ELSEVIER

Blood 142 (2023) 439–442

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

627.AGGRESSIVE LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

Early Results Indicate Acceptable Safety and Promising Efficacy of Venetoclax in Combination with Pola-R-CHP for Untreated High-Risk BCL-2-Positive B-Cell Lymphoma Including Double/Triple Hit Lymphoma

Andrew D. Zelenetz, MD PhD[1], Catherine S. Diefenbach, MD[2], Charles Herbaux, MD PhD[3], Monica Tani[4], Roch Houot, MD PhD[5], Mariana Bastos-Oreiro, MD[6], Herve Tilly, MD[7], Thomas Gastinne, MD[8], Catherine Thieblemont, MD PhD[9], Ethan Troy-Barnes, MBBCh, BAO, MD[10], Stefano Olivieri, PhD[11], Murali Kesavan, MD[10], Manisha Kanwar, MD[10], Simona Barlera, MSc[12], Katerina Hatzi, PhD[13], Yanwen Jiang, PhD[13], Michelle Boyer, PhD BA[10], Franck Morschhauser, MDPhD[14]

[1] Memorial Sloan Kettering Cancer Center, New York, NY
[2] Perlmutter Cancer Center, NYU Langone Health, New York, NY
[3] Centre Hospitalier Universitaire de Montpellier, Montpellier, France
[4] Ematologia, Ospedale Santa Maria delle Croci, Ravenna, Italy
[5] Centre Hospitalier Universitaire de Rennes - Hopital Pontchaillou, Rennes, France
[6] Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain
[7] Centre Henri-Becquerel, Rouen, France
[8] CHU de Nantes, Nantes, France
[9] Hopital Saint-Louis, Paris, France
[10] F. Hoffmann-La Roche AG, London, United Kingdom
[11] F. Hoffmann-La Roche AG, Basel, Switzerland
[12] Parexel International, Milan, Italy
[13] Genentech, Inc., South San Francisco, CA
[14] Centre Hospitalier Régional Universitaire de Lille, Lille, France

Background: The Phase II CAVALLI study assessed the B-cell lymphoma 2 (BCL-2) inhibitor venetoclax (Ven; 800mg for 10 days [Ds]) + rituximab (R), cyclophosphamide (C), doxorubicin (H), vincristine (O) and prednisolone (P; R-CHOP), for first line treatment of diffuse large B-cell lymphoma (DLBCL). The end of treatment (EOT) complete response (CR) rate was 64% in patients (pts) with BCL-2 overexpression by immunohistochemistry (BCL-2 IHC+); there was a 2-year progression-free survival (PFS) benefit compared with R-CHOP (GOYA trial; 78% vs 62%); but a higher incidence of Grade (Gr) 3/4 adverse events (AEs; 86% vs 66%, respectively; Morschhauser et al. Blood 2021).
In the Phase III POLARIX study, polatuzumab vedotin (Pola)-R-CHP had a prolonged PFS vs R-CHOP, establishing Pola-R-CHP as standard of care for untreated DLBCL (Tilly et al. N Engl J Med 2022; Morschhauser et al. EHA 2022). Thus, we explored whether adding Ven to Pola-R-CHP could further improve outcomes in BCL-2 IHC+ DLBCL. Here, we report early safety and efficacy results from a Phase Ib study (BO42203; NCT04790903), evaluating the optimal dose/schedule of Ven+Pola-R-CHP.
Methods: BO42203 is an ongoing open-label, multicenter study of pts with untreated BCL-2 IHC+ DLBCL (including Grade 3b follicular lymphoma). Pts enrolled had an International Prognostic Index (IPI) of 2-5, and BCL-2 IHC+ defined as ≥50% expression (by local pathology).
The primary endpoint is to determine the recommended Phase II dose (RP2D) for Ven+Pola R-CHP based on the rate of dose-limiting toxicity (DLT) during the first 2 cycles (42 Ds), with tolerability assessed by dose modifications/delays and discontinuation. Secondary endpoints include percentage of pts with AEs, and PET-based response rates/duration.
Pts are enrolled in 5 cohorts (n=10 pts each). Safety data are reviewed by an internal monitoring committee (IMC) who can alter the Ven dose/schedule for the next cohort. Pts receive 6 21-D cycles of treatment. Pola-R-CHP is administered on D1 of each cycle at the following doses: Pola 1.8mg/kg, R 375mg/m ^{2}, C 750mg/m ^{2}, H 50mg/m ^{2}, and P 100mg/D for 5 Ds. All pts in Cohort 1 were assigned to Ven 800mg/D for 5 Ds/cycle; doses start on D4 of Cycle 1 and D1 of subsequent cycles (Schedule A) with optional escalation to 10 Ds/cycle from Cohort 2 onwards (Schedule B), depending on IMC assessment.
Results: At the time of analysis (data cutoff: May 2, 2023), 4 cohorts were enrolled (n=40). At baseline, the median age was 64.0 years, 14 (35.0%) pts were female, and 5 (12.5%) had an Eastern Cooperative Oncology Group performance status of 2.

Thirty-six (90.0%) pts had Ann Arbor Stage III-IV; 30 (75.0%) had an IPI score of ≥3; and 10 (25.0%) had poor risk cytogenetics (double/triple hit lymphoma [DHL/THL]).

Thirty-eight pts have completed the DLT period; 2 pts withdrew prior to this due to meningitis and a COVID-related AE. No DLTs have been observed. Gr ≥3 myelosuppression was observed in Cohort 1 after the DLT period: neutropenia (n=5 pts [50.0%]), neutrophil count decreased (n=2 [20.0%]), and febrile neutropenia (n=1 [10.0%]). Hence, after IMC review of Cohorts 1-3 it was decided that Schedule A will be maintained/received by all future pts, as the benefit-risk of increasing the Ven schedule may not be favorable.

Safety and efficacy analyses were performed on Cohorts 1-3 (n=30) as they have reached the EOT. All pts had ≥1 AE; 21 (70.0%) and 11 (36.7%) pts had at least one Gr ≥3 AE (**Table**) and serious AE (SAE), respectively; 2 (6.7%) pts died due to treatment-related SAEs (investigator-assessed; sudden cardiac death [related to Ven] and sepsis [related to Ven+Pola-R-CHP]). AEs leading to dose modification/delay of any drug occurred in 11 (36.7%; 23 events) pts; 21 (91.3%) AEs led to Ven modification in 10 pts (33.3%); and 3 (10.0%) pts had an AE that led to discontinuation of any study drug.

Response was evaluated in 30 pts, with an EOT PET-CT based objective response rate and CR of 86.7% (n=26; including all pts with DHL/THL [n=8; CR: 100%]); 1 pt had progressive disease [PD], and 3 were not assessed due to death (n=2) and early discontinuation (n=1; **Figure**). Three (10.0%) pts died due to PD.

Conclusions: Ven 800mg/D for 5 Ds/cycle + Pola-R-CHP has been determined as the RP2D; early results show acceptable safety and promising efficacy for untreated BCL-2 IHC+ DLBCL. High CR rates were observed across all cohorts at EOT, including pts with DHL/THL. Updated results, including circulating tumor DNA, will be presented.

Disclosures Zelenetz: *Janssen Pharmaceuticals:* Consultancy, Honoraria; *None other than mutual funds (401K):* Current equity holder in publicly-traded company; *Pharmacyclics:* Consultancy, Honoraria; *SAB:* Membership on an entity's Board of Directors or advisory committees; *Lymphoma Research Foundation:* Membership on an entity's Board of Directors or advisory committees; *MEI Pharma Inc:* Consultancy, Honoraria, Research Funding; *F. Hoffmann-La Roche Ltd:* Consultancy, Honoraria, Research Funding; *Abbvie:* Research Funding; *Gilead:* Consultancy, Honoraria; *AstraZeneca:* Consultancy, Honoraria; *BeiGene:* Consultancy, Honoraria, Research Funding; *BMS:* Consultancy, Honoraria. **Diefenbach:** *Gillead:* Current equity holder in publicly-traded company; *OverT Therapeutics:* Current equity holder in private company; *F. Hoffmann-La Roche Ltd/Genentech, Inc., BMS, Merck, Abbvie, Novartis, Celgene, Cargo, Nekktar:* Research Funding; *Genmab, Abbvie, Regeneron, F. Hoffmann-La Roche Ltd/Genentech, Inc., Seattle Genetics, Merck:* Membership on an entity's Board of Directors or advisory committees. **Herbaux:** *AbbVie, F. Hoffmann-La Roche Ltd, AstraZeneca, Janssen:* Honoraria; *AbbVie, Takeda:* Research Funding; *AbbVie, F. Hoffmann-La Roche Ltd, AstraZeneca, Janssen:* Consultancy; *Physician and professor of Hematology at academic center (CHU Montpellier France):* Current Employment. **Tani:** *Abbvie, Jansen-Cilag, Incyte:* Membership on an entity's Board of Directors or advisory committees. **Houot:** *Kite/Gilead, Novartis, Bristol-Myers Squibb/Celgene, ADC Therapeutics, Incyte, Miltenyi:* Consultancy; *Kite/Gilead, Novartis, Incyte, Janssen, MSD, Takeda, F. Hoffmann-La Roche Ltd:* Honoraria. **Bastos-Oreiro:** *SEHH, AMHH:* Membership on an entity's Board of Directors or advisory committees; *BMS, Kite, Novartis, F. Hoffmann-La Roche Ltd, Incyte, Abbvie:* Honoraria, Speakers Bureau; *Incyte, Kite:* Consultancy; *F. Hoffmann-La Roche Ltd, Kite, SEHH, AMHH:* Research Funding; *Gregorio Maranon Hospital:* Current Employment, Membership on an entity's Board of Directors or advisory committees. **Tilly:** *F. Hoffmann-La Roche Ltd:* Honoraria, Research Funding; *BMS, F. Hoffmann-La Roche Ltd, ADC therapeutics:* Membership on an entity's Board of Directors or advisory committees. **Thieblemont:** *Cellectis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses; *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses; *Roche:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses, Research Funding; *Kite:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses; *Kyte, Gilead, Novartis, BMS, Abbvie, F. Hoffmann-La Roche Ltd, Amgen:* Honoraria; *Janssen:* Honoraria, Other: Travel Expenses; *BMS/Celgene:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses, Research Funding; *Gilead Sciences:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses; *Hospira:* Research Funding; *Amgen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses; *Incyte:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Bayer:* Honoraria; *Paris University, Assistance Publique, hopitaux de Paris (APHP):* Current Employment; *AbbVie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel Expenses; *Takeda:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Troy-Barnes:** *F. Hoffmann-La Roche Products Ltd:* Current Employment; *University College London Hospitals NHS Foundation Trust, North Middlesex University Hospital NHS Trust:* Ended employment in the past 24 months; *Whittington Health NHS Trust (honorary contract):* Honoraria. **Olivieri:** *F. Hoffmann-La Roche Ltd:* Current Employment, Current equity holder in private company. **Kesavan:** *F. Hoffmann-La Roche Ltd:* Current Employment; *Oxford university hospitals NHS Trust:* Ended employment in the past 24 months. **Kanwar:** *Viatris:* Ended employment in the past 24 months; *F. Hoffmann-La Roche Ltd:* Current Employment. **Barlera:** *Member of the DSMB for an independent (not sponsored) study conducted at the Mario Negri Institute, no fees:* Other. **Hatzi:** *Genentech, Inc., F. Hoffmann-La Roche Ltd:* Current Employment, Current equity holder in publicly-traded company. **Jiang:** *F. Hoffmann-La Roche Ltd:* Current Employment, Current equity holder in publicly-traded company. **Boyer:** *F. Hoffmann-La Roche Ltd:* Current Employment. **Morschhauser:** *F. Hoffmann-La Roche Ltd, Gilead, AbbVie:* Membership on an entity's Board of Directors or advisory committees; *F. Hoffmann-La Roche Ltd, AbbVie, BMS, Genmab, Gilead, Novartis:* Consultancy.

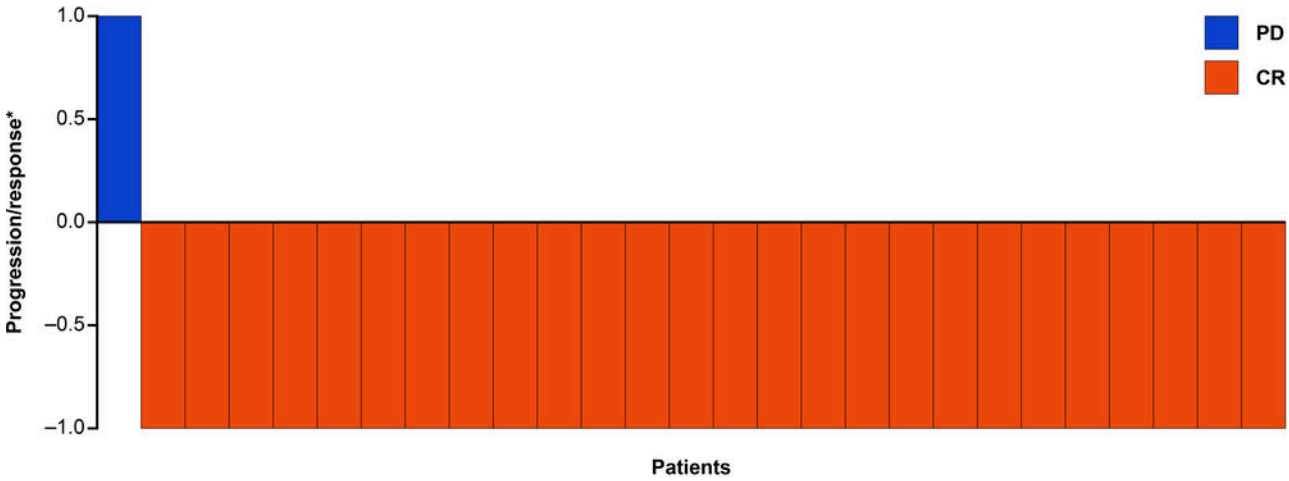
OffLabel Disclosure: Venetoclax plus Pola-R-CHP is an investigational combination. Venetoclax (Venclexta) is a BCL-2 inhibitor indicated: for the treatment of adult pts with CLL or SLL; in combination with azacitidine, or decitabine, or low-dose cytarabine for the treatment of newly diagnosed AML in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemo. Polatuzumab vedotin (Pola) is a CD79b-directed antibody-drug conjugate indicated: in combination with a rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult patients who have previously untreated DLBCL, NOS or HGBL and who have an IPI score of 2 or greater; and in combination with bendamustine and a rituximab product for the treatment of adult pts with relapsed or refractory DLBCL, NOS after at least two prior therapies.

Table. Most common* Grade ≥3 AEs† in the first three cohorts.

n, (%)	Cohort 1 (n=10)	Cohort 2 (n=10)	Cohort 3 (n=10)	Total (n=30)
Patients with ≥1 AE	8 (80.0)	8 (80.0)	5 (50.0)	21 (70.0)
Total number of events‡	37	22	28	87
Blood and lymphatic system disorders	**5 (50.0)**	**4 (40.0)**	**3 (30.0)**	**12 (40.0)**
Neutropenia	5 (50.0)	3 (30.0)	3 (30.0)	11 (36.7)
Anemia	1 (10.0)	2 (20.0)	1 (10.0)	4 (13.3)
Febrile neutropenia	1 (10.0)	1 (10.0)	1 (10.0)	3 (10.0)
Thrombocytopenia	1 (10.0)	1 (10.0)	1 (10.0)	3 (10.0)
Leukopenia	0 (0)	1 (10.0)	0 (0)	1 (3.3)
Investigations	**3 (30.0)**	**3 (30.0)**	**2 (20.0)**	**8 (26.7)**
Lymphocyte count decreased	1 (10.0)	1 (10.0)	1 (10.0)	3 (10.0)
Neutrophil count decreased	2 (20.0)	1 (10.0)	0 (0)	3 (10.0)
WBC count decreased	1 (10.0)	1 (10.0)	1 (10.0)	3 (10.0)
ALT increased	0 (0)	0 (0)	1 (10.0)	1 (3.3)
AST increased	0 (0)	0 (0)	1 (10.0)	1 (3.3)
Infections and infestations	**2 (20.0)**	**1 (10.0)**	**2 (20.0)**	**5 (16.7)**
Sepsis	0 (0)	1 (10.0)	1 (10.0)	2 (6.7)
COVID-19	0 (0)	0 (0)	1 (10.0)	1 (3.3)
Diverticulitis	0 (0)	0 (0)	1 (10.0)	1 (3.3)
Infection	1 (10.0)	0 (0)	0 (0)	1 (3.3)
Pseudomonal bacteremia	0 (0)	0 (0)	1 (10.0)	1 (3.3)
Stoma site infection	1 (10.0)	0 (0)	0 (0)	1 (3.3)
Gastrointestinal disorders	**2 (20.0)**	**1 (10.0)**	**1 (10.0)**	**4 (13.3)**
Diarrhea	1 (10.0)	1 (10.0)	1 (10.0)	3 (10.0)
Dysphagia	1 (10.0)	0 (0)	0 (0)	1 (3.3)

*Most common is defined as AEs, per MedDRA system organ class, that occurred in >10.0% of total pts across all three cohorts.
†Investigator text for AEs encoded using MedDRA version 26.0; only treatment-emergent AEs are displayed.
‡Multiple occurrences of the same AE in an individual are counted separately.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, medical dictionary for regulatory activities; pts, patients; WBC, white blood cell.

Figure. Objective response rate by PET-CT at EOT



*A positive number indicates progression; a negative number indicates response. At EOT, 26 patients had achieved CR, 1 patient had PD (but had achieved PR at Cycle 4), 2 patients had died (due to SAEs), and 1 patient had discontinued prior to treatment completion.
CR, complete response; EOT, end of treatment; PET-CT, positron emission-computed tomography; PD, progressive disease; PR, partial response; SAE, serious adverse event.

Figure 1

https://doi.org/10.1182/blood-2023-174855