DKN-01 and tislelizumab as a second-line (2L) investigational therapy in advanced DKK1 high gastroesophageal adenocarcinoma (GEA): DisTinGuish Trial

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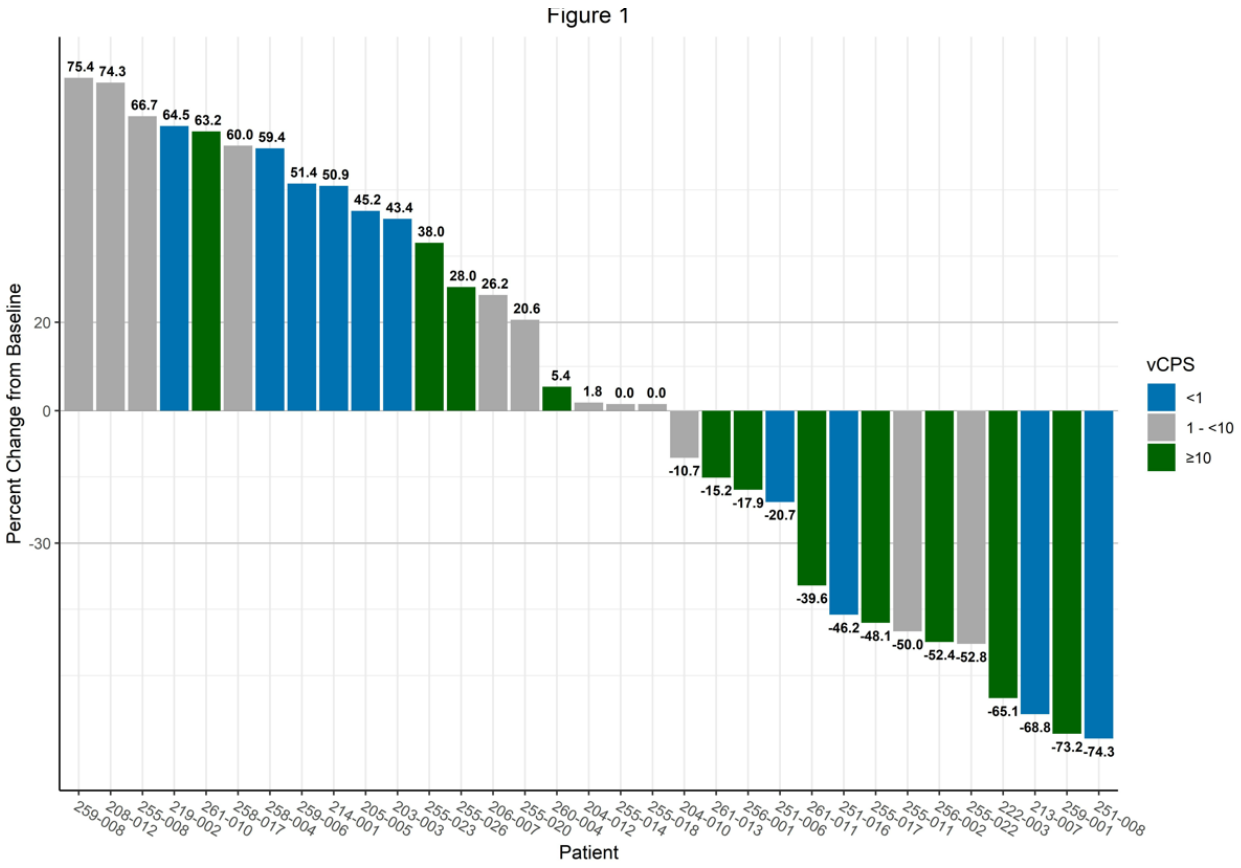
Background: Elevated tumoral DKK1 expression is seen in approximately one third of previously treated GEA and has been associated with more aggressive disease and shorter overall survival. DKN-01 (D) is a targeted anti-DKK1 mAb which has demonstrated improved clinical outcomes in previously treated GEA pts with elevated tumoral DKK1 expression when used in combination with an anti-PD1 antibody.

Methods: DisTinGuish (NCT04363801) is a Phase 2a single arm 2-part trial; Part A is reported separately; Part B investigated two dosing cohorts of D (300 mg and 600 mg) + tislelizumab (TS) as 2L therapy for DKK1-high GEA pts. Primary objective was to examine safety and tolerability and secondary objectives evaluated multiple efficacy endpoints including overall response rate (ORR) and disease control rate (DCR) in a modified intent to treat (mITT) population (>1 dose D).

Results: 52 pts enrolled between 27 Oct 2020 and 7 Jun 2022; (D-300 mg, 24 pts; D-600 mg 28 pts). Median age was 63 (29, 76); 41 males (79%). 18 pts (35%) had gastroesophageal junction (GEJ) adenocarcinoma; 34 pts (65%) had gastric cancer (GC). 22 pts from US, 30 pts from Republic of Korea. 49 pts have PD-L1 visually-estimated combined positive score (vCPS) results: <1 n=13 (27%); 1-<10 n=22 (45%); ≥10 n=14 (29%). 38 pts with genomic profiling: Wnt activating mutations in 12 pts, no MSI-H. 4 pts were IO experienced. Median number of cycles 2 (1, 19). 12 pts remain on therapy. 19 pts (37%) experienced D-related adverse events (AE); 74% were G1/2. Most common regimen related AEs: fatigue, nausea, AST increased. 3 pts (6%) had serious D-related AEs [vomiting, fatigue, dehydration]. No G5 TRAEs. No D-related AE led to D-dose reduction or discontinuation. Preliminary ORR in response evaluable IO naive mITT (n=36) was 25% and DCR 44%. mITT ORR by vCPS (Figure 1): <1: [n=11; PR-3 (27%), SD-1, PD-7]; 1-<10: [n=12; PR-1 (8%), SD-3, PD-8 (1 PD pt -> irPR)]; ≥10: [n=11; PR-5 (45%), SD-3, PD-3]. 6 of 9 responders remain on therapy, median DoR not reached. Median PFS: 1.4 mos (vCPS <1: 1.4 mos, 1-<10: 1.4 mos, ≥10: 2.9 mos).

Conclusions: The combination of D + TS represents a well-tolerated, active chemotherapy-free combination in previously treated DKK1-high IO naïve GEA pts. Encouraging durable activity was observed particularly in DKK1 high/vCPS≥10 cohort: ORR 45%, DCR 73%. Updated ORR, DoR, PFS and additional correlative biomarker evaluation will be reported.

Figure 1.



Based on data as of 30Jun2022