

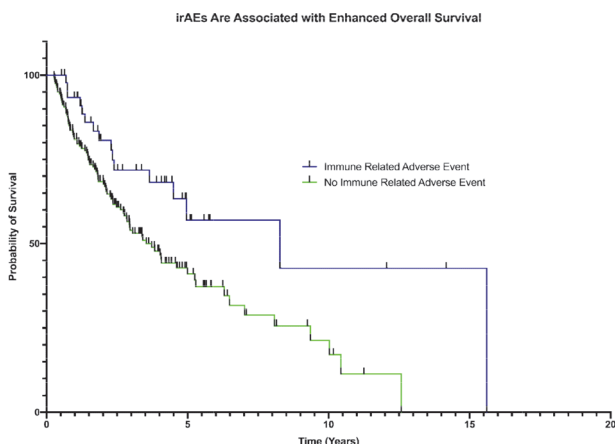
IMMUNE-RELATED ADVERSE EVENTS ASSOCIATED WITH IMMUNE CHECKPOINT INHIBITOR THERAPY ARE ASSOCIATED WITH ENHANCED SURVIVAL AND DISEASE-SPECIFIC INCIDENCE

¹Eric Vick*, ²Inas Abuali, ¹Andrew Kelleher, ¹Sarah Ludvigsen, ¹Nathanael Moore, ³Nicholas Arias, ²Shuchi Gulati, ²Trisha Wise-Draper. ¹University of Cincinnati Medical Center, Cincinnati, OH, USA; ²University of Cincinnati Medical Center and Cancer Center, Cincinnati, OH, USA; ³University of Cincinnati, Cincinnati, OH, USA

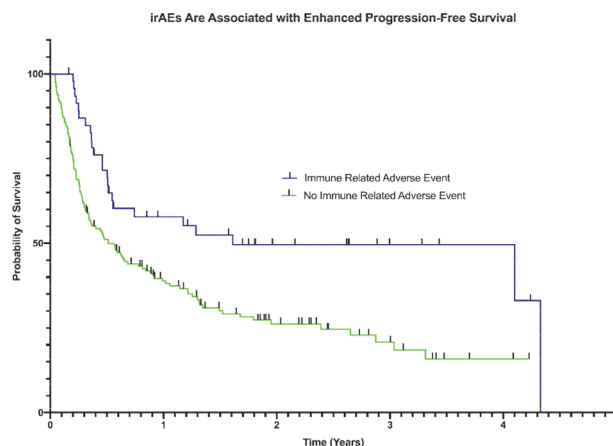
Background Immune checkpoint inhibitors (ICIs) are now approved for several cancer types due to superior outcomes compared to chemotherapy. PD-1/PD-L1 and CTLA-4 inhibitors reactivate T-cell mediated anti-tumor immunity but may also lead to immune-related adverse events (irAEs). Growing evidence suggests the onset of irAEs could be correlated with the efficacy of ICIs.¹⁻² In this study, we investigated patterns and incidence of irAEs and their relationship to overall survival (OS) and progression-free survival (PFS) in multiple cancer types.

Methods The electronic medical record was queried at the University of Cincinnati Medical Center for the administration of ICIs for the identification of irAEs. Data on new irAEs diagnosed after administration of at least one dose of ICI was collected along with relevant demographic and clinicopathologic variables including treatment type, cancer type, staging information, and the administration of immune suppression following the identification of an irAE either inpatient or outpatient. Univariate and multivariate analysis were conducted and survival analysis was determined according to log-rank testing.

Results Of our 210 initial patients, the median age was 64 (range 22–93), 37% were female, 72% had ECOG 0-1, and 79% were white. Cancer types included melanoma 24%, non-small cell lung cancer (NSCLC) 34%, small cell lung cancer 2%, renal cancer 12%, urothelial cancer 11%, head and neck cancers 12%, and 16% other primaries while 19% remained on ICI at the time of data entry. The most common ICIs were pembrolizumab, nivolumab, followed by ipilimumab-nivolumab, ipilimumab, and durvalumab. The overall incidence of irAEs was 22.6%. Overall survival and progression-free survival was improved for those who suffered an irAE (median

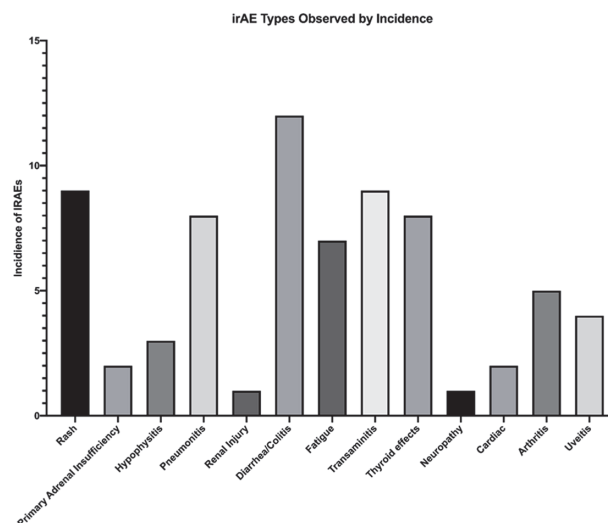


Abstract 252 Figure 1 irAEs are associated with enhanced overall survival overall survival of patients who suffered at least one irAE demonstrated increased median survival of 8.3 years compared to 3.5 years from diagnosis for a mix of malignancies. The hazard ratio for this finding was 0.56, with a p-value of 0.0092 by Mantel-Cox log-rank test



Abstract 252 Figure 2 irAEs are associated with enhanced progression-free Similarly, progression-free survival of patients who suffered at least one irAE demonstrated increased median survival of 1.6 years compared to 0.51 years from initiation of treatment with a checkpoint inhibitor for a mix of malignancies. The hazard ratio for this finding was 0.51, with a p-value of 0.0018 by Mantel-Cox log-rank test

OS 8.3 vs. 3.5 years, HR 0.56, p=0.0092; median PFS 5.0 vs 2.5 years, HR 0.57, p=0.0052) (figure 1 and 2 respectively). ICI treatment in NSCLC was associated with decreased overall irAE events by univariate analysis (Odds Ratio 0.39, 95% CI 0.17 - 0.86). Our multivariate analysis showed ICI treatment in hepatocellular carcinoma to be significantly associated with irAEs, however, this was likely due to low enrollment (n=4) and was not significant by univariate analysis. The most common irAE overall was diarrhea/colitis (figure 3).



Abstract 252 Figure 3 irAE Types Observed by Incidence In our cohort, 47 patients suffered a total incidence of 71 irAEs the most common individual event of which was colitis of all grades (12/71). Rash and transaminitis occurred the second most frequently (9/71 respectively), and pneumonitis/thyroiditis was the third most frequent (8/71 respectively) which together represented 65% of all irAEs in this cohort

Conclusions In our data set, irAEs were associated with increased OS and PFS regardless of disease site. ICI treatment of NSCLC was associated with significantly fewer irAEs compared to other malignancies. Further research is needed to

determine irAE type-specific incidence, the incidence of multiple irAEs in a single patient, and response to corticosteroid therapy.

Acknowledgements We would like to thank the Department of Hematology/Oncology of the University of Cincinnati, the University of Cincinnati Cancer Center, and the Department of Internal Medicine of the University of Cincinnati for their support.

Ethics Approval Considered and Approved by the University IRB Approval #2019-0610.

REFERENCES

1. Weber JS, Hodi FS, Wolchok JD, et al. Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma. *J Clin Oncol* 2017;**35**(7):785–792.
2. Yamauchi I, Yasoda A, Matsumoto S, et al. Incidence, features, and prognosis of immune-related adverse events involving the thyroid gland induced by nivolumab. *PLoS ONE*. 2019;**14**(5):e0216954.

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0252>

253

ANTI-TIGIT ANTIBODIES REQUIRE ENHANCED FcγR CO-ENGAGEMENT FOR OPTIMAL T AND NK CELL-DEPENDENT ANTI-TUMOR IMMUNITY

¹Rebecca Ward*, ²Elena Paltrinieri, ¹Marilyn Marques, ¹Priyadarshini Iyer, ³Sylvia Dietrich, ⁴Jeremy Waight, ¹Mark Bushell, ⁵Nicholas Wilson, ¹Jennifer Buell, ¹David Savitsky, ¹Dhan Chand. ¹Agenus Inc, Lexington, MA, USA; ²Pyxis Oncology, Cambridge, MA, USA; ³Dragonfly Therapeutics Inc, Waltham, MA, USA; ⁴GlaxoSmithKline, King of Prussia, Pennsylvania, USA; ⁵Gilead Sciences, San Carlos, CA, USA

Background T-cell immunoreceptor with Ig and ITIM domains (TIGIT) is an important negative regulator of the immune response to cancer that contributes to resistance/relapse to anti-PD-1 therapy.¹ In clinical trials, anti-human (h) TIGIT antibodies have shown promising activity in combination with anti-PD-1/PD-L1 antibodies for the treatment of various solid tumors.² However, the optimal format for anti-TIGIT antibodies remains controversial. Here we describe a novel Fcγ receptor (FcγR)-dependent mechanism of action that is critical for enhancing T and NK cell anti-tumor immunity, and, further informs on the optimal design of anti-TIGIT antibodies.

Methods We investigated a panel of Fc-silent, Fc-competent, and Fc-engineered anti-mouse (m) TIGIT antibody variants in syngeneic murine CT26 tumor-bearing or B16F10 pseudo-metastases models. To further elucidate the relative contribution of T and NK cells in controlling tumor growth, we assessed the activity of Fc-engineered anti-TIGIT antibodies in NK cell-depleted or T cell-deficient (Nu-Foxn1nu) CT26 tumor-bearing mice. Immune-related pharmacodynamic changes in the tumor microenvironment were assessed by flow cytometry. We further validated these findings in primary human T and NK cell activation assays using Fc-engineered anti-human TIGIT antibodies.

Results The Fc-engineered anti-mTIGIT antibody, which demonstrates enhanced binding to mouse FcγRIV, was the only variant to deliver single agent anti-tumor activity. The Fc-enhanced variant outperformed the Fc-competent variant while the Fc-inert variant had no anti-tumor activity. Tumor control by anti-mTIGIT antibodies was not dependent on Treg depletion, but rather on increased frequency of CD8+ T cells and activated NK cells (Ki67, IFNγ, CD107a and TRAIL) in the tumor microenvironment. Concordant with observations in the mouse, Fc-engineered anti-hTIGIT antibodies with improved binding to FcγRIIIA demonstrate superior T and NK cell

activation in PBMC-based assays compared to a standard hIgG1 variant. Notably, superior activity of the Fc-engineered anti-hTIGIT antibody was observed from PBMC donors that express either high or low affinity FcγRIIIA. Blockade of FcγRIIIA or depletion of CD14+ and CD56+ cells reduced the functional activity of the Fc-enhanced anti-TIGIT antibody, confirming the requirement for FcγR co-engagement to maximize T cell responses.

Conclusions Our data demonstrate the importance of FcγR co-engagement by anti-TIGIT antibodies to promote immune activation and tumor control. First generation anti-TIGIT antibodies are not optimally designed to co-engage all FcγRIIIA variants. However, Fc-enhanced anti-TIGIT antibodies unlock a novel FcγR-dependent mechanism of action to enhance T and NK cell-dependent anti-tumor immunity and further improve therapeutic outcomes.

REFERENCES

1. Johnston RJ, et al., The immunoreceptor TIGIT regulates antitumor and antiviral CD8(+) T cell effector function. *Cancer Cell* 2014; **26**:923–37.
2. Rodriguez-Abreu D, et al., Primary analysis of a randomized, double-blind, phase II study of the anti-TIGIT antibody tiragolumab (tira) plus atezolizumab (atezo) versus placebo plus atezo as first-line (1L) treatment in patients with PD-L1-selected NSCLC (CITYSCAPE). *Journal of Clinical Oncology* 2020; **38**:15_suppl, 9503–9503.

<http://dx.doi.org/10.1136/jitc-2020-SITC2020.0252>

254

CTLA-4 BLOCKADE PROMOTES TREG GLUCOSE METABOLISM AND REDUCES TREG FUNCTIONAL STABILITY IN GLYCOLYSIS-DEFECTIVE TUMORS

¹Roberta Zappasodi*, ¹Inna Serganova, ¹Ivan Cohen, ¹Masatomo Maeda, ¹Yasin Senbabaoglu, ¹Masahiro Shindo, ¹Rachana Maniyar, ¹Mayuresh Mane, ¹Avigdor Leftin, ²McLane Watson, ¹Svena Verma, ¹Matthew Lubin, ¹Myat Kyaw Ko, ¹Arnab Ghosh, ¹Mohsen Abu-Akeel, ¹Ellen Ackerstaff, ¹Jason Koutcher, ³Ping-Chih Ho, ²Greg Delgoffe, ¹Ronald Blasberg, ¹Jedd Wolchok, ¹Taha Merghoub. ¹Memorial Sloan Kettering Cancer Center, New York, USA; ²University of Pittsburgh, Pittsburgh, PA, USA; ³University of Lausanne, Lausanne, Switzerland

Background Durable clinical responses to immune checkpoint blockade (ICB) occur in a limited fraction of patients. We thus hypothesized that the characteristic tumor metabolic switch towards aerobic glycolysis could contribute to ICB resistance. High glucose consumption and lactate production by tumor cells can indeed restrict nutrient availability for tumor-infiltrating T cells, which also rely on glycolysis to proliferate and function. Therefore, we investigated whether targeting tumor glucose metabolism potentiates ICB anti-tumor activity.

Methods We modeled tumor-selective glycolysis inhibition by knocking down the critical glycolytic enzyme lactate dehydrogenase A (LDHA-KD) in the murine metastatic breast carcinoma 4T1 and melanoma B16, which are known immune-refractory tumor models. Anti-CTLA-4 and anti-PD-1 were tested in immunocompetent mice orthotopically implanted with control vs. LDHA-KD tumor cells. Changes in glucose metabolism were assessed by Seahorse and fluorescent-glucose flow-cytometry staining. Changes in immune cells were measured by multiparameter flow cytometry. Glucose-dependent effects of anti-CTLA-4 in regulatory T cells (Tregs) were tested in standard suppression assays with increasing glucose concentration (0.5–10 mM). Pearson correlations between glycolysis and intra-tumor immune-cell infiltration by CIBERSORT immune-deconvolution method were analyzed in bulk RNA-