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# Precision Immuno-Oncology for advanced NSCLC patients treated with PD(L)1 immune checkpoint inhibitors (ICIs)

An analysis of the first 100 pts from the **PIONeeR Project**

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**On behalf of the PIONeeR consortium**

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Gustave Roussy Cancer Campus, Villejuif, France

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# DISCLOSURE INFORMATION

## Personal financial interests:

Astra-Zeneca, Bayer, Bristol-Myers Squibb, Boehringer–Ingelheim, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Novartis, Merck, Mirati, MSD, Pierre Fabre, Pfizer, Seattle Genetics and Takeda

## Institutional financial interests:

Abbvie, ACEA, Amgen, Astra-Zeneca, Bayer, Bristol-Myers Squibb, Boehringer–Ingelheim, Eisai, Eli Lilly Oncology, F. Hoffmann–La Roche Ltd, Genentech, Ipsen, Ignyta, Innate Pharma, Loxo, Novartis, Medimmune, Merck, Mirati, MSD, Pierre Fabre, Pfizer, Sanofi-Aventis and Takeda

## Non-financial interests:

Principal Investigator for Astra-Zeneca, BMS, Merck, Pierre Fabre and F. Hoffmann-La Roche, Ltd, sponsored trials (or ISR)

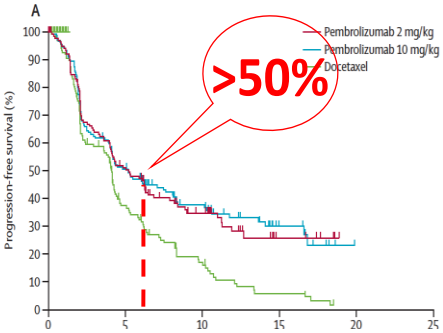
# PIONeeR

Background, Rational & Objectives

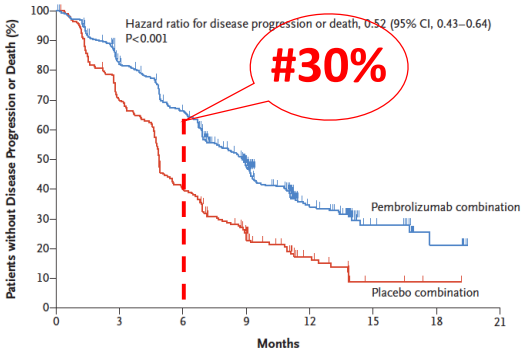
# PD-(L)1i in 1st & 2nd line for advanced NSCLC pts

## Long-term benefit is the goal but primary resistance occur w/o available predictive biomarker(s)

Ex. Pembrolizumab 2nd line in advanced NSCLC (Herbst R, et al. Lancet 2015)



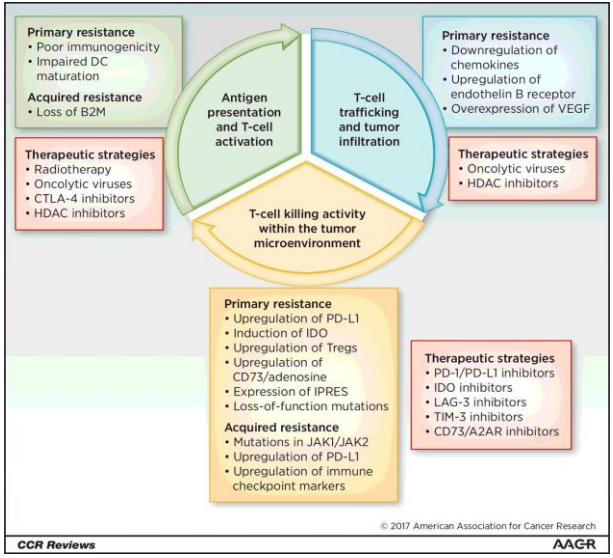

Ex. Pembrolizumab with chemotherapy 1st line line in advanced NSCLC (Ghandi L, et al. NEJM 2018)




*KN010 and KN189 studies have been choosen to illustrate the rational and data are comparable with other types of PD-(L)1 inhibitors alone or in combination with chemotherapy*

# PD-(L)1i in 1st & 2nd line for advanced NSCLC pts

## Proposed mechanisms of resistance




**Distribution** in advanced NSCLC?

►IO naive (primary resistances)?

►IO pretreated (secondary resistances)?

**Predictive value** for efficacy of next generation IO drugs?

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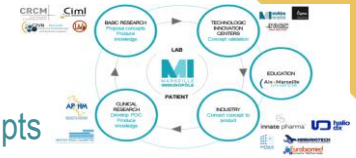
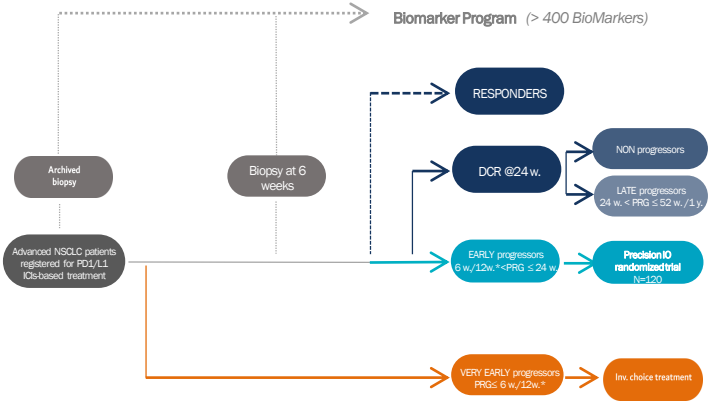
# The PIONeeR project

## Understand, Predict and Overcome resistances to PD-(L)1i in adv. NCSLC pts

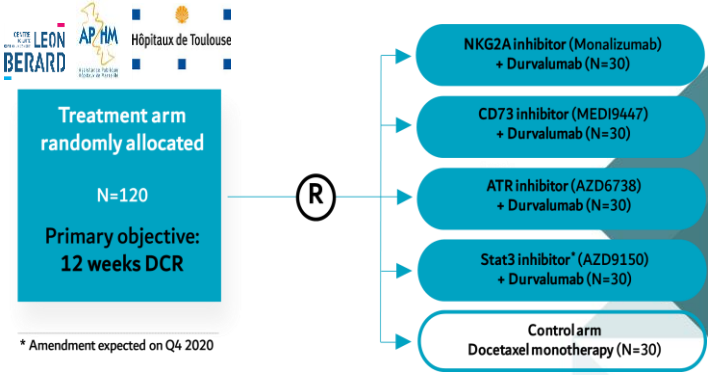


**Understand and Predict**: PIONeeR biomarkers trial




* *Related to 1st line IT+CT*

**Overcome**: PIONeeR umbrella trial




* Amendment expected on Q4 2020

# PIONeeR Biomarkers

Patients & Methods

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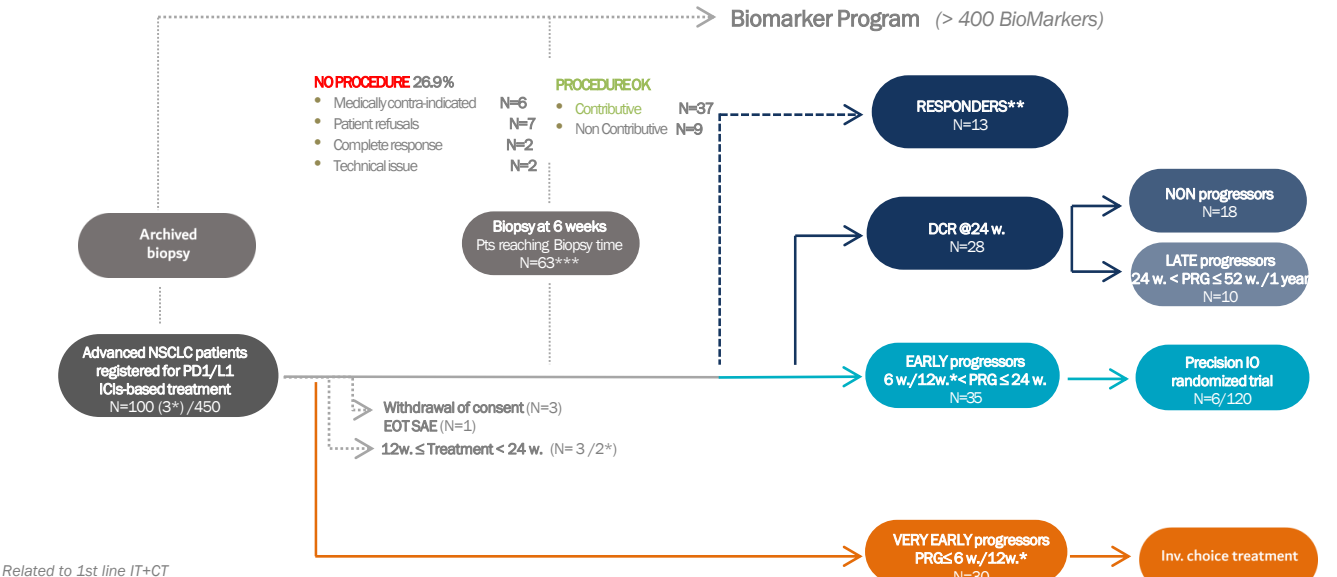
# PIONeeR Biomarkers

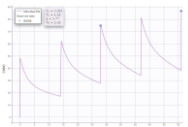
## Design and Flow Chart



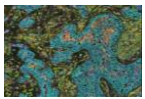

** Related to 1st line IT+CT*
*** Based on RECIST v1.1, irrespective of the study period*
**** Including 3 Very Early Progressors , with a radiologic progression (inclusion in clinical trial)*

# PIONeeR Biomarker program

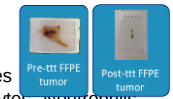
> 400 biomarker data planned at VS & 6W – 123 analyzed VS for at least 33 pts



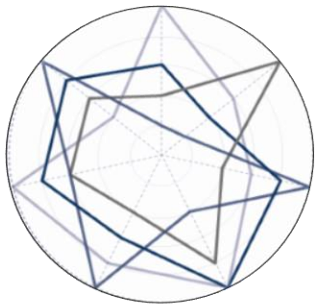
**Drug response**
- PK/PD modelling from longitudinal data



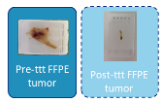
**Immune cells infiltration**
- Mplx IHC, incl. CD3/CD8 cell densities
- Mplx IHC, incl. Monocytes, Granulocytes, Neutrophils
- Mplx Innate Immunity

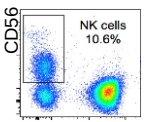



Testing initiated
Data available
To be initiated

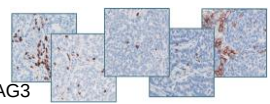


**Sensitivity to immune effectors**
- Immune gene expression signatures

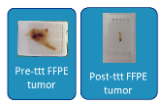


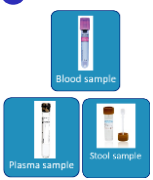




**Peripheral markers**
- Circulating immune cells
- Soluble markers
- Endothelial markers
- ctDNA
- Microbiome



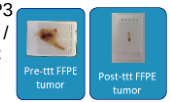
**Immune checkpoints**
- Immunoscore® IC PD-L1/CD8
- Mplx TCE: CD3/CD8/PD1/TIM3/LAG3

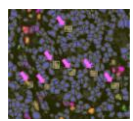



**Tumor foreigness**
- TMB
- T-cell clonality

**Immune suppression**
- Treg – CD4/FOXP3
- Mplx PMN-MDSC / Mononuclear MDSC



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# PIONeeR Biomarkers

## Statistical Analyses

**Endpoints and statistical methods**

- Overall response: binary endpoint, odds ratios (and their 95% CI) estimated using Firth's penalized maximum likelihood logistic regression
- Progression-free and Overall survival: time-to-event endpoint, hazard ratios (and their 95% CI) estimated using Firth's penalized maximum likelihood Cox regression

**Exploratory analyses**

- In the case of a continuous biomarker with a statistically significant impact on PFS or OS in multivariate analysis, a cutoff value was determined using a widespread and straightforward method to select a cutoff value that minimizes the P-value

**R software version 3.6.0**

# PIONeeR Biomarkers

Results on the first 100 patients included

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# PIONeeR Biomarkers: First 100 patients analysis

## Baseline Patients' demographics

| | | N - %* (* *Same number as n=100)* |
|---|---|---|
| Sex | Male / Female | **64 / 36** |
| Age | <70yrs / ≥70yrs | **69 / 31** |
| ECOG PS | 0-1 / 2-3 | **96 / 3** |
| Histology | Adenocarcinoma (w oncogene driver / w *KRAS*m)<br>Squamous Cell C.<br>Others/Unknown | **57 (9 / 28)**<br>**18**<br>**25** |
| Smoking history | Never / Former<br>Current | **8 / 49**<br>**40** |
| Line of PD-(L)1 therapy | 1st line / 2nd line<br>3rd line or more | **3 / 87**<br>**10** |
| Type of PD-(L)1 drug received | Pembrolizumab (alone/w chemo)<br>Nivolumab<br>Atezolizumab | **34/4**<br>**36**<br>**26** |

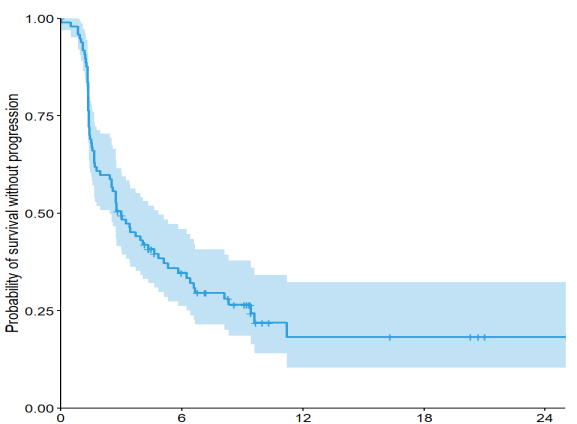
# PIONeeR Biomarkers: First 100 patients analysis

## Outcomes (ITT population)

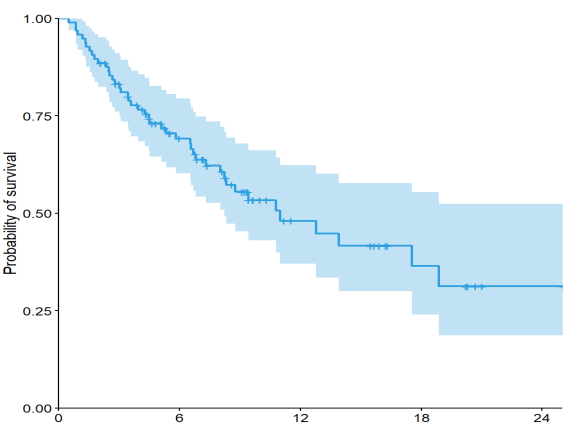
Median length of follow-up: **6.55 months** (range 0.01 – 26.15)

**Overall Response Rate**: **13%** (95%CI 7.1% – 21.2%)

**Median PFS** (71 events): **3.0 m** (95%CI 2.4 – 4.8)




Median **OS** (44 events): **11.0 m** (95%CI 8.2 – NR)



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# PIONeeR Biomarkers: First 100 patients analysis

## Clinical Characteristics[$] & Biomarkers associated with **Objective Response**

| Timepoint | Biomarker | Non-Responders | | Responders | | *P-value* |
|---|---|---|---|---|---|---|
| | | N valid | Mean | N valid | Mean | |
| Pre-treatment | PD-L1+ tumor cell percentage* | 70 | 14% | 11 | 33% | ***0,045*** |
| | Cytotoxic T cells CD3+/CD8+ density in the Tumor | 43 | 298 cells/mm² | 7 | 383 cells/mm² | ***0,041*** |
| | Cytotoxic T cells at TSI (Tumor-Stroma Interface) | 26 | 178 cells/mm² | 4 | 511 cells/mm² | ***0,041**** |
| | Effective T cell density in the Tumor | 43 | 116 cells/mm² | 7 | 172 cells/mm² | ***0,008*** |
| | Regulatory T-cell density in the Stroma | 49 | 18 cells/mm² | 7 | 70 cells/mm² | ***0,010*** |
| | Tissue factor blood concentration (endothelial activation) | 28 | 21,6 fM | 6 | 8,8 fM | ***0,046*** |
| 6 weeks | Neutrophils in the Stroma | 9 | 16 cells/mm² | 2 | 73 cells/mm² | ***0,036*** |

[$], Sex, age, ECOG PS, Histological subtypes, Smoking status, line of therapy and type of PD-(L)1 drug were not found to significantly influence the likelihood of response; * PD-L1 TC expression (<1% vs ≥1%) was significant in multivariate analysis, HR: 4,1 [1,3;14]; ** p-value F-test

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# PIONeeR Biomarkers: First 100 patients analysis

## Clinical Characteristics associated with **Progression Free** & **Overall Survival**

| | **Median PFS (months)** | **HR (95%CI), *p-value*** |
|---|---|---|
| ECOG PS (2/3 vs 0/1)* | **1,22** [0,49;NA] vs **3,22** [2,53;5,32] | **10.8** [2.9 – 30.4], *p=0.002* |
| Histological Subtype (Others *vs* ADC) | **1,51** [1,35;3,45] vs **4,63** [2,53;11,20] | **2.24** [1.3 – 3.9], *p=0.007* |
| Type of PD-(L)1i (Pembro. vs Nivo.) | **3,22** [1,77;NA] vs **2,56** [1,54;4,07] | **0.58** [0.34 – 1.0], *p=0.049* |
| PD-L1 TC expression (<1% vs ≥1%)* | **2,25** [1,58;3,71] vs **6,60** [2,99;NA] | **2.0** [1.2 – 3.5], p=0.004 |

| | **Median OS (months)** | **HR (95%CI), *p-value*** |
|---|---|---|
| ECOG PS (2/3 vs 0/1)* | **3,09** [0,49;NA] vs **12,78** [8,31;NA] | **3.9** [1.1 – 10.3], *p=0.041* |

Sex, age, Smoking status, and line of therapy were not found to significantly influence the risk of progression; * Significant in multivariate analysis

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# PIONeeR Biomarkers: First 100 patients analysis

## Biomarkers associated with **Progression Free & Overall Survival**

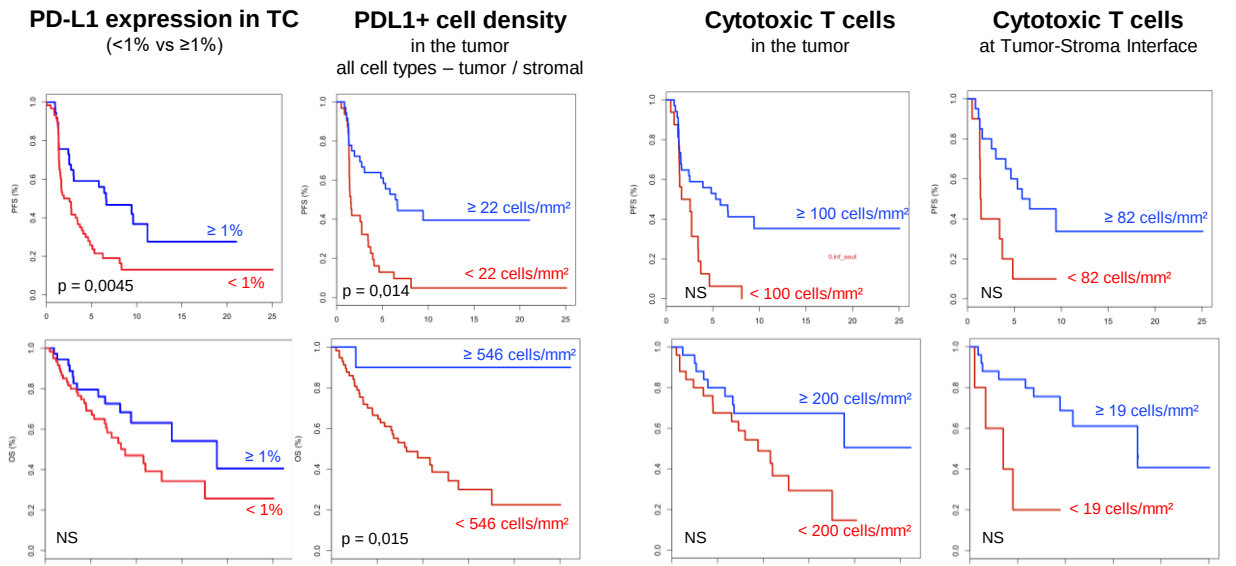
| | Hazard Ratio PFS [95% IC] | *p-value* |
|---|---|---|
| PD-L1 expression in TC (%) * | 0,98 [0,96;0,99] | *0,0209* |
| Circulating Activated T cells * ** | 1,06 [1,02;1,10] | *0,0008* |
| Serum IL6 * | 1,00 [1,00;1,01] | *0,047* |
| Cytotoxic T cells in the tumor ** | 1,00 [1,00;1,01] | *0,047* |

| | Hazard Ratio OS [95% IC] | *p-value* |
|---|---|---|
| Circulating T cells * | 0,99 [0,99;0,99] | *0,039* |
| Circulating Activated T cells * | 1,07 [1,03;1,12] | *0,001* |
| Serum IL6 * | 1,00 [1,00;1,01] | *0,037* |
| Serum TNFα * | 1,04 [1,01;1,09] | *0,031* |

* Multivariate analysis stratified on Sex, Age, ECOG PS, Histology, Smoking history, Line of PD-(L)1 therapy, Type of PD-(L)1 drug received, PDL1 1%; ** Multivariate analysis stratified on Sex, Age, ECOG PS, Histology, Smoking history, PDL1 1%

# PIONeeR Biomarkers: First 100 patients analysis

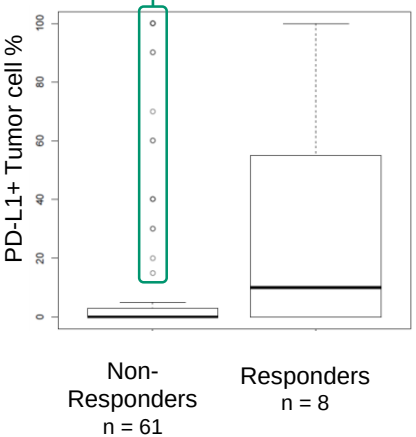
## Examples of biomarkers associated with **Progression Free Survival** & **Overall Survival**

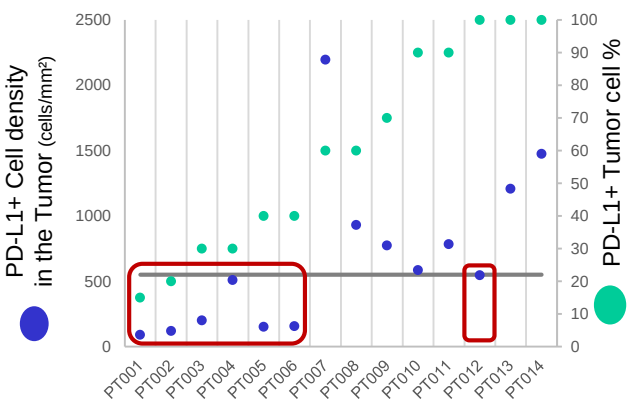


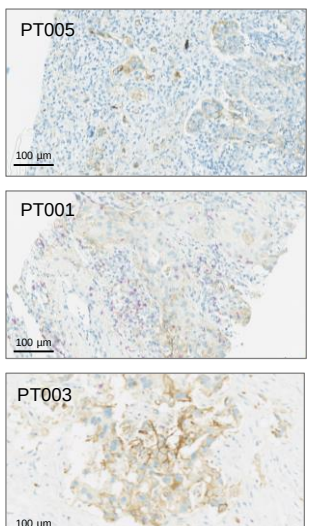
# PIONeeR Biomarkers: First 100 patients analysis

## Example: PD-L1 positive cell density: a potential new and potent predictive biomarker?

16 Non-responders pts w PD-L1+ ≥ 15% TC

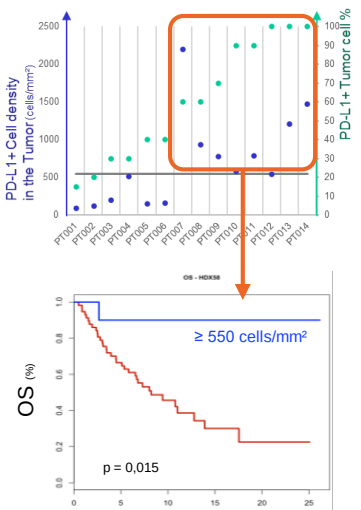


# PIONeeR Biomarkers: First 100 patients analysis

## Example: PD-L1 positive cell density: a potential new and potent predictive biomarker?




550

Immune profiling

| | PT007 | PT009 | PT008 | PT010 | PT013 | PT011 | PT014 | |
|---|---|---|---|---|---|---|---|---|
| PD-L1+ TC % | 60 | 70 | 60 | 90 | 100 | 90 | 100 | PDL1 expression |
| PD-L1+ cell density | 2197 | 775,75 | 930,66 | 586,24 | 1208,6 | 784,41 | 1476,8 | |
| Cytotoxic T cells | 1579,8 | 563,32 | | 459,7 | | 680 | 160 | TI* Anti-tumor Immune cells |
| Cytotoxic T cells PD1+ | 111,92 | 36,37 | | 26,88 | | 190 | 7,7 | |
| monocytes | 369,87 | 206,52 | | 66,3 | 275,91 | 810 | 502,68 | |
| Granulocytes | 43,54 | 6,4 | | 30,11 | 28 | 110 | 149,35 | |
| Neutrophilis | 29,44 | 3,29 | | 12,64 | 23,06 | 67 | 38,43 | |
| Periph Cells | 2320,0 | 1371,0 | 2303,0 | 614,0 | | 1193,0 | 1059,0 | Circulating Immune cells |
| Periph Activ. T Cells | 6,3 | 5,4 | 6,7 | 12,2 | | 8,6 | 11,8 | |
| Serum IL6 | 13,2 | | | | | 186,87 | 58,06 | Cytokines |
| Serum TNAα | 0 | | | | | 0 | 0 | |
| Mono. MDSC | 2,46 | 4,5 | | 0 | 28,83 | 1,2 | 27,73 | Suppressive Immune cells |
| PMN MDSC | 5,27 | 1,56 | | 15,91 | 4,94 | 27 | 110,65 | |
| Treg | 86,99 | 19,3 | 115,85 | 79,09 | 0 | 74,68 | 8,47 | |
| Exhausted T cells | 644,29 | 72,15 | | 51,32 | | 100 | 31 | Immune CP expression |
| Effector T cells | 186,77 | 201,41 | | 173,15 | | 110 | 29 | |

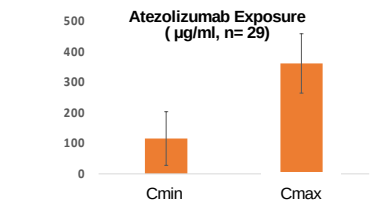
Min Max

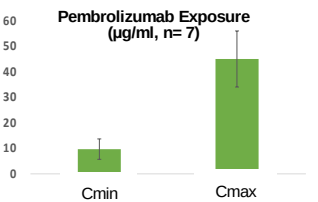
* TI : Tumor Infiltrating; ** IC : Immune Cells

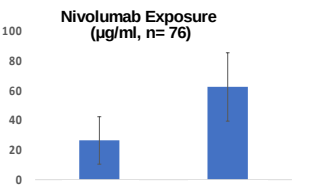
# PIONeeR Biomarkers: First 100 patients analysis

## PK/PD modelling preliminary results

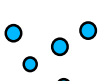
- Large inter-patient variability on both peak levels and through levels



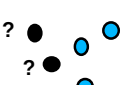



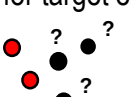

- Identification of individual PK parameters and PK/PD modeling (ongoing)
- Identification of outlier patients with trough levels below the required threshold for target engagement



5 PD patients
despite adequate cell density




2 assayed for nivolumab trough levels




Both showed nivolumab trough levels **below** the threshold associated with efficacy

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# PIONeeR Biomarkers: First 100 patients analysis

## Evolution of immune profile before and 6 weeks after PD-(L)1 treatment

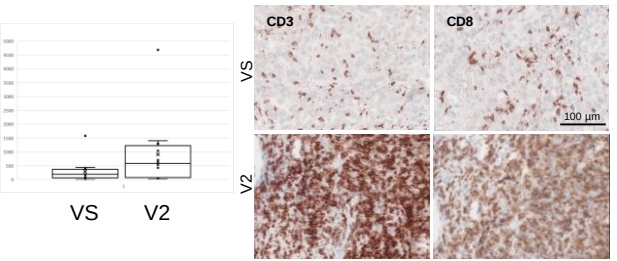
| Marker | N valid | Log2 Fold Change | VS Mean | V2 Mean | *P-value* |
|---|---|---|---|---|---|
| PD-L1+ cell density in the tumor | 21 | **2,4** | 219 | 548 | *0,002* |
| Cytotoxic Tcells density in the tumor | 21 | **1,4** | 310 | 952 | *0,007* |
| CD8+-PD-L1+ cells proximity index in the tumor | 21 | **2,1** | 6,3 | 42,8 | *0,0009* |
| Regulatory Tcells in tumor parenchyma | 21 | **1,6** | 32 | 75 | *0,002* |
| Regulatory Tcells in the stroma | 17 | **1,7** | 24 | 97 | *0,01* |
| Exhausted T cells in the tumor | 12 | **2,3** | 34 | 238 | *0,004* |

# PIONeeR Biomarkers: First 100 patients analysis

## Lymphocytes infiltration increases after treatment.

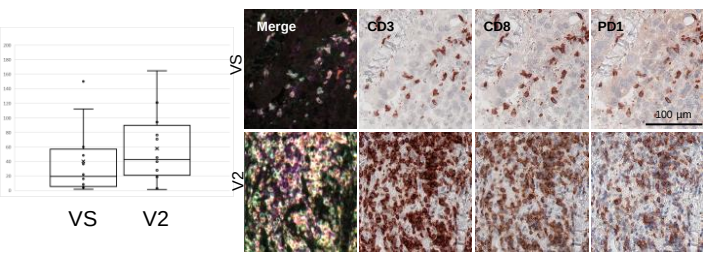
### Cytotoxic Tcells

CD3+ CD8+



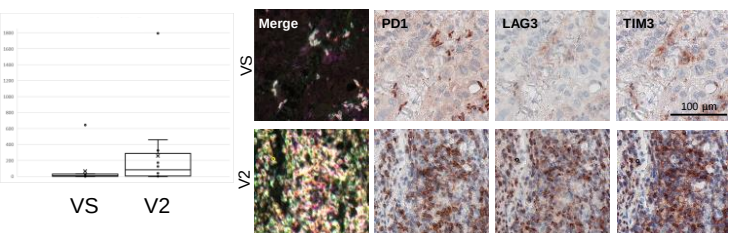

### PD1-expressing Cytotoxic T cells

CD3+ CD8+ PD1+



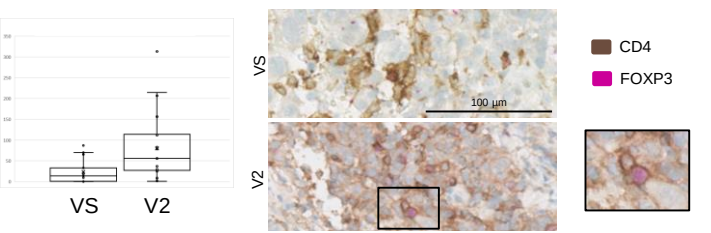

### Exhausted Tcells

CD3+ CD8+ PD1+ LAG3+ TIM3+




### Tregs in Parenchyma

CD4+ FOXP3+



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# PIONeeR Biomarkers: First 100 patients analysis

## Conclusions

PIONeeR biomarkers is the **first and the largest** study to provide with >400 biomarkers assessed in advanced NSCLC treated with PD-(L)1 inhibitors in monotherapy or in combinaison with chemotherapy

Some **clinical** factors predicted the outcomes on PD-(L)1 inhibitors

- **ECOG PS** remains the strongest to predict OS

**Biomakers** are therefore mandatory and PIONeeR suggested a predictive value for:

- PDL1 tumor expression, with **PDL1 positive cell density** possibly superior
- Density of **Cytotoxic T cells** in the tumor
- Density of Immunosuppressive cells: **Treg**, MDSC

The study is still **ongoing** and additional patients as well as analyses will provide with additional data in order to design an '***immunogram***' helping to drive the IO management of advanced NSCLC

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