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POSTER ABSTRACTS

626.AGGRESSIVE LYMPHOMAS: PROSPECTIVE THERAPEUTIC TRIALS

Golcadomide (GOLCA; CC-99282), a Novel CELMoD Agent, Plus R-CHOP in Patients (pts) with Previously Untreated Aggressive B-Cell Lymphoma (a-BCL): Safety and Efficacy Results from Phase 1b Dose Expansion

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Introduction

Up to 40% of pts with diffuse large B-cell lymphoma (DLBCL) relapse after first-line chemo-immunotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). CELMoD agents such as GOLCA potently degrade target proteins Ikaros/Aiolos, resulting in antiproliferative, apoptotic, and immunomodulatory activity. GOLCA preferentially distributes to tissues and lymphoid organs. In a phase 1 study, GOLCA demonstrated a manageable safety profile with promising clinical activity as monotherapy in relapsed/refractory non-Hodgkin lymphoma (Michot et al. Blood 2021). CC-220-DLBCL-001 (NCT04884035) is an ongoing open-label, multicenter, dose escalation and expansion trial to assess safety and preliminary efficacy of CELMoD agents + R-CHOP for untreated a-BCL. GOLCA demonstrated a manageable safety profile in the dose escalation phase (Munoz et al. ICML 2023 abstract 438); we report combined results from the GOLCA dose escalation and expansion phases.

Methods

Eligible pts were ≥ 18 years, had untreated a-BCL with measurable disease (Lugano 2014), ECOG performance status ≤ 2 and International Prognostic Index (IPI) score 0-5 (2-5 in dose expansion). Pts were treated with R-CHOP plus GOLCA in 21-day (D) cycles (C) for up to 6C, or until disease progression/unacceptable toxicity/study withdrawal/physician decision. During dose escalation, pts received GOLCA at dose levels (DL): 0.2 mg D1-7 (DL-1), 0.4 mg D1-7 (DL1), and 0.4 mg D1-10 (DL2). DL2 met the dose-limiting toxicity threshold and was not continued in the expansion phase. During dose expansion, pts were randomized 1:1 to R-CHOP plus GOLCA at DL-1 or DL1. The primary endpoint for the expansion phase was safety of GOLCA at the recommended phase 2 dose (DL1) (based on adverse events [AEs]); secondary endpoints included overall response rate (ORR) and complete metabolic response (CMR) rate (assessed at end of treatment [EoT] by PET-CT [Lugano 2014]). Circulating tumor DNA (ctDNA) was measured at C1D1, C2D1, C3D1, and EoT using the PhasED-Seq assay.

Results

Across escalation and expansion, 78 pts were treated (DL-1, n = 35; DL1, n = 37; DL2, n = 6). Median age was 63.0 years, 56.4% were male, most had high-intermediate/high IPI (3-5) score at diagnosis (64.1%), Ann Arbor stage III-IV disease (83.3%), and germinal center B cell as cell of origin (51.3%); 83.3% pts had DLBCL histology. At data extraction (May 25, 2023), across

escalation and expansion, 38 pts had treatment ongoing, 31 completed treatment, and 35 continued to follow-up. A total of 3 pts discontinued due to AEs, 1 each at DL-1, DL1, and DL2.

In the safety population (n = 78), median GOLCA relative dose intensity (RDI) was 99.4%; 82.1% of pts received RDI ≥ 85%. RDI for CHOP components was > 90%. A total of 73 (93.6%) pts had ≥ 1 treatment-emergent AE (TEAE); 70 (89.7%) pts had ≥ 1 TEAE considered related to GOLCA; 65 (83.3%) pts had ≥ 1 grade 3/4 TEAE, 62 (79.5%) pts had ≥ 1 grade 3/4 TEAE considered related to GOLCA. The most frequently occurring grade 3/4 TEAEs were neutropenia (76.9%) and thrombocytopenia (32.1%) (**Table**). A total of 30 (38.5%) pts had serious TEAEs, most frequently febrile neutropenia (preferred term: 11 pts, 14.1%); 12 (15.4%) pts had serious TEAEs of infection or infestation (system organ class); 6 pts (7.7%) had venous thromboembolisms considered related to GOLCA (4 deep vein thrombosis, 1 superficial thrombosis, 1 pulmonary embolism). Treatment-related AEs leading to GOLCA dose reduction or discontinuation occurred in 11 (14.1%) pts and 6 (7.7%) pts, respectively.

After a median follow-up time of 4.1 months (range 0.3-12.3) and among all treated pts with EoT response available, 21/25 had CMR; together, 14/14 pts who received GOLCA 0.4 mg (DL1 and DL2) achieved CMR at EoT (**Figure**). Among efficacy-evaluable pts (n = 56), ORR was 91.1% (95% CI 80.4-97.0). Pts treated with GOLCA at DL-1 and DL1 who were ctDNA high-risk (≥ 2.5 log hGE/mL) responded to study treatment (CMR-PMR) and had early decreases in ctDNA (Kaplan et al. ASH 2023).

Conclusions

GOLCA demonstrated a manageable safety profile, showed good combinability with R-CHOP, and did not compromise delivery of curative treatment. Efficacy results and substantial ctDNA decrease indicate robust clinical activity in frontline DLBCL, with a high CMR rate at EoT, particularly among patients treated at DL1.

Study support

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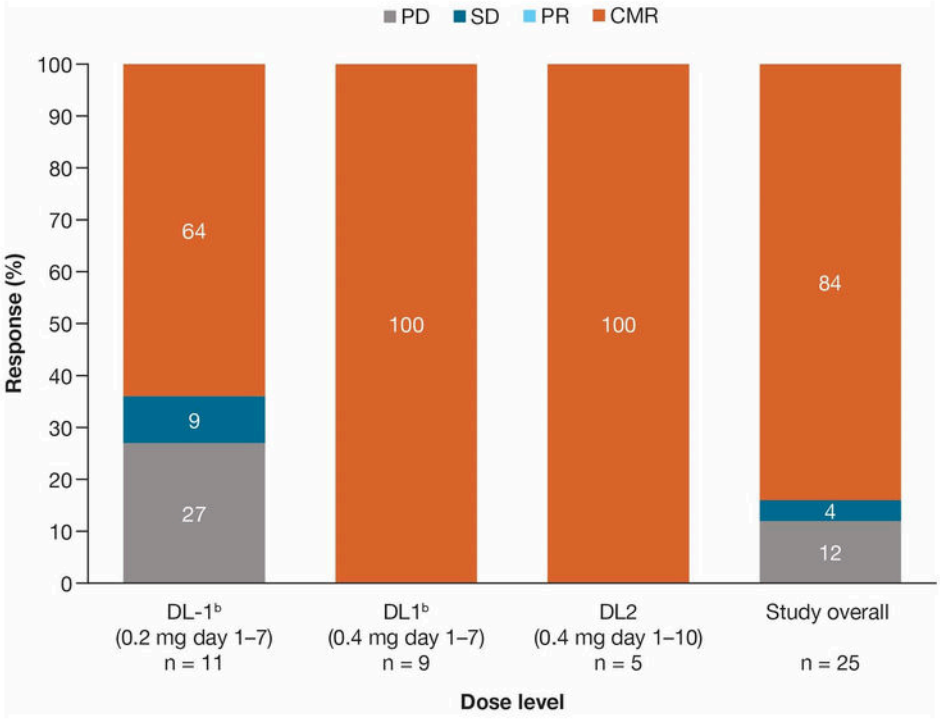
Table. Grade 3/4 TEAEs of interest[a]

System organ class Preferred term, n (%)	DL-1[b] (0.2 mg D1–7) n = 35	DL1[b] (0.4 mg D1–7) n = 37	Overall[c] (all doses) N = 78
Patients with ≥ 1 grade 3/4 TEAE	**31 (88.6)**	**29 (78.4)**	**65 (83.3)**
Blood and lymphatic system disorders	**30 (85.7)**	**28 (75.7)**	**63 (80.8)**
Neutropenia	28 (80.0)	27 (73.0)	60 (76.9)
Thrombocytopenia	4 (11.4)	17 (45.9)	25 (32.1)
Anemia	5 (14.3)	12 (32.4)	20 (25.6)
Febrile neutropenia	4 (11.4)	6 (16.2)	11 (14.1)
Lymphopenia	4 (11.4)	4 (10.8)	10 (12.8)
Infections and infestations[d]	**7 (20.0)**	**4 (10.8)**	**12 (15.4)**

Figure. ORR in patients with disease at EoT



[a]TEAEs were defined as any AE occurring or worsening after first dose of study treatment and up to 28 days after last dose of GOLCA or R-CHOP. Patients with multiple occurrences of TEAEs were counted only once in each category. System organ class and preferred terms were coded using Medical Dictionary for Regulatory Activities v26.0 or higher. TEAEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5; [b]Included patients treated with the dose specified during both escalation and expansion phases; [c]Included 6 patients treated with DL2 (0.4 mg D1–10) who did not continue into the expansion phase; [d]Included 1 case of COVID-19 in the DL-1 population.

AE, adverse event; CMR, complete metabolic response; D, day; DL, dose level; EoT, 6–8 weeks after end of treatment; GOLCA, golcadomide; ORR, overall response rate; PD, progressive disease; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; SD, stable disease; TEAE, treatment-emergent adverse event.

Figure 1

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