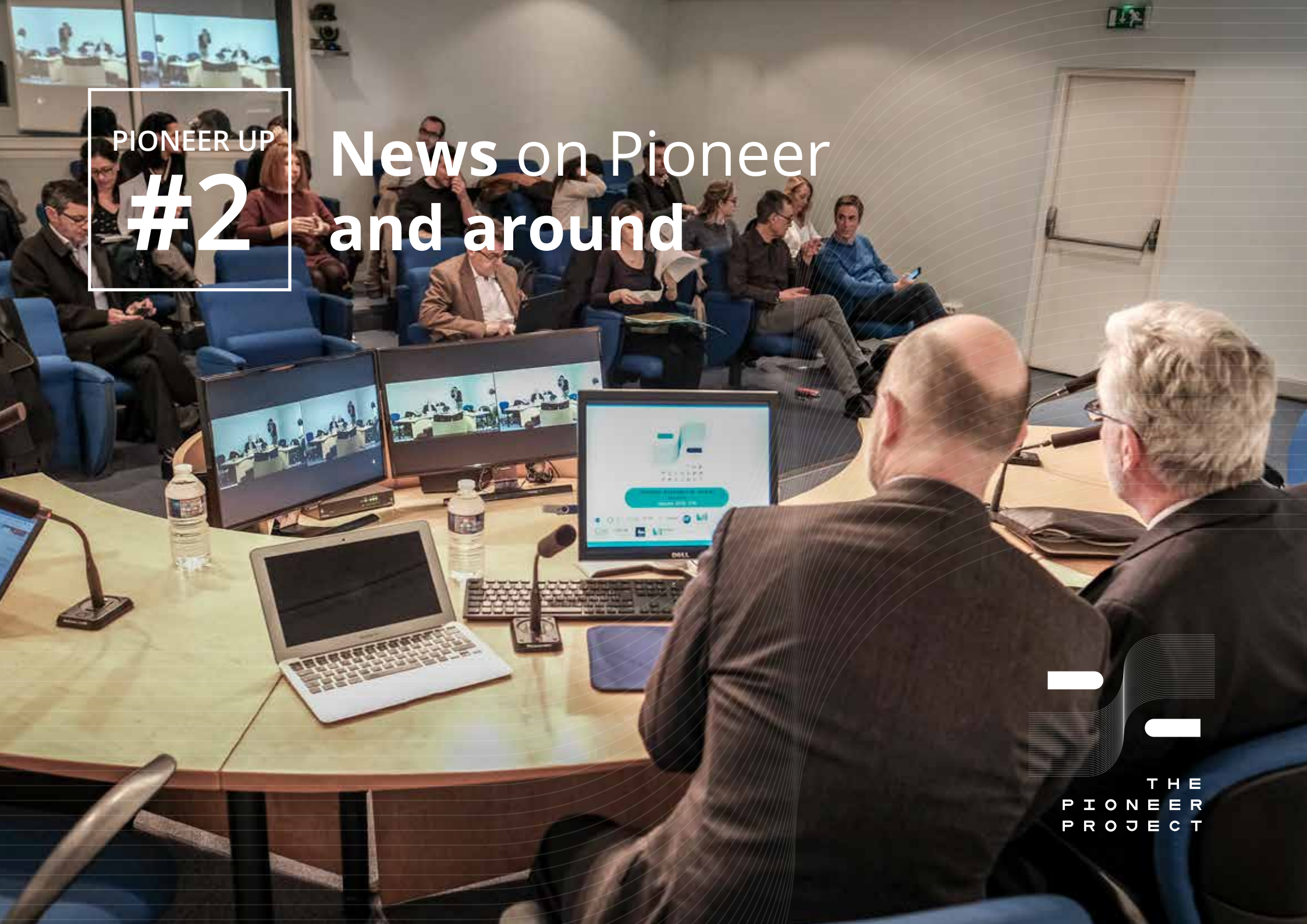


PIONEER UP

#2

News on Pioneer **and around**

THE PIONEER PROJECT

EDITO

Dear all,

Following on the expectations that we awoke around our poster presented at the World Conference in Lung Cancer last September in Barcelona, I am pleased to share with you the latest news from The Pioneer Project. As we approach our two-year anniversary and prepare for a midway evaluation by the National Agency for Research next year, we can be proud of the progress we have achieved. Today, we have recruited 91 patients across 11 centres in the biomarker component of the study, and more centres should rapidly join our challenge. Crucially, we have recently recruited our first two patients to the Pioneer clinical trial, a critical leap forward towards the success of this project.

We will also take this opportunity to review advances in immuno-oncology that we deem important in the framework of The Pioneer Project and the treatment of lung cancers. We were particularly encouraged by recent studies opening for consideration the use of immunotherapy as first-line treatment for advanced non-small cell lung cancer, and alerted by findings suggesting that tumour mutational burden is not a good predictive marker for response to immunotherapy in all circumstances, highlighting the need for new predictive biomarkers that we hope to reveal in our common endeavour.

Thank you all, scientists, clinicians, caretakers, patients, for your commitment to this ambitious adventure,

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

Fabrice BARLESI
Professor of Medicine at Aix-Marseille University
Head of Multidisciplinary Oncology and Therapeutic Innovation at AP-HM
Coordinator of the Center for Early Phase Cancer Trials CLIP2/INCa
Co-founder of the Marseille Immunopole Cluster
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

Lung Cancer Prevention/Interception

A detailed analysis of the molecular and cellular events that lead to carcinogenesis suggests immunotherapy could be used to prevent at risk individuals from developing lung cancer.

After the efforts of the Nelson trials to achieve early lung cancer detection[1], research led by Jérôme Galon now argues for the possibility to prevent cancer development altogether using immunotherapy. Published in the journal Nature, the study examined 122 biopsies from 77 former or current smokers to dissect the sequence of events in the lung tissue and the immune system that lead to carcinogenesis towards squamous cell carcinoma (SCC)[2].

Gene expression data defined four distinct molecular steps of progression: (1) normal tissue, (2) low-grade lesions, (3) high-grade lesions, and finally, (4) invasive squamous cell carcinoma. Each of these steps is characterized by a series of molecular events that were further investigated. For instance, the authors show that immune sensing starts as soon as low-grade lesions appear and most importantly, an anti-tumour immune response appears together with immune suppression mechanisms early on, in pre-cancerous, high-grade lesions. This implies that immunotherapy-based approaches could be used not only as treatments, but also as chemopreventives for individuals at risk of developing lung cancer.

Combinations around PD1(L1) immune checkpoint inhibitors

Chemotherapy plus immunotherapy : the right strategy as first line treatment for extensive stage small cell lung cancer patients (SCLC)

A new study addressed the combination of immunotherapy with chemotherapy in SCLC. Presented at the IASLC 2019 World Conference on Lung Cancer, the CASPIAN trial was performed on 537 patients to compare 1st line durvalumab combined with standard-of-care chemotherapy (SoC, etoposide plus either cisplatin or carboplatin chemotherapy) to SoC alone[3]. The combination treatment improved overall survival: the risk of death was reduced by 27%, with a median OS extended from 10.3 months to 13.0 months. At 18 months, the OS rate was 33.9% with the combination treatment versus 24.7% with the SoC. In terms of safety, the profile of the combination was consistent with previous results obtained for chemotherapy or immunotherapy alone.

Together with the IMpower133 trial published last year[4], these results are particularly promising given the aggressive nature of this disease. Of note, this trial opens the possibility to choose an anti-PD-L1 combination with either cisplatin or carboplatin chemotherapy backbones.

1 De Koning H. et al. Effects of volume CT lung cancer screening: mortality results of the NELSON randomised- controlled population based trial. J. Thorac. Oncol. 2018. 13(10):S185.
2 Mascaux C. et al. Immune evasion before tumour invasion in early lung squamous carcinogenesis. Nature 2019. 571:570-575.
3 Paz-Ares L. et al. Overall Survival with Durvalumab Plus Etoposide-Platinum in First-Line Extensive-Stage SCLC: Results from the CASPIAN Study. WCLC 2019. PL02.11.
4 Horn L. et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. NEJM 2018. 379:2220-2229

Combination immunotherapy for frail, trial-excluded populations

Many knowledge gaps persist when it comes to treating frail cancer patients, who are today underrepresented in most clinical trials. CheckMate 817 assessed the efficacy of 1st line nivolumab plus ipilimumab in advanced non-small cell lung cancer (NSCLC) patients who presented either an ECOG performance status of 2 or co-morbidities such as asymptomatic untreated brain metastases, hepatic or renal impairment, or HIV. The study was presented at the IASLC 2019 World Conference on Lung Cancer, and showed no increase in adverse events of any grade in frail populations (67% TRAEs in the frail population vs. 77% in the general population)[5].

In terms of activity, the efficacy of the combination treatment was slightly lower in the frail population than in the population of patients with ECOG performance status of 0 or 1, but still showed a response rate of 24%, and 57% of patients still in response at 1-year.

Finally, like in the general population, high PD-L1 expression and high TMB were predictive of a better response to treatment. A step towards prospective trials for this significant portion of patients in need of an appropriate cancer treatment.

No benefit from anti-PD-1/anti-CTLA-4 combination in stage IV previously treated SqNSCLC

As part of the Lung-MAP precision medicine trial, a study compared the effect of nivolimumab in combination with ipilimumab vs. nivolimumab alone on a total of 252 patients with stage IV previously treated SqNSCLC[6]. The results, which were presented at the IASLC 2019 World Conference on Lung Cancer, showed no difference whatsoever in OS, PFS and response across the two arms: 10.0 months vs. 11.0 mean OS, 3.8 months vs. 2.8 months mean PFS and 18% vs. 17% RECIST 1.1 response rate, in combination vs. single treatment, respectively. Moreover, outcomes were similar across TMB subgroups and PD-L1 expression levels. The study was closed following these disappointing results.

Immunotherapy as first-line treatment in advanced NSCLC

Atezolizumab improves survival in chemotherapy-naïve patients.

In the quest for alternatives to chemotherapy as first line-treatment for advanced NSCLC, the IMpower 110 trial studies atezolizumab monotherapy as an alternative to a platinum-based treatments in treatment-naïve, PD-L1-selected patients. Interim results presented at the ESMO 2019 Meeting showed that for those patients with high PD-L1 expression on tumour cells (≥50%) or on tumour-infiltrating lymphocytes (≥10%), the anti-PD-L1 presents a real advantage: median OS was 15.7 months in the immunotherapy-treated patients versus 13.1% in the platinum treated patients, and median PFS was respectively 8.1 and 5.0 months. While no advantage was observed under the above PD-L1 expression cut-offs, atezolizumab represents a promising first-line treatment for advanced NSCLC with PD-L1 expression.

5 Barlesi F. et al. CheckMate 817: First-Line Nivolumab + Ipilimumab in Patients with ECOG PS 2 and Other Special Populations with Advanced NSCLC. WCLC 2019. OA04.02
6 Bazhenova L. et al. A Phase III Randomized Study of Nivolumab/Ipilimumab vs Nivolumab for Previously Treated Stage IV Squamous Cell Lung Cancer. WCLC 2019. OA04.01.

Anti-PD-1/anti-CTLA-4 as a first line option regardless of PD-L1 status

Following on last year's positive results on PFS of a nivolumab plus low-dose ipilimumab combination in non-small cell lung cancer patients[7], the latest results of CheckMate-227 were presented at the ESMO 2019 Meeting regarding overall survival. This trial addressed whether or not a nivolumab plus low ipilimumab combination could substitute chemotherapy as a first line treatment for patients with advanced NSCLC. Patients were enrolled in two arms depending in their level of expression of PD-L1. In PD-L1 positive patients (≥ 1%), the 2-year overall survival rates were 40.0% for the immunotherapy combo versus 32.8% for chemotherapy; median duration of OS was 17.1 months versus 14.9 months, respectively. Strikingly, PD-L1 negative patients (< 1%) also benefitted from the combination immunotherapy with a 17.1-month long median duration of OS versus 13.9 with chemotherapy[8]. Importantly, no new safety concerns were revealed. These results suggest that this immunotherapy combination is a valid frontline option for the treatment of advanced NSCLC whatever the expression level of PD-L1.

Predictive biomarkers

Rising skepticism around the use of TMB as a universal predictive marker of response to immunotherapy in NSCLC

Previous research has identified tumour mutational burden (TMB) as a potentially good predictive factor of response to single or combination anti-PD-1(L1)/anti-CTLA-4 immunotherapy. However, recent studies with conflicting results suggest TMB might not be a universal marker after all.

In favour of its predictive properties, a retrospective study presented at the ESMO 2019 Meeting in Barcelona found an improved OS, PFS and ORR to pembrolizumab monotherapy in high TMB patients (≥175 mutations per exome) with treated or untreated NSCLC (Keynote 010 and Keynote 042 trials, respectively)[9]. In contrast, two studies presented at the latest IASLC World Conference on Lung Cancer and a third presented at the ESMO 2019 Meeting concluded that TMB cannot predict response rate, PFS or OS in advanced nonsquamous or squamous NSCLC patients treated with pembrolizumab which in this case was combined with platinum-based chemotherapy. These analyses were performed on data from Keynote 021, Keynote 189 and Keynote 407 trials[10,11,12]. Of note, all these studies measured TMB by whole-exome sequencing of tumours and matched normal DNA, and all encountered difficulties in measuring TMB in a substantial number of patient samples (38% to 76%).

These contradicting findings point towards the need to better understand the circumstances under which TMB can be used as a predictive marker for response to immunotherapy.

7 Hellmann M. et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. NEJM 2018, May 31.
8 Hellmann M. et al. Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer. NEJM 2019, Sept 28.
9 Herbst RS et al. Association between tissue TMB (tTMB) and clinical outcomes with pembrolizumab monotherapy (pembro) in PD-L1-positive advanced NSCLC in the KEYNOTE-010 and -042 trials. ESMO 2019. LBA79
10 Langer CJ et al. KEYNOTE-021: TMB and Outcomes for Carboplatin and Pemetrexed With or Without Pembrolizumab for Nonsquamous NSCLC. WCLC 2019. OA04.05.
11 Garassino MC et al. Evaluation of TMB in KEYNOTE-189: Pembrolizumab Plus Chemotherapy vs Placebo Plus Chemotherapy for Nonsquamous NSCLC. WCLC 2019. OA04.06.
12 Paz-Ares L et al. Pembrolizumab (pembro) plus platinum-based chemotherapy (chemo) for metastatic NSCLC: tissue TMB (tTMB) and outcomes in KEYNOTE-021, 189, and 407. ESMO 2019. LBA80

Follow-up studies after immunotherapy

Low-grade pneumonitis should not deter from use of durvalumab.

To follow up on the positive results of the PACIFIC phase 3 trial, which showed efficacy of durvalumab on Stage III non-small cell lung cancer (NSCLC) patients who had no progression after chemoradiotherapy (CRT), an exploratory analysis of the data was presented at the ESMO 2019 Meeting to specifically investigate efficacy in patients who developed pneumonitis : OS, PFS, and TTDM (time to death or distant metastasis) were all consistent with results for the total population[13]. Treatment benefit with durvalumab versus placebo was therefore maintained regardless of the occurrence of pneumonitis.

Effectiveness, safety and health-related quality of life in lung cancer patients treated with nivolumab

Nivolumab has already demonstrated efficacy and safety in patients previously treated for advanced NSCLC in two phase 3 trials, CheckMate 017 and CheckMate 057. To support and extend these results, the EVIDENS prospective study followed clinical characteristics and health-related quality of life (HRQoL) for a minimum of 17-months after treatment in a population of 1,462 lung cancer patients. While previous reports showed that baseline patient and tumour characteristics from EVIDENS were representative of a standard advanced NSCLC population, the latest update presented at the ESMO 2019 Meeting shows that effectiveness and safety outcomes are consistent with results of the aforementioned trials, confirming that nivolumab is a valuable treatment option in the management of advanced NSCLC.

Importantly, the study also explores safety and HRQoL in subgroups of patients to reveal that ECOG PS, smoking status, EGFR mutation status and TRAEs are independent predictors of survival, and that elderly patients (≥70 years old) benefit as much from a nivolumab treatment as younger patients (<70)[14].

The corresponding poster was granted the price for best poster of the lung cancer session at ESMO 2019.

Revisiting the results from the JAVELIN Lung 200 trial

Follow up studies of failed clinical trials can be very informative in terms of trial design and interpretation. JAVELIN Lung 200 was a randomized, open-label, phase III study, that did not meet its primary endpoint in terms of overall survival (OS) with second-line avelumab vs docetaxel in patients with PD-L1+ NSCLC. In hindsight however, OS may have been affected by the larger proportion of patients in the docetaxel arm who received a subsequent checkpoint inhibitors (anti-PD-1, anti-PD-L1 or anti-CTLA-4). A poster presented at the ESMO 2019 Meeting performed a post-hoc inverse probability weighting analysis and showed that hazard ratios for OS with avelumab vs docetaxel were lower than in the primary analysis both in the PD-L1+ and in the total population[15]. This analysis suggests that that the primary

13 Vansteenkiste J et al. Efficacy of durvalumab in patients with stage III NSCLC who experience pneumonitis (PACIFIC). ESMO 2019. 1459PD
14 Barlesi F et al. Effectiveness and safety of nivolumab in the treatment of lung cancer patients in France: Updated survival and subgroup analysis from the real-world EVIDENS study. ESMO 2019. 1494P.
15 Barlesi F et al. Assessing the impact of subsequent checkpoint inhibitor (CPI) treatment on overall survival: Post hoc analyses from the phase III JAVELIN Lung 200 study of avelumab vs docetaxel in platinum-treated locally advanced/metastatic non-small cell lung cancer (NSCLC). ESMO 2019. 1492P.

OS analysis in this study was indeed impacted by the relatively high proportion of patients in the docetaxel arm who received a subsequent checkpoint inhibitor, adding a word of caution when concluding on trial data.

Resistance to Immune Checkpoint Inhibitors

Understand, predict and overcome anti-PD-1/-L1 resistance in NSCLC

Despite PD-1(L1) immune checkpoint inhibitors leading to a spectacular reduction in tumour volume and a significant lengthening of life expectancy in 20% of NSCLC patients, lung cancer remains the leading cause of cancer deaths worldwide, as most patients are or become resistant to these treatments.

These resistances are the focus of The Pioneer Project, which was presented in a poster at the IASLC 2019.

The poster highlighted the 3 missions of the study :

1. understand the biological mechanisms behind these resistances,
2. elucidate the best way to predict them by multiparametric analysis of an exhaustive panel of biomarkers (PIONeeR biomarker program),
3. define therapeutic strategies to combat them, by combining the anti-PD-L1 durvalumab® with four drug candidates modulating the action of several players of immunity (PIONeeR randomized trial).

While the biomarkers program is now well under way, the randomized trial has just enrolled its first two patients.

The Pioneer Project inside-out

A word from those working behind the scenes for the advancement of The Pioneer Project

Dr. Jacques Le Treut, MD

Pneumo-oncologist at the European Hospital, Marseille

Immunotherapy has transformed the way we function: not only are these treatments more efficient than what was available before, but they are also better tolerated. It really is a revolution. A revolution that is only just starting and should find its way through combination treatments.

Today, our major problem is giving access to treatment associations to our patients. For now, the one way we can do this is through clinical trials and The Pioneer Project is an excellent opportunity that offers tremendous treatment combination options. It is our duty as clinicians to give these options to our patients. To date, we have included 7 patients from the European Hospital to the biomarker component of the study, and are actively working towards referring more patients, although it isn't always easy to convince them of the interest of participating in clinical research.

We are also looking forward to including patients in the Pioneer clinical trial, which should hopefully start very soon.

Statistics

11 centres are currently recruiting patients to the biomarker component of the project.

2 new centres will also join soon, while several others are currently waiting for approval.

[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, [10]Centre Hospitalier du Pays d'Aix, [11]Centre Hospitalier de Bastia

As of December 11th, 2019, a total of 91 patients have been included in the biomarker component of The Pioneer Project.

Investigator	Associated center	Status	Date	Number of patients screened	Number of patients included
Pr BARLESI	Hôpital NORD - Marseille	Active	20/02/2018	71	60
Pr MAZIERES	Hôpital Larrey/Oncopôle - Toulouse	Active	08/10/2018	7	7
Dr LE TREUT	Hôpital Européen - Marseille	Active	11/10/2018	7	7
Dr FOA	Hôpital Saint Joseph - Marseille	Active	16/10/2018	7	7
Dr PEROL	Centre Léon Bérard - Lyon	Active	31/10/2018	2	2
Dr AUDIGIER VALETTE	Hôpital Sainte Musse - Toulon	Active	08/11/2018	2	2
Dr HOMINAL	Centre Hospitalier - Annecy	Active	21/11/2018	1	1
Dr FALCHERO	Hôpital Nord-Ouest - Villefranche-sur-Saône	Active	28/11/2018	1	1
Dr DOMERGUE	Centre Hospitalier - Vallées de l'Ariège	Activated	04/12/2018	0	0
Dr BARRE	Centre Hospitalier - Cahors	Active	11/12/2019	3	3
Dr ZAHI	Centre Hospitalier Général - Montauban	Active	14/01/2019	1	1
Dr MARTINEZ	Centre Hospitalier du Pays d'Aix			0	0
Dr BORY	Centre Hospitalier de Bastia			0	0
TOTAL				**102**	**91**

Biomarker program

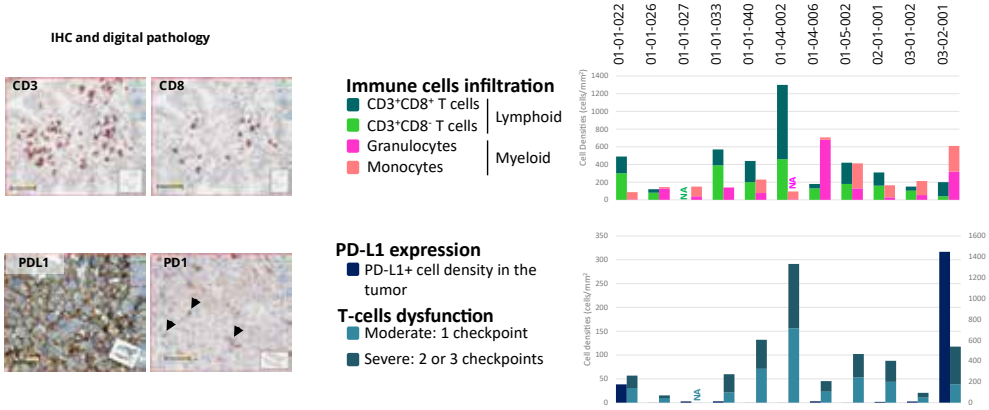
While collection and analysis of patient samples continues, a preliminary biomarker analysis was performed and presented by HalioDx at the SITC meeting 2019[1].

More than 20 biomarkers were analysed on 11 patients at baseline, before the start of their PD1(L1) inhibitor treatment, as a proof of concept of the performances of Immunogram[2] to identify relevant combinations of biomarkers that predict response to ICI treatment.

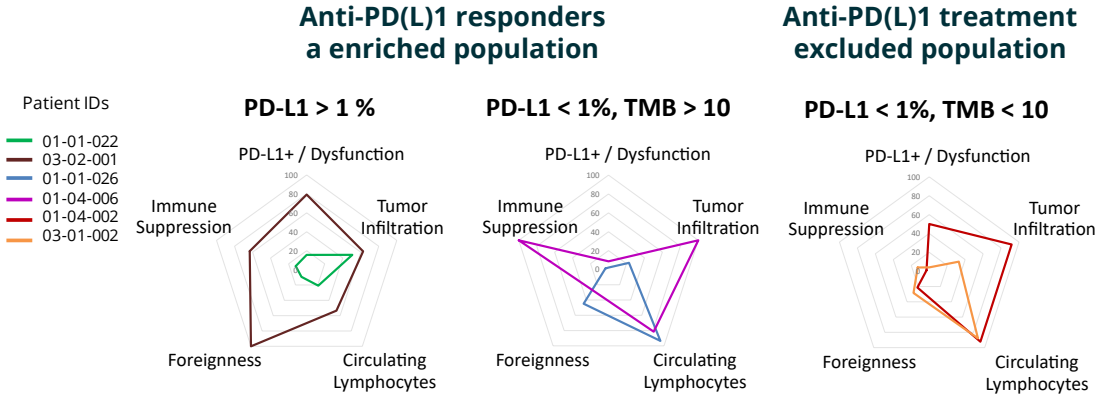
As an example, these are the kind of data obtained for individual patients for immune infiltration and the analysis of PDL1 and other immune checkpoints.

1 Monville F et al. Immunogram to decipher PD1/L1 ICI resistance: a proof of concept in advanced NSCLC patients of the PIONeeR Project. SITC 2019. Poster P117.
2 Blank CU et al. The "Cancer Immunogram". Science 2016. 351: 658-660

Data acquisition and distribution across patients



From the data for the complete set of 20 biomarkers, scores are derived to draw an immunogram for each individual patient.



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.

Modifications

The Pioneer Project team reacts promptly to the changes required to move the project forward.

Work package 1: clinical trial

Two experimental arms were changed:

- New regulatory approvals were obtained,
- The supply of all experimental molecules was adjusted,
- The delay caused by these modifications was limited to six months.

An additional amendment should follow in 2020, when a new experimental arm is added

Work package 2: biomarkers

Since November 2019, the French social security system covers a treatment combining an anti-PD1 (Merck's Keytruda®) with chemotherapy as 1st line for advanced NSCLC patients:

- Regulatory approvals were anticipated,
- Patient inclusion started as soon as the coverage was in place.

This modification will enable comparison of biomarkers predicting resistance in patients receiving immunotherapy in 1st and 2nd/3rd line.

Work package 3

This work package aims to **explore new target pathways to reprogram immune effectors in favour of an anti-tumour immunity**.

This package originally included two target molecules: BTLA and KLRG1.

While the BTLA work plan remains unchanged, several studies published in 2018 have shown that the expression profile of KLRG1 raises many questions [1,2,3,4,5].

The WP has therefore been reoriented to exclude KLRG1 and instead include two new tasks:

Identify ligands for natural cytotoxicity receptors (NCRs) NKp46 and NKp44. NCRs are involved in the activation of NK cells by tumour cells. Starting from a panel of tumour cell lines that elicit activation of primary human NK cells, the main objective is to uncover ligands for these receptors that might be activated therapeutically against tumour cells.

Explore the role of B cells in anti-tumour immunity. B lymphocytes organized in structures related to germinal centers mainly infiltrate the invasion front of many solid tumors. The aim is to analyze the function of these infiltrated B lymphocytes.

1 Thommen DS et al. A transcriptionally and functionally distinct PD-1+ CD8+ T cell pool with predictive potential in non-small-cell lung cancer treated with PD-1 blockade. Nat Med 2018. 24:994–1004
2 Savas P et al. Single-cell profiling of breast cancer T cells reveals a tissue-resident memory subset associated with improved prognosis. Nat Med 2018. 24:986–993
3 Duhen T et al. Co-expression of CD39 and CD103 identifies tumor-reactive CD8 T cells in human solid tumors. Nat Comm 2018.2724
4 Guo X et al. Global characterization of T cells in non-small-cell lung cancer by single-cell sequencing. Nat Med 2018. 24:978–985
5 Zheng C et al. Landscape of Infiltrating T Cells in Liver Cancer Revealed by Single-Cell Sequencing. Cell 2018. 169(7): 1342-1356

Upcoming events

Pioneer Project inside

February 7, 2020

Scientific Advisory Board & Broad General Assembly including members of the National Agency for Research (ANR)

Spring 2020

Midway evaluation of the project by the ANR

Meetings for 2020

April 24-29, 2020

AACR Annual Meeting, San Diego, USA

CONTACTS

Coordination

Marie ROUMIEUX
marie.roumieux@univ-amu.fr

Promoter

Alexandra GIULIANI
alexandra.giuliani@ap-hm.fr

Pharmacovigilance

Julie BRUNET
julie.brunet@ap-hm.fr

Samples logistics

Maryannick LE RAY
maryannick.le-ray@ap-hm.fr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PROJET FINANCÉ PAR L'ANR
PROJECT FUNDED BY THE ANR
INVESTIR L'AVENIR
A*Midex
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