divergent outcomes associated with increased intratumoral TCR and BCR diversity suggest a host response that may favor opposing T and B cell lymphocytic expansion. Regulation of this relationship may be explained by tumor MHC class I expression[3] or the presence of CD141+ cross presenting dendritic cells[7, 8] and tertiary lymphoid structures,[9] currently under investigation. Examination of repertoire modulating therapies is warranted.

Trial Registration This trial (NCT01978184) was approved by the protocol review committee and IRB 13–074 at the University of Pittsburgh and performed in full accordance with the guidelines for good clinical practice and the Declaration of Helsinki. Written informed consent was obtained from all patients prior to any protocol treatment.

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261 ASSOCIATION OF T-CELL–INFLAMED GENE EXPRESSION PROFILE AND PD-L1 STATUS WITH EFFICACY OF PEMBROLIZUMAB IN PATIENTS WITH ESOPHAGEAL CANCER FROM KEYNOTE-180

[1]Manish Shah*, [2]Takashi Kojima, [3]Daniel Hochhauser, [4]Peter Enzinger, [5]Judith Raimbourg, [6]Antoine Hollebecque, [7]Florian Lordick, [8]Sung-Bae Kim, [9]Masahiro Tajika, [10]Heung Tae Kim, [11]A Craig Lockhart, [12]Hendrick-Tobias Arkenau, [13]Farid El-Hajbi, [14]Per Pfeiffer, [15]Pooja Bhagia, [15]Z Alexander Cao, [15]Jared Lunceford, [15]Shailaja Suryawanshi, [15]Mark Ayers, [15]Matt Marton, [16]Ken Kato. *[1]Weill Cornell Medical College, New York, NY, USA; [2]National Cancer Center Hospital East, Chiba, Japan; [3]University College London Hospitals, London, UK; [4]Dana-Farber Cancer Institute, Boston, MA, USA; [5]Institut de Cancérologie de l'Ouest, St Herblain, France; [6]Institut Gustave Roussy, Villejuif, France; [7]University Cancer Center Leipzig, Leipzig, Germany; [8]Asan Medical Center, Seoul, Korea, Republic of; [9]Aichi Cancer Center Hospital, Aichi, Japan; [10]National Cancer Center, Goyang, Korea, Republic of; [11]University of Miami, Miami, FL, USA; [12]Sarah Cannon Research Institute, London, UK; [13]Centre Oscar-Lambret, Lille, France; [14]Odense University Hospital, Odense, Denmark; [15]Merck and Co., Inc., Kenilworth, NJ, USA; [16]National Cancer Center Hospital, Tokyo, Japan*

Background Key biomarkers under investigation for the ability to predict response to monotherapy PD-1 inhibitors such as pembrolizumab include PD-L1, TMB, MSI, and T-cell–inflamed gene expression profile (GEP). The KEYNOTE-180 trial (NCT02559687) was a single-arm phase 2 study of pembrolizumab as third-line or greater therapy in advanced/metastatic esophageal/gastroesophageal junction adenocarcinoma or squamous cell carcinoma (SCC). ORR was 9.9% and median DOR was NR at the primary analysis. We investigated the relationship in KEYNOTE-180 between response to pembrolizumab and T-cell–inflamed GEP or PD-L1 expression by histology.

Methods Patients received pembrolizumab 200 mg Q3W for ≤2 years until disease progression, toxicity, or withdrawal. The end points for this analysis were ORR, DOR, and PFS per RECIST v1.1 by central review and OS in the SCC and adenocarcinoma populations by GEP (non-low [≥−1.540] or low [<−1.540]; cutoff prespecified) and PD-L1 (CPS ≥10 or <10). Tumor GEP was determined using the NanoString nCounter Analysis System. PD-L1 expression was characterized using PD-L1 IHC 22C3 pharmDx. Data cutoff date was July 30, 2018.

Results Of 121 total patients, 118 had an evaluable GEP score and 121 had an evaluable PD-L1 CPS. Fifty-one patients (42.1%) had $GEP^{non\text{-}low}$tumors, 58 (48.0%) had CPS ≥10 tumors, and 31 (25.6%) had $GEP^{non\text{-}low}$/CPS ≥10 tumors; 63 patients (52.1%) had SCC and 58 (47.9%) had adenocarcinoma. ORR was 15.4% with $GEP^{non\text{-}low}$ and 13.5% with GEP^{low} among patients with SCC and 12% and 0% among patients with adenocarcinoma, respectively (table 1). ORR was 20% with CPS ≥10 and 7.1% with CPS <10 among patients with SCC and 4.3% and 5.7%, respectively, among patients with adenocarcinoma (table 2). Median OS was slightly higher among patients with SCC in the $GEP^{non\text{-}low}$ subgroup and the CPS ≥10 subgroup versus GEP^{low} and CPS <10 subgroups, respectively (tables 1, 2); this trend was reversed among patients with adenocarcinoma (tables 1, 2). Median PFS ranged from 1.9 to 2.1 across histology/biomarker subgroups. Median DOR was NR regardless of GEP or CPS status (tables 1, 2).

Abstract 261 Table 1 Response by GEP status and histology
[a]Analysis by biomarker status was not possible because of the small sample size.

	ORR			
	SCC N = 63		Adenocarcinom N = 55	
	$GEP^{non\text{-}low}$ n = 26	GEP^{low} n = 37	$GEP^{non\text{-}low}$ n = 25	GEP^{low} n = 30
ORR, n (%)	4 (15.4)	5 (13.5)	3 (12.0)	0
Median PFS, months (95% CI)	2.1 (1.9-4.1)	2.1 (1.9-3.8)	2.0 (1.1-2.1)	1.9 (1.6-2.0)
Median OS, months (95% CI)	7.7 (5.7-10.5)	6.2 (4.2-12.0)	3.9 (2.3-8.7)	4.2 (3.1-7.2)
	DOR			
	$GEP^{non\text{-}low}$ (n = 7)		GEP^{low} (n = 5)	
Median DOR,[a] months (range)	NR (2.1 to 25.1+)		NR (4.2 to 18.7+)	

[a]Analysis by biomarker status was not possible because of the small sample size.

Abstract 261 Table 2 Response by PD-L1 status and histology
[a]Analysis by biomarker status was not possible because of the small sample size.

	ORR			
	SCC N = 63		Adenocarcinoma N = 58	
	CPS ≥10 n = 35	CPS <10 n = 28	CPS ≥10 n = 23	CPS <10 n = 35
ORR, n (%)	7 (20.0)	2 (7.1)	1 (4.3)	2 (5.7)
Median PFS, months (95% CI)	2.0 (1.9-3.8)	2.1 (1.9-3.8)	2.0 (1.2-2.1)	1.9 (1.7-2.0)
Median OS, months (95% CI)	7.5 (5.1-10.5)	6.1 (4.2-10.0)	3.5 (2.0-12.1)	3.9 (3.4-6.3)
	DOR			
	CPS ≥10 (n = 8)		CPS <10 (n = 4)	
Median DOR,[a] months (range)	NR (4.2 to 25.1+)		NR (2.1 to 17.3+)	

[a]Analysis by biomarker status was not possible because of the small sample size.

Conclusions In KEYNOTE-180, data in a small number of patients suggested that measures of inflammation, like PD-L1

and GEP, may enrich for responses to pembrolizumab. In SCC, some trends toward enrichment were observed for both biomarkers, although the trend was stronger for PD-L1 CPS ≥10. In adenocarcinoma, a trend was observed for GEP but not for PD-L1; the small number of responders is limiting, and further studies are needed to understand molecular correlates in adenocarcinoma.

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Trial Registration ClinicalTrials. gov, NCT02559687

Ethics Approval The study and the protocol were approved by the institutional review board or ethics committee at each site.

Consent All patients provided written informed consent to participate in the clinical trial.

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262 TUMORAL DKK1 EXPRESSION CORRELATES WITH BETTER CLINICAL OUTCOMES IN PATIENTS WITH ADVANCED ESOPHAGOGASTRIC CANCER (EGC) TREATED WITH DKN-01

[1]Samuel Klempner*, [2]Michael Kagey, [2]Cynthia Sirard, [2]Cynthia Sirard. *[1]Massachusetts General Hospital, Boston, MA, USA; [2]Leap Therapeutics, Inc., Cambridge, MA, USA*

Background Dickkopf-1 (DKK1) modulates Wnt signaling and contributes to an immune suppressive tumor microenvironment. DKN-01 (D), a neutralizing DKK1 antibody, has demonstrated safety and clinical activity in advanced EGC either as a monotherapy or in combination with paclitaxel (pac) or pembrolizumab (pem). We report response and survival outcomes in EGC patients (pts) by high/low tumoral DKK1 expression treated with D.

Methods We enrolled advanced EGC pts in a Phase 1b/2a study of D as monotherapy or in combination with pac or pem. Tumoral DKK1 mRNA expression was assessed by an in situ hybridization RNAscope assay. 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 were used for survival analysis and logistic regression was used for clinical benefit/response outcome.

Results 69 EGC pts were enrolled to receive D alone or in combination with pac or pem and had tumoral DKK1 expression available. 60 pts (87%) were male, median age 65 (range 28, 81). 59 pts had adenocarcinoma [19 esophageal (28%), 40 GEJ/gastric (58%)] and 10 pts with ESCC. 65% had ≥2 prior therapies (range 1, 5). 23 pts with DKK1 high (H-score ≥ upper-tertile [≥39]) had an ORR of 22% (5 PR/23), DCR of 57% (13/23) while DKK1 low (H-score <39) had an ORR of 2% (1/46) and DCR of 26% (12/46). Median PFS was 12.1 weeks in DKK1 high vs. 6.0 weeks in DKK1 low; HR of 0.58 (95%CI: 0.34, 1.0). Median OS was 31.6 weeks in DKK1 high vs. 18 weeks in DKK1 low; HR of 0.70 (95%CI: 0.38, 1.3). Subgroup of pts (n=9) with immune checkpoint inhibitor (ICI) refractory disease treated with D + pem demonstrated longer PFS and OS for DKK1 high pts (H-score ≥39, n=4) vs DKK1 low (n=5): PFS 12.8 weeks vs 6.0 weeks; HR of 0.16 (95%CI: 0.02, 1.5) and OS 46 weeks vs. 16 weeks, respectively; HR of 0.22 (95%CI: 0.03, 2.0).

Conclusions High levels of tumoral DKK1 expression correlate with improved clinical outcomes in heterogeneous EGC pts treated with D monotherapy or in combination. Previously we have demonstrated greatest clinical benefit in ICI-naïve, DKK1 high G/GEJ adenocarcinoma treated with D + pem.[1] DKK1-high ICI refractory pts treated with D + pem experienced longer PFS and OS compared with pts with low DKK1 expression. DKK1 as a predictive biomarker for DKN-01 is being evaluated in ongoing studies.

Trial Registration NCT02013154

Ethics Approval WIRB (Western Institutional Review Board) Institution's Ethics Board, approval number 20140759

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263 PLEIOTROPIC EFFECTS OF IL-7 IN PROSTATE CANCER PATIENTS RECEIVING SIPULEUCEL-T VACCINATION

[1]Caroline Duault*, [2]Nirasha Ramchurren, [3]Russell Pachynski, [4]Lawrence Fong, [1]Sean Bendall, [1]Mina Pichavant, [1]Bita Sahaf, [5]Chihiro Morishima, [2]Leonard D'Amico, [2]Martin Cheever, [2]Steven Fling, [1]Holden Maecker. *[1]Stanford University – School of Medicine, Stanford, CA, USA; [2]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [3]Washington University, St. Louis, St Louis, MO, USA; [4]University of California, San Francisco, San Francisco, CA, USA; [5]University of Washington, Seattle, WA, USA*

Background Sipuleucel-T (Provenge) is the first therapeutic vaccination approved by the FDA so far, indicated for advanced metastatic prostate cancer patients. Despite an improvement of the overall survival, the benefits of the therapy are still short-term so increasing the duration of the efficacy is necessary. Specifically, T-cell anergy is one of the challenges that we need to overcome to improve the overall efficacy. IL-7 is known to promote the naive T cell activation and to increase the proliferation and activation of the T cell memory subsets. Therefore, in this phase II clinical trial, we tested the therapeutic potential of a human recombinant glycosylated IL-7 after completion of the Provenge therapy on asymptomatic advanced prostate cancer patients.

Methods To get a comprehensive analysis of the immune landscape in these patients, we performed CyTOF analysis on PBMC samples obtained at week 1 (baseline) and week 6 after the beginning of the IL-7 therapy. After stimulation with PMA/Ionomycin, we proceeded to surface and intracellular cytokine staining before acquisition on the CyTOF. The data were then analyzed by expert gating on Cytobank.

Results At 6 weeks post therapy, our data showed an increase in the number of circulating T lymphocytes in the IL-7 cohort, especially CD8 T cells, in accordance with previous literature. Even though of the frequency of CD4 T cells did not increase, the cells showed greater functionalities, with increased expression of IL-2, TNFα and IL-6 upon stimulation by PMA-Ionomycine. Cytotoxic subsets were also positively affected, with increased expression of IFNγ in CD8 T cells, TNFα in NK cells and IL-2 in γδ T cells. Moreover, PD-1 expression was decreased on CD4, CD8 and γδ T cells while CD137 increased on CD4, CD8 and NK cells. In addition, despite a reduction in the pool of circulating monocytes, we observed higher TNFα expression in these cells.