# Leap Therapeutics
# 17 September 2021

# 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.

# DKN-01 Highlights

- DKN-01 in combination with tislelizumab and chemotherapy has demonstrated compelling overall response rates (ORR) as a first line treatment for advanced G/GEJ cancer
  - 68.2% ORR; 90% ORR in DKK1-high patients vs 56% ORR in DKK1-low patients
- Response is correlated with DKK1 expression and independent of PD-L1 expression
  - 79% ORR in patients with PD-L1-low expression (CPS < 5)
  - 100% ORR in DKK1-high, PD-L1 low patients (CPS < 5)
- DKK1 represents an important new therapeutic target in gastroesophageal adenocarcinoma (GEA)
  - Elevated expression associated with aggressive biology, poor response to standard 5-FU therapy and shorter survival
  - 47% ORR in combination with paclitaxel in 2L+ therapy
  - 50% ORR in DKK1-high 2L+ GEA patients in combination with pembrolizumab*

*_Mol Cancer Ther_. 2021 Sep 4:molcanther.0273.2021. doi: 10.1158/1535-7163.MCT-21-0273. Epub ahead of print. PMID: 34482288.

# AGENDA

## Introduction

Dr. Cynthia Sirard

*Chief Medical Officer, Leap*

## DKK1 Biology and DKN-01 Mechanism of Action

Dr. Jaffer Ajani

*Professor, Department of Gastrointestinal (GI) Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX*

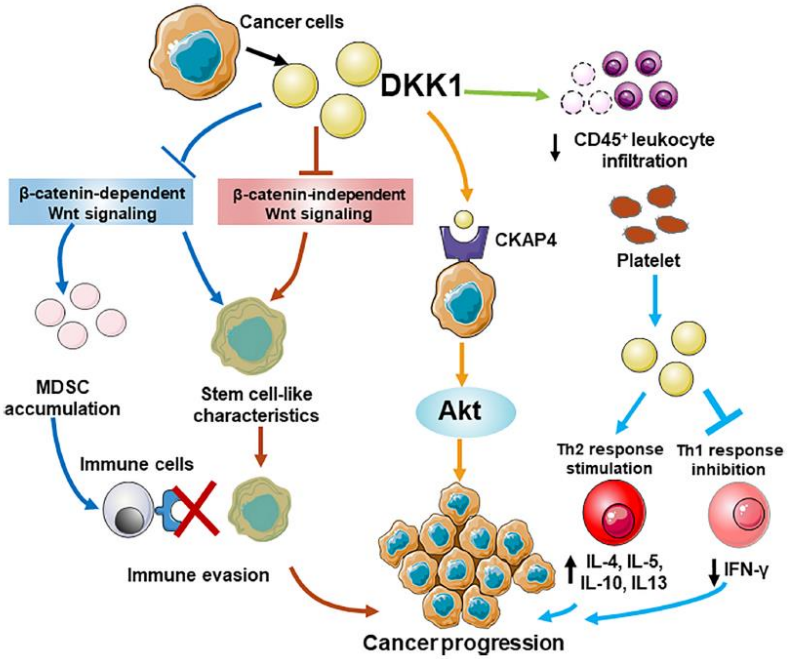
## DisTinGuish Trial Preliminary Results

Dr. Samuel Klempner

*Member of the Faculty at Massachusetts General Hospital and Harvard Medical School and leads the gastric and esophageal program*

## Q&A

# DKK1 is an Important Modulator of the Tumor Microenvironment and Critical Cell Signaling Pathways

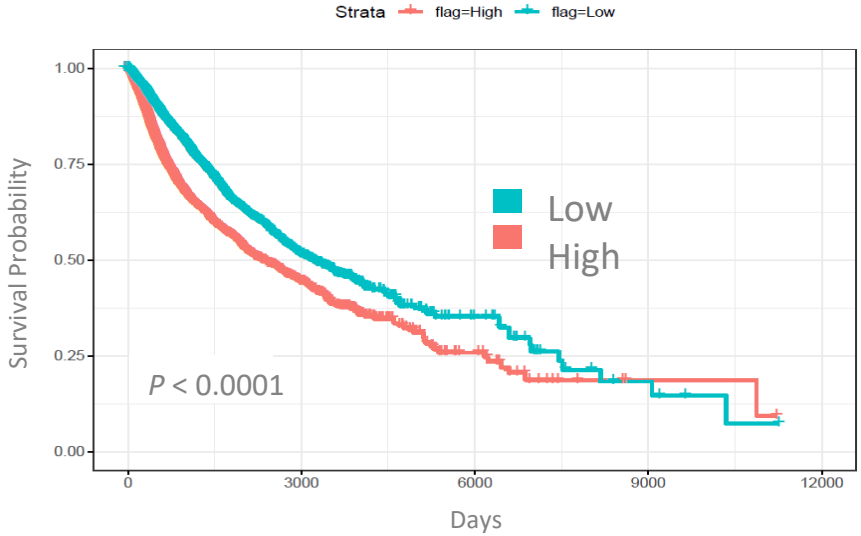



Chu et al, Frontiers in Immunology 2021

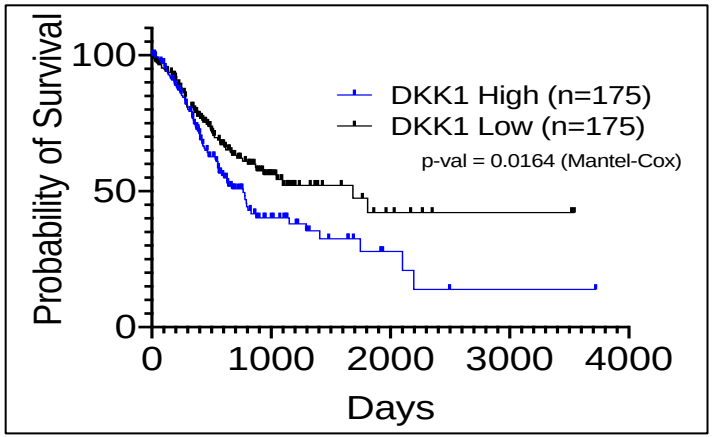
- Leads to the downregulation of NK Cell ligands and reduction of NK Cell anti-tumor activity
- Enhances activity of MDSCs which suppress the immune response against the tumor
- Activates PI3K/Akt signaling through the CKAP4 receptor on tumor cells, resulting in cancer cell survival and proliferation
- Increases angiogenesis through VEGFR2 signaling on tumor cells

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

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




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




~2.5 years shorter OS in DKK1-high patients



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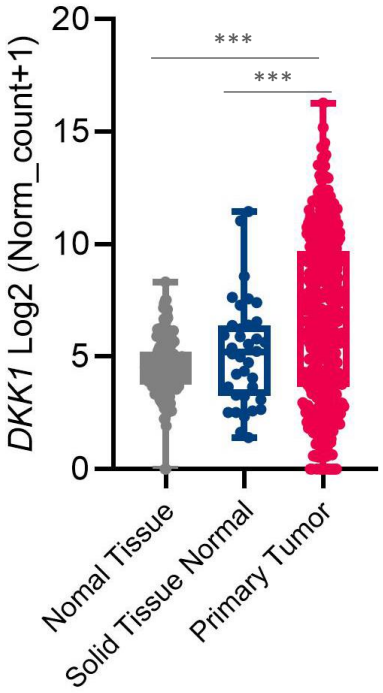
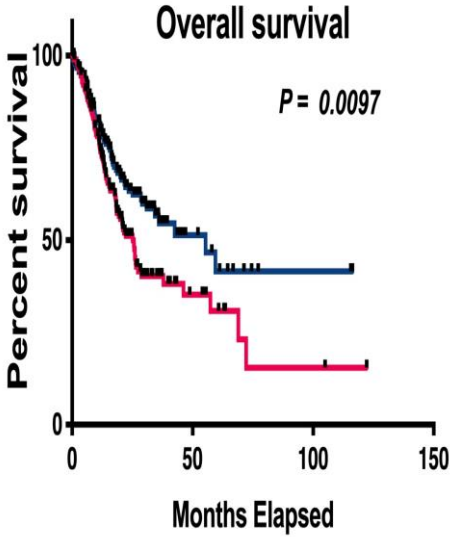
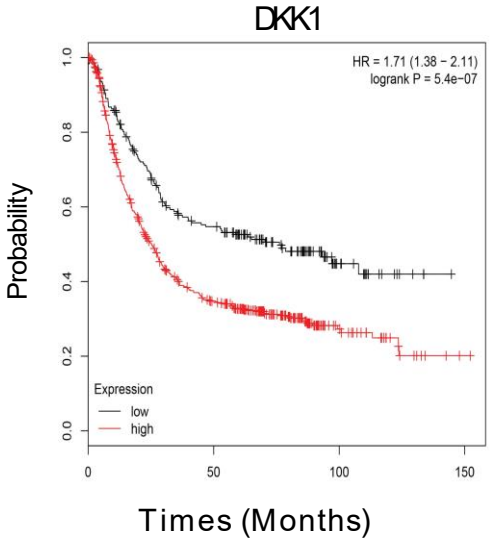
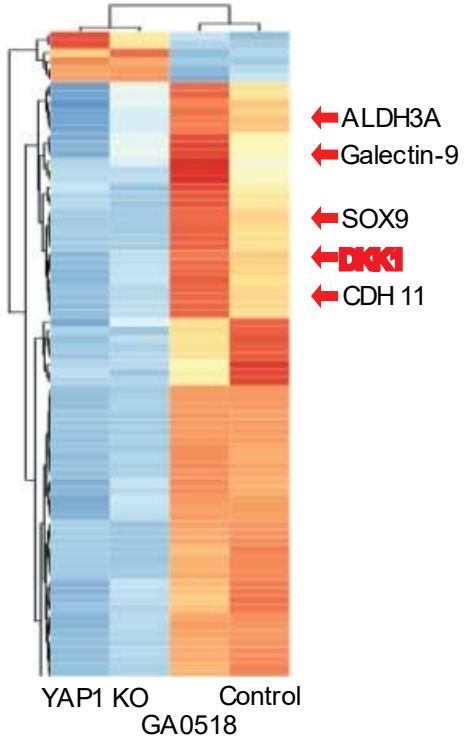
# DKK1 is Highly Expressed in Gastric Cancer and Associated with Poor Survival

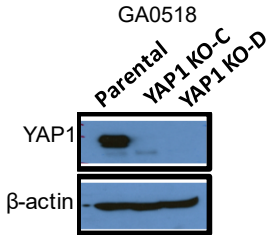


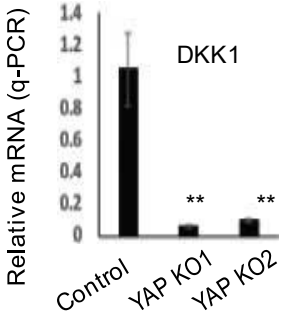



# RNAseq Revealed DKK1 is Potentially a Target of YAP1 and KO YAP1 Decreased DKK1 Expression and Transcription

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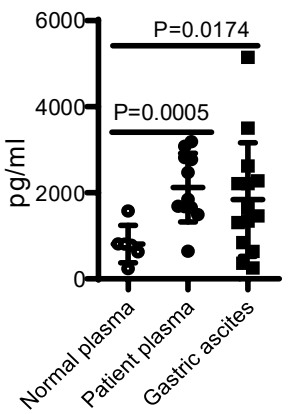


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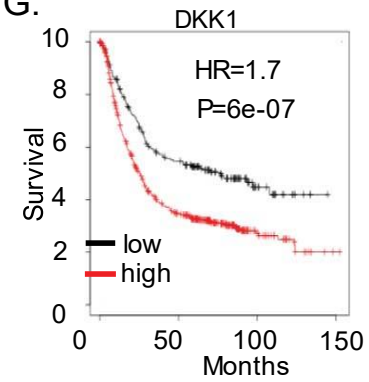


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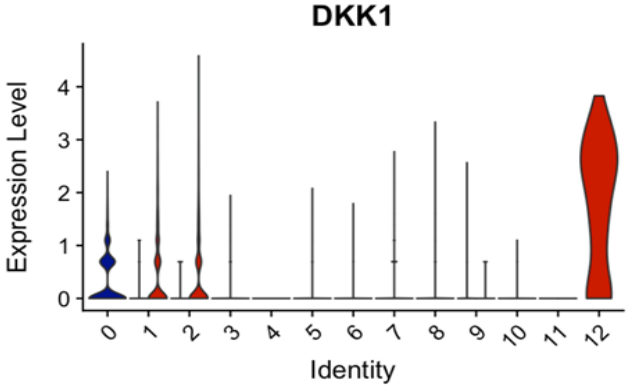
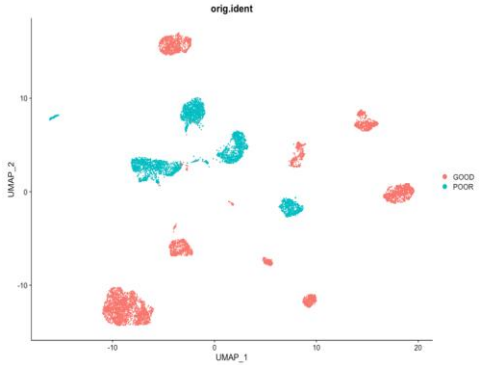
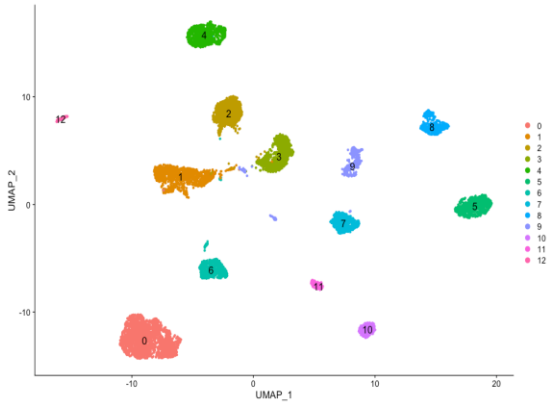
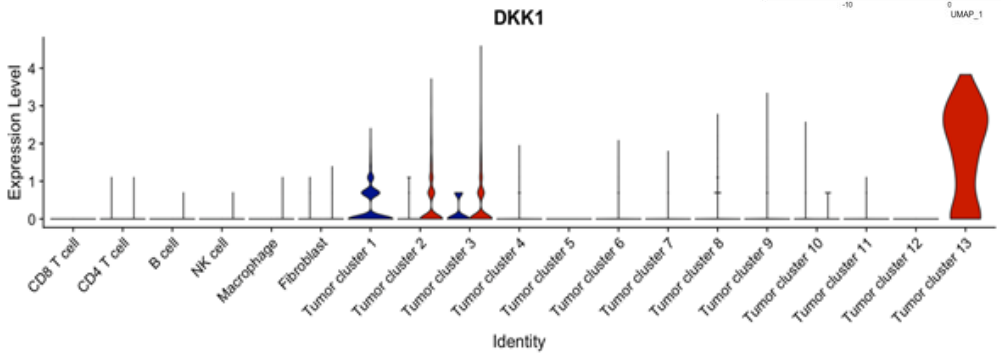
# DKK1 is Expressed in 13 Tumor Clusters by scRNAseq Associated with Poor Survival Tumor Cluster




Blue, good prognosis
Red, poor prognosis

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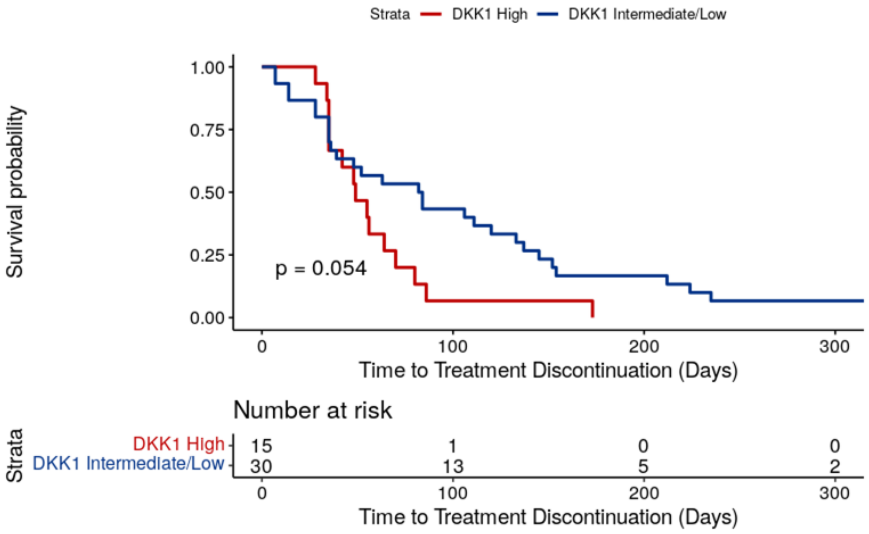
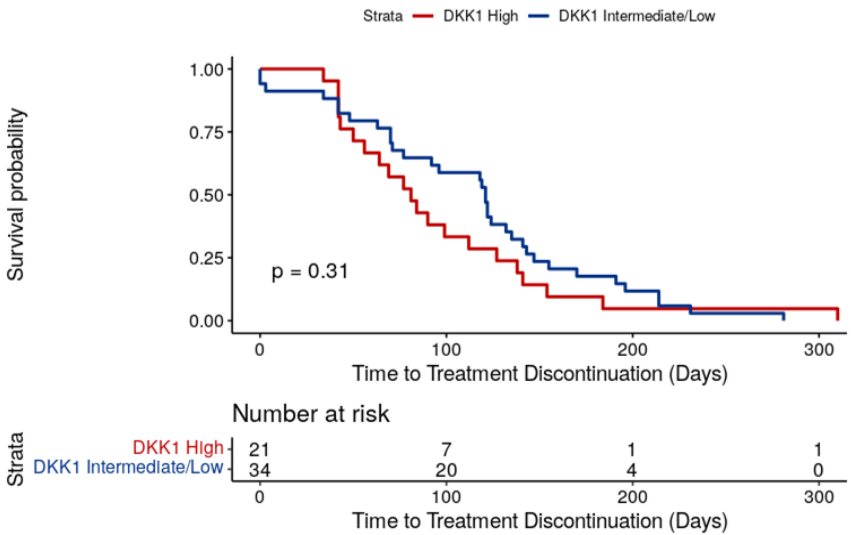
# Elevated DKK1 Is Associated with Poor Response to Standard Therapies in GEJ/Gastric Cancer Patients

## Paclitaxel-Based Regimens




## Platinum + Fluoropyrimidine-Based Regimens




- **High DKK1 is defined as the upper tertile of RNA expression**

Real World Evidence from DKK1-high patients demonstrates faster time to treatment discontinuation

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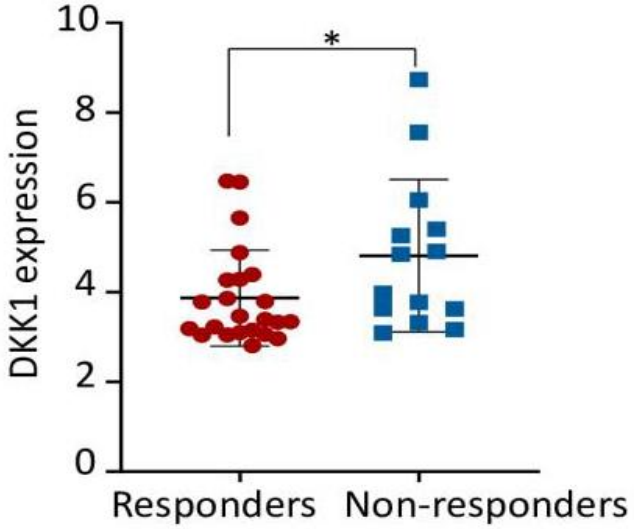
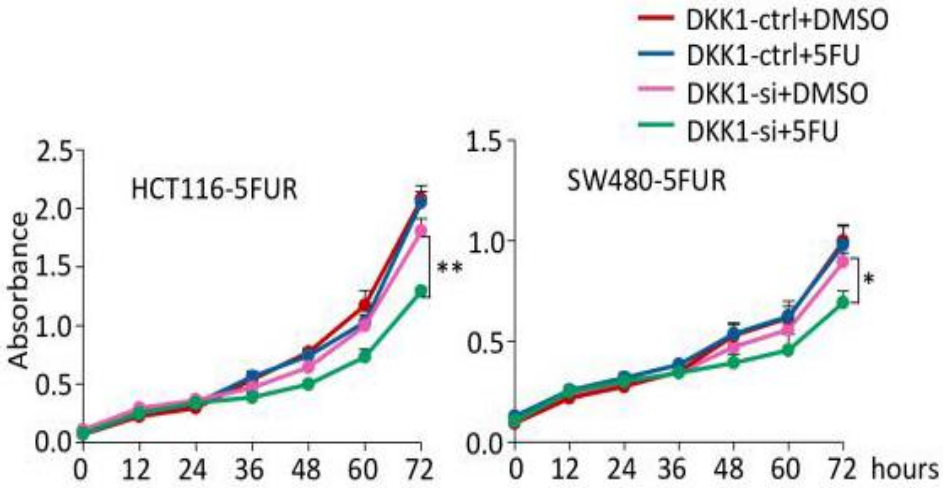
# High DKK1 Is Associated With Poor Response to 5FU

DKK1 was significantly up-regulated in tumors of CRC patients who did not respond to 5FU




Knockdown of DKK1 in CRC cancer cell lines restores 5FU growth inhibition




*Zhao et. al, Carcinogenesis 2021*



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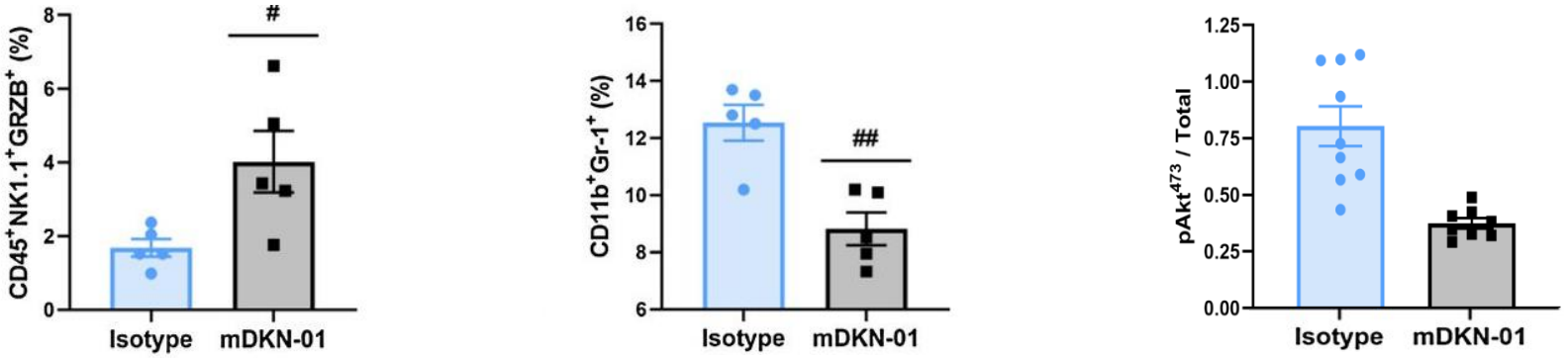
# DKN-01 Targets DKK1 to Enhance Anti-Tumor Immune Response and Modulate Tumor Cell Signaling




*Haas et al; 2021 Mol Cancer Res.: B16 melanoma model #, $P < 0.05$; ##, $P < 0.005$*

- Upregulation of NK Cell activity allows for targeting and clearing of tumor (left)
- Decreased MDSC infiltration in the tumor microenvironment (middle)
- Downregulation of Akt signaling decreases cancer cell survival and proliferation (right)



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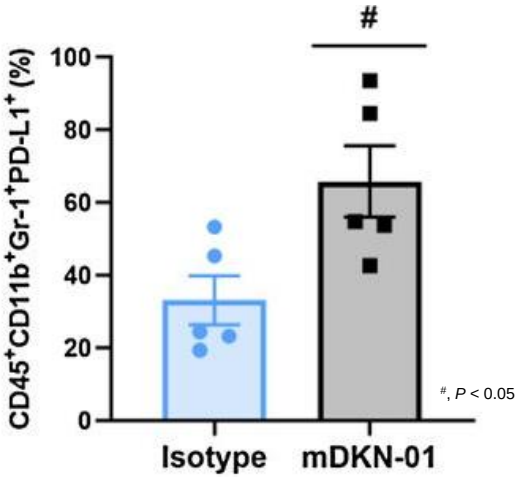
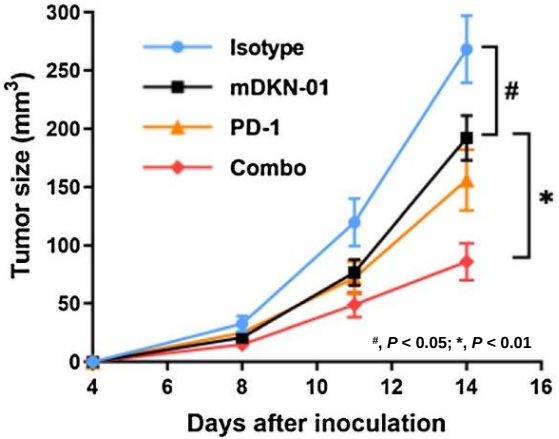
# Dual Blockade of DKK1 and PD-1 Results in an Enhanced Anti-Tumor Effect




*Haas et al; 2021 Mol Cancer Res.: B16 melanoma model*

- In addition to reversing the immunosuppressive tumor microenvironment, DKN-01 upregulates PD-L1 on myeloid cells (left) and increases IFNγ and HLA expression (not shown)

- These changes lead to enhanced tumor growth inhibition seen in combination with anti-PD-1



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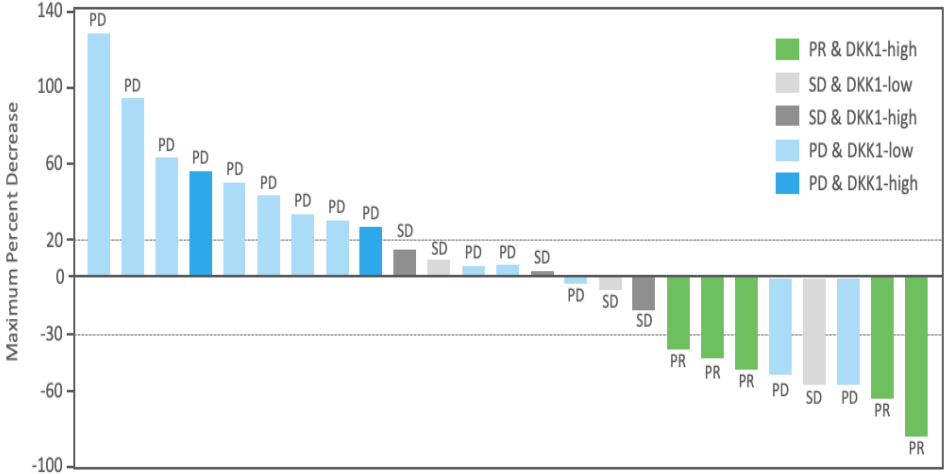
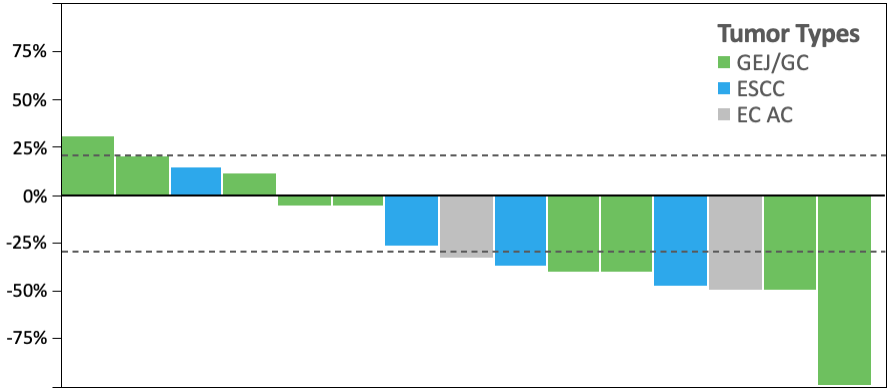
# DKN-01 Preclinical Conclusions

- Overexpression of DKK1 in many cancers is linked to worse prognosis and poor response to standard therapies
- DKK1 is secreted by tumor cells, leading to:
    - Cancer cell signaling, proliferation and angiogenesis through the CKAP4-AKT and VEGFR2 pathways
    - Impaired NK cell activity and enhancement of MDSC activity resulting in an immunosuppressive tumor microenvironment
- Preclinically, DKN-01 reverses the pro-tumorigenic microenvironment and inhibits oncogenic PI3K/AKT signaling
- DKN-01 increases PD-L1 expression and has additive activity with anti-PD-1 across multiple pre-clinical cancer models

# DisTinGuish Trial

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




| 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)

| 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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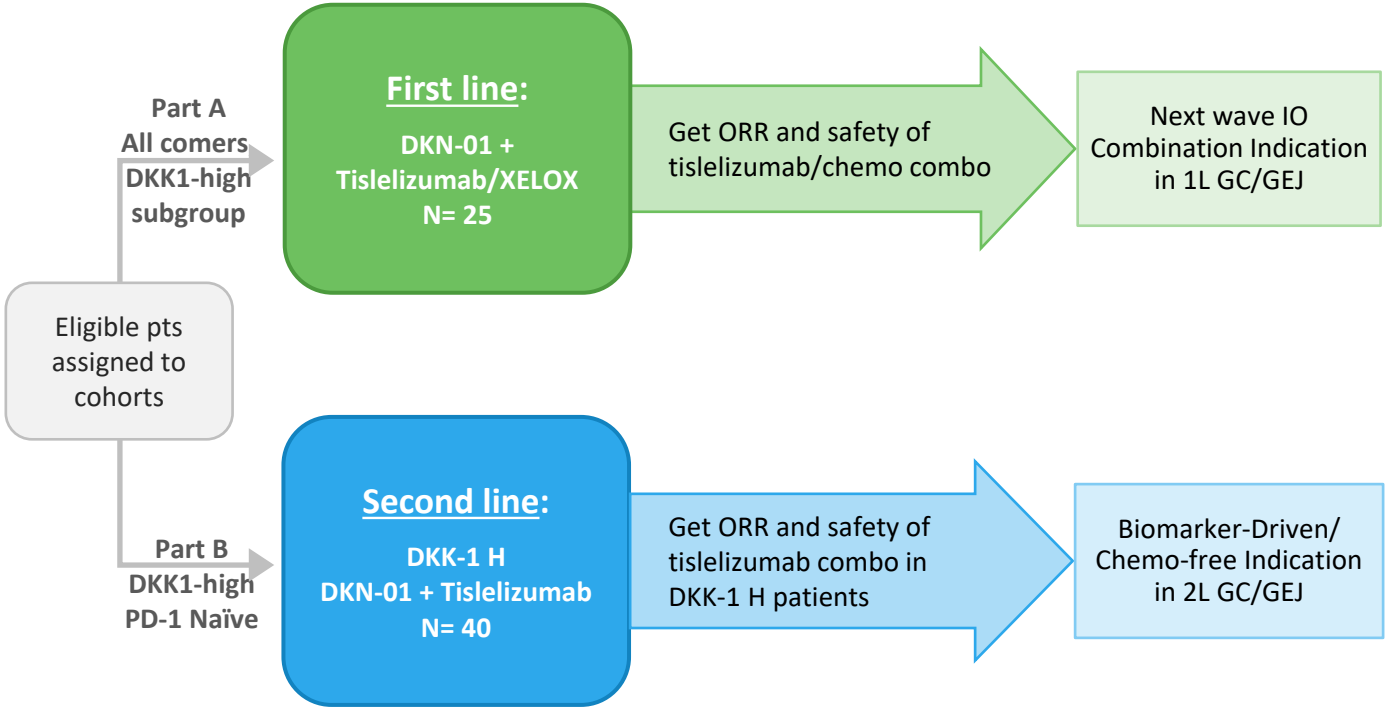
# Study Design in Patients with Advanced Gastric/GEJ Adenocarcinoma

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






BeiGene

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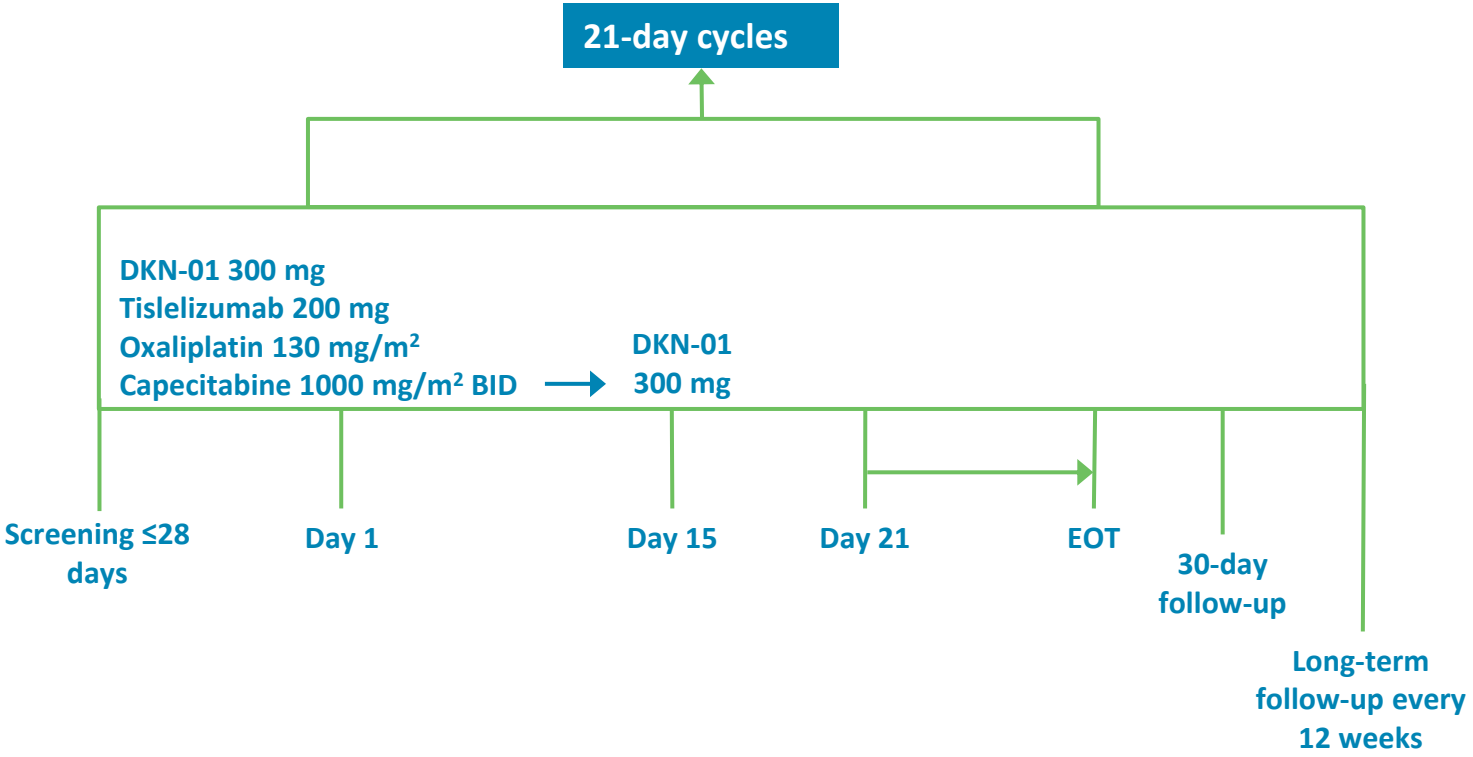
# DisTinGuish Trial Part A: First-line DKN-01 + Tislelizumab + CAPOX in Advanced GC/GEJ Adenocarcinoma



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# Study Methods

- **Design:** Phase 2a study of DKN-01 + tislelizumab + capecitabine/oxaliplatin (CAPOX) as first-line therapy for advanced GEJ/GC patients
- **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
- **Analysis by PD-L1 expression**: comparison between PD-L1 CPS (≥5 vs <5)

# Demographic and Clinical Characteristics

- 25 GEA patients were enrolled
  - 17 patients (68%) had GEJ
  - 8 patients (32%) had 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 Characteristics

- 22 patients (88%) had PD-L1 expression available
  - 5 patients (23%) were CPS <1
  - 16 patients (73%) were CPS <5
  - 2 patients (9%) were CPS ≥10
- 15 patients (60%) had TMB data available
  - 13 patients (87%) were < 10 mut/Mb
- 15 patients (60%) had microsatellite status available
  - All 15 patients (100%) were MSS

| | Overall N=25 | DKK1-high (H-score ≥35) N=12 | DKK1-low (H-score <35) N=9 | DKK1 Unknown N=4 |
|---|---|---|---|---|
| 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.
cTumor Mutation Burden and Microsatellite status was determined from plasma ctDNA using the FoundationOne Liquid CDx assay (Foundation Medicine, Cambridge, MA).

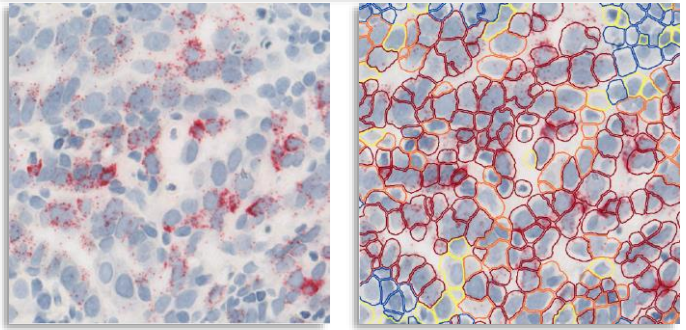
# Disposition and DKN-01 Exposure

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

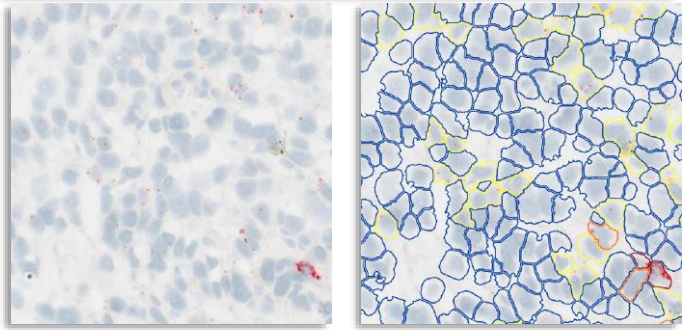
| | Overall N=25 |
|---|---|
| Number of cycles, median (min, max) | 7.0 (1.0, 14.0) |
| Duration on treatment (months), median (min, max) | 5.1 (0.8, 10.1) |
| Reasons for study drug discontinuation, n (%) | |
| Patient request to withdraw | 2 (8) |
| Objective disease progression | 3 (12) |
| Adverse 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 Expression Determined Using RNAscope and Digital Pathology

**DKK1-high Patient (H-score = 108)**



**DKK1-low Patient (H-score = 4)**



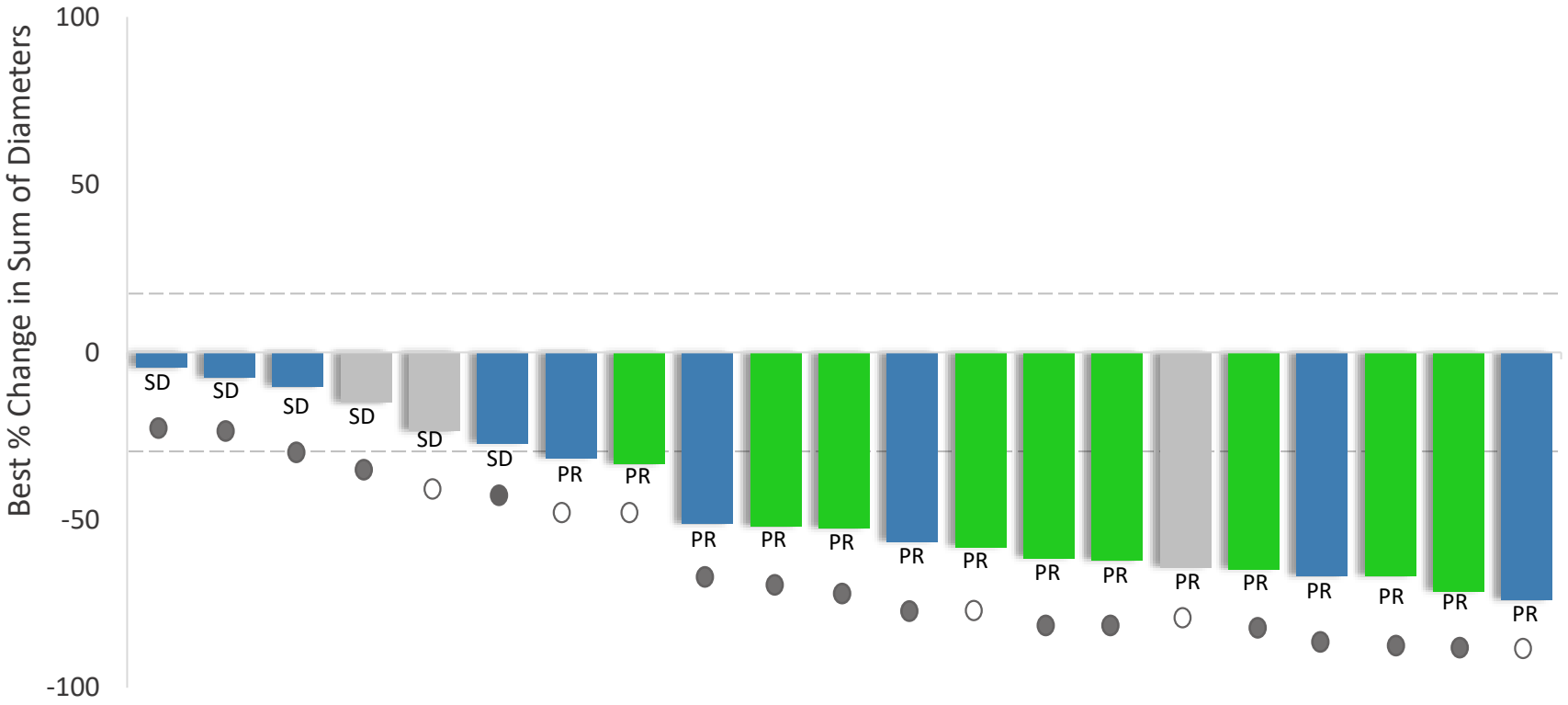
Tumor specimens were stained for DKK1 expression and quantified using a digital image analysis algorithm.[1]

- 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.



1. Flagship Biosciences (Broomfield, CO).

# Best Overall Response by DKK1 Expression



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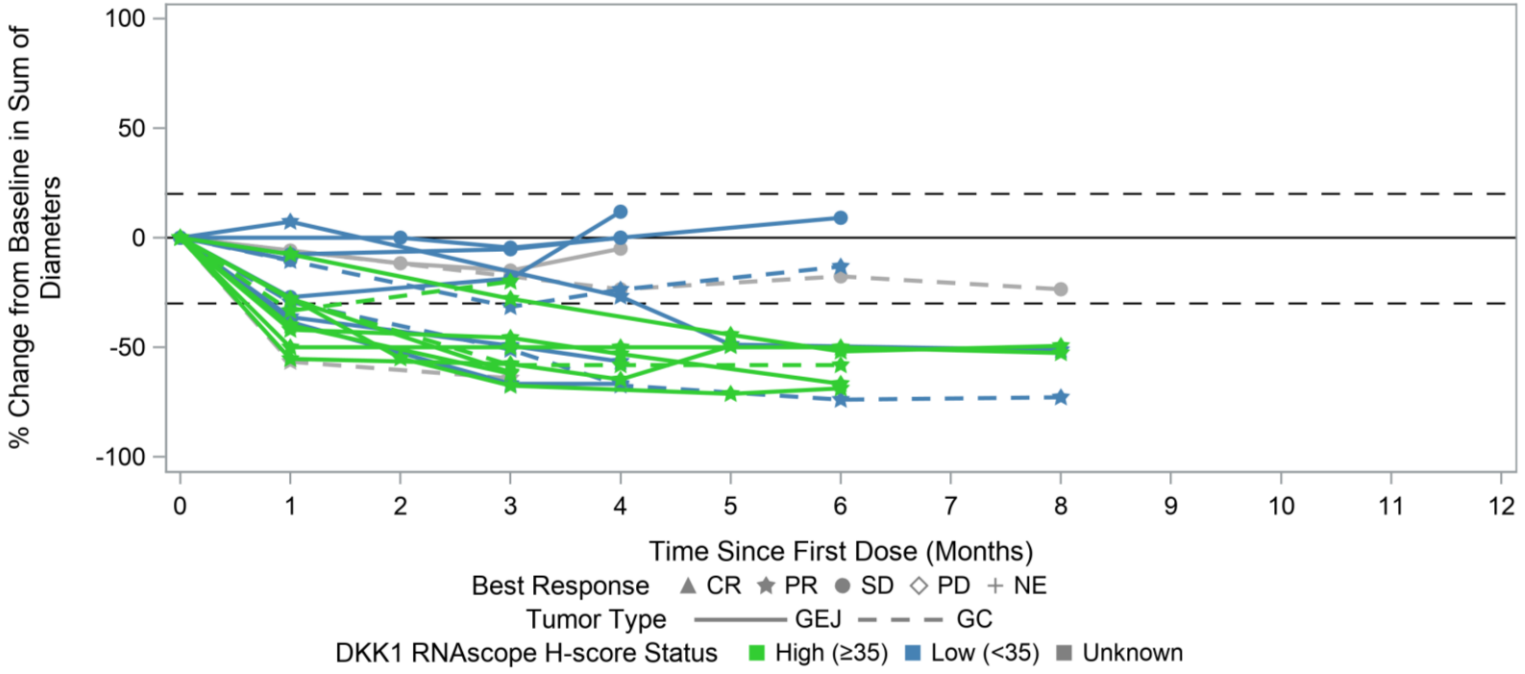
# All Evaluable DKK1-high GC/GEJ had Partial Response

- 90.0% of DKK1-high patients had PR; 7 of 9 responders still on therapy
- 55.6% of DKK1-low patients had PR; 4 of 5 responders still on therapy

| 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 |

# Durable Response by DKK1 Expression



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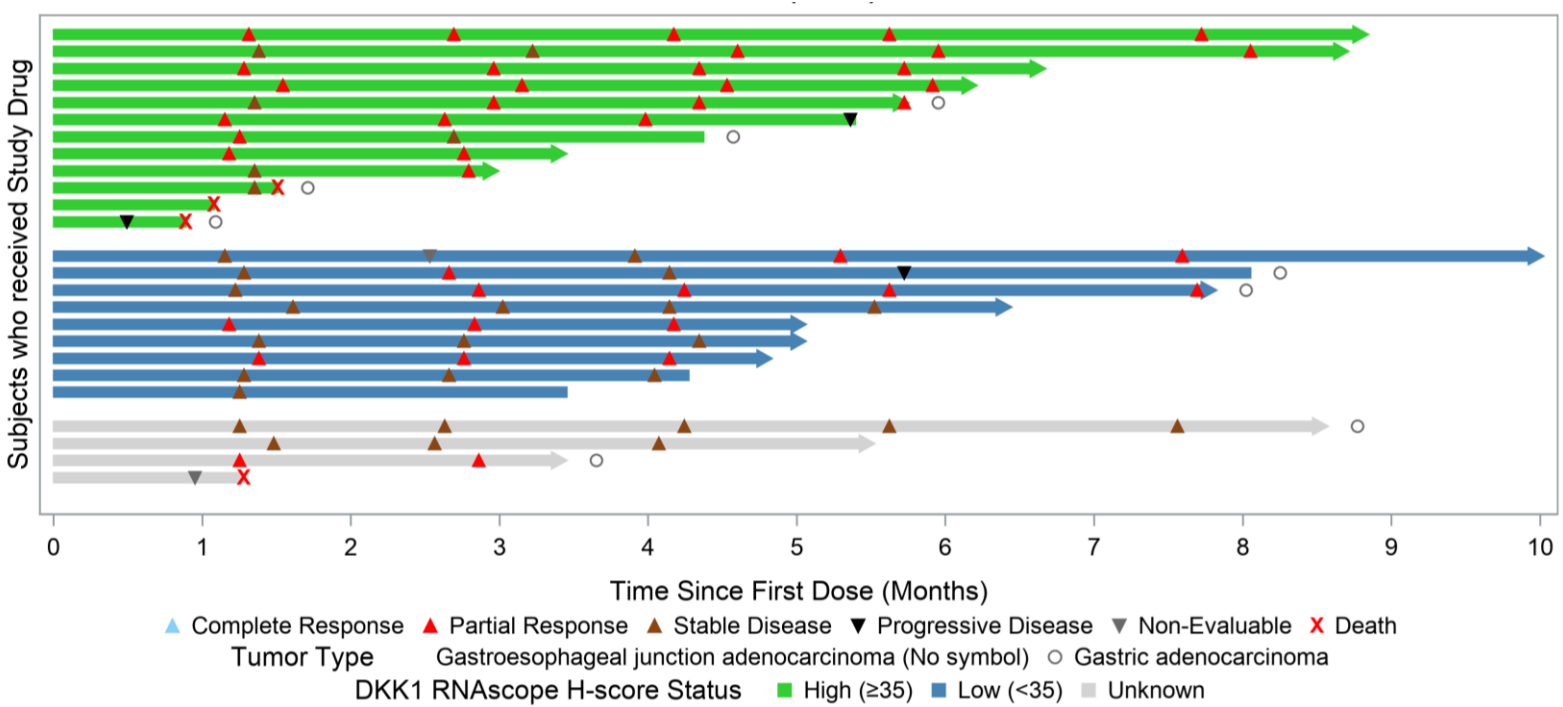
# Duration on Trial by DKK1 Expression




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



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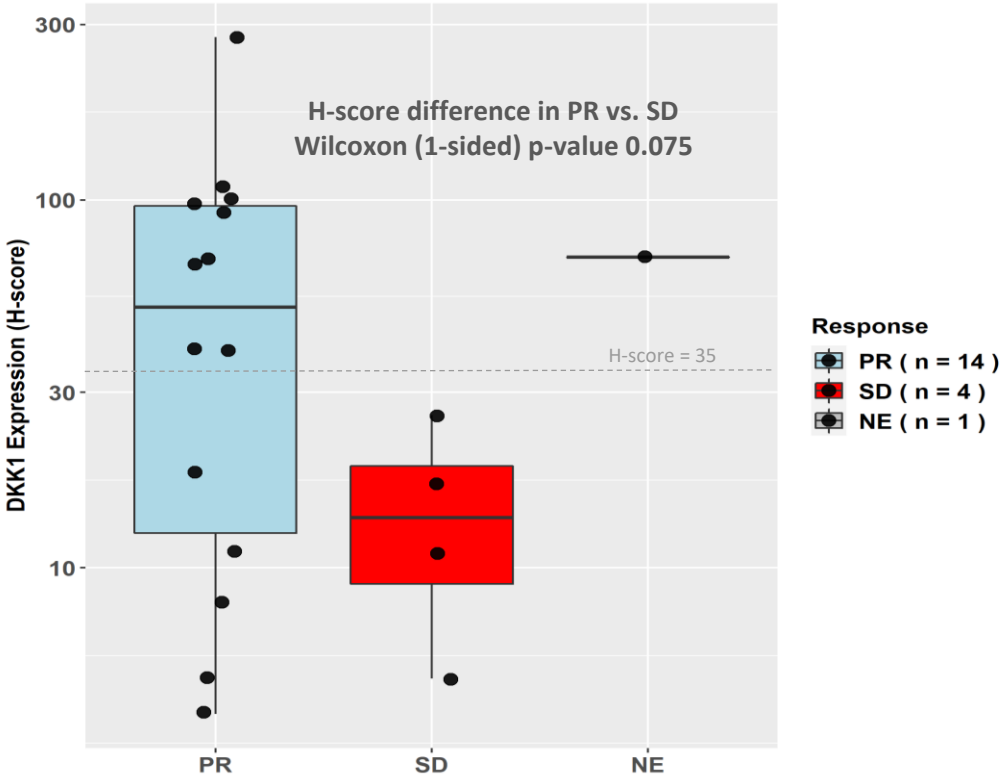
# Tumoral DKK1 Expression Predicts Response to DKN-01 Therapy



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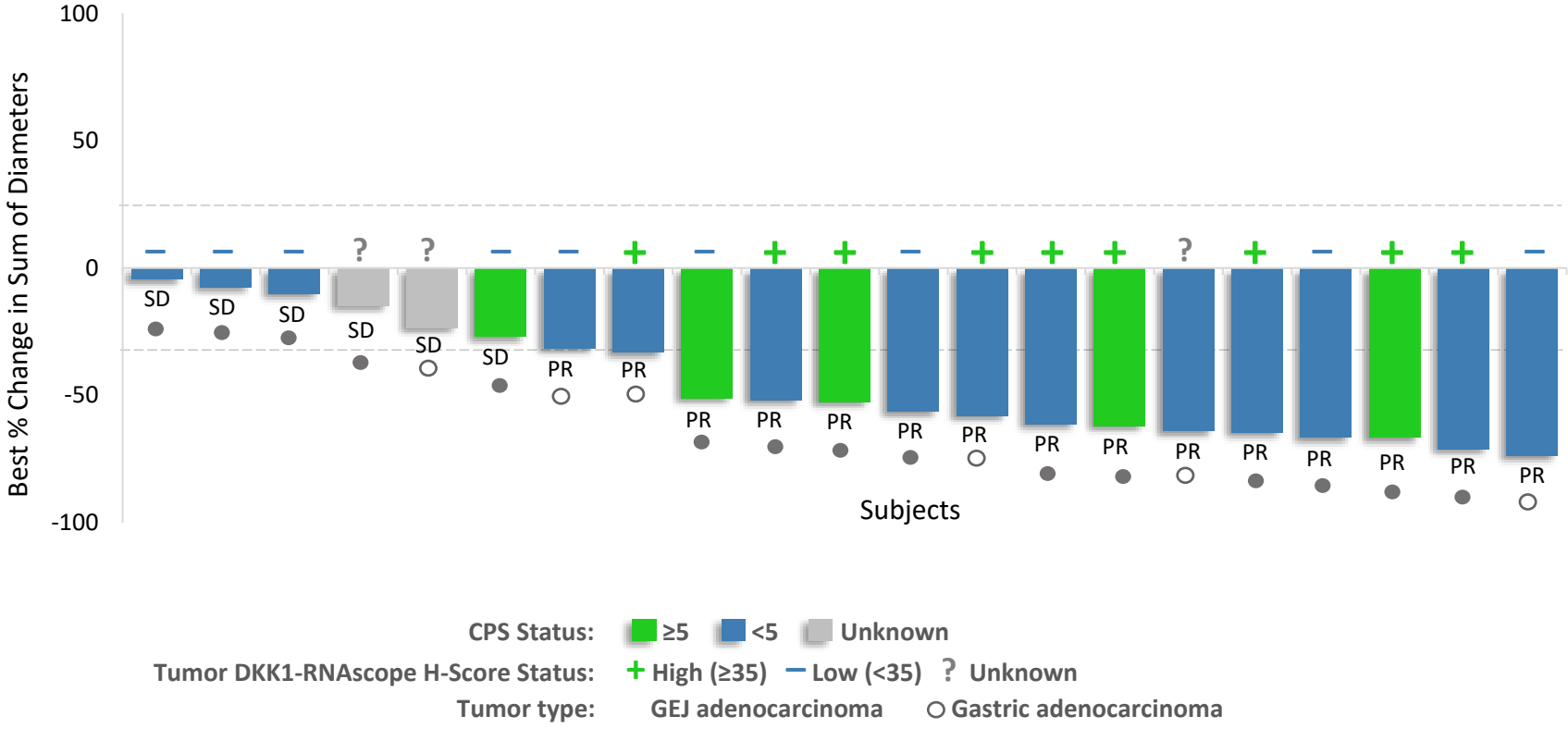
# Best Overall Response by PD-L1 and DKK1 Expression



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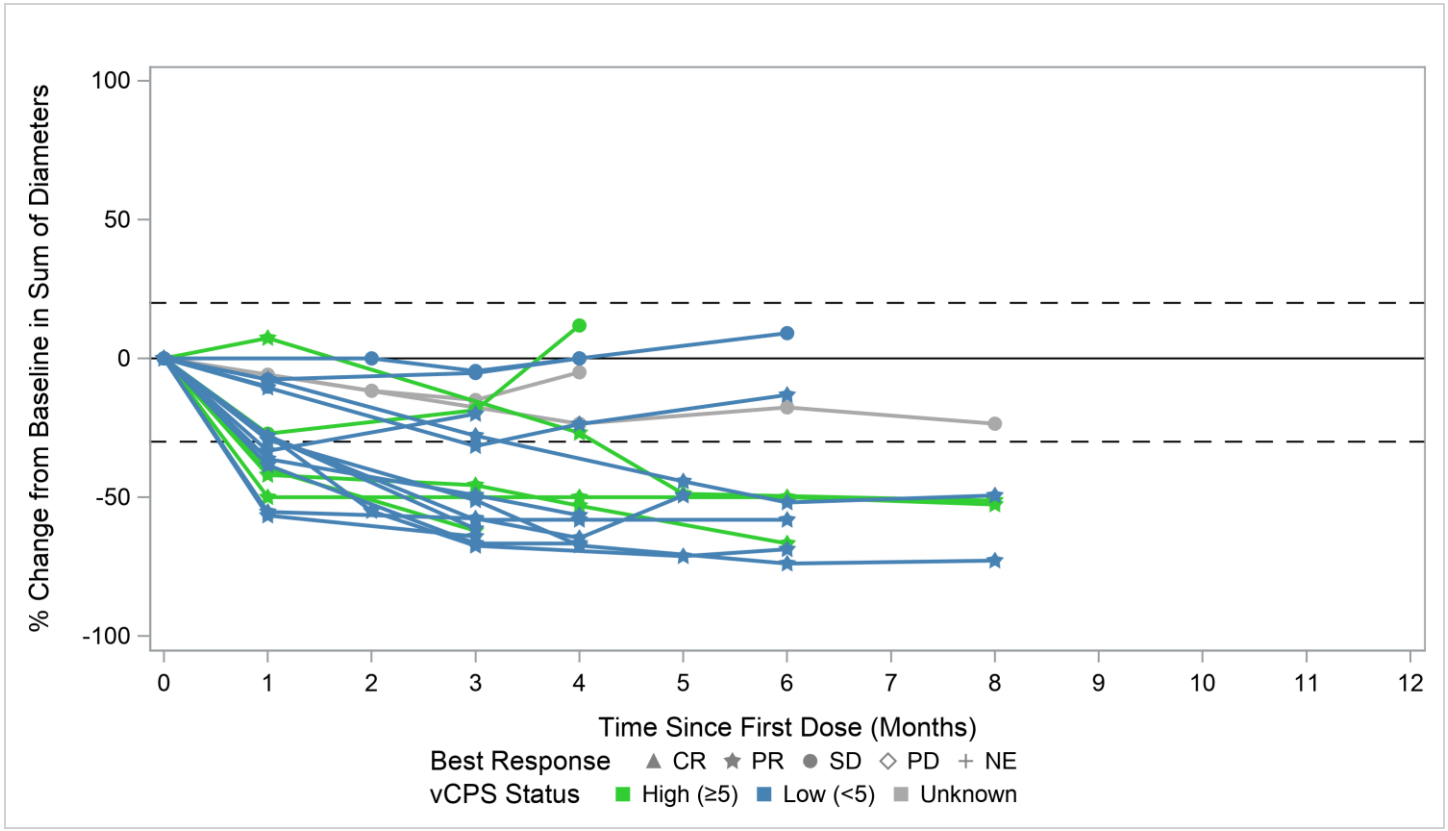
# DKK1 High Patients Respond Regardless of PD-L1 Status

- 79% ORR in patients with PD-L1-low expression (CPS < 5)
  - ***100% ORR in DKK1-high, PD-L1 low patients***
- 67% ORR in patients with PD-L1 high expression (CPS ≥ 5)
  - 75% ORR in DKK1-high, PD-L1 high patients

| 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 |

# Durable Response Independent of PD-L1 Expression



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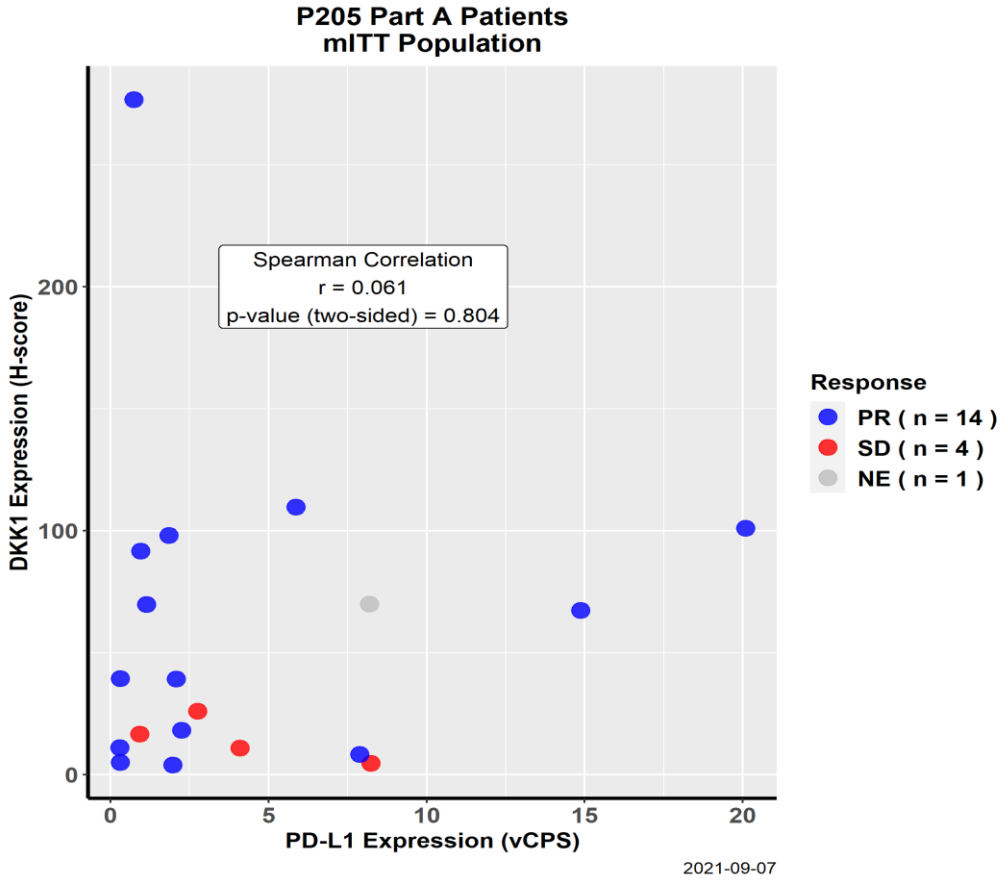
# DKK1 and PD-L1 Expression are not Correlated




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



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# Adverse Events Summary

- 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)

| | Part A Patients N=25 | |
|---|---|---|
| **Preferred Terms** | **No. Patients** | **%** |
| **Deaths 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% |

# PD-1 Antibodies + Chemo in First-Line HER2- GEJ/Gastric Cancer Patients

| | Nivolumab FDA Label[1] Checkmate-649 | | | Nivolumab Lancet Publication[2] Checkmate-649 | | | Tislelizumab | Pembrolizumab Keynote-062 |
|---|---|---|---|---|---|---|---|---|
| | All | CPS ≥ 5 | CPS < 5 | All | CPS ≥ 5 | CPS < 5 | All | CPS ≥ 1 |
| **N** | 789 | 473 | 308 | 603 | 378 | 225 | 15 | 251 |
| **ORR (%) (95% CI)** | 47 (43, 50) | 50 (46, 55) | NR | 58 (54, 62) | 60 (55, 65) | 55 (NR, NR) | 46.7 (21.3, 73.4) | 48.6 (42.4, 54.9) |
| **DOR months (95% CI)** | 8.5 (7.2, 9.9) | 9.5 (8.1, 11.9) | NR | NR | NR | NR | NR | 6.8 (5.5, 8.3) |
| **PFS months (95% CI)** | 7.7 (7.1, 8.5) | 7.7 (7.0, 9.2) | 7.5 (NR, NR) | * | * | * | 6.11 (3.8, NE) | 6.9 (5.7, 7.3) |
| **OS months (95% CI)** | 13.8 (12.6, 14.6) | 14.4 (13.1, 16.2) | 12.4 (NR, NR) | * | * | * | NR | 12.5 (10.8, 13.9) |

*Same as FDA label
NR- not reported

[1]*https://packageinserts.bms.com/pi/pi_opdivo.pdf*
[2]*Lancet: DOI: https://doi.org/10.1016/S0140-6736(21)00797-2*



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# Conclusions

- DKN-01 + tislelizumab + CAPOX was well tolerated and has encouraging response rates as first-line treatment for advanced GC/GEJ
- 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
  - 57% of first-line patients were DKK1 high
- Duration of response and progression-free survival data are not yet mature, expected in first half of 2022