Golcadomide (CC-99282), a Potential First-in-class Oral CELMoD™ Agent, with R-CHOP as First-line Therapy in Aggressive B-cell Lymphoma: Safety and Efficacy in an Open-label, Multicenter, Phase 1b Trial

ABCL-503

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Introduction

- Nearly 60% of patients with diffuse large B-cell lymphoma (DLBCL) are cured with standard of care, first-line (1L) chemo-immunotherapy[1]
  - Up to 40% will have either primary refractory disease or relapse after an initial response, with a higher risk of disease progression or death in patients with a high International Prognostic Index (IPI) score[2]
- The IPI is widely used to predict outcomes; however, it fails to identify patients with inferior prognosis with the lower scores (IPI 1-2; **Figure 1**)[3]
- Patients with DLBCL, an IPI of 1-2, and very high lactate dehydrogenase (≥ 1.3 × upper limit of normal [ULN]) and/or bulky disease (single lesion of ≥ 7 cm maximum diameter) were identified as a high-risk subset[3]

Figure 1. Lymphoma Epidemiology of Outcomes study EFS by IPI group[3]

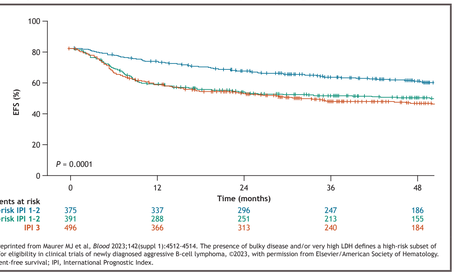
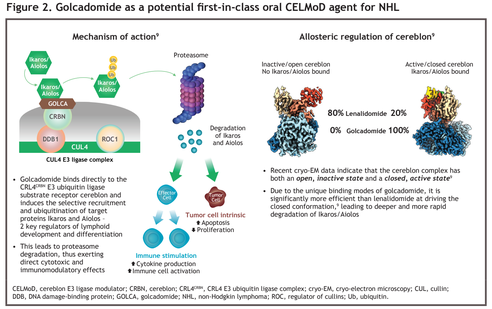


Figure reprinted from Maurer MJ et al, *Blood* 2023;142(suppl 1):4512-4514. The presence of bulky disease and/or very high LDH defines a high-risk subset of IPI 1-2 for eligibility in clinical trials of newly diagnosed aggressive B-cell lymphoma, ©2023, with permission from Elsevier/American Society of Hematology. EFS, event-free survival; IPI, International Prognostic Index.

- Golcadomide, a potential first-in-class oral cereblon E3 ligase modulator (CELMoD™) agent for non-Hodgkin lymphoma (NHL), degrades target proteins Ikaros and Aiolos to produce dual immunomodulatory and direct cell-killing antitumor activity (**Figure 2**)[4-6]
  - Golcadomide degrades Ikaros more potently than lenalidomide and preferentially distributes to lymphoid organs, where it stimulates CD8+ T and natural killer cells with cell-of-origin (COO)-independent cell-autonomous activity (**Figure 3**)
- CC-220-DLBCL-001 (NCT04884035) is an ongoing phase 1b, open-label, multicenter, dose escalation and expansion trial to assess the safety and preliminary efficacy of 1L golcadomide + rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone/-one (R-CHOP) in aggressive B-cell lymphoma (a-BCL)
  - Golcadomide + R-CHOP has shown promising efficacy with high rates of end-of-treatment (EOT) complete metabolic response (CMR) and undetectable minimal residual disease (uMRD) using phased variant enrichment and detection sequencing (PhasED-Seq), and manageable safety in patients with untreated a-BCL, but longer follow-up is needed to assess the durability of response[7,8]
- We report safety and 12-month efficacy results from the golcadomide dose escalation and expansion phases
  - Baseline circulating tumor DNA (ctDNA) levels and EOT uMRD rates are also reported

Figure 2. Golcadomide as a potential first-in-class oral CELMoD agent for NHL

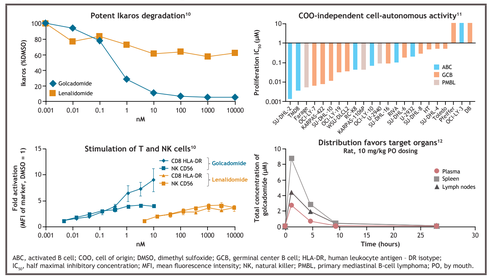


- Golcadomide binds directly to the $CRL4^{CRBN}$ E3 ubiquitin ligase substrate receptor cereblon and induces the selective recruitment and ubiquitination of target proteins Ikaros and Aiolos
- 2 key regulators of lymphoid development and differentiation
- This leads to proteasome degradation, thus exerting direct cytotoxic and immunomodulatory effects

- Recent cryo-EM data indicate that the cereblon complex has both an *open, inactive state* and a *closed, active state*[9]
- Due to the unique binding modes of golcadomide, it is significantly more efficient than lenalidomide at driving the closed conformation,[9] leading to deeper and more rapid degradation of Ikaros/Aiolos

CELMoD, cereblon E3 ligase modulator; CRBN, cereblon; $CRL4^{CRBN}$, $CRL4$ E3 ubiquitin ligase complex; cryo-EM, cryo-electron microscopy; CUL, cullin; DDB, DNA damage-binding protein; GOLCA, golcadomide; NHL, non-Hodgkin lymphoma; ROC, regulator of cullins; Ub, ubiquitin.

Figure 3. Preclinical rationale for golcadomide in DLBCL

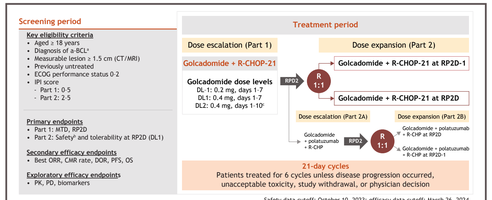


ABC, activated B cell; COO, cell of origin; DMSO, dimethyl sulfoxide; GCB, germinal center B cell; HLA-DR, human leukocyte antigen - DR isotype; IC_{50}, half maximal inhibitory concentration; MFI, mean fluorescence intensity; NK, natural killer; PMBL, primary mediastinal B-cell lymphoma; PO, by mouth.

Methods

- The study design of CC-220-DLBCL-001 is shown in **Figure 4**
- Key eligibility criteria included a diagnosis of a-BCL, at least 18 years of age, measurable lesion of ≥ 1.5 cm by CT or MRI, no prior treatment, and an IPI score of 0-5 (Part 1) or 2-5 (Part 2)
- Part 1 was a dose escalation phase to determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D) of golcadomide, which served as the primary endpoints
- Part 2 was a dose expansion phase designed to further assess the safety and preliminary efficacy of golcadomide + R-CHOP
  - Patients were randomized 1:1 to receive golcadomide + R-CHOP at 1 of 2 RP2D, 0.2 mg or 0.4 mg, for 21-day cycles
- Secondary endpoints included best objective response rate, CMR, duration of response, progression-free survival (PFS), and overall survival
- Phamacodynamics (PD), pharmacokinetics, and selected biomarkers served as exploratory endpoints

Figure 4. CC-220-DLBCL-001 study design:1L golcadomide + R-CHOP in a-BCL[8]



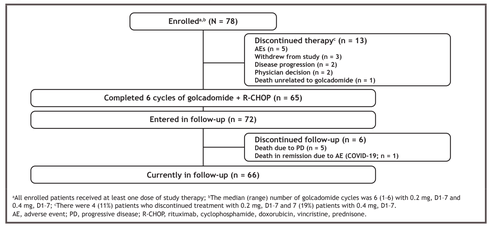
*a-BCL defined according to WHO 2016 classification, including DLBCL, high-grade BCL with *MYC* and *BCL2* and/or *BCL6* rearrangements, primary mediastinal BCL, primary cutaneous DLBCL-leg type, ALK-positive large BCL, EBV-positive DLBCL, and grade 3b FL[13]; †Safety-analysis population included all enrolled patients who received ≥ 1 dose of study drug; ‡Patients in dose level 2 met the dose-limiting toxicity threshold, and this dose was not continued in the expansion phase.

a-BCL, aggressive B-cell lymphoma; ALK, anaplastic lymphoma kinase; BCL, B-cell lymphoma; CMR, complete metabolic response; DL1/DL-1, dose-level 1; DL2, dose-level 2; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; EBV, Epstein-Barr virus; FL, follicular lymphoma; IPI, International Prognostic Index; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; R, randomization; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHP, rituximab, cyclophosphamide, doxorubicin, and prednisone; RP2D, recommended phase 2 dose; WHO, World Health Organization.

Results

- Patient disposition is shown in **Figure 5**
- At the efficacy data cutoff (March 26, 2024), the median (range) follow-up was 12.6 (0.7-22.4) months in the overall population
- Patients had similar baseline characteristics between the 2 treatment groups, with a higher proportion of females in the 0.4 mg group than in the 0.2 mg group (**Table 1**)
- Grade 3/4 treatment-emergent adverse events (TEAEs) were common, occurring in 91% and 92% of the 0.2 mg and 0.4 mg treatment groups, respectively (**Table 2**)
  - For both treatment groups, the most common TEAEs (occurring in ≥ 15% of patients) included neutropenia, thrombocytopenia, anemia, and febrile neutropenia
- Across treatment groups, the median relative dose intensity of golcadomide + R-CHOP ranged from 93% to 99% (**Table 2**)

Figure 5. CC-220-DLBCL-001 patient disposition



[a]All enrolled patients received at least one dose of study therapy; [b]The median (range) number of golcadomide cycles was 6 (1-6) with 0.2 mg, D1-7 and 0.4 mg, D1-7; [c]There were 4 (11%) patients who discontinued treatment with 0.2 mg, D1-7 and 7 (19%) patients with 0.4 mg, D1-7.
AE, adverse event; PD, progressive disease; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

Table 1. Baseline characteristics

	0.2 mg, D1-7 (n = 35)	0.4 mg, D1-7[a] (n = 37)
Age, median (IQR), years	62.0 (52.0-69.0)	63.0 (53.0-69.0)
Female	12 (34)	20 (54)
IPI at enrollment		
Low and low-intermediate risk (0-2)	13 (37)	11 (30)
Low-intermediate (1-2) with high-risk disease	8 (23)	4 (11)
High-intermediate risk (3)	16 (46)	16 (43)
High risk (4-5)	6 (17)	10 (27)
High-risk disease[b]	30 (86)	30 (81)
Cell of origin[c]		
GCB	18 (51)	18 (49)
ABC/non-GCB	12 (34)	12 (32)
Other[d]	5 (14)	7 (19)
Histology		
ALK-positive large BCL	0	1 (3)
Grade 3b FL	4 (11)	1 (3)
EBV-positive DLBCL NOS	1 (3)	0
DLBCL NOS	28 (80)	32 (87)
Double-hit lymphoma[e]	2 (6)	3 (8)

Data are n (%) unless otherwise noted. [a]Represents the pooled population from 0.4 mg, D1-7 from dose escalation plus RP2D in dose expansion; [b]Defined as IPI 3-5 or IPI 1-2 with ≥ 1 lesion with maximum diameter ≥ 7 cm and/or screening LDH ≥ 1.3 × ULN; [c]Determined by immunohistochemistry; [d]Includes unclassified, not done, or unknown; [e]High-grade BCL with *MYC* and *BCL2* and/or *BCL6* rearrangements.
ABC, activated B-cell-like; ALK, anaplastic lymphoma kinase; BCL, B-cell lymphoma; D, day; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; FL, follicular lymphoma; GCB, germinal center B-cell-like; IPI, International Prognostic Index; IQR, interquartile range; LDH, lactate dehydrogenase; NOS, not otherwise specified; RP2D, recommended phase 2 dose; ULN, upper limit of normal.

Table 2. Grade 3/4 TEAEs and treatment exposure

Grade 3/4 TEAEs	0.2 mg, D1-7 (n = 35)	0.4 mg, D1-7 (n = 37)
Grade 3/4 TEAE[a]	32 (91)	34 (92)
Blood and lymphatic disorders	32 (91)	33 (89)
Neutropenia	30 (86)	33 (89)
Thrombocytopenia	7 (20)	22 (59)
Anemia	7 (20)	15 (41)
Febrile neutropenia	7 (20)	9 (24)
Infections and infestations	7 (20)	7 (19)
Pneumonia	3 (9)	3 (8)
Nervous system disorders	2 (6)	3 (8)
Syncope	1 (3)	2 (5)
Gastrointestinal disorders	3 (9)	5 (14)
Diarrhea	2 (6)	3 (8)
Vomiting	0	3 (8)
Pulmonary embolism and deep vein thrombosis[b,c]	5 (14)	3 (8)

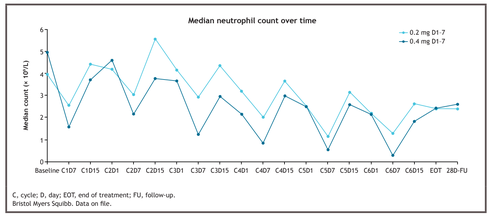
[a]System organ classes with events occurring in > 5% of the total patient population are shown. System organ class and preferred terms coded using Medical Dictionary for Regulatory Activities version 26.0 or higher. TEAEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5; [b]From different system organ classes (vascular disorders, nervous system disorders, and pulmonary disorders); [c]Includes all-grade events.
D, day; TEAE, treatment-emergent adverse event.

Median relative dose intensity

	0.2 mg, D1-7 (n = 35)	0.4 mg, D1-7 (n = 37)
Golcadomide, %	98	97
Cyclophosphamide, %	98	99
Doxorubicin, %	99	99
Vincristine, %	93	99

- The nadir and recovery of the median neutrophil count were similar between the 0.2 mg and 0.4 mg treatment groups, and occurred in a predictable fashion (**Figure 6**)
  - Only 2 (3%) patients had an absolute neutrophil count of < 1000 cells/μL by the start of the next cycle

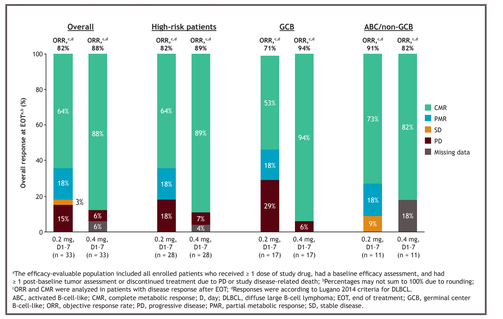
Figure 6. Neutrophil count over time



C, cycle; D, day; EOT, end of treatment; FU, follow-up.
Bristol Myers Squibb. Data on file.

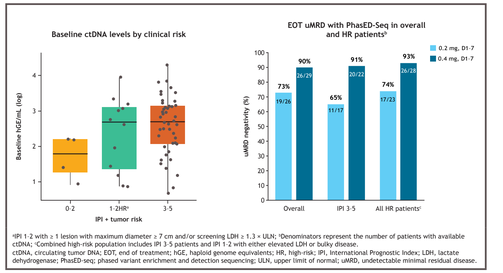
- Golcadomide (0.4 mg, D1-7) resulted in a high rate of CMR at EOT, independent of COO (**Figure 7**)
- Analysis of ctDNA levels by clinical risk and uMRD at EOT supports the efficacy of 0.4 mg golcadomide + R-CHOP in patients with high-risk DLBCL (**Figure 8**)
  - Among patients treated with 0.4 mg, D1-7 with available ctDNA data, 90% achieved uMRD at EOT
- Golcadomide (0.4 mg, D1-7) + R-CHOP resulted in durable CMRs and encouraging rates of PFS and OS at 1 year, in both the overall cohort and in patients with high-risk disease (**Figure 9**)

Figure 7. Efficacy of 0.2 mg and 0.4 mg, D1-7



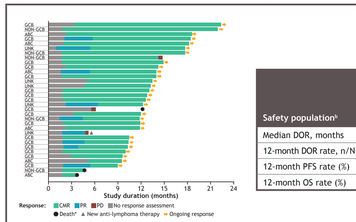
[a]The efficacy-evaluable population included all enrolled patients who received ≥ 1 dose of study drug, had a baseline efficacy assessment, and had ≥ 1 post-baseline tumor assessment or discontinued treatment due to PD or study disease-related death; [b]Percentages may not sum to 100% due to rounding; [c]ORR and CMR were analyzed in patients with disease response after EOT; [d]Responses were according to Lugano 2014 criteria for DLBCL.
ABC, activated B-cell-like; CMR, complete metabolic response; D, day; DLBCL, diffuse large B-cell lymphoma; EOT, end of treatment; GCB, germinal center B-cell-like; ORR, objective response rate; PD, progressive disease; PMR, partial metabolic response; SD, stable disease.

Figure 8. Baseline ctDNA levels and EOT uMRD by clinical risk



[a]IPI 1-2 with ≥ 1 lesion with maximum diameter ≥ 7 cm and/or screening LDH ≥ 1.3 × ULN; [b]Denominators represent the number of patients with available ctDNA; [c]Combined high-risk population includes IPI 3-5 patients and IPI 1-2 with either elevated LDH or bulky disease.
ctDNA, circulating tumor DNA; EOT, end of treatment; hGE, haploid genome equivalents; HR, high-risk; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PhasED-Seq, phased variant enrichment and detection sequencing; ULN, upper limit of normal; uMRD, undetectable minimal residual disease.

Figure 9. Treatment response[a] in patients at 0.4 mg, D1-7



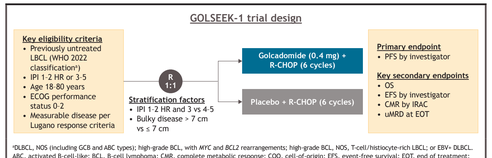
Safety population[b]	0.4 mg, D1-7 (n = 37)	0.4 mg, D1-7 high risk patients (n = 31)
Median DOR, months	NR	NR
12-month DOR rate, n/N (%)	32/33 (97)	27/28 (96)
12-month PFS rate (%)	85	86
12-month OS rate (%)	91	93

*Two patients achieved CMR but did not have an EOT efficacy assessment due to treatment unrelated death (COVID-19 and cardiac arrest).
[a]Determined by immunohistochemistry; [b]The safety-analysis population included all enrolled patients who received ≥ 1 dose of study drug.
ABC, activated B-cell-like; CMR, complete metabolic response; D, day; DOR, duration of response; EOT, end of treatment; GCB, germinal center B-cell-like; NR, not reached; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; UNK, unknown.

Conclusions

- Golcadomide + R-CHOP demonstrated a manageable safety profile, and the addition of golcadomide to R-CHOP did not compromise the delivery of curative treatment
- Golcadomide (0.4 mg D1-7) combined with R-CHOP resulted in:
  - High rates of durable CMRs irrespective of COO, with promising 12-month PFS rates in the overall and high-risk populations
  - High EOT uMRD rates with high rates of durable responses
    - Baseline ctDNA levels were similar in patients with high-risk IPI 1-2 and IPI 3-5, supporting prior observations that these groups have similar prognoses[7,8]
- These data support the ongoing randomized phase 3 GOLSEEK-1 trial (NCT06356129) of golcadomide + R-CHOP versus R-CHOP alone as 1L treatment in patients with high-risk large B-cell lymphoma[15]

GOLSEEK-1 trial design



†DLBCL, NOS (including GCB and ABC types); high-grade BCL, with *MYC* and *BCL2* rearrangements; high-grade BCL, NOS, T-cell/histiocyte-rich LBCL; or EBV+ DLBCL.
ABC, activated B-cell-like; BCL, B-cell lymphoma; CMR, complete metabolic response; COO, cell-of-origin; EFS, event-free survival; EOT, end of treatment; GCB, germinal center B-cell-like; HR, high-risk; IPI, International Prognostic Index; IRAC, Independent Response Adjudication Committee; LBCL, large B-cell lymphoma; NOS, not otherwise specified; OS, overall survival; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R, randomized; uMRD, undetectable minimal residual disease; WHO, World Health Organization.

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