MOLECULAR AND IMMUNOGENOMICS FEATURES ASSOCIATED WITH COMPLETE RESPONSE AND SURVIVAL AFTER NEOADJUVANT CHEMO-IMMUNOTHERAPY FOR MUSCLE-INVASIVE BLADDER CANCER

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Background Bladder cancer patients treated with immunotherapy have varied response and survival.1–3 In the Phase II LCCC1520 trial, neoadjuvant chemo-immunotherapy (pembrolizumab with gemcitabine plus cisplatin) induced pathologic complete response (pCR) in 14 of 39 muscle-invasive bladder cancer patients.4 In this correlative analysis, we identify molecular features associated with pCR and survival in patients with and without pCR.

Methods Associations of TMB, tumor neoantigens, antigen presentation, immune checkpoint gene expression, immune gene signature expression, and TCR repertoire diversity with response and survival were evaluated pre-and post-treatment. Predicted neoantigens were identified using the Landscape of Effective Neoantigens Software.5 25 patients with neoantigen data were divided into discovery (14 patients) and validation (11 patients) sets. Effective neoantigen count (ENC) was calculated by binning neoantigens by expression level score, binding affinity score, and normalized expression level, then identifying the subset in which neoantigen count was most strongly associated with pCR in the discovery set. Using elastic net modeling with 10-fold cross-validation, pCR was predicted from antigen presentation, immune checkpoint, and immune gene signature expression, TMB and ENC.

Results Pre-treatment features associated with pCR response included TMB (p=0.015) and PD-L1 expression (p=0.008); expression of antigen presentation genes TAP1 (p=0.009), TAP2 (p=0.013), B2M (p=0.018), and HLA-DRB1 (p=0.011); and signatures of T cell infiltration (p=0.005) and interferon gamma activation (p=0.001; figure 1). Pre-treatment TIGIT expression was associated with pCR (p=0.018), survival (p=0.026), and PD-1 expression (p=3.3E-5). Pre-treatment CD8+ TIGIT+ T cell percentage from flow cytometry was associated with complete response (p=0.048). ENC was calculated as the number of neoantigens with an expression level score above 90th percentile, a binding affinity below 90th percentile, and an upper quadrant normalized log2 TPM expression above 40th percentile. Pre-treatment ENC was positively associated with complete response in the discovery (p=0.036) and validation sets (p=0.042, ROC-AUC = 0.867, ROC-AUC p = 0.021; figure 2). The final elastic net model—comprised of HLA-DRB1 expression, Ayers IFNG signature, and ENC—predicted complete response in the validation set (p=0.017, ROC-AUC=0.933, ROC-AUC p=0.009). Post-treatment ENC (p=0.005) and TAP1 (p=0.003) and TAP2 (p=0.015) expression were negatively associated with survival among patients without complete response (figure 3).

Conclusions We identify pre-treatment and post-treatment features associated with response and survival in the LCCC1520 trial of pembrolizumab with gemcitabine plus cisplatin neoadjuvant therapy for muscle-invasive bladder cancer. Key features of a predictive model included neoantigen and antigen presentation estimates. We propose that tumor antigen presentation is a major driver of response and survival with neoadjuvant chemo-immunotherapy.

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REFERENCES

Ethics Approval The study was reviewed and approved by the institutional review boards at each participating institution and conducted in accordance with ethical principles per the Declaration of Helsinki.

Abstract 560 Figure 1 Pre-treatment features associated with complete response. Features associated with complete response include TMB (A) and PD-L1 expression (B); immunogenic signatures Ayers_T_cell_inflamed_GEP (C) and Ayers_IFNG (D); and expression of antigen presentation genes TAP1 (E), TAP2 (F), B2M (G), and HLA-DRB1 (H). Pre-treatment TIGIT expression is associated with complete response (I), survival (J), and PD-1 expression (K). Pre-treatment CD8+ TIGIT+ T cell percentage from flow cytometry is associated with complete response (L).
Abstract 560 Figure 2  Effective neoantigen count predicts complete response. Pre-treatment effective neoantigen count is positively associated with complete response in the discovery (A) and validation sets (B,C). The final elastic net model predicts complete response in the discovery (D) and validation (E,F) sets. The final model features, which also have beta coefficient confidence intervals not spanning zero in 10-fold cross validation, are Ayers_IFNG, HLA2 (HLA-DRB1), and effective neoantigen count (G).

Abstract 560 Figure 3  Features associated with survival in patients without complete response. From post-treatment sequencing data, effective neoantigen count (A) and TAP1 (B) and TAP2 (C) expression are negatively associated with survival among patients without complete response.