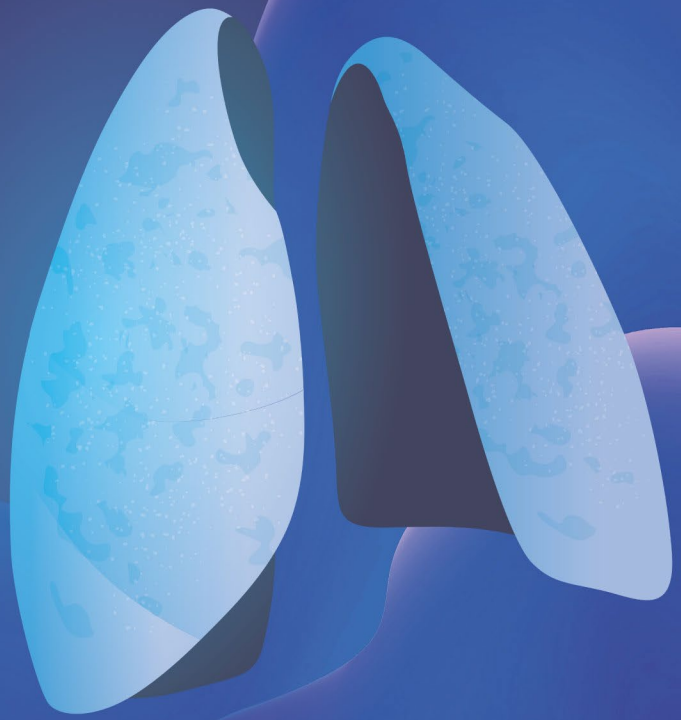

Novedades & Claves en CÁNCER de PULMÓN 2024

Biomarcadores pronósticos

Ana Cardeña Gutiérrez

Hospital Universitario Nuestra Señora de Candelaria

Organizado por:

GECP lung cancer research

Patrocinado por:

Bristol Myers Squibb™

Johnson&Johnson

Factores pronósticos

≠ *BIOMARCADORES*

Edad, sexo, estadio TNM, ECOG, pCR

Biomarcadores pronósticos que no abordaremos

Las mutaciones driver

Índice

- Biomarcadores séricos.
- PD-L1 y TMB
- ¿Futuro?
  - NGS (nuevos paneles)
  - Biopsia líquida (ctDNA, exosomas, epigenética)
  - IT y biomarcadores emergentes (microbiota, BMI)

Organizado por:
GECP
lung cancer research

Biomarcadores séricos

¿Qué sabemos?

2010

2018

Índice	Definición	Mal pronóstico
NLR: Neutrophil-to-Lymphocyte Ratio	$\frac{\text{Recuento de neutrófilos}}{\text{Recuento de linfocitos}}$ =	NLR ≧3
ALI: Advanced Lung Cancer Inflammation Index.	$\frac{\text{IMC x Albúmina (g/L)}}{\text{NLR}}$ =	ALI <18
A/G: Albumin-to-Globulin Ratio.	$\frac{\text{Albúmina(g/L)}}{\text{Globulina sérica (g/L)}}$ =	A/G <1
LIPI : Lung Immune Prognostic Index	= dNLR LDH (U/L) dNLR = $\frac{\text{Neutrófilos}}{\text{Leucociotos - Neutrófilos}}$	Buen pco. dNLR<3 y LDH N Pco. Intermedio: dNLR ≧3 **ó** LDH >250 U/L Mal pco: dNLR ≧3 **y** LDH >250 U/L

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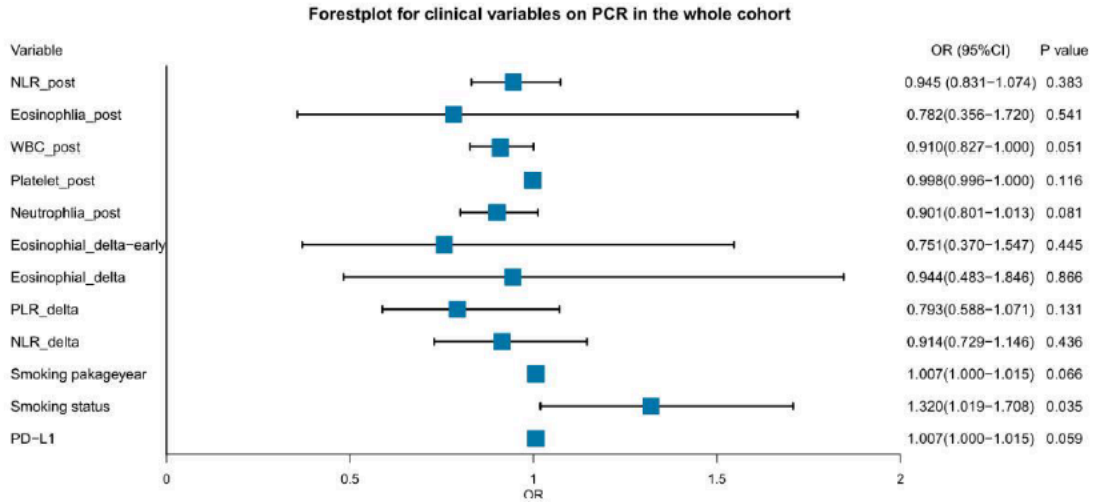
EP.08B.1 Zhou H et al. WCLC 2024

3.



EP.13D.05 Wang N et al. WCLC 2024

"CAPTRA-LUNG" database (NCT03334864)

EP.13D.03 Liao Y.-T et al. WCLC 2024

Meeting Abstract: 2024 ASCO Annual Meeting I

FREE ACCESS | Lung Cancer—Non–Small Cell Metastatic | May 29, 2024

Analysis of the LIPI score as a prognostic factor in advanced non-small cell lung cancer.

Authors: Eduardo Richardet, Pablo Perea, Matias Molina, Ignacio Magi, Santos Depetris, and Martin Eduardo Richardet | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 42, Number 16_suppl
https://doi.org/10.1200/JCO.2024.42.16_suppl.e20612

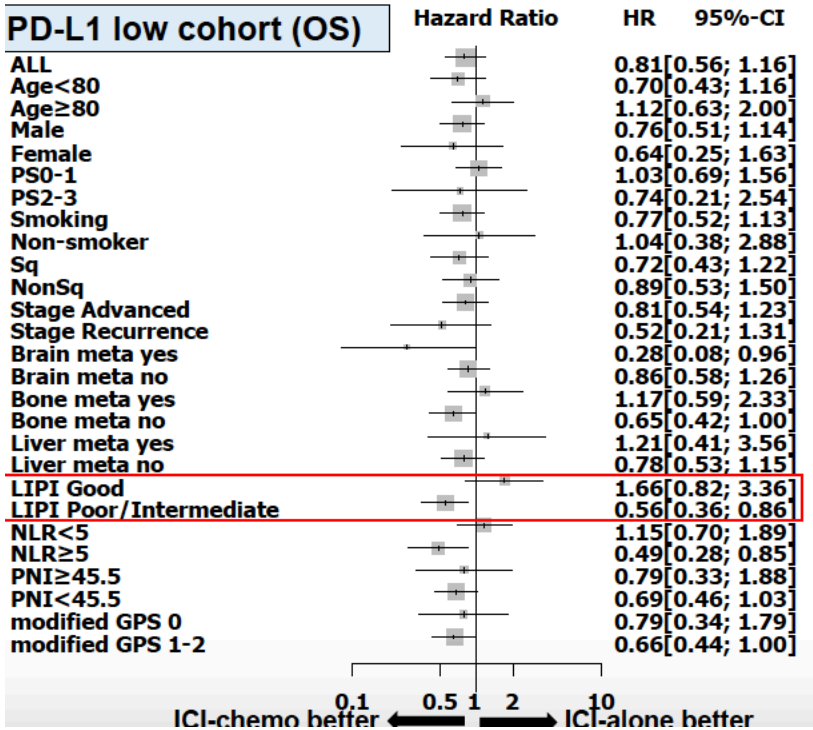
1327P - Lung immune prognostic index (LIPI) as a guide for addition of chemotherapy in immunotherapy in elderly patients (Pts) with non-small cell lung cancer (NSCLC): NEJ057

Date

14 Sep 2024

Presenters

OSAMU HONJO



Organizado por:

GECP lung cancer research

Retrospective evaluation of inflammatory biomarkers in patients affected by unresectable stage III NSCLC: final results of NEUTRALITY trial

1251P

Emanuela Olmetto[1], Chiara Mattioli[1], Saverio Caini[2], Marco Del Riccio[3], Pietro Garlatti[1];,Giovanna Finocchiaro[4], Paolo Borghetti[5], Giulio Metro[6], Sara Pilotto[7], Francesco Grossi[8], Gabriella Farina[9], Fausto Meriggi[10], Andrea Sbrana[11], Elisa Roca[12], Angelo Delmonte[13], Alessandro Russo[14], Marianna Macerelli[15], Marco Perna[16], Alessio Bruni[17], Vieri Scotti[1]

1. Radiation Oncology Unit, Azienda Ospedaliera Universitaria Careggi, University of Florence, Florence, Italy; 2. Cancer Risk Factors and Lifestyle Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy; 3. Department of Health Sciences, University of Florence, Florence, Italy; 4. Medical Oncology and Hematology Unit, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; 5. Radiation Oncology Department, ASST Spedali Civili and Brescia University, Brescia, Italy; 6. Medical Oncology, S. Maria Della Misericordia Hospital, Perugia, Italy; 7. Section of Innovation Biomedicine-Oncology Area, Department of Engineering for Innovaion Medicine (DIMI), University of Verona and University and Hospital Trust (AOUI) of Verona, Italy; 8. Unit of Medical Oncology, Department of Medicine and Surgery, University of Insubria, ASST dei Sette Laghi, Varese, Italy; 9. Department of Oncology, ASST Fatebenefratelli Sacco, Milano, Lombardia, Italy; 10. UO di Oncologia Medica, Casa di Cura Poliambulanza, Brescia, Italy; 11. Service of Pneumo-Oncology, Azienda Ospedaliero-Universitaria Pisana, University of Pisa, Pisa, Italy; 12. Thoracic Oncology—Lung Unit, Ospedale Pederzoli, Peschiera d/G, Verona, Italy; 13. Department of Medical Oncology, IRCCS Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" (IRST), Meldola, Italy; 14. Department of Onco-Hematology, Papardo Hospital, Messina, Italy; 15. Department of Medical Oncology, Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy; 16. Medical Oncology Unit - Florence, Department of Oncology, Azienda USL Toscana Centro, Italy; 17. Radiotherapy Unit, Department of Oncology and Hematology, University Hospital of Modena, Italy

e.olmetto@gmail.com

BACKGROUND

Neutrality trial aims to analyze the prognostic role of blood biomarkes such as **NLR** (neutrophils to lymphocytes ratio), **SII** (Systemic Inflammatory Index - NLR x platelets), **dNLR** (derived NLR - neutrophil to leukocytes - neutrophil ratio) and **LIPI** (Lung Immune Prognostic Index) in stage III NSCLC patients treated with radio-chemotherapy (RT-CHT) followed by Durvalumab in the Italin expanded access program (Cohort A), and in patients treated with RT-CHT alone before the introduction of the Pacific regimen (Cohort B).

METHODS

NEUTRALITY is a retrospective multicentric observational study (ESR-19-20410). Blood count tests were recorded at the end of RT-CHT for Cohort B and during Durvalumab course for Cohort A. Different cut-offs of NLR, dNLR and SII were considered, based on the median values observed. Three LIPI index groups were analyzed: good (dNLR ≤ 3 and LDH ≤ UNL), intermediate (dNLR>; 3 or LDH ≥ UNL) and poor (dNLR>; 3 and LDH ≥ UNL). We performed a Cox-Regression analysis to correlate these biomarkers to Overall Survival (OS) and Progression-Free Survival (PFS).

First author has no conflict of interest to declare
This work received the unconditional support of AstraZeneca

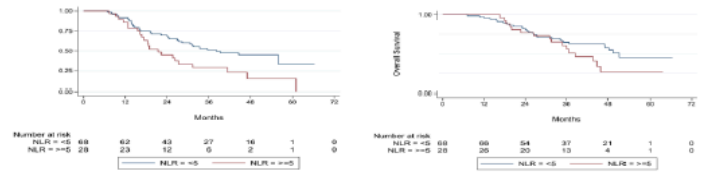
Table 1: Patient characteristics

	Cohort A Patients (%) 96	Cohort B Patients (%) 94
Sex		
M	62 (64.5%)	66 (70%)
F	34 (35.5%)	28 (30%)
Smoke		
Yes	85 (88%)	85 (90%)
No	9 (12%)	9 (10%)
Age years		
Median	68 y	66 y
Range	44-83	42-84
Histology		
Adenocarcinoma	54 (56%)	49 (52%)
Squamocellular	39 (41%)	39 (41%)
Others	3 (3%)	6 (7%)
PD-L1 Expression		
0	12 (12.5%)	11 (12%)
1-49	41 (43%))	15 (16%)
≥ 50	30 (31%)	9 (10%)
Not tested	13 (13.5%)	59 (62%)
Stage Disease		
IIIA	35 (36.5%)	39 (41%)
IIIB	48 (50%)	44 (47%)
IIIC	13 (13.5%)	11 (12%)
ECOG PS		
0	59 (61.5%)	60 (64%)
1	35 (37.5%)	34 (36%)
2	1 (1%)	0

RESULTS

Overall 190 pts (96 in Cohort A and 94 in Cohort B) were enrolled from 35 Italian centers. Details of patients are shown in Table 1. After a median FUP of 48,8 months, for Cohort A we observed a significant correlation between NLR using a cut-off of 5, SII and dNLR as continous variable, with PFS: p 0.017, p 0.03 and p 0.018, respectively. No correlation was found with OS. The good LIPI group showed an increased PFS compared to intermediate and poor group, as expected. No significant correlation was found between these biomarkers and PFS and OS in Cohort B.

Figure 1: Correlation between PFS and NLR in the cohort A and B



CONCLUSIONS

Our analysis suggests that blood inflammatory biomarkers can have a prognostic role for unresectable stage III NSCLC patients treated as per Pacific regimen.

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PD-L1 y TMB

Biomarcadores predictivos

¿Qué sabemos?

- PD-L1: La heterogeneidad intratumoral y la variabilidad en las técnicas de medición pueden afectar su precisión como biomarcador.
- TMB: Aplicación rutinaria limitada debido a la falta de estandarización y consenso sobre los puntos de corte óptimos (aunque ≧10 es el más usado).

PD-L1 y TMB

Biomarcadores predictivos

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¿Novedades?

- Combinación con otros biomarcadores emergentes: radiómica, inteligencia artificial y marcadores séricos y genómicos con valor PRONÓSTICO.

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1301P – A prognostic clinical and circulating biomarker model to identify futile chemo-radiotherapy (CRT) in stage III NSCLC

Rianne D.W. Vaes[1*], Lizza Hendriks[2], Ruud Houben[1], Juliette Degens[3], Francesco Cortiula[3,4], Dirk De Ruysscher[1]

[1] Department of Radiation Oncology (MAASTRO), GROW School for Oncology and Reproduction, Maastricht University Medical Center, Maastricht, The Netherlands | [2] Department of Pulmonary Diseases, GROW School for Oncology and Reproduction, Maastricht University Medical Center+, Maastricht, The Netherlands | [3] Department of Pulmonary Diseases, Zuyderland Medical Center, The Netherlands | [4] Department of Medical Oncology, University Hospital of Udine, Udine, Italy

Introduction

- Chemoradiotherapy (CRT) followed by adjuvant durvalumab is standard of care for fit patients with unresectable stage III non-small cell lung cancer (NSCLC)
- More than half of patients with stage III NSCLC treated with CRT and adjuvant durvalumab will relapse during or after the treatment
- There are no prognostic tools available to identify patients with stage III NSCLC who are at higher risk of early mortality during and after CRT and therefore would urgently need alternative treatments

Objective: To build an actionable prognostic model to identify patients who may not benefit from CRT without durvalumab

Methods

Study design: Single center observational study (prospective MAASTRO biobank project) (2003-2019; NTCT01084785)

Patient population: Patients with unresectable stage III NSCLC treated with curative intent platinum-doublet chemotherapy and radiotherapy (60-66 Gy, 2 Gy/fraction)

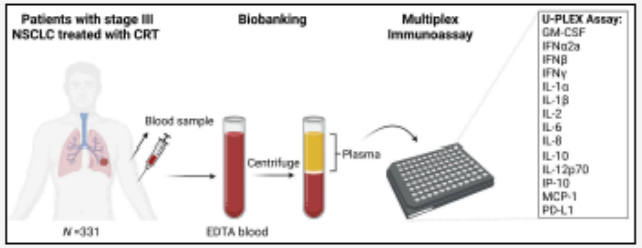


Figure 1: Summary study design. Blood was collected before the start of RT. The U-plex multi-array electrochemiluminescence platform of MesoScaleDiscovery (MSD) was used to measure the EDTA-plasma concentrations of the indicated immune-related proteins.

Statistics: OS was calculated from start of RT. Blood biomarker concentrations were dichotomized by use of the 1-year overall survival (OS) as a cutoff point. Multivariable logistic regression analysis was performed to identify variables predicting OS.

Results

Patient characteristics

	N = 331
Gender (male, %)	209 (63.1%)
Age (years, ±SD)	64.9 (±9.4)
BMI (kg/m², ±SD)	25.0 (±4.5)
Performance status (n, %)*	
0	121 (36.6%)
1	168 (50.8%)
2	32 (9.7%)
3 or 4	10 (3.0%)
Histology (n, %)**	
Adenocarcinoma	78 (23.7%)
Squamous carcinoma	100 (30.4%)
Large cell carcinoma	73 (22.2%)
Unspecified NSCLC	78 (23.7%)
Tumor staging (n, %)***	
Stage IIIA	144 (43.5%)
Stage IIIB	146 (44.1%)
Stage IIIC	41 (12.4%)
Chemoradiation (n, %)	
Concurrent	221 (67.4%)
Sequential	107 (32.6%)
Radiotherapy	
Total dose (Gy, ±SD)	62.6 (±9.15)
Death (*n*, %)	283 (85.5%)
Median overall survival (months)	22.0 (95% CI: 17.6-26.4)
Median follow up	139.0 (95% CI: 119.4-158.6)

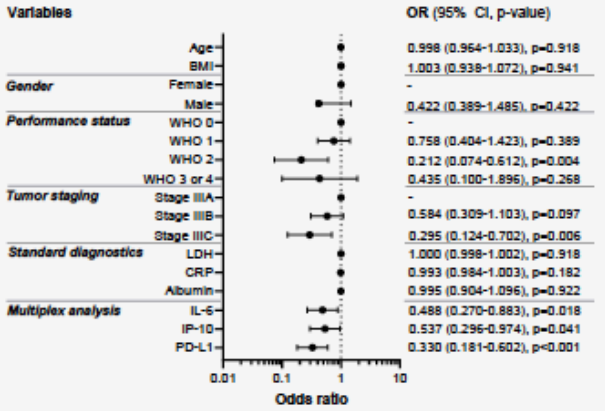
** Missing data, n=1; ** Missing data, n=2; *** According to the AAJC 8th edition*

Dichotomization of blood biomarkers based on 1-year OS as cut-off

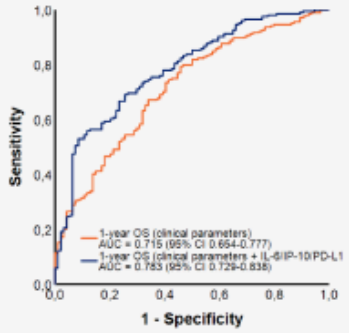
Analyte	OR (95% CI)	p-value	Median OS < cut-off (Months)	Median OS ≥ cut-off (Months)
GM-CSF	0.639 (0.343-1.193)	0.160	23.0	21.0
IFN-γ	0.705 (0.444-1.120)	0.139	26.0	18.0
IL-1β	0.663 (0.398-1.106)	0.116	26.0	21.0
IL-2	0.834 (0.493-1.411)	0.498	24.0	18.0
IL-6	0.332 (0.206-0.534)	<0.001*	36.0	13.0
IL-8	0.473 (0.279-0.802)	0.005*	32.0	18.0
IL-10	0.710 (0.447-1.127)	0.146	26.0	20.0
TNF-α	0.461 (0.279-0.761)	0.002*	33.0	18.0
IP-10	0.436 (0.270-0.705)	<0.001*	27.0	13.0
MCP-1	0.659 (0.410-1.060)	0.085	26.0	20.0
PD-L1	0.252 (0.154-0.413)	<0.001*	33.0	10.0

IFNα2a, IL12p70, IL-1a, and IFN8 were excluded; <15% of samples in detection range or analyte could not be detected

Higher concentrations of IL-6, IP-10 (CXCL10), and PD-L1 were significantly associated with a poorer OS. Multivariable logistic regression analysis with 1-year OS as dependent variable. The backward stepwise regression approach was used to eliminate blood biomarkers from the model to obtain a reduced model with the best fit for predicting 1-year OS. The most powerful prognostic factors for 1-year OS are IL-6, IP-10, and circulating PD-L1.

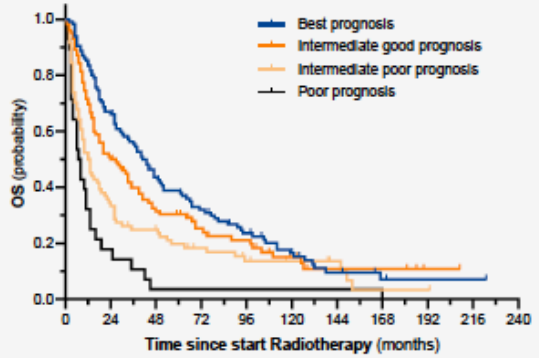


Evaluation of the multivariable prognostic model



Receiver operating curve (ROC) for predicting prognosis in patients with stage III NSCLC treated with CRT. The clinical and circulating biomarker model can better predict 1-year OS vs the clinical model (AUC = 0.783 vs AUC = 0.715, respectively)

Risk groups based on 1-year OS cut-off values of IL-6, IP-10, and PD-L1



Risk group	Median OS (95% CI)
Best prognosis	41.00 (95% CI 32.45-49.55)
Intermediate good prognosis	24.00 (95% CI 11.57-36.43)
Intermediate poor prognosis	12.00 (95% CI 7.92-16.08)
Poor prognosis	6.00 (95% CI 2.42-9.58)
Overall	22.00 (95% CI 17.56-26.44)

Patients in the 'poor prognosis' group (IL-6, IP-10, and PD-L1 above cut-off value; 9.1% of total) had a median OS of 6.0 months.

Conclusion

- The circulating blood biomarkers IL-6, IP-10 (CXCL10), and PD-L1 are the most powerful prognostic factors for 1-year OS
- This prognostic clinical and circulating biomarker model may identify patients who are at higher risk of early mortality during and after CRT
- These patients may benefit from alternative treatments other than curative intent CRT

Correspondence:
Rianne D.W. Vaes Email: rianne.vaes@maastro.nl

#1320P

I3LUNG: Digital pathology predicts PD-L1 expression in metastatic NSCLC patients treated with immunotherapy

Arsela Prelaj[1,3], Matteo Sacco[2], Vanja Miskovic[1,3], Daniele Lorenzini[1], Francesco Trovò[3], Aleksandra Zec[3], Laila Roisman[4], Leonardo Provenzano[1], Claudia Proto[1], Andrea Spagnoletti[1], Cecilia Silvestri[1], Alba Meya[6], Alessandra Pedrocchi[3], Evangelos Sarris[7], Enriqueta Felip[8], Filippo G.M. De Braud[1], Martin Reck[9], Giuseppe Lo Russo[1], Alexander T. Pearson[2], Marina Chiara Garassino[2]

1. Fondazione IRCCS – Istituto Nazionale dei Tumori, Milan, Italy; 2. University of Chicago Department of Medicine - Section of Hematology/Oncology, Chicago, United States of America, 3. Politecnico di Milano, Milan, Italy 4. Shaare Zedek Medical Center, Jerusalem, Israel, 5. UNIMI - Università degli Studi di Milano Statale, Milan, Italy, 6. MEDSIR - Medica Scientia Innovation Research, Barcelona, Spain, 7. Metropolitan Hospital, Athens, Greece, 8. Vall d'Hebron University Hospital, Barcelona, Spain, 9. Airway Research Center North, German Center for Lung Research, LungenClinic, Grosshansdorf, Germany

I3LUNG

Funded by the European Union

BARCELONA 2024 ESMO congress

BARCELONA SPAIN 13-17 SEPTEMBER 2024

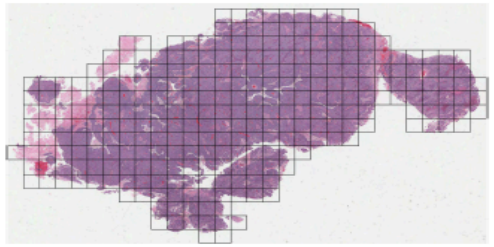
I3LUNG

I3LUNG is a project funded by the European Union through the Horizon 2020 program that aims to develop Artificial Intelligence (AI)-based tools to predict the response of advanced non-small cell lung cancer (NSCLC) patients to immune checkpoint inhibitors (ICIs). The project brings together a consortium of 16 partners from 10 countries (Belgium, Denmark, Italy, Germany, Greece, Spain, Sweden, Switzerland, the United States, and Israel). Utilizing patient data, which includes digital pathology slides (DPS), genomics, radiomics, along with other patient characteristics, the overall goal is to develop a platform to guide therapeutic decisions in immuno-oncology for both healthcare professionals and patients.

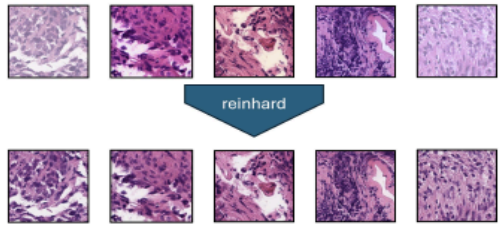
INTRODUCTION

- Immunotherapy (IO) is the new standard of care for patients with advanced NSCLC, yet only 30-50% of patients benefit from it long-term.
- A better understanding of tumor features could help guide treatment decisions.
- To date, Programmed Death-Ligand 1 (PD-L1) remains the only biomarker used to predict IO efficacy, demonstrating its unique predictive ability, even if not perfect.
- A specific morphology has been found to be associated with PD-L1 expression, introducing new scenarios for the biological interpretation of the immune response.
- Utilizing AI and machine learning processes to analyze DPS could help create decision making tools for more individualized prediction of response.

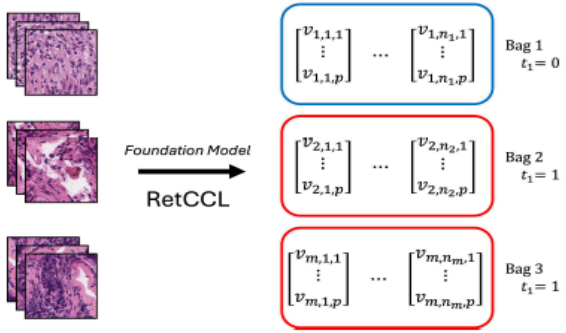
METHODS



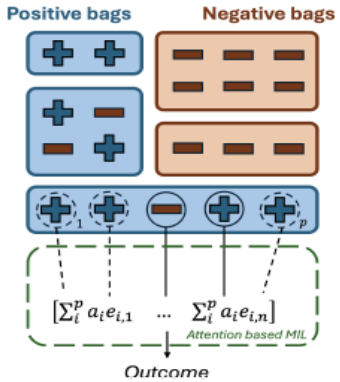
Digital Pathology whole slide images are very large images, and to feed them into Artificial Neural Network-based models we extracted square tiles [299x299px] at 10x magnification from the whole slide images.



Reinhard normalization was employed to reduce batch effect.



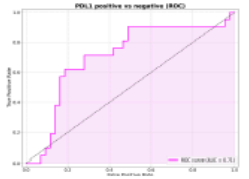
Large-scale AI models, known as foundation models, are developed using vast datasets and a training approach called self-supervised learning. This method does not rely on manually labeled data. Instead, it presents the model with a complex task inherent to the data itself. By solving this task, the model learns to identify and extract important features from the input information on its own.
For this task, we used RetCCL, a model trained on TCGA and PAIP datasets.
Once processed through RetCCL, tiles are converted into vectors of biologically relevant features.



Slides are now converted into bags of vectors.
Assuming that not all tiles are equally relevant for our task, we need a model able to learn not only the patterns associated with a certain outcome, but also which tiles to focus on to find those patterns.
For this goal, we used an Attention-Based Multiple Instance Learning model, which employs the attention mechanism to infer the importance of each tile vector.

RESULTS

- Among the 2188 pt enrolled in the I3LUNG retrospective cohort, 474 patients had available DPS and PD-L1 status to be considered for the present analysis.
- PD-L1 expression was high (>50%), low (1-49%) and negative in 145 (37%), 129 (32%) and 127 (31%) patients within the training cohort, respectively, and 24 (33%), 23 (32%) and 26 (35%) among the validation cohort, respectively.
- PD-L1 high vs low/negative status through DPS were able to be predicted with an area under the curve (AUC) of 0.69; while for PD-L1 positive vs negative an AUC of 0.71 was achieved.



CONCLUSIONS

- To our knowledge, this is the largest series to date demonstrating a correlation between morphological features and PD-L1 expression in lung cancer.
- Data suggests that PD-L1 high and negative have different morphological phenotype.
- This rapid and generalizable model underscores the potential for morphological features to serve as valuable biomarkers in elucidating the mechanisms of immune responses.
- Within I3LUNG integration of genomic and radiomic data will probably allow to improve the ability to assess patient prognosis at diagnosis.

ACKNOWLEDGEMENTS

We sincerely thank the patients and their families for their invaluable participation in this study. This project has received funding from the European Union's Horizon Europe research and innovation programme. We are grateful for the collaborative efforts of our consortium partners. Their expertise has been crucial to the success of the I3LUNG project.

Corresponding Author email: Arsela.Prelaj@istitutotumori.mi.it

Arsela Prelaj DOIs: AstraZeneca, Training of personnel, Advisory Board, coordinating PI; BMS, Advisory Board, Local PI; Italfarma, Training of personnel; Janssen, travel grant, Advisory Board; Lilly, Invited Speaker, Local PI; MEDSIR, Invited Speaker; Novartis, Invited Speaker; Roche, Invited Speaker, Local PI; Bayer, Local PI; MSD, Local PI; SPECTRUM, Coordinating PI

Scan here to view a plain language summary of this study.

Organizado por: GECP lung cancer research

PD-L1 y TMB

Biomarcadores predictivos, y potencialmente pronósticos en combinación con otros biomarcadores.

¿Qué sabemos?

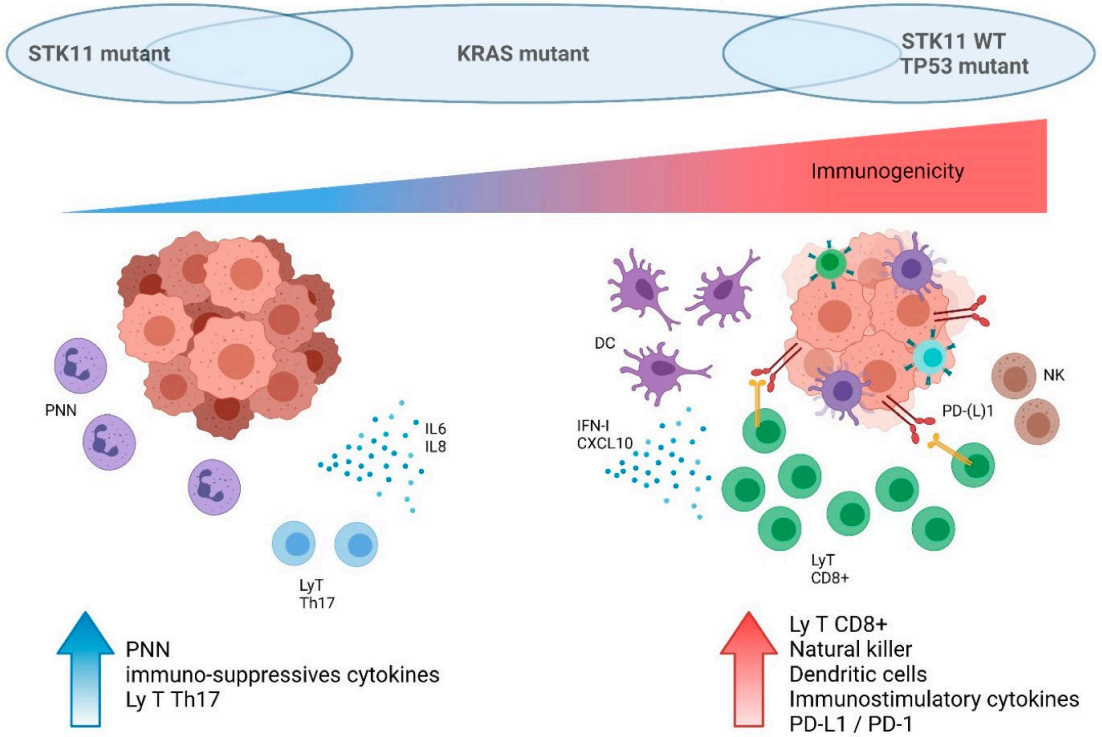
- PD-L1: La heterogeneidad intratumoral y la variabilidad en las técnicas de medición pueden afectar su precisión como biomarcador.
- TMB: Aplicación rutinaria limitada debido a la falta de estandarización y consenso sobre los puntos de corte óptimos.

¿Novedades?

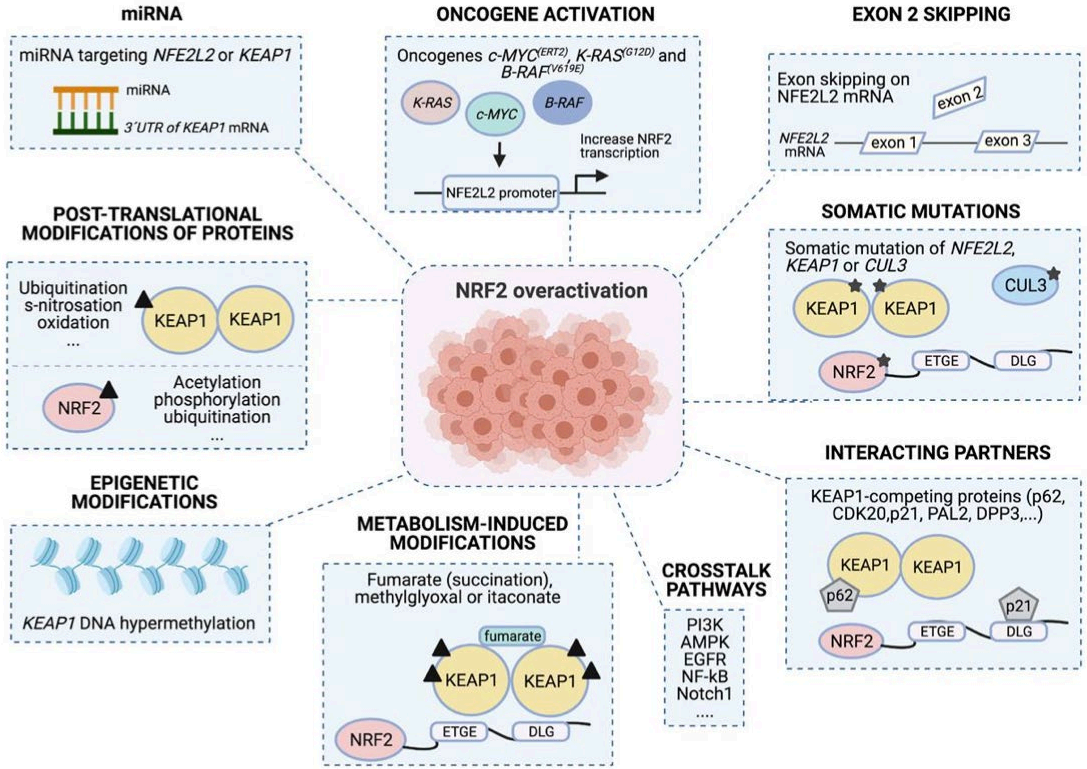
- Combinación con otros biomarcadores emergentes: radiómica, inteligencia artificial y marcadores séricos y genómicos con valor PRONÓSTICO.

- Mutaciones en STK11, KEAP1 y SMARCA4.

Organizado por:
GECP lung cancer research



Pons-Tostivint,E. Cells 2021,10,3129



Sánchez-Ortega,M. Cells 2021, 10, 1879

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lung cancer research

Impact of KRAS, STK11, and KEAP1 co-mutations on survival outcome and response to chemoimmunotherapy in patients with metastatic NSCLC

ESMO congress
FPN: 1339P

Utsav Joshi[1], Suman Gaire[2], Sumeet Yadav[3], Pravash Budhathoki[1], Chengu Niu[4], Soon Khai Low[5], Vishakha Agrawal[6], Michael Shafique[1]

[1]H. Lee Moffitt Cancer Center [2]Mt. Sinai Hospital [3]Mayo Clinic [4]Rochester General Hospital [5]Medical College of Wisconsin [6]University of South Florida

MOFFITT CANCER CENTER

BACKGROUND

- Clinical trials have demonstrated benefit of combination chemo-IO in metastatic NSCLC (mNSCLC) without targetable mutations.
- Limited retrospective studies have shown benefit of chemo-IO in KRAS mutated NSCLC, but the response in the presence of STK11 or KEAP1 mutations and the impact on OS have not been systematically analyzed.
- This analysis leverages data from the AACR GENIE database to evaluate OS and assess the impact of these mutations on treatment outcomes.

METHODS

Patient population:

- Patients with stage IV NSCLC with documented KRAS, STK11, and KEAP1 mutation status based on NGS performed between 2014 and 2018.
- Key exclusion- Stage I-III NSCLC with adjuvant or neoadjuvant therapy prior to disease progression.

Endpoints:

- The primary outcome was OS.

Statistical approach:

- KM curves, log-rank test, and multivariate Cox proportional hazard regression were used.

FUTURE DIRECTIONS FOR RESEARCH

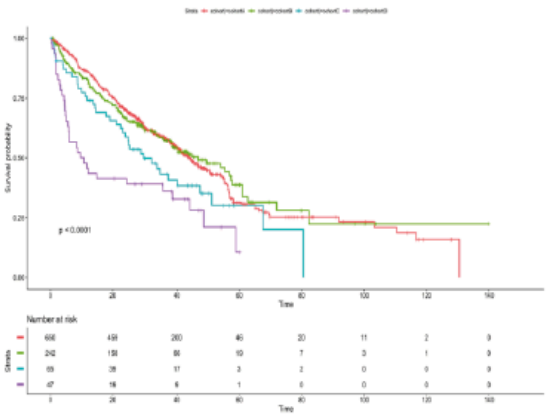
- Future trials should evaluate the role of chemo-IO in KRAS mutated mNSCLC with KEAP1 and/or STK11 co-mutations.
- Exploring personalized treatment strategies, such as optimizing the combination and sequencing of chemo-IO and targeted therapies, may help enhance the efficacy of treatments for patients with different KRAS mutation profiles.

RESULTS

Table 1- Baseline characteristics of the study population.

	$KRAS^{wt}/STK11^{wt}/KEAP1^{wt}$	$KRAS^{mut}/STK11^{wt}/KEAP1^{wt}$	$KRAS^{wt}/STK11^{mut}$ or $KEAP1^{mut}$	$KRAS^{mut}/STK11^{mut}/KEAP1^{mut}$
	659 (64.7%)	242 (24.1%)	65 (6.5%)	47 (4.7%)
Age at sequencing, Median (Range)	62.6 (30.1,85.2)	67.1 (38.6,83.4)	67.8 (50.9,82.1)	65.9 (50.8,79.3)
Sex:				
Female	404 (62.2%)	165 (68.2%)	47 (72.3%)	24 (51.1%)
Male	246 (37.8%)	77 (31.8%)	18 (27.7%)	23 (48.9%)
Cancer stage at diagnosis:				
Stage I-III	186 (29.4%)	102 (43.0%)	22 (33.8%)	13 (27.7%)
Stage IV	459 (70.6%)	138 (57.0%)	43 (66.2%)	34 (72.3%)
Smoking history:				
Current/former smoker	399 (61.4%)	219 (90.5%)	63 (96.9%)	47 (100%)
Never smoker	251 (38.6%)	23 (9.5%)	2 (3.1%)	0
PD-L1 expression:				
Yes	120 (18.5%)	57 (23.6%)	17 (26.2%)	6 (12.8%)
No	120 (18.5%)	32 (13.2%)	10 (15.4%)	14 (29.8%)
Unknown	410 (63.1%)	153 (63.2%)	38 (58.5%)	27 (57.4%)
Systemic therapy:				
Chemotherapy only	287 (44.2%)	52 (21.5%)	13 (20.0%)	10 (21.3%)
Immune checkpoint inhibitors only	12 (1.8%)	10 (4.1%)	4 (6.2%)	2 (4.3%)
chemotherapy and immune checkpoint inhibitors	105 (16.2%)	53 (21.9%)	14 (21.5%)	12 (25.0%)

Figure 1- KM estimate of OS of cohort A-D



Main takeaway:
Overall survival is significantly **compromised in patients with STK11 and/or KEAP1 co-mutations with KRAS** mutation, and those with **KRAS-only or triple mutations derive greater benefit from chemo-IO** compared to chemotherapy alone.

Figure 2- KM estimate of OS of cohort A-D
A) Chemo+IO B) Chemo only

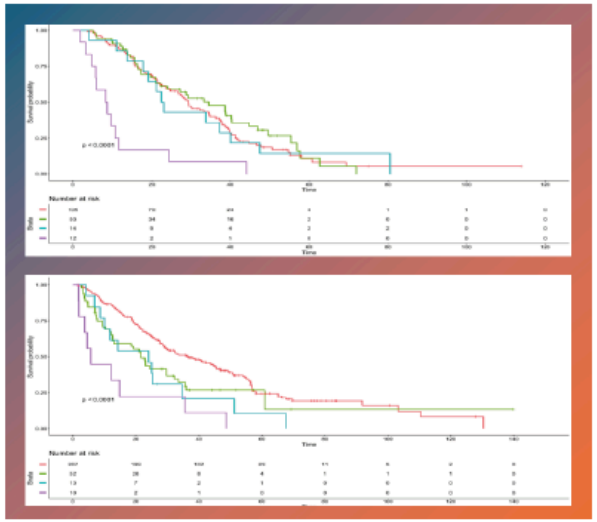


Table 2- Overall survival with different comutations.

Mutation status	Median OS (months) – Chemo + IO	Median OS (months) – Chemo only	3- year OS (%) – Chemo + IO	3-year OS (%) – Chemo only
$KRAS^{wt}/STK11^{wt}/KEAP1^{wt}$	29.31 (N=105)	36.5 (N=287)	39.9	51.3
$KRAS^{mut}/STK11^{wt}/KEAP1^{wt}$	34.51 (N=53)	21.6 (N=52)	47.8	26.7
$KRAS^{mut}/STK11^{mut}$ or $KEAP1^{mut}$	22.78 (N=14)	23.9 (N=13)	35.7	20.5
$KRAS^{mut}/STK11^{mut}/KEAP1^{mut}$	8.47 (N=12)	5.6 (N=10)	8.3	11.1

Table 3- Multivariate analysis adjusting for clinico-demographic factors

Comutations	HR (95% CI)	P value
Cohort A- $KRAS^{wt}/STK11^{wt}/KEAP1^{wt}$		
Cohort B- $KRAS^{mut}/STK11^{wt}/KEAP1^{wt}$	1.34 (1.06,1.67)	0.01
Cohort C- $KRAS^{mut}/STK11^{mut}$ or $KEAP1^{mut}$	1.67 (1.18,2.35)	0.003
Cohort D- $KRAS^{mut}/STK11^{mut}/KEAP1^{mut}$	4.08 (2.78,5.99)	<0.001

LIMITATIONS

- Retrospective nature of the study
- Small sample size within certain comutation subgroups
- Could not establish why an OS difference existed among the triple wild type population between chemo-IO and chemo alone

Correspondence: Utsav.joshi@moffitt.org
Disclosure: None

Organizado por:
GECP lung cancer research

Retrospective analysis of change in frequency of *STK11* mutation in lung adenocarcinomas over a 10-year period

Deevyashali Parekh[1], Alina Basnet[1], Dean Pavlick[2], Jeffrey S Ross[2], Stephen Graziano[1]

Upstate Medical University, Syracuse, NY[1], Foundation Medicine Inc., Boston, MA[2]

BACKGROUND

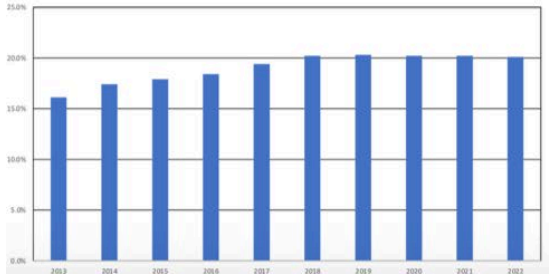
- Inactivating mutations in *STK11* associated with ↓ efficacy of ICIs in Lung Adenocarcinoma
- We queried for a change in *STK11* mutation frequency over the past 10 years potentially reflecting the emergence of acquired resistance mutations

METHODS

- ≥50 ng DNA extracted from 40 μm of FFPE sections
- Sequencing performed on 324 cancer-related genes and 28 common cancer gene introns
- FDA-approved (F1CDx) hybrid capture-based sequencing using adaptor ligation-based libraries
- Short variants, rearrangements, and copy number changes were assessed
- TMB calculated from 0.80 Mb sequenced DNA

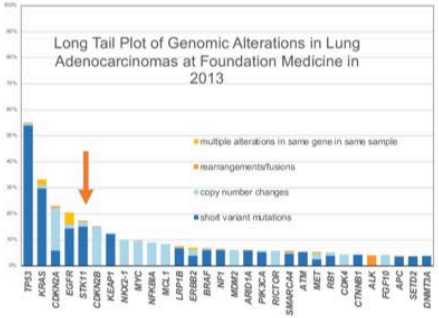
RESULTS

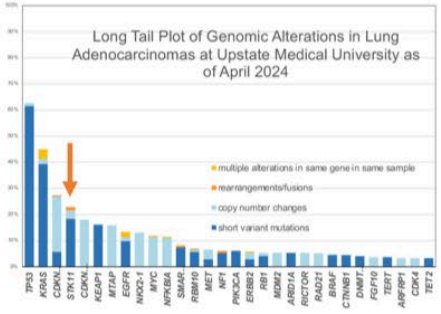
Frequencies of *STK11* GA in Lung Adenocarcinomas from 2013 to 2022 at Foundation Medicine

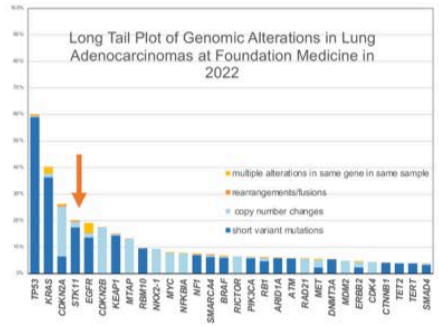


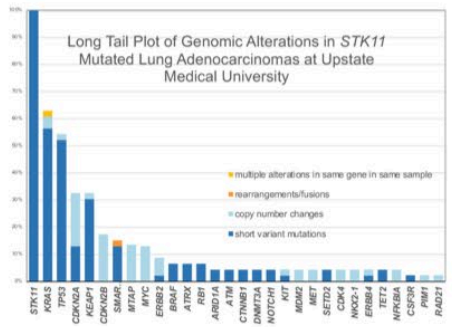
RESULTS

- *STK11* inactivating GA in LA significantly ↑ during the study period from 2013 to 2022 (16.1% vs 20.1%; p=0.0005)
- ↑ predominantly in *KRAS* wild type LA (10.1% vs 15.5%; p<0.0001)
- *STK11* GA frequency ↓ in KRAS mutated LA over the 10-year period (29.9% vs 27.0%, P=0.25)
- *KEAP1* GA frequency ↑ 12.6% to 14.9% (p= 0.076), combined *STK11* and *KEAP1* GA ↑ 4.8% to 8.0% (p=0.0006)
- Over the last 6 years, the frequencies of MSI-high status, TMB and PD-L1 expression did not significantly change over the observation period



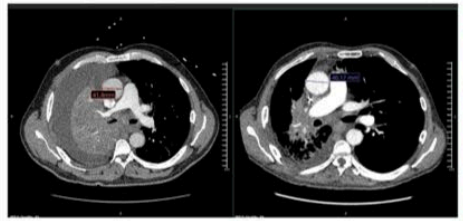




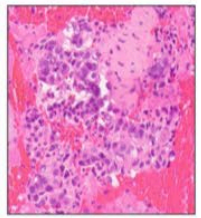


CASE EXAMPLES

- 59-year-old male with MS Stable low TMB (6 mutations/Mb) Stage IV Lung Adenocarcinoma with *STK11* D194H and KRAS G12C mutations
- PD-L1 IHC was 1% TPS
- Treated with Pembrolizumab.
- Discontinued Pembrolizumab 7 months into treatment for progression

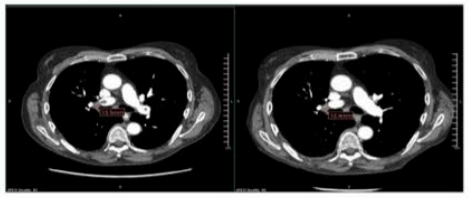


(L) Pre-treatment CT Thorax w contrast; (R) 6-months into treatment

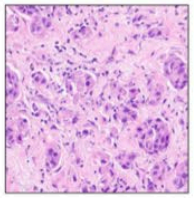


Needle biopsy showing LA

- 75-year-old male with MS Stable, PD-L1 0% TPS, low TMB (1 mutation//Mb) Stage IV Lung Adenocarcinoma with *STK11* A318fs*18 and *KRAS* G12F mutations treated with Pembrolizumab.
- Amplifications of *AKT3, CDK4, MDM2 and loss of CDKN2A/B* and *MTAP* also identified
- Discontinued Pembrolizumab 6 months into treatment for progression



(L) Pre-treatment CT Thorax w contrast; (R) 4-months into treatment

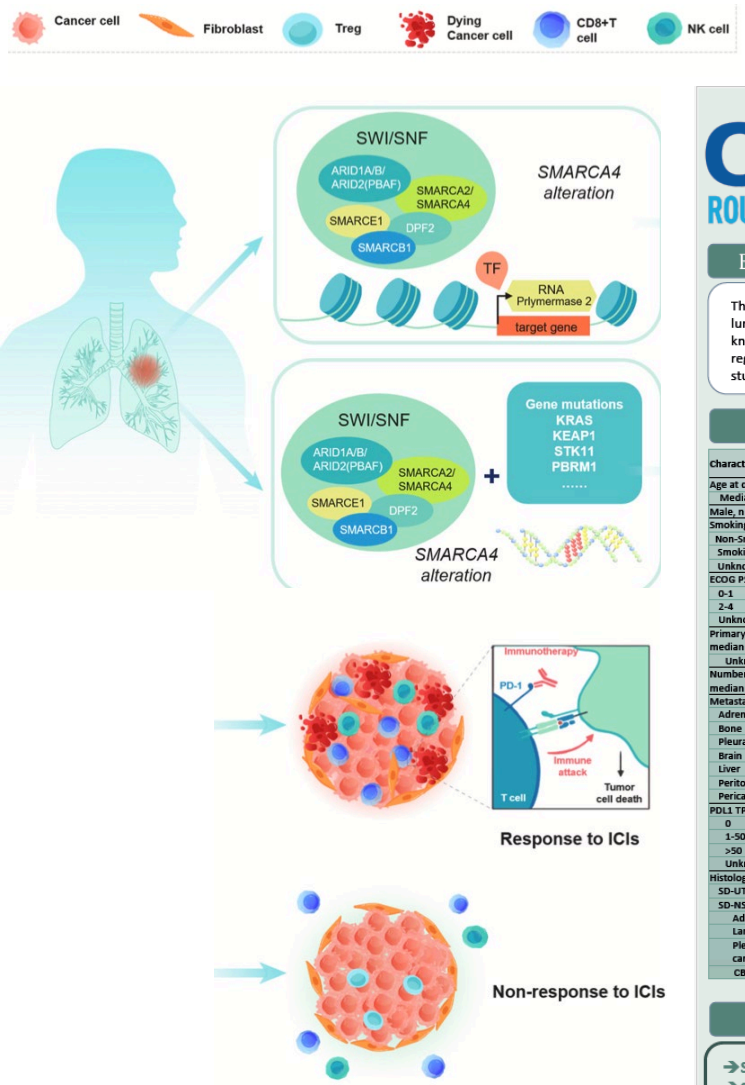


Pleural biopsy of LA

CONCLUSIONS

- ↑ use of ICIs in Lung Adenocarcinoma leading to significant ↑ in *STK11* GA, predominantly in *KRAS* –ve population
- STK11 GA associated with ↓ RR and PFS
- Novel therapies focused on potential restoration of *STK11* function by HDAC/CoREST inhibition hence *STK11* in LA requires further study

Organizado por: GECP lung cancer research



SMART: French multicenter study on clinical characteristics and treatment outcomes in patients with SMARCA4-deficient thoracic tumor

1390P

Duparc Inès[a], Castanet Elora[b], Cousin Sophie[b], Basse Clémence[c], Fallet Vincent[d], Baldacci Simon[e], Demontrond Pierre[f], Arpin Dominique[g], Leite Ferreira Dimitri[h], Oulkhouir Youssef[i], Fournel Pierre[j], Piton Nicolas[k], Guisier Florian[a]

[a] Centre Hospitalier Universitaire de Rouen, Department of Pulmonology; [b] Medical Oncology Department, Institut Bergonié, Bordeaux; [c] Thorax Institute Curie Montsouris, Institut Curie, Paris Saclay University, Versailles, France; [d] Hospital Tenon, Department of Pulmonology, Paris, France; [e] Univ. Lille, CHU Lille, Thoracic Oncology Department, [f] Department of Medical Oncology, Centre François Baclesse, [g] Department of Pulmonology de Villefranche-sur-Saône; [h] Department of Pulmonology & Thoracic Oncology, CHU de Caen, [i] Department of Pulmonology, CHU d'Anger; [j] Département d'Oncologie Médicale, Institut de Cancérologie Lucien Neuwirth, Saint-Étienne; [k] CHU de Rouen, Pathology

SCAN ME

BACKGROUND

The *SMARCA4* gene encodes BRG1, an ATPase subunit of the SWI/SNF complex, which is responsible for chromatin remodeling. The loss of BRG1 expression is observed in 5-10% of non-small cell lung cancers (SD-NSCLC). An undifferentiated SMARCA4-deficient thoracic tumor type (SD-UT) has been described, which is considered distinct from SD-NSCLC. This tumor type was formerly known as SMARCA4-deficient sarcoma and was reclassified in 2021 by the World Health Organization (WHO). These two tumor types are relatively uncommon, with a lack of available data regarding their clinical characteristics. The prognosis for these patients is poor, with a low response rate to chemotherapy and uncertain sensitivity to immune checkpoint inhibitors (ICI). This study aimed to describe the clinical characteristics of these patients, as well as their prognosis and treatment outcomes in the era of anti-PD1/PD-L1 immunotherapy.

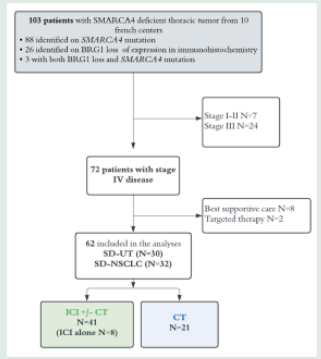
METHODS

RETROSPECTIVE MULTICENTER STUDY

Inclusion criteria	Exclusion criteria
✓ Age > 18 years. ✓ Stage IV thoracic tumor diagnosed between January 2015 and June 2024. ✓ SMARCA4 deficiency: loss of BRG1 expression (immunohistochemistry) and/or pathogenic variant in the *SMARCA4* gene.	× Undifferentiated SMARCA4-deficient tumors without a thoracic target, × No data available or explicit refusal to collect data × First line = best supportive care or targeted therapy

OUTCOME

➔ Describe the clinical and anatomopathological features of these patients.
➔ Prognosis and treatment outcomes in the setting of anti-PD1/PD-L1 immunotherapy (all data censored at 36 months).



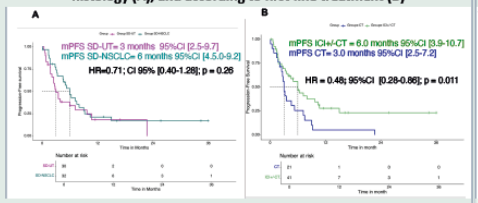
RESULTS

Characteristics	All (n=62)
Age at diagnosis, Median [Q1 - Q3]	61 [49 - 67]
Male, n (%)	47 (76)
Smoking Status, n (%)	
Non-Smoking	2 (3)
Smoking	55 (89)
Unknown	5 (8)
ECOG PS at Diagnosis, n (%)	
0-1	50 (80)
2-4	12 (20)
Unknown	0
Primary tumor size, mm, median [Q1-Q3]	54.5 [30.25 – 80]
Unknown	6
Number of metastatic sites, median [Q1-Q3]	2 [1 – 3]
Metastatic organs, n (%)	
Adrenal gland	23 (37)
Bone	23 (37)
Pleura	20 (32)
Brain	11 (17)
Liver	7 (11)
Peritoneum	7 (11)
Pericardium	2 (6)
PDL1 TPS, n (%)	
0	27 (44)
1-50	11 (26)
>50	10 (24)
Unknown	14 (23)
Histology, n (%)	
SD-UT	30 (48)
SD-NSCLC	32 (52)
Adenocarcinoma	23 (37)
Large cell carcinoma	4 (6)
Pleomorphic carcinoma	2 (3)
CBNPC-NOS	3 (5)

PFS

Median follow up was 16.2 months 95%CI [11.5-NA]
Median PFS was **4.7 months CI95% [3.2-7.2]**

Kaplan-Meier estimate for Progression-Free Survival according to histology (A), and according to first-line treatment (B)



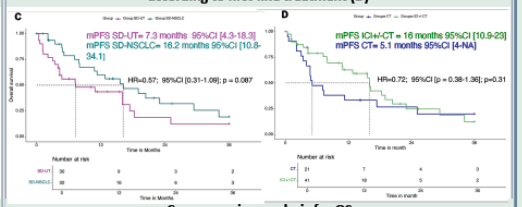
Cox regression analysis for PFS

N = 62 Parameters	Univariate analysis HR [95% CI]	p-value	Multivariate analysis HR [95% CI]	p-value
Age	0.99 [0.97-1.02]	0.789		
Male gender	0.89 [0.46-1.72]	0.731		
SD-NSCLC histology	0.72 [0.40-1.27]	0.258		
OMS				
<2	REF	-	REF	-
≥2	0.86 [0.91-3.75]	0.08	1.15 [1.05-4.42]	0.09
First line treatment				-
CT	REF	-	REF	-
ICI+/-CT	0.48 [0.26-0.86]	0.01	0.43 [0.24-0.79]	0.006
PDL1 (TPS)				
0	REF	-		
1-50 %	0.72 [0.33–1.58]	0.417		
>50 %	0.73 [0.33-1.06]	0.435		
Metastatic sites				
Adrenal gland	0.82 [0.45-1.50]	0.528		
Bone	1.05 [0.59-1.89]	0.856		
Pleural	1.46 [0.78-2.73]	0.233		
Brain	1.06 [0.51-2.22]	0.873		
Liver	1.31[0.55-3.10]	0.055		
Peritoneum	1.73 [0.72-4.11]	0.217		
Pericardial	2.88 [0.67-12.3]	0.153		

OS

Median follow up was 30.8 months 95%CI [20.5-NA]
Median OS was **12.8 months CI95% [7.3-19.0]**

Kaplan-Meier estimate for Overall Survival according to histology (C), and according to first-line treatment (D)



Cox regression analysis for OS

N = 62 Parameters	Univariate analysis HR [95% CI]	p-value	Multivariate analysis HR [95% CI]	p-value
Age	0.99 [0.97-1.01]	0.601		
Male gender	1.05 [0.48-2.28]	0.902		
SD-NSCLC Histology	0.57 [0.31-1.08]	0.088	0.53 [0.26-1.05]	0.072
OMS				
<2	REF	-		
≥2	2.38 [1.08-5.29]	0.003	2.09 [0.83-5.25]	0.116
First line treatment				
CT	REF	-		
ICI+/- CT	0.72 [0.38-1.36]	0.312		
PDL1 (TPS)				
0 %	REF			
1-49 %	0.62 [0.27-1.43]	0.267		
>50 %	0.42 [0.14-1.19]	0.102		
Metastatic sites				
Adrenal gland	0.80 [0.41-1.53]	0.497		
Bone	1.02 [0.54-1.92]	0.952		
Pleural	1.38 [0.71-2.68]	0.340		
Brain	0.98 [0.45-2.14]	0.957		
Liver	2.65 [1.08-2.51]	0.003	2.50 [1.00-6.24]	0.051
Peritoneum	2.81 [1.13-7.00]	0.002	3.55 [1.24-10.14]	0.02
Pericardial	9.64 [2.05-45.8]	0.004	3.48 [0.5-22.12]	0.184

CONCLUSION

➔ **SMARCA4-deficient thoracic tumors** mostly affect smokers, males, and relatively young patients.
➔ **SD-NSCLC** are predominantly adenocarcinomas and TTF1 negative (70%)
➔ **SMARCA4-deficient thoracic tumors** have a poor prognosis particularly SD-UT and a limited response to systemic treatment; however, **immunotherapy ± CT is associated with better PFS then CT alone**

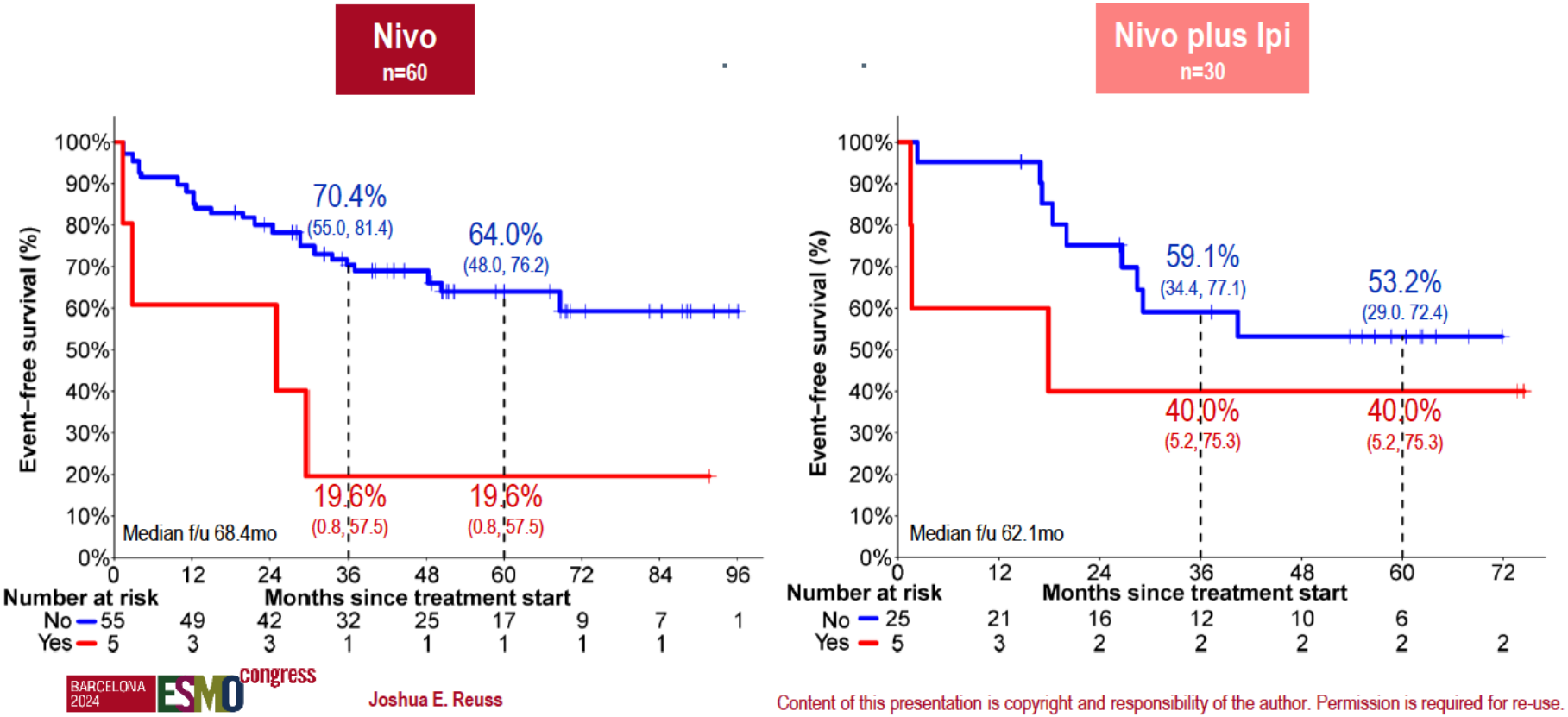
RELATED ARTICLES

Articles	Shi et al. 2024	Wang et al. 2024	Lin et al. 2023	Shinno et al. 2022	Velut et al. 2022
N° of patients	29 SD-UT & 104 SD-NSCLC	25 SD-TT	13 SD-UT & 12 SD-NSCLC	5 SD-UT & 7 SD-NSCLC	7 SD-UT
Treatment	ICI+CT. vs. CT. (1st line)	Anti-PD1+/-CT. vs. CT. alone (any line)	ICI+CT. vs. CT (1st line)	ICI+/- CT. vs. CT alone (1st line)	Anti-PD1 in 7 SD-NSCLC vs. in 77 non SD-NSCLC
Results	Improved PFS with 1st line ICI	No significant difference in OS	Improved PFS with ICI in the SD-UT group (no significant difference in SD-NSCLC group)	Improved PFS with 1st line ICI	Shorter OS in SD-NSCLC

Tiang Y. Cancer Letters 554 (2023) 216022

EFS analysis by key molecular subgroups

EFS by *KRAS* co-mutation w/ *STK11*, *KEAP1*, and/or *SMARCA4* status (No/Yes)



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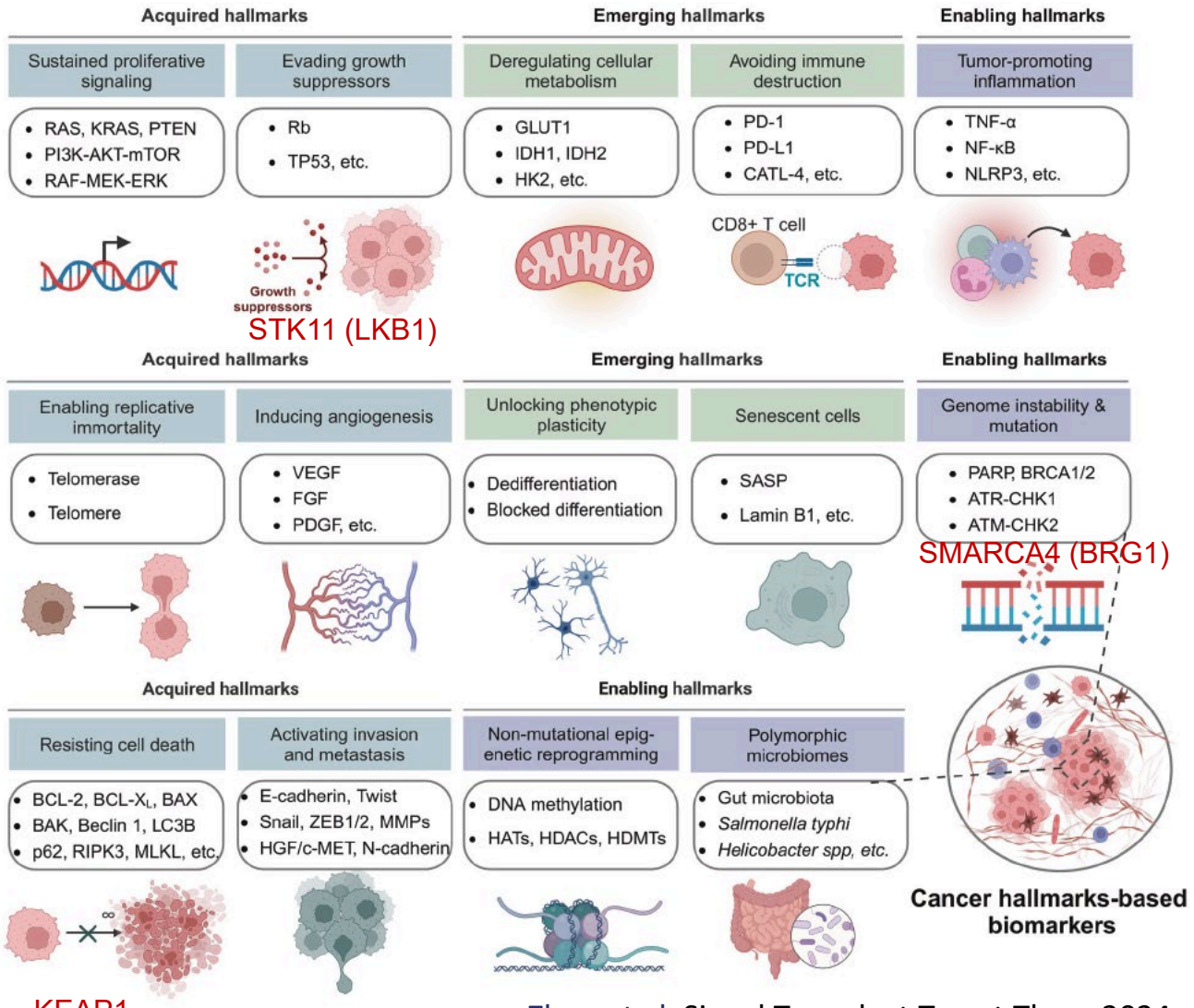


Zhou et al. Signal Transduct Target Ther . 2024

Organizado por:
GECP lung cancer research

Mutaciones con impacto pronóstico en cáncer de pulmón

KRAS (especialmente G12C), comunes en CNMP y tienen importante valor **pronóstico** y terapéutico

TP53, presente en aprox. 50% de los NSCLC y casi todos los SCLC. Asociada a peor **pronóstico** (especialmente en combinación con otras mutaciones como KRAS).
RB, pérdida característica en SCLC.

CDKN2A/2B: genes supresores tumorales cuya pérdida se asocia a peor **pronóstico** en cáncer de pulmón.

TERT. La activación de la telomerasa → biomarcador **pronóstico** en tumores carcinoides

TERT functions in cancer formation

Transcriptional regulations
- *TERT* promoter mutation

Telomere maintenance
- influence telomerase activity
- influence telomerase assembly
- influence recruiting telomerase to telomere

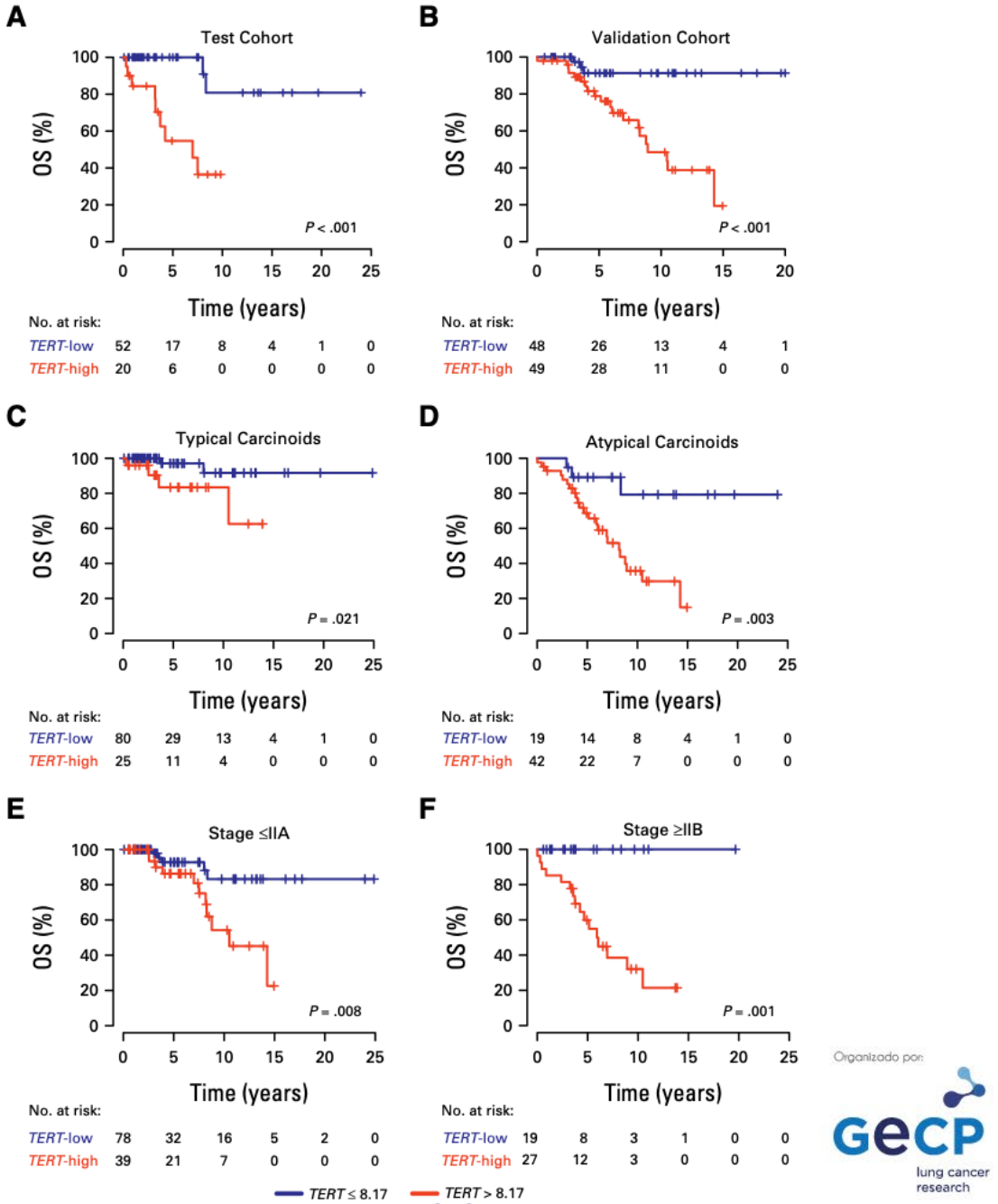
As a therapeutic target
- small molecular inhibitors
- TERT vaccine

Post-translational modifications (PTMs) of TERT
- Phosphorylation
- Ubiquitination
- SUMOylation

Non-canonical functions
- proliferation, apoptosis, cell cycle
- tumor initiating cell formation
- EMT
- induce cancer cell invasion
- influence transcriptional factors activity

up-stream → down-stream

Liu, M et al. Cell Death Dis 15, 90 (2024)



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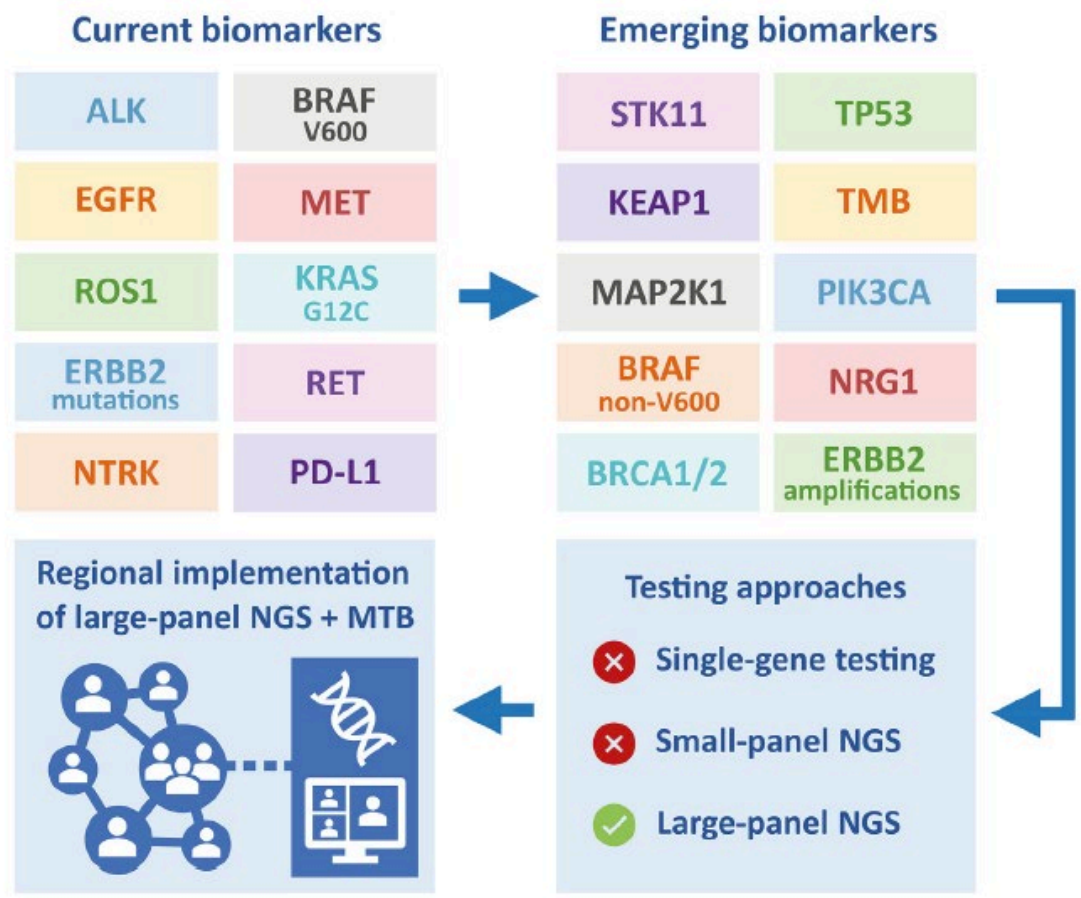
Lisa Werr et al. JCO 43, 214-225(2025)

NGS

Next-generation sequencing



De Jager VD et al. Lancet Reg Health Eur. 2024

- **Ventajas de ampliar paneles**
  - Detección de múltiples alteraciones de forma simultánea.
  - Facilita la identificación de mutaciones accionables.
  - Mejora la comprensión de la heterogeneidad tumoral.
- **Limitaciones**
  - No identifica alteraciones epigenéticas.
  - Pueden pasar por alto genes no mutados del microambiente tumoral.

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Biopsia líquida

- MRD – ctDNA
- Exosomas
- Perfiles de metilación DNA
- Tasa de mutaciones somáticas (SMR)

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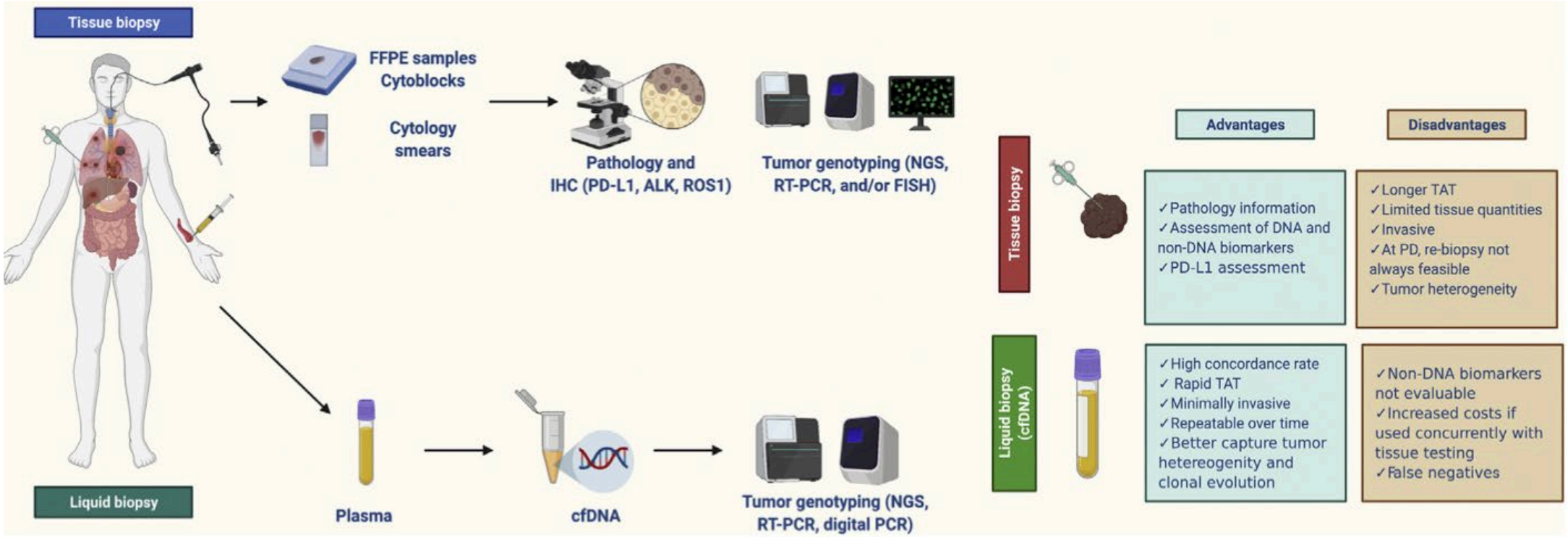
MRD - ctDNA

- Detección de la enfermedad mínima residual (MRD): La detección de ctDNA tras el tratamiento permite identificar pacientes con mayor riesgo de recaída precoz.
- Monitorización de respuesta al tratamiento: Las fluctuaciones en los niveles de ctDNA reflejan de manera dinámica la eficacia de las terapias administradas, permitiendo ajustes en tiempo real.



Rolfo C et al. J ThoracOncol 2021

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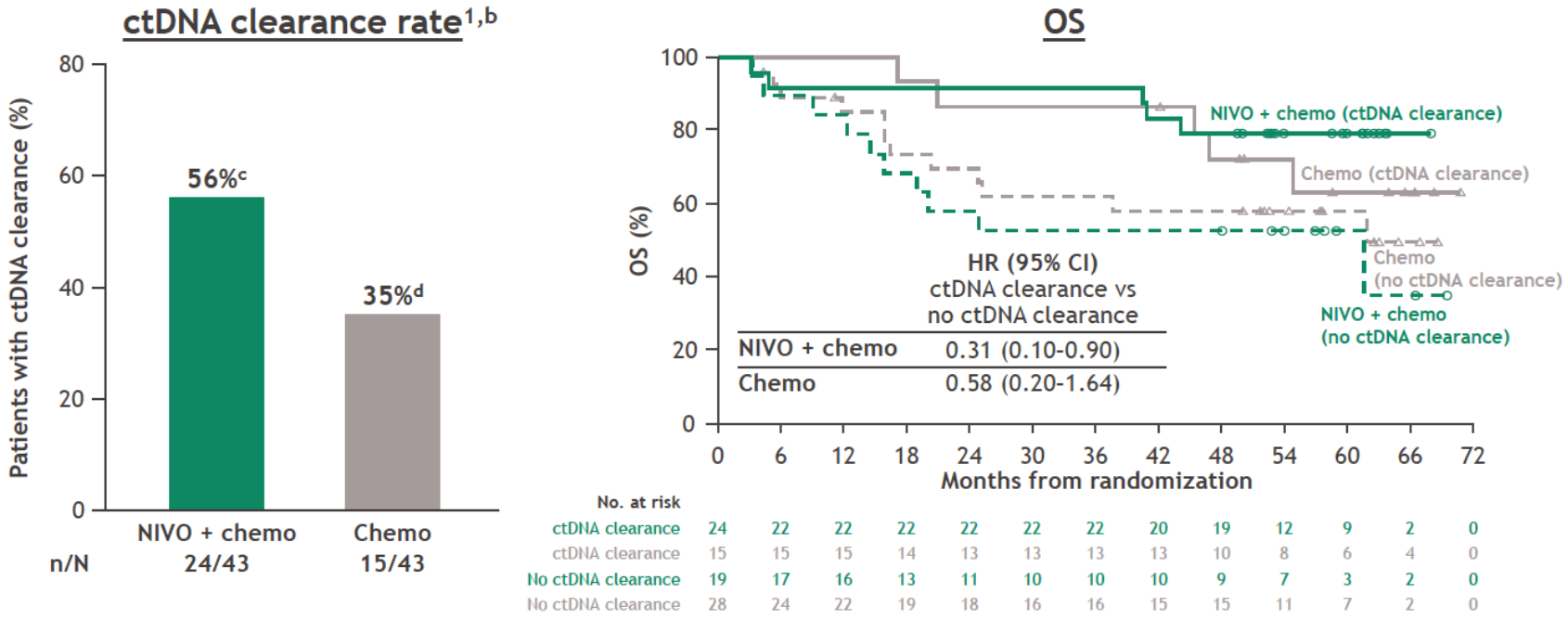
ctDNA clearance rate and OS by ctDNA clearance

- Among concurrently randomized patients, 89 (25%) had evaluable ctDNA levels, and 86 (24%) had detectable ctDNA levels at baseline[1,a]



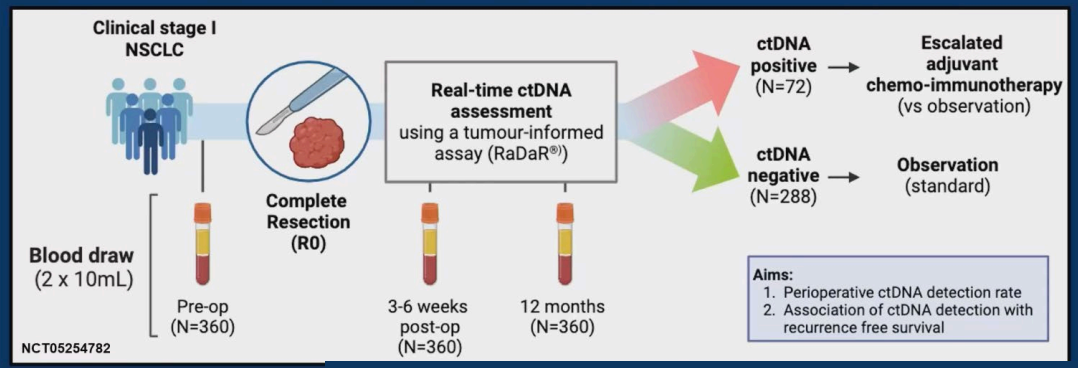
Minimum/median follow-up, 49.1/57.6 months.

[a]The main reasons for sample attrition were lack of tissue for WES and lack of quality control pass for tissue and plasma. [b]ctDNA clearance was defined as pre-surgical change from detectable ctDNA levels before cycle 1 to undetectable ctDNA levels before cycle 3. Analysis was performed using a WES tumor-guided personalized ctDNA panel (ArcherDX Personalized Cancer Monitoring). [c,d]95% CI: [c]40-71; [d]21-51. 1. Forde PM, et al. *N Engl J Med* 2022;386:1973-1985.

Spicer J. Abstract number LBA8010 (ASCO 2024).

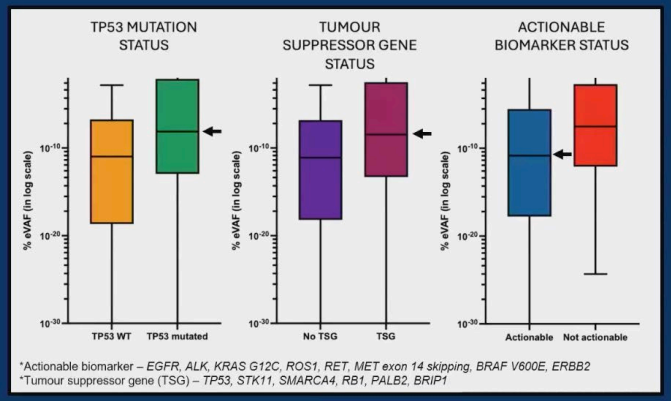
ctDNA-Lung-DETECT

Multicentre investigator-initiated prospective study in Toronto, Canada



Pre-operative ctDNA detection and genomic variants

- Higher estimated variant allelic fraction (eVAF) in plasma was associated with presence of alterations in TP53 (p<0.0001) and other tumour suppressor genes (p=0.0002)
- Presence of actionable biomarkers was associated with lower eVAF than non-actionable biomarkers (p=0.02)



Conclusion

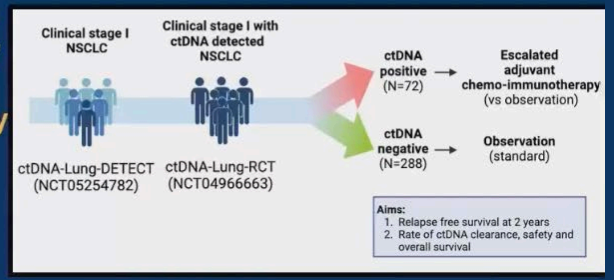
In this study of patients with **clinical stage I** NSCLC:

- Pre-operative ctDNA was detected in 22.7% using a tumour-informed assay
- Post-operative ctDNA was only detected in the setting of pathologic upstaging (occult N2 disease)
- In patients with pathologic stage I NSCLC, pre-operative ctDNA was detected in 14.0%
- Recurrence-free survival was significantly associated with detection of pre-operative ctDNA [HR 3.69, 95% CI: 1.12-12.1]
- Pathologic invasive tumour size but not radiographic size associated with pre-operative ctDNA detection
- ctDNA detection was more frequent in patients with high risk pathologic features and tumour suppressor alterations

Pre-operative ctDNA identifies stage I NSCLC patients at higher risk of relapse that may benefit from intensified curative therapy

Demonstration of the clinical utility of this approach is underway

More sensitive assays are needed to increase the value of this promising technology in clinical practice



Khan S, abstract 8018 (ASCO 2024)

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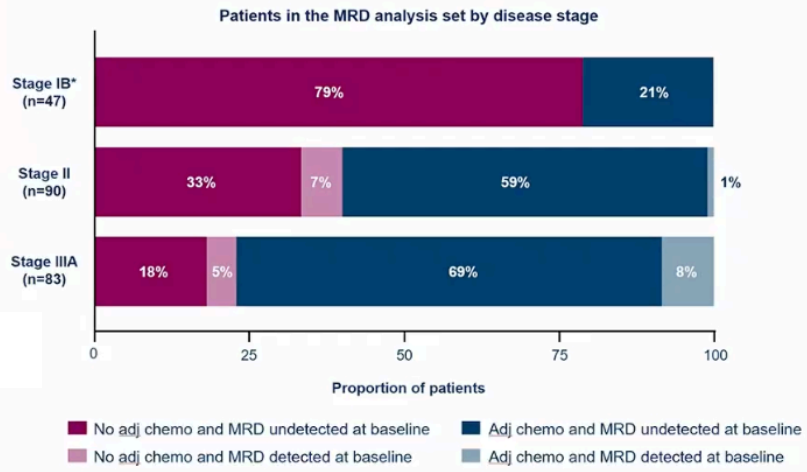
Baseline MRD Status in the ADAURA Study



Rates of MRD detection were low

- Stage IB: 0%
- Stage II: 8%
- Stage IIIA: 13%

Baseline MRD assays were drawn at randomization/C1D1 **after adjuvant chemotherapy if given**

- MRD was less likely to be detectable in patients who had received adjuvant chemotherapy.

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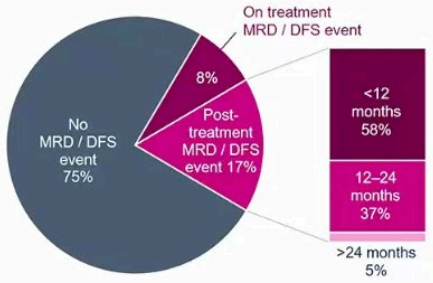
Can plasma MRD predict risk of recurrence after completion of adjuvant osimertinib?



Most MRD or DFS events (68%) occurred after end of TKI treatment

Of these more than half occurred in the first year off TKI

Longitudinal MRD Status

- NPV only 78%
- Median 4.7 months lead-time from MRD to DFS event

Do landmark MRD+ patients require longer course therapy?

Could longitudinal MRD testing reduce the risk of shorter course or deferred adjuvant therapy?

John et al, ASCO 2024; Herbst et al. J Clin Oncol. 2023 Apr 1; 41(10): 1830–1840.

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PRESENTED BY: Julia Rotow, MD

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ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

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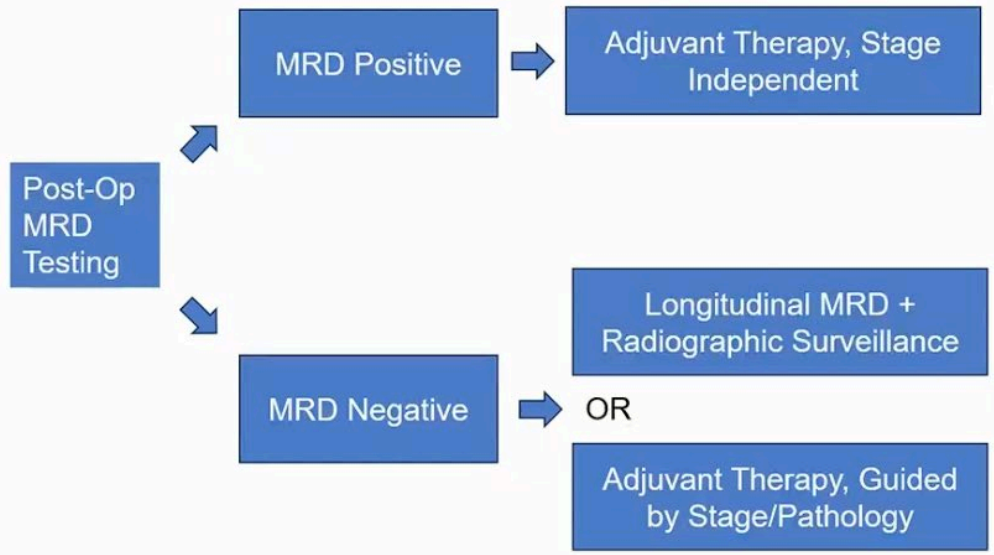
Prospective studies are need to understand how best to modify therapy based on MRD findings



Long-course or indefinite therapy?

Decision Informed By:

- Sensitivity of MRD assay
- Safety and efficacy of adjuvant regimen
- Patient preferences around QoL

PRESENTED BY: Julia Rotow, MD

Avances en ctDNA como biomarcador en cáncer de pulmón

1. Extrachromosomal Circular DNAs (eccDNAs) en NSCLC (Kang et al. EP.03D.03., WCLC 2024)

- Los eccDNAs son segmentos genómicos extracromosómicos que influyen en la expresión génica y están asociados con características específicas del tumor en NSCLC.
- En pacientes con tejido tumoral recurrente (RCT), eccDNAs derivados de CILP2 están sobreexpresados y correlacionados con peor pronóstico.
- Estos eccDNAs podrían actuar como oncogenes y ser potenciales biomarcadores pronósticos y terapéuticos en NSCLC.

2. Fracción tumoral de ctDNA (TF) como biomarcador pronóstico y guía terapéutica (*Dall'Olio et al. 4MO, ESMO 2024*)

- El ctDNA TF correlaciona con carga tumoral y volumen metabólico tumoral (MTV) en NSCLC avanzado.
- Altos niveles de TF (>5%) se asocian con peor pronóstico, menor supervivencia global (HR 0.55; IC 95%: 0.37–0.79) y progresión libre de enfermedad (HR 0.44; IC 95%: 0.29–0.65).
- TF es útil para seleccionar estrategias: inmunoterapia combinada con quimioterapia mejora resultados en pacientes con TF alto, mientras que inmunoterapia sola no es inferior en TF bajo.

Exosomas

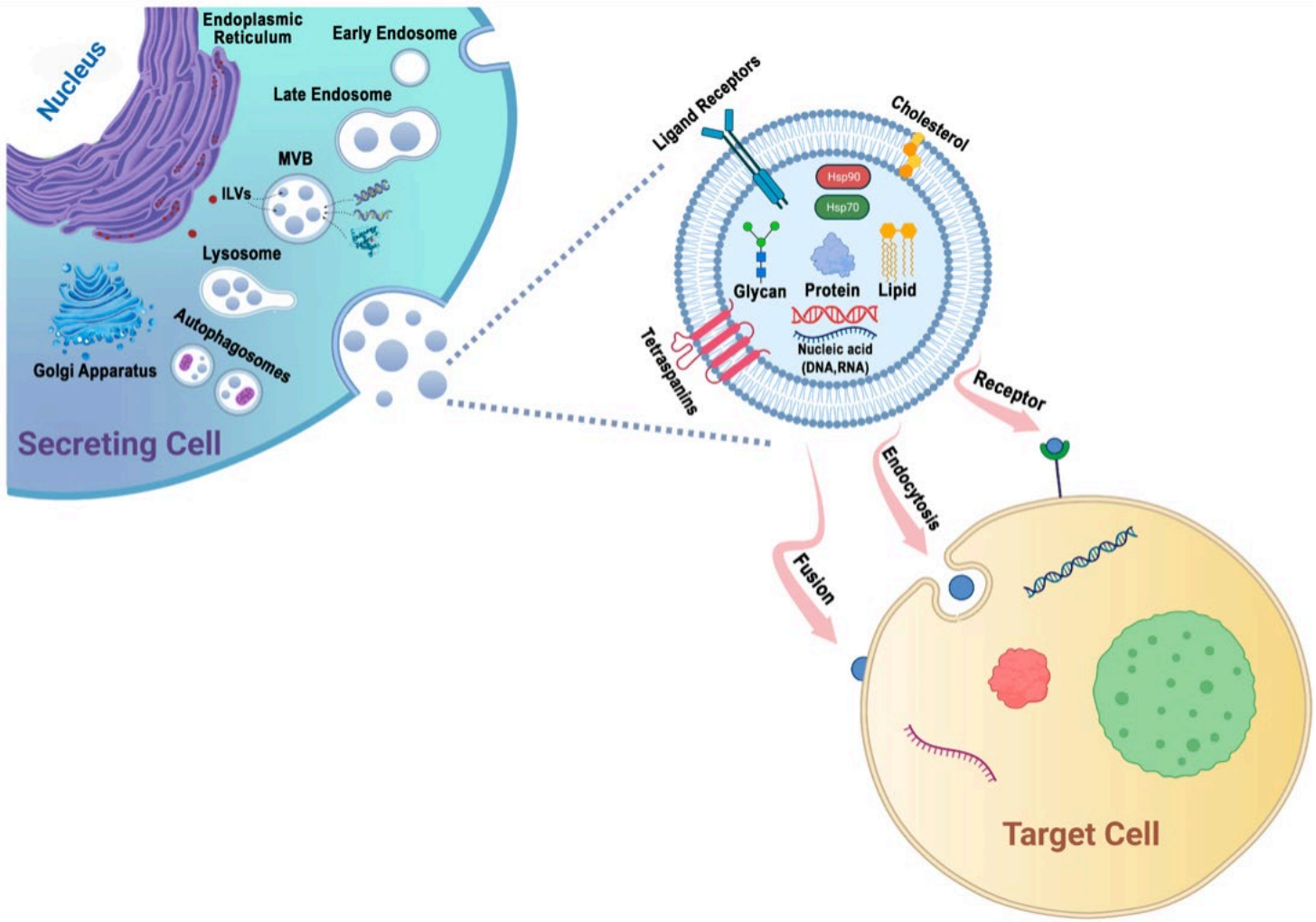
- Vesículas extracelulares liberadas por células tumorales
- Transportan material genético y proteínas reflejando el estado tumoral.
- Papel clave en la comunicación celular y la progresión tumoral.

<u>miRNAs asociados a exosomas</u>:

- Ejm. miR-21 y miR- 155 asociados con peor pronóstico en cáncer de pulmón.

<u>Aplicaciones clínicas</u>:

- Biomarcadores líquidos para diagnóstico y **pronóstico**.
- Potenciales herramientas para monitorizar tratamientos.
- Uso emergente como terapias dirigidas.



Rahimian S. Biomedicines 2024, 12(1), 123

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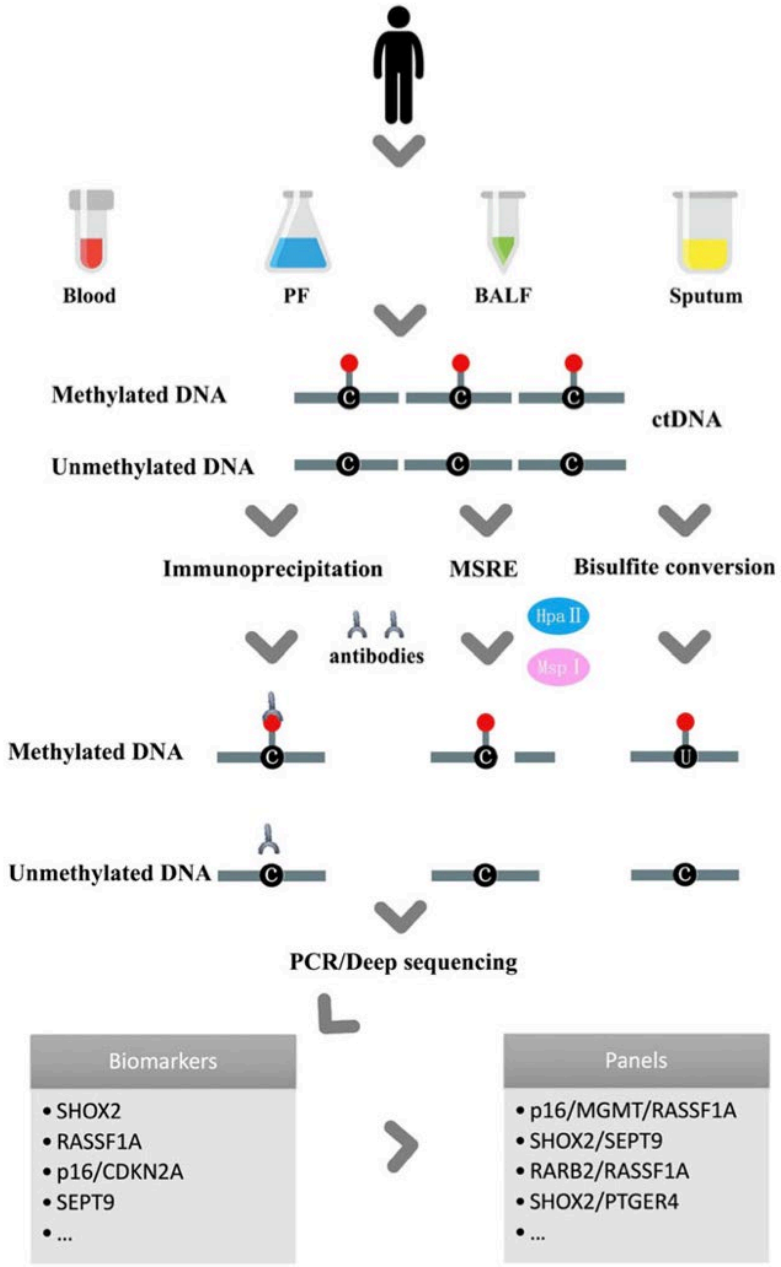
Epigenética

Perfiles de metilación del DNA en sangre

- Detección en biopsia líquida: los perfiles de metilación pueden identificarse en ctDNA, proporcionando información sobre cambios epigenéticos asociados al cáncer.
- Aplicación: ayudan a la detección temprana, clasificación tumoral y predicción de respuesta a tratamientos.
- Proyecto **EPILUNAR** está desarrollando estrategias epigenéticas para personalizar la inmunoterapia en cáncer de pulmón mediante análisis de sangre e inteligencia artificial.



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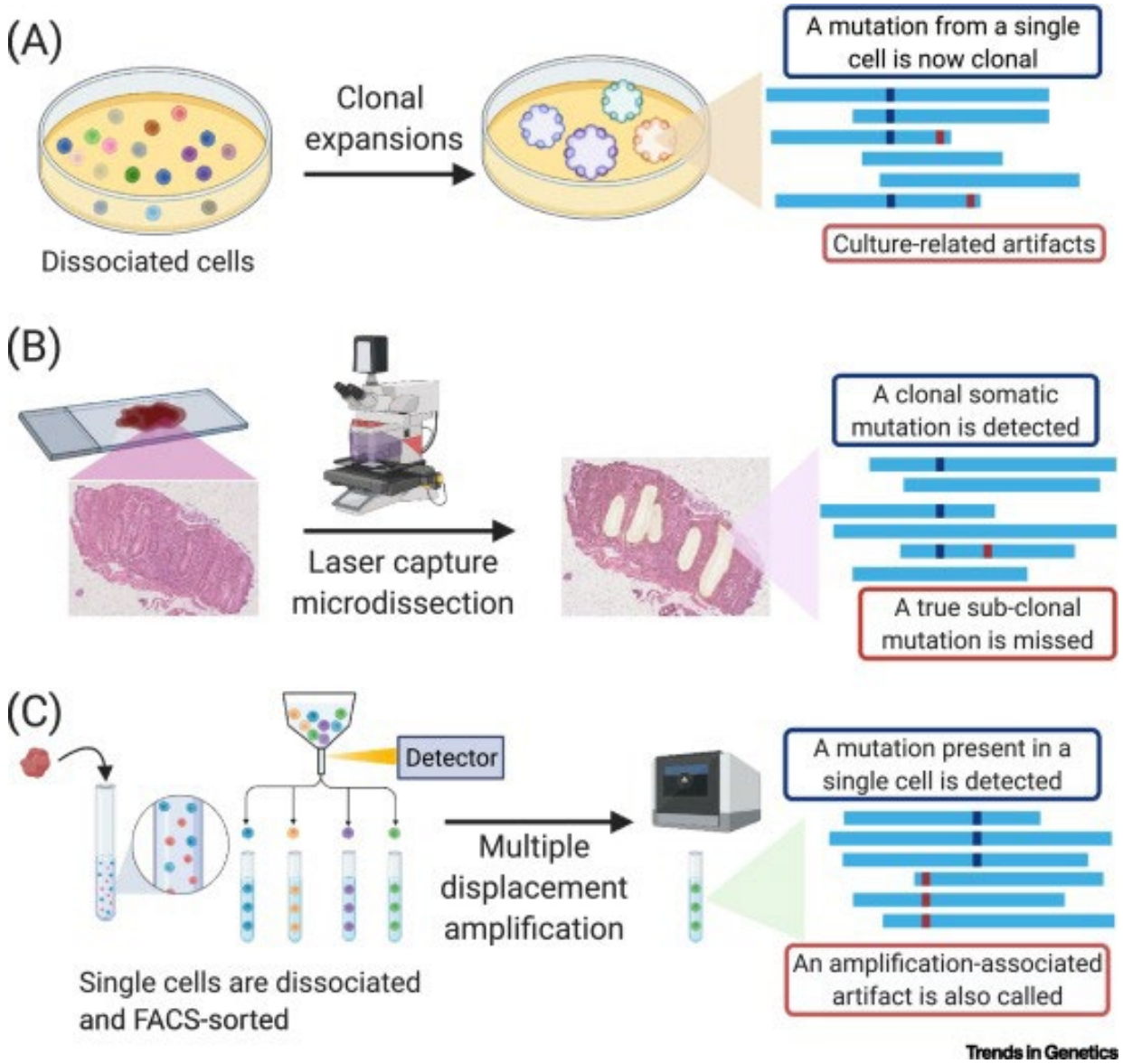
SMR

Número de mutaciones somáticas por megabase en el genoma tumoral.

TMB es similar, pero éste representa la carga mutacional total. Ambos términos se utilizan en ocasiones de manera intercambiable.

Valor pronóstico



Olafsson S. Trends in Genetics, October 2021, Vol. 37, No. 10

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IT y biomarcadores emergentes

Microbiota

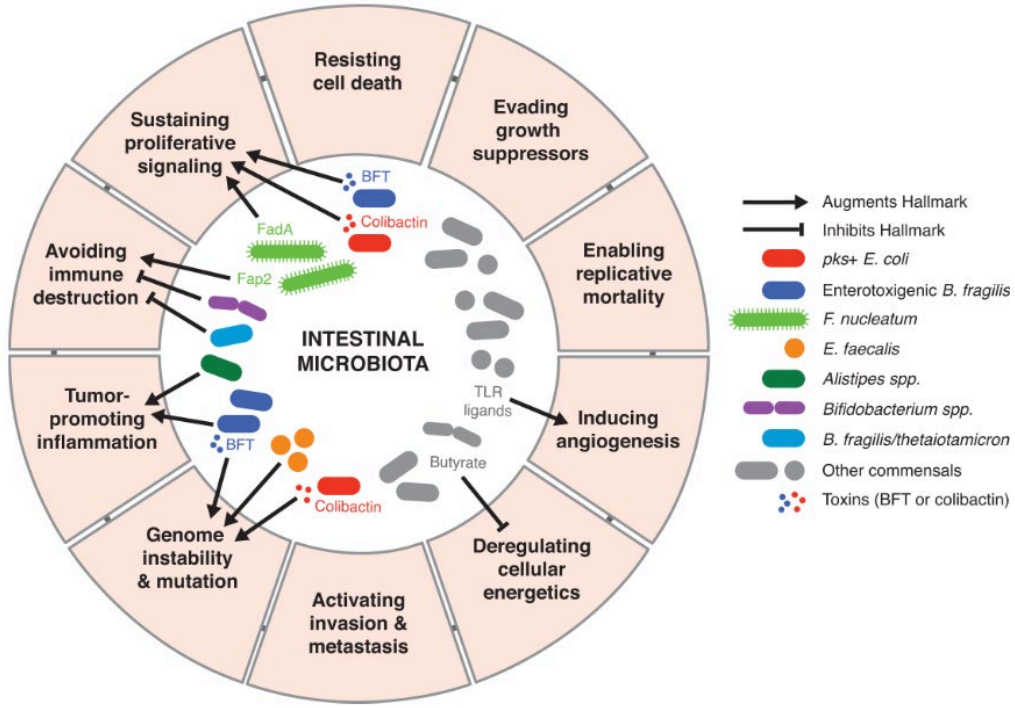
Tabaquismo → Inflamación local → Disbiosis.

Análisis del lavado bronquioalveolar en pacientes con cáncer de pulmón:
↑TM7-3 , Capnocytophaga and Sediminibacterium.

↓ Microbacterium y Stenotrophomonas.

Cáncer de pulmón resecado y microbiota intestinal:

- Alistipes y Bacteroides (buen pronóstico)
- O. splanchnicus (relacionada con mayor probabilidad con progresión tumoral)
- El perfil de microbiota intestinal en estos pacientes se relaciona con VO2 max y la tolerancia al ejercicio.
- También existe relación con la respuesta a los tratamientos onco-específicos (en particular, a inhibidores de checkpoint inmunológicos)



Fulbright LE PLoS Pathog 13(9): e1006480

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Biomarcador	Características
Biomarcadores séricos compuestos (NLR, LIPI)	Indicadores de inflamación asociados a mal pronóstico en cáncer avanzado. Simples de medir mediante análisis de sangre.
PD-L1 y TMB	Valor predictivo de respuesta a inhibidores de checkpoint. Valor pronóstico controvertido en solitario pero mayor impacto pronóstico en combinación con otros biomarcadores.
STK11, KEAP1, SMARCA4, ARID1	Mutaciones asociadas a resistencia a inmunoterapia y peor pronóstico. Uso clínico limitado aún.
TP53, CDKN2A/2B, TERT	TP53 y CDKN2A/2B peor pronóstico, TERT peor pronóstico tumores carcinoides.
ctDNA, MRD, TF, eccDNAs, SMR, perfil metilación, exosomas	ctDNA permite monitorización en tiempo real y detección de MRD. El resto, marcadores prometedores.
Radiómica e Inteligencia Artificial	Herramientas emergentes para combinar datos clínicos y moleculares.
Microbiota tumoral e intestinal	Diferentes perfiles asociados a peor pronóstico.

Conclusiones

PD-L1 como biomarcador combinado.

Importancia del ctDNA y su relación con factores pronóstico clave como la pCR.

STK11, KEAP1 y SMARCA4 se consolidan como marcadores pronóstico en CNMP.

Nuevos biomarcadores emergentes.