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

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Abstract 1835

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

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

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)

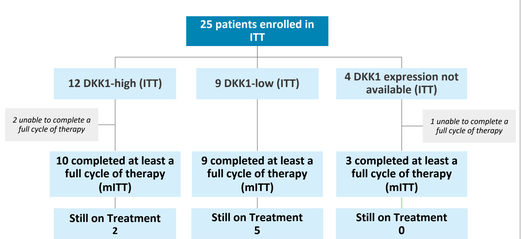
Analysis by Tumoral DKK1 expression: comparison DKK1-high (H-score ≥35) vs DKK1-low

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: June 30, 2022

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

RESULTS

Baseline Characteristics

DKK1 Expression

- 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

- 72.7% had vCPS <5, only 2 patients had vCPS ≥10

MSS / TMB

- No MSI-H and only 2 patients with TMB≥ 10 mut/Mb

	Overall (N=25)	DKK1-high (N=12)	DKK1-low (N=9)	DKK1 unknown (N=4)
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)
Male, n (%)	19 (76.0%)	8 (66.7%)	8 (88.9%)	3 (75.0%)
ECOG Performance Status, n (%)				
0	14 (56.0%)	6 (50.0%)	5 (55.6%)	3 (75.0%)
1	11 (44.0%)	6 (50.0%)	4 (44.4%)	1 (25.0%)
Gastric Adenocarcinoma, n (%)	8 (32.0%)	4 (33.3%)	2 (22.2%)	2 (50.0%)
Months Since First Diagnosis, median (min, max)	1.0 (0.7, 25.1)	1.0 (0.8, 1.4)	13.1 (1.1, 25.1)	0.8 (0.7, 0.9)
GEJ Adenocarcinoma, n (%)	17 (68.0%)	8 (66.7%)	7 (77.8%)	2 (50.0%)
Months Since First Diagnosis, median (min, max)	1.6 (0.6, 20.7)	1.3 (0.6, 3.1)	1.8 (0.6, 11.8)	11.2 (1.6, 20.7)
Liver Involvement, n (%)				
Yes	7 (28.0%)	5 (41.7%)	1 (11.1%)	1 (25.0%)
No	18 (72.0%)	7 (58.3%)	8 (88.9%)	3 (75.0%)
Prior Systemic Therapies – Advanced/Metastatic, n (%)	0	0	0	0
Tumor PD-L1: vCPS[a], n (%)	22	12	9	1
vCPS < 1	5 (22.7%)	2 (16.7%)	2 (22.2%)	1 (100%)
vCPS ≥1	17 (77.3%)	10 (83.3%)	7 (77.8%)	0
vCPS <5	16 (72.7%)	8 (66.7%)	7 (77.8%)	1 (100%)
vCPS ≥5	6 (27.3%)	4 (33.3%)	2 (22.2%)	0
vCPS <10	20 (90.9%)	10 (83.3%)	9 (100%)	1 (100%)
vCPS ≥10	2 (9.1%)	2 (16.7%)	0	0
Tumor Mutation Burden,[b] n (%)	19	10	7	2
<10	17 (89.5%)	8 (80.0%)	7 (100%)	2 (100%)
≥10	2 (10.5%)	2 (20.0%)	0	0
Undetermined	6	2	2	2
Microsatellite status,[b] n (%)	19	10	7	2
Microsatellite Stability (MSS)	19 (100%)	10 (100%)	7 (100%)	2 (100%)
Missing	6	2	2	2

[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).

Safety Outcomes

- 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, appetite decreased, headache, platelet count decreased
- Five patients experienced seven Grade ≥3 DKN-01-related adverse events:
  - Diarrhoea (1), neutrophil count decreased (1), hypophosphatemia (2), pulmonary embolism (2)
- No Grade 4 treatment-related 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

Summary of Adverse Events

Preferred Terms	Patients (N=25) No. Patients (%)
TEAEs leading to death*	3 (12%)
Any adverse event	25 (100%)
DKN-01-related	14 (56%)
Grade ≥ 3 events	16 (64%)
DKN-01-related	5 (20%)
Serious adverse events	10 (40%)
DKN-01-related	2 (8%)
Events leading to DKN-01 discontinuation	3 (12%)
DKN-01-related	1 (4%)
Events leading to DKN-01 dose reduction	2 (8%)

*within 30 days of last dose

First-line Therapy 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)

Best Overall Response, n (%)					
	Complete Response	Partial Response	Stable Disease	Progressive Disease	Non-Evaluable
mITT population (N=22)	1 (5)	14 (64)	6 (27)	0	1 (5)
DKK1-high (N=10)	0	9 (90)	0	0	1 (10)
DKK1-low (N=9)	1 (11)	4 (44)	4 (44)	0	0
DKK1 unknown (N=3)	0	1 (33)	2 (67)	0	0

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

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

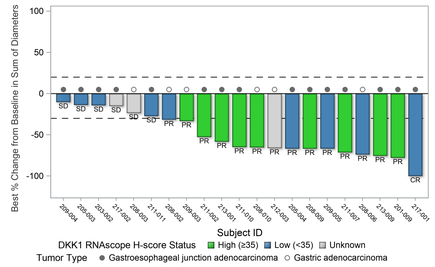
PD-L1-low expression (vCPS <5, n=14)

- 79% (11/14) ORR in PD-L1-low patients
- 100% (6/6) ORR in DKK1-high, PD-L1-low patients

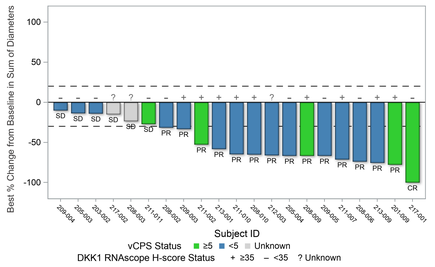
PD-L1-high expression (vCPS ≥5, n= 6)

- 67% (4/6) ORR in PD-L1-high patients
- 75% (3/4) ORR in DKK1-high, PD-L1-high patients

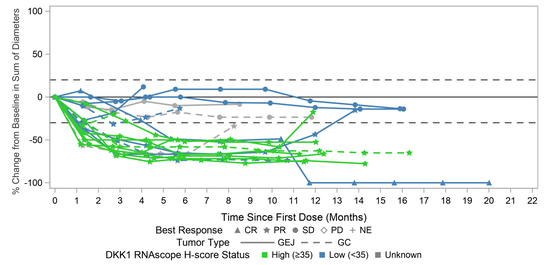
Response by DKK1 Expression (mITT, N=21)



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

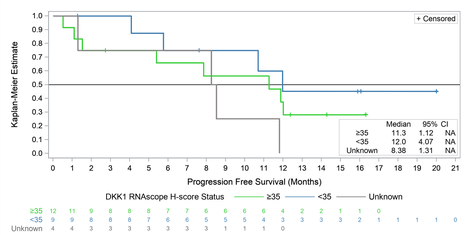


Durability of Clinical Benefit by DKK1 Expression (mITT, N=21)



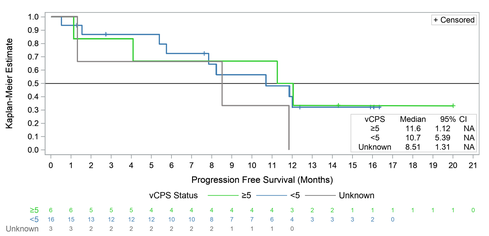
Progression-free Survival by DKK1 Expression (ITT, N=25)

- Median PFS: Overall 11.3 mo, DKK1-high 11.3 mo, DKK1-low 12.0 mo



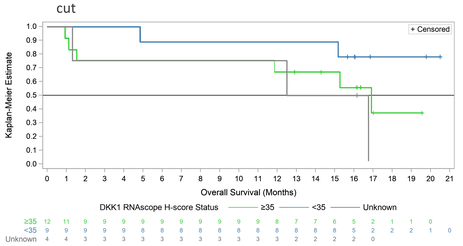
Progression-free Survival by PD-L1 Expression (ITT, N=25)

- Median PFS: Overall 11.3 mo, vCPS <5 10.7 mo, vCPS ≥5 11.6 mo



Overall Survival by DKK1 Expression (ITT, N=25)

- Median OS is not mature with 14/25 pts (56%) still alive at the data cut



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

Disposition and Exposure

- Median duration of treatment: 11.3 mo
- 7 patients remain on therapy

	Patients (N=25)
Number of cycles, median (min, max)	14.0 (1.0, 27.0)
Duration on treatment (months), median (min, max)	11.3 (0.76, 20.50)
Reasons for study drug discontinuation, n (%)	
Patient request to withdraw	2 (8%)
Objective disease progression	11 (44%)
Adverse event	3 (12%)
Investigator decision	1 (4%)
Other reasons	1 (4%)
Reasons for study discontinuation, n (%)	
Withdrawal of consent	1 (4%)
Death	11 (44%)
Other reasons	1 (4%)
Duration on Study (months), median (min, max)	15.7 (0.92, 20.50)

DKK1 and PD-L1 Expression

- DKK1 expression and PD-L1 expression are not correlated

vCPS: Visually-Estimated Combined Positive Score; PD-L1: Programmed Death-Ligand 1
*Highest vCPS was 20 on a scale of 0->100

CONCLUSIONS

- DKN-01 and tislelizumab + CAPOX was well tolerated and active in first-line treatment for advanced GEA patients
- High and durable overall response rate in unselected and aggressive subgroups (DKK-high and PD-L1-low)
- Overall median PFS of 11.3 months exceeds benchmark results in unselected patients
  - 11.3 months in DKK1-high and 12.0 months in DKK1-low
  - 10.7 months in CPS-low and 11.6 months in CPS-high
- Median OS is not mature with only 44% of patients deceased as of the data cut with a median duration on study of 15.7 months (0.92, 20.50)
- Phase 2 randomized controlled study of DKN-01 +/- tislelizumab and chemotherapy (CAPOX or mFOLFOX6) in first-line GEA is underway

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.

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