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Blood 142 (2023) 858–860

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

626.AGGRESSIVE LYMPHOMAS: PROSPECTIVE THERAPEUTIC TRIALS

Glofitamab (Glofit) Plus R-CHOP Has a Favorable Safety Profile and Induces High Response Rates in Patients with Previously Untreated (1L) Large B-Cell Lymphoma (LBCL) Defined As High Risk By Circulating Tumor DNA (ctDNA) Dynamics: Preliminary Safety and Efficacy Results

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Background: Up to one-third of patients (pts) with 1L LBCL treated with R-CHOP do not achieve long-term remission or cure depending on disease stage. Outcome prediction beyond the International Prognostic Index (IPI) score is difficult due to the lack of reproducibility of common biomarkers. ctDNA offers potential as a sensitive biomarker to identify newly diagnosed pts with suboptimal chemoimmunotherapy responses. Reduction of ctDNA levels after 1-2 therapy cycles in pts with 1L diffuse LBCL (DLBCL) is associated with improved survival (Kurtz et al. J Clin Oncol 2018). Whether early intervention can improve outcomes of pts with elevated on-treatment ctDNA levels is unknown. Glofitamab, a CD20xCD3 bispecific antibody, engages and redirects T cells to eliminate B cells and has received FDA and EMA approval as monotherapy for relapsed/refractory DLBCL after ≥2 prior lines of therapy. Glofit + R-CHOP has favorable safety and efficacy in 1L DLBCL (Topp et al. ASH 2022). We report initial safety and efficacy from a Phase II open-label prospective trial (NCT04980222) evaluating glofit + R-CHOP in pts with 1L LBCL defined as high risk by ctDNA dynamics.

Methods: Eligible pts had 1L CD20+ LBCL, Eastern Cooperative Oncology Group performance status 0-2, and IPI 0-5 (IPI 0 for pts with bulky disease; IPI 2-5 for USA pts). During ctDNA screening, pts received R-CHOP on Day (D)1 of Cycle (C)1 and C2 (21-day cycles). In pts defined as high risk by ctDNA (<2-log [100×-fold] reduction in plasma ctDNA after 1 R-CHOP cycle), R-CHOP was continued to C6, and glofitamab was administered as step-up dosing in C3 (D8, 2.5mg; D15, 10mg), at target dose (30mg) on D8 of C4-6, and on D1 of C7-10 (21-day cycles). Hospitalization for the first dose of glofitamab to assess cytokine release syndrome (CRS) was at the investigator's discretion; granulocyte colony-stimulating factors were advised for neutropenia prophylaxis. Real-time ctDNA analysis was performed centrally (AVENIO Oncology Assay for Non-Hodgkin's Lymphoma; Stokowski et al. ASH 2022). The primary endpoint was complete response (CR) at end of treatment (EOT). Responses were investigator-assessed after C2 and at EOT by positron emission tomography using Lugano criteria

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(Cheson et al. J Clin Oncol 2014). CRS was graded by ASTCT criteria (Lee et al. Biol Blood Marrow Transplant 2019); other adverse events (AEs) were assessed by CTCAE v5.0.

Results: At data cut-off (May 25, 2023), of 121 pts screened, 24 (19.8%) were defined as high risk by ctDNA (low risk, 47 [38.8%] pts; missing/not evaluable, 49 [40.5%] pts) and received ≥1 dose of study drug from C3D1 (safety population). Of the 24 high-risk pts, 15 reached the EOT assessment (14 pts completed treatment; 1 pt discontinued due to progressive disease [PD]), and 9 pts were ongoing on treatment. Of 24 pts, 2 pts had double-hit and 4 pts had triple-hit cytogenetics; median age was 61.5 years (range: 39-77); 15 (62.5%) pts had IPI 1-2 (IPI 1: 12.5%, IPI 2: 50.0%) and 9 (37.5%) pts had IPI 3-5 (IPI 3: 25.0%, IPI 4: 8.3%, IPI 5: 4.2%). In the safety population, 20 (83.3%) pts had AEs of any Grade (Gr); 15 (62.5%) pts had Gr 3/4 AEs, including neutropenia (11 [45.8%] pts); febrile neutropenia was not observed (**Table**). The most common (>20%) treatment-emergent AEs (any Gr) were neutropenia (13 [54.2%] pts) and diarrhea (6 [25.0%] pts). No Gr 5 AEs were reported. Nine (37.5%) pts experienced 17 serious AEs (14 glofitamab-related) including 7 CRS events.Gr ≥3 glofitamab-related AEs occurred in 8 (33.3%) pts. CRS events occurred in 5 (20.8%) pts: 4 (16.7%) pts had Gr 1 fever, 1 (4.2%) pt had Gr 2 fever and hypotension. CRS events occurred early and resolved at data cut-off; treatment (tocilizumab and dexamethasone) was administered for the Gr 2 CRS event only. One (4.2%) pt had a non-immunotoxic Gr 3 neurologic AE (presyncope, glofitamab-unrelated) that resolved by data cut-off. One pt died due to PD during treatment follow-up after discontinuing glofitamab. The interim CR rate was 46.7% (95% confidence interval [CI]: 21.3-73.4); CR at EOT was 80.0% (95% CI: 51.9-95.7) and the interim and EOT overall response rate were both 93.3% (95% CI: 68.1-99.8) (**Figure**) **.**

Conclusions: Glofit + R-CHOP in 1L LBCL defined as high risk by ctDNA, had a manageable safety profile and induced high response rates at the interim analysis and at EOT. Dynamic on-treatment risk assessment using ctDNA offers potential to identify high-risk pts with LBCL, independent of baseline characteristics.

Disclosures Falchi: *Roche:* Consultancy, Research Funding; *Genmab:* Consultancy, Research Funding; *Genentech:* Consultancy, Other: Advisory Board, Research Funding; *Abbvie:* Consultancy, Other: Advisory Board, Research Funding; *Seagen:* Other: Advisory Board; *ADC Therapeutics:* Other: Advisory Board; *AstraZeneca:* Consultancy. **Jardin:** *Janssen, Gilead, AbbVie, F. Hoffmann-La Roche Ltd, BMS, Takeda:* Honoraria. **Haioun:** *F. Hoffmann-La Roche Ltd France, Janssen-Cilag, Gilead Sciences, Miltenyi Biotec, Amgen, Takeda, Celgene:* Honoraria. **Joergensen:** *Janssen:* Consultancy; *Roche:* Consultancy; *SOBI:* Consultancy; *Incyte:* Consultancy; *Gilead:* Consultancy; *Genmab:* Consultancy; *AstraZeneca:* Consultancy; *Orion:* Consultancy; *Abbvie:* Consultancy. **Bastos-Oreiro:** *F. Hoffmann-La Roche Ltd, Kite, SEHH, AMHH:* Research Funding; *BMS, Kite, Novartis, F. Hoffmann-La Roche Ltd, Incyte, Abbvie:* Honoraria, Speakers Bureau; *Incyte, Kite:* Consultancy; *Gregorio Maranon Hospital:* Current Employment, Membership on an entity's Board of Directors or advisory committees; *SEHH, AMHH:* Membership on an entity's Board of Directors or advisory committees. **Mou:** *University of Iowa Hospitals and Clinics:* Current Employment. **Budde:** *AstraZeneca:* Consultancy, Research Funding; *ADC Therapeutics:* Consultancy; *Amgen:* Research Funding; *Roche:* Consultancy; *Merck:* Research Funding; *MustangBio:* Research Funding; *Novartis, Gilead, F. Hoffmann-La Roche Ltd, BeiGene, Genentech, Inc.:* Consultancy. **Bartlett:** *ADC Therapeutics, Foresight Diagnostics, Kite, F. Hoffmann-La Roche Ltd / Genentech, Inc., Seattle Genetics:* Membership on an entity's Board of Directors or advisory committees; *ADC Therapeutics, Autolus, BMS/Celgene, Forty Seven, Gilead/Kite Pharma, Janssen, Merck, Millennium, Pharmacyclics, F. Hoffmann-La Roche Ltd / Genentech, Inc., Seattle Genetics:* Research Funding; *Washington University School of Medicine:* Current Employment. **Zaucha:** *Pierre Fabre, Takeda, BMS, Gilead, Novartis, Pfizer, Amgen, F. Hoffmann-La Roche Ltd, Astra Zeneca, Abbvie:* Honoraria; *BMS:* Research Funding; *Medical University of Gdańsk:* Current Employment; *MSD:* Research Funding. **Martin Garcia-Sancho:** *Takeda:* Consultancy, Honoraria; *ADC Therapeutics America:* Consultancy, Honoraria; *Miltenyi:* Consultancy, Honoraria; *Ideogen:* Consultancy, Honoraria; *AbbVie:* Consultancy, Honoraria; *F. Hoffmann-La Roche Ltd, BMS / Celgene, Kyowa Kirin, Novartis, Gilead / Kite, Incyte, Lilly, ADC Therapeutics America, Miltenyi, Ideogen, Abbvie, Sobi:* Consultancy; *F. Hoffmann-La Roche Ltd, BMS/Celgene, Janssen, Gilead/Kite, Takeda, Eusa Pharma, Abbvie:* Honoraria; *Incyte:* Consultancy, Honoraria; *Lilly:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria; *Gilead / Kite:* Consultancy, Honoraria; *Kyowa Kirin:* Consultancy, Honoraria; *Clinigen:* Consultancy; *Eusa Pharma:* Consultancy, Honoraria; *Roche:* Consultancy, Honoraria; *Bristol Myers Squibb:* Consultancy, Honoraria. **Shah:** *Genentech, Inc.:* Current Employment. **Rees:** *Roche Products Ltd:* Current Employment. **McCord:** *F. Hoffmann La Roche Ltd:* Current equity holder in publicly-traded company; *Genentech, Inc.:* Current Employment. **Bazeos:** *F. Hoffmann La Roche Ltd:* Current Employment. **Tandon:** *F. Hoffmann La Roche Ltd:* Current Employment, Current holder of *stock options* in a privately-held company. **Doral:** *Genentech, Inc.:* Current Employment; *F. Hoffmann La Roche Ltd:* Current equity holder in publicly-traded company. **Troy-Barnes:** *Whittington Health NHS Trust (honorary contract):* Honoraria; *University College London Hospitals NHS Foundation Trust, North Middlesex University Hospital NHS Trust:* Ended employment in the past 24 months; *F. Hoffmann-La Roche Products Ltd:* Current Employment.

OffLabel Disclosure: Glofitamab (Columvi) is a CD20xCD3 T-cell-engaging bispecific antibody approved for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma or large B-cell lymphoma after 2 or more prior lines of therapy.

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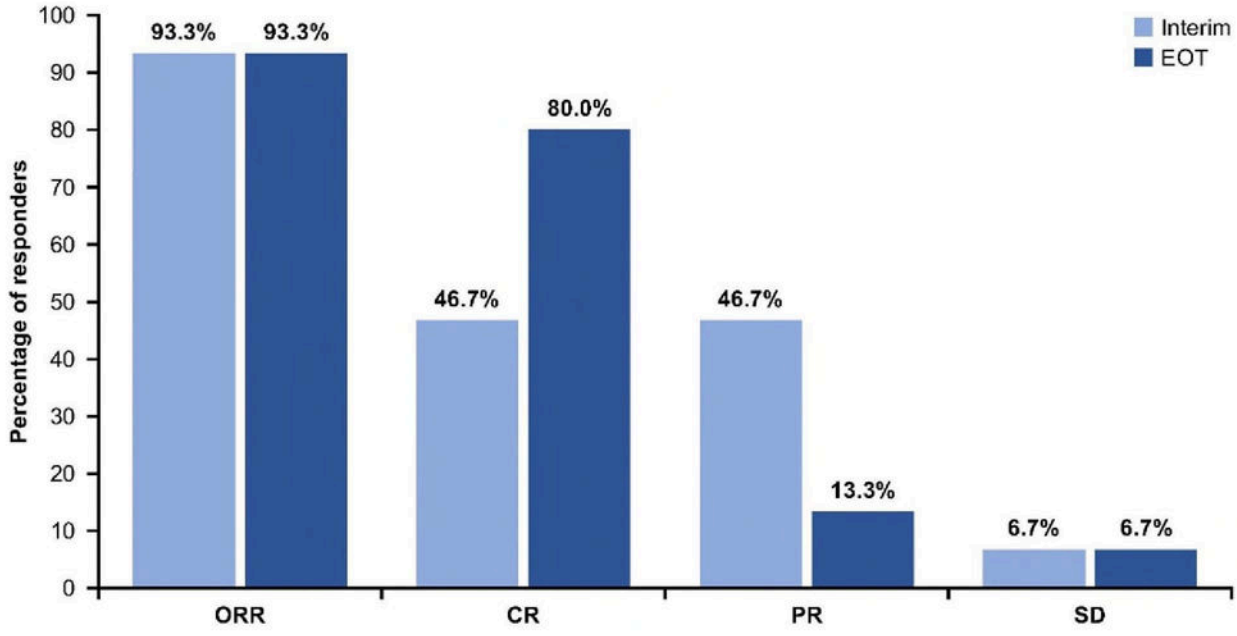
Table: Summary of AEs by highest NCI CTCAE grade (occurring in >10% of patients)

	Patients (N=24)		
n (%)	All Grades	Grade 1–2	Grade 3–4
Neutropenia*	13 (54.2)	2 (8.3)	11 (45.8)
Diarrhea	6 (25.0)	6 (25.0)	0
Cytokine release syndrome	5 (20.8)	5 (20.8)	0
COVID-19	4 (16.7)	4 (16.7)	0
Peripheral neuropathy	4 (16.7)	4 (16.7)	0
Anemia	4 (16.7)	3 (12.5)	1 (4.2)
Fatigue	3 (12.5)	3 (12.5)	0
Pruritis	3 (12.5)	3 (12.5)	0
Platelet count decreased	3 (12.5)	2 (8.3)	1 (4.2)

*Neutropenia: amalgamated outputs of neutropenia and neutrophil count decreased; multiple occurrences of the same AE in one individual are counted once at the highest grade for that AE.
AEs, adverse events; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute.

Figure: Response rates in patients at the interim analysis* and at EOT (n=15)



*Interim analysis was performed at the end of Cycle 2.
CR, complete response; EOT, end of treatment; ORR, overall response rate; PR, partial response; SD, stable disease.

Figure 1

https://doi.org/10.1182/blood-2023-173953

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