184 DISTINCT IMMUNOTHERAPY IMMUNE RESPONSE PHENOTYPES IN NON-SMALL CELL LUNG CANCER PRESENT WITH UNIQUE GENOMIC ALTERATION PROFILES

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Background Biomarkers for predicting response to immune checkpoint inhibitors (ICPIs) in non-small cell lung cancer (NSCLC) are currently limited to PD-1/PD-L1 expression and tumor mutational burden (TMB), but these markers do not capture the full complexity of the tumor microenvironment (TME) and immune escape mechanisms. We have previously described immune gene expression signatures that characterize the TME including tumor immunogenic score (TIGS), cell proliferation (CP), and cancer testis antigen burden (CTAB). By integrating PD-L1, TMB, TIGS, CP, and CTAB with patient outcome data, we were able to classify NSCLC tumor samples into four immune response phenotypes (IRPs) that had differing responses to ICPIs: tumor dominant (CTAB/CP/TMB high), proliferative (CP high), inflamed (TIGS high), and checkpoint (TIGS/PD-L1/TMB high). Although we have previously characterized the immune gene expression and response to ICPIs of these four IRP groups, their underlying genomic alterations have yet to be described. Here, we performed an analysis to characterize the genomic features that are enriched in each IRP group.

Methods IRPs were defined previously using a discovery cohort of 5,450 real world FFPE tumors of 37 histologies tested by comprehensive genomic and immune profiling. Mutations, copy number alterations (gain/loss) and TMB were assessed with DNA-seq, while gene fusions and immune gene expression were assessed with RNA-seq. We extracted data for 2,202 NSCLC patient tumors from the discovery cohort and tested for differences in genomic alteration frequencies between the four IRP groups using Fisher's exact test. Multiple testing corrected p-values <0.05 were considered significantly different.

Results Tumor-dominant phenotype tumors had the highest number of significantly enriched alteration frequencies including *TP53*, *STK11*, *PIK3CA*, *CDKN2A* mutations, *EGFR* exon 1 and 8 fusions, and *APC*, *KIT*, *MYCL*, *PIK3R1*, and *SOX2* copy number variants. Proliferative phenotype tumors were mostly enriched for copy losses in *BRCA2*, *FBXW7*, *TET2*, *RB1*, *PTCH1*, and *BAP1*. Inflamed phenotype tumors had higher frequencies of *EGFR* L858R mutations. Checkpoint phenotype tumors had higher frequencies of *KRAS* G12C and G12V and *BRAF* V600E mutations.

Conclusions In NSCLC, all IRPs were found to be significantly enriched for distinct genomic alterations (GAs), with the tumor-dominant phenotype having the highest number of enriched GAs. Enriched alterations are in line with the gene expression-based phenotypes of each sub-group and provide additional insight into the mechanisms underlying the previously described differential response to immunotherapy.

Ethics Approval Ethics approval for this study was obtained from WCG IRB (Study #1340120), an independent institutional review board, including waiver of informed consent.

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