

HYPOXIA REDUCTION IN COMBINATION WITH ANTI-ANGIOGENIC THERAPY REMODELS THE PDAC MICROENVIRONMENT<http://dx.doi.org/10.1136/jitc-2022-SITC2022.1142>Arthur Liu*, Michael Curran. *UT MD Anderson Cancer Center, Houston, TX, USA*

Background Pancreatic cancer patients remain largely unresponsive to single agent immune checkpoint blockade (ICB) therapy. This refractory state originates from PDAC's unique immunosuppressive microenvironment that is densely populated by suppressive myeloid cells, exhibits poor vascularity, and is highly hypoxic. We previously showed that the hypoxia-activated prodrug TH-302 (Evoxofosamide) reduces intratumoral hypoxia through a tissue remodeling process, initiates tumor vasculature reorganization, and sensitizes aggressive, spontaneous murine models of prostate cancer to ICB.¹ In a clinical trial testing the combination of TH-302 with cytotoxic T-lymphocyte-associated protein (CTLA-4) blockade (NCT03098160) a subset of metastatic, immune checkpoint blockade refractory patients showed prolonged progression free survival.² While these studies highlight hypoxia as therapeutically tractable, we lack complete understanding of the contribution of the tumor vasculature to hypoxia reduction therapy, as well as the downstream consequences of hypoxia reduction on the cellular composition of the tumor microenvironment and the associated sensitivity, or lack thereof, to immunotherapy. We hypothesized that anti-angiogenic therapy and Evoxofosamide could cooperate to normalize tumor vasculature and diminish hypoxia.

Methods TH-302 and a vascular endothelial growth factor receptor-2 (VEGFR-2) blocking antibody were used to treat several syngeneic murine models, including orthotopic pancreatic cancer and a transplantable model of prostate cancer. Immunofluorescence and flow cytometry were used to assess intratumoral hypoxia, vessel normalization, and tumor immune infiltrate. RNA-sequencing analysis of bulk tumor samples was done to determine changes in gene signatures.

Results We find that Evoxofosamide with anti-VEGFR-2 (DC101) significantly extends mouse survival. Combination therapy reduces intratumoral hypoxia, improves vessel integrity, and increases intratumoral DNA damage. In response to the improved metabolic microenvironment, CD8 T cells gain enhanced effector function and lose expression of exhaustion-associated features. Like other anti-angiogenic regimens, combination DC101 and TH-302 leads to an increased frequency of PD-L1 expressing cells within the tumor, however blockade of PD-1 failed to prolong survival. Bulk-tumor RNA sequencing and tumor infiltrating lymphocyte analysis implicates immature myeloid cells as mediators of therapy resistance.

Conclusions Evoxofosamide and DC101 utilize unique yet complementary mechanisms to improve the survival of mice challenged with pancreatic or prostate tumors. This combination relieves hypoxic stress and simultaneously reinvigorates T cell function, but may facilitate de novo MDSC infiltration. Future work will determine the underlying factors that shape the tumor immune microenvironment and influence immunotherapy responses.

REFERENCES

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