PIONEER STUDY PRECISION IMMUNO-ONCOLOGY FOR ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS WITH PD1/L1 ICI RESISTANCE

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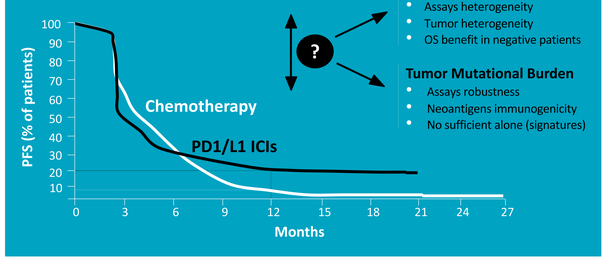
THE PIONEER PROJECT

Background

In the management of advanced Non-Small Cell Lung Carcinoma (NSCLC), PD1/L1 Immune Checkpoint Inhibitors (ICIs) have been shown to increase Overall Survival (OS) over standard 2nd-line chemotherapy (CT). While this long-term increase in OS is driven by about 20% of patients, others display disease progression during the first weeks.



PDL1 tumor expression
- Assays heterogeneity
- Tumor heterogeneity
- OS benefit in negative patients

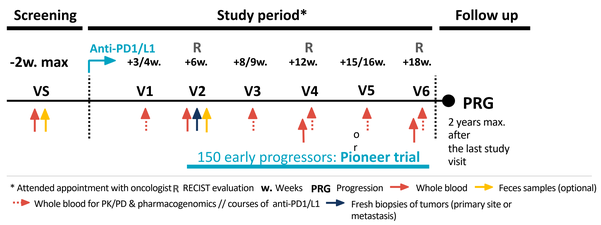
Tumor Mutational Burden
- Assays robustness
- Neoantigens immunogenicity
- No sufficient alone (signatures)

Challenge

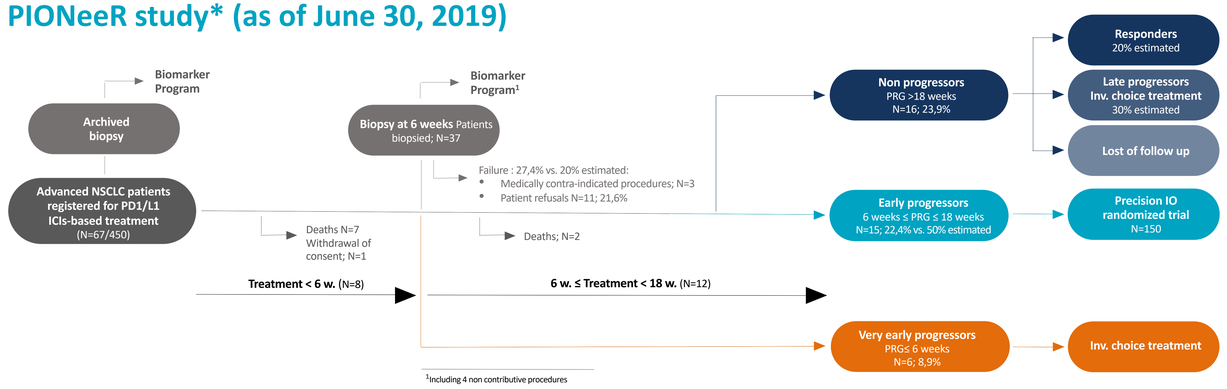
- **Understand** biological background behind resistances to ICIs through a comprehensive multiparametric biomarkers strategy (PIONeeR biomarkers program).
- **Overcome** resistances through clinical assessment of rescue IO combinations (PIONeeR randomized trial).

PIONeeR biomarkers program (design)

N= 450 patients with stage IV or recurrent NSCLC, eligible if:
- Archived pre-ICI tumor block available.
- Planned for 1st line PD1/L1 ICIs-CT combo or 2nd/3rd line PD1/L1 ICIs (Nivolumab, Pembrolizumab or Atezolizumab).



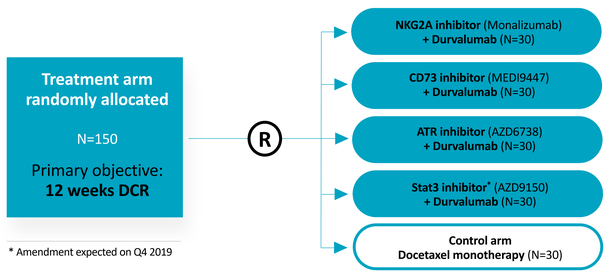
PIONeeR study* (as of June 30, 2019)



*Descriptive statistics in both protocols: distribution of markers' expression, evaluation of predictive value on treatment response and evaluation of prognostic value on PFS.

PIONeeR randomized umbrella trial

NCT03833440: FPFV: July, 2019 (inclusion on, 24 months); LPLV: Q4 2022, 3 centers in France.

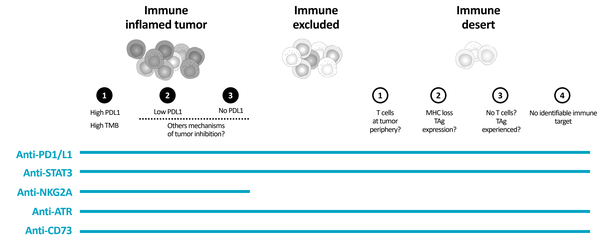


* Amendment expected on Q4 2019

Primary endpoint: DCR at 12 weeks

- Valuable way to early assess the activity of the combination regimens in a metastatic setting.
- Relevant target to overtake with combo in advanced NSCLC patients progressing on 1st line or 2nd line PD1/L1 ICIs-based therapies: 12-w DCR is low (10%) with standard 3rd line CT.

Potential rescue pathways targeted by drugs investigated in the umbrella trial

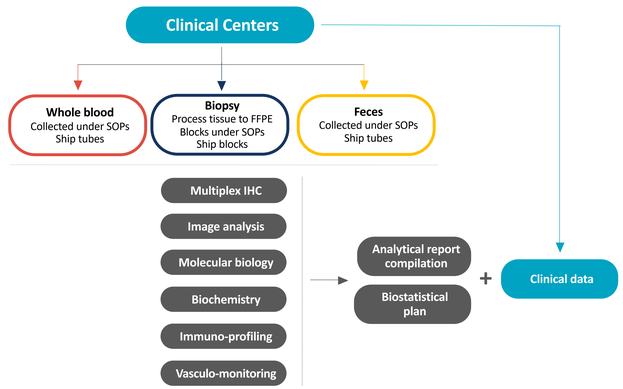


Bayesian design

- **Adaptive** : quickly stop arms without evidence of efficacy (futility rules) and/or select promising arms (efficacy rules).
- **Interim analyses** : after 10 patients included/arm, then every 5 patients/arm.

PIONeeR biomarkers program (logistics)

NCT03493581: FPFV: April, 2018.
LPLV: Q4 2020, 3 centers & 10 satellites in France.



Multiparametric biomarkers analysis

- **Blood:** circulatory immune effector cells, cytokines, endothelial activation, PK-PD relationships
- **Tumors & Microenvironment:** immunomodulatory status (dual/multiplex IHC, digital pathology: Immunoscore® IC, Brightplex), tumor foreignness (NGS: TMB, T cell clonality); immune profile (RNAseq)
- **Feces:** impact of gut microbiome in ICIs resistance.

Next steps

- **1st administration** within the PIONeer trial (Q3 2019).
- **New centers** in France (Q3-Q4 2019).

References

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- Herbst R et al. ESMO IO 2018
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