885 ENHANCING IMMUNE CHECKPOINT INHIBITOR EFFICACY WITH ANTI-ANGIOGENICS IN OVARIAN CANCER

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Background Clinical data from our group supports that ovarian cancer (OC) patients respond better to immune checkpoint blockade (ICB) when targeting both PD-1 and CTLA4 compared to anti-PD-1 alone (33% v. 10%, respectively),[1] yet there is still room to improve dual-ICB response. Bevacizumab is approved as a front-line therapy for OC and targets vascular endothelial growth factor A (VEGF-A). VEGF has been shown to have both anti-tumor and immunomodulatory effects as it induces macrophage infiltration and M2 polarization[2] and directly suppresses T-cell activation, proliferation, and cytotoxic activity.[3,4] Here we aim to determine if priming the immunosuppressive tumor microenvironment (TME) with anti-VEGF enhances the response of T-cell stimulating ICB.

Methods We developed a patient avatar model by administering *ex vivo* expanded tumor infiltrating lymphocytes (TILs) into immunodeficient mice harboring a patient-matched, patient-derived xenograft (PDX).[5,6] Autologous TIL reactivity was validated by flow cytometry and ELISA. Preclinical *in vivo* studies were performed to evaluate if the efficacy of dual-ICBs (nivolumab and ipilimumab) could be enhanced through priming with anti-VEGF (bevacizumab). *Ex vivo* culture systems using donor ascites specimens and viable tumor slices were evaluated to further evaluate this combination in OC.

Results Six distinct PDX/TIL models were developed. Co-culture of TILs with autologous tumor cells resulted in HLA-dependent IFNγ production by TILs with a parallel impact on TIL activation phenotype. In response to IFNγ, PD-L1 expression was increased on tumor cells, suggesting antitumor activity might be improved via PD-1 blockade.[5] As proof-of-concept, anti-PD-1 efficacy was tested in PDX/TIL models (n=3).[5] Anti-PD-1 reduced tumor burden and increased survival in two models compared to TIL treatment alone. Next, we tested the hypothesis that the efficacy of dual-ICBs could be enhanced through TME priming with anti-VEGF (n=3). Results revealed increased efficacy of dual-ICB with anti-VEGF priming in 2 models. Immunohistochemistry and flow cytometry analysis support that the TILs in the combination ICB +/- anti-VEGF have increased anti-tumor activity.

To better delineate the activity of dual-ICB and anti-VEGF in an intact TME, *ex vivo* cultures were used. OC ascites significantly increased the secretion of T-cell effector and myeloid cell associated immunosuppressive molecules in response to ICB treatment, and CD11b+ tumor associated macrophages (TAMs) significantly reduced T-cell activation. In tumor slice cultures, combination treatment with dual-ICB and anti-VEGF reduced overall tumor burden.

Conclusions This data supports the notion that, in addition to the effect of anti-VEGF priming, modulation of the immunosuppressive myeloid population may further enhance ICB efficacy.

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Ethics Approval Surgical or biopsy samples were obtained with informed consent from the Hospital of the University of Pennsylvania in accordance with the IRB (#702679). PDX studies were carried out in accordance with animal ethics guidelines approved by the University of Pennsylvania IACUC (#806002) protocol and in the regulations of the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC).

Consent Written informed consent was obtained from the patients for the collection and use of de-identified biospecimens in this research. A copy of the written consent is available for review by the Editor of this journal.

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