina-R.[6] The ROMULUS study design was later amended to include treatment arms of pola combined with G (pola-G), because G was being compared with R in two large phase III studies for previously untreated DLBCL and indolent NHL,[5,7] potentially altering standard of care.

Here, we describe the safety, tolerability, and biologic and clinical activity of pola (1.8 mg/kg)-G in adult patients with R/R DLBCL and R/R FL. Eligible patients had a histologically confirmed diagnosis of R/R DLBCL, or R/R FL grade 1-3a. Patients with a current/past history of central nervous system lymphoma, current grade ≥1 peripheral neuropathy (PN), and prior use of any mAb, radioimmunoconjugates, or ADC within 4 weeks of cycle 1, day 1 were excluded. Study design and methods are described in the Supplement.

Between February 2015 and April 2017, 88 patients received pola-G: nine patients in the safety run-in (R/R DLBCL: n = 5; R/R FL: n = 4), 79 in the expansion cohorts (R/R DLBCL: n = 40; R/R FL: n = 39: Supplementary Figures 1 and 2). Nine patients with R/R FL discontinued the study: 1/4 (25.0%) of the safety run-in cohort, 8/39 (20.5%) in the expansion. Twenty-nine patients with R/R DLBCL discontinued the study: 3/5 (60.0%) within the safety run-in, 26/40 (65.0%) in the expansion (Supplementary Figure 2). Thirty-one patients with R/R DLBCL and 36 patients with R/R FL were evaluable for response by independent review committee (IRC).

In patients with R/R FL, 14 (38.9%) had a Follicular Lymphoma International Prognostic Index 2 (FLIPI2) score in the high-risk category 3-5 (no patients had FLIPI2 score 5); 6/39 (15.4%) patients had bulky disease (Supplementary Table 1). Prior R was reported for 38/39 (97.4%) patients with R/R FL, 16 (42.1%) of whom were refractory; prior vinca alkaloid use was reported in 27/39 (69.2%) patients (Supplementary Table 1). In patients with R/R DLBCL, 23 (59.0%) had an International Prognostic Index (IPI) score 3-5; 9/40 (22.5%) patients had bulky disease. All but one patient (39/40; 97.5%) had prior R therapy; 31/37 (83.8%) patients with available data were refractory to prior R. All patients with R/R DLBCL had prior vinca alkaloid use (Supplementary Table 1).

In patients with R/R FL, median duration of pola and G treatments was 4.8 months (range 0.0-6.0 months) and 4.9 months (range 0.0-6.0 months), respectively. Median number of treatment cycles was 8 (range 1-8). Overall, 65.9% of patients received >95% of the planned pola dose intensity (adjusted for delays and reductions); 95.3% received >95% of planned G dose. The median duration of follow-up for patients with R/R FL (n = 43) was 12.3 months (range 0.46–23.46 months).

In patients with R/R DLBCL, median treatment duration for both pola and G was 2.1 months (range 0.0-6.2 months). Median number of treatment cycles was 4 (pola; range 1-8) and 4 (G; range 1-8). Overall, 67.4% of patients received >95% of the planned pola dose intensity (adjusted for delays and reductions); 95.6% received >95% of planned G dose. The median duration of follow-up for patients with R/R DLBCL (n = 44) was 12.2 months (range 0.10–19.29 months).

In patients with R/R FL, the nature and severity of reported adverse events (AEs) were consistent with the known safety profiles of single-agent pola and G (Supplementary Table 2). Of

pola-G-treated R/R FL patients, 42/43 (97.7%) experienced ≥1 AE. Most frequently reported AEs (any grade) were fatigue (n = 23/43; 53.5%), constipation (n = 14/43; 32.6%), and diarrhea (n = 14/43; 32.6%). Within the safety run-in, 3/4 (75.0%) patients experienced ≥1 grade 3-4 AE (neutropenia [n = 2/4; 50.0%], infusion-related reactions [n = 1/4; 25.0%], and sinusitis [n = 1/4; 25.0%]). Grade 3-4 AEs occurred in 18/39 (46.2%) expansion cohort patients, most commonly neutropenia (n = 6/39; 15.4%). The median time to Grade ≥3 neutropenia was 1.76 months (range 0.54–2.66 months) and the median duration of the first Grade ≥3 neutropenia was 0.23 months.

Grade ≤2 PN events were experienced by 5/39 (12.8%) expansion cohort patients; there were no grade 3-5 PN events. At data cut-off (April 10, 2017), 17/39 (43.6%) PN events (any grade) were resolved. Serious adverse events (SAEs) occurred in 9/43 (20.9%) patients, most commonly (>10%) infections and infestations; 6/43 (14%) had an AE leading to discontinuation of any treatment. Most common AEs leading to discontinuation were nervous system disorders (n = 2/43; 4.7%), including grade 2 PN (n = 1) and grade 2 peripheral sensory neuropathy (n = 1). At data cut-off, 5/43 (11.6%) patients with R/R FL had died. Progressive disease (PD) was the primary cause of death in four patients; one death was due to an AE (pneumonia).

Overall, 43/45 (95.6%) patients with R/R DLBCL who were administered pola-G experienced ≥1 AE. Most frequently reported AEs (any grade) were diarrhea (n = 16/45; 35.6%), nausea (n = 15/45; 33.3%), and fatigue (n = 14/45; 31.1%). Within the safety run-in, 4/5 (80.0%) patients experienced ≥1 grade 3-4 AE (neutropenia [n = 2/5; 40.0%], anemia [n = 1/5; 20.0%], pleural effusion [n = 1/5; 20.0%], gastric perforation [n = 1/5; 20.0%], and pericardial effusion [n = 1/5; 20.0%]). Grade 3-4 AEs occurred in 23/40 (57.5%) patients in the expansion, most commonly neutropenia (n = 8/40; 20.0%), thrombocytopenia (n = 4/40; 10.0%), anemia (n = 2/40; 5.0%), and pleural effusion (n = 2/40; 5.0%) (Supplementary Table 2). The median time to Grade ≥3 neutropenia was 1.41 months (range 0.5–5.4 months) and the median duration of the first Grade ≥3 neutropenia was 0.15 months. As with the R/R FL cohort, there were no grade 3-5 PN events. Grade ≤2 PN events occurred in 9/40 (22.5%) expansion cohort patients; at data cut-off, 10/24 PN events (any grade) had resolved. SAEs were reported for 19/45 (42.2%) patients; most frequently reported (>10%) SAEs

were infections and infestations (n = 5/45; 11.1%) and respiratory, thoracic, and mediastinal disorders (n = 5/45; 11.1%). Of all patients with R/R DLBCL, 6/45 (13.3%) had an AE leading to discontinuation of any treatment. The most common AE leading to discontinuation was neutropenia: one patient with associated fever, one without (n = 2/45; 4.4%). At data cut-off, 23/45 (51.1%) patients with R/R DLBCL had died; 19 deaths were due to PD, one death was due to an AE (cardiac failure); primary cause of death not determined for the remaining three patients.

In patients with R/R FL, IRC-assessed complete response (CR) rate at end of treatment by positron emission tomography/computed tomography (PET/CT) was 36.1% (n = 13/36; 90% CI 22.9-51.2). Secondary endpoint analysis showed IRC-assessed objective response rate (ORR; CR or partial response [PR]) by PET/CT and CT alone was 66.7% (n = 24/36; 90% CI 51.7-79.5) (Table 1). Additional secondary endpoint analyses are detailed in Table 1. Investigator (INV)-assessed best overall response (BOR) was 72.1% (n = 31/43; 90% confidence interval [CI] 58.7-83.0). INV-assessed median DOR was 8.5 months (interquartile range [IQR] 6.3-9.7 months; Supplementary Figure 3); median PFS 11.5 months (IQR 7.8-12.4). Overall survival (OS) was 92.6% at 12 months; 81.2% at 18 months (median not reached by data cut-off date; Supplementary Figure 4).

There were no IRC-assessed CRs at end of treatment by PET/CT within the R/R DLBCL cohort (primary endpoint; Table 1). Other secondary efficacy endpoints are presented in Table 1. INV-assessed BOR was 40.9% (n = 18/44; 90% CI 28.4-54.4) for patients with R/R DLBCL. INV-assessed median DOR was 3.7 months (range 0.03-15.3; Supplementary Figure 3); median PFS 2.8 months (95% CI 1.5-6.3); median OS 10.7 months (IQR 3.2-not estimable; Supplementary Figure 4). Estimated probability of being alive at 18 months was 38.1% (95% CI 20.8-55.4).

In summary, the overall safety profile of pola-G in patients with R/R DLBCL and R/R FL was in line with previous data in this pre-treated patient population. With a pola dose 1.8 mg/kg, the efficacy of pola-G in R/R DLBCL was modest for ORR and PFS, with no advantage of G over R, emphasizing the need for combination with R and chemotherapy in this setting. The modest response rates are likely due to the differences in dose, duration of treatment, and anti-CD20 agents when comparing the Pola-R and Pola-G cohorts. In contrast, anti-tumor activity was observed in patients with R/R FL in terms of INV-assessed ORR, PFS, and OS. Pola-G is being investigated further as a

backbone for targeted chemotherapy combinations with a third drug, lenalidomide (NCT02600897) or venetoclax (NCT02611323), in R/R DLBCL and R/R FL.

AUTHOR CONTRIBUTIONS

T.P. and J.H. contributed to the conception and design of the study; M.B. contributed to the conception, design, data collection, and data analysis; T.P., A.I.C., J.E., C.D., D.R., J.H., and I.W.F. contributed to the collection and assembly of data, and data analysis/interpretation; A.C. and F.M. contributed to data analysis and interpretation; T.P., A.I.C., J.E., A.C., and C.D. contributed to the treatment of study patients; J.C. contributed to the statistical analysis and interpretation of the clinical data.

ROLE OF FUNDING SOURCE

The study 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 the funder. The corresponding author had full access to the data in the study and had final responsibility for the decision to submit for publication.

ROLE OF MEDICAL EDITOR

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TABLE 1 Overview of anti-tumor activity

IRC-assessed response	**R/R FL (n = 36)**		**R/R DLBCL (n = 31)**	
	PET/CT	**CT[a]**	**PET/CT**	**CT[a]**
CR, n (%)	13 (36.1)	5 (13.9)	0.0 (0.0)	2 (6.5)
90% CI	22.9-51.2	5.6-27.0	0.0-9.21	1.2-19.0
ORR, n (%)	24 (66.7)	24 (66.7)	6 (19)	8 (25.8)
90% CI	51.7-79.5	51.7-79.5	8.8-34.5	13.5-41.8
INV-assessed response	**R/R FL (n = 39)**		**R/R DLBCL (n = 37)**	
	PET/CT	**CT[a]**	**PET/CT**	**CT[a]**
CR, n (%)	14 (35.9)	8 (20.5)	6 (16.2)	4 (10.8)
90% CI	23.2-50.3	10.6-34.0	7.3-29.5	3.8-23.1
ORR, n (%)	25 (64.1)	25 (64.1)	8 (21.6)	8 (21.8)
90% CI	49.7-76.8	49.7-76.8	11.2-35.6	11.2-35.6

	R/R FL	**R/R DLBCL**
Best CR (INV-assessed)	(n = 43)	(n = 44)
n (%)	16 (37.2)	8 (18.2)
90% CI	24.9-50.9	9.4-30.4
BOR (INV-assessed)	(n = 43)	(n = 44)
n (%)	31 (72.1)	18 (40.9)
90% CI	58.7-83.0	28.4-54.4
PFS	(n = 43)	(n = 44)
Median PFS	11.5	2.8
IQR	7.8-12.4	1.5-6.3
OS	(n = 43)	(n = 45)
Median OS	NE	10.7
IQR	–	3.2-NE
DOR	(n = 31)	(n = 18)
Median DOR	8.5	3.7
IQR	6.3-9.7	3.3-NE

Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; FL, follicular lymphoma; INV, investigator; IQR, interquartile range; IRC, independent review committee; NE, not estimable; ORR,

objective response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; R/R, relapsed/refractory. [a]Response based on CT alone.