GENERALIZABILITY OF PREDICTIVE VERSUS PROGNOSTIC INDICATORS FROM PUBLISHED TRANSCRIPTOMIC ASSOCIATIONS WITH TUMOR RESPONSE TO IMMUNE CHECKPOINT INHIBITION

1Dante Barton*, 1Anne Monette, 2Nicholas Tschemia, 3Alexandria Cogdill, 4Yana Najjar, 5Randy F. Swies, 6Sara Valpiene, 7Erik Wennerberg, 8Praeven Bommardeyy, 9Cara Haymaker, 10Uqba Khan, 11Heather M McGee, 12Wangqi Park, 13Housein A Sater, 14Christine Spencer, 15Maria Asciento, 16Valentin Baran, 17Vinita Popat, 18Daniel Wells, 19Steven Versko, 20Sarah Dehemier, 21Vestmier Thorsen, 22Roberta Zappadossi, 23Nils-Petter Rudqvist, 24Benjamin Vincent*. 1University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; 2Jefferson Medical College, Philadelphia, PA, United States; 3St. Vincent’s University Hospital, Halifax, NS, Canada; 4National Cancer Institute, Bethesda, MD, United States; 5University of Texas MD Anderson Cancer Center, Houston, TX, United States; 6UPMC Hillman Cancer Center, Pittsburgh, PA, United States; 7University of Chicago, Chicago, IL, United States; 8The Christie NHS Foundation Trust, Manchester, UK; 9Institute of Cancer Research, London, UK; 10Replimune Inc, Woburn, MA, United States; 11Well Cornell Medical, New York, NY, United States; 12City of Hope, Duarte, CA, United States; 13Memorial Sloan Kettering Cancer Center, New York, NY, United States; 14Cleveland Clinic, Florida, Stut, FL, United States; 15Parker Institute for Cancer Immunotherapy, San Francisco, CA, United States; 16Pombridge Saint John’s Cancer Institute, Santa Monica, CA, United States; 17Stanford University School of Medicine, Palo Alto, CA, United States; 18University of Texas Westernmost Medical Center, Dallas, TX, United States; 19Immunol, New York, NY, United States; 20Institute for Systems Biology, Seattle, United States; 21Well Cornell Medical College of Cornell University, San Francisco, CA, United States; 22Well Cornell Graduate School of Medical Sciences, San Francisco, CA, United States

Background Clinically actionable biomarkers of immune checkpoint inhibitor (ICI) response are currently limited to specific mutation profiling, immunohistochemistry staining for PD-L1, and tumor mutational burden. Use of the latter two are challenging, as they are incompletely predictive and lack accepted standards for measurement and interpretation. Transcriptomic associations with response have been reported and may add critical information to an integrated biomarker strategy. There is a need for better understanding of the performance of potential biomarkers across multiple datasets and tumor tissue types.

Methods RNA sequencing FASTQ data files from 12 ICI trials (TCGA)14 were processed using a standardized bioinformatics workflow for quality control, mapping, generation of gene expression matrices, and extraction of immunogenomics features. We evaluated 182,5−22 immunogenomics features that have been published or proposed to associate with clinical response to ICI therapy for correlation with response and survival across these datasets, estimating predictive information from the ICI trials and prognostic information from TCGA dataset results.

Results The MIRACLE score was associated with response and survival in most ICI studies, both overall and within melanoma trials (figures 1). Other immunogenomics features had both lower effect sizes of outcome associations and fewer cohorts in which their outcome associations were statistically significant. Features that were associated with outcome in the ICI studies were generally associated with survival in TCGA as well, whether evaluating all tumor tissue types (figure 2) or melanoma only (figure 3). In melanoma, the TIDE score was associated with response to ICIs, but not with overall survival in TCGA, though the effect size was small. Gene expression signatures built from responders versus non-responders in each trial did not yield generalizable associations with response across other trials. Harmonized gene expression data and immunogenomics features extracted in this project are available for review and further analysis in the CRI iAtlas platform (https://cri-iatlas.org).

Conclusions The MIRACLE score performed best in both effect size and frequency of studies where its association with outcome was statistically significant. No features gave substantial predictive rather than prognostic information. We expect that integration of transcriptomic features with clinical features and DNA alterations will be required to provide predictive (rather than just prognostic) information. Methods that train models on prioritization of predictive information and generalizability across studies may be required for optimal biomarker development.

Acknowledgements We would like to thank SITC for funding for this work as part of the Sparkathon TimIOS collaborative project. We would also like to thank the authors of the published datasets we have used in the study.

REFERENCES
Abstract 508 Figure 1  Overall survival associations of selected immunogenomics features. Rows represent selected immunogenomics features and columns represent individual datasets. Results from ICI trials are shown in the left panel, and results from TCGA datasets are shown in the right panel. Row/column intersections represent effect size (triangle direction and color) and statistical significance (triangle size) of associations with overall survival. Column-side colorbars show various dataset features for comparison.

Abstract 508 Figure 2  Predictive versus prognostic information content of selected immunogenomics features. X-axis represents the log10 hazard ratio with 95% confidence interval derived from TCGA data, and Y-axis represents log10 hazard ratio with 95% confidence interval derived from ICI data.

Abstract 508 Figure 3  Predictive versus prognostic information content of selected immunogenomics features, melanoma trials only. X-axis represents the log10 hazard ratio with 95% confidence interval derived from TCGA data, and Y-axis represents log10 hazard ratio with 95% confidence interval derived from ICI data.