A Phase 2 Study (DisTinGuish) of DKN-01 in Combination with Tislelizumab + Chemotherapy as First-Line (1L) Therapy in Patients with Advanced Gastric or GEJ Adenocarcinoma (GEA)

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BACKGROUND

Advanced GEA Treatment Landscape

- Nivolumab plus SOC chemotherapy is approved for patients with 1L advanced GEA[1,2] based on the CheckMate-649 (CM-649) trial (median OS 13.8 mo vs 11.6 mo for chemotherapy alone).[2]
  - The survival benefit was greatest in patients with PD-L1 CPS scores ≥5 (median OS 14.4 mo vs 11.1 mo). [2]
  - Median OS in the CPS <5 patient population was similar to chemotherapy alone (12.4 mo vs 12.3 mo).[1]
- Tislelizumab is an anti-PD1 antibody engineered to minimize binding to FcgR on macrophages.[3]
  - RATIONALE-305 recently reported a median OS of 17.2 mo for tislelizumab + chemotherapy vs 12.6 mo for chemotherapy alone (median PFS 7.2 mo vs 5.9 mo) in the vCPS* ≥ 5 patient population.[4]
- Patients with GEA whose tumors express low or no PD-L1, have poor outcomes and represent up to two-thirds of the patient population with advanced GEA.[5]

DKK1 and DKN-01

- Expression of DKK1 is associated with poor survival and resistance to chemotherapy in multiple tumor types.[6,7]
- DKN-01 is an anti-DKK1 mAb which has demonstrated anti-tumor activity in patients with advanced GEA with low tumor PD-L1 expression,[8] a subset with very limited therapeutic options.
- DKN-01 has immunomodulatory activity, stimulates a pro-inflammatory tumor microenvironment and upregulates PD-L1 levels. [9,10]
- Here we present 2-year survival data for 1L advanced GEA patients who received combination treatment with DKN-01 plus tislelizumab and CAPOX.

METHODS

DisTinGuish Trial (NCT04363801)

Design: Phase 2a single arm multi-cohort trial

- **Part A: DKN-01 + Tislelizumab + CAPOX in 1L Advanced GEA**
- Part B: DKN-01 + Tislelizumab in 2L Advanced GEA
- Part C: Randomized- DKN-01 + Tislelizumab + CAPOX or mFOLFOX6 vs Tislelizumab + CAPOX or mFOLFOX6 in 1L Advanced GEA

Part A Primary objective: safety and tolerability

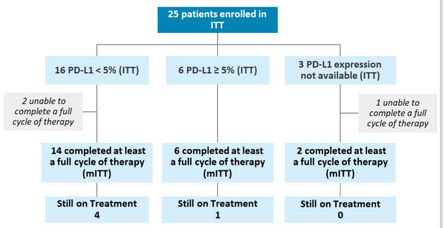
Secondary endpoints: objective response rate (ORR), duration of response (DoR), disease control rate (DCR), progression- free survival (PFS) assessed by investigators and overall survival (OS)

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

Tumor DKK1 and PD-L1 expression: DKK1 RNA expression was performed by chromogenic ISH RNAscope assay; tumors were assigned an H-score (0-300) (Flagship Biosciences, Broomfield, CO; Advanced Cell Diagnostics, Newark, CA); PD-L1 IHC was performed using the SP263 Ab and a vCPS* was reported (Roche Tissue Diagnostics, Tucson, AZ).

Data cut-off: Feb. 3, 2023

1L Advanced GEA Patients
DKN-01 300 mg + Tislelizumab + CAPOX



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

*vCPS: Visually-Estimated Combined Positive Score

RESULTS

Baseline Characteristics

	Patients (N=25)
Age, median (min, max)	61.0 (22.0, 80.0)
Male, n (%)	19 (76%)
Female, n (%)	6 (24%)
Gastric Adenocarcinoma, n (%)	8 (32%)
GEJ Adenocarcinoma, n (%)	17 (68%)
Liver Involvement, n (%)	
Yes	7 (28%)
No	18 (72%)
Tumor PD-L1 expression	
vCPS <5	16 (64%)
vCPS ≥5	6 (24%)
vCPS unknown	3 (12%)
Tumor DKK1 expression	
DKK1 low (H-score <35)	9 (36%)
DKK1 high (H-score ≥35)	12 (48%)
DKK1 unknown	4 (16%)

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

Disposition and Exposure

	Patients (N=25)
Duration on treatment (months), median (min, max)	11.3 (0.76, 24.4)
Reasons for study drug discontinuation, n (%)	
Patient request to withdraw	2 (8%)
Objective disease progression	11 (44%)
Adverse event	4 (16%)
Investigator decision	2 (8%)
Other reasons	1 (4%)
Reasons for study discontinuation, n (%)	
Withdrawal of consent	1 (4%)
Death	18 (72%)
Duration on Study (months), median (min, max)	18.7 (0.92, 24.6)

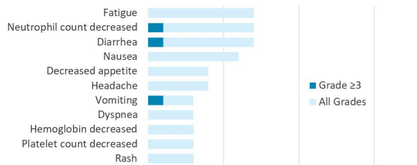
Safety Outcomes

- Combination DKN-01+ tislelizumab + CAPOX was well tolerated with manageable toxicity
- Most AEs related to DKN-01 were low-grade (76%)

Preferred Terms	Patients (N=25) No. Patients (%)
TEAEs leading to death*	3 (12%)
Any adverse event	
DKN-01-related	15 (60%)
Grade ≥ 3 events	17 (68%)
DKN-01-related**	6 (24%)
Serious adverse events	11 (44%)
DKN-01-related	3 (12%)
Events leading to DKN-01 discontinuation	4 (16%)
DKN-01-related	1 (4%)
Events leading to DKN-01 dose reduction	2 (8%)

*within 30 days of last dose; **diarrhea (1), vomiting (1), neutrophil count decreased (1), blood phosphorus decreased (2), pulmonary embolism (2)

Adverse Events Related to DKN-01 Reported in ≥ 10% of Patients



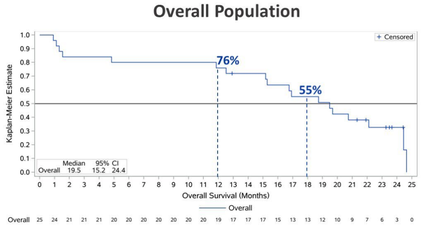
First-line Therapy Efficacy Outcomes

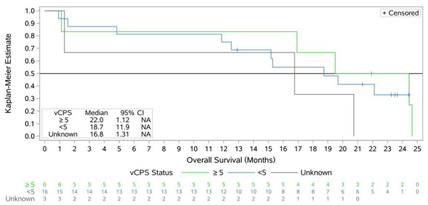
	Progression-free Survival (months)	Overall Survival (months)
	median (95% CI)	median (95% CI)
Overall (n=25)	11.3 (5.75, 12.0)	19.5 (15.2, 24.4)
vCPS < 5 (n=16)	10.7 (5.39, NA)	18.7 (11.9, NA)
vCPS ≥ 5 (n=6)	11.6 (1.12, NA)	22.0 (1.12, NA)

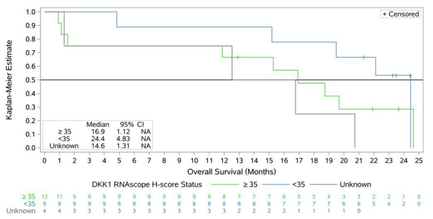
Best Overall Response, n (%)

		Objective Response Rate	Complete Response	Partial Response	Stable Disease	Progressive Disease	Non-Evaluable
mITT population (N=22)		**73% (49.8, 89.3)**	1 (5%)	15 (68%)	5 (23%)	0	1 (5%)
PD-L1 Expression	vCPS < 5 (N=14)	**86% (57.2, 98.2)**	0	12 (86%)	2 (14%)	0	0
	vCPS ≥ 5 (N=6)	**67% (22.3, 95.7)**	1 (17%)	3 (50%)	1 (17%)	0	1 (17%)
	Unknown (N=2)	**0%**	0	0	2 (100%)	0	0

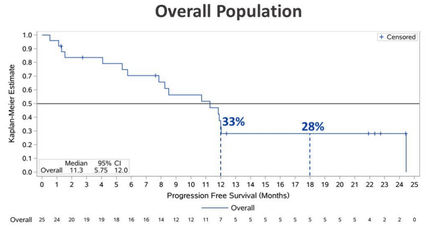
Overall Survival (ITT, N=25)

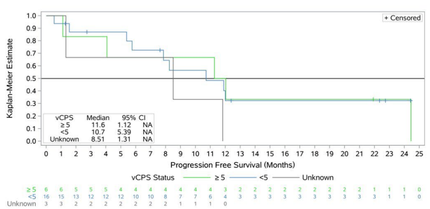


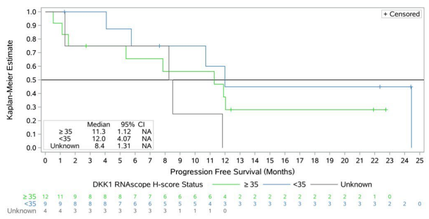




Progression-free Survival (ITT, N=25)

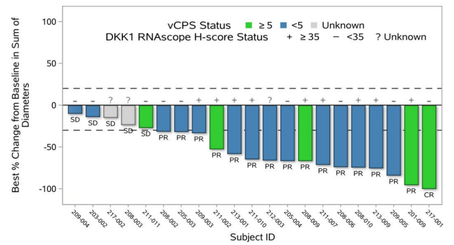




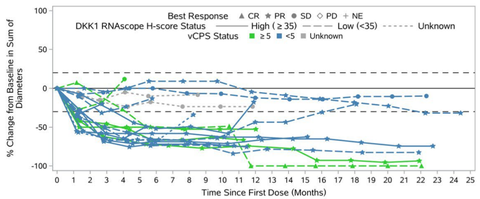


DKK1-high: H-score ≥35; | DKK1-low: H-score <35 | mITT: modified intent-to-treat population defined as all patients who received more than one dose of DKN-01 | PD-L1: Programmed Death-Ligand 1 | vCPS: Visually-Estimated Combined Positive Score

Response (mITT, N=21)



Duration of Clinical Benefit (mITT, N=21)



CONCLUSIONS

- **At 2 years of follow-up, the median OS with DKN-01 + tislelizumab + CAPOX exceeded the historical control in CM-649,[2] both in the overall population (19.5 vs 13.8 months) and in the PD-L1 low-subgroup (18.7 vs 12.4 months).**
  - **Percentage of patients alive at 12 and 18 months in DisTinGuish vs CM-649 is 76% vs 55% and 55% vs ~35%, respectively.**
- **Median PFS is consistently longer by ~3 months over historical controls for both the overall population (11.3 vs 7.7 months) and for the PD-L1 low subgroup (10.7 vs. 7.5 months)**
- **DKN-01 + tislelizumab + CAPOX showed a durable ORR in the mITT population (73%) and, importantly, in the PD-L1 low-subgroup (86%).**
- **The Phase 2 randomized controlled study of DKN-01 +/- tislelizumab and chemotherapy (CAPOX or mFOLFOX6) in first-line GEA is ongoing (NCT04363801)**

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