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205 PD-1/PD-L1-1/CTLA-4 INHIBITOR THERAPY FOLLOWING PROGRESSION ON A DIFFERENT PD-1/PD-L1 INHIBITOR: A CASE SERIES

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Background There are increasing numbers of immune checkpoint inhibitors (CPI) targeting the PD-1/PDL-1 and CTLA-4 pathways, which are approved in a wide variety of tumor types. A case series has previously described the sequential use of first line CPI, followed by second line CPI in renal cell carcinoma and melanoma patients, and both patient populations had progressive disease. There is still a lack of data on the safety and efficacy of challenging a patient who has previously progressed on a CPI with a different class of CPI, in other tumor types.

Methods We retrospectively collected data from patients treated with a CPI, who were subsequently challenged with another CPI, at a single institution. Exclusion criteria included patients with renal cell carcinoma and melanoma. Patient characteristics, immune-related adverse effects (irAEs), cancer type, tumor proportion score if available, treatment type, treatment response/progression per RECIST v1.1, and survival data were collected.

Results We identified 11 patients with various pathologies who received sequential CPI after progressing on first line CPI (table 1). Cancer types included non-small cell lung cancer (n=5), head and neck cancer (n=2), urothelial carcinoma (n=1), Merkel cell carcinoma (n=1), poorly differentiated carcinoma (n=1), and hepatocellular carcinoma (n=1). The tumor proportion score was available in 6 patients. Out of these patients, all were metastatic at the time of second line CPI. First line CPIs were all PD(L)-1 inhibitors, second line CPIs were all PD(L)-1 inhibitors except for one patient who received a CTLA-4 inhibitor in combination with a PD-1 inhibitor. Out of these patients, 3 patients who were trialed with second line CPI had stable disease, 5 patients had progression of disease, 1 patient had an irAE leading to discontinuation of CPI, and 2 patients died from adverse events unrelated to CPI. Out of 3 patients with stable disease on second line CPI, 2 patients had stable disease for over 2 years, and 1 patient had stable disease for over 1 year.

Conclusions Despite concerns that sequential immunotherapy may not be efficacious, 3 out of 11 patients did significantly benefit with the long-term stable disease. We need further large-scale prospective studies and research to know more about tumor characteristics, the mechanism of resistance in immuno-oncology to help us identify patients who would benefit from sequential immunotherapy.

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206 AN IMMUNE-COMPETENT TUMOR ORGANOID PLATFORM TO TEST NOVEL IMMUNE CHECKPOINT COMBINATIONS TARGETING THE RECEPTOR CD47 IN TRIPLE NEGATIVE BREAST CANCER

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Background Immune checkpoint blockade therapy targeting PD-L1 has recently been approved for metastatic triple negative breast cancer (TNBC) patients. However, a 7% response rate calls for better models and strategies to stimulate TNBC immunogenicity to increase patient response. Overexpression of the receptor CD47 impairs innate and adaptive tumor immunosurveillance when engaged to its counter receptor SIRPα or ligand thrombospondin-1. Co-expression of CD47 and PD-L1 is implicated with disease progression in TNBC patients. We examined through murine models and tumor organoid platforms whether targeting CD47 sensitizes TNBC tumors to PD-L1 therapy, focusing on the modulation of cellular bioenergetics as a potential mechanism and potentially predict response.

Methods The effects of targeting CD47 and PD-L1 were examined through orthotopic syngenic 4T1 and EMT-6 TNBC murine models. Due to predicting patient therapeutic response challenges, tumor organoid platforms investigated mechanisms of tumor sensitization to anti-PD-L1 by targeting CD47. Organooids were constructed by embedding murine TNBC tumor tissue and AH1 CD8+ T cells in a specialized ECM mimicking hydrogel. Immunohistochemistry was performed on organoids, human and murine TNBC tumor tissue. Cellular bioenergetics was analyzed through Seahorse® bioanalyzer.

Results Staining of human TNBC biopsies found elevated CD47 expression, signifying a potential therapeutic target. Targeting CD47 or in combination with anti-PD-L1 resulted in decreased tumor volume and weight in a TNBC murine model. The decrease in tumor burden was correlated with...
increased intratumoral granzyme B secreting CD8+ T cells. Additionally, targeting CD47 within organoids increased IFNγ and granzyme B released, indicating enhanced CD8+ T cell cytolytic capacity. Differential cellular bioenergetics was observed between cancer and T cells suggesting a shift in metabolism in the tumor microenvironment. CD47 targeted T cells had an increased glycolytic rate compared to WT T cells. Conversely CD47 targeted TNBC cells had a decreased glycolytic rate, which may be correlated with decreased PD-L1 expression. 

Conclusions Targeting CD47 enhanced granzyme B and IFNγ expression suggesting potential mechanisms to increase tumor immunogenicity. CD47 targeted monotherapy or combination with anti-PD-L1 preserves T cell bioenergetics and antitumor function, resulting in decreased TNBC tumor burden. Alternatively, CD47 targeted TNBC had a decreased glycolytic rate and decreased PD-L1 expression, which is reported to regulate glycolysis through Akt/mTOR signaling. Targeting CD47 on T cells enhances their bioenergetics and antitumor function while decreasing TNBC cell bioenergetics, making them more susceptible to immune cell killing. Our data indicates that CD47 targeted monotherapy or combination with anti-PD-L1 may enhance TNBC patient response and improve overall survival.

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Ethics Approval Animal studies were approved by the Institutional Care and Use Committee, Wake Forest Health Sciences.

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207 SMALL MOLECULE INHIBITORS OF SEC61 COTRANSLATIONAL TRANSLLOCATION REGULATE THE PHAGOCYTOSIS CHECKPOINT MOLECULE CD47

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Background Many tumor cells escape immune cell clearance by overexpressing CD47, a multi-pass transmembrane protein, which binds signal regulatory protein α (SIRPα) on macrophages leading to decreased phagocytic activity. Blockade of CD47/SIRPα interactions enhances macrophage phagocytosis and is being targeted with antibody-based drugs, some of which are used in combination therapies in clinical trials. A novel method to target CD47 is through the inhibition of cotranslational translocation of transmembrane proteins. Immediately after exiting the ribosome, signal sequences that are unique to each protein are directed through the Sec61 channel into the ER for extracellular expression. 3 Several Sec61-targeting compounds have been identified to suppress translocation in a signal sequence-specific manner. 5 We previously described Sec61 inhibitors capable of selectively targeting immune checkpoint proteins and enhancing T cell function. 3 Here, we demonstrate the blockade of CD47 expression on tumor cells and enhancement of macrophage phagocytosis with small molecule inhibitors of Sec61.

Methods Sec61-dependent expression of target proteins was assayed using HEK293 cells overexpressing constructs comprised of signal sequences fused to a luciferase reporter. Stimulated PBMCs or tumor cells were incubated with Sec61 inhibitors, and surface expression of checkpoint molecules were examined by flow cytometry. Necrotic and apoptotic cells were assessed by Annexin V and 7AAD labeling. Human CD14+ monocytes were differentiated to M1- or M2-type macrophages. Jurkat or SKBR3 cells were incubated with Sec61 inhibitors, labeled with a pH sensitive dye and co-cultured with macrophages to assess phagocytosis.

Results We identified Sec61 inhibitors that block select immune checkpoint proteins. Compounds demonstrated either selective or multi-target profiles in transient transfection screens, which was supported by decreased protein expression on activated T cells. KZR-9275 targeted multiple checkpoint molecules, including PD-1, LAG-3 and CD73, along with a potent inhibition of the CD47 signal sequence reporter. CD47 surface expression was decreased on Jurkat and SKBR3 cells following 72 hours of compound treatment. KZR-9275 treatment of SKBR3 cells induced a minor increase in apoptotic cells, which was not detected in Jurkat cells. Increased macrophage phagocytosis, especially with M2-type macrophages, was observed when Jurkat or SKBR3 cells were pre-treated with KZR-9275.

Conclusions Our findings demonstrate that Sec61 inhibitors can block the expression of CD47, a phagocytosis checkpoint protein, on tumor cells and subsequently modulate macrophage phagocytic activity. Small molecule inhibitors of Sec61 provide an opportunity to target multiple checkpoint proteins on various cell populations. Future in vivo tumor models will assess the efficacy of Sec61 inhibitors to provide combination-like therapy.

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208 E7777 (DENILEUKIN DIFTITOX) ENHANCES ANTI-TUMOR ACTIVITY AND SIGNIFICANTLY EXTENDS SURVIVAL BENEFIT OF ANTI-PO-1 IN SYNGENEIC SOLID TUMOR MODELS

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Background Regulatory T cell (Tregs) inhibit activity of anti-tumor T cells, and have been shown to limit checkpoint inhibitor effectiveness. Depletion of Tregs seems desirable during immunotherapy, but chronic Treg depletion with antibody therapies can lead to serious autoimmune adverse events. Compared to antibodies, the fusion protein E7777 (IL-2/diphtheria toxin) has a relatively short half-life in circulation, which allows for transient and selective Treg depletion. The potential therapeutic benefit of combining E7777 with anti-PD-1 was tested in syngeneic solid tumor models.

Methods CT26 colon and H22 liver cancer tumors were implanted subcutaneously in immunocompetent BALB/c mice. E7777 (2.5 mcg/mouse, i.v.) was given on a Q7Dx3 schedule. Anti-murine PD-1 was given (100 mcg/mouse, i.v.) Q4Dx5.

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