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 (PIONeeR) trial

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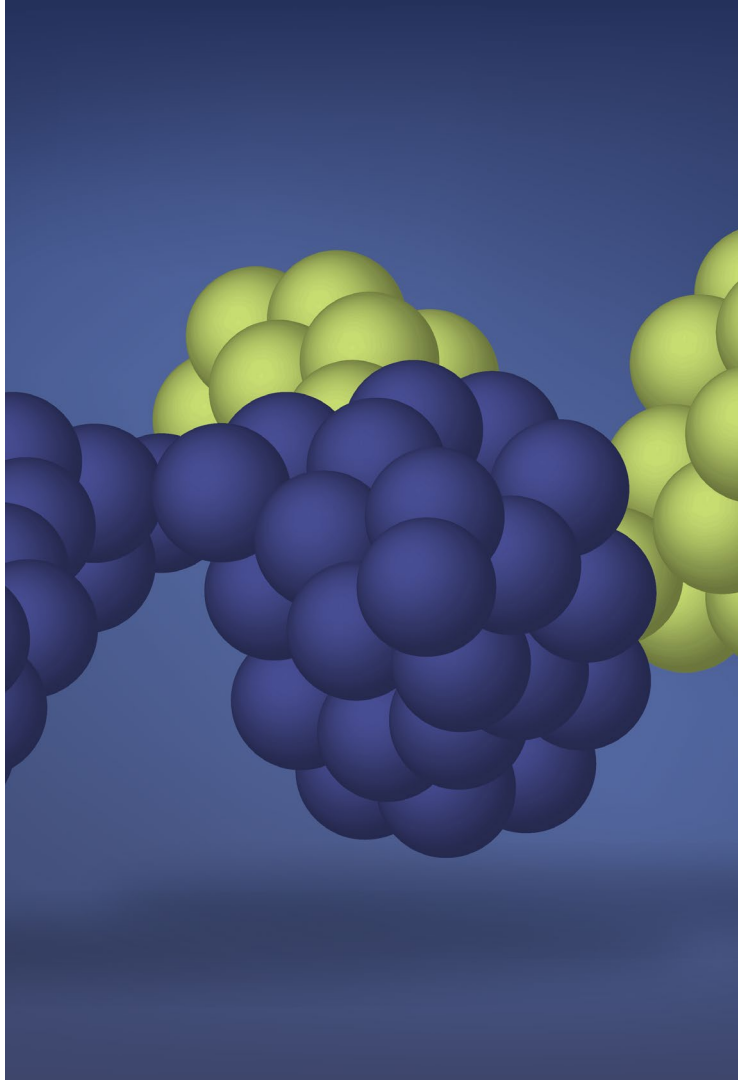
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE



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:

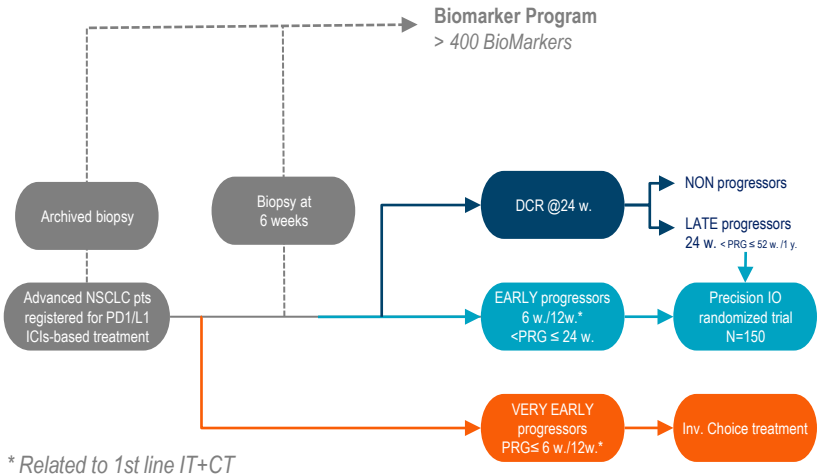
- Principal Investigator for Astra-Zeneca, BMS, Innate Pharma, Merck, Pierre Fabre and F. Hoffmann-La Roche, Ltd, sponsored trials (or ISR)

No other conflicts of interest

THE PIONEER STUDY DESIGN

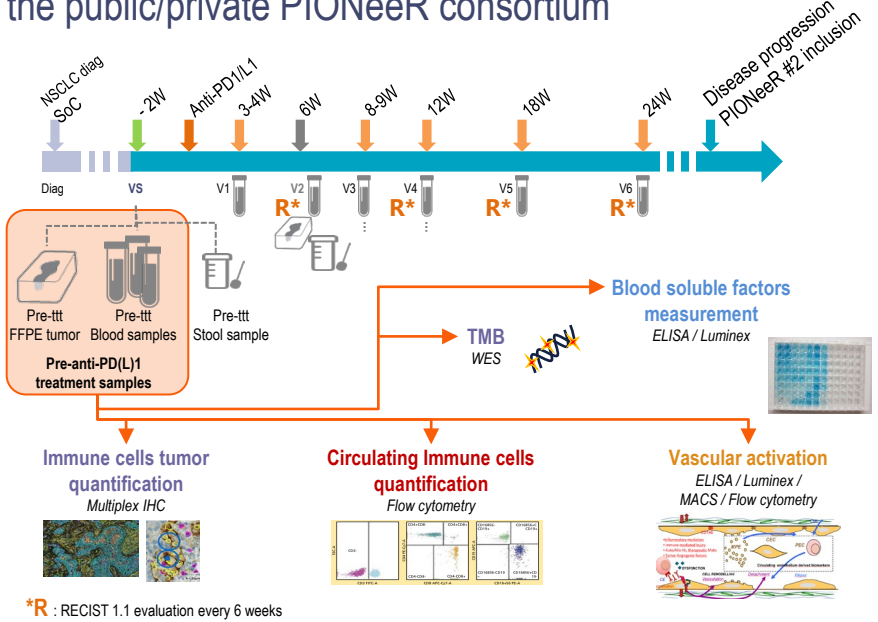
Assess, Understand & Overcome ICI resistances in advanced NSCLC

Baseline, On-treatment & Progression biopsies
Both 2nd and 1st 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

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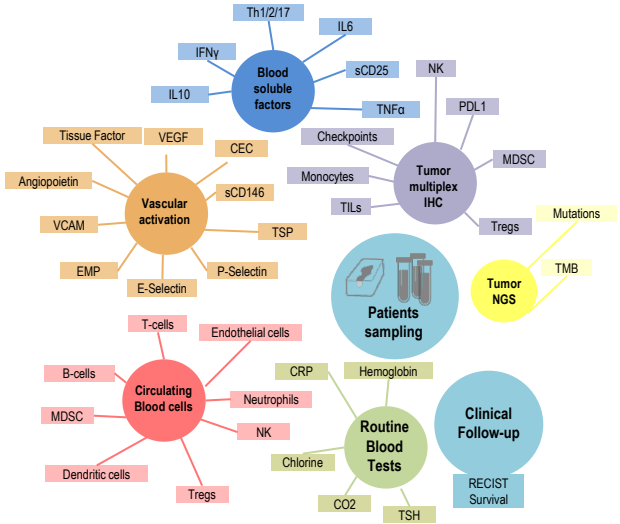
Barlesi F, et al. WCLC 2019 (P1.04-30); Barlesi F, et al. ESMO 2020 (LBA53), Leca et al, SITC 2021, Ghezali et al, SITC 2022 (p 701)

GENERATE A MULTIMODAL PREDICTIVE SIGNATURE

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



374 biomarkers

Biomarkers association with Early Progression
UV / MV

Control variables (mv) : sex, age, ECOG, smoking status, histology and PD-L1 expression

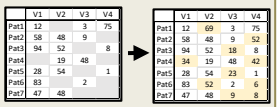
association with Early Progression status

Classification task through logistic regression

association with Progression Free Survival

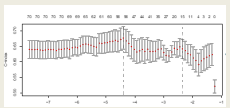
Survival analysis – Cox regression

Missing values imputation



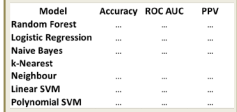
Missing values (53%) were imputed by median (continuous variable) or mode (categorical variable)

LASSO-based biomarker selection



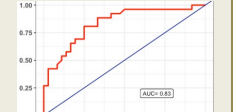
Biomarkers incrementation to reach the best AUC predicting 1Y PFS

Model selection



Machine learning models applied to selected biomarkers to select the most predictive model

Model performance assessment



Cross validation to assess the accuracy, the robustness and the precision of the model

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Benzekry, Clin Pharm Ther, 2020, Artificial intelligence and mechanistic modeling for clinical decision making in oncology
Greillier L, et al. AACR 2022 (LB120)

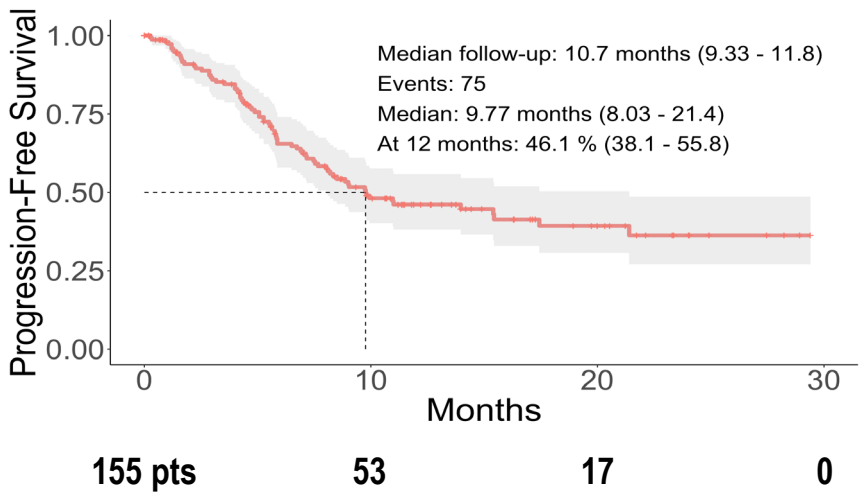
PATIENTS CHARACTERISTICS & OUTCOMES

Overall, 350 pts included to date - Focus on the 1st line setting*

To date, 155 pts treated with Chemo/Pembrolizumab

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

PFS outcomes in line with reported results



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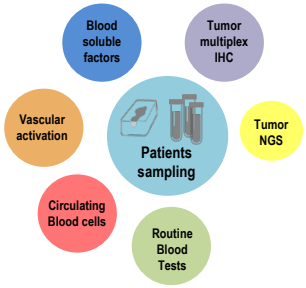
** See Greillier L, et al. AACR 2022 (LB120) for the results for the 2nd line setting*



RESULTS: STANDARD ANALYSIS

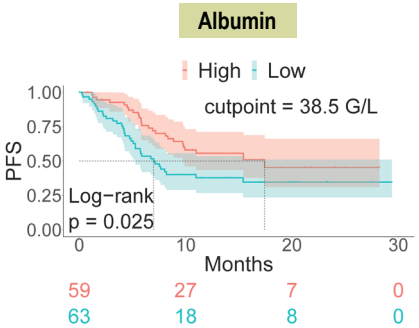
Biomarkers associated with PFS (1st line setting only)

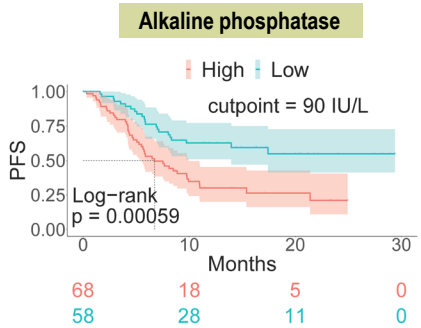
Global Table (Univariate/Multivariate Analyses)

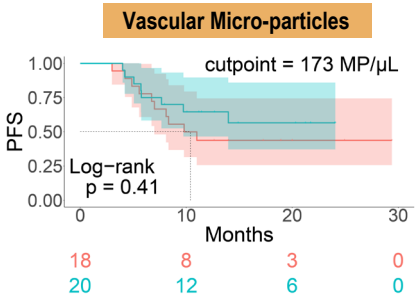
	UV		MV	
Variable	HR	p	HR	p
Albumin	0.71 (0.55 - 0.92)	**	0.47 (0.31 - 0.7)	***
Alkaline phosphatase	1.5 (1.3 - 1.8)	****	1.4 (1.2 - 1.7)	***
C reactive protein	1.6 (1.3 - 2.1)	***	1.9 (1.3 - 2.7)	***
Chlorine	0.66 (0.51 - 0.85)	**	0.6 (0.43 - 0.82)	**
Circulating Monocytes	1.4 (1.1 - 1.7)	*	1.6 (1.2 - 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)	*

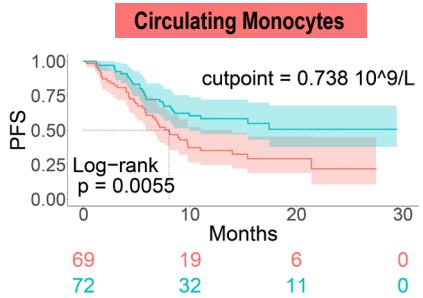
UV= univariable, MV = multivariable, **** = p<0.0001, *** = p<0.001, ** = p<0.01, * = p<0.05

Selected PFS curves









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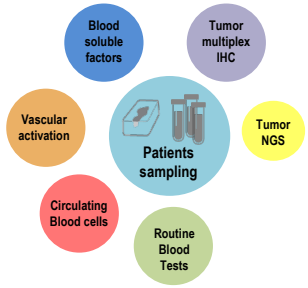
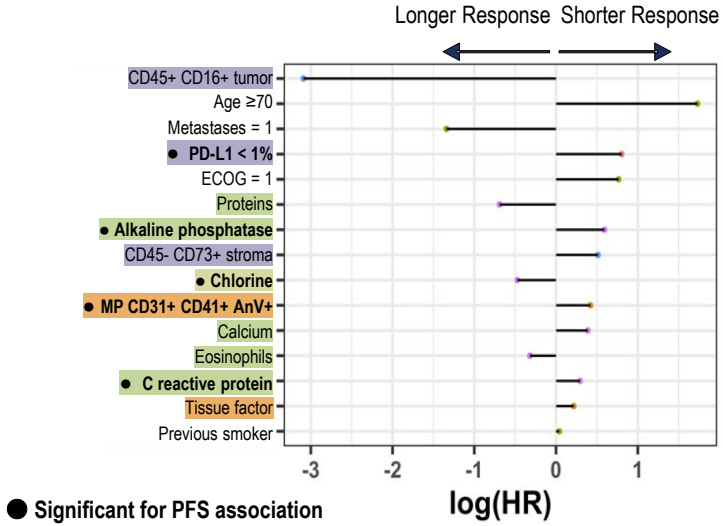
RESULTS: MACHINE LEARNING

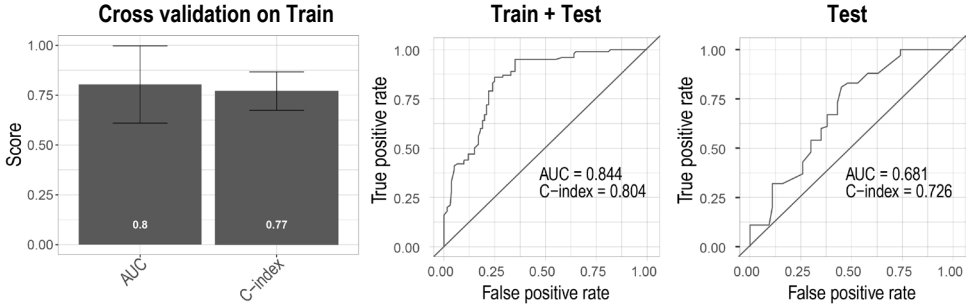
Biomarkers associated with PFS (1st line setting only)



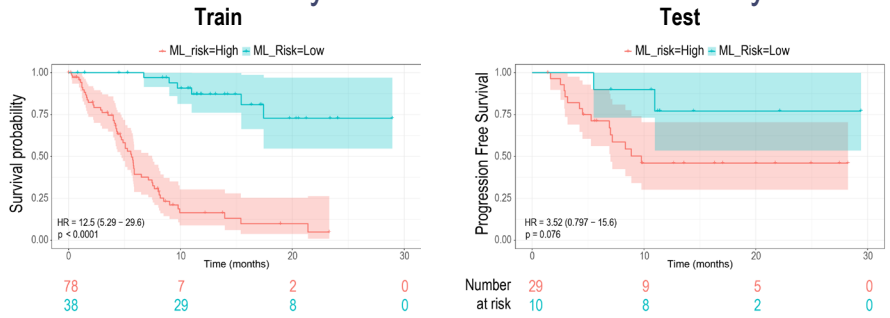
A 15-biomarkers signature



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



Prediction of the 1-year PFS with 83% sensitivity



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CONCLUSIONS

A multimodal signature predicts the 1st 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

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- OncoGard : Dr. A. Serre
- Nîmes Hospital : Dr. S. Van Hulst
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Lyon (& area)

- Léon Bérard Center Medical Oncology Department : Dr. M. Pérol
- Villefranche Hospital : Drs. L. Falchero, L. Odier
- Annecy Hospital : Dr. S. Hominal

Toulouse (& area)

- Toulouse CHU Thoracic Oncology Department : Pr. J. Mazières
- Cahors Hospital : Dr. P. Barre
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