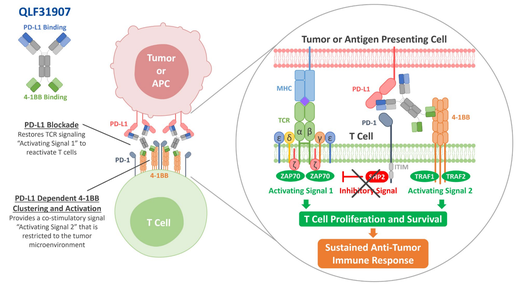
Background

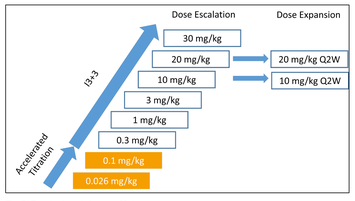
- Clinical development of agonistic 4-1BB monoclonal antibodies is limited by their narrow therapeutic window or unsatisfactory efficacy. Development of novel molecules with improved efficacy and restricted 4-1BB activation to tumor microenvironment is crucial[1].
- QLF31907 is a bispecific antibody targeting PD-L1 and 4-1BB and showed restricted activation of 4-1BB in preclinical studies.



Method

- This was a phase 1, open-label, dose-escalation/dose-expansion of QLF31907 in patients with advanced solid tumors and lymphoma.

Figure 1. Study Design



The DLT evaluation window was 28 days

Primary Study Endpoints

- Dose-limiting toxicity (DLT) (for dose escalation part) and objective response rate (ORR) (for dose expansion part)

Inclusion Criteria

- Histologically confirmed solid tumors or relapsed/refractory (r/r) lymphoma;
- Failed in or intolerable to standard therapy;
- At least 1 measurable lesion.

Exclusion Criteria

- Patients previously treated with 4-1BB agonists or 4-1BB recombinant;
- History of autoimmune diseases;
- History of hepatitis and liver cirrhosis.

Results

- As of 18 Apr 2024, 38 patients were enrolled from 5 centers across China.
- Median age was 58 years and 52.6% patients had an ECOG PS of 1.
- Five (13.1%) patients had r/r lymphoma. 36 (94.8%) patients had stage IV disease.
- 31.6% patients previously received ≥3 lines therapies and 57.9% patients previously received PD-1/PD-L1 therapy.

Table 1. Baseline Characteristics

	0.026mg/kg (N=1)	0.1mg/kg (N=1)	0.3mg/kg (N=3)	1mg/kg (N=3)	3mg/kg (N=3)	10mg/kg (N=12)	20mg/kg (N=12)	30mg/kg (N=3)	Total (N=38)
Age, median (Q1,Q3), year	36.0 (36.0, 36.0)	43.0 (43.0, 43.0)	56.0 (38.0, 58.0)	61.0 (54.0, 64.0)	61.0 (53.0, 70.0)	57.0 (49.5, 60.0)	61.0 (57.5, 66.5)	53.0 (35.0, 68.0)	58.0 (52.0, 61.0)
Sex, n (%)									
Male	1 (100.0)	1 (100.0)	2 (66.7)	2 (66.7)	2 (66.7)	5 (41.7)	11 (91.7)	3 (100.0)	27 (71.1)
ECOG PS, n (%)									
0	0	1 (100.0)	1 (33.3)	2 (66.7)	0	4 (33.3)	8 (66.7)	2 (66.7)	18(47.4)
1	1 (100.0)	0	2 (66.7)	1 (33.3)	3 (100.0)	8 (66.7)	4 (33.3)	1 (33.3)	20 (52.6)
Tumor type, n (%)									
NSCLC	1 (100.0)	0	3 (100.0)	2 (66.7)	1 (33.3)	2 (16.7)	5 (41.7)	0	14 (36.8)
EC	0	0	0	0	0	2 (16.7)	6 (50.0)	1 (33.3)	9 (23.7)
CC	0	0	0	1 (33.3)	0	2 (16.7)	0	0	3 (7.9)
Melanoma	0	0	0	0	1 (33.3)	1 (8.3)	0	0	2 (5.3)
HNSCC	0	0	0	0	0	2 (16.7)	1 (8.3)	2 (66.7)	5 (13.1)
Lymphoma	0	1 (100.0)	0	0	1 (33.3)	3 (25.0)	0	0	5 (13.1)
Current clinical stage, n (%)									
III	0	0	1 (33.3)	0	0	0	1 (8.3)	0	2(5.3)
IV	1 (100.0)	1 (100.0)	2 (66.7)	3 (100.0)	3 (100.0)	12 (100.0)	11 (91.7)	3 (100.0)	36 (94.8)
Lines of previous anticancer therapy, n (%)									
1	1 (100.0)	0	1 (33.3)	2 (66.7)	1 (33.3)	5 (41.7)	6 (50.0)	1 (33.3)	17 (44.7)
2	0	0	0	1 (33.3)	0	3 (25.0)	4 (33.3)	1 (33.3)	9 (23.7)
≥3	0	1 (100.0)	2 (66.7)	0	2 (66.7)	4 (33.3)	2 (16.7)	1 (33.3)	12 (31.6)

ECOG, Eastern Cooperative Oncology Group; NSCLC, Non-Small Cell Lung Cancer; EC, Esophageal cancer; CC, Cervical Cancer; HNSCC, Head and Neck Squamous Cell Carcinoma;

Safety

- Dose-limiting toxicities (DLTs) were observed in 1 patient (20 mg/kg): myalgia and platelet count decreased.
- All patients experienced treatment-emergent adverse events (TEAEs) (treatment-related, 92.1%). The most common TEAE was anemia (73.7%), followed by hypertriglyceridemia (50.0%) and hypoalbuminemia (36.8%).
- Twenty-four (63.2%) patients experienced grade≥3 TEAEs (treatment-related, 31.6%). The most common grade≥3 TEAE was pneumonia (13.2%).
- TEAEs leading to treatment discontinuation occurred in 6 (15.8%) patients (treatment-related, 7.9%).
- TESAEs occurred in 20 (52.6%) patients (treatment-related, 26.3%).

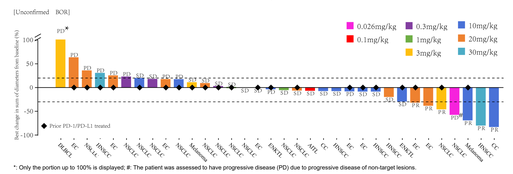
Table 2. Safety Profile

	0.026mg/kg (N=1)	0.1mg/kg (N=1)	0.3mg/kg (N=3)	1mg/kg (N=3)	3mg/kg (N=3)	10mg/kg (N=12)	20mg/kg (N=12)	30mg/kg (N=3)	Total (N=38)
TEAEs, n (%)	1 (100.0)	1 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	12 (100.0)	12 (100.0)	3 (100.0)	38 (100.0)
TRAEs, n (%)	0	1 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	12 (100.0)	12 (100.0)	1 (33.3)	35 (92.1)
Grade≥3 TEAEs, n (%)	1 (100.0)	1 (100.0)	2 (66.7)	1 (33.3)	3 (100.0)	7 (58.3)	8 (66.7)	1 (33.3)	24 (63.2)
TESAEs, n (%)	1 (100.0)	0	1 (33.3)	1 (33.3)	2 (66.7)	6 (50.0)	7 (58.3)	2 (66.7)	20 (52.6)
TEAEs leading to treatment discontinuation, n (%)	0	0	0	0	1 (33.3)	0	4 (33.3)	1 (33.3)	6 (15.8)
TEAEs in >20% patients, n (%)									
Anemia	0	1 (100.0)	2 (66.7)	3 (100.0)	2 (66.7)	10 (83.3)	8 (66.7)	2 (66.7)	28 (73.7)
Hypertriglyceridemia	1 (100.0)	1 (100.0)	1 (33.3)	2 (66.7)	1 (33.3)	9 (75.0)	3 (25.0)	1 (33.3)	19 (50.0)
Hypoalbuminemia	0	1 (100.0)	1 (33.3)	2 (66.7)	2 (66.7)	5 (41.7)	3 (25.0)	1 (33.3)	15 (39.5)
White blood cell count decreased	0	1 (100.0)	1 (33.3)	2 (66.7)	2 (66.7)	5 (41.7)	2 (16.7)	0	13 (34.2)
AST increased	0	1 (100.0)	0	2 (66.7)	2 (66.7)	4 (33.3)	3 (25.0)	1 (33.3)	13 (34.2)
Hyponatremia	0	0	2 (66.7)	0	2 (66.7)	4 (33.3)	4 (33.3)	0	12 (31.6)
Hypercholesterolemia	0	0	0	0	1 (33.3)	7 (58.3)	3 (25.0)	1 (33.3)	12 (31.6)
ALT increased	0	1 (100.0)	0	2 (66.7)	2 (66.7)	4 (33.3)	3 (25.0)	0	12 (31.6)
Platelet count decreased	0	1 (100.0)	1 (33.3)	1 (33.3)	1 (33.3)	5 (41.7)	3 (25.0)	0	12 (31.6)
Neutrophil count decreased	0	1 (100.0)	0	2 (66.7)	1 (33.3)	7 (58.3)	1 (8.3)	0	12 (31.6)
Pyrexia	0	1 (100.0)	1 (33.3)	0	1 (33.3)	5 (41.7)	3 (25.0)	1 (33.3)	12 (31.6)
Cough	0	1 (100.0)	1 (33.3)	1 (33.3)	2 (66.7)	2 (16.7)	3 (25.0)	0	10 (26.3)
Sinus Tachycardia	1 (100.0)	0	1 (33.3)	2 (66.7)	2 (66.7)	1 (8.3)	3 (25.0)	0	10 (26.3)
Hypokalemia	0	0	1 (33.3)	1 (33.3)	0	2 (16.7)	4 (33.3)	0	8 (21.1)
Hyperuricemia	0	1 (100.0)	0	1 (33.3)	1 (33.3)	2 (16.7)	3 (25.0)	0	8 (21.1)

TRAEs, treatment-related adverse events; TESAEs, treatment-emergent serious adverse events; TEAEs, treatment-emergent adverse events; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase;

Efficacy

- Six (15.8%) patients had partial responses (PR) (3 PRs were confirmed). Stable disease was observed in 20 (52.6%) patients. Disease control rate (DCR) was 60.5% (23/38).
- Two patients had PRs lasting for more than 1 year and are still on treatment: 1 with PD-1/PD-L1 naïve cervical cancer (Case 1, PR>20 months) and 1 with PD-1/PD-L1 treated melanoma (Case 2, PR>15 months).



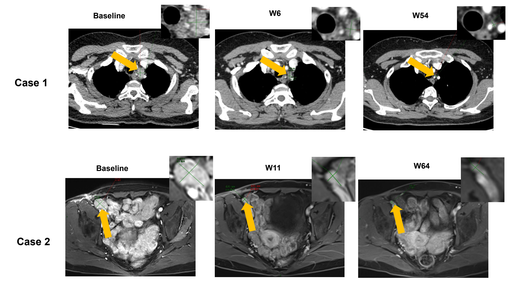
*: Only the portion up to 100% is displayed; #: The patient was assessed to have progressive disease (PD) due to progressive disease of non-target lesions.

Figure 2. Best Change in Target Lesion Size from Baseline

Case Presentation (Case 1, Case 2, Case 3)

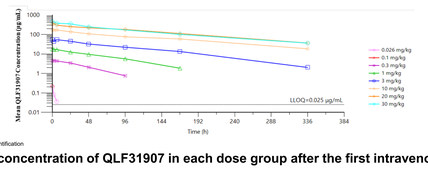
Case	Sex	Age	Dose level	Cancer diagnosis	Previous treatment	Total number of treatment cycles	Best overall response
1	Female	49	10mg/kg	Cervical Cancer	Chemoradiotherapy	21	PR
2	Female	55	10mg/kg	Melanoma	Surgery + Immunotherapy	17	PR
3	Male	63	20mg/kg	NSCLC	Chemoradiotherapy	14	SD

Case Presentation (Case 1 and Case 2)



Pharmacokinetics/pharmacodynamics

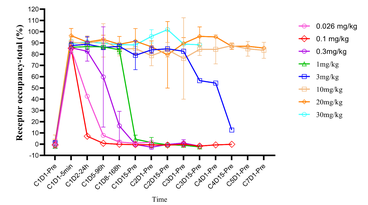
- In the dose range of 0.026-30 mg/kg, the exposure increased proportionally with dose increase.



LLOQ, lower limit of quantification

Figure 3. Mean concentration of QLF31907 in each dose group after the first intravenous infusion

- At 10mg/kg Q2W and above, PD-L1 and 4-1BB receptor occupancy indicated by peripheral blood mononuclear cells (PBMCs) stabilized >80% during the treatment period.



Pre, before QLF31907 injection.

Figure 4. Mean receptor occupancy of PD-L1 and 4-1BB of peripheral T cells in each dose group

Conclusions

- **QLF31907 showed an acceptable safety profile and preliminary clinical activity in heavily pretreated patients with advanced solid tumors and lymphoma.**
- **Encouraging clinical activity was observed in patients who have failed PD-1/PD-L1 therapy and further research on the mechanism is ongoing.**

REFERENCES

1. MAbs. 2023; 15(1): 2167189.

ACKNOWLEDGEMENT

We express our gratitude to the patients, their families, and caregivers for their invaluable participation in this trial, as well as to all investigators and site personnel involved.

CONTACT INFORMATION

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