PD-1/PD-L1/CTLA-4 INHIBITOR THERAPY FOLLOWING AN IMMUNE-COMPETENT TUMOR ORGANOID: 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 population 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 has 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.
increased intratumoral granzyme B secreting CD8+ T cells. Additionally, targeting CD47 within organoids increased IFNy 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 IFNy 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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References

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

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Background Regulatory T cell (Treg) activity inhibits 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 autoimmunity 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.