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http://dx.doi.org/10.1136/jitc-2020-SITC2020.0204

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

Suresh Mukkamala*, Karine Tawagi, Marc Matrana. *Ochsner Clinic Foundation, New Orleans, LA, USA*

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 has had stable disease for over 1 year.

Abstract 205 Table 1 Patient characteristics and response

Tumor Type	Tumor proportion score	1st line CPI	2nd Line CPI	Response
Pelvic mass- poorly differentiated carcinoma	21-30%	Pembrolizumab (PD-1)	Nivolumab (PD-1)	Stable disease for 29 months with ongoing treatment
Hepatocellular carcinoma	N/A	Pembrolizumab (PD-1)	Nivolumab (received ipilimumab (CTLA4) and Nivolumab (PD-1) until Cycle 5)	Stable disease for 30 months with ongoing treatment
Squamous cell lung carcinoma	15%	Durvalumab (PD- L1)	Pembrolizumab (PD-1)	Stable disease for 12 months with ongoing treatment
HPV associated squamous cell carcinoma of tongue	1%	Nivolumab (PD-1)	Pembrolizumab (PD-1)	Progression
HPV associated squamous cell carcinoma of head & neck	N/A	Nivolumab (PD-1)	Pembrolizumab (PD-1)	Progression
Squamous cell lung carcinoma	34%	Durvalumab (PD-L1)	Nivolumab (PD-1)	Progression
Urothelial squamous cell carcinoma	N/A	Pembrolizumab (PD-1)	Nivolumab (PD-1)	Progression
Adeno-squamous lung carcinoma	N/A	Nivolumab (PD-1)	Atezolizumab (PD-L1)	Died of cardiac arrest
Squamous cell carcinoma of lung	20%	Nivolumab (PD-1)	Pembrolizumab (PD-1)	Progression with Nivolumab, Pneumonitis with Pembrolizumab
Squamous cell lung carcinoma	50%	Durvalumab (PD-L1)	Pembrolizumab (PD-1)	Pneumonitis (radiation) unrelated to CPI

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.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0205

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

[1]Elizabeth Stirling*, [1]Ethan Willey-Shelkey, [1]Adam Wilson, [2]Aleksander Skardal, [1]Pierre Triozzi, [3]Masaki Terabe, [1]Lance Miller, [1]Shay Soker, [1]David Soto-Pantoja. *[1]Wake Forest School of Medicine, Winston Salem, NC, USA; [2]The Ohio State University, Columbus, OH, USA; [3]National Cancer Institute, Bethesda, MD, USA*

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 TN-tumor 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. Organoids were constructed by embedding murine TNBC tumor tissue and AH1 CD8+ T cells in a specialized ECM mimicking hydrogel. Immunohistochemistry was performed on organoid, 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