Tumor bulk-RNA seq identifies patients at high risk of progression in non-complete pathological responders

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Researchers from Spain have identified an immune expression signature in surgical specimens associated with disease progression for non-

complete pathological responders patients treated with neo adjuvant chemo-immunotherapy, which could help the follow-up and therapeutic management of these high-risk patients. The research was presented today at the IASLC 2022 World Conference on Lung Cancer in Vienna.

Pathological response is postulated as a surrogate for survival in patients treated with neoadjuvant chemo-immunotherapy. In this sense, non-complete pathological response (non-CPR) patients present higher risk of disease progression compared to complete pathological responders (CPR).

To identify gene expression patterns that may affect long-term outcomes in this high-risk group, a group of Spanish researchers, led by Marta Casarrubios, Instituto de Investigacion Sanitaria Puerta de Hierro-Segovia de Arana (IDIPHISA), Hospital Universitario Puerta de Hierro-Majadahonda, Spain, analysed surgical samples of non-CPR patients and characterized the differences between progressors and non-progressors.

Dr. Casarrubios and colleagues analyzed surgical tissue samples from 36 patients with resectable stage IIIA NSCLC from the NADIM trial (NCT03081689) were analysed. Tumor RNA was sequenced using the Oncomine Immune Response panel which targets 395 genes related to immunological processes. Differential-expressed genes (DEGs) between groups and pathway enrichment analysis were assessed using DESeq2 and Gene Set Enrichment Analysis (GSEA). CIBERSORTx was used to estimate the proportions of immune cells subtypes. Patients were classified into complete pathological responders CPR (n=22) and non-complete pathological responders (n=14). Patients with non-CPR were further categorized as progressors (P, n=5) or non-progressors (NP, n=9) depending on whether they had disease progression or not at 34.2 months from diagnosis. Values with the highest likelihood ratio from the ROC curve analysis were used as thresholds to categorize DEGs or immune cell subsets for each patient into high or low groups.

The researchers report that 22 genes were upregulated in non-CPR patients compared to CPR, most of them related to proliferation (CDKN3, CCNB2, KIAA0101, MKI67, BUB1, CDK1, TOP2A, FOXM1, MELK, MAD2L1), tumor markers (CDKN2A, KRT5, BRCA1,TWIST1), among others (MAGEA3, CEACAM1, CXCL8, TNFRSF18, G6PD, HMBS, DGAT2, ISG15). Further GSEA analysis showed an upregulation of pathways related to antigen processing, TCR coexpression and lymphocyte infiltrate in CPR patients. Non-CPR patients showed an upregulation of proliferation, tumor marker, interferon signaling, housekeeping and tumor antigen pathways. Regarding differences between P and NP, 10 genes were identified as differentially upregulated in P patients: IFI6 and OAS3, involved in interferon signaling; AKT and KRT7 as tumor markers; BST2, ISG15 and IFI27 involved in type I interferon signaling as well as, CD8B, SDHA, HMBS and OAS1. Higher levels of IFI6 (p=0.010), BST2 (p=0.010), CD8B (p=0.019), AKT (p=0.033), OAS3 (p=0.010) and IFI27 (p=0.010) in post-treatment samples of non-CPR patients were associated with lower progression-free survival (PFS). In addition, higher levels of HMBS (p=0.018) and AKT (p=0.003) were associated with lower overall survival (OS).

Patients with high AKT expression present a higher risk of progression (HR: 10.31; 95%CI 1.2-88.8) and death (HR:50.6; 95%CI 3.77-680.5). The median PFS for patients with high AKT was 12.3 months (95%CI 0-32.6) and not reached for those with low AKT. No differences were observed between P and NP patients in the estimated cell proportions. However, higher proportion of activated dendritic cells or neutrophils in non-CPR patients were associated with lower PFS (p=0.019, p=0.053) and OS (p=0.033, p=0.003), respectively.

"The upregulated pathways in surgical samples of CPR patients suggests that an effective immune response to PD-1 blockade was done," said Dr. Casarrubios. "Additionally, we have identified an immune expression

signature in surgical specimens associated to disease progression for non-CPR patients which could help in the follow-up and therapeutic management of these high-risk patients."

Provided by International Association for the Study of Lung Cancer

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