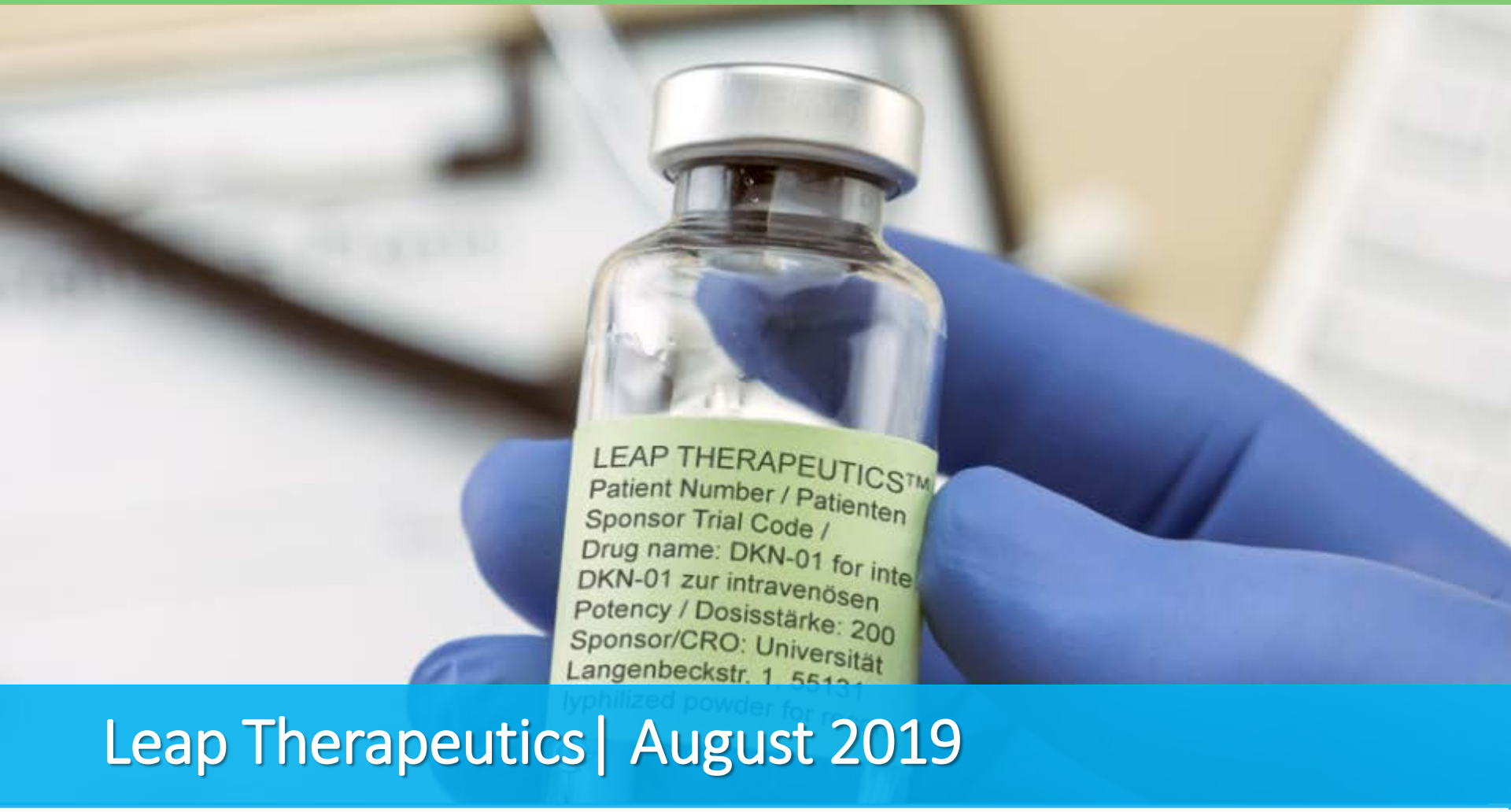


Leap Therapeutics| August 2019

DKN-01 Program Update

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, VP, Clinical Research & Development, Leap

DKK1 Biology and Preclinical Studies
Dr. Walter Newman, VP, Research, Leap

Esophagogastric Cancer
Dr. Samuel Klempner
Assistant Professor, Massachusetts General Hospital Cancer Center and Harvard Medical School

Gynecologic Cancers
Dr. Rebecca Arend
Assistant Professor and Associate Scientist, Gynecologic Oncology Clinic, UAB Comprehensive Cancer Center Experimental Therapeutics Program

Q&A

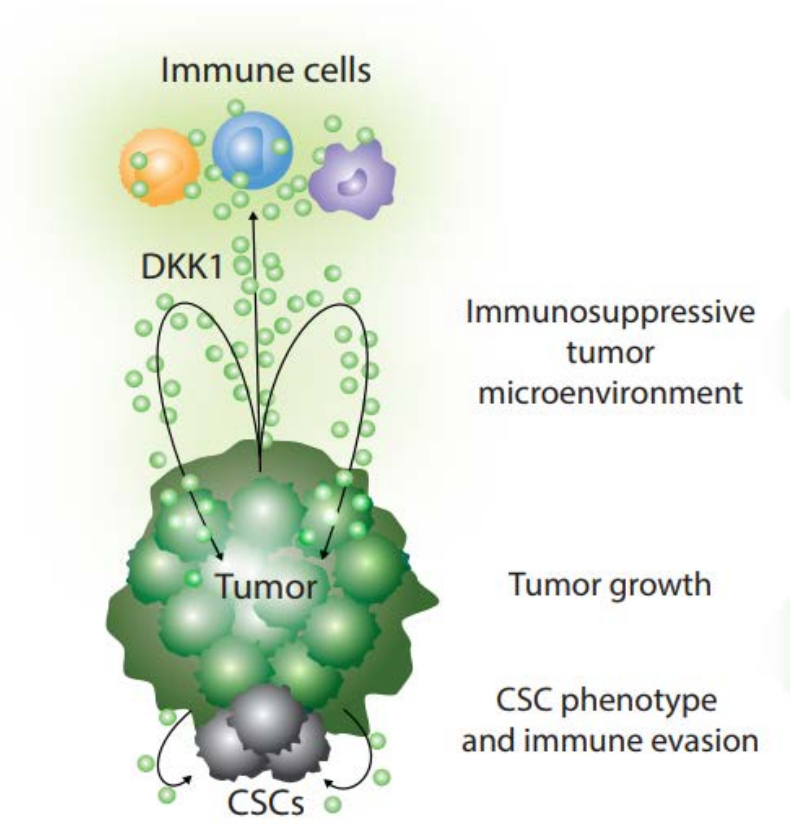
DKN-01

Biology and Preclinical Studies

Walter Newman
Leap Therapeutics

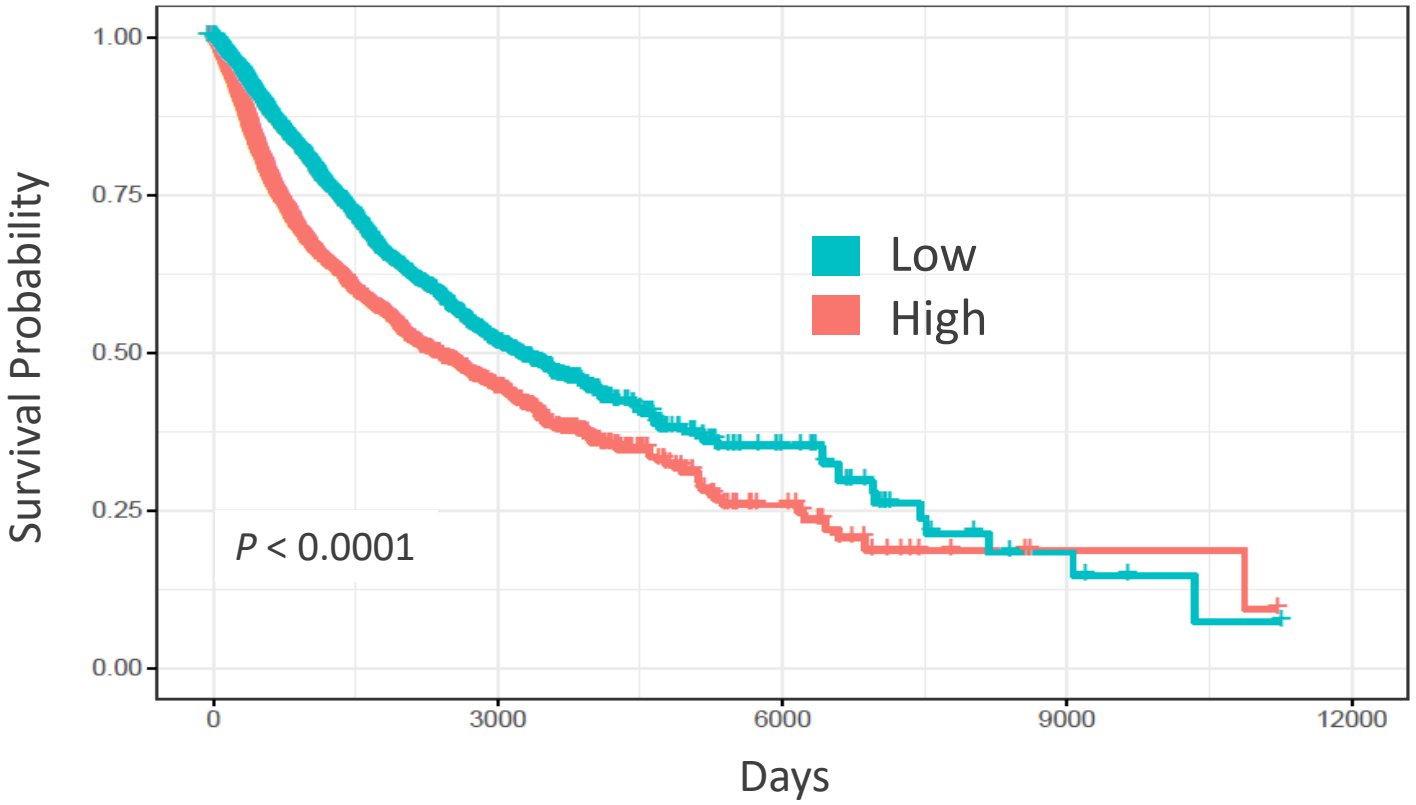
DKK1 in Cancer

- Overexpression of DKK1 linked to poor prognosis
- Tumor cells secrete DKK1 promoting proliferation, metastasis, and angiogenesis
- DKK1 suppresses anti-tumor immune responses
- Neutralizing DKK1 activates an innate immune response in oncology models



High Levels of DKK1 Correlate with Shorter Overall Survival

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

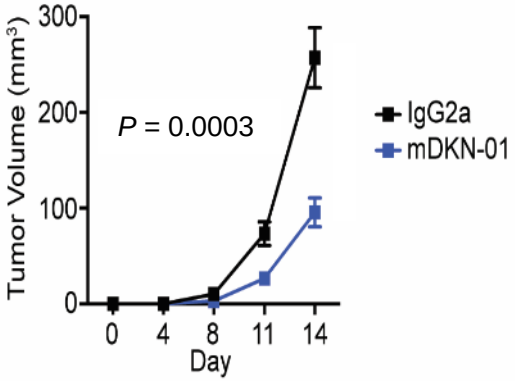


~2.5 year shorter OS in DKK1-high

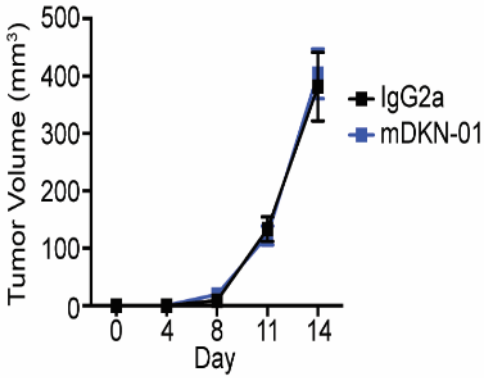
Murine DKN-01 (mDKN-01) Has Immunotherapeutic Activity

- mDKN-01 activity depends on a functioning immune system and NK cells
- mDKN-01 activity stimulates an increase in PD-L1 expression on MDSCs and tumors

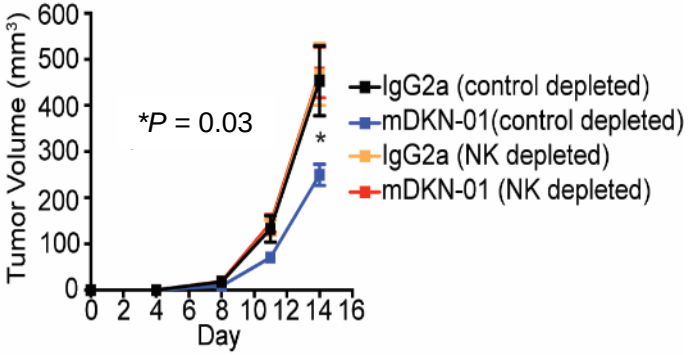
mDKN-01 has Activity in a Melanoma (B16) Syngeneic Model



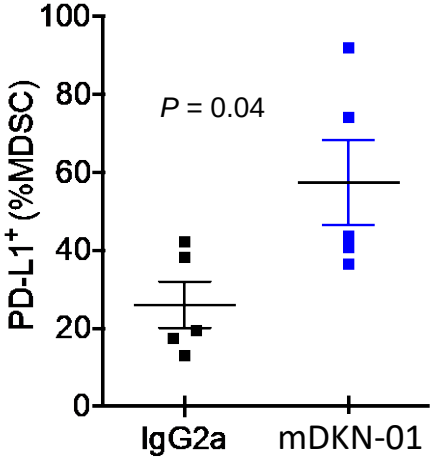
mDKN-01 Does Not Have Activity in a Melanoma (B16) NSG Model



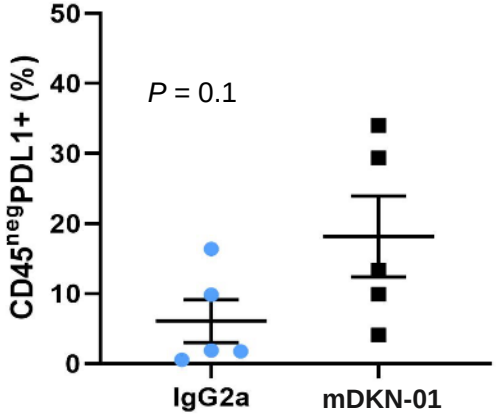
mDKN-01 Efficacy Requires NK Cells



Increase in PD-L1 on MDSCs



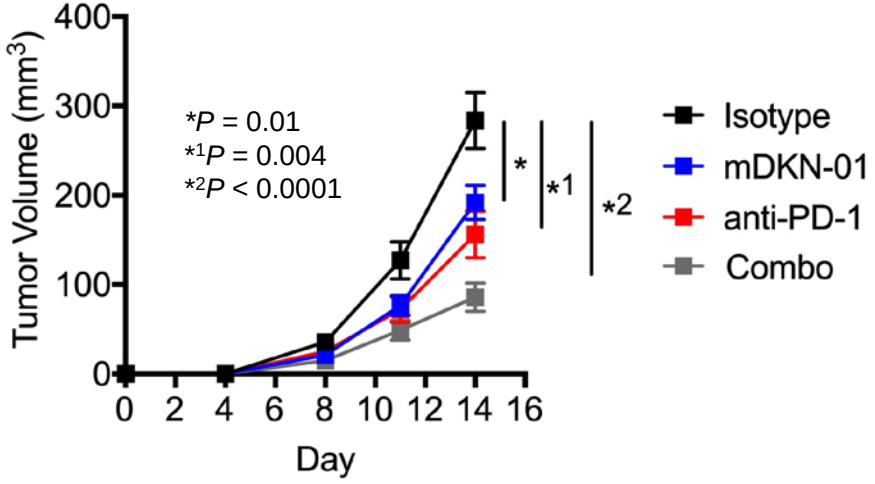
Increase in B16 PD-L1 Expression



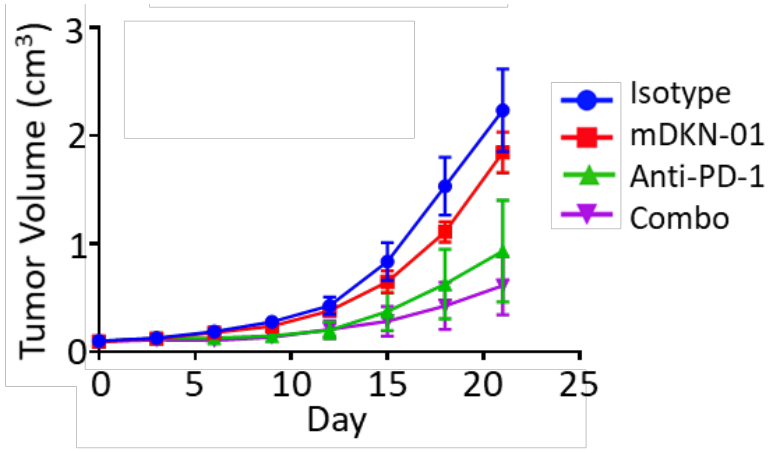
mDKN-01 in Combination with an Anti-PD-1 Antibody

- Murine DKN-01 (mDKN-01) has additive activity with an anti-PD-1 antibody in two syngeneic melanoma models and one triple negative breast cancer model

B16 Melanoma

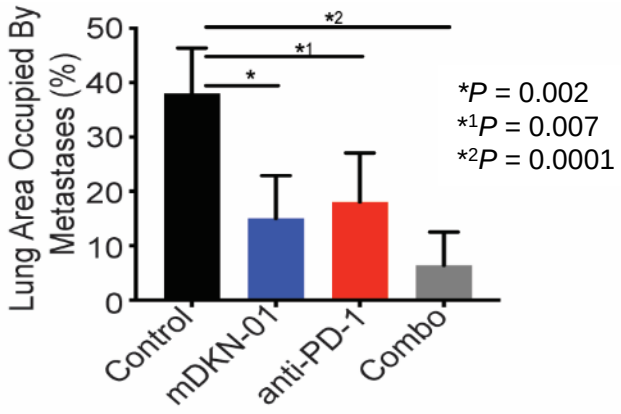


Melanoma BRAF^{V600E}-PTEN$^{-/-}$



Hanks et al. 2019

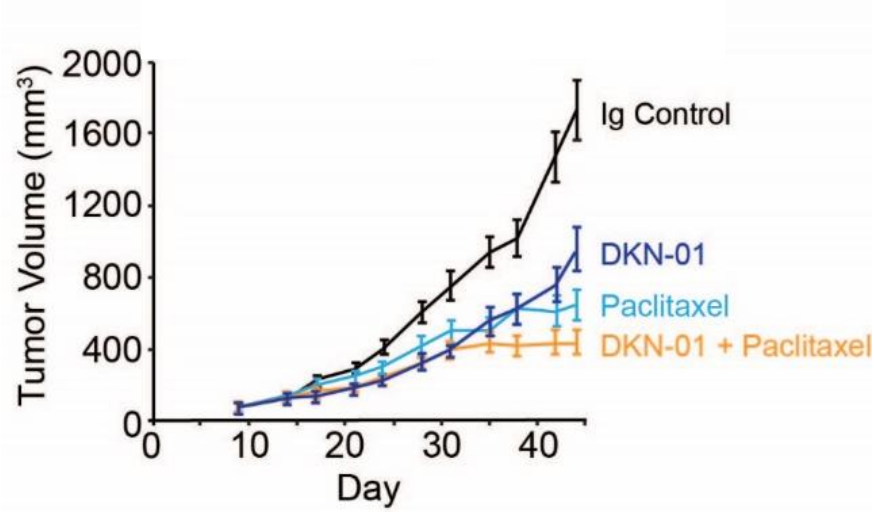
Lung Metastasis in 4T1 Breast Cancer



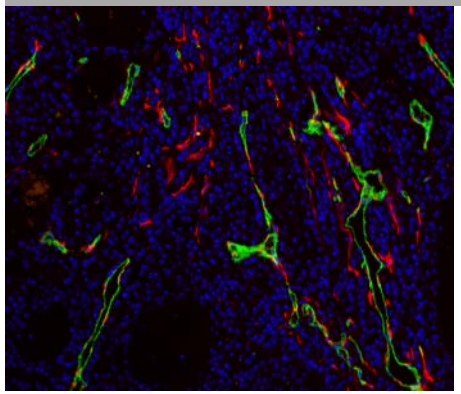
DKN-01 in Combination with Paclitaxel

- DKN-01 has monotherapy and additive efficacy in combination with paclitaxel
- DKN-01 reduces density of blood vessels in tumors

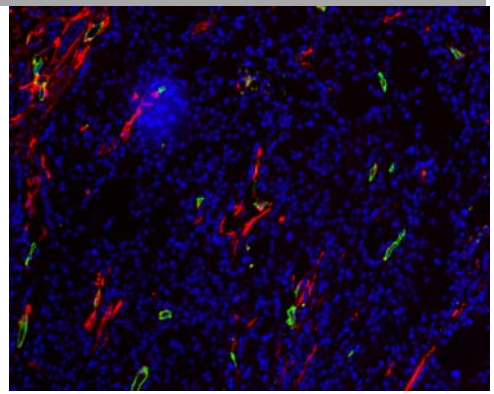
NSCLC (A549) Xenograft



Hoechst: stains all cell nuclei
CD31: stains endothelial cells
SMA: stains myofibroblasts and pericytes
GLUT1: stains hypoxic cells



Control IgG4



DKN-01

DKN-01

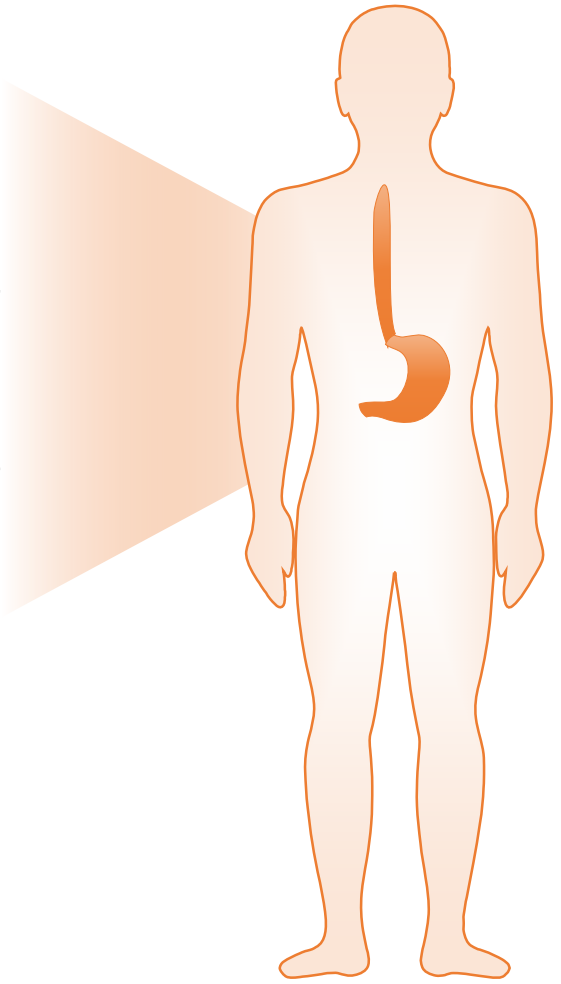
Esophagogastric Malignancies

Dr. Samuel Klempner
Massachusetts General Hospital Cancer Center
Harvard Medical School

Esophagogastric Cancer

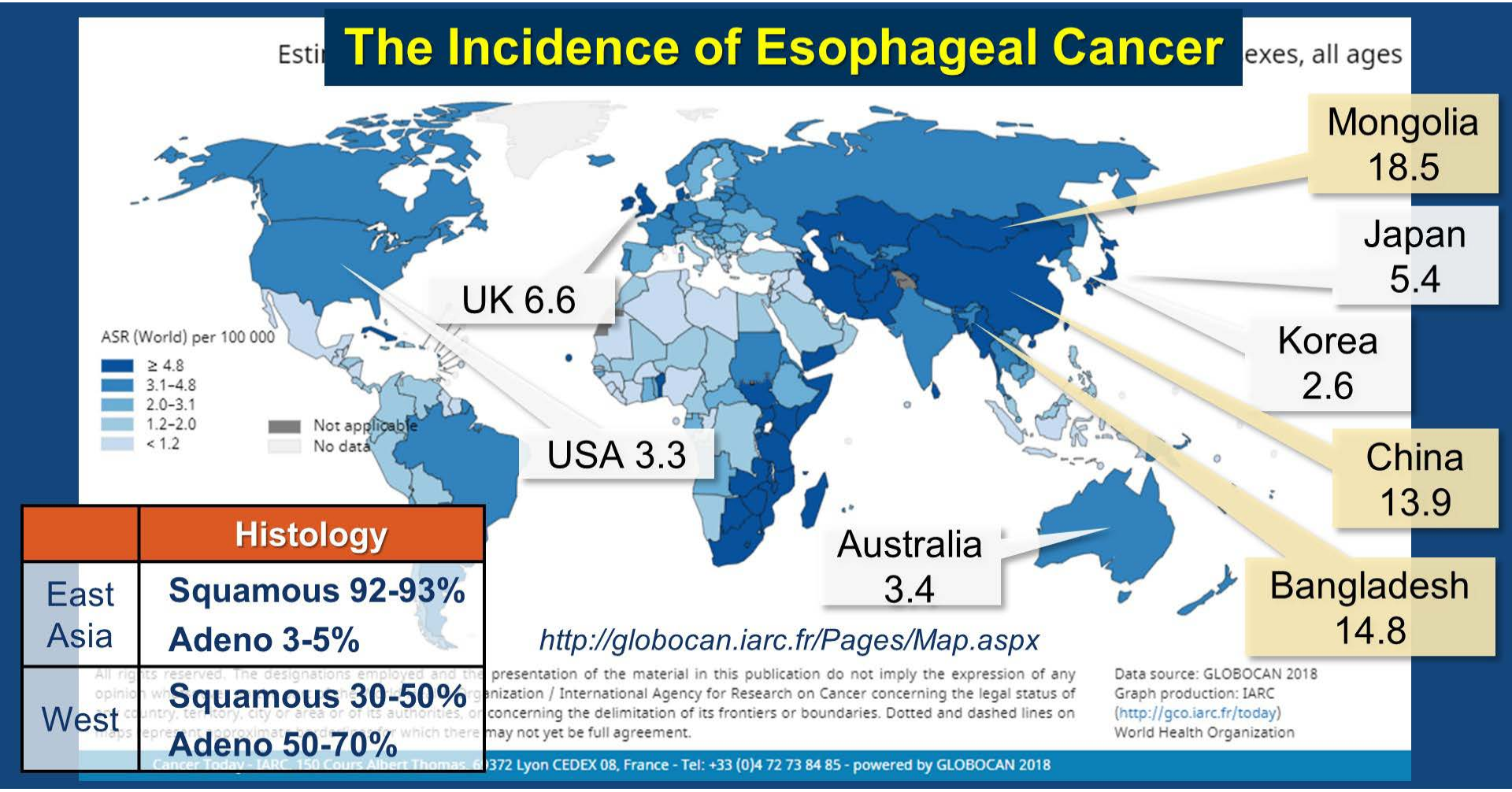
New Cases Each Year*

	Esophageal Cancer	Gastric Cancer
US	17,290	26,240
Worldwide	572,034	1,033,701



* SEER: US in 2018
GLOBOCAN: Global Cancer Statistics 2018

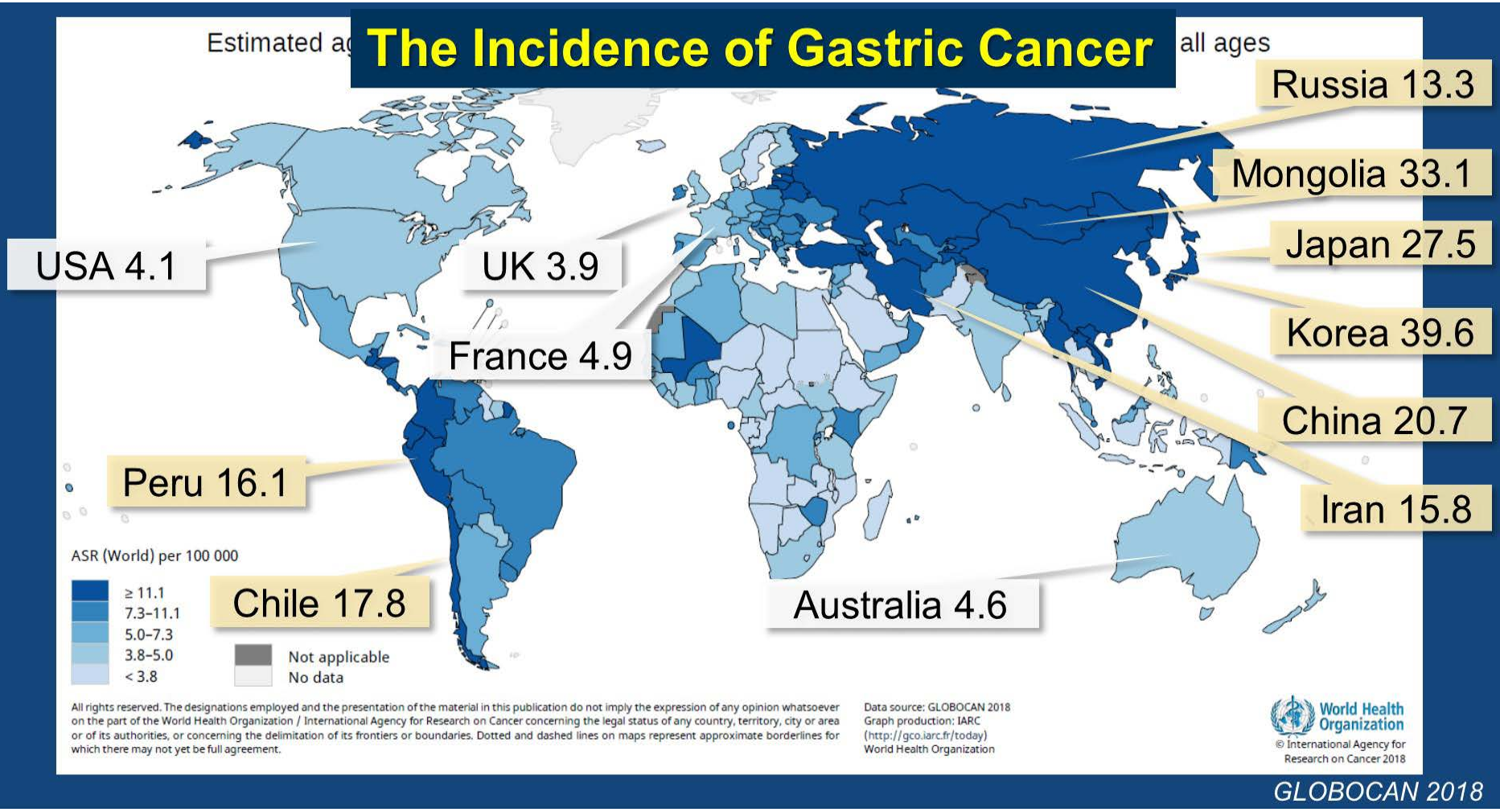
Esophageal Cancer is a Global Unmet Need



	Histology
East Asia	Squamous 92-93% Adeno 3-5%
West	Squamous 30-50% Adeno 50-70%

Source: WHO GLOBOCAN Database, 6/2019

Gastric Cancer is a Global Problem



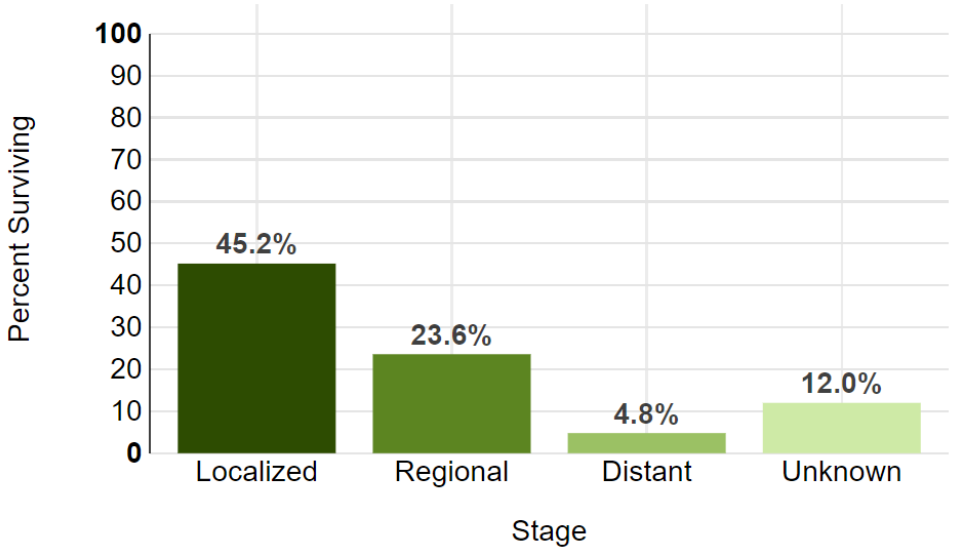
Source: WHO GLOBOCAN Database, 6/2019

Esophagogastric Cancer

Grim Prognosis and Poor Quality of Life

- At diagnosis >50% percent of patients have advanced disease
- Limited treatment options available
- Standard of care has limited activity

5-Year Survival By Stage

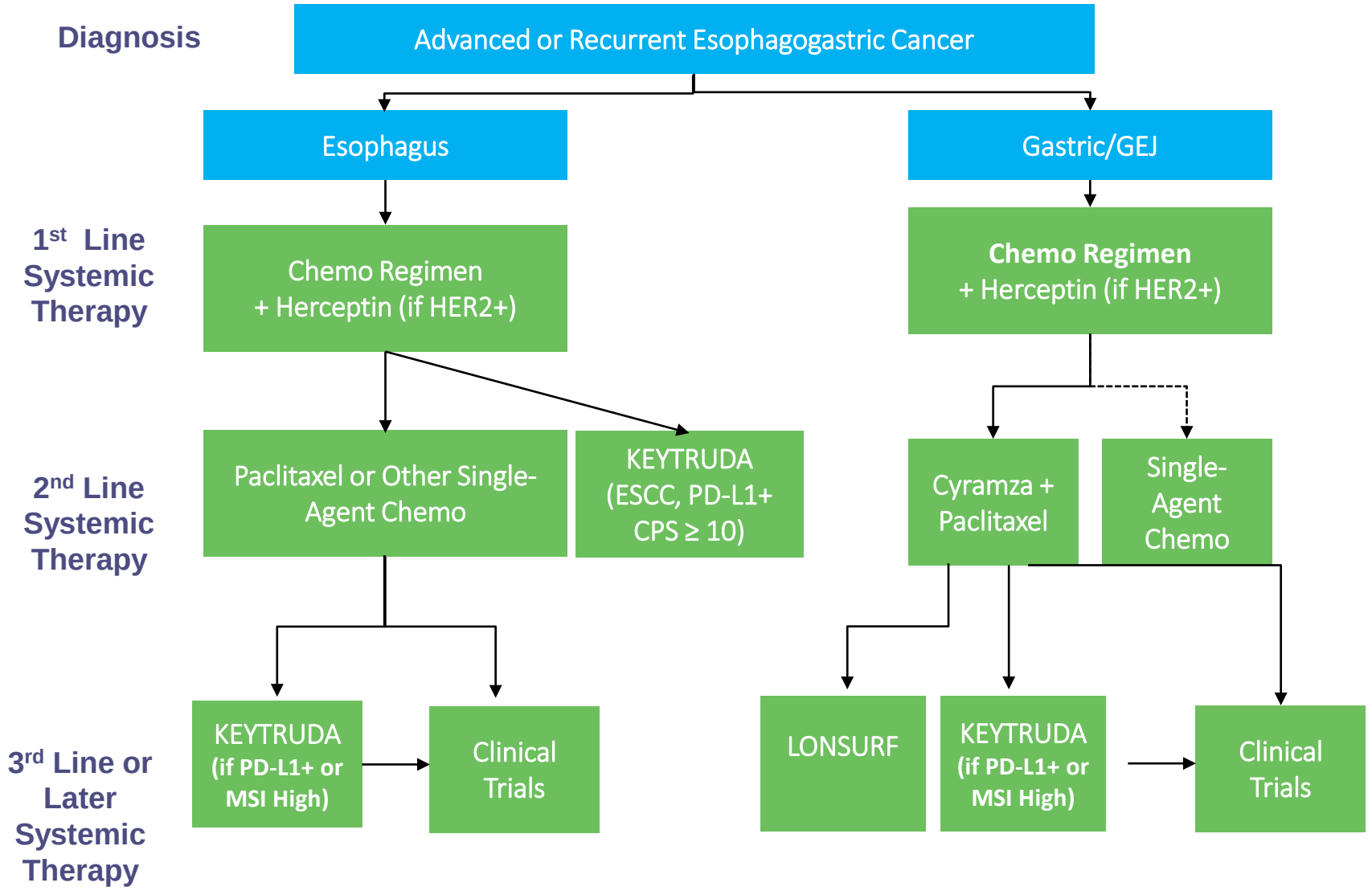


Source: SEER

Challenges in Caring for Advanced EGC Patients

- Highly symptomatic disease complicates number of patients appropriate for clinical trials
- Nutritional Status: complicated by prior surgical treatment and/or tumor location.
- Several large studies suggest only 40% of US EGC patients receive second line therapy
- Inter and intra-tumoral heterogeneity limit success of small molecule targeted therapies and trastuzumab.

Treatment Paradigm for Esophagogastric Cancer



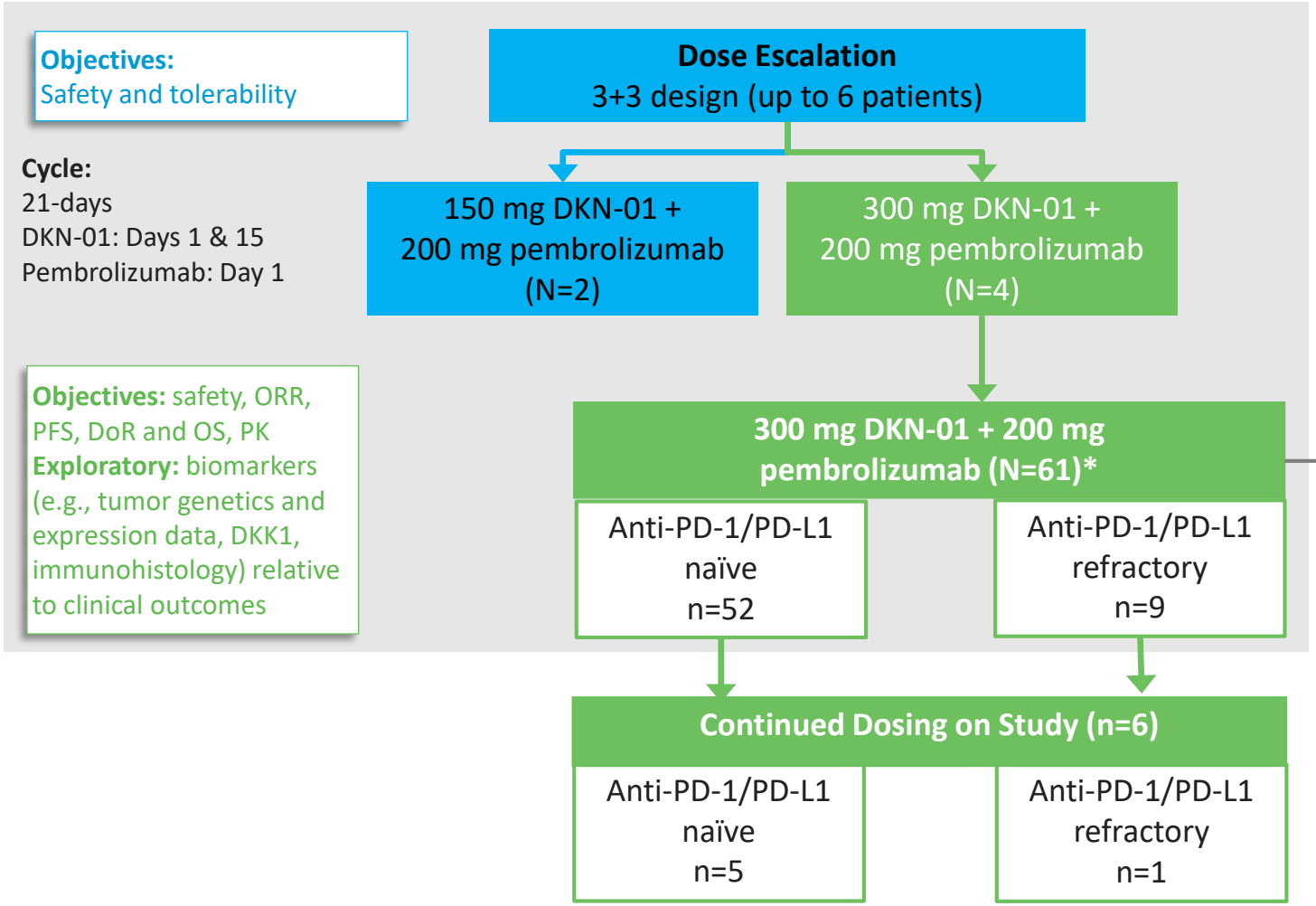
Benchmark Studies in Esophagogastric Cancer Patients

Response Rates and Overall Survival Remain Low

	Second Line		Third Line +
	KN-181 Pembro mono (EA+ESCC)	KN-061 Pembro mono (GEJ/GC)	KN-059 Pembro mono (GEJ/GC)
N	314	296	259
ORR (%)	13.1	11.1	11.6
ORR in MSS Pts (%)	NR	9.3	9.0
PFS months (95% CI)	2.1 (2.1, 2.2)	1.5 (1.4, 1.6)	2.0 (2.0, 2.1)
OS months (95% CI)	7.1 (6.2, 8.1)	6.7 (5.4, 8.9)	5.6 (4.3, 6.9)

KEYNOTE-731 Study Flow Diagram

Esophagogastric Cancer – DKN-01/Pembrolizumab



*Total N includes 4 patients from dose escalation

DKK1-high Patients Live Longer

Esophagogastric Cancer – DKN-01/Pembrolizumab

- Heterogeneous, heavily pretreated esophagogastric population
- Patients with high tumoral DKK1 have improved outcomes
- DKK1-high GEJ/GC patients have 50% ORR, median PFS of 5.1 months (22.1 weeks) and OS of 7.3 months (31.6 weeks)
- PD-L1 CPS scores do not predict efficacy in GEJ/GC
- DKK1-high correlates with longer PFS independent of PD-L1 CPS
- DKK1-high has a stronger association to efficacy outcomes than number of prior therapies
- IO refractory GEJ/GC patients with DKK1-high tumors had a best response of SD, whereas those with DKK1-low tumors had PD

Baseline Demographics

Esophagogastric Cancer – DKN-01/Pembrolizumab

	150 mg DKN-01 (+pembrolizumab)	300 mg DKN-01 (+pembrolizumab)	
		Anti-PD-1/PD-L1 naïve	Anti-PD-1/PD-L1 refractory
N	2	52	9
Median Age (range)	68 (67, 69)	64.5 (28, 81)	62 (40, 74)
Sex (Male)	1 (50.0)	49 (94.2)	6 (66.7)
ECOG PS			
0	–	13 (25.0)	–
1	2 (100)	39 (75.0)	9 (100)
Cancer			
Esophageal	1 (50.0)	18 (34.6)	4 (44.4)
Squamous Cell	–	4 (7.7)	1 (11.1)
Adenocarcinoma (AC)	1 (50.0)	14 (26.9)	3 (33.3)
Gastroesophageal Junction AC	1 (50.0)	27 (51.9)	5 (55.6)
Gastric AC	–	7 (13.5)	–
Time Since Diagnosis			
Median (range, mos)	51.9 (23.3, 80.5)	11.8 (2.5, 67.6)	24.0 (18.5, 42.4)
Stage at Diagnosis			
Stage I	–	2 (3.8)	–
Stage II	1 (50.0)	6 (11.5)	–
Stage III	–	5 (9.6)	2 (22.2)
Stage IV	1 (50.0)	39 (75.0)	7 (77.8)

Prior Therapies

Esophagogastric Cancer – DKN-01/Pembrolizumab

	150 mg DKN-01 (+pembrolizumab)	300 mg DKN-01 (+pembrolizumab)	
		Anti-PD-1/PD-L1 naïve	Anti-PD-1/PD-L1 refractory
N	2	52	9
Prior Therapy			
Median (range)	3 (3, 3)	2 (1, 5)	4 (2, 5)
1	0	21 (40.4)	–
≥2	2 (100)	31 (59.6)	9 (100)
Type of Prior Therapy			
5-Fluorouracil	2 (100)	49 (94.2)	9 (100)
Platinum	2 (100)	52 (100)	9 (100)
Trastuzumab	0	13 (25.0)	2 (22.2)
Taxane	1 (50.0)	31 (59.6)	8 (88.9)
Ramucirumab	1 (50.0)	15 (28.8)	7 (77.8)
Anti- PD-1/PD-L1	1 (50.0)	0	9 (100)

Baseline Biomarker Demographics

Anti-PD-1/PD-L1 Naïve Esophagogastric Cancer

Cancer, n (%)	Anti-PD-1/PD-L1 naïve (300 mg DKN-01)		
	Overall n=52	ESO (EAC + ESCC) n=18	GEJ/GC n=34
DKK1 RNAScope Tumor Cell Analysis	n=49	n=18	n=31
Median H-Score	17.0	20.5	17.0
PD-L1 Expression	n=45	n=18	n=27
Median CPS	2.0	1.5	2.0
Positive			
CPS 1- <10	18 (40.0)	5 (27.8)	13 (48.1)
CPS ≥ 10	12 (26.7)	5 (27.8)	7 (25.9)
Negative	15 (33.3)	8 (44.4)	7 (25.9)
Unknown	7	–	7
Microsatellite Status	n=40	n=14	n=26
MSS	40	14	26
MSI-H	–	–	–
Unknown	12	4	8
Tumor Mutation Burden	n=24	n=8	n=16
Median	5.0	3.4	5.5
Low (1-10)	22 (91.7)	7 (87.5)	15 (93.8)
Intermediate (≥10- <20)	2 (8.3)	1 (12.5)	1 (6.3)
High (≥20)	–	–	–
Unknown	28	10	18

Summary of Adverse Events

Esophagogastric Cancer – DKN-01/Pembrolizumab

Patients with Adverse Events (AE), n (%)	DKN-01 300 mg + Pembrolizumab (N=61)
Any TEAE	59 (96.7)
TEAE Related to DKN-01	39 (63.9)
TEAE Related to Pembrolizumab	34 (55.7)
G3+ TEAE	39 (63.9)
G3+ TEAE Related to DKN-01	15 (24.6)
G3+ TEAE Related to Pembrolizumab	15 (24.6)
Any TE SAE	25 (41.0)
TE SAE Related to DKN-01	5 (8.2)
TE SAE Related to Pembrolizumab	6 (9.8)
TEAE Leading to Discontinuation of DKN-01	3 (4.9)
TEAE Leading to Discontinuation of Pembrolizumab	4 (6.6)
TEAE Leading to Dose Modification of DKN-01	1 (1.6)
TEAE Thought to Represent Disease Progression	13 (21.3)
TEAE Indicated as DLT or DLT Equivalent	0
TEAE Leading to Death	1 (1.6)

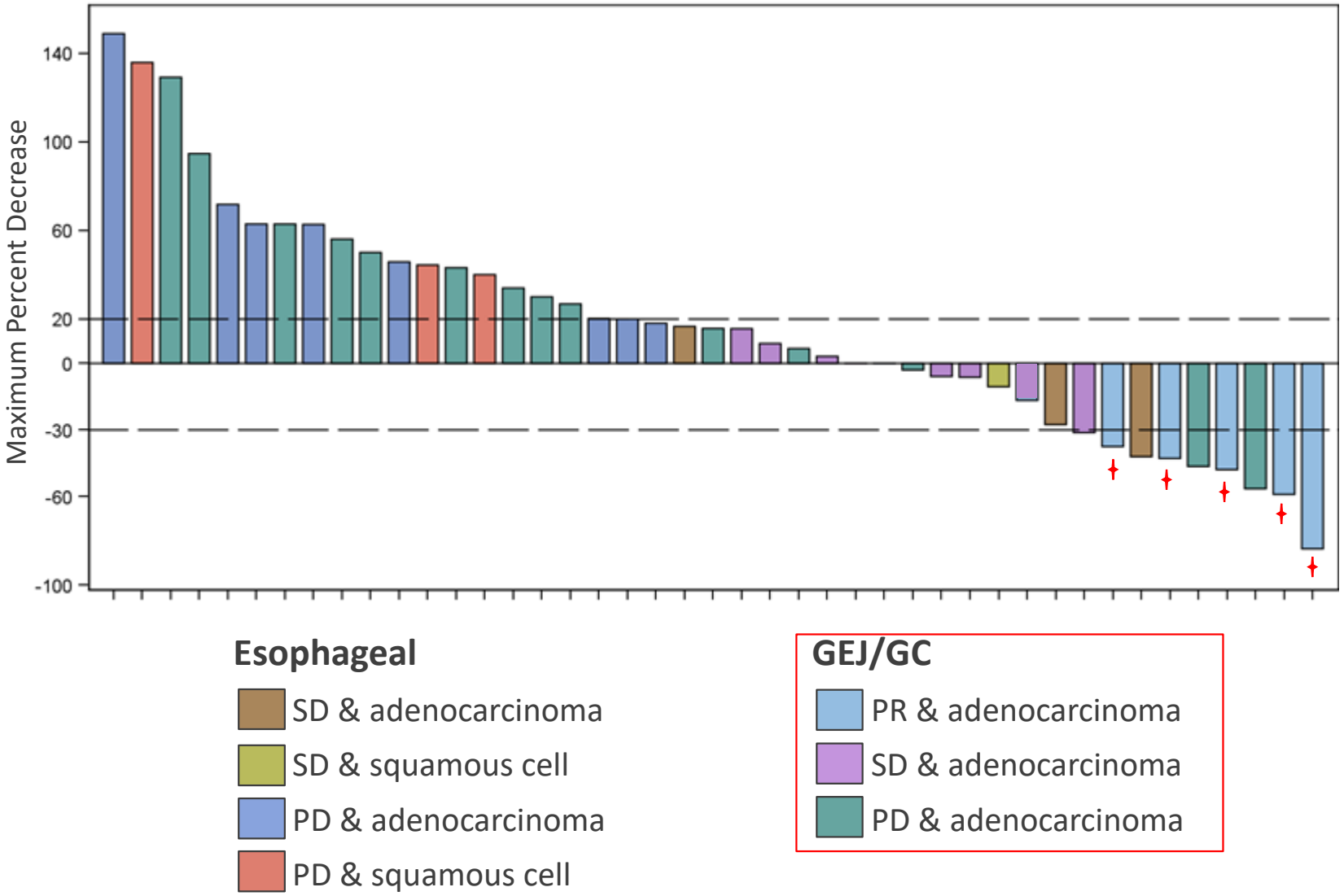
No Additive Toxicity

Esophagogastric Cancer – DKN-01/Pembrolizumab

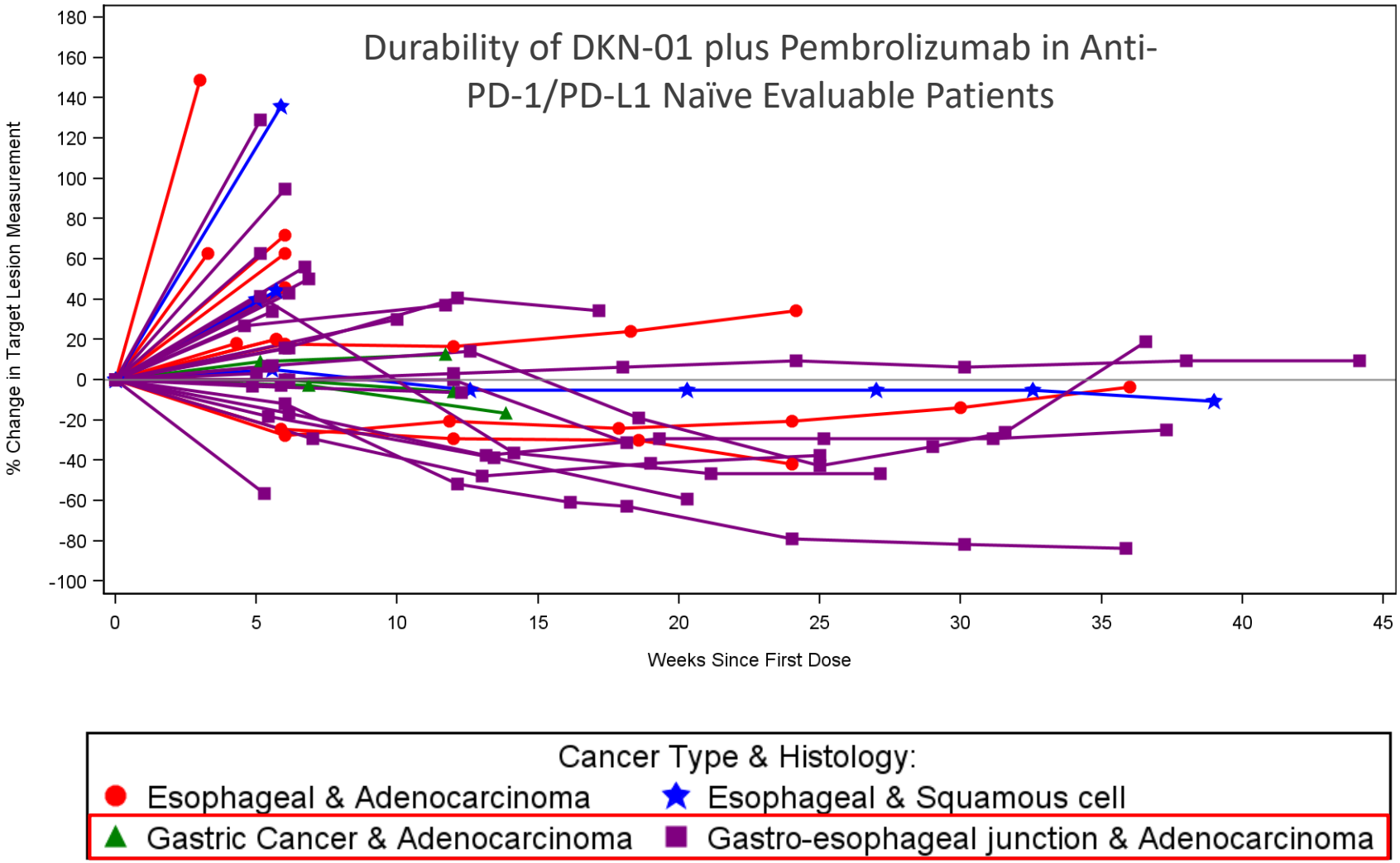
	DKN-01-Related Causality				Pembro-Related Causality			
	TEAE Any Grade		TESAE		TEAE Any Grade		TESAE	
	n	%	n	%	n	%	n	%
Any TEAE	**39**	**64**	**5**	**8**	**34**	**56**	**6**	**10**
≥ Grade 3 TEAE	15	25	–	–	15	25	–	–
DLT	–	–	–	–	–	–	–	–
Discontinuation due to TEAE	3	5	–	–	4	7	–	–
Preferred terms	**#**	**%**	**#**	**%**	**#**	**%**	**#**	**%**
Aspartate aminotransferase increased	9	15	0	0	9	15	0	0
Fatigue	10	16	0	0	9	15	0	0
Alanine aminotransferase Increased	5	8	0	0	5	8	1	2
Blood alkaline phosphatase increased	7	12	0	0	4	7	0	0
Decreased appetite	4	7	0	0	3	5	0	0
Dry skin	0	0	0	0	3	5	0	0
Hyperbilirubinaemia	2	3	0	0	3	5	0	0
Myalgia	2	3	0	0	3	5	0	0
Pruritus	0	0	0	0	3	5	0	0
Anaemia	6	10	0	0	2	3	0	0

All possibly related SAEs occurred in 1. Abdominal pain, dehydration, hypophosphataemia, orthostatic hypotension, pleural effusion, pneumonia and syncope were SAEs reported as at least possibly related to both DKN-01 and pembrolizumab. Alanine aminotransferase increased was an SAE reported for pembrolizumab only.

Greatest Clinical Benefit Seen in GEJ/GC Patients



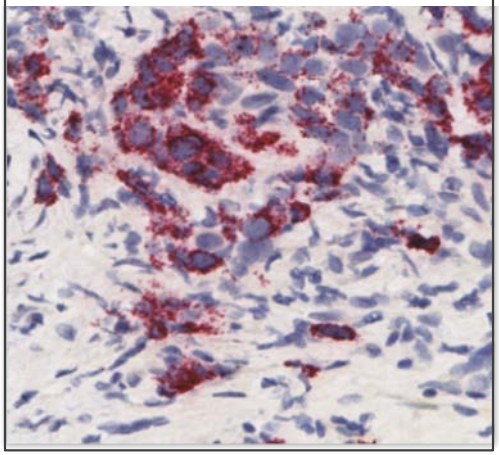
Greatest Clinical Benefit Seen in GEJ/GC Patients



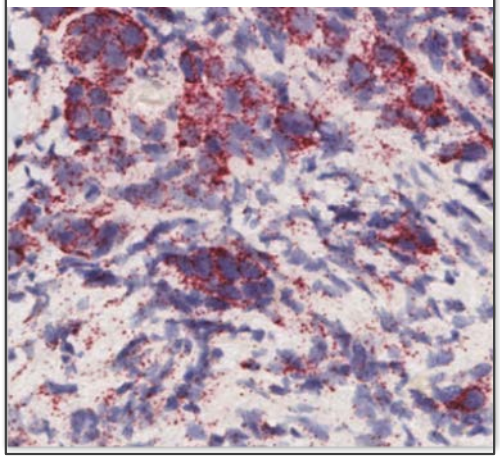
DKK1-RNAscope Assay

Patient with a partial response: DKK1 H-score = 163

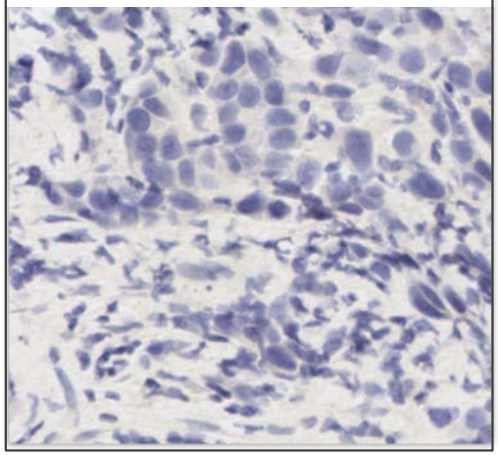
DKK1-high



PPIB (positive control)

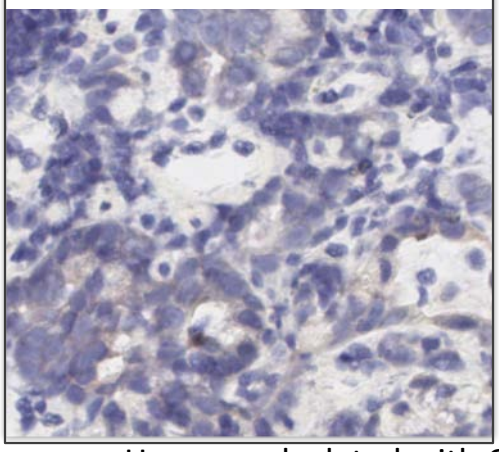


dapB (negative control)

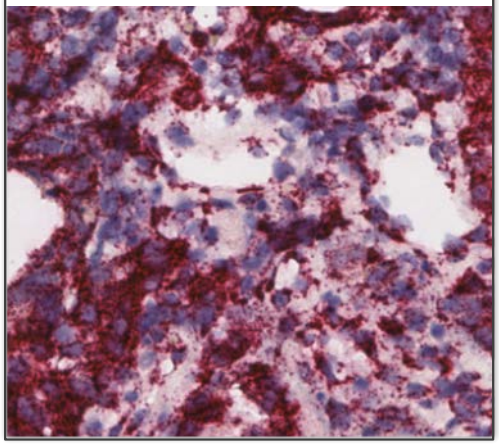


Patient with progressive disease: DKK1 H-score = 7

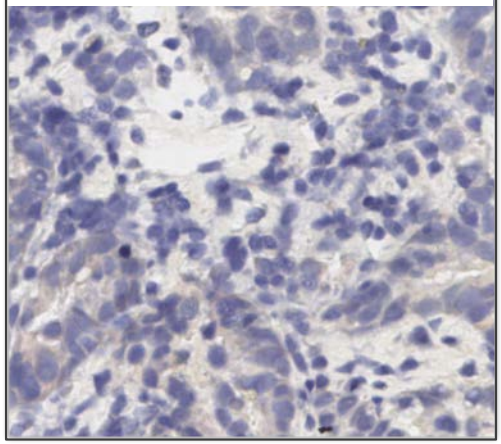
DKK1-low



PPIB (positive control)



dapB (negative control)

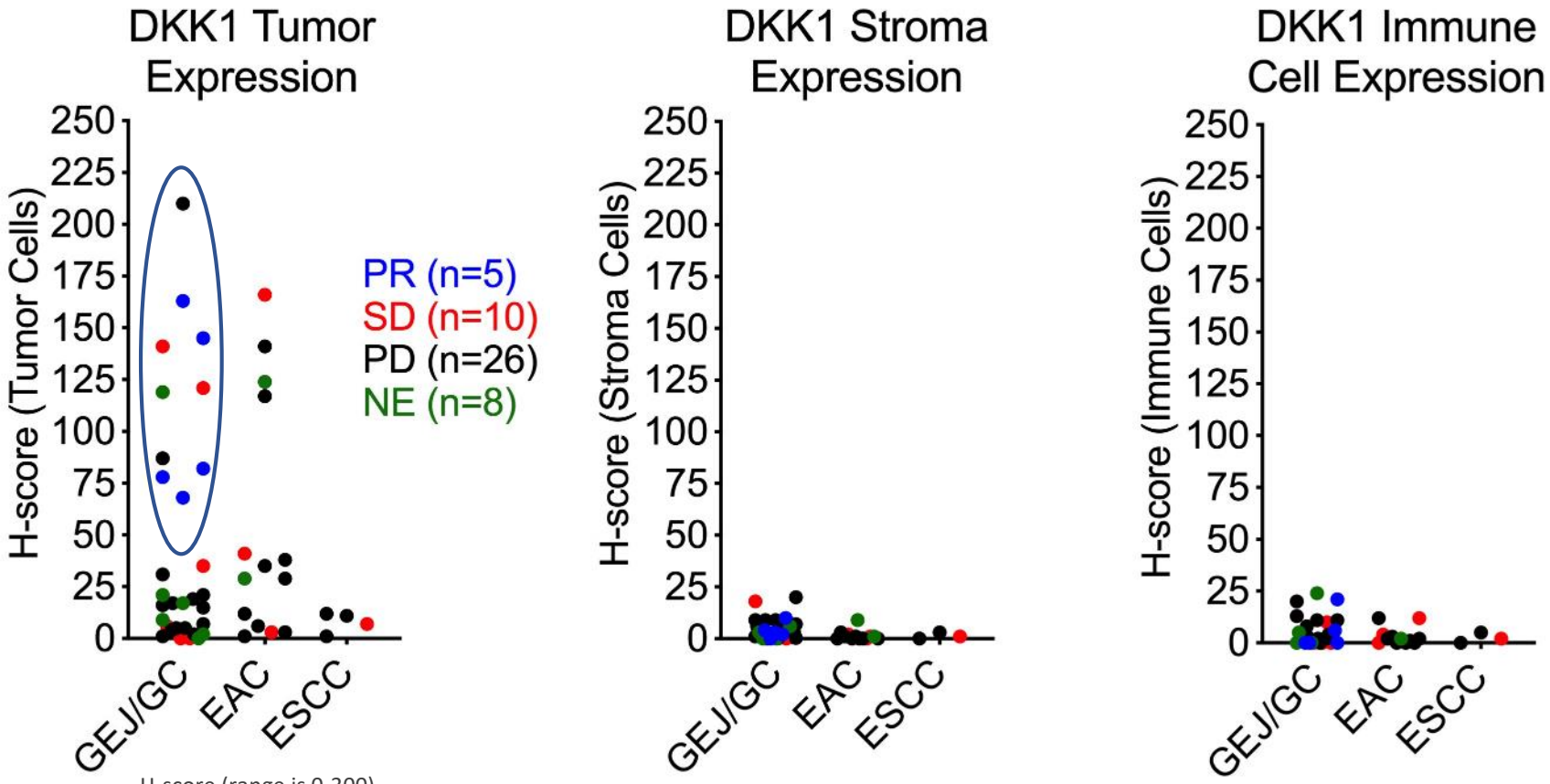


H-score calculated with QuPath software using 3 bins, score range is 0-300

DKK1 Tumor Expression

Anti-PD-1/PD-L1 Naïve Esophagogastric Cancer

- Responding GEJ/GC patients have elevated levels of DKK1
- DKK1 is expressed in tumor cells



H-score (range is 0-300)

- H-score = (%cells in Bin 1)*1 + (%cells in Bin 2)*2 + (%cells in Bin 3)*3
- Bin 1 = 1-3 dots/cell, Bin 2 = 4-9 dots/cell, Bin 3 = ≥10 dots/cell

Screening, archival or an on-treatment biopsy was analyzed depending on availability and quality

Patients dosed at 300 mg DKN-01

Better and More Durable Responses – DKK1-high

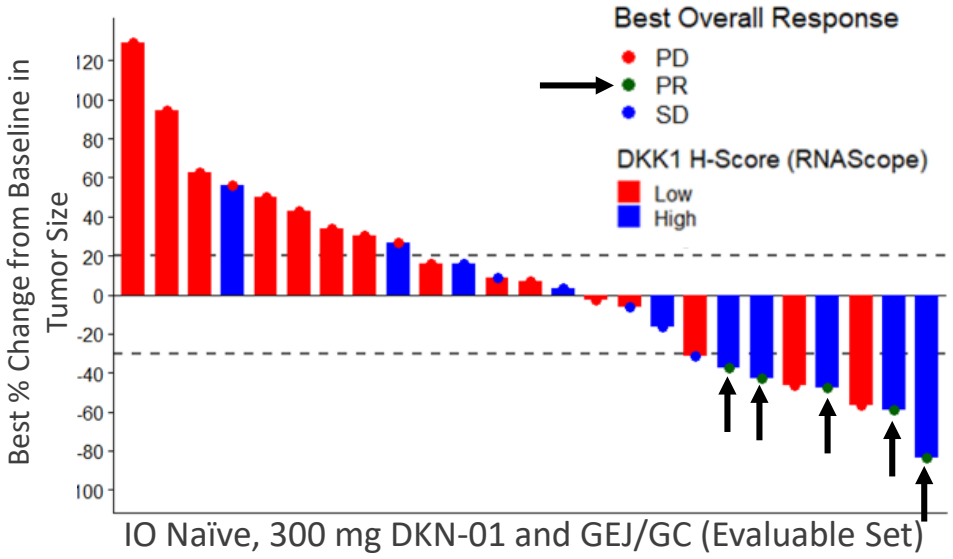
Anti-PD-1/PD-L1 Naïve GEJ/GC Subgroup

Best Overall Response

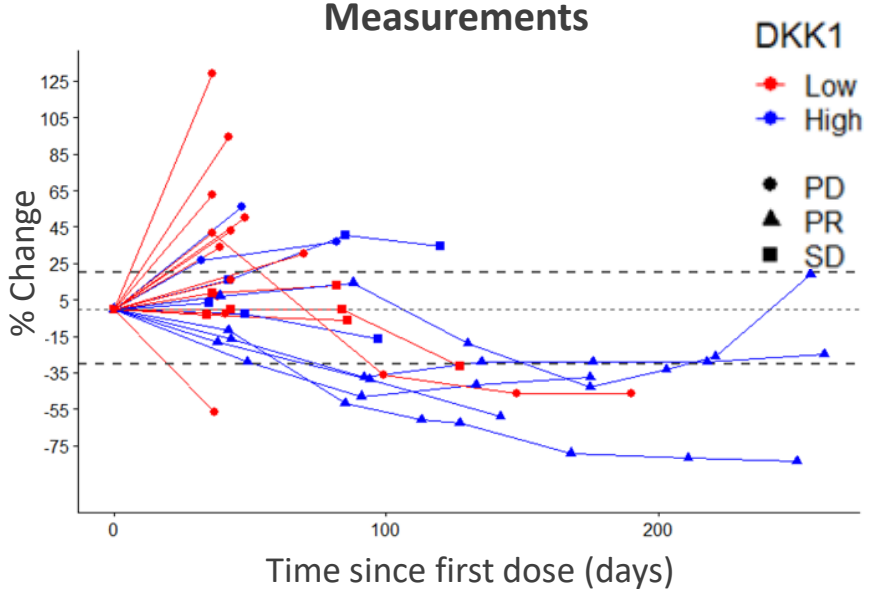
Primary Location	Total (n)	RE* (n)	PR (n)	SD (n)	PD (n)	NE (n)	RE* ORR (n, %)	DCR (n,%)
Overall	52	43	5	12	26	9	5 (11.7)	19 (39.5)
GEJ/GC	**34**	**27**	**5**	**8**	**14**	**7**	**5 (18.5)**	**13 (48.1)**
DKK1 RNAScope*	31							
DKK1-high	11	10	5	3	2	1	5 (50.0)	8 (80.0)
DKK1-low	20	15	0	3	12	5	0 (0.0)	3 (20.0)

*DKK1-high ≥ upper tertile (35)

Best Percent Change from Baseline in Tumor Size



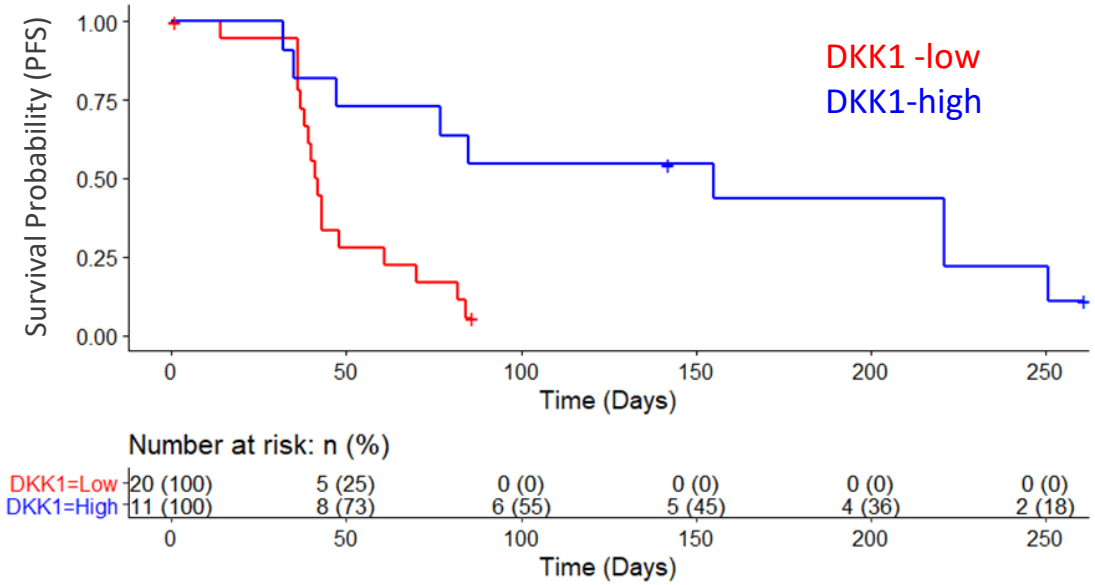
Percent Change in Target Lesion Measurements



Longer PFS Associated with DKK1-high

Anti-PD-1/PD-L1 Naïve GEJ/GC Subgroup

Kaplan-Meier Estimates of PFS

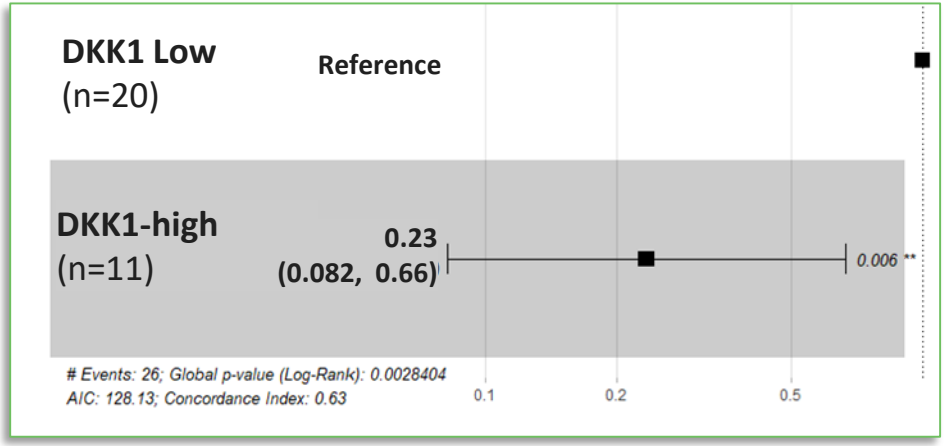


Progression Free Survival

Primary Location	Total (n)	Median PFS (wks, 95%CI)
Overall	52	6.0 (5.7, 10.0)
GEJ/GC	**34**	**7.8 (5.7, 12.1)**
DKK1 RNAScope*	31	
DKK1-high	11	22.1 (5.0, 35.9)
DKK1-low	20	5.9 (5.3, 8.3)

*DKK1-high ≥ upper tertile (35)

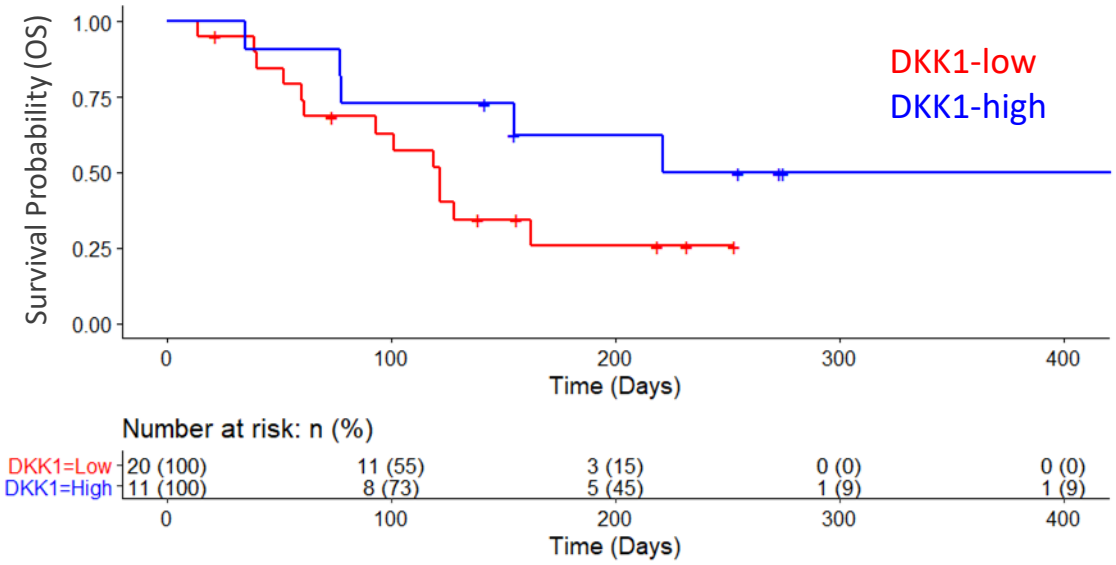
Hazard Ratio



Longer OS Trends with DKK1-high

Anti-PD-1/PD-L1 Naïve GEJ/GC Subgroup

Kaplan-Meier Estimates of OS

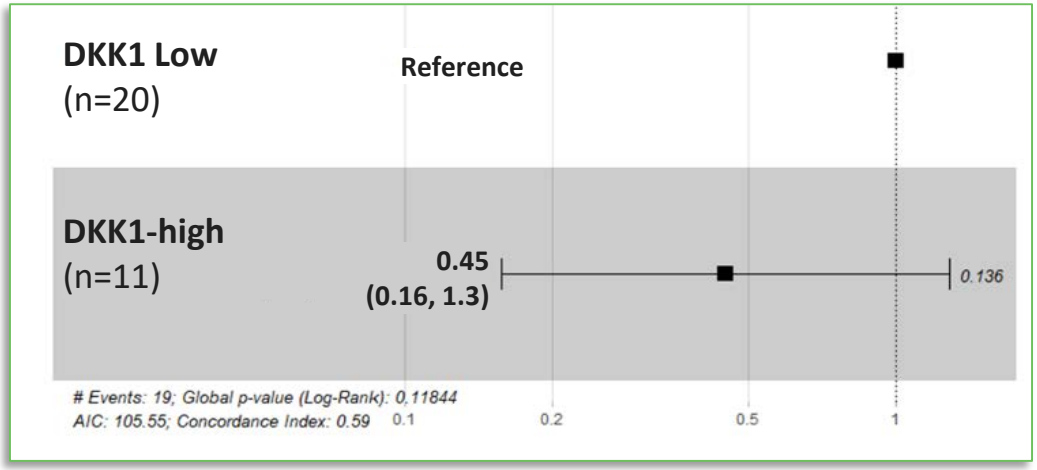


Overall Survival

Primary Location	Total (n)	Median OS (wks, 95%CI)
Overall	52	22.1 (14.1, 60.9)
GEJ/GC	**34**	**22.1 (14.1, 60.9)**
DKK1 RNAScope*	31	
DKK1-high	11	31.6 (11.0, NR)
DKK1-low	20	17.4 (8.7, 23.1)

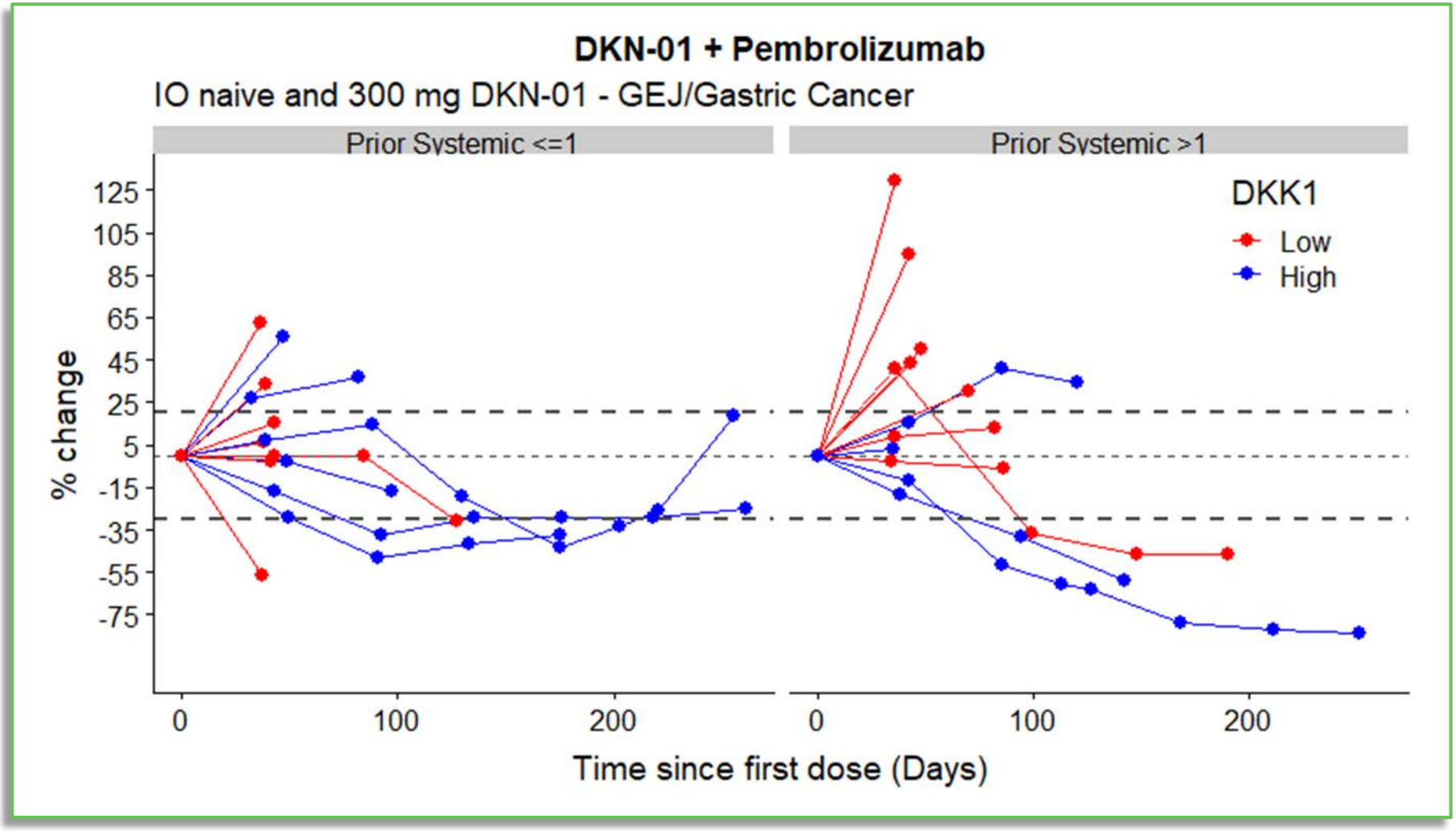
*DKK1-high ≥ upper tertile (35)

Hazard Ratio



DKK1-high Patients Respond Despite Prior Therapies

Anti-PD-1/PD-L1 Naïve GEJ/GC Subgroup



PD-L1 CPS Scores Do Not Predict Clinical Benefit

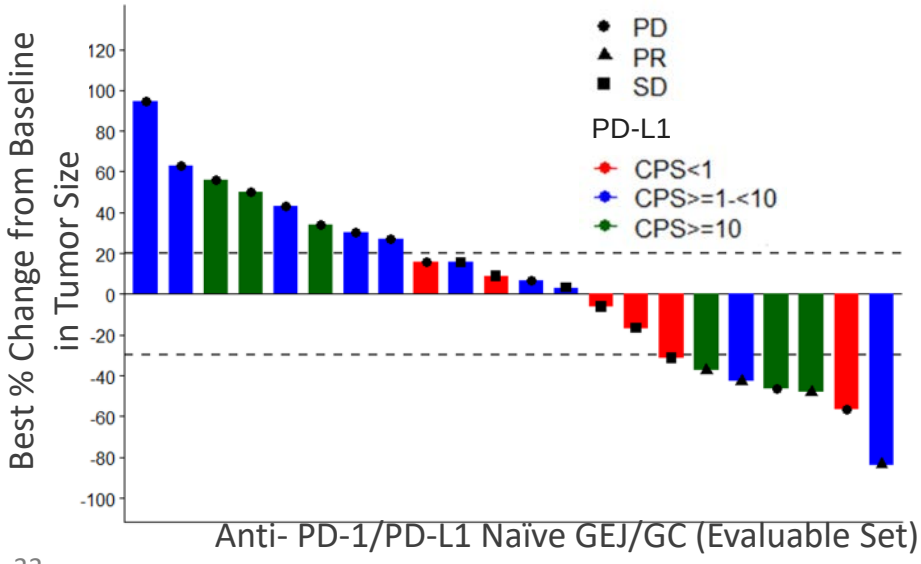
Anti-PD-1/PD-L1 Naïve GEJ/GC Subgroup

Best Overall Response

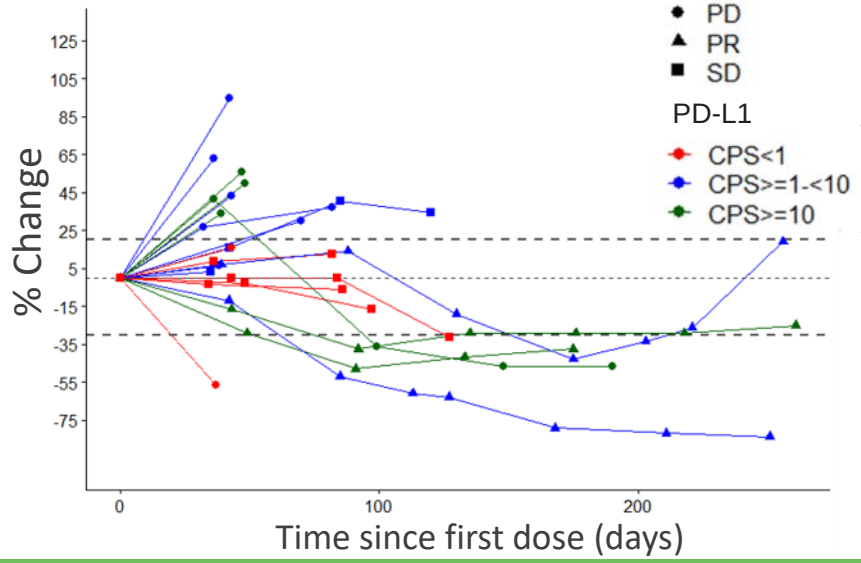
Primary Location	Total (n)	RE* (n)	PR (n)	SD (n)	PD (n)	NE (n)	RE* ORR (n, %)	DCR (n,%)
GEJ/GC	34	27	5*	8	14	7	5 (18.5)	13 (48.1)
PD-L1 Status	27							
Positive	20							
CPS:1-10	13	10	2	2	6	3	2 (20.0)	4 (40.0)
CPS ≥10	7	6	2	0	4	1	2 (33.3)	2 (33.3)
Negative: CPS <1	7	6	0	4	2	1	-	4 (66.7)

* One PR had unknown PD-L1 status

Best Percent Change from Baseline in Tumor Size

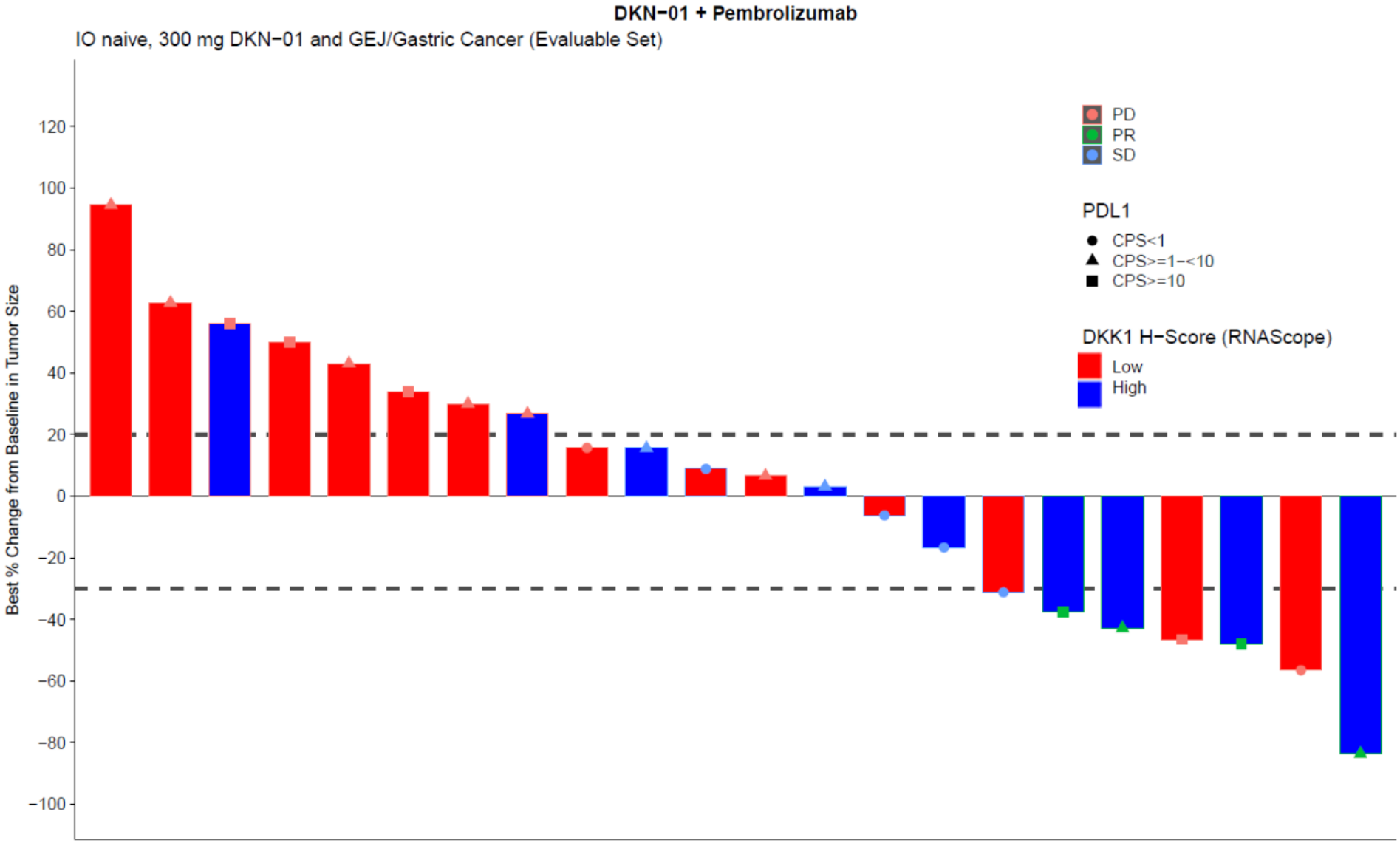


Percent Change in Target Lesion Measurements



DKK1 and PD-L1 CPS – Impact on Best Change in Tumor Burden

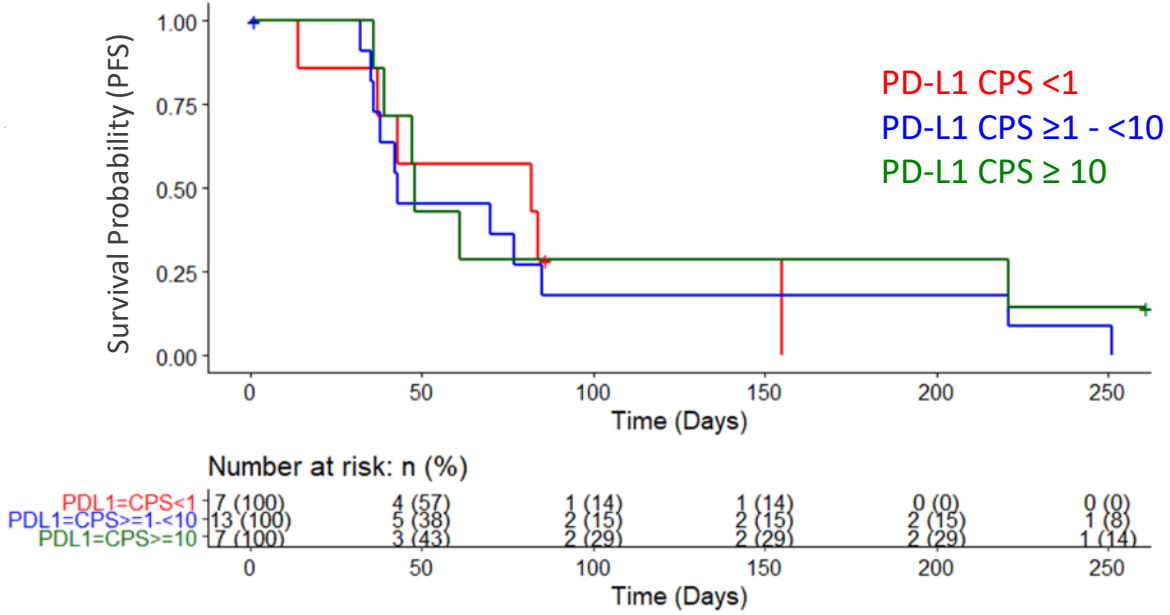
Anti-PD-1/PD-L1 Naïve GEJ/GC Subgroup



PD-L1 CPS Scores Not Associated with PFS

Anti-PD-1/PD-L1 Naïve GEJ/GC Subgroup

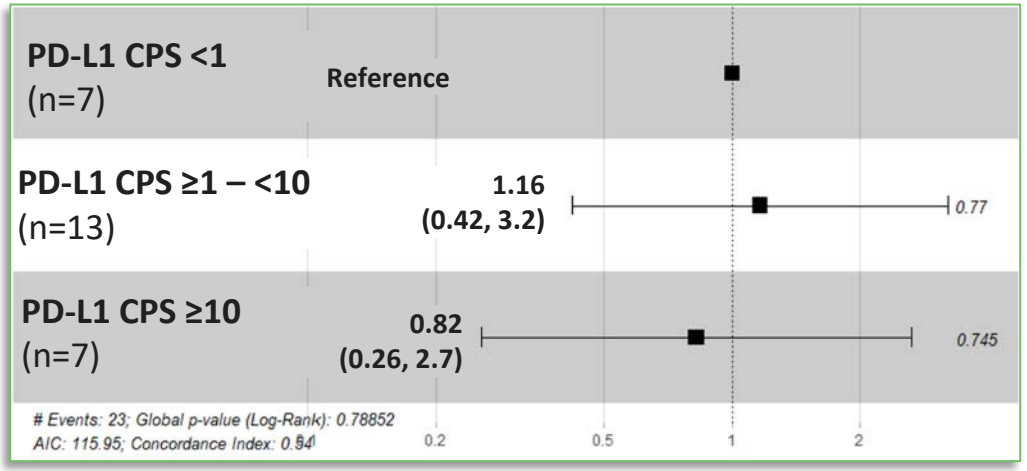
Kaplan-Meier Estimates of PFS by PD-L1 CPS



Progression Free Survival

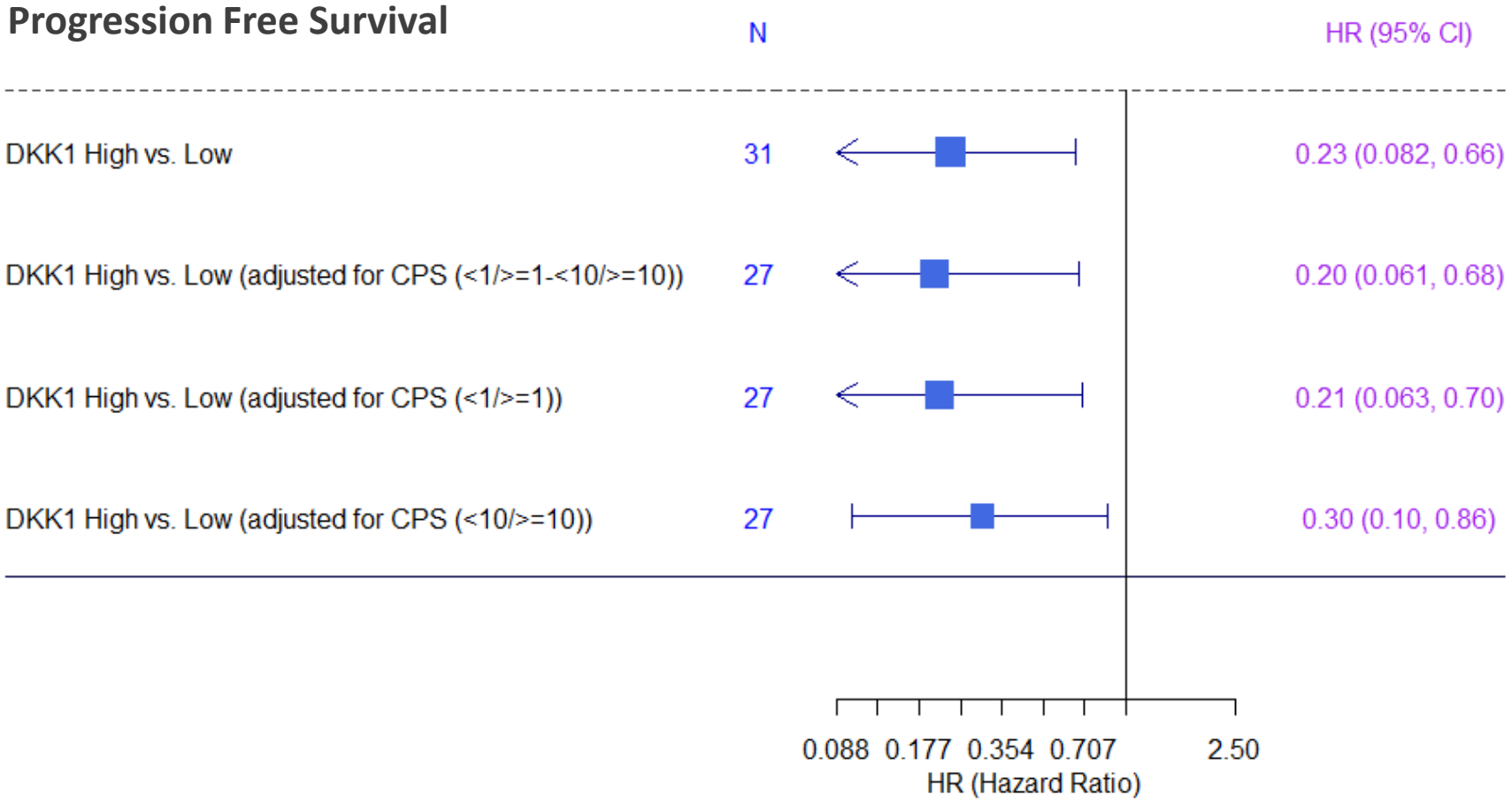
Primary Location	Total (n)	Median PFS (wks, 95%CI)
GEJ/GC	**34**	**7.8 (5.7, 12.1)**
PD-L1 Status	27	
Positive	20	
CPS:1-10	13	6.1 (5.0, 12.1)
CPS ≥10	7	6.9 (5.1, 31.6)
Negative: CPS <1	7	11.7 (2.0, 22.1)

Hazard Ratio by PD-L1 CPS



DKK1-High Correlates with Longer PFS Independent of PD-L1 CPS

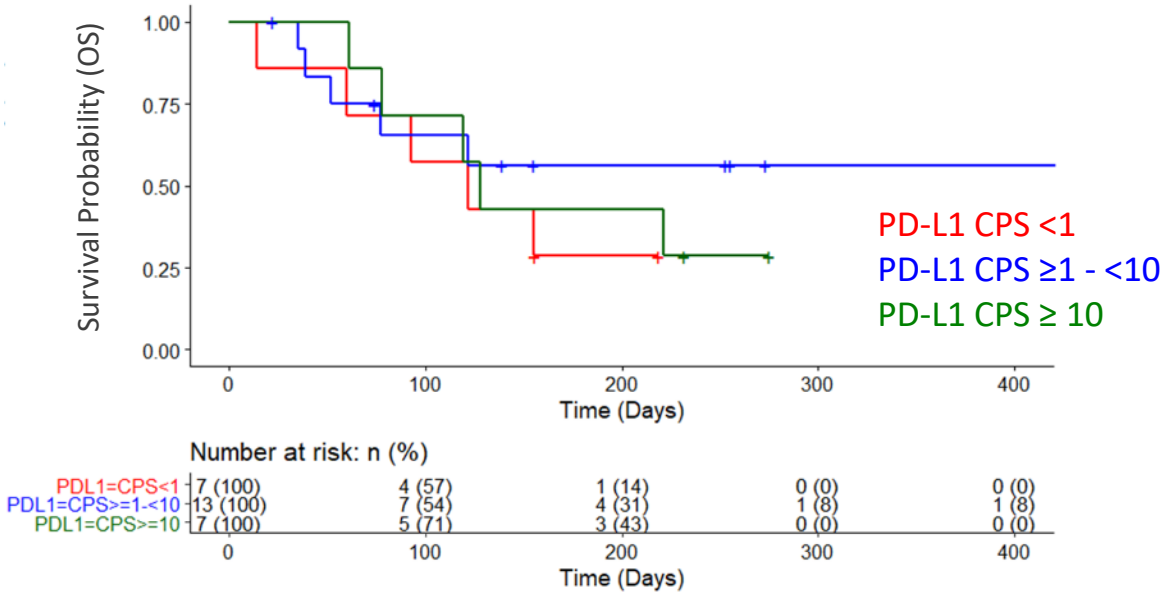
Anti-PD-1/PD-L1 Naïve GEJ/GC Subgroup



PD-L1 CPS Not Associated with OS

Anti-PD-1/PD-L1 Naïve GEJ/GC Subgroup

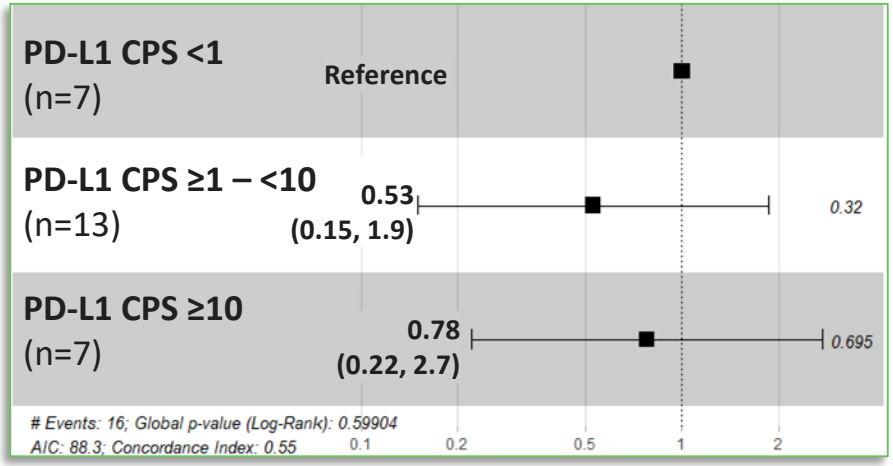
Kaplan Meier Estimate of OS by PD-L1 CPS



Overall Survival

Primary Location	Total (n)	OS (wks, 95%CI)
GEJ/GC	**34**	**22.1 (14.1, 60.9)**
PD-L1 Status	27	
Positive	20	
CPS:1-10	13	>60.9 (5.6, NR)
CPS ≥10	7	18.3 (8.7, NR)
Negative: CPS <1	7	17.4 (2.0, NR)

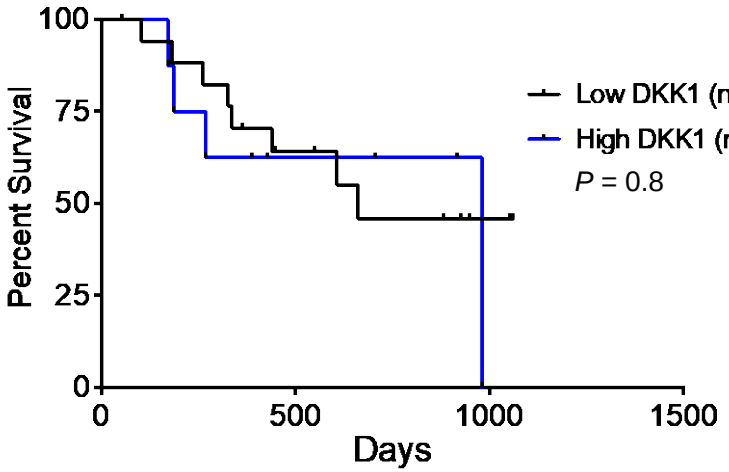
Hazard Ratio by PD-L1 CPS



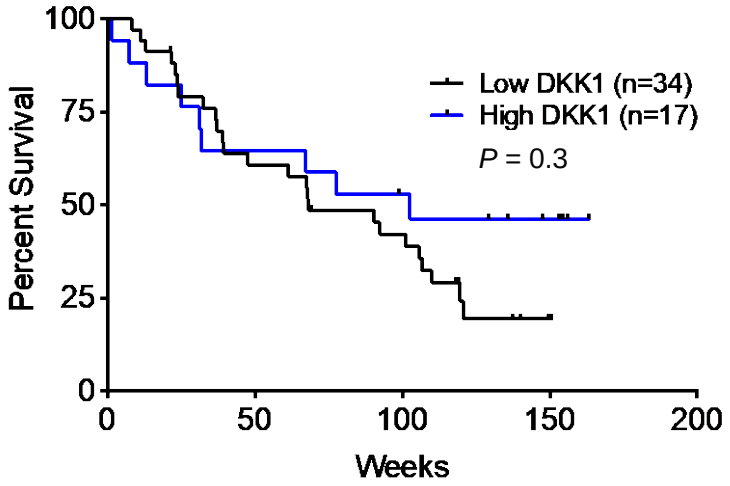
DKK1 Not Predictive of Clinical Outcomes with Anti-PD-1/PD-L1

- DKK1 tumor expression is not associated with overall survival for melanoma patients treated with pembrolizumab or nivolumab[1-2]
- DKK1 expression is not significantly different in responding versus non responding urothelial patients treated with atezolizumab[3]

Overall Survival for Melanoma Patients Treated with Pembrolizumab or Nivolumab[1]



Overall Survival for Melanoma Patients Treated with Nivolumab[2]



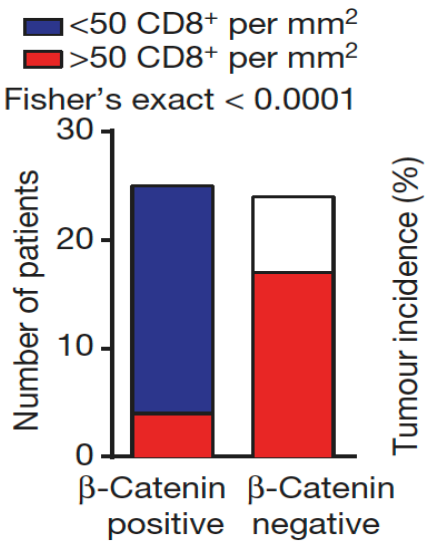
[1]Hugo et al., Cell, 2016
[2]Riaz et al., Cell, 2017
[3]Mariathasan et al., Nature, 2018

Activation of Wnt/β-catenin Signaling Linked to Immune Exclusion and Immune Checkpoint Resistance

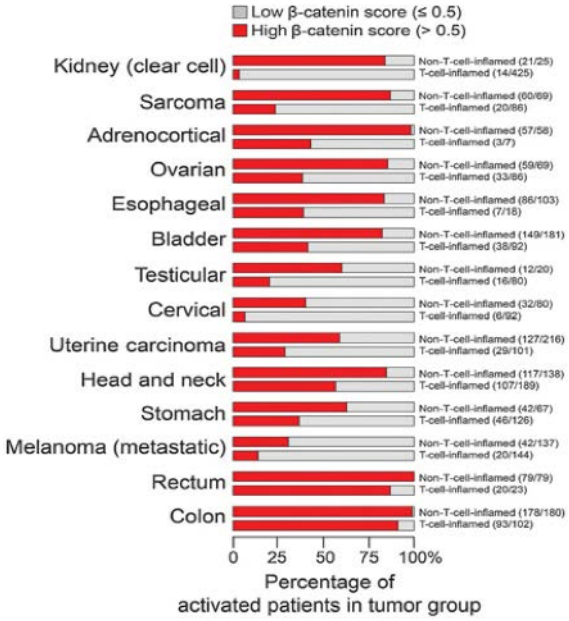
β-catenin Activation Promotes Immune Escape and Resistance to Anti-PD-1 in HCC[1]

"β-catenin-driven tumors were resistant to anti-PD-1…β-catenin activation promotes immune escape and resistance to anti-PD-1 and could represent a novel biomarker for HCC patient exclusion."

β-catenin Positive Melanomas Have Reduced CD8+ Infiltrate[2]

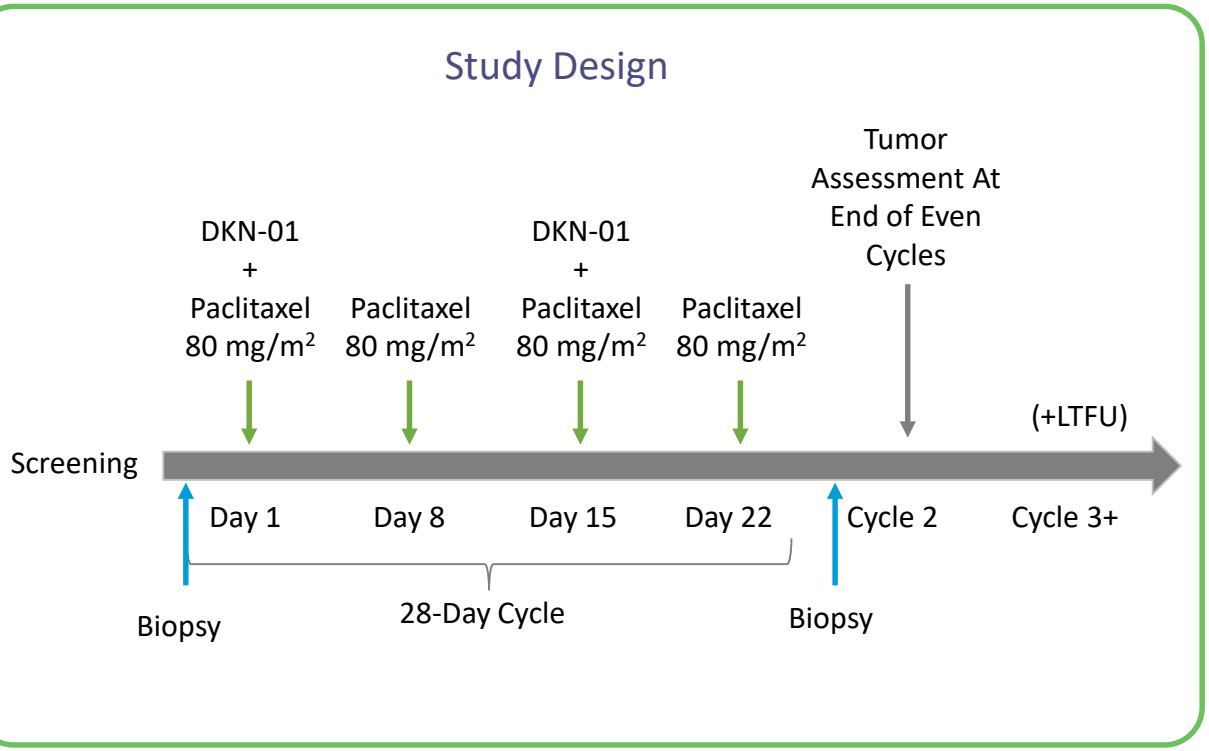


Tumors with Activated Wnt Signaling Are Not T-cell Inflamed[3]



1. Ruiz de Galarreta M, et al. Cancer Discovery, 2019
2. Spranger et. al., Nature, 2015
3. Luke et. al., Clin Canc Res, 2019

DKN-01 Plus Paclitaxel Esophagogastric Study Design



	DKN-01 150 mg + pac N=3	DKN-01 300 mg + pac N=56
Age (median, range)	56 (47, 73)	62.5 (34, 82)
Male (n, %)	3 (100)	43 (76.8)
White	3 (100)	48 (85.7)
Type of Cancer (n, %)		
Esophageal Squamous	-	13 (23.2)
Esophageal AC	1 (33.3)	12 (21.4)
GEJ AC	2 (66.7)	29 (51.8)
Gastric	-	2 (3.6)
Prior Therapy (median, range)	4 (2, 7)	2 (1, 6)
Taxane (n, %)	3 (100)	27 (48.2)
Ramucirumab (n, %)	1 (33.3)	7 (12.5)

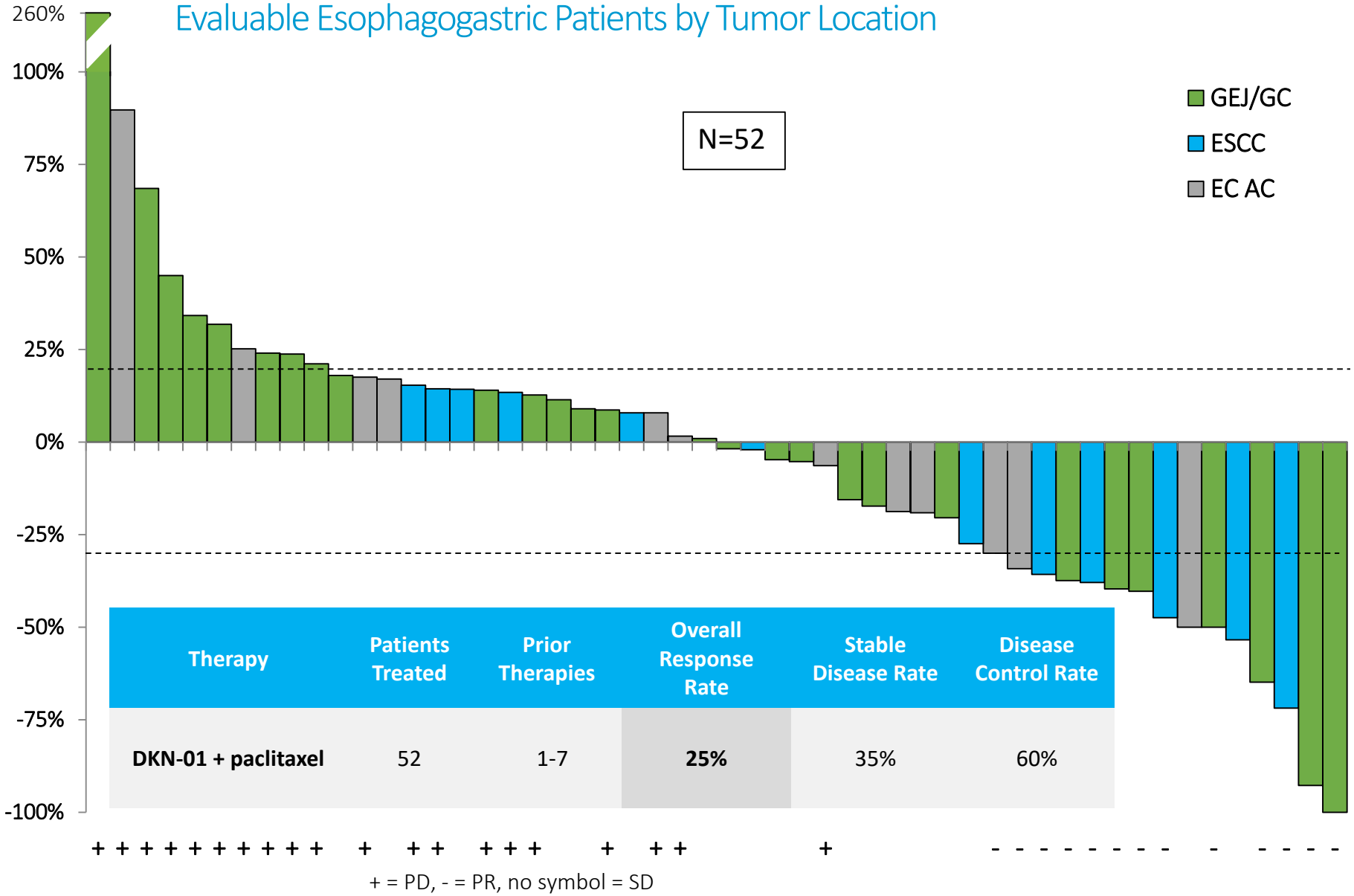
Benchmark Studies in Esophagogastric Cancer Patients

Response Rates and Overall Survival Remain Low

	Second Line			
	KN-181 Chemo mono (EA+ESCC)	KN-061 Pac mono (GEJ+GC)	RAINBOW Pac mono (GEJ+GC)	RAINBOW Ram + Pac (GEJ+GC)
N	314	296	335	330
ORR (%)	6.7	12.5	16.0	27.0
DCR (%)	NR	NR	63.4	79.4
PFS months (95% CI)	3.4 (2.8, 3.9)	4.1 (3.2–4.2)	2.9 (2.8, 3.0)	4.4 (4.2, 5.3)
OS months (95% CI)	7.1 (6.3, 8.0)	8.3 (7.7, 8.8)	7.4 (6.3, 8.4)	9.6 (8.5, 10.8)

Clinical Activity of DKN-01 Plus Paclitaxel:

Evaluable Esophagogastric Patients by Tumor Location



Therapy	Patients Treated	Prior Therapies	Overall Response Rate	Stable Disease Rate	Disease Control Rate
DKN-01 + paclitaxel	52	1-7	**25%**	35%	60%

+ = PD, - = PR, no symbol = SD

DKN-01 Plus Paclitaxel Combination

Esophagogastric Malignancies

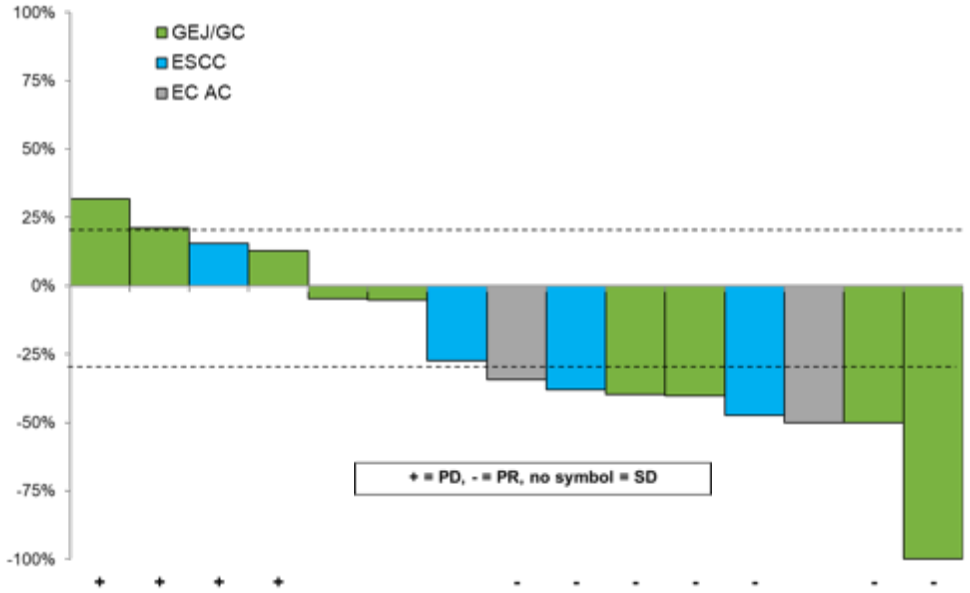
- 14.1 months (61.1 weeks) overall survival in second-line patients

Primary Location	Total (n)	PR (n)	SD (n)	PD (n)	NE* (n)	ND** (n)	Evaluable*** n	ORR (n,%)	DCR (n,%)	**PFS* (weeks, 95% CI)**	**OS (weeks, 95% CI)**
ESCC	13	4	4	4	-	1	12	4 (33.3)	8 (66.7)	13.7 (7.0, 19.6)	31.0 (14.1, 47.3)
Esophageal AC	13	2	4	6	-	1	12	2 (16.7)	6 (50.0)	9.7 (7.9, 19.0)	28.4 (11.1, 55.1)
GEJ/Gastric AC	32	7	10	11	2	2	28	7 (25.0)	17 (60.7)	13.4 (8.0, 18.6)	27.9 (19.0, 35.6)
Overall	58	13	18	21	2	4	52	13 (25.0)	31 (59.6)	13.4 (8.1, 17.0)	27.9 (22.6, 33.3)
Prior Therapy											
1	16	7	4	4	-	1	15	7 (46.7)	11 (73.3)	19.6 (7.9, 40.7)	61.1 (27.9, 131.9)
2	21	3	7	10	1	-	20	3 (15.0)	10 (50.0)	9.7 (7.9, 14.7)	22.6 (14.7, 31.9)
> 2	21	3	8	6	1	3	17	3 (17.6)	11 (64.7)	11.8 (8.0, 15.7)	26.3 (13.1, 34.4)
Prior Taxane Exposure											
Yes	31	4	11	14	-	2	29	4 (13.8)	15 (51.7)	10.1 (8.0, 14.7)	23.1 (16.1, 30.4)
No	27	9	7	7	2	2	23	9 (39.1)	16 (69.6)	15.9 (8.0, 19.1)	31.0 (27.4, 61.1)

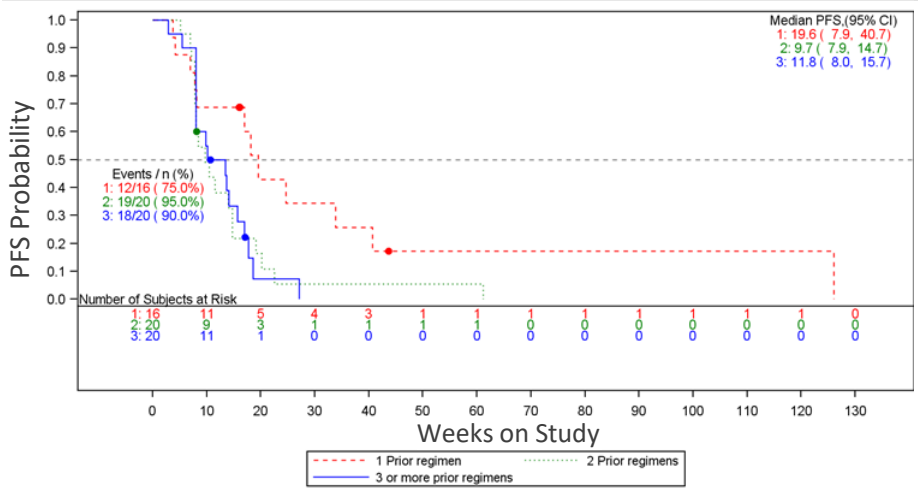
* Subjects with non-measurable disease at baseline are excluded from PFS analysis

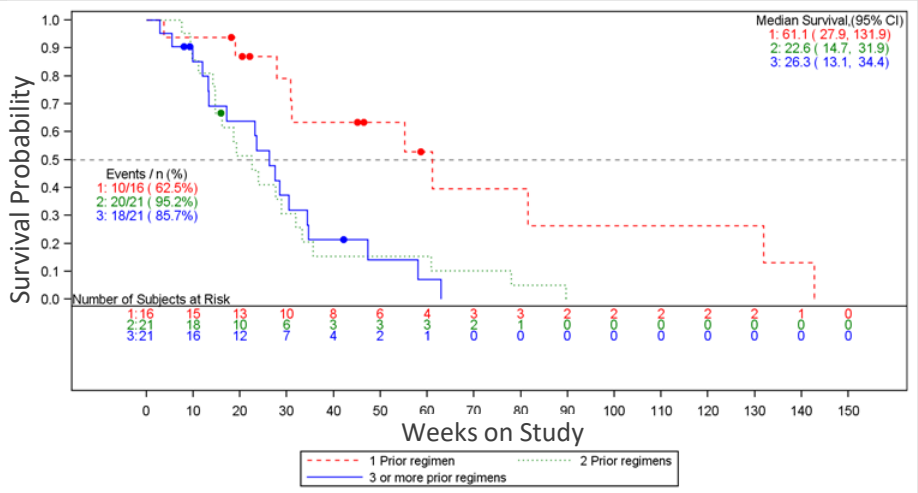
61 Weeks Median Overall Survival in Second Line Therapy Subset

Esophagogastric Patients – DKN-01/Paclitaxel



	All DKN-01 + paclitaxel, 2nd Line
n	15
ORR (%)	46.7
DCR (%)	73.3
PFS (weeks), median (95% CI)	19.6 (7.9, 40.7)
OS (weeks), median (95% CI)	61.1 (27.9, 131.9)





Conclusions

- Esophagogastric cancer patients have low response rates and survival outcomes and are in need of new targeted therapies
- DKN-01 plus paclitaxel combination exceeds the benchmark response rate and survival outcomes expected from paclitaxel alone
- DKN-01 plus pembrolizumab combination therapy extends survival and PFS in the DKK1-high subgroup of PD-1/PD-L1 naïve GEJ/GC patients independent of PD-L1 status
- Totality of DKN-01 data (monotherapy, chemo combination and PD-1 combination) creates a compelling profile and should be evaluated in randomized clinical trials
  - DKN-01 and paclitaxel in second-line or later esophageal cancer
  - DKN-01 and PD-1/PD-L1 antibody in DKK1-high gastric cancer
- Triplet combinations should be considered
  - DKN-01, PD-1/PD-L1 antibody and paclitaxel
  - DKN-01, ramucirumab and paclitaxel

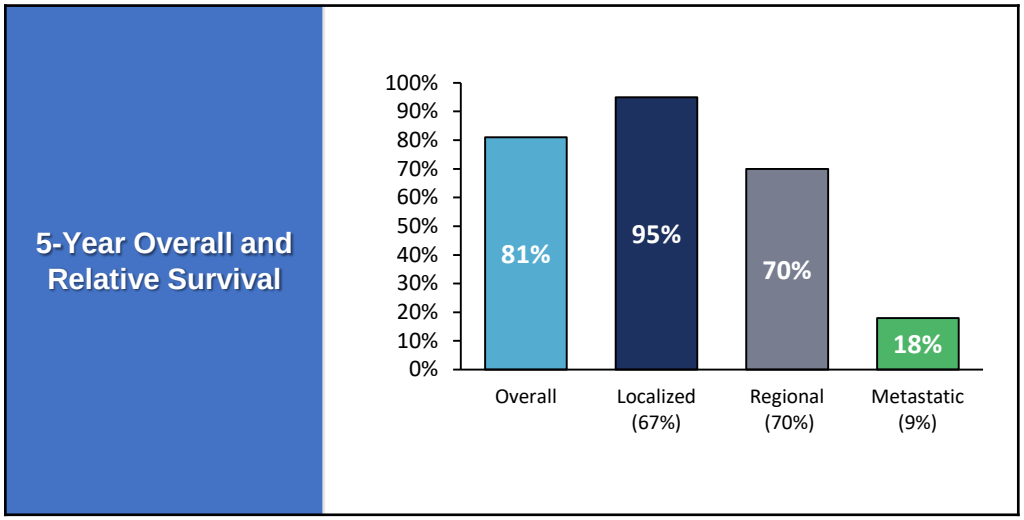
DKN-01

Gynecologic Malignancies

Dr. Rebecca Arend
UAB Comprehensive Cancer Center

Endometrial Cancer

- Most common primary gynecological cancer in the western world, with approximately 62,000 cases estimated in the United States in 2018
- Fourth most common cancer in women in the US and incidence is increasing
- Clinical risk factors include estrogen-only hormone replacement, obesity, chronic anovulation, tamoxifen therapy, nulliparity, early menarche, and late menopause
- Clinically categorized into two subtypes:
  - Type I carcinomas, which account for most cases (70-80%), ae typically associated with a good prognosis, early stage at diagnosis, estrogen signaling, obesity, and low-grade endometrioid histology
  - Type II carcinomas are characterized by high stage at the time of diagnosis, non-endometrioid histology, and poor prognosis



Endometrial Cancer NCCN Guidelines for Patients

Result of imaging	Treatment
Cancer hasn't spread farther than the pelvis or abdomen	**Total hysterectomy and bilateral salpingo-oophorectomy** Before surgery, chemotherapy may be used to shrink the tumor.
Cancer has spread to distant areas of the body	**You may have one or more of these treatments:** •Chemotherapy •External radiation •Hormone therapy •Surgery to help with symptoms (not to cure the cancer)
Cancer has spread beyond the uterus and can't be removed with surgery first	**OPTION 1: External radiation, with or without:** • Internal radiation (brachytherapy) • Chemotherapy
	OPTION 2: Systemic therapy (chemotherapy and/ or hormone therapy)

Wnt Pathway Mutations are Frequent in Endometrial Cancer

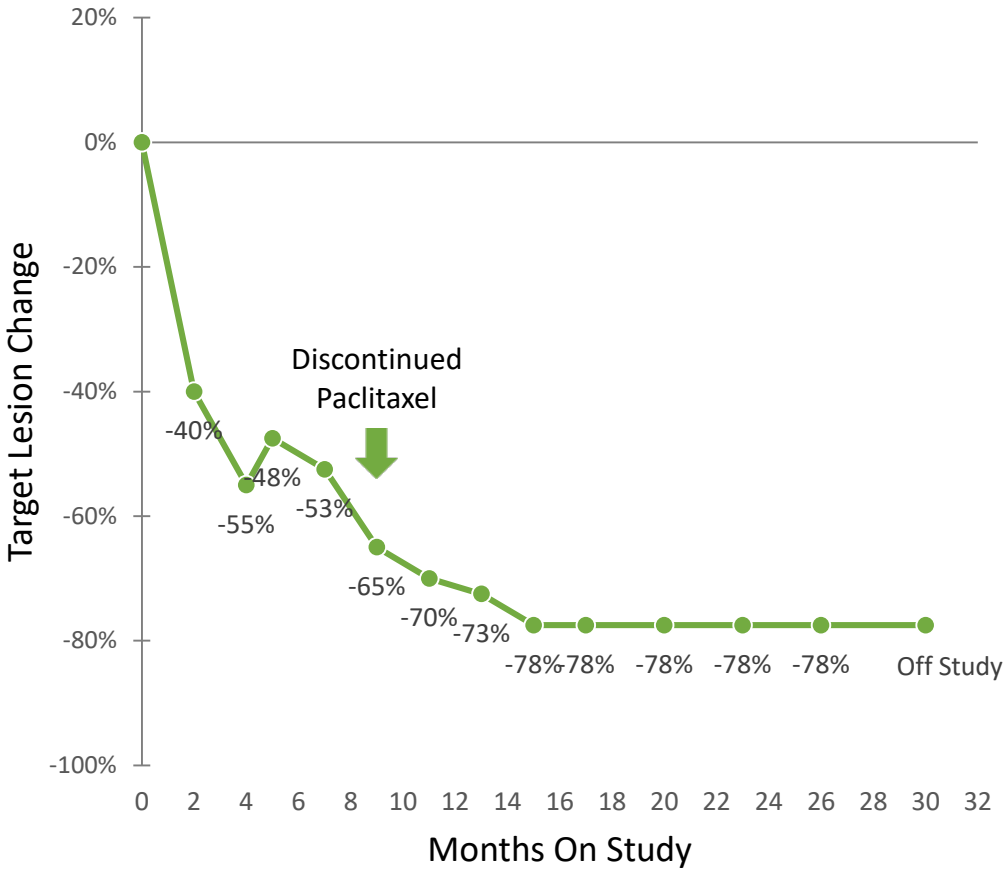
	Endometrioid	Serous	Carcinosarcoma	Clear cell
Bokhman subtype	I	II	II	II
TP53 mutation	Rare	>90%	60–90%	35%
PI3K alterations	*PTEN* mutation (75–85%) *PIK3CA* mutation (50–60%) *PIK3R1* mutation (40–50%)	*PTEN* mutation (11%) *PIK3CA* amplification (45%) *PIK3CA* mutation (35%) *PIK3R1* mutation (12%)	*PTEN* mutation (19%) *PIK3CA* mutation (35%) *PIK3CA* amplification (14%)	*PTEN* loss (80%) *PIK3CA* mutation (18%)
KRAS mutation	20–30%	3%	17%	0%
ERBB alterations	None	*ERBB2* amplification (25–30%)	*ERBB2* amplification (13–20%) *ERBB3* amplification or mutation (13%)	*ERBB2* mutation (12%) *ERBB2* amplification (16%)
FGFR amplification or mutation	*FGFR2* mutation (12%)	*FGFR2* mutation (5%) Frequent *FGFR1* and *FGFR3* amplification	*FGFR3* amplification (20%)	..
Wnt/β-catenin	*CTNNB1* mutation (25%)	*CTNNB1* mutation (3%)	..	..
Other	*ARID1A* mutation (35–40%)	*PPP2R1A* mutation (20%) *FBXW7* mutation (20% of undifferentiated endometrial carcinoma) *LRPB1* deletion Frequent amplifications in *MYC*, *CCNE1*, and *SOX17*	*PPP2R1A* mutation (28%) *FBXW7* mutation (35–40%) *ARID1A* mutation (25%) *CCNE1* amplification (42%) *SOX17* amplification (25%)	*ARID1A* (25%) *TERT* promoter mutations

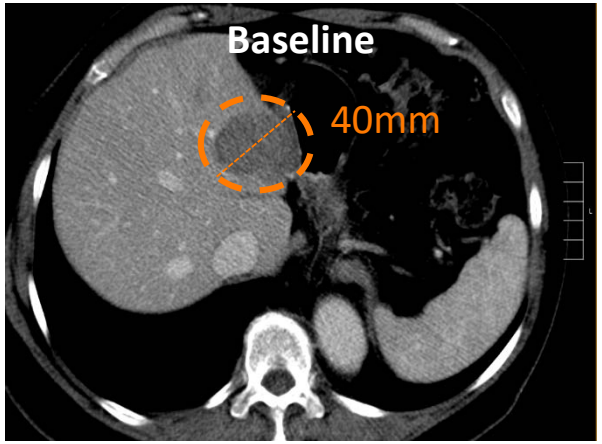
Table 2: Molecular classification of endometrial cancers, by histology

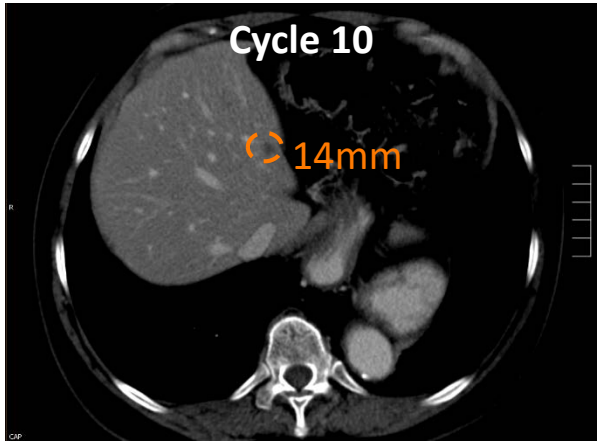
www.thelancet.com Published online September 7, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00130-0

Durable DKN-01 Response

GEJ AC Patient with *CTNNB1* Mutation



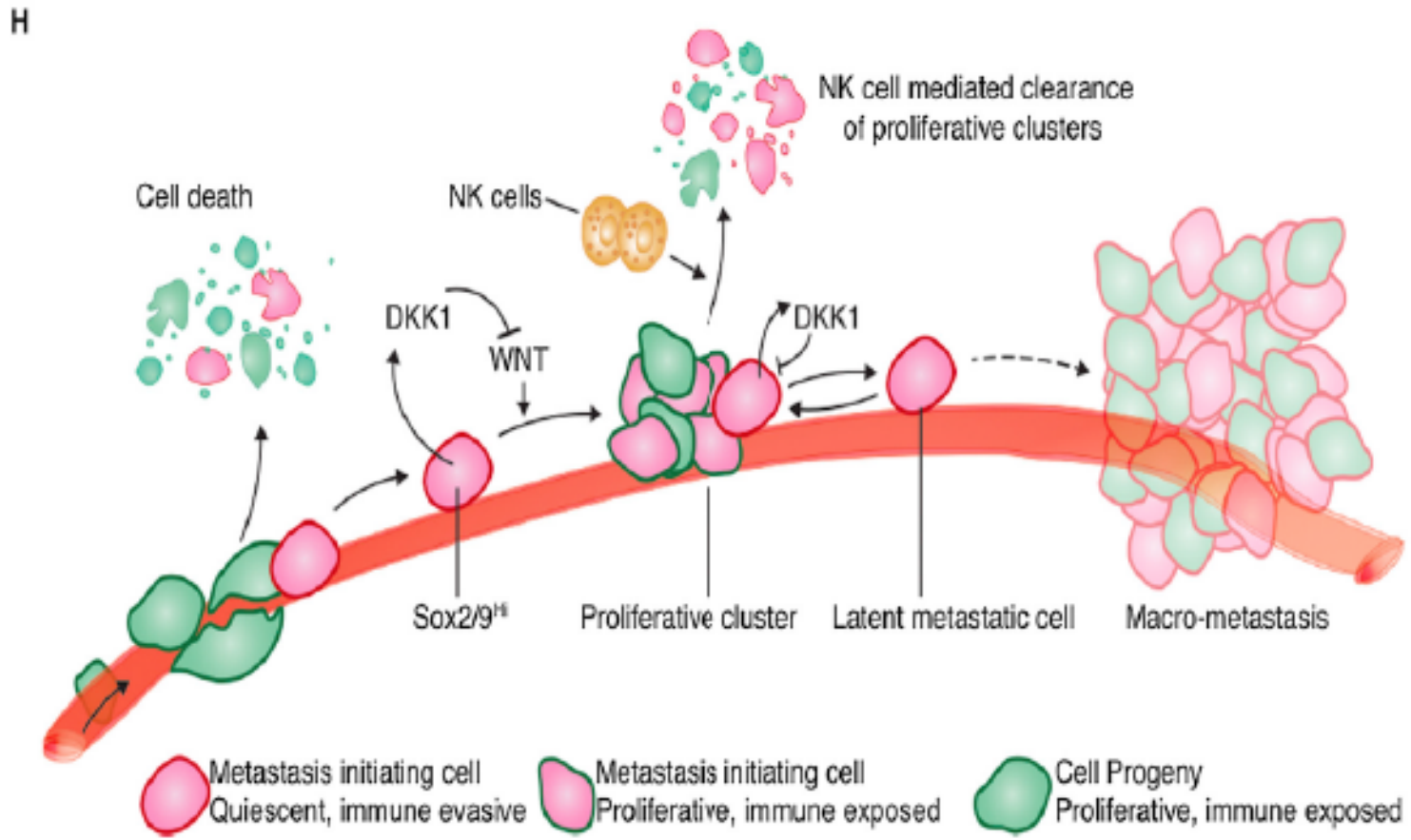




Rationale for Inhibiting DKK1 in Gynecologic Cancers

- DKK1 contributes to tumor growth in gynecologic cancers.
- Elevated levels of DKK1 have been observed in both the serum and tumors from patients with gynecologic cancers.
- Elevated DKK1 serum levels associated with later International Federation of Gynecology and Obstetrics (FIGO) stages for both cancers and lymphatic metastasis for cervical cancer.
- DKK1 expression correlated with worse clinical outcomes, such as advanced FIGO stage and overall survival.
- Nonclinical models have demonstrated that DKK1 promotes ovarian cancer cell invasion and that depletion of DKK1 had efficacy in a murine ovarian tumor reduction model.
- Malignancies with activated Wnt/β-catenin signaling produce higher levels of tumoral DKK1
- Activated Wnt/β-catenin signaling genetic mutations occur early in the oncogenic process and are associated with immune exclusion
- Patients with high tumoral DKK1 have improved outcomes and may serve as an enrichment strategy in future studies

DKK1 and Immune Evasion



Gynecologic Study Design

- Phase 2 basket study study enriched for Wnt signaling alterations explores genetic mutations and DKK1 expression as predictive biomarkers
- Evaluates DKN-01 as monotherapy or in combination with paclitaxel
- Patients with recurrent epithelial endometrial cancer (EEC) or recurrent platinum-resistant/refractory epithelial ovarian cancer (EOC)

Eligibility Criteria:

- Refractory or intolerant to ≥ 1 prior therapy
- Tumor tissue for mandatory pre-treatment and on-treatment evaluation
- Measurable disease
- Patients not eligible to receive paclitaxel received single-agent DKN-01

DKN-01 300 mg monotherapy 28-day cycle

# of pts*	EEC	Mutated	Non-mutated
Total	23	14	9
Evaluable	**12**	**10**	**2**

# of pts	EOC	Mutated	Non-mutated
Total*	15	9	6
Evaluable	**11**	**7**	**4**

DKN-01 300 mg D1 & 15 + Paclitaxel 80 mg (D 1, 8 & 15) 28-day cycle

# of pts*	EEC	Mutated	Non-mutated
Total	28	18	10
Evaluable	**23**	**14**	**9**

# of pts*	EOC	Mutated	Non-mutated
Total	19	10	9
Evaluable	**19**	**10**	**9**

*Evaluable as of 1 May 2019

Primary Objective:

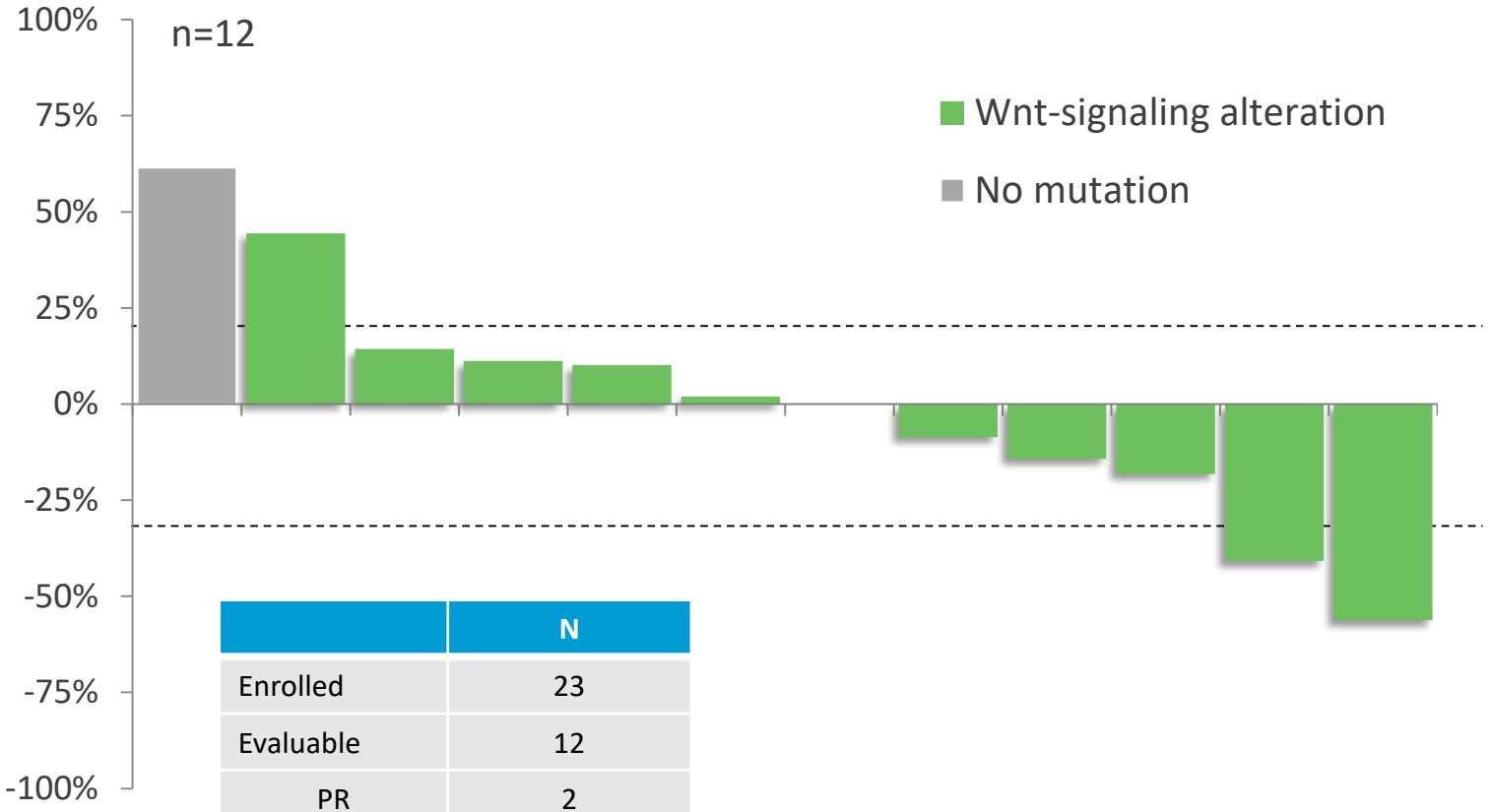
- Objective response rate (ORR)

Secondary Objectives:

- Objective disease control rate (ODCR)
- Overall survival (OS)
- Progression-free survival (PFS)
- Duration of response (DoR)
- Duration of complete response (DoCR)
- Time to treatment failure (TTTF)
- Safety
- PK/PD

Response Associated With Wnt-signaling Genetic Alterations

Endometrial Cancer - DKN-01 Monotherapy

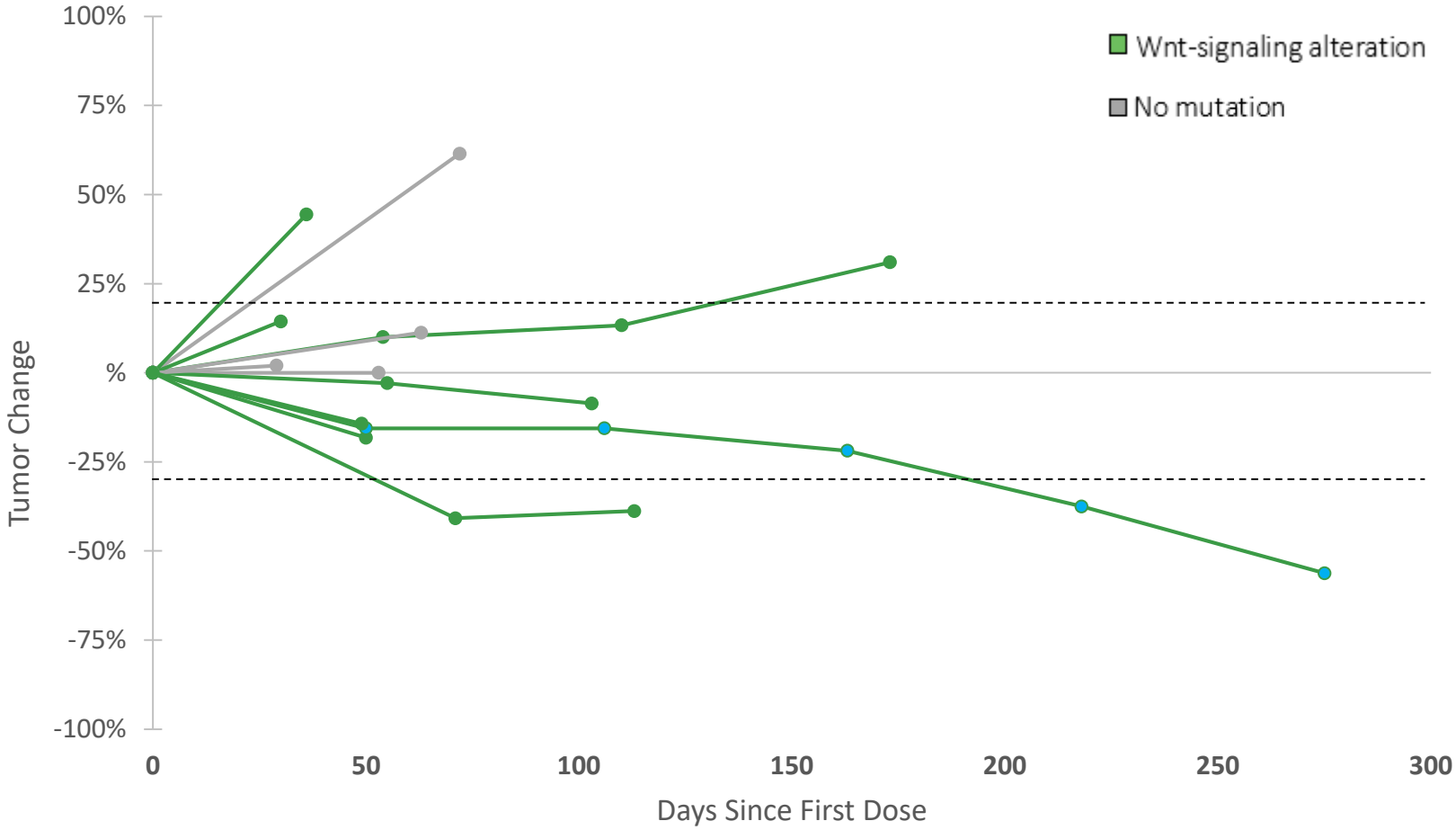


	N
Enrolled	23
Evaluable	12
PR	2
SD	5
PD	5
Non-evaluable	3
Pending Scans	8

Data as of 4-26-2019

Duration on Study is Associated With Wnt-signaling

Endometrial Cancer - DKN-01 Monotherapy

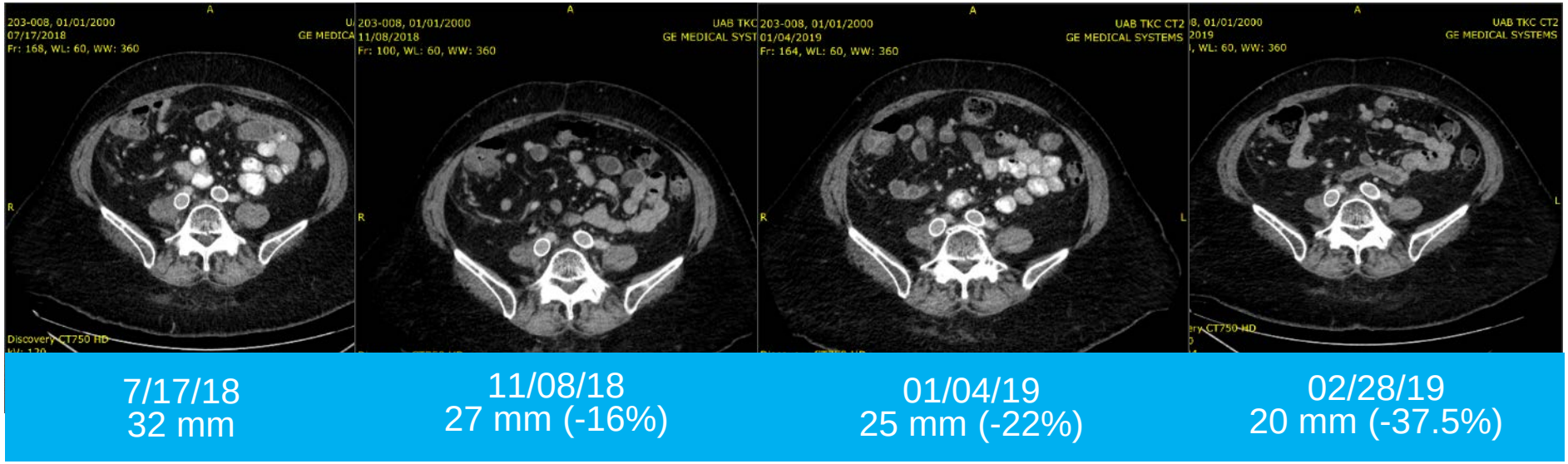


Patients with Wnt Pathway Mutations Respond to DKN-01 Monotherapy

Data as of April 26, 2019.

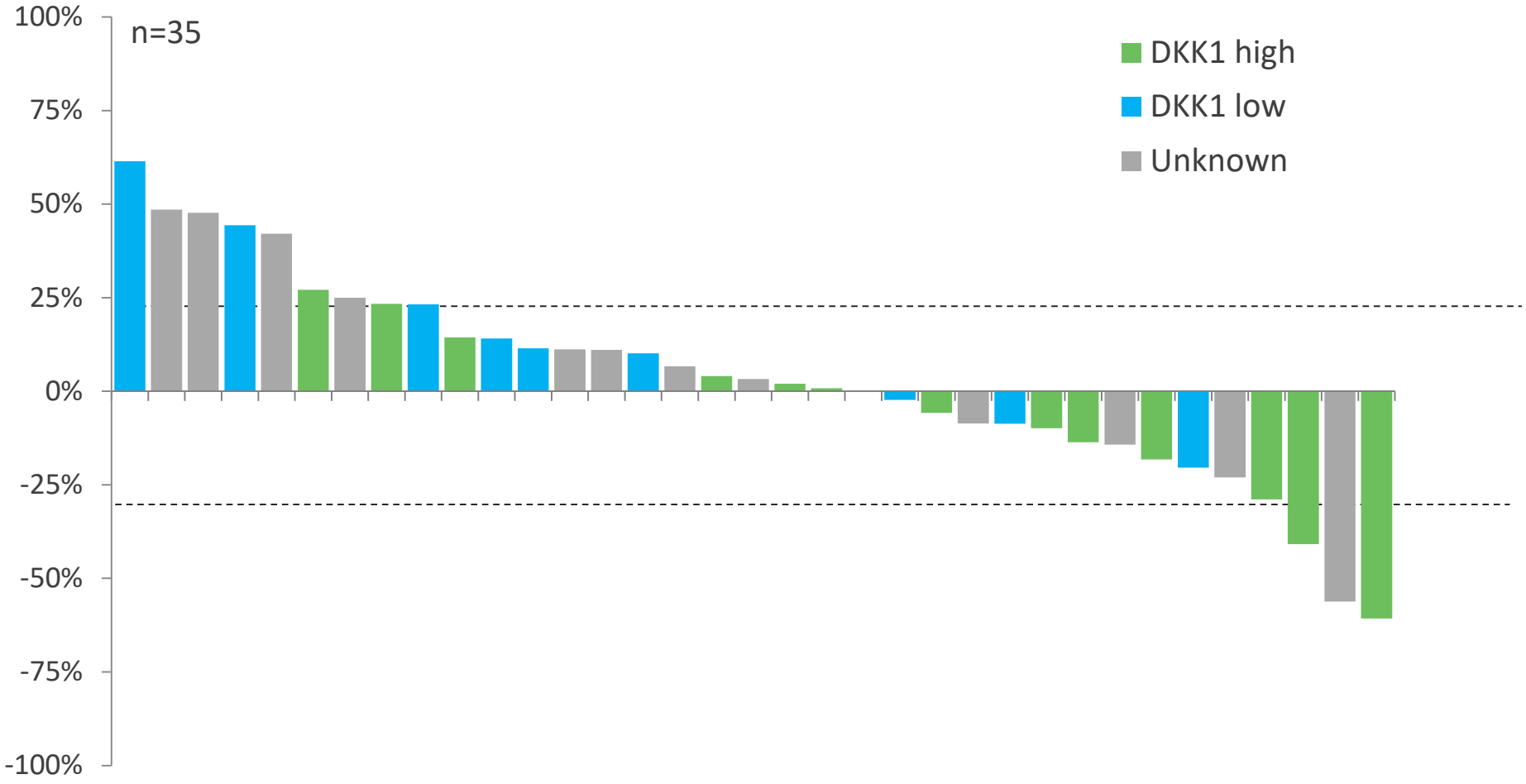
DKN-01 Monotherapy PR in Endometrial Cancer

- 60-year-old with endometrial adenocarcinoma (ER/PR+, HER2-, MSI-H, TMB: 46.65, Wnt signaling alterations: *ARID1A, MLL2*) treated with surgical excision followed by local vaginal cuff brachytherapy with recurrence requiring local radiotherapy then systemic chemotherapy (carboplatin and paclitaxel) complicated by worsening neuropathy and thrombocytopenia
- Enrolled in July 2018, with continued deepening of tumor reduction with each scan, developed partial response (-37.5%) after 8 cycles, confirmed PR after 10 cycles (-56.2%) remains on study in Cycle 14, tolerating therapy well



Responses Seen in Patients with DKK1-high

Endometrial Cancer: DKN-01 Monotherapy or in Combination with Paclitaxel



Data as of 4-26-2019

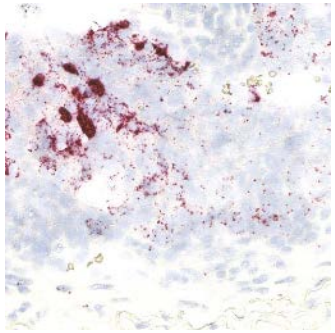
Tumors with Wnt/β-Catenin Activating Mutations Express Higher DKK1

Endometrial Cancer Patients

- Genetic and DKK1 RNAscope data for 25 patients
  (8 patients have a Wnt signaling activating mutation*)

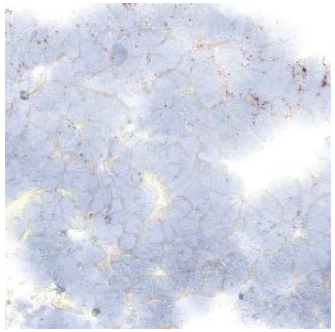
202-005: H-score = 115

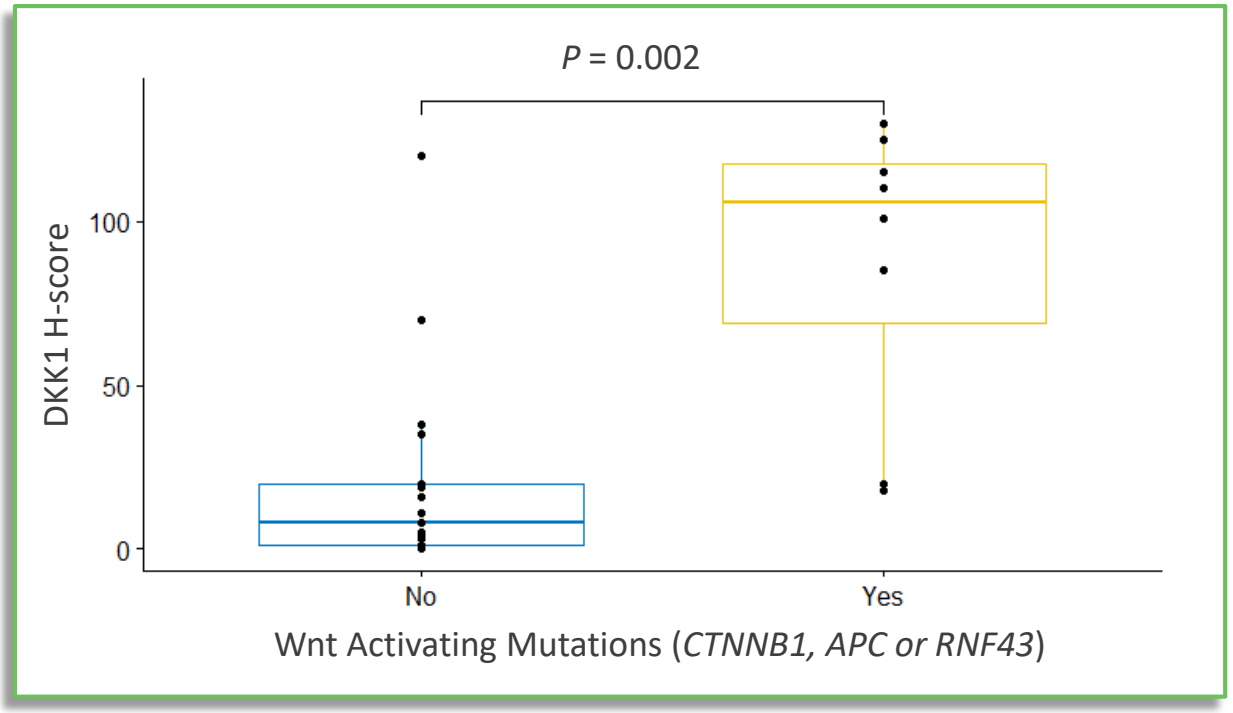
CTNNB1(S37F)



202-006: H-score = 11

No mutation



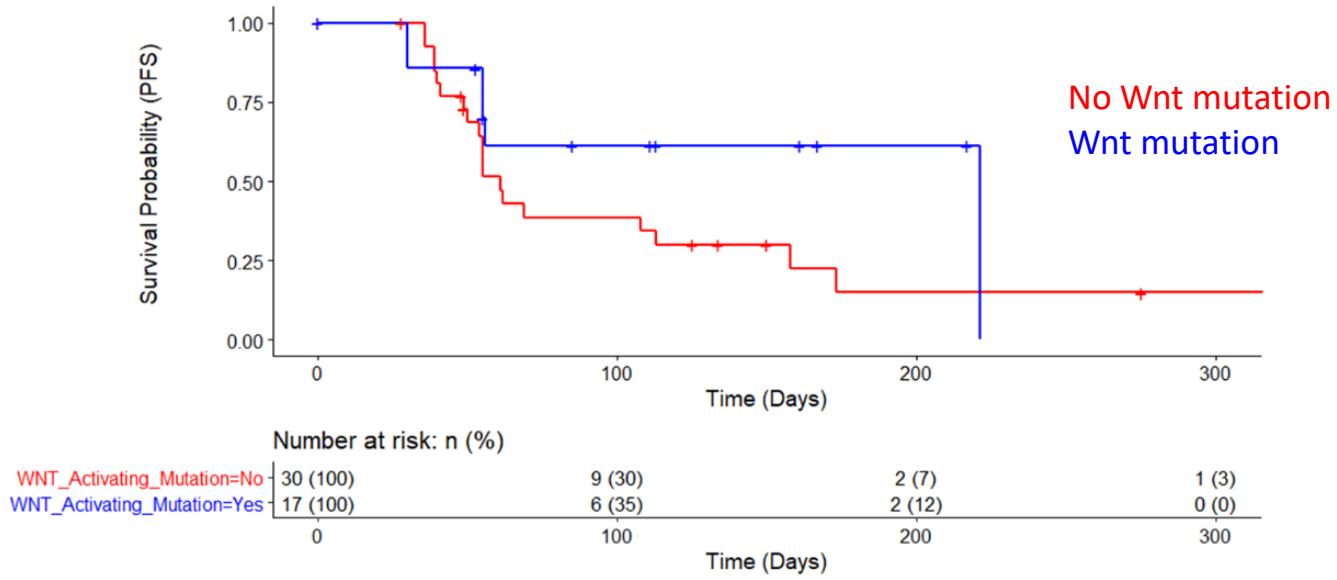


*β-catenin stabilizing, APC or RNF43 truncation

Trend Towards Longer PFS with Wnt/β-catenin Activating Mutations

Endometrial Cancer Patients

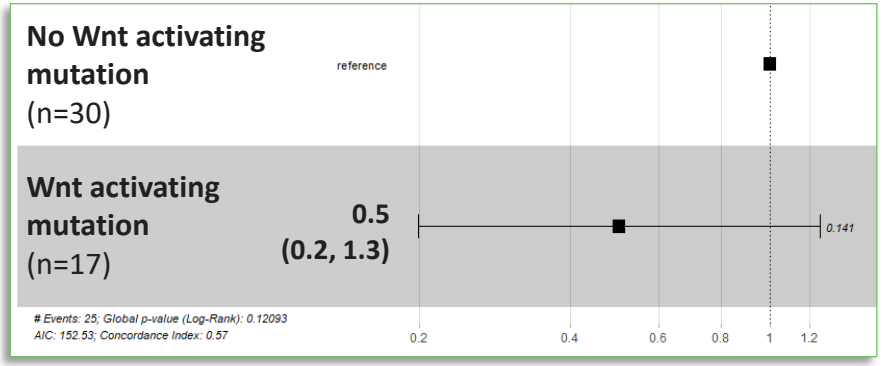
Kaplan Meier Estimate of PFS by Wnt/β-catenin Activating Mutation Status



Progression Free Survival

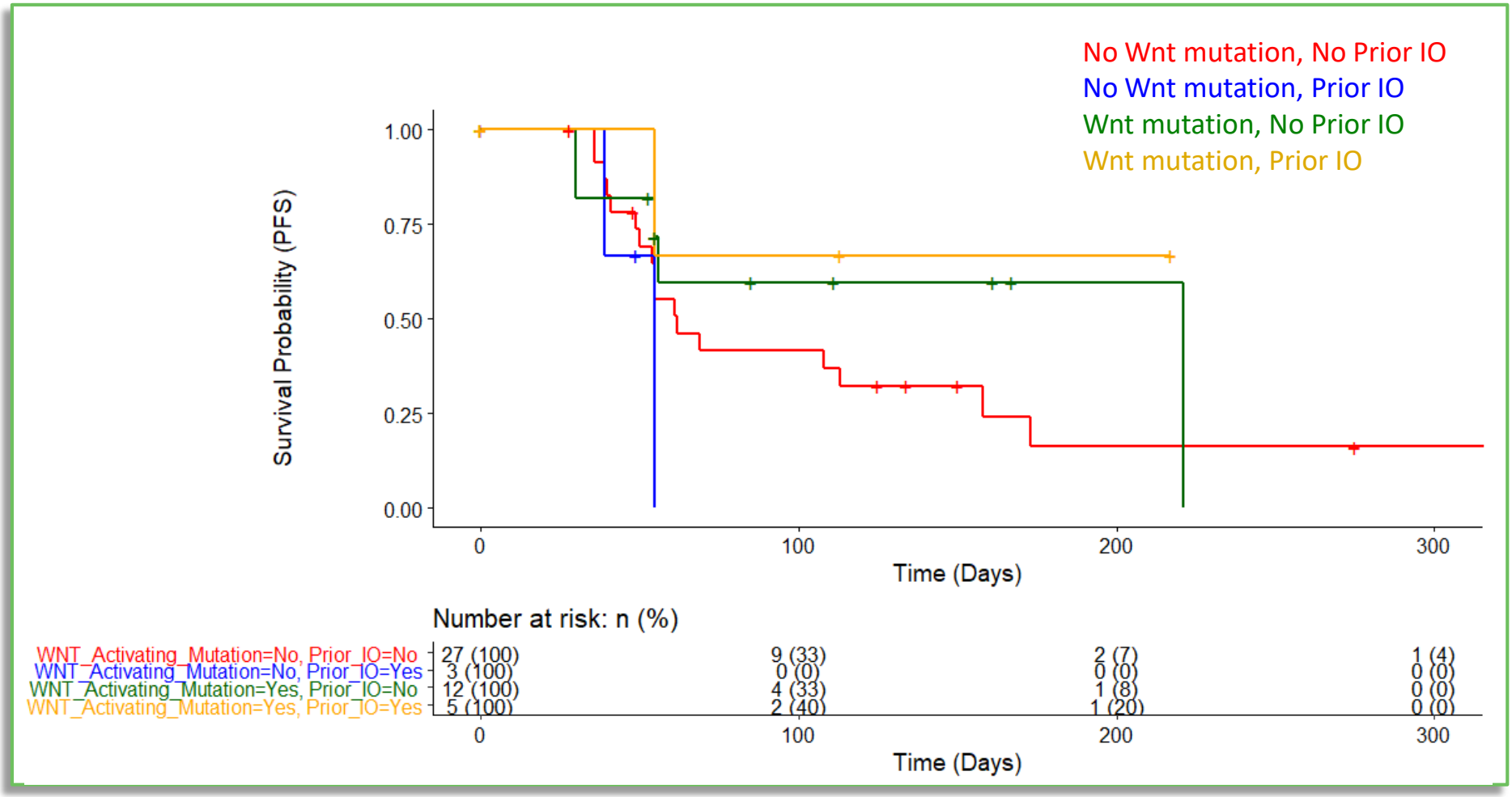
EEC	N	Median PFS (wks, 95%CI)
Wnt Activating Mutations		
No	30	8.7 (7.1, 16.1)
Yes (*CTNNB1, APC or RNF43*)	**17**	**31.6 (7.9, NR)**

Hazard Ratio



Wnt/β-catenin Activating Mutations and Prior IO Therapy: PFS

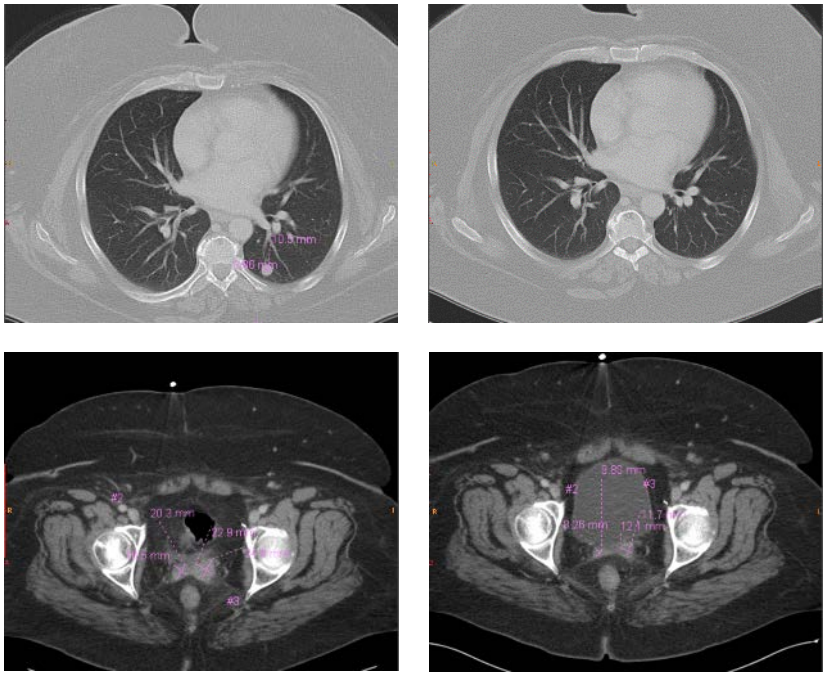
Endometrial Cancer Patients



Best Response in Wnt/β-catenin Activating Mutations (*CTNNB1 & APC*)

Uterine Carcinosarcoma Patient with *CTNNB1* Mutation and Partial Response

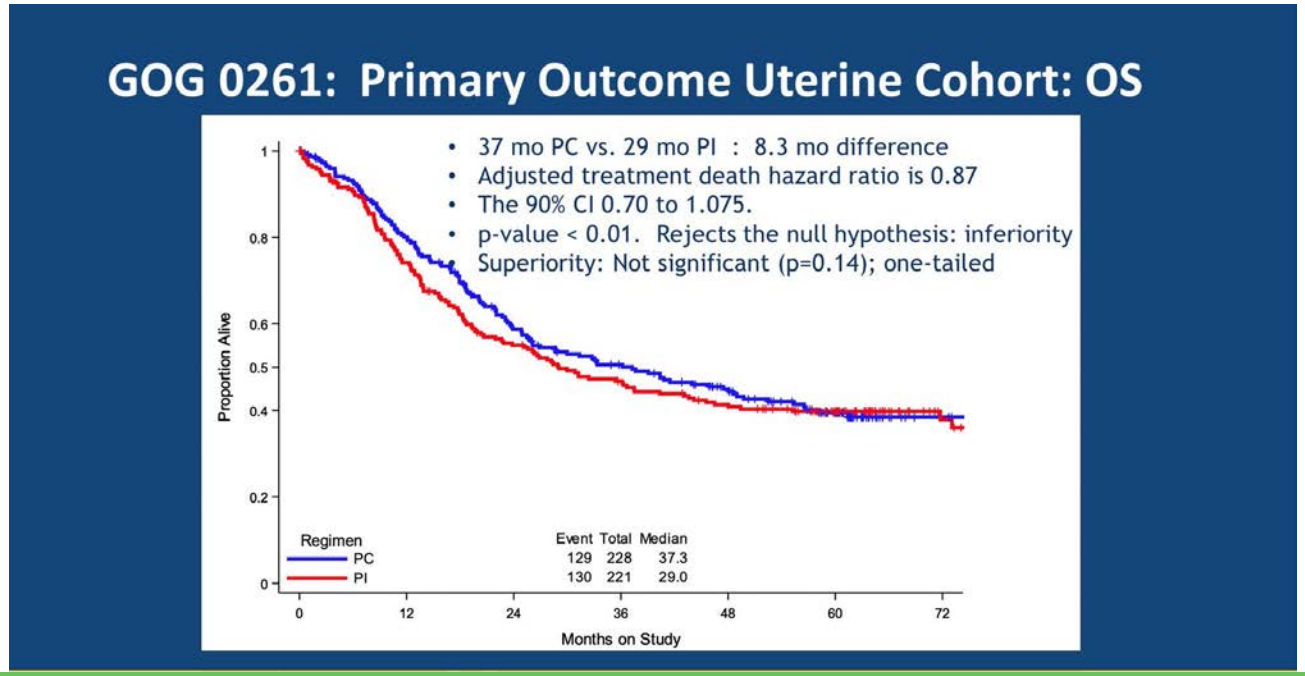
- 46-year-old female
- Recurrent uterine carcinosarcoma
- Previously treated with neoadjuvant/adjuvant (carbo/paclitaxel), debulking surgery and one therapy for advanced recurrent disease (cisplatin/XRT)
- Received DKN-01 + paclitaxel therapy
- First scans reveal PR (-61%) with resolution of lung nodules known to be Wnt driven (*CTNNB1*)



12/19/18 **02/13/19**

Uterine Carcinosarcoma (Malignant Mixed Mullerian Tumor)

- Malignant uterine neoplasm comprised on carcinomatous and sarcomatous elements
- Accounts for < 5% of all uterine cancer
- Aggressive, poor prognosis
  - 50% diagnosed with metastatic disease beyond the pelvis
  - 5-year survival of 9-22% for advance stage disease
- Poor response to chemotherapy



Uterine Carcinosarcoma: Further Study Warranted

- Four patients enrolled in original study groups
  - 3 patients treated with DKN-01 + paclitaxel
  - 1 patient treated with DKN-01 monotherapy
- Two patients with clinical benefit, both with *CTNNB1* mutations
  - One PR (DKN-01 + paclitaxel)
  - One prolonged SD (> 12 months) (DKN-01 monotherapy)
- Three patients with DKK1-high tumors
- Study now enrolling 30 additional patients enriched for Wnt-signaling alterations with higher dose of DKN-01 (600 mg)
  - 10 DKN-01 monotherapy
  - 20 DKN-01 + paclitaxel

Conclusions

- Endometrial cancer and carcinosarcoma patients are in need of new, more effective treatment options
- DKN-01 as a monotherapy and in combination with paclitaxel has generated partial responses and durable clinical benefit in heavily pre-treated patients
- Patients whose tumors have activating Wnt pathway mutations express higher levels of DKK1
- Patients whose tumors have Wnt pathway alterations experience greater clinical benefit
- DKN-01 (300 mg) is safe as a monotherapy or in combination with paclitaxel with no additive toxicities
- Updated data will be presented at IGCS in September 2019


LEAP THERAPEUTICS
Patient Number / Patienten
Sponsor Trial Code /
Drug name: DKN-01 for

DKN-01

DKN-01 Path Forward

- Totality of DKN-01 data (monotherapy, chemo combination and PD-1 combination) creates a compelling profile and should be evaluated further in esophagogastric cancer with randomized clinical trials
  - DKN-01 and paclitaxel in second-line or later esophageal cancer
  - DKN-01 and PD-1/PD-L1 antibody in DKK1-high gastric cancer
- Emerging DKN-01 data in endometrial cancer and carcinosarcoma creates an attractive opportunity
  - Patients whose tumors have activating Wnt pathway mutations express higher levels of DKK1 and have enhanced outcomes
  - Updated data will be presented at IGCS in September 2019
- Expand future indications and combinations through use of biomarker focused Investigator-Initiated and Cooperative Group Studies
  - Prostate Cancer – NYU Langone
  - HCC – University of Mainz
  - Tecentriq combination in EGC/BTC – EORTC and Roche
- Business strategy to identify partner for late-stage development


LEAP THERAPEUTICS
Patient Number / Patienten
Sponsor Trial Code /
Drug name: DKN-01 for

DKN-01

Q&A