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Phase I Study of KN035, a novel fusion Anti-PD-L1 Antibody administered subcutaneously in Patients with Advanced Solid Tumors in the USA

Authors: K. Papadopoulos[1], W. Harb[2], N. Lu[3], X. Ma[3], Y. He[3], L. Yuan[3], M. Fu[3], Y. Lin[3], W. Xu[3], X. Wang[5], P. Wang[5], T. Xu[5], R. Dong[4], J. Gong[3]; [1] Clinical Research Department, South Texas Accelerated Research Therapeutics(START), San Antonio, TX, US, [2] Horizon Oncology Research, LLC., Horizon BioAdvance, Lafayette, IN, US, [3] 3D Medicines Co., Ltd., Beijing, CN, [4] Shanghai HaiHe Pharmaceutical Co., Ltd., Shanghai, CN, [5] Alphamab Oncology INC., Suzhou, CN

Background

- KN035 is a novel fusion protein of anti-PD-L1 single domain antibody and Fc. As a recombinant fusion protein, KN035 consists of two identical polypeptide chain linked via a pair of disulfide bonds. Each chain contains a human IgG1 Fc fragment and humanized single domain antibody Figure 1.
- The single domain antibody (dAb) was obtained from a focused phage library, derived from PBMC of human PD-L1 immunized camel. The dAb was humanized thereafter. Due to two-point mutations, the Fc part has muted effector functions, antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC).
- Pre-clinical study suggested that the binding affinity of KN035 to PD-L1 was 1.45 times higher than that of durvalumab. The binding curve of KN035 and durvalumab with hPD-L1 is shown in Figure 2.
- KN035 is formulated for subcutaneous (SC) injection.
- A phase 1 dose escalation study was performed in the USA to evaluate and characterize the safety and tolerability, MTD, PK,PD and preliminary antitumor activity of single agent KN035 in patients (pts) with locally advanced or metastatic solid tumors.

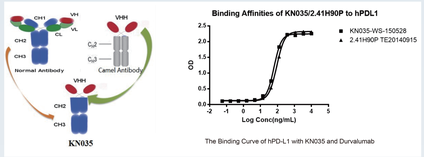


Figure 1

Figure 2

Objectives and Study Population

- Primary Objective: To evaluate and characterize the tolerability and safety profile of single agent KN035 in adult subjects with unresectable advanced carcinoma.
- Secondary Objectives include: To characterize the PK profile, determine maximum tolerated dose (MTD) and to evaluate the antitumor activity of single agent of KN035.
- Study Population Inclusion/Exclusion Criteria:
  - Patients with histological or cytological confirmed advanced carcinoma, who had failed standard therapies, been intolerant to such therapy or considered ineligible for standard therapy.
  - Eastern Cooperative Oncology Group (ECOG) Performance Scale 0 to 1.
  - Adequate hematologic and organ function.
  - Active autoimmune disease, pneumonitis were excluded.
  - Subject will be excluded if subject had prior treatment targeting PD-L1. Prior PD-1 was allowed following a 4 week washout period.

Method

Study Design

- A modified 3+3 dose-escalation design was adopted with the DLT evaluation period of 28 days.
- Planned dose levels at 0.01, 0.03, 0.1, 0.3, 1.0, 2.5, 5 and 10 mg/kg SC weekly.
- Single patient cohorts were planned at the dose levels of 0.01, 0.03 and 0.1 mg/kg/dose; unless a ≥ G2 drug-related AE occurred in the first 28-day cycle, then 2 additional pts would be enrolled. Starting with 0.3 mg/kg, 3 or 6 subjects would be enrolled.
- Severity of adverse events was graded according to Common Terminology Criteria for Adverse Events CTCAE v 4.03.
- Response was evaluated by RECIST 1.1 every 12 weeks.

Results

Baseline Characteristics and Disposition

- As of July 5, 2018, a total of 18 pts have been enrolled, median age 70.5 (range 53-79).
- Patient baseline characteristics and prior therapy exposure are summarized in Table 1.
- Median duration of exposure of KN035 was 9 weeks (range 6- 32 weeks).
- At time of data cut-off, patients had discontinued treatment due to disease progression (n= 11) or adverse events (n= 3) or in the opinion of investigator (n=1) or other (n=1).

Treatment –Emergent adverse events (TEAEs)

- All patients experienced at least one TEAE (Table 2)
- Planned maximum dose of 10 mg/kg has been reached without DLTs within the DLT evaluation window.
- TEAEs Grade ≧ 3 attributed to KN035 were increased aspartate aminotransaminase (n=2), alanine aminotransaminase (n=2)and lymphopenia (n=2).

Table 1 Baseline Demographic and Disease Characteristics

Characteristic	Overall (N=18)
Median Age (years) (range)	70.5 (53-79)
Males, n (%)	13 (72.2)
Race, n (%)	
White	16 (88.9)
Black or African American	2 (11.1)
Cancer Diagnosis, n (%)	
Prostate Cancer	5 (27.8)
Lung Cancer, Non-Small Cell	2 (11.1)
Breast Cancer	2 (11.1)
Bladder Cancer	1 (5.6)
Cervical Cancer	1 (5.6)
Esophageal Cancer	1 (5.6)
Head and Neck Cancer	1 (5.6)
Liver Cancer	1 (5.6)
Melanoma	1 (5.6)
Other	3 (16.7)
Current Disease Primary Stage,	
III	1 (5.6)
IV	17 (94.4)

Table 2 Summary of TEAEs regardless of attribution (occurring in ≥2 patients)

Summary of TEAEs regardless of attribution (occurring in ≥2 patients) N=18	Any grade (100%)	Grade ≥3 (100%)
Any	18 (100)	9 (50)
Lead to withdrawal of study treatment	3 (16.7%)	2 (11.1)
Most Common (≥2 patients)		
Fatigue	7 (38.9)	0(0.0)
Nausea	4 (22.2)	0(0.0)
Alanine aminotransferase	3 (16.7)	2 (11.1)
Aspartate aminotransferase	3 (16.7)	2 (11.1)
Diarrhoea	3 (16.7)	0(0.0)
Abdominal pain	2 (11.1)	2 (11.1)
Constipation	2 (11.1)	0(0.0)
Dry mouth	2 (11.1)	0(0.0)
Salivary hypersecretion	2 (11.1)	0(0.0)
Vomiting	2 (11.1)	0(0.0)
Decreased appetite	2 (11.1)	0(0.0)
Hypokalaemia	2 (11.1)	0(0.0)
Hypomagnesaemia	2 (11.1)	0(0.0)
Hypophosphataemia	2 (11.1)	1(5.6)
Musculoskeletal chest pain	2 (11.1)	0(0.0)
Musculoskeletal stiffness	2 (11.1)	0(0.0)
Blood alkaline phosphatase	2 (11.1)	2 (11.1)
Lymphopenia	2 (11.1)	2 (11.1)
Skin abrasion	2 (11.1)	0(0.0)

Clinical Efficacy

- Tumor response by investigator assessment is summarized in Table 3 & Figure 4.
  - Among 17 pts with first disease assessment completed, 2 pts had confirmed PR, including 1 NSCLC pt at 0.3mg/kg (response duration 9 months) and 1 MSI-H prostate cancer pt at 2.5mg/kg (ongoing response 10 months), and 5 pts achieved SD.

Pharmacokinetics

- The exposure to KN035 was dose-dependent and increased proportionally (Figure 3).
- Average half-life (t1/2) of KN035 was approximately 200 hours.
- Tmax for the KN035 varied from 96 to 168 hrs for dose 1 with intense PK sampling.

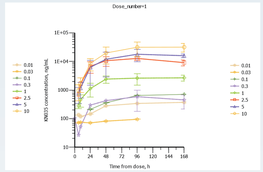


Figure 3

Table 3 Summary of Best Responses

	KN035 0.01 mg/kg weekly (N=1) n (%)	KN035 0.03 mg/kg weekly (N=1) n (%)	KN035 0.1 mg/kg weekly (N=1) n (%)	KN035 0.3 mg/kg weekly (N=3) n (%)	KN035 1.0 mg/kg weekly (N=3) n (%)	KN035 2.5 mg/kg weekly (N=3) n (%)	KN035 5.0 mg/kg weekly (N=3) n (%)	KN035 10.0 mg/kg weekly (N=3) n (%)	Overall (N=18) n (%)
Best Overall Response									
Complete Response (CR)	0	0	0	0	0	0	0	0	0
Partial Response (PR)	0	0	0	1 (33.3)	0	1 (33.3)	0	0	2 (11.1)
Stable Disease (SD)	0	1 (100)	0	1 (33.3)	1 (33.3)	0	1 (33.3)	1 (33.3)	5 (27.8)
Progressive Disease (PD)	1 (100)	0	1 (100)	0	2 (66.7)	2 (66.7)	2 (66.7)	1 (33.3)	9 (50.0)
Not Evaluable (NE)	0	0	0	0	0	0	0	1 (33.3)	1 (5.6)
Overall Response Rate (ORR: CR+PR)	0	0	0	1 (33.3)	0	1 (33.3)	0	0	2 (11.1)
95% CI	(0, 97.5)	(0, 97.5)	(0, 97.5)	(0.8, 90.6)	(0, 70.8)	(0.8, 90.6)	(0, 70.8)	(0, 70.8)	(1.4, 34.7)
Disease Control Rate (DCR: CR+PR+SD)	0	1 (100)	0	2 (66.7)	1 (33.3)	1 (33.3)	1 (33.3)	1 (33.3)	7 (38.9)
95% CI	(0, 97.5)	(2.5, 100)	(0, 97.5)	(9.4, 99.2)	(0.8, 90.6)	(0.8, 90.6)	(0.8, 90.6)	(0.8, 90.6)	(17.3, 64.3)

Figure 4 Response of Evaluable Subjects

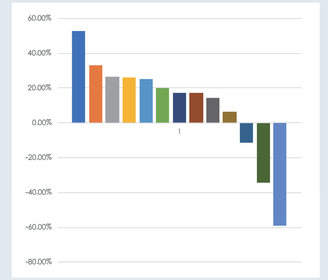
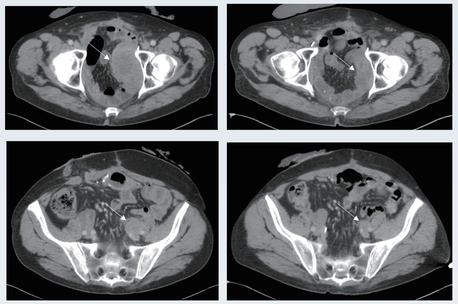


Figure 4

Figure 5 Patient with MSI-H prostate cancer with partial response (37.5% reduction)post cycle 3, ongoing at 10 months



Baseline Cycle 3

Figure 5

Conclusions

- KN035 exhibits a favorable safety profile in patients with advanced malignancies and preliminary results demonstrate encouraging anti-tumor activity.
- Phase 2 study for MSI-H solid tumors and a Phase 3 Study for Biliary Tract Carcinoma are ongoing in China and a global Phase 3 study for hepatocellular carcinoma will start soon.

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