COMBINED ANTI-VEGF, ANTI-CTLA4 AND ANTI-PDL1 TREATMENT INDUCES STRONG IMMUNE RESPONSES IN PATIENTS WITH CHOLANGIOCARCINOMA: RESULTS FROM A CLINICAL TRIAL/IN DEPTH CORRELATIVE STUDIES AND MOUSE STUDIES

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Background The addition of durvalumab (anti-PD-L1) to chemotherapy with gemcitabine and cisplatin has become standard of care for patients with cholangiocarcinoma. Both anti-CTLA4/anti-PD-L1 and anti-VEGF/anti-PDL1 are FDA approved immune checkpoint inhibitor regimens. Here we tested the combination of anti-CTLA4 + anti-VEGF + anti-PD-L1 in patients with cholangiocarcinoma (CCA).

Methods In this open-label phase II study patients with histologically confirmed HCC and CCA were treated with 300 mg tremelimumab, 7.5 mg/kg bevacizumab and 1150 mg durvalumab on day 1 followed by 7.5 mg/kg bevacizumab and 1150 mg durvalumab every 3 weeks. Primary objective was the 6-month progression-free survival (PFS). Secondary endpoints include safety and correlative studies including single cell RNA-sequence analysis of PBMC, spectral flow cytometry analysis using a 22-color pan-immunological panel and a 25-color T cell-specific panel and multiplex serum cytokine analysis as well as bulk mRNA analysis from paired tumor biopsies. Immune and tumor responses were tested in mice with subcutaneously injected SB1 cholangiocarcinoma cells after treatment with anti-VEGF/anti-CTLA4 and anti-PD-L1.

Results A total of 7 patients (6 CCA and 1 HCC) were enrolled into this study before the study was halted for unexpected high rates of immune related AEs. 4/7 patients developed grade 3 AEs including 2 patients with myositis, 1 patient with colitis, 1 patient with hepatitis, 2 patients with thyroiditis and 1 patient who developed a myocarditis, myositis, myasthenia gravis and immune thrombocytopenia. Here we present the unexpected clinical responses in CCA with 2/6 CCA patients demonstrating long-lasting partial responses (10.3 and 3.5 months) and a median OS of 13.6 months despite early treatment discontinuation. Analysis of immune correlates are ongoing. Preliminary spectral flow cytometry results demonstrated a significantly higher frequency of regulatory T cells (Tregs), proliferating CD4+ and CD8+ T cells, as well as non-classical monocytes following anti-VEGF/anti-CTLA4/anti-PD-L1 treatment. Within the CD8 T cell compartment, a CD39+Ki67+PD-1hi fraction expanded in the anti-VEGF/anti-CTLA4/anti-PD-L1 treated cohort. 10x single cell sequencing analysis confirmed the findings of the flow cytometric analysis and revealed expanded TCR clonotypes in the treated cohort. In murine studies anti-VEGF, anti-CTLA-4 and anti-PD-L1 combination resulted in marked tumor control in tumor-bearing mice mimicking results we obtained in patients with CCA.

Conclusions Here, we show that combined anti-VEGF, anti-CTLA4 and anti-PD-L1 induces exceptional immunological and therapeutic responses in patients with cholangiocarcinoma. The study is continuing to enroll with a modified dosing schedule. Murine studies will help better to further elucidate the immunological mechanism.

Trial Registration NCT03937830

Ethics Approval This study has been approved by the NIH review board (#NCI-19-C-0094)