A Phase 2 Study (DisTinGuish) of DKN-01 in Combination with Tislelizumab + Chemotherapy as First-Line (1L) Therapy in Patients with Advanced Gastric or GEJ Adenocarcinoma (GEA)

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BACKGROUND

Advanced GEA Treatment Landscape

- Neoadjuvant or adjuvant chemotherapy is approved for patients with stage III/IV advanced or recurrent GEA (excluding locally advanced) with platinum (cisplatin or carboplatin) and/or 5-fluorouracil (5-FU) for chemotherapy-naïve patients.

- The current standard of care for patients with metastatic GEJ cancer is 5-FU and cisplatin or carboplatin (GEMOX or cisplatin, respectively). Interim analysis of patients with stage III/IV disease showed a median OS of 13.9 months with this regimen.

- Tislelizumab is a PD-1 antibody engineered to inhibit T-cell co-stimulation.

- NMSC 1818 recently reported a median OS of 17.2 months with first-line pembrolizumab + chemotherapy or 14.6 months for chemotherapy alone (median 7.2 vs 5.9 months in the pembrolizumab arm) in patients with stage IV GEA.

- Patients with ECOG performance status 0-1, prior chemotherapeutic treatments on 5-FU, prior PD-L1/CTLA-4 agents, and prior PD-1/PD-L1/PD-L2 agents were excluded.

DKK1 and DKN-01

- DKK1 is a Wnt decoy receptor associated with poor survival and resistance to chemotherapy in multiple tumor types.

- DKN-1 is an oral small molecule drug that competitively inhibits the interaction between Wnt signaling proteins with DKK1 and possesses activity in patients with advanced EGC with low tumor PD-1 expression, a subset with very limited therapeutic options.

- DKN-1 has immunomodulatory activity, stimulates a pro-inflammatory tumor microenvironment and augments PD-L1 levels.

- Here we present 3-year survival data for 3L advanced gastric patients who received combination treatment with DKN-1 plus ramucirumab and CAPOX.

METHODS

DisTinGuish Trial (NCT04363801)

Design: Phase 2a, open-label, multicenter trial.

Part 1: DKN-1 + Tislelizumab + CAPOX in Advanced GEA

Part 2: DKN-1 + Tislelizumab + 5-FU/5-FU, Advanced GEA

Part 3: DKN-1 + Tislelizumab + CAPOX on neoadjuvant 5-FU/5-FU in Tislelizumab + CAPOX or Infusion 5-FU, Advanced GEA

Primary end points: safety, tolerability, and efficacy.

Secondary end points: objective response rate (ORR), duration of response (DOR), disease-control rate (DCR), progressionfree survival (PFS), and overall survival (OS).

Analytical endpoints: immune-related T-cell (IT) safety population and modified IT (mIT) population.

Tumor DNA and PD-L1 expression: DKK1 mRNA expression was performed by blinded central lab. DKK1 mRNA levels may be used as a biomarker to identify potential bottleneck or management strategies for patients with advanced gastric cancer.

- Advanced GEA Patients

- DKN-01 300 mg + Tislelizumab + CAPOX

Safety Outcomes

- Combination DKN-1

- DKN-1 + Tislelizumab + CAPOX vs. chemotherapy

- Most reactive (n=240)

- Other reactive (n=240)

- Smallest reactive (n=240)

Adverse Events Related to DKN-01 Reported in ≥10% of Patients

- Adverse event: nausea, vomiting, abdominal pain, diarrhea, fatigue, constipation

RESULTS

Baseline Characteristics

- Age, median (min, max): 63 (13, 80)


- Body weight: median (min, max): 75 (45, 200)

- Performance status: median (min, max): 1 (0, 3)

- Prior chemotherapy treatment: median (min, max): 2 (0, 3)

- Prior radiotherapy treatment: median (min, max): 1 (0, 3)

First-line Therapy Efficacy Outcomes

- Overall (N=25)

- Overall Population

- Progression-free Survival (ITT, N=25)

- By PD-L1 Expression

- By DKK1 Expression

- Overall Population

- Duration of Clinical Benefit (mITT, N=21)

- Response (mITT, N=21)

- mITT (N=21)

- Overall Survival (ITF, N=25)

- Progression-free Survival (ITT, N=25)

- By PD-L1 Expression

- By DKK1 Expression

- Safety Outcomes

- By PD-L1 Expression

- By DKK1 Expression

- CONCLUSIONS

- At 2 years of follow-up, the 2-year OS rate on DKN-01 + Tislelizumab + CAPOX was 58% vs 44% for historical controls in CM646 (both in the overall population: 13.5 vs 13.1 months) and for the PD-L1 low subgroup (9.1 vs 7.8 months).

- Percentage of patients alive at 12 and 18 months in the Infusion arms of CM646 was 74% vs 55% and 76% vs 56%, respectively.

- mITT PFS was consistently longer by 7 months over historical controls for both the overall population (11.3 vs 7.7 months) and for the PD-L1 low subgroup (10.7 vs 3.9 months).

- DKN-01 + Tislelizumab + CAPOX showed a durable ORR in the mITT population (73%) and a progression-free survival of 24.4 months.

- The Phase 2 randomized controlled study of DKN-01 + Tislelizumab and chemotherapy (CAPOX) in first-line GEA is ongoing (NCT04363801)