PFS in mTNBC. Here we present the correlative genomic and immunologic analyses from this study.

Methods This trial (https://clinicaltrials.gov/ct2/show/NCT02768701) recruited 40 patients with largely pretreated mTNBC. Response was defined as >30% decrease in imaging-assessed disease burden. Clinical benefit was defined as treatment response or stable disease. Tumor specimens were collected prior to enrollment, and peripheral blood mononuclear cell (PBMC) samples taken prior to cyclophosphamide and before each cycle of pembrolizumab. RNA sequencing was performed on tumor samples for gene expression and immune repertoire reconstruction. Targeted sequencing of the T-cell beta chain, Ig kappa, lambda and heavy chain (TRB, IGH, and IGL, respectively) on PBMCs captured the peripheral immune repertoire. Whole exome sequencing was performed on tumor samples with PBMCs serving as a matched normal.

Results Of 40 patients enrolled, 31 patients had tumor RNA-seq and at least 15 had matched PBMC-derived immune chains capturing both pre and post treatment. When preliminary RNA-seq samples (n=22) revealed upregulation in B-cell receptor pathways and related gene signatures (figure 1), we updated our planned analysis to exclude tumor specimens collected from lymph nodes. In our final analysis, response to therapy (4 of 25, 16%) was associated in tumor RNA-Seq with gene pathways involving programmed cell death and MAPK activation, while non-responding tumors were enriched in G-protein signaling and inhibition of insulin secretion (figure 2a,b, table 1). Immune gene signatures related to NK cells and B-cell activation, signaling and interaction with T follicular helper cells,3,7,8 were associated with response (figure 2g).

Pre-treatment immune repertoire measures demonstrated a significant association between increased peripheral IGH abundance and richness, and both future clinical benefit and response to therapy (figure 3a-d).

Conclusions Response to CI therapy was associated with immunogenicomic features of programmed cell death and B-cell activation. Pre-treatment circulating immunoglobulin diversity measures (high IGH abundance and IGH richness) also correlated with future response to therapy. Taken together, these data suggest that B-cell activity contributes significantly to response to CI therapy in mTNBC.

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Trial Registration Clinical Trials. gov: NCT02768701.

Ethics Approval All patients provided written informed consent, and the study was approved by each institution’s institutional review board (No. NCT02768701).

REFERENCES


Abstract 258 Figure 3 Tumor and peripheral immune repertoire diversity. A-D: In tumor RNA-Seq, higher IGH chain abundance and richness was associated with both clinical benefit (A, C) and response (B, D) (n=31). E-F: Inter-group comparisons showed fewer TRB chain similarities between patients who derived clinical benefit (E) or response (F) versus those who did not, in pre-treatment PBMC samples. G-I: Univariate Cox proportional hazards models for PFS showing immune diversity measures derived from pre-treatment tumor RNA-Seq (G), PBMC-derived amplicon sequencing pre-pembrolizumab (H), and PBMC-derived amplicon sequencing pre-pembrolizumab (I)
Methods MORPHEUS-PDAC, MORPHEUS-TNBC and MOR- 
PHEUS-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 sel (16 mg SC on D1 every 28-day cycle for C1-4 
and every third cycle thereafter). Patients also received gem (1000 
mg/m²) and nabP (1000 mg/m², 125 mg/m² 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, capectabine in TNBC, and regorafenib in 
CRC. Primary endpoints were safety and objective response 
rate (ORR; investigator-assessed RECIST 1.1). PD-L1 and 
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 immunose- 
quencing 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 × 10^4±0.76 total CDR3s) repertoire com- 
pared to a paucity of TCR Vβ clones (2±1 uCDR3s of 43 
±60 total CDR3s). Patients with a higher than median TCR 
Vβ Diversity 50 Index (D50, proportion of uCDRs that 
made 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 BCR IgH D50 also had a 
reduced lymph node ratio (p = 0.039) and greater overall 
Survival (p = 0.0241). Given the dichotomy of the TCR and BCR 
repertoire diversity and association with clinical outcome, we 
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 

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

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, 2.163 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.