# Preliminary Safety, Tolerability and Efficacy 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 aberrated solid tumors


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## Background

### KN026: Bispecific HER2-Targeted Antibody

- Fully humanized, IgG1-like antibody, binds to two distinct HER2 epitopes, the same domains as trastuzumab (ECD4) and pertuzumab (ECD2).
- Crosslinking multiple HER2 receptors on the cell surface and promote HER2 internalization.
- Recruit immune cells to destroy HER2-overexpressing target cells.
- Increased presence of KN026 on tumor cells leads to increased tumor killing by effector functions.
- IgG1 Fc fragment of KN026 binds to FcγRIIIa and mediates potent ADCC.

### KN046: Bispecific PD-L1 and CTLA-4 Antibody

- Recombinant humanized PD-L1/CTLA-4 domain antibody Fc fusion protein.
- Blocking CTLA-4 with B7 and PD-L1 with PD-1.
- Limited peripheral distribution reduces treatment-associated on-target off-tumor toxicity.
- IgG1 Fc domain, CTLA-4 blocking-mediated Treg cells deletion.

### KN026 in combination with KN046

- Activation of HER2 pathway interferes STING pathway, key component in innate immunity.
- Blocking HER2 pathway lift the inhibition to the innate immunity
- Anti-tumor activity further enhanced by activation of adaptive immunity by KN046.

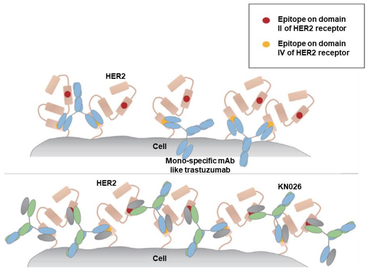



Figure 1. Mechanism of action of KN026

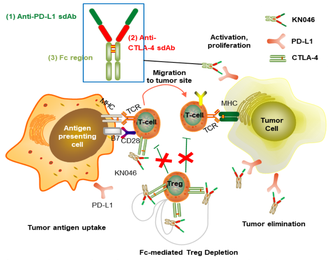



Figure 2. Mechanism of action of KN046

## Study Design

- KN046-IST-02 is a dose escalation and expansion study of KN026 in combination with KN046 in Chinese pts with solid tumors who have failed available standard of care.
- Status of HER2 pathway aberration (HER2 mutation, HER2 amplification and/or HER2 overexpression)
- Three ascending doses examined
  - DL1: KN026 20 mg/kg Q2W + KN046 3 mg/kg Q2W; DL2: KN026 20 mg/kg Q2W with loading on Days 1, 8 of Cycle 1 + KN046 5 mg/kg Q3W; DL3: KN026 30 mg/kg Q3W with loading on Days 1, 8 of Cycle 1 + KN046 5 mg/kg Q3W.
- Tumor response was evaluated Q8W per RECIST 1.1. Primary endpoint was DLT and key secondary endpoints were efficacy parameters (ORR, DOR, PFS).

## Results

### Safety

- 26 pts enrolled. 18 pts HER2-positive (HER2 IHC3+ or IHC2+/FISH+)
- No dose limiting toxicities (DLTs).
- 23.1% pts experienced ≥Grade 3 treatment related AEs: neutrophil count decreased (1), platelet count decreased (1), anemia (1), immune-mediated endocrinopathy (1), pneumonia (1) and infusion related reaction (1).
- The most common (frequency ≥ 15%) KN026 or KN046 related TEAEs were infusion related reaction (n=11, 44.0%), anaemia (n=9, 36.0%), white blood cell count decreased (n=6, 24.0%), diarrhea (n=5, 20.0%), AST increased (n=5, 20.0%), platelet count decreased (n=5, 20.0%), rash (n=5, 20.0%) and ALT increased (n=4, 16.0%).

| | 20 mg/kg Q2W + 3 mg/kg Q2W (N=19) | 20 mg/kg Q2W + 5 mg/kg Q3W (N=3) | 30 mg/kg Q3W + 5 mg/kg Q3W (N=4) | Total (N=26) |
|---|---|---|---|---|
| Gender, n% | | | | |
| Male | 11 (57.9%) | 3 (100%) | 3 (75.0%) | 17 (65.4%) |
| Female | 8 (42.1%) | 0 | 1 (25.0%) | 9 (34.6%) |
| Race, n% | | | | |
| Asian | 19 (100%) | 3 (100%) | 4 (100%) | 26 (100%) |
| Age (years) | | | | |
| n | 19 | 3 | 4 | 26 |
| Median | 56.0 | 56.0 | 52.5 | 55.5 |
| Treatment ongoing | 11 (57.9%) | 1 (33.3%) | 4 (100%) | 16 (61.5%) |
| Treatment termination | 8 (42.1%) | 2 (66.7%) | 0 | 10 (38.5%) |
| Adverse Event | 1 (5.3%) | 0 | 0 | 1 (3.8%) |
| Death | 0 | 2 (66.7%) | 0 | 2 (7.7%) |
| Objective Disease Progression | 5 (26.3%) | 0 | 0 | 5 (19.2%) |
| other | 2 (10.5%) | 0 | 0 | 2 (7.7%) |

Table 1. Patient demographics and disposition (as of 3-Sep-2020)

| | 20 mg/kg Q2W+3 mg/kg Q2W (n=19) | 20 mg/kg Q2W+5 mg/kg Q3W (n=3) | 30 mg/kg Q3W+5 mg/kg Q3W (n=4) | Total (n=26) |
|---|---|---|---|---|
| Subjects with at least 1 TEAE | 16 (84.2%) | 3 (100%) | 2 (50.0%) | 21 (80.8%) |
| Related to KN026 | 16 (84.2%) | 3 (100%) | 2 (50.0%) | 21 (80.8%) |
| Related to KN046 | 15 (78.9%) | 3 (100%) | 1 (25.0%) | 19 (73.1%) |
| Subjects with at least 1 TEAE of CTCAE grade 3 or 4 | 6 (31.6%) | 2 (66.7%) | 0 | 8 (30.8%) |
| Related to KN026 | 4 (21.1%) | 1 (33.3%) | 0 | 5 (19.2%) |
| Related to KN46 | 5 (26.3%) | 1 (33.3%) | 0 | 6 (23.1%) |
| Subjects with at least 1 IRR | 6 (31.6%) | 1 (33.3%) | 2 (50.0%) | 9 (34.6%) |
| Related to KN026 | 6 (31.6%) | 1 (33.3%) | 2 (50.0%) | 9 (34.6%) |
| Related to KN046 | 3 (15.8%) | 0 | 1 (25.0%) | 4 (15.4%) |
| Subjects with at least 1 irAE | 9 (47.4%) | 0 | 0 | 9 (34.6%) |
| Subjects with at least 1 CTCAE grade ≥ 3 irAE | 1 (5.3%) | 0 | 0 | 1 (3.8%) |
| Subjects with at least 1 treatment-emergent SAE | 3 (15.8%) | 2 (66.7%) | 0 | 5 (19.2%) |
| Related to KN026 | 3 (15.8%) | 0 | 0 | 3 (11.5%) |
| Related to KN046 | 3 (15.8%) | 0 | 0 | 3 (11.5%) |
| Subjects with at least 1 CTCAE grade ≥3 treatment-emergent SAE | 2 (10.5%) | 2 (66.7%) | 0 | 4 (15.4%) |
| Related to KN026 | 2 (10.5%) | 0 | 0 | 2 (7.7%) |
| Related to KN046 | 2 (10.5%) | 0 | 0 | 2 (7.7%) |
| Subjects with at least 1 TEAE leading to drug withdrawn | 3 (15.8%) | 2 (66.7%) | 0 | 5 (19.2%) |
| Related to KN026 | 2 (10.5%) | 0 | 0 | 2 (7.7%) |
| Related to KN046 | 3 (15.8%) | 0 | 0 | 3 (11.5%) |
| Subjects with at least 1 TEAE Leading to Death | 0 | 2 (66.7%) | 0 | 2 (7.7%) |
| Related to KN026 | 0 | 0 | 0 | 0 |
| Related to KN046 | 0 | 0 | 0 | 0 |

Table 2.KN026+KN046 Safety Summary (as of 3-Sep-2020)

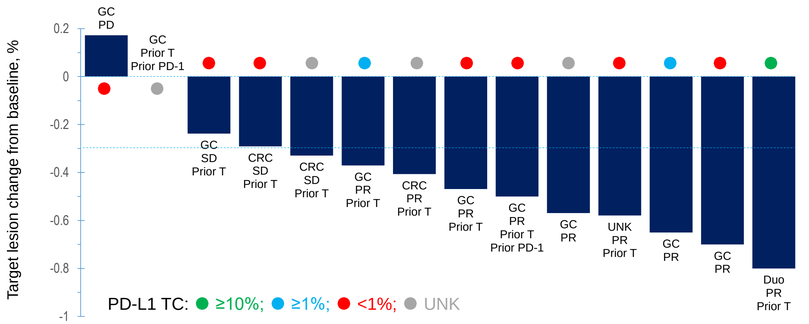
## Results

### Efficacy

| | 20 mg/kg Q2W + 3 mg/kg Q2W (N=13) | 20 mg/kg Q2W + 5 mg/kg Q3W (N=1) | 30 mg/kg Q3W + 5 mg/kg Q3W (N=0) | Total (N=14) |
|---|---|---|---|---|
| Best Overall Response | | | | |
| Complete Response (CR) | 0 | 0 | 0 | 0 |
| Partial Response (PR) | 8 (61.5%) | 1 (100%) | 0 | 9 (64.3%) |
| Stable Disease (SD) | 8 (61.5%) | 0 | 0 | 8 (32.0%) |
| Progressive Disease (PD) | 2 (15.4%) | 0 | 0 | 2 (14.3%) |
| Not Evaluable (NE) | 0 | 0 | 0 | 0 |
| Objective Response Rate (ORR) | 8 (61.5%) | 1 (100%) | NA | 9 (64.3%) |
| 95% CI | 31.6%, 86.1% | 2.5%, 100.0% | NA | 35.1%, 87.2% |
| Disease Control Rate (DCR) | 12 (92.3%) | 1 (100.0%) | NA | 13 (92.9%) |
| 95% CI | 64.0%, 99.8% | 2.5%, 100.0% | NA | 66.1%, 99.8% |

Note: CR: complete response, including confirmed and unconfirmed. PR: partial response, including confirmed and unconfirmed. CBR: clinical benefit response. SD: stable disease; PD: progressive disease; NE: not evaluable; ORR = CR+PR; DCR=CR+PR+SD

Table 3. Summary of efficacy results in HER2-positive solid tumors (as of 3-Sep-2020 )




Prior T: previously treated by trastuzumab; Priro PD-1: previously treated by anti-PD1 agent; Duo: duodenum; UNK: unknown origin;

Figure 3. KN026 in combined with KN046 in late line HER2-positive solid tumors (as of 3-Sep-2020 )

## Conclusion

- KN026 in combination with KN046 was well tolerated in patients with solid tumors. Treatment related adverse events (TRAEs) were generally mild and moderate in severity.
- 23.1% of ≥ Grade 3 TRAEs.
- No new safety signals from respective monotherapies were identified.
- Encouraging antitumor activity was observed in HER2-positive solid tumors, regardless of prior treatments from trastuzumab and/or anti-PD-1 agent.
- Objective response was 64.3% and disease control rate was 92.9%.

***KN026 combined with KN046 is well tolerated and has demonstrated profound anti-tumor activity in HER2-positive solid tumors preliminarily***

- **Of 14 evaluable HER2-Positive pts, the objective response rate was 64.3% and disease control rate was 92.9%.**
- **Responses were observed in patient who failed previous HER2 and/or ICI treatment**
- **No DLTs were observed in all 3 dose levels，No pts experienced LVEF decreased or other clinically meaningful cardiac AEs，Minimal lung toxicity**
- **Majority of AEs were Grade 1 or 2. Grade 3 or above treatment related AEs 23.1%**


**Clinical trial information:**NCT04040699


**Corresponding author email:** linshenpku@163.com



**Reference:** Shiying Wu, Qian Zhang, Fei Zhang et al. HER2 recruits AKT1 to disrupt STING signalling and suppress antiviral defence and antitumour immunity. Nature Cell Biology, 21, 1027–1040 (2019).