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COMPLEX MARKERS OF SURVIVAL FROM PEMBROLIZUMAB: THE POTENTIAL PREDICTIVE ROLE OF TUMOR MUTATIONAL BURDEN (TMB) AND KRAS

Yong Hee Lee*, Carrie Hoefer, Paul DePietro, Mary Nesline. *OmnSeq, Buffalo, NY, USA*

Background Pembrolizumab, with or without chemotherapy, is NCCN guideline-recommended treatment for NSCLC cancer patients depending on tumor PD-L1 status by IHC. PD-L1 IHC provides guidance for treatment selection for response, but does not accurately predict survival benefit from pembrolizumab. Emerging evidence suggests TMB and other genomic markers (KRAS, STK11, TP53 mutations), may have clinical utility for predicting survival benefit.

Methods We identified a cohort of metastatic EGFR/ALK wild type NSCLC patients (n=116) whose tumors underwent comprehensive profiling (June 2017-March 2019) for genomic variants, TMB and PD-L1 IHC 22C3 prior to selection of pembrolizumab (n=43), pembrolizumab + chemotherapy (n=41), or chemotherapy only (excluding subsequent targeted therapy or immunotherapy) (n=32) at Roswell Park Comprehensive Cancer Center, with at least one year of follow up. TMB was assessed using a 1.75 Mb capture of 409 oncogenes with full exon coverage (DNA-Seq), with 'high' TMB interpreted as ≥ 10 mutations/Mb. Electronic pharmacy records were curated to create pre and post-test treatment histories for each patient. Cox regression analysis evaluated OS with pembrolizumab monotherapy or pembrolizumab + chemotherapy vs chemotherapy only, adjusting for covariates including oncogenic driver mutations, TMB, PD-L1 IHC demographics, clinicopathologic characteristics, prior treatment, and performance status. Using the same model, we then assessed overall survival for each treatment group by TMB, KRAS, STK11, and TP53 mutant status.

Results Overall, 47% of tumors were PD-L1 high, 47% TMB high, 34% KRAS mutant (codons 12, 13, 60, 61), 52% TP53 mutant and 16% STK11 mutant. As expected, pembrolizumab with or without chemotherapy significantly improved overall survival (OS) compared to chemotherapy alone; with TMB, smoking, and ECOG status identified as significant covariates. PD-L1 IHC status was not associated with OS for any treatment. TMB high status was significant for OS benefit with pembrolizumab either as monotherapy [HR=0.02; CI=0.01–0.40; p=0.01] or in combination with chemotherapy [HR=0.20; CI=0.04–0.95; p=0.04]. KRAS mutant status was independently significant for OS benefit from pembrolizumab + chemotherapy [HR=0.01; CI=0.01–0.79; p=0.04] but not for pembrolizumab monotherapy or chemotherapy alone. Among patients who received pembrolizumab monotherapy, there was a trend toward increased risk of death in those with STK11 mutations [HR=17.54; CI=0.35–1,000; p=0.15], whereas TP53 mutant status trended toward survival benefit [HR=0.18; CI=0.02–1.53; p=0.11].

Conclusions Data comparing pembrolizumab treatments with chemotherapy and independent marker associations suggest TMB has predictive power for determining overall survival benefit from pembrolizumab, while KRAS, STK11, and TP53 mutational status demonstrated potential prognostic relevance for NSCLC.

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B-CELL RECEPTOR HEAVY CHAIN REPERTOIRE PROFILING USING AN AUGMENTED TRANSCRIPTOME

Eric Levy*, Pamela Milani, Gabor Bartha, Charles Abbott, Robert Power, Rena McClory, Robin Li, John West, John Lyle, Sean Boyle, Richard Chen. *Personalis, Inc., Menlo Park, CA, USA*

Background Comprehensive profiling of the tumor and tumor microenvironment (TME) is a critical tool for furthering our understanding of tumor progression and response to treatment, including immunotherapies. To address this challenge, we developed an augmented, immuno-oncology-optimized exome/transcriptome platform, ImmunoID NeXT™, which provides a more comprehensive view of the tumor and TME from limited FFPE tumor biopsies. We have recently added the ability to profile the B-cell receptor (BCR) heavy chain. Here, we show that ImmunoID NeXT is now able to accurately and reproducibly profile abundant B-cell clones and provide information on the diversity of B-cells in tumor samples.

Methods We analyzed multiple replicates of PBMCs to examine the reproducibility of BCR sequence identification using ImmunoID NeXT. Utilizing a standalone BCR sequencing approach, we further evaluated the concordance of top clones to those identified by ImmunoID NeXT. In addition, we analyzed the reproducibility of BCR sequences in patient-derived FFPE samples. Finally, we used ImmunoID NeXT to profile the B-cell clonal diversity across over 500 solid tumor samples.

Results Reproducibility in PBMC samples was very high, with abundances of clones shared between replicates being very concordant ($R^2 > 0.92$, $R^2 > 0.86$, and $R^2 > 0.97$ for IgG, IgM, and IgA, respectively). When comparing to a standalone BCR sequencing method that profiles IgM and IgG, we observed highly concordant abundances ($R^2 > 0.72$ and $R^2 > 0.82$ in IgM and IgG, respectively), as well as strong overlaps of top clones. When comparing subsequent curls of a tumor FFPE sample, we also achieved a high concordance of clonal abundances ($R^2 > 0.92$, $R^2 > 0.93$, and $R^2 > 0.76$ for IgG, IgM, and IgA, respectively). Finally, we observed differences in clonal diversity of B-cell repertoires across over 500 solid tumor samples.

Conclusions We demonstrate that ImmunoID NeXT can be used to reproducibly, sensitively, and accurately profile high-abundance BCR heavy chain clones, including coverage of all major isotypes. In addition, we show how ImmunoID NeXT can profile the diversity of the BCR repertoire across a variety of tumor samples. Combined with the platform's TCR profiling capabilities, ImmunoID NeXT can provide insight into the diversity of the immune repertoire, contributing to its ability to provide comprehensive analysis of both the tumor and TME from a single FFPE sample.

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THE PROGNOSTIC AND PREDICTIVE IMPLICATIONS OF THE 12-CHEMOKINE SCORE IN MUSCLE INVASIVE BLADDER CANCER

¹Roger Li*, ¹Logan Zemp, ¹Anders Berglund, ¹Jasreman Dhillon, ¹Ryan Putney, ¹Youngchul Kim, ¹Rohit Jain, ¹Daniel Grass, ¹Jingsong Zhang, ¹Michael Poch, ¹Julio Pow-Sang, ¹Wade Sexton, ¹Scott Gilbert, ¹Shari Pilon-Thomas, ¹José Conejo-García, ²Colin Dinney, ¹James Mulé. ¹H. Lee Moffitt Cancer Center, Tampa, Florida, USA; ²MD Anderson Cancer Center, Houston, TX, USA

Background Emerging evidence from studies in sarcoma and melanoma immune checkpoint blockade (ICB) trials