

successfully determined main cancer immune-subtypes associated with survival across multiple cancer types in TCGA.¹

Methods RNA sequencing data from 1092 patients were uniformly reprocessed harmonized, and annotated with predefined clinical parameters. We defined a comprehensive set of immunogenomics features, including immune gene expression signatures associated with treatment outcome,^{1,2} estimates of immune cell proportions, metabolic profiles, and T and B cell receptor repertoire, and scored all compendium samples for these features. Elastic net regression models with parameter optimization done via Monte Carlo cross-validation and leave-one-out cross-validation were used to analyze the capacity of an integrated immunogenomics model to predict durable clinical benefit following ICB treatment.

Results Our preliminary analyses confirmed an association between the expression of an IFN-gamma signature in tumor (1) and better outcomes of ICB, highlighting the feasibility of our approach.

Conclusions In line with analysis of pan-cancer TCGA datasets using this strategy (1), we expect to identify analogous immune subtypes characterizing baseline tumors from patients responding to ICB. Furthermore, we expect to find that these immune subtypes will have different importance in the model predicting response and survival. Results of this study will be incorporated into the Cancer Research Institute iAtlas Portal, to facilitate interactive exploration and hypothesis testing.

REFERENCES

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Combination immunotherapies

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HIGH-RESOLUTION MAPS OF HETEROGENEOUS ANTIGEN EXPRESSION IN GLIOBLASTOMA AND IMPLICATIONS FOR IMMUNOTHERAPY

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Background Glioblastoma (GBM) remains an almost universally fatal brain tumor. While CAR T cell immunotherapy has shown promising clinical efficacy, therapeutic failure may reflect our incomplete understanding of target antigen expression. We previously examined variations in antigen expression at the level of individual patients (inter-patient or inter-tumor heterogeneity), focusing on immunotherapy targets IL13R α 2, HER2 and EGFR. We concluded that antigen expression diverged from expectations from random expression. Because antigen escape may arise from GBM cell heterogeneity, we have mapped target antigen expression within individual tumors (intra-tumor heterogeneity).

Methods Serial sections from a 43 patient cohort were immunostained (DAB with hematoxylin counterstain) for target antigens IL13R α 2, HER2 and EGFR. Each section was annotated directly from the slide by a neuropathologist. Sections were scanned (0.46 μ m/pixel; Hamamatsu), and then working within Fiji/ImageJ, images were segmented by color deconvolution into hematoxylin (nuclei) and DAB layers. Images of nuclear layers were aligned, and used to align the DAB layers. Two schemes were used to examine the spatial distributions of the three target antigens. When tumor domains could be identified, we determined expression of each antigen as optical density (OD). In the second scheme, a 10 μ m grid was superimposed on each section, and OD was determined for each position and assembled into spreadsheets (Origin v2019b). Maps for expression were generated from the OD in each position.

Results Approaching these maps from the perspective of antigen escape, we examined the extent to which expression of target antigens was spatially mixed, how rapidly antigen dominance could shift (spatial frequency), and whether spatial distributions were arrayed in a coordinated manner.

When tumor domains could be identified, we calculated the Shannon diversity index (H) for each domain within a section. While values of H clustered within some tumors, usually values of H varied widely.

The superimposed grid was used to examine heterogeneity within entire tumor sections. Expression was intermixed, and EGFR and IL13R α 2/HER2 displayed complementary expression patterns. In tumors with large EGFR+ areas, IL13R α 2+/HER2+ areas could overlap, while when EGFR+ areas were smaller, IL13R α 2+ and HER2+ areas were more distinct. Borders could be quite diffuse, or quite sharp (a few cell diameters).

Conclusions Our results indicate that expression of IL13R α 2, HER2 and EGFR is highly heterogeneous and not always spatially distinct. Because GBM tumors adapt to the selection pressures of immunotherapies, we suggest that combination therapies should be designed accordingly, and immunotherapies targeting IL13R α 2/HER2 could benefit from inclusion of EGFR.

Completed clinical trial

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AVID200, FIRST-IN-CLASS TGF-BETA1 AND BETA3 SELECTIVE INHIBITOR: RESULTS OF A PHASE 1 MONOTHERAPY DOSE ESCALATION STUDY IN SOLID TUMORS AND EVIDENCE OF TARGET ENGAGEMENT IN PATIENTS

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Background AVID200 is a rationally designed first-in-class receptor ectodomain trap that inhibits transforming growth factor-beta (TGF-beta) isoforms -beta1 and -beta3 with pM