PIONEER UP

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# Immuno-Oncology & Lung cancer **Highlights 2018**

THE PIONEER PROJECT

# Immuno-Oncology and Lung cancer - Highlights 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].

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[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