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

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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 and 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


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 biospecimens. 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. Using 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 (R²>0.92, R²>0.86, and R²>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 (R²>0.72 and R²>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 (R²>0.92, R²>0.93, and R²>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

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Background: Emerging evidence from studies in sarcoma and melanoma immune checkpoint blockade (ICB) trials...
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1. demonstrated enhanced efficacy in tumors harbouring tertiary lymphoid structures (TLS)\(^1–3\) - lymph node like aggregates in the tumor microenvironment postulated to recruit lymphocyte infiltration and coordinate tumor antigen presentation and lymphocyte priming. Previously, our group described a 12-chemokine metagene signature that reflects strong intratumoral chemotactic signalling and accurately predicts the presence of TLS in colorectal carcinoma.\(^4\) Grounded in these works, we attempted to correlate high 12CK signature with TLS formation in the context of muscle invasive bladder cancer (MIBC), and then sought to define its prognostic implications and its ability to predict response to ICB.

**Methods** A total of 130 MIBC samples were arrayed on Affymetrix microarrays and 12CK scores were assessed. Scores were normalized using 12CK>1 to denote 12CK-High (n=24). We then investigated the presence of TLS with the associated immune cellular infiltration evaluated by immunohistochemistry and gene signature deconvolution method (xCell).\(^5\)

12CK were also correlated with survival in our institutional cohort and validated using data from TCGA. Finally, 12CK scores were extracted from the IMVIGOR210 study to examine its ability to predict response to ICB.\(^6\)

**Results** Type III TLS, consisting of germinal center-like structures and discrete T-cell zones were found in 7/22 12CK-High vs. 0/21 12CK-Low tumors (p=0.009) (figure 1a). Additionally, a more robust immune-environment was seen in 12CK-High tumors, consisting of increased infiltration of CD4+ T lymphocytes (p=0.1), CD8+ T lymphocytes (p=0.02), activated dendritic cells (p=0.047), and B lymphocytes (p=0.006) on immunohistochemistry (figure 1b). Furthermore, on xCell deconvolution, M1 macrophage, NK cells, CD8+ Tem, CD4+ Tem, and memory B cells were enriched in 12CK-High tumors, suggesting both a heightened innate and adaptive immune response (figure 1c, d).

Kaplan-Meier survival analyses of our internal cohort revealed improved PFS (HR 0.25, p=0.003), CSS (HR 0.25, p=0.003), and OS (HR 0.55, p=0.03) amongst 12CK-High patients (figure 2a-c). From the TCGA, similar improvements were found in PFS (HR 0.55, p=0.007), CSS (HR 0.40, p=0.002), and OS (HR 0.59, p=0.01) in 12CK-High patients (figure 2d-f). From the IMVIGOR-210 study, complete responders exhibited significantly higher 12-CK scores than all other groups (figure 2g). Strikingly, the 12CK-High signature conferred a median overall survival benefit of almost 1 year in the atezolizumab-treated patients (figure 2h).

**Conclusions** In muscle invasive bladder cancer, 12CK-High scores corresponded with formation of TLS in the TME; favourable prognosis in surgically treated MIBC patients; and CR in atezolizumab-treated patients.

**REFERENCES**