782-G THE CORRELATION OF TUMOR IMMUNE MICROENVIRONMENT WITH RESPONSE TO NEOADJUVANT CHEMOTHERAPY RESPONSE IN UNDIFFERENTIATED PLEIOMORPHIC SARCOMAS: AN ANALYSIS OF THE NEOSARCOMICS STUDY

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Background Undifferentiated pleiomorphic sarcoma (UPS) is the predominant and most aggressive subtype of soft tissue sarcoma (STS). Patients with high-grade UPS frequently undergo anthracycline-based neoadjuvant chemotherapy (NACT). Our recent multidimensional analysis revealed two distinct UPS entities differentiated by immune phenotypes, prognostic implications, and molecular characteristics.[1] This study aimed to discern the relationship between the tumor microenvironment and the histological response to NACT, as well as the influence of neoadjuvant chemotherapy on the tumor immune microenvironment (TIME) in UPS patients.

Methods 31 participants with UPS from the NEOSARCOMICS study (NCT02789384) underwent six cycles of standard neoadjuvant chemotherapy (doxorubicin combined with ifosfamide). A favorable histological response was identified by the presence of less than 10% viable tumor cells in the surgical specimen. Tumor microenvironment analysis incorporated RNA sequencing (using deconvolution analysis) and multiplex immunofluorescence. Plasma proteomic profiling employed the Olink technology as we previously described.[2]

Results 13 patients (41%) had good histological response. Transcriptomic analysis of the pre-NACT tumor samples revealed a differential expression of 1574 genes between NACT responders and non-responders. Immunity pathways were predominantly observed in the NACT-resistant group, while the E2F signaling pathway was more pronounced in sensitive tumors. To delineate immune cell disparities between these groups, we used a six-color IHC panel, identifying T cells, B cells, and myeloid cells, including tumor-associated macrophages. Notably, CD8+ T cells and myeloid cells were significantly more abundant in patients with resistant tumors (CD8 T cells: 301/mm² vs 47/mm², p=0.002; CD45+CD14+ cells: 670/mm² vs 118/mm²), corroborating the RNA-seq findings. Plasma proteome analysis before NACT onset confirmed activation of immunity and downregulation of cell cycle pathways in non-responders and identified specific cytokines associated with NACT response and outcomes.

Conclusions Our findings suggest that the immune composition of TIME could be a predictive biomarker for NACT response in UPS. Specifically, the higher infiltration of CD8+ T cells and myeloid cells as well as the activation of immunity and downregulation of cell cycle pathways are linked to reduced NACT effectiveness.

Trial Registration NCT02789384

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Ethics Approval NEOSARCOMICS obtained ethics approval by the CPP Bordeaux Sud Ouest. All patients gave informed consent.

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