A TRANSCRIPTOMICS-BASED RESPONSE PREDICTOR IDENTIFIES POTENTIAL RESPONDERS AMONG PATIENTS WITH NEGATIVE STANDARD MARKERS FOR RESPONSE TO IMMUNE CHECKPOINT BLOCKERS

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Background Immune checkpoint blockers (ICB) are revolutionizing cancer treatment, approved for increasingly more cancer types. The most common biomarkers currently used to select patients for ICB are TMB, microsatellite stability and PDL1 presentation. However, some patients that do not meet the criteria of these markers still respond to ICBs. This calls for complementary biomarkers that could better identify responders to ICBs and importantly, discover responders where the standard biomarkers fail to do so. Here, we focus on predicting response to anti-PD1 in patients with negative markers for response to ICBs.

Methods We employ ENLIGHT, a transcriptomic-based precision oncology platform, which follows SELECT in identifying and utilizing clinically relevant genetic interactions to predict a patient’s response to targeted therapies and ICB. ENLIGHT generates an individual ICB response score calculated from pre-treatment tumor mRNA expression, using a 10-gene signature. Patients with a score above a predetermined threshold are considered matched by ENLIGHT to anti-PD1 treatments. We have previously shown, based on more than 1000 cases analyzed retrospectively, that this signature can identify responders to anti-PD1 with high accuracy. We also described a real world case of a cancer patient, who was negative to all 3 markers, but had an exceptional response to ENLIGHT-matched anti-PD1 + anti-CTLA4 treatment. Here, we use ENLIGHT to perform a retrospective analysis of mRNA data from 107 patients that had low TMB (< 10) or microsatellite stable tumors and were treated with anti-PD1, to specifically assess ENLIGHT’s performance in this biomarker-negative group of patients.

Results Patients who responded to anti-PD1 treatments have significantly higher ENLIGHT Matching Scores (EMS) in both datasets (figure 1A). Correspondingly, ENLIGHT is highly predictive of response to anti-PD1 among patients with negative ICB markers in the two datasets we studied (ROC AUCs of 0.77 and 0.845, figure 1B). It is important to note that ENLIGHT has not been trained on any of these datasets and is applied as-is using the original parameters published in. Remarkably, we find that patients who are ENLIGHT-Matched to anti-PD1 are 11 times more likely to respond than patients who are not (22% vs. 2%, p<0.01, figure 1C).

Conclusions ENLIGHT is a powerful tool for predicting response to anti-PD1 treatment in patients with negative standard biomarkers for ICB, a currently unmet need with considerable clinical importance.

REFERENCES

Abstract 157 Figure 1 ENLIGHT’s performance in predicting response to anti-PD1 treatments in patients with negative immune biomarkers. (A) Swarmplot of the score produced by ENLIGHT. (ENLIGHT Matching Score (EMS), Xaxis) among responders (blue) and non-responders (orange) to anti-PD1 for each dataset denoted on the x axis. Blue dashed line denotes the binary threshold to classify a patient as ENLIGHT-Matched or ENLIGHT-Unmatched as fixed in [1] on independent data. P value was calculated using man-h Whitney U test. (B) ROC curve of ENLIGHT’s anti-PD1 response prediction in the Kim et al. (red) and Rose et al. (blue) datasets. Dashed line represents the curve of a random classifier. (C) Response Probability (percent of patients that actually responded) among ENLIGHT-Matched and ENLIGHT-Unmatched patients. Black dashed line denotes the overall response rate in the dataset. P value was calculated using one sided difference in proportion test. All 40 patients in the Kim et al. (gastric cancer) were microsatellite stable and all 67 patients in the Rose et al. (urothelial cancer) were TMB low (<10).

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