sequencing data sets from human and murine tumors treated with ICB.

Results Comparison of ICB activity in LDHA-KD vs. control tumor-bearing mice revealed improved anti-tumor effects and overall survival in the setting of glycolysis-defective tumors specifically upon CTLA-4 blockade. Anti-tumor CD8+ T-cell responses correlated with Treg phenotypic and functional destabilization in anti-CTLA-4-treated LDHA-KD tumors. CTLA-4 blockade led to CTLA-4 and CD25 downregulation associated with increased IFN-gamma and TNF-alpha production in Tregs from glycolysis-defective vs. control tumors. We next mimicked high- vs. low-glycolysis tumor microenvironment (TME) in vitro using control vs. LDHA-KD tumor co-cultures with Tregs, control vs. LDHA-KD tumor-conditioned media or directly modulating glucose concentrations. In these assays, we observed that CTLA-4 blockade promotes IFN-gamma±TNF-alpha production and glucose uptake by Tregs and more efficiently counteracts Treg suppression and enhances CD28 co-stimulation at higher glucose concentrations. Lastly, by interrogating transcriptomic data from human melanoma and murine 4T1 tumors, we found that CTLA-4 blockade promotes immune-cell infiltration and metabolic fitness especially in glycolysis-defective tumors.

Conclusions Our findings indicate that increasing glucose availability in the TME may improve anti-CTLA-4 therapeutic activity and reveal a new mechanism through which CTLA-4 blockade interferes with Treg immunosuppression in a glucose-dependent manner. These results suggest that CTLA-4 blockade can be more effective in tumors with low glycolysis and/or can be best exploited in combination with inhibitors of tumor glycolysis.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0254

255 EFFICACY OF SEQUENTIAL IMMUNE CHECKPOINT INHIBITION (ICI) IN PATIENTS WITH GENITOURINARY MALIGNANCIES

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Background Immune checkpoint inhibitors (ICI) have become a standard of care for treatment of both metastatic renal cell carcinoma (mRCC) and metastatic urothelial carcinoma (mUC). Additional treatment with ICI following disease progression on first-line therapy has become increasingly common for patients with severe disease, but the clinical outcomes of sequential therapy have not been well studied. We report here the clinical outcomes in a cohort of patients with mRCC and mUC who received two regimens of ICI-based therapy.

Methods We performed a retrospective review of 31 mRCC patients and 11 mUC with follow-up data available who received at least 1 dose of a 2nd ICI-based regimen at the Winship Cancer Institute of Emory University from 2015–2020. Radiographic responses were determined using response evaluation criteria in solid tumors version 1.1 (RECISTv1.1). An objective response (OR) was defined as a complete response (CR) or partial response (PR). Clinical benefit (CB) was defined as an objective response or stable disease (SD) > 6 months.

Results Most patients were white (81%) and male (69%). 31 had mRCC (table 1) and 11 had mUC (table 2). Overall most patients (58%) received anti-PD-1 (Programmed cell death protein 1) monotherapy as first line, with anti-PD-L1 (Programmed death-ligand 1) monotherapy (33%) and anti-PD-1/CTLA-4 (Cytotoxic T-lymphocyte-associated protein 4) combination therapy (9%) being less prevalent. Patients spent an average of 27.1 weeks on first ICI therapy. Second ICI-based treatment was most commonly anti-PD-1/CTLA-4 (62%), followed by anti-PD-1 monotherapy (38%). A subset of patients (33%) had clinical benefit with combination anti-PD-1/CTLA-

Abstract 255 Table 1 Demographics and treatment data for patients with metastatic renal cell carcinoma

Variable		n (%)
Gender	Male	22 (71)
	Female	9 (29)
Race	White/Asian	27 (87)
	Black	5 (13)
Clear-cell histology	Yes	24 (77)
	No	7 (23)
Prior Lines of Therapy	1	13 (42)
	2	7 (23)
	3+	11 (35)
Number of distant metastatic sites	1-2	9 (29)
	3	10 (32)
	4+	12 (39)
First ICI regimen	PD-1 monotherapy	23 (74)
	PDL-1 monotherapy	4 (13)
	PD-1/CTLA4 combination	4 (13)
Reason for d/c 1st ICI Regimen	Progression	26 (84)
	Toxicity	3 (10)
	Completion	2 (6)
Second ICI Regimen	PD-1 monotherapy	6 (19)
	PD-1/CTLA4 combination	25 (81)
Best Radiographic Response to 2nd ICI Regimen	PD	18 (60)
	SD	7 (23)
	PR	4 (13)
Response Rate: 16.7%	CR	1 (3)
CB Rate: 40.0%	NE	1

Abstract 255 Table 2 Demographics and treatment data for patients with urothelial cell carcinoma

Variable		n (%)
Gender	Male	7 (64)
	Female	4 (36)
Race	White/Asian	9 (81)
	Black	2 (19)
Prior Lines of Therapy	0-2	4 (36)
	3-4	6 (55)
	5+	1 (9)
Number of distant metastatic sites	1-2	6 (54)
	3	2 (19)
	4+	3 (27)
First ICI regimen	PD-1 monotherapy	1 (9)
	PDL-1 monotherapy	10 (91)
Reason for d/c 1st ICI Regimen	Progression	10 (91)
	Toxicity	0
	Completion	1 (9)
Second ICI Regimen	PD-1 monotherapy	10 (91)
	PD-1/CTLA4 combination	1 (9)
Best Radiographic Response to 2nd ICI Regimen	PD	6 (60)
	SD	4 (40)
	PR	0
Response Rate: 0%	CR	0
CB Rate 40%	NE	1

4-based second ICI therapy, with 4 (10%) having PR and one (2%) having CR of disease following second ICI-based treatment. Patients spent an average of 21.4 weeks on the second ICI regimen. The response rate for the entire cohort was 11.9% (16.7% for RCC and 0% for UC).The CB rate for the entire cohort was 40% (40% for RCC and 40% for UC). Immune-related adverse events were experienced in a subset of patients (28%).

Conclusions Although we observed a low OR rate to a second ICI-based regimen, a select subset of patients did have CB from a second ICI-regimen. Current studies exploring the addition of CTLA4 inhibitors to anti-PD-1 therapy may provide insight into the greater efficacy of treatment within a subset of patients. Further analysis of a larger cohort receiving sequential immunotherapy is necessary to better identify patients who may be more likely to derive CB from sequential ICI.

Ethics Approval This retrospective study was approved by the Emory University Institutional Review Board.

Consent Not applicable.

Acknowledgements Research reported in this publication was supported in part by the Breen Foundation.

Trial Registration Not applicable.

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Not applicable

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0255

256 SINGLE-AGENT ZALIFRELIMAB (ANTI-CTLA-4) SHOWS CLINICAL BENEFIT IN RARE TUMORS – CASE REPORT FROM PHASE 2 STUDY (NCT03104699)

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Background Zalifrelimab is a fully human monoclonal antibody against cytotoxic T-lymphocyte -associated protein 4 (CTLA-4). Preliminary data demonstrated clinical benefit and tolerability, as monotherapy, in patients with recurrent solid tumors including rare tumor types. Previously presented Phase I data reported one durable complete response in recurrent cutaneous angiosarcoma (cAS).[1] Here we report additional clinical responses from an ongoing Phase 2 study of zalifrelimab monotherapy including clinical benefit in rare solid tumors.

Methods In an ongoing, phase 2 study (NCT03104699), the safety and efficacy of zalifrelimab, as monotherapy, was evaluated in patients who progressed on prior anti-PD-1/L1 treatment. All patients were treated intravenously (IV) with zalifrelimab at 1 mg/kg every 3 weeks until disease progression or up to 2 years.

Results Overall, 44 patients were treated and 29 patients were response-evaluable at the time of report. In patients with refractory solid tumors treated with zalifrelimab, we report a disease control rate (CR, PR, and SD) of 51.7%, objective response rate (ORR) of 10.3% (3/29), disease stabilization of 41.3% (12/29). Clinical activity was observed in five solid tumors considered rare, including; cAS (N=1), glucagonoma (N=1), chondrosarcoma (N=1), spindle-cell sarcoma (N=1) and fibroblastic sarcoma (N=1). In these rare tumors, durable partial responses of 45 and 30 weeks were observed in cAS of the scalp with lymph node metastases and glucagonoma, respectively. Both patients remain on zalifrelimab with no evidence of disease progression. Additionally, durable disease stabilization was observed in a patient with spindle-cell sarcoma. Patients with chondrosarcoma and fibroblastic sarcoma progressed on therapy. Zalifrelimab was well tolerated with the most commonly reported treatment-related adverse events including fatigue, nausea, anemia, diarrhea and vomiting, consistent with the drug class. Most events were mild or moderate and resolved with standard treatments.

Conclusions Our data demonstrates the potential for Zalifrelimab to promote meaningful clinical benefit in difficult to treat tumors, including patients that progress on prior PD-1/PD-L1 therapy or chemotherapy. Notably, responses were observed in rare tumor types such as recurrent cutaneous angiosarcoma and glucagonoma. Treatment with zalifrelimab is safe and well tolerated in patients with advanced malignancies.

Trial Registration NCT03104699.

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http://dx.doi.org/10.1136/jitc-2020-SITC2020.0256

Clinical trials completed

257 DEVELOPMENT OF A DIAGNOSTIC PLATFORM WHICH MATCHES THERAPIES TO THE TUMOR MICROENVIRONMENT DOMINANT BIOLOGY

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Background Tumor microenvironment (TME)-targeting agents such as anti-angiogenic therapies and check-point inhibitors (CPIs), have shown both promise and variability in effectiveness depending on the tumor type. For immune-targeting agents like CPIs, efforts to identify features or biomarkers that predispose responding patients include but are not limited to genomic stability, tumor mutation burden, and PD-L1 expression. Oncologie is developing a RNA-based platform that identifies subsets of patients based on multiple aspects of the biological processes (dominant biology) existing within the tumor microenvironment.

Methods RNA data from publicly available sources including microarray, RNASeq exome and whole RNA were analyzed with respect to gene signatures that describe four different microenvironmental phenotypes. Phenotypes were then evaluated for relationships to clinical efficacy endpoints. From these RNA signatures and driven by machine learning methodologies, drug-specific algorithms were developed and applied to retrospectively to clinical data. Comparative analyses were explored between gene signatures, commonly used biomarkers (eg. presence of microsatellite DNA, expression levels of PD-L1, etc) and within-patient metadata to better understand better how this approach can be utilized in prospective clinical studies.

Results Attributes in RNA expression identified using Oncologie's platform have retrospectively characterized responders to CPIs or anti-angiogenic drugs, demonstrating a relationship between clinical response and biomarker positive and negative patient populations. Exploratory data summarizing the use of the this platform demonstrates its utility for enriching