Preliminary safety, efficacy and pharmacokinetics (PK) results of KN046 (bispecific anti-PD-L1/CTLA4) from a first-in-human study in subjects with advanced solid tumors

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BACKGROUND

KN046 is a novel bispecific domain antibody fused with human IgG1 Fc, which blocks both PD-L1 interaction with PD-1 and CTLA-4 interaction with CD80/CD86. The wild type IgG1 Fc portion of KN046 preserves intact effector functions, such as ADCC that may lead to depletion of Tregs in tumor microenvironments.

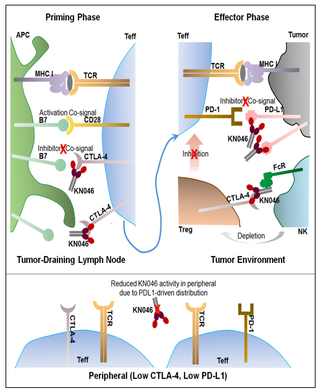

Figure 1. Mechanism of action of KN046

- Blocking CTLA-4 with B7 restores T effector cell function in lymph nodes and deletes Treg (inhibitory T cell) in tumor microenvironment
- Blocking PD-L1 with PD-1 restore T cell effector function at tumor site
- Binds PD-L1 more strongly than CTLA-4, which enables KN046 targeting tumor microenvironment with PD-L1 high expression
- Limited peripheral distribution reduces treatment-associated on-target off-tumor toxicity
- With wide type of IgG1 Fc domain, CTLA-4 blocking-mediated Treg cells deletion was retained via Fc effector function

OBJECTIVES

Primary objectives

- To determine the maximum tolerated dose (MTD) or a biological effective dose (BED), and the recommended Phase II dose (RP2D) of KN046 when administered as a single agent in subjects with advanced solid tumors

METHODS

The dose-escalation was based on the traditional “3+3” dose-escalation design followed by dose expansion after safety and tolerability was confirmed.

Dose limiting toxicity (DLT) evaluation period is 28 days.

Efficacy evaluation was performed by RECIST 1.1 every 8 weeks.

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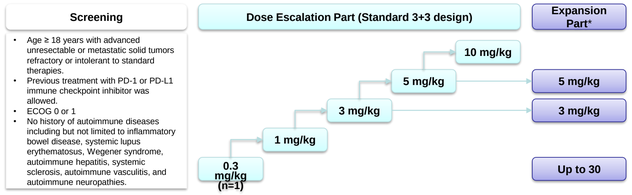


Note: * Cohort expansion will be proposed to enroll approximately 30 subjects based on available safety, pharmacokinetics and preliminary efficacy data and the agreement between sponsor and SMC.

Figure 2. Study design

RESULTS

As of April 30, 2019, 23 pts had been enrolled (0.3 mg/kg, n=1; 1 mg/kg, n=3; 3 mg/kg, n=13; and 5 mg/kg, n=6).

Table 1. Patient demographics, disease characteristics and treatment duration

	0.3mg/kg Q2W (n=1)	1.0mg/kg Q2W (n=3)	3.0mg/kg Q2W (n=13)	5.0mg/kg Q2W (n=6)	Total (n=23)
Gender, n (%)					
Male	0	0	3 (23.1%)	2 (33.3%)	5 (21.7%)
Female	1 (100%)	3 (100%)	10 (76.9%)	4 (66.7%)	18 (78.3%)
Age (years)					
Median (Range)	43.0 (43, 43)	62.0 (40, 66)	69.0 (40, 77)	61.5 (54, 74)	65.0 (40, 77)
ECOG, n (%)					
0	1 (100%)	3 (100%)	7 (53.8%)	4 (66.7%)	15 (65.2%)
1	0	0	6 (46.2%)	2 (33.3%)	8 (34.8%)
Lines of Chemotherapy					
≤ Line 2	1 (100%)	3 (100%)	9 (69.2%)	6 (100%)	18. (78.3%)
> Line 2	0	0	4 (30.8%)	2 (33.3%)	6 (26.1%)
Duration of Treatment (weeks)					
Mean (SD)	4.0 (NA)	18.0 (5.29)	7.8 (5.28)	9.8 (8.45)	9.5 (6.85)
Median	4.0	16.0	7.0	6.5	7.0
Min, Max	4, 4	14, 24	2, 24	2, 24	2, 24

1 DLT was observed at 5 mg/kg dose (a grade 3 immune-related hepatitis without elevation in total bilirubin; reversible in two weeks).

The most common (≥ 13%) treatment-emergent AEs (TEAE) were Fatigue (5, 21.7%), Nausea (4, 17.4%), Dry mouth (3, 13.0%) and Hypotension (3, 13.0%). Immune-related TEAEs (Hepatic function abnormal, Hyperthyroidism, Autoimmune colitis, Autoimmune arthritis, Pruritis, Arthralgia, Abdominal pain, Nausea, Rash, Psoriasis and Transaminases increased) were observed in 8 pts (Table 2).

Table 2 Summary of safety results

	0.3 mg/kg Q2W	1.0 mg/kg Q2W	3.0 mg/kg Q2W	5.0 mg/kg Q2W	Total
Subjects with ≥ Grade 1 TEAE	1 (100%)	3 (100%)	11 (84.6%)	6 (100%)	21 (91.3%)
Subjects with ≥ Grade 3 TEAE	0	2 (66.7%)	4 (30.8%)	5 (83.3%)	11 (47.8%)
Subjects with ≥ Grade 1 TRAE	1 (100%)	2 (66.7%)	6 (46.2%)	5 (83.3%)	14 (60.9%)
Subjects with ≥ Grade 3 TRAE	0	2 (66.7%)	2 (15.4%)	2 (33.3%)	6 (26.1%)
irAE of any grade	0	2 (66.7%)	4 (30.8%)	2 (33.3%)	8 (34.8%)
Subjects with Grade 3/4 irAE	0	2 (66.7%)	1 (7.7%)	2 (33.3%)	5 (21.7%)
Hepatic function abnormal	0	1 (33.3%)	0	1 (16.7%)	2 (8.7%)
Autoimmune colitis	0	0	0	1 (16.7%)	1 (4.3%)
Autoimmune arthritis	0	0	1 (7.7%)	0	1 (4.3%)
Abdominal pain†	0	1 (33.3%)	0	0	1 (4.3%)

Note: †The patient was excluded of immune related colitis via endoscopy and KN046 treatment continued

11 subjects were evaluable for efficacy as of the cut-off date. One PT with NSCLC from 3 mg/kg cohort had confirmed completed response. One PT with pancreatic cancer from 5 mg/kg cohort had initial long-term stable disease (25 weeks) and transitioned to partial response at 6th cycle. Two PTs (TNBC and nivolumab refractory RCC) from 1 mg/kg cohort had shown long-term stable disease (14 and 30 weeks, respectively). One PT (Rectal cancer) from 5 mg/kg cohort had shown long-term stable disease (16 weeks)(Figure 3 and 4).

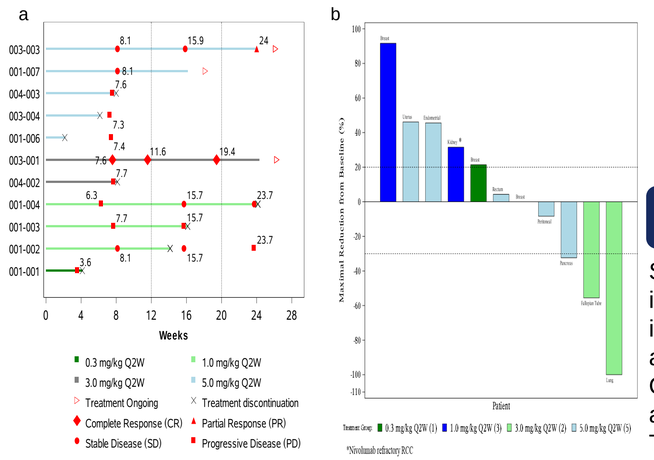
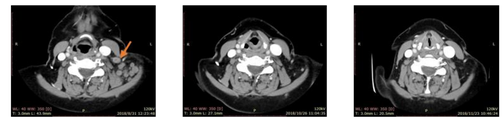


Figure 3. Efficacy summary

Screening/baseline **Week 8** **Week 12**



- History: 57-year-old female patient with stage IV NSCLC progress disease after chemoradiotherapy (Carboplatin and Taxol).
- Outcome: CR (by RECIST 1.1) for > 24 weeks at cutoff

Figure 4. Complete response in a patient with NSCLC

Pharmacokinetics following the first 60- or 90- minutes infusion and dose proportionality of KN046 have been characterized in 13 subjects (Table 3 and Figure 5).

Table 3 Summary of safety results

Parameter, mean (SD)	0.3 mg/kg Q2W (n=1)	1.0 mg/kg Q2W (n=3)	3.0 mg/kg Q2W (n=3)	5.0 mg/kg Q2W (n=6)
Cmax (μg/mL)	6.4	25.6 (10.1)	63.3 (22.7)	103.2 (17.1)
AUC_{0-t} (μg/mL*h)	495.7	2219.6 (618.4)	5510.7 (1484.4)	8564.0 (2127.0)
t1/2 (h)	59.0	101.0 (20.1)	148.1 (36.9)	192.8 (49.6)
CL (mL/h)	35.6	30.0 (1.7)	30.0 (2.0)	25.4 (3.8)
Vz (mL)	3031.0	4356.5 (871.3)	6467.3 (1943.6)	6885.5 (1124.9)

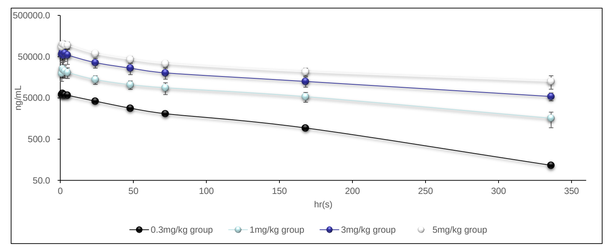


Figure 5. Concentration-time profile by dose cohort (Mean ± SD)

CONCLUSIONS

Single agent KN046 has an acceptable safety profile and is in line with previously reported safety data from other immune checkpoint inhibitors. Preliminary efficacy results are promising. PK data from initial 4 cohorts support Q2W schedule. 3 and 5 mg/kg Q2W have been declared as recommended phase 2 doses for further exploration. The study is currently ongoing at dose expansion phase 3 mg/kg Q2W.