460 **SPATIAL DISTRIBUTION OF INFILTRATING T LYMPHOCYTES WITH IMMUNOSCORE® CR T CELLS EXHAUSTION TEST HELPS STRATIFICATION OF NSCLC PATIENTS TREATED WITH PD1/PDL1 INHIBITORS IN THE PIONEER PROJECT**

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Background PD1/L1 Immune Checkpoint Inhibitors (ICI) have significantly improved long-term outcome in about 20% of advanced Non Small Cells Lung Cancer (NSCLC) patients (pts), but 80% present primary or secondary resistance. The PIONeeR project (NCT03493581) aims to predict the response/resistance to PD1/L1 ICIs in advanced NSCLC pts through a comprehensive agnostic multiparametric and longitudinal biomarkers assessment. Data presented here are a focus on the quantification of tumor infiltration by lymphocytes, their activation as potential markers of the resistance to treatment by ICI.

Methods Advanced NSCLC pts with available archived tumor tissue at screening visit (VS), treated with standard PD1/L1 ICIs (nivolumab, pembrolizumab or atezolizumab), alone (2nd line or more) or combined with chemotherapy (1st line), were re-biopsied at 6 weeks (V2) of treatment. PD1/L1 ICIs overall response rate (ORR) was assessed by RECIST 1.1 every 6 weeks. The multiplex IHC test "Immunoscore® CR T Cells Exhaustion" (IS TCE) quantifies cytotoxic lymphocytes expressing three checkpoints: PD1, LAG3, TIM3, extrapolating their exhaustion status, both in the stroma and parenchyma. The unsupervised neural-network-based machine learning algorithm SOM (Self-Organizing Maps) was used to classify samples based on the 27 IS TCE variables. Statistical significance of survival differences between groups was evaluated using the log-rank test.

Results Among the first 100 pts, (male (64%), smokers (91,8%), <70yrs (69%), with an ECOG PS0/1 (97%), treated in 2nd line setting (86%)), 79 VS + 30 V2 biopsies were tested with IS TCE. SOM clustering highlighted four distinct clusters: a group with moderate T-cells infiltration (group 1), hot tumors with high T cells infiltration in both stroma and parenchyma (group 2), cold tumors with very low T cells infiltration (group 3), and finally, a highly distinguishable group with important T-cells density in stroma only (group 4). None of the 11 responders was present in the Group 3, "Cold" cluster. The four groups presented different Progression Free Survival (PFS) rates (p=5,2e-4) with better relapse-free survival Groups 1 and 2. Additionally, V2/VS ratios showed lymphocytes recruitment induced by the treatment in parenchyma only: no significant lymphocytes recruitment was observed in the stromal compartment. Interestingly, the most recruited lymphocyte populations expressed PD1.

Conclusions IS TCE test may help stratifying and predicting responders to anti PD1/L1 therapy through checkpoint expressing lymphocytes quantification and spatial distribution. Additional tests performed on the PIONeeR cohort to explore other aspects of the immune response to cancer should complete these results.

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Ethics Approval The study is conducted in accordance with Good Clinical Practice and the French applicable regulatory requirements (Public Health Code, article L.1121-1/La loi n° 2012–300 du 5 mars 2012 relative aux recherches impliquant la personne humaine (dite loi Jardé), the applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinski. The study was approved by the French Ethic Committee, CPP Ouest II - Angers, ref. CPP: 2028/08, Ref ANSM (French competent authority) 2018020500208, 2018072600120, 2019083000148. Freely given written informed consent was signed and obtained from each individual participating in the study, before any study specific procedure was undertaken and after the provision of information about the study by the investigator during a physician-patient consultation and sufficient time for reflection.

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