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A Phase 1, Dose-escalation Study of QLF32101, a CLL1/CD3 Bispecific Antibody, in Patients with Relapsed/Refractory Acute Myeloid Leukemia

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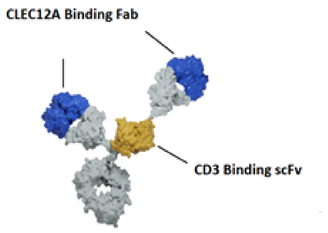
INTRODUCTION

- Acute myeloid leukemia (AML) remains difficult to treat due to the heterogeneity of the disease, lack of specific target, and presence of leukemic stem cells (LSCs) that mediates relapse after conventional treatments. C-type lectin-like molecule-1 (CLL1), a myeloid lineage antigen highly expressed by AML cells and LSCs but not expressed by normal hematopoietic stem cells, is a promising target[1,2].
- QLF32101 is a bispecific antibody engineered with a fragment antigen binding (Fab) arm, which binds with high affinity to CLL1 expressed on AML cells and LSC, and a single chain variable fragment (scFv) binds with low affinity to CD3 expressed on T cells. The Fc region was engineered to avoid toxicity caused by Fcγ receptor-mediated T cell activation and avoid antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).

QLF32101 Structure

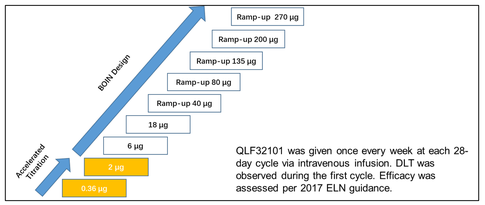


AIM

- This is an ongoing phase 1 study to assess the safety, tolerability, pharmacokinetics /pharmacodynamics (PK/PD), and preliminary efficacy of QLF32101 in patients with relapsed/refractory(r/r) AML. ClinicalTrials.gov Identifier: NCT05703204

METHOD

Figure 1. Study design



ClinicalTrials.gov Identifier: NCT05703204

Patient Population

Inclusion Criteria

- Patients with histologically or cytologically confirmed r/r AML, had no standard therapy or intolerable to standard therapy were enrolled;
- ECOG PS 0 to 2;
- Adequate organ functions.

Exclusion Criteria

- Patients with M3 subtype (FAB classification);
- Central nervous system (CNS) involvement;
- History of any active autoimmune disease.

RESULTS

- As of April 22, 2024, 18 patients received QLF32101 at doses 0.36-40 ug QW. The median age was 61.5 (range: 52.0-66.0) years.
- All patients had r/r AML. Five (27.8%) patients had AML with recurrent genetic abnormalities and four (22.2%) patients had AML, not otherwise specified.
- Fifteen (83.3%) patients had an ECOG PS≥1.

Table 1 Baseline demographics and disease characteristics

	0.36 ug (N = 1)	2 ug (N = 1)	6 ug (N = 3)	18 ug (N = 6)	40 ug (N = 7)	Total (N = 18)
Age, median (Q1, Q3), year	22.0 (22.0,22.0)	65.0 (65.0,65.0)	52.0 (38.0,53.0)	65.0 (62.0,66.0)	61.0 (34.0,71.0)	61.5 (52.0,66.0)
Sex, n (%)						
Male	0 (0.0)	0 (0.0)	2 (66.7)	3 (50.0)	2 (28.6)	7 (38.9)
ECOG PS, n (%)						
0	0 (0.0)	0 (0.0)	1 (33.3)	2 (33.3)	0 (0.0)	3 (16.7)
1	1 (100.0)	1 (100.0)	2 (66.7)	2 (33.3)	6 (85.7)	12 (66.7)
2	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	1 (14.3)	3 (16.7)
AML, NOS（WHO）	1 (100.0)	0 (0.0)	1 (33.3)	2 (33.3)	0 (0.0)	4 (22.2)
AML with recurrent genetic abnormalities (WHO)	0 (0.0)	1 (100.0)	2 (66.7)	1 (16.7)	1 (14.3)	5 (27.8)
M2 (FAB)	0 (0.0)	0 (0.0)	2 (66.7)	2 (33.3)	2 (28.6)	6 (33.3)
M4-M5 (FAB)	1 (100.0)	1 (100.0)	1 (33.3)	2 (33.3)	3 (42.9)	8 (44.4)
Relapsed/Refractory AML with WHO criteria, n (%)						
Refractory AML	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (14.3)	2 (11.1)
Relapsed AML	0 (0.0)	0 (0.0)	0 (0.0)	4 (66.7)	4 (57.1)	8 (44.4)
Relapsed/Refractory AML	16	1 (100.0)	2 (66.7)	2 (33.3)	2 (28.6)	8 (44.4)
Platelet count <50 ×10⁹/L	0 (0.0)	1 (100.0)	2 (66.7)	5 (83.3)	5 (71.4)	13 (72.2)
Neutrophil count ＜1 ×10⁹/L	0 (0.0)	1 (100.0)	1 (33.3)	3 (50.0)	5 (71.4)	10 (55.6)
CLL1 %, median (Q1, Q3)	42.0 (42.0, 42.0)	78.4 (78.4, 78.4)	68.65 (49.4, 87.9)	84.4 (53.1, 95.6)	86.15 (68.75, 91.75)	78.4 (49.4, 87.9)

ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization; AML, acute myeloid leukemia; NOS, not other specified; PS, performance status.

Safety

- DLTs were observed in 1 patient (40 ug cohort, events: sepsis, cytokine release syndrome and pulmonary alveolar hemorrhage).
- The most common grade ≥3 hematologic treatment-emergent adverse events (TEAEs) were leukopenia (55.6%; treatment-related, 11.1%) and neutropenia (55.6%; treatment-related, 22.2%).
- The most common grade ≥ 3 non-hematologic TEAE was hypokalemia (38.9%; treatment-related, 22.2%)
- CRS of any grade occurred in 88.9% (16/18) of patients (grade≥3, 1 patient).

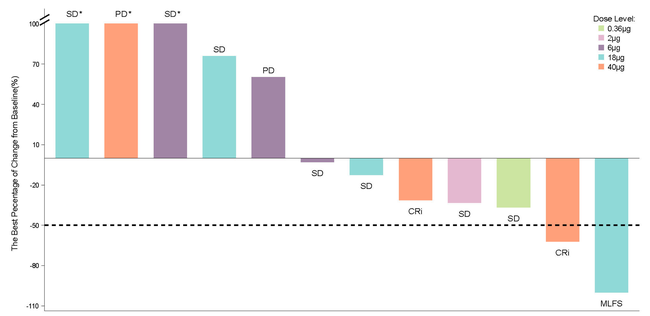
Table 2 Grade ≥3 Adverse Events in >1 Patient

	TEAEs (Gr≥3)	TRAEs (Gr≥3)
Any AE, n (%)	17 (94.4)	13 (72.2)
Hematologic AEs		
Leukopenia	10 (55.6)	2 (11.1)
Neutropenia	10 (55.6)	4 (22.2)
Thrombocytopenia	8 (44.4)	2 (11.1)
Anemia	8 (44.4)	0
Lymphopenia	6 (33.3)	4 (22.2)
Non-hematologic AEs		
Hypokalemia	7 (38.9)	4 (22.2)
Infectious pneumonia	4 (22.2)	0
Abnormal liver function	3 (16.7)	3 (16.7)
Upper respiratory tract infection	3 (16.7)	0
Sepsis	2 (11.1)	1 (5.6)

TEAEs, treatment emergent adverse events; TRAEs, treatment-related adverse events

Efficacy

- Two (11.1%) patients achieved complete remission with incomplete count recovery (CRi) at dose of 40 μg, of whom one revealed ≥50% reduction in blasts compared with baseline.
- One patient (5.6%) achieved morphological leukemia free state (MLFS) at a dose of 18 μg.
- Seven patients (38.9%) achieved stable disease (SD) and 2 patients (11.1%) had progressive disease (PD).



*: Only the portion up to 100% is displayed.

Figure 2. The Best Percentage of Change from Baseline in Bone Marrow Blasts

Case Presentation - 40 ug cohort

- 61 years/Female R/R AML-M5, Baseline BM blast **6.4%**;
- Medical history: hypertension, leukopenia, neutropenia, thrombocytopenia, anemia.

QLF32101

22Dec2023	27Dec2023	C1D1 1Jan2024	C2D1 31Jan2024	C3D1 28Feb2024	C4D1 27Mar2024
Step dose-1 10ug	Step dose-2 20ug	Cycle 1 40ug QW	Cycle 2 40ug QW	Cycle 3 40ug QW	Cycle 4 40ug QW

Safety	TEAEs	Notes
CRS	CRS (Gr2)： Step-dose 1(10ug) C1D1 40ug	Tocilizumab+methylprednisolone, CRS recovered in 1 day
≥ Grade 3 hematologic	Neutropenia (Gr4)： C1D1 , C1D8	Target-related
≥ Grade 3 Non-hematologic	Liver injury (Gr3)： Step-dose 10ug C1D1 40ug	Recovered ≤Grade 2 in 2 days
	Hypokalemia (Gr3)： Step-dose 10ug	Recovered in 1 day

Efficacy	Baseline	C2D1	C3D1	C4D1
Blast cell	6.4%	26.6%	21.2%	4.4%
ANC, 10^9/L	0.39	0.18	2.12	3.00
PLT, 10^9/L	42	24	22	30
Extramedullary disease	none	none	none	none
2017 ELN	/	PD	SD	CRi

✓ The patient experienced Gr2 CRS and Gr3 liver injury after step-dose1 and C1D1 and recovered quickly. Treatment was continued without CRS occurrence and good tolerance could be established.

✓ The patient had PD after the first cycle of treatment. The BM blast cells decreased after 2 cycles of persistent treatment and a CRi was achieved after 3 cycles QLF32101 treatment(PLT didn't recover).

Pharmacodynamics

- T cell activation was demonstrated by post-dose CD69+ T cell upregulation in peripheral blood.
- Significant T cell activation could be observed at dose levels 6-40 μg, which driving T-cell mediated lysis to CLL1 positive blasts.

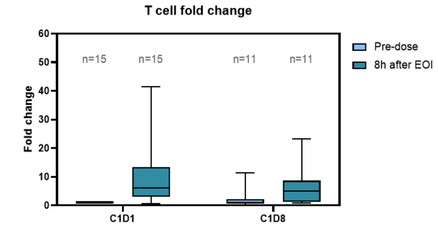


Figure 4. Changes of CD69+ T Cell

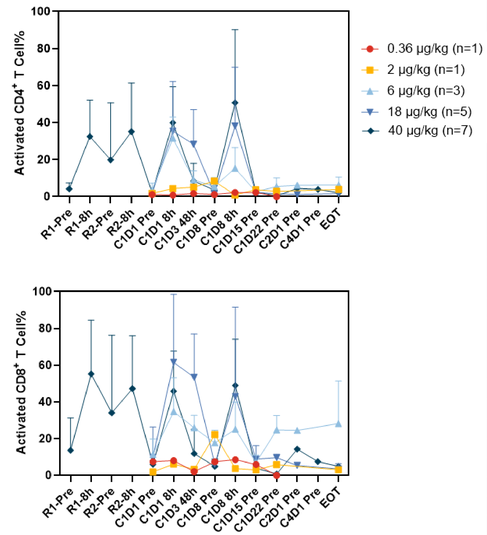


Figure 5. Activated peripheral blood T cells change from baseline

CONCLUSIONS

- **Preliminary data of QLF32101 dosed up to 40 μg provide early evidences of acceptable safety profile, drug tolerability, and anti-leukemic activity.**

REFERENCES

1. J Clin Invest. 2020 Apr 1; 130(4): 1552–1564.
2. J Hematol Oncol. 2019 Apr 24;12(1):41.

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