

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, IGK, IGL, and IGH, 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,<sup>3-7</sup> 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 immunogenomic 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).

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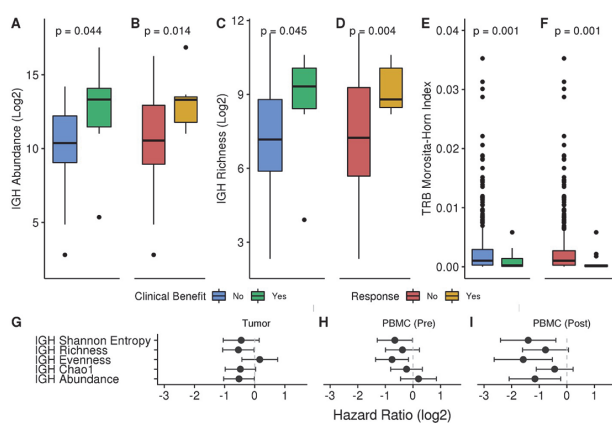
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## PHASE IB/II OPEN-LABEL, RANDOMIZED EVALUATION OF ATEZOLIZUMAB (ATEZO) + SELICRELUMAB (SELI) + GEMCITABINE+NAB-PACLITAXEL (GEM+NABP) OR BEVACIZUMAB (BEV) VS CONTROL IN MORPHEUS-PDAC, -TNBC AND -CRC

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**Background** The MORPHEUS platform comprises multiple randomized Phase Ib/II trials to identify early safety and efficacy signals for treatment combinations across cancers. Seli interacts with CD40 on antigen presenting cells, resulting in activation and priming of CD8 T-cells. Atezo (anti-PD-L1) +seli (CD40 agonist) was evaluated with gem+nabP for pancreatic ductal adenocarcinoma (PDAC), or with bev for triple-negative breast cancer (TNBC) and colorectal cancer (CRC).



**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 post-pembrolizumab (I)

**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<sup>2</sup>) and nabP (1000 mg/m<sup>2</sup>, 125 mg/m<sup>2</sup> 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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### T CELL INFILTRATING REPERTOIRE DIVERSITY IS ASSOCIATED WITH ENHANCED SURVIVAL FOLLOWING NEOADJUVANT THERAPY IN PATIENTS WITH RESECTABLE PANCREATIC CANCER

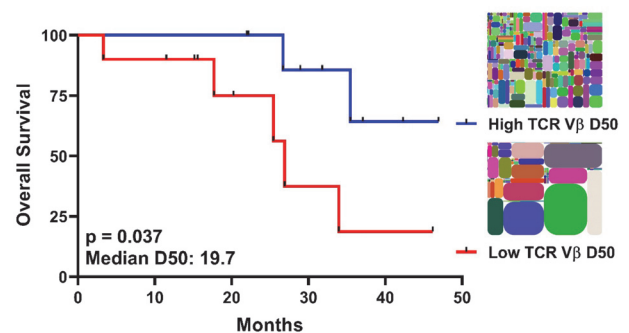
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**Background** Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy, characterized by a desmoplastic stromal reaction and an immunosuppressive tumor microenvironment (TME)<sup>1</sup>. The metabolic stress within the PDAC TME promotes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

**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.<sup>4</sup> Utilizing multiplex immunohistochemistry and dimer avoidance multiplex PCR-NGS<sup>5</sup> 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,<sup>6</sup> was associated with improved overall survival ( $p = 0.035$ ). Bulk tumor immunosequencing revealed a clonally expanded T cell receptor (TCR) V $\beta$  ( $115 \pm 84$  unique CDR3s (uCDR3s) of  $3.3 \times 10^4 \pm 2.4$  total CDR3s) and B cell receptor (BCR) IgH ( $9.8 \times 10^4 \pm 5.2$  uCDR3s of  $1.4 \times 10^5 \pm 0.76$  total CDR3s) repertoire compared to a paucity of TCR V $\delta$  clones ( $2 \pm 1$  uCDR3s of  $43 \pm 60$  total CDR3s). Patients with a higher than median TCR V $\beta$  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 V $\beta$  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 V $\beta$ :BCR IgH CDR3s and found that patients with a higher than median TRC V $\beta$ :BCR IgH ratio had a greater Evan's Grade histopathologic response ( $p = 0.069$ ).

**Conclusions** PDAC TIL repertoire with high TCR V $\beta$  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 V $\beta$  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 V $\beta$  Diversity 50 ( $n=10$ , 0.2163 HR; 95 CI [0.458, 1.021]). Representative tree maps of high and low TRC V $\beta$  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