1135PD Characterization of the immune tumor microenvironment (TME) to inform personalized medicine with immuno-oncology (IO) combinations


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Methods: The Cancer Genome Atlas (TCGA) RNA data (melanoma, NSCLC, RCC, UC, SCCHN, GEJ) were normalized and grouped as inflamed (INF), intermediate (INT), or non-INF. Binary associations of PD1 with IO targets (LAG3, IDO1, FOXP3, GITR, CSF1R, KIRDL1, CTLA4) were studied. Unsupervised clustering and pt-level gene expression profiling (GEP) were performed. A separate set of tumors was analyzed by IHC (N = 128). IHC results were integrated into an algorithm for IO combination selection.

Results: TCGA analysis showed associations of IO targets and PD1 (mean Pearson r = 0.62 ± 0.03; P < 0.0001). Unsupervised clustering revealed discrete groups of INT tumors with high T-cell energy, regulatory T cell, or myeloid signatures. Pt-level GEP showed INT/low-PDL1 tumors as most likely to have outlier IO targets suggestive of functional relevance. IHC showed clustering of IO targets by INF level, with outliers in INT/low-INF tumors and variability by tumor type. Observations were verified by selected IHC markers showing significant association of expression level and INF score: IDO1, LAG3 (non-INF vs INT P = 0.17–1.9E-04; INT vs INF P = 0.001–0.03); FOXP3, GITR, NKp46 (INT vs INF P = 0.001–0.049). CSF1R did not show significant associations. These data aided in the design of the ADAPt1Ve biomarker trial that InformS Evolution of therapy (ADVISE, NCT03335540), where prospective treatment selection (nivolumab + second IO agent) is driven by analysis of pretreatment biopsies. Initial clinical implementation will also be presented.

Conclusions: Translational data reveal potentially actionable biomarkers, which are being assessed in the ongoing ADVISE trial as an initial clinical foray into personalized IO therapy.

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