DKN-01 and Tislelizumab ± Chemotherapy as First-line (1L) or Second-line (2L) Investigational Therapy in Advanced Gastroesophageal Adenocarcinoma (GEA): DisTinGuish Trial

Samuel J Klempner, Joseph Chao, Hope Elizabeth Uronis, Cynthia A. Sirard, Michael Kagey, Jason Baum, James Song, Jin Wang, In-Ho Kim, Keun Wook Lee, Do-Youn Oh, Bassam Bassam Sonbol, Zev A. Wainberg, Jaffer A. Ajani

The Angeles Clinic and Research Institute, Los Angeles, CA; City of Hope Comprehensive Cancer Center, Duarte, CA; Duke Univ, Durham, NC; HeathCare Pharmaceuticals, Inc., Cambridge, MA; Leap Therapeutics, Inc., Cambridge, MA; BeiGene, Beijing, China; BeiGene (Shanghai) Co., Ltd., Shanghai, China; Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea; Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea; Department of Internal Medicine, Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, South Korea; Mayo Clinic Cancer Center, Division of Hematology/Oncology, Mayo Clinic Arizona Phoenix, Phoenix, AZ; UCLA Medical Center–Santa Monica, Santa Monica, CA; The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Despite recent approval of anti-PD-1 antibodies as 1L therapy in HER2(-) advanced GEA, benefit remains modest and limited largely to PD-L1(+) patients (pts), primarily those with combined positive scores (CPS) ≥5. Thus novel therapeutic approaches are needed for this pt population. DKN-01 is a targeted anti-DKK1 mAb which has demonstrated improved clinical outcomes in pts with elevated tumoral DKK1 expression, a subset of pts with more aggressive disease and shorter overall survival.

Methods: DisTinGuish (NCT04363801) is a Phase 2a single arm 2-part trial; Part A investigated DKN-01 (D) + tislelizumab (TS) + CAPOX as 1L therapy for pts with advanced HER2(-) GEA regardless of DKK1 status; Part B investigated two dosing cohorts of D (300 mg and 600 mg) + TS as 2L therapy for DKK1-high advanced GEA pts. Primary objective was to examine safety and tolerability and secondary objectives evaluated multiple efficacy endpoints including overall response rate (ORR) in a modified intent to treat (mITT) population (>1 dose D).

Results: Forty-nine pts enrolled between 01 Sept 2020 and 15 Sept 2021; 25 pts in Part A and 24 pts in Part B (D-300 mg). Key clinicopathologic features and efficacy outcomes are shown in Table. The most common D-related AEs were low grade (G1/2) fatigue, nausea, and diarrhea. Nine pts had D-related ≥G3 toxicities, elevated AST/ALT, elevated alkaline phosphatase, hypophosphatemia, hyponatremia, lymphopenia, neutropenia, diarrhea, vomiting, fatigue all occurring in 1 pt and pulmonary embolism in 2 pts (one G5 event). No new safety signals were observed in Part A or B1. Duration of response (DoR), median PFS and median OS have not been reached for Part A. Last pt enrolled in Part B1 on 15 Sept 2021.

Conclusions: The combination of D/TS + CAPOX represents a well-tolerated, active 1L combination, particularly for DKK1-high patients consistent with the proposed mechanism of action. Activity appears to be independent of PD-L1 status. Part B1 is aligned with biomarker enrichment and efficacy and biomarker data will be presented along with updated Part A efficacy data. Clinical trial information: NCT04363801.

	Part A 1L D/TS + CAPOX				Part B1 2L D/TS
	Overall (n=25)	DKK1-high (n=12)	DKK1-low (n=9)	DKK1-unknown (n=4)	DKK1-high (n=24)
Age (median, yrs)	61.0	62.5	56.0	65.0	61.0
United States/South Korea	25/ --	12/ --	9/ --	4/ --	10/ 14
ECOG PS: 0/ 1	14/ 11	6/ 6	5/ 4	3/ 1	10/ 14
Gastric/ GEJ	8/ 17	4/ 8	2/ 7	2/ 2	15/ 9
DKK1 RNAscope H-score, median	39.0	70.0	11.0	N/A	110.0
PD-L1 (vCPS[a])	n=22	n=12	n=9	n=1	n=16
<5	16	8	7	1	10
≥5	6	4	2	0	6
Median duration on study (months; min, max)	6.8 (1.4, 11.4)	5.4 (1.4, 10.7)	6.8 (3.8, 11.4)	6.3 (1.5, 10.3)	N/A
ORR (RE mITT[b]), %	71[c]	100	56	33	N/A

[a]vCPS: visually-estimated Combined Positive Score [b]Response evaluable (RE) mITT (had post baseline imaging and received > 1 dose DKN-01) [c]n =21: Not