DKN-01 in Combination with Tislelizumab and Chemotherapy as a First-line Therapy in Unselected Patients with Advanced Gastroesophageal Adenocarcinoma (GEA): DisTinGuish Trial

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Poster # 1384P

Abstract # 2218

BACKGROUND

Dickkopf-1 (DKK1)

- DKK1 modulates Wnt signaling[1]
- Overexpression of DKK1 is linked to poor prognosis[1]
- Tumor cells secrete DKK1 promoting proliferation, metastasis and angiogenesis[1]
- DKK1 suppresses anti-tumor immune responses through the downregulation of NK cell function and enhancement of MDSC activity[2,3]
- Promotes activation of Akt signaling through CKAP4 receptor[4]

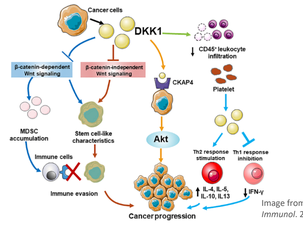


Image from: Chu HY, et al. *Front Immunol*. 2021;12:658097

DKN-01

- Humanized monoclonal antibody [IgG4] targeting DKK1
- Activates innate immune response in preclinical models characterized by increased infiltration of NK cells and reduced MDSC function[5]
- In vivo, DKN-01 downregulates Akt activity and upregulates PD-L1 expression in tumors[5]
- DKN-01 in combination with the anti-PD1 antibody, pembrolizumab, has demonstrated safety and clinical activity in advanced, previously treated DKK1-high GEA; high tumoral DKK1 expression was associated with longer PFS (22.1 weeks vs 5.9 weeks)[6]
- 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.[7]
- We report response and survival outcomes in GEA patients treated with a DKN-01 combined with tislelizumab and chemotherapy as first-line therapy.

METHODS

Design: Phase 2a study of DKN-01 + tislelizumab + capecitabine/oxaliplatin (CAPOX) in advanced GEA patents

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)

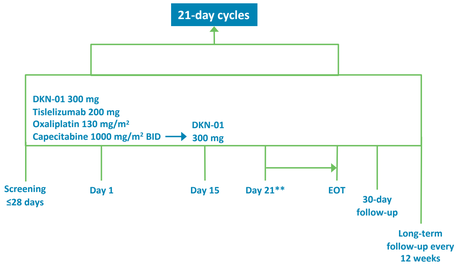
Primary efficacy endpoint: objective response rate (ORR)

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

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

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

DisTinGuish Trial Part A*
First-line DKN-01 + Tislelizumab + CAPOX in Advanced GEA
(NCT04363801)



*The DisTinGuish Trials has two parts. Part A is reported here. Part B is evaluating second-line treatment with 300 or 600 mg DKN-01 + tislelizumab in 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).
**Safety review after the first 5 patients have enrolled and completed one cycle

RESULTS

Demographic & Clinical Characteristics

- 25 GEA patients were enrolled
  - → 17 patients (68%) had gastroesophageal junction (GEJ) adenocarcinoma
  - → 8 patients (32%) had gastric cancer (GC)
- 21 patients had RNAscope DKK1 expression available
  - → 12 patients (57%) DKK1-high (8 GEJ, 4 GC)
  - → 9 patients (43%) DKK1-low (7 GEJ, 2 GC)

	Overall N=25	DKK1-high (H-score ≥35) N=12	DKK1-low (H-score <35) 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)
Gender (male), n (%)	19 (76)	8 (67)	8 (89)	3 (75)
ECOG Performance Status, n (%)				
0	14 (56)	6 (50)	5 (56)	3 (75)
1	11 (44)	6 (50)	4 (44)	1 (25)
GEJ Adenocarcinoma	17 (68)	8 (67)	7 (78)	2 (50)
Stage at Initial Diagnosis, n (%)				
Stage I	1 (4)	1 (8)	0	0
Stage III	3 (12)	1 (8)	2 (22)	0
Stage IV	9 (36)	6 (50)	3 (33)	0
Unknown	4 (16)	0	2 (22)	2 (50)
Months Since First Diagnosis, median	1.2 (0.2, 20.3)	1.0 (0.6, 2.4)	1.0 (0.2, 7.1)	10.9 (1.4, 20.3)
GC Adenocarcinoma, n (%)	8 (32)	4 (33)	2 (22)	2 (50)
Stage at Initial Diagnosis				
Stage III	1 (4)	0	1 (11)	0
Stage IV	7 (28)	4 (33)	1 (11)	2 (50)
Months Since First Diagnosis, median	0.7 (0.4, 25.0)	0.6 (0.4, 0.7)	12.9 (0.8, 25.0)	0.4 (0.3, 0.6)
Prior Systemic Therapies, n (%)				
Adjuvant	2 (8)	0	1 (11)	1 (25)
Neoadjuvant	2 (8)	0	2 (22)	0
Adjuvant/neoadjuvant	3 (12)	0	2 (22)	1 (25)
Tumor PD-L1: vCPS[a], n (%)	22 (88)	12 (100)	9 (100)	1 (25)
CPS < 1	5 (23)	2 (17)	2 (22)	1 (100)
CPS <5	16 (73)	8 (67)	7 (78)	1 (25)
CPS ≥5[b]	6 (27)	4 (33)	2 (22)	0
Tumor Mutation Burden,[c] n (%)	15 (60)	7 (58)	7 (78)	1 (25)
<10	13 (87)	5 (71)	7 (100)	1 (100)
≥10	2 (13)	2 (29)	0	0
Missing	10 (40)	5 (42)	2 (22)	3 (75)
Microsatellite status,[c] n (%)	15 (60)	7 (58)	7 (78)	1 (25)
Microsatellite Stability (MSS)	15 (100)	7 (100)	7 (100)	1 (100)
Missing	10 (40)	5 (42)	2 (22)	3 (75)

[a]vCPS: visually-estimated Combined Positive Score, also known as Tumor Area Positivity (TAP) score (Ventana Medical Systems, Oro Valley, AZ).
[b]Two patients had vCPS ≥10.
[c]Tumor Mutation Burden and Microsatellite status was determined from plasma ctDNA using the FoundationOne Liquid CDx assay (Foundation Medicine, Cambridge, MA).

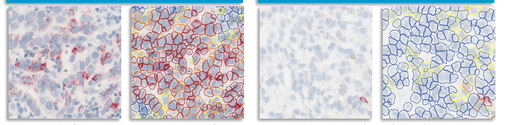
Disposition & Exposure

- Mean duration of treatment: 5 months
- Longest duration to date on study: 10+ months
- 16 patients remain on therapy

	Overall N=25
Number of cycles, median (min, max)	7.0 (1.0, 14.0)
Duration on treatment (months), median (min, max)	5.1 (0.8, 10.1)
Reasons for study drug discontinuation, n (%)	
Patient request to withdraw	2 (8)
Objective disease progression	3 (12)
Adverse event	3 (12)
Other reasons	1 (4)
Reasons for study discontinuation, n (%)	
Withdrawal of consent	0
Death	4 (16)
Duration on study (months): median, (min, max)	5.6 (1.4, 10.4)

DKK1 RNAscope Tumor Biopsy Examples

DKK1-high Patient (H-score = 108) | **DKK1-low Patient (H-score = 4)**

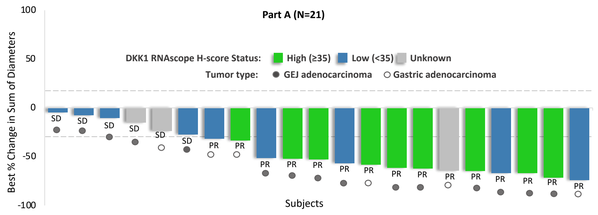


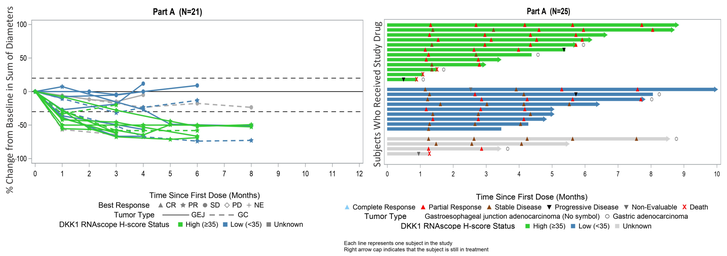
Sectioned slides from tumor specimens were stained for DKK1 mRNA at Flagship Biosciences (Broomfield, CO) and expression was quantified using a digital image analysis algorithm.[8] Blue circles (no DKK1 staining), yellow circles (low DKK1 staining), orange circles (medium DKK1 staining) and red circles (high DKK1 staining). An H-score was calculated by determining the percentage of cells expressing low, medium and high levels of DKK1 with the following formula. H-score = (%low)+2*(%medium)+3*(%high). H-score range: 0 to 300.

Best Overall Response by DKK1 Expression

- mITT population included 22 patients; response evaluable (RE) mITT population was 21 patients
- ORR in mITT was 68.2% (15 PR, 6 SD, 1 NE) and DCR was 96%
- DKK1-high mITT ORR was 90%; 7 of 9 responders still on therapy
- DKK1-low mITT ORR was 55.6%; 4 of 5 responders still on therapy
- Median DoR and PFS were not reached

Best Overall Response, n (%)				
	Partial Response	Stable Disease	Progressive Disease	Non-Evaluable
mITT population (N=22)	15 (68.2%)	6 (27.3%)	0	1 (4.5%)
DKK1-high (N=10)	9 (90.0%)	0	0	1 (10.0%)
DKK1-low (N=9)	5 (55.6%)	4 (44.4%)	0	0
DKK1 unknown (N=3)	1 (33.3%)	2 (66.7%)	0	0





Safety

- Most common DKN-01-related adverse events: fatigue, nausea, diarrhoea, neutrophil count decreased, platelet count decreased
- Grade ≥3 DKN-01-related adverse events (5 patients): diarrhoea (1), neutrophil count decreased (1), blood phosphorus decreased (1), pulmonary embolism (2)
- Grade 5: pulmonary embolism (1)

Summary of Adverse Events

	Part A Patients N=25	
Preferred Terms	No Patients	%
Death within 30 days of last dose	3	12%
Any adverse event	25	100%
Grade ≥ 3 events	13	52%
DKN-01-related	5	20%
Serious adverse events	7	28%
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	1	4%
Drug-related adverse events		
DKN-01-related	14	56%
Tislelizumab-related	16	64%
Capecitabine-related	23	92%
Oxaliplatin-related	22	88%
Regimen-related	23	92%

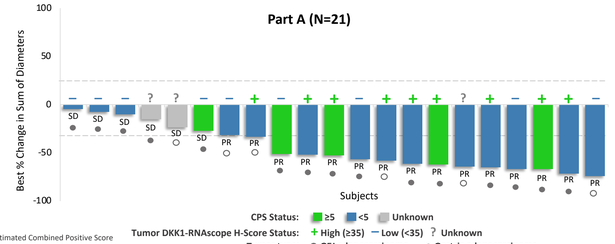
DKN-01 Related Adverse Events with ≥10% Incidence

	Part A Patients N=25	
Preferred Terms	No Patients	%
DKN-01 Related		
Fatigue	8	32%
Nausea	5	20%
Diarrhoea	5	20%
Neutrophil count decreased	5	20%
Platelet count decreased	5	20%
Hemoglobin decreased	4	16%
Decreased appetite	3	12%
Headache	3	12%
DKN-01 Related Grade ≥ 3	5	20%
Diarrhoea	1	4%
Neutrophil count decreased	1	4%
Blood phosphorus decreased	1	4%
Pulmonary embolism	2	8%
Any DKN-01+Tislelizumab regimen-related Grade ≥ 3	9	36%
Diarrhoea	3	12%

Best Overall Response by PD-L1 and DKK1 Expression

- In the RE mITT, similar ORR regardless of PD-L1 vCPS score (<5 vs ≥5) overall (79% vs 67%) and in DKK1-high patients (100% vs 75%), respectively
- Double negative patients (DKK1-low and PD-L1 vCPS <5) have an ORR 57%

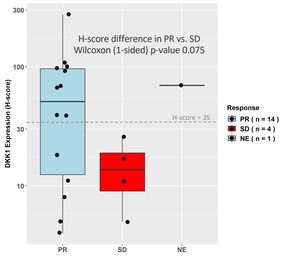
Best Overall Response, n (%)				
	Partial Response	Stable Disease	Progressive Disease	Non-Evaluable
PD-L1 CPS ≥5 (N=6)	4 (67%)	1 (17%)	0	1 (17%)
DKK1-high (N=4)	3 (75%)	0	0	1 (25%)
DKK1-low (N=2)	1 (50%)	1 (50%)	0	0
PD-L1 CPS <5 (N=14)	11 (79%)	3 (21%)	0	0
DKK1-high (N=6)	6 (100%)	0	0	0
DKK1-low (N=7)	4 (57%)	3 (43%)	0	0
DKK1 unknown (N=1)	1 (100%)	0	0	0



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

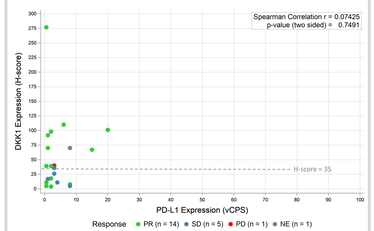
Association of DKK1 Expression with Response

- Tumoral DKK1 expression is predictive of response to DKN-01 therapy



Correlation of DKK1 RNAscope H-score with vCPS

- DKK1 and PD-L1 expression are not correlated



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

CONCLUSIONS

DKN-01 + tislelizumab + CAPOX was well tolerated and has encouraging response rates as first-line treatment for advanced GEA

- Improved ORR outcomes in the overall population compared to current standard of care in an unselected PD-L1 population
- Efficacy driven by enhanced ORR in the DKK1-high patients, an aggressive subpopulation
  - All 9 RE mITT DKK1-high patients had partial responses
- Response correlates with DKK1 expression and is independent of PD-L1 expression
- Duration of response and progression-free survival data are not yet mature, expected in first half of 2022

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