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 \( (4 \text{ of } 25, 16\%) \) 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, \(^{1-7} \) 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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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 PBCM-derived amplicon sequencing pre-pembrolizumab (l).
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/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, capcitabine in TNBC, and regorafenib in CRC. Primary endpoints were safety and objective response rate (ORR; investigator-assessed RECIST 1.1). PD-L1 and CDR3s and found that patients with a higher than median TRC V\text{b} repertoire diversity and association with clinical outcome, we further analyzed the individual ratio of TRC V\text{b}:BCR IgH CDR3s and found that patients with a higher than median TRC V\text{b}:BCR IgH ratio had a greater Evans’ grade histopathologic response (p = 0.069).

Conclusions PDAC TIL repertoire with high TCR V\text{b} diversity is associated with decreased positive lymph node ratio and greater overall survival following neoadjuvant therapy. The