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

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Jianming Xu,[1] Shukui Qin,[2] Yun Zhang,[1] Yaoyue Zhang,[1] Ru Jia,[1] Rongrui Liu,[1] Gairong Zhang,[1] Chuanhua Zhao,[1] Ni Lu,[3] Huilong Liu,[3] Siying Xu,[3] Wenlian Xu,[3] Amanda Fu,[3] Walt Cao,[3] Haolan Lu,[3] David Liu,[3] Xiaoxiao Wang,[4] Pilin Wang,[4] Ting Xu,[4] John Gong[3]

[1]5th Medical Center of PLA, Beijing, China; [2]Nanjing Medical University Bayi Hospital, Nanjing, China; [3]3DMedicines Co. Ltd. Sichuan, China; [4]Alphamab Co. Ltd. Suzhou, China

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.
- 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 EC_{50} of KN035 to PD-L1 was determined at 90.082 ng/ml.
- KN035 is formulated for subcutaneous (SC) injection owning to its high solubility and concentration.

OBJECTIVE AND STUDY POPULATION

- A Phase I clinical trial, KN035-CN-001, was performed in China to evaluate the safety, tolerability, pharmacokinetics and preliminary effect of single agent KN035 administered subcutaneously to subjects with advanced solid tumors. This was divided into three phases (dose escalation, dose expansion-1 and dose expansion-2).
  - The primary objective of the dose-escalation phase was to assess the safety, tolerability and maximum tolerated dose (MTD).
  - The secondary objective of the dose-escalation phase was to evaluate the PK profile, immunogenicity and clinical activity of single agent of KN035.
- Key eligibility criteria:
  - Eligible patients had a histologically or cytologically confirmed advanced carcinoma, failed or were intolerant to standard therapies, refused such therapies, or was not amenable to standard therapies approach,
  - ECOG PS of 0 or 1,
  - Measurable disease per RECIST v1.1.
- Patients reported here were from the dose escalation phase only.
  - All patients in dose-escalation phase who received any study treatment were included in the safety population.
  - Patients in dose-escalation phase with baseline tumor assessment and at least one on-treatment tumor assessment were included in the efficacy population.

METHOD

Study design

- A modified 3+3 dose-escalation design was adopted with the DLT evaluation period of 28 days.
- Planned dose levels were at 0.1, 0.3, 1.0, 2.5, 5.0 and 10.0 mg/kg SC weekly.
- One patient was planned for the 0.1 and 0.3 mg/kg dose cohorts in absence of drug related grade 2 AE. Starting at 1.0 mg/kg cohort, traditional 3+3 design was followed.
- Severity of adverse events was graded according to Common Terminology Criteria for Adverse Events CTCAE v4.03.
- Tumor response was evaluated by investigators every 12 weeks per RECIST v1.1.

RESULTS

Baseline Characteristics and Disposition

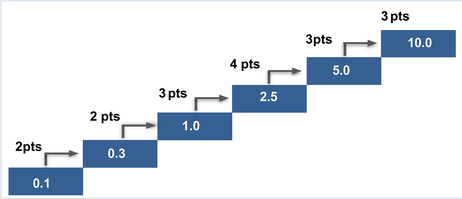
- As of May 1, 2019, a total of 17 patients were enrolled.
- Median duration of exposure of KN035 was 18 weeks (range 1- 71).
- At the time of data cut-off, 16 patients had discontinued treatment due to disease progression (n=15) or consent withdrawal (n=1).
- The study population had advanced cancers with majority received ≥ 2 lines of prior systemic treatment (Table 1).
- Patient disposition by dose level is shown in Figure 1.

Table 1. Baseline Demographics and Clinical Characteristics

Baseline characteristics[a]	N=17
Median age(range), years	49 (24-64)
Gender, n(%)	
Male	15 (88.2%)
Female	2 (11.8%)
ECOG PS, n(%)	
0	2 (11.8%)
1	15 (88.2%)
TNM stage, n(%)	
III	2 (11.8%)
IV	15 (88.2%)
Prior Treatment	
Prior radiotherapy, n (%)	7 (41.2%)
No. of prior systemic regimens, n (%)	
＜ 2	8 (47.1%)
≥ 2	9 (52.9%)

[a]Tumor types included biliary tract cancer (n=3), renal cell cancer (n=2), urothelial cancer (n=3), gastrointestinal cancer (n=3), hepatic cell cancer (n=2), thymic cancer (n=2), non-small cell lung cancer (n=1) and ovarian cancer (n=1).
ECOG PS: Eastern Cooperative Oncology Group performance status; TNM: tumor nodes metastasis; No.: number.

Figure 1. Dose escalation



Doses in mg/Kg; Pts: patients; 1 patient at dose of 0.1 and 1 patient at dose of 0.3 mg/kg did not complete PK blood collection and were replaced.

Safety

- As of cutoff date, 17 patients received any study treatment and were evaluable for safety assessment.
- No DLT was observed.
- No treatment-related SAE was observed.
- No Grade 5 treatment-related AE was observed.
- Only one Grade 3-4 treatment-related AE (Grade 3 dermatitis) was observed.
- The safety results are summarized in Table 2.

Table 2. Safety Summary

Adverse Events	Safety Population (N=17)
Any grade, n(%)	100 (100%)
Treatment-related	13 (76.5%)
Grade 3-4, n(%)	6 (35.3%)
Treatment-related[a]	1 (5.9%)
Grade 5, n(%)	1 (5.9%)
Treatment-related	0
Serious AE, n(%)	3 (17.6%)
Treatment-related	0
Leading to permanent discontinuation of treatment	1 (5.9%)
Treatment-related	0

[a] one subject in 0.3mg/kg group who experienced Grade 3 adverse event of immune-related dermatitis and completely recovered after study drug withheld.

- No unexpected safety signal was observed.
- Treatment-related adverse events with the highest prevalence are listed in Table 3.

Table 3. Common Treatment-Related AEs[a] (≥10% of patients), n(%)

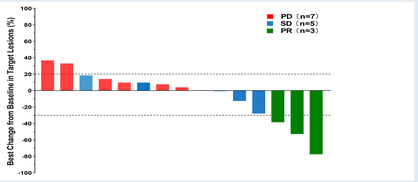
	N=17	
	Any Grade	Grade 3-4
ALT increased[b]	6 (35.3%)	0
AST increased[b]	6 (35.3%)	0
Dermatitis/rash	3 (17.6%)	1 (5.9%)
Blood bilirubin increased	3 (17.6%)	0
Injection site reaction	2 (11.8%)	0

[a]AE categories that only included an event with frequency of ≥10% of 17 patients are listed;
[b]Of note, 5 of 17 (29.4%) patients were diagnosed with hepatic cancer cell or biliary tract cancer.
AE: adverse event; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

Clinical Activity

- At the data cutoff, 15 treated patients were considered as efficacy evaluable patients.
- Three patients (20.0%) had confirmed PR as best overall response (Table 4) , including one renal cell cancer patient at 2.5 mg/kg and one Intrahepatic cholangiocarcinoma patient at 5.0 mg/kg (ongoing response), and one biliary tract cancer patient at 10.0 mg/kg, 5 patients achieved SD.
- The best percentage change in target lesion is presented in Figure 2.

Figure 2. Tumor Response to KN035



PD: progressive disease; PR: partial response; SD: stable disease.

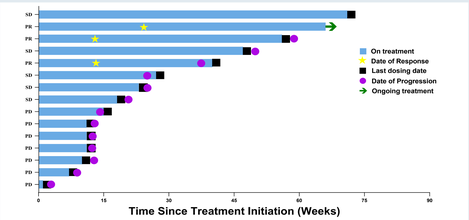
- The response data by dose level to KN035 is presented in Table 4.

Table 4. Best Overall Response

	0.1 mg/kg (N=1)	0.3 mg/kg (N=2)	1.0 mg/kg (N=3)	2.5 mg/kg (N=3)	5.0 mg/kg (N=3)	10.0 mg/kg (N=3)	In total (N=15)
BOR							
CR	0	0	0	0	0	0	0
PR	0	0	0	1	1	1	3 (20.0%)
SD	0	0	2	2	1	0	5 (33.3%)
PD	1	2	1	0	1	2	7 (46.7%)
ORR	0	0	0	1	1	1	3 (20.0%)
DCR	0	0	2	3	2	1	8 (53.3%)

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate; DCR: disease control rate.

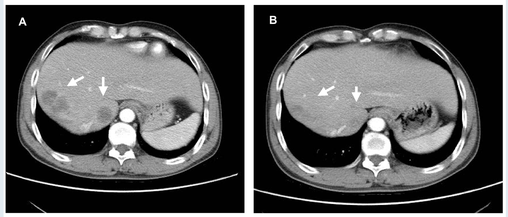
Figure 3. Tumor Response, Tumor Progression and Duration of Treatment



PD: progressive disease; PR: partial response; SD: stable disease.

- Tumor response, Tumor progression and Duration of Treatment are displayed in Figure 3.
- Investigator-assessed response was ongoing in one of three patients with PR as best overall response.
  - Duration of response exceeded 24 weeks in all three patients and two patients had exceeded 40 weeks.

Figure 4. Patient with intrahepatic cholangiocarcinoma with PR (52.75% reduction) in cycle 16



Baseline Cycle 16

- Patient ID C01013 diagnosed with intrahepatic cholangiocarcinoma with intrahepatic metastasis at baseline was treated with KN035 at a dose of 5.0 mg/kg for more than 15 months and remained on treatment. The patient had a first Partial Response after six months of treatment, and after then the tumor burden continued to decrease.
- Baseline image shown in A and image after 16 cycles is shown in B.

CONCLUSIONS

- KN035 exhibited a tolerable safety profile in patients with advanced malignancies.
  - No DLT was observed; MTD was not reached.
  - No related SAE, no grade 4-5 related AEs, only 1 grade 3 related AE was observed.
  - No new safety signal was identified beyond the established safety profile.
- KN035 showed preliminary efficacy in patients with advanced malignancies with a confirmed ORR of 20% by investigator assessment per RECIST v1.1.
- Further clinical development of KN035 is warranted. A phase 2 study in MSI-H solid tumor and a phase 3 study in Biliary Tract Cancer are ongoing in China.

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QR CODE AND CONTACT INFORMATION

- For questions or comments on this poster, please contact Dr. Xu Jianming at *Jmxu2003@yahoo.com*.