DKN-01 in Gynecologic Cancers

March 22, 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.

AGENDA

Leap Therapeutics

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Q&A

DKN-01 in Gynecologic Malignancies

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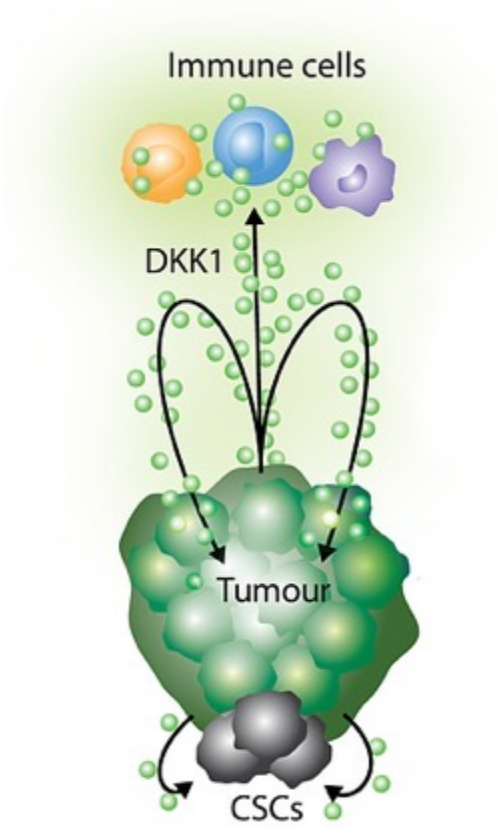
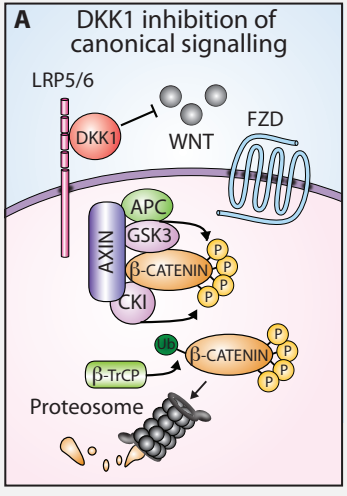
DKK1 in Cancer



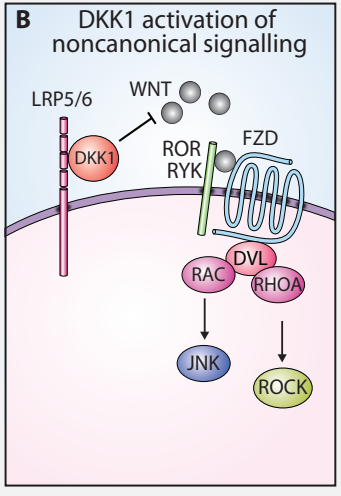
- Overexpression of DKK1 linked to poor prognosis
- Tumor cells secrete DKK1 promoting proliferation, metastasis and angiogenesis
- DKK1 suppresses anti-tumor immune responses
- Neutralizing DKK1 activates an innate immune response in oncology models

DKK1 is an Important Target Regulating Key Signaling Pathways

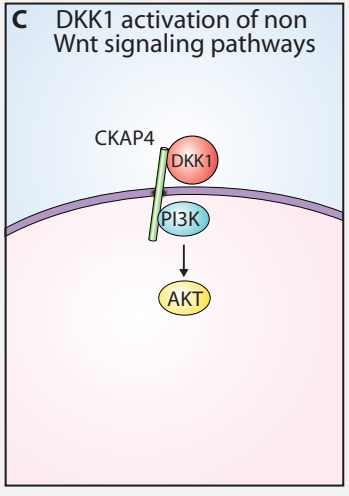
DKK1 inhibits canonical Wnt signaling



DKK1 indirectly activates noncanonical signaling



DKK1 activates PI3K/AKT signaling



Malladi et al., *Cell*, 2016; D'Amico et al., *J Exp Med*, 2016; Kimura et al., *J Clin Invest*, 2016; Krause et at., *Cell Death Dis*, 2014; Tao et al., *Dig Liver Dis*, 2013; Thudi et al., *Prostate*, 2011; Wang and Zhang, *Clin Exp Metastasis*, 2011

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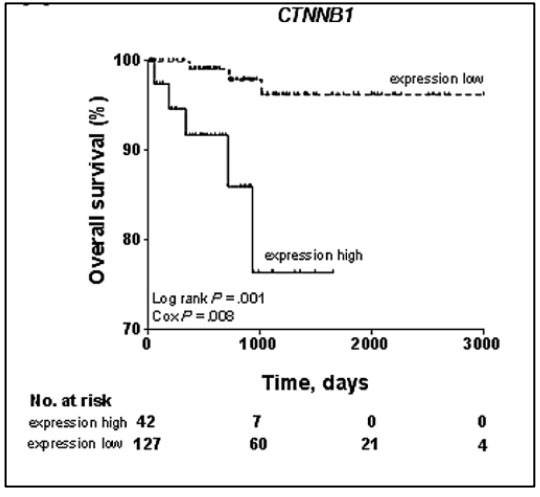
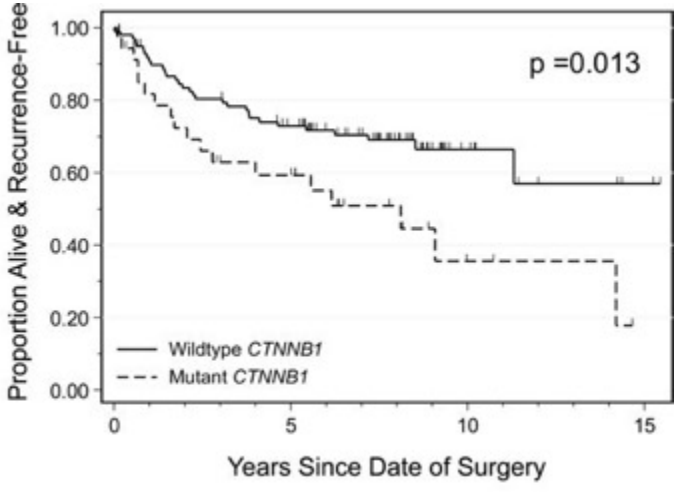
Wnt/ß-Catenin Activation is Associated With Poor Outcomes in EEC



Liu et al; 2014 Natl Cancer Inst

- *CTNNB1* exon 3 mutations characterize an aggressive subset of low-grade and low-stage EEC occurring
- Higher expression levels of *CTNNB1* were associated with poor overall survival



Kurnit et al; 2017 Mod Pathol

- Recurrence-free survival for endometrioid endometrial cancer patients, grade 1-2 and stage I-II
- Analysis limited to identify higher risk patients in an otherwise lower-risk setting
- *CTNNB1* exon 3 mutations were associated with significantly worse recurrence-free survival.

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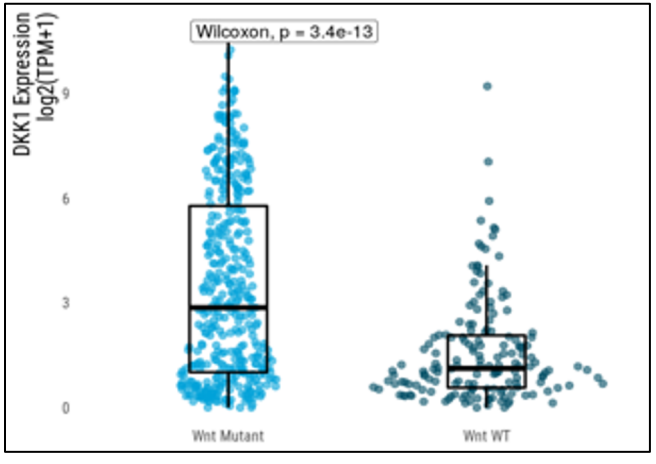
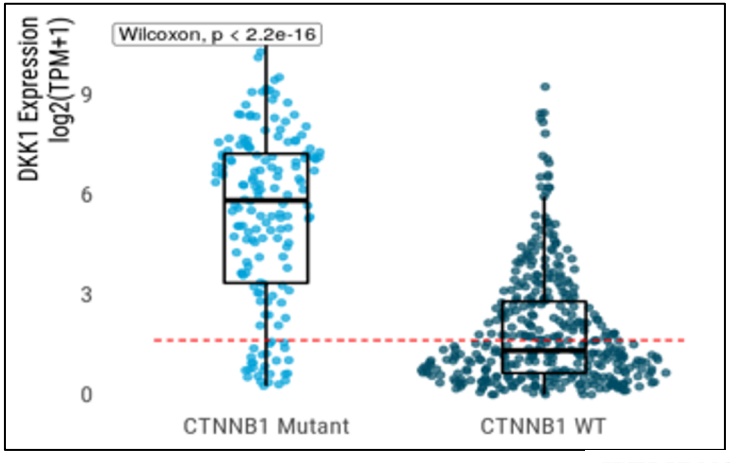
Activation of Wnt/ß-catenin-Dependent Signaling Results in Increased Expression of DKK1





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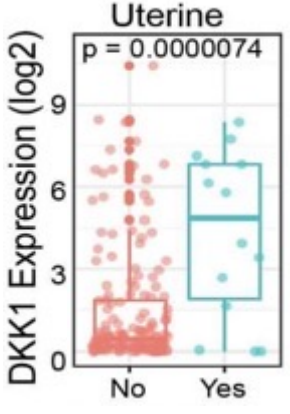

Stabilizing *CTNNB1* Mutant

Real World Evidence (RWE) in endometrioid endometrial cancer patients (Tempus)
*Wnt activating mutations include CTNNB1, AXIN1/2, APC, ZNRF3, RNF43, RSPO2/3

TCGA data.
Alterations to S33, S37, T41 or S45

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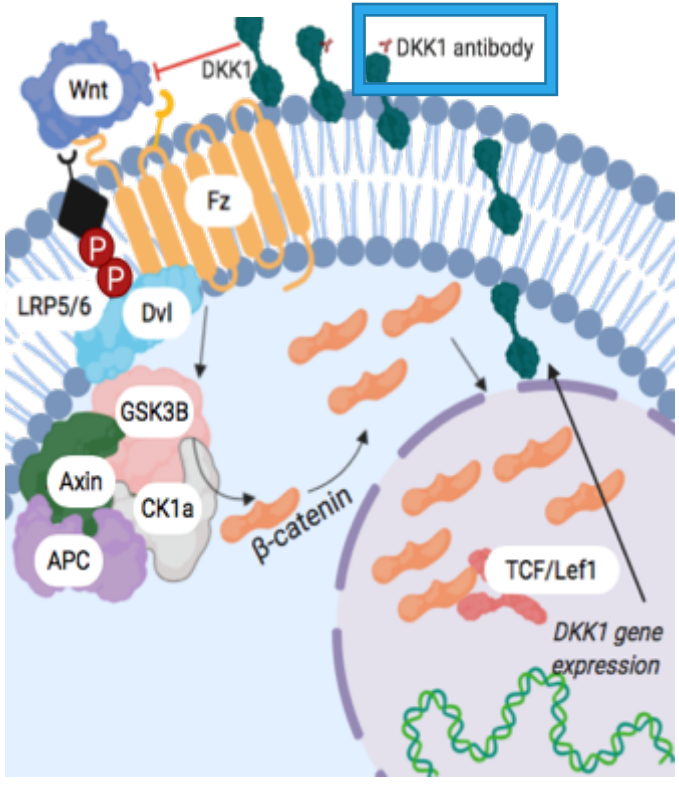
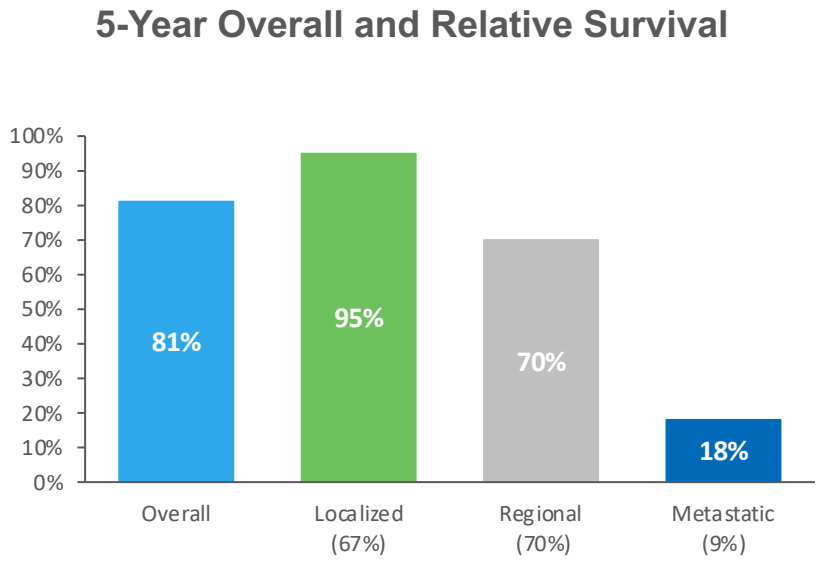
DKN-01: A Humanized Monoclonal Antibody [IgG4] Targeting DKK1

- Humanized monoclonal antibody [IgG4] against DKK1
- DKN-01 Mechanism of Action:
  - (1) Direct anti-tumor effects
  - (2) Activates innate immune response
  - (3) Acts as an anti-angiogenic agent
- GEJ/GC tumors with DKK1-high expression have demonstrated better clinical outcomes compared with DKK1-low tumors following treatment with DKN-01 + pembrolizumab
  - ORR: 50 vs 0%
  - DCR: 80 vs 20%
  - PFS: 22.1 vs 5.9 weeks



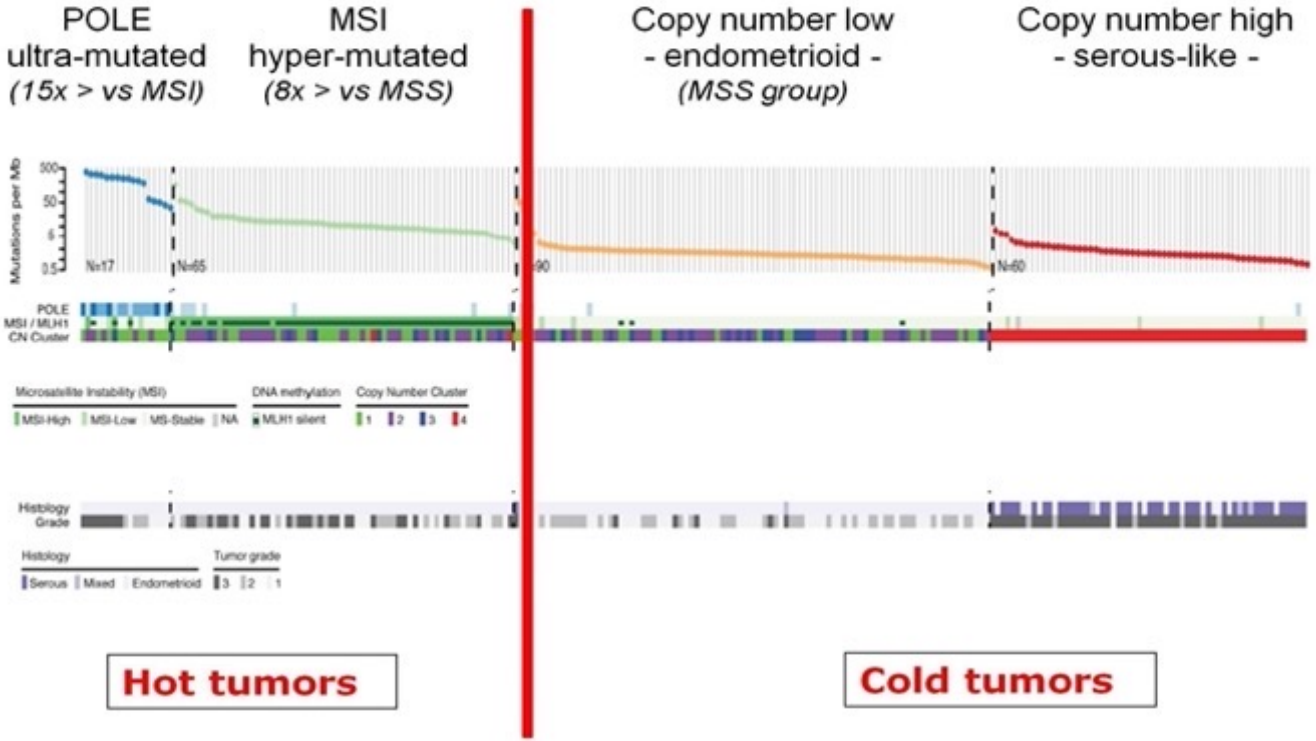
Endometrial Cancer

- Most common gynecological cancer in the western world
- ~62,000 annual cases in the United States and the incidence is increasing
- Fourth most common cancer in women in the US
- Clinical risk factors include estrogen-only hormone replacement, obesity, chronic anovulation, tamoxifen therapy, nulliparity, early menarche, and late menopause



Endometrial Cancer (EC) – Four molecular subtypes

(Integrated genomic, transcriptomic and proteomic characterization)

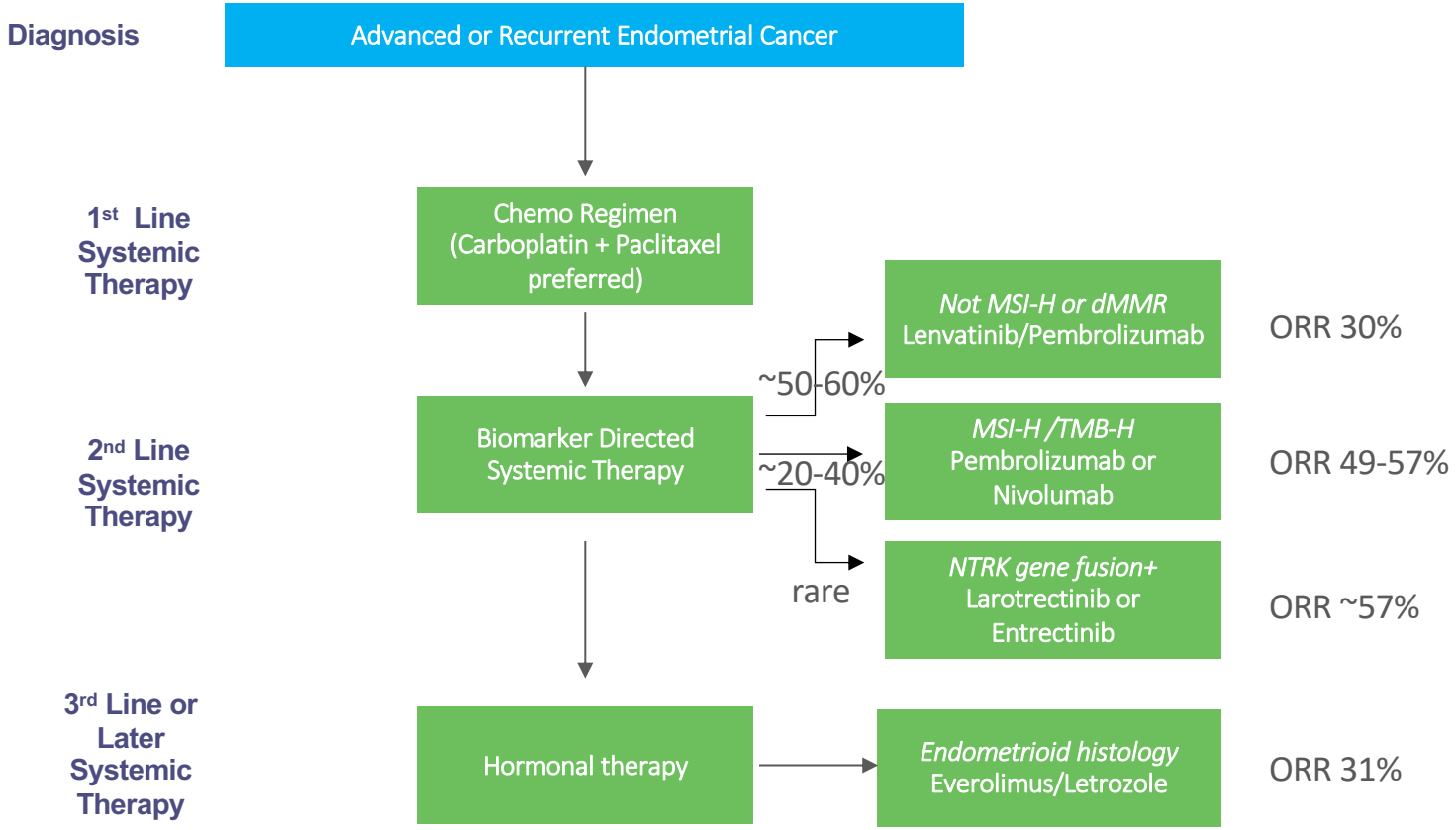


GOG 210 Endometrioid (Cosgrove 2018)

Kandoth et al., Nature 2013

Incidence: 49% CNS, 4% POLE mutant, 39% MMR deficient, 8% copy number altered (CNA).
Cancer-specific mortality: 5%=CNS ; 2.6% =POLE tumors; 7.6%=MMR deficient tumors; 19% with CNA tumors.

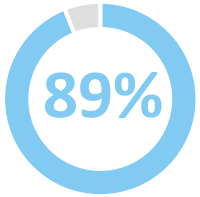
Treatment Paradigm for Advanced Endometrial Cancer



Single Agent Activity in Endometrial Cancer

Class	Drug name	ORR (%)	DCR (%)	mPFS (mos)
Anti-PD(L)-1: MSS/refractory PD-L1+	pembrolizumab	13	26	1.8
	dostarlimab	20	-	-
	durvalumab	6	-	-
	avelumab	3	-	-
Anti-angiogenic	bevacizumab	13.5	63.5	4.2
	lenvatinib	14.3	-	5.4
mTOR	everolimus	9	36	2.8
Cytotoxic Chemotherapies	doxorubicin	22	77	3.2
	paclitaxel	26.7	53.4	-
	ifosfamide	12.5	-	-
	PLD	11.5	71	-
	oxaliplatin	13.5	42.3	-
	ixabepilone	12	60	2.9

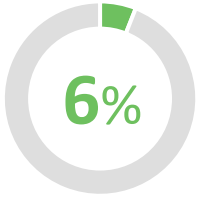
Pembrolizumab + Lenvatinib Data



Grade ≥3 Treatment-Emergent AEs[1]

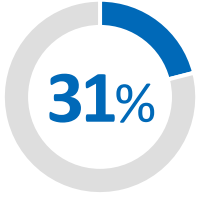
Any Grade Treatment-Emergent AEs[1]

Most common AE's with LENVIMA + KEYTRUDA treated patients:
hypertension (64.0%), hypothyroidism (57.4%), diarrhea (54.2%), nausea (49.5%), decreased appetite (44.8%), vomiting (36.7%), weight decrease (34.0%), fatigue (33.0%), arthralgia (30.5%), proteinuria (28.8%), anemia (26.1%), constipation (25.9%) and urinary tract infection (25.6%).



FATAL ADVERSE REACTIONS[1]

Including gastrointestinal disorders: 1.2%, cardiac disorders: 0.5%, general disorders: 1.5%, infections: 0.7%, decreased appetite: 0.2%, neoplasms, nervous system, psychiatric, renal, reproductive, or respiratory disorders: 0.2% each



LENVIMA DISCONTINUATION[1]

KEYTRUDA discontinuation 19%[1,2]:
Most common AE's leading to discontinuation of KEYTRUDA: adrenal insufficiency, colitis, pancreatitis and muscular weakness (2% each).

AE's leading to interruption of KEYTRUDA (49%)[2]:
fatigue (14%), diarrhea, and decreased appetite (6% each), rash (5%), renal impairment, vomiting, increased lipase, decreased weight (4% each), nausea, increased blood alkaline phosphatase, and skin ulcer (3% each), adrenal insufficiency, increased amylase, hypocalcemia, hypomagnesemia, hyponatremia, peripheral edema, musculoskeletal pain, pancreatitis, and syncope (2% each).

AE's leading to reduction or interruption of LENVIMA (88%)[2]:
fatigue (32%), hypertension (26%), diarrhea (18%), nausea, palmar-plantar erythrodysesthesia, vomiting (13% each), decreased appetite (12%), musculoskeletal pain (11%), stomatitis (9%), abdominal pain, hemorrhages (7% each), renal impairment, decreased weight (6% each), rash, headache, increased lipase, and proteinuria (5% each).

AGENT	POPULATION	n	ORR	CR	PR	SD	mPFS
Len + Pembro KN-775	Post platinum-based therapy, all-comers (dMMR + pMMR)	411	31.9%	6.6%	25.3%	47.0%	7.2 months
	Post platinum-based therapy, pMMR	346	30.3%	5.2%	25.1%	48.6%	6.6 months

[1]KEYNOTE-775 data presented at SGO 2021
[2]FDA Approves LENVIMA® (lenvatinib) plus KEYTRUDA® (pembrolizumab) Combination Treatment for Patients with Certain Types of Endometrial Carcinoma. *https://www.eisai.com/news/2019/news201967.html*

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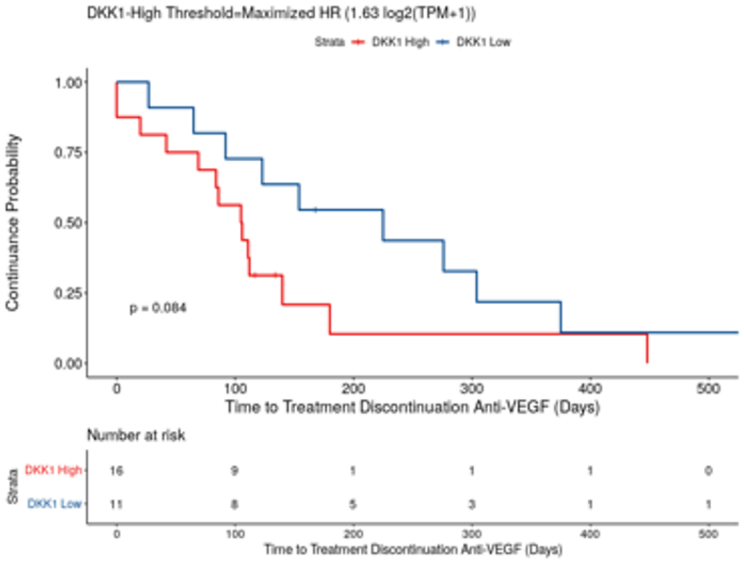
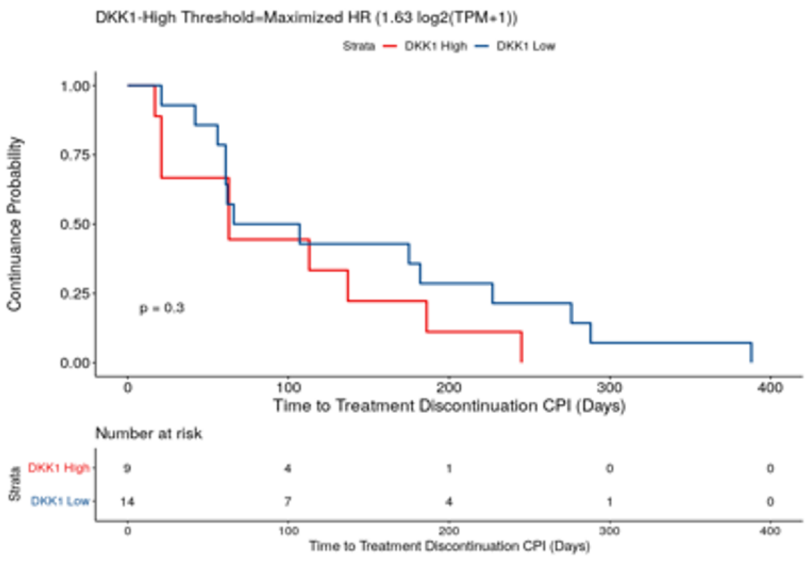
High DKK1 Is Associated With Poor Response to anti-VEGF and anti-PD-(L)1 in Endometrioid Endometrial Cancer Patients

Anti-VEGF treatment



PD-(L)1 treatment



- TTD: Time to treatment discontinuation
- Threshold for DKK1 high vs low mRNA expression devised using an optimal cutoff to maximize hazard ratio across multiple treatment regimens

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DKN-01 Phase 2 Study Design

Primary objective:

Objective response rate (ORR)

Secondary objectives:

Exploring genetic mutations in the Wnt signaling pathway and tumoral DKK1 expression as predictive biomarkers

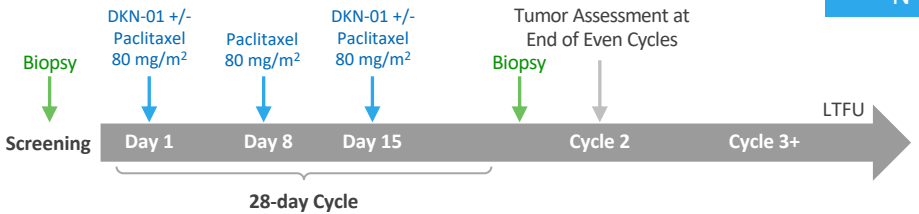
Eligible Patients

- Recurrent EEC
- Recurrent platinum-resistant/refractory EOC
- Recurrent MMMT
- ≥ 1 prior therapy
- Measurable disease
- 50% in each group with Wnt signaling alteration

DKN-01 300 mg Monotherapy N=52
- EEC N=29
- EOC N=14
- MMMT N=9

DKN-01 300 mg + Paclitaxel 80 mg N=59
- EEC N=24
- EOC N=19
- MMMT N=16

Data as of 28 Sep 2020. EEC: epithelial endometrial cancer; EOC: epithelial ovarian cancer; MMMT: carcinosarcoma (malignant mixed Mullerian tumor)



Basket study (NCT03395080) evaluating DKN-01 as monotherapy or in combination with paclitaxel in advanced gynecologic malignancies

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Wnt Genetic Groups

Wnt Signaling Alterations

Genes that are associated with the Wnt signaling pathway, either directly or tangentially

Genes: ***CTNNB1, APC, AXIN1/2, RNF43, ZNRF3, RSPO2/3,*** *WISP3, TNKS2, TERT, SOX9, SOX2, SLIT2, PAX5, NOTCH1, MLL2, LTK, LRP1B, GSK3B, GREM1, FOXP1, FBXW7, FAM123B, CREB, CDH20, CDC73, ARID1A* and *APCDD1*

Wnt Activating Mutations

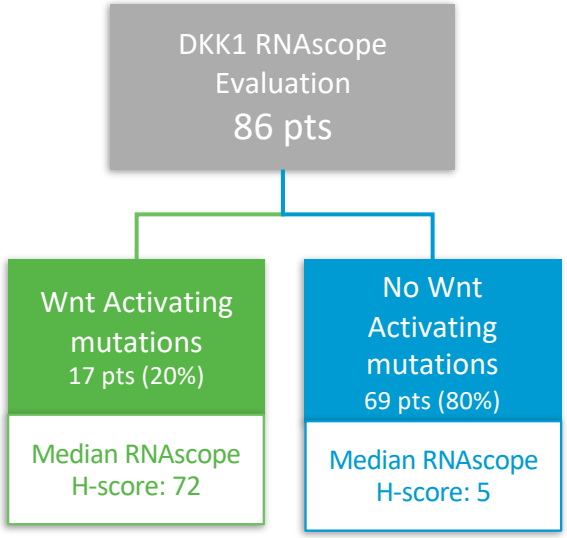
A well defined subgroup of the genes associated with Wnt Signaling Alterations

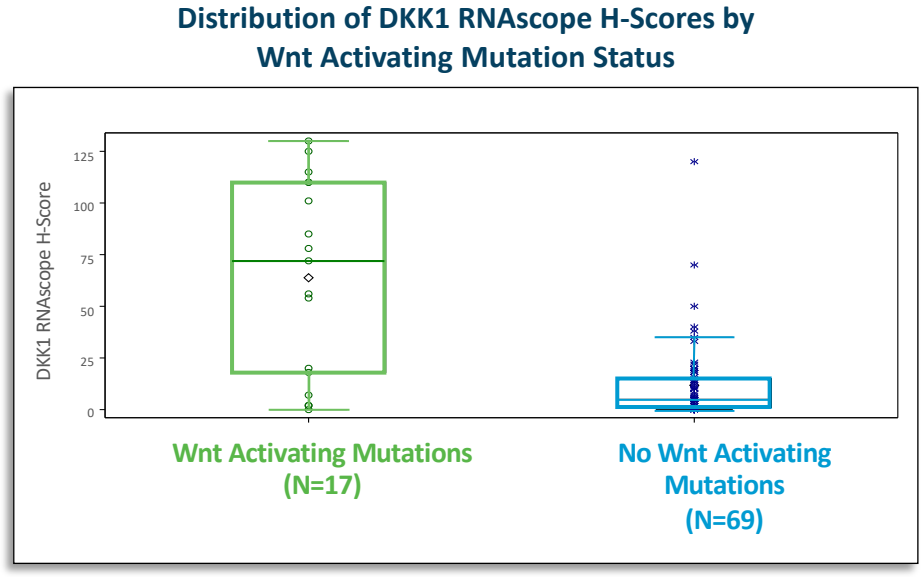
- Alterations that result in active Wnt/β-catenin dependent signaling
- Genes: ***CTNNB1, APC, AXIN1/2, RNF43, ZNRF3, RSPO2/3***

Gene	Genetic alteration
***CTNNB1* (β-catenin)**	Protein stabilizing alteration (missense mutation of S33, S37, T41 or S45; exon 3 missense mutation or inframe deletion of all or part of exon 3)
APC	Loss of function alteration (truncation or deletion)
AXIN1/2	Loss of function alteration (truncation or deletion)
RNF43	Loss of function alteration (truncation or deletion)
ZNRF3	Loss of function alteration (truncation or deletion)
RSPO2	Fusion protein (EIF3E-RSPO2)
RSPO3	Fusion protein (PTPRK-RSPO3)

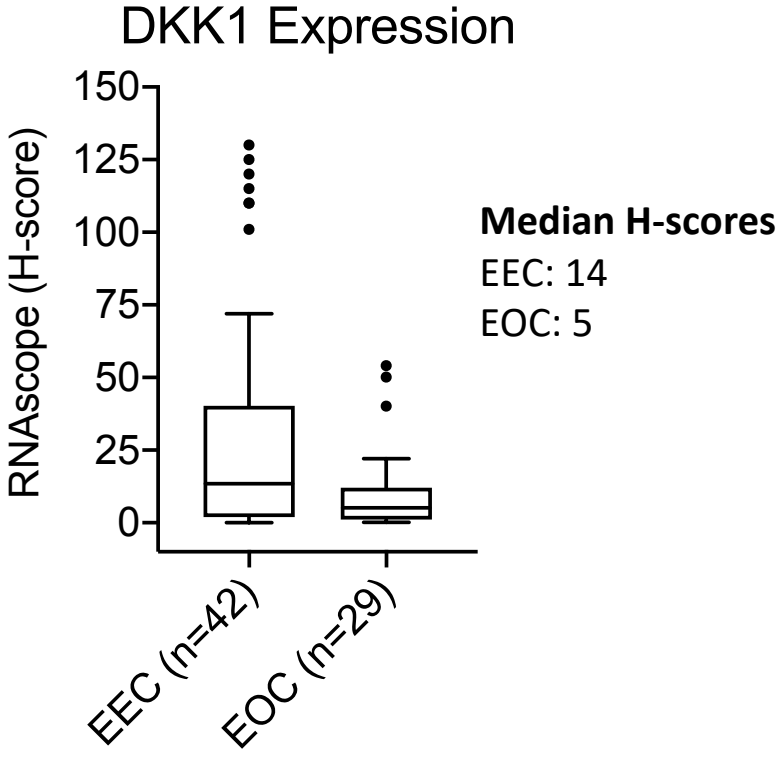
DKK1 High Expression Is Associated with Wnt Activating Mutations

- Overall, 21% had Wnt Activating Mutations; most common mutation CTNNB1 (16%)
- Tumors with Wnt activating mutations have 14.4 times higher DKK1 expression

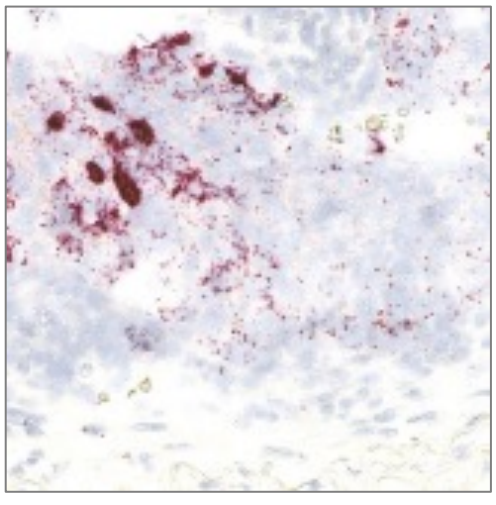




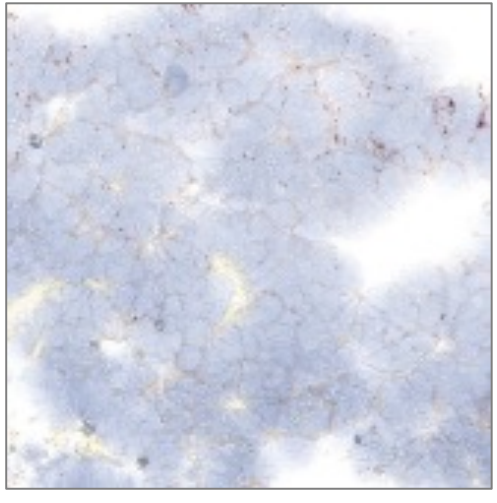
Endometrial Cancer Patients have Higher DKK1 Expression than Ovarian Cancer Patients



Median H-scores
EEC: 14
EOC: 5



H-score = 115
CTNNB1(S37F)



H-score = 11
No mutation

DKN-01 Was Well Tolerated as Monotherapy and in Combination with Paclitaxel

- Related SAEs:
  - DKN-01 monotherapy: 5.8%
  - DKN-01 + paclitaxel combination: 6.8%
- No TEAEs which led to death

Most Common DKN-01 Related TEAEs

Monotherapy:
- Nausea (28.8%)
- Fatigue (26.7%)
- Constipation (11.5%)

Combination therapy:
- Fatigue (30.5%)
- Anemia (27.1%)
- Diarrhoea (23.7%)
- Nausea (16.9%)
- Neutropenia (11.9%)

DKN-01 Related TESAEs

Monotherapy:
- Acute kidney injury (1.9%)
- Dyspnoea (1.9%)
- Nausea (1.9%)
- Oedema peripheral (1.9%)

Combination therapy:
- Anemia (1.7%)
- Colitis (1.7%)
- Hypokalemia (1.7%)
- Paresthesia (1.7%)

Endometrial Cancer

Demographics & Baseline Tumor Characteristics

Patient Characteristics	EEC Mono (n=29)	EEC Combo (n=24)	All EEC (n=53)
Age (yrs), median	63.0	64.5	63.0
White, n	27 (93%)	21 (88%)	48 (91%)
Stage at diagnosis, n (%)			
I	12 (41%)	7 (29%)	19 (36%)
II	4 (14%)	1 (4%)	5 (9%)
III	3 (10%)	9 (38%)	12 (23%)
IV	10 (35%)	7 (29%)	17 (32%)
EEC type, n (%)			
Clear cell	1 (4%)	0	1 (2%)
Endometrioid	23 (79%)	11 (46%)	34 (64%)
Serous	5 (17%)	8 (33%)	13 (25%)
Mixed epithelial tumor	0	1 (4%)	1 (2%)
Other	0	4 (17%)	4 (7%)
Tumor Grade, n (%)			
G1	6 (21%)	6 (25%)	12 (23%)
G2	11 (38%)	1 (4%)	12 (23%)
G3	9 (31%)	14 (58%)	23 (43%)
Unknown	3 (10%)	3 (13%)	6 (11%)
Prior radiation therapy	19 (65.5%)	16 (66.7%)	35 (66.0%)
Prior systemic therapies, median	2	4	3
>2 prior systemic therapies, n	13 (45%)	16 (67%)	29 (55%)
Prior Taxanes, n	28 (97%)	24 (100%)	52 (98%)
Prior Platinum, n	28 (97%)	24 (100%)	52 (98%)
Prior VEGF Inhibitors, n	7 (24%)	7 (29%)	14 (26%)
Prior PARP Inhibitors, n	1 (3%)	3 (13%)	4 (8%)
Prior Immunotherapy, n	5 (17%)	6 (25%)	11 (21%)
Prior Hormonal Therapy, n	12 (41%)	10 (42%)	22 (42%)

Tumor Genetics	EEC Mono (n=29)	EEC Combo (n=24)	All EEC (n=53)
Wnt Altered, n (%)	21 (72%)	16 (67%)	37 (70%)
Wnt Activated, n (%)	9 (31%)	7 (29%)	16 (30%)
ARID1A	11 (38%)	6 (25%)	17 (32%)
MLL2	8 (28%)	5 (21%)	13 (25%)
CTNNB1	6 (21%)	5 (21%)	11 (21%)
CREBBP	4 (14%)	3 (13%)	7 (13%)
RNF43	2 (7%)	2 (8%)	4 (8%)
SOX9	3 (10%)	0	3 (6%)
PAX5	3 (10%)	0	3 (6%)
APC	2 (7%)	1 (4%)	3 (6%)
PI3K/AKT, n (%)	25 (86%)	17 (71%)	42 (79%)
PTEN	18 (62%)	10 (42%)	28 (52%)
PIK3CA	13 (45%)	10 (42%)	23 (43%)
RNAscope analysis population	22	20	42
RNAscope H-score, median	9	18	14
Microsatellite status, n (%)	21 (72%)	22 (92%)	43 (80%)
MSS	18 (62%)	19 (79%)	37 (70%)
MSI-H	2 (7%)	3 (13%)	5 (9%)
MSI-L	1 (3%)	0	1 (2%)
Unknown/missing	8 (28%)	2 (8%)	10 (19%)
TMB, n (%)	21 (72%)	22 (92%)	43 (81%)
Low (0 to < 6)	15 (52%)	12 (50%)	27 (51%)
Intermediate (≥ 6 to < 20)	4 (14%)	7 (29%)	11 (21%)
High (≥ 20)	2 (7%)	3 (13%)	5 (9%)
Unknown	8 (27%)	2 (8%)	10 (19%)

Endometrial Cancer

DKN-01 Monotherapy

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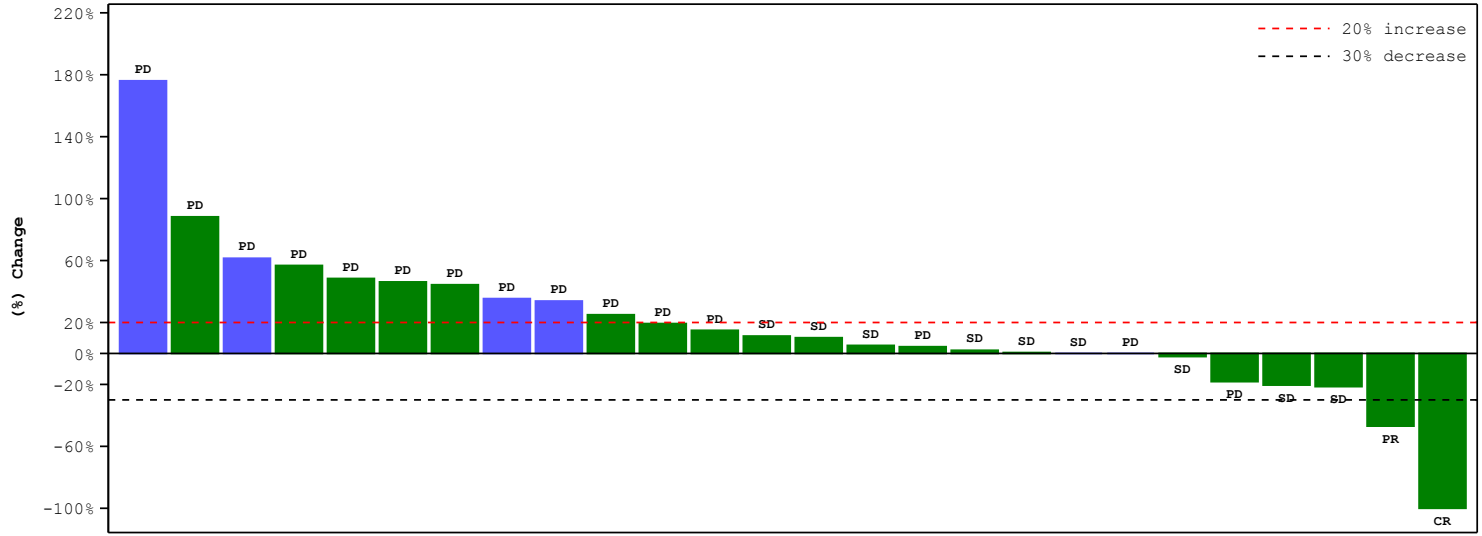
DKN-01 Monotherapy - Endometrial Cancer Overall Response

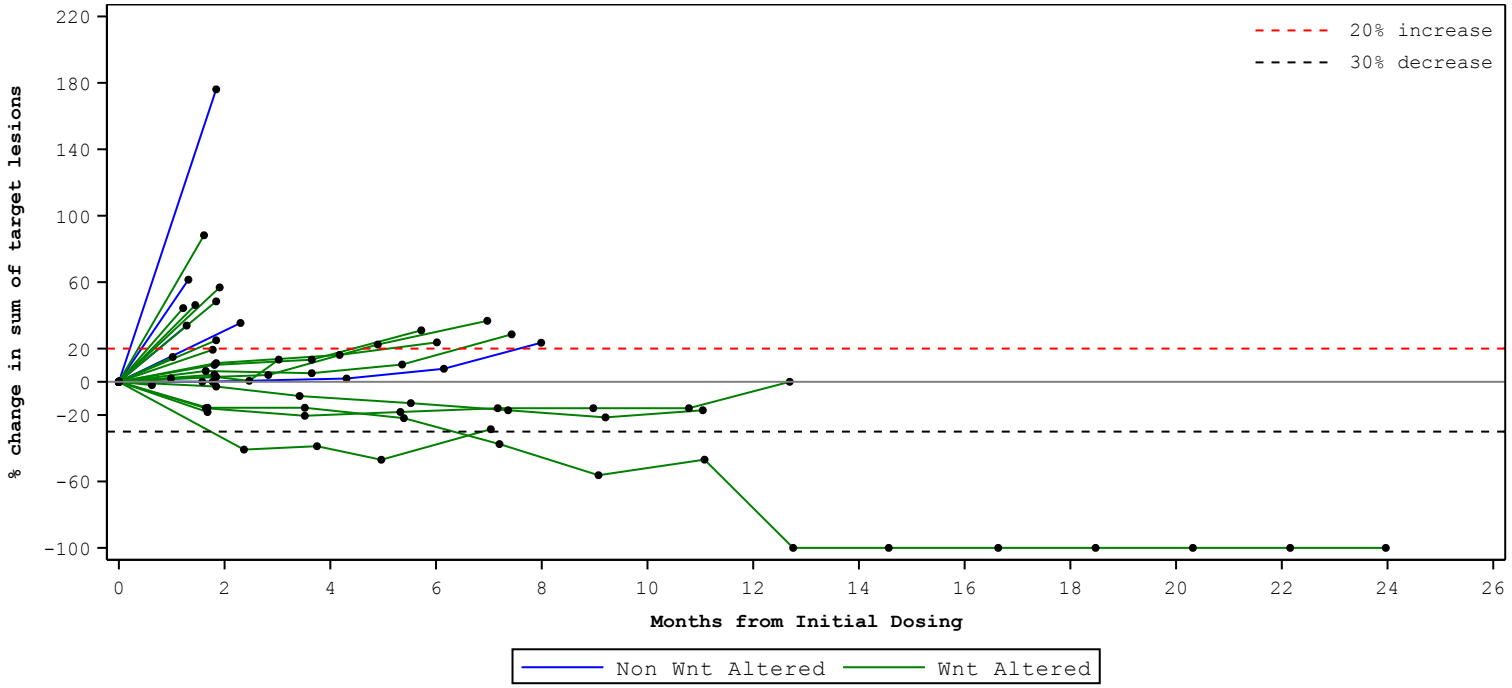
- Endometrial cancers with alterations in the Wnt signaling pathway had greater clinical activity than in those without Wnt pathway alterations (ORR: 10% vs 0%, DCR: 48% vs 13%)



	Status	N	ORR	DCR	CR	PR	SD	PD	NE
EEC monotherapy	Wnt altered	21	10%	48%	1	1	8	10	1
	Non - Wnt altered	8	0%	13%	0	0	1	5	2

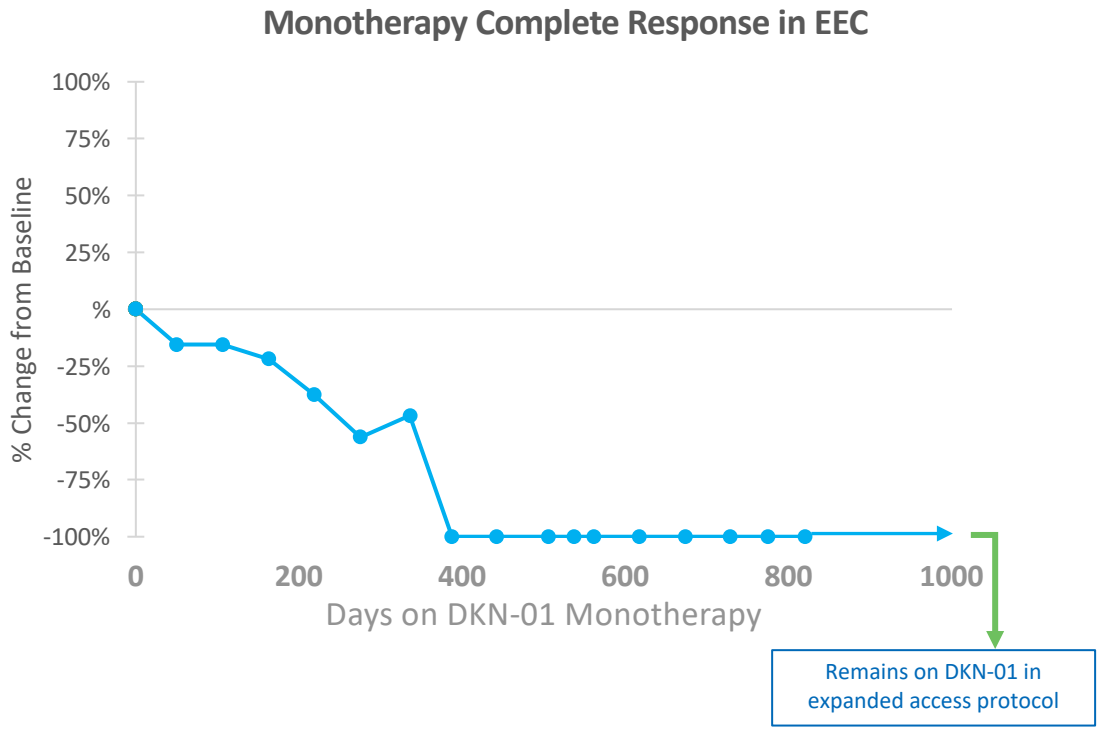
DKN-01 Monotherapy - Endometrial Cancer Durable Clinical Benefit

- Endometrial cancers with alterations in the Wnt signaling pathway had more durable clinical benefit than in those without Wnt pathway alterations



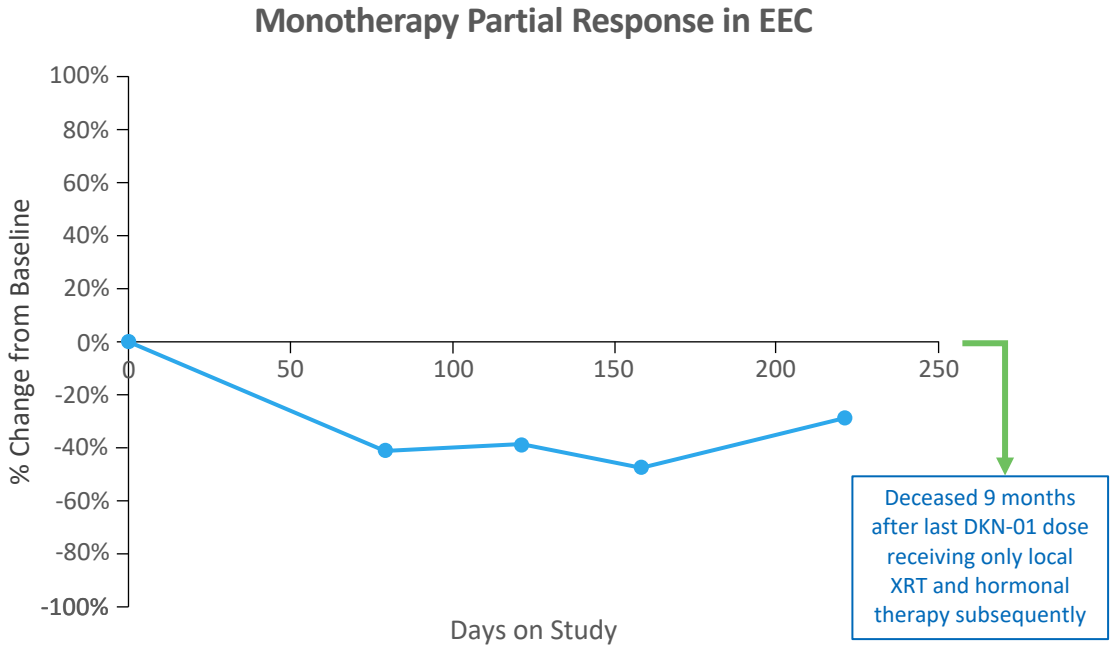
Monotherapy Complete Response in Endometrial Cancer Patient

- Resection followed by vaginal cuff brachytherapy. Recurred in right psoas muscle and received local XRT, then carboplatin and paclitaxel which was poorly tolerated with neuropathy and thrombocytopenia
- Enrolled in July 2018 biopsy revealed MSI-H and Wnt signaling alterations: ARID1A, MLL2, PIK3CA
- Deepening of tumor reduction with each scan, developed PR (-37.5%) after 8 cycles, cPR after 10 cycles (-56.2%); CR after 14 cycles, cCR after 16 cycles
- Continues on DKN-01 monotherapy with no evidence of residual disease



Monotherapy Partial Response in Endometrial Cancer Patient

- Resection followed by local vaginal brachytherapy then systemic chemotherapy (carboplatin/paclitaxel) to which she experienced substantial toxicity
- Tumor growth within 1 month of discontinuing chemotherapy
- Tumor genetics revealed MSS, TMB: 3.78, PIK3CA, Wnt alteration SOX9
- DKK1 RNAscope H-score: 19
- Developed PR after 2 cycles of monotherapy (-41%), confirmed PR after 4 cycles
- Experienced dosing delays and ultimately developed progressive disease after ~7 months on therapy



Endometrial Cancer:
Tumoral DKK1 as a Biomarker

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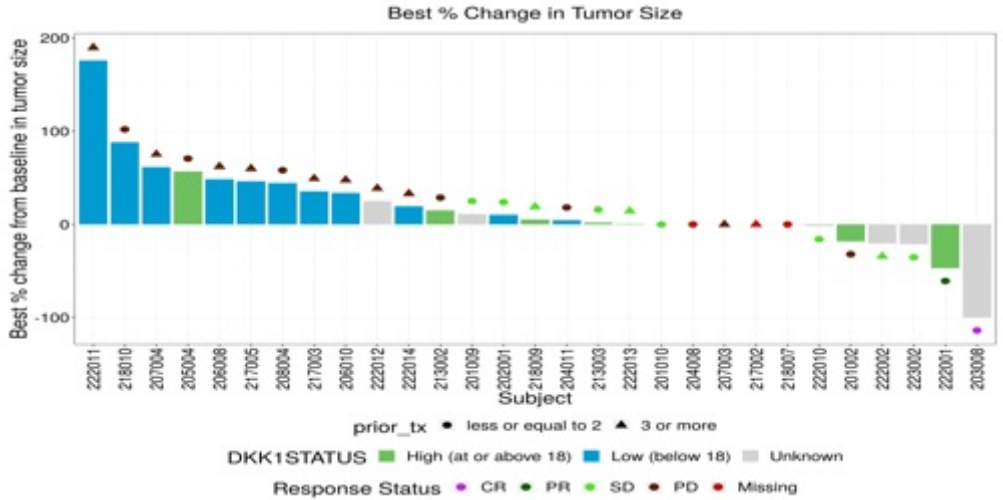
DKN-01 Monotherapy - Overall Response by DKK1 Tumoral Expression

- Endometrial cancer with DKK1-high* tumoral expression have better ORR (14% vs 0%) and clinical benefit (57% vs. 7%) after DKN-01 treatment compared with low DKK1 tumors
- 7 patients with unknown DKK1 expression had an additional complete responder and overall DCR 86%; 3 of these patients with durable SD had Wnt activating mutations



	Status	N	ORR	DCR	CR	PR	SD	PD	NE
EEC monotherapy	DKK1-high (≥18)*	7	14%	57%	0	1	3	3	0
	DKK1-low (<18)	15	0%	7%	0	0	1	11	3
	Unknown	7	14%	86%	1	0	5	1	0

*H score ≥ 18, upper tertile of overall study population

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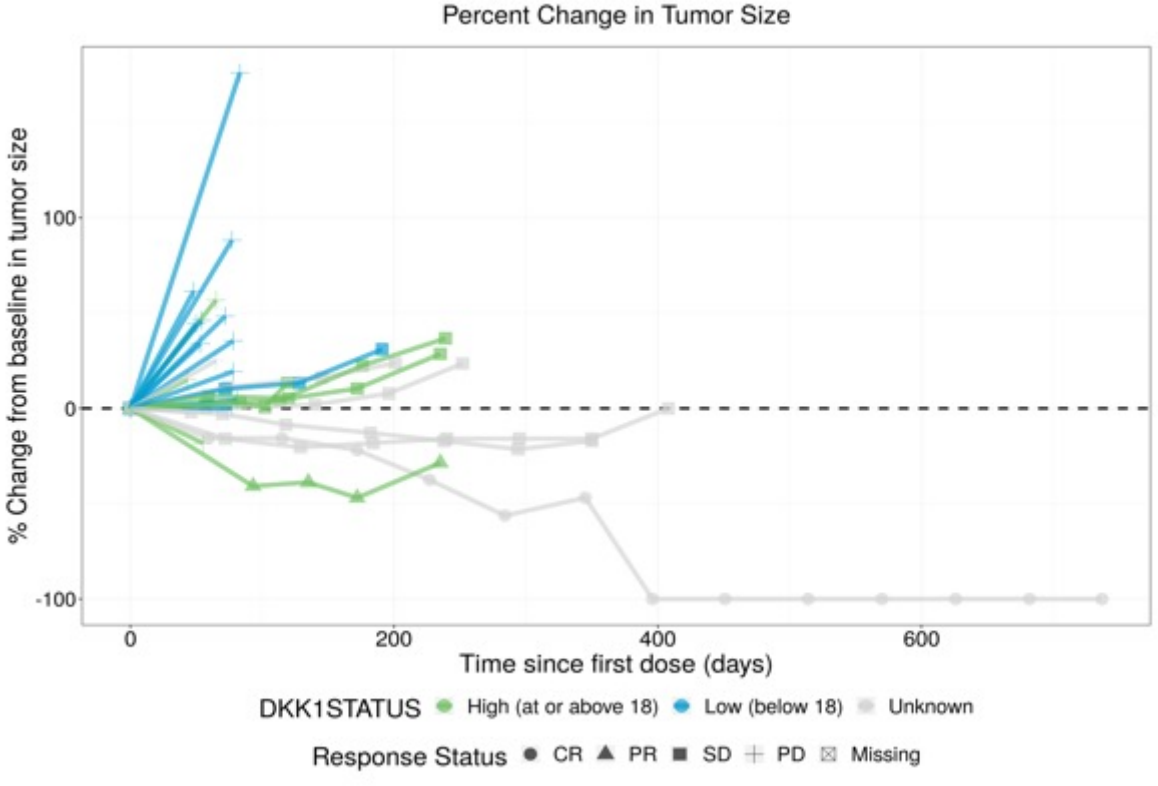
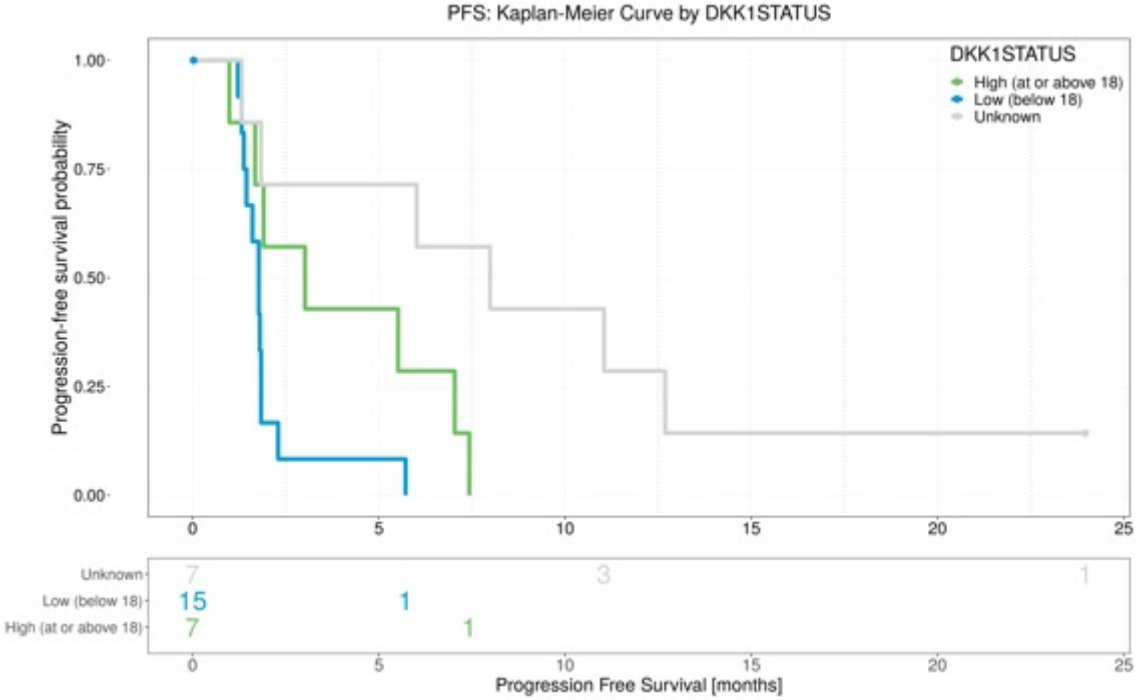
DKN-01 Monotherapy - Durable Clinical Benefit in DKK1-high Tumors

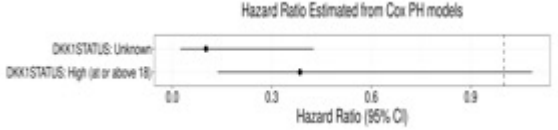
- High tumoral DKK1 expression have more durable clinical benefit after DKN-01 monotherapy compared with DKK1-low tumors



DKN-01 Monotherapy - Improved PFS with High Tumoral DKK1 Expression

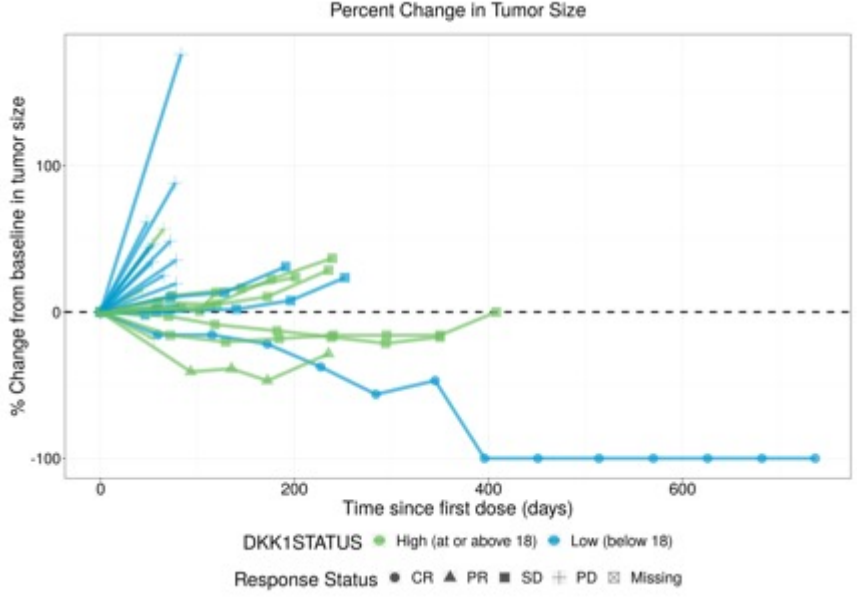
- Tumors with high DKK1 have longer PFS (3.0 vs 1.8 mo [HR 0.39; 95% CI: 0.14, 1.1]) after DKN-01 monotherapy compared with DKK1-low tumors

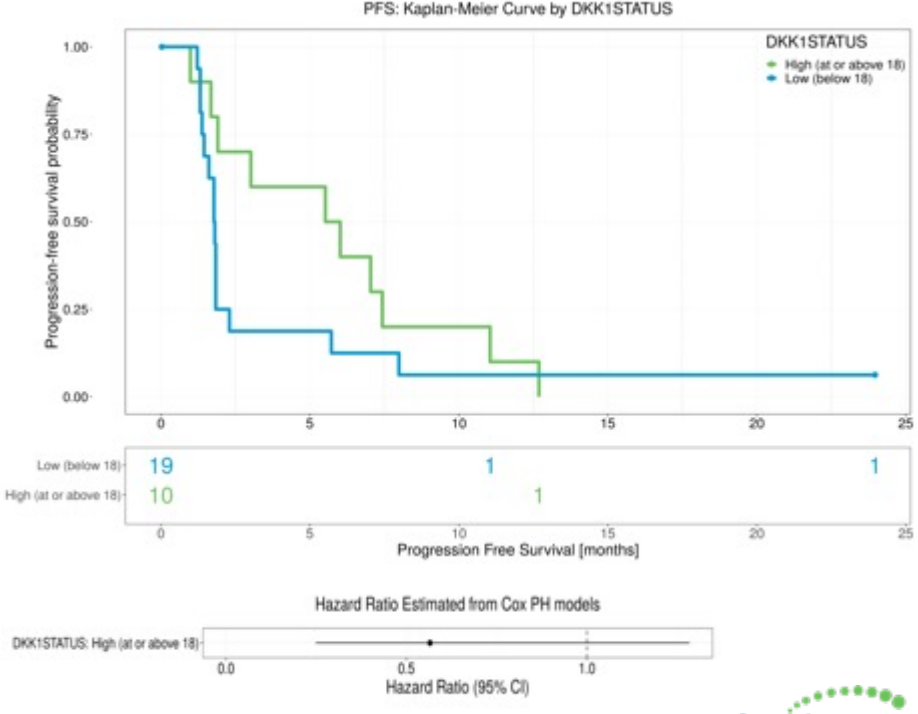




DKN-01 Monotherapy Sensitivity Analysis

- Sensitivity analysis reflecting 3 patients with known Wnt activating mutations considered to be DKK1-high
- Strengthens PFS compared to DKK1 low to 5.8 mos vs 1.8 mos (HR 0.565, 95% CI: 0.25, 1.28)





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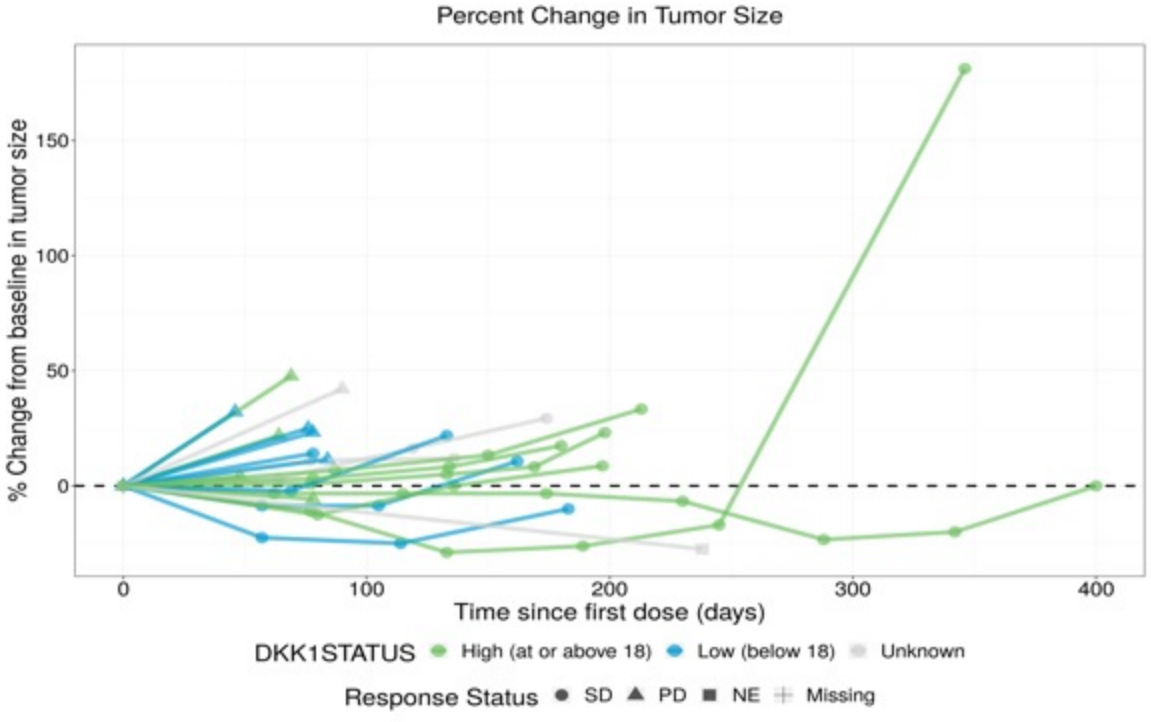
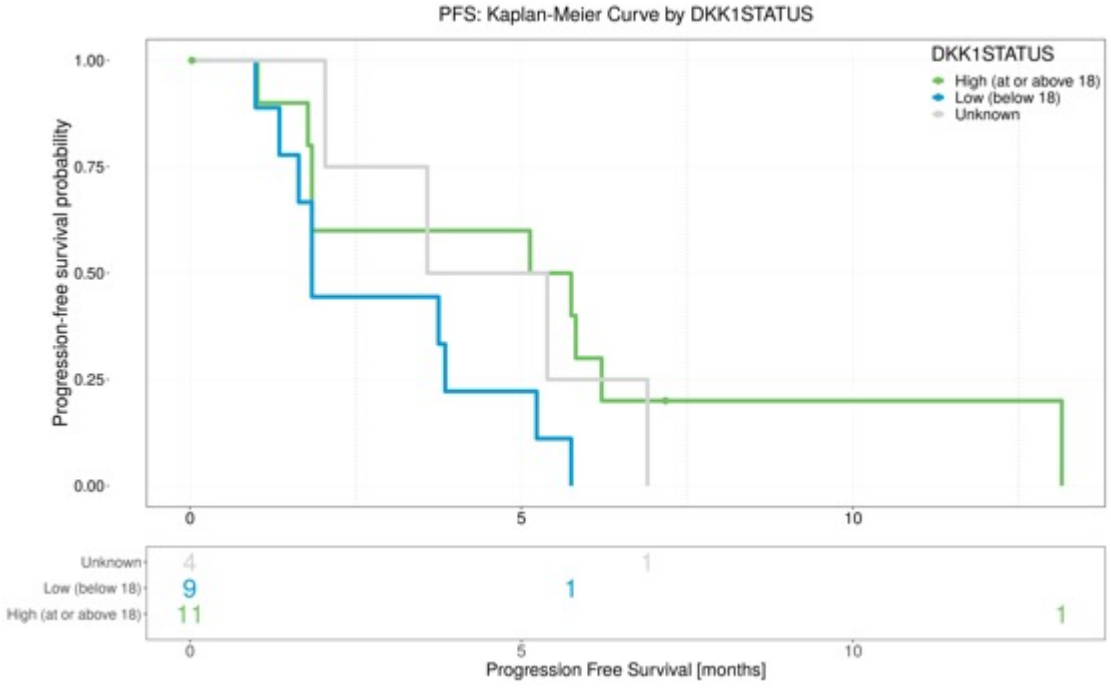
DKN-01 + Paclitaxel - Durable Clinical Benefit with High DKK1 Tumoral Expression

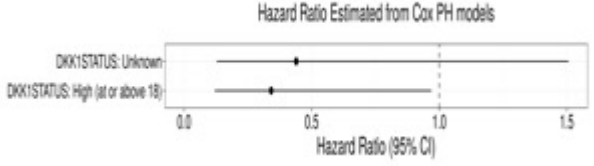
- Endometrial cancer with DKK1 high tumoral expression have more durable clinical benefit after DKN-01 + paclitaxel compared with DKK1-low tumors



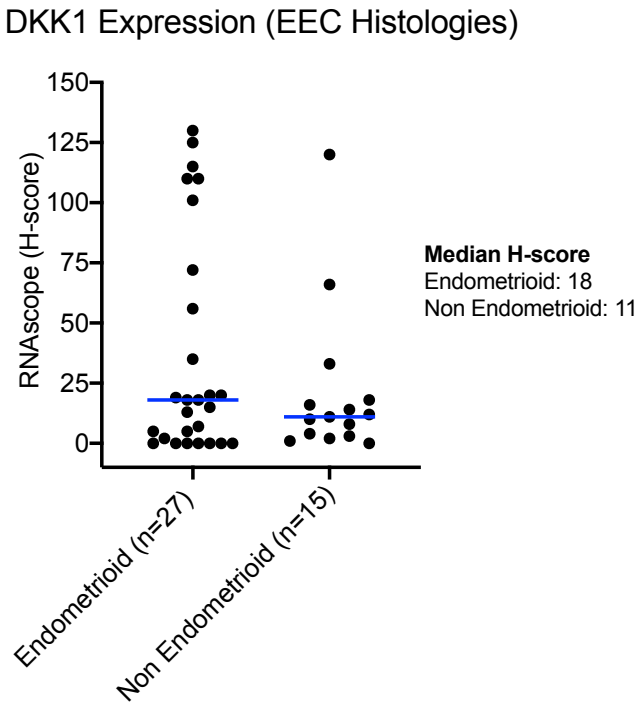
DKN-01 + Paclitaxel - Improved PFS with High Tumoral DKK1 Expression

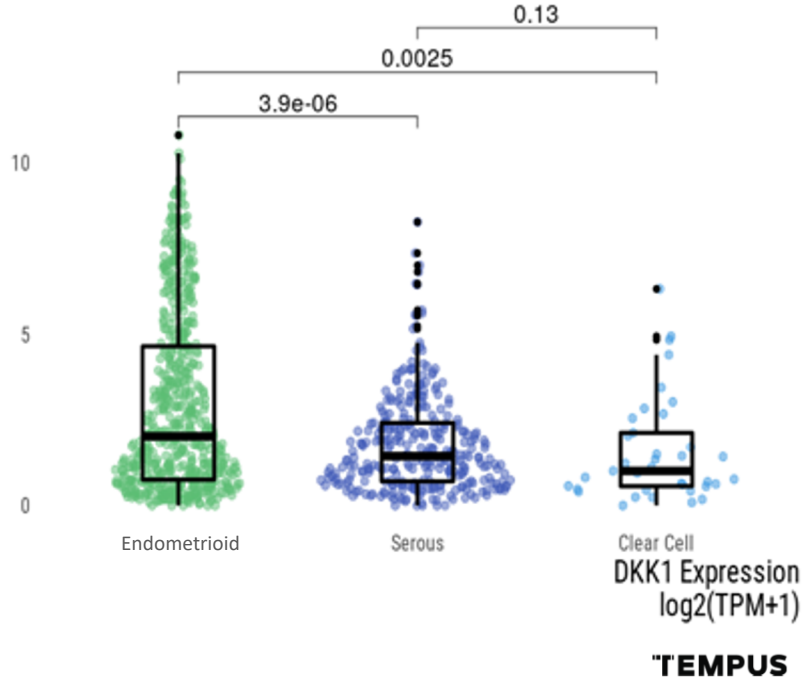
- Tumors with high DKK1 have longer PFS (5.4 vs 1.8 mo [HR 0.34; 95% CI: 0.12, 0.97]) after DKN-01 + paclitaxel compared with DKK1-low tumors





DKK1 Expression is Higher in Endometrioid Endometrial Carcinoma

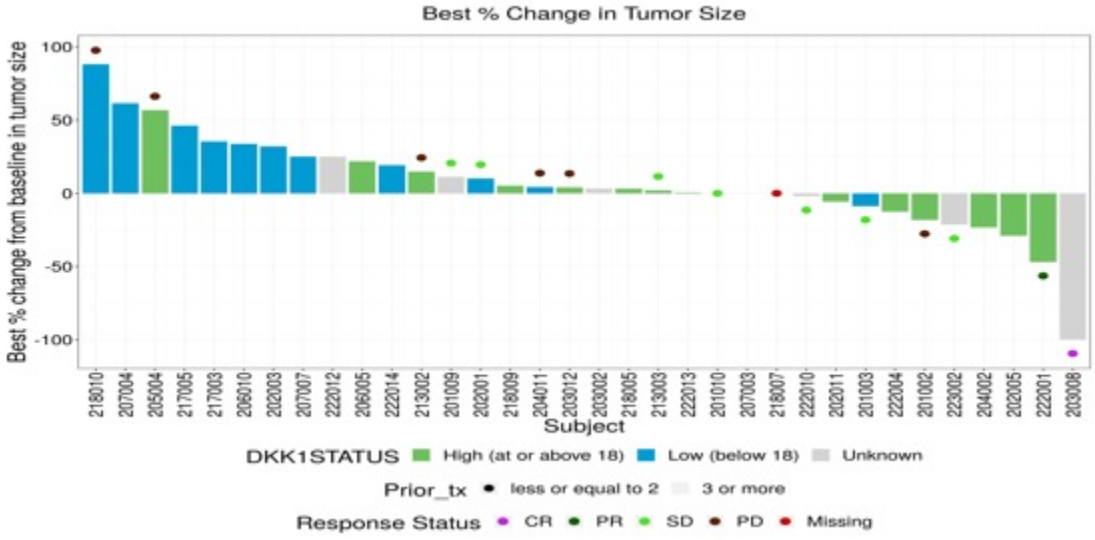


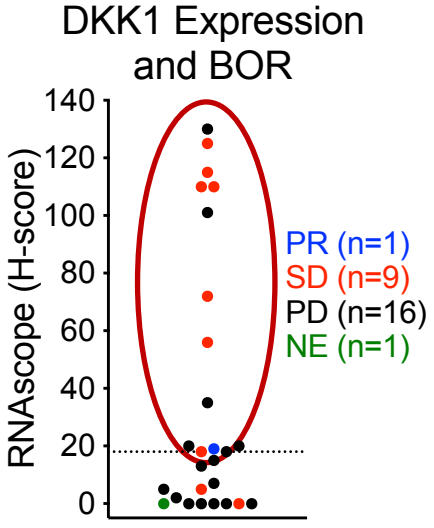


Non-endometrioid histologies: serous (n=9), clear cell (n=1), mixed epithelial tumor (n=1) and other (n=4)

Pooled Endometrial Cancer - Overall Response in Endometrioid Histology by Tumoral DKK1 Expression

- Tumors with high DKK1 have better ORR (7% vs. 0 %) and DCR (57% vs 15%) after DKN-01 treatment compared with DKK1-low tumors





	Status	N	ORR	DCR	CR	PR	SD	PD	NE
All Endometrioid EEC	DKK1-high (≥18)*	14	7%	57%	0	1	7	6	0
	DKK1-low (<18)	13	0%	15%	0	0	2	10	1
	Unknown	7	14%	86%	1	0	5	1	0

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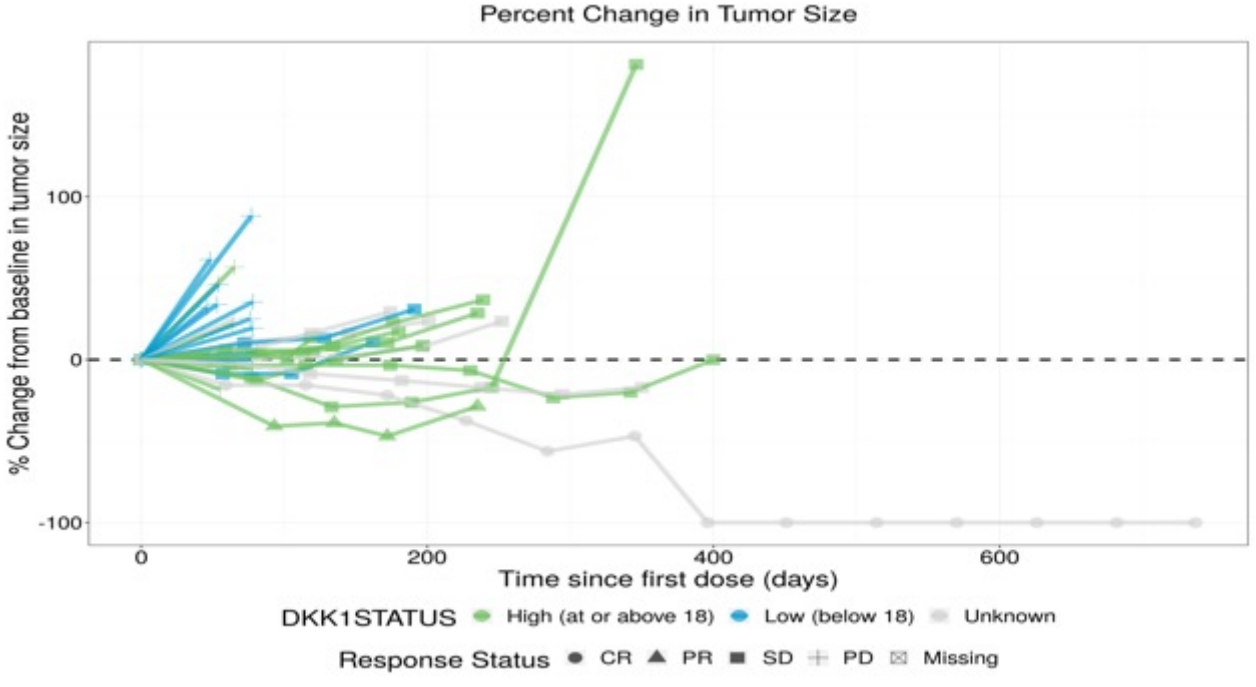
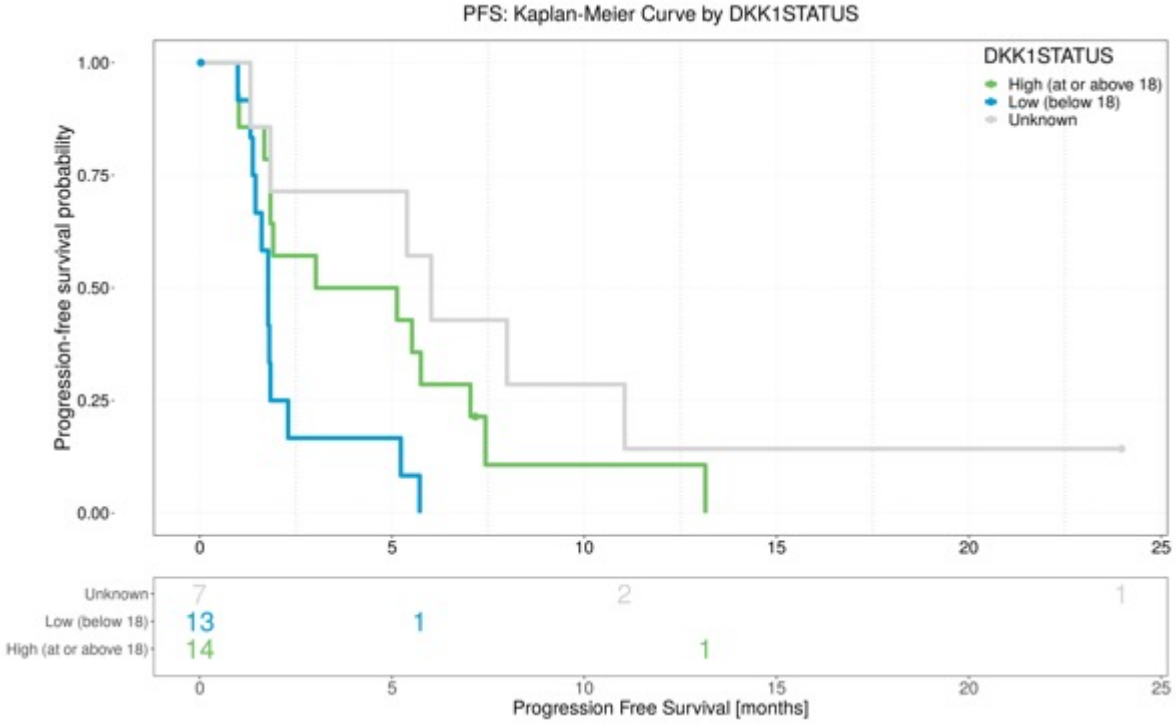
Pooled Endometrial Cancer - Durable Clinical Benefit in Endometrioid Histology by DKK1 Tumoral Expression

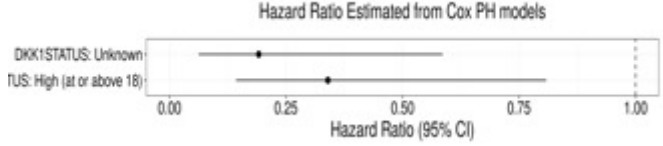
- Endometrial cancer with DKK1 high tumoral expression have more durable clinical benefit after DKN-01 treatment compared with low DKK1 tumors



Pooled Endometrial Cancer - PFS in Endometrioid Histology by Tumoral DKK1 Expression

- Tumors with high DKK1 have better PFS (4.1 vs 1.8 mo [HR 0.34; 95% CI: 0.14, 0.81]) after treatment compared with low DKK1 tumors





Conclusions

- DKN-01 (anti-DKK1 antibody) is safe and well tolerated as either a monotherapy or in combination with paclitaxel

- DKN-01 monotherapy demonstrated clinical activity in unselected heavily-pretreated endometrial cancer patients including a complete response

- High tumoral DKK1 expression in endometrial cancer population demonstrated greater response, durable clinical benefit and progression free survival
  - DKN-01 monotherapy in DKK1-high vs DKK1-low
    - ORR: 14% vs 0%
    - DCR: 57% vs 7%
    - PFS: 3.0 vs 1.8 mos [HR 0.39; 95% CI: 0.14, 1.1]

- Greatest benefit and highest tumoral DKK1 expression in endometrioid histology
  - Pooled endometrioid data with DKK1-high demonstrated longer PFS at 4.1 vs. 1.8 mos for DKK-1-low tumors [HR 0.34; 95% CI: 0.14, 0.81]

- Future gynecologic development will focus on DKK1-high endometrial cancer patients, with monotherapy or in combination with anti-PD-1 therapy

Q&A

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