A Phase 1/2 Multicenter Investigator-Initiated Trial of DKN-01 as Monotherapy or in Combination with Docetaxel for the Treatment of Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Abstract # 321876

David R. Wise[1], Russel K. Pachynski[2], Samuel R. Denmeade[3], Rahul R. Aggarwal[4], Victor Adorno Febles[1,5], Arjun V. Balar[1], Minas P. Economides1, Cynthia Loomis[6], Shanmugapriya Selvaraj[6], Michael Haas[7], Michael Kagey[7], Walter Newman[7], Cynthia A. Sirard[7], Andrea B. Troxel[8], Sarah Griglun[1], Dayna Leis[1], Nina Yang[1], Viktoriya Aranchiy[1], Sabrina Machado[1], Erika Waalkes[1], Gabrielle Gargano[1], Ezeddin Fedal[9], Fang-Ming Deng[9], Qinghu Ren[9], Luis Chiriboga[9], Jonathan Melamed[9]

1 Laura & Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY 2 Washington University School of Medicine, St. Louis, MO; 3 The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD; 4 UCSF Cancer Center, San Francisco, CA; 5 New York Harbor Veterans Healthcare System, New York, NY; 6 Department of Pathology, NYU Langone Health, New York, NY; 7 Leap Therapeutics, Inc., Cambridge, MA; 8 Division of Biostatistics, Department of Population Health at NYU Grossman School of Medicine, New York, NY 9 Department of Pathology, New York University School of Medicine, New York, NY

Background

- Dickkopf-1 (DKK1) is a secreted Wnt signaling modulator that is upregulated in prostate cancers with low Androgen Receptor (AR) expression and co-occurring mutations in Wnt signaling family genes.
- DKN-01, a potent humanized monoclonal IgG4 antibody with neutralizing activity against DKK1, delays prostate cancer growth in pre-clinical modes in an NK-cell dependent manner.
- These data provided the rationale for a prospective clinical trial testing DKN-01 in patients with mCRPC.
- Here, we report the safety and efficacy results of the phase 1 dose escalation cohorts.

Study Design

Treatment Groups

Phase 1b *Dose Escalation*

Cohort 1A

DL	DKN-01	Docetaxel
1	300 mg	75 mg/m2
2	600 mg	75 mg/m2
-1	150 mg	75 mg/m2

Phase 2 *Dose Expansion*

***Cohort 1B* (N = 33)**

- Pre-docetaxel
- Measurable disease required
- Docetaxel + DKN-01

Cohort 2A

DL	DKN-01
1	300 mg
2	600 mg
-1	150 mg

***Cohort 2B* (N = 27)**

- Post-docetaxel or taxane ineligible
- Measurable disease not required
- DKN-01 monotherapy

- This is an investigator-initiated parallel-arm non-randomized phase 1/2 clinical trial testing DKN-01 alone or in combination with docetaxel 75 mg/m2 for men with mCRPC who progressed on ≥1 AR signaling inhibitor.
- Eligible patients who had progressed on or were intolerant of docetaxel were assigned to the monotherapy cohort whereas taxane-naïve patients were assigned to the DKN-01 plus docetaxel combination cohort.
- DKK1 status was determined by RNA in-situ expression.
- The primary endpoint of the phase 1 dose escalation cohorts was safety, characterized by dose-limiting toxicity (DLT). A secondary endpoint of the study was to correlate anti-tumor activity, DKK1 expression (cutoff H-score ≥ 1), and clinical evidence of aggressive variant prostate cancer (AVPC).

RESULTS

Table 1 – Baseline Characteristics

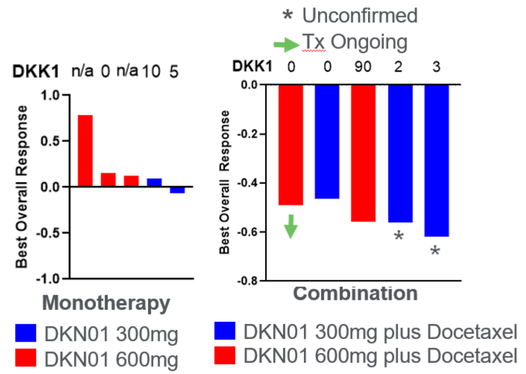
Characteristics	DKN-01 Docetaxel	300mg N/A n=4	600mg N/A n=3	300mg 75mg/m2 n=3	600mg 75mg/m2 n=3
Age (median)		64.5	74	66	68
Adenocarcinoma, n (%)		4 (100)	3 (100)	3 (100)	1 (33)
Neuroendocrine Carcinoma, n (%)		0	0	0	2 (67)
Aggressive Variant (AVPC), n (%)		1 (25)	0	1 (25)	3 (100)
APC mutation, n (%)		1 (25)	1 (33)	1 (33)	0
CTNNB1 mutation, n (%)		0	2 (67)	0	0

Table 2 – Selected Adverse Events

DKN-01	300mg		600mg		300mg		600mg	
Docetaxel	N/A		N/A		75mg/m²		75mg/m²	
	n=4		n=3		n=3		n=3	
	Grade		Grade		Grade		Grade	
	All	≥3	All	≥3	All	≥3	All	≥3
TEAE in ≥1 patient , n								
Neutropenia	0	0	0	0	2	2	1	1
Fatigue	3	0	1	0	2	0	2	1
Anemia	0	0	1	1	1	1	0	0
Atrial fibrillation	0	0	0	0	1	1	0	0
CPK increased	0	0	0	0	1	1	0	0
Clostridium Difficile	0	0	0	0	1	1	0	0
Hypotension	0	0	0	0	1	1	0	0
Acute kidney injury	0	0	1	1	0	0	0	0
Anorexia	1	0	2	1	0	0	1	0
Hematuria	0	0	1	1	1	0	0	0
Creatinine increased	0	0	1	1	0	0	0	0

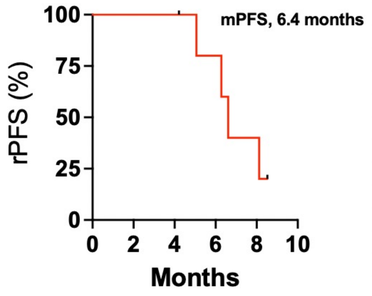
- Events noted in Table 2 are events that occurred with Grade 3 severity in at least 1 patient in at least 1 cohort
- No DKN-01 related Grade ≥ 3 adverse events occurred in either cohort.
- No unexpected Docetaxel-related Grade ≥ 3 AEs were observed
- No DLTs were observed and the maximum tolerated dose was not achieved
- No DKN-01 dose reductions occurred
- 1 SAE occurred in the monotherapy cohorts (AKI) and 1 SAE occurred in the combination cohort (C. Difficile Colitis), neither of which were related to study drugs.

Figure 1 – Best Radiographic Response



Best overall RECIST v1.1 response for DKN-01 monotherapy (left) and combination DKN-01 plus docetaxel (right). DKK1 in-situ RNA expression (H score)

Figure 2– rPFS



rPFS (n=6), pts treated with DKN-01 plus Docetaxel.

Table 3 – DKK1 Expression

DKK1 Expression	n = 24
H-Score 0	14 (58.3)
H-Score ≥1	10 (41.7)
H-Score ≥10	5 (20.8)
H-Score ≥35	3 (12.5)

DKK1 mRNA expression determined by RNA in-situ hybridization in mCRPC biopsy specimens.

CONCLUSIONS

- DKN-01 600mg was well tolerated and selected as the recommended phase 2 dose as monotherapy and in combination with docetaxel.
- DKN-01 in combination with docetaxel showed promising clinical activity in prostate cancers regardless of DKK1 expression and was particularly promising in patients with AVPC.
- Further accrual into the phase 2 portion of this study is ongoing alongside preclinical and correlative studies aiming to investigate the mechanism of action of this combination therapeutic strategy.
- DKN-01 plus Docetaxel activity was observed in DKK1 low mCRPC prompting a protocol amendment to no longer require DKK1/Wnt biomarker+.
- Retrospective correlation of anti-tumor activity with DKK1/Wnt biomarker status will be performed.

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@DrDaveWise