Methods MORPHEUS-PDAC, MORPHEUS-TNBC and MORPHEUS-CRC enrolled 1L metastatic (m) PDAC, 2L locally advanced or mTNBC or 3L mCRC patients, respectively. Experimental arm patients received atezo (840 mg IV q2w) and seli (16 mg SC on D1 every 28-day cycle for C1-4 and every third cycle thereafter). Patients also received gem (1000 mg/m^2) and nabP (1000 mg/m^2, 125 mg/m^2 respectively, IV on D1, 8, 15 every 28-day cycle) in PDAC or bev (10 mg/kg IV q2w) in TNBC and CRC. Control treatments were gem +nabP in PDAC, capecitabine in TNBC, and regorafenib in CRC. Primary endpoints were safety and objective response rate (ORR; investigator-assessed RECIST 1.1). PD-L1 and CD8/panCK IHC were tested in all biopsies.

Results All treated patients were safety evaluable. MORPHEUS-PDAC (20-week interim analysis): 9 patients received atezo+seli +gem+nabP and 4 received control. Treatment-related adverse events (TRAEs) were seen in all. Treatment-related serious AEs (SAEs) occurred in 6 patients (67%) receiving atezo+seli+gem +nabP and 1 (25%) receiving control. Confirmed ORRs: 44% (95%CI:14–79) and 25% (95%CI:6–81), respectively. MORPHEUS-TNBC (27-week interim analysis): 6 patients received atezo+seli+bev and 24 received control. TRAEs were seen in 5 patients (83%) receiving atezo+seli+bev and 18 (75%) receiving control. Treatment-related SAEs occurred in 1 patient in each arm (17% and 4%, respectively). Confirmed ORRs: 17% (95% CI:0.4–64) and 21% (95%CI:7–42), respectively. All 6 patients receiving atezo+seli+bev were PD-L1 negative (SP142 IHC assay) at baseline; the only patient with partial response (PR) showed upregulation of PD-L1 expression at week 3. MORPHEUS-CRC (18-week interim analysis): 6 patients received atezo+seli+bev and 13 received control. TRAEs were seen in all patients receiving atezo+seli+bev and 12 (92%) receiving control. Treatment-related SAEs occurred in 3 patients (50%) receiving atezo+seli+bev and 1 (8%) receiving control. No responses occurred in either study arm. Paired biopsies for 3 patients (60%) receiving atezo+seli+bev suggest on-treatment increases in CD8 T-cell infiltration into tumors.

Conclusions Toxicities related to the atezo+seli combinations were consistent with individual study treatments. Preliminary efficacy was observed for atezo+seli+gem+nabP in PDAC. Together with preliminary evidence of on-treatment pharmacodynamic effects in CRC and TNBC tumor samples, CD40 agonist strategies warrant further investigation.

Trial Registration MORPHEUS-PDAC: NCT03193190; MORPHEUS-TNBC: NCT03424005; MORPHEUS-CRC: NCT03555149.

Ethics Approval The trial was conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent. Protocol approval was obtained from independent review boards or ethics committees at each site.

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260 T CELL INFILTRATING REPERTOIRE DIVERSITY IS ASSOCIATED WITH ENHANCED SURVIVAL FOLLOWING NEOADJUVANT THERAPY IN PATIENTS WITH RESECTABLE PANCREATIC CANCER

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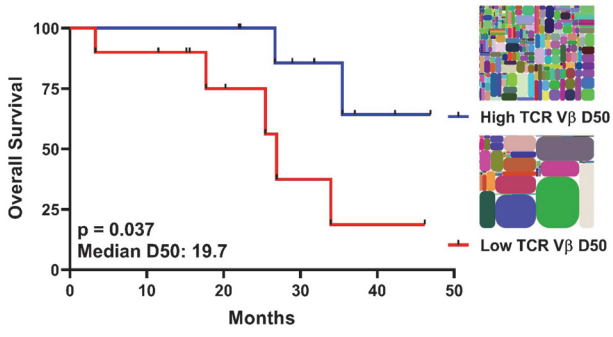
Background Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy, characterized by a desmoplastic stromal reaction and an immunosuppressive tumor microenvironment (TME)[1]. The metabolic stress within the PDAC TME promotes autophagy, a form of programmed cell survival associated with chemotherapeutic resistance and immune evasion.[2,3]

Methods We conducted a randomized phase II study of preoperative gemcitabine and nab-paclitaxel with or without autophagy inhibition with oral hydroxychloroquine (HCQ) in patients with resectable PDAC. Autophagy inhibition increased Evans Grade histopathologic response and immune infiltrate.[4]Utilizing multiplex immunohistochemistry and dimer avoidance multiplex PCR-NGS[5] in a subset of RNA extracted FFPE tumor specimens, we evaluated the adaptive immune response and immune correlates of response.

Results Patients receiving HCQ had a greater CD4/CD8 immune infiltration (p = 0.033). Independent of treatment, a higher tumor immune infiltration score,[6] was associated with improved overall survival (p = 0.035). Bulk tumor immunosequencing revealed a clonally expanded T cell receptor (TCR) Vβ (115±84 unique CDR3s (uCDR3s) of 3.3 × 10^4±2.4 total CDR3s) and B cell receptor (BCR) IgH (9.8 × 10^4±5.2 uCDR3s of 1.4 × 10^5±0.76 total CDR3s) repertoire compared to a paucity of TCR Vδ clones (2±1 uCDR3s of 43 ±60 total CDR3s). Patients with a higher than median TCR Vβ Diversity 50 Index (D50, proportion of uCDR3s that make up 50% of the total CDR3s) had significantly higher tumor CD4 (p = 0.003) and CD8 (p = 0.031) counts. Patients with a higher than median TRC Vβ D50 also had a reduced lymph node ratio (p = 0.039) and greater overall survival (p = 0.037, figure 1). Conversely, patients with a higher than median BCR IgH D50 had worse overall survival (p = 0.0241). Given the dichotomy of the TCR and BCR repertoire diversity and association with clinical outcome, we further analyzed the individual ratio of TRC Vβ:BCR IgH CDR3s and found that patients with a higher than median TRC Vβ:BCR IgH ratio had a greater Evan's Grade histopathologic response (p = 0.069).

Conclusions PDAC TIL repertoire with high TCR Vβ diversity is associated with decreased positive lymph node ratio and greater overall survival following neoadjuvant therapy. The



Abstract 260 Figure 1 Following neoadjuvant therapy, patients with resectable pancreatic cancer with a higher than median intratumoral TCR Vβ Diversity 50 (n=9, 4.624 HR; 95 CI [0.971, 21.83]) have greater overall survival compared to patients with lower than median intratumoral TCR Vβ Diversity 50 (n=10, 0.2163 HR; 95 CI [0.458, 1.021]). Representative tree maps of high and low TRC Vβ D50, where each rounded rectangle represents a unique CDR3, with the size of the rectangle corresponding to the relative frequency of the CDR3 clones across the entire repertoire

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

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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