Novedades y Claves en Cáncer de Pulmón 2022

Biomarcadores pronósticos

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Con la colaboración de:

Bristol Myers Squibb™

Janssen Oncology

PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Organizado por:

GECP lung cancer research

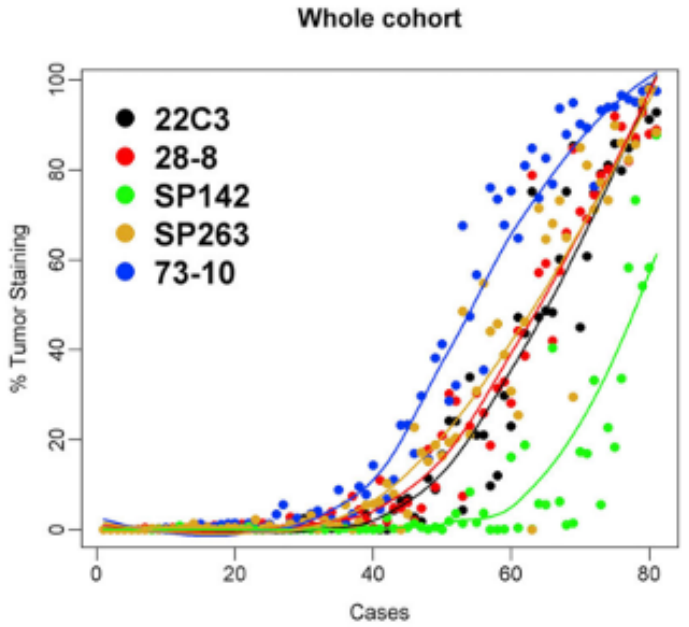
- ❑ PD-L1
- ❑ TMB
- ❑ Firmas genéticas
- ❑ Mutaciones de posibles genes de resistencia a ICI
- ❑ ctDNA, TILs, CD8
- ❑ Microbioma
- ❑ CPCP

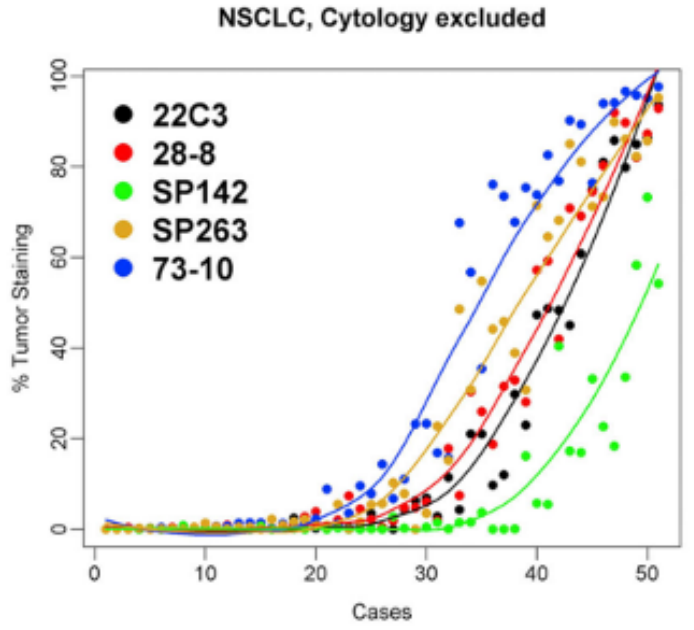
PDL1

Table 1. Immunotherapies Approved in the Frontline Setting for the Treatment of Advanced/Metastatic NSCLC

PD-L1 Expression	Regimen[a]	Pivotal Trial	Histology
PD-L1 ≥ 1%[b,c]	Nivolumab + ipilimumab	CheckMate 227	NSQ/SQ
	Pembrolizumab monotherapy	KEYNOTE-024 KEYNOTE-042	NSQ/SQ
PD-L1 ≥ 50%[d-g]	Atezolizumab monotherapy	IMpower110	NSQ/SQ
	Cemiplimab-rwlc monotherapy	EMPOWER-LUNG 1	NSQ/SQ
	Pembrolizumab monotherapy[h]	KEYNOTE-024	NSQ/SQ
Regardless of PD-L1 expression[b,c,d,i]	Atezolizumab + bevacizumab, paclitaxel, and carboplatin	IMpower150	NSQ
	Atezolizumab + paclitaxel protein-bound and carboplatin	IMpower130	NSQ
	Nivolumab + ipilimumab + 2 cycles platinum-doublet chemotherapy	CheckMate 9LA	NSQ/SQ
	Pembrolizumab + pemetrexed and platinum chemotherapy	KEYNOTE-189	NSQ
	Pembrolizumab + carboplatin and either paclitaxel or paclitaxel protein-bound	KEYNOTE-407	SQ
	Sintilimab + pemetrexed and platinum chemotherapy	ORIENT-11	NSQ
	Sintilimab + gemcitabine and platinum chemotherapy	ORIENT-12	SQ
	Tislelizumab + platinum-based chemotherapy	RATIONALE 304	NSQ
	Tislelizumab + carboplatin-based chemotherapy	RATIONALE 307	SQ
	Camrelizumab + pemetrexed and carboplatin	CameL	NSQ
	Camrelizumab + paclitaxel and carboplatin	CameL-Sq	SQ

Type of PD-L1 assay
Type of tissue tested (fresh vs. archival).
PD-L1 expression cutoffs
Type of cells (tumor vs. immune vs. both) tested for PD-L1 expression.
Vary between tumor sites (primary versus metastases)
Temporal dynamism (previous therapies).





Mino-Kenudson. JTO 2022. Tsao. J Thorac Oncol. 2018

research

TMB

Table 2. Tissue-Based Evaluation of TMB as Predictive Biomarker for ICI Therapies in Phase 3 Trials Involving NSCLC

Line of Tx	Clinical Trial	Analysis	Study Therapy	Reference Therapy	Assay	Cutpoint	Survival	Hazard Ratio		Ref
								High TMB	Low TMB	
Anti-PD-1 or PD-L1 vs. chemo										
1L	CM-26	E	Nivo	Chemo	WES	243 mut/exome	PFS	0.62 (0.38-1.00)	1.82 (1.30-2.55)	160
1L	KN-042	E	Pembro	Chemo	WES	175 mut/exome	PFS	0.75 (0.59-0.95)	1.27 (1.04-1.55)	161
1L	MYSTIC	E	Durva	Chemo	F1CDx	10 mut/Mb	OS	0.70 (0.47-1.06)	1.26 (0.90-1.77)	29
2L	KN-010	E	Pembro	Chemo	WES	175 mut/exome	PFS	0.59 (0.40-0.87)	1.09 (0.72-1.63)	161
2/3L	POPLAR	E	Atezo	Chemo	F1	16.2 mut/Mb	PFS	0.49 (0.19, 1.3)	1.28 (0.77, 2.12)	162
						9.9 mut/Mb	PFS	0.49 (0.25-0.93)	2.41 (1.24-4.67)	
Anti-PD1 or PD-L1 + anti-CTLA-4 vs. chemo										
1L	CM-227	P	Nivo + Ipi	Chemo	F1CDx	10 mut/Mb	PFS	0.58 (0.41-0.81)	1.07 (0.84-1.35)	27,28
						10 mut/Mb	OS	0.68 (0.51-0.91)	0.75 (0.59-0.94)	
1L	MYSTIC	E	Durva + Treme	Chemo	F1CDx	10 mut/Mb	OS	0.72 (0.48-1.09)	1.39 (1.00-1.92)	29
Anti-PD1 + chemo vs. chemo										
1L	KN-189	E	Pembro + Chemo	Chemo	WES	175 mut/exome	PFS	0.32 (0.21-0.51)	0.51 (0.35-0.74)	163
1L	KN-407	E	Pembro + Chemo	Chemo	WES	175 mut/exome	PFS	0.57 (0.41-0.81)	0.68 (0.48-0.96)	163
1L	RATIONALE-307[a]	E	Tisle + Chemo	Chemo	OncoScreen	10 mut/Mb	PFS	0.44 (0.27-0.72)	0.57 (0.36-0.91)	32
						12 mut/Mb		0.34 (0.19-0.62)	0.61 (0.40-0.93)	
						14 mut/Mb		0.29 (0.13-0.65)	0.57 (0.39-0.82)	
Anti-PD-1 + anti-CTLA-4 + chemo vs. chemo										
1L	CM-9LA	E	Nivo + Ipi + Chemo	Chemo	F1CDx	10 mut/Mb	PFS	0.74 (0.51-1.08)	0.75 (0.55-1.02)	33
							OS	0.49 (0.34-0.70)	0.83 (0.63-1.10)	
Anti-PD-L1 + anti-CTLA-4 vs. ICI										
1L	MYSTIC	E	Durva + Treme	Durva	F1CDx	10 mut/Mb	OS	1.00 (0.65-1.54)	1.09 (0.79-1.50)	29

[a]Enrolling squamous cell carcinoma only.
Tx, therapy; L, line; E, exploratory; P, prospective; ICI, immune checkpoint inhibitor; chemo, chemotherapy; nivo, nivolumab; pembro, pembrolizumab; durva, durvalumab; atezo, atezolizumab; ipi, ipilimumab; treme, tremelimumab; tisle, tislelizumab; F1, FoundationOne; F1CDx, FoundationOne CDx; PD-1, programmed cell death protein 1; PFS, progression-free survival; TMB, tumor mutational burden; OS, overall survival; PD-1, programmed cell death protein 1; WES, whole exome sequencing; KN, KeyNote; CM, CheckMate.

Mino-Kenudson. JTO 2022

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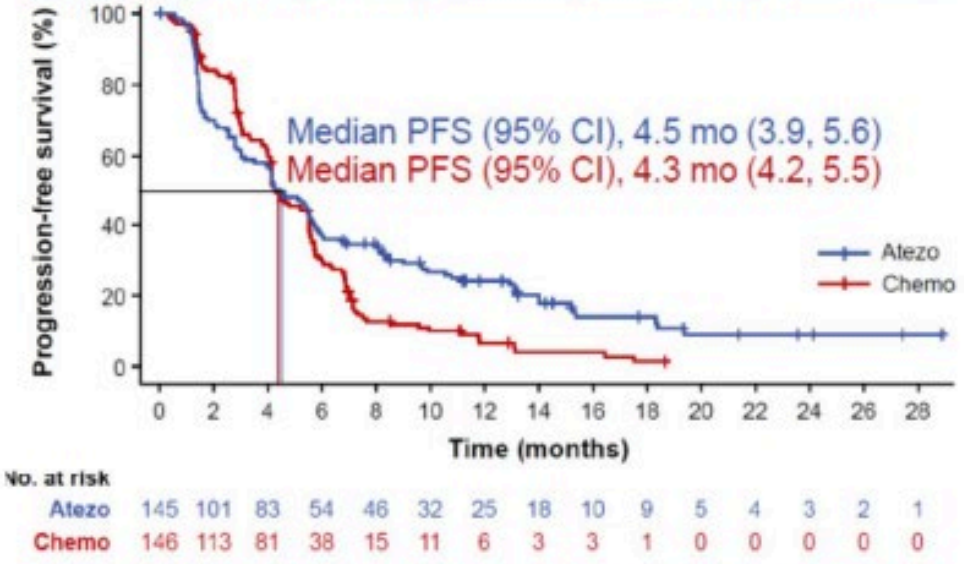
Mino-Kenudson. JTO 2022

TMB

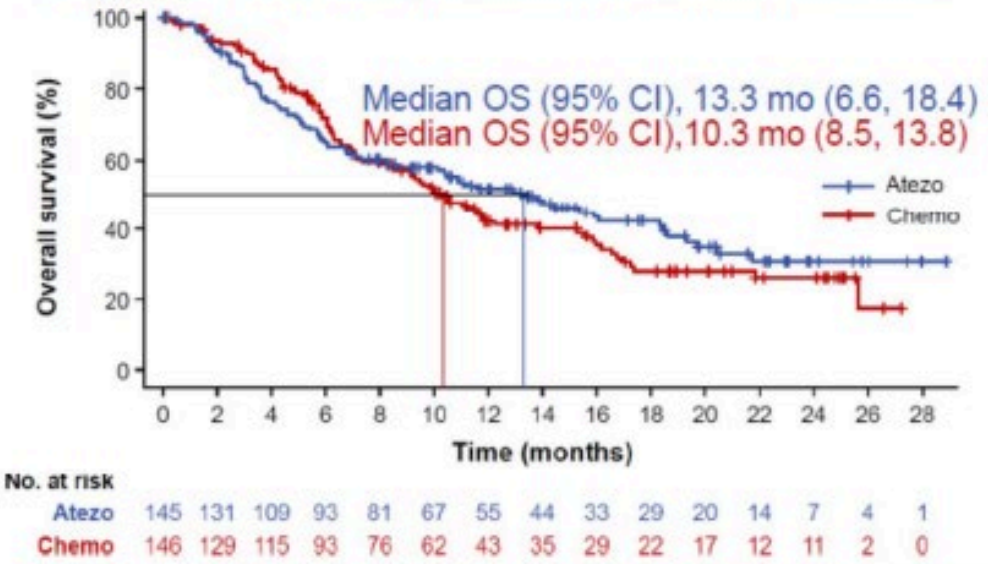
B-FAST

PFS and OS in the bTMB ≥16 population

	Atezo (n=145)	Chemo (n=146)
PFS events, n (%)	119 (82)	124 (85)
Stratified HR (95% CI)	0.77 (0.59, 1.00); *P*=0.053	



	Atezo (n=145)	Chemo (n=146)
OS events, n (%)	82 (57)	88 (60)
Stratified HR (95% CI)	0.87 (0.64, 1.17); *P*=0.35[a]	



Although progression rates were initially higher in the atezo vs chemo arm, PFS benefit was seen with atezo after 4 months

Confirmed ORR for bTMB ≥16 was 25.5% (95% CI: 18.7, 33.4) for atezo vs 17.8% (12.0, 25.0) for chemo

Organizado por:

GECP lung cancer research

Dziadziuszko, ESMO 2021

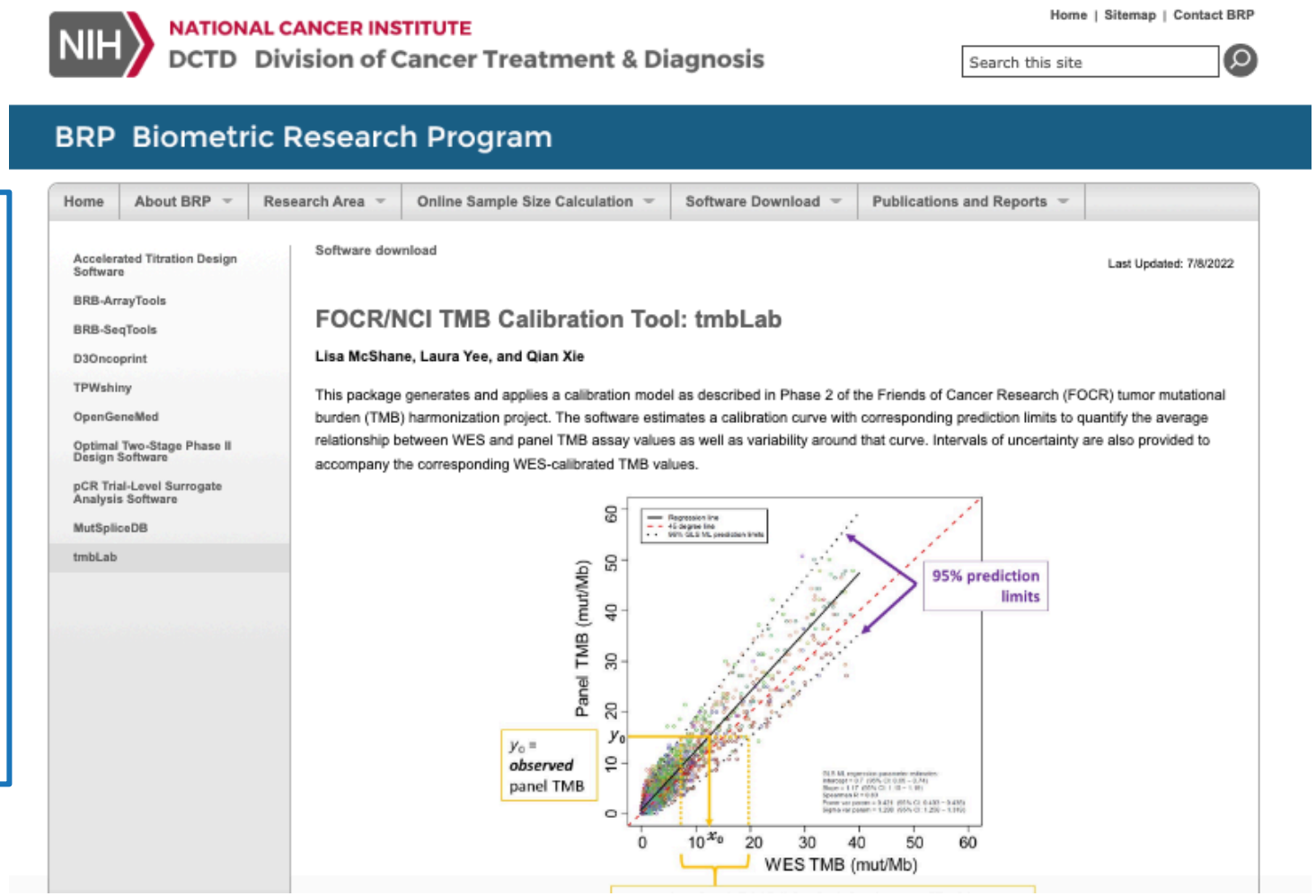
TMB

Establishing guidelines to harmonize tumor mutational burden (TMB): in silico assessment of variation in TMB quantification across diagnostic platforms: phase I of the Friends of Cancer Research TMB Harmonization Project

1. Reporting of TMB in mut/Mb to ensure consistency.

2. Standardization of analytical validation studies for TMB estimation to include assessment of analytical accuracy, precision, and sensitivity.

3. Assurance of consistency across panels by alignment of panel TMB values to whole exome sequencing–derived universal reference standards.



Merino DM. Journal for ImmunoTherapy of Cancer 2020.

https://brb.nci.nih.gov/tmbLab/

FIRMAS GENÉTICAS

Table 4. Main Transcriptomic Signatures Predictive of Response or Resistance to ICIs in NSCLC

Studies	Tumors (No. of Cases With RNAseq Data Available)	Platforms or Panels	Transcriptomic Signatures (GEP)	Pathways Involved	Clinical Validation *p* Values, AUC, and/or Hazard Ratios (95% Confidence Interval)
Ott et al.[83]	20 cancers including SCLC (n = 8)	NanoString platform (custom 680-gene panel)	18-gene T-cell-inflamed GEP (*CD3D, IDO1, CIITA, CD3E, CCL5, GZMK, CD2, HLA-DR, CXCL13, IL2RG, NKG7, HLA-E, CXCR6, LAG3, TAGAP, CXCL10, STAT1, GZMB*)	T-cell-activated TME, IFN-γ signaling, antigen presentation, chemokines, T-cell cytotoxic activity, and adaptive immunity	Higher scores associated with ORR (p = 0.012) and longer PFS (p = 0.017) in patients treated with pembrolizumab (KEYNOTE-028 trial)
Fehrenbacher et al.[85]	NSCLC (n = 224)	Fluidigm-based gene expression platform	8-Gene T-effector and IFN-γ GEP (*CD8A, GZMA, GZMB, IFNγ, EOMES, CXCL9, CXCL10*, and *TBX21*)	T-effector and IFN-γ signaling	Higher Teff/IFN-γ scores associated improved OS (HR 0·43 [0.24-0.77]) vs. Teff/IFN-γ low (HR 1·10 [0.68-1.76]) in patients treated with atezolizumab (POPLAR trial)
Higgs et al.[86]	NSCLC (n = 97)	Pan-transcriptome sequencing	4-Gene IFN-γ GEP (*IFNγ, CD274, LAG3*, and *CXCL9*)	IFN-γ signaling	IFN-γ+ (vs. IFN-γ−) scores associated ORR 37.5 (21.7-56.3) vs. 6.2 (2.0-15.8); median OS: 22.7 mo (9.5-NR) vs. 6.5 (4.3-14.2); median PFS: 7.5 mo (2.7-14.6) vs. 1.4 (1.3-2.4) in patients treated with durvalumab
Damotte et al.[87]	NSCLC (n = 38)	NanoStringPanCancer IO 360-gene panel	5-Gene TIS (*CXCL9, CXL10, CXCL11, TAP1*, and *PSMB9*)	IFN-γ signaling and antigen processing	High TIS scores associated with improved OS (HR = 0.36 [0.14, 0.90], p = 0.02) in PD-1 inhibitor responders
Hwang et al.[88]	NSCLC (n = 21)	Oncomine Immune Response Research Assay (395 immune-related gene panel)	M1 (*CBLB, CCR7, CD27, CD48, FOXO1, FYB, HLA-B, HLAG, IFIH1, IKZF4, LAMP3, NFKBIA*, and *SAMHD1)* and peripheral T cell (*HLA-DOA, GPR18*, and *STAT1*) signatures	T-cell activation, antigen presentation, tumor-associated macrophages	Longer PFS associated with high M1 and peripheral T-cell GEP scores (p = 7.84e−5 and p = 8.29e−3) in patients treated with anti-PD-1 monotherapy. Positive predictive values (AUC) for peripheral T-cell signature: 0.94.
Ranganath et al.[89]	NSCLC (n = 67)	In-house RT-qPCR panel	27-Gene IO score		IO score associated with PFS (HR 0.21 [0.085-0.54], $p < 0.001$)
Leng et al.[90]	526 TCGA-LUAD and 438 LUAD cohort data sets (GSE30219, 3121, 50081)	Pan-transcriptome sequencing	7 Genes (*DUT, TYMS, YWHAG, MGMT, POLH, RAD1*, and *RAD17*) from 8 DDR GEPs	DDR pathways	Low-risk score associated with better survival (HR 1.912 [1.421-2573]); positive predictive values (AUC) 0.71
Jang et al.[92]	NSCLC (n = 87 LUADs, 101 SCCs, and 35 NSCLCs for validation)	Pan-transcriptome sequencing and validation with the Nanostring platform (PanCancer Immune Profiling Panel of 770 mRNA sets)	59-Gene signature (IR score)	Good TiME (higher expression of immune-regulatory molecules, increased cytolytic activity, higher interferon-g signature, and abundant immune cells) vs. bad TiME	"Good-TiME" associated with high response score to PD-1 inhibitors; positive predictive values (AUC) 0.702 (p = 0.039)

Mino-Kenudson. JTO 2022

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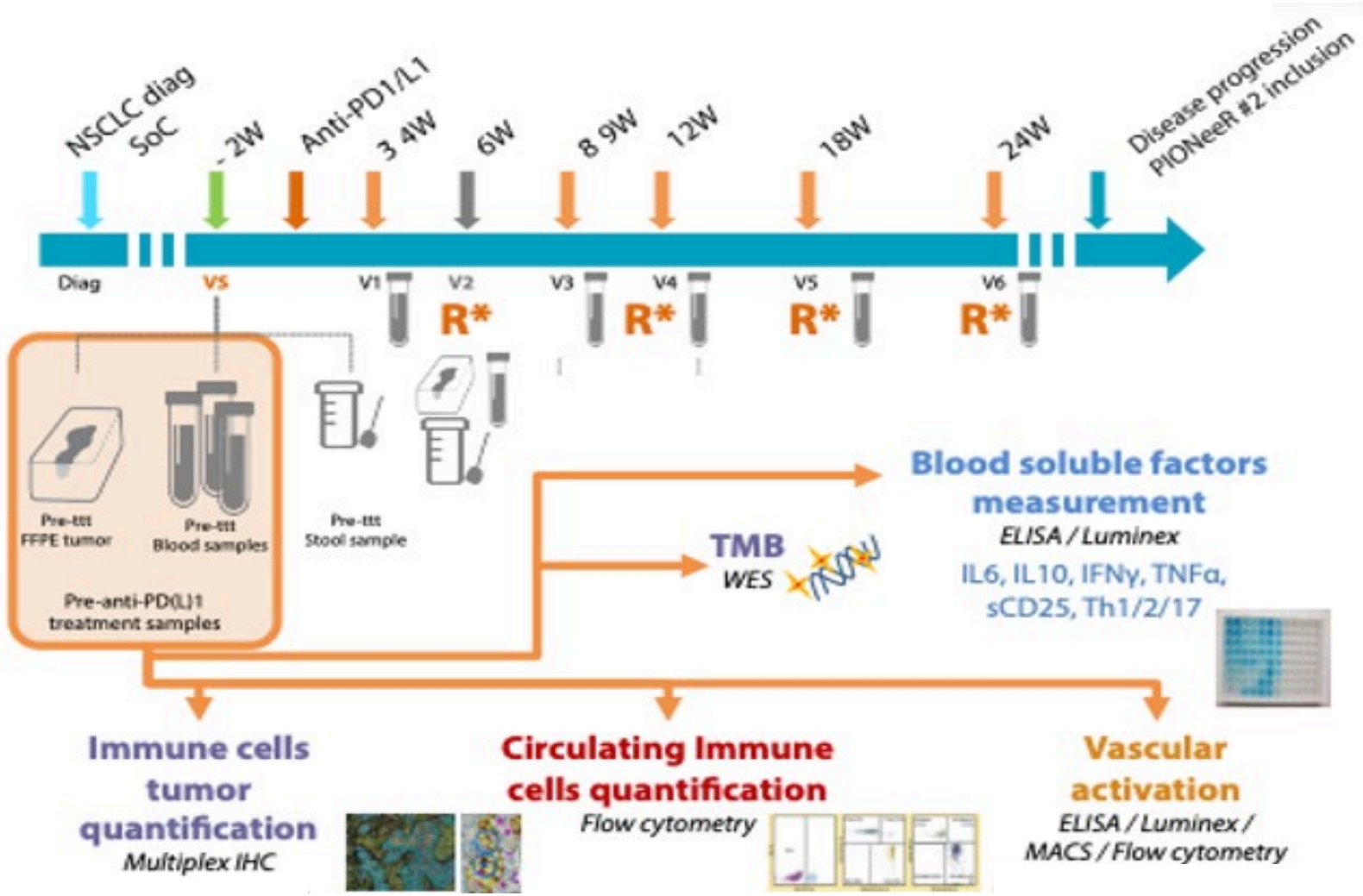
PIONeeR Comprehensive biomarkers analysis to explain resistances to PD1-L1 ICIs: The precision immuno-oncology for advanced non-small cell lung cancer (PIONeeR) trial



Greillier. AACR 2022

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GECP lung cancer research

FIRMAS GENÉTICAS

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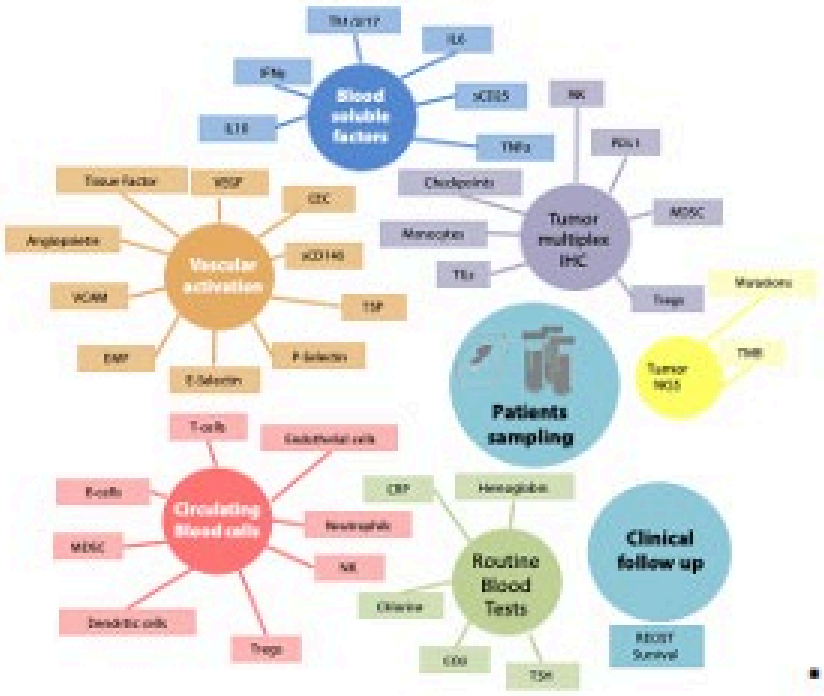
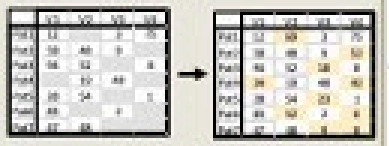


374 biomarkers

Biomarkers association with Early Progression
UV / MV

- **association with Early Progression status** — Classification task through logistic regression
- **association with Progression Free Survival** — Survival analysis – Cox regression

Missing values imputation

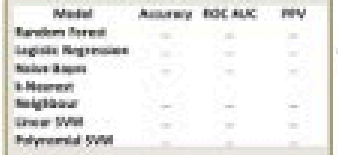


- 22 dropped biomarkers (>90% missing values or estimated imputation error >70%)
- Remaining missing values (33%) imputed through chained random forests

LASSO-based biomarker selection

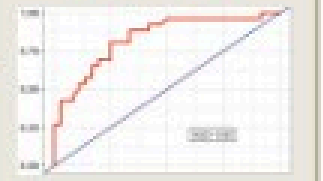
Biomarkers incrementation to reach the best AUC predicting Early Progression

Model selection



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

Model performance assessment



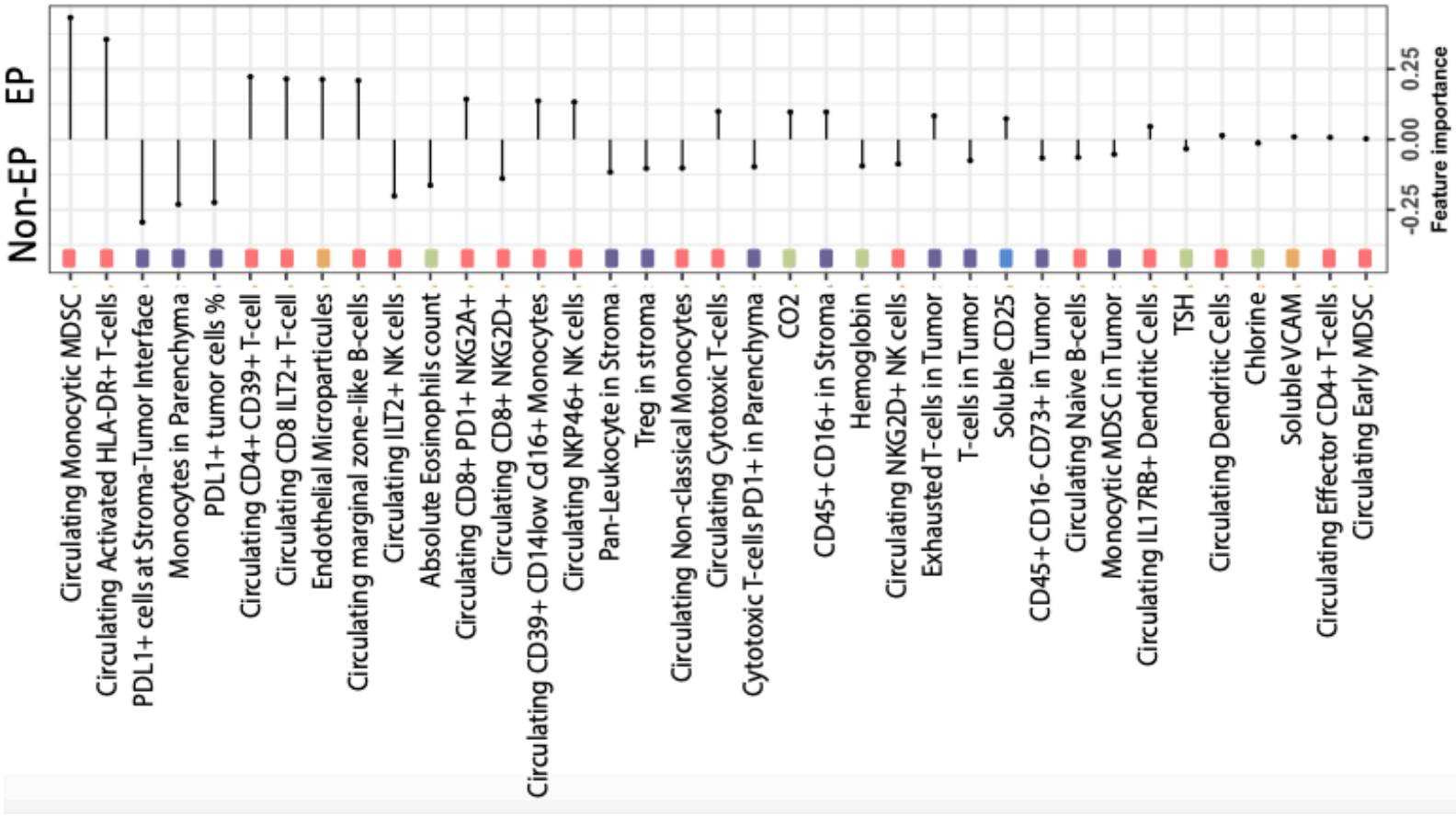
Cross validation to assess the accuracy, the robustness and the precision of the model

Greillier. AACR 2022

FIRMAS GENÉTICAS

PIONeeR Comprehensive biomarkers analysis to explain resistances to PD1-L1 ICIs: The precision immuno-oncology for advanced non-small cell lung cancer (PIONeeR) trial

Figure 8: EP signature description



Color code

- Circulating blood cells
- Tumor biomarker
- Vascular origin
- Routine blood tests
- Soluble immune marker

The best predictive model includes markers of diverse origins: immune, vascular, biochemical.
It highlights the complexity of ICI-response and the complementarity of blood and tumor samples for its prediction.

Greillier. AACR 2022

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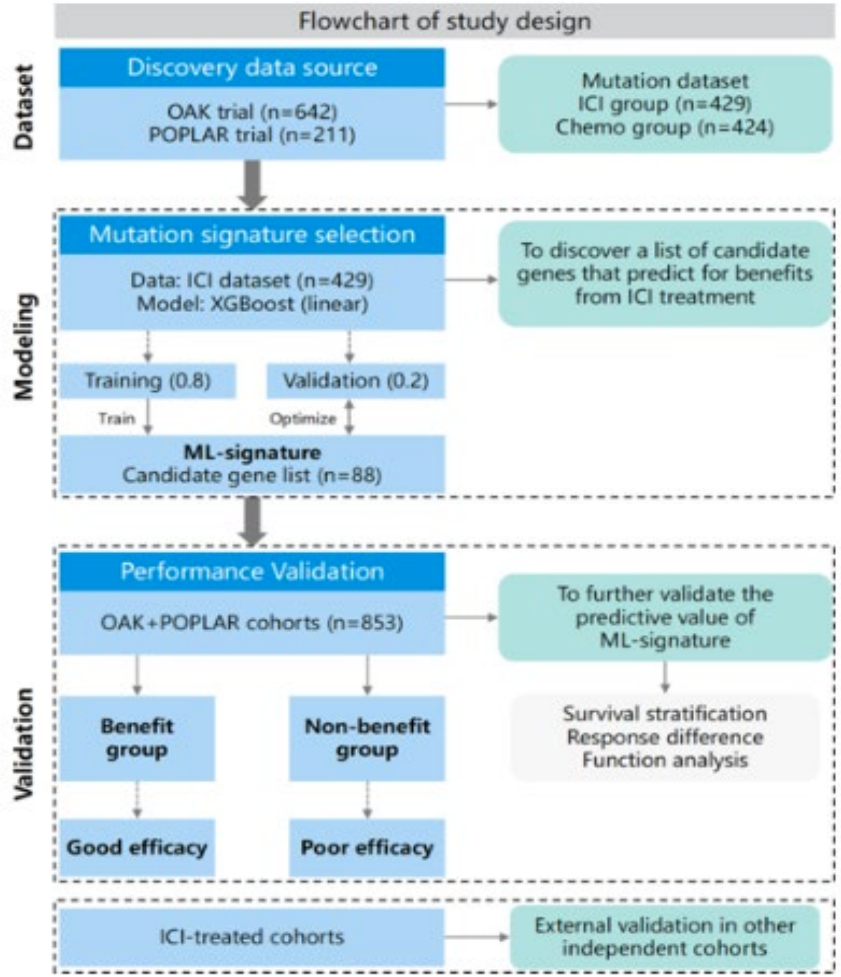
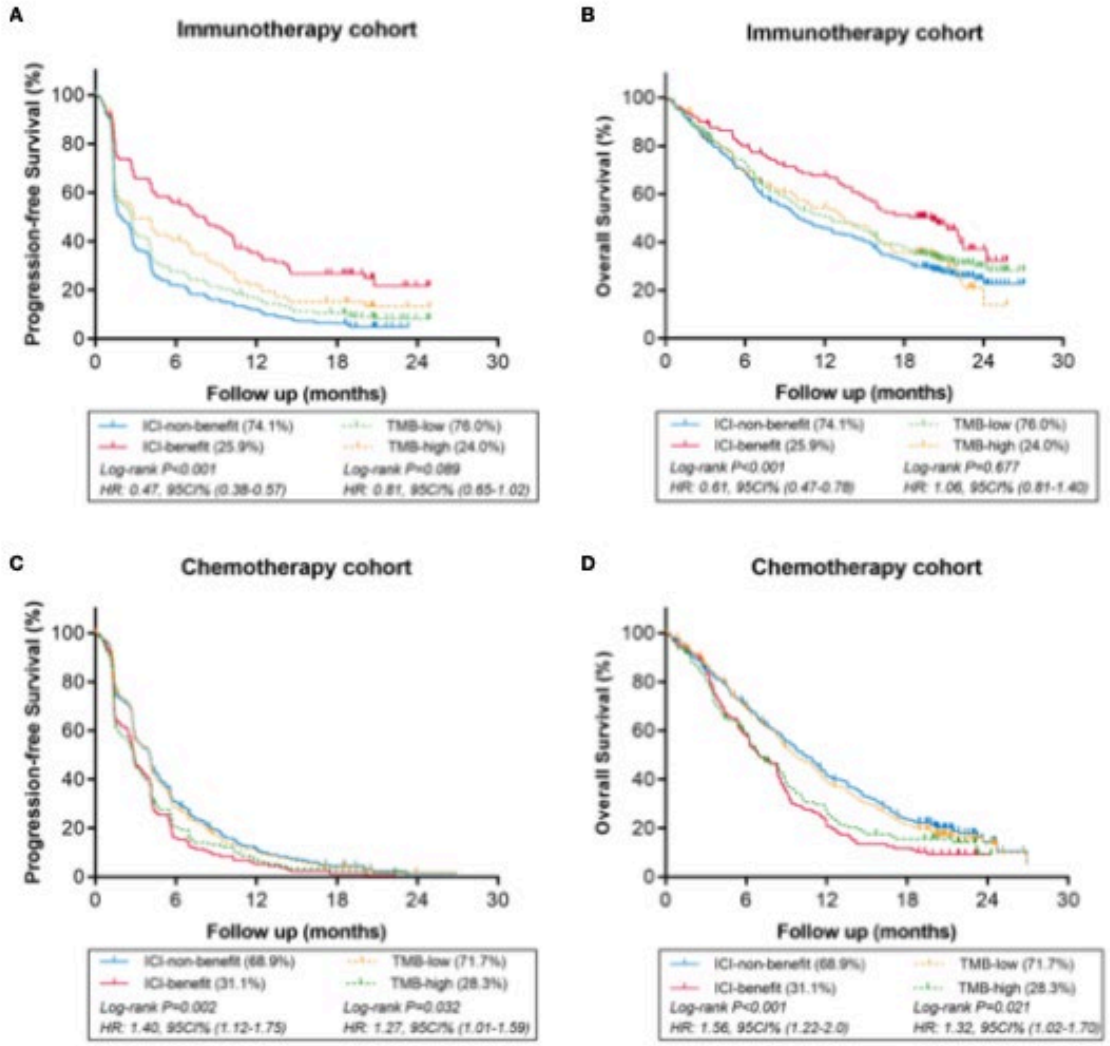
Predictive mutation signature of immunotherapy benefits in NSCLC based on machine learning algorithms





Liu. Front Immunol 2022

Organizado por:

GECP lung cancer research

Posibles genes de resistencia a ICI

FDA pooled anlalysis: Outcomes of 1L therapy in patients with advanced NSCLC according to KRAS mutation status & PD-L1 expression.

Study Therapy	Interpretation of Response	ORR		Median OS, mo	
		KRASwt	*KRASm*	*KRASwt*	*KRASm*
ICI alone	***KRASwt < KRASm*** (n=127) (n=30)	29%	57%	15	28
ICI+chemo	***KRASwt ≈ KRASm*** (n=145) (n=59)	48%	41%	23	21

Herbst et al Ann. Oncol. 2019

Gadgeel et al Ann. Oncol. 2019

Nakajima. ASCO 2022

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12 Randomized 1L Trials of ICI+Chemo, ICI Alone, or Chemo Alone Arms Submitted for Marketing Approval
N = 8888

***KRAS* mutation status reported**
N = 1430 (16%)

	KRASwt N = 875 (61%)	*KRASm* N = 555 (39%)	*KRAS G12C* N = 157 (11%)
PD-L1 TPS, %			
Negative (<1%)	40	36	37
Low (1-49%)	32	32	32
High (≥50%)	27	31	31
Treatment Arm, %			
ICI+Chemo	35	39	37
ICI alone	27	24	29
Chemo alone	36	36	34

	KRASwt (N=875)	*KRASm* (N=555)	*KRAS G12C* (N=157)
Gender Male, %	64	54	55
Age, median (range)	65 (32 – 87)	64 (32 – 89)	66 (39 – 86)
≥65 years, %	49	46	52
Race, %			
White	88	90	85
Asian	6	5	4
Black/African American	3	2	3
Histology, %			
Non-squamous	95	98	99
Smoking Status, %			
Ever smoked	85	93	97
Baseline CNS mets, %	9	9	6

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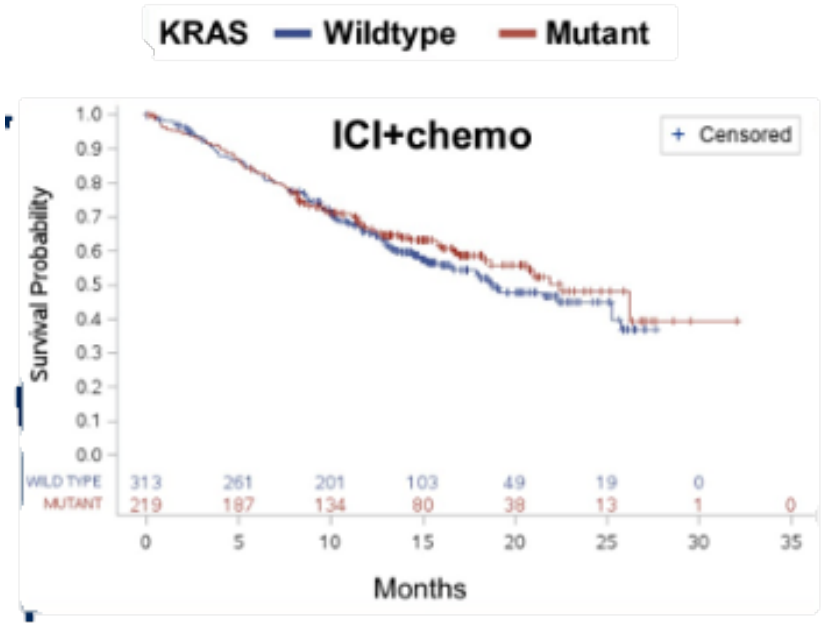
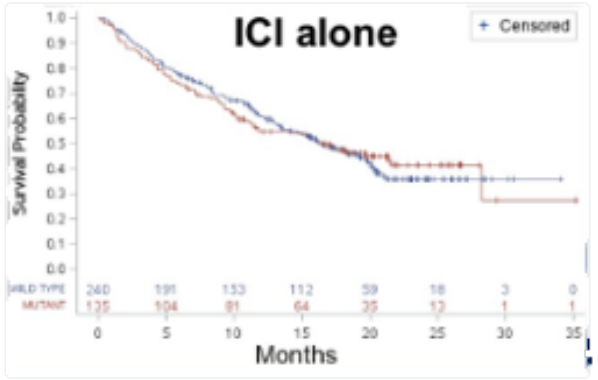
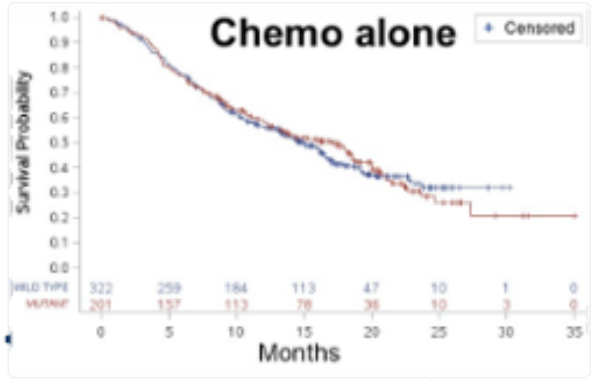
	ORR (95% CI)		
	KRASwt N=875	***KRASm*** N=555	***KRAS G12C*** N=157
ICI+Chemo	**51%** (46, 57)	**46%** (39, 53)	**47%** (33, 60)
ICI alone	**33%** (27, 40)	**37%** (29, 46)	**33%** (20, 49)
Chemo alone	**32%** (33, 60)	**33%** (20, 49)	44% (31, 59)

Study Therapy	Median OS, mos (95% CI)		
	KRASwt	***KRASm***	***KRAS G12C***
ICI+chemo	**18.7** (16.0, 25.2) N=313	**22.4** (18.2, NE) N=219	**20.8** (11.3, NE) N=58
	HR 1.12 (95% CI: 0.86, 1.46)		
ICI alone	**16.4** (13.4, 19.7) N=240	**16.2** (11.1, NE) N=135	**11.8** (8.2, NE) N=45
	HR 1.01 (95% CI: 0.76, 1.34)		
Chemo alone	14.9 (12.2, 16.6) N=322	17.1 (12.3, 18.9) N=201	17.5 (10.7, 21.1) N=54
	HR 1.02 (95% CI: 0.81, 1.29)		







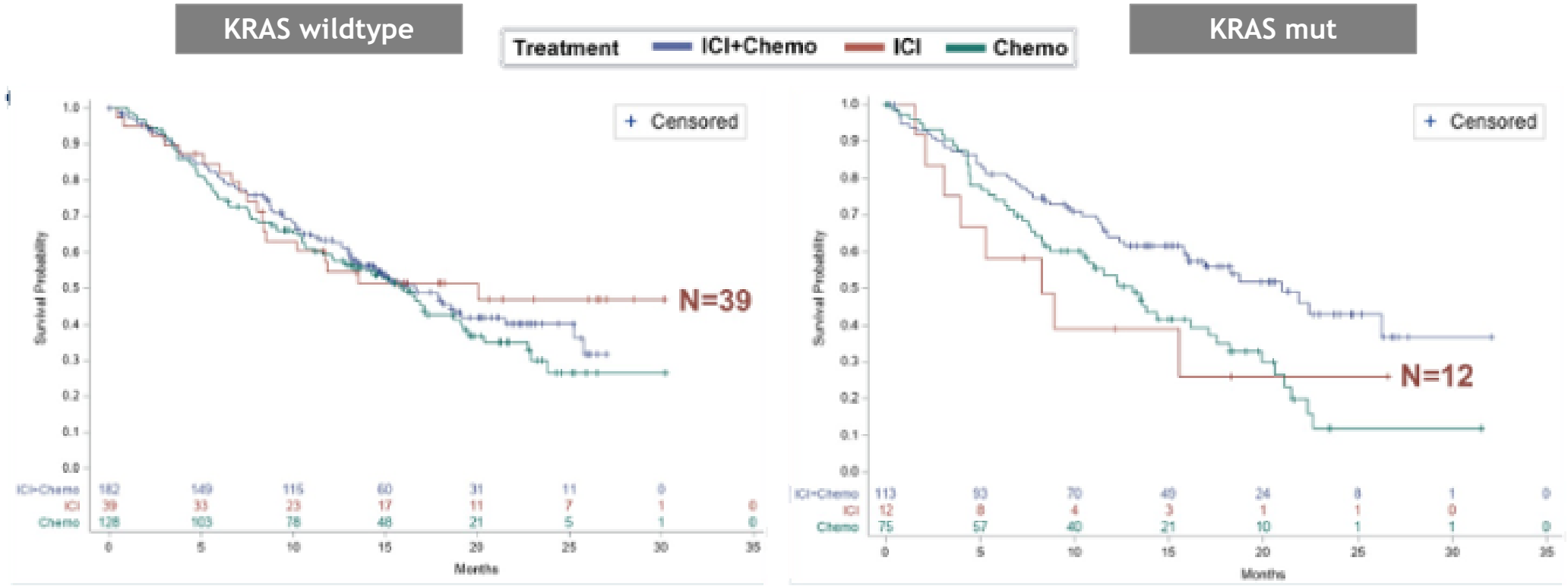
Organizado por:

GECP lung cancer research

Posibles genes de resistencia a ICI

FDA pooled anlalysis: Outcomes of 1L therapy in patients with advanced NSCLC according to KRAS mutation status & PD-L1 expression.

OS in PD-L1 negative



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Nakajima. ASCO 2022

Posibles genes de resistencia a ICI

FDA pooled anlalysis: Outcomes of 1L therapy in patients with advanced NSCLC according to KRAS mutation status & PD-L1 expression.

KRAS was only determined in 16% of patients (157 ptes with G12C mut)

Co-mutations with KEAP1, ST11 or TP53 were not studied.

All subgroups appear to benefit from the addition of IT regardless of PDL1 expression and KRAS mutational status.

Data will be needed later to define and determine if there is a subgroup of KRAS mutated patients who will benefit more from a targeted therapy than from treatment including first-line ICI

Nakajima. ASCO 2022

Posibles genes de resistencia a ICI

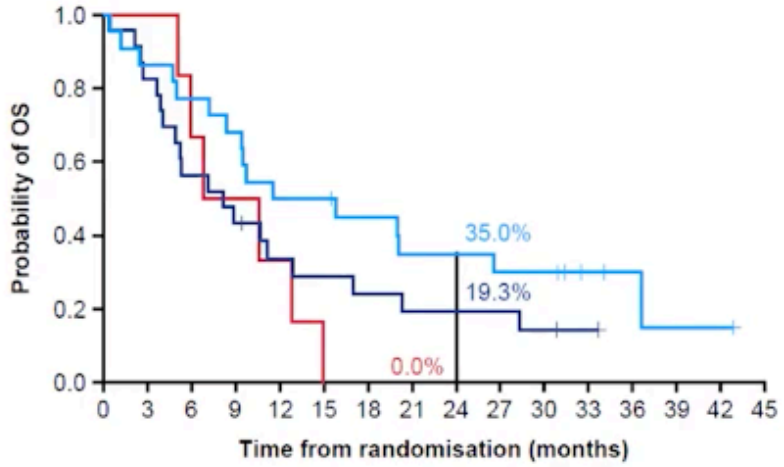
Association Between KRAS/STK11/KEAP1 Mutations and Outcomes in POSEIDON: Durvalumab +/- Tremelimumab + Chemotherapy in mNSCLC

OS by *KEAP1* Mutation Status

OS benefit observed for T+D+CT vs CT in KEAP1m with HR 0.43 (small sample size)

*KEAP1*m

	T+D+CT	D+CT	CT
Events, n/N	16/22	19/23	6/6
mOS, mo (95% CI)	**13.7** (7.2–26.5)	**8.1** (4.0–12.9)	**8.7** (5.1–NE)
HR* (95% CI)	**0.43** (0.16–1.25)	**0.77** (0.31–2.15)	–

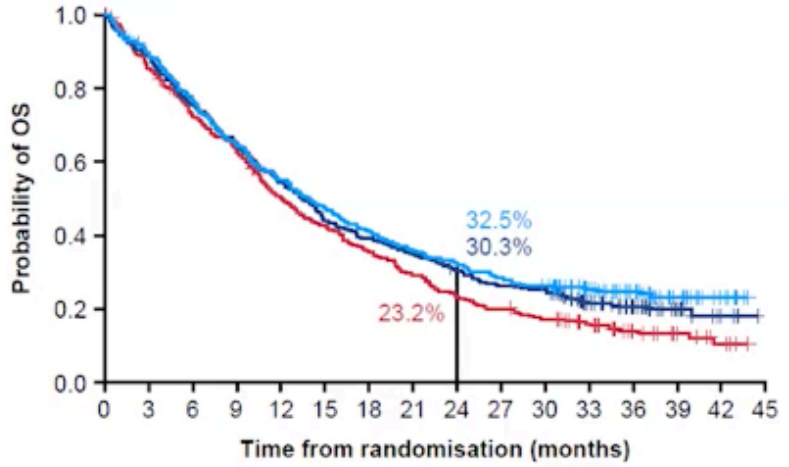


No. at risk

T+D+CT	22	19	17	15	11	11	9	7	7	6	6	3	2	1	1	0
D+CT	23	19	13	10	7	6	5	4	4	4	3	1	0	0	0	0
CT	6	6	4	3	2	0	0	0	0	0	0	0	0	0	0	0

*KEAP1*wt

	T+D+CT	D+CT	CT
Events, n/N	226/303	241/307	262/312
mOS, mo (95% CI)	**14.0** (11.8–16.1)	**13.5** (11.7–14.9)	**12.2** (10.6–13.9)
HR* (95% CI)	**0.79** (0.66–0.94)	**0.85** (0.71–1.01)	–



No. at risk

T+D+CT	303	268	230	194	165	142	123	108	97	85	78	57	38	19	8	0
D+CT	307	272	230	198	165	134	119	106	91	79	76	49	33	15	5	0
CT	312	264	221	192	153	129	108	88	70	61	51	38	21	13	6	0

HR (95% CI) vs CT in NSQ *KEAP1*m was 0.33 (0.10–1.15) with T+D+CT and 0.67 (0.23–2.17) with D+CT

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Posibles genes de resistencia a ICI

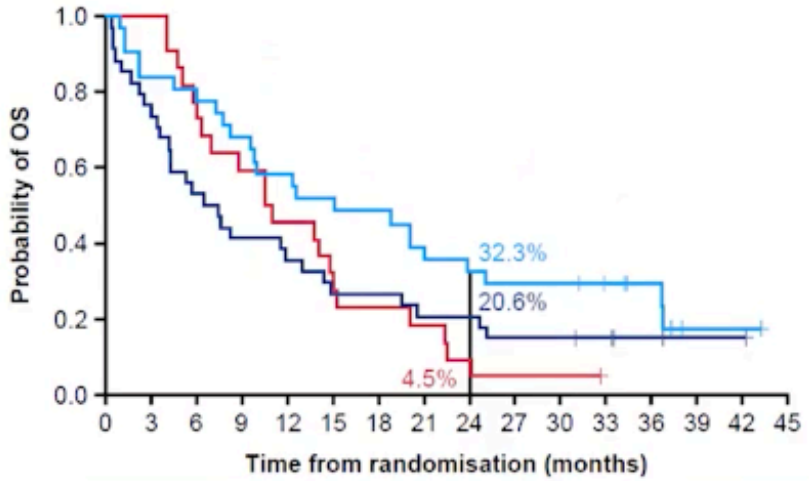
Association Between KRAS/STK11/KEAP1 Mutations and Outcomes in POSEIDON: Durvalumab +/- Tremelimumab + Chemotherapy in mNSCLC

OS by *STK11* Mutation Status

OS benefit observed for T+D+CT vs CT in STK11m with HR 0.56 and estimated 32.3% alive at 2 yrs vs 4.5%

*STK11*m

	T+D+CT	D+CT	CT
Events, n/N	24/31	29/34	21/22
mOS, mo (95% CI)	**15.0** (8.2–23.8)	**6.9** (3.6–12.9)	**10.7** (6.0–14.9)
HR* (95% CI)	**0.56** (0.30–1.03)	**1.03** (0.59–1.84)	–

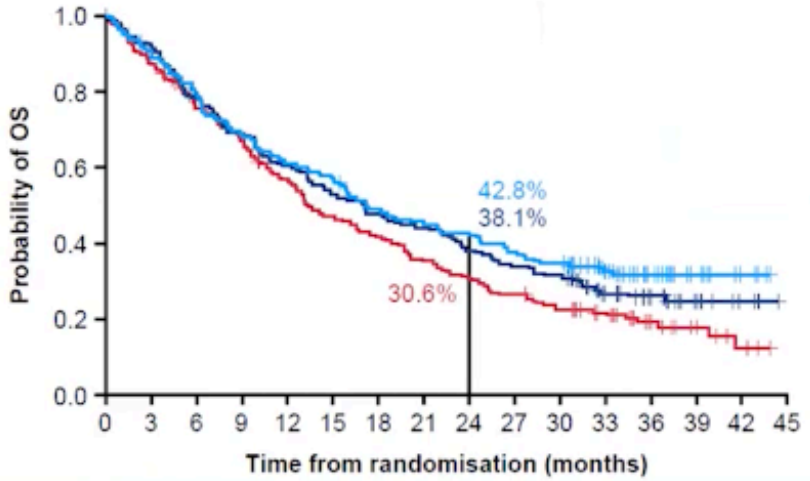


No. at risk

T+D+CT	31	26	24	21	18	15	15	11	10	9	9	7	5	1	1	0
D+CT	34	26	18	14	12	9	9	7	7	5	5	4	2	1	0	0
CT	22	22	16	13	10	6	5	4	1	1	1	0	0	0	0	0

*STK11*wt

	T+D+CT	D+CT	CT
Events, n/N	118/177	123/169	141/179
mOS, mo (95% CI)	**17.2** (14.9–22.1)	**17.1** (13.3–22.3)	**13.4** (11.5–17.5)
HR* (95% CI)	**0.73** (0.57–0.93)	**0.81** (0.64–1.04)	–



No. at risk

T+D+CT	177	159	140	120	107	100	85	79	74	65	60	40	25	11	5	0
D+CT	169	155	130	114	100	87	79	73	63	56	52	33	23	10	4	0
CT	179	154	131	116	97	80	71	60	52	45	37	29	15	8	4	0

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Posibles genes de resistencia a ICI

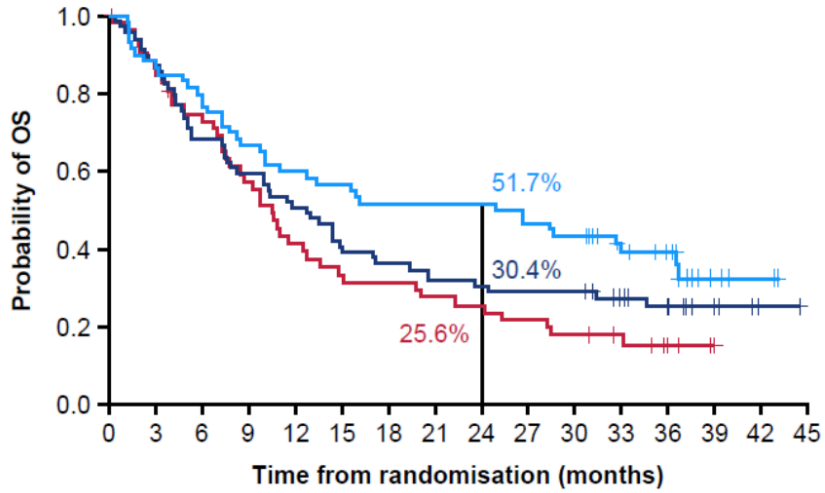
Association Between KRAS/STK11/KEAP1 Mutations and Outcomes in POSEIDON: Durvalumab +/- Tremelimumab + Chemotherapy in mNSCLC

OS by *KRAS* Mutation Status

OS benefit observed for T+D+CT vs CT in KRASm with HR 0.56 and estimated 51.7% alive at 2 yrs vs 25.6%

*KRAS*m

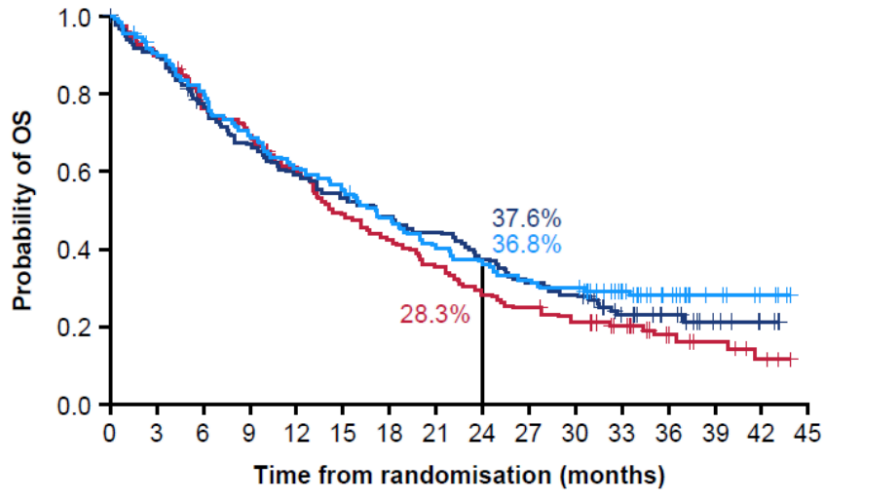
	T+D+CT	D+CT	CT
Events, n/N	38/60	51/69	43/53
mOS, mo (95% CI)	**25.7** (9.9–36.5)	**12.6** (7.5–16.9)	**10.4** (7.5–13.6)
HR* (95% CI)	**0.56** (0.36–0.88)	**0.80** (0.53–1.21)	–



No. at risk																
T+D+CT	60	53	46	40	36	34	31	31	31	28	26	17	14	4	2	0
D+CT	69	61	47	41	35	27	25	22	21	20	20	14	9	4	1	0
CT	53	44	37	29	21	17	16	14	13	11	9	7	3	0	0	0

*KRAS*wt

	T+D+CT	D+CT	CT
Events, n/N	104/148	101/134	119/148
mOS, mo (95% CI)	**17.1** (13.4–20.1)	**17.1** (12.3–22.6)	**14.4** (12.6–18.3)
HR* (95% CI)	**0.80** (0.62–1.04)	**0.86** (0.66–1.12)	–



No. at risk																
T+D+CT	148	132	118	101	89	81	69	59	53	46	43	30	16	8	4	0
D+CT	134	120	101	87	77	69	63	58	49	41	37	23	16	7	3	0
CT	148	132	110	100	86	69	60	50	40	35	29	22	12	8	4	0

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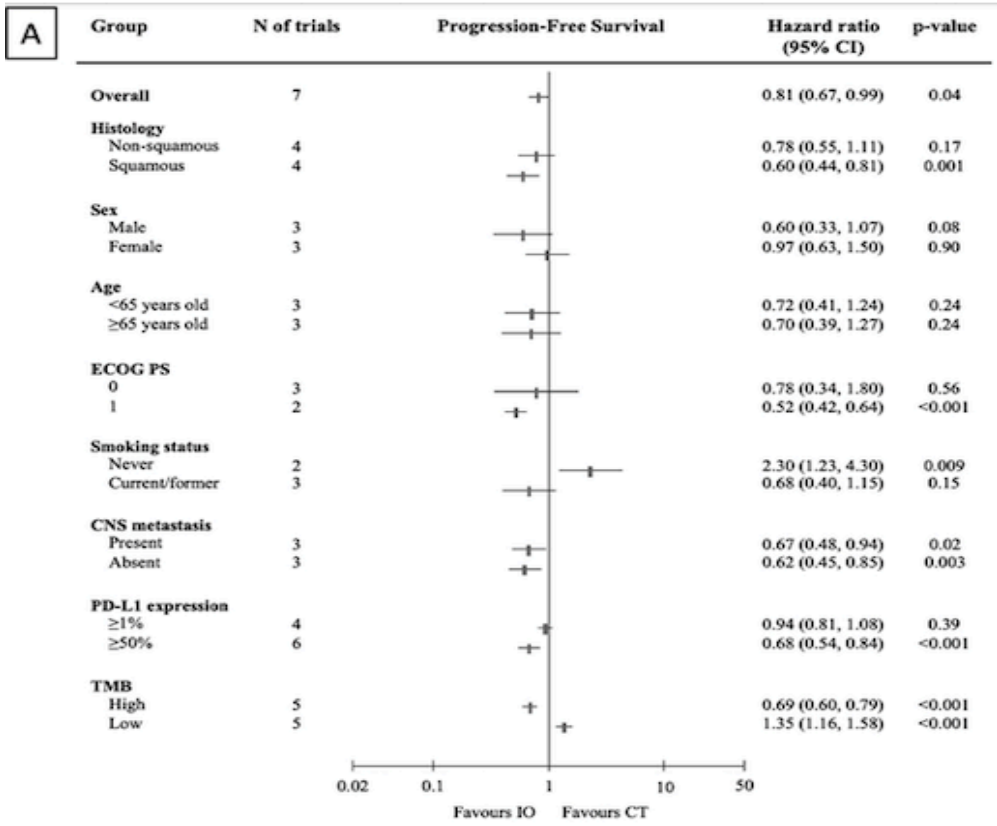
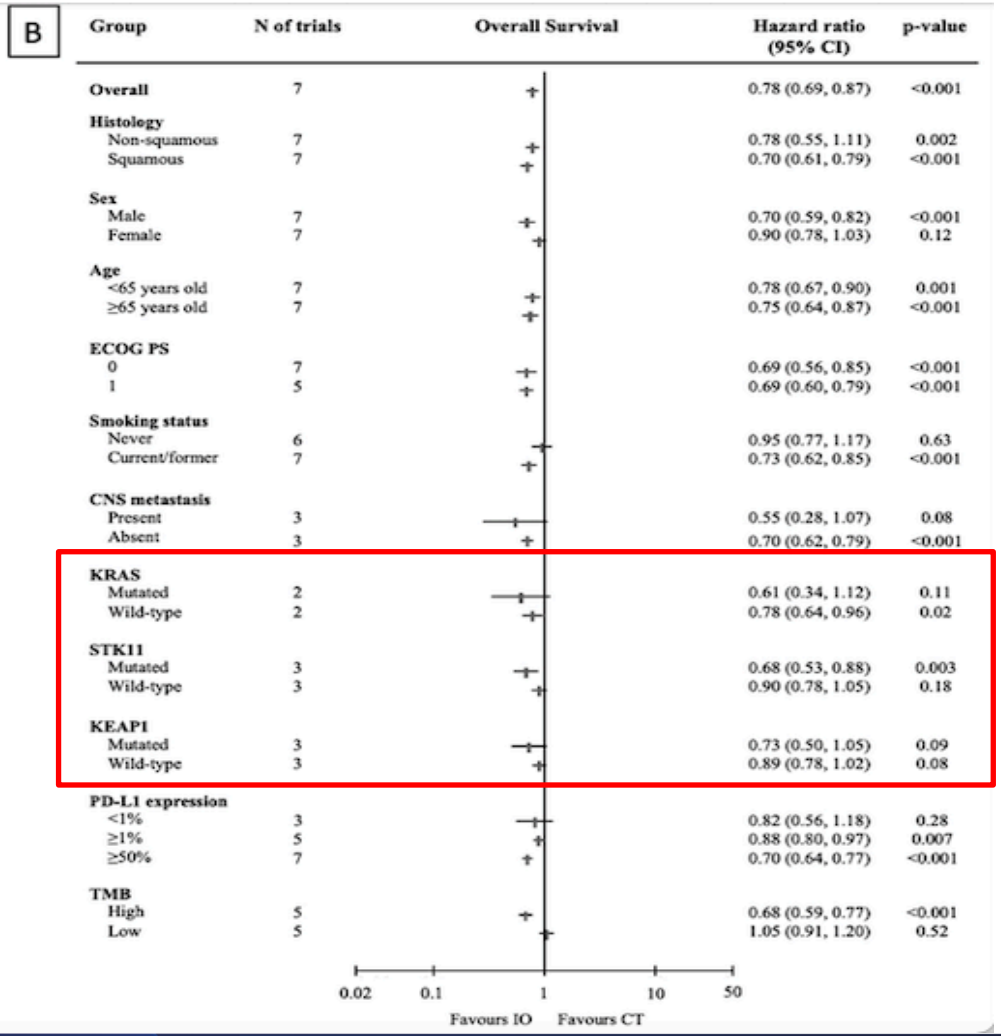
Posibles genes de resistencia a ICI

Predictors of survival to immunotherapy and chemoimmunotherapy in non-small cell lung cancer: A meta-analysis

ICI vs ChT





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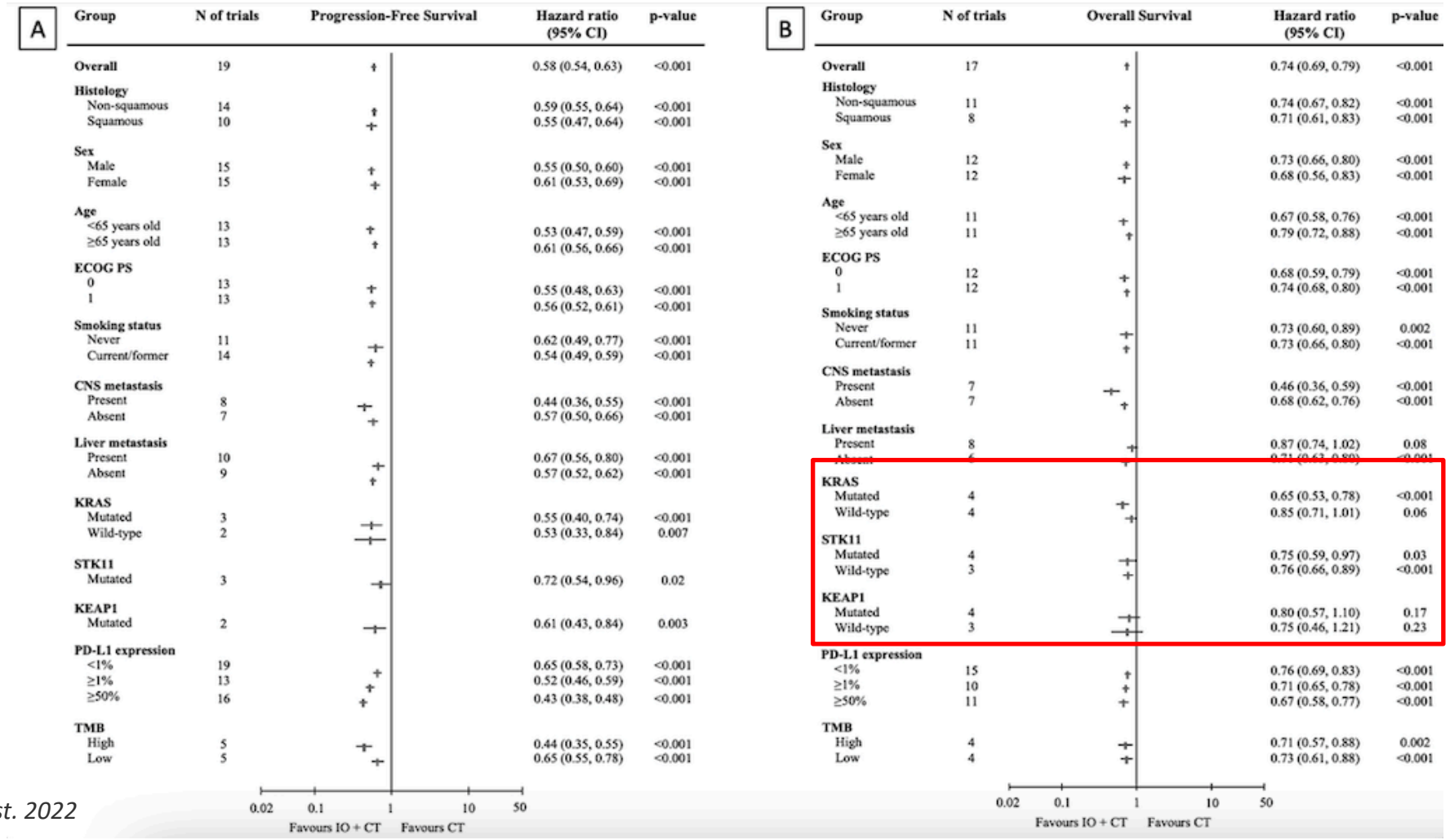
Posibles genes de resistencia a ICI

Predictors of survival to immunotherapy and chemoimmunotherapy in non-small cell lung cancer: A meta-analysis

ICI + Cht vs ChT



A

Group	N of trials	Hazard ratio (95% CI)	p-value
Overall	19	0.58 (0.54, 0.63)	<0.001
Histology			
Non-squamous	14	0.59 (0.55, 0.64)	<0.001
Squamous	10	0.55 (0.47, 0.64)	<0.001
Sex			
Male	15	0.55 (0.50, 0.60)	<0.001
Female	15	0.61 (0.53, 0.69)	<0.001
Age			
<65 years old	13	0.53 (0.47, 0.59)	<0.001
≥65 years old	13	0.61 (0.56, 0.66)	<0.001
ECOG PS			
0	13	0.55 (0.48, 0.63)	<0.001
1	13	0.56 (0.52, 0.61)	<0.001
Smoking status			
Never	11	0.62 (0.49, 0.77)	<0.001
Current/former	14	0.54 (0.49, 0.59)	<0.001
CNS metastasis			
Present	8	0.44 (0.36, 0.55)	<0.001
Absent	7	0.57 (0.50, 0.66)	<0.001
Liver metastasis			
Present	10	0.67 (0.56, 0.80)	<0.001
Absent	9	0.57 (0.52, 0.62)	<0.001
KRAS			
Mutated	3	0.55 (0.40, 0.74)	<0.001
Wild-type	2	0.53 (0.33, 0.84)	0.007
STK11			
Mutated	3	0.72 (0.54, 0.96)	0.02
KEAP1			
Mutated	2	0.61 (0.43, 0.84)	0.003
PD-L1 expression			
<1%	19	0.65 (0.58, 0.73)	<0.001
≥1%	13	0.52 (0.46, 0.59)	<0.001
≥50%	16	0.43 (0.38, 0.48)	<0.001
TMB			
High	5	0.44 (0.35, 0.55)	<0.001
Low	5	0.65 (0.55, 0.78)	<0.001

0.02 0.1 1 10 50

Favours IO + CT Favours CT

B

Group	N of trials	Hazard ratio (95% CI)	p-value
Overall	17	0.74 (0.69, 0.79)	<0.001
Histology			
Non-squamous	11	0.74 (0.67, 0.82)	<0.001
Squamous	8	0.71 (0.61, 0.83)	<0.001
Sex			
Male	12	0.73 (0.66, 0.80)	<0.001
Female	12	0.68 (0.56, 0.83)	<0.001
Age			
<65 years old	11	0.67 (0.58, 0.76)	<0.001
≥65 years old	11	0.79 (0.72, 0.88)	<0.001
ECOG PS			
0	12	0.68 (0.59, 0.79)	<0.001
1	12	0.74 (0.68, 0.80)	<0.001
Smoking status			
Never	11	0.73 (0.60, 0.89)	0.002
Current/former	11	0.73 (0.66, 0.80)	<0.001
CNS metastasis			
Present	7	0.46 (0.36, 0.59)	<0.001
Absent	7	0.68 (0.62, 0.76)	<0.001
Liver metastasis			
Present	8	0.87 (0.74, 1.02)	0.08
Absent	6	0.71 (0.63, 0.80)	<0.001
KRAS			
Mutated	4	0.65 (0.53, 0.78)	<0.001
Wild-type	4	0.85 (0.71, 1.01)	0.06
STK11			
Mutated	4	0.75 (0.59, 0.97)	0.03
Wild-type	3	0.76 (0.66, 0.89)	<0.001
KEAP1			
Mutated	4	0.80 (0.57, 1.10)	0.17
Wild-type	3	0.75 (0.46, 1.21)	0.23
PD-L1 expression			
<1%	15	0.76 (0.69, 0.83)	<0.001
≥1%	10	0.71 (0.65, 0.78)	<0.001
≥50%	11	0.67 (0.58, 0.77)	<0.001
TMB			
High	4	0.71 (0.57, 0.88)	0.002
Low	4	0.73 (0.61, 0.88)	<0.001

0.02 0.1 1 10 50

Favours IO + CT Favours CT

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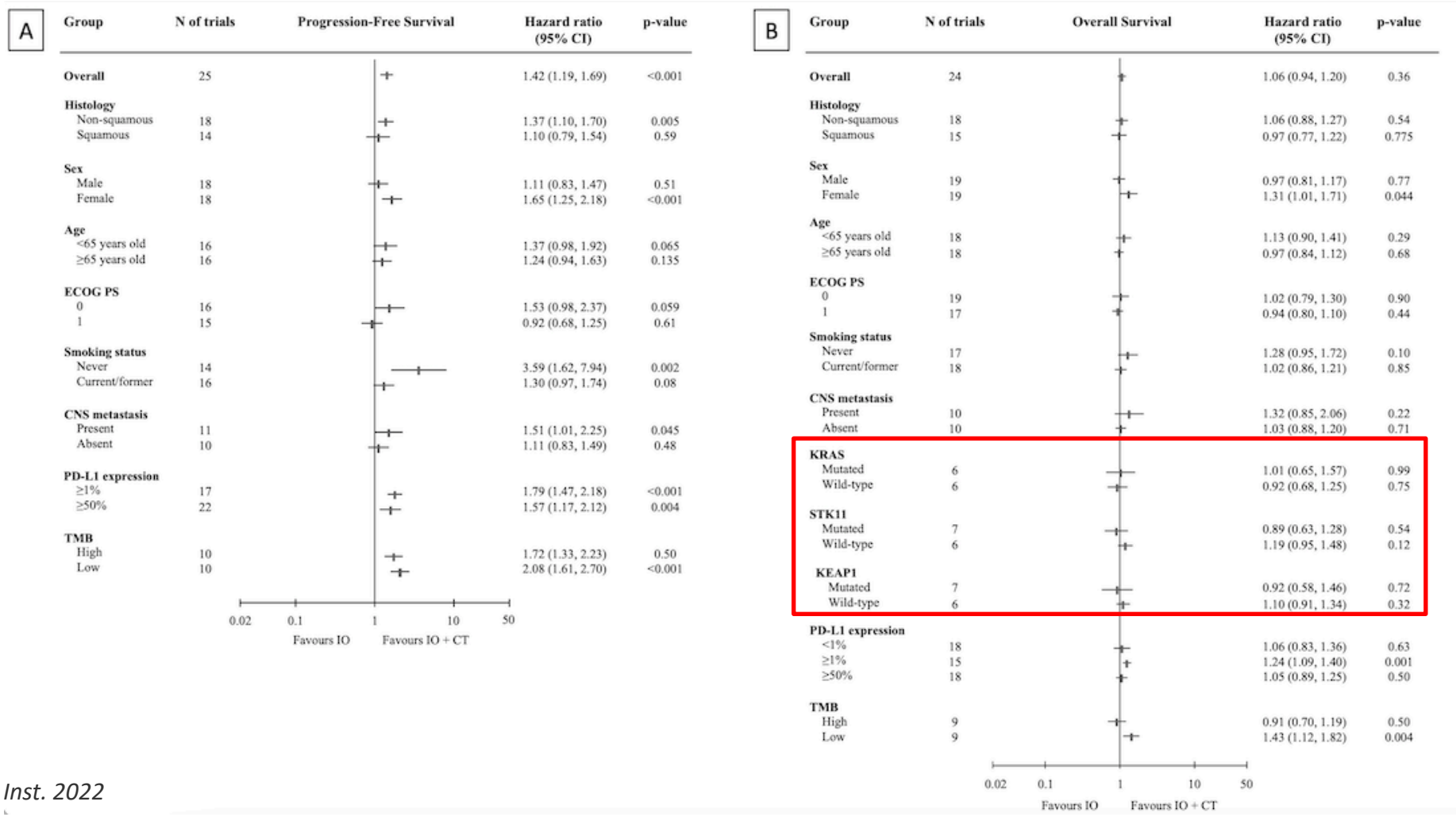
Posibles genes de resistencia a ICI

Predictors of survival to immunotherapy and chemoimmunotherapy in non-small cell lung cancer: A meta-analysis

ICI + Cht vs ICI



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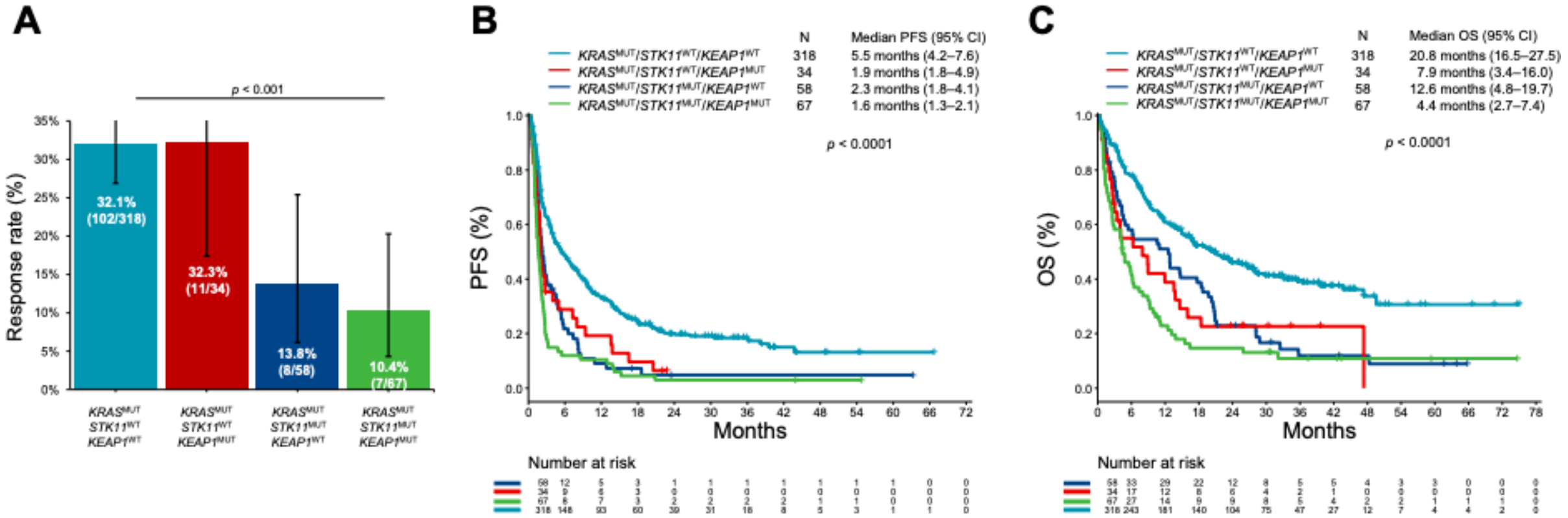
Posibles genes de resistencia a ICI

Diminished Efficacy of Programmed Death- (Ligand)1 Inhibition in STK11- and KEAP1-Mutant Lung Adenocarcinoma Is Affected by KRAS Mutation Status



Ricciuti. J Thorac Oncol. 2022

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ctDNA

NADIM II

TABLE 1. HR and Corresponding 95% CI According to Each Biomarker (TMB, PD-L1, and ctDNA levels at baseline)

Biomarker	No.	Deaths	Progressions	HR (PFS)[a]	95% CI[a]	*P*[a]	HR (OS)[a]	95% CI[a]	*P*[a]
TMB ≥ 10 mut/Mb	29	6	6	1.67	0.41 to 6.83	.474	2.13	0.37 to 12.40	.399
PD-L1 ≥ 1%	28	5	8	0.64	0.17 to 2.40	.508	0.35	0.06 to 2.12	.252

Organizado por:

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Provencio. JCO 2022

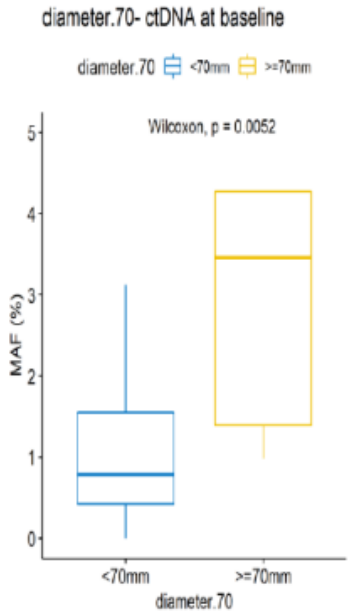
ctDNA

NADIM II

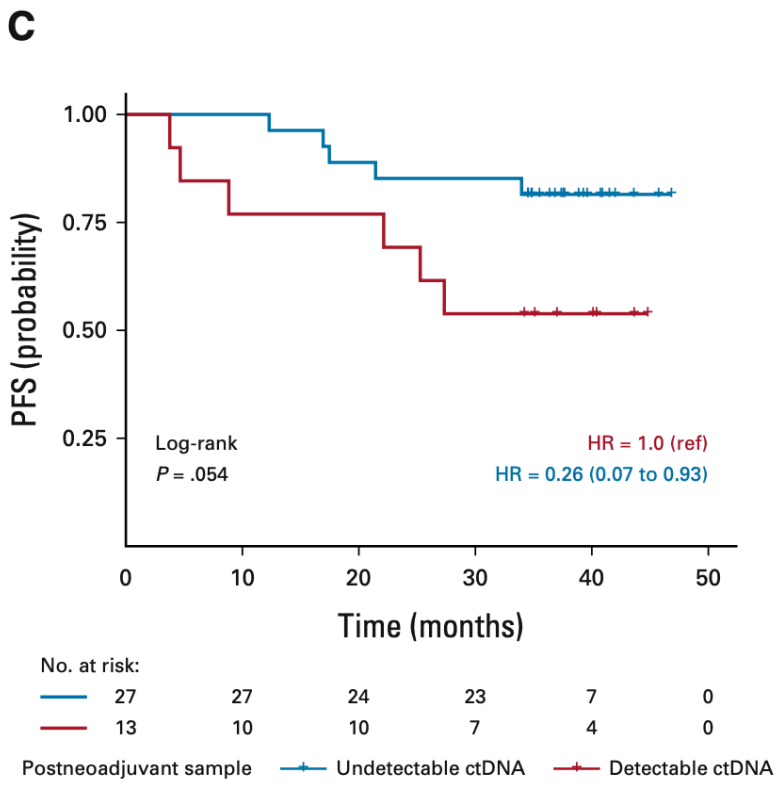
TABLE 1. HR and Corresponding 95% CI According to Each Biomarker (TMB, PD-L1, and ctDNA levels at baseline)

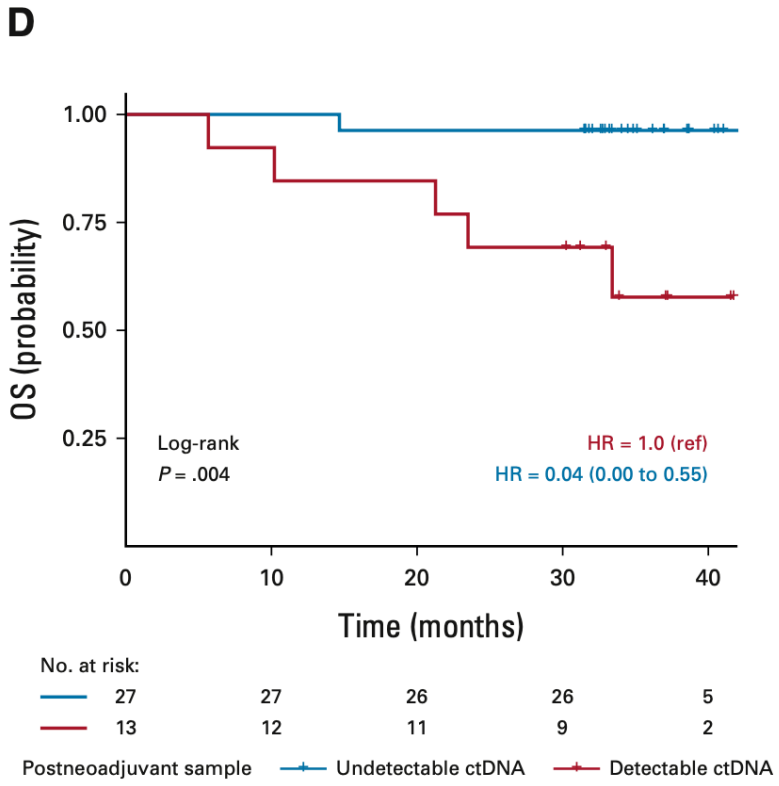
Biomarker	No.	Deaths	Progressions	HR (PFS)[a]	95% CI[a]	P[a]	HR (OS)[a]	95% CI[a]	P[a]
TMB ≥ 10 mut/Mb	29	6	6	1.67	0.41 to 6.83	.474	2.13	0.37 to 12.40	.399
PD-L1 ≥ 1%	28	5	8	0.64	0.17 to 2.40	.508	0.35	0.06 to 2.12	.252

Pre-treatment ctDNA levels were significantly associated with tumor size (maximum diameter ≥ 70mm)



Median follow up time was 26.1 (IQR: 17.6-30.9) months



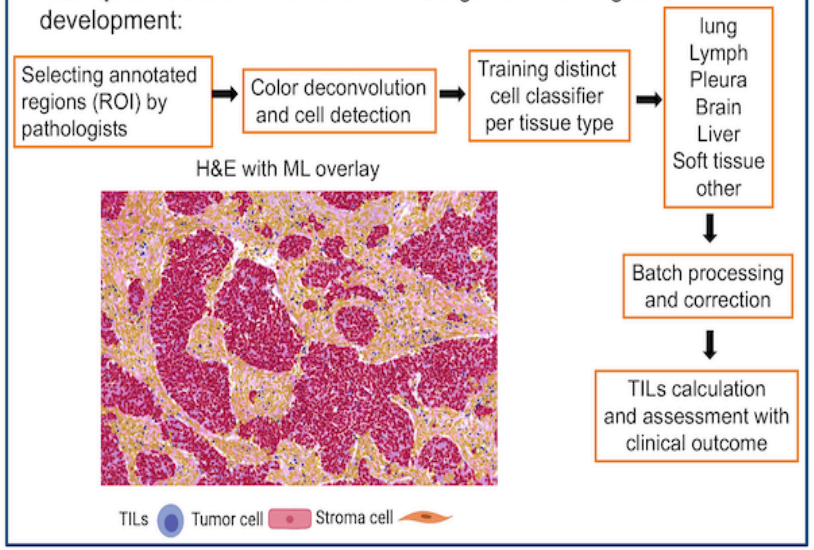


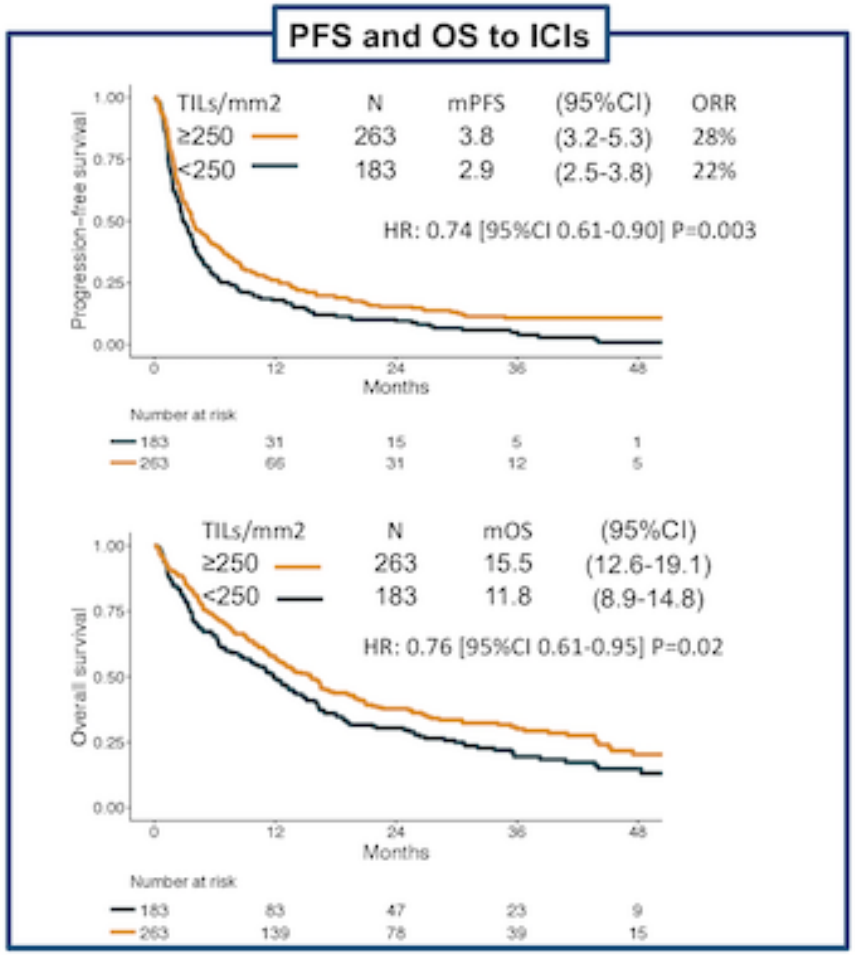
TILS

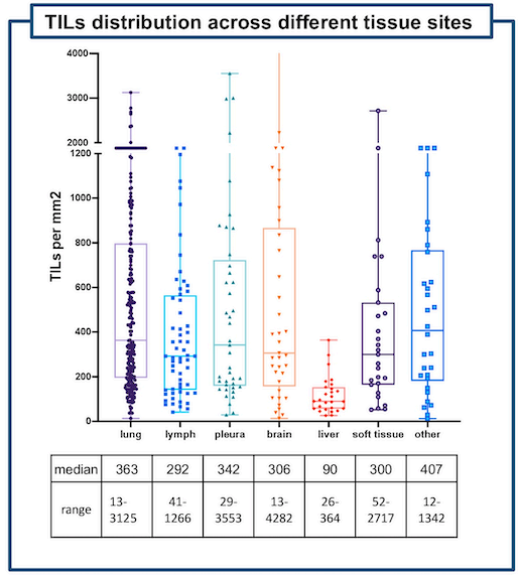
Digital quantification of lymphocytic infiltration on routine H&E images and immunotherapy response in NSCLC

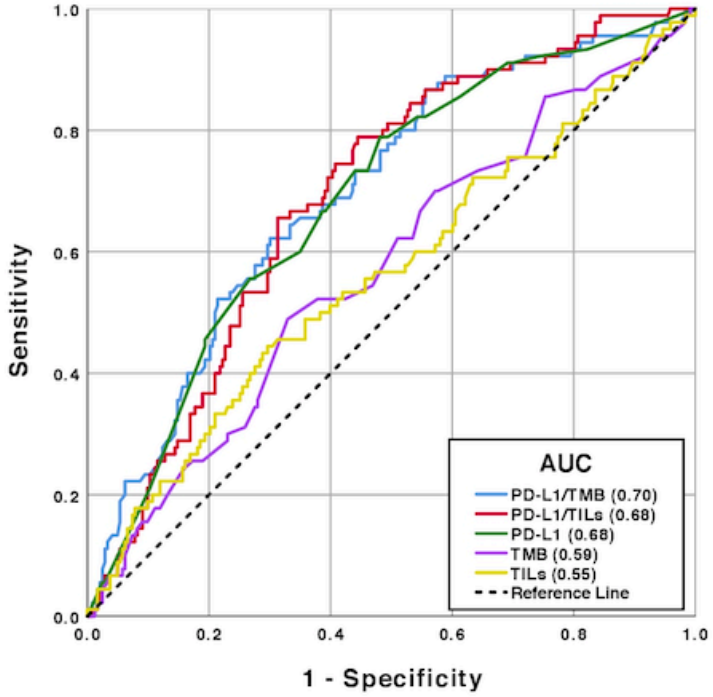
Method

- **Patients**: The study included 446 patients diagnosed with advanced primary and metastatic NSCLC between August 2014 and May 2019 treated with PD-(L)1 inhibitors at DFCI, who also had Oncopanel (panel NGS) analysis. Clinicopathological data and clinical endpoints (PFS, OS, ORR) were retrieved from each patient's chart. PD-L1 protein expression by IHC and TMB were also obtained, having been previously performed.
- **TILs quantification**: Flowchart of ML algorithm training and development:





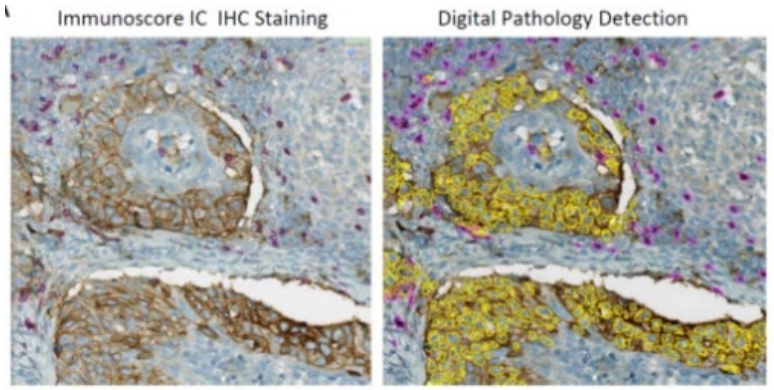




Rakaee. ASCO 2022

CD8

Efficacy of anti-PD1/PD-L1 immunotherapy in non-small cell lung cancer is dependent upon Immunoscore immune checkpoint CD8 and PD-L1 status

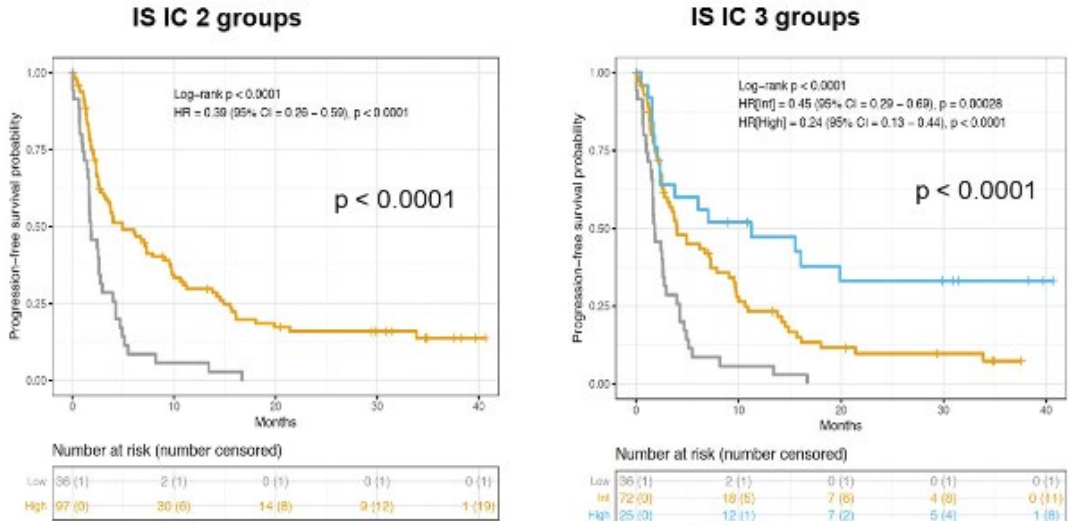


variable	coef
CD8.Tumor	-0.295
CD8.Free.TR	-0.093
CD8.Tumor_nn.20um.clust	-0.166
PDL1.Tumor_nn.20um.prox	-0.375
CD8.Tumor_nn.20um.prox	0.000
PDL1.Tumor_nn.20um.clust	0.000
PDL1.Tumor	-0.029

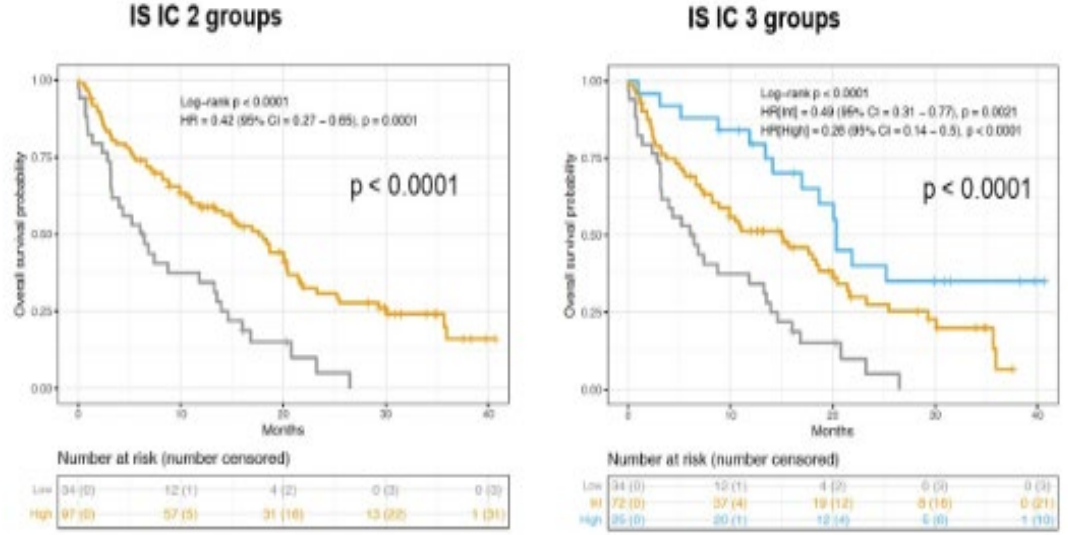
density

distance

Significant parameters of Immunoscore IC used to categorized into 2 or 3 groups



OS



Galon. ASCO 2022.

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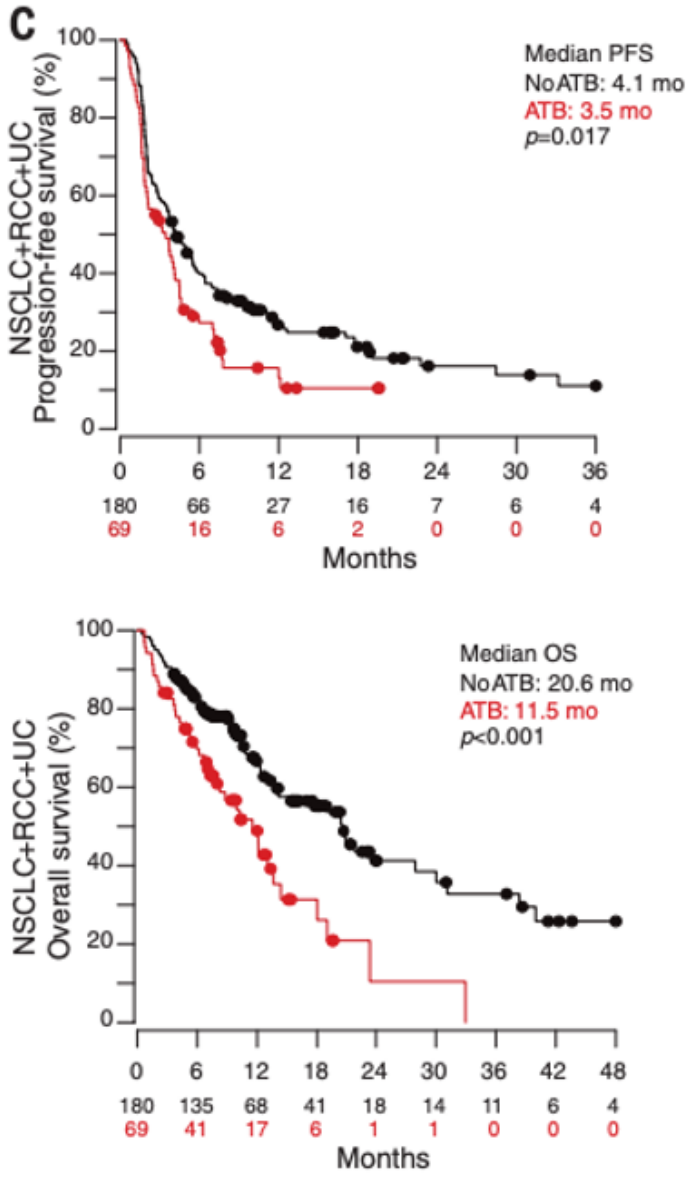
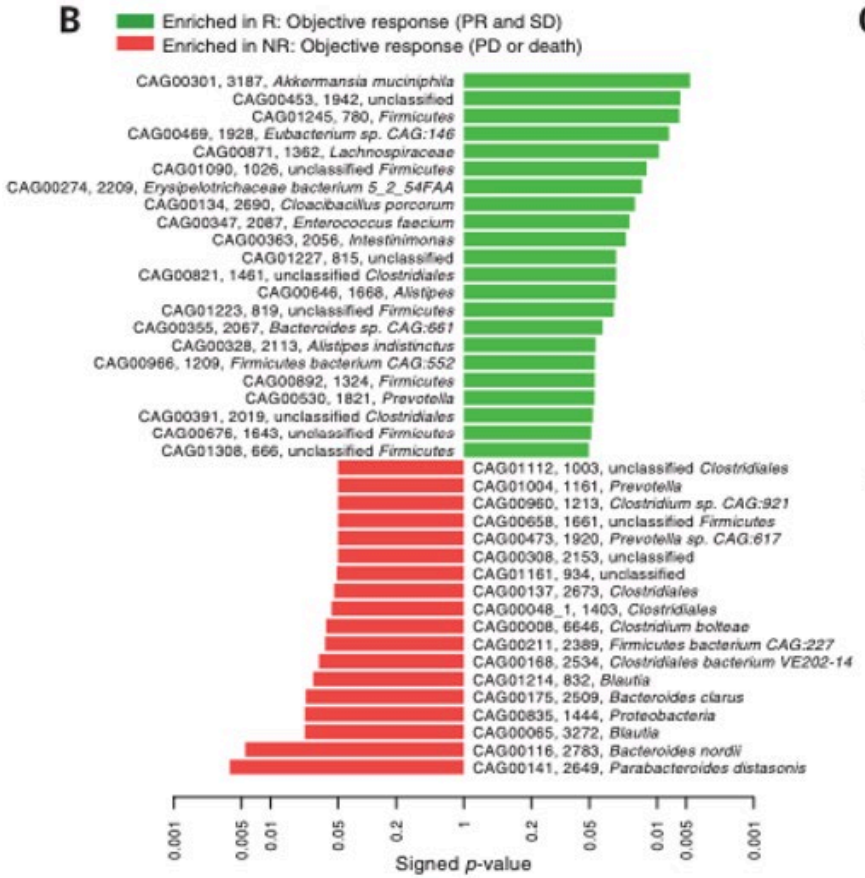
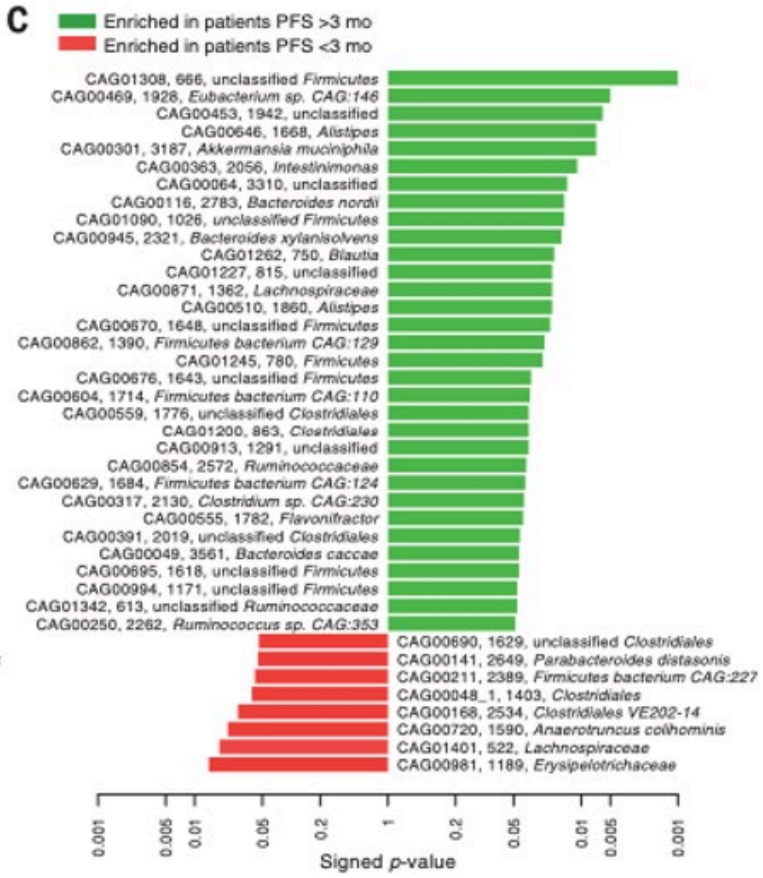
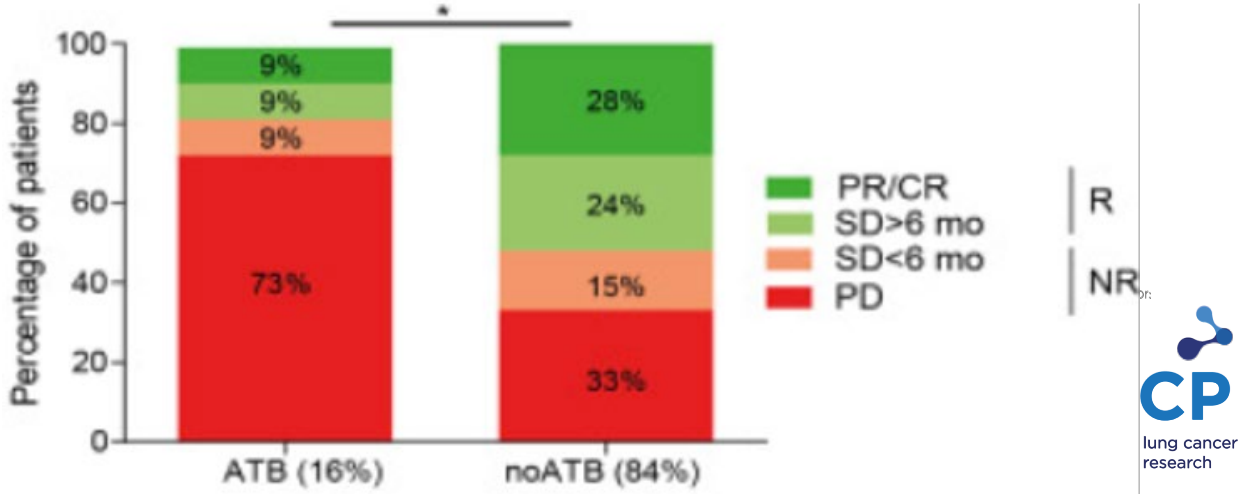
Microbioma







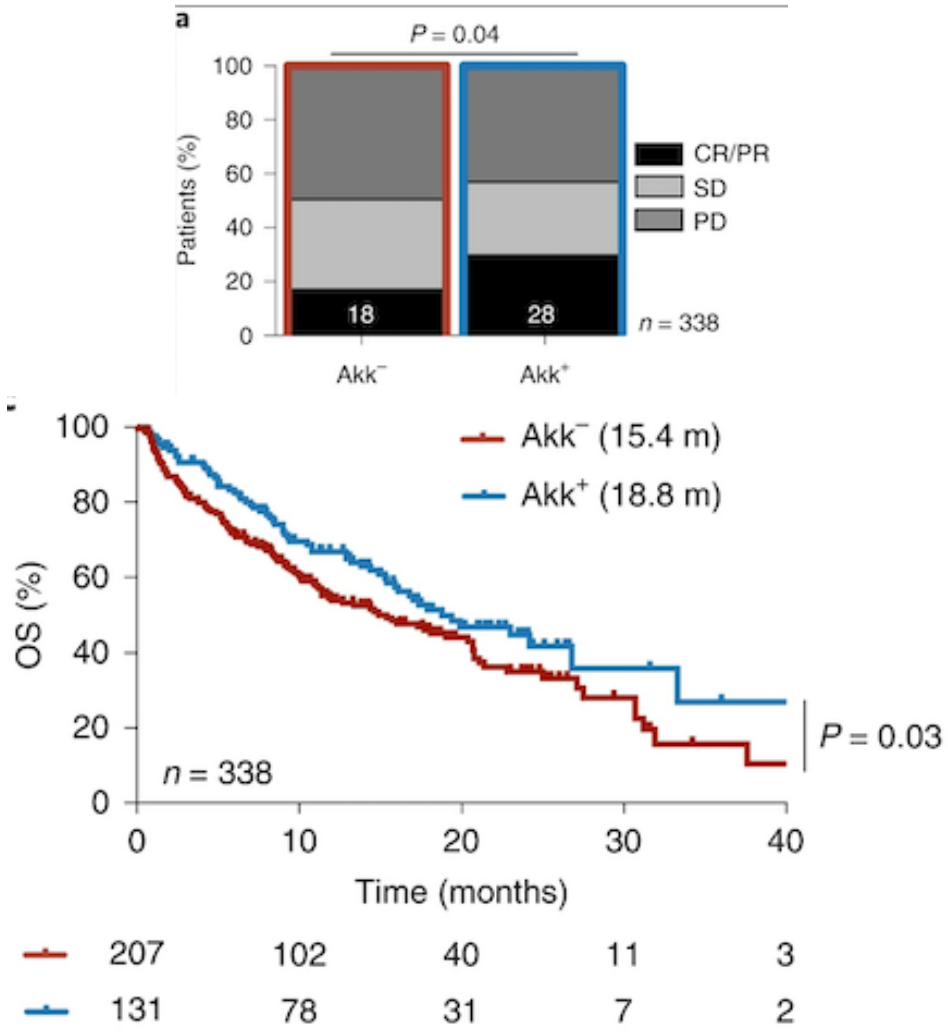


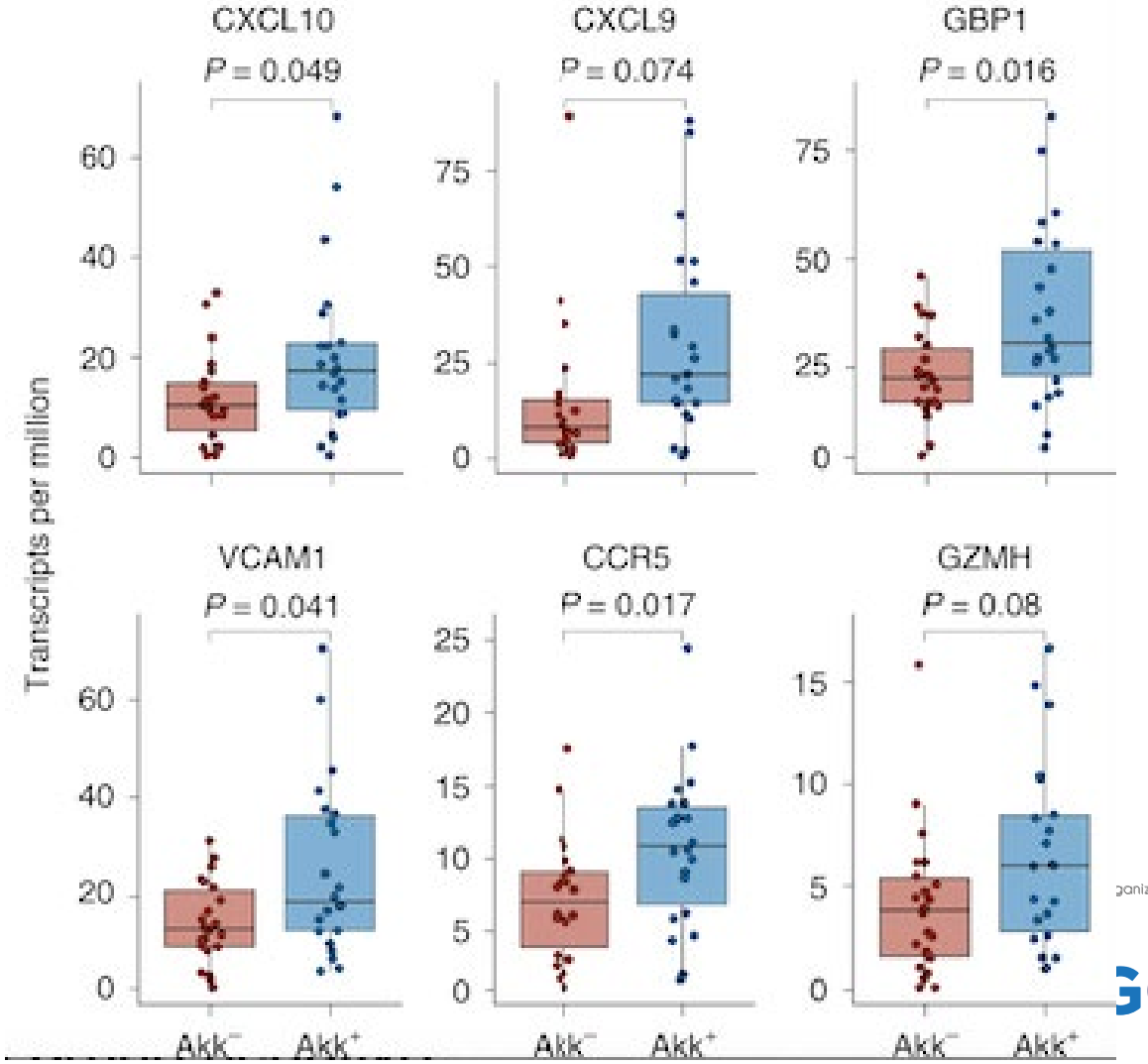
Routy. Science 2018. Derosa. Cancer Discov 2021.

CP lung cancer research

Microbioma

Intestinal Akkermansia muciniphila predicts clinical response to PD-1 blockade in advanced non-small cell lung cancer patients.

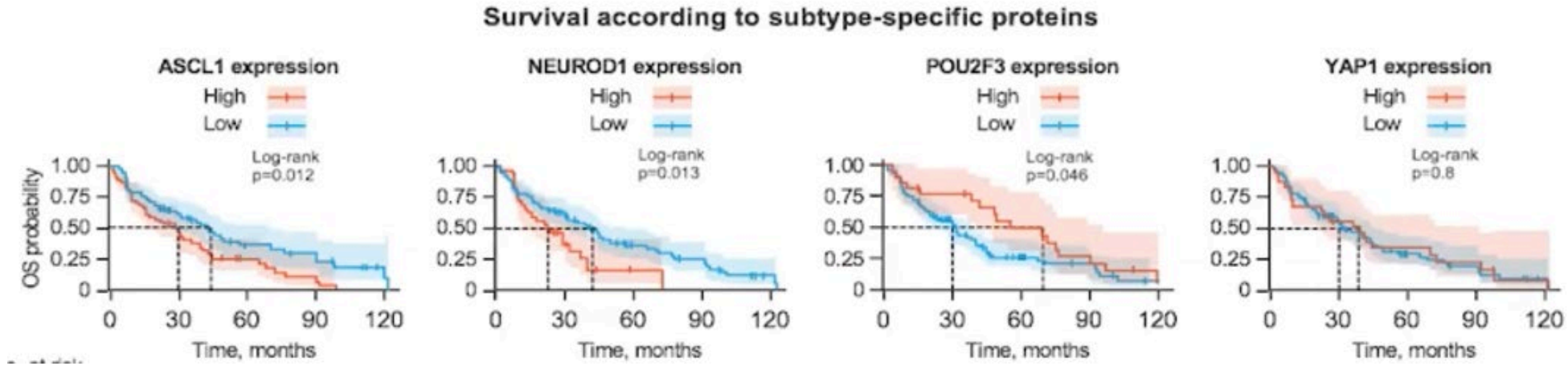


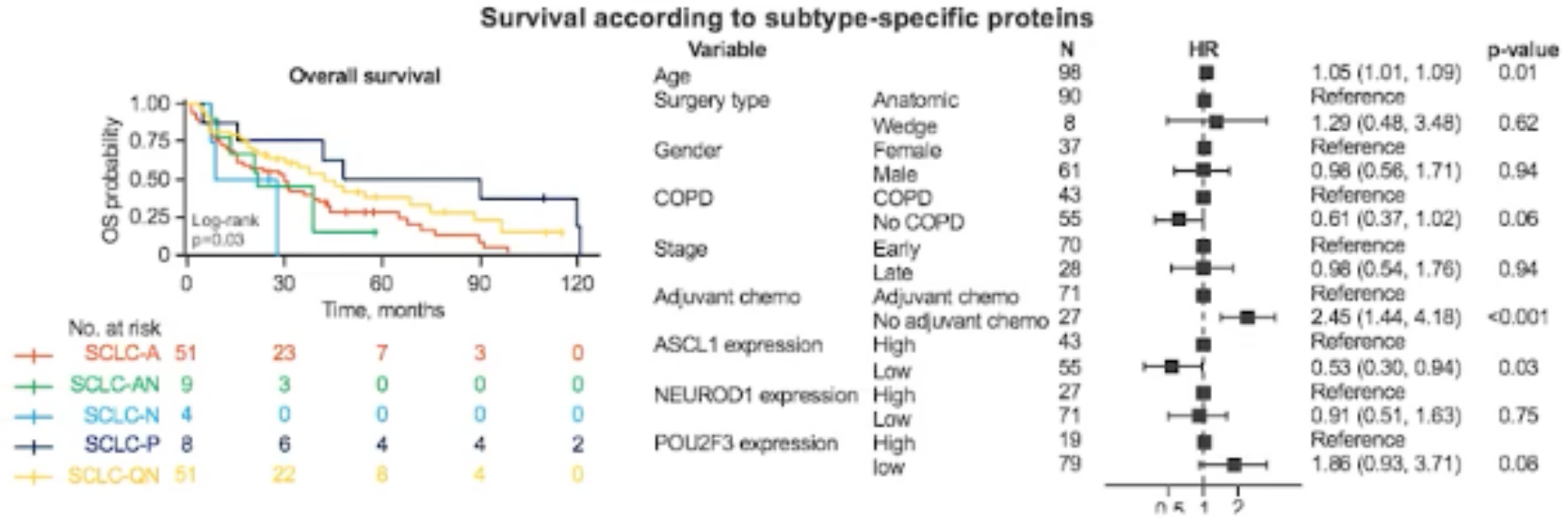


Derosa. Nat Med 2022.

SCLC

Molecular Subtypes of Surgically Resected Small Cell Lung Cancer: Expression Pattern and Prognostic Relevance





Megyesfalvi. IASCL 2022

Organizado por:
GECP lung cancer research

… conclusiones

- ❑ PDL1 continúa siendo el biomarcador más empleado.
- ❑ Enfoque combinado de múltiples biomarcadores para un mejor desempeño predictivo.
- ❑ Biomarcadores prácticos y fácilmente implementables en la práctica clínica.
- ❑ Estudios prospectivos de validación.