The Pioneer Project at the SITC 2022 Annual Meeting

The Pioneer Project [1], a major international Hospital-University Research (RHU) project that addresses the critical challenge of resistance to PD-1/L1 immune checkpoint inhibitors (ICIs) in advanced non-small cell lung cancers (NSCLC), presented 2 posters at the SITC 2022 Annual Meeting, one focusing on the biomarker component of the study (to predict primary or secondary resistance to PD-1/L1 inhibitors), the other one on the exploratory program (to uncover new pathways that might rescue immune checkpoint inhibitor resistance in pre-clinical settings).

Interim data on the signature of Early Progression on 2nd line patients included in the biomarker component of The Pioneer Project, has been presented at AACR 2022 annual meeting. Upcoming interim data presentation on clinic-biological data will occur at the ESMO Immuno-Oncology Congress 2022 (Geneva, Switzerland, 7-9 December 2022) with a mini-oral presentation featuring Prof. Fabrice BARLESI on Thursday, Dec 8, 2022, 14:40 - 14:45 CET, in room B: “Comprehensive biomarkers (BMs) analysis to predict efficacy of PD1/L1 immune checkpoint inhibitors (ICIs) in combination with chemotherapy: a subgroup analysis of the Precision Immuno-Oncology for advanced Non-Small CELL Lung CancER (PIONeeR) trial (ID 345)”.

Poster presented at SITC 2022:

Title: Brightplex® TCE and Brightplex® MDSC assays combination improve advanced NSCLC patient stratification under anti-PD1/L1 immunotherapy in the PIONeeR project
Presenter: Jacques Fieschi, PhD, Veracyte
Date/Time: November 10, 2022, 9:00 a.m.-9:00 p.m. ET
Poster #: 701

Title: Anti-HVEM mAB therapy improves antitumoral immunity both in vitro and in a novel mice model expressing human HVEM and BTLA molecules using HVEM expressing tumors
Presenter: Laurent Gorvel, PhD, CRCM
Date/Time: November 10, 2022, 9:00 a.m.-9:00 p.m. ET
Poster #: 1107 (Eposter only)

[1] Precision Immuno-Oncology for advanced Non-Small Cell Lung Cancer Patients with PD1(L1) ICI Resistance.
Biomarker data presented at SITC 2022:

We previously showed (SITC 2021) that quantifying T-lymphocytes within tumor stroma and parenchyma respectively with Brightplex® T-Cell Exhaustion assay highlighted 27% of patients with no infiltration that would not benefit from PD1/L1 ICIs.

Here, we hypothesize that myeloid cells evaluation through Brightplex® Myeloid-Derived Suppressor Cells (MDSC) assay [2] may refine the stratification of these advanced NSCLC patients regarding PD1/L1 benefit.

Brightplex® T-Cell Exhaustion assay applied to PDL1 <50% patients confirmed the four previously described Spatial Tumor-infiltrating lymphocytes (TILs) subtypes with association to progression free survival (PFS): Cold, Stromainfiltrated, Parenchyma Hot and Hot subtype.

Brightplex® MDSC assay refines this stratification, particularly in Parenchyma Hot and Stromainfiltrated subtypes through tumor myeloid cells spatial distribution. Myeloid lineage couldn't help to the TILs Hot subtype stratification.

Cell populations associated to poor prognostic were opposite in Parenchyma Hot and Stromainfiltrated subtypes. This strengthens the hypothesis that immune cells spatial distribution within the tumor compartments is crucial and may reveal different immune pathways in tumors to be considered to explain ICI resistance.

Finally, we propose a classification based on three assays including PDL1 IHC to guide patients regarding PD1/L1 ICIs administration:

- 41% of patients identified with these tests would not benefit of PD1/L1 ICIs
- 17% of patients present PDL1 ≥ 50% and benefit of PD1/L1 ICIs
- Within the 42% of unclassified patients, the median PFS is better than in the general population (6.3 months vs 5.4). This population of patients still needs to be explored and better stratified through additional biomarkers.

New pathways data presented at SITC 2022:

HVEM, or TNFRSF14, is a TNF-receptor family member largely expressed by healthy immune and non-immune cells and participates to immune homeostasis. HVEM is expressed on immune cells and also upregulated in numerous solid and hematologic malignancies such as melanoma, digestive cancers or breast cancer. HVEM network of interactors is complex and induces either cell activation or inhibition. Indeed, HVEM binding to BTLA (B and T lymphocyte attenuator) and CD160 (BY55) triggers co-inhibitory signals whereas LIGHT (TNFSF14) and Lymphotoxin-α (LTα) are co-stimulatory ligands. Like PD-1 and CTLA-4, BTLA is an important co-inhibitory receptor expressed by B and T cells. Therefore, targeting the HVEM-BTLA axis is a promising but complex immunotherapy strategy.

Here, we propose a preclinical study of both CIS and TRANS effects of the anti-HBaxis mAb on the activation of the immune system against tumor cells in vitro and in a cutting edge humanized BTLa and HVEM syngeneic mouse model for tumor growth control assays. Anti-HBaxis mAb treatment demonstrated that anti-tumor immune response was strengthened, delayed tumor growth or eradicated tumors and induced a tumor specific memory immune response in pre-clinical mouse model. Therefore, HVEM-BTLA axis targeting is a great addition to the available arsenal of immunotherapies.

This work benefits from a government grant handled by the French National Research Agency (ANR) as part of the France 2030 investment plan, under the reference ANR-17-RHUS-0007. A partnership of AMU, AP-HM, CNRS, Inserm, Centre Léon Bérard, InstitutPaoli-Calmettes, Gustave Roussy, AstraZeneca, Veracyte, Innate Pharma & ImCheck Therapeutics, sponsored by AP-HM and initiated by Marseille Immunopole. Drug supply when applicable is funded by AstraZeneca.

The Pioneer Project at a glance

In search of robust biomarkers to predict primary or secondary resistance to PD-1/L1 inhibitors, The Pioneer Project has undertaken the study of over 400 comprehensive agnostic and longitudinal biological parameters in advanced NSCLC patients treated with anti-PD-1/L1 immunotherapy. While the biomarker component of The Pioneer Project progresses to understand and predict the resistance to ICIs, an umbrella clinical trial, which includes several combination immunotherapies for patients that progress under anti-PD1/L1, is currently recruiting patients, aiming to overcome these resistances. Finally, the study also includes an exploratory program to uncover new pathways that might rescue immune checkpoint inhibitor resistance in pre-clinical settings.

Winner of the 3rd University-Hospital Research in Health call for projects in the “France 2030” program, this major international research project, called The Pioneer Project, was launched in November 2017. This 6-year [3] project is coordinated by Fabrice BARLESI, Professor of Medicine at Université Paris-Saclay, DG of Gustave Roussy Institute and co-founder of the French cluster Marseille Immunopôle. As of October 31, 2022, 482 patients have been screened, of which 438 have entered the biomarker component of the project (97.3% of total inclusions). In parallel, 109 patients have been screened for and 75 have entered the PIONeeR umbrella clinical trial (62.5% of total inclusions). A 1 year-extension of the inclusion period has been allowed to make possible the objective of 150 patients included in the umbrella clinical trial triggering an additional 1 year-extension of the whole project.

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[3] Initially a 5-year project. Extension period granted, notably linked to the Covid crisis.

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