DKN-01 in combination with tislelizumab and chemotherapy as a first-line therapy in unselected patients with advanced gastroesophageal adenocarcinoma (GEA): DisTinGuish Trial

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Background

Dickkopf-1 (DKK1) modulates Wnt signaling and contributes to an immune suppressive tumor microenvironment. DKN-01 (D), a neutralizing DKK1 antibody, in combination with an anti-PD1 antibody, has demonstrated safety and clinical activity in advanced previously treated DKK1-high GEA. We report response and survival outcomes in GEA patients (pts) treated with D + tislelizumab (T) + capecitabine/oxaliplatin (CAPOX) as a first line therapy.

Methods

We enrolled advanced GEA pts in a Phase 2a study of D + T + CAPOX (NCT04363801). Tumoral DKK1 mRNA expression was assessed by a chromogenic in situ hybridization RNAscope assay and assigned an H-score (0-300). Objective response rate (ORR) [primary efficacy objective], duration of response (DoR), disease control rate (DCR), and progression free survival (PFS) were evaluated in a modified intent to treat (mITT) population (completed ≥ 1 cycle) as well as compared between DKK1 high (H-score ≥35) and low groups.

Results

Twenty-five GEA pts were enrolled. Median age was 61 (22, 80); 19 males, 6 females. 17 pts (68%) had gastroesophageal junction (GEJ) adenocarcinoma; 8 pts (32%) had gastric cancer (GC). 18 GEA pts had RNAscope DKK1 expression available; 9 pts DKK1-high [5 GEJ, 4 GC) and 9 pts DKK1-low [7 GEJ, 2 GC]. Mean duration of treatment 3 mos, longest duration to date on study 7 mos, 19 pts remain on therapy. Most common D + T + CAPOX regimen related TEAEs were G1/2: anemia, thrombocytopenia, fatigue, diarrhea, nausea each in 3 pts. No related G3/4 toxicities; overall four G5 events; 1 related event pulmonary embolism. mITT analysis included 22 pts. Preliminary ORR in response evaluable (RE) mITT was 68% (13 PR, 6 SD, 1 NE, 2 pending first scan) and DCR 100%. In RE DKK1 high pts (n=7) there was an ORR of 100% (6 PR, 1 NE) compared with DKK1 low pts (n=9) ORR of 56% (5 PR, 4 SD). Median DoR and PFS were not reached.

Conclusions

D + T + CAPOX was well tolerated and has encouraging early activity as first line treatment for advanced GEA (unselected for PD-L1), with a preliminary ORR of 68% and DCR of 100%. Higher ORR in biomarker RE population: DKK1 high compared with DKK1 low (ORR 100% vs 56%). Updated ORR, DoR, PFS and PD-L1 expression will be reported.