Background Cytotoxic T lymphocyte (CTL) plays a crucial role in anti-cancer immunity. Progression of CTL to exhausted T lymphocyte (ETL) cells that overexpress inhibitory receptors can substantially decrease effector cytokines production and diminish the cytolytic activity in tumor microenvironment (TME). However, while the activity levels of CTL and ETL are considered important determinants of Immune checkpoint inhibitor (ICI) response, it has been repeatedly observed that their predictive power of the latter is quite limited. Studying this conundrum on a large scale across the TCGA cohort, we find that ETL and CTL activity (estimated based on conventional gene signatures in the bulk tumor expression) is strongly positively correlated in most cancer types. We thus hypothesized that their limited predictive power may arise due to their high concordance in the bulk expression, such that their opposing associations with response effectively cancel each other.

Methods Aiming to better characterize these two CD8+ immune states as ICI response biomarkers, we analyzed several melanoma single cell expression datasets via an interaction linear regression model and identified 13 genes whose expression state decouples the CTLs and ETLs.

Results We further tested and validate this decoupling signature in several melanoma bulk expression ICI cohorts by first demonstrating that in high-decoupling-score patient groups, the correlation between ETL and CTL activities is indeed markedly lower than in the low-decoupling-score patient groups. Second, the performance of CTL activity in predicting ICI response is significantly better in the high-decoupling-score than that in the low one. Finally, importantly, in the high decoupling score, CTL activity is a better predictor of melanoma patients ICI response than state-of-art ICI prediction methods.

Conclusions These results demonstrate the utility of a new decoupling score for boosting the power of CTL activity in predicting ICI response in melanoma.