SYSTEMIC IMMUNE PROFILING OF ADVANCED BILIARY TRACT CANCER PATIENTS DEFINES ALTERED CYTOKINES AND IMMUNE CELL POPULATIONS

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Background Biliary tract cancers (BTCs) are aggressive malignancies often refractory to chemotherapy and immunotherapy. There is urgent need to identify novel, data-driven therapeutic targets to change the course of disease. It is also challenging to procure substantial quantities of tissue for research from patients with advanced or metastatic disease. Thus, we posit that peripheral blood holds particular value for exploring immune landscapes in patients with advanced BTC. We hypothesized actionable immunotherapy targets can be identified from blood that are suited to improve outcomes for BTC patients.

Methods We examined a comprehensive panel of immune biomarkers in pre-treatment blood from 79 patients with advanced BTC on a national, randomized Phase II clinical trial of atezolizumab ± cobimetinib in advanced metastatic BTC (NCI10139). A cohort of 12 healthy donors was obtained as a comparator. Blood was processed via ficoll and density gradient centrifugation. PBMCs and plasma were cryopreserved prior to analysis by bioplex assay and multiparameter flow cytometry (n=23 colors). Analysis of 45 peripheral soluble factors was performed on a Luminex 100. Flow cytometric analysis was conducted on a Cytex Aurora and analyzed using FlowJo software. Comparisons of normal versus BTC patient samples were conducted via unpaired two-tailed t tests.

Results Bioplex analysis of 45 peripheral soluble factors revealed significant elevations in BTC plasma compared to normal donors for several factors including IL-6, IL-18, eotaxin/CCL11, IP-10/CXCL10, MIP-1β/CCL9, IFN-γ, PDGF-BB, PIGF-1, and SCF (p's<0.01). Our comprehensive flow panel captured 27 phenotypically defined cell populations encompassing T/B lymphocytes, monocytes, NK cells, and myeloid cells. Only 6 cell populations were significantly different between BTC patients and normal donors (figure 1). Patients with advanced BTC had higher frequencies of T cells expressing inhibitory checkpoint molecules compared to healthy donors. Namely, higher frequencies of CD4+PD-1+ T cells, CD8+PD-1+ T cells, CD4+BTLA+ T cells, and CD8+BTLA+ T cells (p's<0.01) were evident. In addition, BTC patients had more monocytes (CD11b+CD11c+CD14+CD16+HLA-DR+), and M2 macrophages (CD11b+CD11c+CD16+CD33+CD14+) (p's<0.03) versus healthy donors. Ongoing analysis will determine associations between biomarkers and overall survival in the patient cohort using the Cox proportional hazard model for time-to-event outcomes.

Conclusions To our knowledge, this work represents the most comprehensive analysis of peripheral immune biomarkers in BTC patients to date. These data suggest that cytokine mediators and/or distinct immune checkpoints deserve further investigation as actionable targets in patients with BTC.

Ethics Approval Patient samples were collected as part of a study approved by the National Cancer Institute's (NCI) Cancer Therapy Evaluation Program (CTEP), as well as central and local institutional review boards (IRBs). All patients and healthy donors gave informed consent before participation in these studies.

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Abstract 18 Figure 1 Several immune biomarkers are elevated in the peripheral blood of biliary tract cancer patients compared to normal donors, including (a) percent of CD45% cells that are phenotypically defined as M2 macrophages (CD11b+CD11c+CD16+CD33+CD14+), (b) percent of CD45% cells that are BTLA+CD8+ T cells, (c) soluble MIP-1β/CCL9, and (d) soluble IL-6.