Preliminary Efficacy and Safety Results of KN026 (a HER2-targeted Bispecific Antibody) in Combination with KN046 (an anti-PD-L1/CTLA-4 Bispecific Antibody) in Patients (pts) with HER2-positive Gastrointestinal Tumors

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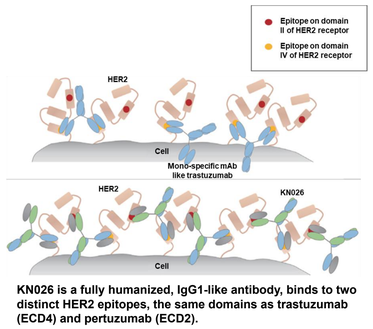
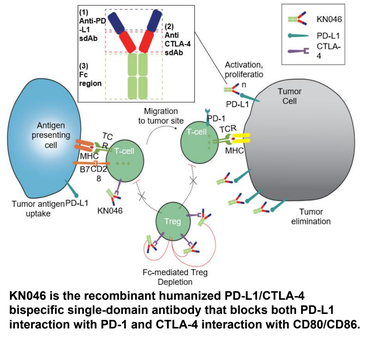
BACKGROUND

- KN026 is a novel bispecific antibody that simultaneously binds to two distinct HER2 epitopes. KN046 is a novel bispecific antibody that blocks both PD-L1 interaction with PD-1 and CTLA-4 interaction with CD80/CD86.
- Both preclinical and clinical studies have suggested a coordination of engagement of innate and adaptive immunity with the combination of an anti-HER2 antibody and an immune checkpoint blockade.
- The study assessing the safety, tolerability and preliminary efficacy for KN026 in combination with KN046 in pts with HER2 aberrated solid tumors was reported in 2020 SITC. Here we mainly reported the efficacy in patients with HER2-positive (IHC 3+ or HER2 gene amplification) gastrointestinal tumors and the safety of KN026 combined with KN046 (NCT04040699).

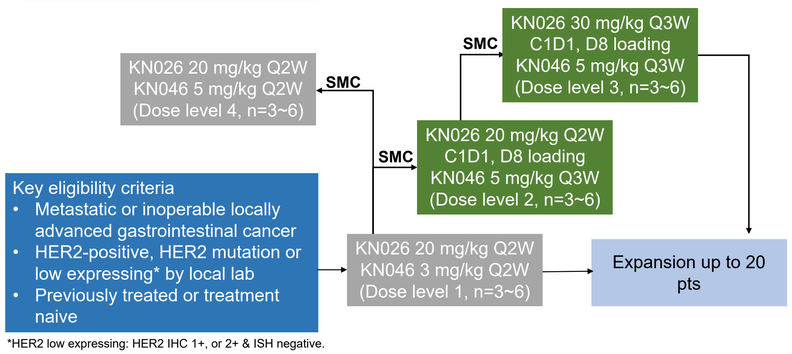


KN026 is a fully humanized, IgG1-like antibody, binds to two distinct HER2 epitopes, the same domains as trastuzumab (ECD4) and pertuzumab (ECD2).



KN046 is the recombinant humanized PD-L1/CTLA-4 bispecific single-domain antibody that blocks both PD-L1 interaction with PD-1 and CTLA-4 interaction with CD80/CD86.

STUDY DESIGN



*HER2 low expressing: HER2 IHC 1+, or 2+ & ISH negative.

Primary endpoint

- Dose escalation: DLT
- Dose expansion: ORR and DOR

Second endpoint:

- 6-month PFS rate (PFSR-6m), PFSR-12m, CBR
- 6-month OS rate (OSR-6m), OSR-12m
- AE
- Relationship between biomarker and clinical efficacy

Demographics & Baseline characteristics

	GC/GEJ			Other GI*	Total
	First line (n=7)	Late line (n=24)	Total (n=31)	(n=13)	(N=44)
Sex					
Male	4 (57.1%)	18 (75.0%)	22 (71.0%)	8 (61.5%)	30 (68.2%)
Female	3 (42.9%)	6 (25.0%)	9 (29.0%)	5 (38.5%)	14 (31.8%)
Age（years）					
Mean（SD）	55.7(4.11)	57.9(9.74)	57.4(8.78)	52.0(11.62)	55.8(9.88)
Median （Min，Max）	55.0 (49, 62)	56.0 (38, 74)	56.0 (38, 74)	54.0 (29, 70)	56.0 (29,74)
ECOG					
0	2 (28.6%)	1 (4.2%)	3 (9.7%)	2 (15.4%)	5 (11.4%)
1	5 (71.4%)	23 (95.8%)	28 (90.3%)	11 (84.6%)	39 (88.6%)
Distant metastasis	5 (71.4%)	21 (87.5%)	26 (83.9%)	13 (100%)	39 (88.6%)
Prior HER2 treatment	0	12 (50.0%)	12 (38.7%)	9 (69.2%)	21 (47.7%)

*All patients with other GI disease had received prior treatment

Safety (related AE ≥ 10%)

Preferred Term	Any grade (N = 44)	Grade ≥ 3 (N=44)
Subjects with at least 1 KN026 or KN046 related TEAE	40 (90.9%)	8 (18.2%)
Anemia	17 (38.6%)	2 (4.5%)
Infusion related reaction	16 (36.4%)	1 (2.3%)
AST increased	12 (27.3%)	0
Diarrhea	12 (27.3%)	0
ALT increased	11 (25.0%)	0
Rash	9 (20.5%)	0
Blood bilirubin increased	8 (18.2%)	0
White blood cell count decreased	8 (18.2%)	0
Neutrophil count decreased	6 (13.6%)	1 (2.3%)
Platelet count decreased	6 (13.6%)	1 (2.3%)

RESULTS

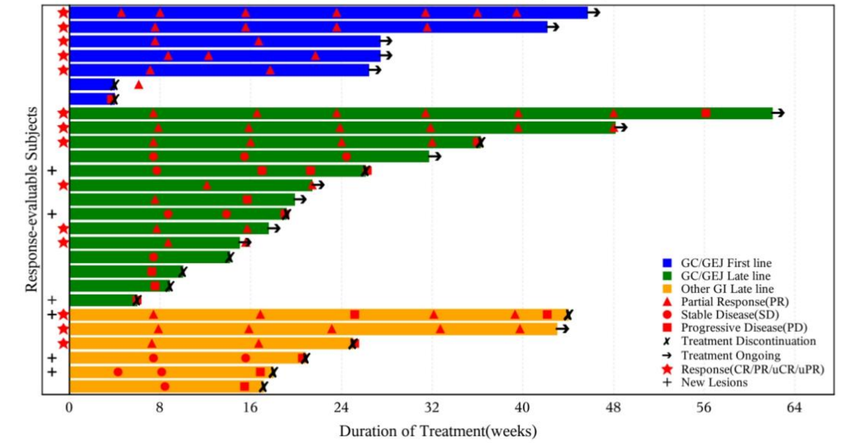
- As of 8 May 2021, a total of 44 patients were enrolled, and there were 25, 3, 13 and 3 patients in dose level 1 (DL1), DL2, DL3 and DL4 respectively. 34 patients (77.3%) were HER2-positive.
- 36 patients were evaluable, and the ORR was 38.9% with median DOR (mDOR) 11.2 months (mo). For all 44 patients, median PFS (mPFS) was 4.8 mo, and the OSR-12m were 72.4%.
- There were 34 patients with HER2 positive. 27 patients of them were evaluable, and the ORR was 51.9% with mDOR 11.2 mo. The CBR was 55.6%. For all 34 HER2-positive patients, mPFS was 5.8 mo, and PFSR-6m was 39.5%. mOS wasn't reached and OSR-12m was 78.1%.
- There were 24 HER2-positive GC/GEJ patients and 21 patients of them were evaluable. In 21 HER2-positive GC/GEJ patients, ORR was 71.4% for 7 first-line patients and 42.9% for 14 late-line patients with mDOR 11.2 mo, and ORR was 40.0% for 10 patients with prior trastuzumab. The CBR was 71.4% for first-line patients and 50.0% for late-line patients. mPFS was 8.3 mo for 24 HER2-positive GC/GEJ patients and 4.4 mo for 17 late-line patients. PFSR-6m was 85.7% and 46.2% for first-line and late-line patients, respectively. OSR-12m was 79.5% for all HER2-positive GC/GEJ patients and 62.2% for late-line patients.
- The most commonly reported related TEAEs were anemia (38.6%), infusion related reaction (36.4%), AST increased (27.3%), diarrhea (27.3%), ALT increased (25.0%) and rash (20.5%). Grade ≥ 3 related TEAE occurred in 8 patients (18.2%), and the most common was anemia (4.5%).

CONCLUSIONS

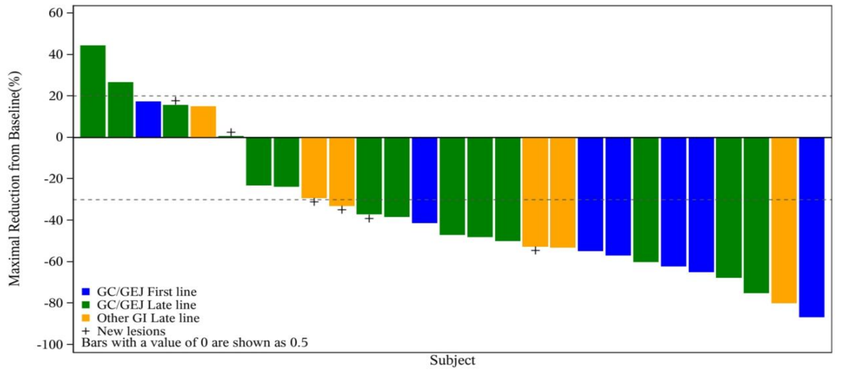
- KN026 combined KN046, as chemo-free therapy, demonstrated great clinical efficacy with a high ORR of 51.9% in HER2 positive GI patients, and a clinical meaningful ORR of 71.4% for first-line GC/GEJ patients and 42.9% for late-line GC/GEJ patients. AEs of the combined therapy were tolerated. Pivotal trials in HER2-positive GC/GEJ are planned.

Efficacy Outcomes (HER2-positive patients)

	GC/GEJ			Other GI	Total
	First line (n=7)	Late line (n=14)	Total (n=21)	(n=6)	(N=27)
ORR (%, 95% CI)	71.4 (29.0, 96.3)	42.9 (17.7, 71.1)	52.4 (29.8, 74.3)	50.0 (11.8, 88.2)	51.9 (31.9, 71.3)
DCR (%, 95% CI)	85.7 (42.1, 99.6)	78.6 (49.2, 95.3)	81.0 (58.1, 94.6)	100 (54.1, 100)	85.2 (66.3, 95.8)
CBR (%, 95% CI)	71.4 (29.0, 96.3)	50.0 (23.0, 77.0)	57.1 (34.0, 78.2)	50.0 (11.8, 88.2)	55.6 (35.3, 74.5)
mDOR (months, 95% CI)	NE (NE, NE)	11.2 (6.6, NE)	11.2 (6.6, NE)	4.1 (4.1, NE)	11.2 (4.1, NE)
	GC/GEJ			Other GI	Total
	First line (n=7)	Late line (n=17)	Total (n=24)	(n=10)	(N=34)
mPFS (months, 95% CI)	NE (0.9, NE)	4.4 (1.7, NE)	8.3 (3.6, NE)	4.8 (3.4, 5.8)	5.8 (3.6, NE)
PFSR-6m (95% CI)	85.7 (33.4, 97.9)	46.2 (18.2, 70.4)	57.2 (31.4, 76.4)	14.3 (0.7, 46.5)	39.5 (18.6, 59.8)
PFSR-12m (95% CI)	NE (NE, NE)	30.8 (6.3, 60.6)	42.9 (14.5, 69.0)	NE (NE, NE)	31.6 (11.9, 53.5)
OSR-6m (95% CI)	100 (100, 100)	93.3 (61.3, 99.0)	95.5 (71.9, 99.3)	87.5 (38.7, 98.1)	93.1 (75.0, 98.2)
OSR-12m (95% CI)	NE (NE, NE)	62.2 (7.2, 91.8)	79.5 (31.7, 95.5)	72.9 (27.6, 92.5)	78.1 (48.8, 91.9)



Swimlane Plot (HER2-Positive evaluable patients)



Waterfall Plot (HER2-Positive evaluable patients)