DKN-01 and Tislelizumab as a Second-line (2L) Investigational Therapy in Advanced DKK1-high Gastroesophageal Adenocarcinoma (GEA): DisTinGuish Trial

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Abstract #553

BACKGROUND

Advanced GEA Treatment Landscape

- Anti-PD-1 antibodies + chemotherapy have recently been approved as first-line therapy in HER2(-) advanced GEA.[1] However, benefit remains modest and largely limited to PD-L1(+) patients, primarily those with combined positive score (CPS) ≥5.
- Current second line (2L) standard of care includes cytotoxic chemotherapy (e.g., taxane) +/- combination with ramucirumab.
- KEYNOTE-061, which compared pembrolizumab to paclitaxel as a 2L therapy, failed to demonstrate improvement in progression-free survival (median PFS: pembrolizumab 1.5 months vs paclitaxel 4.1 months) or overall survival (median OS: pembrolizumab 9.1 months vs paclitaxel 8.3 months) in patients with CPS ≥1.[2]
  - Post hoc analysis with CPS ≥ 10 revealed an ORR 24.5% for pembrolizumab vs 9.1% for paclitaxel; median OS: 10.4 months for pembrolizumab vs 8.0 months for paclitaxel.[2]
  - Patients with CPS <1 had ORR 2% for pembrolizumab vs 10.4% for paclitaxel; median OS: 4.8 months for pembrolizumab vs 8.2 months for paclitaxel.[2]

DKN-01 + Tislelizumab

- DKN-01 is a targeted anti-DKK1 mAb that has demonstrated improved clinical outcomes in patients with elevated tumoral DKK1[3]—a subset of patients with more aggressive disease and shorter overall survival.[4]
- Tislelizumab is an anti-PD-1 mAb with high affinity and specificity for PD-1, designed to minimize binding to FcγR on macrophages and thereby potentially avoid antibody-dependent phagocytosis.[5]

METHODS

DisTinGuish Trial (NCT04363801)

Design: Phase 2a, single arm, 2-part trial

- Part A: First-line DKN-01 300 mg + Tislelizumab + CAPOX in Advanced GEA (reported separately)
- Part B: Second-line DKN-01 300 or 600 mg + Tislelizumab in Advanced GEA with High Tumoral DKK1 Expression (reported here)

Primary objective: safety and tolerability

Secondary efficacy endpoints: objective response rate (ORR), duration of response (DoR), disease control rate (DCR), progression-free survival (PFS) assessed by investigators and overall survival (OS)

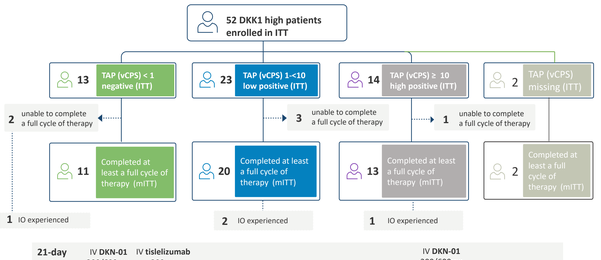
Analysis populations: intent-to-treat (ITT) (safety) and modified ITT (mITT) (completed >1 cycle)

Tumoral DKK1 mRNA expression: DKK1-high = H-score ≥35 assessed by a chromogenic *in situ* hybridization RNAscope assay and assigned an H-score (0-300) (Flagship Biosciences, Broomfield, CO; Advanced Cell Diagnostics, Newark, CA)

Follow-up: end of treatment, 30 days after end of treatment, every 12 weeks thereafter

Data cut-off: Sept 6, 2022

Second-line DKN-01 300 or 600 mg + Tislelizumab in Advanced GEA Patients with High Tumoral DKK1 Expression



Tumor Area Positive (TAP) or vCPS: <1 (negative), 1-<10 (low positive), ≥10 (high positive). TAP score methodology has been previously referred to as visually-estimated combined positive score (vCPS)

RESULTS

Baseline Characteristics

- 52 pts enrolled between 27 Oct 2020 and 7 Jun 2022
- vCPS results (n=50): 13 (25%) pts <1, 23 (44%) pts 1-<10, 14 (27%) pts ≥10
- Genomic profiling (n=49): 15 pts with Wnt activating mutations, no MSI-H, TMB <10 (87%)
- 4 pts had prior anti-PD-1/PD-L1 therapy

	Overall (N=52)	B1 (300 mg DKN-01) (N=24)	B2 (600 mg DKN-01) (N=28)
Age, median (min, max)	63.0 (29.0, 76.0)	61.0 (41.0, 68.0)	63.5 (29.0, 76.0)
Male, n (%)	**41 (78.8%)**	20 (83.3%)	21 (75.0%)
Female, n (%)	11 (21.2%)	4 (16.7%)	7 (25.0%)
Region			
United States	22 (42.3%)	10 (41.7%)	12 (42.9%)
South Korea	30 (57.7%)	14 (58.3%)	16 (57.1%)
ECOG Performance Status, n (%)			
0	16 (30.8%)	8 (33.3%)	8 (28.6%)
1	36 (69.2%)	16 (66.7%)	20 (71.4%)
Primary Location			
Stomach (Gastric)	34 (65.4%)	15 (62.5%)	19 (67.9%)
Gastroesophageal Junction (GEJ)	18 (34.6%)	9 (37.5%)	9 (32.1%)
Prior Systemic Therapies			
Advanced/Metastatic, n (%)	51 (98.1%)	24 (100%)	27 (96.4%)
Chemotherapy			
Platinum	47 (90.4%)	21 (87.5%)	26 (92.9%)
Pyrimidine analogues	43 (82.7%)	19 (79.2%)	24 (85.7%)
Taxane	9 (17.3%)	5 (20.8%)	**4 (14.3%)**
Immunotherapy	4 (7.7%)	0	4 (14.3%)
Tumor PD-L1: vCPS (TAP)[a], n (%)	50 (96.2%)	22 (91.7%)	28 (100.0%)
TAP < 1	13 (25.0%)	9 (37.5%)	4 (14.3%)
TAP 1-<10	23 (44.2%)	10 (41.7%)	13 (46.4%)
TAP ≥ 10	14 (26.9%)	3 (12.5%)	11 (39.3%)
unknown	2 (3.8%)	2 (8.3%)	0
Tumor Mutation Burden,[b] n (%)	47 (90.4%)	22 (91.7%)	25 (89.3%)
<10	41 (87.2%)	20 (90.9%)	21 (84.0%)
≥10	6 (12.8%)	2 (9.1%)	4 (16.0%)
Undetermined	5 (9.6%)	2 (8.3%)	3 (10.7%)
Microsatellite status,[b] n (%)	49 (94.2%)	23 (95.8%)	26 (92.9%)
Microsatellite Stability (MSS)	46 (93.9%)	21 (91.3%)	25 (96.2%)
Missing (not tested)	3 (6.1%)	2 (8.7%)	1 (3.8%)
Her2 positive, n(%)	9 (18.4%)	1 (4.5%)	8 (29.6%)

[a]vCPS: visually-estimated Combined Positive Score, also known as Tumor Area Positivity (TAP) score (Ventana Medical Systems, Oro Valley, AZ).
[b]Tumor Mutation Burden and Microsatellite status was determined from plasma ctDNA using the FoundationOne Liquid CDx assay (Foundation Medicine, Cambridge, MA).

Disposition and Exposure

- Median duration of treatment: 1.46 months
- 10 (19.2%) patients remain on therapy

	B1 (300 mg DKN-01) (N=24)	B2 (600 mg DKN-01) (N=28)
Number of cycles, median (min, max)	2.0 (1.0, 22.0)	2.0 (1.0, 15.0)
Duration on treatment (months), median (min, max)	1.43 (0.59, 15.93)	1.48 (0.33, 10.28)
Reasons for study drug discontinuation, n (%)	21 (87.5%)	21 (75.0%)
Patient request to withdraw	1 (4.2%)	3 (10.7%)
Objective disease progression	15 (62.5%)	13 (46.4%)
Adverse event	3 (12.5%)	4 (14.3%)
Investigator decision	1 (4.2%)	0
Other reasons	1 (4.2%)	1 (3.6%)
Reasons for study discontinuation, n (%)	18 (75.0%)	16 (57.1%)
Withdrawal of consent	6 (25.0%)	1 (3.6%)
Death	12 (50.0%)	14 (50.0%)
Lost to follow-up	0	1 (3.6%)
Duration on Study (months), median (min, max)	2.61 (0.79, 15.97)	4.58 (0.33, 10.28)

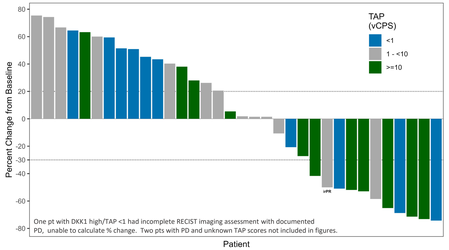
Second-line Therapy Efficacy Outcomes in the Anti-PD-1/PD-L1-naïve Population

Objective Response Rate (ORR) (mITT)

- ORR in response evaluable anti-PD-1/PD-L1-naïve mITT (n=43)
  - ORR: 27% and DCR: 43%
- DKK1 high/TAP ≥ 10 pts: ORR 55%, DCR 73%
- DKK1 high/TAP <1 pts: ORR 27%, DCR 36%
- DKK1 high/TAP 1-<10 pts: ORR: 8%, DCR 31%
- Overall, 7 of 10 responders remain on therapy
- 4 of 6 responders (DKK1 high/TAP ≥ 10 pts) remain on therapy

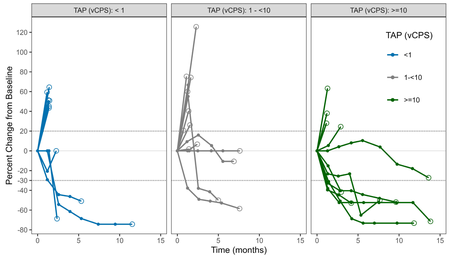
Best Overall Response (mITT n=43), n (%)					
TAP/vCPS	Partial Response	Stable Disease	Progressive Disease	Non-Evaluable	ORR
<1 (n=11)	3	1	7	0	27%
1-<10 (n=18)	1	3	9	5	8%
≥10 (n=12)	6	2	3	1	55%
Unknown (n=2)	0	0	2	0	0%

Response by PD-L1 Expression (TAP/vCPS) (mITT, N=43)



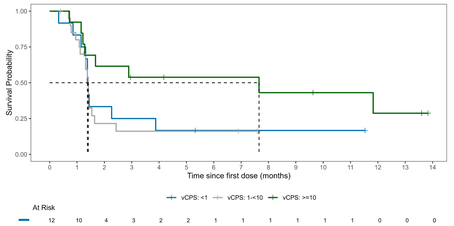
One pt with DKK1 high/TAP <1 had incomplete RECIST imaging assessment with documented PD, unable to calculate % change. Two pts with PD and unknown TAP scores not included in figures.

Durability of Clinical Benefit by PD-L1 Expression (TAP/vCPS) (mITT, N=43)



Progression-free Survival (PFS) by PD-L1 Expression (TAP/vCPS) (ITT, N=46*)

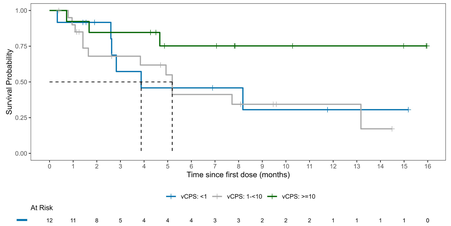
- Median PFS: 1.4 mo overall (vCPS <1: 1.4 mo, 1-<10: 1.4 mos, ≥10: 7.7 mo)



* 2 pts with unknown TAP scores not included

Overall Survival (OS) by PD-L1 Expression (TAP/vCPS) (ITT, N=46*)

- Median OS: 7.7 mo overall (vCPS <1: 3.9 mos, 1-<10: 5.2 mos, ≥10: not reached)



* 2 pts with unknown TAP scores not included

TAP: Tumor Area Positive; vCPS: Visually-Estimated Combined Positive Score; PD-L1: Programmed Death-Ligand 1

Safety Outcomes

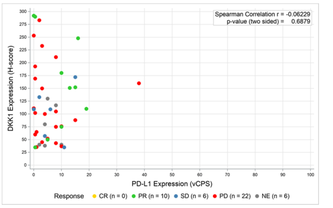
- Combination DKN-01 + tislelizumab was well tolerated with manageable toxicity
- Higher DKN-01 dose (600 mg) was not associated with higher frequency of adverse events
- Most common regimen-related TEAEs: fatigue 7 (13.5%), nausea 5 (9.6%), pruritus 3 (5.8%), rash 3 (5.8%) and AST increased 3 (5.8%)
- Regimen-related serious TEAEs: 4 pts (7.7%): vomiting, fatigue, dehydration and immune-mediated hepatitis
- No Grade 5 treatment-related TEAEs
- No DKN-01-related TEAEs leading to study drug discontinuation or dose reduction

Summary of Adverse Events

	B1 (300 mg DKN-01) (N=24)	B2 (600 mg DKN-01) (N=28)
	No. Patients (%)	No. Patients (%)
Any adverse event	24 (100%)	24 (85.7%)
Grade ≥3 events*	13 (54.2%)	15 (53.6%)
Serious adverse events*	13 (54.2%)	13 (46.4%)
Events leading to DKN-01 discontinuation*	3 (12.5%)	5 (17.9%)

*Grade ≥3 DKN-01-related TEAEs in 5 pts (9.6%); AST increased (1), ALT increased (1), blood alkaline phosphatase increased (1), blood sodium increased (1), vomiting (1), fatigue (1) and dehydration (1); DKN-01-related serious TEAEs: 3 pts (vomiting, fatigue and dehydration).
* AEs leading to DKN-01 discontinuation, none were DKN-01 related: abdominal pain (2), malignant gastrointestinal obstruction (1), dyspnoea (1), immune-mediated hepatitis (1), chronic kidney disease (1), fatigue (1) and hip fracture (1).
TEAE: treatment-emergent adverse event

DKK1 and PD-L1 Expression Are Not Correlated



CONCLUSIONS

- **The combination of DKN-01 and tislelizumab represents a well-tolerated, active chemotherapy-free combination in previously treated DKK1-high anti-PD-1/PD-L1-naïve GEA pts**
- **Encouraging durable activity was observed in 2L anti-PD-1/PD-L1-naïve GEA pts with DKK1 high (H-score ≥35) and TAP high (≥10)**
  - **ORR: 55% and DCR 73%**
  - **PFS: 7.7 months**
  - **OS: not reached**
- **DKK1 and PD-L1 expression are independent biomarkers**
- **A Phase 2 randomized controlled study of tislelizumab and chemotherapy (CAPOX or mFOLFOX6) +/- DKN-01 in first-line GEA is underway (NCT04363801)**

References: 1. OPDIVO (nivolumab) injection prescribing information. Bristol-Myers Squibb Company, August 2021. 2. Shitara K, et al. *Lancet.* 2018;392(10142):123-133. 3. Klempner SJ, et al. *Mol Cancer Ther.* 2021; 11:2240-2249. 4. Kagey MH, He X. *Br J Pharmacology.* 2017;174:4637–4650. 5. *Xu J*, et al. Clin Cancer Res. 2020;26(17):4542-4550.

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