DKN-01 in Combination with Pembrolizumab in Patients with Advanced Gastroesophageal Adenocarcinoma (GEA): Tumoral DKK1 Expression as a Predictor of Response and Survival

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BACKGROUND

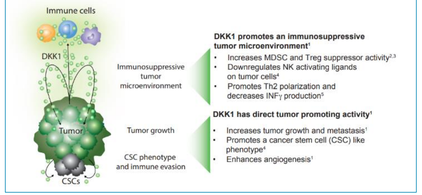
Dickkopf-1 (DKK1)

- Modulator of Wnt signaling
- Tumor cells secrete DKK1; elevated DKK1 expression is associated with poor prognosis
  - → Immunosuppressive tumor microenvironment
  - → Promotes proliferation, metastasis, and angiogenesis

DKN-01

- Humanized monoclonal antibody [IgG4] targeting DKK1
- Activates innate immune response in preclinical models
- In GEA cancer patients treated with DKN-01 + pembrolizumab, high tumoral DKK1 was associated with longer PFS
- DKN-01 + pembrolizumab has demonstrated safety and clinical activity in advanced GEA
- We report response and survival outcomes in anti-PD-1/anti-PD-L1-naïve GEA patients by high/low tumoral DKK1 expression

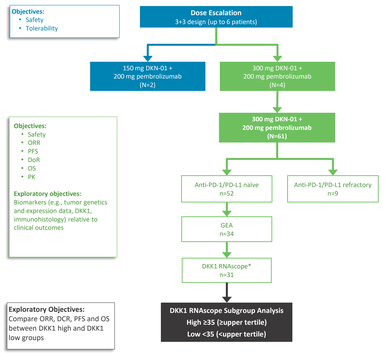
Model for DKK1 Cancer-Promoting Activity[1-5]



METHODS

We enrolled advanced anti-PD-1/PD-L1 naïve gastroesophageal/gastric adenocarcinoma (GEA) patients in a Phase 1b/2a study of DKN-01 + pembrolizumab (NCT02013154). Tumoral DKK1 mRNA expression was assessed by an in-situ hybridization RNAscope assay. PD-L1 IHC was done using the Dako 22C3 antibody. Objective response rate (ORR), disease control rate (DCR), progression free survival (PFS) and overall survival (OS) were compared between DKK1 high and low groups. Kaplan-Meier method and Cox-PH model was used for survival analysis and logistic regression was used for clinical benefit/response outcome.

KEYNOTE-731 Study Flow Diagram
Esophagogastric Cancer – DKN-01/Pembrolizumab



*Most of the biopsies were obtained during screening.

RESULTS

Patient Disposition: DKK1 GEA Subset

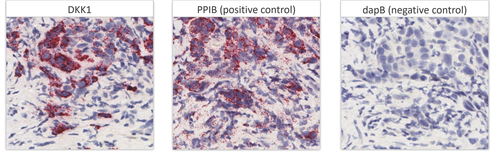
- 34 patients were enrolled to receive 300 mg DKN-01 + pembrolizumab
- 31 patients had DKK1 expression available
  - → One third of patients were considered DKK1 high (H-score ≥ 35)
  - → Among patients who had known MSI status, all were MSS

Gastro-esophageal adenocarcinoma/GEA with DKK1 H-score (IO naïve)	Overall N = 31	DKK1 High (H-Score >upper-tertile*) N=11	DKK1 Low (H-Score <upper-tertile*) N=20
Age, median (min, max)	63 (28, 80)	59 (45, 80)	66 (28, 78)
Gender (male), n(%)	28 (90)	10 (91)	18 (90)
ECOG Performance Status			
0	6 (19)	3 (27)	3 (15)
1	25 (81)	8 (73)	17 (85)
Diagnosis, n(%)			
GEJ Adenocarcinoma	26 (84)	10 (91)	16 (80)
GC Adenocarcinoma	5 (16)	1 (9)	4 (20)
Stage at Initial Diagnosis, n(%)	IV: 27 (87)	IV: 9 (82)	IV: 18 (90)
Time Since First Diagnosis, n (%)			
≤12 months	15 (48)	4 (36)	11 (55)
>12 month	16 (52)	7 (64)	9 (45)
Prior Systemic Therapies, n(%)			
Prior Taxane	16 (52)	6 (56)	10 (50)
Prior Trastuzumab	10 (32)	3 (27)	7 (35)
Prior Ramucirumab	10 (32)	4 (36)	6 (30)
Baseline Tumor Burden (Sum of target lesions at baseline in mm), median (min, max)	53 (16, 195)	44 (22, 110)	59 (16, 195)
Neutrophils:Lymphocytes Ratio > 4, n:N (%)	14/28 (50)	7/10 (70)	7/18 (39)
Tumor PD-L1: CPS, n			
CPS < 1 (Negative)	7	1	6
CPS ≥ 1 - <10 (Positive, Low)	13	6	7
CPS ≥ 10 (Positive, High)	7	3	4
Missing	4	1	3
Tumor Mutation Burden, n			
≤ 5	7	3	4
>5-<10	7	3	4
≥10	1	0	1
Missing	16	5	11

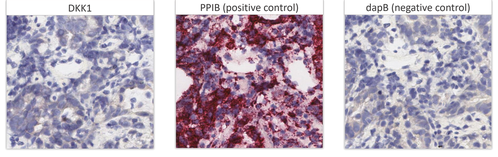
*Upper-tertile: 35; No significant differences were seen between DKK1 high and low groups for the baseline characteristics above (Fisher's test was used for categorical variables; Wilcoxon Rank Sum was used for continuous variables)

DKK1 RNAscope Tumor Biopsy Images

Patient with a partial response: DKK1 H-score = 163



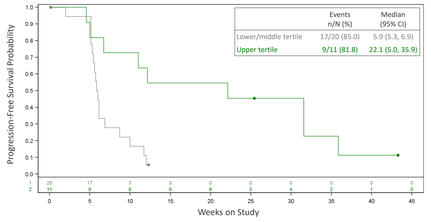
Patient with progressive disease: DKK1 H-score = 7



Pre-treatment biopsies from GEA cancer patients treated with a DKN-01 pembrolizumab combination were analyzed for DKK1 expression by RNAscope (in situ hybridization). Tumor DKK1 mRNA levels were quantified using QuPath software or manually by calculating a H-score (range 0 to 300). H-score = 1*(%cells with 1-3 dots) + 2*(%cells with 4-9 dots) + 3*(%cells with ≥10 dots). Peptidyl-prolyl cis-trans isomerase B (PPIB). Bacillus subtilis dihydrodipicolinate reductase (dapB).

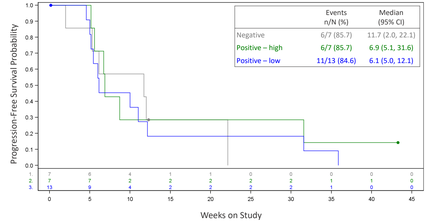
Progression-Free Survival

- Median PFS was longer in DKK1 high (22.1 weeks) vs. DKK1 low (5.9 weeks); HR: 0.23 (95% CI: 0.082, 0.66)
- Adjusted (for PD-L1 expression) HR for DKK1 high was 0.20 (95% CI: 0.061, 0.68; n=27)
- Adjusting for baseline tumor burden did not alter the association of high DKK1 with longer PFS (DKK1 high vs. low (adjusted for sum of target lesions at baseline as <median vs. >= median) HR: 0.24 (95% CI: 0.084, 0.7)



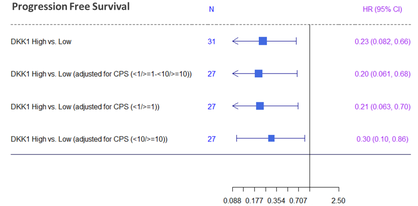
Progression-Free Survival by PD-L1 CPS Status

- PFS was not associated with PD-L1 CPS expression



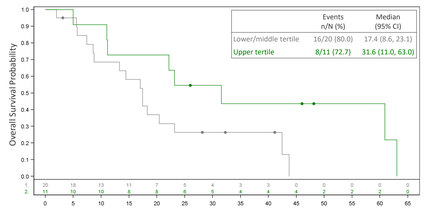
Multivariable Analysis

- DKK1 high correlates with longer PFS independent of PD-L1 CPS expression



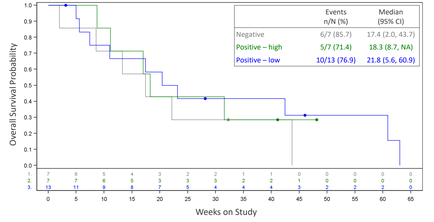
Overall Survival

- Median OS was longer in DKK1 high (31.6 weeks) vs. DKK1 low (17.4 weeks); HR: 0.4 (95% CI: 0.15, 1.1)



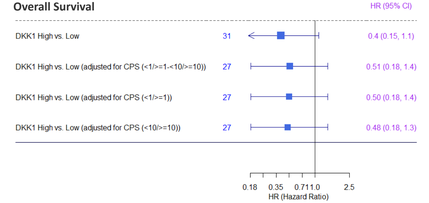
Overall Survival by PD-L1 CPS Status

- OS was not associated with PD-L1 CPS expression



Multivariable Analysis

- DKK1 high trends toward longer OS independent of PD-L1 CPS expression

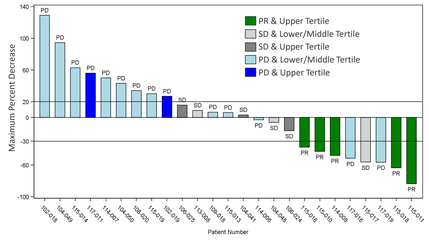


Best Overall Response

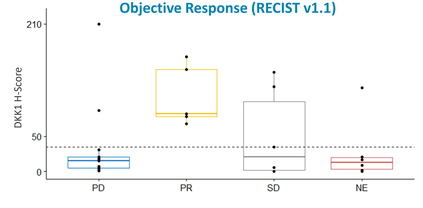
- 25 of 31 patients were response-evaluable (RE)
- 22 of 31 patients were RE and had both DKK1 and PD-L1 expression available
- DKK1 high had an ORR of 50% (5 PR/10) and DCR of 80% (8/10)
- DKK1 low had an ORR of 0% (0/15) and DCR of 20% (3/15)
- DKK1 high (vs. low) had an OR of 16 (95% CI: 2.2, 118.3; n=25) and adjusted (for PD-L1 CPS ≥10 vs. <10) OR of 17.6 (95% CI:1.6, 194.4; n=22) for clinical benefit/response (PR/SD vs. PD)

Primary Location	Total (n)	RE* (n)	PR (n)	SD (n)	PD (n)	NE (n)	RE* ORR (n, %)	DCR (n,%)
DKK1 RNAscope*	31							
DKK1-high	11	10	5	3	2	1	5 (50)	8 (80)
DKK1-low	20	15	0	3	12	5	0 (0)	3 (20)

*DKK1-high ≥ upper tertile (35)



Objective Response (RECIST v1.1)



CONCLUSIONS

- GEA patients with high tumoral DKK1 expression have improved clinical outcomes when treated with DKN-01 + pembrolizumab
- Improvements in response/clinical benefit and PFS were observed independent of PD-L1 expression
- DKK1 high patients trended toward longer OS, irrespective of PD-L1 expression in this early-phase trial
- Tumoral DKK1 will be evaluated as a predictive biomarker for DKN-01 treated GEA patients prospectively in future studies

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