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

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Abstract # 292

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.
- Standard of care first-line therapy with chemo + nivolumab had a response rate of 47% and PFS of 7.7 mo.[1]
- In a Phase 2 study, tislelizumab + chemo as first-line therapy for G/GEJ adenocarcinoma had an ORR of 47% and PFS of 6.1 months.[2] A phase 3 study BGB-A317-305 comparing tislelizumab + chemo vs. placebo + chemo as a 1L therapy is ongoing.

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 a 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.[2]

METHODS

DisTinGuish Trial (NCT04363801)

Design: Phase 2a single arm 2-part trial

Primary objective: safety and tolerability

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

Analysis populations: intent-to-treat (ITT) (safety population) and modified ITT (mITT) (completed >1 dose DKN-01)

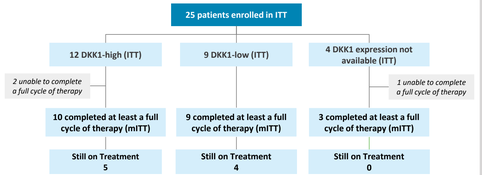
Analysis by DKK1 expression: comparison between DKK1- high (H-score ≥35) and DKK1-low groups

Tumoral DKK1 mRNA expression: 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

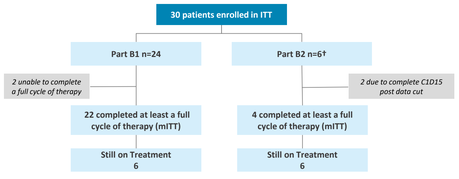
Data cut-off: Dec. 10, 2021

Part A: First-line DKN-01 300 mg + Tislelizumab + CAPOX in Advanced GEA Patients Regardless of Tumoral DKK1 Expression



21-day cycles: IV DKN-01 (300 mg) on Days 1 and 15, IV tislelizumab (200 mg) on Day 1, IV oxaliplatin (130 mg/m^2) on Day 1, and oral capecitabine (1000 mg/m^2 twice daily) on Days 1-15

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



21-day cycles: Part B1: IV DKN-01 (300 mg) on Days 1 and 15 and IV tislelizumab (200 mg) on Day 1. **Part B2:** IV DKN-01 (600 mg) on Days 1 and 15 and IV tislelizumab (200 mg) on Day 1.

*Locally advanced/metastatic DKK1-high gastric or gastroesophageal adenocarcinoma patients who have received only one prior systemic treatment with a platinum + fluoropyrimidine–based therapy (±HER2 therapy, if applicable).
†Open to enrollment, planned n=24

RESULTS

Demographic & Clinical Characteristics

DKK1 Expression in First-line

- Elevated DKK1 common in previously untreated G/GEJ adenocarcinoma (57% DKK1-high)
- DKK1-high more frequently associated with liver involvement in previously untreated patients (41.7% vs 11.1%)

PD-L1 Expression

- First-line (Part A): 72.7% had vCPS <5, only 2 patients had vCPS ≥10
- Second-line (Part B): preliminary analysis showed 72.7% with vCPS <5, only 3 patients had vCPS ≥10

MSS / TMB

- No MSI-H and only 4 patients with TMB≥ 10 mut/Mb (2 in IL, 2 in 2L)

	Part A				Part B – DKK1-high	
	Overall (N=25)	DKK1-high (N=12)	DKK1-low (N=9)	DKK1 unknown (N=4)	Part B1 (N=24)	Part B2 (N=6)
Age, median (min, max)	61.0 (22.0, 80.0)	62.5 (22.0, 71.0)	56.0 (35.0, 80.0)	65.0 (36.0, 80.0)	61.0 (41.0, 68.0)	61.5 (42.0, 65.0)
Male, n (%)	19 (76.0%)	8 (66.7%)	8 (88.9%)	3 (75.0%)	20 (83.3%)	4 (66.7%)
ECOG Performance Status, n (%)						
0	14 (56.0%)	6 (50.0%)	5 (55.6%)	3 (75.0%)	9 (37.5%)	2 (33.3%)
1	11 (44.0%)	6 (50.0%)	4 (44.4%)	1 (25.0%)	15 (62.5%)	4 (66.7%)
Gastric Adenocarcinoma, n (%)	8 (32.0%)	4 (33.3%)	2 (22.2%)	2 (50.0%)	15 (62.5%)	5 (83.3%)
Months Since First Diagnosis, median (min, max)	0.6 (0.3, 24.9)	0.6 (0.4, 0.7)	12.8 (0.8, 24.9)	0.4 (0.3, 0.6)	9.3 (2.4, 39.4)	18.5 (4.2,24.6)
GEJ Adenocarcinoma, n (%)	17 (68.0%)	8 (66.7%)	7 (77.8%)	2 (50.0%)	9 (37.5%)	1 (16.7%)
Months Since First Diagnosis, median (min, max)	0.9 (0.3, 20.3)	0.8 (0.3, 2.4)	0.9 (0.3, 11.2)	10.9 (1.4, 20.3)	7.8 (5.0, 45.4)	4.1 (4.1, 4.1)
Liver Involvement, n (%)						
Yes	7 (28.0%)	5 (41.7%)	1 (11.1%)	1 (25.0%)	15 (62.5%)	1 (16.7%)
No	18 (72.0%)	7 (58.3%)	8 (88.9%)	3 (75.0%)	9 (37.5%)	5 (83.3%)
Prior Systemic Therapies – Advanced/Metastatic, n (%)	0	0	0	0	24 (100%)	6 (100%)
Tumor PD-L1: vCPS[a], n (%)	22	12	9	1	22	–
vCPS < 1	5 (22.7%)	2 (16.7%)	2 (22.2%)	1 (100%)	9 (40.9%)	–
vCPS ≥1	17 (77.3%)	10 (83.3%)	7 (77.8%)	0	13 (59.1%)	–
vCPS <5	16 (72.7%)	8 (66.7%)	7 (77.8%)	1 (100%)	16 (72.7%)	–
vCPS ≥5	6 (27.3%)	4 (33.3%)	2 (22.2%)	0	6 (27.3%)	–
vCPS <10	20 (90.9%)	10 (83.3%)	9 (100%)	1 (100%)	19 (86.4%)	–
vCPS ≥10	2 (9.1%)	2 (16.7%)	0	0	3 (13.6%)	–
Tumor Mutation Burden,[b] n (%)	19	10	7	2	21	–
<10	17 (89.5%)	8 (80.0%)	7 (100%)	2 (100%)	19 (90.5%)	–
≥10	2 (10.5%)	2 (20.0%)	0	0	2 (9.5%)	–
Missing	6	2	2	2	3	–
Microsatellite status,[b] n (%)	19	10	7	2	20	–
Microsatellite Stability (MSS)	19 (100%)	10 (100%)	7 (100%)	2 (100%)	20 (100.0%)	–
Missing	6	2	2	2	4	–

[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).

Tumoral DKK1 mRNA Expression

First-line (Part A) US

Specimens Tested	N	DKK1 High - n (%)
All	21	12 (57%)
GEJ	15	8 (53%)
Gastric	6	4 (67%)

Second-line (Part B) US and South Korea

Specimens Tested	N	DKK1 High - n (%)
All	170	56 (33%)
GEJ	46	17 (37%)
Gastric	124	39 (31%)

Disposition & Exposure

First-line (Part A)

- Median duration of treatment: 8.57 mo
- 9 patients remain on therapy

Second-line (Part B)

- Enrollment continues in Part B2
- 12 patients remain on therapy

	Part A (N=25)	Part B	
		B1 300 mg (N=24)	B2 600 mg (N=6)
Number of cycles, median (min, max)	11.0 (1.0, 20.0)	2.0 (1.0, 11.0)	1.0 (1.0, 2.0)
Duration on treatment (months), median (min, max)	8.57 (0.76, 13.96)	1.43 (0.59, 7.23)	0.76 (0.30, 1.41)
Reasons for study drug discontinuation, n (%)			
Patient request to withdraw	2 (8.0%)	1 (4.2%)	0
Objective disease progression	8 (32.0%)	11 (45.8%)	0
Adverse event	3 (12.0%)	2 (8.3%)	0
Investigator decision	0	2 (8.3%)	0
Other reasons	3 (12.0%)	2 (8.3%)	0
Reasons for study discontinuation, n (%)			
Withdrawal of consent	0	3 (12.5%)	0
Death	5 (20.0%)	9 (37.5%)	0
Other reasons	1 (4.0%)	0	0
Duration on Study (months), median (min, max)	9.2 (0.92,13.96)	2.61 (0.79,7.23)	0.76 (0.30,1.41)

First-line (Part A): Efficacy Outcomes by DKK1 Expression

Overall ORR (mITT): 68% (1 CR, 14 PR)

- DKK1-high: 90% ORR (9 PR, 8 confirmed)
- DKK1-low: 56% ORR (1 CR, confirmed; 4 PR, 3 confirmed)
  - 1 PR (confirmed) went to curative surgery with a pathologic CR
- DKK1-unknown: 33% ORR (1 PR, confirmed)

DKK1-high patients responded regardless of PD-L1 status (mITT)

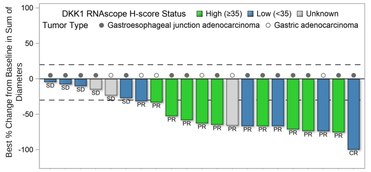
PD-L1-low expression (vCPS <5, n=14)
- 79% (11/14) ORR in PD-L1-low patients
- 100% (6/6) ORR in DKK1-high, PD-L1-low patients

PD-L1-high expression (vCPS ≥5, n= 6)
- 67% (4/6) ORR in PD-L1-high patients
- 75% (3/4) ORR in DKK1-high, PD-L1-high patients

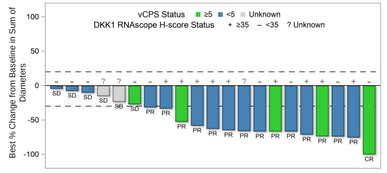
Best Overall Response, n (%)					
	Complete Response	Partial Response	Stable Disease	Progressive Disease	Non-Evaluable
mITT population (N=22)	**1 (4.5%)**	**14 (63.6%)**	6 (27.3%)	0	1 (4.5%)
DKK1-high (N=10)	0	**9 (90.0%)**	0	0	1 (10.0%)
DKK1-low (N=9)	1 (11.1%)	4 (44.4%)	4 (44.4%)	0	0
DKK1 unknown (N=3)	0	1 (33.3%)	2 (66.7%)	0	0

DKK1-high: H-score ≥35; DKK1-low: H-score <35

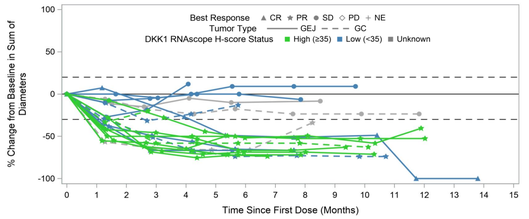
Response by DKK1 Status (mITT, N=21)



Response by PD-L1 Status (mITT, N=21)

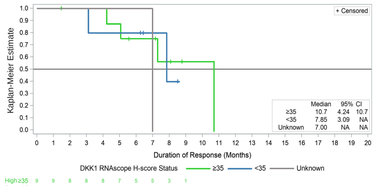


Durability of Clinical Benefit (mITT, N=21)



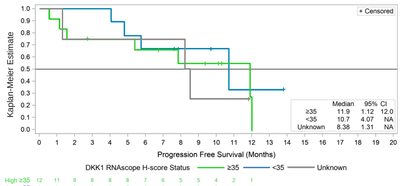
Duration of Response (Responders, N=15)

- Median DoR: 10.7 mo in DKK1-high vs 7.9 mo in DKK1-low patients



Progression-free Survival (ITT, N=25)

- Median PFS ITT was 10.7 mo: DKK1-high 11.9 mo vs DKK1-low 10.7 mo



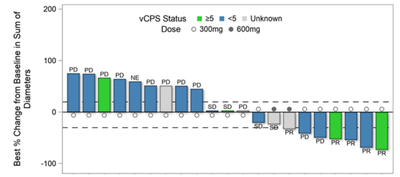
vCPS: Visually-Estimated Combined Positive Score; PD-L1: Programmed Death-Ligand 1

Second-line DKK1-high (Part B): Best Overall Response by PD-L1 Expression

- Study continues to enroll; 12 patients remain on therapy with 4 pending first imaging assessment post baseline
- ORR in evaluable mITT included 5 PR (25%) and an additional irPR

Best Overall Response, n (%)				
	Partial Response	Stable Disease	Progressive Disease	Non-Evaluable
mITT population (N=26)	5 (19%)	4 (15%)	11 (42%)	6 (23%)*
PD-L1 vCPS ≥5 (N=5)	2 (40%)	1 (20%)	1 (20%)	1 (20%)
PD-L1 vCPS <5 (N=15)	2 (13%)	2 (13%)	8 (53%)	3 (20%)
PD-L1 vCPS unknown (N=6)	1 (17%)	1 (17%)	2 (33%)	2 (33%)

* 4 patients in the mITT population (Part B2) have not had their first post-treatment scan



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

Safety

First-line (Part A)

- Combination DKN-01+ tislelizumab + capox was well tolerated with manageable toxicity
- Most common DKN-01-related adverse events were low grade (G1/2):
  - Fatigue, nausea, diarrhoea, neutrophil count decreased, platelet count decreased
- 5 patients experienced six Grade ≥3 DKN-01-related adverse events:
  - Diarrhoea (1), neutrophil count decreased (1), blood phosphorus decreased (2), pulmonary embolism (2)
- No Grade 4 events
- TEAEs leading to death (Grade 5) within 30 days of last dose
  - Pulmonary embolism (1) assessed by the investigator as related to regimen.
  - Aspiration pneumonia (1) and hepatic failure (1) both assessed as possibly related to disease progression.

Second-line (Part B)

- Combination of DKN-01 + tislelizumab was well tolerated at both doses of DKN-01 (300 and 600 mg)
- DKN-01 600 mg cohort continues to enroll
- Most common DKN-01-related adverse events were low grade (G1/2):
  - Fatigue, nausea
- 4 patients experienced seven Grade ≥3 DKN-01-related adverse events included:
  - ALT increased (1), AST increased (2), alkaline phosphatase increased (1), sodium decreased (1), vomiting (1), fatigue (1)
- No Grade 5 toxicities or TEAEs leading to death within 30 days of last dose

Summary of Adverse Events

	Part A (N=25)	Part B – DKK1-high	
		Part B1 (N=24)	Part B2 (N=6)
Preferred Terms	No. Patients (%)	No. Patients (%)	No. Patients (%)
TEAEs leading to death within 30 days of last dose	3 (12%)	0	0
Any adverse event	25 (100%)	23 (96%)	5 (83%)
Grade ≥ 3 events	14 (56%)	13 (54%)	1 (17%)
DKN-01-related	5 (20%)	4 (17%)	0
Serious adverse events	10 (40%)	13 (54%)	1 (17%)
DKN-01-related	2 (8%)	3 (13%)	0
Events leading to DKN-01 discontinuation	3 (12%)	4 (17)%	0
DKN-01-related	1 (4%)	1 (4%)	0
Events leading to DKN-01 dose reduction	1 (4%)	0	0
Drug-related adverse events			
DKN-01-related	14 (56%)	11 (46%)	4 (67%)
Tislelizumab-related	17 (68%)	13 (54%)	3 (50%)
Capecitabine-related	24 (96%)	–	–
Oxaliplatin-related	25 (100%)	–	–
Regimen-related	25 (100%)	–	–

CONCLUSIONS

DKN-01 300 mg + tislelizumab + CAPOX was well tolerated and had encouraging clinical activity as first-line treatment for advanced GEA patients

- **Efficacy driven by enhanced ORR, DoR and PFS in DKK1-high patients, an aggressive subgroup**
- **Response is associated with DKK1 expression and is independent of PD-L1 expression**
- **ORR and PFS in the overall population of this single arm study is reported to be higher than published standard of care in an unselected PD-L1 population; OS not reached**

DKN-01 300 or 600 mg + tislelizumab was well tolerated with clinical responses as second-line treatment for advanced GEA patients with high DKK1 expression

- **This study is ongoing and continuing to enroll in the 600 mg arm**

References: 1. OPDIVO (nivolumab) injection prescribing information. Bristol-Myers Squibb Company, August 2021. 2. Xu J, et al. *Clin Cancer Res*. 2020;26(17):4542-4550. 3. Klempner SJ, et al. *Mol Cancer Ther*. 2021; 11:2240-2249. 4. Kagey MH, He X. *Br J Pharmacology*. 2017;174:4637–4650. **Acknowledgements:** The authors thank the patients, families and physician investigators who participated in the DisTinGuish trial. Poster design and creation by Laurie LaRusso, MS, ELS, Chestnut Medical Communications. **Disclosures:** Dr. Klempner reports consulting/advisory fees from Merck, BMS, Eli Lilly, Natera Oncology, Pieris, Daiichi-Sankyo, Sanofi-Aventis, Foundation Medicine, and stock/equity in Turning Point Therapeutics.