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Pioneer Study: Precision Immuno-Oncology for Advanced Non-Small Cell Lung Cancer Patients with PD1/L1 ICI Resistance

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Background : In the management of advanced Non-Small Cell Lung Carcinoma (NSCLC), both PD1/L1 immune checkpoint inhibitors (ICIs) have been shown to increase overall survival (OS) over standard second-line chemotherapy. While this long-term increase in OS is driven by about 20% of patients, others display disease progression during the first weeks (w.). PIONeeR aims to understand, through a strategy based on a comprehensive biomarkers assessment, and overcome, through rescue IO strategies, the resistance to ICIs. **Method** : Stage IV or recurrent NSCLC patients (n=450), with an archived pre-ICI tumor block, planned for a standard 2nd or 3rd line ICIs monotherapy, will be screened. If eligible, after signing an informed written consent, they will be blood-sampled, every cycle throughout the 18 w. post C1D1, and systematically be re-biopsied (primitive or metastasis tumor) at 6 w. of treatment. Efficacy of ICIs will be assessed by RECIST, after 6, 12 and 18 w. Feces will be self-collected by patients, before and during ICIs, to analyze impact of gut microbiome in resistance to ICIs. Characterization of the specific immune contexture of each patient to potentially predict the efficacy of ICIs will be based on the investigation of tumors and their microenvironment (Immunoscore[®] IC & Multiplex ImmunoHistoChemistry, Tumor Mutational Burden eT cell clonality- ctDNA investigation), effector immune cells, cytokines and endothelial activation (ELISA-Flow cytometry). Protocol's legal and ethical authorizations were obtained on February 2018 (NCT03493581), patient inclusions were enhanced on April 2018 with the activation of 3 main centers ; 10 satellites centers were opened at Q4 2018, inclusions are expected to be completed at Q4 2020. Patients who will progress between 6 and 18 w. (n=150) will be randomized within a precision immuno-oncology experimental masterprotocol using a Bayesian, adaptive design (4 combinations of PDL1i and NKG2Ai, STAT3i, ATRi or CD73i or a control arm). Legal authorizations were obtained on December 2018 (NCT03833440), the inclusion period is expected to last 24 months, from the beginning of Q2 2019. Descriptive

statistics will be used to characterize distributions of marker's expression and to evaluate their predictive value on treatment response and prognostic value on Progression Free Survival., in both protocols. The primary endpoint of the randomized clinical trial is the 12-week Disease Control Rate, assessed in each arm of treatment. **Result** : Section not applicable **Conclusion** : Section not applicable **Keywords** : primary resistance, predictive biomarkers, PD1/L1 inhibitors.