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Preliminary Safety, Tolerability and Efficacy Results of KN046 (an anti-PD-L1/CTLA-4 Bispecific Antibody) in combination with Nab-paclitaxel in Metastatic Triple-negative Breast Cancer (mTNBC)

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Background

TNBC:

- Triple-negative breast cancer (TNBC) is the term used to describe breast cancers that lack ER and PR expression and do not overexpress HER2. Patients with TNBC have poor clinical outcomes.
- In patients with TNBC, the expression of PD-L1 occurs mainly on tumor-infiltrating immune cells rather than on tumor cells and can inhibit anticancer immune responses. The inhibition of PD-1 and PD-L1 has been proved to be a useful treatment strategy.

KN046: Bispecific PD-L1 and CTLA-4 Antibody

- KN046 is a recombinant humanized PD-L1/CTLA-4 domain antibody Fc fusion protein.
- KN046 can block CTLA-4 with B7 and PD-L1 with PD-1 and CD80 simultaneously.
- Limited peripheral distribution of KN046 reduces treatment-associated on-target off-tumor toxicity.
- KN046 reserves IgG1 Fc domain, CTLA-4 blocking-mediated T_{reg} cells depletion.

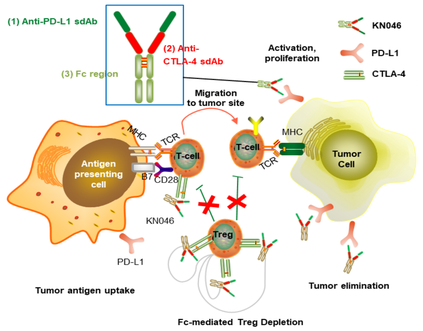

Figure 1. Mechanism of action of KN046

Study Design

Key eligibility criteria:
- Metastatic or inoperable locally advanced TNBC
  - Histologically documented
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

KN046 3 mg/kg or 5 mg/kg IV
- On day 1 and 15 of 28-day cycle

+ *Nab*-paclitaxel 100 mg/m^2 IV
- On day 1, 8 and 15 of 28-day cycle

RECIST 1.1 confirmed disease progression or toxicity

- Eligible patients were 18 years of age or older and received nab-paclitaxel plus KN046 at two dose levels (3 mg/kg Q2W or 5 mg/kg Q2W).
- Tumor response was evaluated Q8W per RECIST 1.1.
- Primary endpoint was ORR and key secondary endpoints were PFS and OS.
- Patients had a representative tumor specimen that could be evaluated for PD-L1 expression on immune cells (SP142 PD-L1 immunohistochemical assay).

Results

Disposition and Exposure:

	KN046 3 mg/kg Q2W +Nab-paclitaxel (N=16)	KN046 5 mg/kg Q2W +Nab-paclitaxel (N=11)	Total (N=27)
Age (years)			
Median (range)	53.5 (35, 70)	45.5 (33, 62)	50.0 (33, 70)
Treatment ongoing	9 (56.3%)	3 (27.3%)	12 (44.4%)
Treatment termination	7 (43.8%)	8 (72.7%)	15 (55.6%)
Adverse Event	3 (18.8%)	0	3 (11.1%)
Death	1 (6.3%)	0	1 (3.7%)
RECIST 1.1 PD	2 (12.5%)	6 (54.5%)	8 (29.6%)
Other reasons	1 (6.3%)	2 (18.2%)	3 (11.1%)
Treatment duration (weeks)			
Median (range)	26.2 (6.0, 81.9)	14.1 (2.0, 56.0)	16.0 (2.0, 81.9)

Table 1. Patient disposition and treatment duration (as of 8-Mar-2021)

Efficacy:

	KN046 3 mg/kg Q2W +Nab-paclitaxel (N=15)	KN046 5 mg/kg Q2W +Nab-paclitaxel (N=10)	Total (N=25)
Best Overall Response			
Complete Response (CR)	2 (13.3%)	0	2 (8.0%)
Partial Response (PR)	5 (33.4%)	3 (30.0%)	8 (32.0%)
Stable Disease (SD)	8 (53.3%)	6 (60.0%)	14 (56.0%)
Progressive Disease (PD)	0	1 (10.0%)*	1 (4.0%)
Objective Response Rate (ORR)	7 (46.7%)	3 (30.0%)	10 (40.0%)
95% CI	21.3%, 73.4%	6.7%, 65.2%	21.1%, 61.3%
Disease Control Rate (DCR)	15 (100%)	9 (90.0%)	24 (96.0%)
95% CI	78.2%, 100.0%	55.5%, 99.7%	79.6%, 99.9%

Note: CR&PR: including confirmed and unconfirmed. ORR = CR+PR; DCR=CR+PR+SD
* PSCC (primary squamous cell carcinoma) patient was mis-enrolled.

Table 2. Summary of best of responses (as of 8-Mar-2021)

- From Jun. 2019 through Mar. 2021, 27 patients (all female) were enrolled. 15 patients had been treated with neoadjuvant or adjuvant taxane and anthracycline chemotherapy
- At the time of data cutoff, the median follow-up was 13.7 months.
- At the time of data cutoff, a total of 14 patients had disease progression or died. The median PFS were 7.3 (95% CI: 3.7, NE) months in ITT population and 13.8 (95% CI: 1.6, NE) months in PD-L1 positive subgroup, respectively
- At the time of the data cutoff, 5 patients had died and 4 patients were lost visited. The median OS was not reached. 15-month OS rates were 73.4% (95% CI: 46.1%, 88.4%) in ITT population and 77.1% (95% CI: 34.5%, 93.9%) in PD-L1 positive subgroup, respectively.

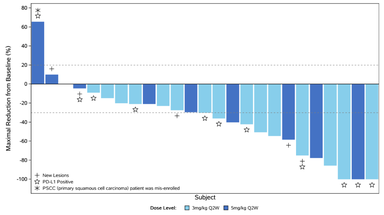

Figure 2. Waterfall plot (as of 8-Mar-2021)

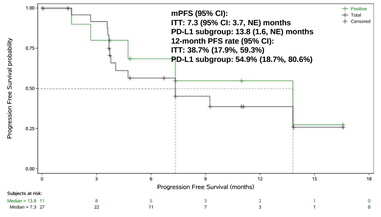

Figure 3a. Kaplan-Meier plot of PFS (as of 8-Mar-2021)

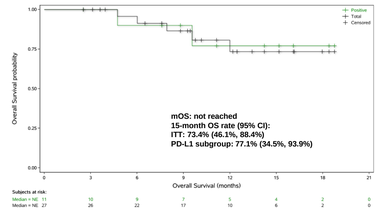

Figure 3b. Kaplan-Meier plot of OS (as of 8-Mar-2021)

Results

Safety:

- Among patients in the safety population, adverse events (AEs) related to KN046 occurred in 100% of 27 patients. The frequency of grade 3 or 4 AEs was 48.1%. No KN046 treatment related leading to death.
- Immune related adverse events (irAEs) occurred in 11 (40.7%) patients. All the events were of grade 1 or 2 except that 3 patients experienced two grade 3 immune-mediated hepatic disorders and one grade 3 rash.

Preferred Term	KN046 3 mg/kg Q2W +Nab-paclitaxel (N=16)		KN046 5 mg/kg Q2W +Nab-paclitaxel (N=11)		Total (n=27)	
	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades
Subjects with at least 1 KN046 related TEAE	8 (50.0%)	16 (100%)	5 (45.5%)	11 (100%)	13 (48.1%)	27 (100%)
Aspartate aminotransferase increased	2 (12.5%)	6 (37.5%)	2 (18.2%)	7 (63.6%)	4 (14.8%)	13 (48.1%)
Alanine aminotransferase increased	0	7 (43.8%)	0	6 (54.5%)	0	13 (48.1%)
Pyrexia	0	5 (31.3%)	0	4 (36.4%)	0	9 (33.3%)
Neutrophil count decreased	3 (18.8%)	7 (43.8%)	0	1 (9.1%)	3 (11.1%)	8 (29.6%)
Anaemia	0	6 (37.5%)	0	1 (9.1%)	0	7 (25.9%)
White blood cell count decreased	2 (12.5%)	7 (43.8%)	0	0	2 (7.4%)	7 (25.9%)
Rash	0	5 (31.3%)	1 (9.1%)	2 (18.2%)	1 (3.7%)	7 (25.9%)
Infusion related reaction	1 (6.3%)	4 (25.0%)	0	1 (9.1%)	1 (3.7%)	5 (18.5%)
Hyponatraemia	1 (6.3%)	4 (25.0%)	0	1 (9.1%)	1 (3.7%)	5 (18.5%)
Diarrhoea	0	3 (18.8%)	0	1 (9.1%)	0	4 (14.8%)
Hypothyroidism	0	2 (12.5%)	0	2 (18.2%)	0	4 (14.8%)
Vomiting	0	3 (18.8%)	0	1 (9.1%)	0	4 (14.8%)
Gamma-glutamyltransferase increased	1 (6.3%)	2 (12.5%)	1 (9.1%)	1 (9.1%)	2 (7.4%)	3 (11.1%)
Dermatitis allergic	0	2 (12.5%)	0	1 (9.1%)	0	3 (11.1%)
Hepatic function abnormal	3 (18.8%)	3 (18.8%)	0	0	3 (11.1%)	3 (11.1%)
Hyperglycaemia	0	3 (18.8%)	0	0	0	3 (11.1%)
Hypocalcaemia	0	3 (18.8%)	0	0	0	3 (11.1%)
Hypokalaemia	2 (12.5%)	3 (18.8%)	0	0	2 (7.4%)	3 (11.1%)

Table 3. The most common (≥ 10%) KN046 related TEAEs (as of 8-Mar-2021)

Conclusion

- We report here the primary results from a phase 2 trial of KN046 in patients with mTNBC. Administered as first-line treatment, the combination of KN046 with nab-paclitaxel was well tolerated and showed favorable clinical efficacy in PD-L1 positive patients. Preliminary overall survival data is encouraging.
- Combination therapy with KN046 plus nab-paclitaxel had a safety profile that was consistent with the known toxic effects of each agent. Consistent with observations from other trials of KN046, no new adverse-event signals were observed. Majority of ≥ Grade 3 TRAEs were hepatotoxicity and hematotoxicity, which were reversible after symptomatic treatment.

Clinical trial information: *NCT03872791*

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KN046 combined with nab-paclitaxel is well tolerated and has demonstrated favorable clinical efficacy in PD-L1 positive TNBC.

- **Of 25 evaluable TNBC pts, the objective response rate was 40.0% and disease control rate was 96.0%.**
- **Median PFS in pts with PD-L1 positive (IC PD-L1≥1%) was 13.8 months and 15-month OS rate was 77.1%.**
- **The frequency of grade 3 or 4 AEs (related to KN046) was 48.1%. KN046 related SAEs occurred in 4 patients (14.8%).**
- **Immune related adverse events (irAEs) occurred in 40.7% of patients. Only 3 patients experienced grade 3 irAEs.**