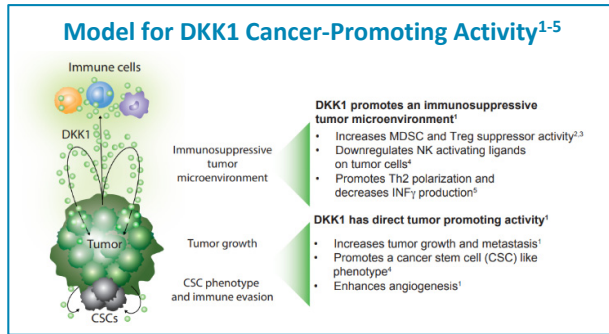


# Tumoral DKK1 Expression Correlates with Better Clinical Outcomes in Patients with Advanced Esophagogastric Cancer (EGC) Treated With DKN-01

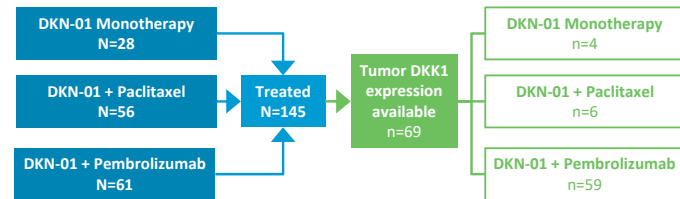
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## BACKGROUND

Dickkopf-1 (DKK1) modulates Wnt signaling and contributes to an immune suppressive tumor microenvironment. DKN-01, a neutralizing DKK1 antibody, has demonstrated safety and clinical activity in advanced EGC either as a monotherapy or in combination with paclitaxel or pembrolizumab. Previously, we demonstrated greatest clinical benefit in anti-PD-1/PD-L1-naïve, DKK1-high GEJ/GC adenocarcinoma pts treated with DKN-01 + pembrolizumab. We report response and survival outcomes in EGC pts treated with DKN-01 by high vs low tumoral DKK1 expression, with a focus on anti-PD-1/PD-L1-refractory GEJ/GC pts.



## METHODS

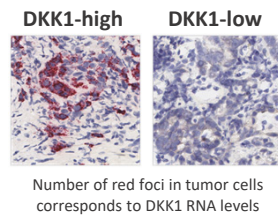


**Study Design:** Phase 1b/2a study of DKN-01 monotherapy or combined with paclitaxel or pembrolizumab (NCT02013154) in advanced EGC pts

**Tumoral DKK1 RNA Expression:** Assessed by a chromogenic in-situ hybridization RNAscope assay. DKK1 tumoral RNA levels 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  $\geq 10$  dots).

**DKK1-high:**  
H-score  $\geq$  upper-tertile ( $\geq 39$ )

**DKK1-low:**  
H-score < upper-tertile (<39)

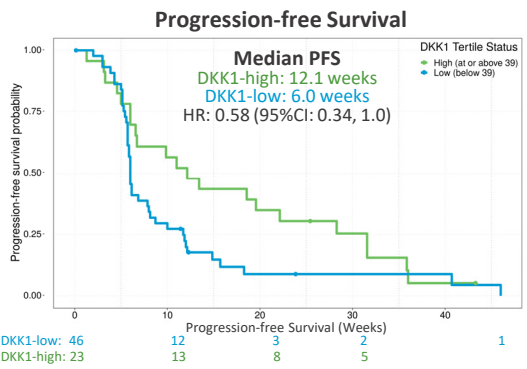
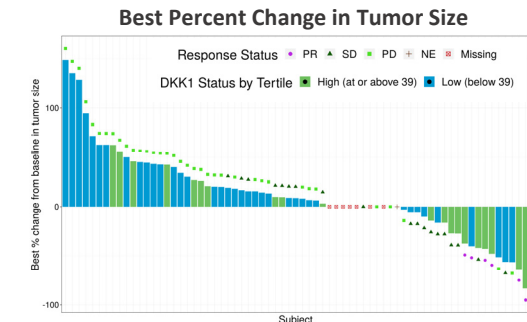


**Endpoints:** Objective response rate (ORR), disease control rate (DCR), progression free survival (PFS) and overall survival (OS) compared between DKK1-high and DKK1-low groups

**Statistical Analysis:** Kaplan-Meier method and Cox-PH model for survival analysis and logistic regression for clinical benefit/response outcome

## DKK1 High vs Low: All Patients (N=69)

- ORR: DKK1-high 22% (5 PR/23) vs DKK1-low 2% (1/46)
- DCR: DKK1-high 57% (13/23) vs DKK1-low 26% (12/46)
- Longer PFS and trend toward longer OS in DKK1-high vs DKK1-low

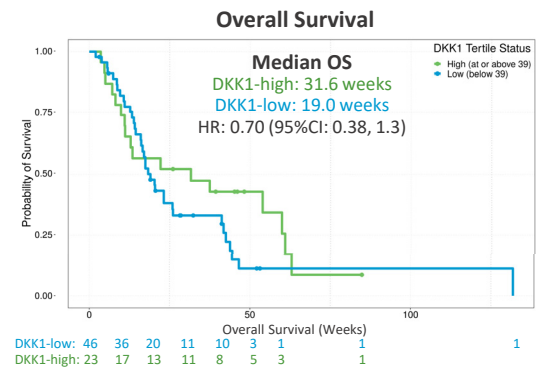
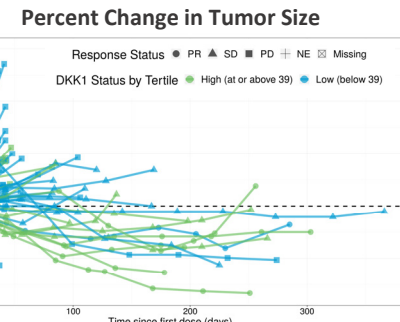


## Baseline Patient Characteristics

- 69 pts had tumoral DKK1 expression available
- 65% had  $\geq 2$  prior therapies (range 1 to 5)

	Overall N=69	DKK1-high* N=23	DKK1-low* N=46
Age, median (min, max)	65 (28, 81)	65 (48, 81)	64.5 (28, 81)
Gender (male), n(%)	60 (87%)	19 (82.6%)	41 (89.1%)
Diagnosis, n(%)			
EAC	19 (27.5)	7 (30.4)	12 (26.1)
ESCC	10 (14.5)	2 (8.7)	8 (17.4)
GEJ/GC	40 (58)	14 (60.9)	26 (56.5)
Stage III-IV at Diagnosis, n(%)	60 (87)	19 (83)	41 (89)
Months First Diagnosis, median (min, max)	14.9 (2.5, 80.5)	16.8 (3.2, 80.5)	12.1 (2.5, 39.6)
Prior Systemic Therapies, median	2	3	2

EAC: esophageal adenocarcinoma; ESCC: esophageal squamous cell carcinoma; GEJ/GC: gastroesophageal junction or gastric adenocarcinoma  
\*DKK1-high = upper tertile of patients with RNAscope H-scores  $\geq 39$ ; DKK1-low = H-score < upper tertile (<39)



## Tumor Characteristics

- No notable differences in baseline MSS, TMB, PD-L1 expression between groups

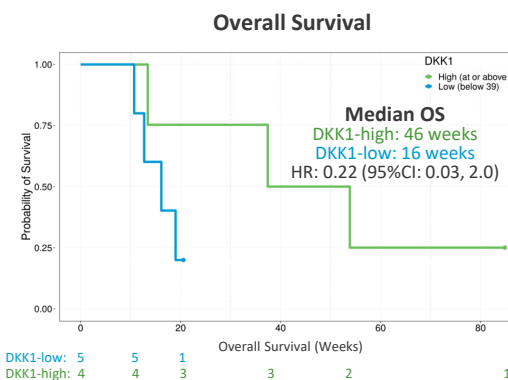
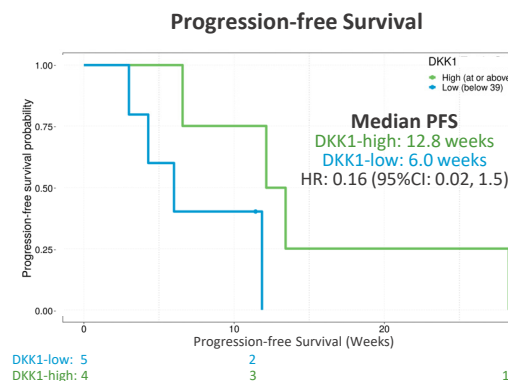
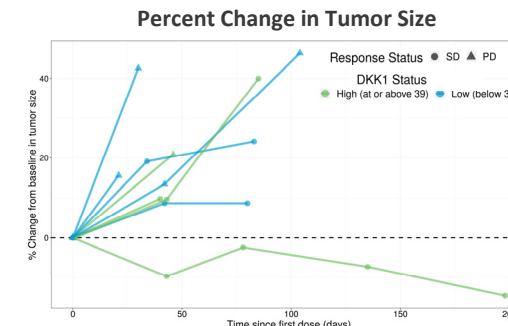
	Overall N=69	DKK1-high* N=23	DKK1-low* N=46
Neutrophils:Lymphocytes Ratio >4, n (%)	38 (55.1)	15 (65.2)	23 (50.0)
Microsatellite Status, n (%)			
MSI-H	2 (2.9)	1 (4.4)	1 (2.2)
MSS	48 (69.6)	14 (60.9)	34 (73.9)
Unknown	19 (27.5)	8 (34.8)	11 (23.9)
Tumor PD-L1: CPS, n (%)			
CPS < 1 (Negative)	19 (27.5)	6 (26.1)	13 (28.3)
CPS $\geq 1$ - <10 (Low Positive)	22 (31.9)	8 (34.8)	14 (30.4)
CPS $\geq 10$ (High Positive)	14 (20.3)	5 (21.7)	9 (19.6)
Unknown	14 (20.3)	4 (17.4)	10 (21.7)
Tumor Mutation Burden, n (%)			
$\leq 5$	16 (23.2)	6 (26.1)	10 (21.7)
>5-<10	11 (15.9)	6 (26.1)	5 (10.9)
$\geq 10$	4 (5.8)	1 (4.4)	3 (6.5)
Missing	38 (55.1)	10 (43.5)	28 (60.9)

\*\*DKK1-high = upper tertile of patients with RNAscope H-scores  $\geq 39$ ; DKK1-low = H-score < upper tertile (<39)

## RESULTS

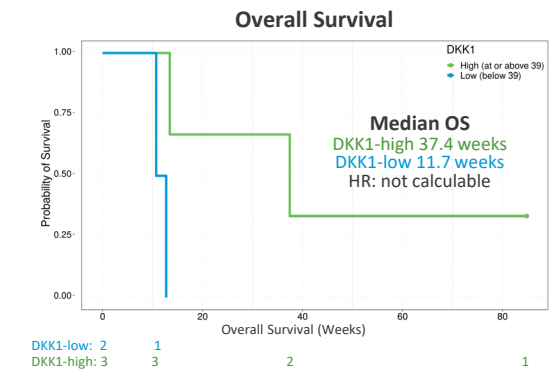
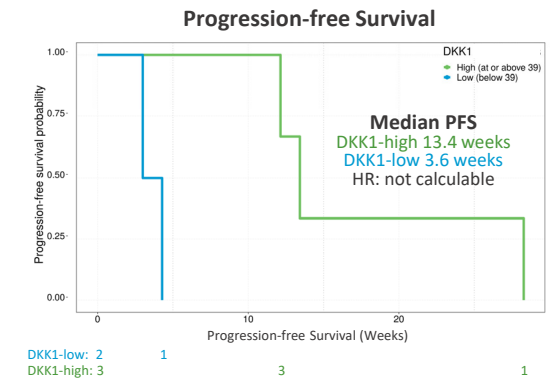
### DKK1 High vs Low: Anti-PD-1/PD-L1-Refractory Patients (N=9)

- Longer PFS and OS for DKK1-high (n=4) vs DKK1-low (n=5)
- All pts in this group treated with DKN-01 + pembrolizumab



### DKK1 High vs Low: Anti-PD-1/PD-L1-Refractory Patients with GEJ/GC (N=5)

- Longer PFS and OS for DKK1-high (n=3) vs DKK1-low (n=2)
- All pts in this group treated with DKN-01 + pembrolizumab



## CONCLUSIONS

- High levels of tumoral DKK1 expression correlated with improved clinical outcomes in heterogeneous EGC pts treated with DKN-01 monotherapy or in combination.
- DKK1-high PD-1/PD-L1-refractory pts treated with DKN-01 + pembrolizumab experienced longer PFS and OS compared with DKK1-low pts
- DKK1 tumoral expression as a predictive biomarker for response to DKN-01 therapy in combination with tislelizumab is being evaluated in a Phase 2 study (NCT04363801)