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Development and preliminary clinical activity of QL1706 (PSB205), a combination of anti-PD1 and anti-CTLA-4 antibodies manufactured together as a single product

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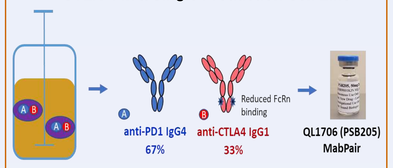
Introduction

- The MabPair platform enables the delivery of antibody combination therapy in a single bifunctional product. MabPair molecules such as QL1706 (PSB205) can be specifically engineered to achieve the optimal level of target coverage for two different molecules such as anti-PD-1 and anti-CTLA-4 monoclonal antibodies, which can be translated into improved efficacy with good tolerability(Figure 1).

Figure 1. Co-expression of anti-PD1 and anti-CTLA-4 in a Single Production Cell Line



- This was a phase I, open-label, dose escalation and expansion study to evaluate the safety, tolerability, MTD, PK and primary clinical activity of QL1706 in patients with advanced malignancy tumors.

Objectives

Primary objectives

To determine the safety, tolerability, DLTs, and RP2D of QL1706 in patients with advanced malignant tumors.

Secondary objectives

To assess the PK, preliminary efficacy and immunogenicity of QL1706 in patients with advanced malignant tumors.

Exploratory objectives

To explore the correlation between QL1706 exposure and functional RO, and the correlation between biomarkers and QL1706 efficacy in patients with advanced malignant tumors

Methods

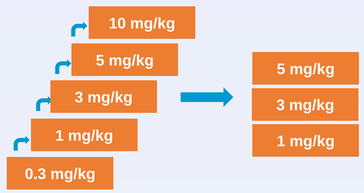
Patient Eligibility

- Age ≥ 18 years.
- ECOG performance status 0 or 1.
- Patients with pathological diagnosis of advanced/metastatic malignant tumor have progressed disease on standard therapy or for which no effective therapy is available.
- Measurable disease per RECIST V1.1.

Methods

Study Design

Figure 2. Dose escalation and dose expansion



QL1706 were administered every 3 weeks via intravenous infusion.

Results

Baseline characteristics

- A total of 47 patients with solid tumors between March 31 and December 20, 2020, were enrolled, with 16 and 31 patients in the dose-escalation and expansion cohorts, respectively. Of the patients, 25 (53.2%) had nasopharyngeal carcinoma (NPC), 20 (42.6%) had NSCLC, one (2.1%) had thyroid cancer and one (2.1%) had mucinous adenocarcinoma of the umbilical canal. The median of prior lines of therapy was 2.0 (ranging 0-5).

Safety and Tolerability

- Two patients in the 10 mg/kg group experienced DLT, including one case with grade 3 decreased platelet count complicated with grade 1 gingival bleeding and one case with grade 4 immune-mediated nephritis. Thus, the maximum tolerated dose (MTD) was determined as 5mg/kg Q3W.
- Treatment related adverse events (TRAEs) occurred in 31 (66.0%) of the 47 patients. The most frequently reported TRAEs were listed in Table 1. Most patients experienced grade 1 TRAEs (38.3%), especially in those who receiving 5 mg/kg (50%).
- Immune-related adverse events (irAEs) of any grades occurred in 16 (34.0%) of 47 patients. The most common (≥5%) irAEs were pruritus (23.4%), rash (21.3%), hyperthyroidism (10.6%), and hypothyroidism (10.6%) .

Efficacy

- As shown in Table 2, of 35 patients with available data for efficacy analysis, resulting in an ORR of 28.6% and a DCR of 48.6%

Results and Conclusions

Table 1. Treatment related adverse events occurring in ≥5% QL1706-treated patients

Adverse event	1 mg/kg (N=6) [a]		3 mg/kg (N=6) [a]		5 mg/kg (N=28)			10 mg/kg (N=6)			Total (N=47) [b]			
	Grade 1	Grade 2	Grade 1	Grade 2	Grade 1	Grade 2	Grade≥ 3[c]	Grade 1	Grade 2	Grade≥ 3[d]	Grade 1	Grade 2	Grade≥ 3	Any Grades
TRAEs, n(%)	2 (33.3)	3 (50.0)	1 (16.7)	1 (16.7)	14 (50.0)	3 (10.7)	2 (7.1)	1 (16.7)	1 (16.7)	3 (50.0)	18 (38.3)	8 (17.0)	5 (10.6)	31 (66.0)
Pruritus	2 (33.3)	0	1 (16.7)	1 (16.7)	6 (21.4)	0	0	1 (16.7)	0	0	10 (21.3)	1 (2.1)	0	11 (23.4)
Rash	2 (33.3)	0	2 (33.3)	0	4 (14.3)	1 (3.6)	0	0	1 (16.7)	0	8 (17.0)	2 (4.3)	0	10 (21.3)
AST increased	1 (16.7)	0	0	0	5 (17.9)	0	1 (3.6)	0	0	0	6 (12.8)	0	1 (2.1)	7 (14.9)
Fatigue	1 (16.7)	0	0	0	4 (14.3)	0	0	0	1 (16.7)	0	5 (10.6)	1 (2.1)	0	6 (12.8)
Hypothyroidism	0	2 (33.3)	1 (16.7)	0	0	1 (3.6)	0	0	1 (16.7)	0	1 (2.1)	4 (8.5)	0	5 (10.6)
Hyperthyroidism	0	1 (16.7)	0	0	3 (10.7)	0	0	1 (16.7)	0	0	4 (8.5)	1 (2.1)	0	5 (10.6)
ALT increased	0	1 (16.7)	0	0	0	1 (3.6)	0	2 (33.3)	0	0	2 (4.3)	2 (4.3)	0	4 (8.5)
Pyrexia	0	0	0	0	2 (7.1)	0	0	1 (16.7)	1 (16.7)	0	3 (6.4)	1 (2.1)	0	4 (8.5)
Infusion related reaction	0	0	0	0	1 (3.6)	1 (3.6)	0	0	0	1 (16.7)[e]	1 (2.1)	1 (2.1)	1 (2.1)	3 (6.4)

a :No Grade≥ 3 TRAE occurred in the dose level. b :No TRAE occurred in the 0.3 mg/kg (N=1). c :One patient experienced myocarditis (grade 3). d :One patient experienced platelet count decreased (grade 3) and immune-mediated nephritis (grade 4), one patient experienced platelet count decreased (grade 4). e :Grade 4.

- For the 20 patients with **no prior immunotherapy**, the PR and SD rates were 40.0% (n=8) and 25.0% (n=5), respectively, with an ORR of 40.0% (n=8) and a DCR of 65.0% (n=13).
- Of the 10 patients who **had received prior anti-PD-1/PD-L1 therapy**, two (20.0%) achieved PR, and one (10.0%) achieved SD, resulting in an ORR of 20.0% and a DCR of 30.0%.

Table 2. Best objective response according to RECIST v1.1

	All patients(n=35)	NPC(n=20)	NSCLC(n=14)
CR, n (%)	0	0	0
PR, n (%)	10 (28.6)	7 (35.0)	3 (21.4)
SD, n (%)	7 (20.0)	2 (10.0)	5 (35.7)
PD, n (%)	18 (51.4)	11 (55.0)	6 (42.9)
ORR, n (%)	10 (28.6)	7 (35.0)	3 (21.4)
DCR, n (%)	17 (48.6)	9 (45.0)	8 (57.1)

Figure 3. Tumor response. The best objective responses of target lesions from the baseline

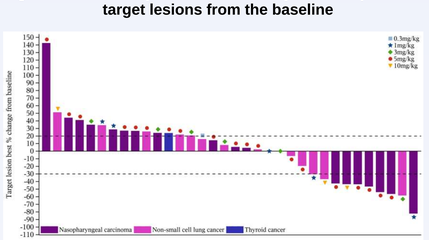


Figure 4. Individual patient's duration of treatment

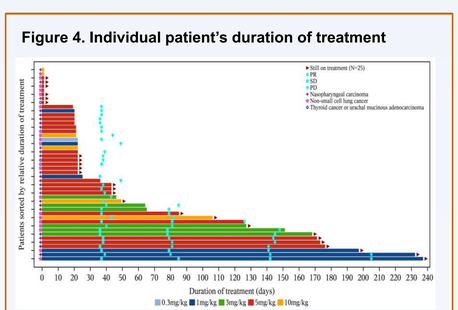
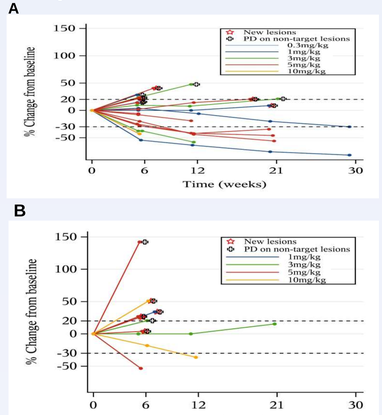
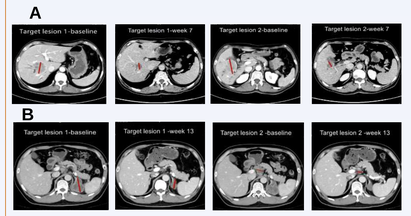


Figure 5. Percentage change from baseline in tumor shrinkage



Percentage change from baseline in tumor shrinkage in patients naïve to prior immunotherapy (A) and in patients with prior anti-PD-1/PD-L1 therapy (B).

Figure 6. Representative partial tumor responses in NPC and NSCLC patients who were refractory to prior immunotherapy

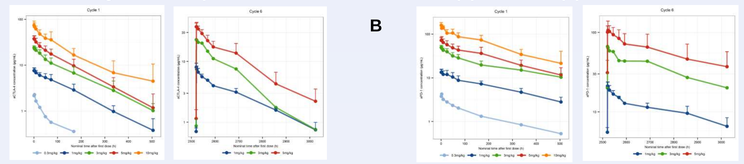


(A):The sum of diameters for all target lesions was 101 mm at baseline and 47 mm at week 7 (-53.5%).(a NPC patient in 5 mg/kg that was refractory to prior PD-L1/TGFβ bispecific inhibitor therapy)
(B):The sum of diameters for all target lesions was 77 mm at baseline and 49 mm at week 13 (-36.4%). (a non-small cell lung cancer patient in 10 mg/kg that was refractory to prior nivolumab and 4-1BB inhibitor therapy)

Pharmacokinetic analysis

- The exposure of both aCTLA-4 and aPD-1 increased as the dose increased following single- and multiple-dose administration(Figure 7).
- Both aCTLA-4 and aPD-1 might exhibit linear PK characteristics at single doses ranging from 0.3 to 10 mg/kg.
- The corresponding mean $t_{1/2}$ of aCTLA-4 were 104-121 h (4-5 days) and 111-190 h (5-8 days), respectively. No significant accumulation of aCTLA-4 was observed following multiple dosing.
- The mean $t_{1/2}$ of aPD-1 were 147-227 h (6-9 days) following single dose administration .

Figure 7. Mean plasma concentrations of aCTLA-4(A) and aPD-1(B)



Mean (+SD) plasma concentrations of aCTLA-4 (A) and aPD-1(B) as a function of time following dosing in Cycle 1 and at steady state (Cycle 6) shown on log10 scale in μg/mL across dose levels from 0.3 mg/kg to 10 mg/kg Q3W.

Pharmacodynamics analysis

- A sustained high percentage of PD-1 receptor occupancy rate was observed in all dosing groups throughout the treatment cycle(Figure 8).
- The increase of KI67+ cells in CD4 and CD8 T cell population was more significant in the 5mg/kg and 10 mg/kg group than in the lower dose groups(Figure9). In addition, there was a dose dependent upregulation of ICOS on CD4 T cells, a well-recognized surrogate for CTLA-4 blockades. The highest increase of ICOS+CD4 T cells over the baseline was observed in 5mg/kg and 10 mg/kg group(Figure 10).

Figure 8. PD-1 Receptor occupancy in circulating CD3 T cells after QL1706 treatment.

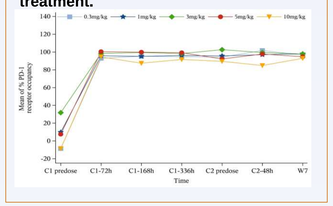
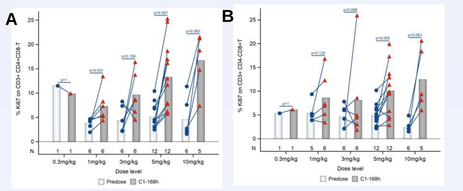
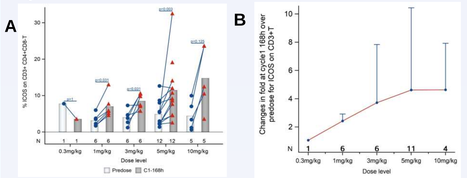


Figure 9. Proliferation of CD4 and CD8 T cells after QL1706 treatment



Proliferation of CD4 and CD8 T cells after QL1706 treatment. The percentage of Ki67+ CD4 T cells (A) and CD8 T cells (B) before treatment or 168 hours post treatment were compared in each patient and linked by a line. The mean value of Ki67+ percentage in each dose group were shown as light bar (Predose) and grey bar (168 hr post treatment), respectively.

Figure 10: The expansion of ICOS+CD4+CD8- T cells after QL1706 treatment.



(A):The percentage of ICOS+ CD4 T cells before or 168 hours after treatment were compared and linked by a line.(B):The average fold of increase on ICOS+ CD4 T cell in each dose group was shown. The number of samples analyzed in each group was listed on the x-axis

Conclusions

- Based on the overall assessment of tolerability, PK, and pharmacodynamics, the regimen of 5 mg/kg Q3W was selected as RP2D for further investigation of QL1706 in advanced solid malignancies.
- MabPair technology represents a new approach in delivering antibody combination therapy with a single vial product. QL1706, the first MabPair product with dual blockades of PD-1 and CTLA-4, was evaluated in a phase 1 trial and showed an acceptable safety profile and early evidence of clinical anti-tumor activity in advanced solid malignancies.

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