AACR VIRTUAL SPECIAL CONFERENCE
ENDOMETRIAL CANCER: NEW BIOLOGY DRIVING RESEARCH AND TREATMENT
November 9-10, 2020

AACR
American Association for Cancer Research
FINDING CURES TOGETHER

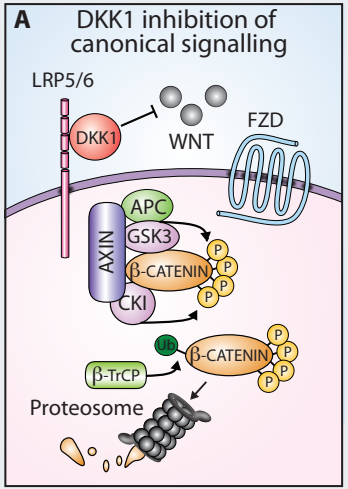
Patients with recurrent epithelial endometrial cancers (EEC) and Wnt signaling alterations demonstrated greater clinical benefit when treated with DKN-01 monotherapy

Rebecca C. Arend, MD, MSPH
University of Alabama at Birmingham
rarend@uabmc.edu

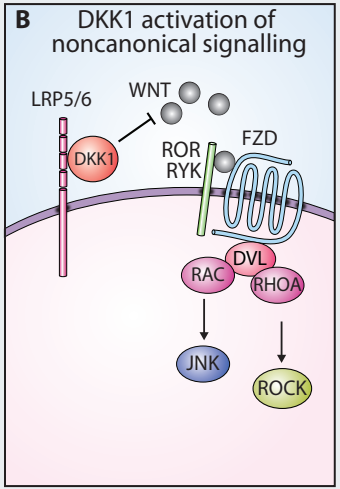
UAB MEDICINE
The University of Alabama at Birmingham

Model of DKK1 Regulation of Signaling Pathways

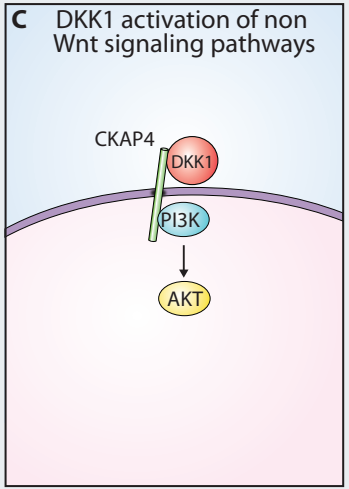
DKK1 inhibits canonical Wnt signaling



DKK1 indirectly activates noncanonical signaling

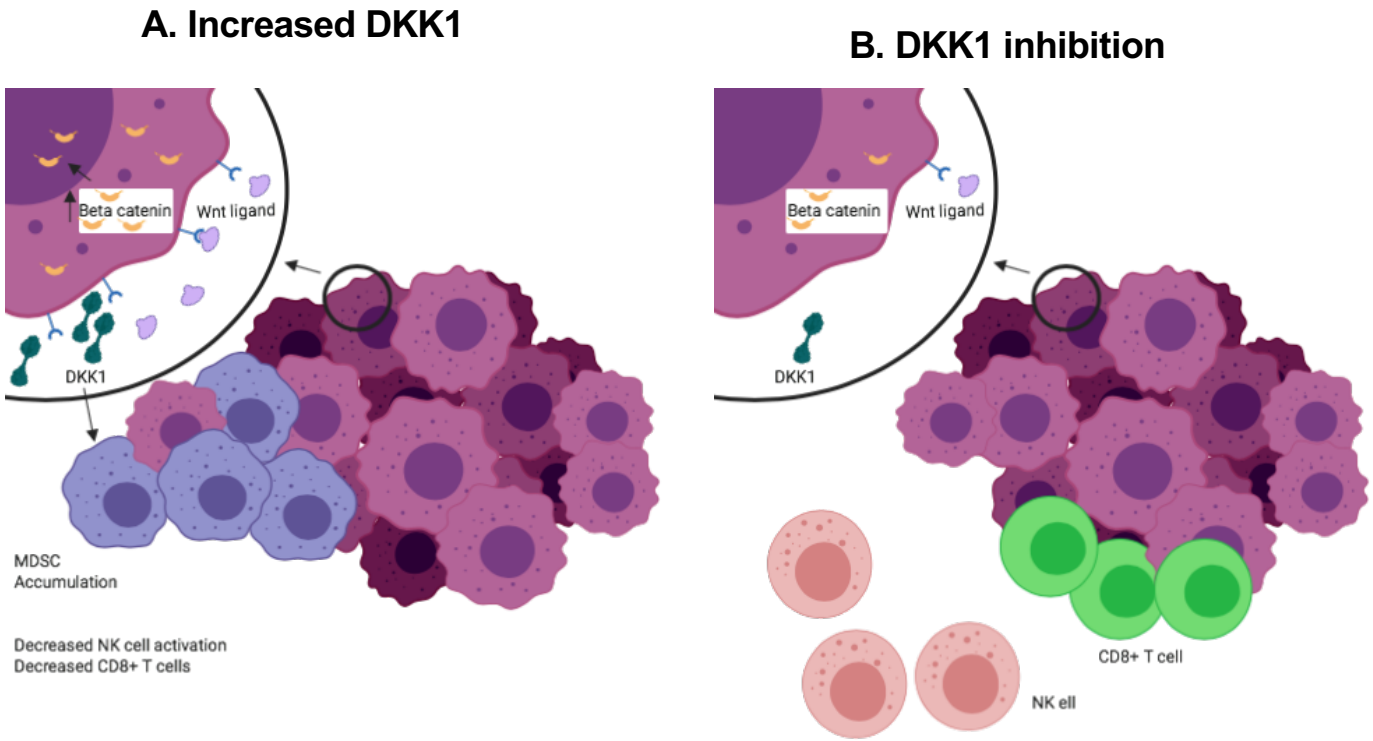


DKK1 activates PI3K/AKT signaling



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

DKK1 Decreases Activated NK Cells Increases MDSC Accumulation

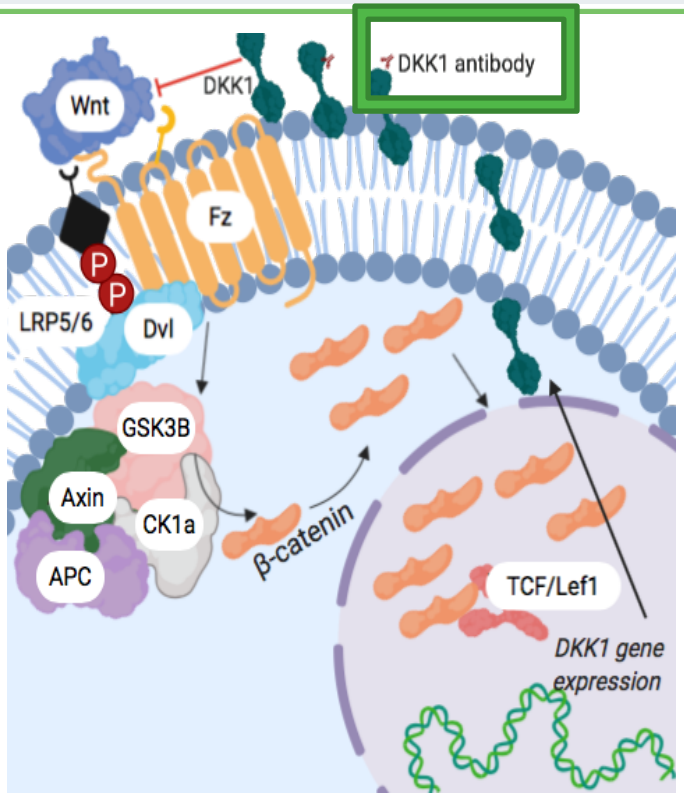


DKN-01: A Humanized Monoclonal Antibody [IgG4] Targeting DKK1

(1) Direct anti-tumor effects
(2) Activates innate immune response
(3) Acts as an anti-angiogenic agent

- Tumors with Wnt activating mutations are associated with higher levels of tumoral DKK1 expression.

- High tumoral DKK1 was associated with longer PFS and OS in patients with esophagogastric cancer treated with DKN-01 and pembrolizumab.



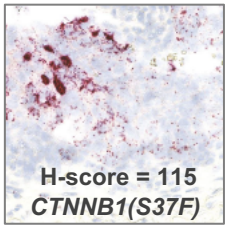
DKK1 High Expression Is Associated with Wnt Activating Mutations

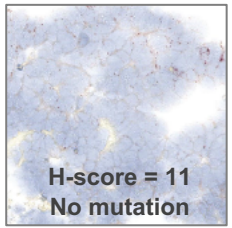
- Tumors with Wnt activating mutations have 14.4 times higher DKK1 expression

DKK1 RNAscope Evaluation
86 pts

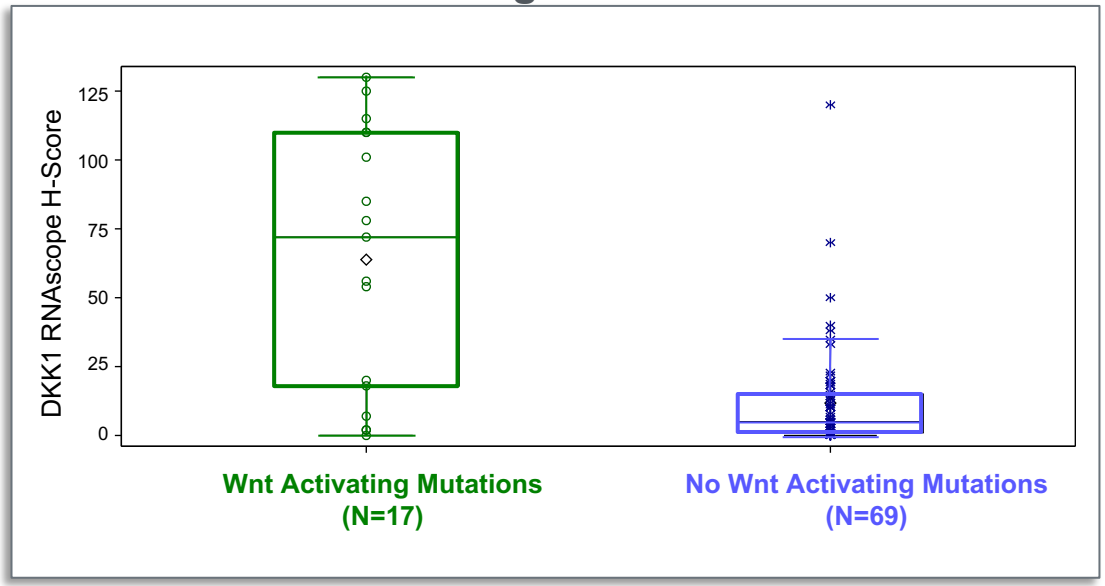
Wnt Activating mutations
17 pts (20%)
Median RNAscope H-score: 72

No Wnt Activating mutations
69 pts (80%)
Median RNAscope H-score: 5





Distribution of DKK1 RNAscope H-Scores by Wnt Activating Mutation Status



Phase 2 Study Design

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

Primary objective:

Objective response rate (ORR)

Secondary objectives:

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

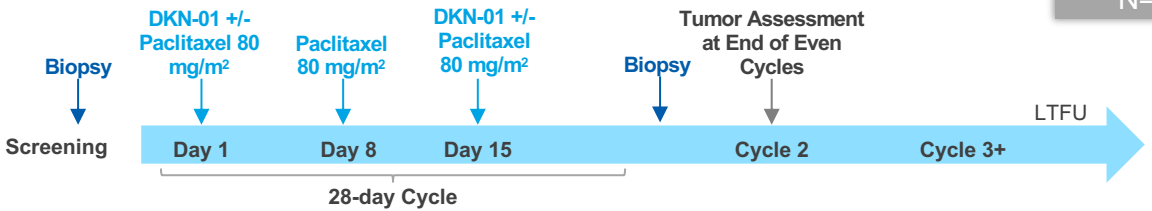
Data as of 28 Sept 2020. EEC: epithelial endometrial cancer; EOC: epithelial ovarian cancer; MMMT: carcinosarcoma (malignant mixed Mullerian tumor)

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=25
- EOC N=19
- MMMT N=15



NCT03395080

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/b-catenin dependent signaling
- Genes: ***CTNNB1, APC, AXIN1/2, RNF43, ZNRF3, RSPO2/3***

Gene	Wnt Activating Genetic Mutation
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)

Demographics

Demographics	Wnt Altered (n=21)	Wnt Activating* (n=9)	Non-Wnt Altered (n=8)
Age (yrs), median	62.0	55.0	63.5
White, n	20	8	7
Stage at diagnosis, n			
I	9	3	3
II	3	1	1
III	2	1	1
IV	7	4	3
Weeks since diagnosis, median	126.71	186.14	124.43
EEC type, n			
Clear cell	1	0	0
Endometrioid	14	8	6
Serous	3	1	2
Unknown	3	0	0

	Wnt Altered (n=21)	Wnt Activating* (n=9)	Non-Wnt Altered (n=8)
Tumor Grade, n			
G1	5	4	1
G2	9	3	2
G3	5	1	4
Unknown	2	1	1
Prior systemic therapies, median	2.0	3.0	4.0
≥3 prior systemic therapies, n	10	6	6
Prior Taxanes, n	20	9	8
Prior Platinum, n	20	9	8
Prior VEGF Inhibitors, n	4	2	3
Prior PARP Inhibitors, n	0	0	1
Prior Immunotherapy, n	5	3	0
Prior Hormonal Therapy, n	9	5	3

*Wnt activating is a subset of Wnt altered

Tumor Characteristics

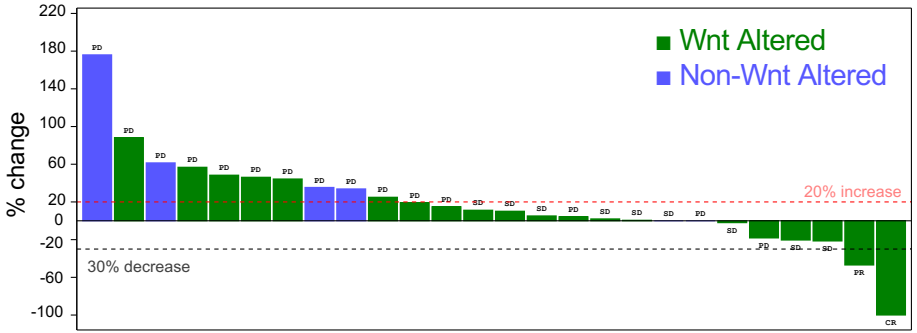
	Wnt Altered (n=21)	Wnt Activating* (n=9)	Non-Wnt Altered (n=8)
Wnt genes, n#	**21 (72.4)**	**9 (31.0)**	**8 (27.6)**
ARID1A	11	—	—
MLL2	8	—	—
APC	7	2	—
CTNNB1	6	6	—
CREBBP	4	—	—
RNF43	3	2	—
SOX9	3	—	—
PAX5	3	—	—
PI3K/AKT, n#	**19 (65.5)**	**9 (31.0)**	**6 (20.7)**
PTEN	14	6	4
PIK3CA	9	5	4

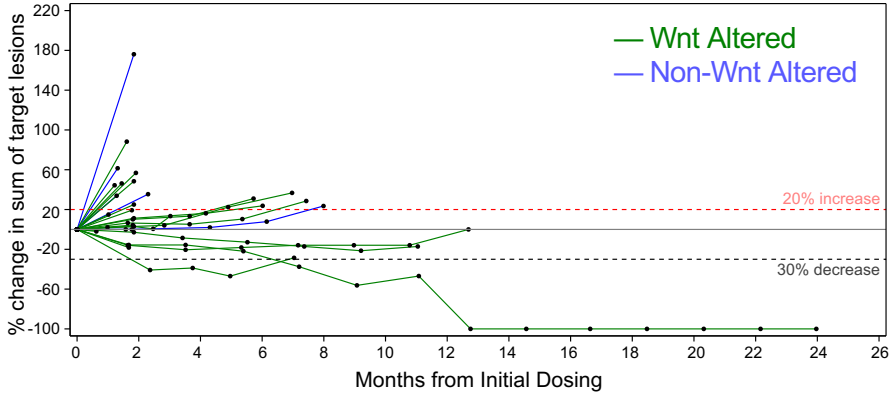
	Wnt Altered (n=21)	Wnt Activating* (n=9)	Non-Wnt Altered (n=8)
RNAscope H score, median (tertile 1, tertile 2)#	15.0 (7.0, 35.0)	64.0 (7.0-110.0)	0.0 (0.0, 2.0)
Microsatellite status, n#			
MSS	13	6	5
MSI-H	2	0	0
MSI-L	1	0	0
Unknown	5	3	3
TMB, n#			
Low (0 to < 6)	11	5	4
Intermediate (≥ 6 to < 20)	3	1	1
High (≥ 20)	2	0	0
Unknown	5	3	3

*Wnt activating is a subset of Wnt altered
n (%) is calculated from total 29 patients in EEC subset

Clinical Response by Wnt Alteration Status

- Greater and more durable clinical activity in EEC pts with Wnt signaling alterations: 1 CR, 1 PR (ORR 10%) and 8 SD (ODCR 50%) vs 1 SD (ODCR 17%)

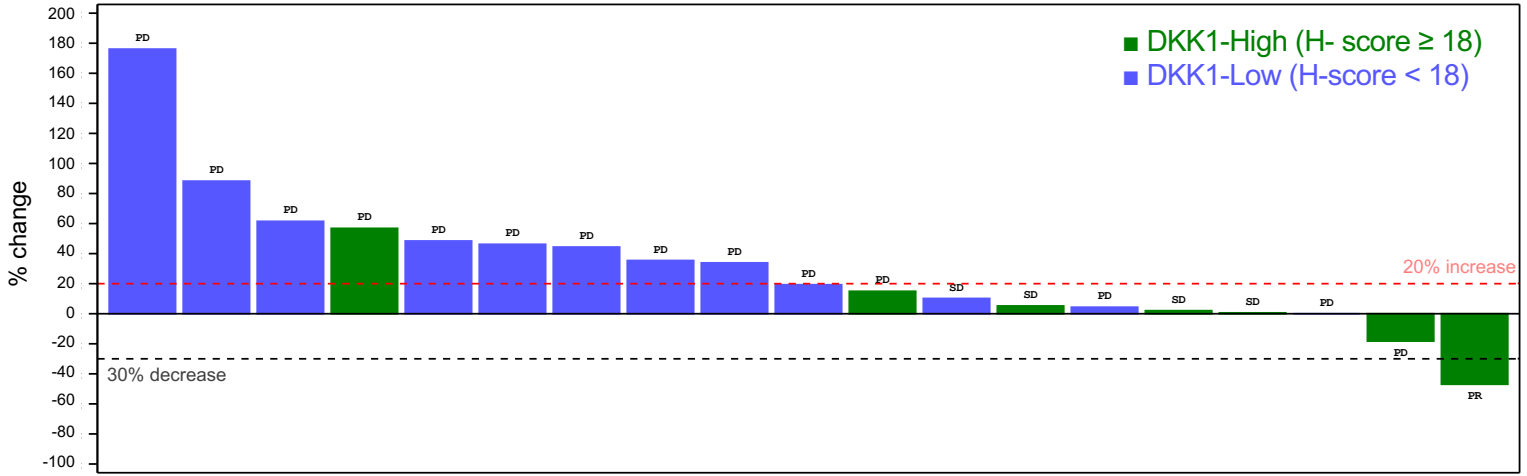




EEC	Evaluable	CR	PR	SD	PD
Wnt Signaling Alterations (n)	20	1	1	8	10
No Identified Wnt Alterations (n)	6	0	0	1	5

Tumoral DKK1 Expression and Clinical Activity

- Higher tumoral expression of DKK1 is associated with greater clinical activity:
  DKK1-high: ORR 14.3%; ODCR: 57.1% vs DKK1-low: ORR: 0%; ODCR: 8.3%

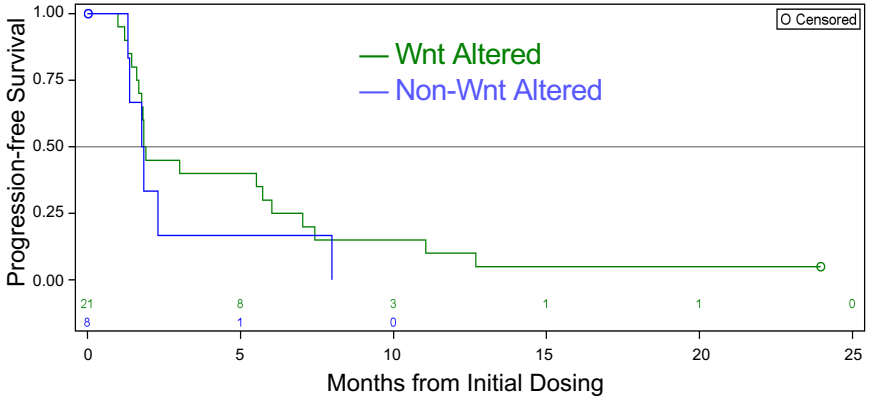


EEC	Evaluable	CR	PR	SD	PD
DKK1-High (H-score ≥ 18) (n)	7	0	1	3	3
DKK1-Low (H-score < 18) (n)	12	0	0	1	11

Progression-free Survival by Wnt Mutation Status

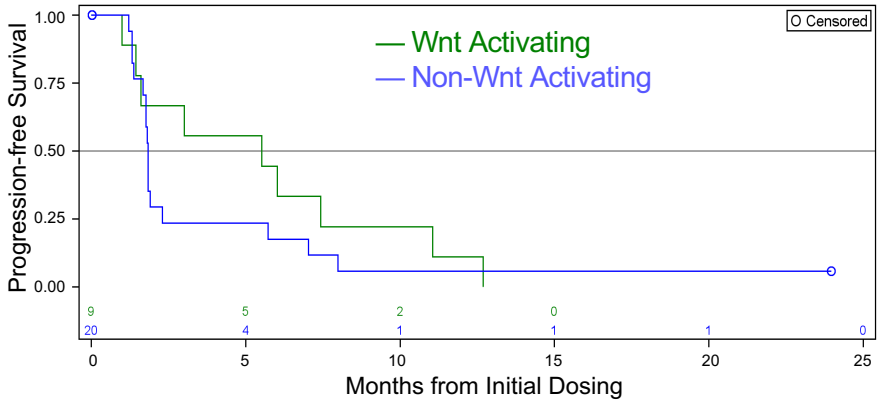
- Longest PFS in pts with Wnt activating mutations compared to those without:
  Median 5.5 months (95% CI: 1.0, 11.1) vs 1.8 months (95% CI: 1.4, 2.3)

Wnt Signaling Alteration Status



	Subjects	Event	Censored	Median Survival	95% CL	
Wnt Altered	21	19	2	1.875	1.610	6.020
Non Wnt Altered	8	6	2	1.810	1.320	7.990

Wnt Activating Mutation Status

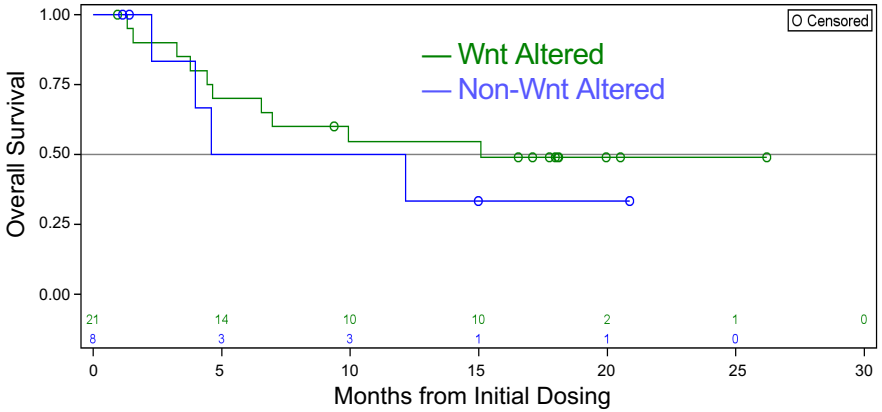


	Subjects	Event	Censored	Median Survival	95% CL	
Wnt Activating	9	9	0	5.520	0.990	11.05
Non Wnt Activating	20	16	4	1.840	1.380	2.300

Overall Survival by Wnt Mutation Status

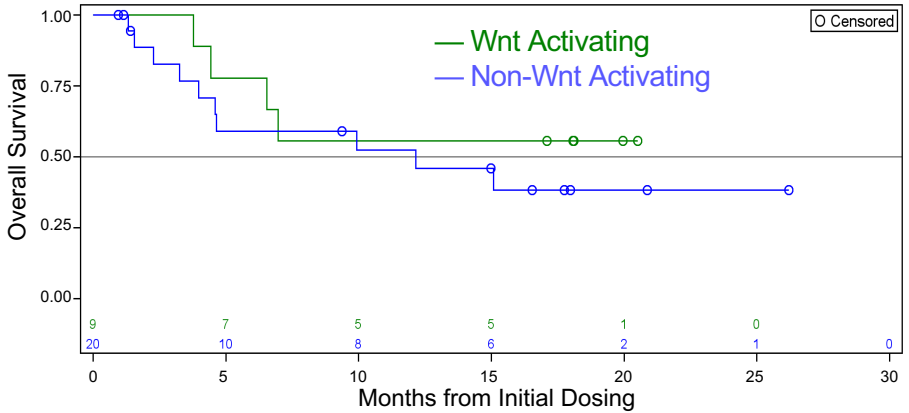
- Longest OS in pts with Wnt activating mutations compared to those without
  Median not reached (NR) vs 12.2 months (95% CI: 3.3, NE)

Wnt Signaling Alteration Status



	Subjects	Event	Censored	Median Survival	95% CL	
Wnt Altered	21	10	11	15.09	4.440	.
Non Wnt Altered	8	4	4	8.380	2.270	.

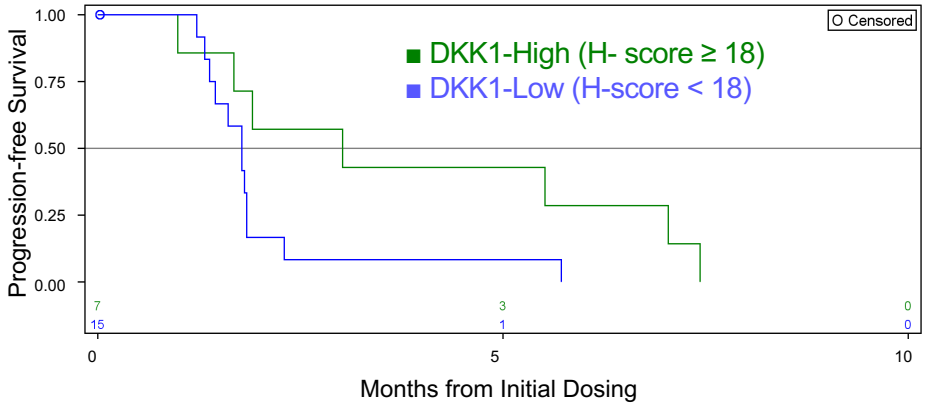
Wnt Activating Mutation Status



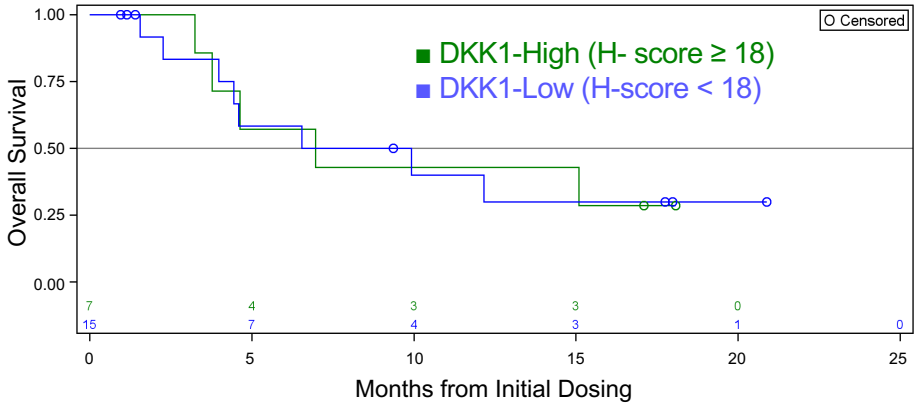
	Subjects	Event	Censored	Median Survival	95% CL	
Wnt Activating	9	4	5	.	3.780	.
Non Wnt Activating	20	10	10	12.16	3.250	.

Tumoral DKK1 Expression and Survival

- Higher tumoral expression of DKK1 is associated with longer PFS than DKK1-low (3.0 vs 1.8 months), but not OS (7.0 vs 8.2 months)



	Subjects	Event	Censored	Median Survival	95% CL	
Upper Tertile (H-Score Value >=18)	7	7	0	3.020	0.990	7.040
Lower/Middle Tertile (H-Score Value <18)	15	12	3	1.780	1.320	1.840



	Subjects	Event	Censored	Median Survival	95% CL	
Upper Tertile (H-Score Value >=18)	7	5	2	6.970	3.250	.
Lower/Middle Tertile (H-Score Value <18)	15	8	7	8.235	2.270	.

Conclusions

- DKN-01 has single agent activity in endometrial cancer
- EEC has a high prevalence of Wnt signaling alterations (72%), including a subgroup with Wnt activating mutations (~30%)
- Wnt activating mutations are associated with higher tumoral DKK1 expression
- CTNNB1 mutations in EEC have been correlated with aggressive biology and shorter survival
- EEC pts with Wnt signaling alterations or elevated tumoral DKK1 treated with DKN-01 monotherapy experienced greater and more durable clinical benefit
- Subgroup of pts with Wnt activating mutations and treated with DKN-01 experienced longer PFS and OS when compared to those without similar mutations: PFS: 5.5 mos vs 1.8 mos and OS: NR vs 12.2 mos, respectively
- Further study with DKN-01 is warranted in EEC in pts with Wnt activating mutations and/or elevated tumoral DKK1

Thank you/Acknowledgements…

My co-authors

Cesar Castro – Massachusetts General Hospital, Boston, MA

Ursula Matulonis – Dana-Farber Cancer Institute, Boston, MA

Erika Hamilton – Sarah Cannon Research Institute/Tennessee Oncology, Nashville,TN

Camille Gunderson – Univ. of Oklahoma Health Sciences Center, Oklahoma City, OK

Kristopher LyBarger – Sarah Cannon-Research Institute at HCA Midwest, Kansas City, MO

Howard M. Goodman – Florida Cancer Specialists, West Palm Beach, FL

Linda R. Duska – Univ. of Virginia Health System, Charlottesville, VA

Haider Mahdi – Cleveland Clinic, Cleveland, OH

Adam C. El Naggar – West Cancer Center, Memphis, TN

Michael Kagey – Leap Therapeutics, Inc., Cambridge, MA

Lisa M. Barroilhet – Univ. of Wisconsin Hospitals and Clinics, Madison, WI

William Bradley – Froedtert and Medical College of Wisconsin, Milwaukee, WI

Jasgit Sachdev – HonorHealth Research Institute, Scottsdale, AZ

Cynthia A. Sirard – Leap Therapeutics, Inc., Cambridge, MA

Michael Birrer – Univ. of Arkansas, Little Rock, AR

David M. O'Malley – Ohio State University, Columbus, OH

- My lab members:
  - Carly Scalise PhD
  - Jhalak Dholakia MD
  - Mckenzie Foxall
  - Jill Hyde RN
  - Alba Martinez MS
  - Ashwini Katre MS
- LEAP Therapeutics Team
- ***AND*** especially all the patients