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.

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Combination immunotherapies

P855

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

P856

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

potency. TGF-beta signaling is highly immunosuppressive in the tumor microenvironment and has been associated with immune checkpoint inhibitor resistance.¹⁻⁴ TGF-beta1 and -beta3 are most closely associated with cancer progression whereas TGF-beta2 is required for normal cardiac function and hematopoiesis. Accordingly, selective targeting of TGF-beta1 and -beta3 by AVID200 may improve the efficacy of immunotherapy while avoiding toxicities associated with earlier generations of non-selective TGF-beta inhibitors.

Methods This open-label, multicenter Phase 1 study (NCT03834662) evaluated safety, tolerability and dose-limiting toxicities (DLTs) of sequential escalating doses of AVID200 (Q3W IV) to establish the recommended Phase 2 dose. Patients with documented, locally advanced or metastatic solid tumors without other treatment options were eligible. The primary objective was safety and tolerability; secondary objectives included preliminary anti-tumor activity, pharmacokinetics (PK), and assessment of pharmacodynamic biomarkers indicative of target modulation. PK was assessed by enzyme immunoassay. Ability of AVID200 to selectively sequester and neutralize its target was assessed by TGF-beta quantification per ELISA, as well as cell-based IL-11 release functional evaluation of TGF-beta signal inhibition. In addition, phosphorylation of SMAD2, a downstream target of TGF-beta, was assessed by immunohistochemistry in skin biopsies at screening and Cycle 1, Day 4 (C1D4).

Results Enrollment to all planned cohorts is complete: A total of 13 patients with ECOG 0-1 received AVID200 across the three planned dose levels of 180 (N=7), 550 (N=3), and 1100 mg/m² (N=3) (~5, 15, and 30 mg/kg). The MTD was not reached. Grade 3 study drug-related AEs were reported in two patients (diarrhea, lipase elevation); no related Grade 4 or 5 AEs were observed. Serum exposure was dose-proportional. AVID200 sequestered circulating endogenous active TGF-beta at all dose levels. Moreover, AVID200 in patient plasma potentially neutralized TGF-beta1- and -3 - but not -beta2 - mediated signaling. SMAD2 phosphorylation in skin biopsies was detectably reduced at C1D4 across all dose levels. Three of nine patients evaluated for response had a best response of stable disease (SD), including one prolonged SD which was ongoing at six months at time of writing.

Conclusions AVID200 has been well tolerated as monotherapy and engaged its target in patients providing proof-of-principle that selective and potent inhibition of TGF-beta1 and -beta3 is feasible in the clinic. The results warrant evaluation of AVID200 in combination with anti-PD(L)1 and other anti-cancer therapies.

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Trial Registration Clinicaltrials.gov NCT03834662

Ethics Approval The study was approved by START-Midwest's IRB (approval number STMW2018.19), University Health Network's Research Ethics Board (approval number 18-6104), and The University of Texas MD Anderson Cancer Center's IRB (approval number 2018-1079).

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Immune-stimulants and immune modulators

P857

ONM-500 – A NOVEL STING-ACTIVATING THERAPEUTIC NANOVACTION PLATFORM FOR CANCER IMMUNOTHERAPY

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Background Efficacy of cancer vaccines requires the induction of tumor antigen-specific cytotoxic T-lymphocytes (CTL) to effectively clear established tumors. Orchestration of antigen presentation, co-stimulatory signaling, and innate cytokine signals are necessary steps for tumor-specific T-cell activation. The ONM-500 nanovaccine platform¹⁻² utilizes a novel pH-sensitive polymer that forms an antigen-encapsulating nanoparticle and functions both as a carrier for antigen delivery of both peptide and protein antigens to dendritic cells and acts as an adjuvant, activating the stimulator on interferon genes (STING) pathway and generating a CD8+ CTL response. Peptide antigens have translational challenges due to complex formulations and/or HLA-type-specific antigen sequence recognition, processing and presentation. Full-length protein antigens alleviate HLA subtype limitation, allowing coverage of multi-immunogenic T cell epitopes in patients. Pairing ONM-500 adjuvant with the full-length E6 and E7 oncoproteins from human papillomavirus (HPV) cancers shows great potential to treat HPV-associated cancer in patients.

Methods Based on the previously demonstrated STING-dependent T cell activation by ONM-500 [1], the nanovaccine was formulated with full-length HPV16 E6 and E7 proteins (recombinant), and the nanoparticle properties and antigen loading were characterized. In vivo lymph node accumulation following subcutaneous administration was evaluated using fluorescent nanovaccines. Direct binding of ONM-500 to

Abstract P857 Figure 1