REFERENCES

1. Lanzkron S, Carroll CP, Haywood C Jr. The burden of emergency department use for sickle-cell disease: an analysis of the national emergency department sample database. *Am J Hematol*. 2010;85(10):797-799. doi:10.1002/ajh.21807
2. Morris CR, Kato GJ, Poljakovic M, et al. Dysregulated arginine metabolism, hemolysis-associated pulmonary hypertension, and mortality in sickle cell disease. *JAMA*. 2005;294(1):81-90. doi:10.1001/jama.294.1.81
3. Morris CR, Kuypers FA, Larkin S, Vichinsky EP, Styles LA. Patterns of arginine and nitric oxide in patients with sickle cell disease with vaso-occlusive crisis and acute chest syndrome. *J Pediatr Hematol Oncol*. 2000;22(6):515-520.
4. Onalo R, Cooper P, Cilliers A, et al. Randomized control trial of oral arginine therapy for children with sickle cell anemia hospitalized for pain in Nigeria. *Am J Hematol*. 2021;96(1):89-97. doi:10.1002/ajh.26028
5. Morris CR, Kuypers FA, Lavrisha L, et al. A randomized, placebo-controlled trial of arginine therapy for the treatment of children with sickle cell disease hospitalized with vaso-occlusive pain episodes. *Haematologica*. 2013;98(9):1375-1382. doi:10.3324/haematol.2013.086637
6. Morris CR, Brown LA, Reynolds M, et al. Impact of arginine therapy on mitochondrial function in children with sickle cell disease during vaso-occlusive pain. *Blood*. 2020;136:1402-1406. doi:10.1182/blood.2019003672

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Received: 9 June 2021 | Revised: 27 October 2021 | Accepted: 28 October 2021

DOI: 10.1002/ajh.26400

Safety and efficacy of polatuzumab vedotin + obinutuzumab for relapsed/refractory non-Hodgkin lymphomas: A phase IB/II study

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; www.clinicaltrials.gov), 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 versus 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 Appendix S1.

Between February 2015 and April 2017, 88 patients received pola-G: 9 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: $n = 39$: Figures S1 and S2). 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 (Figure S2). 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 (Table S1). 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 (Table S1). In patients with R/R DLBCL, 23 (59.0%) had an International Prognostic Index 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 (Table S1).

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 0.5–23.5 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 0.1–19.3 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 (Table S2). 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 1.8 months (range 0.5–2.7 months) and the median duration of the first Grade ≥3 neutropenia was 0.2 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 (14.0%) 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 4 patients; 1 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%) (Table S2). The median time to Grade ≥3 neutropenia was 1.4 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: 1 patient with associated fever, 1 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, 1 death was due to an AE (cardiac failure); primary cause of death not determined for the remaining 3 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% confidence interval [CI] 22.9–51.2). Secondary endpoint analysis showed IRC-assessed objective response rate (ORR; CR or partial response) 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% CI 58.7–83.0). INV-assessed median DOR was 8.5 months (interquartile range [IQR] 6.3–9.7 months; Figure S3); 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; Figure S4).

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 months; Figure S3); median PFS 2.8 months (95% CI 1.5–6.3); median OS 10.7 months (IQR 3.2–not estimable; Figure S4). 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 of 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.

ACKNOWLEDGMENTS

The authors would like to thank the participating patients and their families, study investigators, and research nurses. 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.

TABLE 1 Overview of anti-tumor activity

IRC-assessed response	R/R FL ($n = 36$) PET/CT	R/R FL ($n = 36$) CT[a]	R/R DLBCL ($n = 31$) PET/CT	R/R DLBCL ($n = 31$) CT[a]
CR, *n* (%) 90% CI	13 (36.1) 22.9–51.2	5 (13.9) 5.6–27.0	0.0 (0.0) 0.0–9.21	2 (6.5) 1.2–19.0
ORR, *n* (%) 90% CI	24 (66.7) 51.7–79.5	24 (66.7) 51.7–79.5	6 (19) 8.8–34.5	8 (25.8) 13.5–41.8
INV-assessed response	**R/R FL ($n = 39$) PET/CT**	**R/R FL ($n = 39$) CT[a]**	**R/R DLBCL ($n = 37$) PET/CT**	**R/R DLBCL ($n = 37$) CT[a]**
CR, *n* (%) 90% CI	14 (35.9) 23.2–50.3	8 (20.5) 10.6–34.0	6 (16.2) 7.3–29.5	4 (10.8) 3.8–23.1
ORR, *n* (%) 90% CI	25 (64.1) 49.7–76.8	25 (64.1) 49.7–76.8	8 (21.6) 11.2–35.6	8 (21.6) 11.2–35.6
	R/R FL		**R/R DLBCL**	
Best CR (INV-assessed) *n* (%) 90% CI	($n = 43$) 16 (37.2) 24.9–50.9		($n = 44$) 8 (18.2) 9.4–30.4	
BOR (INV-assessed) *n* (%) 90% CI	($n = 43$) 31 (72.1) 58.7–83.0		($n = 44$) 18 (40.9) 28.4–54.4	
PFS Median PFS, months IQR	($n = 43$) 11.5 7.8–12.4		($n = 44$) 2.8 1.5–6.3	
OS Median OS, months IQR	($n = 43$) NE –		($n = 45$) 10.7 3.2–NE	
DOR Median DOR, months IQR	($n = 31$) 8.5 6.3–9.7		($n = 18$) 3.7 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.

The corresponding author had full access to the data in the study and had final responsibility for the decision to submit for publication. Third-party medical writing assistance, under the direction of the authors, was provided by Angela Rogers, PhD, and Claire Lavin, PhD, on behalf of Ashfield MedComms, an Ashfield Health company, and was funded by F. Hoffmann-La Roche Ltd.

CONFLICT OF INTERESTS

Tycel Phillips has received research support from AbbVie and Pharmacyclics, and reports advisory board participation for Genentech, Inc., Bayer, Gilead, Pharmacyclics, Incyte, and Seattle Genetics. Mark Brunvand has no disclosures; the clinical and intellectual work on this paper was performed prior to employment with the Cigna Corporation and does not reflect the opinions or support of the Cigna Corporation. Andy I. Chen has acted as a consultant and has received research funding from Genentech, Inc. James Essell has nothing to disclose. Annalisa Chiappella reports advisory board participation for Celgene, Janssen, and iQone, and has received lecture fees from Celgene, Janssen, F. Hoffmann-La Roche Ltd, and Servier. Catherine Diefenbach has served as a consultant/advisory board participant for Bristol-Myers Squibb, Celgene, Merck, 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. Ji Cheng is an employee of F. Hoffmann-La Roche Ltd. David Ramies was a consultant to Genentech, Inc. at the time the study was carried out. Jamie Hirata is an employee of Genentech, Inc. Franck Morschhauser 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. Ian W. Flinn 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.

AUTHOR CONTRIBUTIONS

Tycel Phillips and Jamie Hirata contributed to the conception and design of the study; Mark Brunvand contributed to the conception, design, data collection, and data analysis; Tycel Phillips, Andy I. Chen, James Essell, Catherine Diefenbach, David Ramies, Jamie Hirata, and Ian W. Flinn contributed to the collection and assembly of data, and data analysis/interpretation; Annalisa Chiappella and Franck Morschhauser contributed to data analysis and interpretation; Tycel Phillips, Andy I. Chen, James Essell, Annalisa Chiappella, and Catherine Diefenbach contributed to the treatment of study patients; Ji Cheng contributed to the statistical analysis and interpretation of the clinical data.

DATA AVAILABILITY 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).

Tycel Phillips[1], Mark Brunvand[2], Andy I. Chen[3], James Essell[4], Annalisa Chiappella[5], Catherine Diefenbach[6], Ji Cheng[7], David Ramies[8], Jamie Hirata[9], Franck Morschhauser[10], Ian W. Flinn[11]

[1]*Division of Hematology and Oncology, University of Michigan Medical School, Ann Arbor, Michigan, USA*
[2]*Cigna Corporation, Bloomfield, Connecticut, USA*
[3]*Division of Hematology/Medical Oncology, Oregon Health & Science University, Portland, Oregon, USA*
[4]*Blood Cancer Center, Oncology Hematology Care Inc., Cincinnati, Ohio, USA*
[5]*Department of Hematology, Città della Salute e della Scienza Hospital and University, Torino, Italy*
[6]*Department of Medicine, Division of Hematology and Medical Oncology, Perlmutter Cancer Center at New York University Langone Health, New York, New York, USA*
[7]*Product Development - Biostatistics, F. Hoffmann-La Roche Ltd, Mississauga, Ontario, Canada*
[8]*Division of Oncology, Genentech, Inc., South San Francisco, California, USA*
[9]*Product Development - Oncology, Genentech, Inc., South San Francisco, California, USA*
[10]*Department of Hematology, University Lille, Centre Hospitalier Régional Universitaire Lille, Groupe de Recherche sur les formes Injectables et les Technologies Associées, Lille, France*
[11]*Department of Medical Oncology, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, Tennessee, USA*

Correspondence
Tycel Phillips, University of Michigan Medical School, 1301 Catherine St, Ann Arbor, MI 48109, USA.
Email: tycelp@med.umich.edu

ORCID

Tycel Phillips https://orcid.org/0000-0003-2143-9672
Ian W. Flinn https://orcid.org/0000-0001-6724-290X

REFERENCES

1. Coiffier B, Gisselbrecht C, Bosly A, et al. 10 years follow-up of the GELA LNH98.5 study, first randomized study comparing R-CHOP to CHOP chemotherapy in patients with diffuse large B-cell lymphoma. *Blood*. 2009;114:3741.
2. Becnel MR, Nastoupil LJ. Follicular lymphoma: past, present, and future. *Curr Treat Options Oncol*. 2018;19:32.
3. Genentech, Inc. POLIVY™ (polatuzumab vedotin-piiq) for injection, for intravenous use. 2019. Accessed November 29, 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761121s000lbl.pdf
4. European Medicines Agency. POLIVY summary of product characteristics. Accessed January 12, 2021. https://www.ema.europa.eu/en/documents/product-information/polivy-epar-product-information_en.pdf
5. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. *N Engl J Med*. 2017;377:1331-1344.
6. Morschhauser F, Flinn IW, Advani R, et al. Polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed or refractory non-Hodgkin lymphoma: final results from a phase 2 randomised study (ROMULUS). *Lancet Haematol*. 2019;6:e254-e265.
7. Vitolo U, Trněný M, Belada D, et al. Obinutuzumab or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated diffuse large B-cell lymphoma. *J Clin Oncol*. 2017;35(31):3529-3537.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Received: 12 September 2021 | Revised: 24 October 2021 | Accepted: 28 October 2021

DOI: 10.1002/ajh.26406

Kinetics of anti-SARS-CoV-2 neutralizing antibodies development after BNT162b2 vaccination in patients with amyloidosis and the impact of therapy