BOLOGNA 16/JAN/2024

New drugs in Hematology

Non-Hodgkin Lymphoma

Golcadomide (CC99282)

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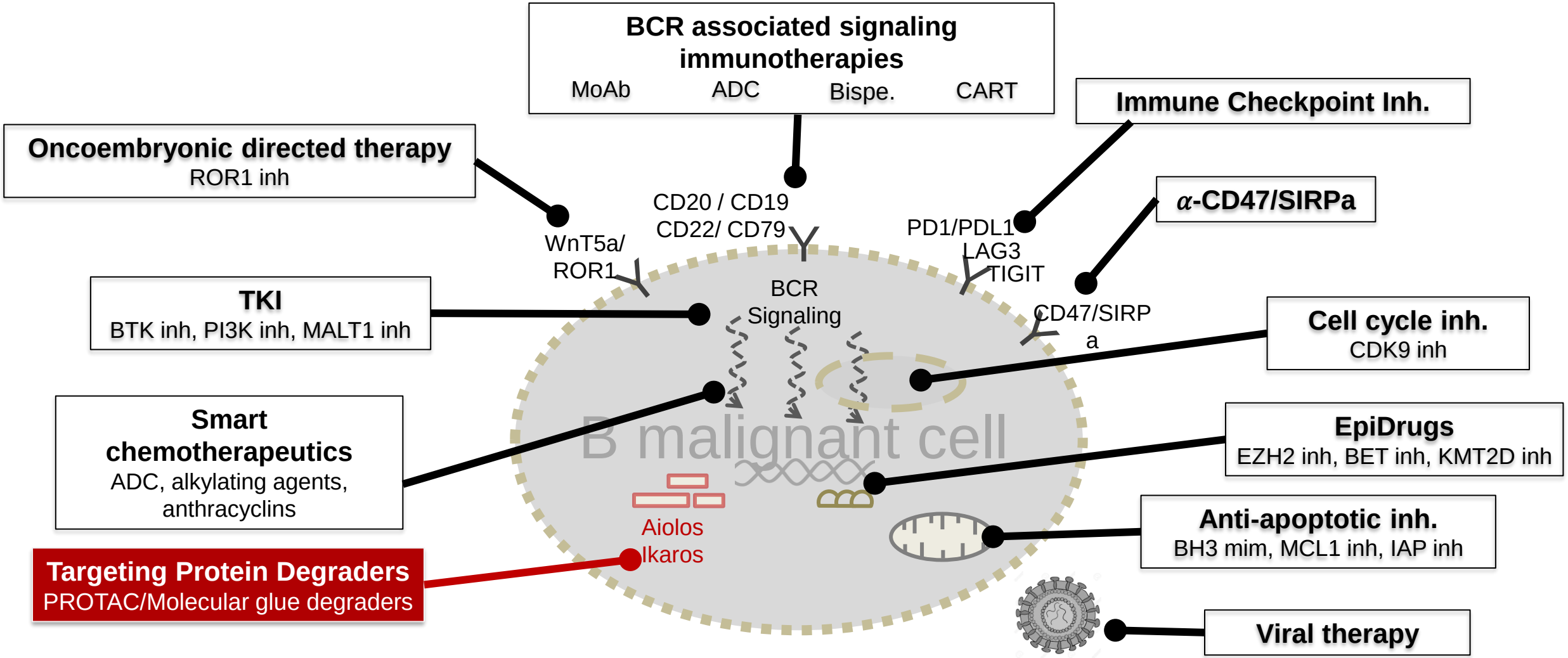
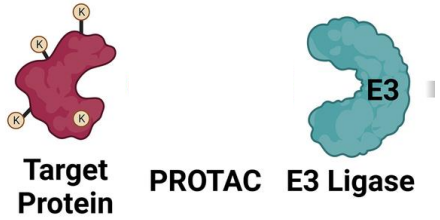
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Astex	x						
Glaxosmithkline	x						x
Ideogen							x
MSD							x
Therakos/Mallinckrodt						x	
Regeneron						x	
BMS							x

Main new therapeutics targets in large B-cell lymphoma



Targeted Protein Degraders (TPD), general summary mechanism of action

Resulting in the catalytic proteasomal degradation of their targets



Preliminary Efficacy evaluation in humans of protein degraders targeting Aiolos/Ikaros pathways in RR DLBCL

summary of reported data (for study ≥ 20 subjects)

Drug in monotherapy	Number of subjects	Method	Median previous line (range)	Post ASCT	Post CAR-T	ORR (CR)	References
LEN (CC5013)	N=153	Retrospective study	2 (1-6)	17%	N/A	29% (24%)	Broccoli A, Oncologist, 2019
LEN (CC5013)	N= 600	Meta-analysis	Not specified	Not specified	N/A	33% (16%)	Jia Li, Front Oncol, 2021
AVA (CC122)	N=97	Phase 1b	3 (1-13)	19%	N/A	28% (9%)	Carpio C, Blood 2020
GOL (CC99282)	N=28	Phase 1a	3 (1-8)	20%	28%	32% (11%)	Michot JM, EHA 2022
GOL (CC99282)	N=46	Phase 1b	4 (1-11)	N/A	N/A	42% (19%)	Chavez J, ASH 2023

Efficacy and safety of golcadomide, a novel cereblon E3 ligase modulator (CELMoD) agent, combined with rituximab in a phase 1/2 open-label study of patients with relapsed/refractory non-Hodgkin lymphoma

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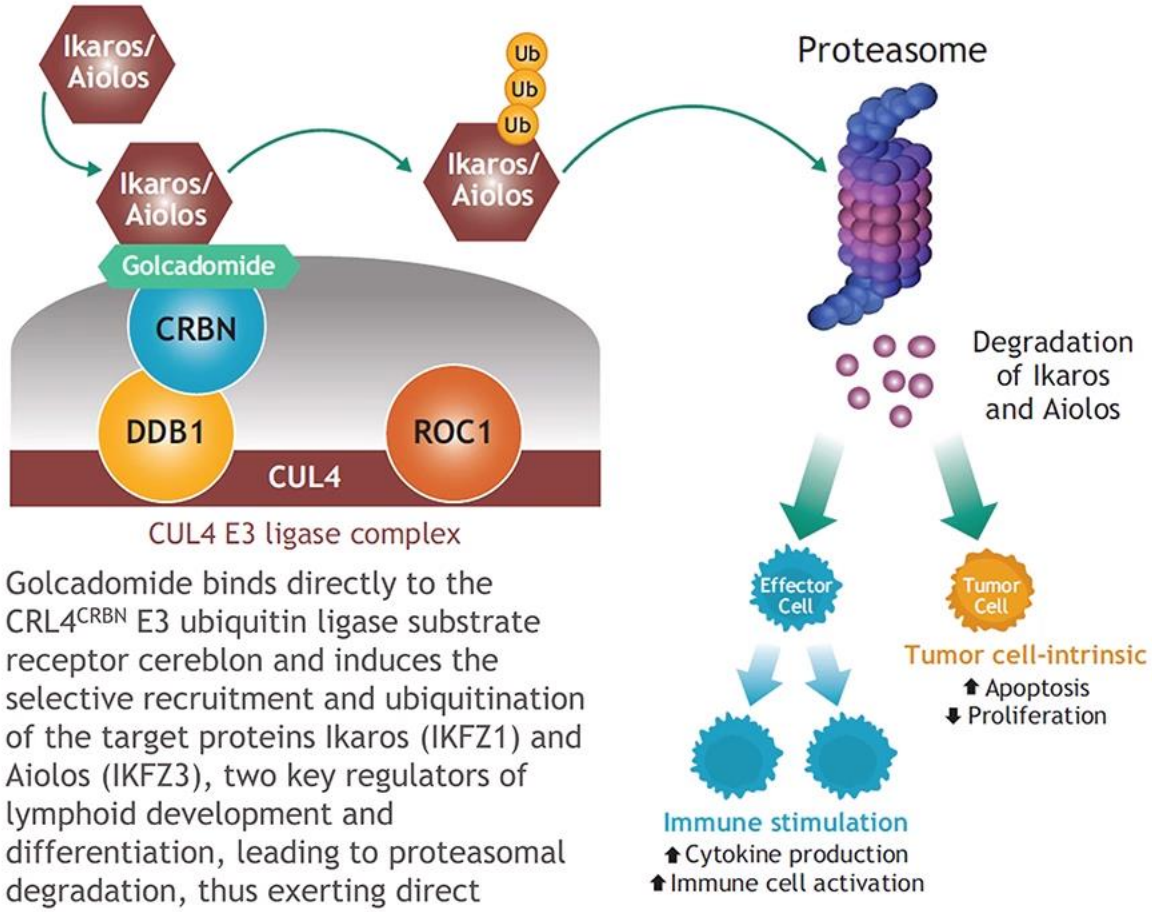
Figure 1. Golcadomide is a potent first-in-class lymphoma CELMoD with pleotropic MoA

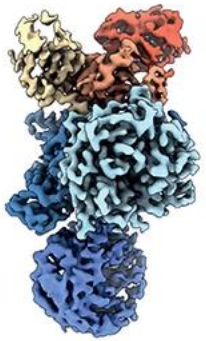


Golcadomide binds directly to the CRL4^{CRBN} E3 ubiquitin ligase substrate receptor cereblon and induces the selective recruitment and ubiquitination of the target proteins Ikaros (IKFZ1) and Aiolos (IKFZ3), two key regulators of lymphoid development and differentiation, leading to proteasomal degradation, thus exerting direct cytotoxic and immunomodulatory effects

Allosteric regulation of cereblon[1]

Inactive/open cereblon
No Ikaros/Aiolos bound

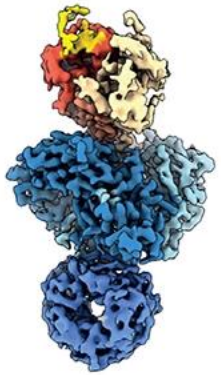
Active/closed cereblon
Ikaros/Aiolos bound



75% **Lenalidomide** 25%

50% **Iberdomide** 50%

0% **Golcadomide** 100%

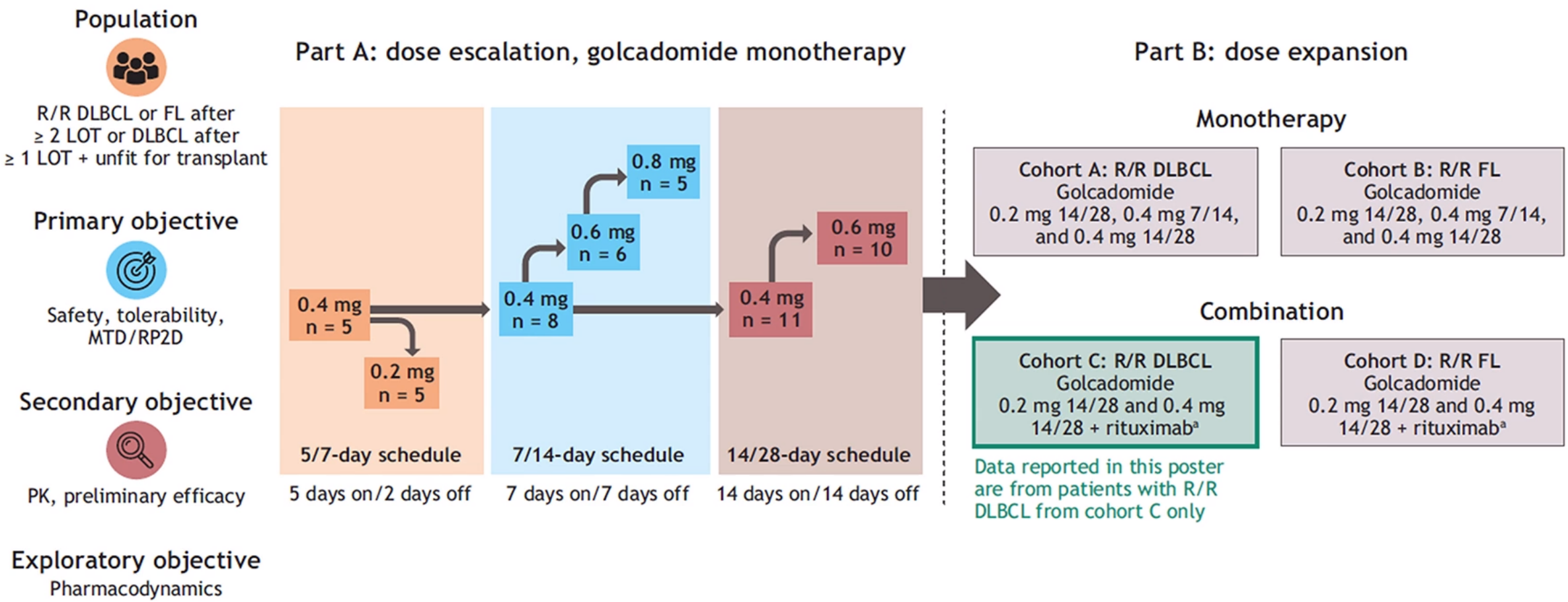


- Recent cryo-EM data indicates that the cereblon complex has both an ***open, inactive state*** and a ***closed, active state***, and that IMiDs and CELMoDs drive the closed conformation[1]
- Due to the unique binding modes of golcadomide, it is more efficient than lenalidomide at driving the closed conformation,[1] leading to deeper and more rapid degradation of Ikaros/Aiolos

1. Watson ER, et al. *Science* 2022;378:549-553.

CELMoD, cereblon E3 ligase modulator; CRBN, cereblon; cryo-EM, cryogenic electron microscopy; CUL4, cullin 4; DDB1, DNA damage-binding protein 1; IMiD, immunomodulatory drug; MoA, mechanism of action; ROC1, regulator of cullins 1; Ub, ubiquitin.

Figure 2. CC-99282-NHL-001 study design



[a]Rituximab dosing was 375 mg/m^2 IV on Days 1, 8, 15, and 22 of Cycle 1, and Day 1 of Cycles 2-5.
DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IV, intravenous; LOT, line of therapy; MTD, maximum tolerated dose; PK, pharmacokinetics; R/R, relapsed or refractory; RP2D, recommended phase 2 dose.

Table 1. Demographics and baseline characteristics

Characteristic	Part B cohort C Golcadomide + RTX (N = 46)
Age, years, median (range)	64 (20-86)
Sex, male, n (%)	30 (65)
Diagnosis, n (%)[a]	
DLBCL	43 (93)
Double-hit positive[b]	3 (7)
Triple-hit positive[c]	3 (7)
Cell of origin, n (%)	
GCB	11 (24)
ABC	7 (15)
Unknown[d]	28 (61)
Time from initial diagnosis to first dose, months, median (range)	23 (1-219)
ECOG PS score, n (%)	
0	15 (33)
1	24 (52)
2	5 (11)
Treatment history	
No. of prior lines of systemic anti-cancer therapy, median (range)	4 (1-11)
Prior stem cell transplant, n/N (%)[e]	5/44 (11)
Prior CAR T cell therapy, n/N (%)[e]	27/44 (61)
Best response to last regimen, n (%)[a]	
CR or PR	12 (26)
Never achieved objective response	24 (52)
Missing/unknown	7 (15)

Data cutoff: September 7, 2023.
[a]Diagnosis and prior therapies missing for 3 patients.. [b]Double hit is defined as positive case of MYC + BLC2 or MYC + BCL6. [c]Triple hit is defined as positive case of MYC + BCL2 + BCL6. [d]Includes unclassified, not done, unknown, and missing. [e]Data are from the safety population of n = 44.
ABC, activated B-cell-like; CAR, chimeric antigen receptor; CR, complete response; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B cell; PR, partial response; RTX, rituximab.

Table 4. TEAEs related to golcadomide reported in ≥ 2 patients at the 0.2-mg and 0.4-mg doses

- In the safety population neutropenia was the most TEAE, occurring in 22 (50%) patients, all of which were grade 3/4
  - All neutropenia was considered related to golcadomide, comprising 10/24 (42%) patients treated at the 0.2-mg and 12/20 (60%) patients treated at the 0.4-mg dose level
  - Febrile neutropenia occurred in 2 (5%) patients, 1 patient at each dose level
  - Granulocyte colony-stimulating factors were used in 22 (50%) patients

TEAE, n (%)	Golcadomide 0.2 mg + RTX (n = 24)		Golcadomide 0.4 mg + RTX (n = 20)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Patients with at least one TRAE	16 (67)	11 (46)	14 (70)	12 (60)
Neutropenia	10 (42)	10 (42)	12 (60)	12 (60)
Diarrhea	4 (17)	0	0	0
Constipation	2 (8)	0	2 (10)	0
Anemia	1 (4)	0	3 (15)	3 (15)
Asthenia	2 (8)	1 (4)	1 (5)	0
Fatigue	1 (4)	0	2 (10)	1 (5)
Pyrexia	1 (4)	0	2 (10)	1 (5)
Lymphopenia	0	0	3 (15)	0
Thrombocytopenia	0	0	3 (15)	3 (15)

- Six patients had SAEs related to golcadomide; the only SAEs occurring in > 1 patient were pneumonia and pyrexia (both n = 2)
- Four grade 5 TEAEs occurred (infection, n = 3; tubulo-interstitial nephritis, n = 1); only 1 (pneumonia) was considered related to study treatment
- TEAEs led to golcadomide discontinuation in 5 (11%) patients (0.2 mg, n = 3; 0.4 mg, n = 2) and rituximab discontinuation in 5 (11%) patients

RTX, rituximab; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

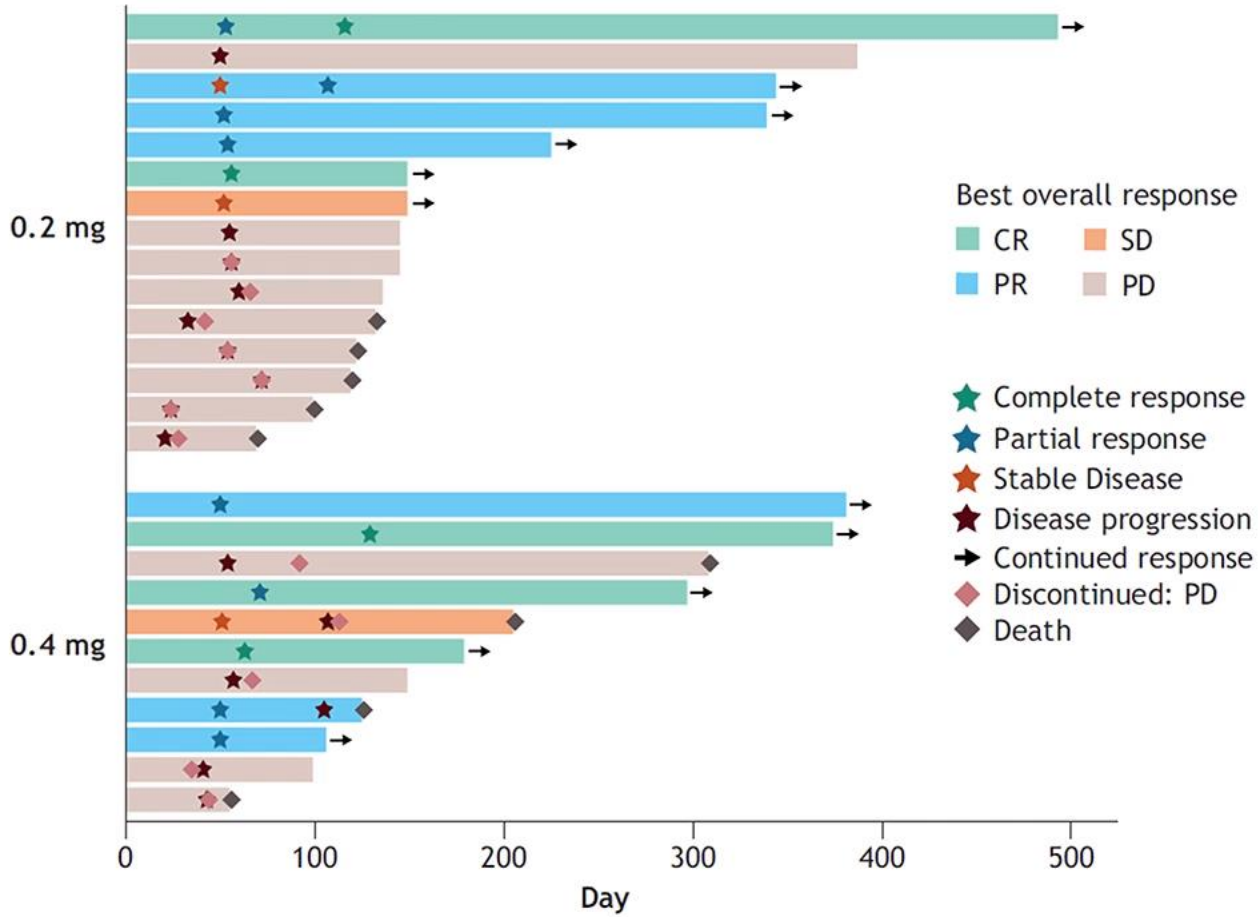
Table 3. Best overall response in the efficacy evaluable population at the 0.2-mg and 0.4-mg doses

Response, n (%)	Efficacy-evaluable population		
	0.2 mg (n = 15)	0.4 mg (n = 11)	Overall (n = 26)
Overall response rate	5 (33)	6 (55)	11 (42)
Complete response 95% CI	2 (13) 1.7-40.5	3 (27) 6.0-61.0	5 (19) 6.6-39.4
Partial response 95% CI	3 (20) 4.3-48.1	3 (27) 6.0-61.0	6 (23) 9.0-43.6
Stable disease 95% CI	1 (7) 0.2-31.9	1 (9) 0.2-41.3	2 (8) 0.9-25.1
Progressive disease 95% CI	9 (60) 16.3-67.7	4 (36) 30.8-89.1	13 (50) 29.9-70.1

- Median duration of golcadomide treatment was 8 weeks (range, 2.4–68), and median follow-up was 5.9 weeks (range, 0.3–16.2)
- In the efficacy-evaluable population (n = 26), overall response rate (CR + PR) was 42% (n = 11), with CR occurring in 19% (n = 5) of patients

CI, confidence interval; CR, complete response; PR, partial response.

Figure 3. Disposition for individual efficacy evaluable patients at 0.2 and 0.4mg doses[a]



- Median duration of response was 7.5 months (range, 1.8–14.5), including a durable response > 14 months in 1 patient

[a]Each bar shows time from treatment start to earliest of death date, cutoff date, and last known alive date. Continued response is defined as censored duration of response/duration of stable disease. First assessment shown for best overall response for ongoing patients and up to treatment discontinuation for discontinued patients. First efficacy assessment in C3D1 and every 2 cycles during active treatment.

Pharmacodynamic biomarkers and ctDNA support the mechanism of action and clinical efficacy of golcadomide (CC-99282) combined with R-CHOP in previously untreated aggressive B cell lymphoma

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CC-220-DLBCL-001 study design

Screening period

Key eligibility criteria

- Age ≥ 18 years
- Diagnosis of a-BCL
- Measurable lesion ≥ 1.5 cm (CT/MRI)
- Previously untreated
- ECOG PS 0-2
- IPI score
  - Part 1: 0-5
  - Part 2: 2-5

Primary endpoints

- Part 1: MTD, RP2D
- Part 2: Safety and tolerability at RP2D

Secondary efficacy endpoints

- Best ORR, CMR rate, TTR, DOR, PFS, OS

Treatment period

Dose escalation (part 1)

GOLCA + R-CHOP-21
(n = 78)

GOLCA dose levels
- DL-1: 0.2 mg days 1-7
- DL1: 0.4 mg days 1-7
- DL2: 0.4 mg days 1-10

Dose expansion (part 2)

R[a]

GOLCA + R-CHOP-21 at RP2D-1

GOLCA + R-CHOP-21 at RP2D[b]

- Additional details on trial design, patient population, and results are presented in poster 4459[1]

a-BCL defined according to WHO 2016 classification, including: DLBCL, high-grade B cell lymphoma 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.[2]

[a]Randomization for the purpose of dose optimization; [b]The safety review committee may reconsider the RP2D in regard to emergent AEs experienced from cycle 1 day 1 through completion of cycle 6.

a-BCL, aggressive B-cell lymphoma; ALK, anaplastic lymphoma kinase; CMR, complete molecular response; DL, dose level; DOR, duration of response; EBV, Epstein-Barr virus; FL, follicular lymphoma; IPI, International Prognostic Index; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R, randomization; R-CHOP-21, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone in 21-day cycles; RP2D, recommended phase 2 dose; RP2D-1, 1 step below recommended phase 2 dose; TTR, time to response.

1. Hoffman MS, et al. Poster presentation at the American Society of Hematology (ASH) Annual Meeting; December 9-12, 2023; San Diego, CA, USA. Poster 4459; 2. Swerdlow SH, et al. *Blood* 2016;127:2375-2390.

Kaplan M, et al. ASH 2023 [Presentation #1631]

Methods

Translational analyses

- Biomarker data from Part 1 and Part 2 were combined
  - DL1 and dose-reduced DL2 (DL2 reduced to DL1 by C1D7) data were combined for analysis
- Data cutoff was July 24, 2023 for Ikaros and immunophenotyping, and May 10, 2023 for ctDNA

Ikaros

- Ikaros levels in peripheral blood were measured by flow cytometry in CD3+ T cells and CD19+ B cells (CERBA Research, Zwijnaarde, Belgium)
  - ≥ 200 cells in gate were required for analysis

Immunophenotyping

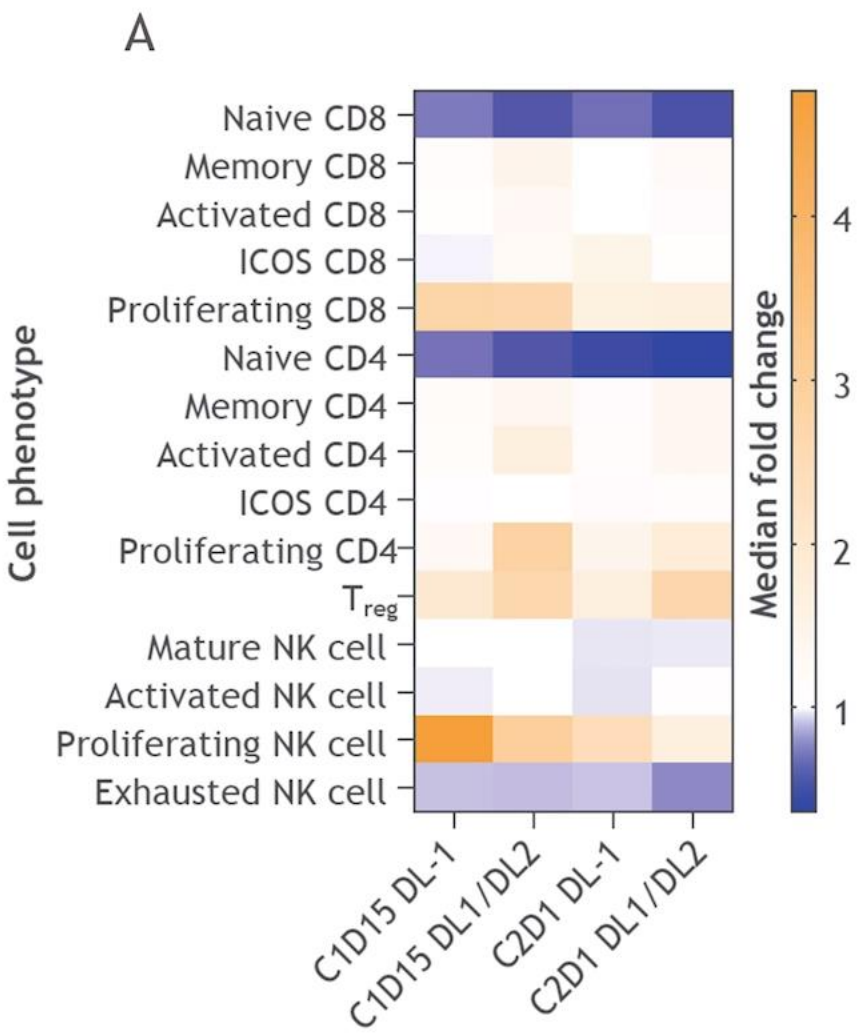
- Modulation of T cell and NK cell subsets in peripheral blood was measured using flow cytometry (Q^2 Solutions, Durham, NC)

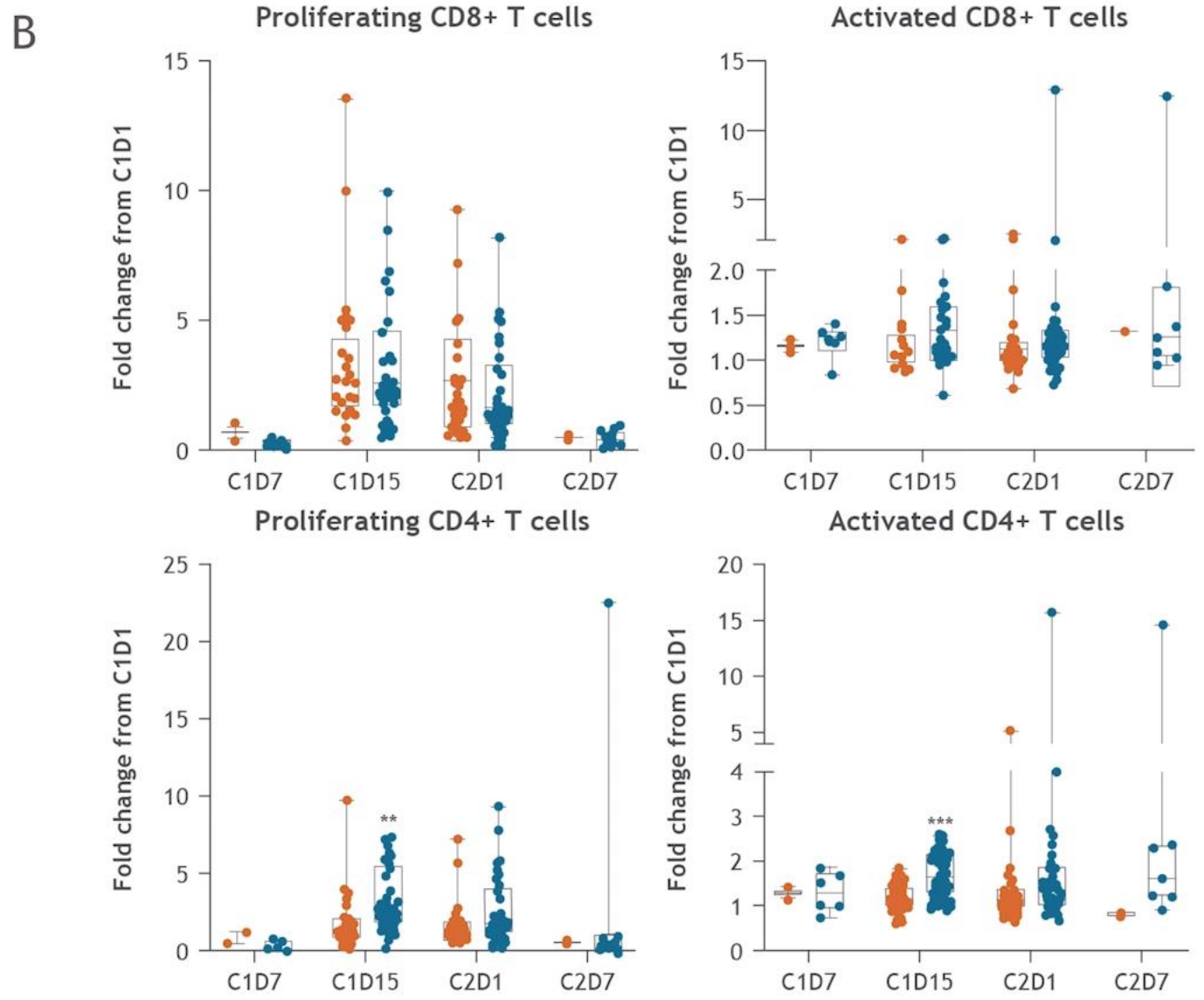
ctDNA

- Baseline and on-treatment ctDNA levels were measured using PhasED-Seq (Foresight Diagnostics, Aurora, CO), an off-the-shelf next-generation sequencing assay to detect a defined panel of phased variants in NHL[1]
- Proportions of patients reaching pre-defined changes in ctDNA levels[2] and maintenance of MRD negativity (undetectable ctDNA or < 0.00002% variant allele fraction) over time were analyzed

C, cycle; D, day; MRD, minimal residual disease; NHL, non-Hodgkin lymphoma; PhasED-Seq, phased variant enrichment and detection sequencing.
1. Kurtz DM, et al. *Nat Biotech* 2021;39:1537–1547; 2 Kurtz DM, et al. *J Clin Oncol 2018*;36:2845–2853.

Peripheral immunophenotyping of T cells and NK cells with GOLCA + R-CHOP





Median fold changes are as a percentage of gate.
*P < 0.05; **P < 0.01; ***P < 0.001.

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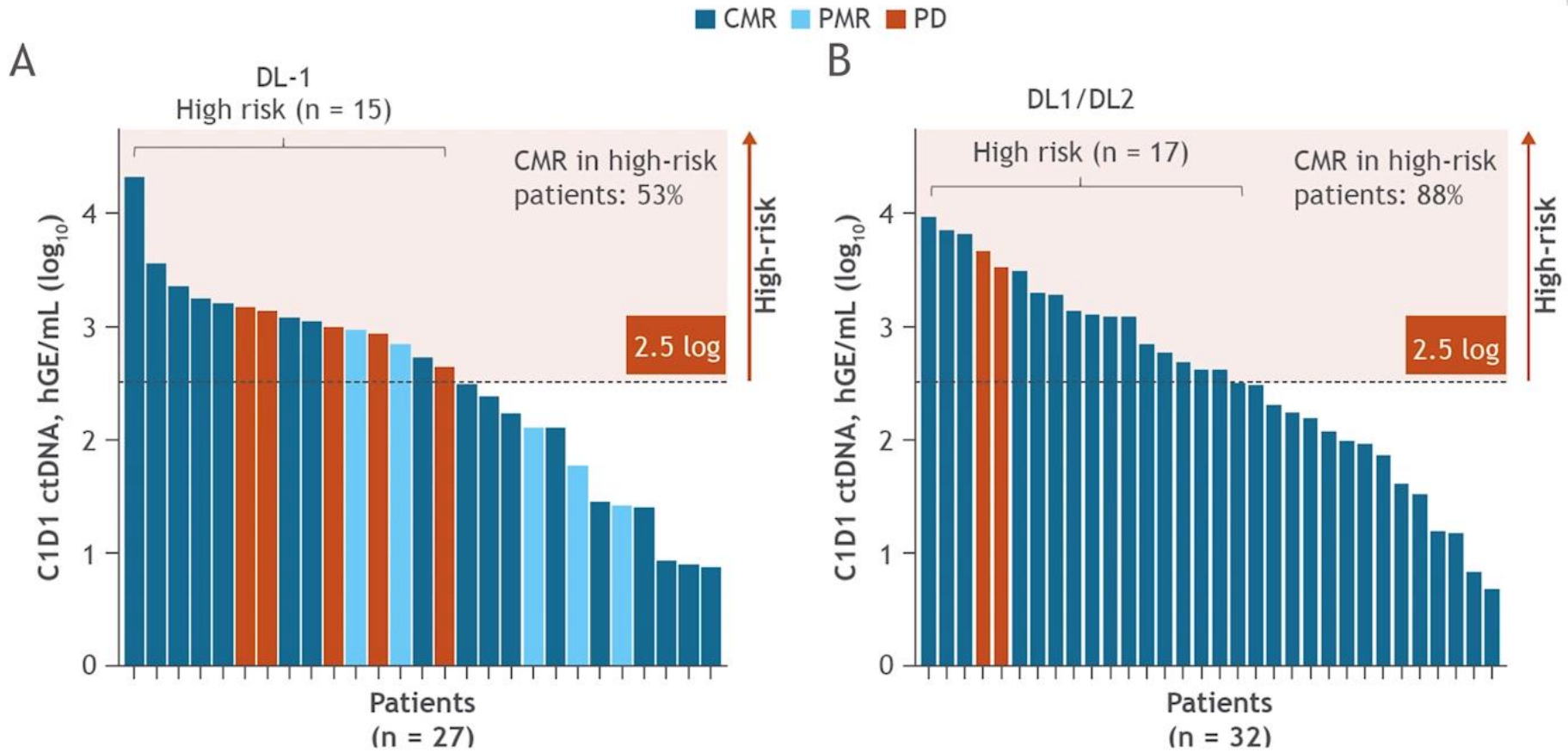
Association of baseline ctDNA levels with risk and response



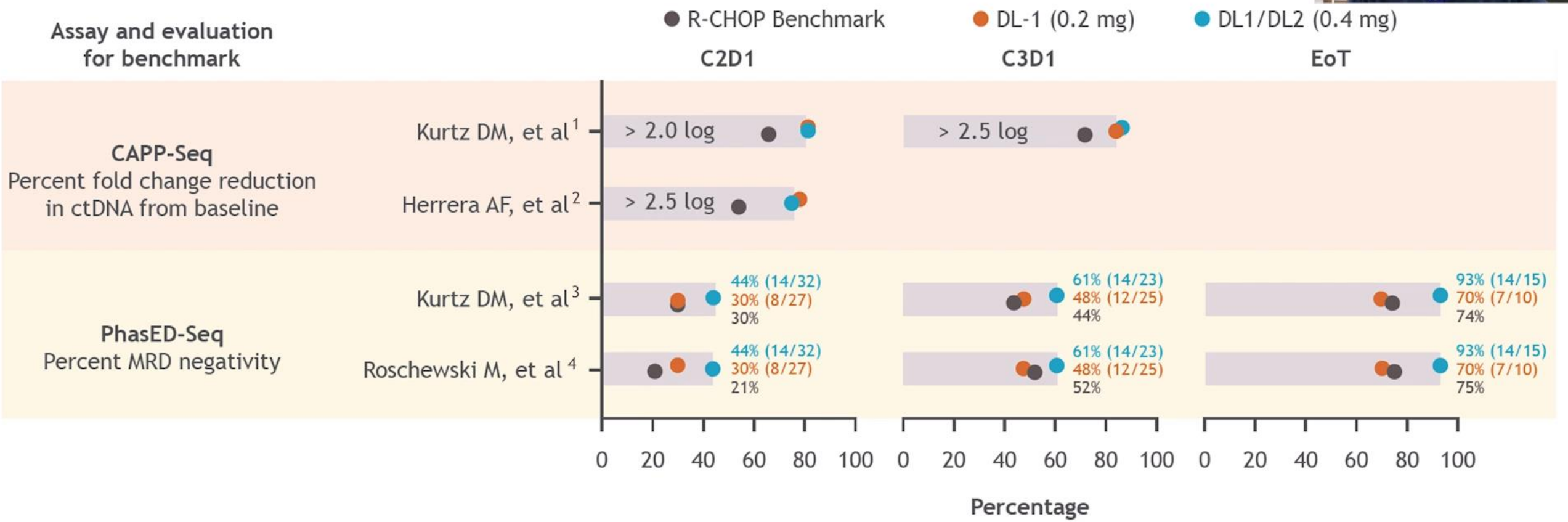
- The number of patients with high-risk disease, defined as patients with > 2.5-log baseline ctDNA[1], were balanced between DL-1 and DL1/DL2 groups and the CMR rate was significantly higher with DL1/DL2 versus DL-1 ($P < 0.05$)

hGE, haploid genome equivalents; PMR, partial molecular response; PD, progressive disease; NE, not evaluable.

1. Kurtz DM, et al. *J Clin Oncol* 2018;36:2845-2853.

Kaplan M, et al. ASH 2023 [Presentation #1631]

Proportion of patients meeting published response benchmark criteria



- The proportion of patients who had ctDNA reductions below predefined thresholds by each cycle or who achieved MRD negativity was higher overall in the GOLCA DL1/DL2 group
  - The DL1/DL2 group exceeded published benchmark criteria defined by both fold changes on-treatment and MRD negativity[1-4]

CAPP-Seq, cancer personalized profiling by deep sequencing.

1. Kurtz DM, et al. *Nat Biotech* 2021;39:1537–1547; 2. Herrera AF, et al. *Blood* 2022;140(suppl S1):36(28):1297–1300; 3. Kurtz DM, et al. *J Clin Oncol 2018*;36:2845–2853; 4. Roschewski M, et al. *Blood* 2022;140(suppl S1):785–786.

Kaplan M, et al. ASH 2023 [Presentation #1631]

Conclusion golcadomide for NHL

- **Safety favorable**
  - > At this time no « off target » AE (skin rash / thrombosis) as observed with other drugs such as LEN
  - > Neutropenia leading AE to manage
- **Confirmed promising efficacy in monotherapy for RR DLBCL (and RR FL)**
  - > Recent data ASH2023 : 41 ORR (19% PR) for RR DLBCL
  - > Quality of responses by long reponders observed (protein degrader class avantage over ITK?)
- **Combination data with R-CHOP phase 1b data was promising and phase 3 R-CHOP frontline expected**

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