

15th MADRID
on **Lung** CONGRESS
CANCER
23&24
November 2023

#15CongressGECP

SESSION VII:
OPEN QUESTIONS FOR IMMUNOTHERAPY IN NSCLC

Critical evaluation of potential predictive factors

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Disclosures

- **Empleo**
Sanidad de Castilla y León (SACYL)
- **Honorarios como conferenciante**
Kyowa Kirin, Pierre-Fabre, Takeda, AstraZeneca, Bristol-Myers Squibb, Novartis, Roche, Pfizer
- **Consultoría**
Roche, Astra-Zeneca, Boehringer Ingelheim, Novartis, Takeda
- **Proyectos de investigación financiados**
Roche, Bristol-Myers Squibb, MSD, Boehringer Ingelheim, AstraZeneca
- **Viaje a reuniones-congresos y alojamiento**
Takeda, Pfizer, Pierre-Fabre, Roche
- **Acciones cotizadas**
Ninguna



Puntos a tratar

- ➔ Biomarcadores “convencionales”
 - PD-L1
 - TMB
- ➔ Biomarcadores no convencionales
 - Tabaquismo, sexo, LIPI
- ➔ Biomarcadores emergentes
 - Co-mutaciones, microbiota, aneuploidía...
- ➔ Búsqueda de nuevos biomarcadores
 - Transcriptómica, IA...

Savage Chickens

by Doug Savage





Factor predictivo de respuesta



“Afección u observación que ayuda a predecir si el cáncer de una persona responderá a un tratamiento específico...”

Diccionario del cáncer del NCI



...hablando de la inmunoterapia



...hablando de la inmunoterapia





...hablando de la inmunoterapia





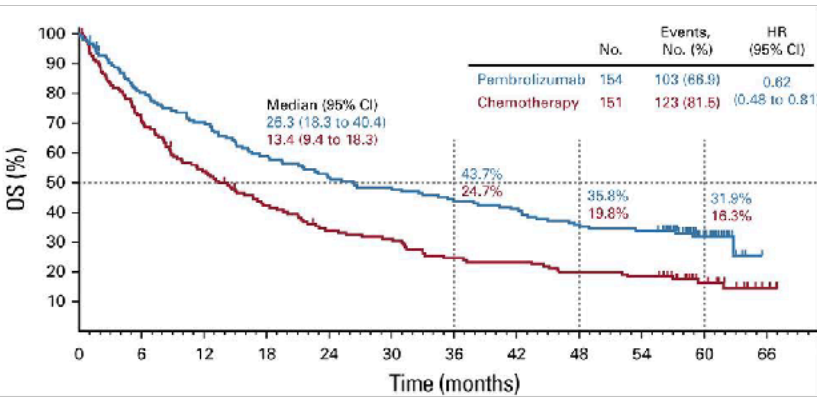
¿En qué basamos nuestras decisiones?



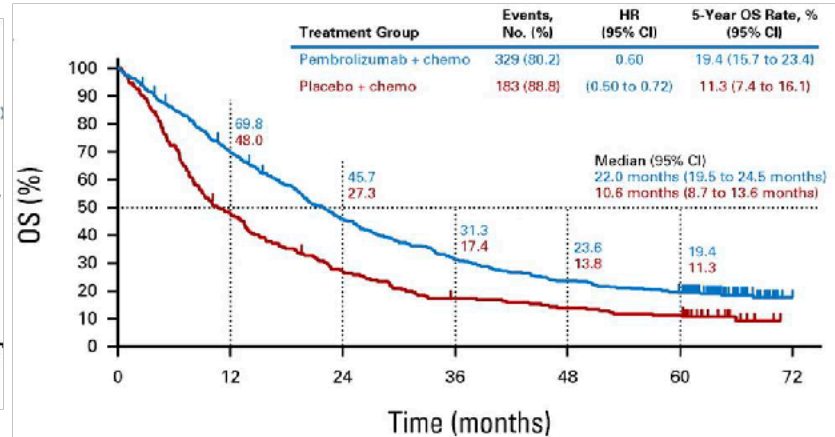


La inmunoterapia con inhibidores de punto de control (CPIs) es la espina dorsal del tratamiento del cáncer de pulmón

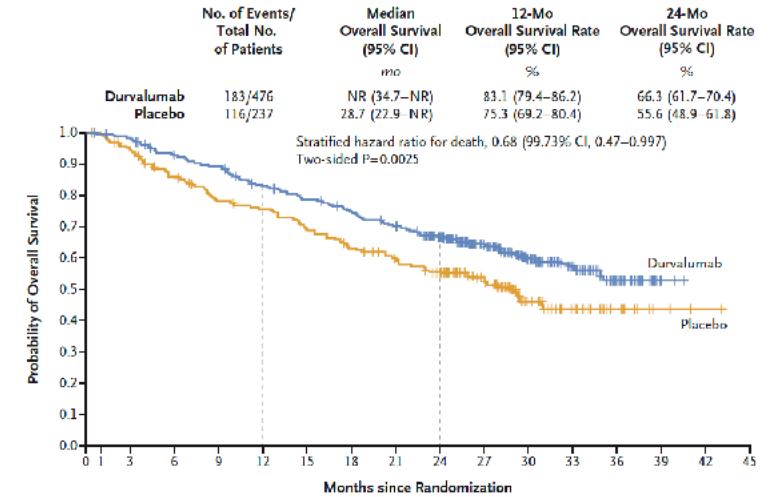
KEYNOTE 024



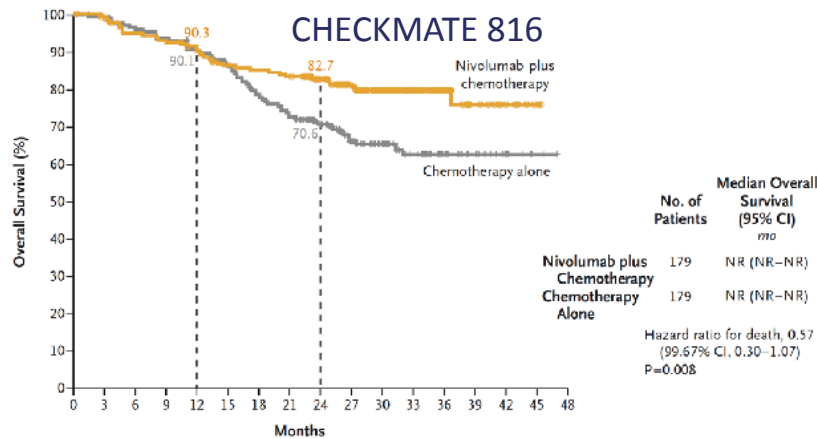
KEYNOTE 189



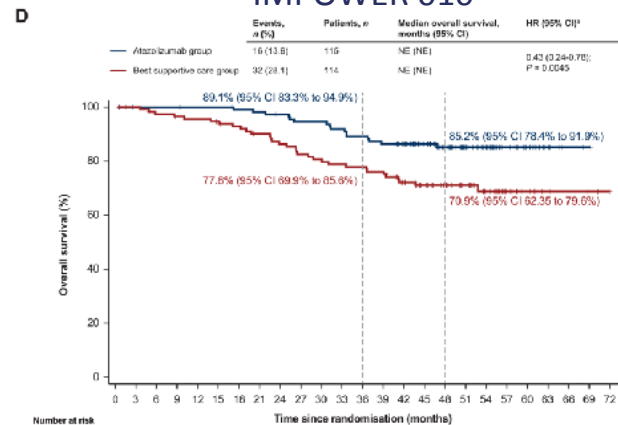
PACIFIC



CHECKMATE 816



IMPOWER 010

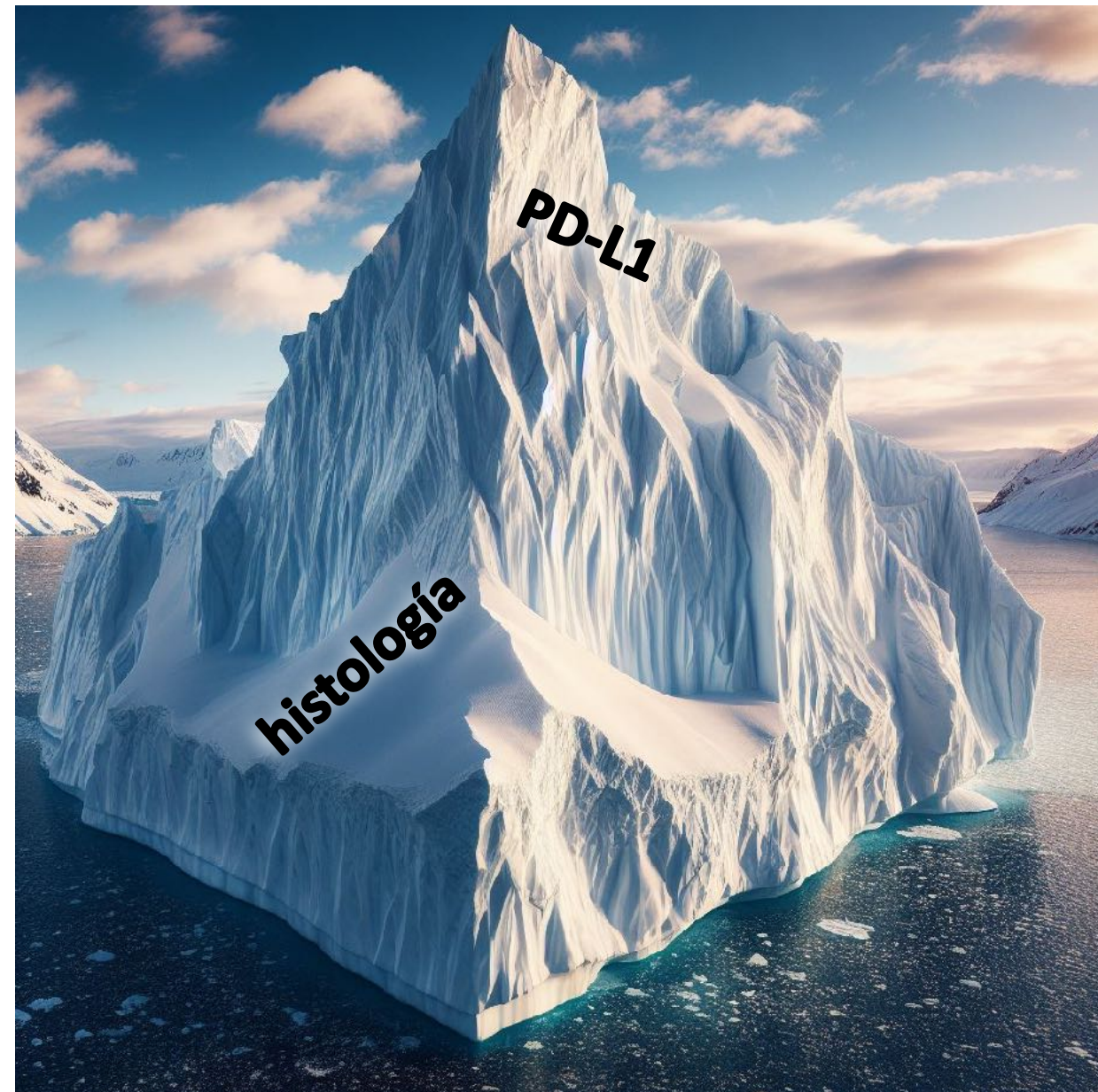


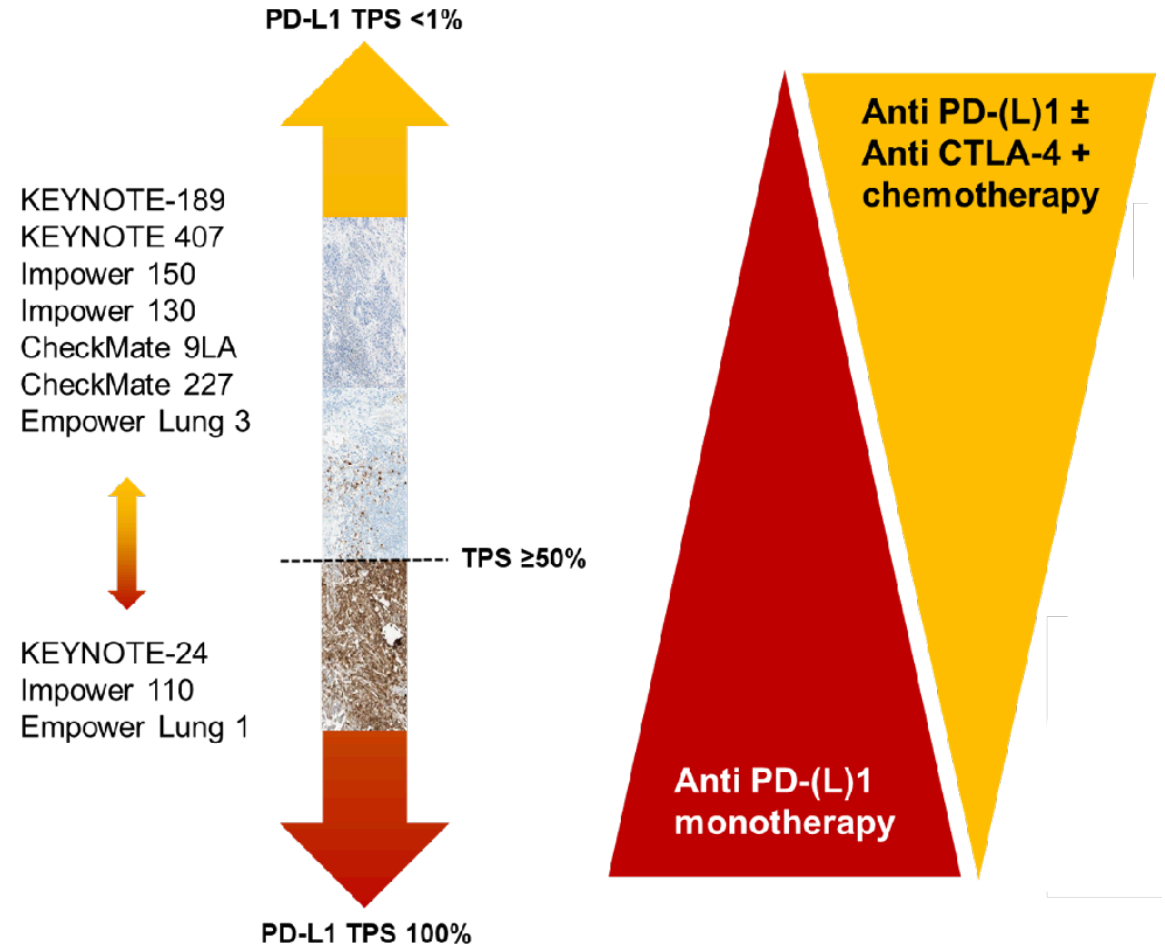
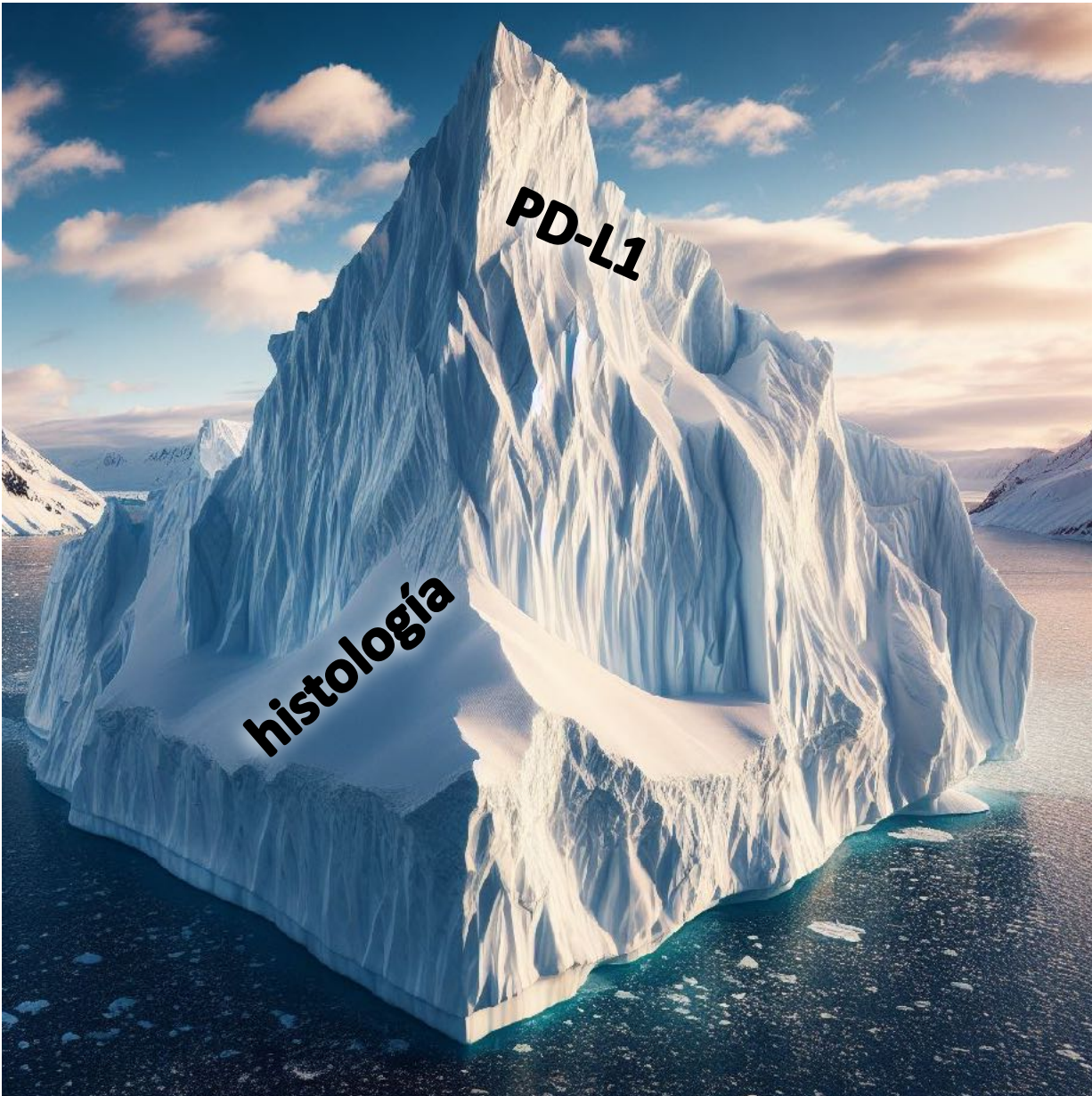
...exceptuando situaciones como ciertos *drivers*, contraindicación para IO...



1

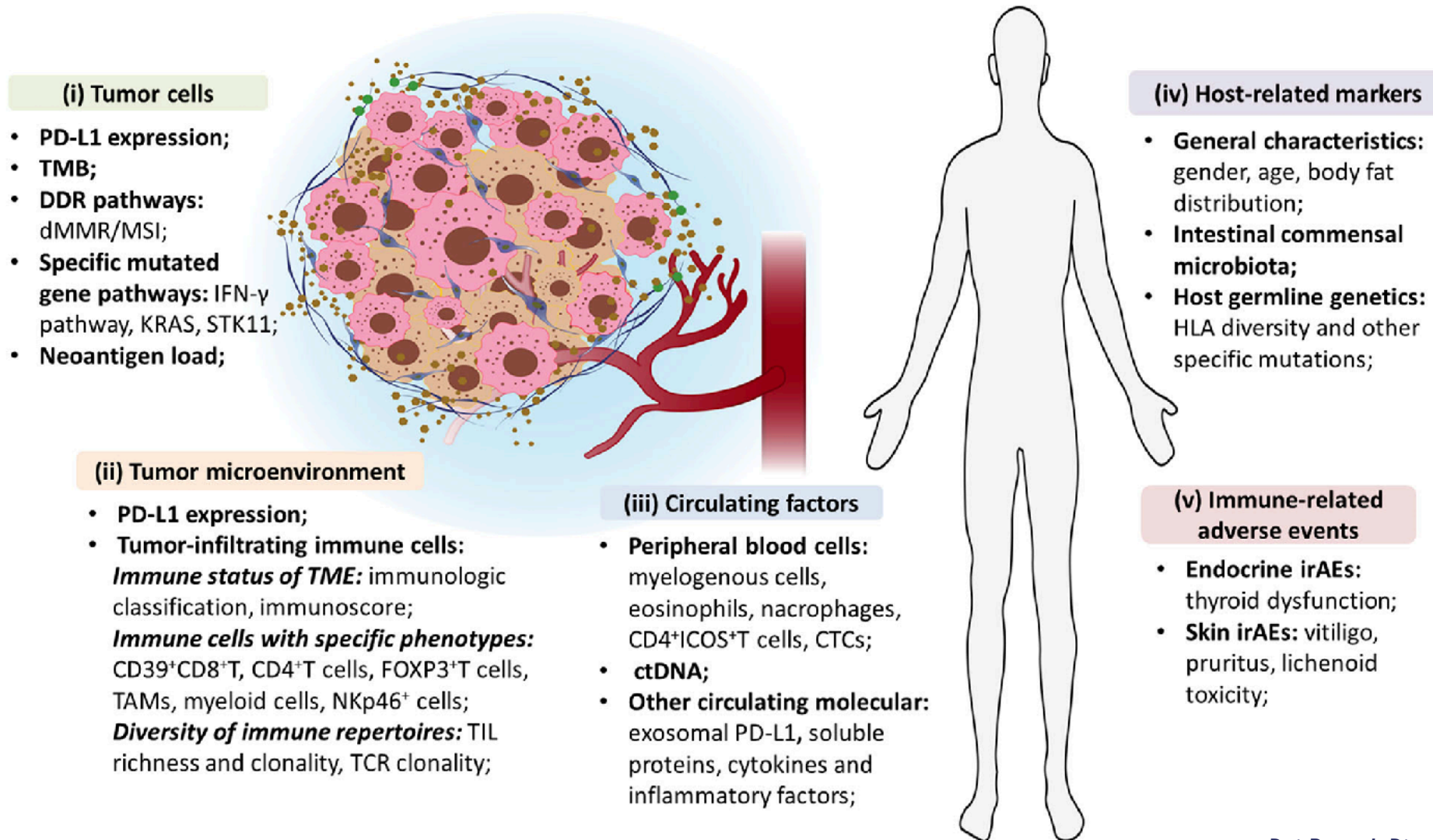
“Convencionales”





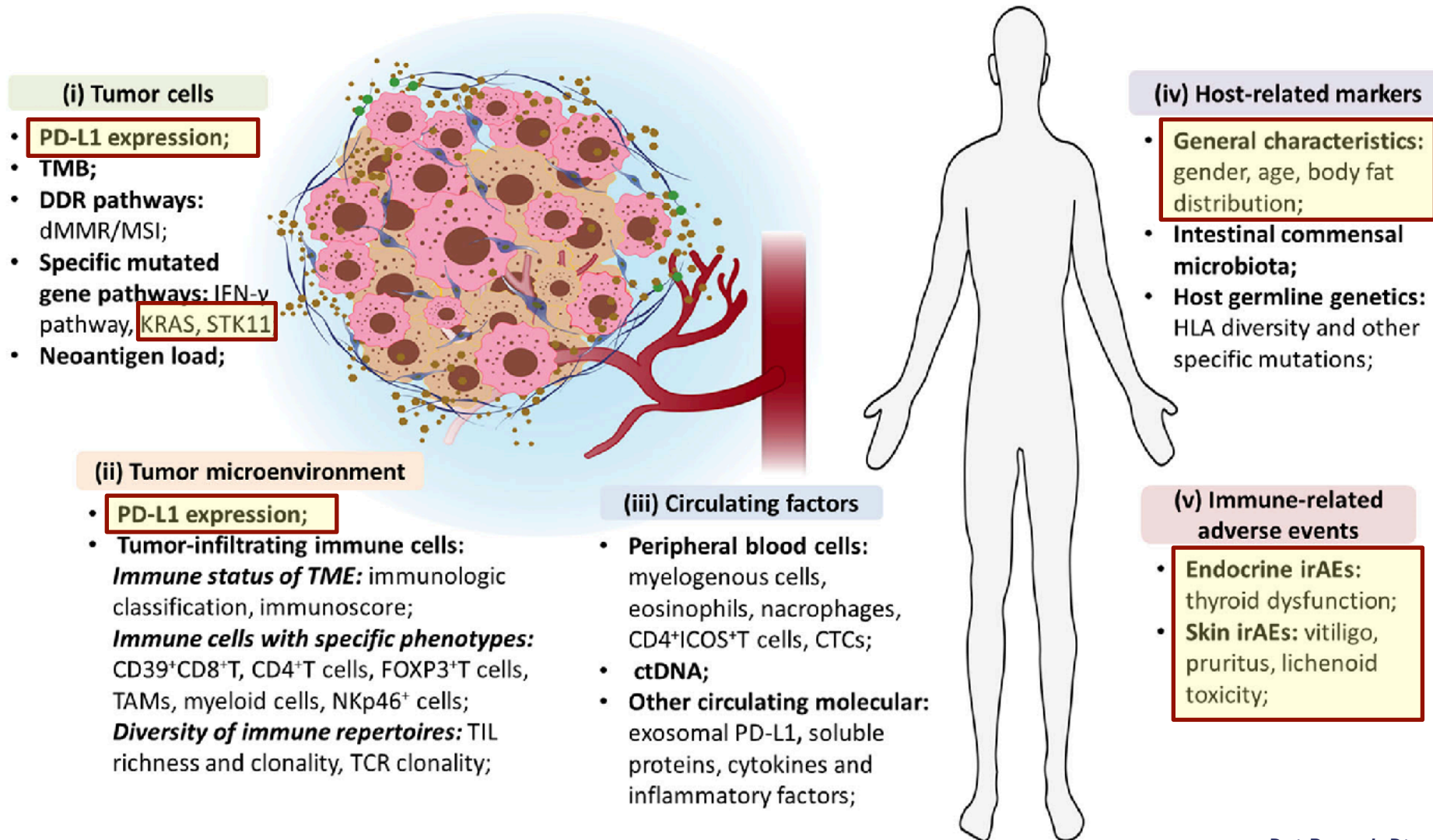


¿Factores predictivos de respuesta a inmunoterapia?





¿Factores predictivos de respuesta a inmunoterapia?





¿Es PD-L1 el factor predictivo ideal?

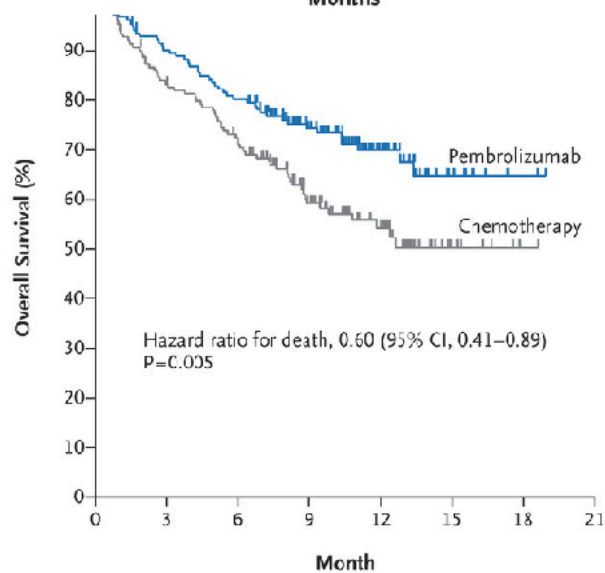
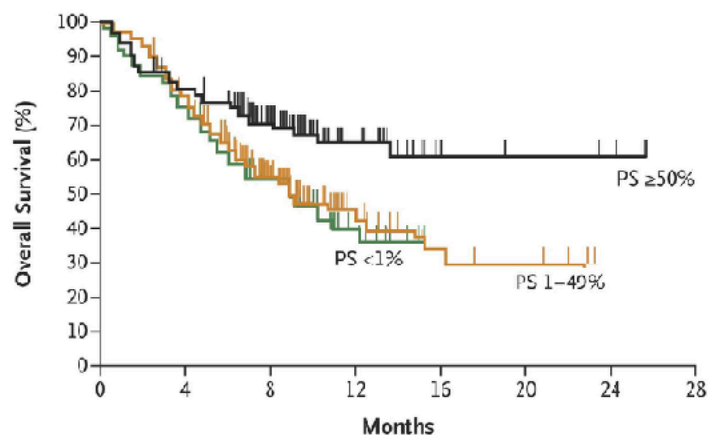
¿Cuál es el punto de corte óptimo?



¿Es PD-L1 el factor predictivo ideal?

¿Cuál es el punto de corte óptimo?

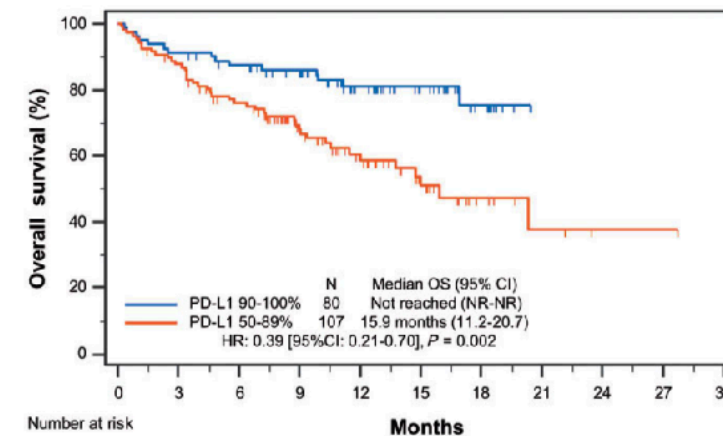
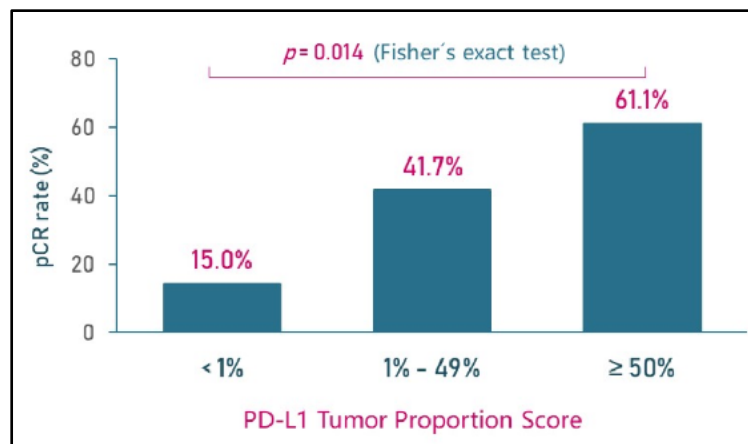
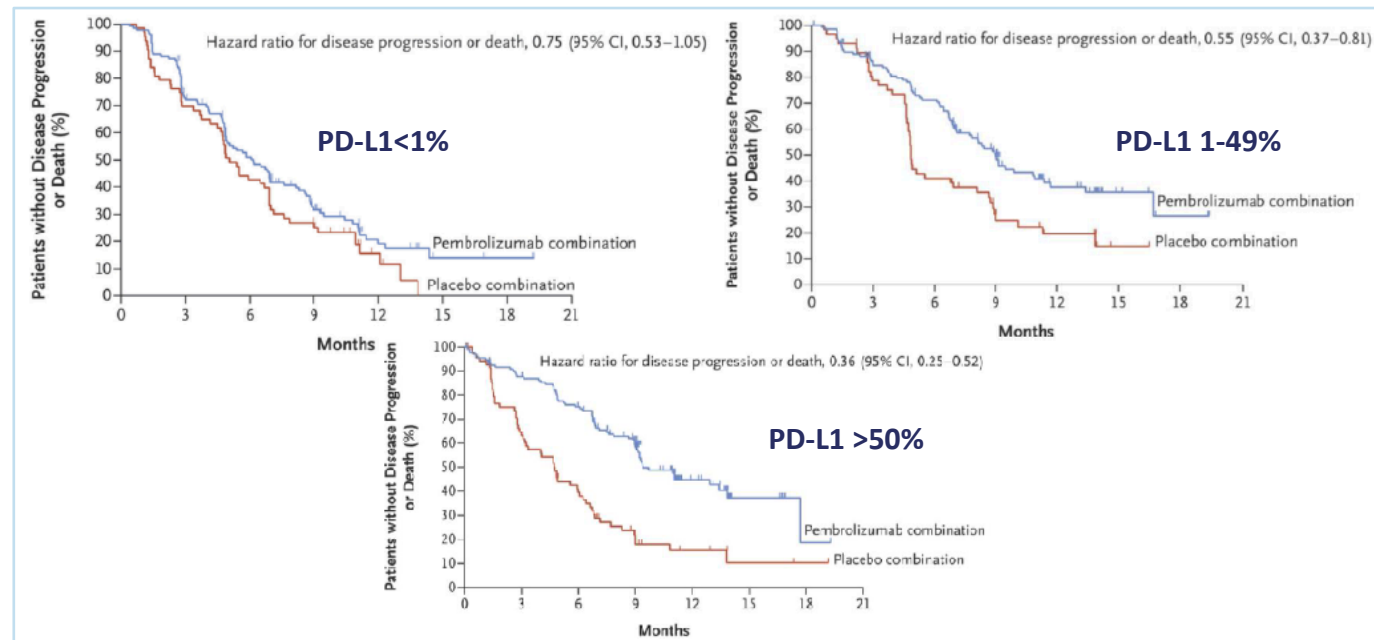
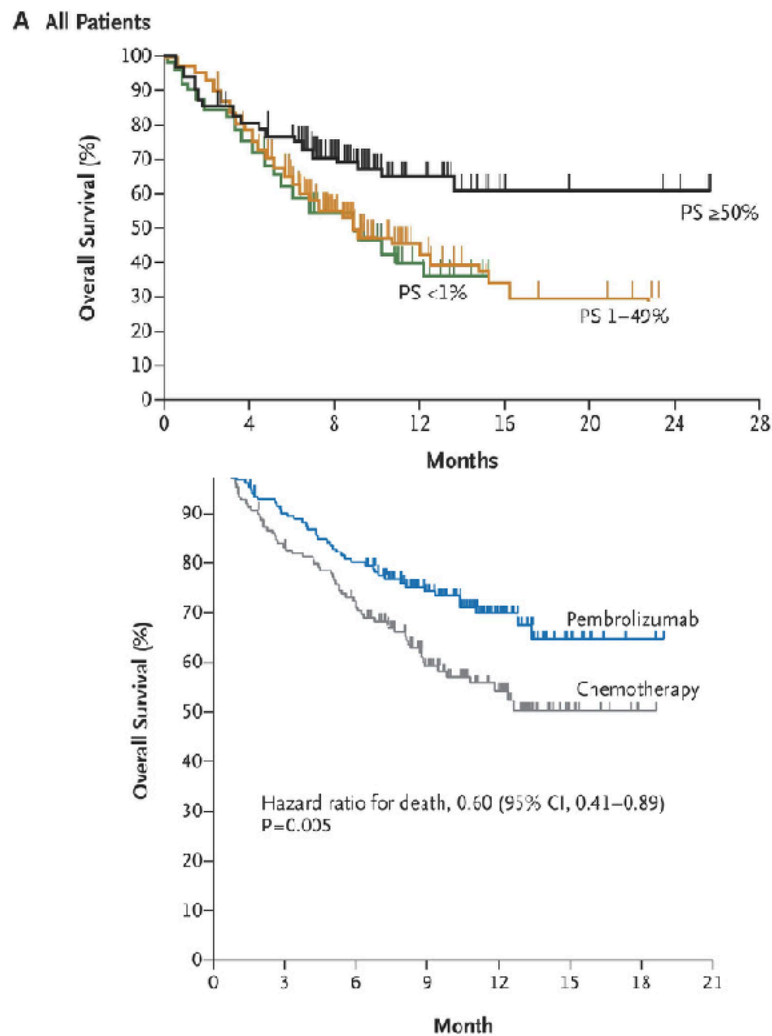
A All Patients





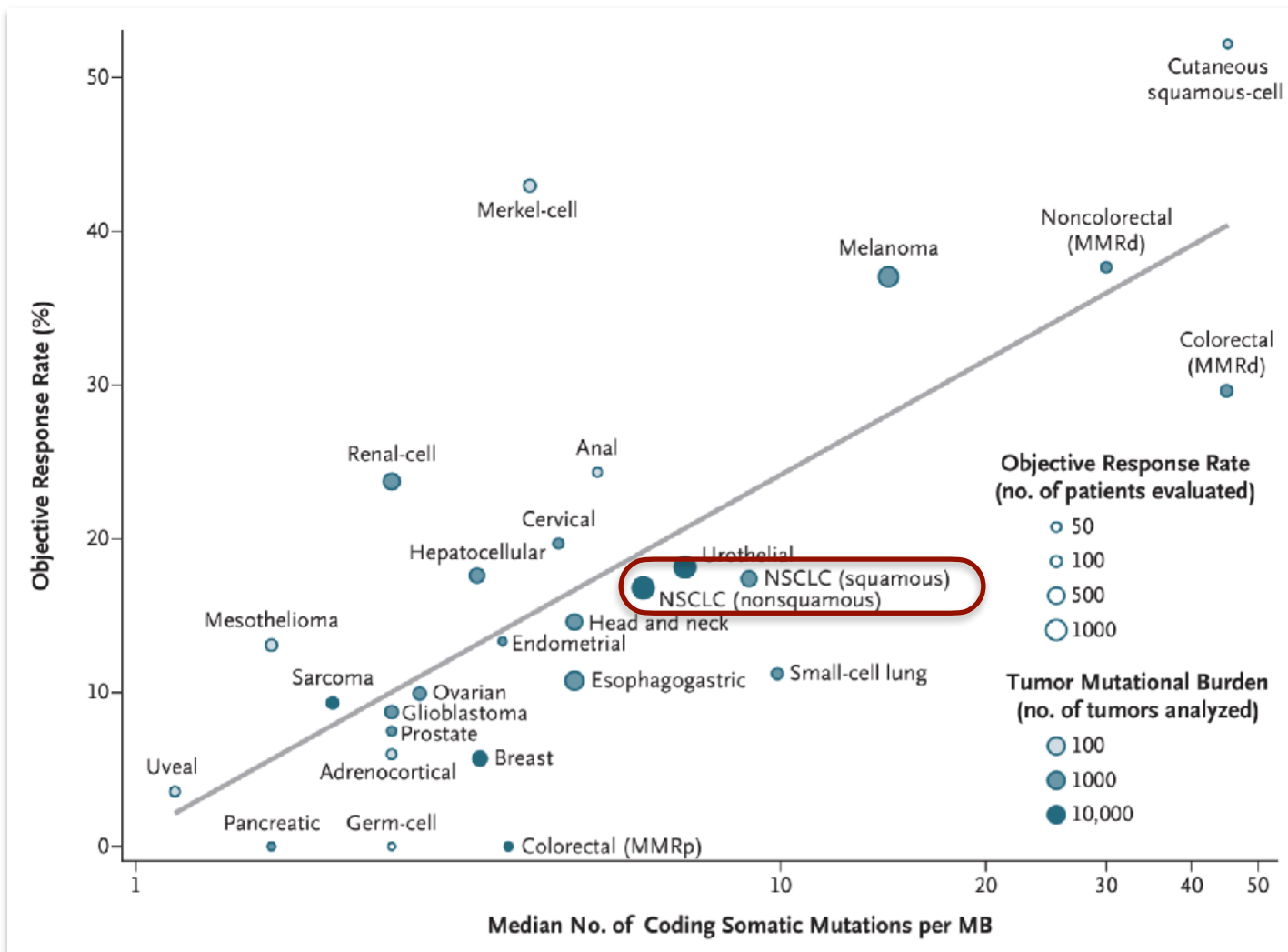
¿Es PD-L1 el factor predictivo ideal?

¿Cuál es el punto de corte óptimo?





...tal vez la TMB

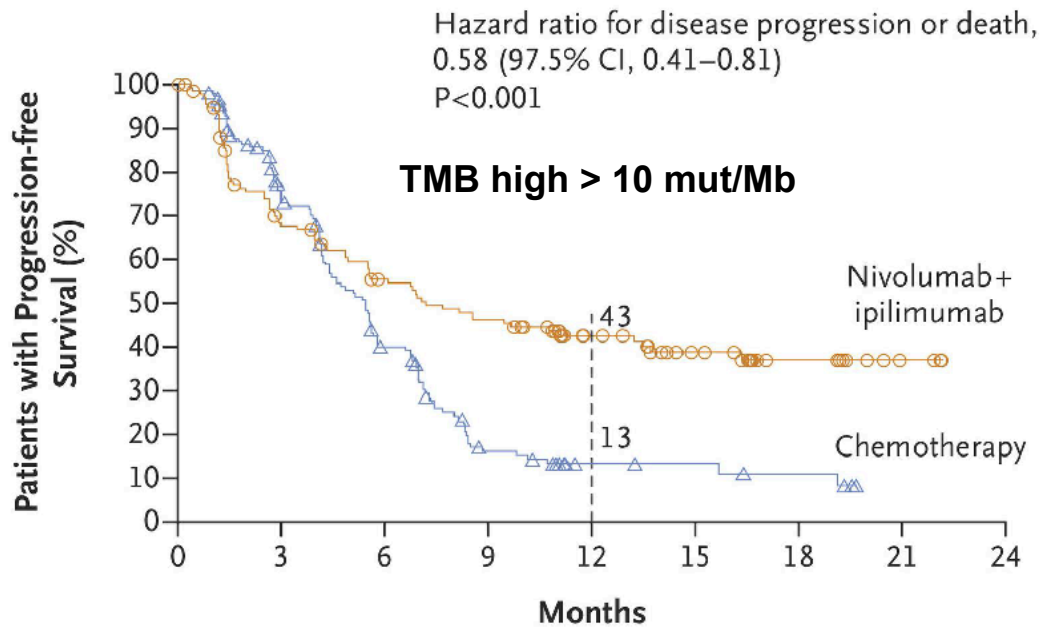


➔ Capacidad predictiva de SLP y TRO





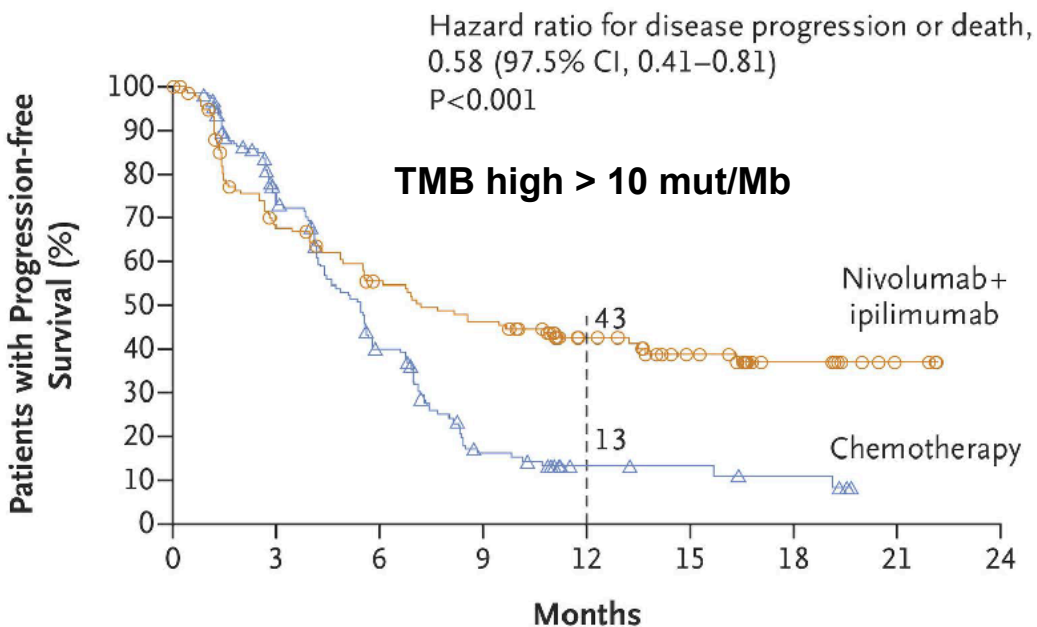
Correlación TMB/eficacia de CPIs



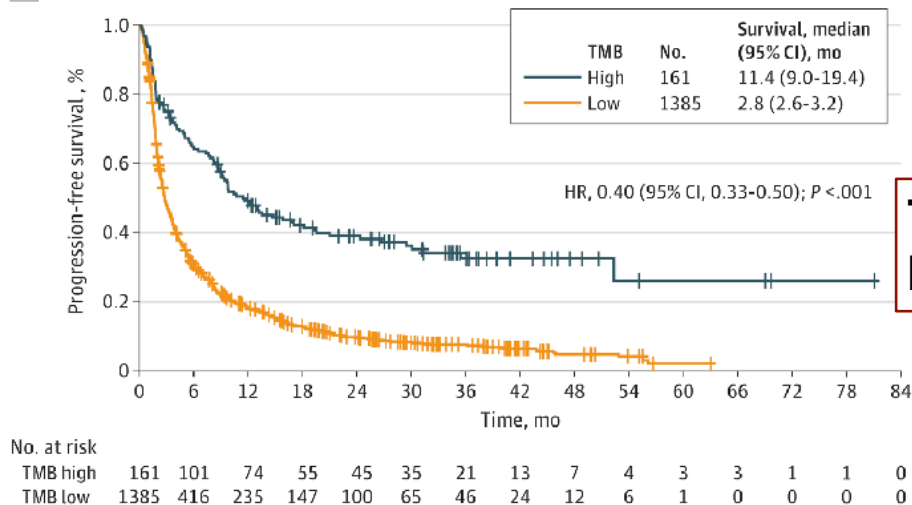


Correlación TMB/eficacia de CPIs

¿Cuál es el umbral de TMB?

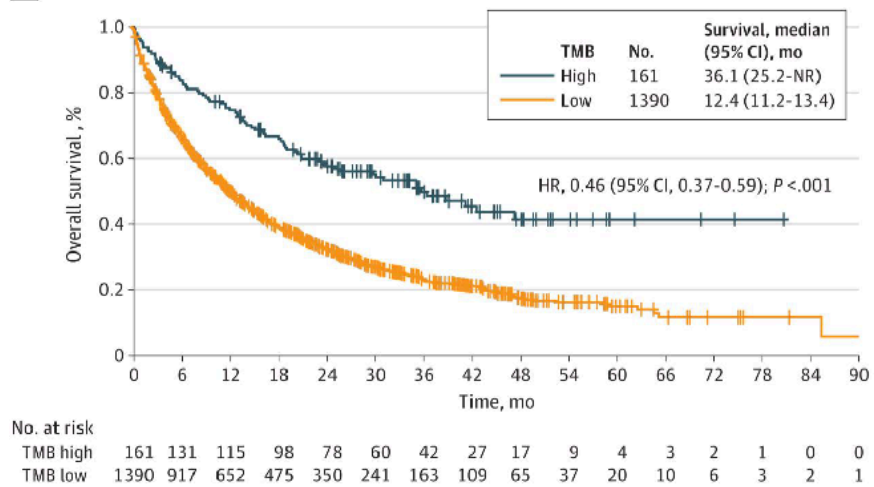


B Progression-free survival

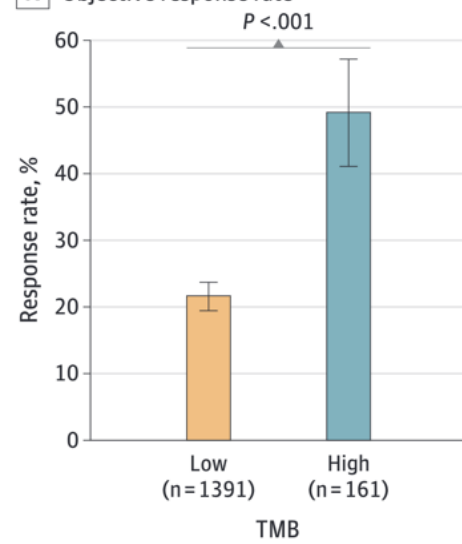


TMB high > 19 mut/Mb by NGS (or >16 by WES)

C Overall survival

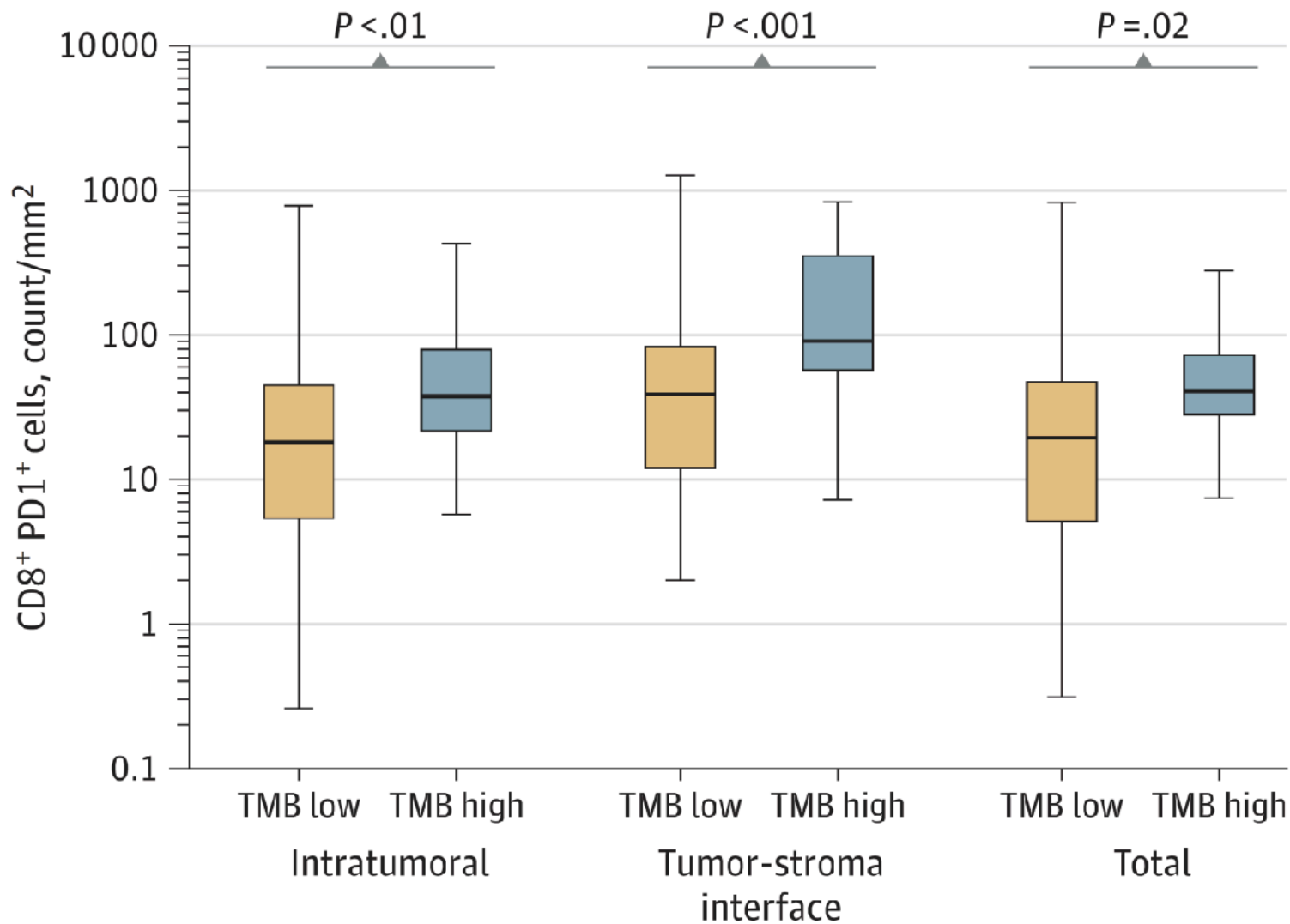


A Objective response rate





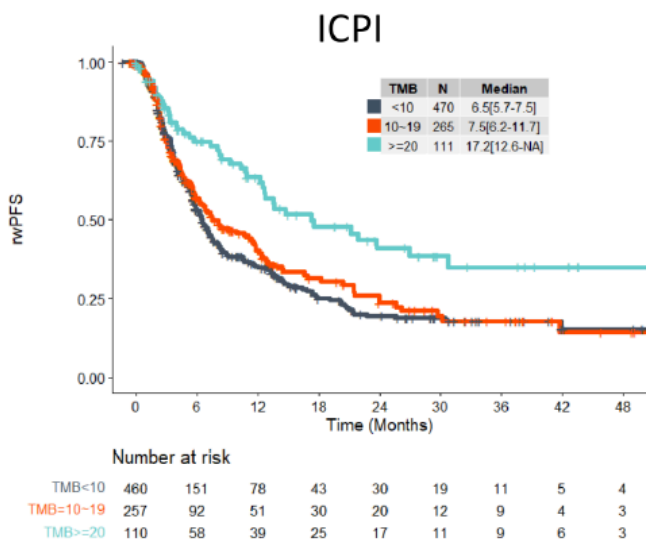
TMB alta: Correlación con Linfos T CD8+ infiltrantes en CPNM



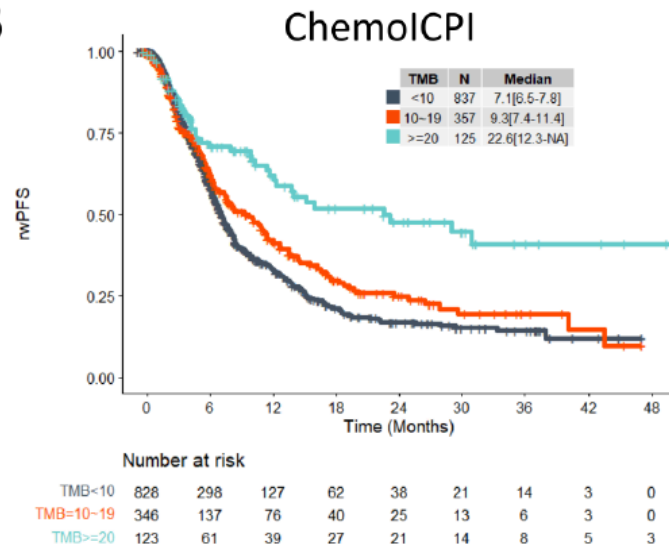


TMB muy alta (≥ 20 mut/Mb por FM CDx) asociado con incremento de SLP y SG con CPIs +/- QT

A



B

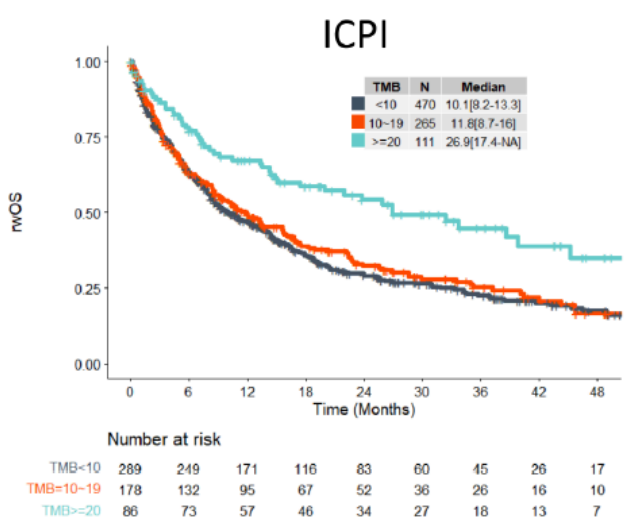


RWD with 2165 pts

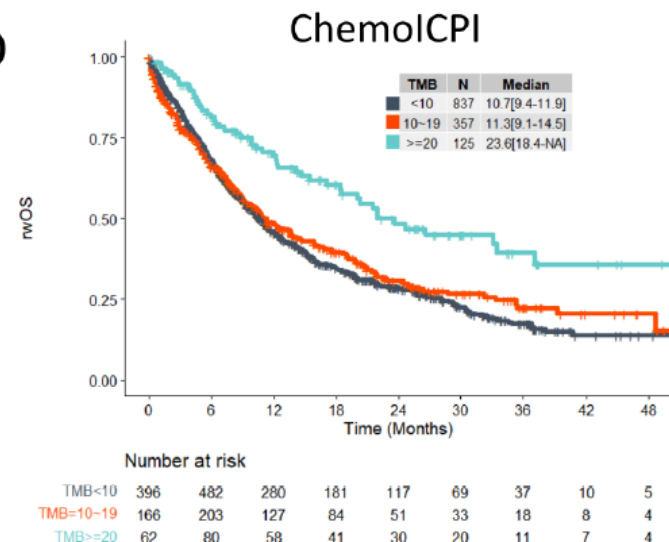
TMB by Foundation Medicine CDx in tissue

PD-L1 $\geq 50\%$ (anti-PD(L)1 monotherapy)			
	TMB <10	TMB 10-19	TMB ≥ 20
mPFS (m)	6.5	7.5	17.2
mOS (m)	10.1	11.8	26.9

C



D



PD-L1<50% (QT + anti-PD(L)1 monotherapy)			
	TMB <10	TMB 10-19	TMB ≥ 20
mPFS (m)	7.1	9.3	22.6
mOS (m)	10.7	11.3	23.6



2

No Convencionales



Lung Immune Prognostic Index

$$dNLR = \frac{\text{absolute neutrophil count}}{[\text{white blood cell} - \text{absolute neutrophil count}]}$$

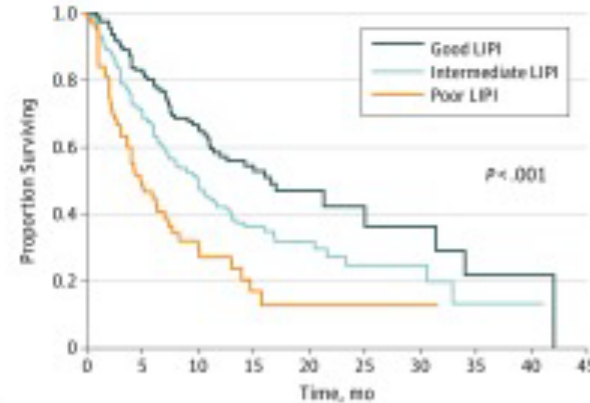


LDH N vs \geq ULN



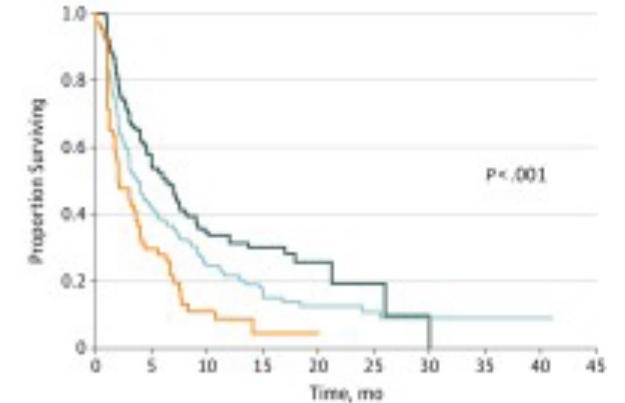
LIPI good = 0 factors
 LIPI intermediate = 1 factor
 LIPI poor = 2 factors

A OS in the immunotherapy pooled cohort



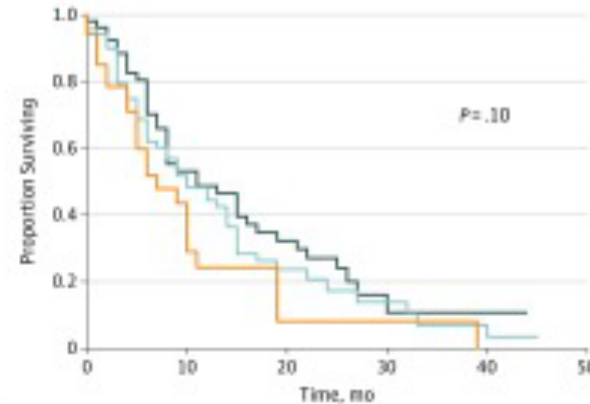
No. at risk	0	5	10	15	20	25	30	35	40	45
Good LIPI	162	118	69	34	12	7	5	3	3	0
Intermediate LIPI	206	125	72	28	15	9	5	2	1	0
Poor LIPI	63	29	13	5	2	1	1	0	0	0

B PFS in the immunotherapy pooled cohort



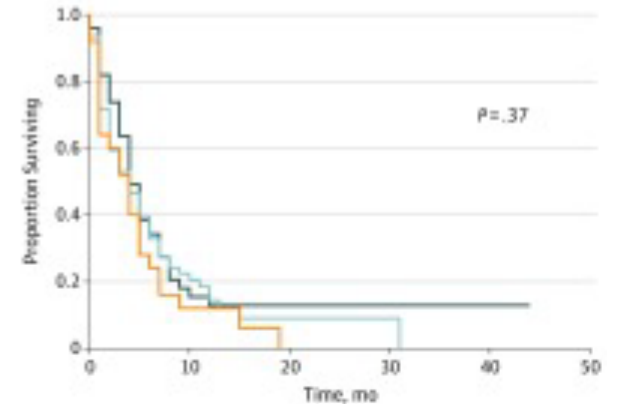
No. at risk	0	5	10	15	20	25	30	35	40	45
Good LIPI	162	84	36	20	6	2	1	0	0	0
Intermediate LIPI	206	75	38	18	8	6	2	2	1	0
Poor LIPI	63	18	5	1	1	0	0	0	0	0

C OS in the chemotherapy cohort



No. at risk	0	10	20	30	40	50
Good LIPI	53	24	13	3	2	0
Intermediate LIPI	70	30	9	4	2	0
Poor LIPI	34	9	1	1	0	0

D PFS in the chemotherapy cohort

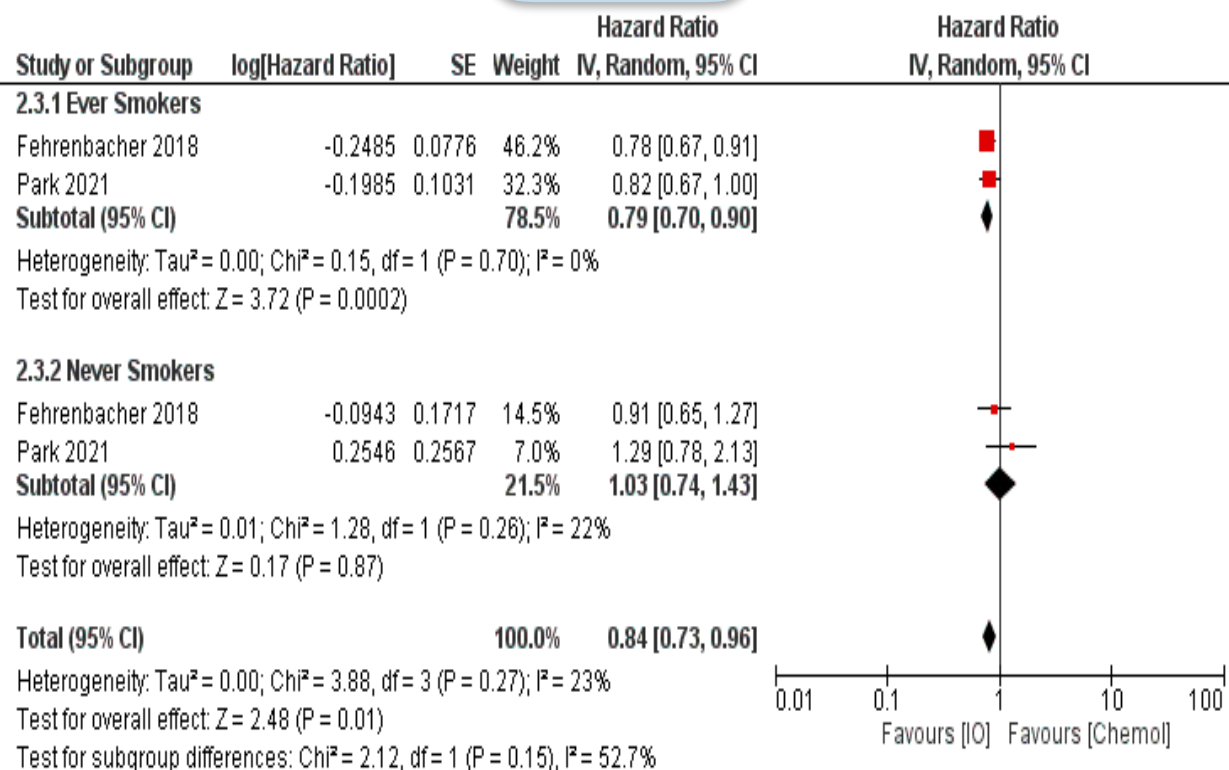


No. at risk	0	10	20	30	40	50
Good LIPI	50	7	4	1	1	0
Intermediate LIPI	64	12	2	1	0	0
Poor LIPI	25	2	0	0	0	0

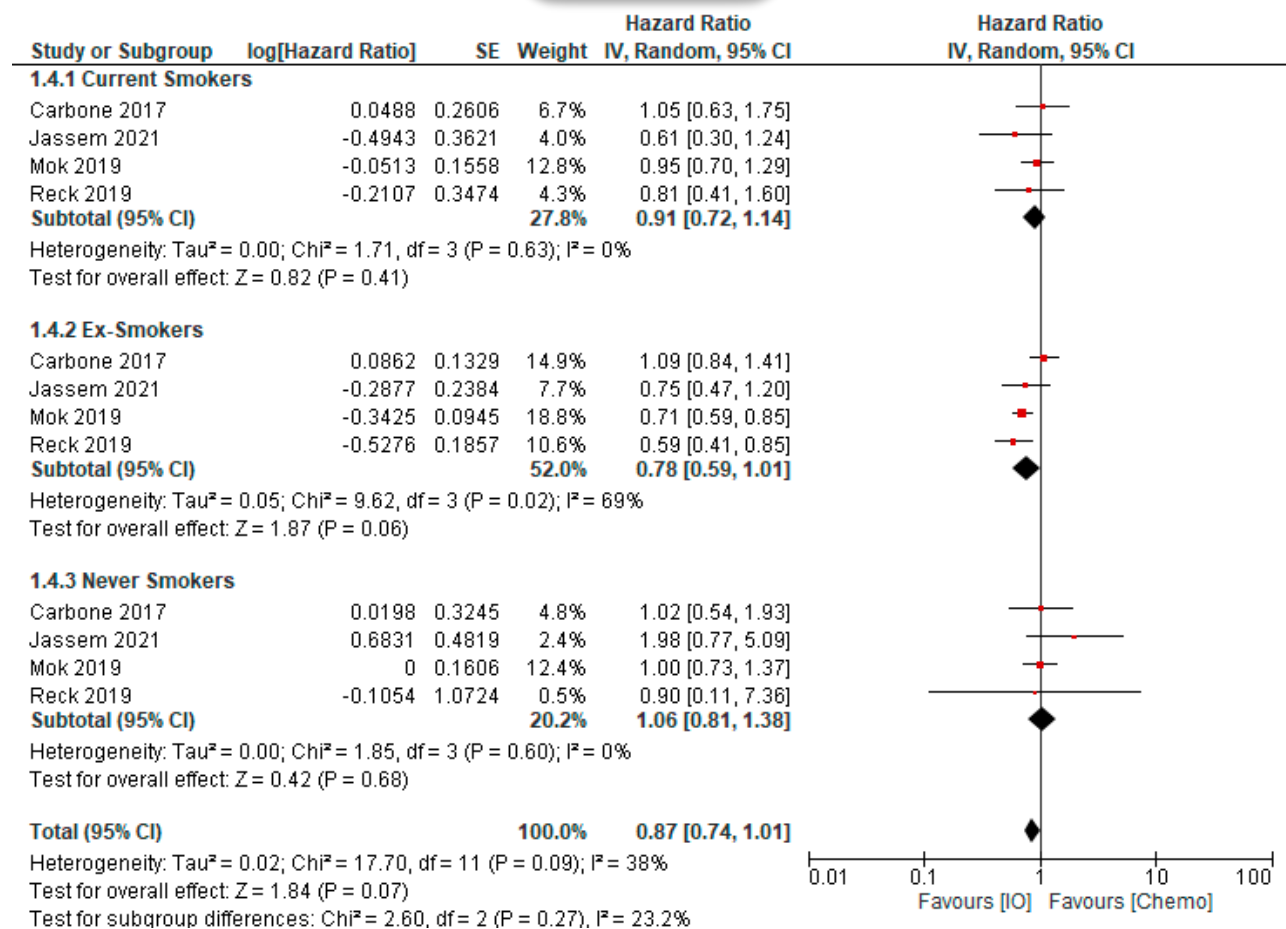


¿El tabaco?

IO 2L



IO 1L

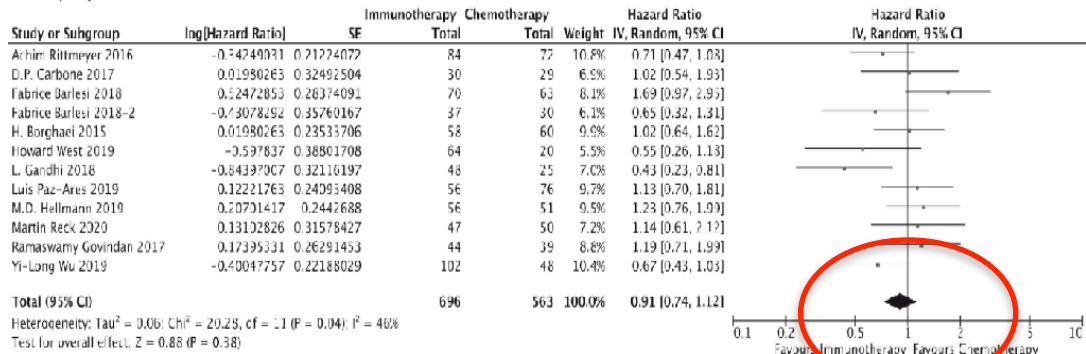




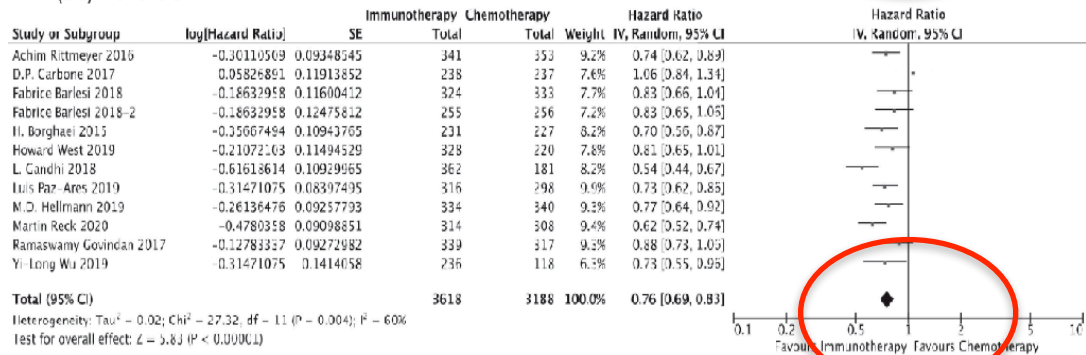
¿El tabaco?

OS: Non smokers and smokers

HR (OS) in non-smokers

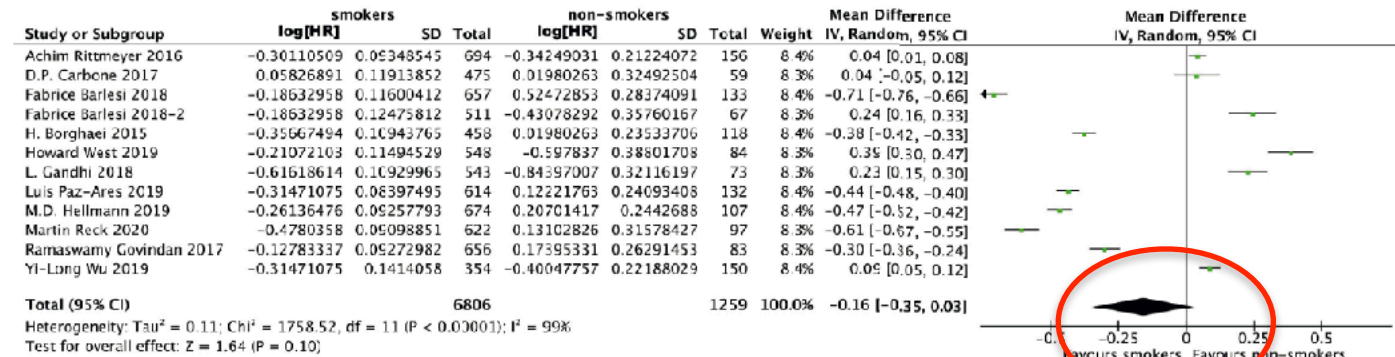


HR (OS) in smokers

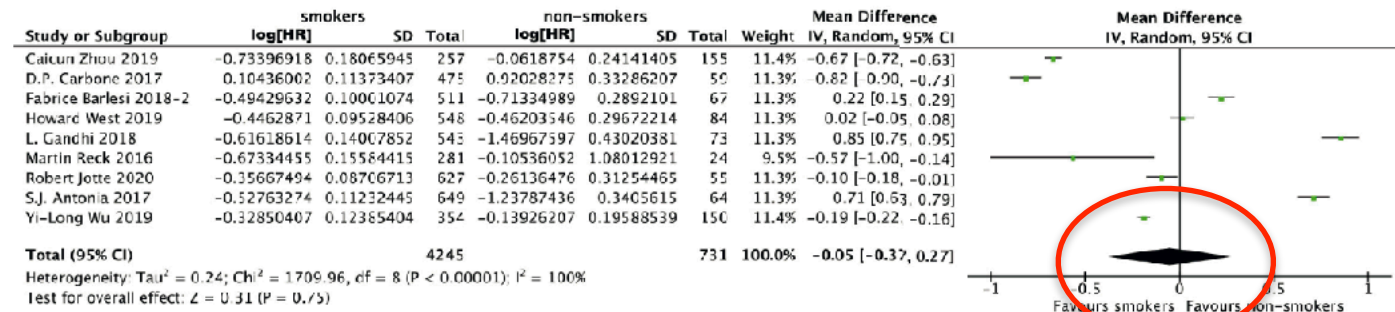


PFS and OS: Non smokers vs smokers

A Comparison of HR (OS) between smokers and non-smokers

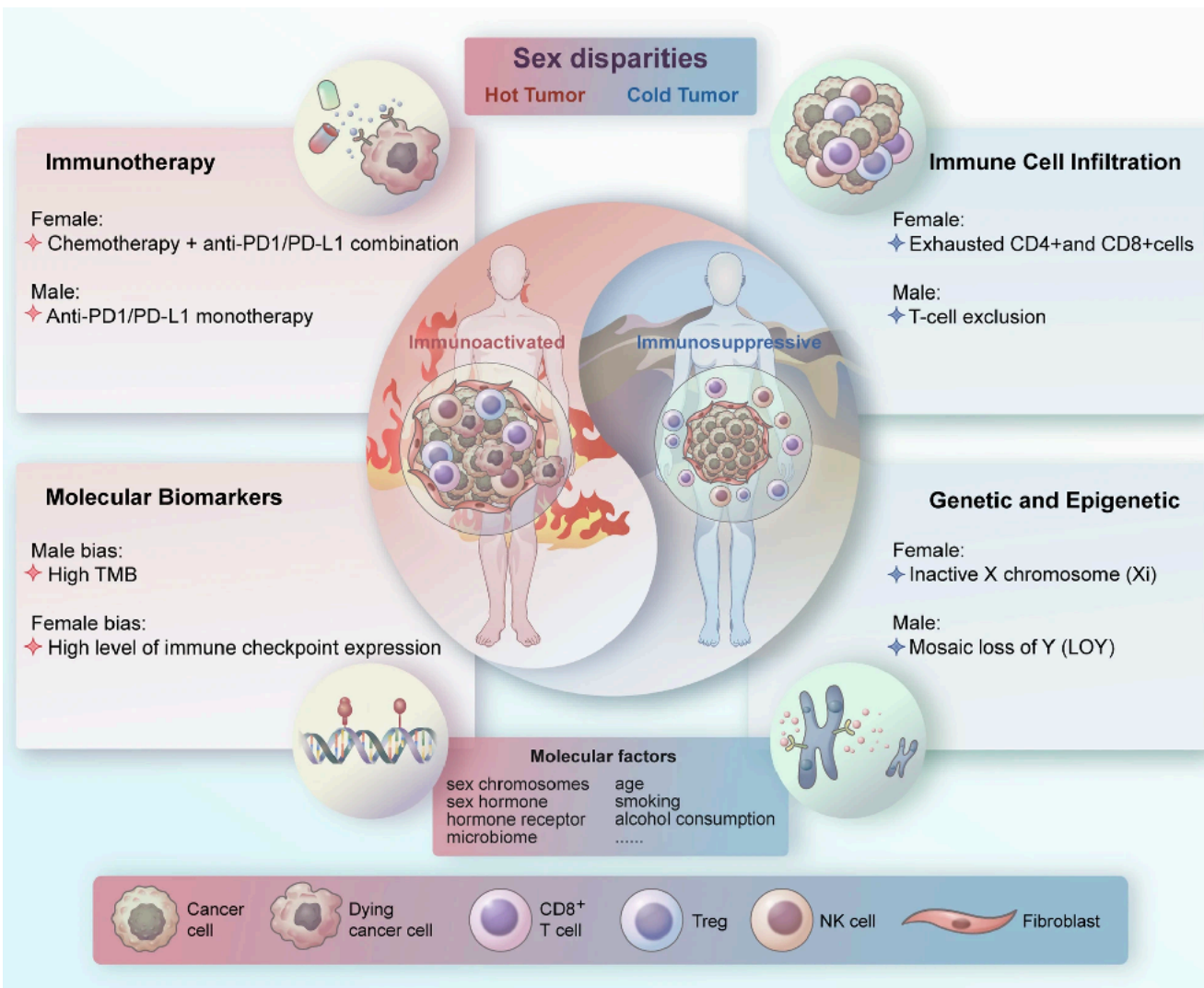


B Comparison of HR (PFS) between smokers and non-smokers



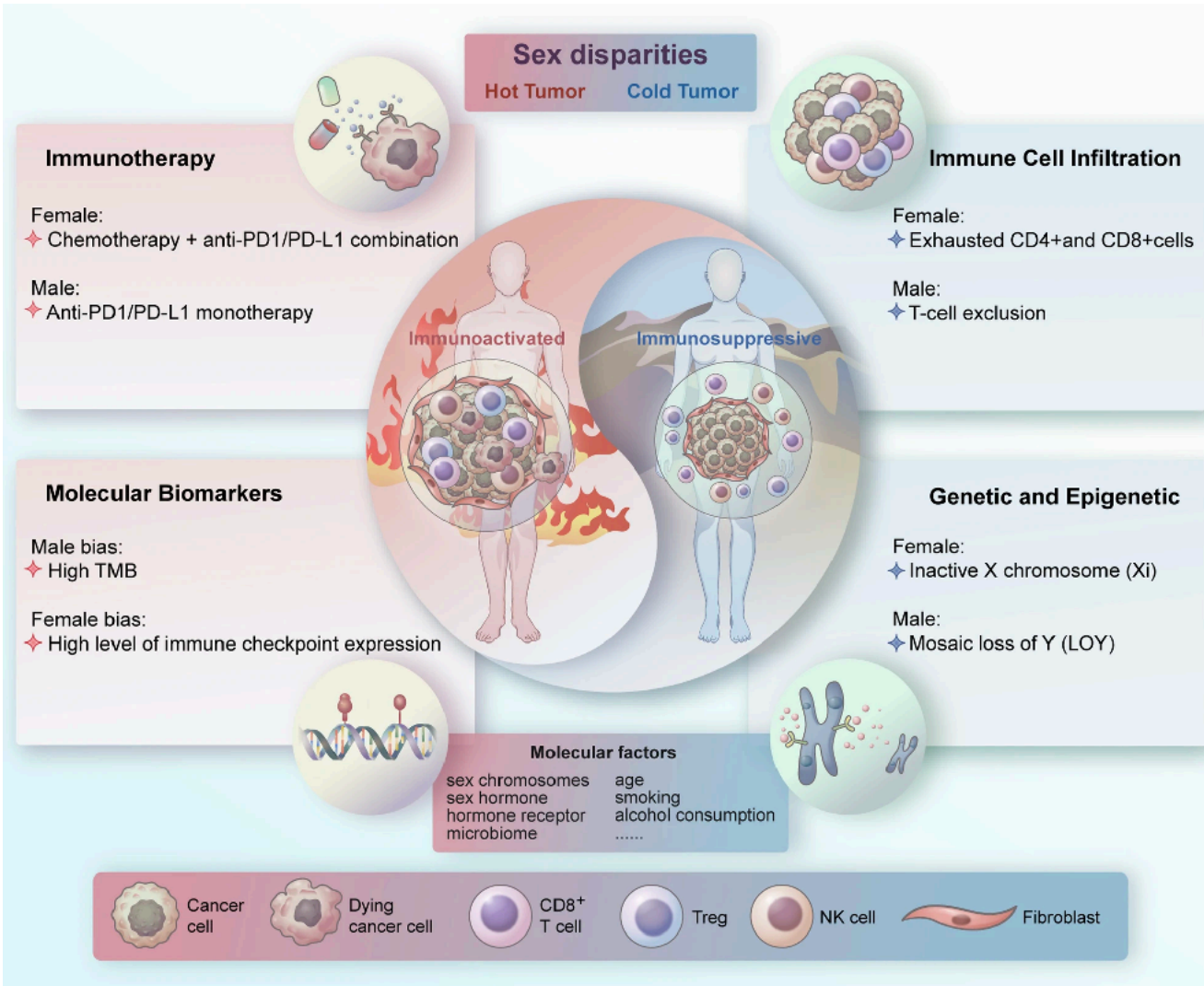


¿Hay un fenotipo tumoral masculino y otro femenino?

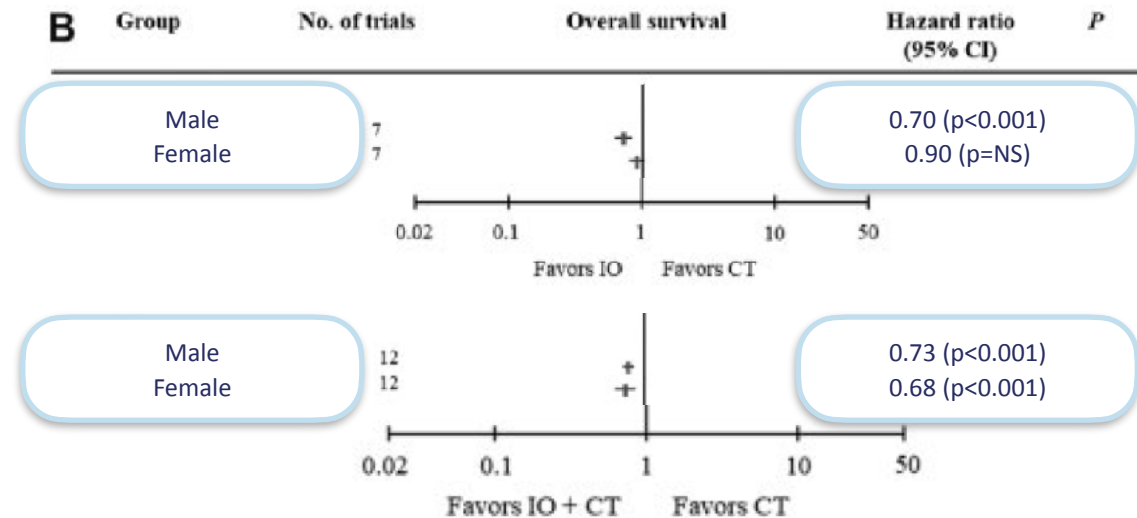




¿Hay un fenotipo tumoral masculino y otro femenino?



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





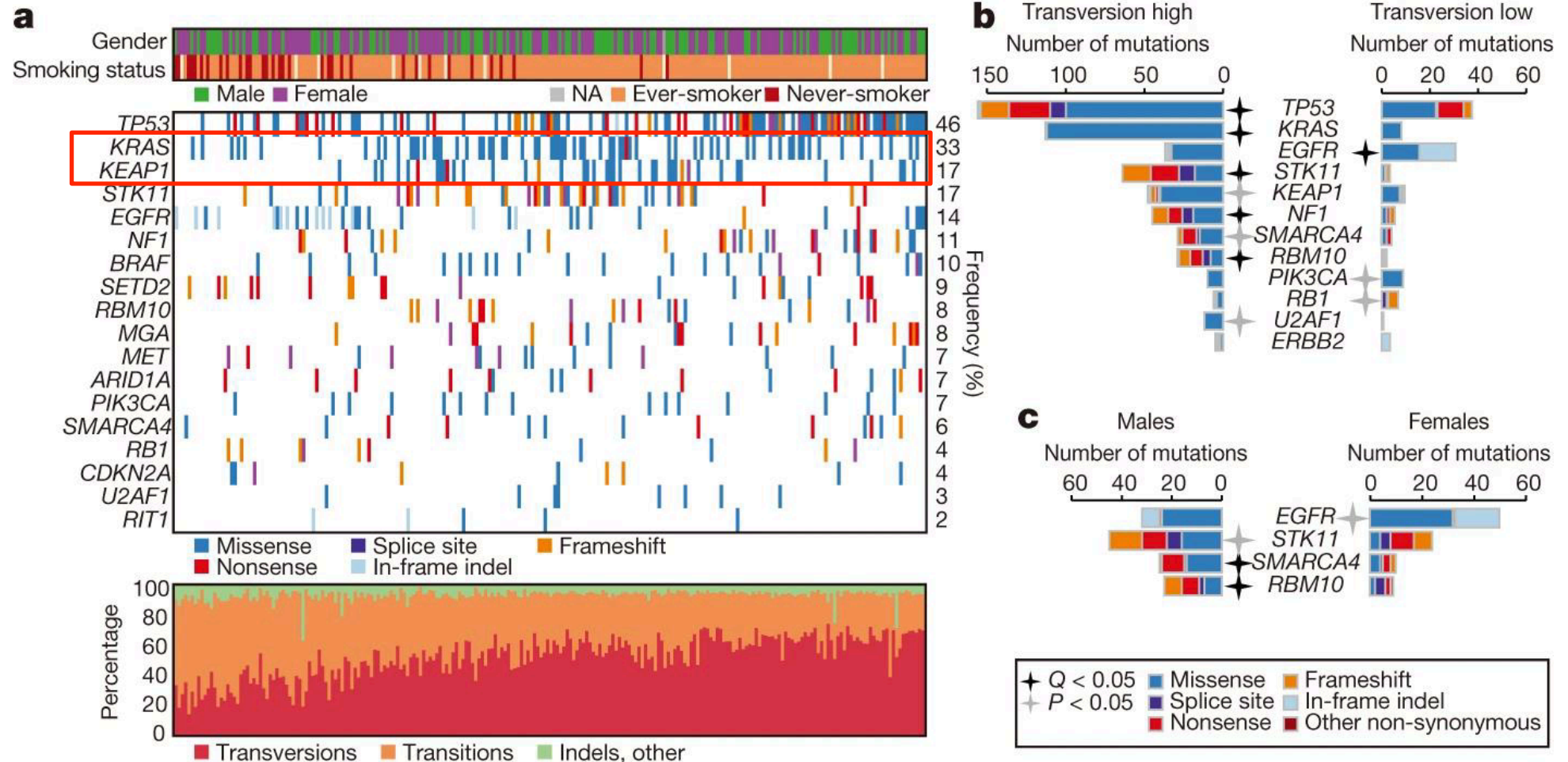
3

Emergentes



Compleja heterogeneidad de CPNM

ADC

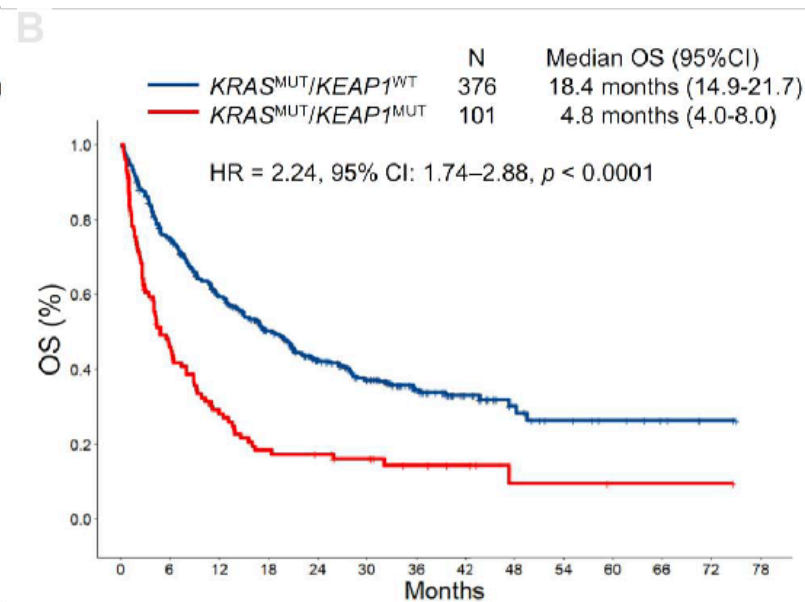
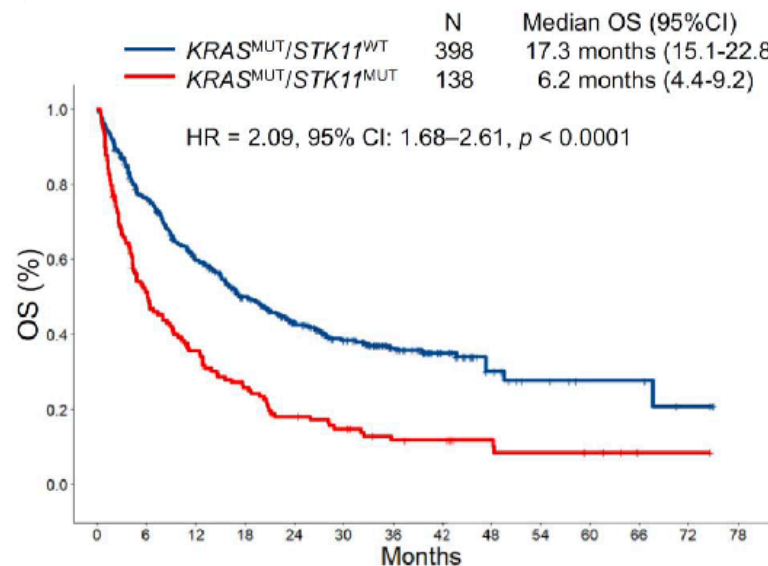
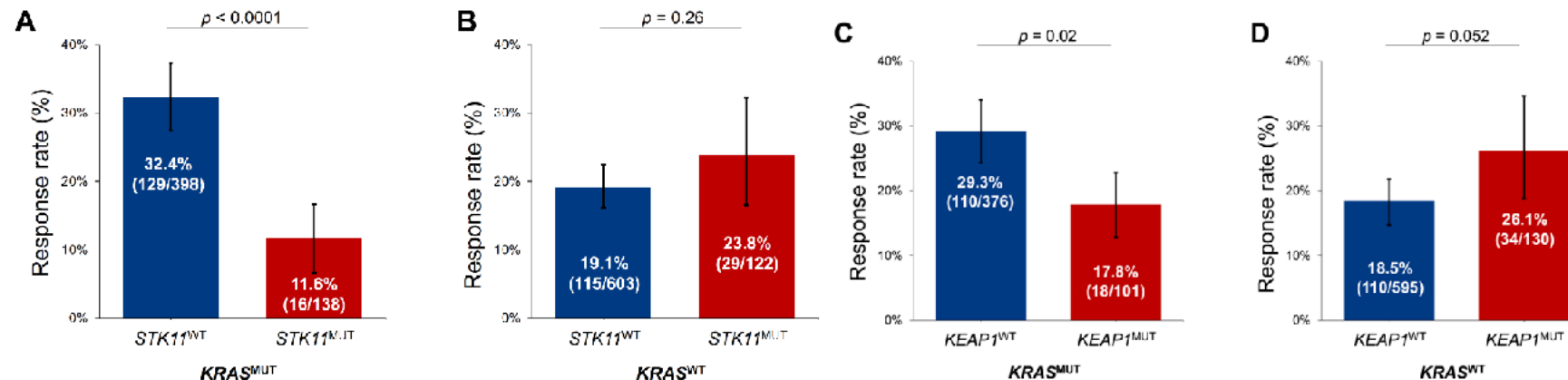




Presencia de co-mutaciones

STK11: Gen regulador de metabolismo, crecimiento y regulación celular. Pérdida en 15% de ADC, relacionada con pérdida de expresión de PD-L1, CD8+ infiltrantes y respuesta a CPIs

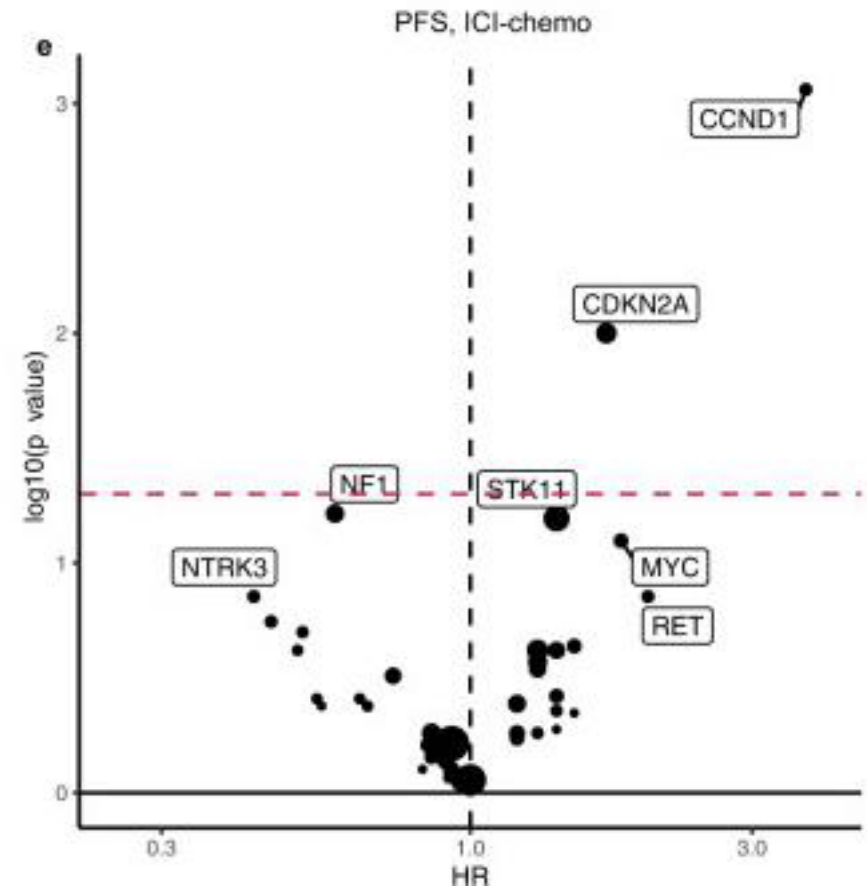
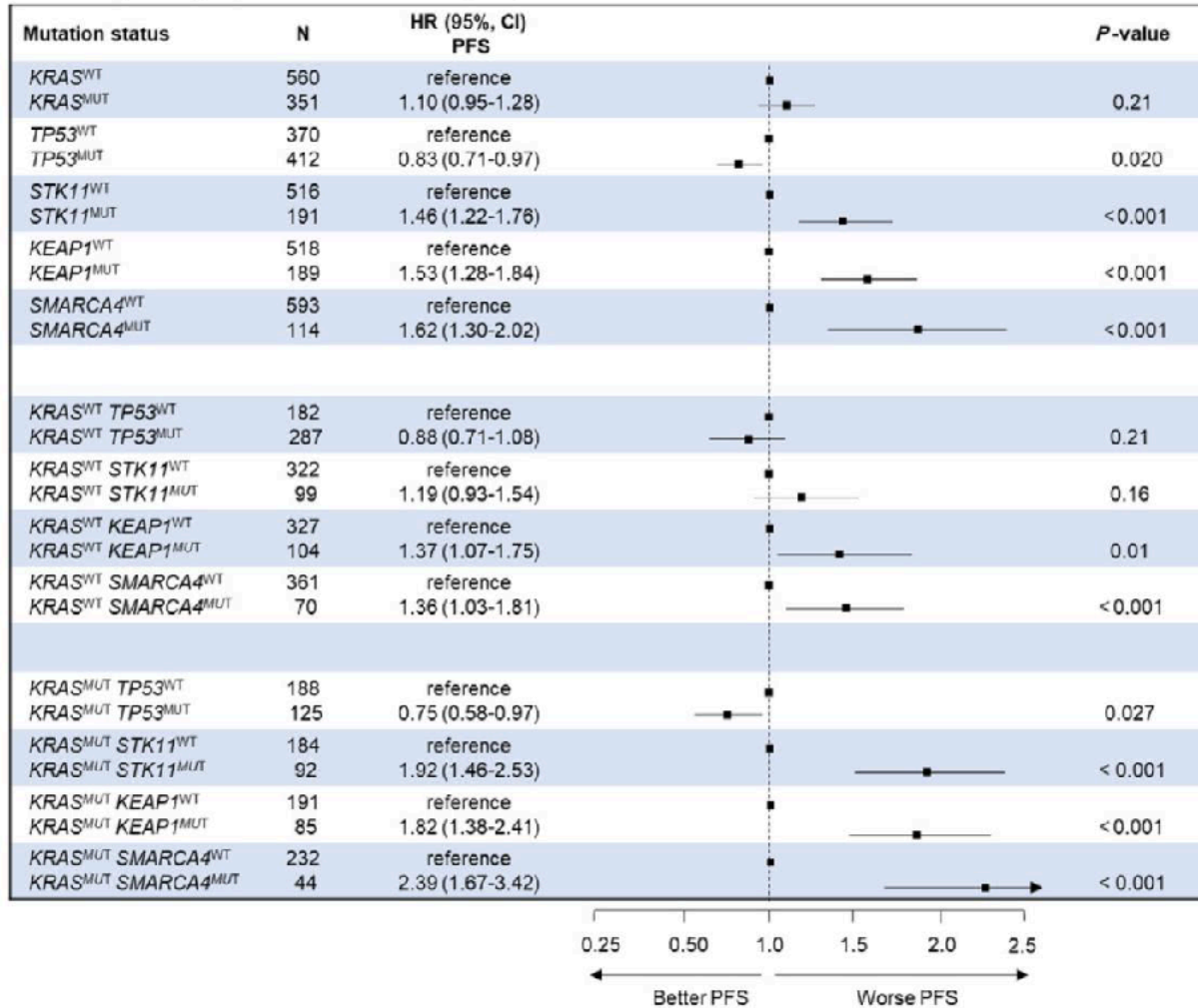
KEAP1: Es un regulador negativo de Nrf2 (regulador de respuesta a daño oxidativo). Pérdida en 20% de ADC, se relaciona con un microambiente tumoral bajo en CD8+ infiltrantes





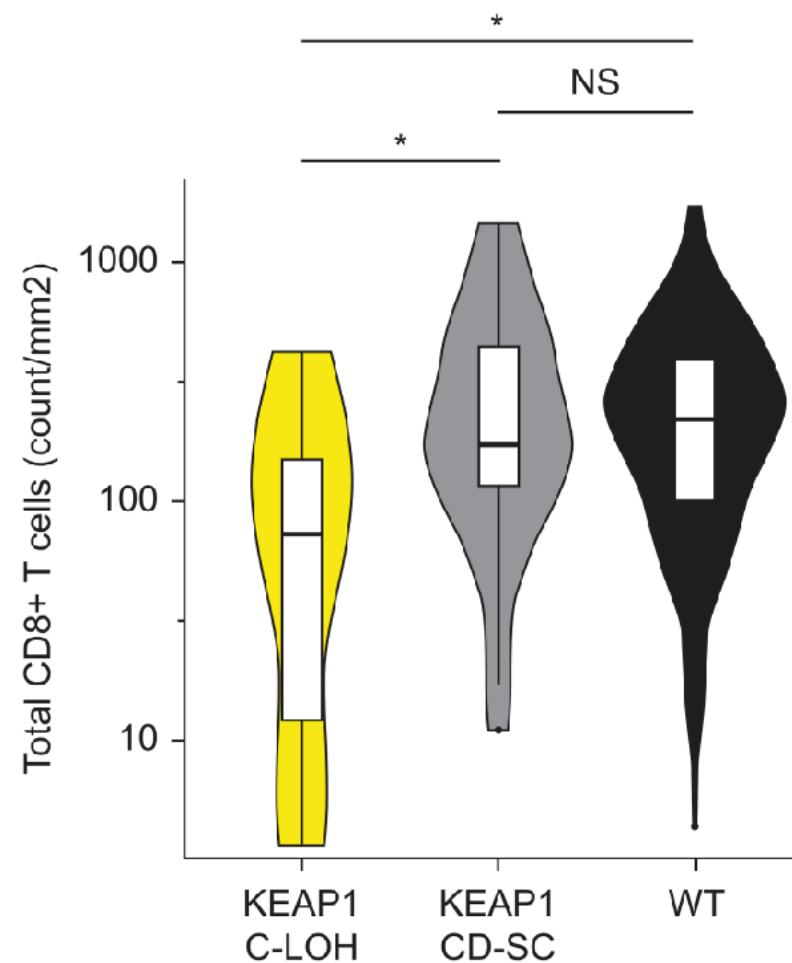
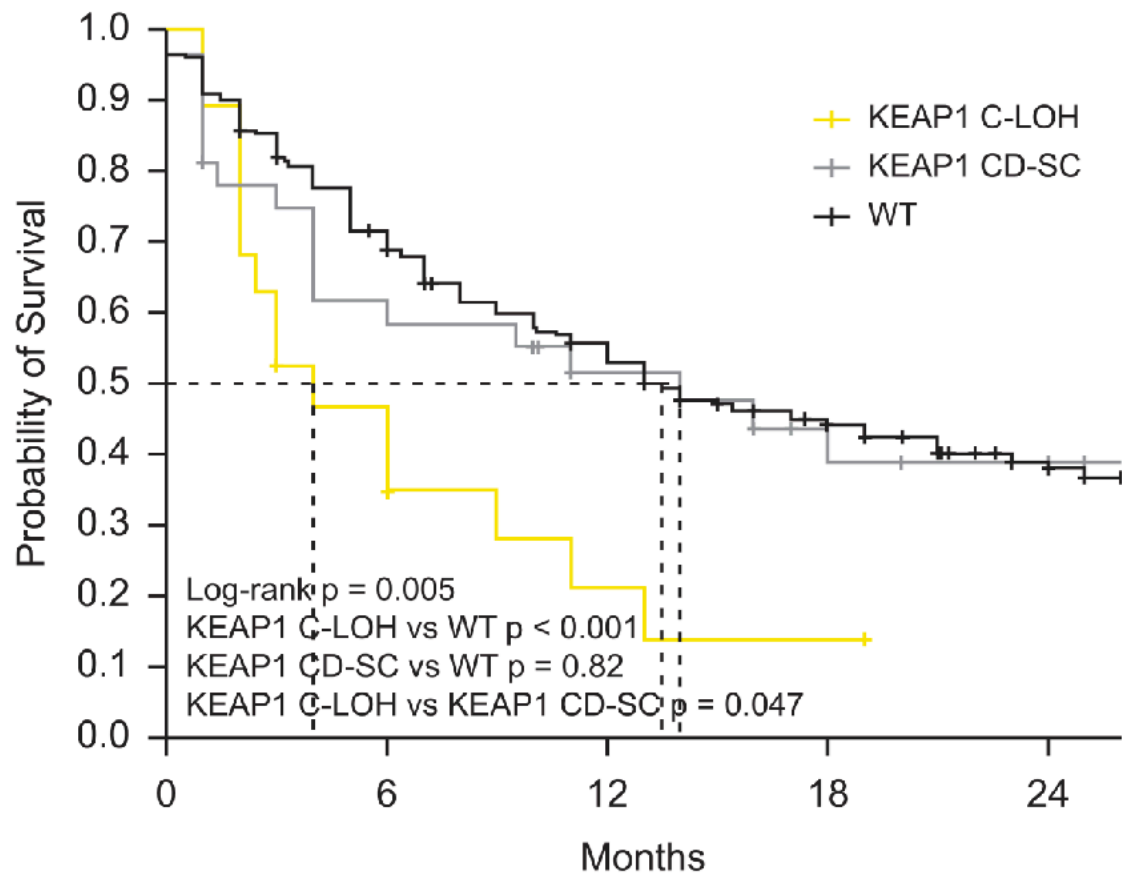
Mutaciones STK11/KEAP1 impactan en la eficacia de QT-CPIs

Forest-plot for progression-free survival (PFS)





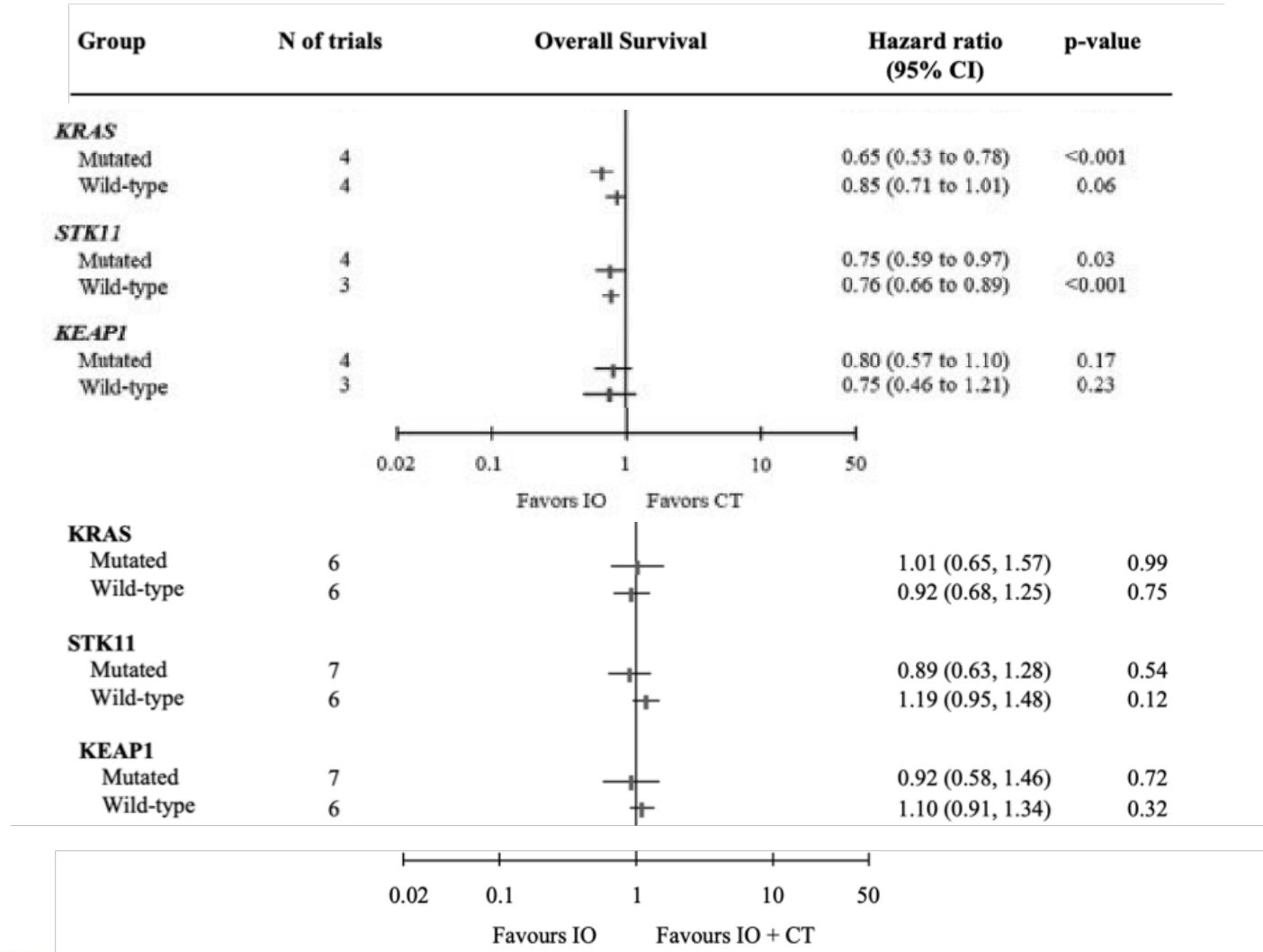
KEAP1 clonal + pérdida de heterocigosidad: Resistencia a inmunoterapia





Mutaciones STK11/KEAP1 ¿qué opción mejor, IO o QT-IO?

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





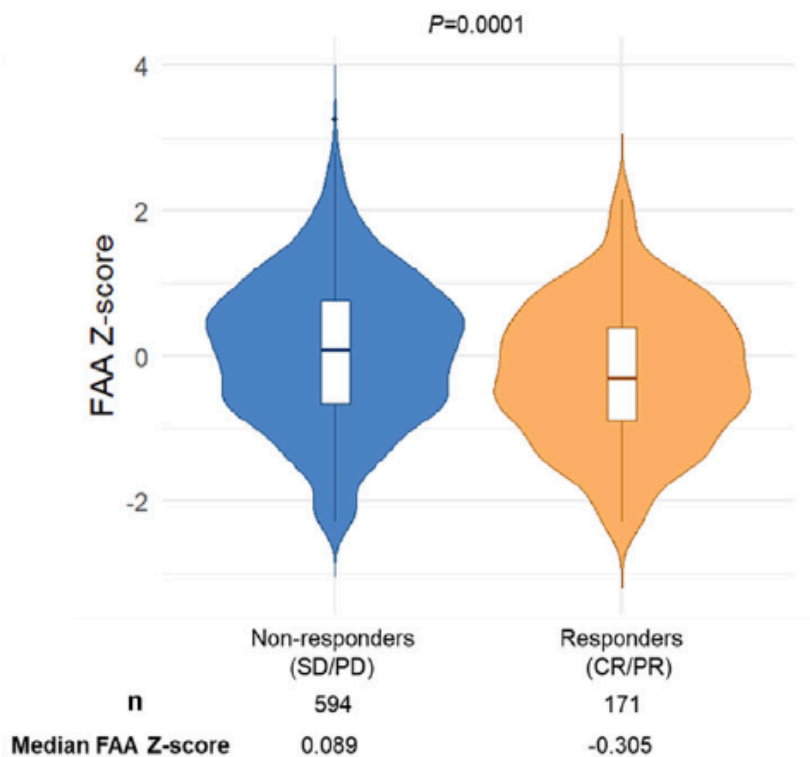
Aneuploidía como factor predictivo de respuesta

n= 2293, secuenciación cromosómica para definir aneuploidía

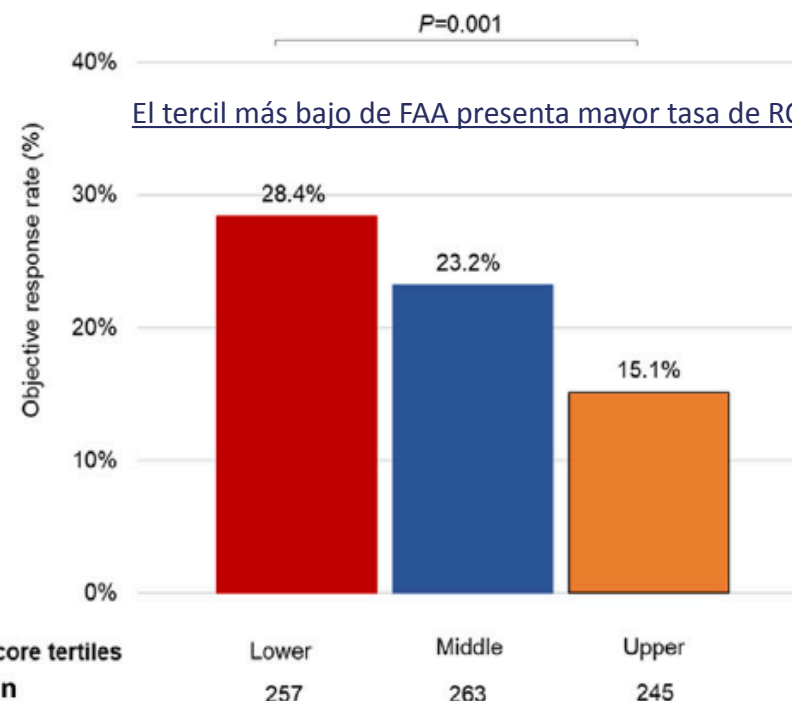
Score FAA (fraction of chromosomal arm alterations): 0-39 (número de brazos cromosómicos alterados)

→ Pequeños 1-12 y 16-20

→ Largos 13-15 y 21-22



La mediana de FAA es menor en pacientes respondedores





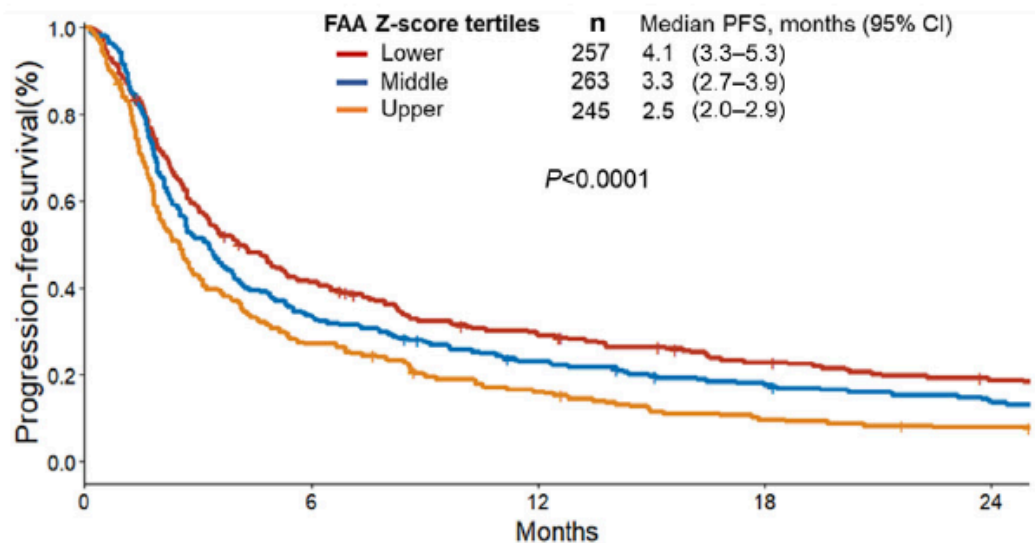
Aneuploidía como factor predictivo de supervivencia

n= 2293, secuenciación cromosómica para definir aneuploidía

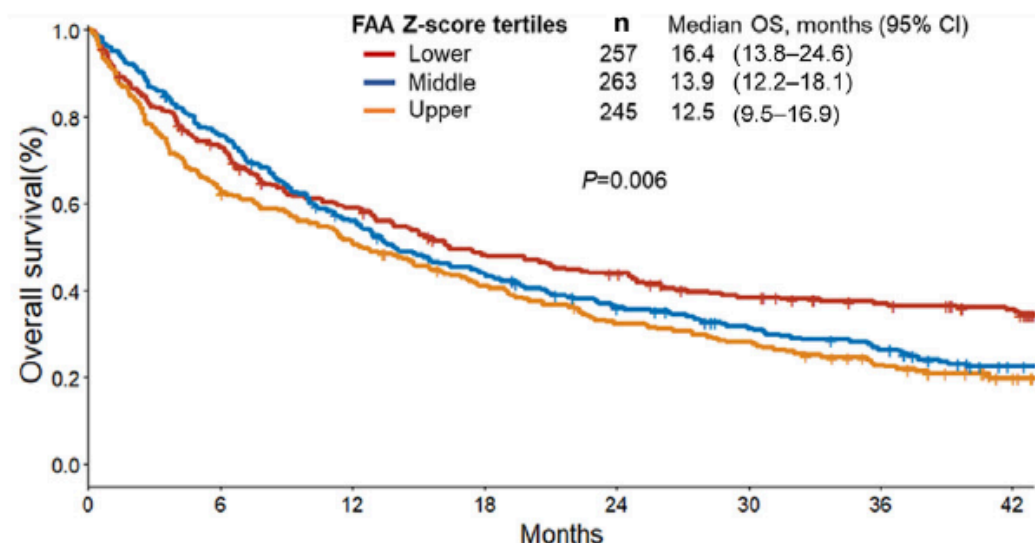
Score FAA (fraction of chromosomal arm alterations): 0-39 (número de brazos cromosómicos alterados)

→ Pequeños 1-12 y 16-20

→ Largos 13-15 y 21-22



Number at risk					
	0	6	12	18	24
Lower	257	104	70	52	41
Middle	263	89	58	44	33
Upper	245	66	38	22	17

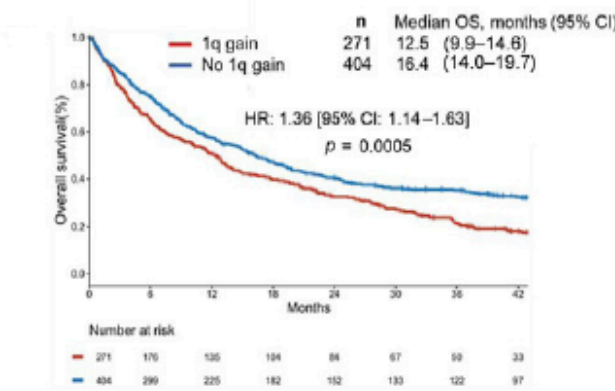
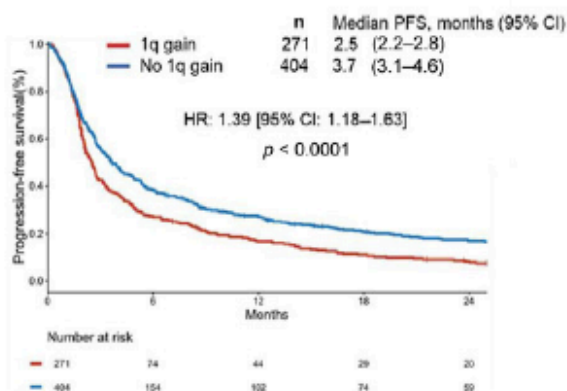
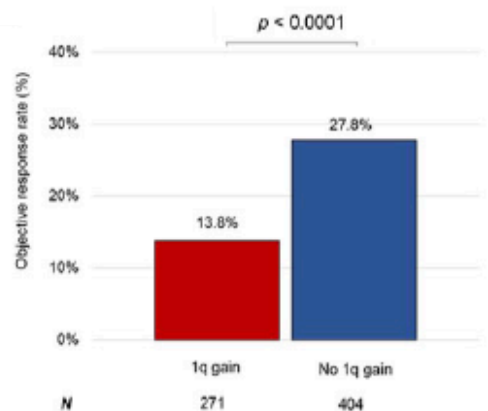
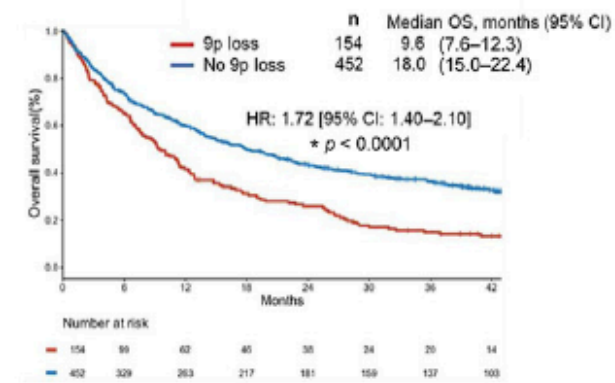
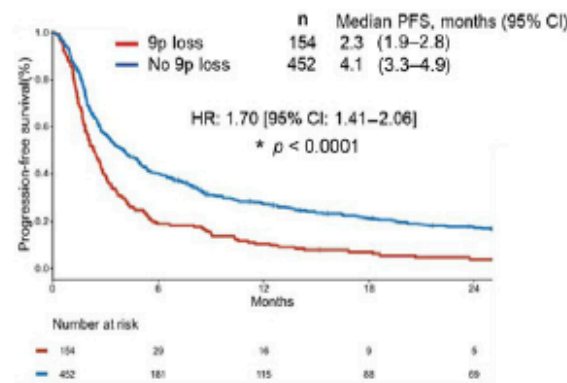
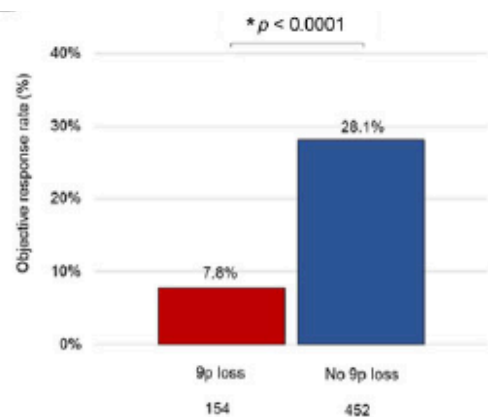
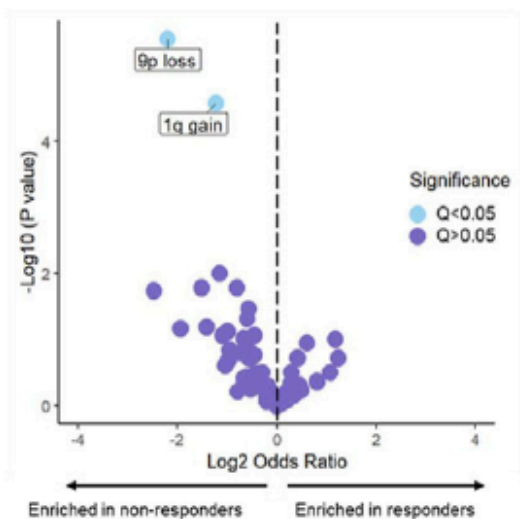


Number at risk								
	0	6	12	18	24	30	36	42
Lower	257	183	145	116	105	88	78	69
Middle	263	197	143	112	88	71	59	39
Upper	245	155	124	97	76	66	50	35



Pérdida de 9p* y ganancia 1q

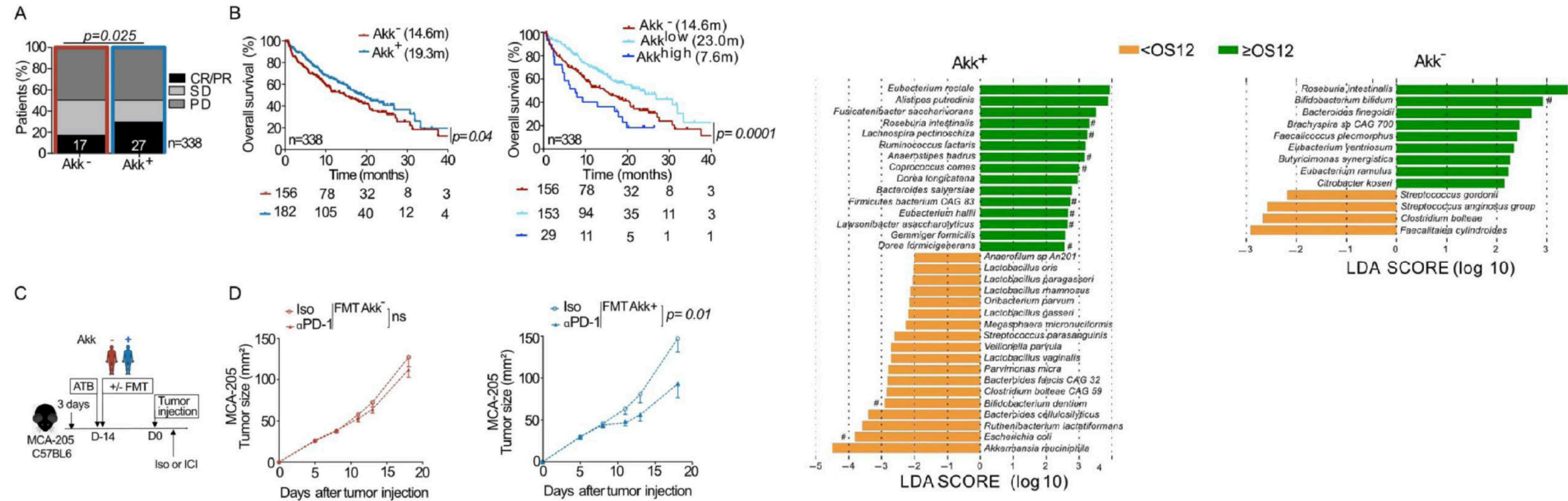
9p loss were enriched for higher TMB levels, KRAS wild-type status, lower PD-L1 expression levels and higher stage 1p gain was consistent with higher PD-L1 levels, lower KRAS mutations



*en 9p asienta CDKN2A



¿Hablamos de microbiota?





4

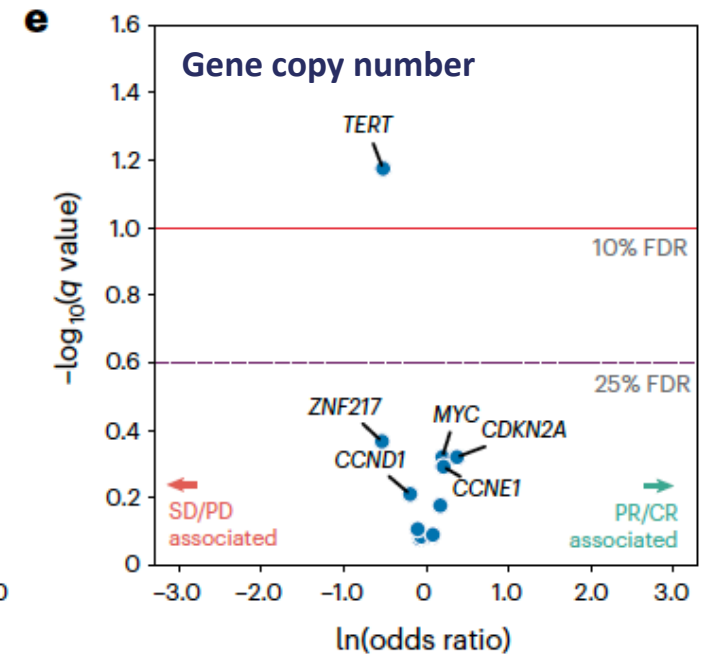
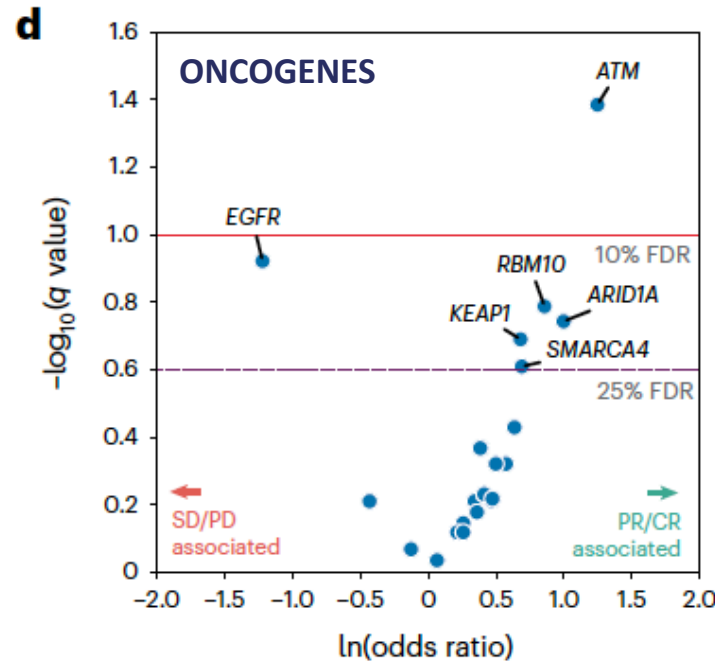
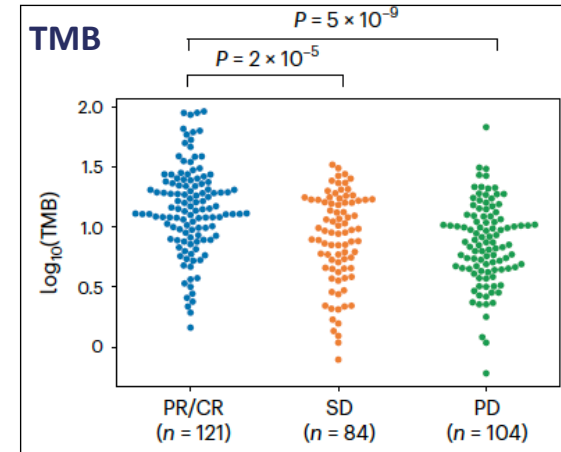
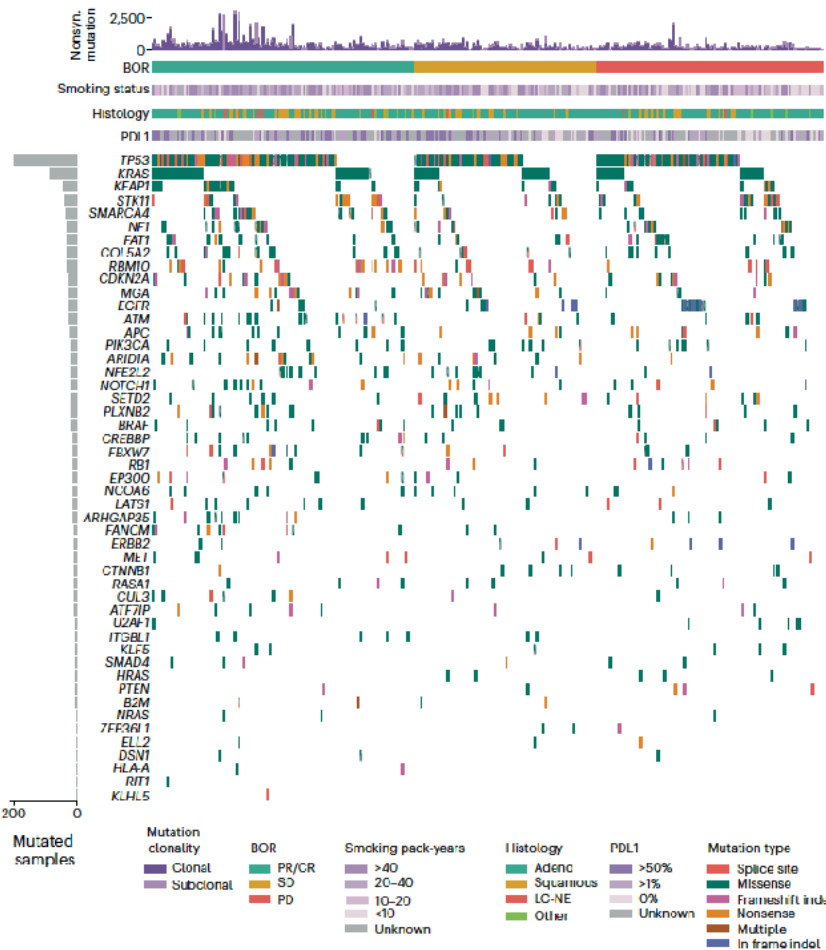
Nuevos biomarcadores



Transcriptomic correlates of ICI efficacy in NSCLC

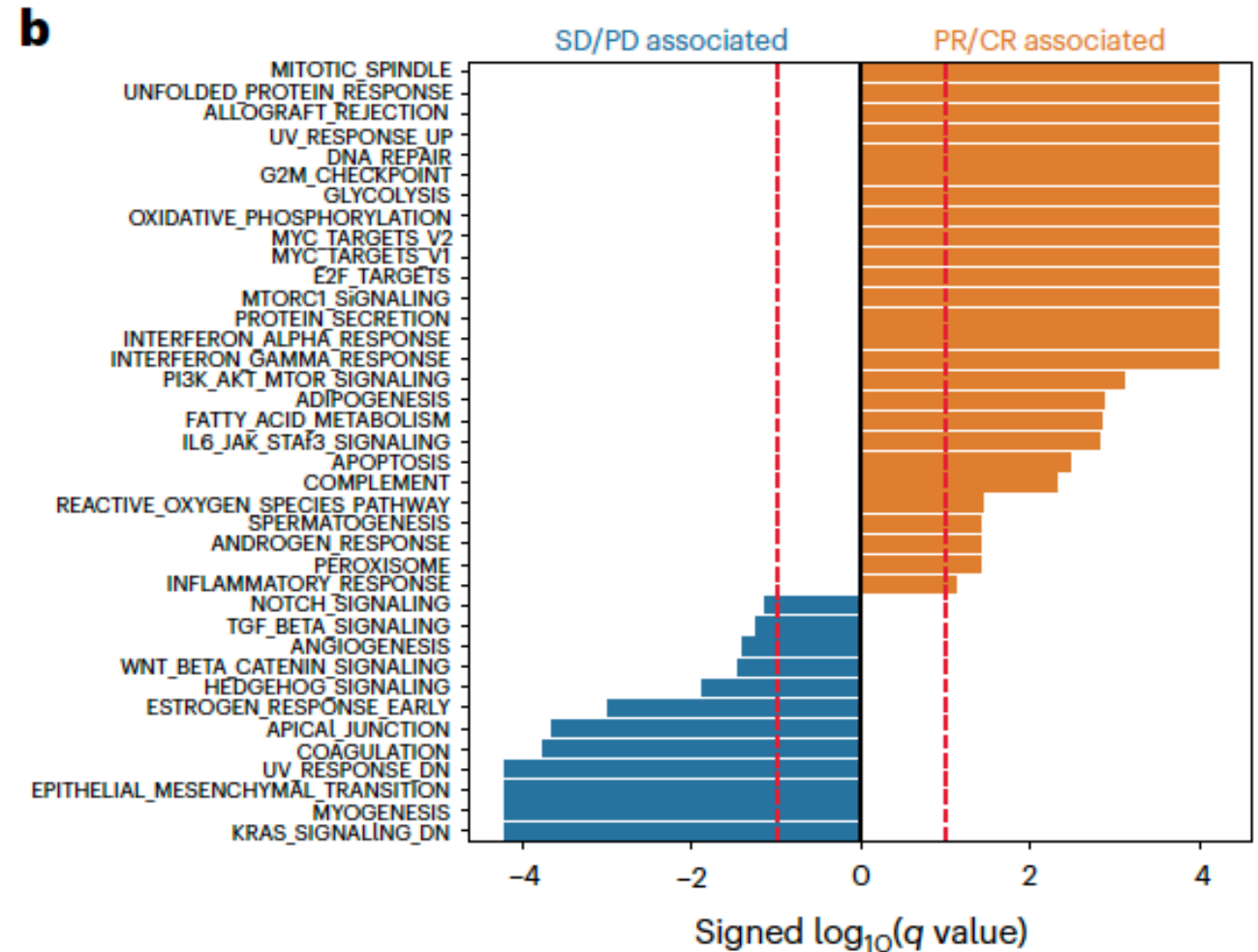
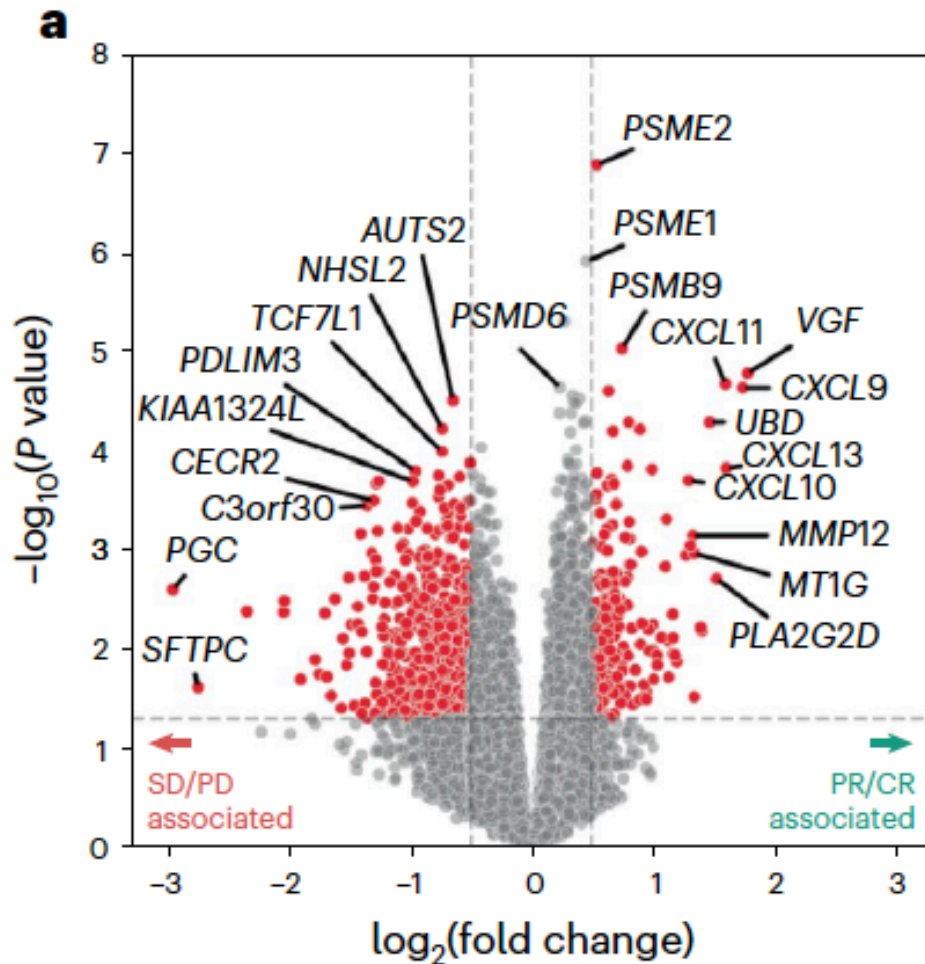
SU2C-MARK NSCLC cohort: 393 pts con WES + RNA-Seq

81% monoterapia; 17% + anti-CTLA4; 1% QT





Transcriptomic correlates of ICI efficacy in NSCLC





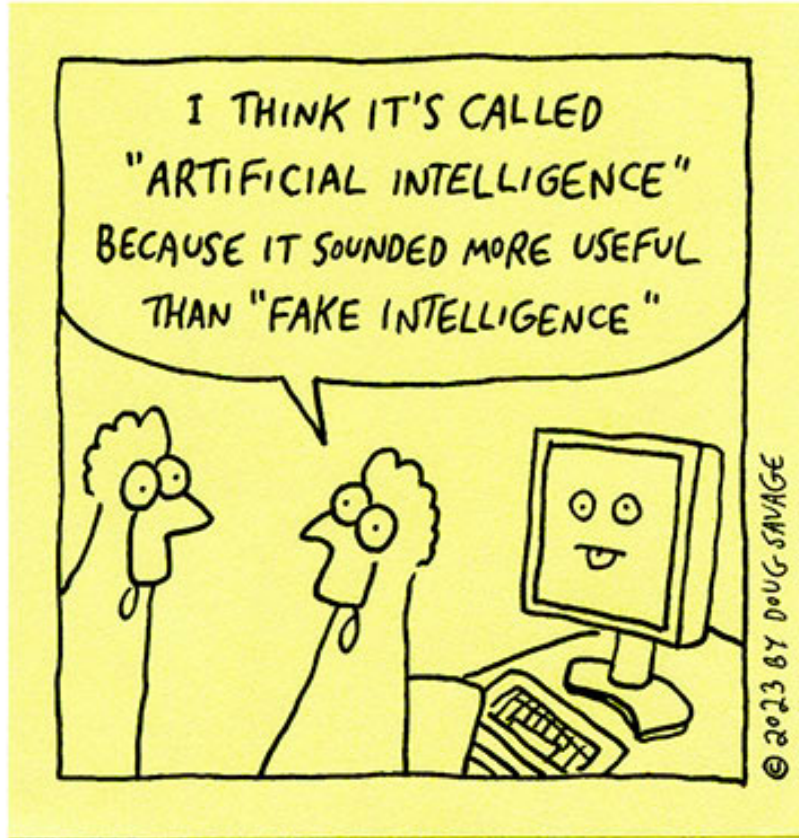
ARTIFICIAL INTELLIGENCE



ARTIFICIAL INTELLIGENCE

Savage Chickens

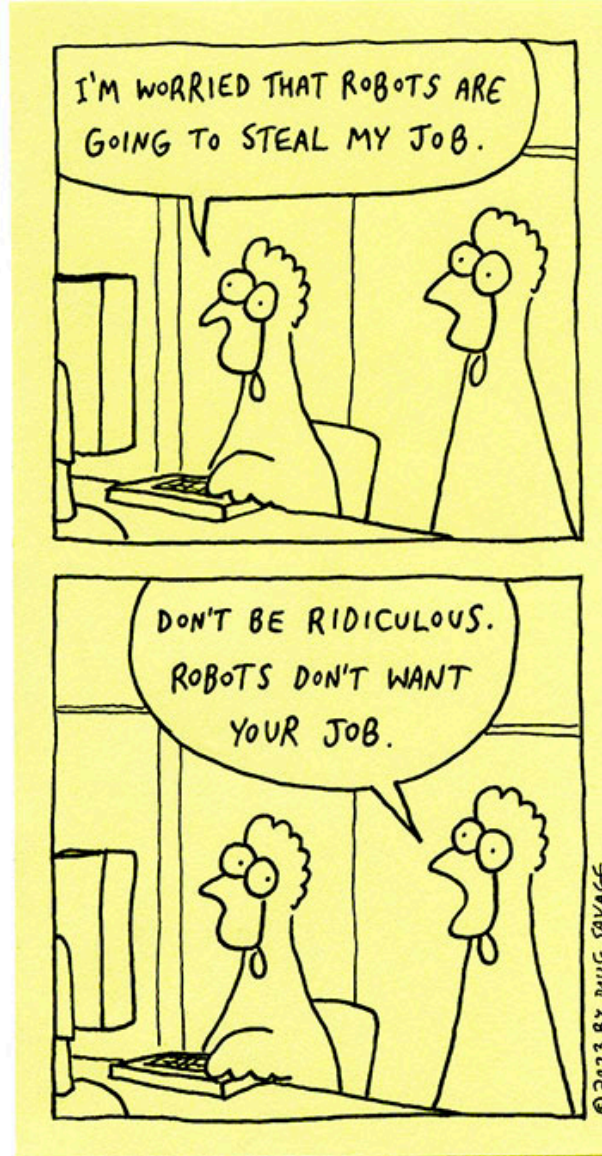
by Doug Savage



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Savage Chickens

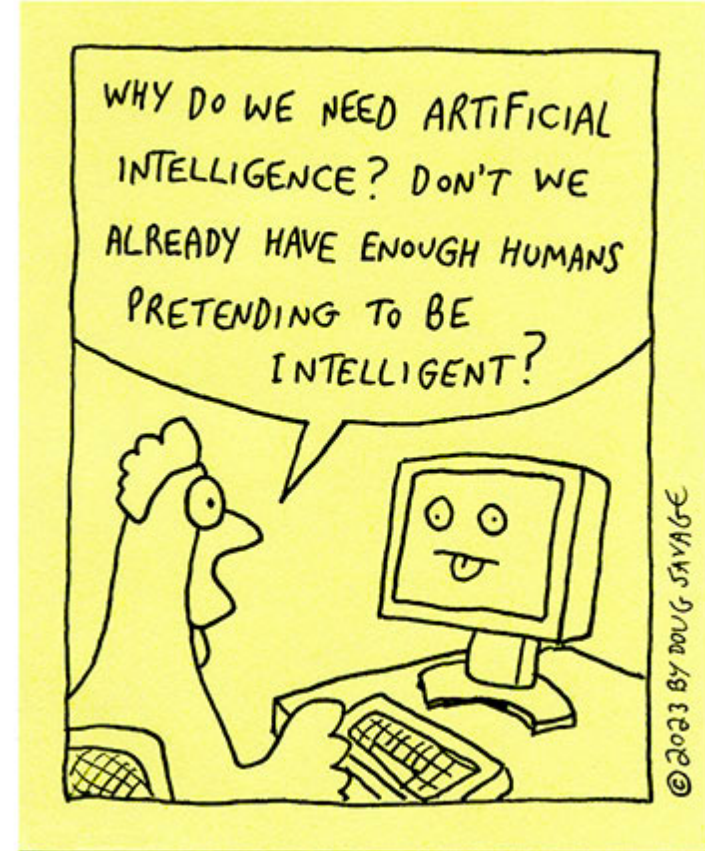
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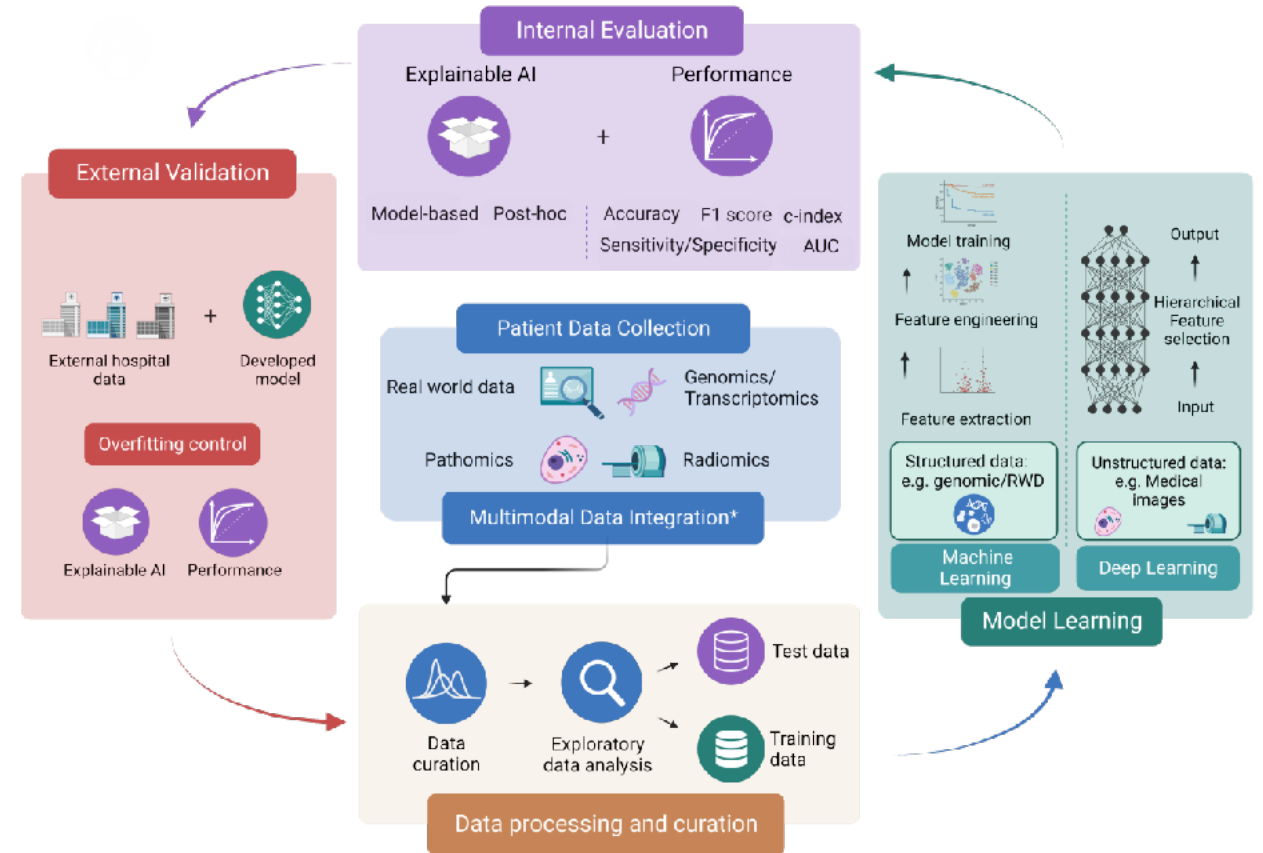


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ARTIFICIAL INTELLIGENCE: Revisión sistemática

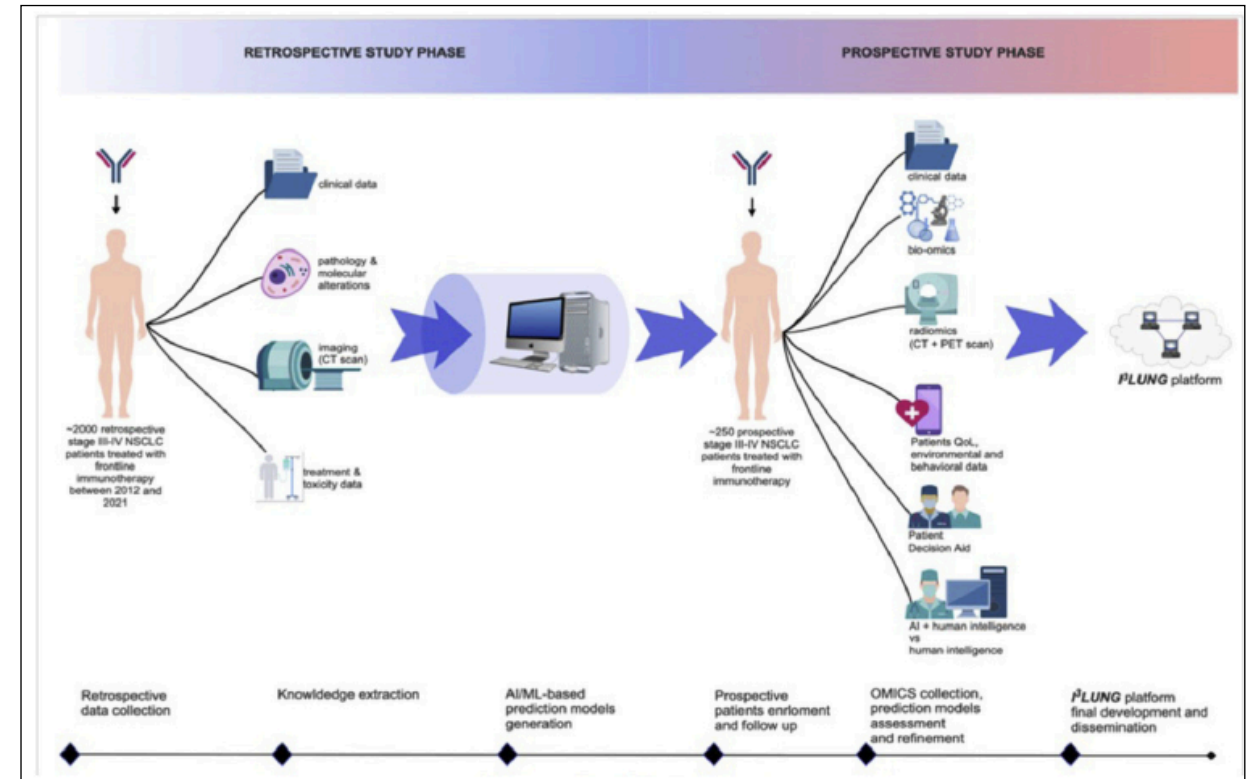
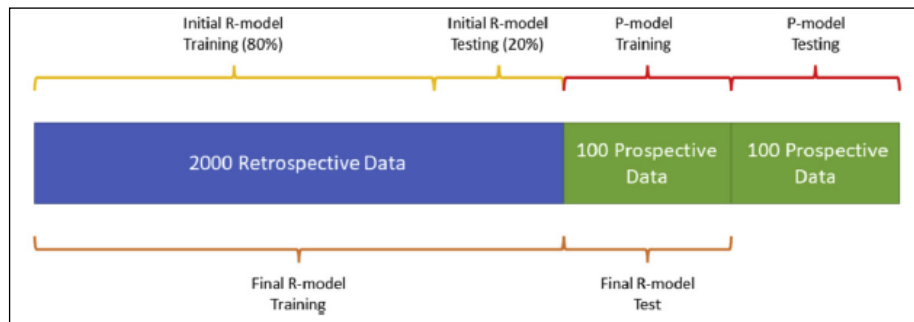
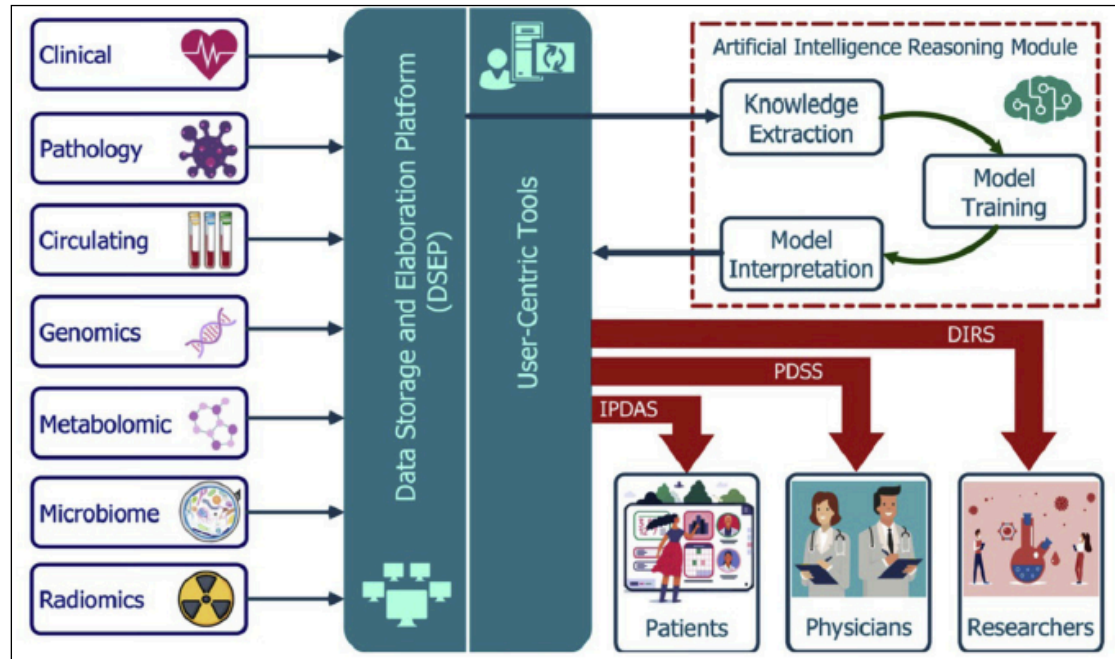
- 90 estudios (80% en el periodo 2021-2022)
- Los tumores más estudiados: CPNM (36%), melanoma (16%), pan-tumor 25%
- 37 estudios incluyen genómica, 20 radiómica, 8 patómica, 20 RWD y 5 multimodales
- Muy prometedores, pero falta de evidencia suficiente para implementar cambios en la práctica clínica
- Desafíos: Escasez de datos, estructura, heterogeneidad de los modelos, estandarización, guías clínicas, integridad de los modelos y generalización, diseño...

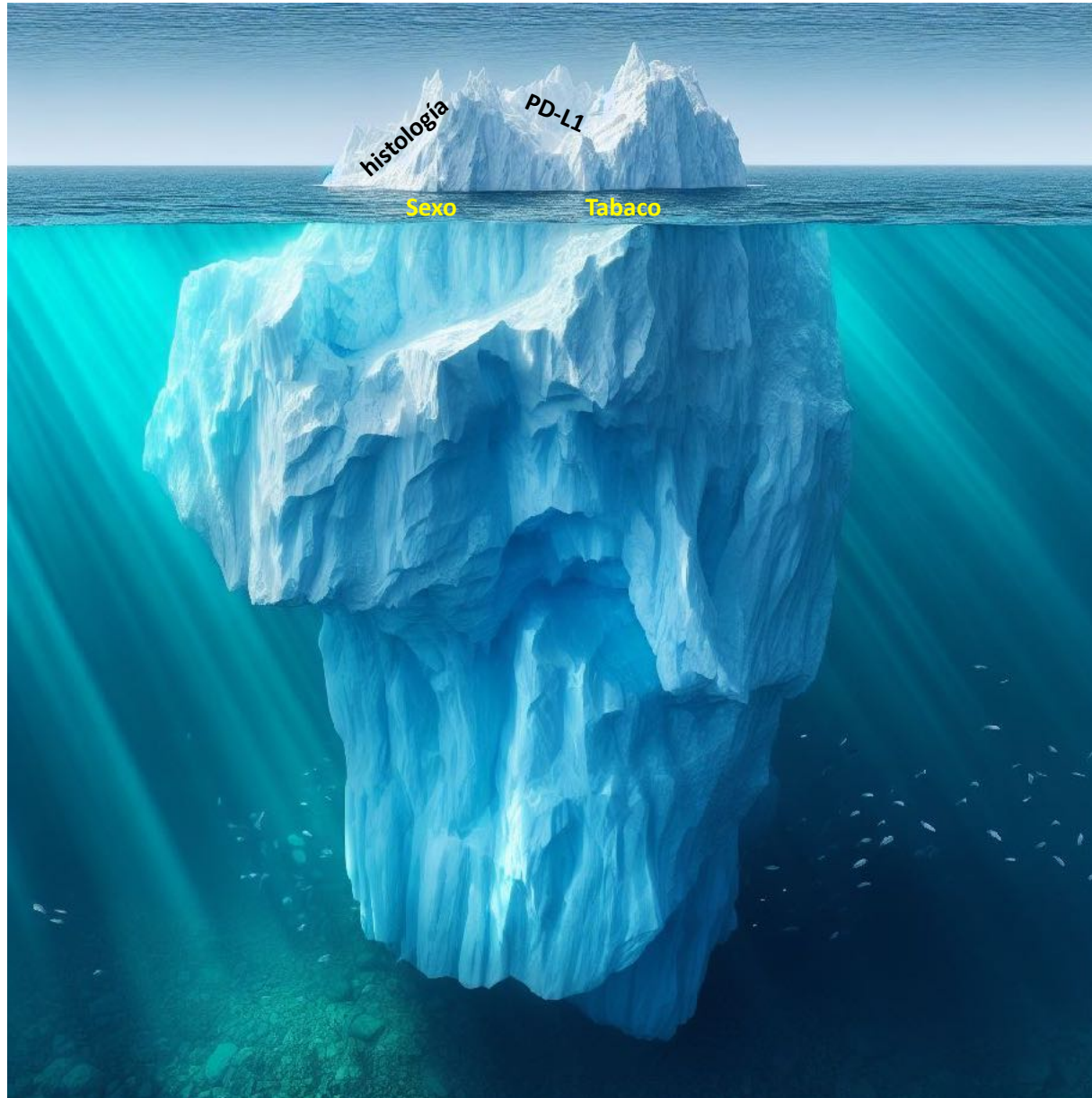


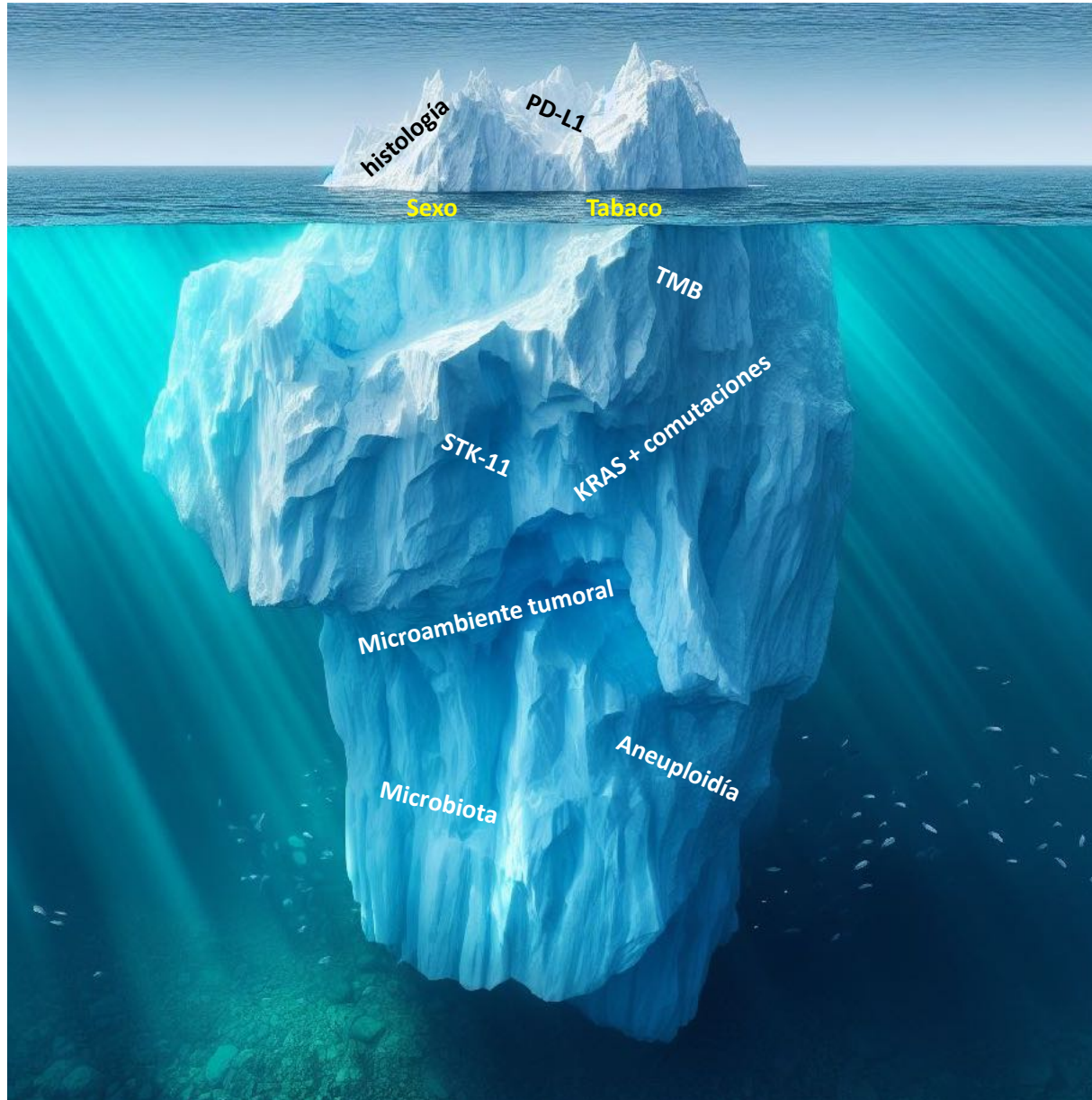


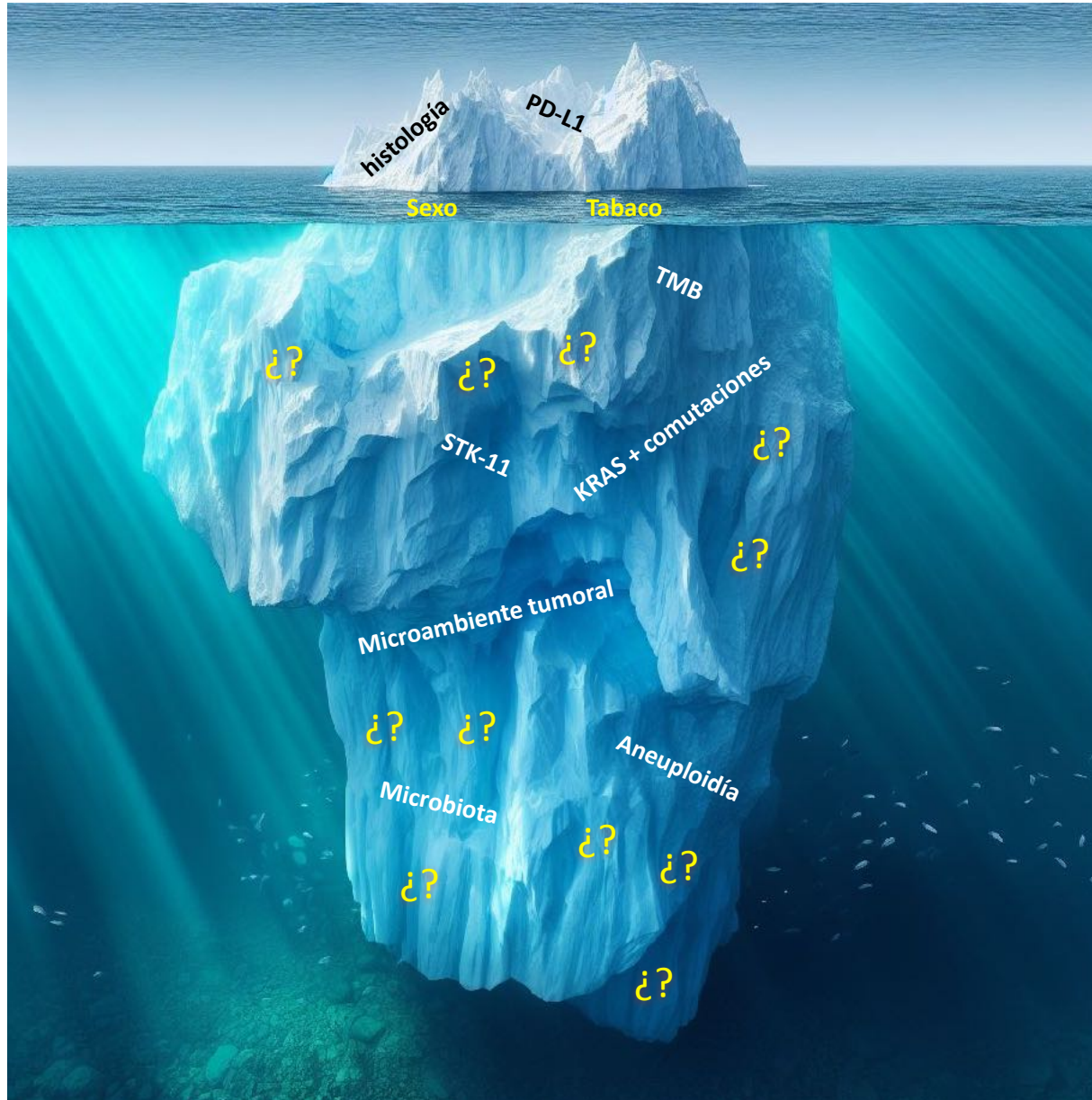
ARTIFICIAL INTELLIGENCE?: Estudio observacional

- I3LUNG is an international, multicenter, retrospective and prospective, observational study of patients with aNSCLC treated with IO, entirely funded by European Union (EU) under the Horizon 2020 (H2020) program



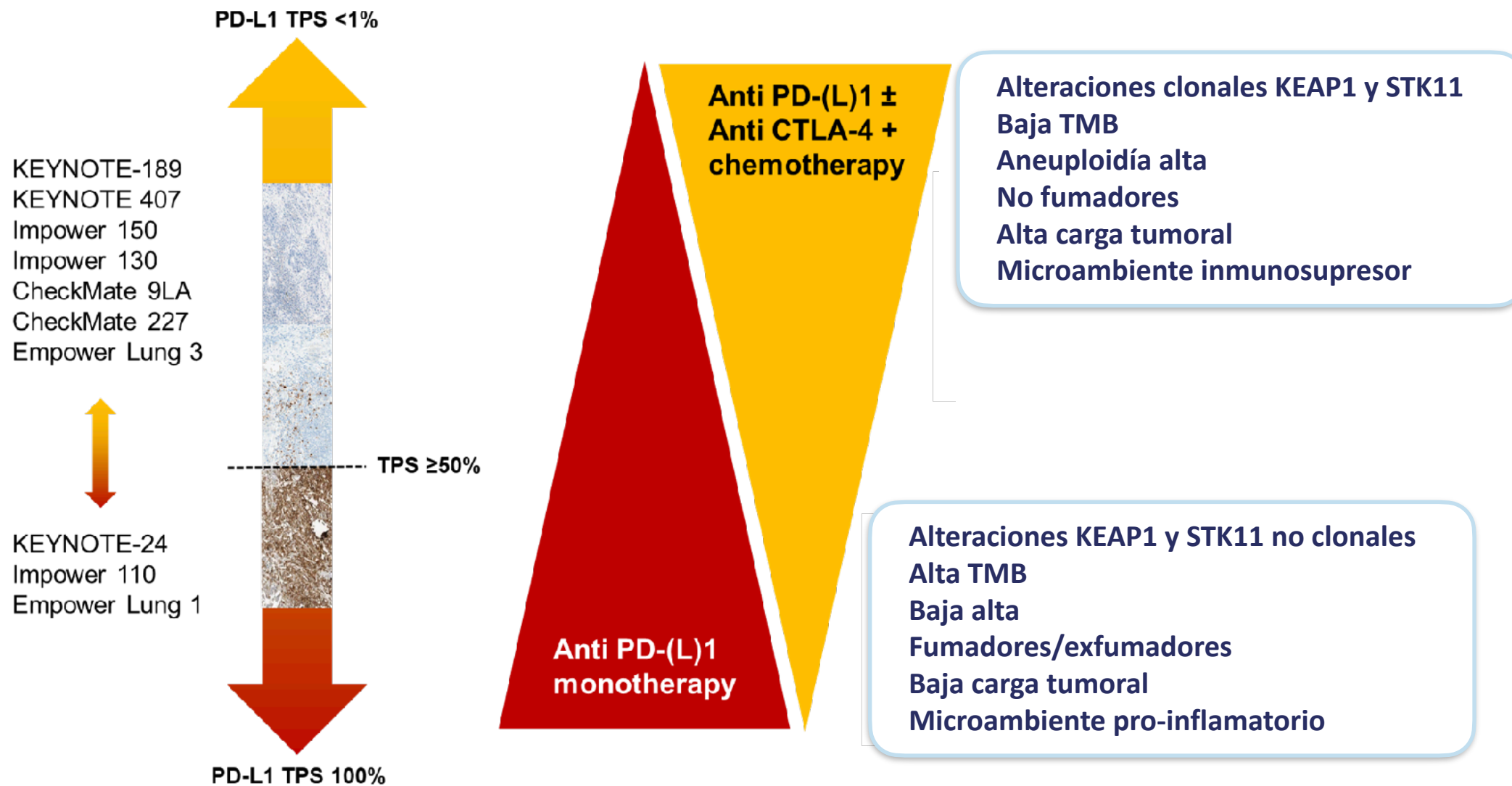








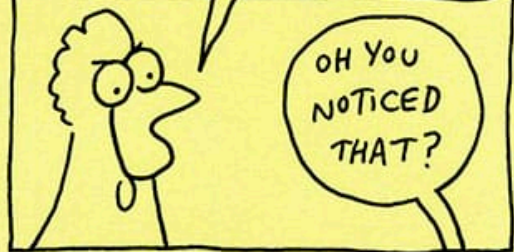
Optimizing treatment selection for immunotherapies in NSCLC



Savage Chickens

by Doug Savage

WE NEED TO TALK ABOUT YOU FALLING ASLEEP DURING THE MEETING.



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Fundación
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Muchas Gracias

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