A Phase 1a Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Preliminary Efficacy of a Modular CLDN18.2-targeting PG CAR-T Therapy (IBI345) in Patients with CLDN18.2+ Solid Tumors (FPN: 1054P)

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Background

- Chimeric antigen receptor (CAR) T-cell therapy holds great promise for the treatment of solid tumors. However, how to avoid or minimize the “on-target off-tumor” effect of CAR-T therapy remains a major issue.
- We developed a P329G (PG) modular and switchable CAR technology, and report the first-in-human clinical results of a CLDN18.2-targeting PG CAR-T product (IBI345) for the treatment of CLDN18.2+ solid tumors.

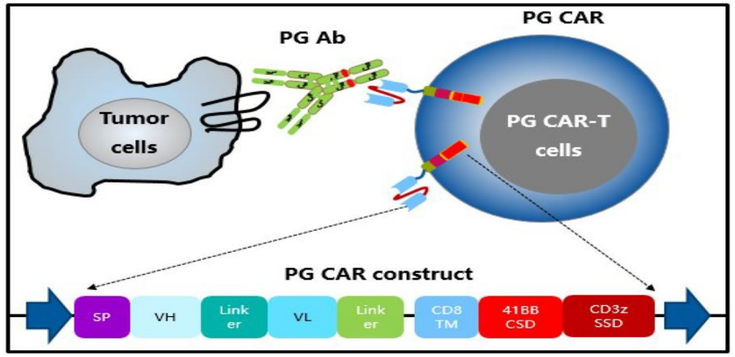

Figure 1. Design of PG CAR-T

Methods

- This phase 1a study (NCT05199519) enrolled CLDN18.2-positive (≥1+, ≥1%) patients (pts) with advanced gastric cancer or pancreatic cancer who failed or were intolerant to standard therapy.
- **Treatment:** Pts received an infusion of IBI345 consisting of one dose of PG CAR-T cells at escalating doses of 50, 250*10^6 cells plus ≥ 1 dose of CLDN18.2-targeting PG antibody (Ab) at a fixed dose of 1mg/kg Q3W after lymphodepletion preconditioning.
- **Objectives:** Safety and tolerability, pharmacokinetics and preliminary efficacy (per RECIST 1.1) of IBI345.

Results

Table 1. Overview of Clinical and Biomarker Results for Each Individual Patient

IBI345 dose	Patient	Age (years)	Gender	Tumor Type	CLDN 18.2 expression	Best overall response
IBI345 PG IgG 1mg/kg + PG CAR-T cells 50*10^6	PT01	69	Male	Esophagogastric junction cancer (EGJC)	1+, 12%; 2+,3%; 3+, 0% H score 18, Low	Partial response (PR)
IBI345 PG IgG 1mg/kg + PG CAR-T cells 250*10^6	PT02	64	Male	Gastric cancer (GC)	1+, 1%; 2+,0%; 3+, 0% H score 1, Low	Stable disease (SD)
	PT03	60	Male	Pancreatic cancer (PC)	1+, 0%; 2+, 5%; 3+, 90% H score 280, High	Stable disease (SD)
	PT04	68	Female	Pancreatic cancer (PC)	1+, 0%; 2+, 0%; 3+, 100% H score 300, High	Progressive disease (PD)

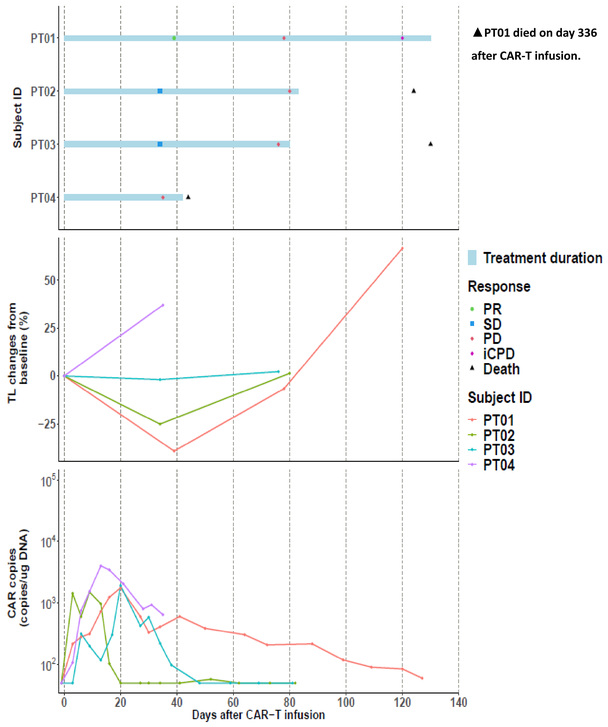

Figure 2. Clinical response and pharmacokinetics profile.
TL: target lesion

Safety: As of Apr 7, 2023, 5 pts were treated with IBI345. All pts experienced treatment related adverse events (TRAEs) while 3 pts (60%) had grade ≥3 TRAEs. Common TRAEs were decreased appetite (4/5, grade ≥3 in 1 pt), neutrophil count decreased (2/5, all grade ≥3), white blood cell count decreased (2/5), pyrexia (2/5), blood creatinine increased (2/5) and vomiting (2/5). No cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) or treatment-related death occurred.

Efficacy: For 4 efficacy-evaluable pts, the objective response rate (ORR) was 25% and disease control rate (DCR) was 75%.

Pharmacokinetics: CAR-T expansion and persistence were detected in all pts, with a median peak of 1,840 copies/μg gDNA (range: 1,500-4,020), a median time to peak of 16 days (range: 9-20), and a median persistence of 45 days (range: 35-127).

Conclusions

IBI345 demonstrated a manageable safety profile and preliminary efficacy in patients with CLDN18.2+ advanced solid tumors. To realize the full potential of this modular CAR-T cell product, the dose and regimen of the P329G Ab and CAR-T cells requires further exploration.

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