Immunogram to decipher PD1/L1 ICI resistance: a proof of concept in advanced NSCLC patients of the PIONeeR Project

Florence Monville[1], Frédéric Vély[3,4], Joseph Ciccolini[2,3], Florence Sabatier[2,3], Stéphane Garcia[2,3], Vanina Leca[1], Marion Fabre[2], Christelle Piperoglou[3], Pernelle Outters[1], Laurent Arnaud[3], Laurent Vanhille[1], Caroline Laugé[1], Anna Martirosyan[1], Aurélie Collignon[1], Marie Roumieux[2], Julien Mazières[5], Maurice Perol[6], Francoise Dignat-George[2,3,7], Eric Vivier[3,4,8], Fabrice Barlesi[2,3], Jacques Fieschi[1]

[1] HalioDx, Marseille/France, [2] Centre de Recherche en Cancérologie de Marseille (CRCM), Inserm U1068 Aix Marseille University, Marseille/France, [3]Assistance Publique des Hôpitaux de Marseille (APHM), Marseille/France , [4] Centre d'Immunologie de Marseille-Luminy (CIML), Marseille/France, [5] CHU Toulouse/France, [6] Centre Léon Bérard, Lyon/France, [7] Vascular Research Center (VRCM), Marseille /France, [8] Innate Pharma, Marseille/France.

This work is supported by **French National Research Agency (17-RHUS-0007)**; a partnership of AMU, AP-HM, CNRS, Inserm, Centre Léon Bérard, Institut Paoli-Calmettes, AstraZeneca, HalioDx, Innate Pharma & ImCheck Therapeutics, sponsored by AP-HM and initiated by Marseille Immunopole.
Drug supply is funded by Innate Pharma and AstraZeneca.

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.

In clinical practice, high PD-L1 expression in tumor cells as well as high Tumor Mutational Burden provide with an enriched population of PD(L)1 inhibitors responders without being sufficiently precise to exclude patients from treatment.

Challenge

Understand biological background behind resistances to PD1/L1 ICIs through a comprehensive multiparametric biomarkers strategy (PIONeeR biomarkers program).

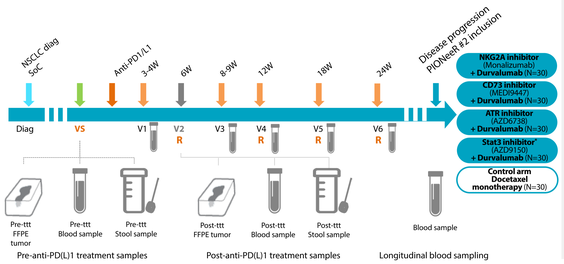
Identify a relevant predictive algorithm based on biomarkers combination adaptable to clinical practice.

Strategy

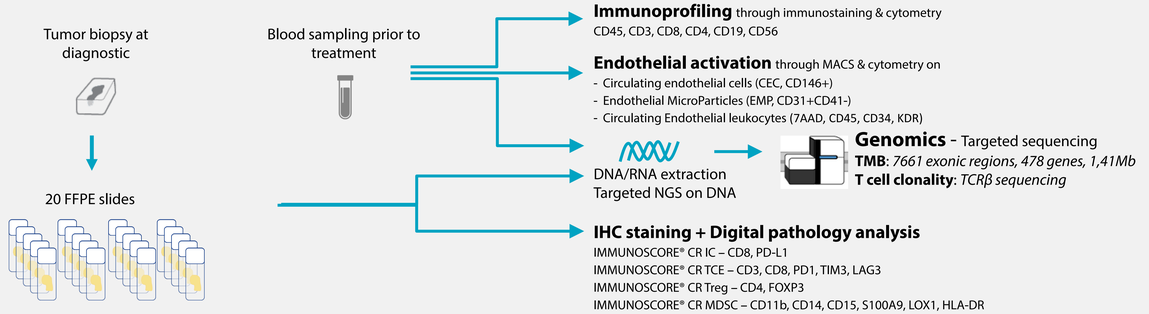
450 patients prospectively collected with stage IV or recurrent NSCLC with first line anti-PD1/L1 immunotherapy.

Preliminary analysis of more than 20 biomarkers on 11 patients at baseline as a proof of concept of Immunogram[1] performances to identify relevant combinations of biomarkers to predict response to ICI treatment.

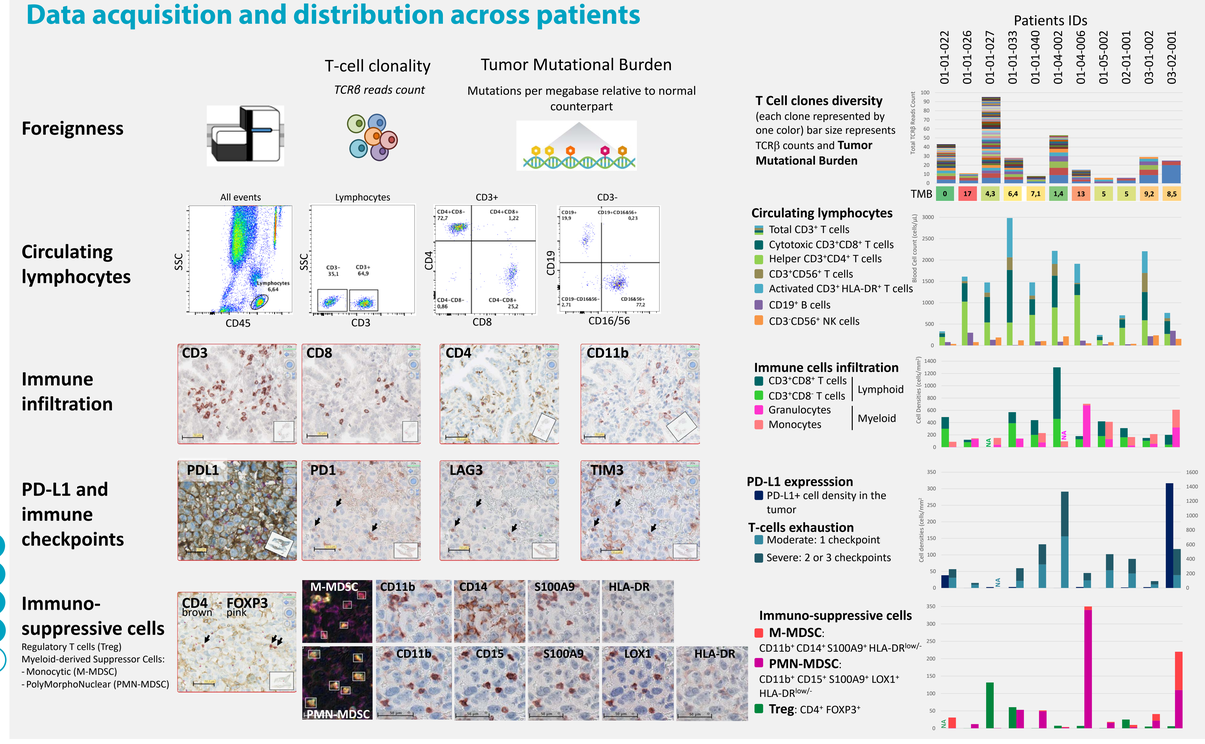
PIONeeR study sampling workflow



Technical workflow for immunoprofiling at baseline



Data acquisition and distribution across patients



Patient groups display heterogeneous immune profiles

Variables were combined in five biological axes to define an Immunogram; five arbitrary scores were calculated:

- Each test results were transformed to fit 0 – 100, where 100 = maximum value observed across the 11 samples
- Each normalized result was weighted as indicated in brackets below

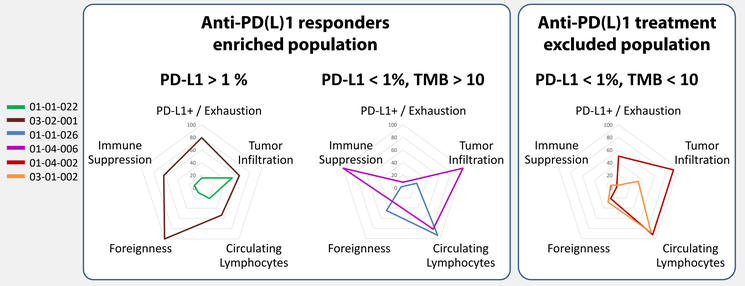
Foreignness : TMB (1/2), TCR clonality (1/2)

Immune suppression within the tumor : Treg *(1/3)*, M-MDSC *(1/3)*, PMN-MDSC *(1/3)*

PD-L1+ / Exhaustion : PD-L1+ cell density (1/2), PD1/LAG3/TIM-triple positive Tcells (1/4), PD1/LAG3/TIM-double positive Tcells (1/4).

Immune infiltration : Tumor Infiltrating Lymphocytes *(1/2)* and Tumor Infiltrating Monocytes *(1/2)*

Circulating lymphocytes : Total CD45+ lymphocytes



Conclusion

This preliminary profiling highlights immunological heterogeneity across patients not evaluated in current clinical practice.

Such analyses confronted to clinical parameters may highlight biological mechanisms explaining resistance to anti-PD(L)1 ICIs.

These profiles will be expanded to additional biomarkers and optimized on more than 400 patients to identify reliable predictive biomarker combinations.

Reference

- Blank CU. et al., Science, 2016

Poster P117