Polatuzumab vedotin plus bendamustine and rituximab or obinutuzumab in relapsed/refractory follicular lymphoma: a phase Ib/II study

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Supplementary material: Polatuzumab vedotin plus bendamustine and rituximab or obinutuzumab in relapsed/refractory follicular lymphoma: A phase Ib/II study

Supplementary Methods

Study assessments and endpoints

Exploratory endpoints included efficacy outcomes by biomarker status (including CD79b expression, which is presented in this analysis), investigator-assessed duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Evaluation of CD79b expression was based on H-scores, which range from 0 to 300 depending on the proportion of cells with staining intensities of 0, 1, 2, or ≥3. Further description of H-score calculation can be found in Sehn, *et al.* J Clin Oncol 2020 (1).

Statistical analyses

The phase Ib safety run-in portion of the study had a planned sample size of 12 patients (Pola-BR, n=6; Pola-BG, n=6). Initiation of phase II was permitted if <2 safety events were observed in each cohort. The sample size of the phase II randomized cohort was determined based on an assumed 25% difference in complete response (CR) rate from 40% with BR to 65% with Pola-BR. With 40 patients per arm, 95% exact Clopper–Pearson confidence intervals (CIs) for estimation of the true CR rate had a margin of error not exceeding ±17% and was able to rule out a true CR of <43% with 95% confidence. Also, the sample sizes of the expansion and randomized arms provided ≥87% likelihood of observing ≥1 adverse event based on true incidence rates of ≥10% and ≥5%, respectively. Efficacy analyses were performed in the intent-to-treat population (i.e., all randomized patients according to original treatment assignment) and the safety-evaluable population comprised all patients who received ≥1 dose of any study treatment. Response rates were reported as percentages with associated 95% Clopper–Pearson (i.e., exact binomial) CIs. PFS and OS were summarized as medians, estimated using Kaplan–Meier methodology with 95% Greenwood's CIs.

Similarly, median DOR was estimated using Kaplan–Meier methodology, but with 95% Brookmeyer and Crowley CIs.

References

1. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. Clin J Oncol. 2020;38(2):155.

Supplementary Tables and Figures

Supplementary Table S1. Full inclusion and exclusion criteria.

Inclusion criteria
Provided a signed informed consent form
≥18 years of age
Judged by the investigator to be able to comply with the study protocol
Grade 1, 2, or 3a histologically confirmed FL
Received ≥1 prior therapy for FL
Relapsed or have become refractory to a prior regimen: • Relapsed to prior regimen(s) following a documented response (CR, CRu, PR) of ≥6 months in duration from completion of treatment • Refractory to any prior regimen (i.e., no response or progression within 6 months of completion of the last dose of therapy)
Response duration to prior bendamustine of >1 year (in patients who have received prior bendamustine and who have relapsed disease after a prior regimen)
≥1 bi-dimensionally measurable lesion on imaging scan (i.e., longest dimension >1.5 cm)
Confirmed availability of archival or freshly collected tumor tissue prior to study enrolment
Life expectancy ≥24 weeks
ECOG PS 0–2
Adequate hematologic function*: • Hemoglobin ≥9 g/dL • ANC ≥1.5 × 10^9/L • Platelet count ≥75 × 10^9/L
Women who were not postmenopausal (i.e., ≥12 months of non-therapy-induced amenorrhea and >45 years old) or surgically sterile (i.e., absence of ovaries and/or uterus) had to agree to remain abstinent or to use single highly effective or combined contraceptive methods† during the treatment period and for ≥12 or ≥18 months after the last dose of rituximab or obinutuzumab, respectively.
Exclusion criteria
Known allergy to humanized or murine MAbs (or recombinant antibody-related fusion proteins) or murine products
Use of bendamustine, rituximab, or obinutuzumab contraindicated
Known sensitivity to the excipient mannitol
Use of any MAb, radioimmunoconjugate, or ADC within 5 half-lives or 4 weeks (whichever is longer)
Radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational agent within 2 weeks prior, with the exception of rituximab if the last dose was received >2 weeks prior
Grade >2 acute, clinically significant treatment-related toxicity from prior therapy (except for alopecia)
Ongoing corticosteroid use >30 mg/day prednisone (or equivalent), except for control of lymphoma symptoms • Patients receiving documented stable doses of corticosteroids ≤30 mg/day prednisone (or equivalent) were permitted
Treatment with CAR T-cell therapy ≤100 days prior
Completion of autologous SCT ≤100 days prior or eligible for autologous SCT
Prior allogeneic SCT
Grade 3b FL or transformation of indolent disease to DLBCL
Primary or secondary CNS lymphoma
Current grade >1 peripheral neuropathy

History of other malignancy that could affect compliance with the protocol or interpretation of results. Exceptions include: • Curatively treated basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix, or ductal carcinoma in situ of the breast • Any other malignancy treated with curative-intent surgery alone that has been in remission without treatment for ≥3 years prior • Patients with low-grade, early-stage prostate cancer not requiring therapy
Significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results (e.g., significant cardiovascular or pulmonary disease)
Active bacterial, viral, fungal, mycobacterial, parasitic, or other infection, or any major episode of infection requiring treatment with IV antibiotics or hospitalization ≤4 weeks prior
Suspected or confirmed latent tuberculosis
Chronic HBV infection (with positive HBsAg serology) • Patients with occult or prior HBV infection (i.e., negative HBsAg and positive HBcAb) may be included if HBV DNA is undetectable. Such patients must be willing to undergo DNA testing on Day 1 of every cycle and monthly for ≥12 months after completion of study treatment
Positive for HCV antibody, with the exception of those for whom PCR is negative for HCV RNA
History of HIV seropositive status
Known HTLV-1 infection
Received a live vaccine ≤28 days prior
Recent major surgery ≤6 weeks prior (other than for diagnosis)
Pregnant or lactating or intend to become pregnant within 12 or 18 months of the last dose of rituximab or obinutuzumab, respectively
Abnormal laboratory values*: • Creatinine >1.5 × ULN or creatinine clearance <40 mL/min • AST or ALT >2.5 × ULN • Total bilirubin ≥1.5 × ULN • INR or PT >1.5 × ULN in the absence of therapeutic anticoagulation • PTT or aPTT >1.5 × ULN in the absence of a lupus anticoagulant
Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding contraindicating the use of an investigational drug, or that may affect interpretation of the results or render the patient at high risk of treatment complications

ADC, antibody–drug conjugate; ALT, alanine aminotransferase; ANC, absolute neutrophil count; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CAR, chimeric antigen receptor; CNS, central nervous system; CR, complete response; CRu, unconfirmed complete response; DLBCL, diffuse large B-cell lymphoma; DNA, deoxyribose nucleic acid; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTLV-1, human T-cell leukemia virus 1; INR, international normalized ratio; IV, intravenous; MAb, monoclonal antibody; PCR, polymerase chain reaction; PR, partial response; PT, prothrombin time; PTT, partial thromboplastin time; RNA, ribonucleic acid; SCT, stem cell transplant; ULN, upper limit of normal. *Unless due to underlying disease. †Defined as a failure rate of <1% per year.

Supplementary Table S2. Summary of treatment exposure (safety-evaluable patients).

	Phase II randomized		Phase Ib/II expansion
	Pola-BR (n=38)	**BR (n=41)**	**Pola-BG (n=26)**
Median no. of cycles completed (range)	5 (1–6)	3 (1–6)	6 (1–6)
Discontinued polatuzumab vedotin, n (%)	9 (20.5)	–	6 (23.1)
Progressive disease	1 (2.3)	–	0
Lack of efficacy	0	–	0
AE	6 (13.6)	–	5 (19.2)
Other	2 (4.5)	–	1 (3.8)
Discontinued bendamustine, n (%)	12 (27.3)	10 (24.4)	7 (26.9)
Progressive disease	1 (2.3)	2 (4.9)	0
Lack of efficacy	0	1 (2.4)	0
AE	9 (20.5)	5 (12.2)	6 (23.1)
Other	2 (4.5)	2 (4.8)*	1 (3.8)†
Discontinued rituximab or obinutuzumab, n (%)	9 (20.5)	9 (22.0)	6 (23.1)
Progressive disease	0	2 (4.9)	0
Lack of efficacy	0	1 (2.4)	0
AE	7 (15.9)	4 (9.8)	5 (19.2)
Other	2 (4.5)	2 (4.8)*	1 (3.8)†
Median dose intensity‡, % (range)			
Polatuzumab vedotin	99.7 (85.0–110.0)	–	99.3 (79.0–102.0)
Bendamustine	100 (78.0–105.0)	100 (74.0–103.0)	99.9 (89.0–102.0)
Rituximab	100 (97.0–117.0)	100 (89.0–103.0)	–
Obinutuzumab	–	–	100 (88.0–103.0)

AE, adverse event; BG, bendamustine plus obinutuzumab; BR, bendamustine plus rituximab; Pola, polatuzumab vedotin. *Physician decision (n=1), patient withdrawal (n=1). †Non-compliance with treatment regimen. ‡Defined as the percentage of expected dose that was received.

Supplementary Table S3. Summary of patient deaths (safety-evaluable patients).

Cause of death, n (%)	**Phase II randomized**		**Phase Ib/II expansion**
	Pola-BR (n=38)	**BR (n=41)**	**Pola-BG**
Progressive multifocal leukoencephalopathy	–	–	1 (3.8)
Acute pulmonary edema	–	–	1 (3.8)
Sepsis	–	1 (2.4)	–
Septic shock	–	1 (2.4)	–
Adenocarcinoma	–	1 (2.4)	–
Cerebrovascular accident	–	1 (2.4)	–
Respiratory failure	1 (2.6)	–	–
Sudden death	1 (2.6)	–	–
Pneumonia	1 (2.6)	–	–
Brain edema	1 (2.6)	–	–
Cardiac arrest	1 (2.6)	–	–
SARS-COV-2 infection-induced pneumonia	1 (2.6)	–	–
Other	2 (5.2)	–	–

AE, adverse event; BG, bendamustine plus obinutuzumab; BR, bendamustine plus rituximab; Pola, polatuzumab vedotin.

Supplementary Figure S1. Kaplan–Meier curve of INV-assessed DOR. A) DOR in randomized Pola-BR and BR arms; B) DOR in Ph Ib/II expansion (Pola-BG) arm. BG: bendamustine plus obinutuzumab; BR, bendamustine plus rituximab; CI, confidence interval; DOR, duration of response; INV, investigator; NE, not evaluable; Pola, polatuzumab vedotin.