
PIONEER UP
#1
News on Pioneer and around
THE PIONEER PROJECT

EDITO

Welcome to all of you,

I am very pleased to share with you this first newsletter *which will allow us to report regularly on the progress made by the RHU The Pioneer Project, and more broadly on the advances in immuno-oncology.*

With the commitment of 11 partner centers, 37 patients included in the biomarker component of the project and the planned inclusion of a first patient in the clinical trial as of March, the RHU has entered a new phase. The composition of our Scientific Committee will be formally announced at the beginning of the year in the media, on our web site and on the Marseille Immunopole twitter blog that I invite you to join.

Thank you to everyone*, first and foremost to the patients who have joined us in this great human, medical and scientific adventure of the The Pioneer Project.*

Fabrice BARLESI

The Pioneer Project

1,825 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

REFERENCES

Management

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Vice-President of the Canceropole PACA

RHU Coordinator

Aix-Marseille University (AMU)

Clinical trial sponsor

Marseille Public University Hospital System (AP-HM)

Project initiator

Marseille Immunopole

Key figures

Total cost: **25 510 000**€
NRA funding: **8 502 000**€
Duration: **60**months

Focus 2018

Lung cancer screening

Further evidence of benefits of CT lung cancer screening for at risk individuals

7 years after the publication of the works of the National Lung Screening Trial[1] in the New England Journal of Medicine, a large-scale randomized study, called NELSON, has confirmed the benefits of CT lung cancer screening for at risk individuals[2]. Presented at the IASLC 2018 conference, this new study demonstrated a highly significant reduction in mortality amongst heavy and ex-heavy smokers (25% for men and 40% to 60% for women).

On November 12, 30 French experts of the IFCT and SIT and the patient association *De l'air !* called on the HAS and the Ministry of Health and Solidarity to rapidly implement this screening program in association with smoking-cessation support[3].

Combinations around PD1(L1) immune checkpoint inhibitors

A number of studies confirm the superiority of the PD1(L1) chemotherapy-PD1(L1) blockade combination in non-small-cell lung cancer patients

At the ASCO 2018 Meeting, a series of studies have demonstrated the superiority of the anti-PD1(L1)-chemotherapy combination vs chemotherapy alone to treat advanced non-small-cell lung cancer (NSCLC). In a phase 3 study involving more than 600 patients with metastatic NSCLC[4], the combination of anti-PD1 pembrolizumab with chemotherapy (an association of pemetrexed and cisplatin) significantly improves survival (more than 20%), response rate (47% compared to 19% for chemotherapy alone) and the duration of response (11.2 months compared to 7.8 months).

These results confirm the multiple immunological benefits of chemotherapy: the induction of immunogenic cell death which promotes the recruitment and activation of T-cells and myeloid-cell-mediated reduced immunosuppression (their metabolic profile making them more sensitive to cytotoxic agent action such as anti-folic acids or platinum salts).

On 6 December 2018, following the positive results of the phase 3 clinical trial conducted in more than 1,200 patients with the same profiles[5], the FDA approved the use of a combination of anti-PDL1 atezolizumab with anti-angiogenic bevacizumab and chemotherapy (a combination of paclitaxel and carboplatin) for patients with metastatic EGF and ALK3 wild-type metastatic NSCLC[6].

[1]The National Lung Screening Trial Research Team. Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening. N Engl J Med 2011, 365:395-409.

[2]Koning H-J. et al. Effects of Volume CT Lung Cancer Screening: Mortality Results of the NELSON Randomised-Controlled Population Based Trial. WCLC2018 Meeting, #PL02.05.

[3]IFCT and SIT joint press release, 12 November 2018.

[4]Gandhi L et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. N Engl J Med 2018; 378:2078-2092.

[5]Socinski M et al. Atezolizumab for First-Line Treatment of Metastatic non-squamous NSCLC. N Engl J Med. 2018; 378:2288-2301.

[6]FDA approves atezolizumab with chemotherapy and bevacizumab for first-line treatment of metastatic non-squamous NSCLC

First benefits of immunotherapy for small cell lung cancer…

In a study conducted on 403 patients with advanced small cell lung cancer (SCLC), the first-line treatment combining atezolizumab with carboplatin and etoposide has improved the overall survival and progression-free survival (12.6% vs 5% at 12 months). Announced at the IALSC-WCLC 2018 conference[7], these results constitute a first not only for immunotherapy but more broadly for the management of this particularly difficult-to-treat disease.

…and stage III non-small-cell lung cancer

Presented at the ESMO and IALSC 2018 conferences[8], the final results of the PACIFIC study mark a significant step in the treatment of locally advanced NSCLC.

At 80% unresectable, the latter represent nearly one third of NSCLC and the benefits of the standard treatment, which combines chemotherapy and radiotherapy, remain limited (5-year survival is 15%).

When administered after chemoradiotherapy, anti-PDL1 durvalumab prolonged progression-free survival by almost a year (11.2 months), regardless of the expression level of the ligand PDL1. These results confirm once more the clinical benefits of the immunogenic effect of chemotherapy and radiotherapy.

Failures of the anti-PD1(L1)-anti-CTL4 duo in first-line in metastatic non-small-cell lung cancer

After the failure of the CheckMate-227 study, the first results of the MYSTIC study in turn demonstrated that the combination of anti-PDL1 durvalumab and anti-CTL4 tremelimumab did not improve patient survival than chemotherapy[9]. These new data highlight the key issues of stratification: the selection of biomarkers (PDL1 expression level, Immunoscore, alone or in combination with targeted immune checkpoints, TMB…), the thresholds used and the required standardization of associated tests. As many parameters which will be evaluated in *The **Pioneer Project***.

Combining immune checkpoint modulators: identifying the right sequence

In August 2018, work carried out by Bernard Fox at the Chiles Research Institute[10] highlighted once again the importance of sequence and timing regarding combination therapies. In a murine model of breast cancer (MMTV-PyMT mouse), the benefits of the simultaneous administration of an anti-PD1 and an anti-OX40 were reduced compared to anti-OX40 alone. In contrast, the administration of the anti-OX40 followed by that of the anti-PD1 (contrary to the reverse sequence) significantly increased the activity of CD8 and CD4 T-cells and animal survival (a 30% gain compared to treatment by anti-OX40 alone). Like the results of the phase 2 clinical study conducted by Eric Vivier and the teams at Innate Pharma and Medimmune/AstraZeneca[17], this work demonstrates the therapeutic potential of combinations with inhibition mechanisms and activation of T and/or NK cells.

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[7] WCLC 2018, Abstract PL02.07

[8] Pascale Tomasini et al. Durvalumab after chemoradiotherapy in stage III non-small cell lung cancer. J Thorac Disc; 2018 April 10; S1032–S1036

[9] AstraZeneca provides update on the Phase III MYSTIC trial of Imfinzi and tremelimumab in Stage IV non-small cell lung cancer, 16 November 2018

[10] David Messenheimer et al. Timing of PD-1 blockade is critical to effective combination immunotherapy with anti-OX40. Clin Cancer Res 2017, 23(20)

Reclassification of solid tumors

Further steps towards precision oncology

In 2017, the FDA[11] granted marketing authorization of anti-PD1 keytruda for the treatment of any unresectable or metastatic MSI-H+ or dMMR+ solid tumors. For the first time in the history of oncology, the marketing approval of a drug was not longer linked to the organ or tissue concerned but to the genetic profile of the tumor.

On 27 November 2018, the FDA[12] marked a new step in the molecular reclassification of solid tumors. Following the spectacular results of the LOXO-101 study (a response rate of 80% in 17 types of unresectable or metastatic solid tumors)[13], the US agency approved the tyrosine kinase inhibitor for the treatment of any TRK fusion solid tumor.

Presented at the IALSC-WCLC 2018 conference, new data from the FLAURA study[14] (which evaluated the third-generation tyrosine kinase osimertinib in EGFR-mutated NSCLC) also marks the dawn of this new precision medicine.

Prognostic and predictive biomarkers

Mutation rate and anti-tumor immune response: two sides of the same coin

On 30 November 2017, the FDA granted marketing approval of the very first companion diagnostic test based on the Tumor Mutational Burden (TMB)[15]. Used to predict the response to targeted therapies or immune checkpoint inhibitors of patients with different solid tumors (including NSCLC), this test has since brought to light the "grey areas" of TMB (false positives and false negatives) which pleads for a multiparameter approach.

As demonstrated by the recent work of Jérôme Galon's team[16], the clonal evolution of the tumor is indeed far from being an independent parameter. The mutation rate also reflects the pressure exerted by the pressure exerted by the tumor immune microenvironment: the immune cells respond to the antigens produced by the tumor which thus try to escape by generating new harmful mutations. The decoding and the clinical evaluation of this dynamic are at the heart of *The Pioneer Project.*

[11] FDA approves immunotherapy for MSI-High or MMR-Deficient tumors. May, 23, 2017

[12] FDA approves Vitrakvi for solid tumors with NTRK gene fusion. November 27, 2018

[13] Alexander Drilon et al. Efficacy of Larotrectinib in TRK Fusion–Positive Cancers in Adults and Children. N Engl J Med 2018; 378:731-739

[14] Jean-Charles Soria et al. Osimertinib in untreated EGFR-mutated advanced Non–Small-Cell Lung Cancer. N Engl J Med 2018; 378:113-125

[15] FDA announces approval, CMS proposes coverage of first breakthrough-designated test to detect extensive number of cancer biomarkers. November 30, 2017

The intra-tumor immune response marks the development of early-stage cancers as advanced tumors

At the heart of the biomarker component of *The Pioneer Project*, Immunoscore® also made its mark in the news in 2018. The eponymous international consortium led by Jérôme Galon had already demonstrated the unmatched prognostic value of this new immunologic parameter in early stage colon cancers. In a new study published in *Cell*[16], Jérôme Galon and collegues demonstrates this time that Immunoscore® can also predict the development of metastatic colon cancers. Despite the extraordinary genetic heterogeneity of metastases in a given patient, the combined values of Immunoscore® and immuno-editing sign the risk of recurrence.

New immune checkpoint inhibitors

NKG2A opens a new class of broad-spectrum immune checkpoint inhibitors

Part of the clinical component of *The Pioneer Project*, the antibody monalizumab targets NKG2A, a receptor expressed on NK cells and CD8 cytotoxic tumor-infiltrating lymphocytes. Recently published in *Cell*[17], the work carried out by Eric Vivier showed that the anti-NKG2A monalizumab potentiates the anti-tumor action of anti-PDL1 durvalumab in a murine model of metastatic cancer (40% vs 60% of survival in favor of the combination).

In a phase 2 clinical trial the association of monolizumab and the anti-EGFR cetuximab also increases the progression-free survival of patients with advanced head and neck cancer (25% compared with 13% for cetuximab alone). Finally, in November of the same year, a Dutch team demonstrated the benefits of the combination of an anti-NKG2A and a therapeutic vaccine in several murine models of cancers[18].

Targeting simultaneously T and NK cells and prone to combine with another immune checkpoint inhibitor, a targeted drug or a therapeutic vaccine, Monalizumab opens a new class of broad-spectrum immune checkpoint inhibitors.

[16]Mihaela Angelova et al. Evolution of metastases in space and time under immune selection. Cell 2018; 175-3, 751-765

[17]Pascal André et al. Anti-NKG2A mAb is a checkpoint inhibitor that promotes anti-tumor immunity by unleashing both T and NK cells. Cell 2018; 175, 1-13

[18]Nadine Van Montfoort et al. NKG2A blockade potentiates CD8 T cell immunity induced by cancer vaccines. Cell 2018, 175-7, 1744-1755

Statistics

As of February 7, 2019, 37 patients had already been included in the biomarker component of the project and the enrollment of the first patient in the clinical trial is expected in March 2019

[1]Hôpital Nord/AP-HM, Hôpital Européen, Hôpital Saint Joseph, [2]Hôpital Larrey/Oncopôle, [3]Centre Léon Bérard, [4]Hôpital Sainte Musse, [5]Centre Hospitalier d'Annecy, [6]Centre Hospitalier des Vallées de l'Ariège, [7]Hôpital Nord-Ouest, [8]Centre Hospitalier, [9]Centre Hospitalier Général

As of February 7, 2019, *The Pioneer Project* benefits from the commitment of 11 partner centers.

Investigator	Associated center	Status	Date	Number of patients screened	Number of patients included
Pr BARLESI	**Hôpital NORD - Marseille**	Active	07/02/2019	35	32
Pr MAZIERES	Hôpital Larrey/Oncopôle - Toulouse	Activated	07/02/2019	0	0
Dr LE TREUT	**Hôpital Européen - Marseille**	Active	07/02/2019	4	3
Dr FOA	**Hôpital Saint Joseph - Marseille**	Active	07/02/2019	1	1
Dr PEROL	Centre Léon Bérard - Lyon	Activated	07/02/2019	0	0
Dr AUDIGIER VALETTE	**Hôpital Sainte Musse - Toulon**	Active	07/02/2019	1	1
Dr HOMINAL	Centre Hospitalier - Annecy	Activated	07/02/2019	0	0
Dr FALCHERO	Hôpital Nord-Ouest - Villefranche-sur-Saône	Activated	07/02/2019	0	0
Dr DOMERGUE	Centre Hospitalier - Vallées de l'Ariège	Activated	07/02/2019	0	0
Dr BARRE	**Centre Hospitalier - Cahors**	Active	07/02/2019	1	0
Dr ZAHI	Centre Hospitalier Général - Montauban	Activated	07/02/2019	0	0
TOTAL				**42**	**37**

Modifications

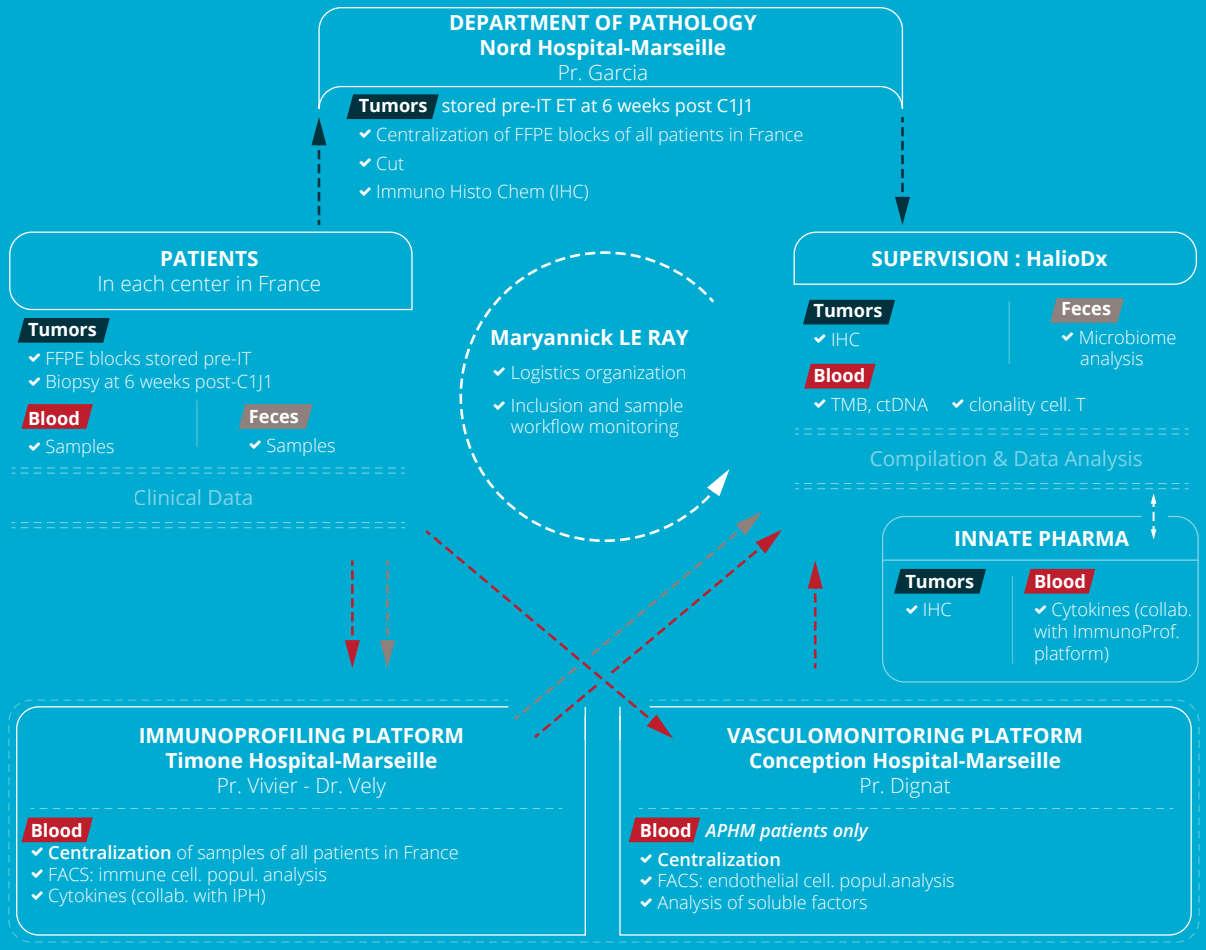
In April 2018, the CXC chemokine receptor 2 antagonist AZD5069 was replaced by AZD6738, a new inhibitor of the ATR serine-threonine kinase (an enzyme which contributes to the protection of tumor cells by facilitating DNA repair during the replication phase).

In a phase 1b clinical study conducted in different types of solid tumors, AstraZeneca has demonstrated the safety of the combination of AZD6738 and chemotherapy (carboplatin with olaparib) or anti-PDL1 durvalumab and obtained early encouraging signs of activity. The AZD6738-durvalumab combination is now evaluated in several hematological malignancies and solid tumors, in particular in anti-PD1(L1)-resistant NSCLC (HUDSON study, NCT03334617).

On the same date, AstraZeneca also informed us that a second drug candidate (STAT3 antisens oligonucleotide AZD9150) would not be available before the end of September 2018.

In order not to delay the initial submission schedule, the corresponding experimental arm was postponed. The amendment relating to the opening of the arm combining durvalumab and AZD9150 has been tabled in February 2019.

Logistics and sample analysis



Governance

Consortium agreement

After validation of the consortium agreement by the National Research Agency (ANR), the grant agreement with the RHU *The Pioneer Project* (the definitive contractual funding arrangement) was signed by Aix-Marseille University within the required timeframe, that is less than one year after the signature of the pre-financing agreement in November 2017.

Scientific Committee

As part of the consortium agreement, *The Pioneer Project* RHU has appointed an independent Scientific Committee.

It includes **Prof. Solange PETERS** (President-elect of the European Society of Medical Oncology and Head of Oncology at the Vaudois University Hospital Center, Switzerland), **Prof. Bernard A. FOX** (Head of Molecular Biology and Immunology at the Chiles Research Institute, University of Providence, USA), **Prof. Martin RECK** (Head of the Departments of Thoracic Oncology and Clinical Studies at the Grosshansdorf Hospital Center, Germany), **Prof. Daniel TAN** (Medical Director of the Radio-Oncology Division of the American-Asian Medical Group and Senior Oncologist at the National Cancer Center Singapore and **Prof. Ming TSAO** (Head of Translational Research Program in Lung Cancer and Laboratory of Medicine and Pathology at the University of Toronto).

The nomination of the Scientific Committee will be formally announced at the begining of 2019.

CONTACTS

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Communication

The Pioneer Project now benefits from a unique identity (freely inspired by the Kaplan-Meier methodology, our logo highlights the project's first mission: to increase the survival rate of NSCLC patients with resistance to anti-PD1/L1). It will be used on all RHU on and off-line communication supports (slideshows, scientific posters ...).

The new web space of *The Pioneer Project* RHU is now online:

www.marseille-immunopole.org/en/the-pioneer-project

Upcoming events

29 March-3 April

AACR Annual Meeting // Atlanta, USA

10-13 April

ELCC Congress // Geneva, Suisse

31 May-4 June

ASCO Annual Meeting // Chicago, USA

7 -10 September

IASLC WCLC World Conference // Barcelona, Espagne

27 september-1st October

ESMO Congress // Barcelona, Espagne

NEXT MEETINGS

Q3/Q4 2019

Third General Assembly and Steering Committee Foundation A*Midex Steering Committee

Q1 2020

Second SAB meeting


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