PIONeeR UP #5 : News on PIONeeR and around

Edito

Dear all,

As the PIONeeR umbrella clinical trial smoothly continues its due course, I am happy to share with you our fifth newsletter, and I will take this

opportunity to inform you of reassuring recent news received from our data and safety monitoring board, which concluded to the continuation of the study without modification. You may also have heard of recent data presented by AstraZeneca at the ESMO Congress 2021 last September, showing that combination of durvalumab with the anti-NKG2A monalizumab in their phase 2 COAST trial extends progression-free survival and improves objective response rate in stage III NSCLC patients. These results are not only extremely encouraging, but also validate the combination approach that we decided to undertake in the PIONeeR trial, which includes one experimental arm that combines durvalumab with monalizumab.

In the meantime, we have now reached 76% of total recruitments in the biomarker component of the study. A new preliminary biomarker data analysis was presented by Veracyte – formerly HalioDX – at the SITC 2021 Annual Meeting last month, suggesting promising new stratification criteria for NSCLC patients treated with immune checkpoint inhibitors, criteria that are currently under validation.

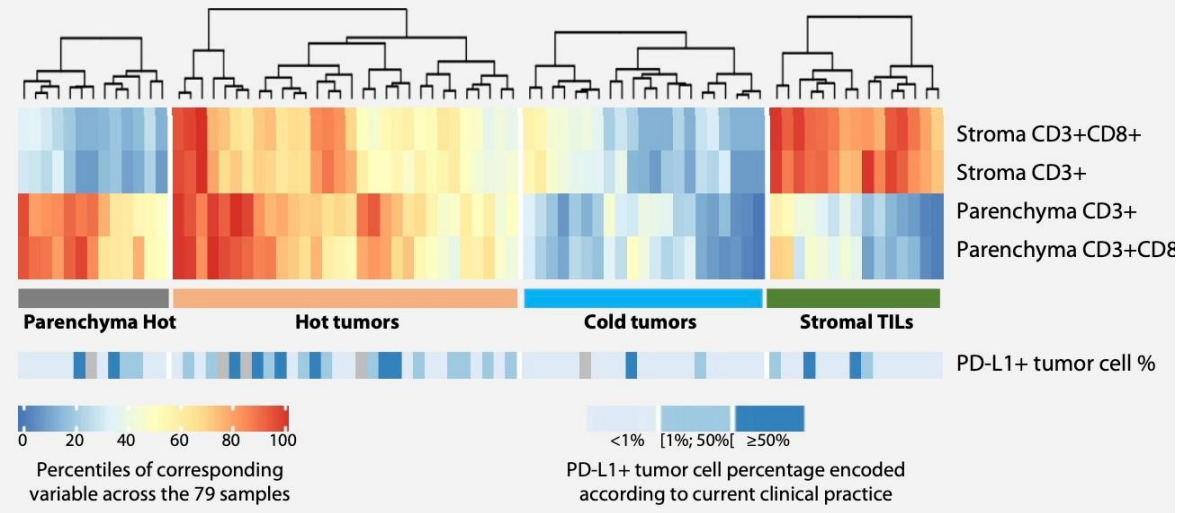
I would like to thank you all, scientists, clinicians, caretakers, patients, for the efforts you put into ensuring the progression of this ambitious project.

Fabrice BARLESI

Preliminary PIONeeR Biomarker data analysis presented at SITC 2021

As we reach 76% of total inclusions in the biomarker component of PIONeeR, analysis performed by Veracyte in biopsies from 79 included patients has pointed towards new possible stratification criteria for NSCLC treatment with PD1/PDL1 inhibitors.

The analysis revealed the existence of four distinct tumor subtypes with respect to the distribution of infiltrating lymphocytes (TILs) in their parenchyma and stroma (see figure below). These subtypes are specifically associated with different ORR and PFS tendencies. While further data analysis continues, combining the data from the spatial distribution of TILs with the level of expression of different immune checkpoints in the parenchyma of the tumors could in some cases be predictive of disease progression.



Hierarchical clustering of 79 NSCLC patients based on CD3+ and CD3+CD8+ cell densities in the parenchyma and the stroma of each tumor.

View the poster

Proven effectiveness of durvalumab plus monalizumab combination in the framework of AstraZeneca's COAST phase 2 trial

Interim results from the large, randomised COAST Phase 2 trial were presented by AstraZeneca at the ESMO Congress 2021 regarding combination of the anti-PD-L1 durvalumab with the anti-NKG2A monalizumab in patients with unresectable, Stage III non-small cell lung cancer (NSCLC) who had not progressed after concurrent chemoradiation therapy. The combination both improved progression-free survival and increased objective response rate (PFS at 10 months was 72.7% with the combination versus 39.2% with durvalumab alone; ORR was 36% versus 18%, respectively).

These positive results support the design of the PIONeeR umbrella trial, which includes one arm that combines durvalumab with monalizumab, and reinforce the validity of the approach undertaken by *The PIONeeR Project* to extend the benefits of immunotherapy to patients who do not respond to durvalumab treatment alone, the current standard of care for stage III NSCLC.

Immuno-oncology and lung cancer highlights: episode 5 (Q4 2021)

An overview of recent advances in immuno-oncology and lung cancer that we deem important in the framework of *The Pioneer Project*, with a particular focus on works presented at the 2021 SITC Annual Meeting.

IMMUNO-ONCOLOGY IN THE ERA OF COVID-19

Data support the safety of COVID-19 vaccination in patients receiving immune checkpoint inhibitors.
Hwang J, Dzimitrowicz H, Shah R, et al. 2021 SITC Annual Meeting. Abstract 625.

GENERAL IMMUNO-ONCOLOGY

Skin toxicity may be predictive of survival benefit from anti-PD(L)1 therapy
Semenov Y, Tang K, Seo J, et al. 2021 SITC Annual Meeting. Abstract 814.

Efficacy and toxicity of single agent immune checkpoint inhibitor treatment in older adults
Nebhan C, Cortellini A, Ma W, et al. 2021 SITC Annual Meeting. Abstract 239.

NON-SMALL CELL LUNG CANCER-SPECIFIC

Biomarkers of resistance to immune checkpoint blockade in NSCLC using high-plex digital spatial profiling
Moutafi M, Martinez-Morilla S, Divakar P, et al. 2021 SITC Annual Meeting. Abstract 240.

Interim analysis of a biomarker-directed randomized phase 2 trial of Pembrolizumab-based combinations for NSCLC
Gutierrez M, Lam W, Hellmann M, et al. 2021 SITC Annual Meeting. Abstract 457.

Read the digest

Clinical research assistant at the Centre Hospitalier of Bastia, Corsica: a portrait of Stéphane Provent

Clinical research assistants play a critical role in satellite centers to recruit patients to the biomarker component of PIONeeR, and to coordinate the logistics between patient data collection and sample handling. Meet Stéphane Provent, clinical research assistant at the Centre Hospitalier and the Clinique Maymard in Bastia.

"It is important for me to participate in clinical research projects such as PIONeeR, contributing to the understanding of resistance to immunotherapy while opening clinical research to patients in Corsica, who, until recently, had no choice other than to fly to Marseille or Paris for such opportunities."

Read his portrait

Statistics : patient recruitment

17 centers are currently recruiting patients to the biomarker component of the project. As of November 30th, 2021, a total of **342 patients** have been included in the biomarker component of The Pioneer Project, adding up to 76% of total

inclusions. In parallel, the PIONeeR clinical trial has recruited 32 patients as of November 30th, 2021, adding up to 26,7% of total inclusions.

Recruiting centres :

Hôpital Nord/AP-HM, Hôpital Européen et Hôpital Saint Joseph (Marseille), Hôpital Larrey/Oncopôle (Toulouse), Centre Léon Bérard (Lyon), Centre Hospitalier Intercommunal Sainte Musse (Toulon), Centre Hospitalier d'Annecy, Centre Hospitalier Vallées de l'Ariège (Foix), Hôpital Nord-Ouest (Villefranche-sur- Saône), Centre Hospitalier Henri Duffaut (Avignon), Centre Hospitalier de Cahors, Centre Hospitalier du Pays d'Aix (Aix-en-Provence), Centre Hospitalier de Montauban, Centre Hospitalier de Bastia, Clinique Maymard (Bastia), ONCOGARD Nîmes et Alès, Centre Hospitalier de Nîmes.

Modifications

A few adjustments were made in the past months to ensure progression of *The Pioneer Project.*

Work package 1: clinical trial

An amended version of the protocol is being reviewed by the regulatory authorities to include a new experimental arm to the PIONeeR clinical trial, which will combine Durvalumab with Savolitinib, a MET kinase inhibitor expected to impact tumor microenvironment, by limiting neutrophil recruitment to tumors and lymph nodes, and therefore potentiating T cell anti-tumor immunity.

Upcoming events

Meetings for 2022

January 21-23, 2022
26ème CPLF (Congrès de Pneumologie de Langue Française), Lille, France

April 8-13, 2022
AACR annual meeting, New Orleans, USA

June 3-7, 2022
ASCO annual meeting, Chicago, USA

The Pioneer Project

2,190 days, 3 countries, over 100 scientists, 8 research labs, 11 hospitals, 25.5 million euros to better understand, predict and overcome anti-PD1/L1 resistance

in non-small-cell lung cancer

“ Better understand and predict resistance

Decipher the mechanisms of resistance to anti-PD1/L1
Identify and validate predictive biomarkers of anti-PD1/L1 response and next generation immune checkpoint inhibitors
Protocol authorization: February 2018

“ Overcome resistances

Evaluate the safety and efficacy of new combinations based on the anti-PDL1 durvalumab in a large-scale exploratory clinical trial
Protocol authorization: December 2018

“ Validate the potential of new immune checkpoint inhibitors

Establish the pre-clinical Proof of Concept of new target-antibody pairs
First in vitro and in vivo evaluation of corresponding antibodies: ongoing