American Society of Hematology
Helping hematologists conquer blood diseases worldwide

ABSTRACT #768

Preliminary anti-leukemia activity from a phase 1 study of CLN-049, a novel anti-FLT3 x anti-CD3 bispecific T-cell engager, in relapsed/refractory (R/R) acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)

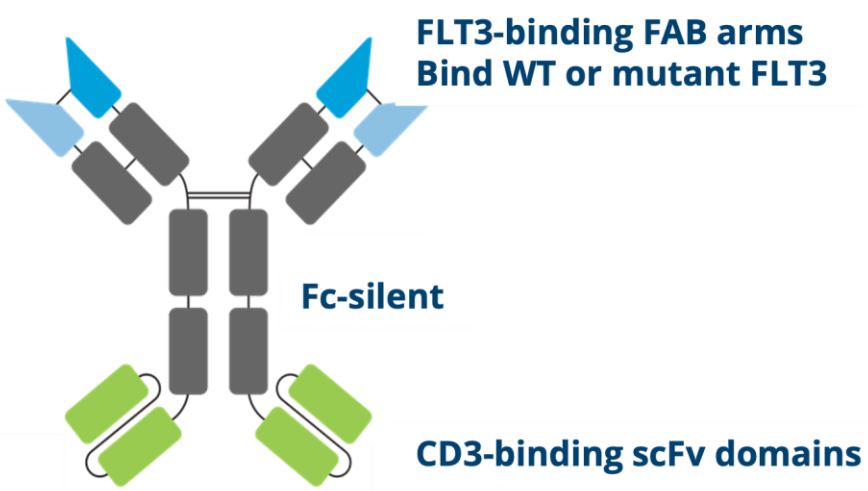
Maher Abdul-Hay, MD, Colin Vale, MD, Onyee Chan, MD, Namrata S Chandhok, MD, Courtney D DiNardo, MD, MSCE, Gary J Schiller, MD, Eunice S Wang, MD, Sanghee Hong, MD, Kimo Bachiashvili, MD, Mohammed S Chaudhry, MD, PhD, Kristy G Kuplast-Barr, BS, Kaida Wu, MD, PhD, Todd Shearer, PhD, Thuy Hoang, PhD, Irina Shapiro, PhD, Máire F Quigley, PhD, Jeffrey A Jones, MD, MPH, MBA, William Blum, MD, David A Sallman, MD, Ghayas C Issa, MD

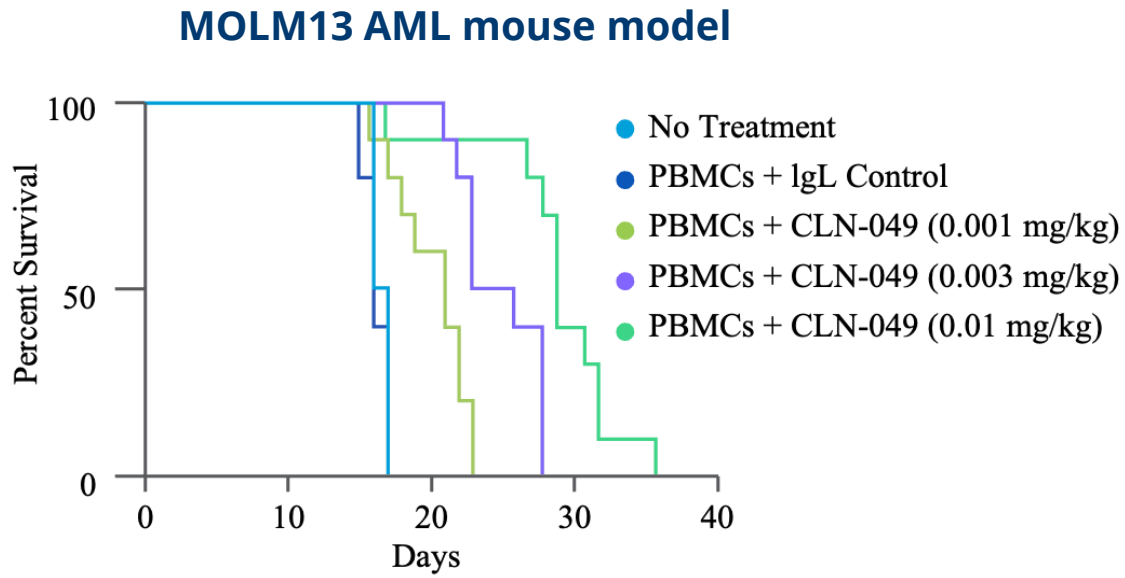
Maher Abdul-Hay

Daiichi - Consultancy (Includes expert testimony); Servier - Consultancy (Includes expert testimony); Abbvie - Consultancy (Includes expert testimony); PureTech - Consultancy (Includes expert testimony); Amgen - Consultancy (Includes expert testimony); Novartis - Consultancy (Includes expert testimony); Incyte - Consultancy (Includes expert testimony); Autolus - Consultancy (Includes expert testimony)

CLN-049: a novel T-cell engager targeting FLT3 in AML

- Development of T-cell–redirecting therapy in AML is limited by a lack of leukemia-associated target antigens
- FLT3 is a compelling cell surface target for immunotherapy that is expressed on >80% of AML blasts and only a limited number of normal hematopoietic precursors and dendritic cells
- CLN-049 is a novel T-cell engager targeting FLT3 that demonstrates AML blast killing preclinically[1,2]





1. Mehta NK, et al. *J Immunother Cancer*. 2022;10:e003882; 2. Abdul-Hay M, et al. EHA Library. 2023;386972;abstr PB1847.
AML, acute myeloid leukemia; FAB, antigen-binding fragment; Fc, crystallizable fragment; FLT3, FMS-like tyrosine kinase 3; IgL, immunoglobulin lambda; scFv, single-chain variable fragment; PMBC, peripheral blood mononuclear cell; WT, wild-type.

CLN-049-001 Part B: an ongoing, open-label, phase 1 FIH dose-escalation study exploring IV CLN-049

Key Eligibility

- Patients aged ≥18 years
- Patients with relapsed or refractory AML or MDS
- ECOG 0 to 2
- **No requirement for baseline testing for FLT3 expression on AML blasts**

Key Primary and Secondary Objectives

- **To assess safety, tolerability, PK, pharmacodynamics, and immunogenicity of IV-administered CLN-049 in patients with R/R AML or MDS**
- To assess the preliminary efficacy of IV CLN-049
- To define the dosing regimen for IV CLN-049 in patients with R/R AML or MDS

Study Efficacy Endpoints

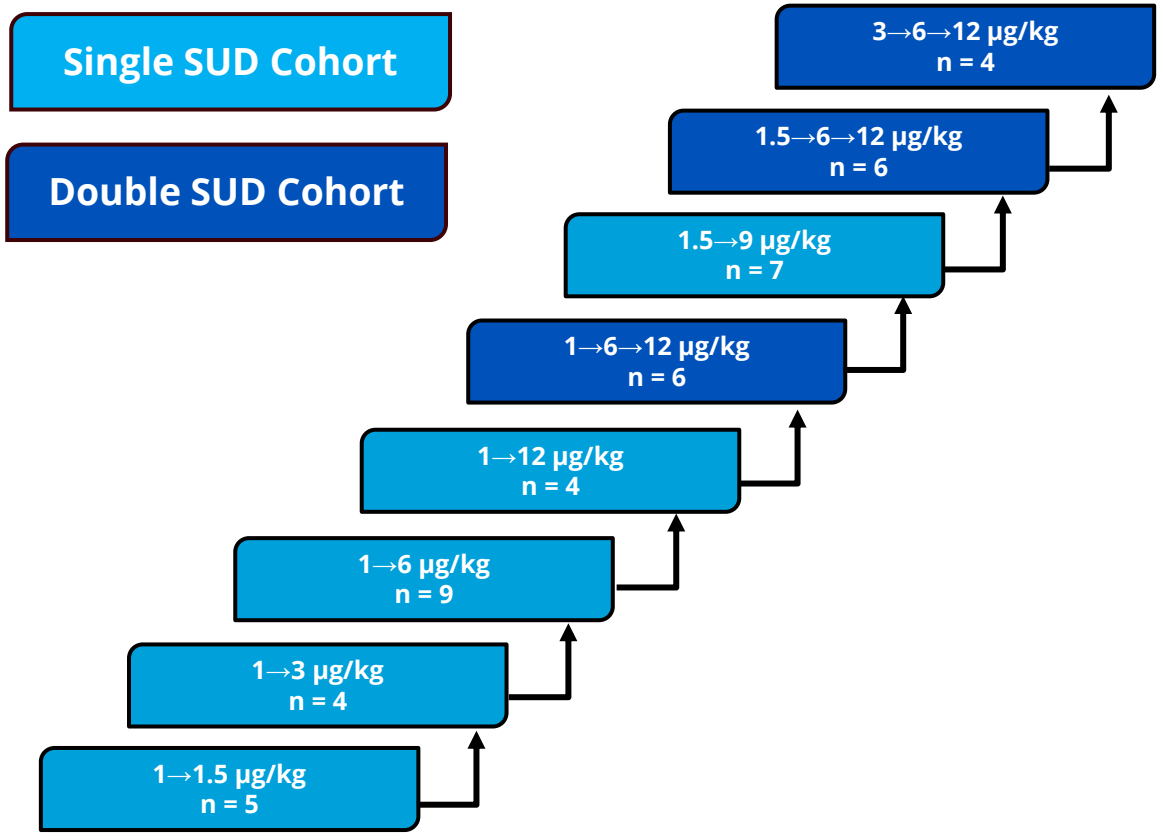
- **Complete response (CR) rate**
- **Composite complete response (CRc) rate**: (CR/CRi/CRh in AML or CR/CRL/CRh in MDS)
- **ORR**: (CRc + MLFS + PR in AML or CRc + PR + HI in MDS)

Response assessed using ELN 2022 (AML) or IWG 2023 (MDS) criteria

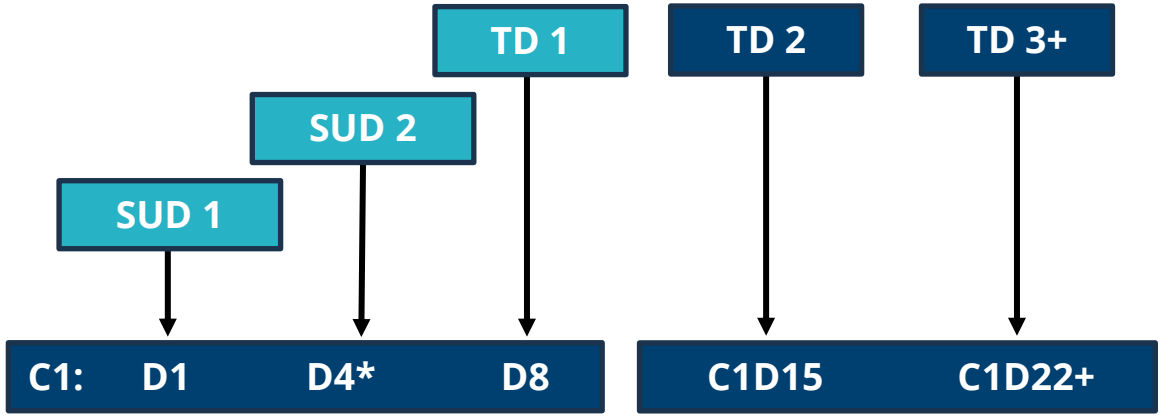
CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete recovery; CRL, complete remission with limited response; ECOG, Eastern Cooperative Oncology Group; ELN, European LeukemiaNet; FIH, first in human; HI, hematologic improvement; IV, intravenous; IWG, International Working Group; MDS, myelodysplastic syndrome; MLFS, morphologic leukemia-free state; ORR, objective response rate; PK, pharmacokinetics; PR, partial response; R/R, relapsed/refractory.

CLN-049-001 Part B: multiple ascending dose 3+3 dose-escalation design and IV dosing schema

Study Design – IV MAD Cohorts



Dosing Schema – IV MAD Cohorts



Premedication:

- Antihistamine + Antipyretic + H2 Blocker + Corticosteroids
- Antihistamine + Antipyretic + H2 Blocker

*Target doses administered Q1W until patients meet protocol-defined treatment withdrawal criteria. *SUD2 only if necessary.*

Patient baseline characteristics

Characteristic	All cohorts N=45	1→6 µg/kg cohort n=9	1.5→9 µg/kg cohort n=7	12 µg/kg cohorts[1] n=20
Diagnosis, n (%)				
AML	39 (87)	9 (100)	5 (71)	19 (95)
MDS/AML	3 (7)	0	2 (29)	0
MDS	3 (7)	0	0	1 (5)
Female, n (%)	19 (42)	8 (89)	0	8 (40)
Age, median (range)	71 (25–84)	66 (43–84)	74 (54–83)	71.5 (25–81)
Race and ethnicity, n (%)				
White/Black/Asian	37 (82) / 2 (4) / 1 (2)	8 (89) / 0 / 0	4 (57) / 1 (14) / 1 (14)	19 (95) / 1 (5) / 0
Hispanic/Not Hispanic	9 (20) / 33 (73)	4 (44) / 4 (44)	1 (14) / 6 (86)	2 (10) / 18 (90)
ECOG at baseline, n (%)				
0	13 (29)	2 (22)	2 (29)	6 (30)
1	24 (53)	4 (44)	4 (57)	10 (50)
2	8 (18)	3 (33)	1 (14)	4 (20)
Prior therapies				
Median (range)	2 (1–8)	2 (1–7)	2 (1–5)	1.5 (1–8)
HMA/Venetoclax as last prior therapy, n (%)	27 (60)	7 (78)	2 (29)	12 (60)
Prior transplant, n (%)	10 (22)	2 (22)	3 (43)	4 (20)
BMA blasts[2] at screening, n (%)				
<30%	27 (60)	6 (67)	4 (57)	12 (60)
≥30–50%	6 (13)	0	2 (28)	3 (15)
>50%	7 (16)	0	1 (14)	4 (20)
Risk at time of diagnosis (AML), n (%)				
Favorable	2 (5)	0	1 (20)	0
Intermediate	6 (15)	1 (11)	2 (40)	1 (5)
Adverse	28 (72)	8 (89)	1 (20)	6 (84)
Cytogenetics/molecular annotation, n (%)				
Any abnormality	39 (87)	9 (100)	6 (86)	18 (90)
Complex cytogenetics	7 (16)	3 (33)	0	3 (30)
–5; –7; –17/abn(17p)	6 (13)	2 (22)	0	4 (20)
FLT3-ITD mutation[3]	6 (13)	2 (22)	0	1 (5)
TP53 mutation[4]	16 (36)	3 (33)	0	11 (55)

[1]12 µg/kg cohorts include 1 → 12 µg/kg, 1 → 6 → 12 µg/kg, 1.5 → 6 → 12 µg/kg, and 3 → 6 → 12 µg/kg dose levels.
[2]Bone marrow biopsy data used where bone marrow aspirate data was not available.
[3]FLT3-ITD identified through cytogenic/molecular annotation in EDC and eligibility packets, or prior treatment with an approved FLT3 inhibitor
[4]TP53 mutation identified through cytogenetic/molecular annotation in EDC and eligibility packets
BMA, bone marrow aspirate; Unknown or not-specified values not shown

Treatment-emergent adverse events by grade

TEAEs by preferred term, >10% of patients in Part B, n (%)	Any grade N=45	Grade ≥3
Patients with ≥1 TEAE	**42 (93.3)**	**35 (77.8)**
Cytokine release syndrome	16 (35.6)	1 (2.2)
Infusion related reaction	15 (33.3)	2 (4.4)
Febrile neutropenia	9 (20.0)	9 (20.0)
White blood cell count decreased	8 (17.8)	8 (17.8)
Pneumonia	8 (17.8)	5 (11.1)
Diarrhoea	7 (15.6)	0
Hypomagnesaemia	7 (15.6)	0
Stomatitis	7 (15.6)	3 (6.7)
Hypokalaemia	7 (15.6)	2 (4.4)
Alanine aminotransferase increased	6 (13.3)	2 (4.4)
Hypotension	6 (13.3)	0
Hypophosphataemia	5 (11.1)	1 (2.2)
Headache	5 (11.1)	0
Fatigue	5 (11.1)	2 (4.4)
Pyrexia	5 (11.1)	0
Nausea[1]	5 (11.1)	0
Neutrophil count decreased	5 (11.1)	5 (11.1)
Platelet count decreased	5 (11.1)	3 (6.7)

- DLT of grade 4 drug-related and reversible transaminitis occurred in 3/45 patients – further details on subsequent slide

[1]One AE of nausea was ungraded at time of Data cutoff
DLT, dose-limiting toxicity; TEAE, treatment-emergent adverse event.

Treatment-emergent adverse events by cohort

TEAEs by preferred term, >15% of patients, n (%)	Single step-up cohorts					Double step-up cohorts			Total N=45
	1→1.5 µg/kg n=5	1→3 µg/kg n=4	1→6 µg/kg n=9	1.5→9 µg/kg n=7	1→12 µg/kg n=4	1→6→12 µg/kg n=6	1.5→6→12 µg/kg n=6	3→6→12 µg/kg n=4	
Patients with ≥1 TEAE	5 (100.0)	4 (100.0)	8 (88.9)	7 (100.0)	4 (100.0)	6 (100.0)	6 (100.0)	2 (50.0)	42 (93.3)
Cytokine release syndrome (CRS)	0	1 (25.0)	2 (22.2)	3 (42.9)	4 (100.0)	3 (50.0)	2 (33.3)	1 (25.0)	16 (35.6)
Infusion-related reaction	1 (20.0)	1 (25.0)	4 (44.4)	3 (42.9)	0	1 (16.7)	3 (50.0)	2 (50.0)	15 (33.3)
Febrile neutropenia	1 (20.0)	1 (25.0)	3 (33.3)	0	1 (25.0)	2 (33.3)	1 (16.7)	0	9 (20.0)
White blood cells decreased	1 (20.0)	1 (25.0)	1 (11.1)	1 (14.3)	2 (50.0)	1 (16.7)	0	1 (25.0)	8 (17.8)
Pneumonia	0	1 (25.0)	2 (22.2)	1 (14.3)	0	2 (33.3)	2 (33.3)	0	8 (17.8)
Diarrhea	0	1 (25.0)	2 (22.2)	0	2 (50.0)	1 (16.7)	1 (16.7)	0	7 (15.6)
Hypomagnesemia	0	1 (25.0)	2 (22.2)	1 (14.3)	2 (50.0)	0	0	1 (25.0)	7 (15.6)
Stomatitis	2 (40.0)	1 (25.0)	1 (11.1)	0	1 (25.0)	2 (33.3)	0	0	7 (15.6)
Hypokalemia	1 (20.0)	1 (25.0)	3 (33.3)	2 (28.6)	0	0	0	0	7 (15.6)

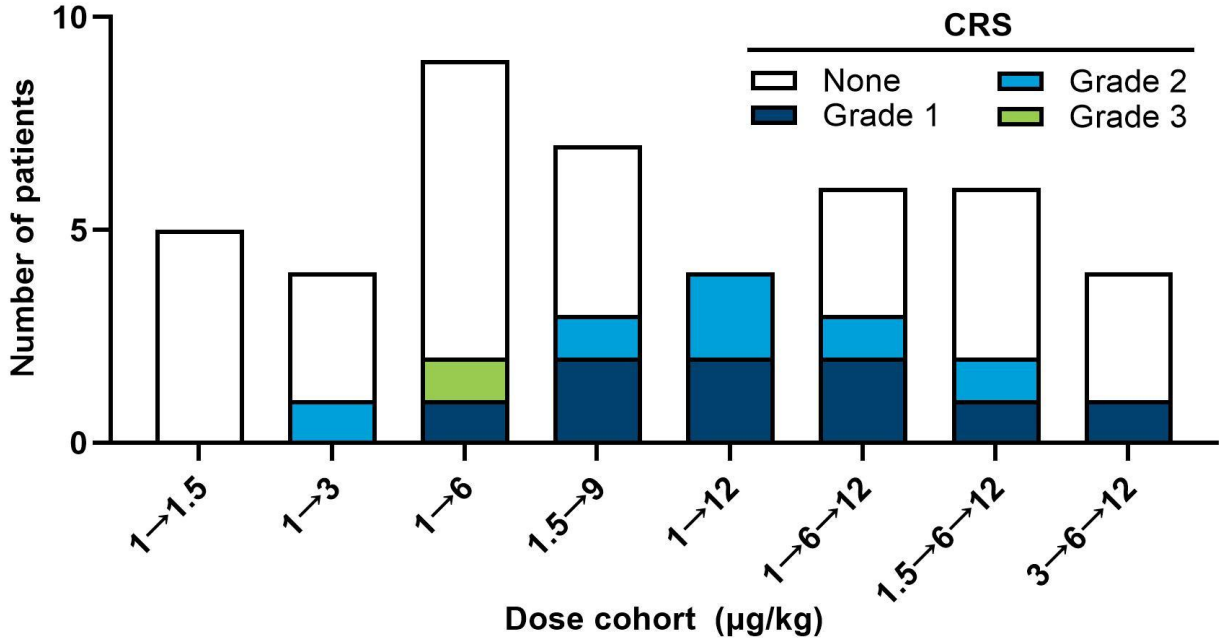
Treatment-emergent adverse events by cohort

TEAEs by preferred term, >15% of patients, n (%)	Single step-up cohorts					Double step-up cohorts			Total N=45
	1→1.5 µg/kg n=5	1→3 µg/kg n=4	1→6 µg/kg n=9	1.5→9 µg/kg n=7	1→12 µg/kg n=4	1→6→12 µg/kg n=6	1.5→6→12 µg/kg n=6	3→6→12 µg/kg n=4	
Patients with ≥1 TEAE	5 (100.0)	4 (100.0)	8 (88.9)	7 (100.0)	4 (100.0)	6 (100.0)	6 (100.0)	2 (50.0)	42 (93.3)
Cytokine release syndrome (CRS)	0	1 (25.0)	2 (22.2)	3 (42.9)	4 (100.0)	3 (50.0)	2 (33.3)	1 (25.0)	16 (35.6)
Infusion-related reaction	1 (20.0)	1 (25.0)	4 (44.4)	3 (42.9)	0	1 (16.7)	3 (50.0)	2 (50.0)	15 (33.3)
Febrile neutropenia	1 (20.0)	1 (25.0)	3 (33.3)	0	1 (25.0)	2 (33.3)	1 (16.7)	0	9 (20.0)
White blood cells decreased	1 (20.0)	1 (25.0)	1 (11.1)	1 (14.3)	2 (50.0)	1 (16.7)	0	1 (25.0)	8 (17.8)
Pneumonia	0	1 (25.0)	2 (22.2)	1 (14.3)	0	2 (33.3)	2 (33.3)	0	8 (17.8)
Diarrhea	0	1 (25.0)	2 (22.2)	0	2 (50.0)	1 (16.7)	1 (16.7)	0	7 (15.6)
Hypomagnesemia	0	1 (25.0)	2 (22.2)	1 (14.3)	2 (50.0)	0	0	1 (25.0)	7 (15.6)
Stomatitis	2 (40.0)	1 (25.0)	1 (11.1)	0	1 (25.0)	2 (33.3)	0	0	7 (15.6)
Hypokalemia	1 (20.0)	1 (25.0)	3 (33.3)	2 (28.6)	0	0	0	0	7 (15.6)

- **Reduction in frequency of CRS at the highest 12 µg/kg TD observed with use of a second SUD**

CRS and associated toxicities

- CRS in 16/45 (35.6%) patients
- Onset usually after a SUD or the first TD
- Nearly all CRS events limited to grade 1 or 2
- Only one grade 3 CRS; no grade 3 events observed in regimens utilizing 2 SUDs
- CRS events were not dose limiting



Additional toxicities associated with CRS

- **ICANS**: 2 patients with grade 1 events that occurred at SUD2 or TD1, each preceded by grade 2 CRS
  - Both events were transient and reversible, and were not dose limiting
- **Transaminitis**: 3 patients with grade 4 events that occurred after TD1 or TD2 in association with grade 1–3 CRS
  - All events were asymptomatic, transient and reversible, and were mitigated by use of a second SUD

Preliminary efficacy data highlights anti-leukemic activity including potential to achieve deep MRD negative responses

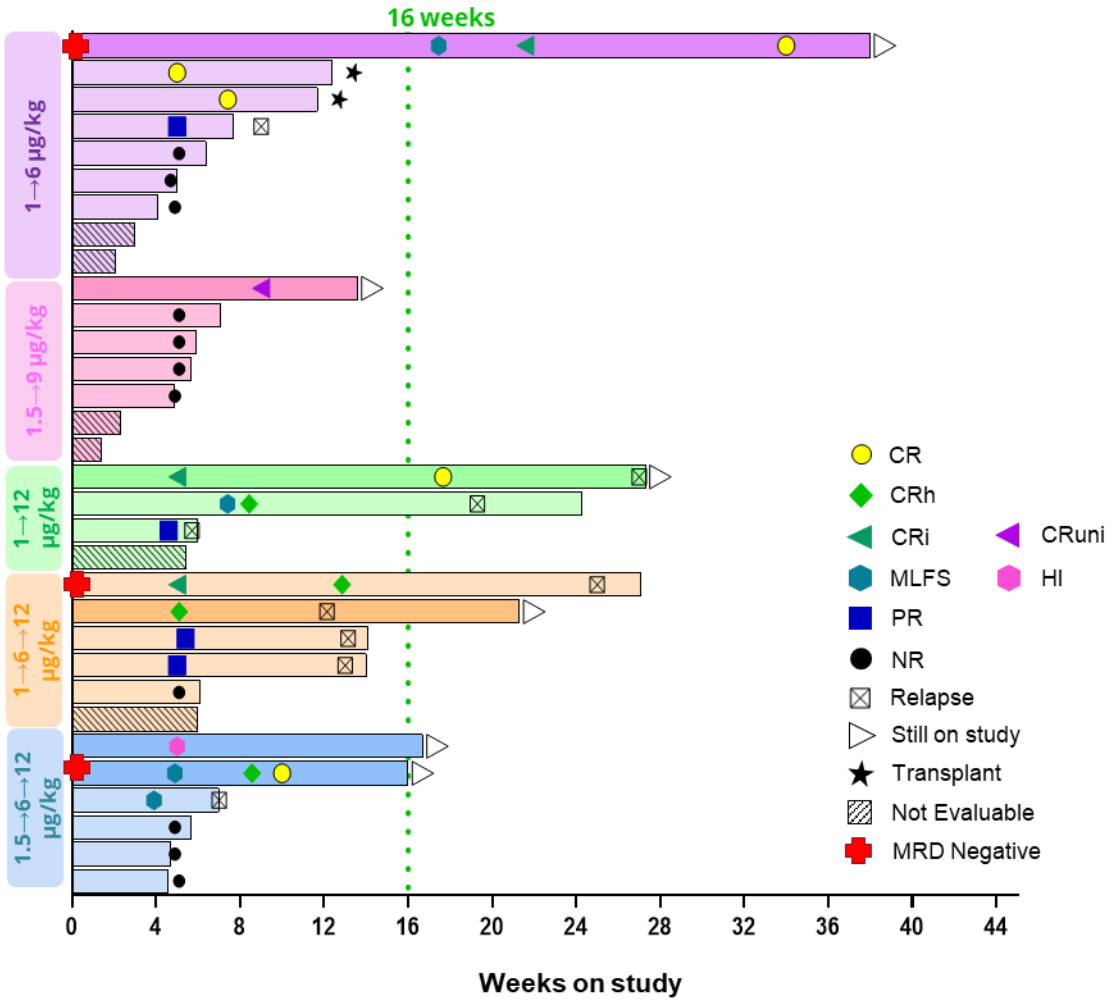
Response rate (best response), n (%)	Single step-up cohorts					Double step-up cohorts[1]		All cohorts n=41	≥6 µg/kg cohorts n=32	12 µg/kg cohorts n=16
	1→1.5 µg/kg n=5	1→3 µg/kg n=4	1→6 µg/kg n=9	1.5→9 µg/kg n=7	1→12 µg/kg n=4	1→6→12 µg/kg n=6	1.5→6→12 µg/kg n=6			
CR	0	0	3 (33)	0	1 (25)	0	1 (17)	5 (12)	5 (16)	2 (13)
CR/CRh	0	0	3 (33)	0	2 (50)	2 (33)	1 (17)	8 (20)	8 (25)	5 (31)
CRc	0	1 (25)	3 (33)	1 (14)	2 (50)	2 (33)	1 (17)	10 (24)	9 (28)	5 (31)
ORR	0	1 (25)	4 (44)	1 (14)	3 (75)	4 (67)	3 (50)	16 (39)	15 (47)	10 (63)

- 8/32 patients treated at a TD of ≥6 µg/kg achieved CR or CRh

➡ **3 were MRD negative by flow cytometry (central laboratory testing)**

[1]Enrollment into 3→6→12 µg/kg cohort ongoing at time of data cutoff; efficacy data not available for this cohort.
MRD, measurable residual disease; PD, progressive disease.

Duration of response at efficacious doses



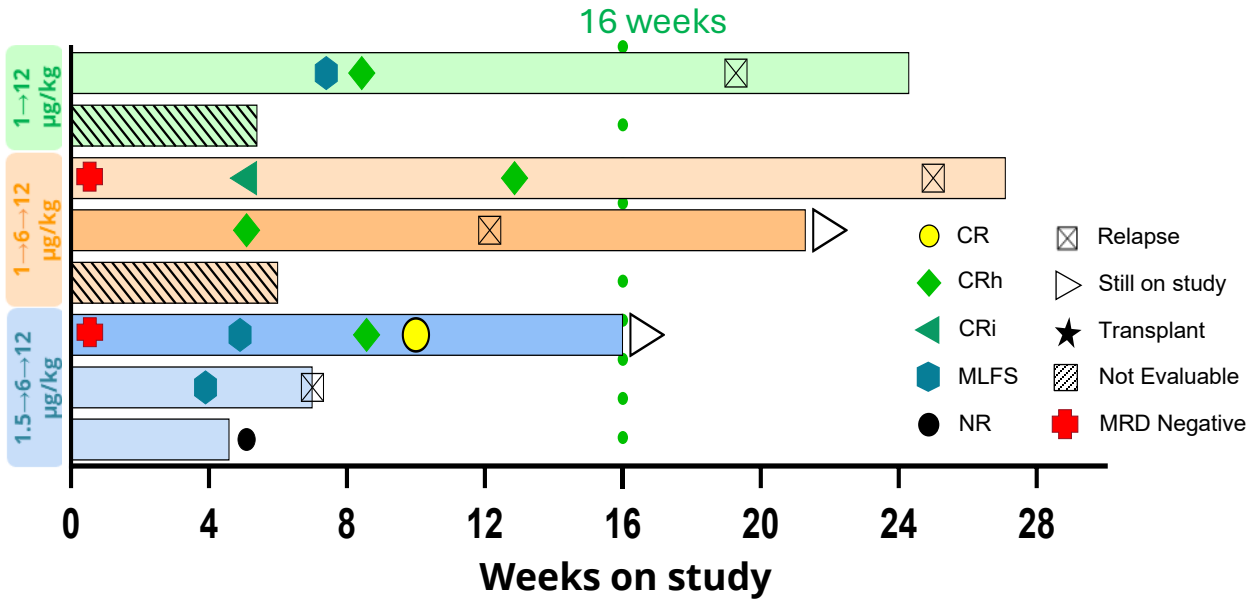
- In 8 patients achieving CR or CRh at a TD of ≥ 6 µg/kg:
  - 5 patients had DoR >16 weeks
  - 1 of these has an ongoing response for >36 weeks
  - 2 additional patients attained CR and proceeded to allo-HSCT
- Early evidence suggests that depth of response will influence DoR:
  - 3 MRD-negative patients all achieved DoR >16 weeks

BM, bone marrow; CRuni, complete remission unilineage; DoR, duration of response; allo-HSCT, allogeneic hematopoietic stem cell transplant; NR, no response.

Anti-leukemic activity independent of baseline genetic risk, including durable responses in *TP53*-mutated AML

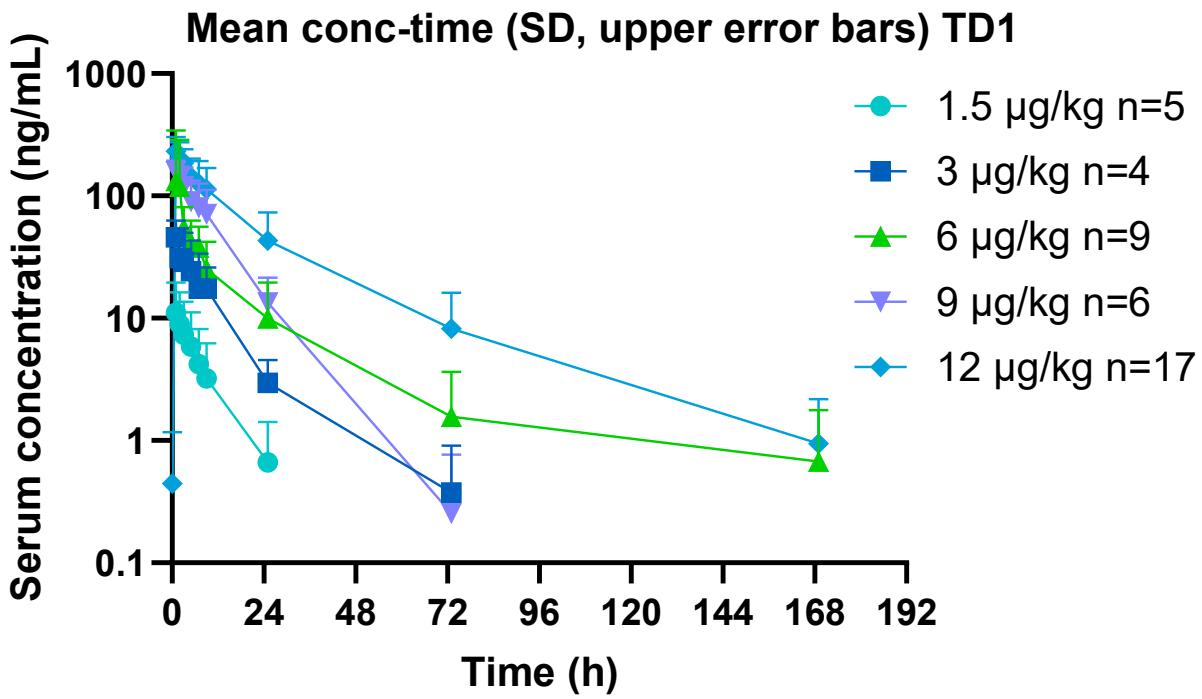
TP53-mutated AML response rate (best response), n (%)	All cohorts n=13	12 µg/kg cohorts n=8
CR	2 (15)	1 (13)
CR/CRh	5 (38)	4 (50)
CRC	5 (38)	4 (50)
ORR	6 (46)	5 (63)

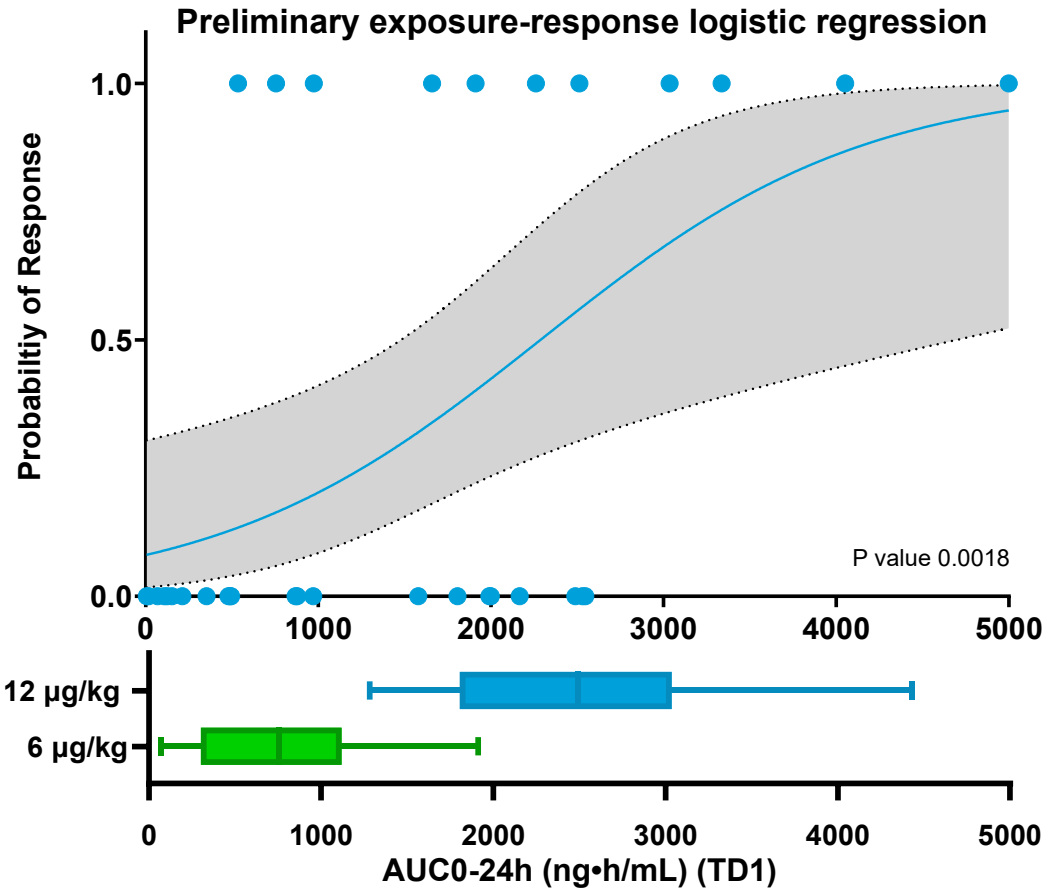
Duration of response in 12 µg/kg cohorts



- **4/8 patients with *TP53*-mutated AML treated at the highest TD of 12 µg/kg achieved CR or CRh**
- **CR/CRh responses were durable beyond 16 weeks in 3 of these patients**

Probability of clinical response is positively associated with higher drug exposures





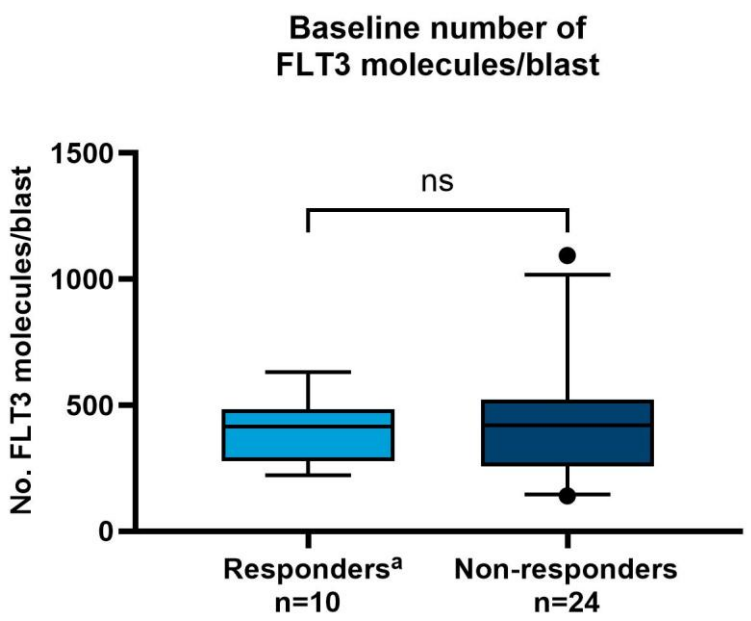
Dose-dependent increase in drug exposure

Statistically significant positive E-R relationship

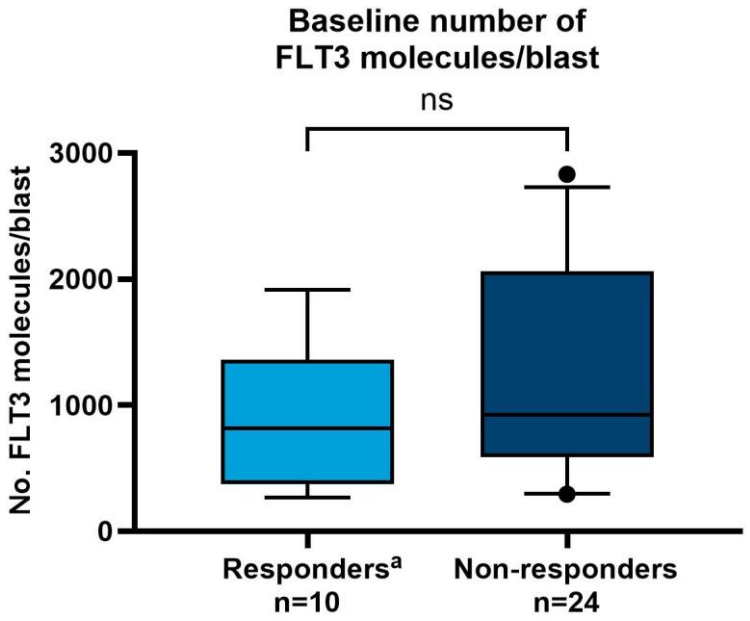
AUC0-24h, area under the concentration-time curve from 0 to 24 hours; E-R, exposure-response; SD, standard deviation; conc, concentration; TD1, target dose 1.
Left graph shows mean (SD, upper error bars) serum concentration-time profiles in nominal time.
Response includes CR, CRi, CRh, MLFS. Logistic regression models the probability of a binary outcome (1-responder, 0-nonresponder) based on a predictor (drug exposure).
Box plot includes median and 25th and 75th percentiles with whiskers at 10th and 90th percentile.

Clinical response is independent of baseline FLT3 expression

Bone marrow aspirate



Peripheral blood



No correlation between response and baseline FLT3 expression as measured by number of FLT3 receptor molecules on FLT3+ blasts

[a]Responders: CR, CRi, CRh, MLFS.

Conclusions

- CLN-049 monotherapy demonstrated promising anti-leukemic activity in a broad, heavily pretreated population of patients with R/R AML and MDS
- At the highest target dose tested of 12 µg/kg, CR/CRh rate was 31%
- The majority of responses were durable beyond 16 weeks
- Safety was favorable with no G3 CRS and no dose-limiting adverse events observed at the highest target dose in regimens utilizing 2 step-up doses
- CLN-049 development will proceed under FDA fast track designation, with expansion cohorts planned in early 2026

Acknowledgements

- Patients and their families/caregivers
- Investigators, nurses, and staff at all sites
- The Cullinan Therapeutics Study Team
- The study was sponsored by Cullinan Therapeutics
- Medical writing support was provided by Peloton Advantage, LLC, an OPEN Health company