DisTinGuish Study Update

January 21, 2022

Leap Therapeutics | Forward Looking Statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based only on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, projections, anticipated events and trends, the economy and other future conditions. Because forward-looking statements relate to the future, they are subject to inherent uncertainties, risks and changes in circumstances that are difficult to predict and many of which are outside of our control. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We assume no obligation to update any forward-looking statements, except as required by applicable law.

AGENDA

Introduction

Dr. Cynthia Sirard

Chief Medical Officer, Leap

Dr. Jason Baum

Vice President and Head of Translational Medicine, Leap

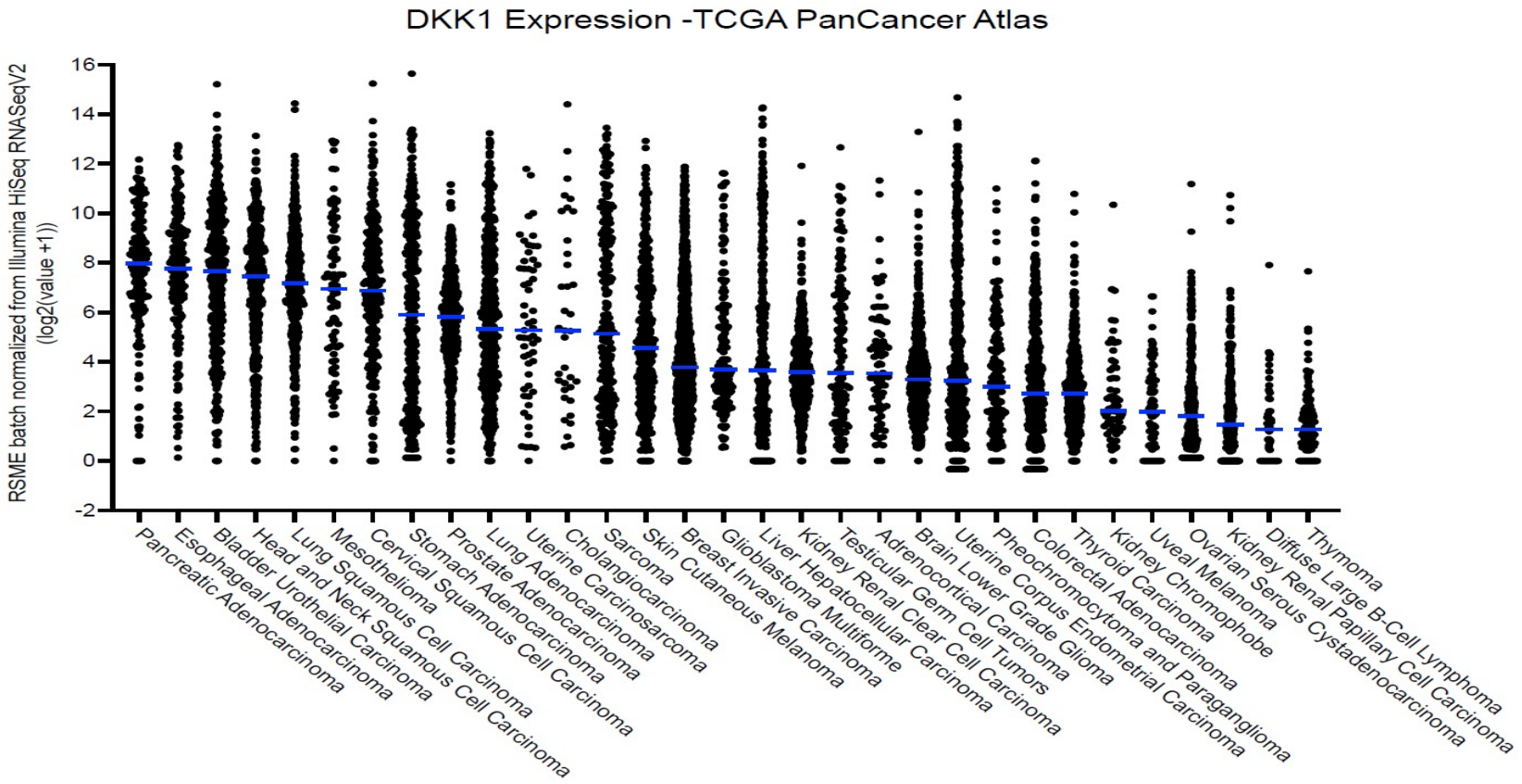
DisTinGuish Trial Preliminary Results

Dr. Samuel Klempner

Associate Professor at Harvard Medical School who leads the gastric and esophageal cancer program at Massachusetts General Hospital Cancer Center

Q&A

DKK1 is Widely Expressed Across Cancer Indications



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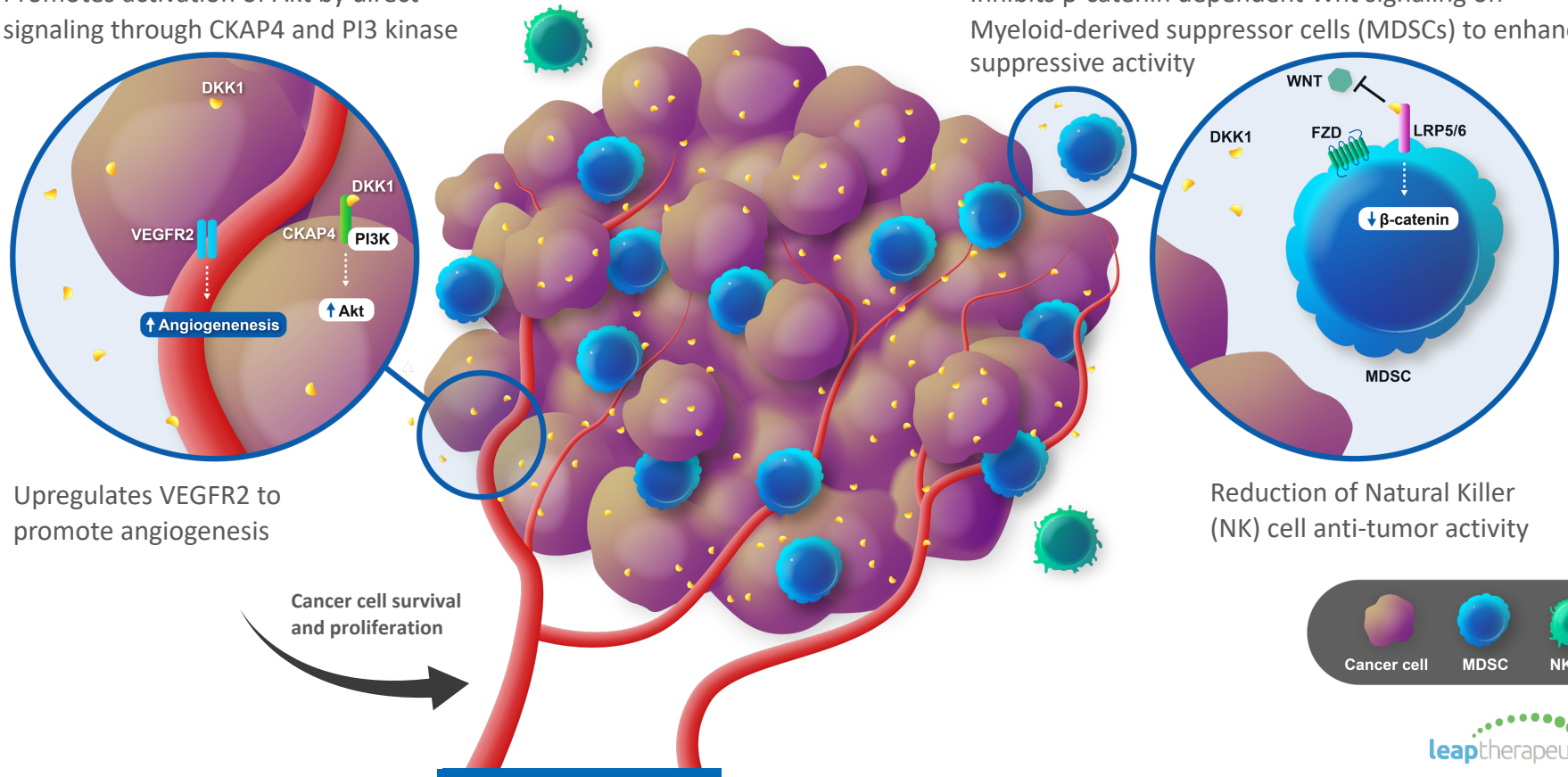
The Role of DKK1 in Cancer

Promotes activation of Akt by direct signaling through CKAP4 and PI3 kinase

Inhibits β-catenin dependent Wnt signaling on Myeloid-derived suppressor cells (MDSCs) to enhance suppressive activity



Upregulates VEGFR2 to promote angiogenesis

Reduction of Natural Killer (NK) cell anti-tumor activity

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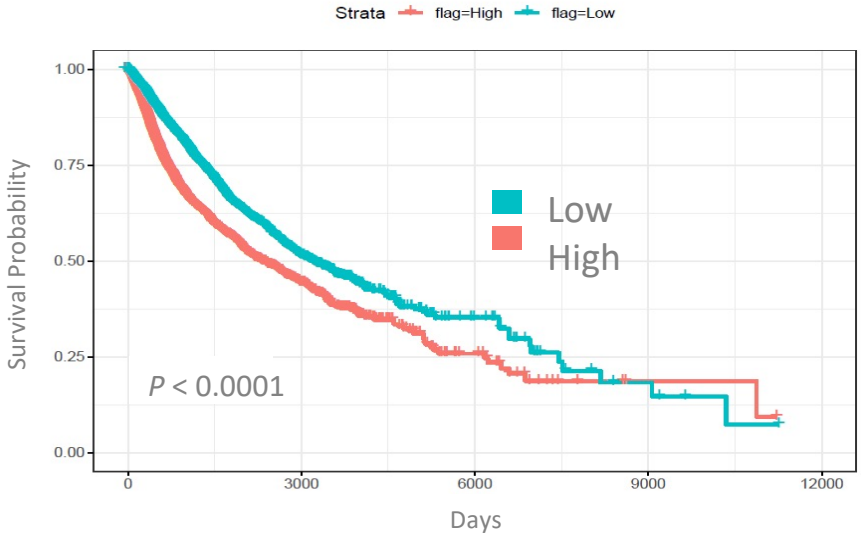
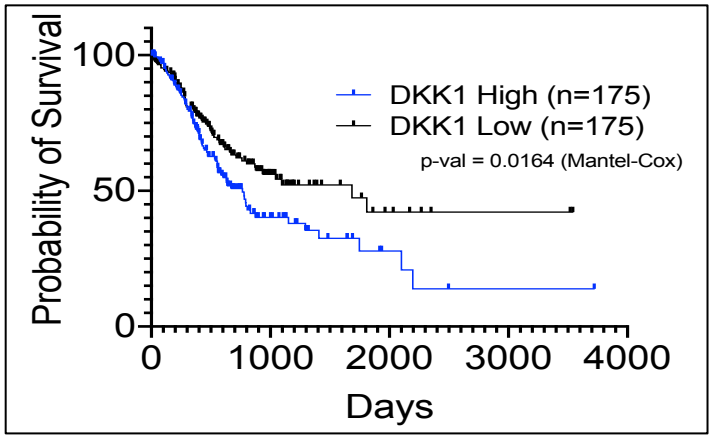
High Levels of DKK1 Correlate with Shorter Overall Survival Across Indications including Gastric and GEJ Cancer

OS for DKK1 High and Low Samples by Median (TCGA Pan-Cancer Dataset)



~2.5 year shorter OS in DKK1-high

OS for DKK1 High and Low Samples by Median (TCGA STAD Dataset)



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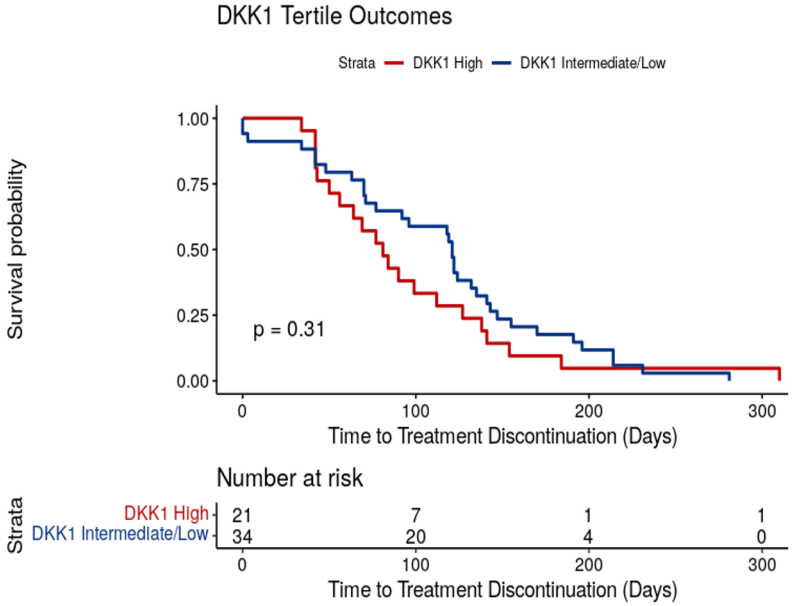
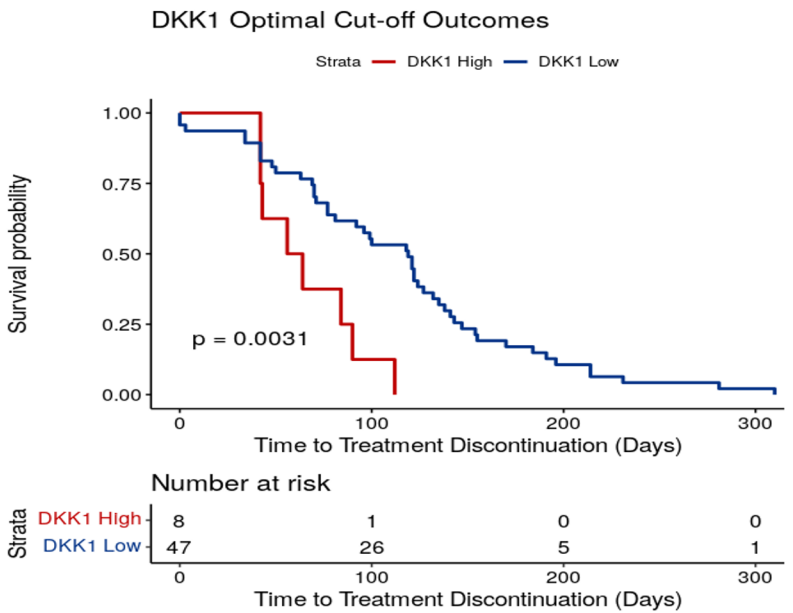
High DKK1 Is Associated with Poor Response to 1L Platinum + Fluoropyrimidine Based Therapies in GC/GEJ Patients





- Real world evidence (RWE) from patients with high DKK1 by RNAseq demonstrated faster time to treatment discontinuation (TTD) of 1L 5FU/capecitabine and platinum-based therapies.

TEMPUS

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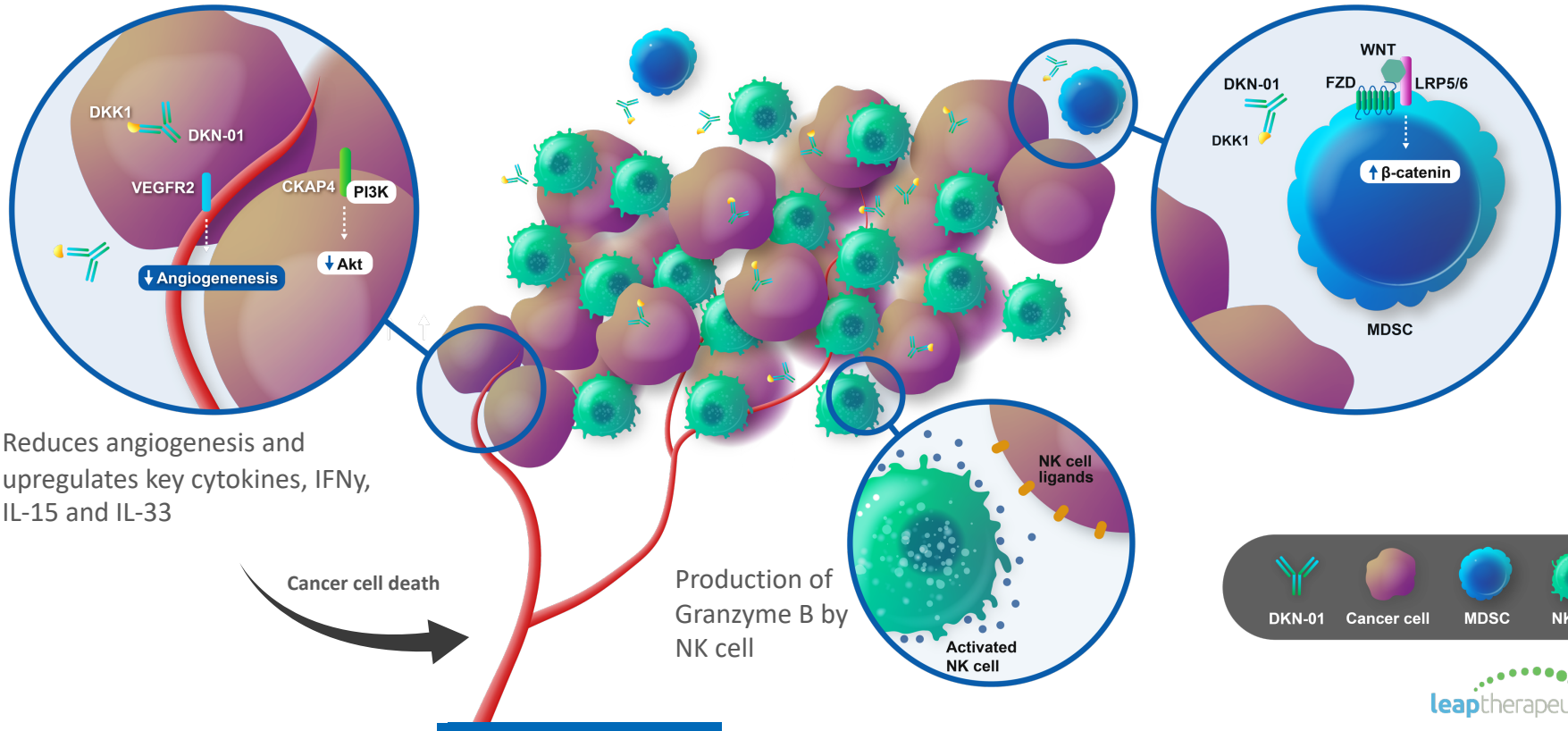
Activity of DKN-01 to Treat Cancer

Downregulation of Akt signaling decreases cancer cell survival and proliferation

β-dependent Wnt signaling reprograms MDSCs and reduces immunosuppressive activity



Reduces angiogenesis and upregulates key cytokines, IFNγ, IL-15 and IL-33

Production of Granzyme B by NK cell

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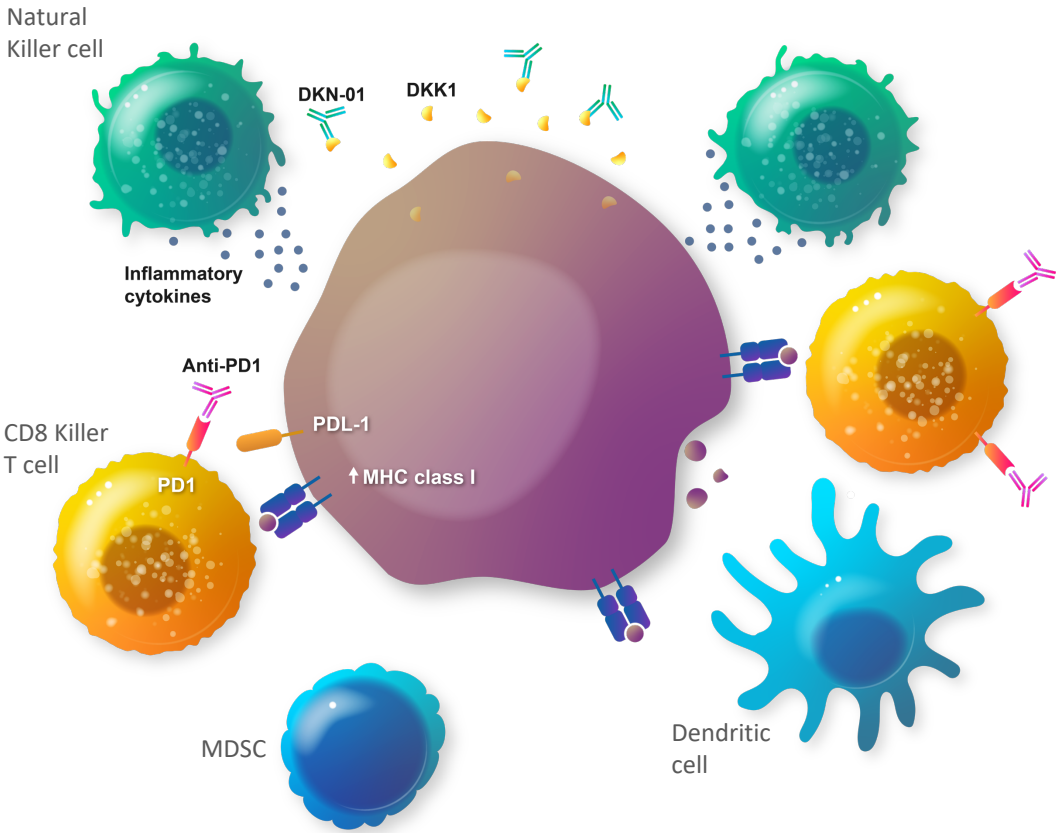
DKN-01 and Anti-PD-1 Cooperativity



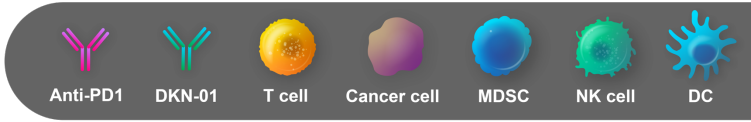
DKN-01 targets innate immunity by activating NK cells and inhibiting MDSC cells

- Dendritic cell and NK activation
- Induces pro-inflammatory cytokines
- Enhances tumor antigen recognition through an increase in MHC class 1 molecules

DKN-01 targets adaptive immunity by increasing PD-L1 expression and T cell infiltration

Anti-PD1 stimulates a CD8 adaptive immunity response

- Arms CD8 T cells to kill tumor cells
- Enhances immune memory for long-term tumor suppression



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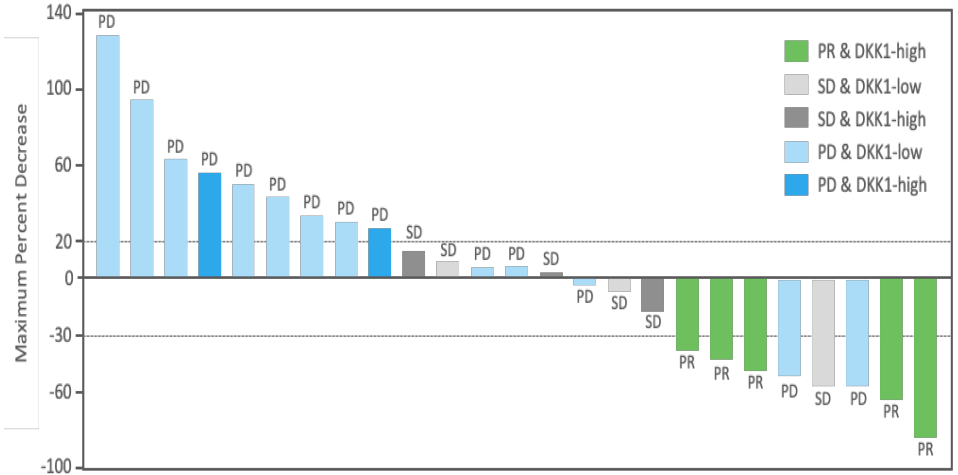
DKN-01 has Previously Demonstrated Activity in GEA in Combination with anti-PD-1 and with Paclitaxel

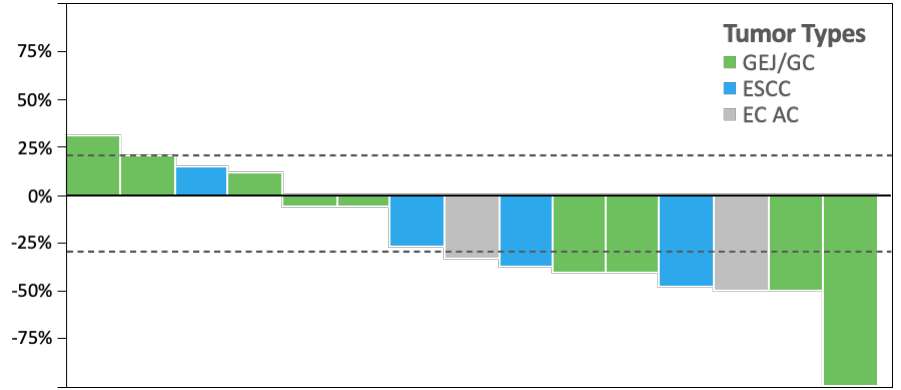
DKN-01 + Pembrolizumab in 2L+



Primary Location	Total (n)	RE* (n)	PR (n)	SD (n)	PD (n)	NE (n)	RE* ORR (n, %)	DCR (n,%)
DKK1 RNAscope*	31							
DKK1-high	11	10	5	3	2	1	5 (50)	8 (80)
DKK1-low	20	15	0	3	12	5	0 (0)	3 (20)

*DKK1-high ≥ upper tertile (35)

DKN-01 + Paclitaxel in 2L



2nd Line	n	ORR (%)	DCR (%)	PFS	OS
DKN-01 + pac	15	46.7%	73.3%	19.6 wks	55.1 wks

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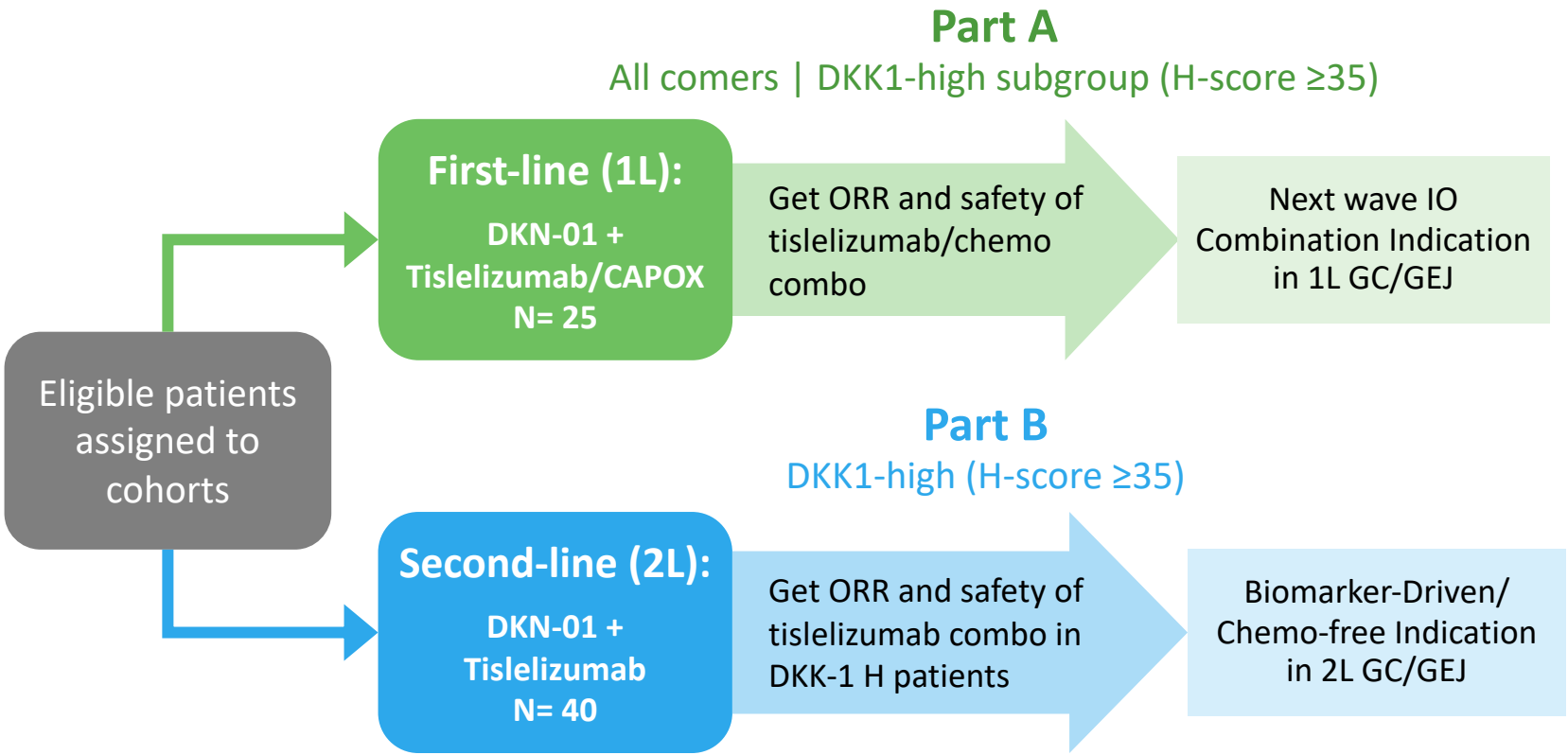
Q&A

Study Design in Patients with Advanced Gastric/GEJ Adenocarcinoma

Assess the Safety and Anti-tumor Activity of DKN-01 in Combination with Tislelizumab +/- Chemo



GEJ: gastroesophageal junction

Overall Demographics

- 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%)

	Part A (1L)				Part B (2L) – 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%)

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

Data as of 10 Dec 2021

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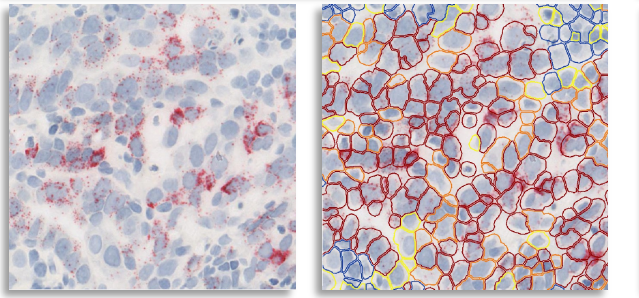
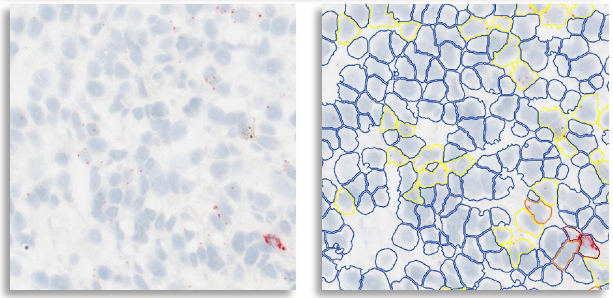
DKK1 Expression Determined Using RNAscope and Digital Pathology

DKK1-high Patient (H-score = 108)



DKK1-low Patient (H-score = 4)



Tumor specimens were stained for DKK1 expression and quantified using a digital image analysis algorithm.[1]

- An H-score was calculated by determining the percentage of cells expressing low, medium and high levels of DKK1. H-score range: 0 to 300.
- Blue circles = no DKK1 staining, yellow circles = low DKK1 staining, orange circles = medium DKK1 staining and red circles = high DKK1 staining.

Tumoral DKK1 mRNA expression

1L (Part A) US

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

2L (Part B) US and ROK

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

1. Flagship Biosciences (Broomfield, CO).

Baseline Tumor Characteristics

PD-L1 Expression

- 1L (Part A): 72.7% had vCPS <5, only 2 patients had vCPS ≥10
- 2L (Part B): preliminary analysis showed 72.7% with vCPS <5, only 3 patients had vCPS ≥10

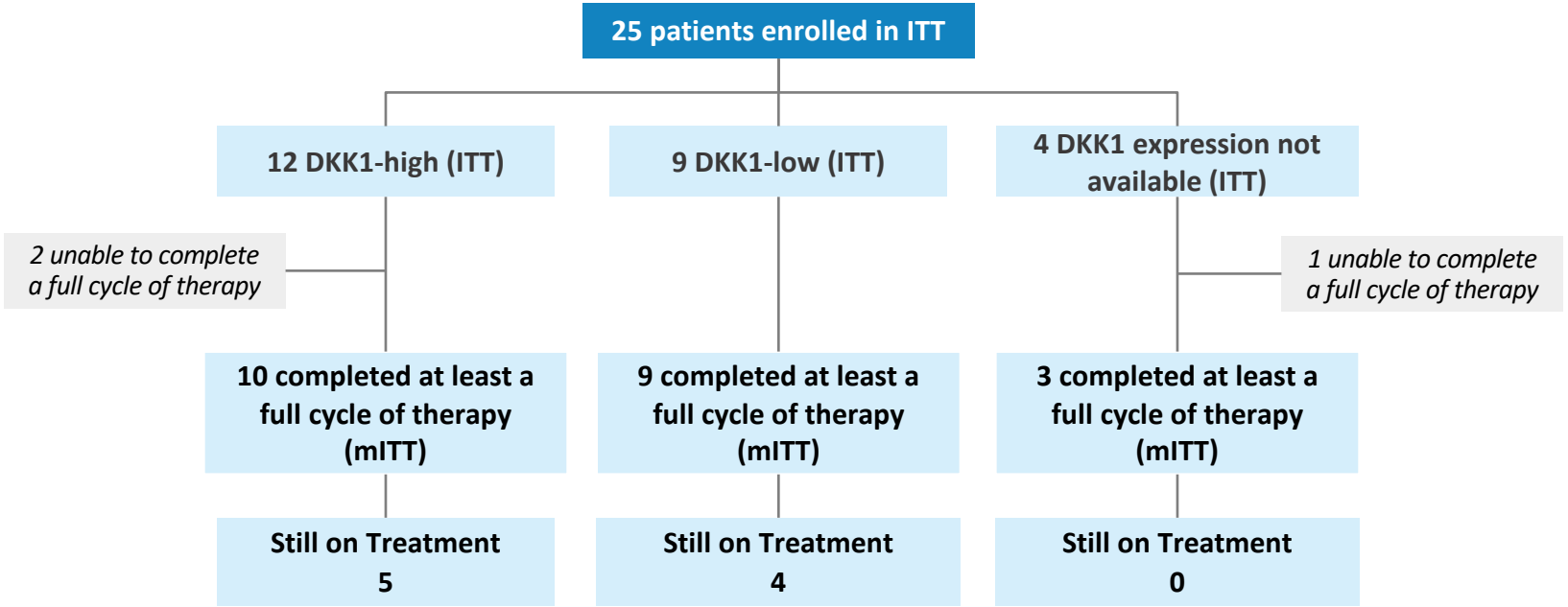
MSS / TMB

- No MSI-H and only 4 patients with TMB≥ 10 mut/Mb (2 in 1L, 2 in 2L)

	Part A (1L)				Part B (2L) – DKK1-high	
	Overall (N=25)	DKK1-high (N=12)	DKK1-low (N=9)	DKK1 unknown (N=4)	Part B1 (N=24)	Part B2[c] (N=6)
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).
[c]Data as of 10 Dec 2021. Part B2 ongoing and not yet available.

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

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

Drug Exposure and Duration on Therapy

1L (Part A)

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

2L (Part B)

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

	Part A (1L) (N=25)	Part B (2L)	
		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)

All Evaluable DKK1-high Patients Had Partial Response

1L GEJ/GC – DKN-01 Plus Tislelizumab Plus Chemotherapy

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

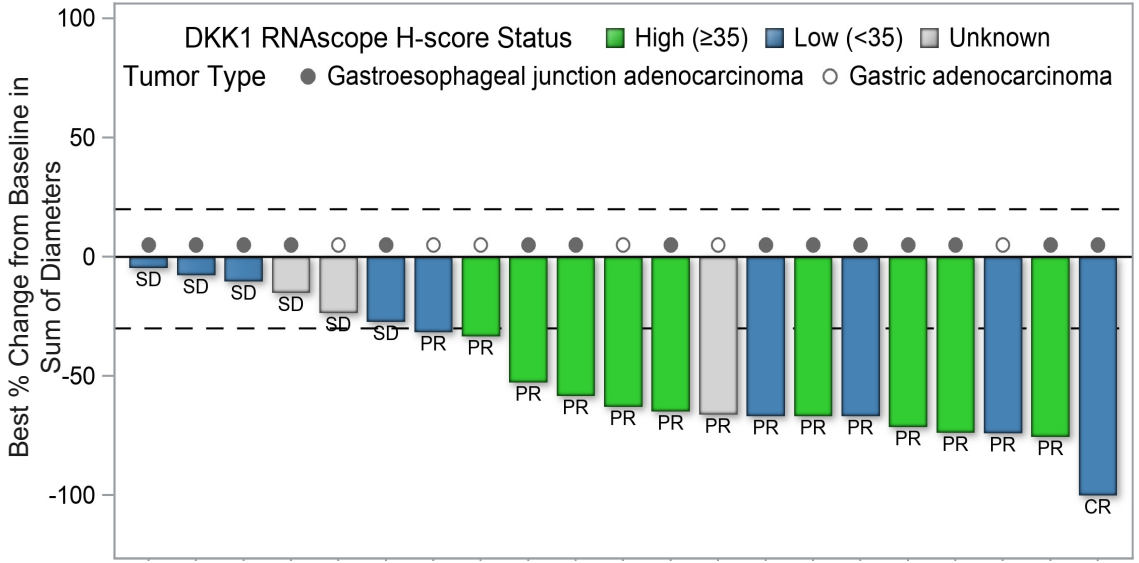
Objective Response Rate (ORR): 68% in mITT Population

1L GEJ/GC – DKN-01 Plus Tislelizumab Plus Chemotherapy

ORR:

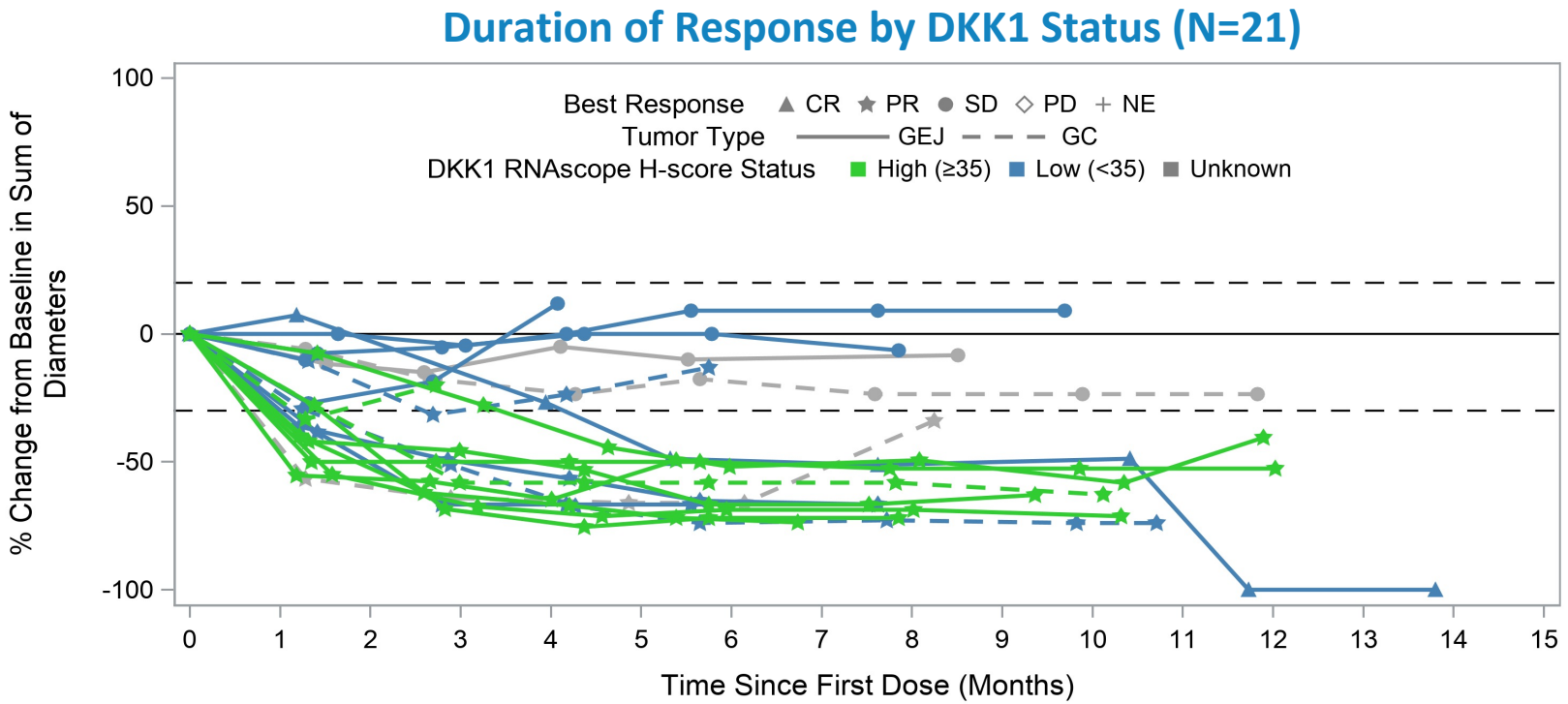
- Overall: 68% (1 CR, 14 PR)
- DKK1-high: 90% ORR (9 PR)
- DKK1-low: 56% ORR (1 CR; 4 PR)
  - 1 PR went to curative surgery with a pathologic CR
- DKK1-unknown: 33% ORR (1 PR)

Response by DKK1 Status (N=21)



Durability of Clinical Benefit

1L GEJ/GC – DKN-01 Plus Tislelizumab Plus Chemotherapy



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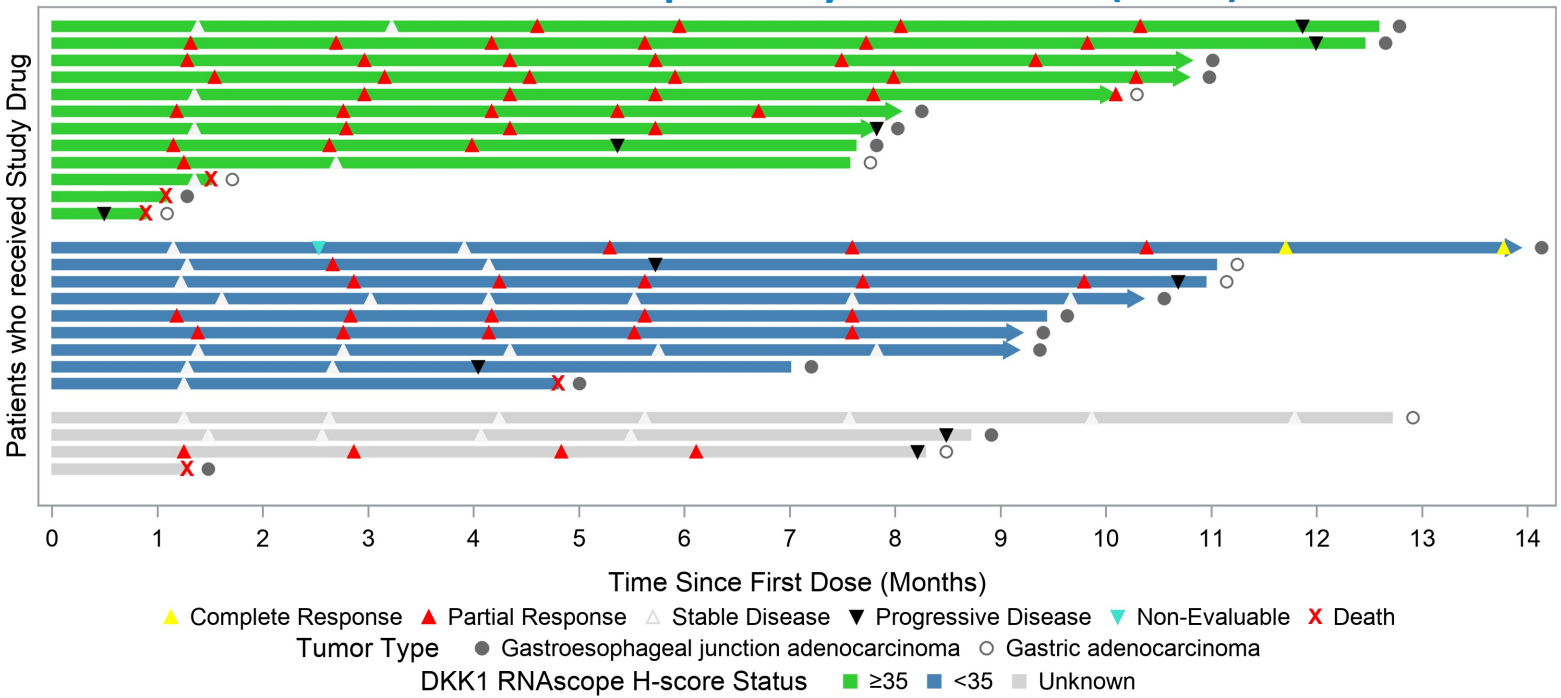
Prolonged Clinical Benefit

1L GEJ/GC – DKN-01 Plus Tislelizumab Plus Chemotherapy

Duration of Response by DKK1 Status (N=25)



Each line represents one patient in the study
Right arrow cap indicates that the patient is still in treatment

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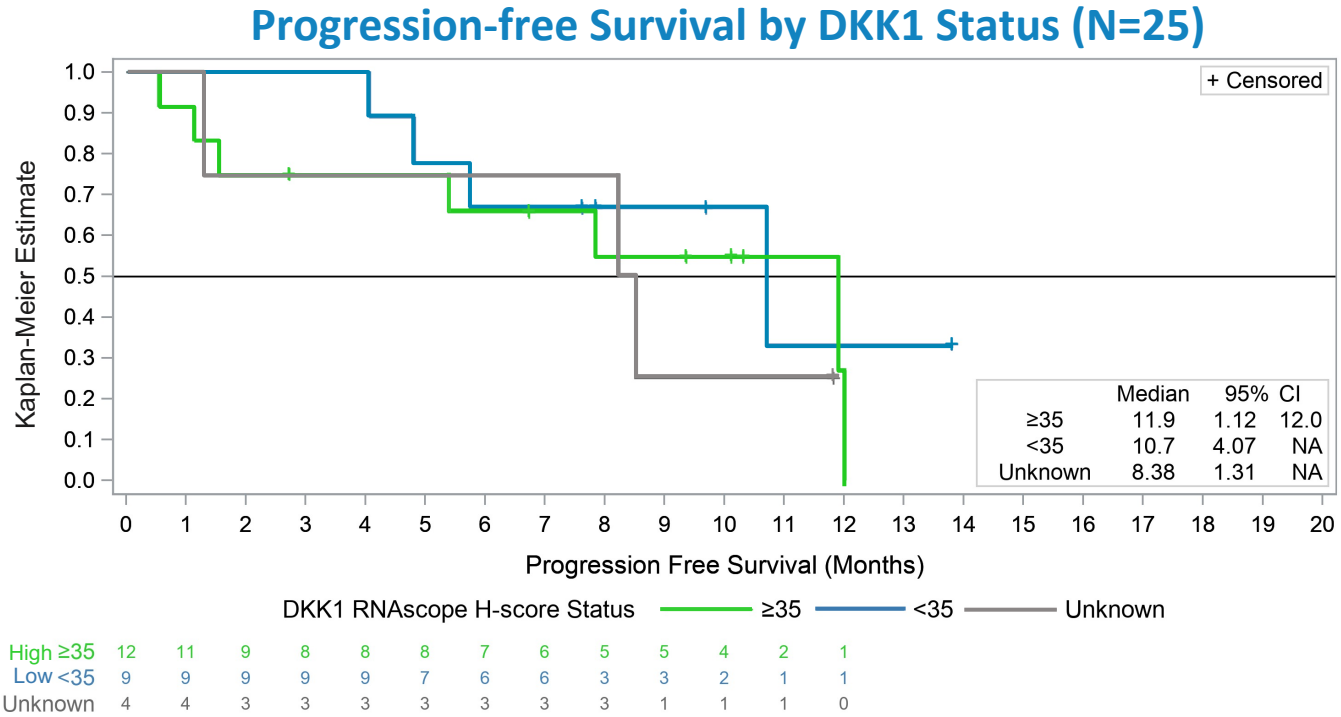
PFS Longer in DKK1-high Patients

1L GEJ/GC – DKN-01 Plus Tislelizumab Plus Chemotherapy

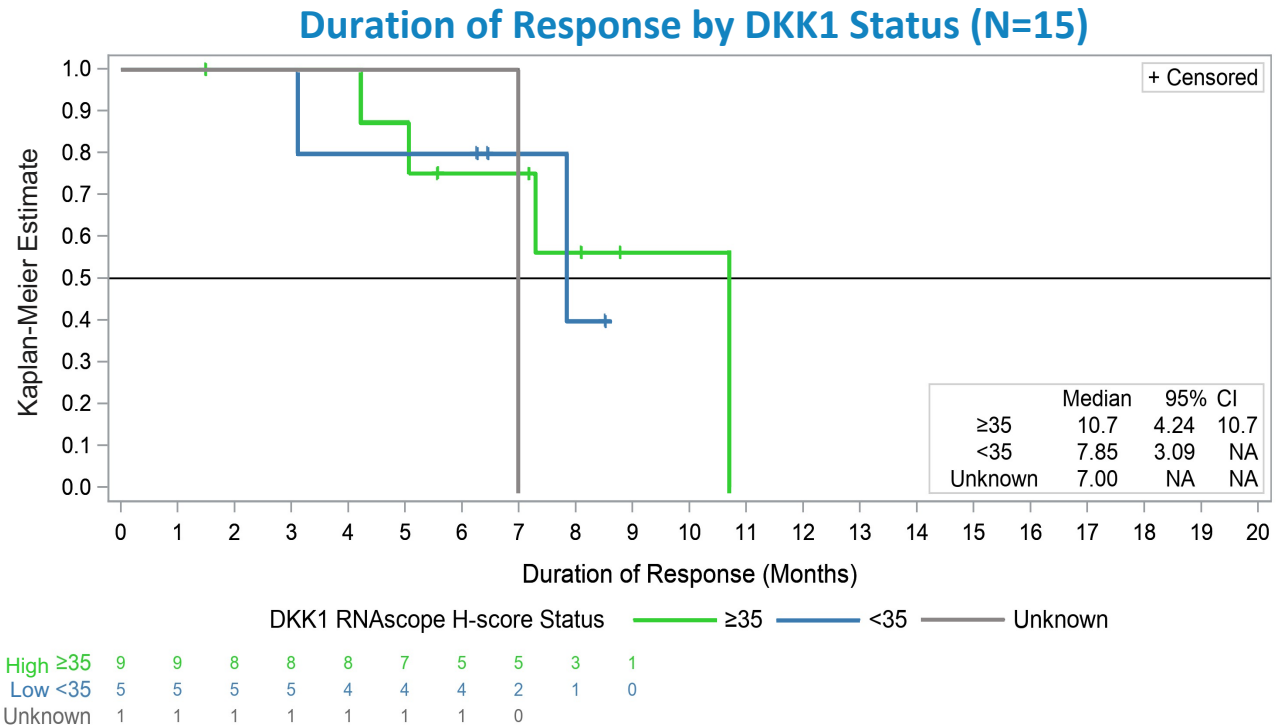
- Median PFS: 10.7 mo
- Median PFS for DKK1-high 11.9 mo vs DKK1-low 10.7 mo



Duration of Response (DoR) Longer in DKK1-high Patients

1L GEJ/GC – DKN-01 Plus Tislelizumab Plus Chemotherapy

- Median DoR 10.7 mo in DKK1-high patients compared with 7.9 mo in DKK1-low patients



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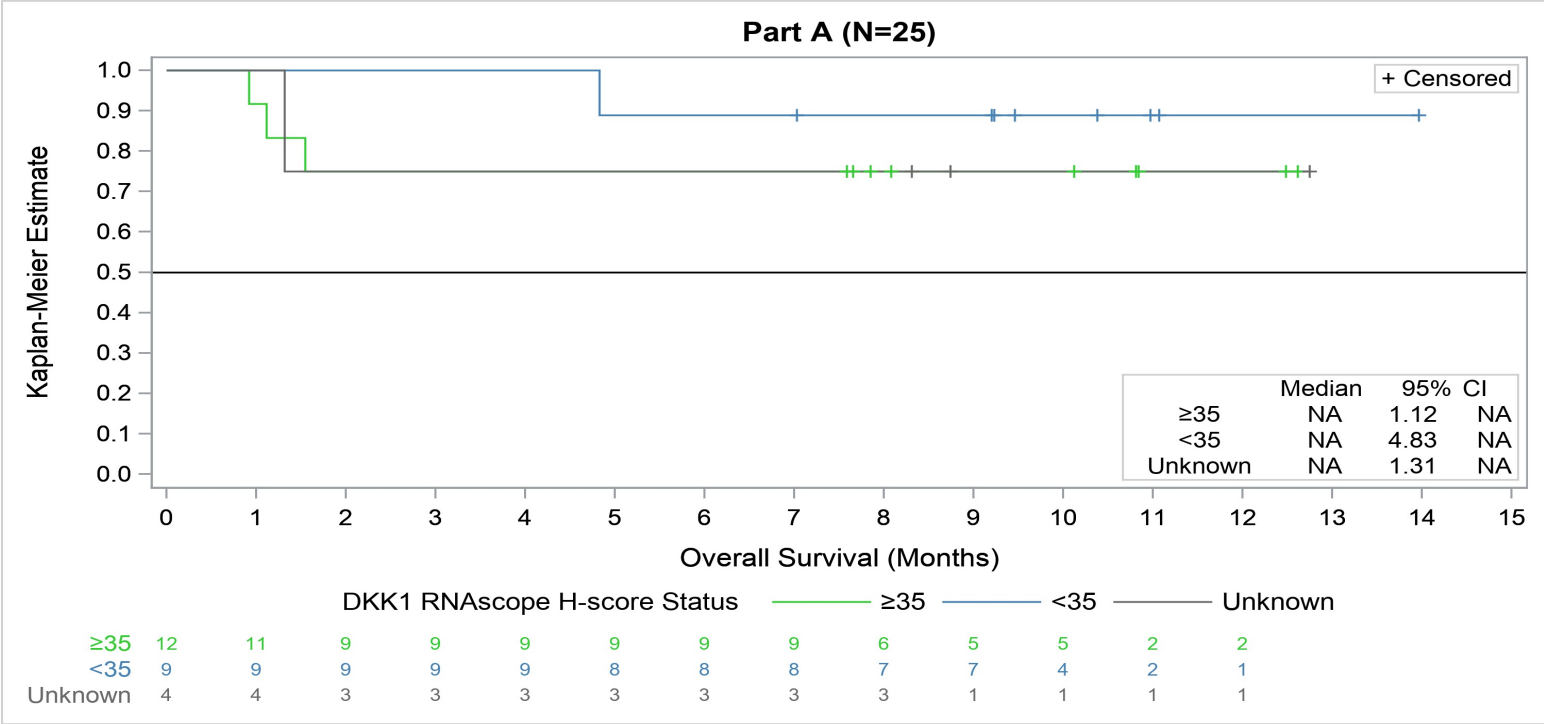
Overall Survival Not Reached

1L GEJ/GC – DKN-01 Plus Tislelizumab Plus Chemotherapy

Overall Survival by DKK1 Status (N=25)



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DKK1-high Patients Respond Regardless of PD-L1 Status

PD-L1-low expression (CPS < 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 (CPS ≥ 5, N=6)

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

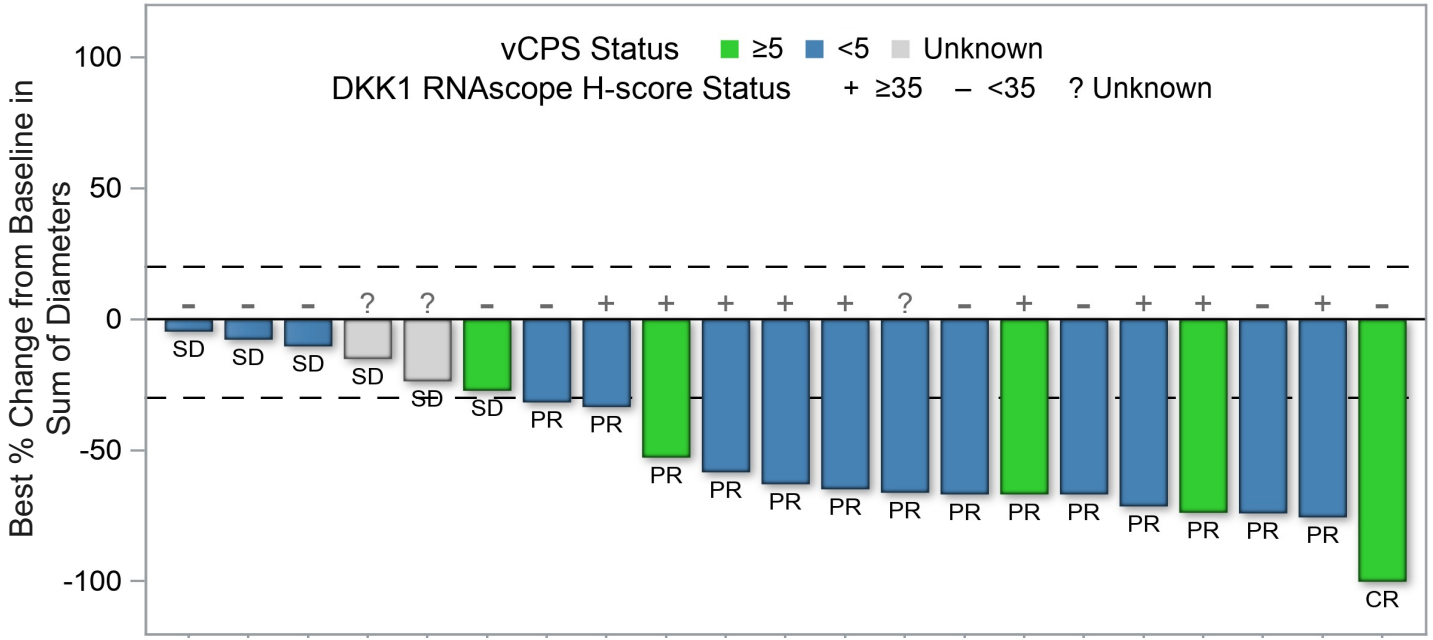
Best Overall Response, n (%)					
	Complete Response	Partial Response	Stable Disease	Progressive Disease	Non-Evaluable
PD-L1 CPS ≥5 (N=6)	1 (17)	3 (50)	1 (17)	—	1 (17)
DKK1-high (N=4)	—	3 (75)	—	—	1 (25)
DKK1-low (N=2)	1 (50)	—	1 (50)	—	—
PD-L1 CPS <5 (N=14)	—	11 (79)	3 (21)	—	—
DKK1-high (N=6)	—	6 (100)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

* Including one pathologic CR

Response Not Correlated to PD-L1 Expression

1L GEJ/GC – DKN-01 Plus Tislelizumab Plus Chemotherapy

Response by PD-L1 Status (N=21)



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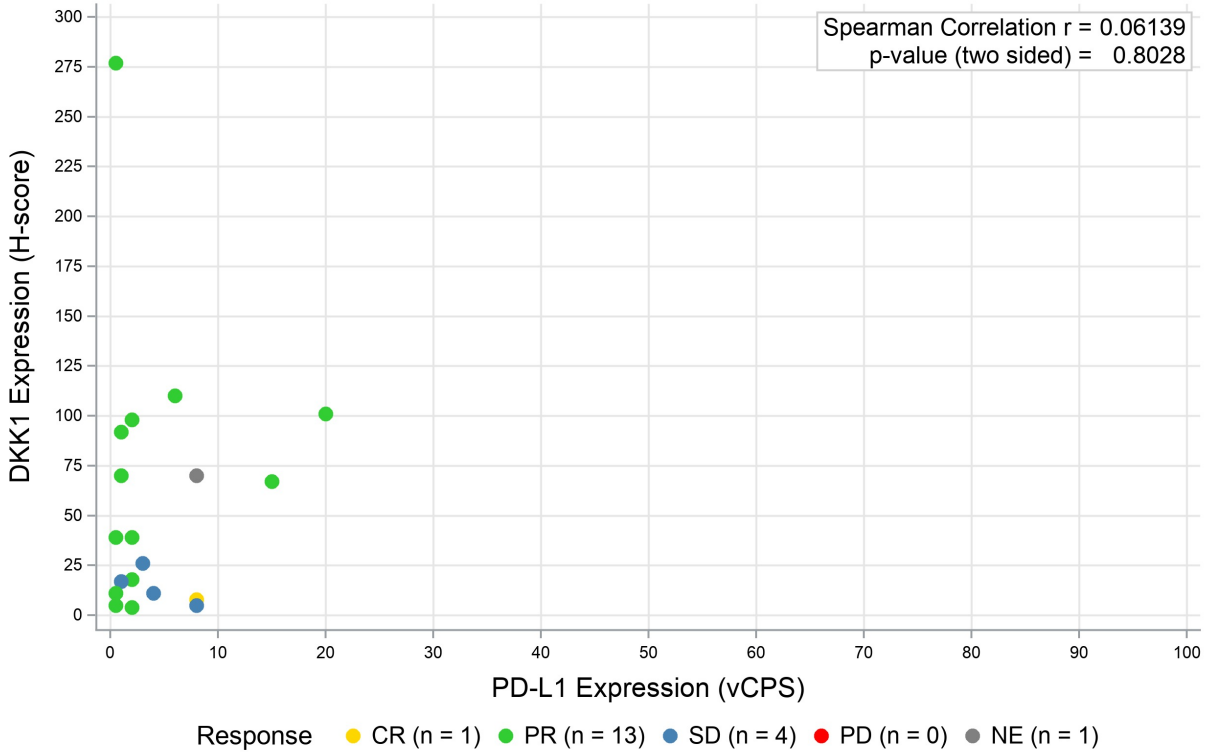
DKK1 and PD-L1 Expression Are Not Correlated in Treatment-naïve G/GEJ Adenocarcinoma

1L GEJ/GC – DKN-01 Plus Tislelizumab Plus Chemotherapy



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

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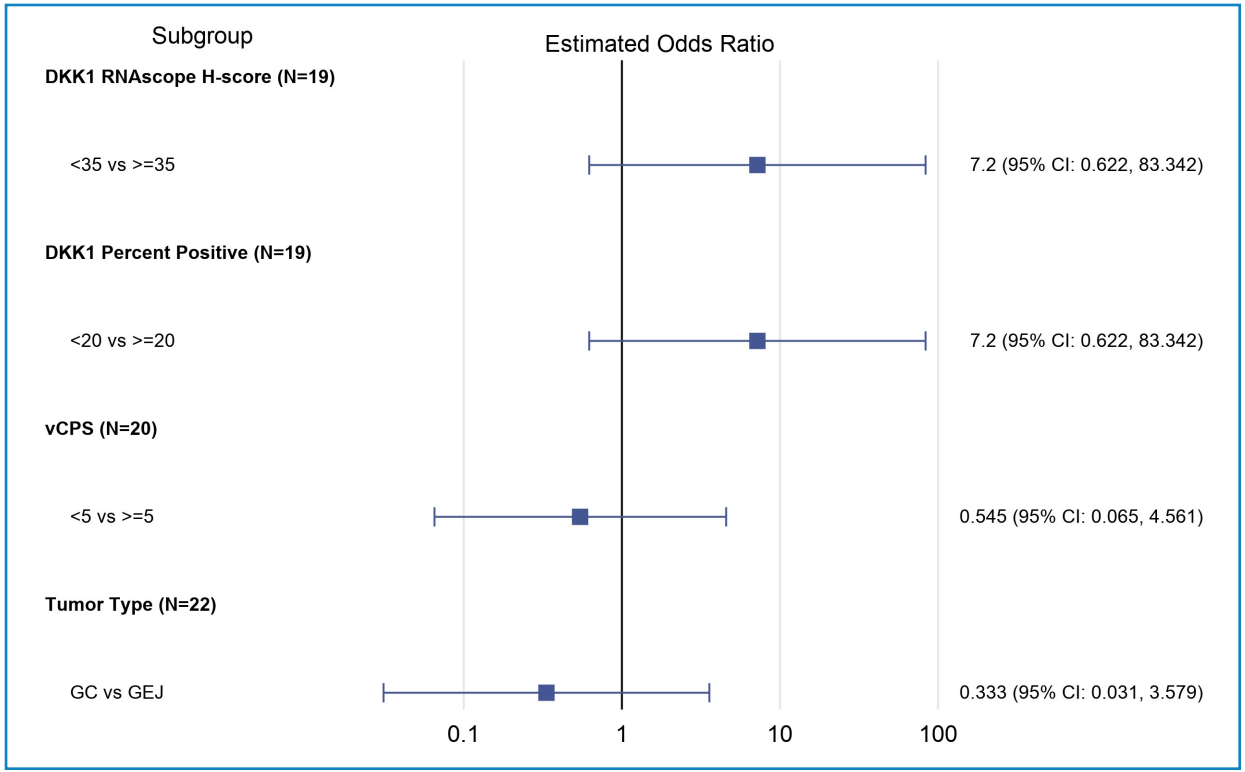
Response Correlated with Tumoral DKK1 Expression

1L GEJ/GC – DKN-01 Plus Tislelizumab Plus Chemotherapy

- Elevated tumoral DKK1 expression (H-score ≥35 or TPS ≥20) associated with better ORR in 1L G/GEJ
- ORR not correlated to PD-L1 CPS high (≥5)



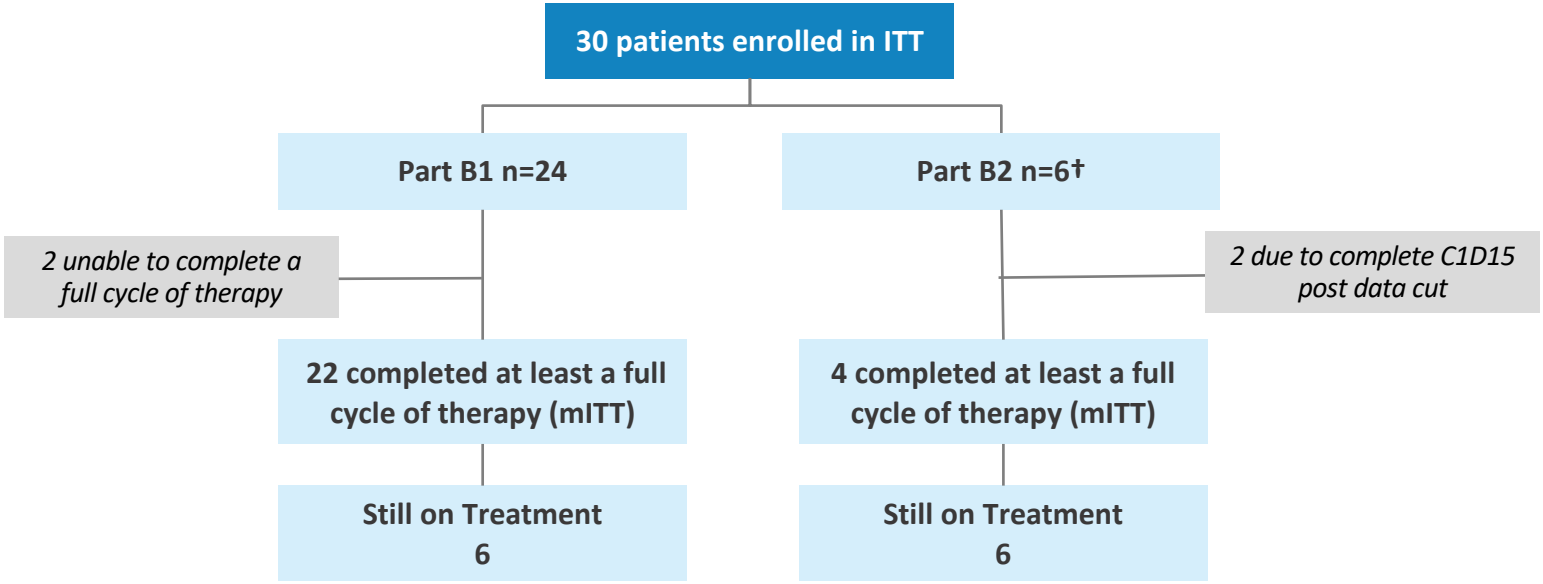
vCPS: Visually-Estimated Combined Positive Score; PD-L1: Programmed Death-Ligand 1; TPS: Tumor Percentage Score

First-line DKN-01 + Tislelizumab + CAPOX – Adverse Events Summary

- 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.

Preferred Terms	Part A (N=25) No. Patients (%)
TEAEs leading to death within 30 days of last dose	3 (12%)
Any adverse event	25 (100%)
Grade ≥ 3 events	14 (56%)
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	1 (4%)
Drug-related adverse events	
DKN-01-related	14 (56%)
Tislelizumab-related	17 (68%)
Capecitabine-related	24 (96%)
Oxaliplatin-related	25 (100%)
Regimen-related	25 (100%)

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

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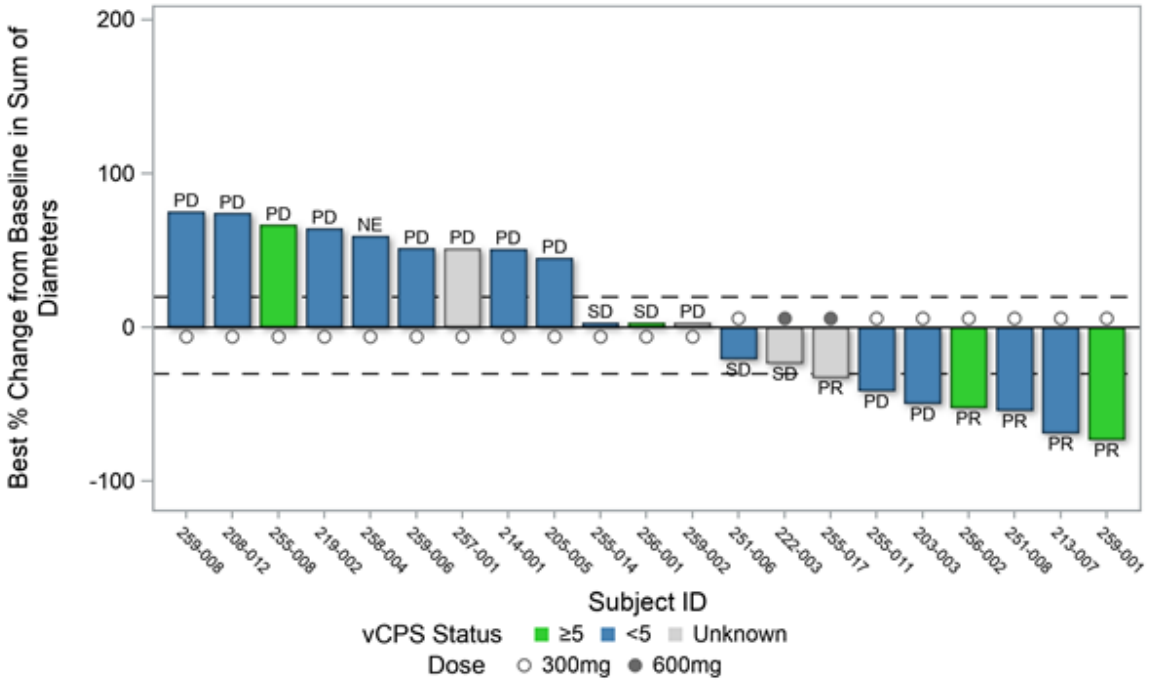
Objective Response Rate by PD-L1 Expression

2L DKK1-high GEJ/GC – DKN-01 Plus Tislelizumab

- Study continues to enroll
- 12 patients remain on therapy with 4 pending first imaging assessment post baseline
- ORR in evaluable mITT includes 5 PR (25%) and 1 irPR

Response by PD-L1 Status (mITT, N=20 evaluable)



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

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Objective Response Rate - Preliminary

2L DKK1-high GEJ/GC – DKN-01 Plus Tislelizumab

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 CPS ≥5 (N=5)	2 (40%)	1 (20%)	1 (20%)	1 (20%)
PD-L1 CPS <5 (N=15)	2 (13%)	2 (13%)	8 (53%)	3 (20%)
PD-L1 CPS unknown (N=6)	1 (17%)	1 (17%)	2 (33%)	2 (33%)

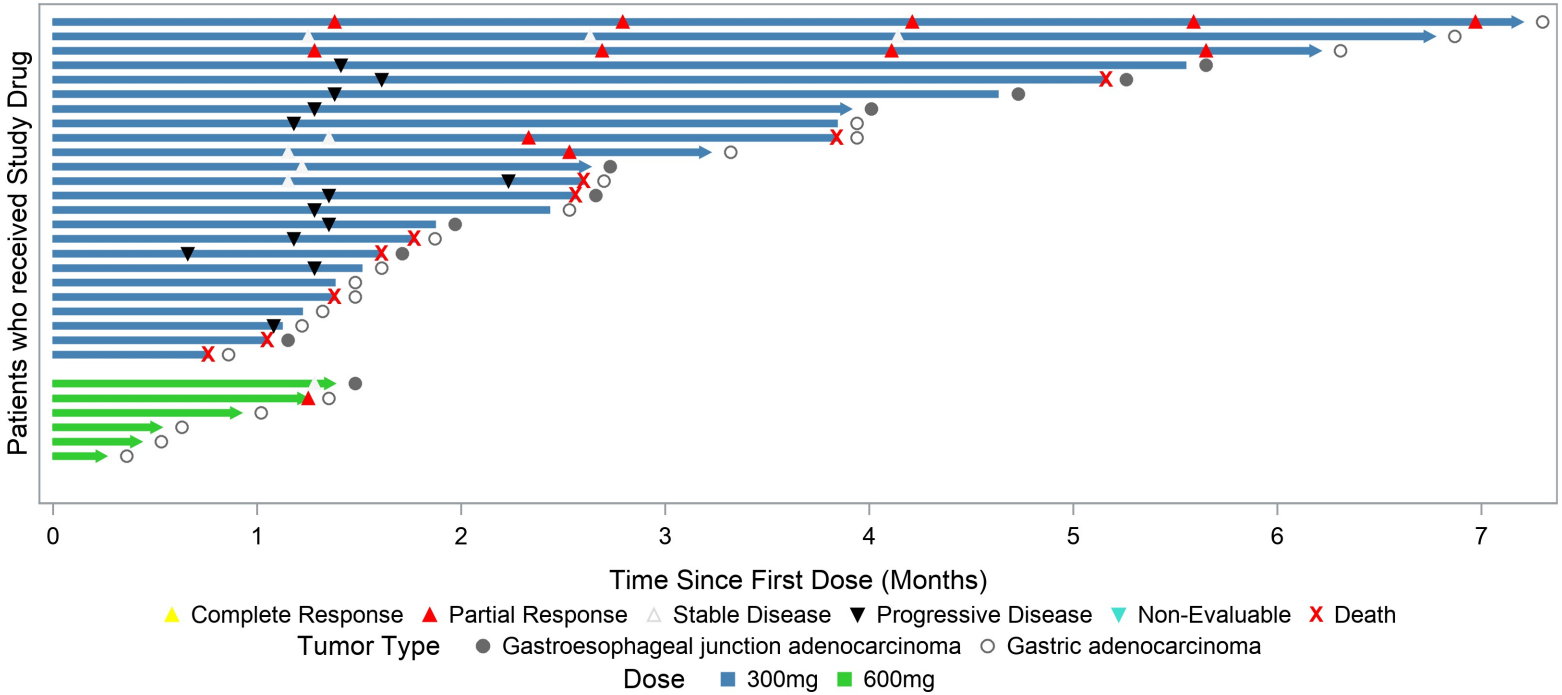
* 4 patients have not had their first post-treatment scan

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

Prolonged Clinical Benefit

2L DKK1-high GEJ/GC – DKN-01 Plus Tislelizumab

Duration of Clinical Benefit by DKN-01 Dose (N=30)



Each line represents one patient in the study
Right arrow cap indicates that the patient is still in treatment

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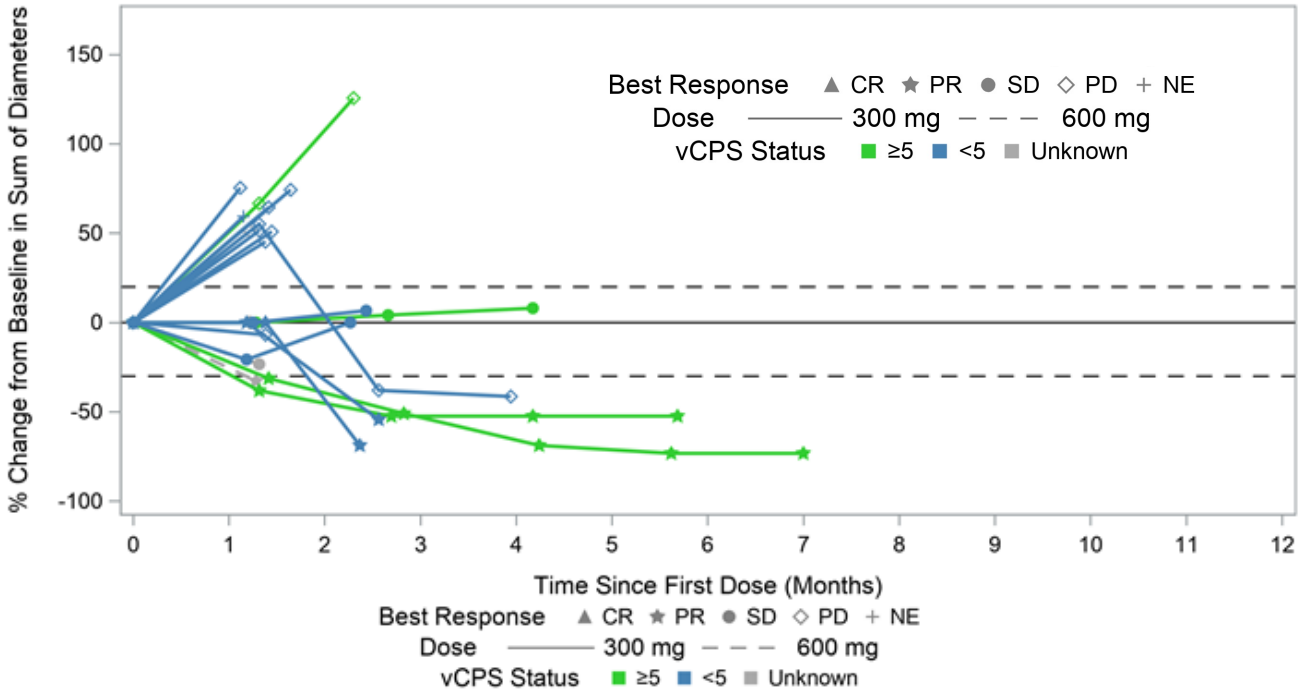
Durability of Clinical Benefit by PD-L1 Expression

2L DKK1-high GEJ/GC – DKN-01 Plus Tislelizumab

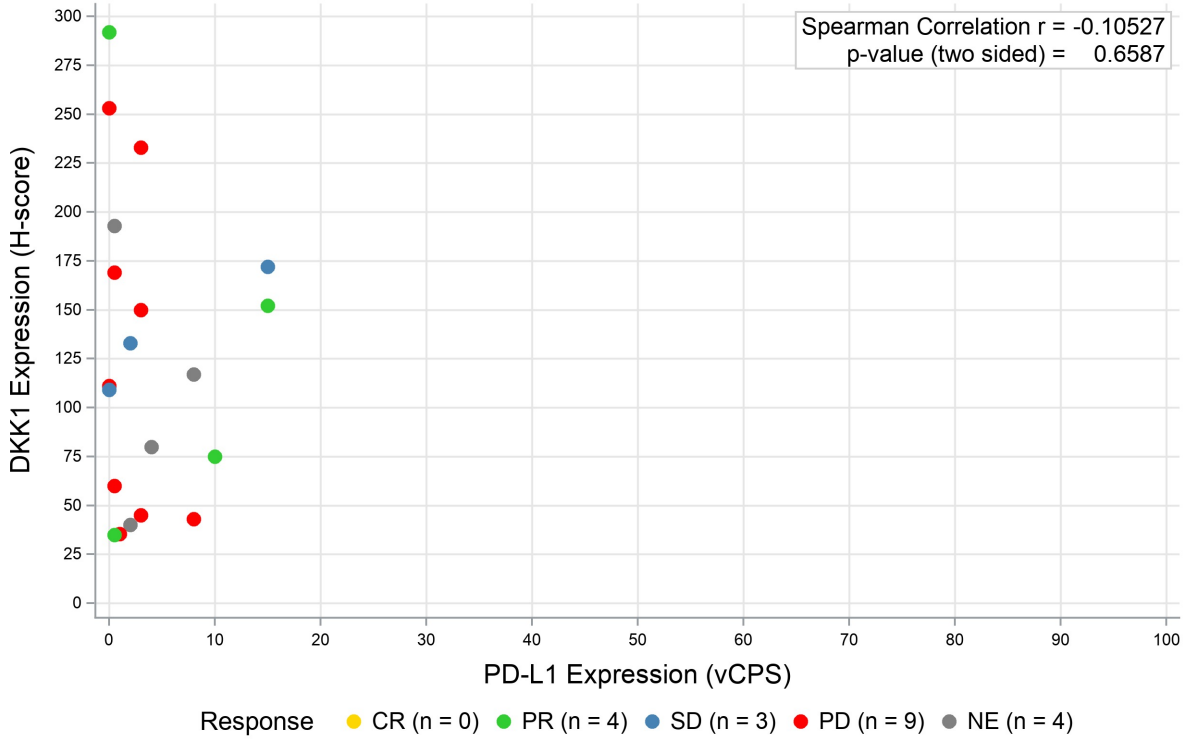
Response by PD-L1 Status (N=20 evaluable)



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

DKK1 and PD-L1 Expression Are Not Correlated in Second-line G/GEJ Adenocarcinoma

2L DKK1-high GEJ/GC – DKN-01 Plus Tislelizumab



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

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Second Line DKN-01 + Tislelizumab – Adverse Events Summary

2L DKK1-high GEJ/GC – DKN-01 Plus Tislelizumab

- 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

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

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

AGENDA

Introduction

Dr. Cynthia Sirard

Chief Medical Officer, Leap

Dr. Jason Baum

Vice President and Head of Translational Medicine, Leap

DisTinGuish Trial Preliminary Results

Dr. Samuel Klempner

Associate Professor at Harvard Medical School who leads the gastric and esophageal cancer program at Massachusetts General Hospital Cancer Center

Q&A