Patients with Recurrent Gynecologic Cancer Whose Tumors Have Activating Wnt Pathway Mutations Respond Better To Dkn-01, A Dickkopf-1 (DKK1) Inhibitor

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#0419

BACKGROUND

Dickkopf-1 (DKK1)

- Modulator of Wnt signaling.
- Mutations in Wnt activating genes (stabilizing β-catenin mutation; e.g., CTNNB1, APC and RNF43) lead to increased DKK1 expression.
- Tumor cells secrete DKK1; elevated DKK1 expression = poor prognosis.
  - → Immunosuppressive tumor microenvironment.
  - → Activates oncologic noncanonical Wnt signaling.
  - → Promotes proliferation, metastasis, and angiogenesis.

DKN-01

- Humanized monoclonal antibody [IgG4] targeting DKK1.
- Activates innate immune response in preclinical models.
- Has anti-angiogenic and direct anti-tumor effects in preclinical models.
- Tumors with Wnt activating mutations are more likely to responded to DKN-01.
- In esophagogastric cancer patients treated with DKN-01 + pembrolizumab, high tumoral DKK1 was associated with longer PFS.

STUDY DESIGN

- Phase 2 basket study (NCT03395080) in advanced gynecologic malignancies
- Activity of DKN-01 as monotherapy or in combination with paclitaxel (physician's choice) in EEC or EOC
- Primary objective: objective response rate (ORR)
- 2-stage Simon Minimax design
- Secondary objective: Exploring genetic mutations in the Wnt signaling pathway and tumoral DKK1 expression as predictive biomarkers

* 2 patients in EEC monotherapy and 2 patients in EEC combination therapy have no available genetics

Data reported are as of 30 July 2019

Eligible Patients
- Recurrent EEC
- Recurrent platinum-resistant/refractory EOC
- ≥ 1 prior therapy
- Measurable disease
- 50% in each group with Wnt mutation

EEC: epithelial endometrial cancer
EOC: epithelial ovarian cancer

DKN-01 300 mg monotherapy 28-day cycle

# of pts*		Wnt Altered	Non-Wnt-Altered
EEC			
Total	30	20	8
Evaluable	23	16	6
EOC			
Total	15	9	6
Evaluable	14	8	6

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

# of pts*		Wnt Altered	Non-Wnt-Altered
EEC			
Total	28	19	7
Evaluable	24	15	7
EOC			
Total	19	11	8
Evaluable	19	11	8

RESULTS

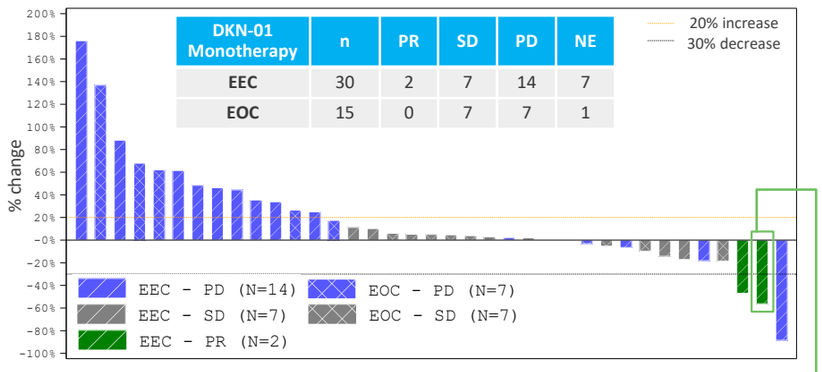
Patient and Cancer Characteristics

	DKN-01 Monotherapy (N=45)		DKN-01 + Paclitaxel (N=47)	
	EEC n=30	EOC n=15	EEC n=28	EOC n=19
Age (yrs), median (min, max)	63.0 (36, 78)	67.0 (43, 87)	64.5 (39, 80)	63.0 (35, 79)
White, n (%)	27 (90.0)	13 (86.7)	25 (89.3)	16 (84.2)
Baseline CA-125 (µg/mL), median (min, max)	48.50 (6.0, 6410.2)	399.00 (9.6, 2833.0)	85.10 (5.5, 7091.0)	419.00 (19.2, 4373.0)
Baseline tumor volume (mm), median (min, max)	67.5 (15, 284)	77 (29, 230)	85.4 (15, 245)	73 (15, 265)
Stage at diagnosis, n (%)				
I	12 (40.0)	0	8 (28.6)	1 (5.3)
II	4 (13.3)	1 (6.7)	1 (3.6)	1 (5.3)
III	3 (10.0)	12 (80.0)	10 (35.7)	14 (73.7)
IV	11 (36.7)	2 (13.3)	9 (32.1)	3 (15.8)
Tumor type, n (%)				
Endometrioid	18 (60.0)	1 (6.7)	9 (32.1)	1 (5.3)
Serous	5 (16.7)	11 (73.3)	8 (28.6)	11 (57.9)
Carcinosarcoma	2 (6.7)	0	1 (3.6)	0
Other	2 (6.7)	2 (13.3)	6 (21.4)	4 (21.1)
Missing	3 (10.0)	1 (6.7)	4 (14.3)	3 (15.8)
≥ 3 prior therapies, n (%)	21 (70.0)	11 (73.3)	23 (82.1)	17 (89.5)
Prior therapies, n (%)				
Taxane	26 (86.7)	13 (86.7)	27 (96.4)	18 (94.7)
Bevacizumab	6 (20.0)	10 (66.7)	8 (28.6)	11 (57.9)
PARP inhibitor	1 (3.3)	4 (26.7)	3 (10.7)	7 (36.8)
Immunotherapy	5 (16.7)	2 (13.3)	5 (17.9)	3 (15.8)
Hormonal	9 (30.0)	1 (6.7)	10 (35.7)	2 (10.5)
Wnt signaling alteration†, n (%)	20 (66.7)	9 (60.0)	19 (67.9)	11 (57.9)
ARID1A	10 (33.3)	5 (33.3)	9 (32.1)	5 (26.3)
Wnt activating mutations	**9 (30.0)**	**2 (13.3)**	**9 (32.1)**	**1 (5.3)**
CTNNB1	**6 (20.0)**	**2 (13.3)**	**7 (25.0)**	**1 (5.3)**
APC	**2 (6.7)**	**0**	**1 (3.6)**	**0**
RNF43	**2 (6.7)**	**0**	**2 (7.1)**	**0**

2 EEC monotherapy pts and 2 EEC combination therapy pts have no available genetics.
†Wnt signaling alterations: **ZNRF3, RSPO2, RNF43, CTNNB1, AXIN1/2, APC,** WISP3, TNKS2, TNKS, TERT, SOX9, SOX2, SLIT2, PAX5, NOTCH1, MLL2, LTK, LRP1B, LRP, GSK3B, GREM1, FOXP1, FBXW7, FAM123B, CREB, CDH20, CDC73, ARID1A, APCDD1.

Efficacy with DKN-01 Monotherapy

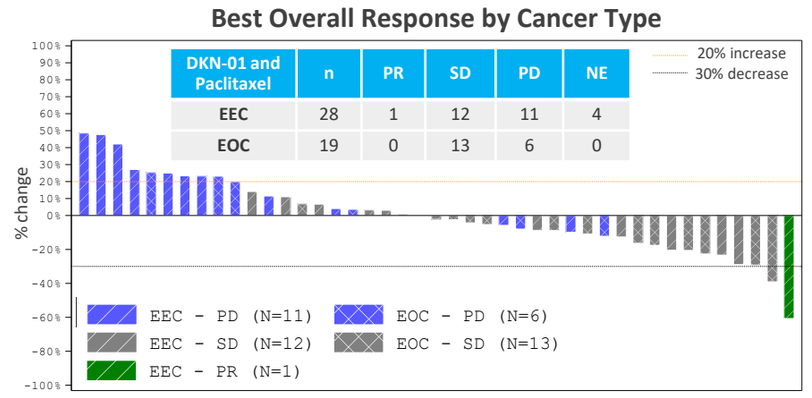
Best Overall Response by Cancer Type



DKN-01 Monotherapy	PFS, days	OS, days
EEC	56 (51, NE)	NYR (141, NYR)
EOC	63.0 (50.0, 112.0)	NYR (NYR, NYR)

Efficacy with DKN-01 + Paclitaxel

Best Overall Response by Cancer Type



DKN-01 + paclitaxel	PFS, days	OS, days
EEC	109.0 (56.0, 164.0)	372.0 (223.0, NE)
EOC	110.0 (56.0, 224.0)	321.0 (229.0, 365.0)

CR in DKN-01 Monotherapy Patient (reported after data cut)

Enrolled July 2018 → **PR -37.5%** after 8 cycles → **cPR -56.2%** after 10 cycles → **CR** after 14 cycles → Currently in Cycle 15

Disposition and Exposure

- Median # cycles: monotherapy 2, combination therapy 4
- Median duration on treatment: monotherapy 43 days, combination 98 days
- Duration on study: monotherapy 127 days, combination 177 days

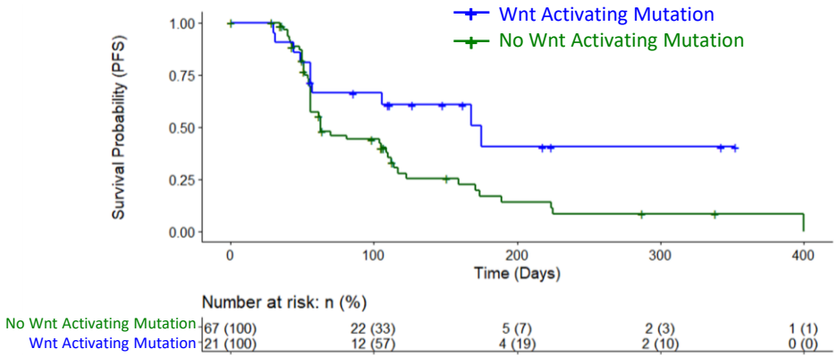
Safety

- DKN-01 was well tolerated as monotherapy and in combination with paclitaxel
- Most common related TEAEs: Monotherapy: nausea (35.5%), fatigue (29.0%); Combination: diarrhoea (31.6%), anemia (31.6%), fatigue (26.3%)
- Related SAEs: Monotherapy: nausea, acute kidney injury; Combination: hypokalemia, anemia and paresthesia

	Monotherapy (n=45)			Combination Therapy (n=47)		
	TEAE Any Grade	TEAE > Grade 3	TESAE	TEAE Any Grade	TEAE > Grade 3	TESAE
Any TEAE	42 (93.3)	18 (40.0)	7 (15.6)	47 (100)	28 (59.6)	18 (38.3)
TEAE Related to DKN-01	31 (68.9)	5 (11.1)	2 (4.4)	38 (80.9)	12 (25.5)	2 (4.3)

Wnt Activating Mutations Associated with Longer PFS

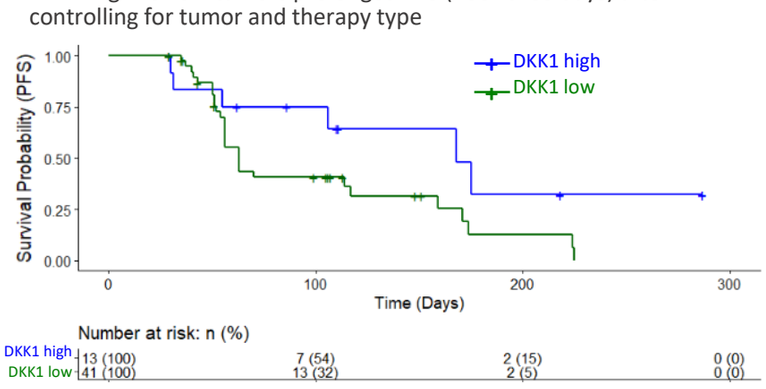
- Longer PFS (175 days vs 63 days) in patients with Wnt activating mutations independent of treatment and tumor type



Wnt activating mutations Yes (N=21) vs No (N=67)	Hazard Ratio (95% CI)
Yes vs No – adjusted for monotherapy/combo	0.45 (0.23, 0.90)
Yes vs No – adjusted for tumor type EEC/EOC	0.44 (0.22, 0.89)
Yes vs No – adjusted for monotherapy/ combo and tumor type EEC/EOC	0.41 (0.20, 0.83)

DKK1 High Tumors Associated with Longer PFS

- 13 of 54 patients (24.1%) were DKK1 high
- DKK1 high vs. low tumors prolonged PFS (168 vs. 63 days) after controlling for tumor and therapy type

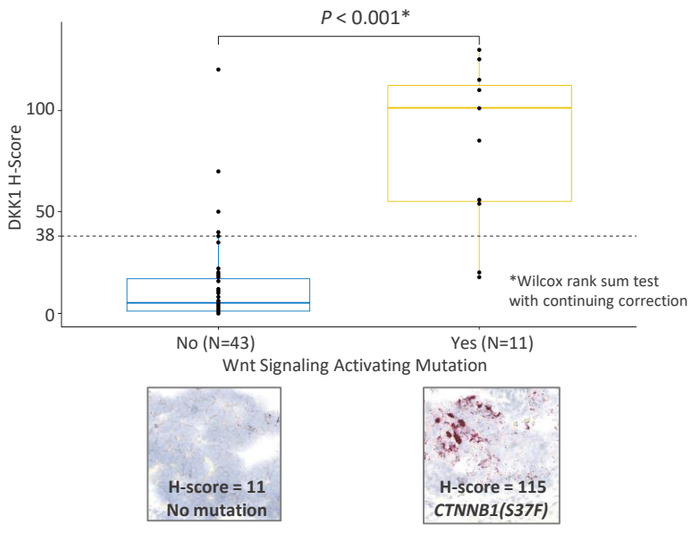


DKK1 H-score* High vs Low (N=13 vs 41)	Hazard Ratio (95% CI)
High vs Low – adjusted for monotherapy/combo	0.39 (0.16, 0.98)
High vs Low – adjusted for tumor type EEC/EOC	0.40 (0.16, 1.0)
High vs Low – adjusted for monotherapy/ combo and tumor type EEC/EOC	0.37 (0.15, 0.93)

*RNA in situ hybridization assay (RNAscope)

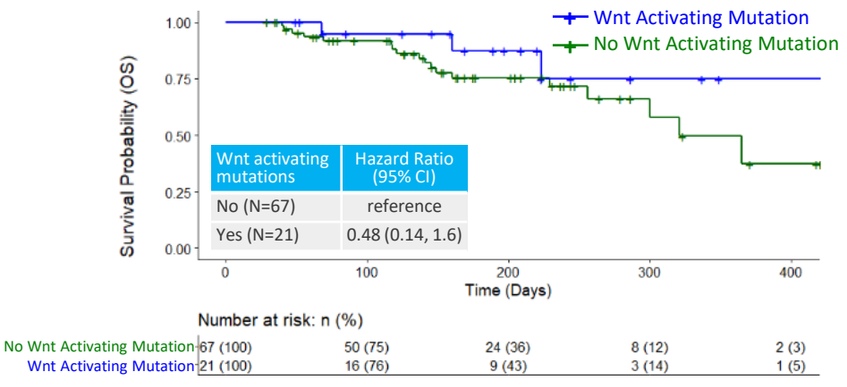
DKK1 High Tumors Associated with Wnt Activating Mutations

- Tumors with Wnt activating mutations have a 20-fold increase in tumoral DKK1



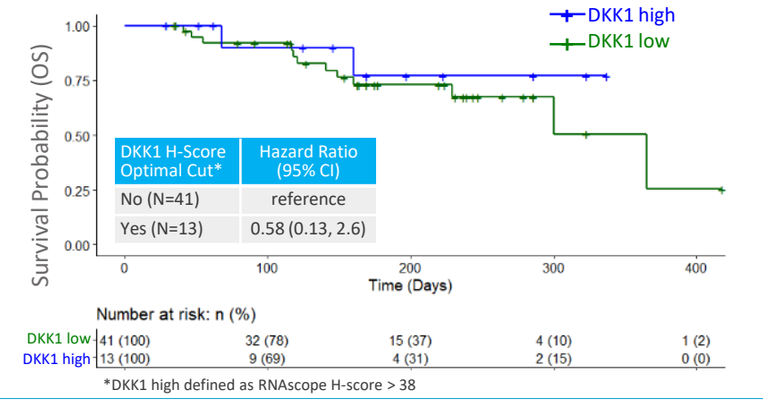
Wnt Activating Mutations Trend Toward Longer OS

- Median OS not yet reached (NYR) vs. 321 days without Wnt activating mutations
- Only 3 of 21 patients with Wnt activating mutations (14.3%) have had events vs. 18 of 67 patients (26.9%) without Wnt activating mutations



DKK1 High* Tumors Trend Toward Longer OS

- DKK1 high vs DKK1 low tumors trend towards longer OS (NYR vs 365 days)
- 2 of 13 (15.4%) DKK1 high patients had events vs. 12 of 41 (29.3%) DKK1 low patients



*DKK1 high defined as RNAscope H-score > 38

CONCLUSIONS

- DKN-01 monotherapy has activity in gynecologic cancers, especially in patients with endometrial cancer (EEC) (proportion of Wnt activating mutations is greater)
  - Monotherapy complete response
- Wnt activating mutations are associated with high levels of tumoral DKK1
- Wnt activating mutation + high tumoral DKK1 → improved clinical benefit and longer PFS; early data trend toward longer OS
- DKN-01 is safe and well tolerated as monotherapy and in combination with paclitaxel

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