



IX SIMPOSIO · SYMPOSIUM | 2024 **BIOPSIA LÍQUIDA · LIQUID BIOPSY**

EL CAMINO A LA ONCOLOGÍA DE PRECISIÓN · THE WAY TO PRECISION MEDICINE

25, 26 Y 27 DE ENERO · JANUARY 25th, 26th and 27th

Proteomic signature to predict response to therapy in NSCLC

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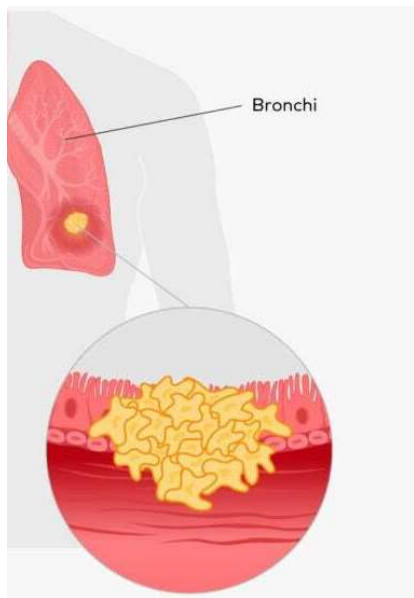
Fundación Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS)
Oncología Médica traslacional (oncomet)

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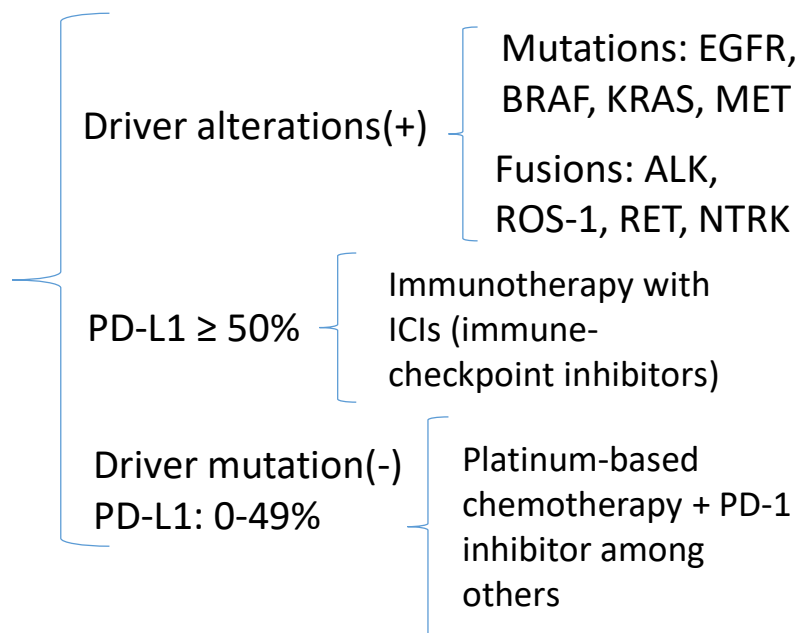
Organizado por:
Organized by:



NON-SMALL CELL LUNG CANCER



- ✓ Most common type of lung cancer (85-90% of all lung cancers)
- ✓ 65% of patients are diagnosed on advanced stages (IV)

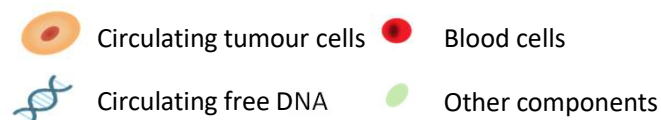
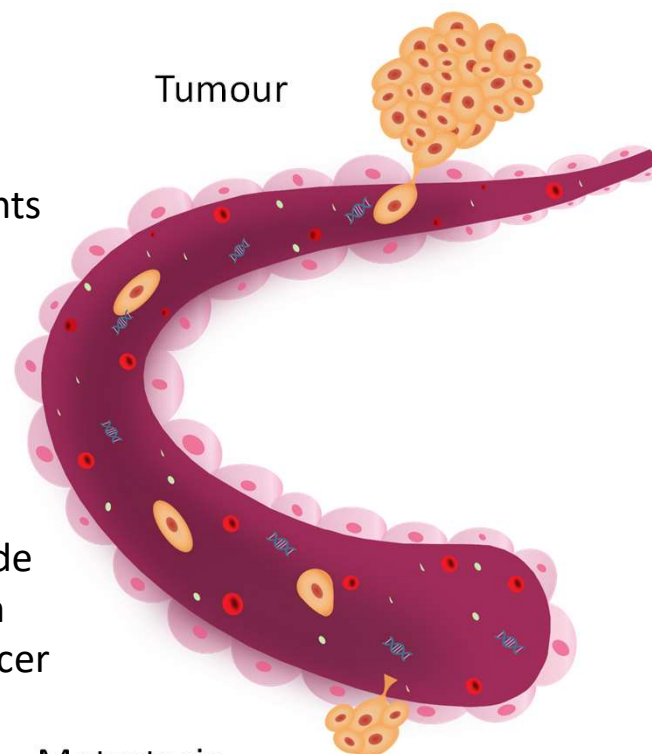


Immune checkpoint inhibitors

<i>anti CTL4</i>	<i>anti PD-1</i>	<i>anti PD-L1</i>
Ipilimumab	Pembrolizumab Cemiplimab Nivolumab (2 nd line)	Atezolizumab

Circulating proteins as alternative to PD-L1 in tissue

- PD-L1 is the only biomarker used in clinics to select patients to be treated with immunotherapy
- Overall response rates are about **30 %**
- Circulating biomarkers provide real-time disease information with the least damage to cancer patients.



Proteomic methods are the most popular for protein biomarkers screening

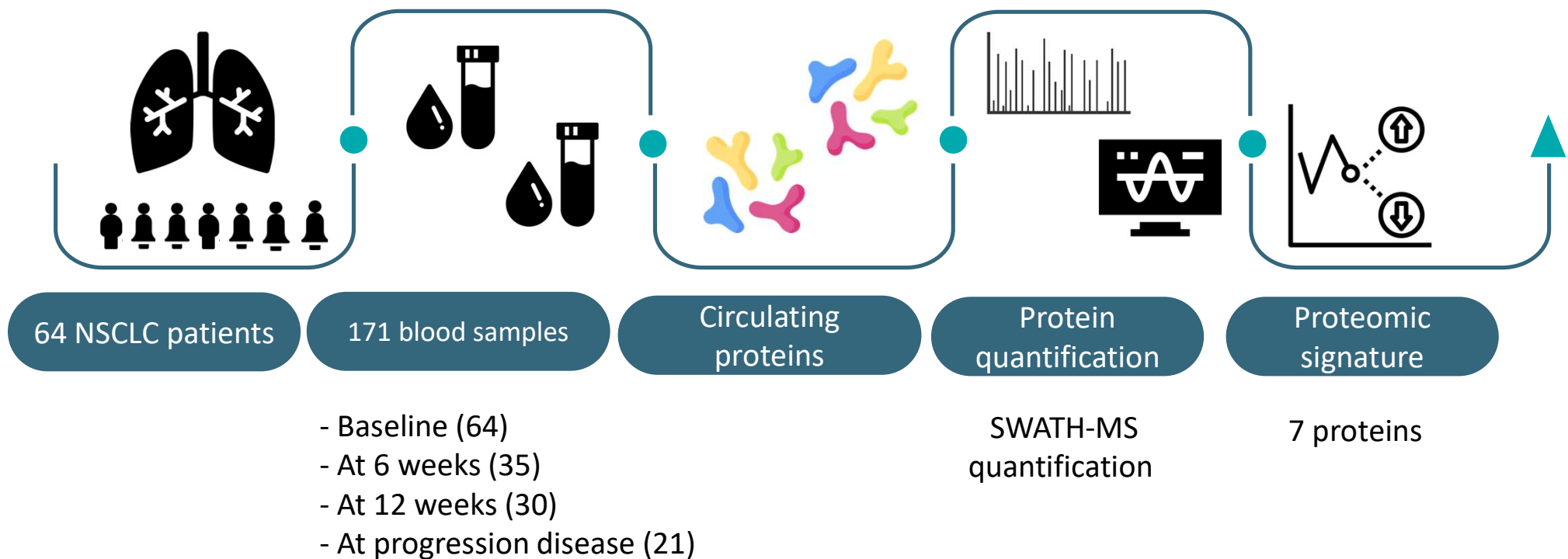
- ✓ Easy measurement and isolation.
- ✓ Easy clinical implementation.
- ✓ Represent tumour microenvironment, such as the immune response and inflammatory status.

Sequential Window Acquisition of All Theoretical Fragment Ion Mass Spectra (SWATH-MS)



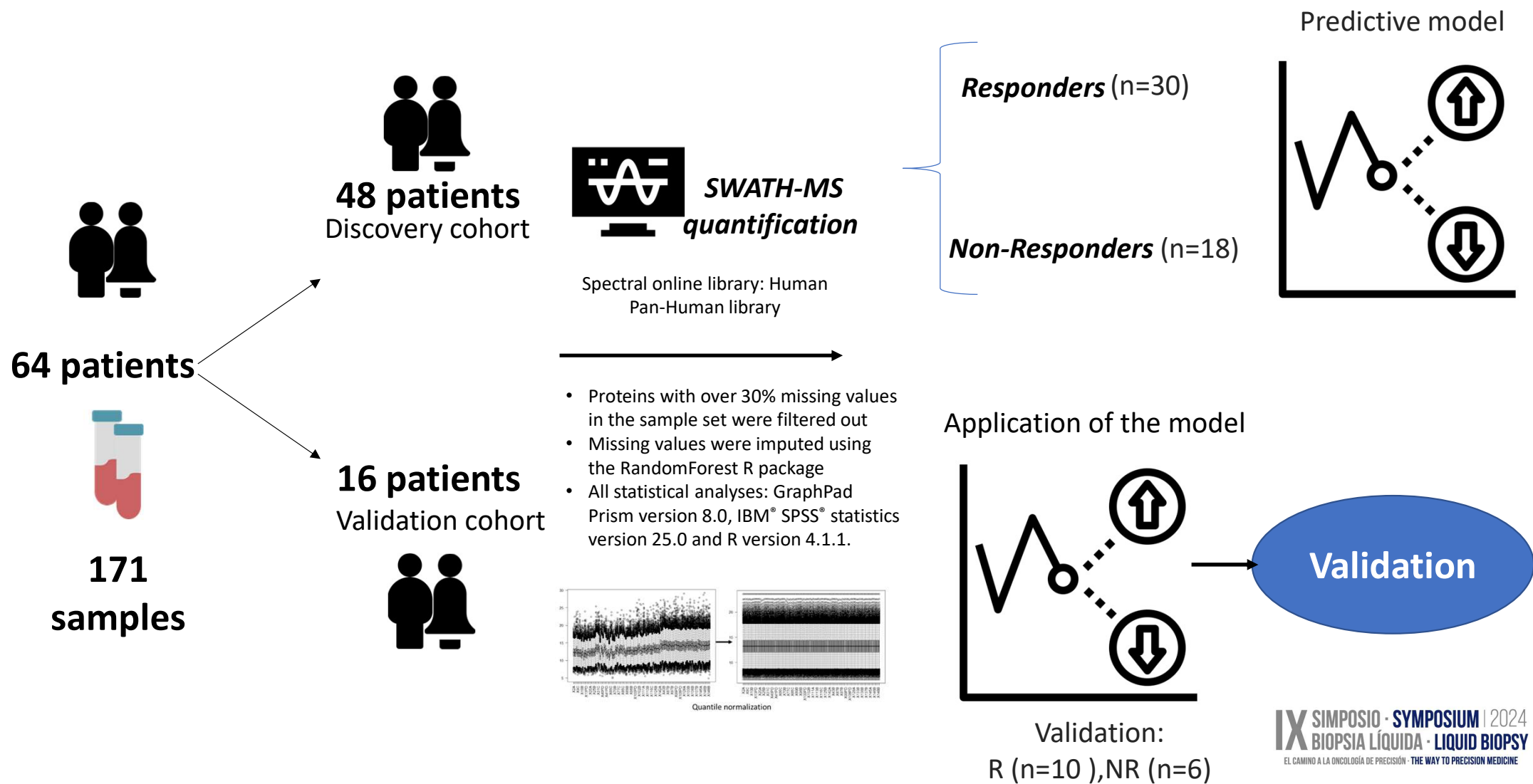
Project scheme

Hypothesis: Plasma proteome analyses have predictive and prognostic value in newly diagnosed NSCLC patients who started pembrolizumab therapy

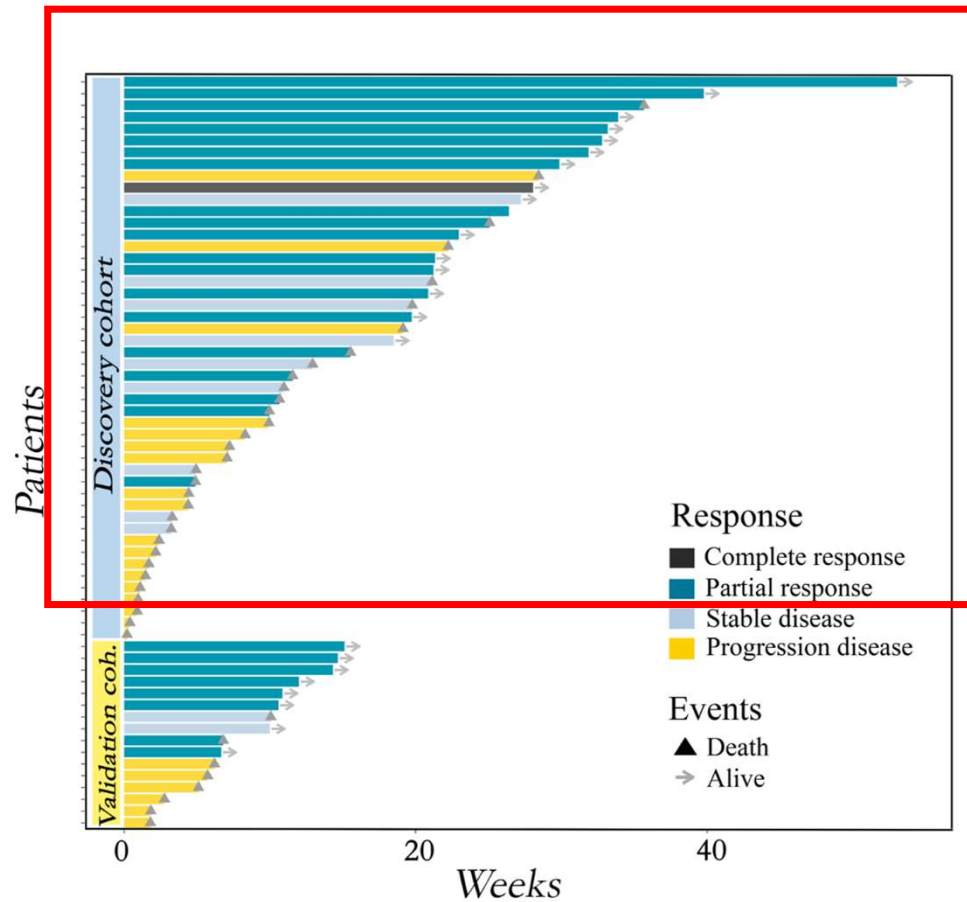
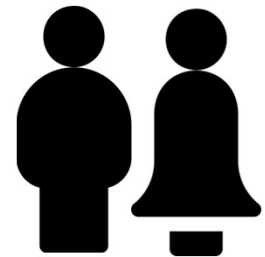


Submitted to: Mondelo et al., Molecular and cellular proteomics (under review)

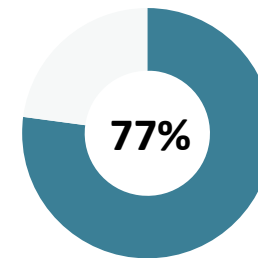
Project procedure



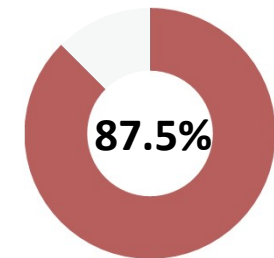
Patients characteristics



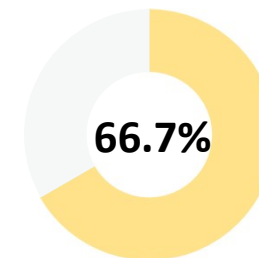
DISCOVERY COHORT N=48



Males



Adenocarcinomas



Immunotherapy in
monotherapy

Protein quantification (Discovery cohort N=48)



DISCOVERY COHORT

7,115 proteins

- ten peptides/protein and a 1% false discovery rate (FDR)
- normalization by quantile

Quality Control

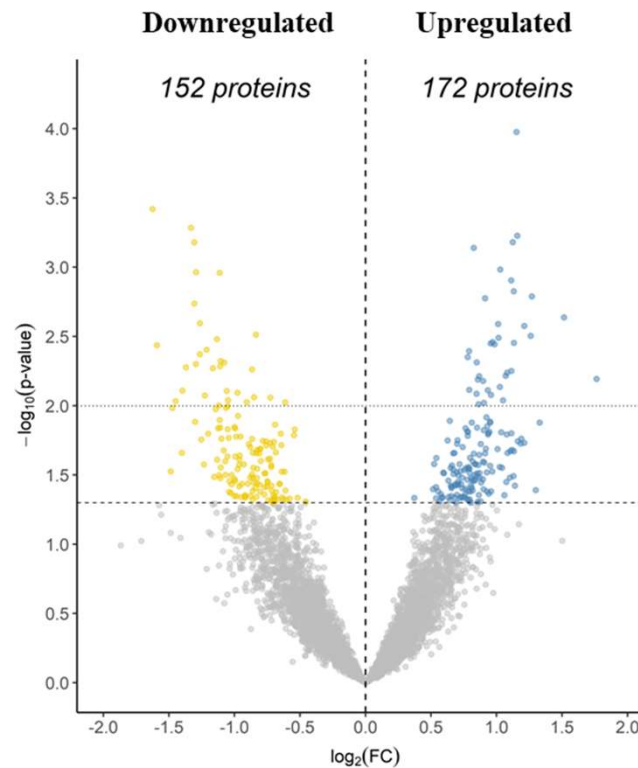
6,364 proteins

p -value < 0.05

- Student's t tests

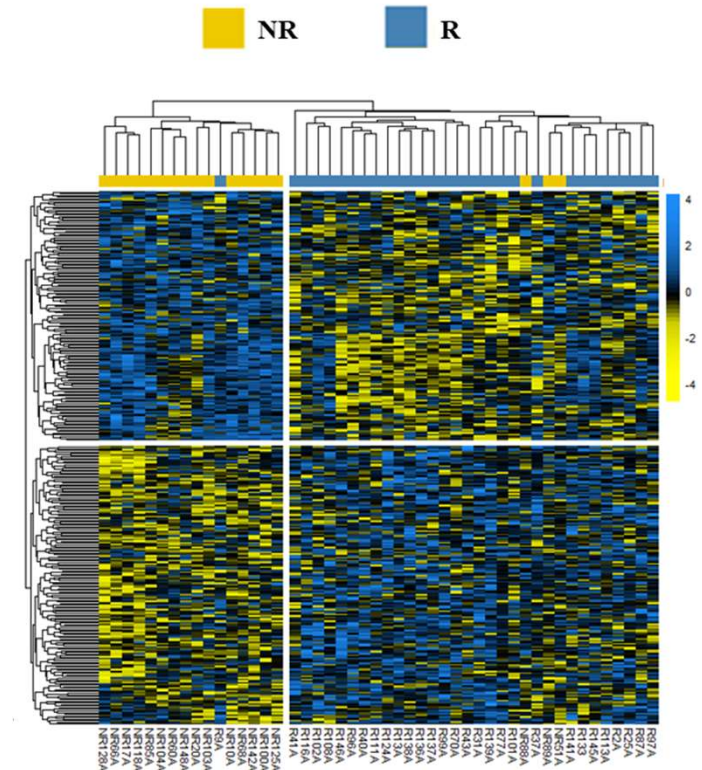
324 differentially expressed proteins

Volcano plot



(responders)

Heatmap

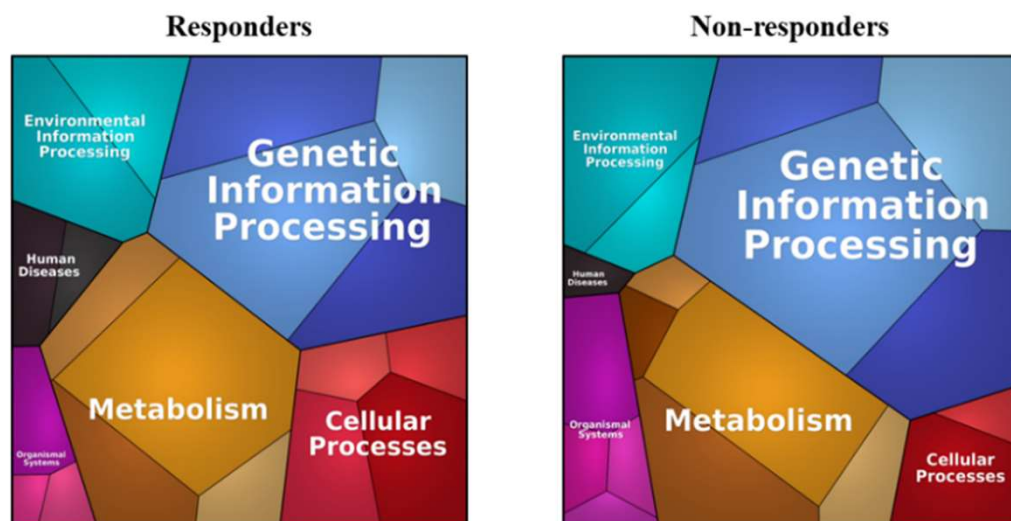


The processing of the samples and the application of the SWATH methodology was carried out at the IDIS Proteomics Platform

Protein quantification

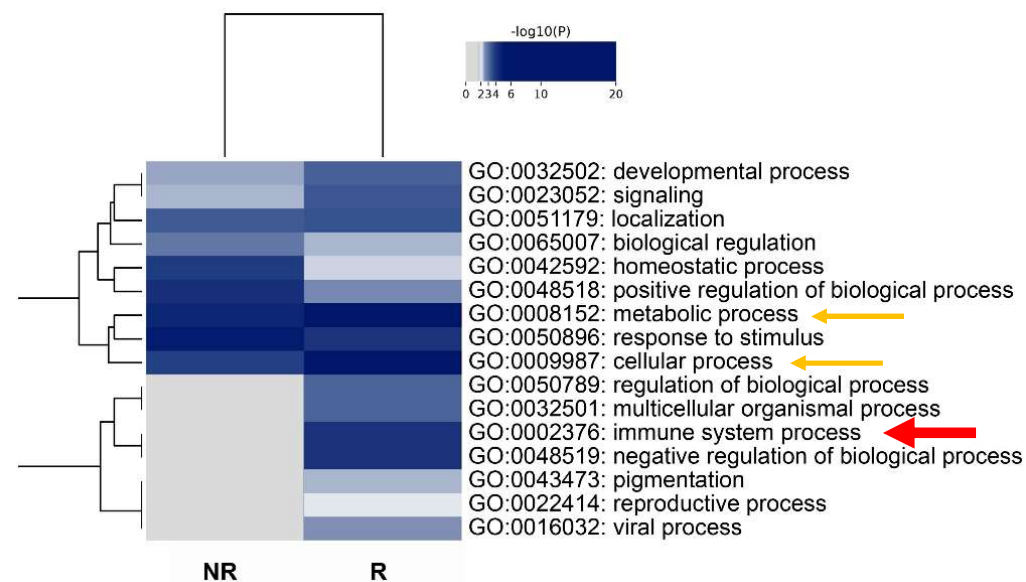
324 differentially expressed proteins $p\text{-value} < 0.05$

Relative protein abundance



Proteomaps tool; www.proteomaps.net

Gene ontology analysis



DEPs between responders and non responders
present some differences in GO pathways.

METASCAPE tool; metascape.org

Protein quantification

DISCOVERY COHORT

7,115 proteins

Quality Control

6,364 proteins

$p\text{-value} < 0.05$

324 differentially expressed proteins

$p\text{-value} < 0.01$

66 differentially expressed proteins

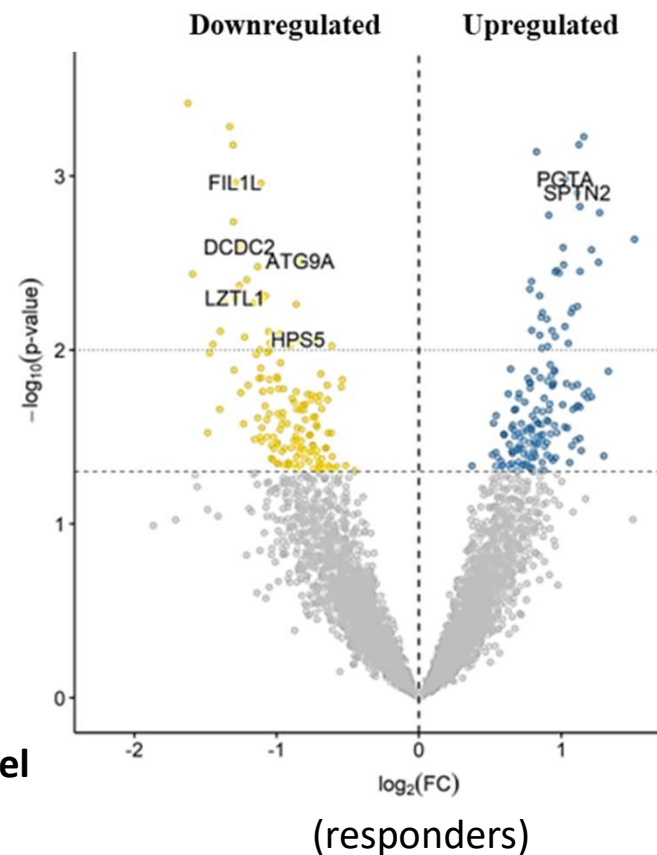
Predictive model

7 proteins

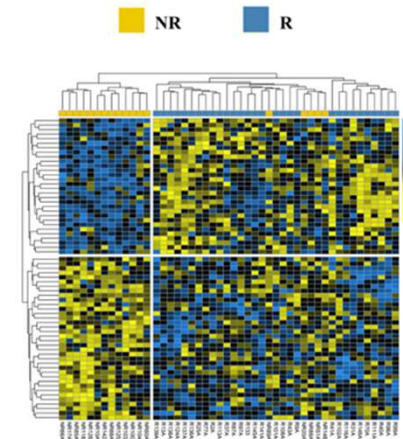
- Student's t tests

- Akaike Information Criterion (AIC)

Volcano plot

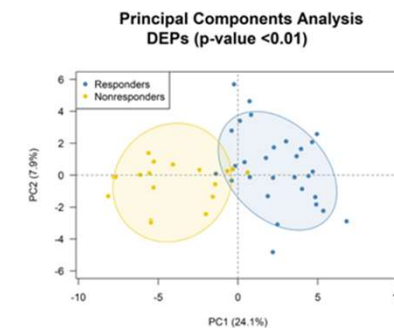


Heatmap



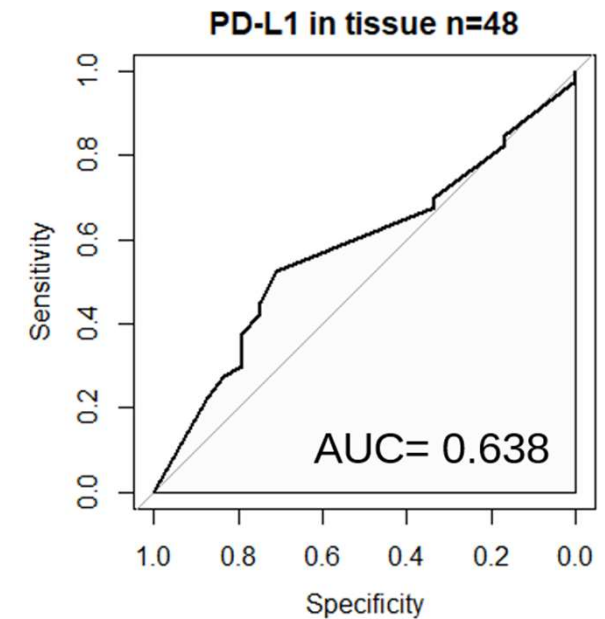
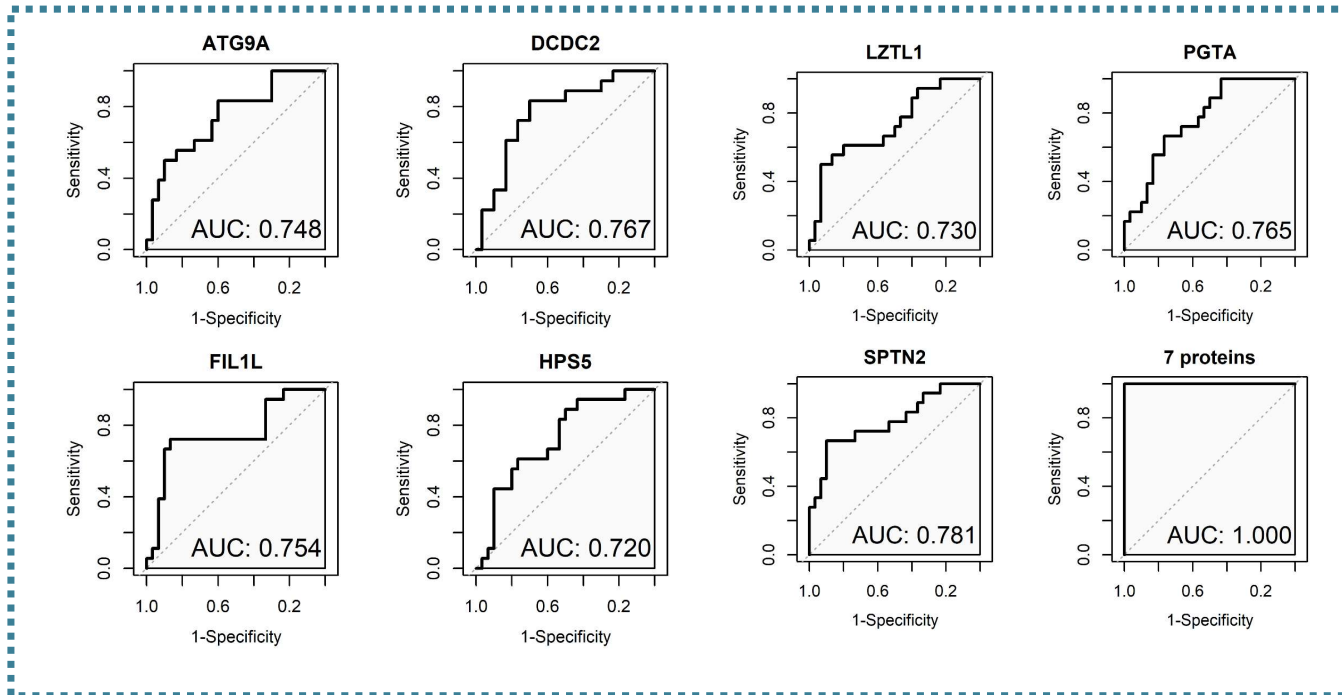
Protein	Name	Gene
SPTN2_Q15020	Spectrin beta chain, non-erythrocytic 2	SPTBN2
PGTA_Q92696	Geranylgeranyl transferase type-2 subunit alpha	RABGGTA
FIL1L_Q4L180	Filamin A-interacting protein 1-like	FILIP1L
ATG9A_Q7Z3C6	Autophagy-related protein 9A	ATG9A
LZTL1_Q9NQ48	Leucine zipper transcription factor-like protein 1	LZTL1
HPS5_Q9UPZ3	BLOC-2 complex member HPS5	HPS5
DCDC2_Q9UHG0	Doublecortin domain-containing protein 2	DCDC2

PCA



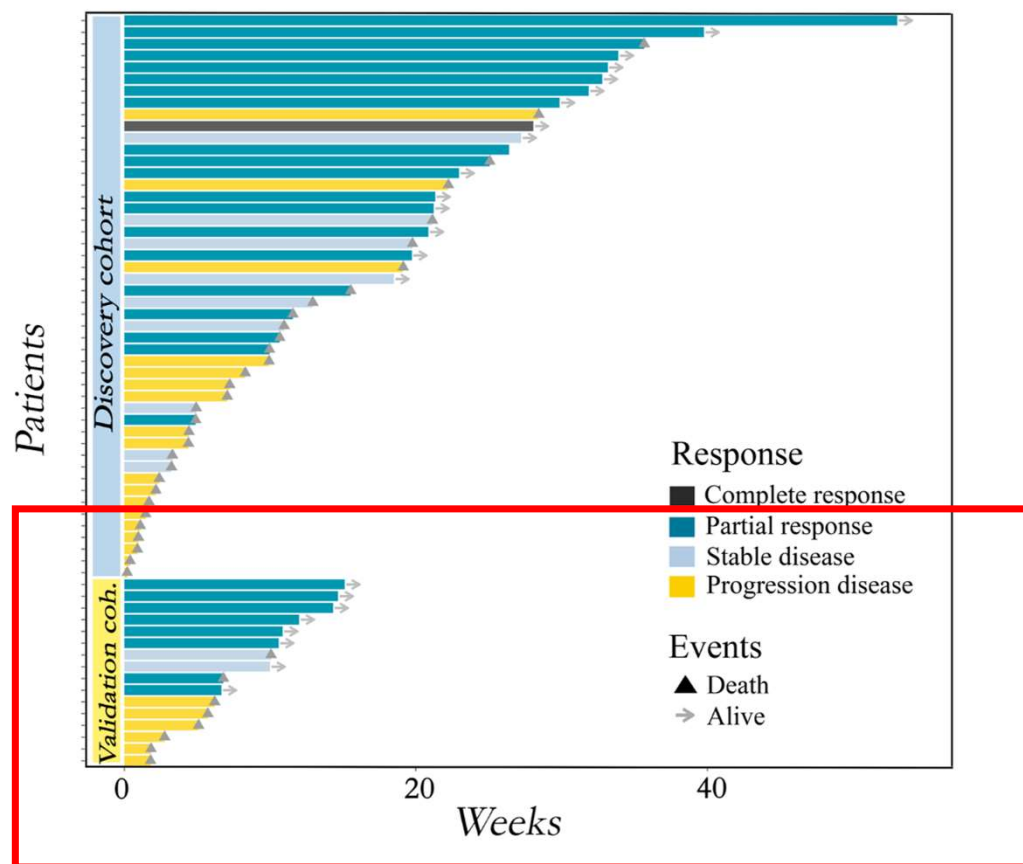
Predictive model

PREDICTIVE MODEL IN PLASMA SAMPLES

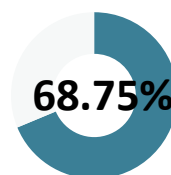


Our protein model allowed us to predict immunotherapy response with a higher AUC than PD-L1 expression in tumour tissue in our **patients' cohort**.

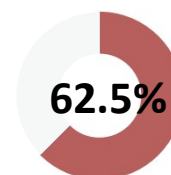
👤 Patients' characteristics (validation cohort)



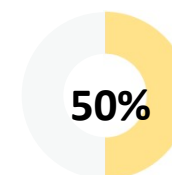
VALIDATION COHORT N=16



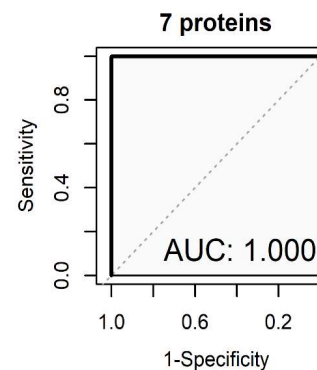
Males



Adenocarcinoma

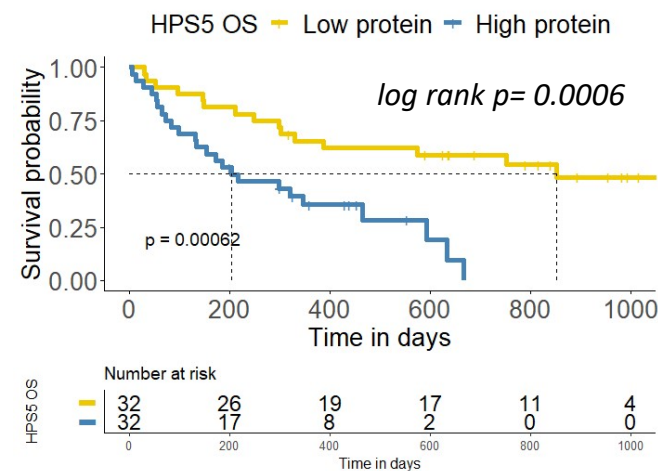
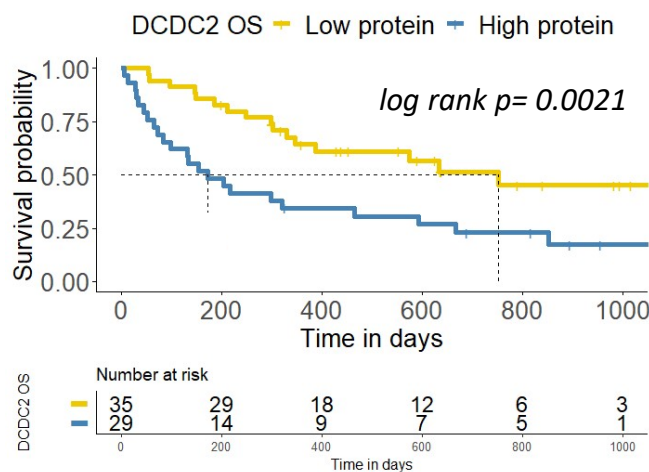
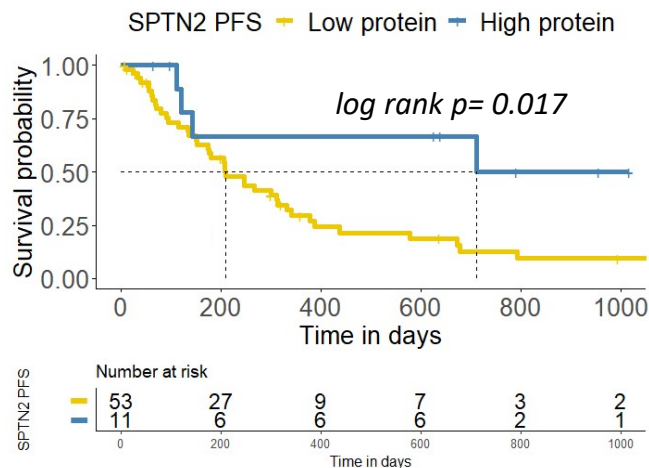
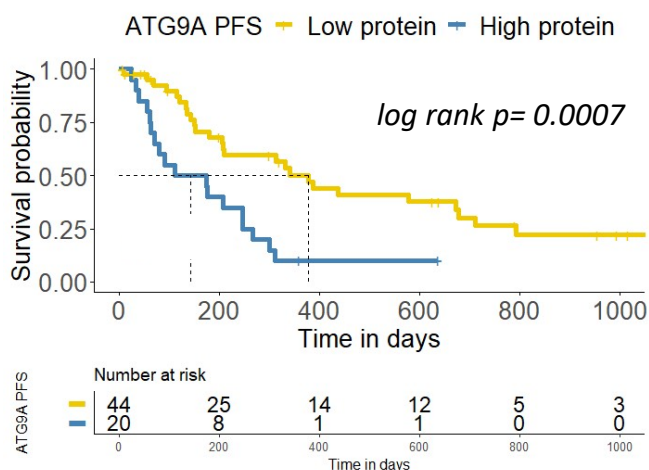


Immunotherapy
in monotherapy



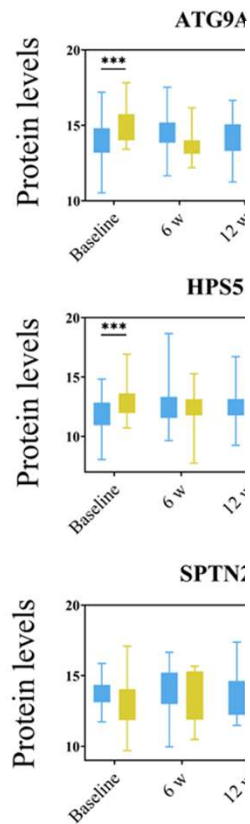
The predictive value of the proteomic model was confirmed in the validation cohort

Global cohort



The levels of 4 proteins at baseline were associated with PFS or OS.

Predictive model



DCDC2

ETL 11

CM2

European Patent Office
80298 MUNICH
GERMANY

Questions about this communication?
Contact Customer Services at www.epo.org/contact



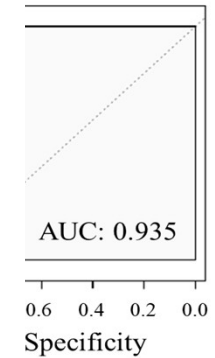
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28046 Madrid
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Date
10.01.2024

Reference 908 111	Application No./Patent No. 23382377.2 - 1111
Applicant/Proprietor Fundación Instituto de Investigación Sanitaria de Santiago de Compostela, et al	

THERAPY

2 weeks



Larger studies should be conducted to provide a more detailed and conclusive interpretation of our data

Diapositiva 13

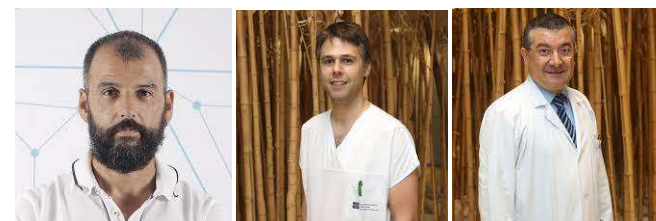
CM2

Por qué existe tanta variación en los niveles a lo largo del tto? no sé, veo prots que suben i bajan pero el modelo sigue funcionando. Quizás hecho de menos en esta gráfica los niveles basales.

Cuenta Microsoft; 18/01/2024

Conclusions

- **The analysis of circulating proteins allowed us to find biomarkers of response to immunotherapy in NSCLC**
- **We were able to develop a signature of response to immunotherapy for NSCLC patients**
- **Larger studies should be conducted to provide a more detailed and conclusive interpretation of our data**
- **This signature can be a complementary tool, to image methodologies, to allow clinicians to follow the response of the patients during treatment**



THANK YOU!

Patients and families

Scientific Researchers:

Susana Bravo
Patricia Mondelo
Roberto Diaz
Laura Muineló
Alica Abalo

Clotilde Costa
Carmen Abuín
Gloria Garcia
Roberto Piñeiro



Oncologist researchers:

Luis-León
Jorge-García
Rafael López

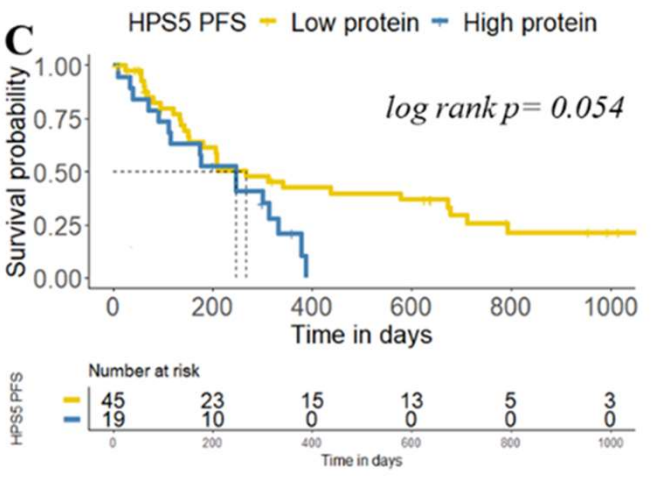
The oncomet group!!!

¡GRACIAS!

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BIOPSIA LÍQUIDA · LIQUID BIOPSY
EL CAMINO A LA ONCOLOGÍA DE PRECISIÓN · THE WAY TO PRECISION MEDICINE

- ATG9A protein is a transmembrane protein that plays an important role in the formation and regulation of autophagosomes, which are cellular structures involved in the process of autophagy. This protein is localized on the membranes of the endoplasmic reticulum and Golgi [44]. **A recent study characterizes novel functions of ATG9A as component of a TNF-induced cell death checkpoint .**
- DCDC2 is a protein expressed in the brain that has been linked to the development of cognitive skills such as reading and language processing. DCDC2 has been found to be localized to the cilia of neurons in the developing brain, where it is involved in the control of ciliogenesis and ciliary length [46,47]. In addition, DCDC2 seems to play a role in the inhibition of canonical Wnt signaling pathway (it is well established that mutations in the canonical WNT-signalling pathway play a major role in various cancers)
- HPS5 is a protein that plays a crucial role in the biogenesis and function of lysosome-related organelle and may be involved in the regulation of general functions of integrins. **Integrins expressed in tumour cells contribute to tumour progression and metastasis by increasing tumour cell migration, invasion, proliferation and survival**
- On the other side FIL1L is a protein that acts as a regulator of the antiangiogenic activity on endothelial cells. The overexpression in endothelial cells leads to inhibition of cell proliferation and migration and increase in apoptosis [50]. **In oncology field, FIL1L has been previously reported as a protein down regulated in ovarian cancer [51].**
- LZTL1 regulates ciliary localization of the BBSome complex [52] **and may have tumour suppressor function in several primary cancer types [53].**

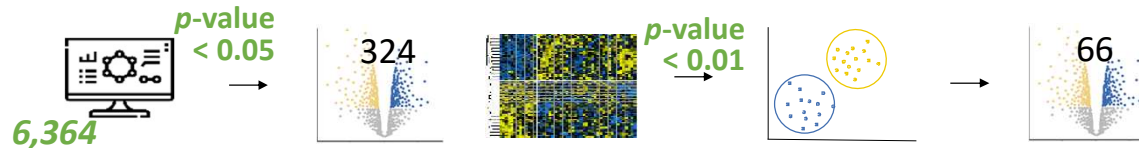
Finally, some limitations should be considered in the present study. Firstly, our study included patients with diverse histological subtypes and under treated with different immunotherapy regimens. This heterogeneity in our cohort, comprising a relatively small number of patients with histologists other than adenocarcinoma, as well as the wide range of treatment regimens, underscores the importance of future investigations focusing on more homogeneous patient populations to facilitate more definitive conclusions. Second, a validation cohort with more patients should be employed to confirm the predictive value of our model and their utility during immunotherapy.



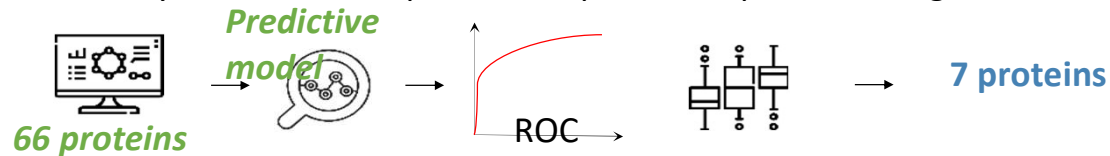
Step 1. Discovery cohort: Plasma protein identification by SWATH-MS analyses



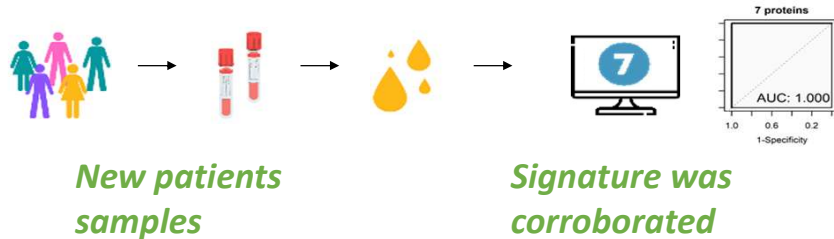
Step 2. Discovery cohort: Differentially expressed between R and NR



Step 3. Discovery cohort: Development of a predictive proteomic signature

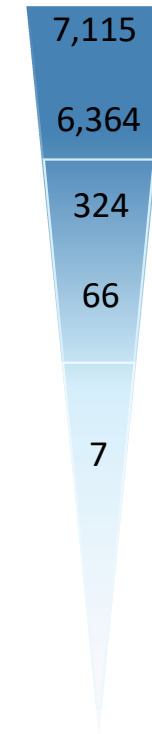


Step 4. Validation cohort: Proteomic signature validation



Proteins

Patients



Discovery cohort

n=48

Validation cohort

n=16