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**3MO - Comprehensive biomarkers (BMs) analysis to predict efficacy of PD1/L1 immune checkpoint inhibitors (ICIs) in combination with chemotherapy: a subgroup analysis of the Precision Immuno-Oncology for advanced Non-Small CELL Lung CancER (PIONeeR) trial**

Fabrice Barlesi, Laurent Greillier, Florence Monville, C Audigier-Valette, S. Martinez, N. Cloarec, Sylvie van Hulst, L. Odier, Frédéric Vely, L. Juquel, et al.

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# ESMO IMMUNO-ONCOLOGY

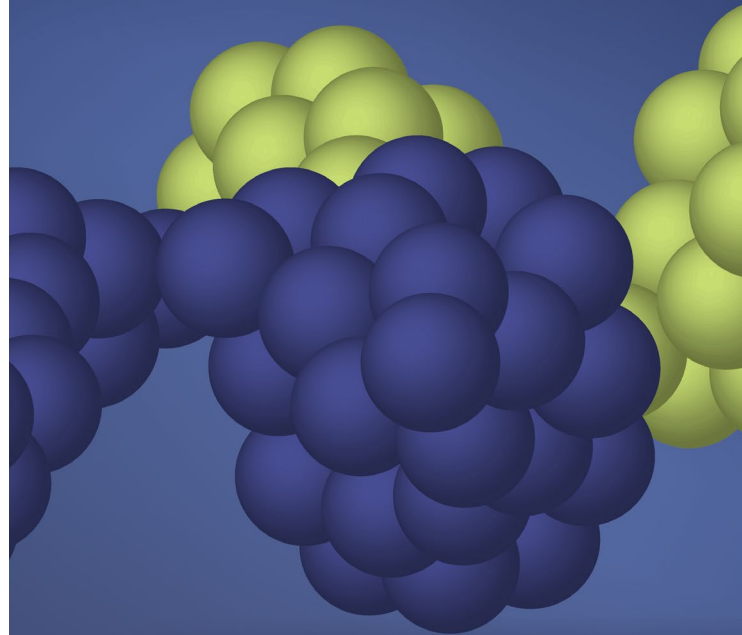
Annual Congress

## COMPREHENSIVE BIOMARKERS ANALYSIS TO PREDICT EFFICACY OF PD1/L1 ICI IN COMBINATION WITH CHEMOTHERAPY

A subgroup analysis of the Precision Immuno-Oncology for advanced Non-Small Cell Lung Cancer (PIONeR) trial

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# DECLARATION OF INTERESTS

Fabrice Barlesi, MD, PhD

## Personal financial interests:

- None (since August 2021)

## 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, MSD, Pierre Fabre, Pfizer, Sanofi-Aventis and Takeda

## Non-financial interests:

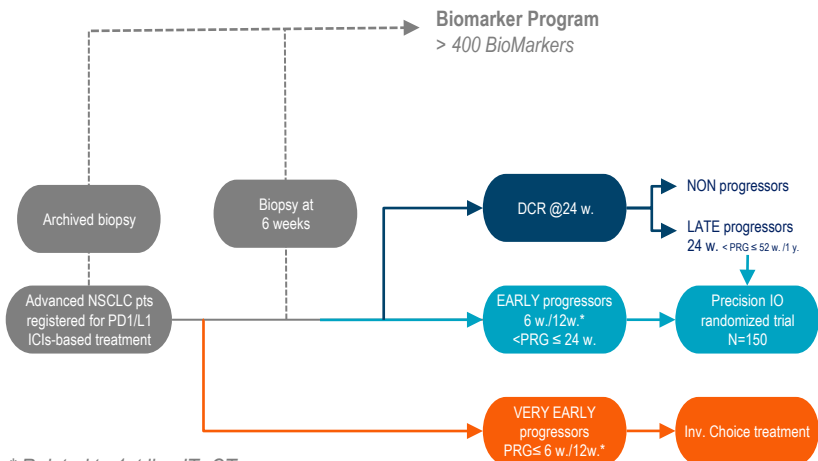
- Principal Investigator for Astra-Zeneca, BMS, Innate Pharma, Merck, Pierre Fabre and F. Hoffmann-La Roche, Ltd, sponsored trials (or ISR)

**No other conflicts of interest**

# THE PIONEER STUDY DESIGN

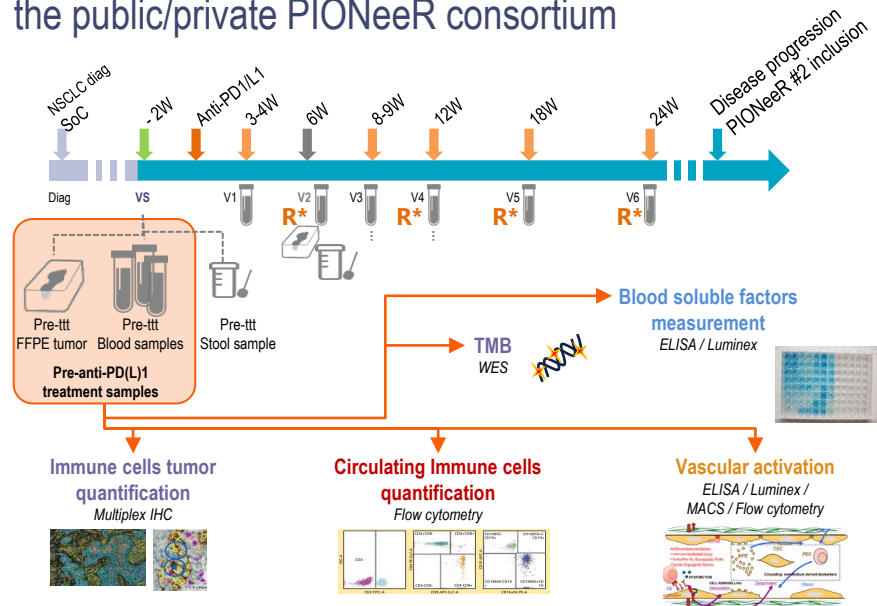
Assess, Understand & Overcome ICI resistances in advanced NSCLC

Baseline, On-treatment & Progression biopsies  
Both 2<sup>nd</sup> and 1<sup>st</sup> line settings



\* Related to 1st line IT+CT

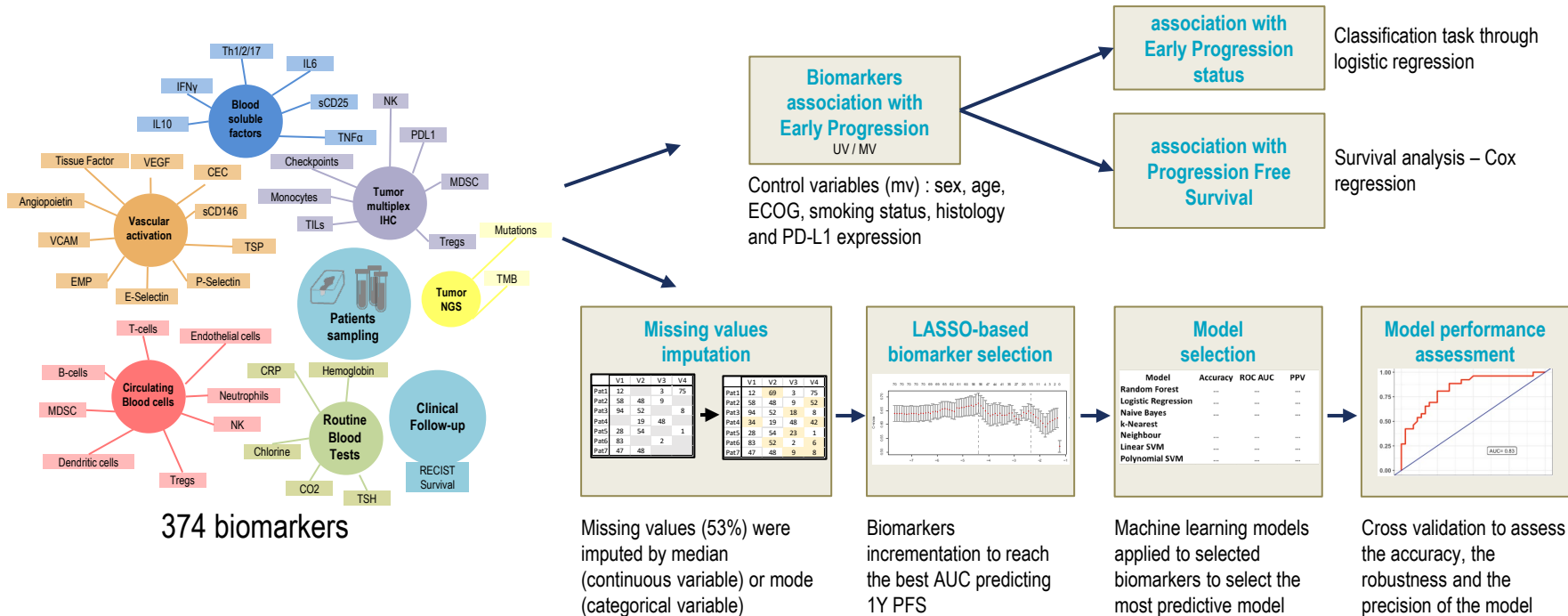
A comprehensive biomarkers assessment, thanks to the public/private PIONeer consortium



\*R : RECIST 1.1 evaluation every 6 weeks

# GENERATE A MULTIMODAL PREDICTIVE SIGNATURE

Aim: predict patients deriving the largest long-lasting PFS benefit



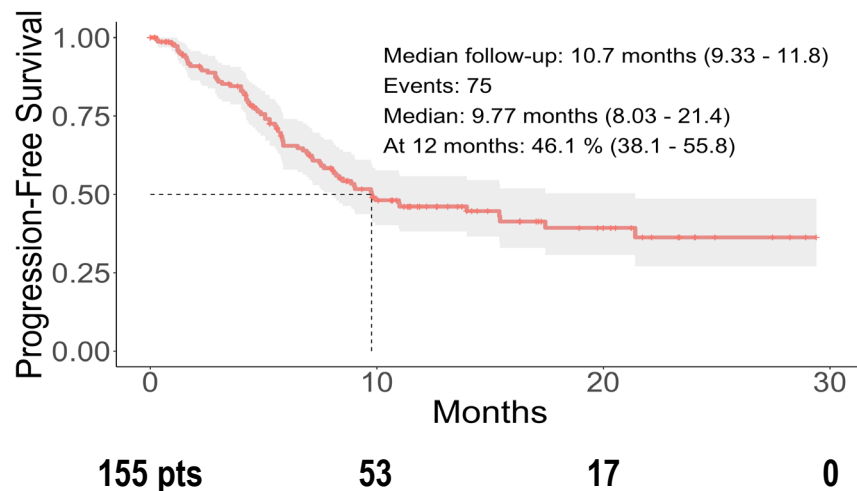
# PATIENTS CHARACTERISTICS & OUTCOMES

Overall, 350 pts included to date - Focus on the 1<sup>st</sup> line setting\*

To date, 155 pts treated with Chemo/Pembrolizumab

PFS outcomes in line with reported results

<b>SEX</b>	M	101 (65%)	<b>PD-L1 EXPRESSION</b>	≥1%	43 (35%)
	F	54 (35%)		<1%	81 (65%)
<b>AGE</b>	<70	127 (82%)	<b>BIOPSY SITE</b>	Not interpretable	31
	≥70	28 (18%)		Metastasis	51 (38%)
<b>ECOG</b>	0	68 (44%)	<b>HISTOLOGY</b>	Primitive tumor	85 (62%)
	1	86 (56%)		Unknown	19
	Unknown	1		ADK	98 (84%)
<b>TOBACCO HISTORY</b>	Current	55 (37%)	<b>TREATMENT</b>	Others	4 (3.4%)
	Never	7 (4.7%)		Squamous	15 (13%)
	Previous	88 (59%)		Unknown	38
<b>RECIST</b>	Unknown	5	<b>RECIST</b>	anti-PD1	6 (3.9%)
				anti-PDL1	0 (0%)
				PEMBRO+CHEMO	149 (96%)
				CR	8 (7.1%)
				PD	4 (3.5%)
		PR	60 (53%)		
		SD	41 (36%)		
		Unknown	42		



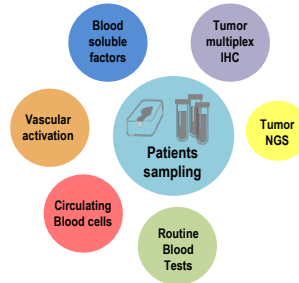
# RESULTS: STANDARD ANALYSIS

## Biomarkers associated with PFS (1<sup>st</sup> line setting only)

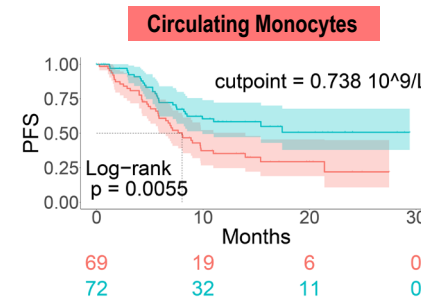
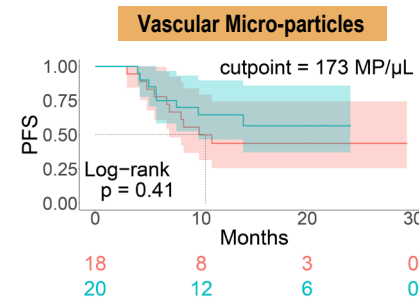
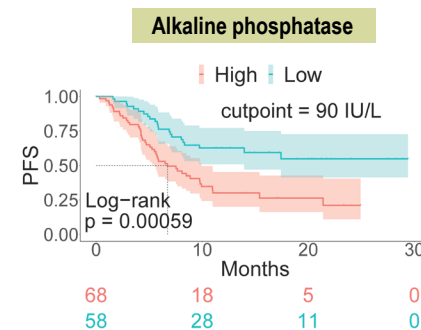
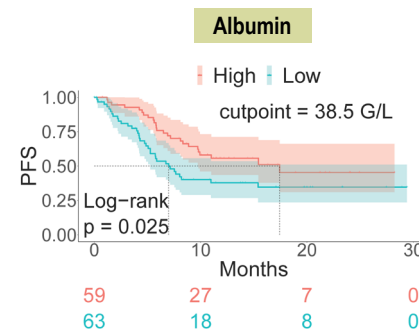
### Global Table (Univariate/Multivariate Analyses)

Variable	UV		MV	
	HR	p	HR	p
Albumin	0.71 (0.55 - 0.92)	**	0.47 (0.31 - 0.7)	***
Alkaline phosphatase	1.5 (1.3 - 1.8)	****	1.4 (1.2 - 1.7)	***
C reactive protein	1.6 (1.3 - 2.1)	***	1.9 (1.3 - 2.7)	***
Chlorine	0.66 (0.51 - 0.85)	**	0.6 (0.43 - 0.82)	**
Circulating Monocytes	1.4 (1.1 - 1.7)	*	1.6 (1.2 - 2.2)	**
VEGFR1	1.4 (1 - 2.1)	*	1.9 (1.2 - 2.8)	**
Platelets	1.3 (1 - 1.6)	*	1.5 (1.2 - 2)	**
ASAT	1.3 (1 - 1.6)	*	1.7 (1.2 - 2.5)	**
PD-L1 ≥ 1%	2.2 (1.2 - 3.8)	**	2.7 (1.3 - 5.7)	**
Prothrombin rate	0.65 (0.49 - 0.87)	**	0.55 (0.35 - 0.87)	*
Total bilirubin	1.5 (1.2 - 1.9)	***	1.6 (1.1 - 2.3)	*
Circulating Neutrophils	1.3 (1 - 1.6)	*	1.4 (1.1 - 2)	*
Vascular Micro-particles	1.6 (1.1 - 2.2)	**	1.7 (1.1 - 2.7)	*
Circulating Leukocytes	1.4 (1.1 - 1.7)	**	1.5 (1 - 2.1)	*
Stromal Monocytic MDSC	0.55 (0.31 - 0.98)	*	0.27 (0.081 - 0.92)	*

UV= univariable, MV= multivariable, \*\*\*\*= p<0.0001, \*\*\*= p<0.001, \*\*= p<0.01, \*= p<0.05

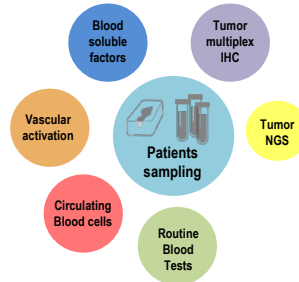


### Selected PFS curves

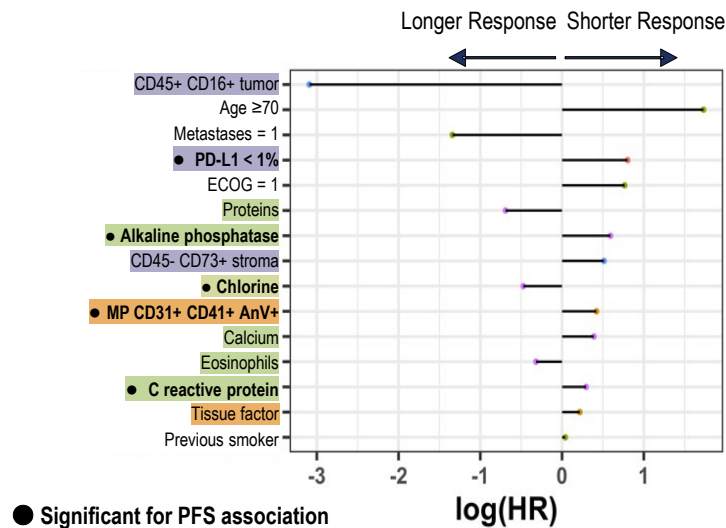


# RESULTS: MACHINE LEARNING

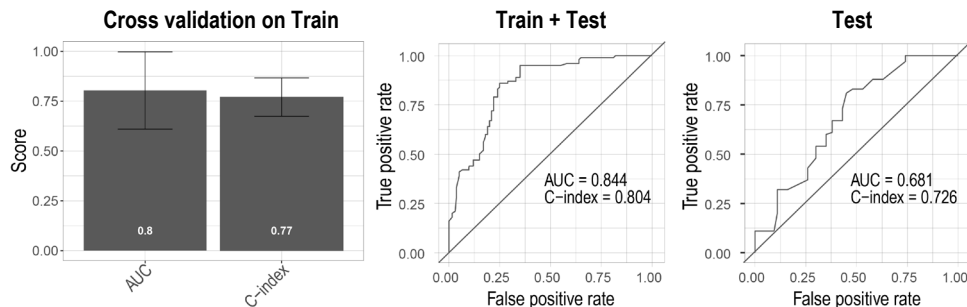
Biomarkers associated with PFS (1<sup>st</sup> line setting only)



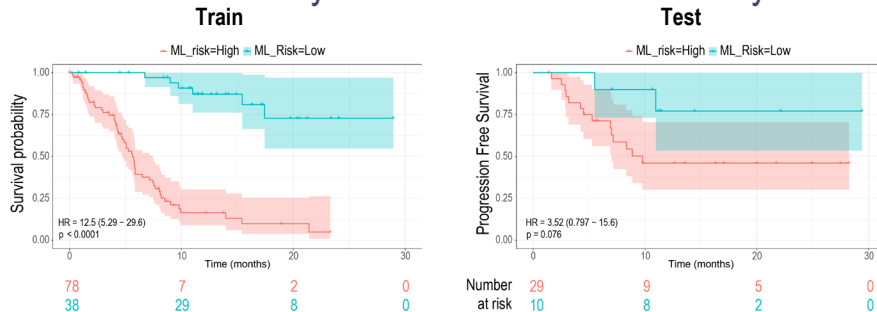
A 15-biomarkers signature



Training set (n=116, 75%), Testing set (n=39, 25%)



Prediction of the 1-year PFS with 83% sensitivity





# CONCLUSIONS

A multimodal signature predicts the 1<sup>st</sup> line chemo/ICI benefit in advanced NSCLC pts

- Our 15-biomarkers signature includes clinical, biological, tissue and circulating biomarkers
- Our predictive algorithm achieves good c-index and AUC in both cross-validation and testing set cohorts
- Variability of the cross-validation results is due to multiple samples still remaining to be processed; the completion of the study is expected in 2023
- The predictive model will be dissected at the pathophysiological level and an external validation will be performed on other cohorts

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## Patients & Families

### Investigators and Study teams

#### Marseille (& area)

- APMH Mult. Oncology & Therap Innov. Dep. : Pr L. Greillier, Dr P Tomasin
- St Joseph Private Hospital : Dr. C. Foa
- Europ. Hospital : Dr. J. Le Treut
- Ste Musse CHI, Toulon : Dr. C. Audigier-Valette
- Maynard Private Hospital, Bastia, Corsica : Dr. A. Frikha
- Bastia Hospital : Dr. P. Bory
- Aix-Pertuis Hospital : Dr S. Martinez
- OncoGard : Dr. A. Serre
- Nîmes Hospital : Dr. S. Van Hulst
- Avignon Hospital : Dr. N. Cloarec

#### Lyon (& area)

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- Annecy Hospital : Dr. S. Hominal

#### Toulouse (& area)

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- Cahors Hospital : Dr. P. Barre
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- CHIVA center : Drs. F. Romagné, L. Lebas

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- Oncology Phase I Unit CLIP<sup>2</sup> labeled (CEPCM) : M. Le Ray, Dr. A. Pelletier
- Pathology Dep. : Drs. JP. Dales, L. Juquel & team
- ImmunoProfiling Platform : Dr. F. Vély, A. Pouchin
- VasculoMonitoring Platform : Pr. F. Sabatier, L. Arnaud
- Data Management : R. Malkoun

## Veracyte

- J. Fieschi, F. Monville, L. Ghezali & team

## Innate Pharma

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## Inserm – Inria (COMPO Team)

- Biostatistics – Machine Learning : S. Benzekry, M. Karlsen, P. Dufosse & team

## Institut Paoli Calmettes – CRCM & ImCheck Therapeutics

- D. Olive & teams

## Léon Bérard Center

- Methodologists: Dr. D. Pérol, S. Chabaud, C. Cropet

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