Safety and Efficacy of a DKK1 Inhibitor (DKN-01) as Monotherapy or in Combination with Paclitaxel in Patients with Wnt Activated Recurrent Gynecologic Malignancies

Rebecca Arend,[a] Cesar Castro,[b] Ursula Matulonis,[c] Erika Hamilton,[d] Camille Gunderson,[e] Kristopher LyBarger,[f] Howard M. Goodman,[g] Linda R. Duska,[h] Haider Mahdi,[i] Adam C. ElNaggar,[j] Michael Kagey,[k] Cynthia A. Sirard,[k] Michael Birrer[k]

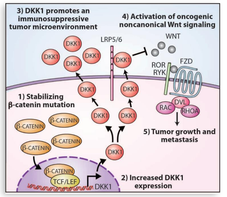
[a]University of Alabama at Birmingham, Birmingham, AL, USA; [b]Massachusetts General Hospital, Boston, MA, USA; [c]Dana-Farber Cancer Institute, Boston, MA, USA; [d]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [e]The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA; [f]Sarah Cannon-Research Institute at HCA Midwest, Kansas City, MO, USA; [g]Florida Cancer Specialists, West Palm Beach, FL, USA; [h]University of Virginia Health System, Charlottesville, VA, USA; [i]Cleveland Clinic, Cleveland, OH, USA; [j]West Cancer Center, Memphis, TN, USA; [k]Leap Therapeutics, Inc., Cambridge, MA, USA

65

BACKGROUND

Dickkopf-1 (DKK1)

- DKK1 is a modulator of Wnt signaling.[1]
- Elevated DKK1 tumoral expression is associated with poor prognosis.[1]
- DKK1 contributes to an immunosuppressive tumor microenvironment.[1]
- Tumor cells secrete DKK1 promoting proliferation, metastasis, and angiogenesis.[1]
- Gynecologic endometrioid tumors have a high prevalence of stabilizing β-catenin mutations[2,3]
- Activation of canonical Wnt signaling (e.g. stabilizing β-catenin mutations) results in increased DKK1 expression.[4-6]



DKN-01

- DKN-01 is a humanized monoclonal antibody [IgG4] targeting DKK1.
- DKN-01 activates an innate immune response in nonclinical models.[7,8]
- DKN-01 has anti-angiogenic and direct anti-tumor effects in nonclinical models.[9]
- Tumors with Wnt pathway alterations are more aggressive and have responded to DKN-01.[9]
- Elevated DKK1 levels may predict response to DKN-01.[10]

STUDY DESIGN

- Phase 2 basket study (NCT03395080) study enriched for Wnt signaling alterations explores genetic mutations and DKK1 expression as predictive biomarkers in advanced gynecologic malignancies
  - Evaluates DKN-01 activity as monotherapy or in combination with paclitaxel
- Patients with recurrent epithelial endometrial cancer (EEC) or recurrent platinum-resistant/refractory epithelial ovarian cancer (EOC)
- 2-stage Simon Minimax design[11]
  - Stage 1 is ongoing; available data on first 38 evaluable patients (4 Mar 2019)

Eligibility Criteria:
- Recurrent EEC
- Recurrent platinum-resistant/refractory EOC
- 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

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

Wnt mutation status

# of pts*	EEC	Mutated	Non-mutated
Total	11	8	3
Evaluable	5	4	1

# of pts	EOC	Mutated	Non-mutated
Total*	10	6	4
Evaluable	7	4	3

# of pts*	EEC	Mutated	Non-mutated
Total	23	12	11
Evaluable	12	8	4

# of pts*	EOC	Mutated	Non-mutated
Total	18	9	9
Evaluable	14	6	8

*Total enrolled as of 4 Feb 2019, evaluable as of 4 Mar 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

DEMOGRAPHICS

Patient & Tumor Characteristics

- Heavily pretreated patients; range 1–10 prior therapies; all received prior platinum and taxane
- Majority of patients tumors were TMB low
- 35 of 62 (56%) patients with Wnt pathway alterations:
  - Activating mutations: CTNNB1: 10 pts; APC: 2 pts
  - Most common mutation ARID1A: 17 pts

Patient Demographics	DKN-01 Monotherapy N=23	DKN-01 + Paclitaxel N=41
Age (yrs), median (min, max)	66 (43, 78)	64 (35, 80)
White, n (%)	19 (90.5)	35 (85.4)
Primary diagnosis, n (%)		
Epithelial endometrial cancer (EEC)	11 (52.4)	23 (56.1)
Epithelial ovarian cancer (EOC)	10 (47.6)	18 (43.9)
Platinum-sensitive	1	0
Platinum-resistant	3	8
Platinum-refractory	5	6
Unknown	1	4
Baseline CA125 (µg/mL)*, median (min, max)	114.80 (9.6, 1810.0)	215.50 (6.0, 7091.0)
Number of prior therapies, median (min, max)	3 (1, 10)	4 (1, 9)
Prior therapies, n		
Platinum	21	41
Taxane	21	41
Bevacizumab	5	15
PARP inhibitor	1	8
Tumor Characteristics	**EEC / EOC**	**EEC / EOC**
Tumor mutational burden, n	N=7 / N=8	N=17 / N=14
Low (0-5 Muts/Mb)	5 / 6	11 / 11
Intermediate (6-20 Muts/Mb)	1 / 2	4 / 3
High (>20 Muts/Mb)	1 / 0	2 (11.8) / 0
Microsatellite status, n (%)	N=11 / N=8	N=21 / N=15
MSS	10 / 8	19 / 15
MSI-H	1 / 0	2 / 0
Wnt pathway altered*	8 / 6	12 / 9

Data as of 4 Mar 2019
*Wnt alterations: CTNNB1, ARID1A, APC, RNF43, CREBBP, MLL2, FBXW7, TERT, NOTCH1, LRP1B, SOX2
^as of 23 Jan 2019

Number of Prior Therapies Among the 38 Evaluable Patients

1-2	3-6	7-9
N=13	N=19	N=6

Data as of 4 Mar 2019

EXPOSURE

Drug Exposure and Study Disposition

- Majority of patients remain on treatment as of 23 Jan 2019

	DKN-01 Monotherapy N=18	DKN-01 + Paclitaxel N=30	Total N=48
Number of cycles, median (min, max)	2.0 (1, 8)	3 (1, 8)	2.0 (1, 8)
Duration on treatment (days), median (min, max)	48.0 (8, 226)	68.5 (8, 222)	54.0 (8, 226)
Reasons for study drug discontinuation, n (%)			
Adverse event	0	0	0
Clinical progression	1 (5.6)	5 (16.7)	6 (12.5)
Objective disease progression	2 (11.1)	4 (13.3)	6 (12.5)
Patient withdrew consent	0	3 (10.0)	3 (6.3)
Reasons for study discontinuation, n (%)			
Adverse event	0	0	0
Death	1 (5.6)	4 (13.3)	5 (10.4)
Lost to follow up			
Patient withdrew consent	0	3 (10.0)	3 (6.3)
Duration on post-treatment follow up (days), median (min, max)	97.0 (38, 98)	40.5 (7, 166)	51.0 (7, 166)
Duration on study (days): median, (min, max)	50.0 (8, 226)	98.5 (8, 247)	85.0 (8, 247)

Data as of 23 Jan 2019

SAFETY

- DKN-01 was safe and well tolerated as a monotherapy and in combination with paclitaxel
- Majority of adverse events were Grade 1-2
- DKN-01 related ≥ Grade 3 events
  - DKN-01 monotherapy: nausea
  - DKN-01 + paclitaxel: anemia, neutropenia and fatigue

Adverse Events with ≥10% Incidence: DKN-01 Monotherapy

	Regardless of DKN-01 Causality				DKN-01 Related Causality			
	TEAEs Any Grade N=17		TEAEs ≥ Grade 3 N=17		TEAEs Any Grade N=17		TEAEs ≥ Grade 3 N=17	
	#	%	#	%	#	%	#	%
Any								
Serious	1	5.9	1	5.9	1	5.9	1	5.9
Preferred Terms								
Fatigue	6	35.3	0	0	5	29.4	0	0
Nausea	6	35.3	1	5.9	6	35.3	1	5.9
Arthralgia	3	17.6	0	0	0	0	0	0
Abdominal distension	2	11.8	0	0	2	11.8	0	0
Chills	2	11.8	0	0	1	5.9	0	0
Constipation	2	11.8	0	0	1	5.9	0	0
Decreased appetite	2	11.8	0	0	2	11.8	0	0
Dizziness	2	11.8	0	0	2	11.8	0	0
Headache	2	11.8	0	0	1	5.9	0	0
Pollakuria	2	11.8	0	0	1	5.9	0	0
Vomiting	2	11.8	0	0	2	11.8	0	0

Data as of 23 Jan 2019

Adverse Events with ≥10% Incidence: DKN-01 + Paclitaxel Therapy

	Regardless of DKN-01 Causality				DKN-01 Related Causality			
	TEAEs Any Grade N=30		TEAEs ≥ Grade 3 N=30		TEAEs Any Grade N=30		TEAEs ≥ Grade 3 N=30	
	#	%	#	%	#	%	#	%
Any								
Serious	7	23.3	6	20.0	1	3.3	1	3.3
Preferred Terms								
Fatigue	9	30.0	1	3.3	7	23.3	1	3.3
Alopecia	8	26.7	0	0	2	6.7	0	0
Diarrhoea	7	23.3	0	0	6	20.0	0	0
Nausea	7	23.3	0	0	5	16.7	0	0
Anaemia	6	20.0	4	13.3	6	20.0	3	10.0
Dyspnoea	6	20.0	1	3.3	3	10.0	0	0
Headache	5	16.7	0	0	3	10.0	0	0
Vomiting	5	16.7	0	0	2	6.7	0	0
Abdominal distension	4	13.3	0	0	1	3.3	0	0
Cough	4	13.3	0	0	1	3.3	0	0
Dizziness	4	13.3	0	0	3	10.0	0	0
Hypokalaemia	4	13.3	0	0	3	10.0	0	0
Neutropenia	4	13.3	1	3.3	2	6.7	1	3.3
Chills	3	10.0	0	0	2	6.7	0	0
Decreased appetite	3	10.0	0	0	1	3.3	0	0
Hot flush	3	10.0	0	0	2	6.7	0	0
Hyperglycaemia	3	10.0	1	3.3	2	6.7	0	0
Hypomagnesaemia	3	10.0	0	0	2	6.7	0	0
Hyponatraemia	3	10.0	1	3.3	0	0	0	0
Pyrexia	3	10.0	0	0	3	10.0	0	0

Data as of 23 Jan 2019

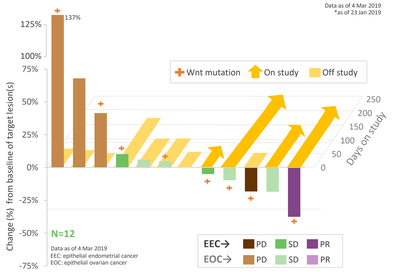
EFFICACY

Best Overall Response: DKN-01 Monotherapy

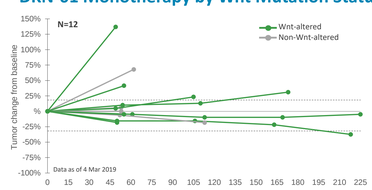
- 12 of 21 patients enrolled are evaluable with post-baseline imaging (4 March 2019)
- 1 PR after 8 cycles of therapy; 6 pts with SD; 7 of 12 evaluable patients with clinical benefit; 5 of 7 with Wnt alterations; 4 of 7 with tumor volume reductions
- 4 of 12 evaluable patients were on DKN-01 monotherapy for 150+ days

Best Overall Response, ITT (n=21)	Endometrial Cancer (n=11)		Ovarian Cancer (n=10)	
Wnt Genetics	Wnt-Altered n=8	Non-Altered n=3	Wnt-Altered n=6	Non-Altered n=4
Evaluable	4	1	4	3
Partial response (PR)	1	0	0	0
Stable disease (SD)	2	0	2	2
Stable disease > 6 weeks	2	0	2	2
Objective disease control (ODR)	3	0	2	2
Duration of clinical benefit* (weeks), median (95% CI)	17.1 (NA, NA)	NA	NA (8.1, NA)	NA
Progressive disease (PD)	1	1	2	1
Not evaluable	0	1	0	0
Pending first evaluation	4	1	2	1

Data as of 4 Mar 2019
*as of 23 Jan 2019



Percent Change in Target Lesion Measurements: DKN-01 Monotherapy by Wnt Mutation Status

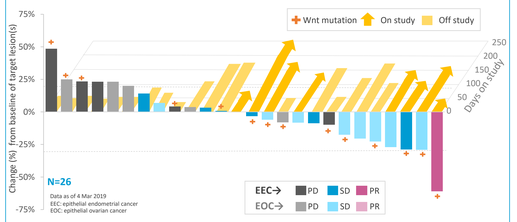


Best Overall Response: DKN-01 + Paclitaxel Therapy

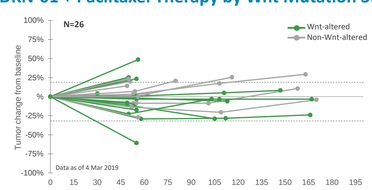
- 26 of 41 patients enrolled are evaluable with post-baseline imaging (4 March 2019)
- Duration of clinical benefit prolonged in patients with Wnt-altered tumors (23 Jan 2019)

Best Overall Response, ITT (n=41)	Endometrial Cancer (n=23)		Ovarian Cancer (n=18)	
Wnt Genetics	Wnt-Altered n=12	Non-Altered n=11	Wnt-Altered n=9	Non-Altered n=9
Evaluable	8	4	6	8
Partial response (PR)	1	0	0	0
Stable disease (SD)	3	3	4	5
Stable disease > 6 weeks	3	3	4	5
Objective disease control (ODR)	4	3	4	5
Duration of clinical benefit* (weeks), median (95% CI)	23.9 (NA, NA)	15.5 (15.1, 15.9)	NA (7.7, NA)	10.4 (3.9, 17.0)
Progressive disease (PD)	4	1	2	3
Not evaluable	1	1	0	0
Pending first evaluation	3	6	3	1

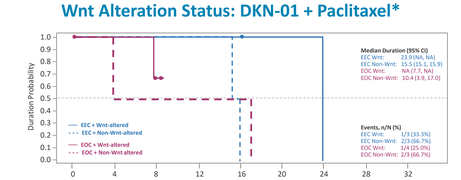
Data as of 4 Mar 2019
*as of 23 Jan 2019



Percent Change in Target Lesion Measurements: DKN-01 + Paclitaxel Therapy by Wnt Mutation Status

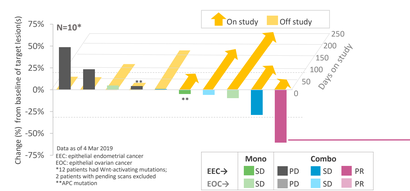


Duration of Clinical Benefit by Tumor Type and Wnt Alteration Status: DKN-01 + Paclitaxel*



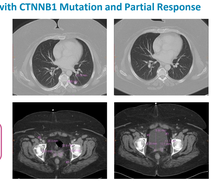
*as of 23 Jan 2019

Best Response in Wnt-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)

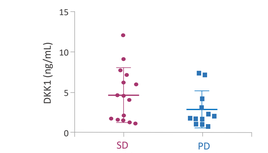


BIOMARKERS

DKK1 Screening Plasma Levels

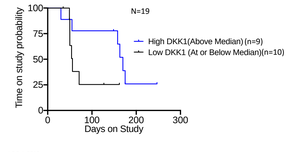
- Patients with stable disease have higher screening plasma DKK1 levels in an early analysis
- High screening plasma DKK1 levels are associated with longer time on therapy in the DKN-01 + paclitaxel group

DKK1 Plasma at Screening: All Groups



Data as of 6 Feb 2019

Time on Study by DKK1 Screening Plasma Levels (DKN-01 + Paclitaxel)



Data as of 6 Feb 2019

CONCLUSIONS

- Partial responses and durable clinical benefit with DKN-01 monotherapy and in combination with paclitaxel
- Partial response and stable disease observed in patients with carcinosarcoma, a difficult to treat population
- Patients whose tumors have Wnt pathway alterations experience greater duration of clinical benefit when treated with DKN-01 plus paclitaxel
- High baseline plasma DKK1 levels are associated with longer time on therapy in the DKN-01 plus paclitaxel group
- DKN-01 is safe as a monotherapy or in combination with paclitaxel with no additive toxicities
- 24 newly enrolled patients currently in cycle 1 or 2 are not yet evaluable for initial efficacy assessment; 23 of 38 (61%) evaluable patients remained on treatment (70+ days); 12 (32%) remain on therapy (median duration 150+ days)
- A higher dose of DKN-01 and an expansion population (carcinosarcoma) are under consideration

SCAN TO REQUEST REPRINT

References:

1. Kagey M and He X. *Br J Pharmacol*. 2017;174:4637–4650.
2. Liu Y, et al. *J Natl Cancer Inst*. 2014;1(9): dju245.
3. McConechy MK, et al. *Mod Pathol*. 2014;27:128–134.
4. Chamorro MN, et al. *EMBO*. 2005; 24:73-84.
5. Nixda A, et al. *Oncogene*. 2004; 23:8520-8526.
6. Leap Therapeutics unpublished data
7. Haas M, et al. *Cancer Res*. 2018;78(13 Suppl):Abstract nr 1710.
8. Haas, M, et al. *J ImmunoTherapy Cancer*. 2018;6 (Suppl 1):115 P474.
9. Kagey M, et al. *Cancer Res*. 2017;77(13 Suppl):Abstract nr 369.
10. Klempner SJ, et al. *Ann Oncology*. 2018;29(8):viii222.
11. Simon, R. *Control Clin Trials*. 1989;10(1):1-10.