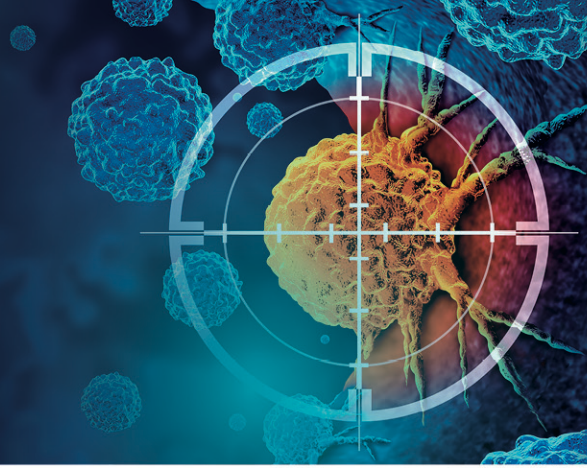
XVIII SIMPOSIUM

BASES BIOLÓGICAS DEL CÁNCER E INNOVACIÓN TERAPÉUTICA

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER



Cáncer de pulmón: ¿Qué biomarcadores *cambian* nuestra decisión cada día?

Dr. Rafael López Castro, Hospital Clínico Universitario de Valladolid

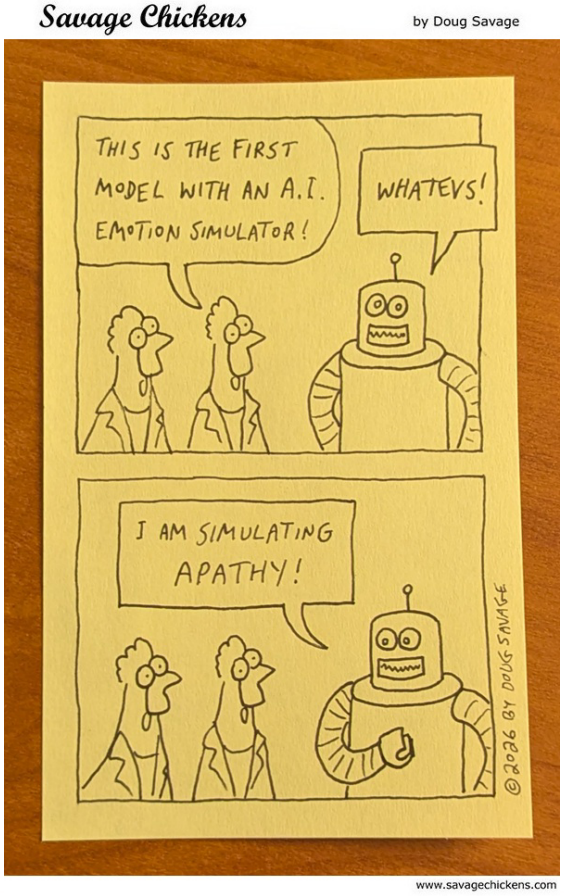
Conflictos de interés

- **Empleo**
  Sanidad de Castilla y León (SACYL)
- **Honorarios como conferenciante**
  Pierre-Fabre, Takeda, AstraZeneca, BMS, Roche, Pfizer, Sun Pharma
- **Consultoría**
  Roche, Astra-Zeneca, Takeda, Amgen, Johnson&Johnson, Pfizer, BeOne
- **Proyectos de investigación/EECC financiados**
  Roche, GSK, PharmaMar, AstraZeneca
- **Viaje a reuniones-congresos y alojamiento**
  Takeda, Pfizer, Pierre-Fabre, Roche, MSD
- **Acciones cotizadas**
  Ninguna

Declaración

- Las opiniones emitidas por el autor de esta presentación deben considerarse dentro de un contexto educacional y no constituyen recomendaciones clínicas ni sustituyen el juicio clínico independiente, las guías vigentes y la individualización terapéutica.

- Para la elaboración de esta presentación se han empleado herramientas de IA con fines fundamentalmente ilustrativos, bibliográficos y de corrección de estilo



¿Para qué nos sirven los biomarcadores?



Imagen creada con Google Gemini

¿Para qué nos sirven los biomarcadores?



Imagen creada con Google Gemini

La búsqueda de “esos” biomarcadores

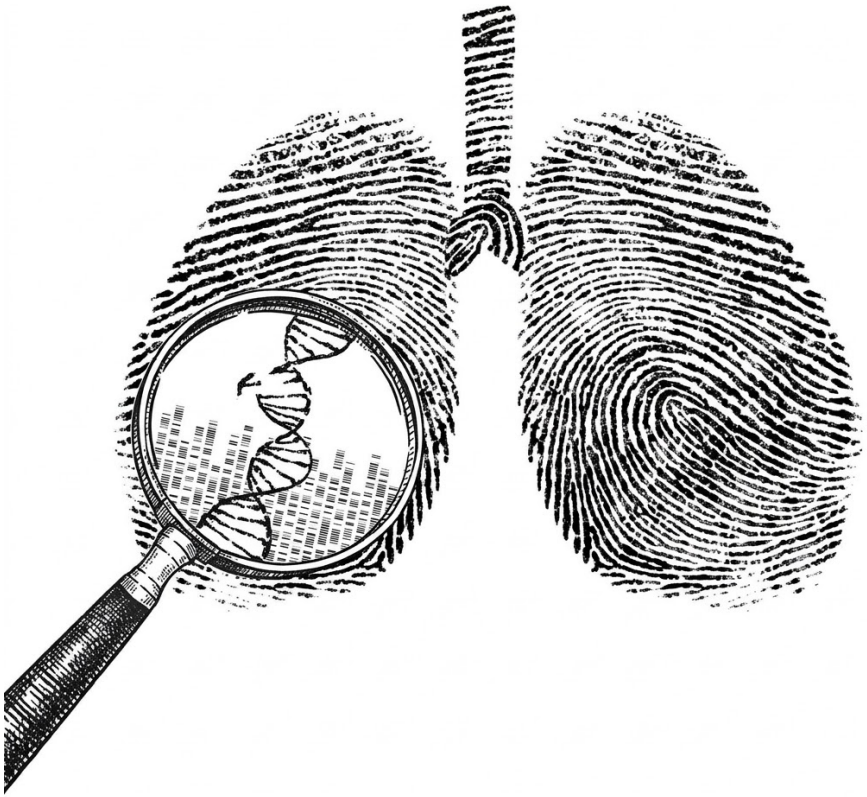
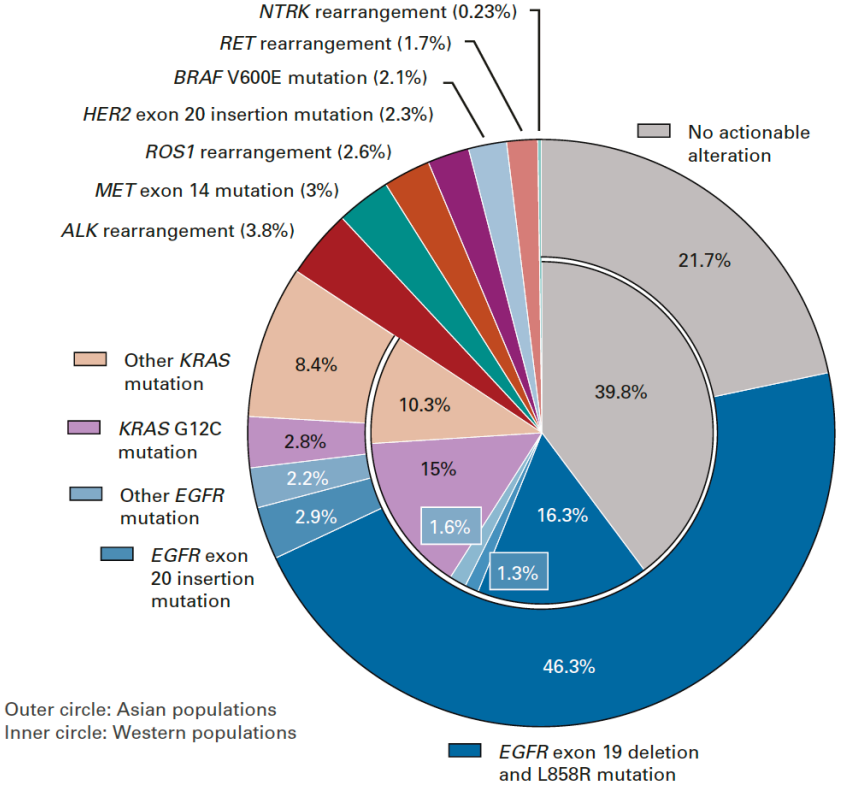
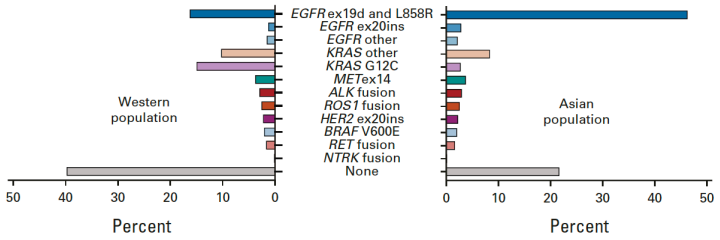


Imagen creada con Google Gemini

Alteraciones *driver* en CPNM

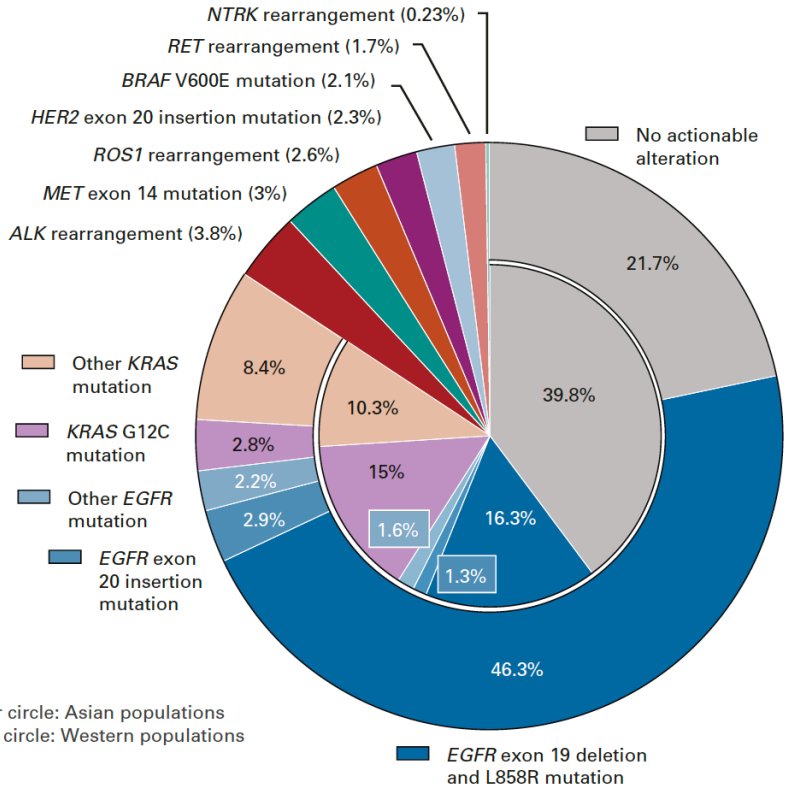


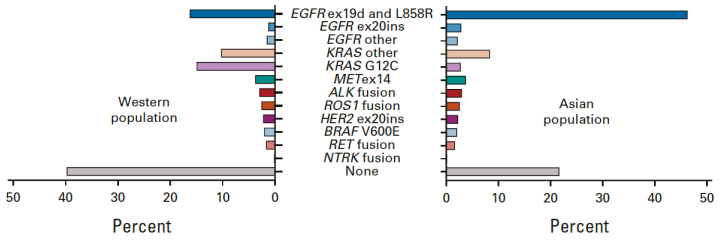


EGFR comunes	16.3%
EGFR ex20ins	1.6%
EGFR otros	1.3%
ALK	3.8%
KRAS G12C	15 %
KRAS No-G12C	10.3%
METex14	3 %
ROS1	2.6%
BRAF V600E	2.1%
RET	1.7%
NTRK	0.23%
HER2 ex20ins	2.3%
TOTAL:	**60.2%**
Resto:	**39.8%**

Tan A et al. JCO 2022

Alteraciones *driver* en CPNM tratables en 1L*



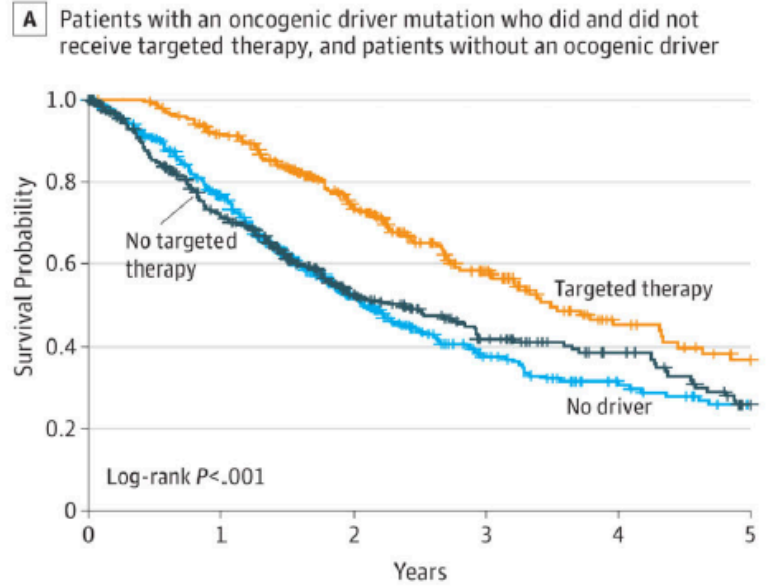


EGFR comunes	16.3%
~~EGFR ex20ins~~	~~1.6%~~
EGFR otros	1.3%
ALK	3.8%
~~KRAS G12C~~	~~15 %~~
~~KRAS No-G12C~~	~~10.3%~~
~~METex14~~	~~3 %~~
ROS1	2.6%
BRAF V600E	2.1%
RET	1.7%
NTRK	0.23%
~~HER2 ex20ins~~	~~2.3%~~
TOTAL:	**28.03%**
Resto:	**71.97%**

*** Con terapia financiada en indicación 1L en SNS**

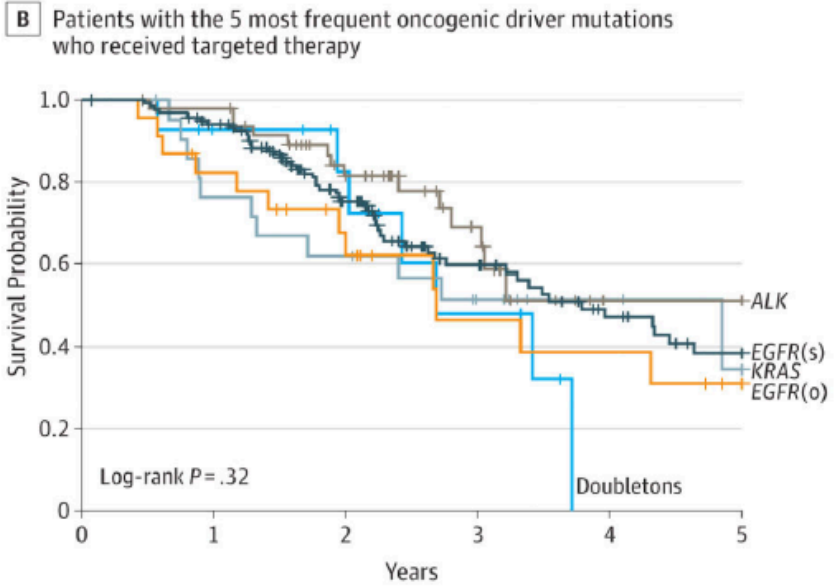
Tan A et al. JCO 2022

Diagnosticar y tratar el driver tiene valor pronóstico



No. at risk

Patients with oncogenic driver						
No targeted therapy	318	205	110	64	43	20
Targeted therapy	260	225	143	72	36	23
Patients with no driver	360	250	122	59	36	23



No. at risk by oncogenic driver

EGFR(s)	136	122	72	38	24	16
EGFR(o)	23	18	12	6	5	2
ALK	49	46	31	14	2	2
KRAS	22	16	13	8	4	2
Doubletons	14	11	8	4		

Kris MG et al. JAMA. 2014 May 21; 311(19): 1998–2006.

Implicaciones clínicas en enfermedad con *driver:* afectación SNC

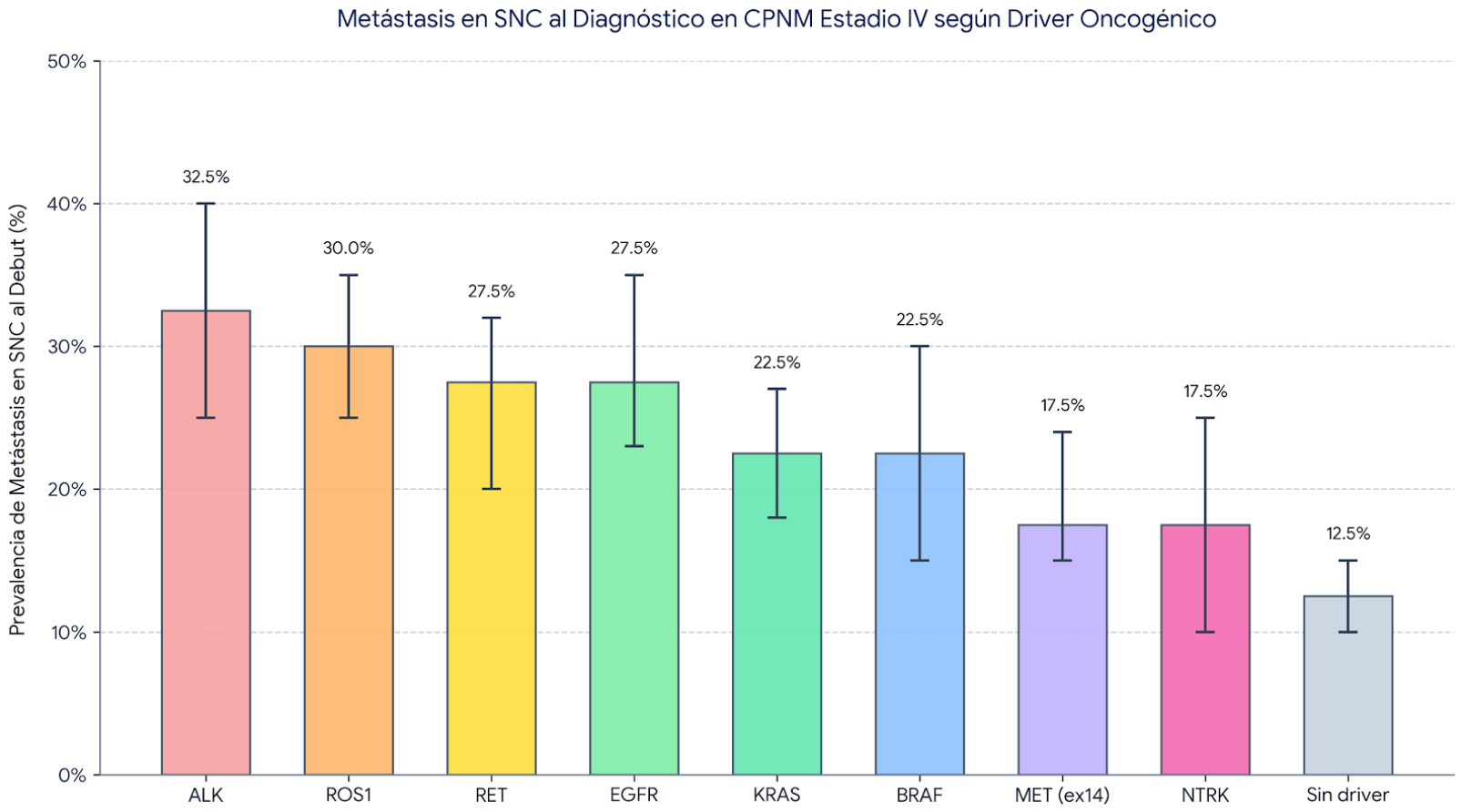
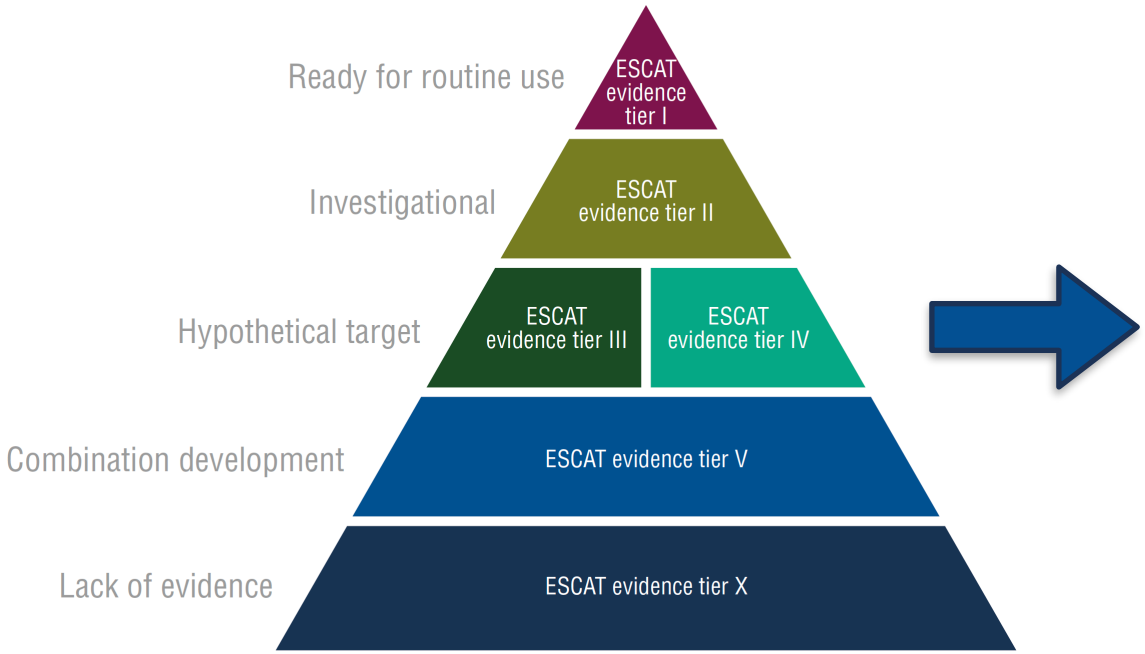


Imagen creada con Google Gemini basándose en datos de ensayos clínicos con inhibidores de cada diana. Limitación metodológica en los % debido al propio diseño de los estudios

ESCAT: ESMO Scale of Clinical Actionability for molecular Targets



Gene	Alteration	ESCAT
	ESCAT TIER EVIDENCE I	
EGFR	Common mutations (Del19, L858R)	IA
	Acquired T790M exon 20	IA
	Uncommon (G719X exon 18, L861Q exon 21, S768I exon 20)	IB
EGFR	Exon 20 insertion	IA ↑
ALK	Fusions	IA
ROS1	Fusions	IA/IB
BRAF	Mutations (V600E)	IA/IB IA ↑
RET	Fusions	IB
KRAS^{G12C}	Mutations ex 14 skipping	IA/IB ↑
ERBB2 (HER2)	Mutations	IB ↑
NTRK 1/2/3	Fusions	IC
	ESCAT TIER EVIDENCE II-III	
MET	Focal amplifications (de novo/acquired resistance)	IIB
ERBB2	Amplifications	IIB
NRG1	Fusions	IIB/IIIA
BRCA 1/2	Mutations	IIIA
PIK3CA	Hotspot mutations	IIIA/IV

Basado en Mateo J, et al. Annals of Oncology 2018;29(9):1895-1902; Mosele F, et al. Ann Oncol 2020; Adaptación realizada con Google Gemini

Lo más importante: El diagnóstico

Recommendations for the use of next-generation sequencing (NGS) for patients with advanced cancer in 2024: a report from the ESMO Precision Medicine Working Group

Gene	Alteration	Estimated prevalence	ESCAT score	Drug class matched
EGFR	• Common mutations • Acquired T790M • Exon 20 insertions • Uncommon mutations	• 15% Caucasian/30% Asian • 60% (after 1st gen TKI) • 2% • 10%	IA IA IA IB	• 3rd gen EGFR TKI (+/- CT); EGFR-MET biAb + 3rd gen TKI • 3rd gen TKI • EGFR-MET biAb + CT • 2nd / 3rd gen EGFR TKI
ALK	Fusions	5%	IA	ALK TKI
ROS1	Fusions	1-2%	IA	ROS1 TKI
RET	Fusions	1-2%	IA	RET TKI
NTRK1/2/3	Fusions	<1%	IC	TRK inhibitors
KRAS	Mutations (p. G!2C)	12%	IA	KRAS G12C TKI
BRAF	Mutations (p. V600E)	2%	IB	BRAF TKI + MEK TKI
MET	Mutations exon14 skipping	3%	IB	MET TKI
ERBB2	Hotspot mutations	3%	IIB	• TKI • Anti-HER2 ADC
MET	Focal amplifications	• 5% as primary • 15% as AR on EGFR TKIs	IIB	• MET TKI • MET TKI + 3rd gen EGFR TKI; EGFR-MET biAb + 3rd gen EGFR TKI
NRG1	Fusions	<1%	IIB	Anti-HER2/HER3 biAb

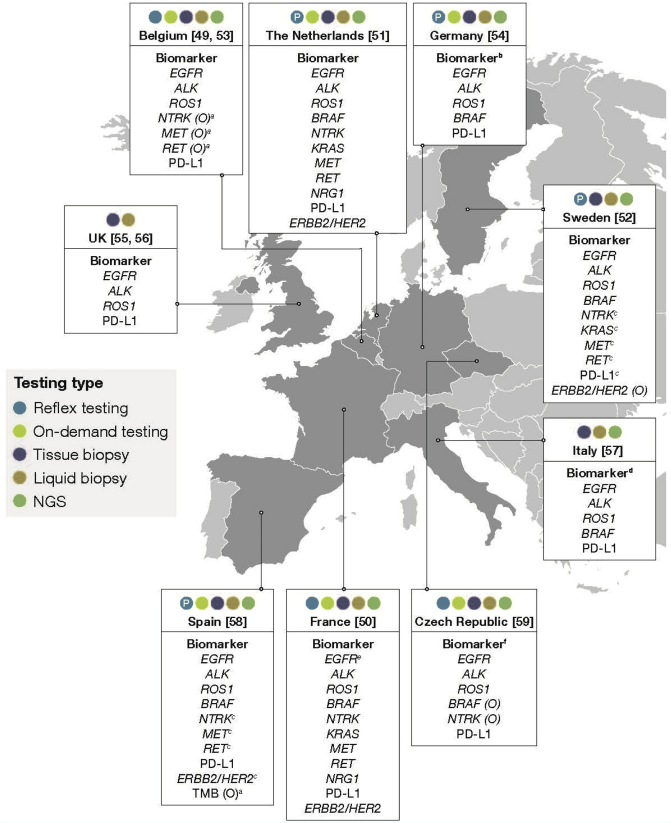
Adaptado de Mosele MF et al. Ann Oncol. 2024 Jul;35(7):588-606

Situación actual (EU)

The evolving landscape of biomarker testing for non-small cell lung cancer in Europe

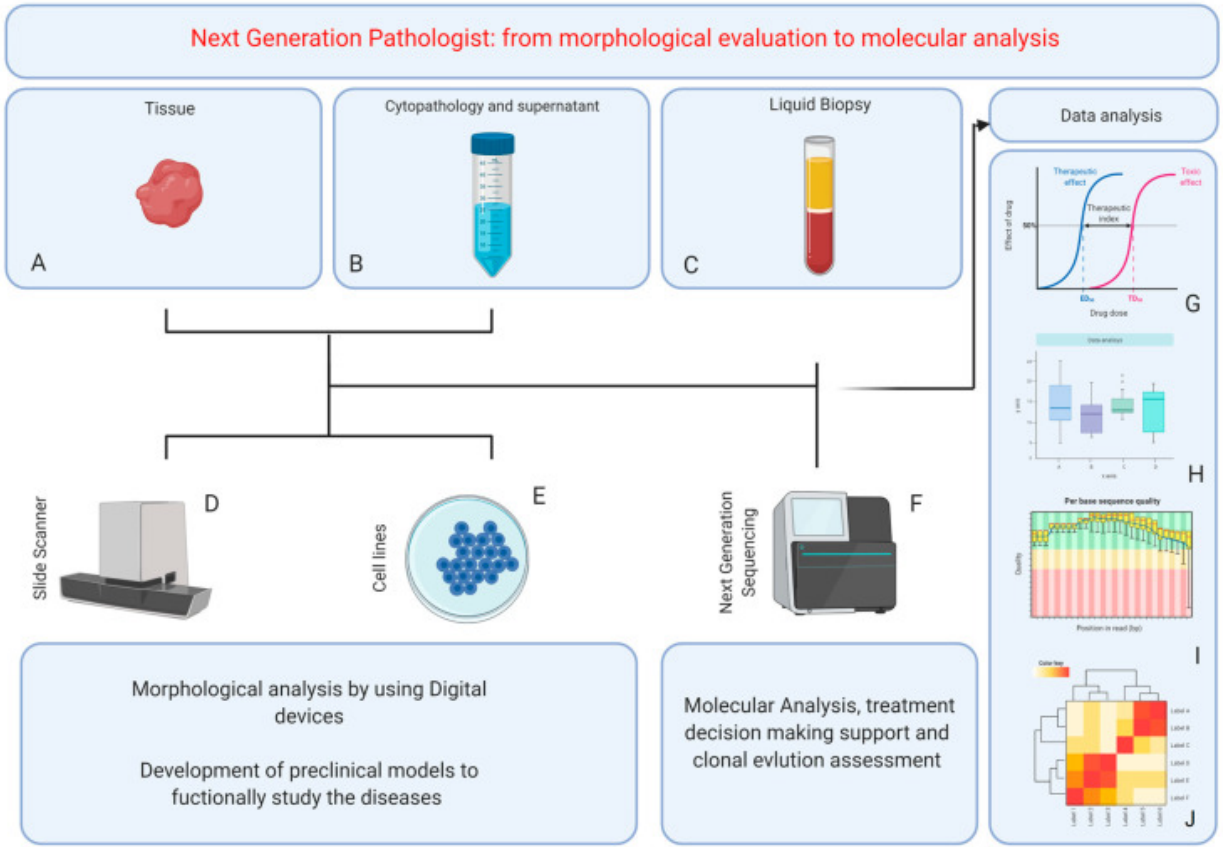
Country-specific guidelines for biomarker testing in advanced or recurrent NSCLC

How are these guidelines translated into clinical practice?



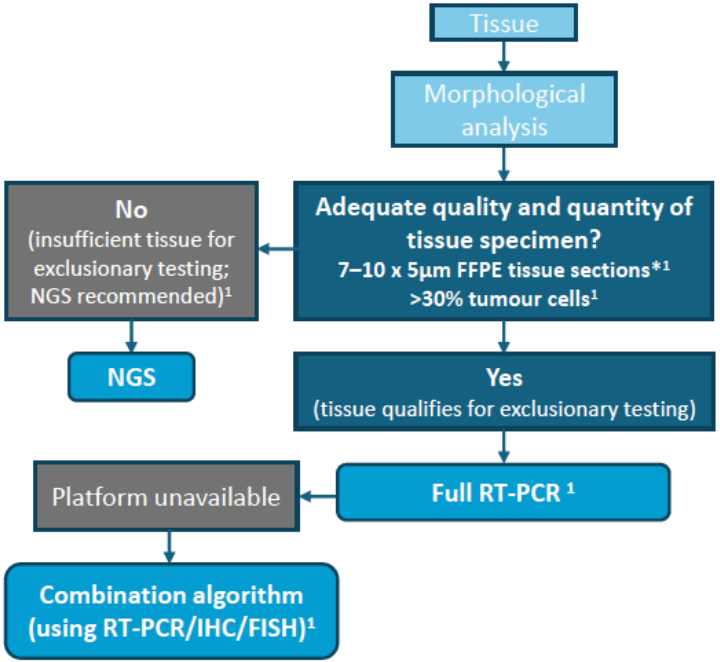
Kerr KM, et al. Lung Cancer. 2021 Apr:154:161-175

Papel de Anatomía Patológica y Biología Molecular



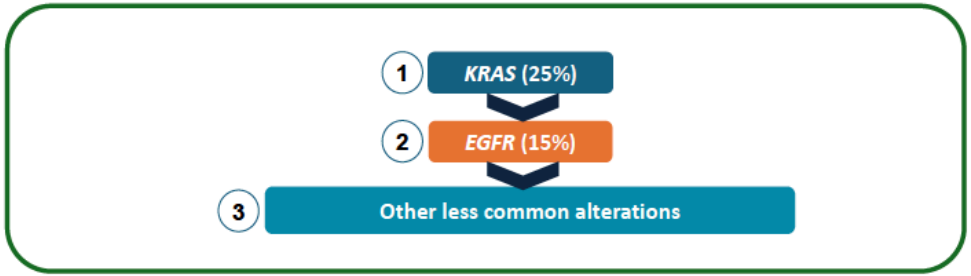
Angerilli V, et al. Diagnostics (Basel) . 2021 Feb 18;11(2):339

Algoritmos NO basados en NGS



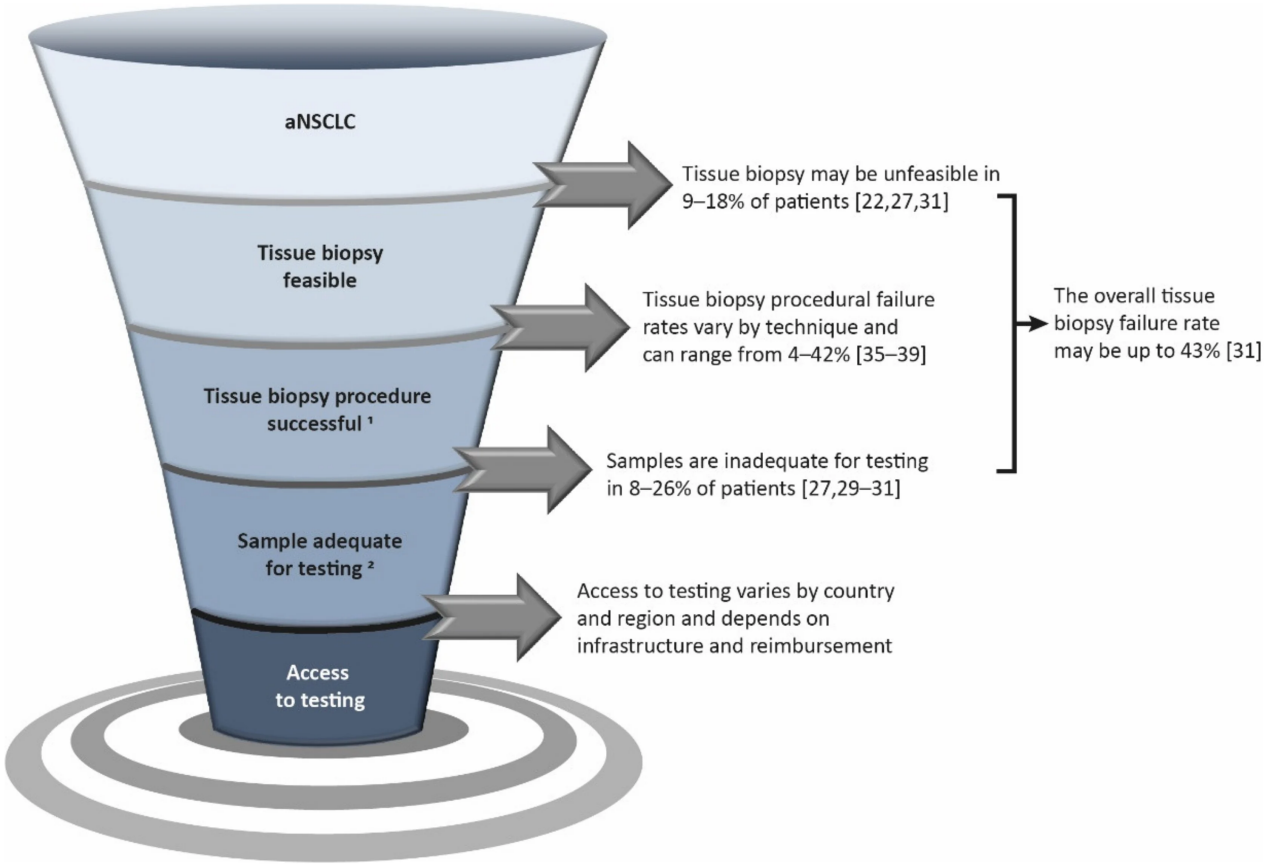
- The resources and technology available in each laboratory may impact the choice of diagnostic tests performed
- If NGS is unavailable, **alternative algorithms** based on **exclusionary testing†** can be considered to inform treatment decisions in patients[2,3]
- It is important to evaluate the **quality and quantity of tissue** and ensure there is **sufficient material** available for all the tests before proceeding with **sequential exclusionary testing**

The **testing sequence** of genes should be based on the **prevalence of the genetic alteration** in patients with NSCLC[2]



Unpublished data provided by Professor Umberto Malapelle; 2. Pakkala S, et al. JCI Insight 2018;3:e120858; 3. Pennell NA, et al. JCO Precis Oncol 2019;10.1200/PO.18.00356.

Las limitaciones del tejido

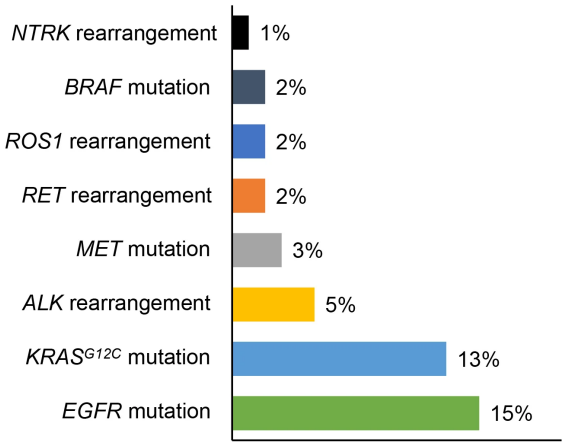


Malapelle U, et al. J Mol Pathol. 2021;2:255–73.

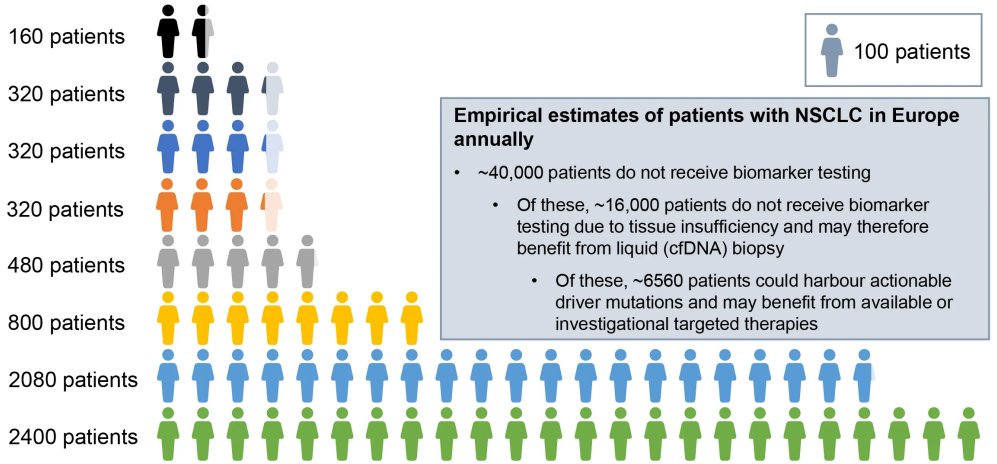
Perspectiva sobre biopsia líquida para el diagnóstico de biomarcadores (EU)

XVIII SIMPOSIUM BASES BIOLÓGICAS DEL CÁNCER E INNOVACIÓN TERAPÉUTICA
MÁS DE 20 AÑOS DE AVANCES EN LA COMPRENSIÓN EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER

Frequencies of NSCLC driver alterations



Estimated number of patients with NSCLC without adequate tissue biopsy who could theoretically benefit from using liquid biopsy for molecular diagnosis



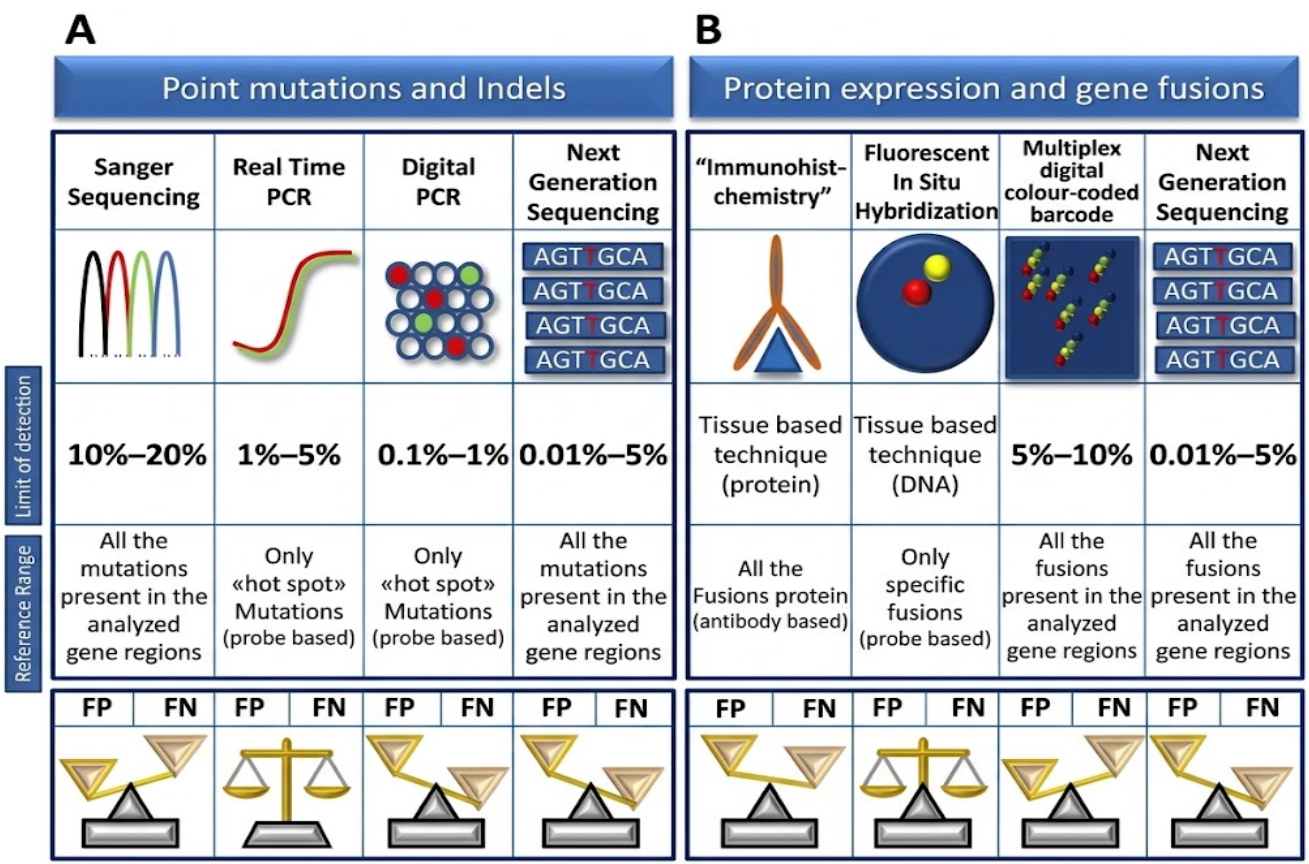
ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene; cfDNA, circulating free DNA; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene homolog; MET, hepatocyte growth factor receptor; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; RET, rearranged during transfection; ROS1, ROS proto-oncogene 1.

Tissue biopsy may be unfeasible or inadequate for molecular analysis in an estimated **~16000 NSCLC patients annually**

With a molecular diagnosis based on liquid biopsy, **~6560 NSCLC patients annually** could benefit from targeted treatments

Malapelle U, et al. J Mol Pathol. 2021;2:255–73.

Main techniques utilised to detect NSCLC biomarkers



*A qualitative scale of the FP to FN risk ratio associated with each technique is presented along the bottom of this figure.FN, false negative; FP, false positive; PCR, polymerase chain reaction; RT, real time.

Adaptado de Passiglia F, et al. J Thorac Oncol. 2019;14:2046–52.

Coste de las determinaciones

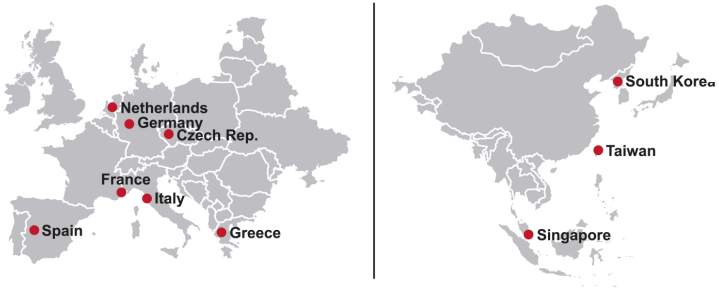
The Journal of Pathology: Clinical Research
J Pathol Clin Res March 2025; **11**: e70018
Published online in Wiley Online Library
(wileyonlinelibrary.com). DOI: 10.1002/2056-4538.70018

ORIGINAL ARTICLE

Costs of biomarker testing in advanced non-small cell lung cancer: a global study comparing next-generation sequencing and single-gene testing

Umberto Malapelle[1], Chien-Chin Chen[2], Enrique de Álava[3,4], Paul Hofman[5], Daniel Kazdal[6,7], Tae-Jung Kim[8], Tony Kiat Hon Lim[9], Aleš Ryška[10], Angelica A Saetta[11], Ed Schuuring[12], Giancarlo Troncone[1], Michele Biscuola[3], Yi-Lin Chen[13], Gek San Tan[9], Charles Hugo Marquette[14], Maria Michelli[11], Arja ter Elst[12], Hana Vošmiková[10], Joshua Kapp[15], Sebastian Gonzalez-McQuire[15], Andromachi Giannopoulou[15†], Jean Marie Franzini[16], Victoria Lucia Rabsiun Aramburu[16], Anna Baggi[16] and Albrecht Stenzinger[6,7*]

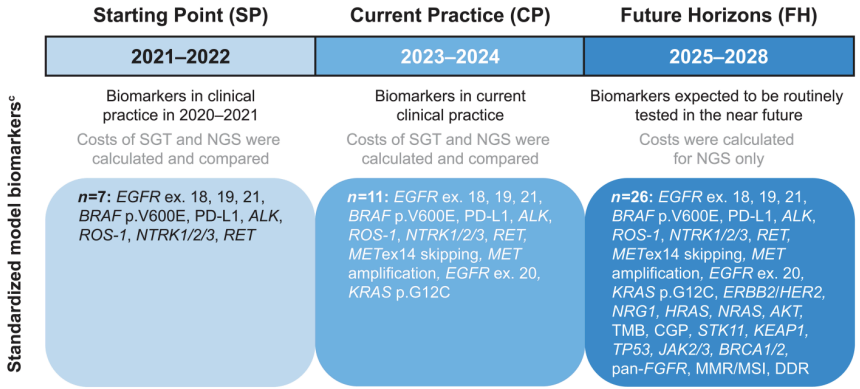
Center locations



Data collected from each center

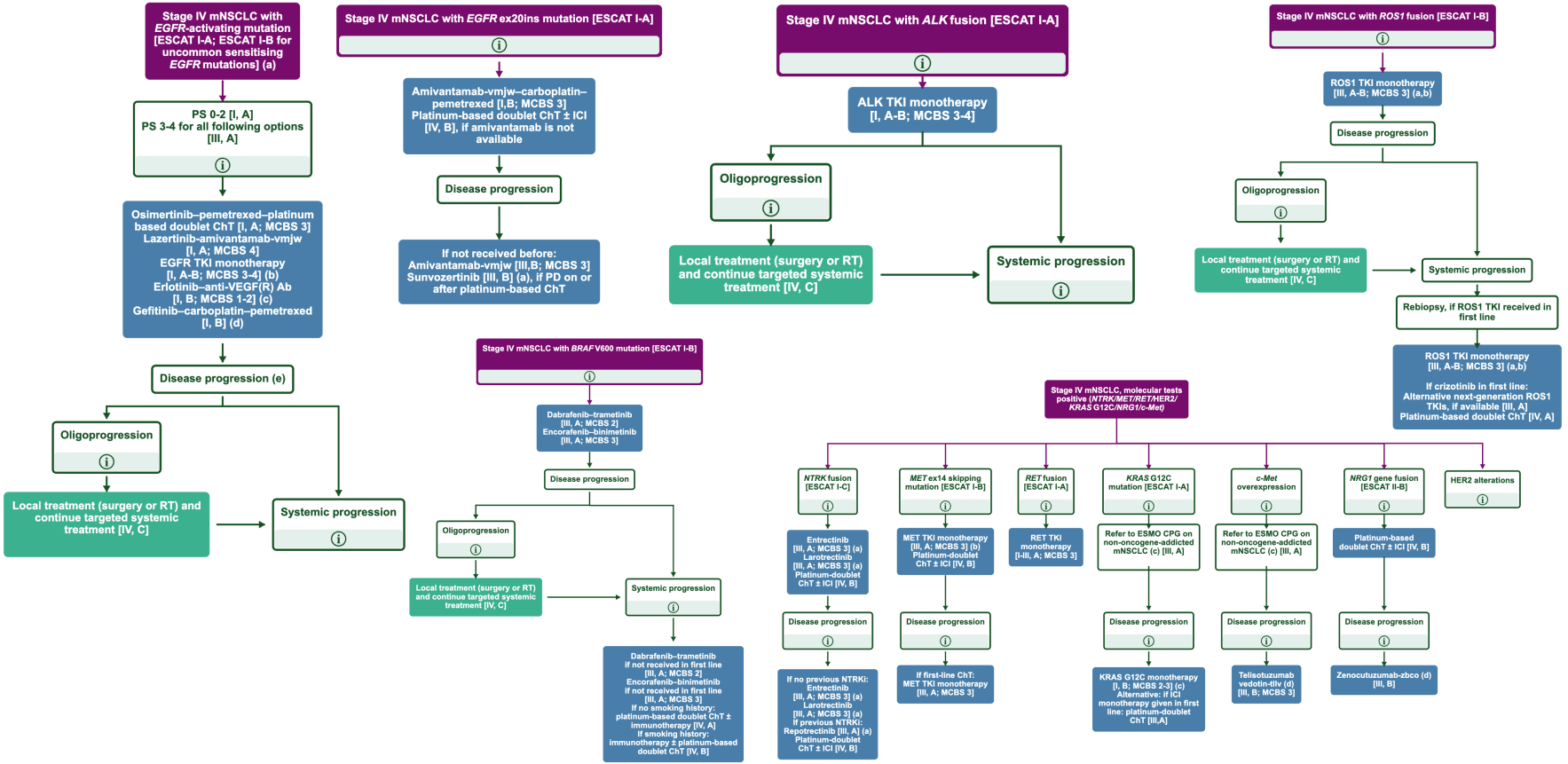
Variable	Data collected
Patients	Number of patients with newly diagnosed non-squamous aNSCLC who received testing in 2021
Biomarkers and testing techniques	Set of biomarkers tested SGT techniques used to test each biomarker NGS panels used to test biomarkers Proportions of patients who received tests for each biomarker
Retests	Frequency and technique used for retests for confirming results (confirmatory retesting) or following failed/inconclusive tests (indeterminate retesting)
Consumable costs	Consumable costs for each biomarker/testing technique combination
Equipment costs	Investment costs Payback period/depreciation Maintenance costs Software costs Proportion of time allotted for equipment to non-squamous aNSCLC Equipment saturation (for NGS only)
Personnel costs	Personnel time for non-squamous aNSCLC genomic testing activities Average annual salary for each type of personnel involved in genomic testing activities

Testing costs included personnel costs, consumable costs, equipment costs, and overheads



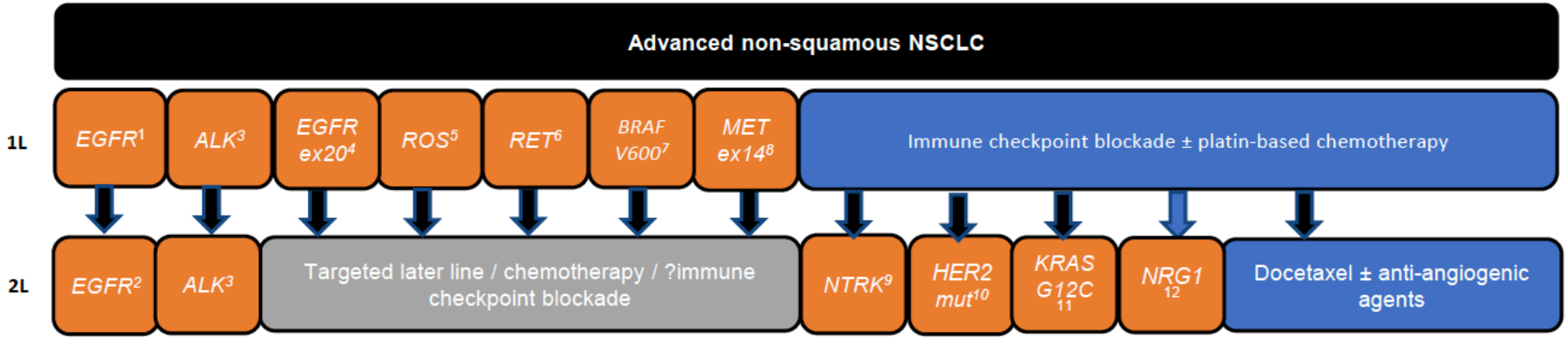
"Mean per-patient costs decreased for NGS relative to SGT over time, with real-world model ***costs 18% lower for NGS*** than for SGT"

ESMO living guidelines Oncogene-addicted metastatic NSCLC



ESMO living guidelines: Oncogene-Addicted Metastatic Non-small Cell Lung Cancer 2026

Terapias dirigidas para CPNM avanzado (2026)



[1] 1st line: Osimertinib ± Cht, Amivantamab and Lazertinib;
[2] 2nd line: Amivantamab + ChT, +Dapopotamab deruxtecan, &Sacituzumab tirumotecan; &Ivonescimab + ChT
&Savolitinib and Osimertinib in case of MET amplification
[3] Crizotinib, Alectinib, Brigatinib, Lorlatinib,+Ensartinib
[4] Amivantamab + Cht, +Sunvozertinib
[5] Crizotinib, Entrectinib, Repotrectinib
[6] Selpercatinib, Pralsetinib
[7] Dabrafinib + Trametinib, Encorafenib + Binimetinib
[8] Tepotinib, *Capmatinib, &Savolitinib

[9] Larotrectinib, Entrectinib, Repotrectinib
[10] Trastuzumab deruxtecan, +Zongertinib, +Sevabertinib
[11] Sotorasib, Adagrasib
[12] +Zenocutuzumab

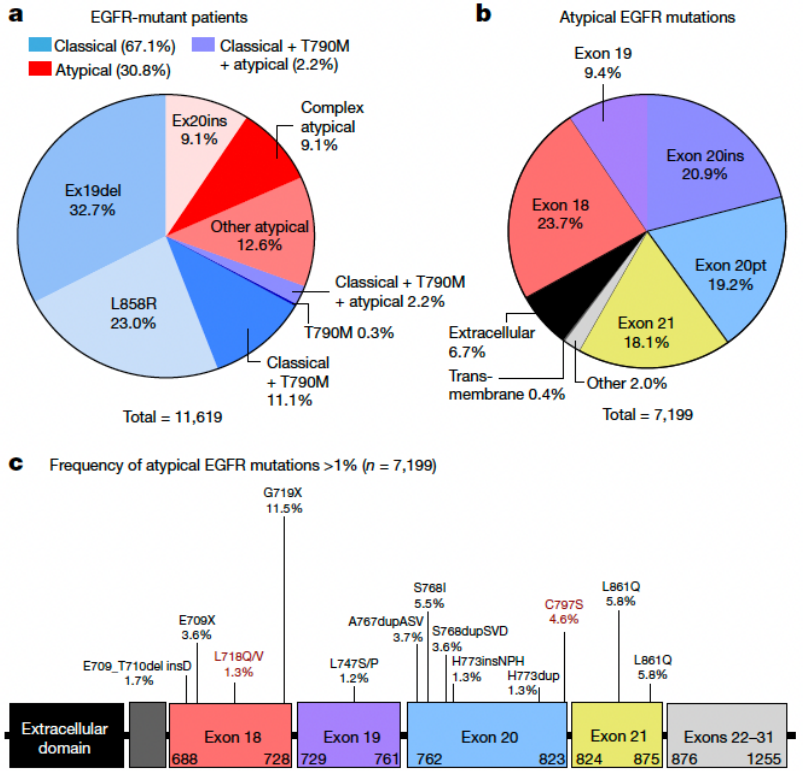
*EMA 2nd line only;
+ FDA only;
& China only
O Not yet fully approved

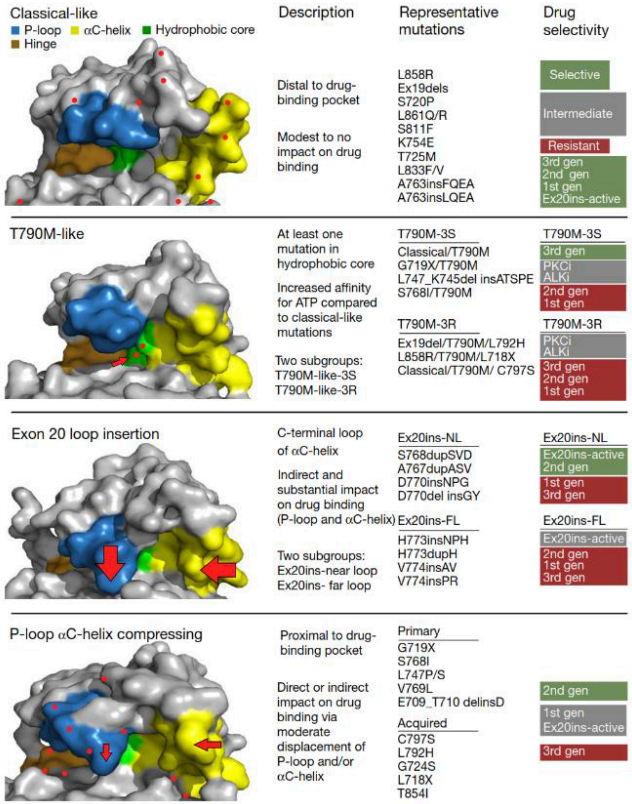
Cortesia Dr. Rolf Stahel

EGFR

Mutaciones EGFR

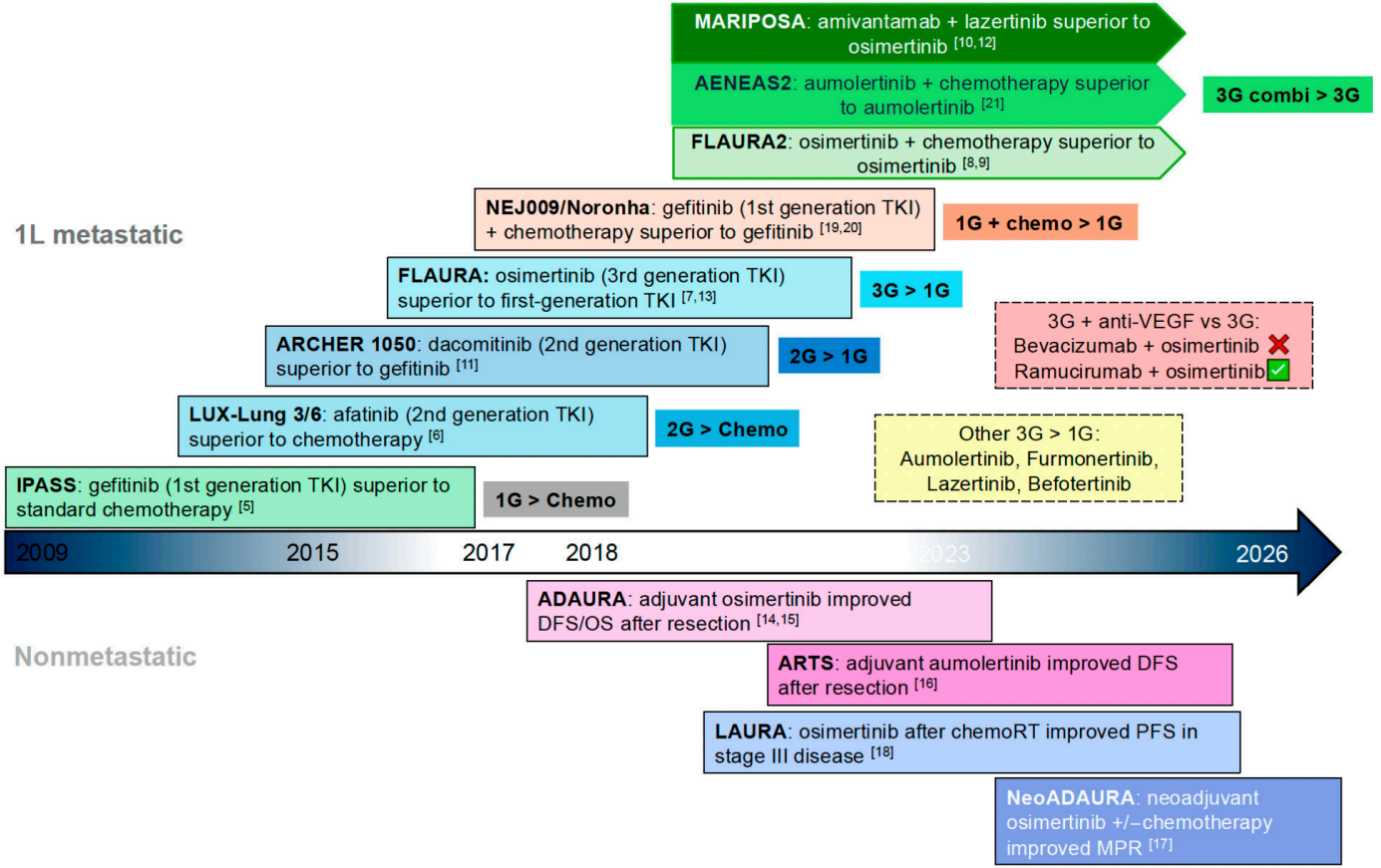
Clasificación estructural de mutaciones EGFR: Clásicas, T790M-like, Exon Exon 20 loop insertion y PACC





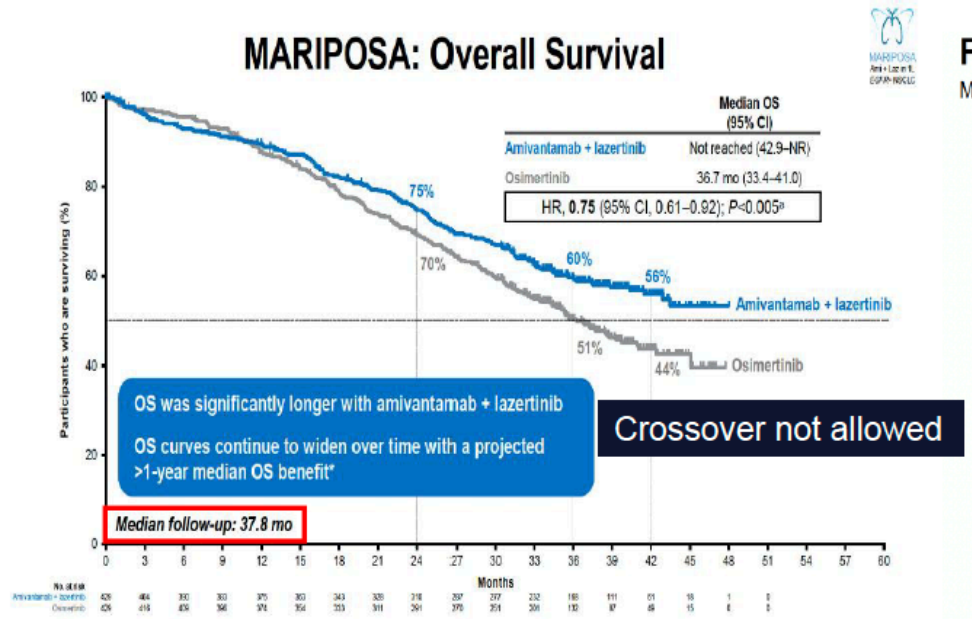
Robichaux et al. Nature, 2021

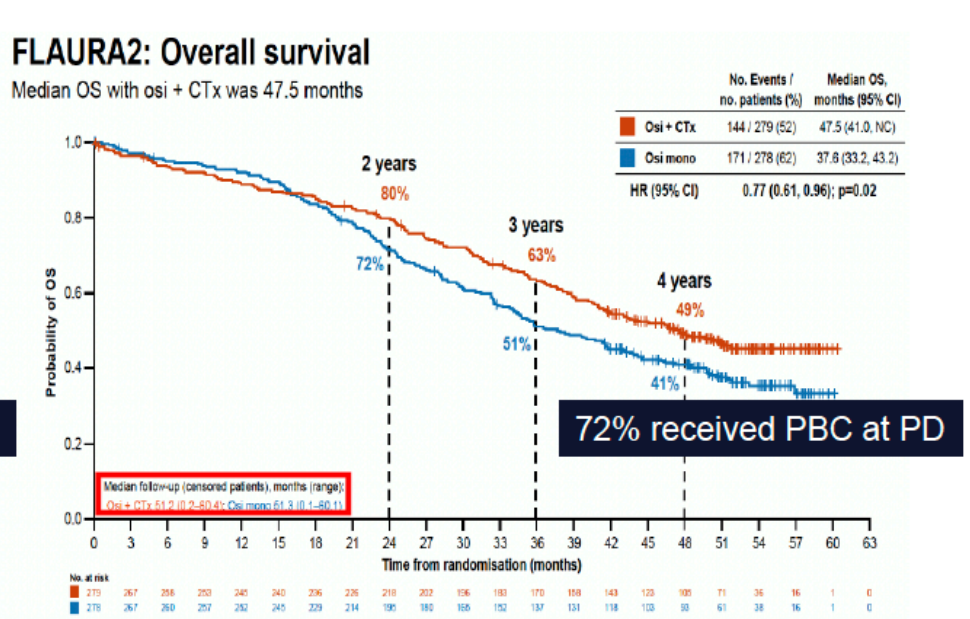
EGFR: Evolución del tratamiento



Uehara Y et al. Cancers (Basel) . 2026 Jul 25;18(15):2401

Incremento de supervivencia con combos 1L

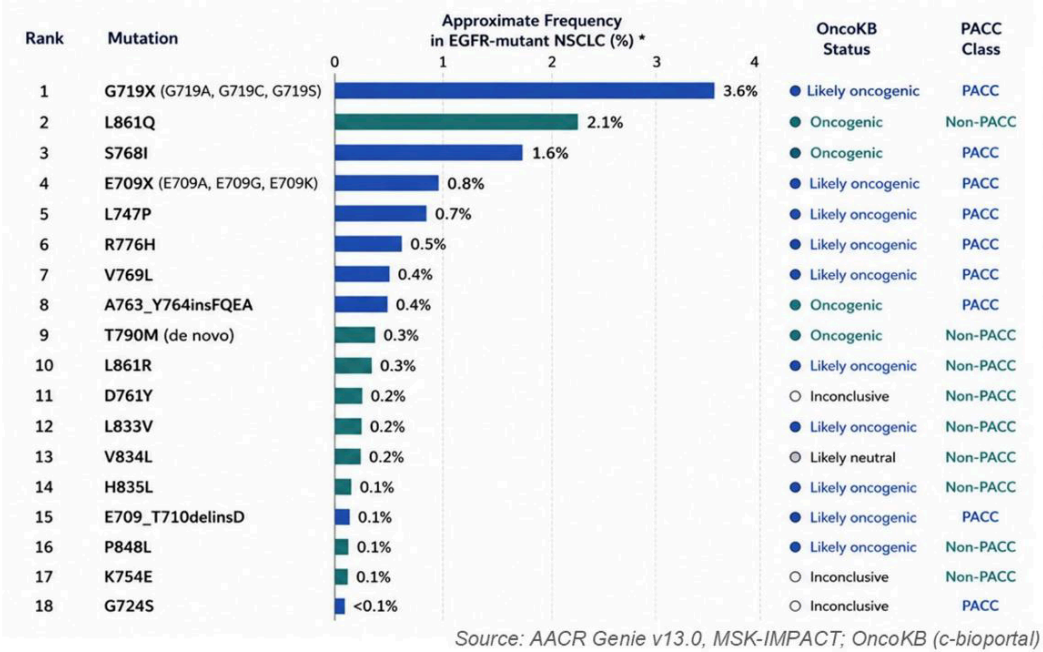




Yang et al. ELCC 2025; Planchard. D et al. WCLC 2025

EGFR mutaciones *raras*

Diversidad de mutaciones atípicas de EGFR frecuencia de mutaciones compuestas



Source: AACR Genie v13.0, MSK-IMPACT; OncoKB (c-bioportal)

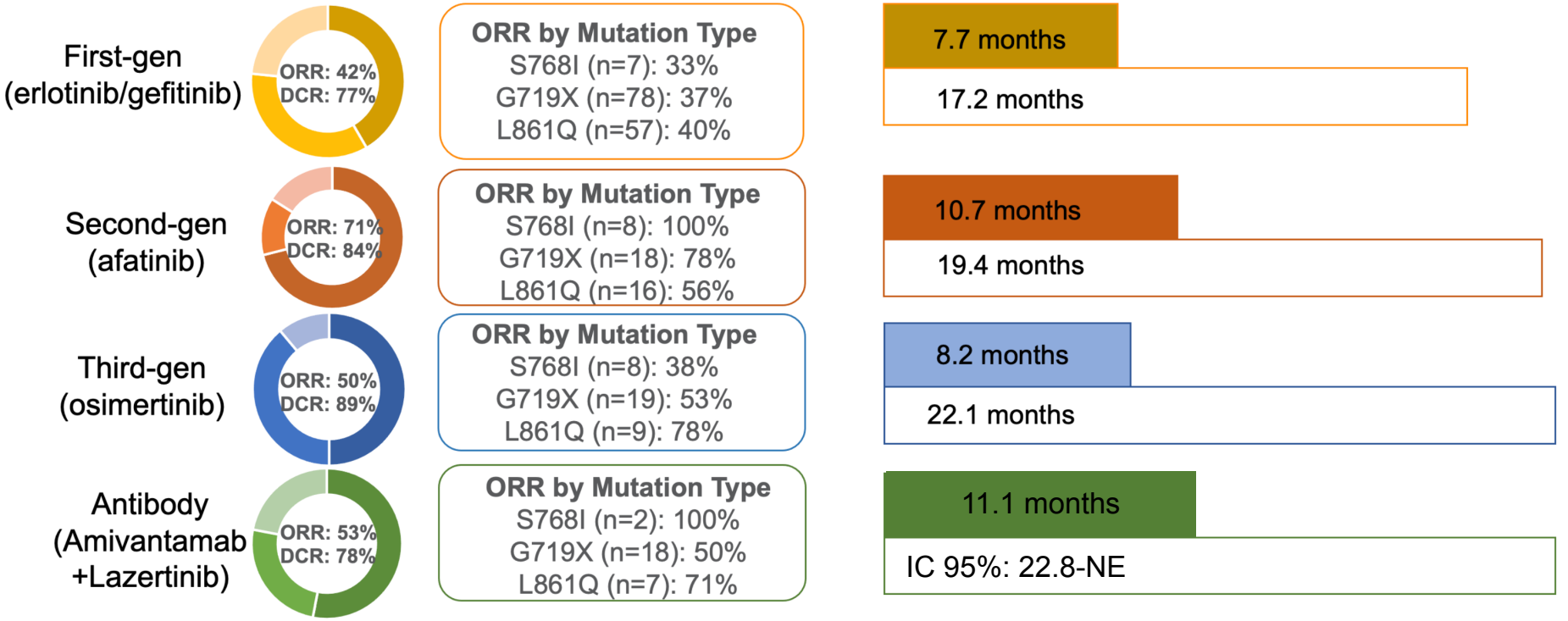
Frequency of classical-uncommon, & uncommon-uncommon mutations

	L858R	del19	G719C/S/A	L861Q	Total
E709A/G/K	9	0	3	1	13
T790M	5	3	1	0	9
S768I	5	0	5	0	10
L833V	4	0	0	0	4
R776C/G	2	0	0	0	2
Other mutation	13	5	5	3	24
Compound (+)	38	8	14	4	62
Compound (-)	157	163	1	7	328
Total	195	171	15	11	390
Compound %	**19.5**	**4.7**	**93.3**	**36.4**	**15.9**

- L858R needs dimerization for oncogenesis
  - Has weaker oncogenic potential than del19
  - Explains its increased compound mutations frequency vs del 19
- G719X has weaker kinase activity likely oncogenic potential
  - Explaining its occurrence in “cis”with classical mutations

Courtey of Daniel Tan (ASCO 2026); Kohsaka et al. Sci Trans Med (2017)

Eficacia de ITKs en EGFR *Uncommon*



Chiu et al. JCO 2014, Yang et al. Lancet Oncol 2015, Cho et al. J Clin Oncol 2020; Bar et al. JTO, 2020; Tomasini P et al. J Clin Oncol. 2026 Jan;44(1):54-65.

EGFR ex20ins

PAPILLON: El estándar en 2026

Key eligibility criteria

- Treatment-naïve,[a] locally advanced or metastatic NSCLC
- Documented *EGFR* Ex20ins
- ECOG PS 0 or 1

Stratification factors

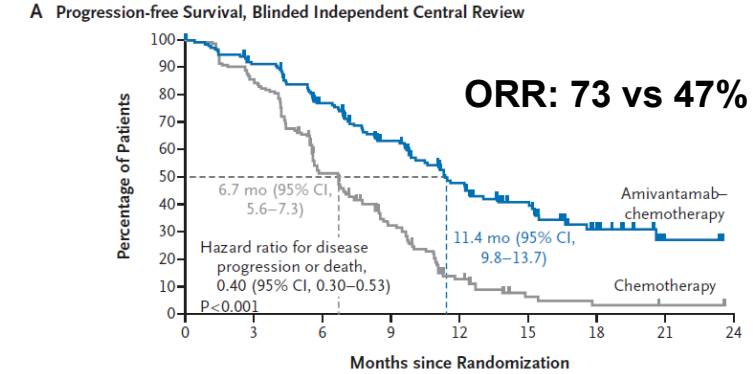
- ECOG PS
- History of brain metastases[b]
- Prior EGFR TKI use[a]

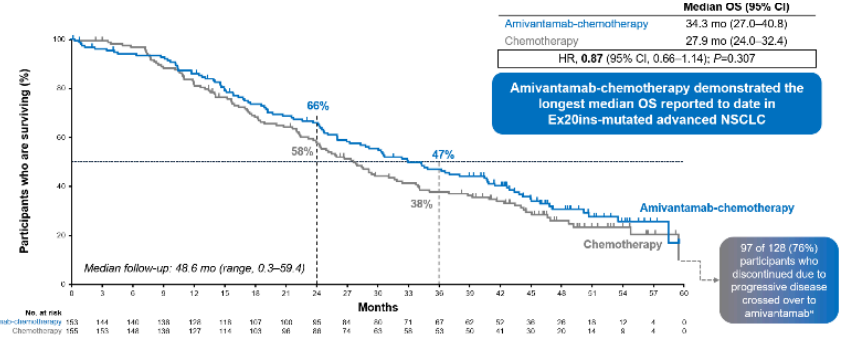
1:1 Randomization (N=308)

- **Amivantamab-chemotherapy** (n=153)
- **Chemotherapy** (n=155)

Crossover to 2L amivantamab monotherapy

- Crossover permitted only after BICR-confirmed disease progression
- Amivantamab monotherapy given Q3W



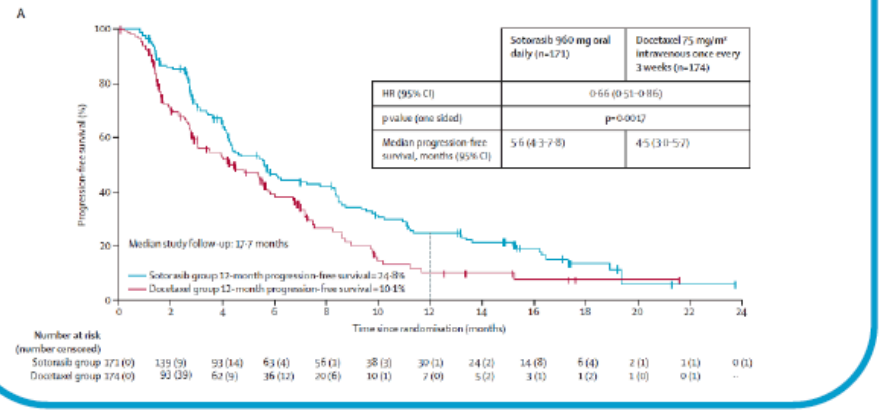


Zhou et al. NEJM (2023); Kim et al. WCLC (2026)

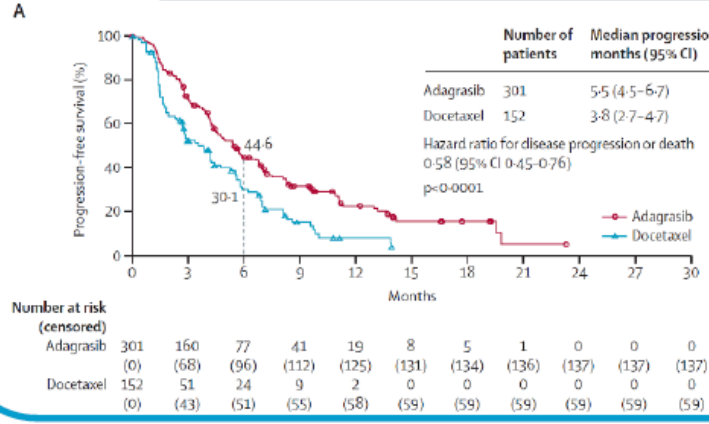
KRAS G12C

Primera generación de inhibidores KRAS G12C (off)

CodeBreaK 200



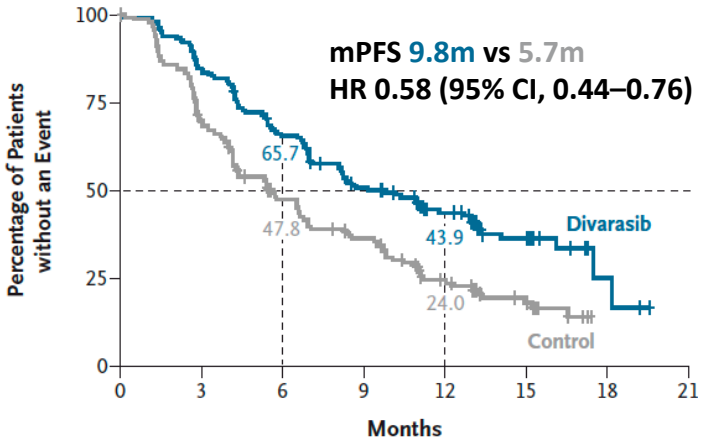
KRYSTAL-12



Agent	Trial	Line	ORR	mPFS	PFS HR	mOS	OS HR	Cross over
Sotorasib	CodeBreaK 200	2L+	28%	5.6mo	0.66	10.6mo	1.01	34%
Adagrasib	KRYSTAL-12	2L+	32%	5.5mo	0.58	Not reported	Not reported	29%

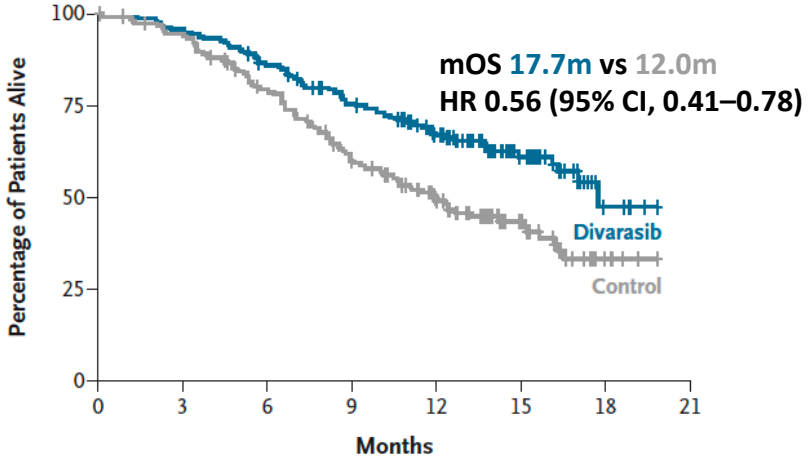
DeLangen et al Lancet (2023); Barlesi et al. Lancet (2025)

Divarasib vs sotorasib/adagrasib



No. at Risk

Divarasib	167	142	108	80	53	27	3	0
Control	171	116	73	54	26	14	0	0



No. at Risk

Divarasib	167	160	142	120	95	41	6	0
Control	171	159	128	94	65	31	6	0

Skoulidis F et al. N Engl J Med. 2026 Oct 25.

Estrategias futuras

1

Immunotherapy combinations
- **CODEBREAK 101**: Sotorasib+pembrolizumab
- **KRYSTAL-7**: Adagrasib+pembrolizumab

Chemotherapy combinations
- **CODEBREAK 101**: Sotorasib+carboplatin-pemetrexed
- **CODEBREAK 202**: Sotorasib+carboplatin-pemetrexed

EGFR inhibitor combinations
- **KROCUS**: Fulzerasib+cetuximab
- **(CODEBREAK101**: Sotorasib+panitumumab)

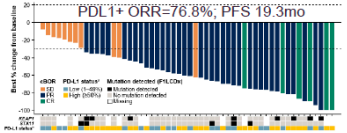
2

Vertical strategies, targeting:
-SHP2
-EGFR
-SOS1
-MEK

Horizontal strategies, targeting:
-mTOR
-CDK 4/6
-WEE1

3

KRASCENDO 170 Divarasib + Pembro (1L)

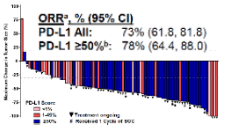


PDL1- uORR=69.6%; PFS NR

trAEs:
- G3 ALT 23%
- G3 AST 17.9%
- Dose interruption 69.2%
- Discontinuation 12.8%

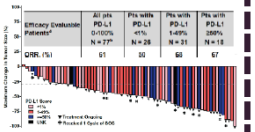
TRAE G3+ ALT/AST: 23%

Olomorasib + pembrolizumab (1L)



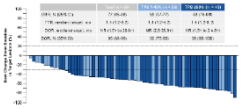
TRAE G3+ ALT/AST: 16.5%

Olomorasib + pembrolizumab + platinum-pemetrexed (1L)

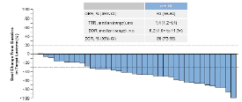


TRAE G3+ ALT/AST: 11.9%

Calderasib + pembrolizumab



Calderasib + pembrolizumab + platinum-pemetrexed

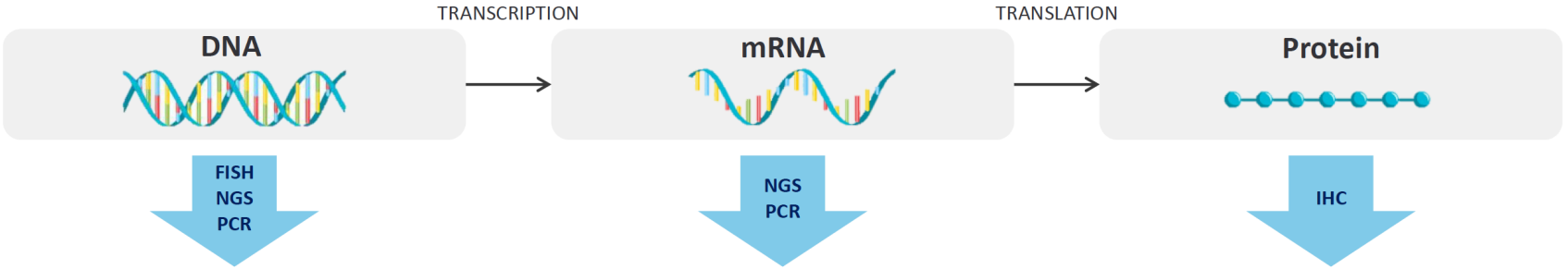


TRAE G3+ ALT/AST: 3%
TRAE G3+ ALT/AST: 5%

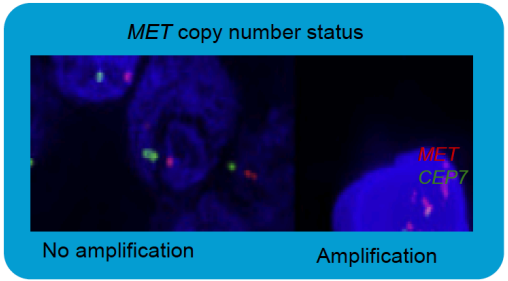
Cortesía S. Popat

MET ex14

Diferentes métodos diagnósticos para diferentes alteraciones MET

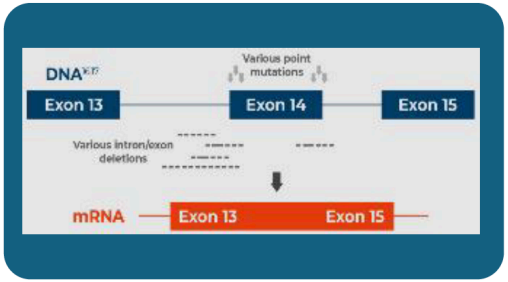


MET amplification[4]

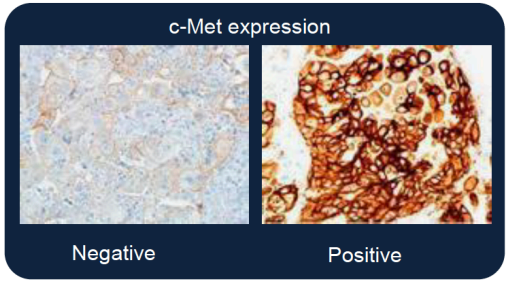


MET amplification lacks a consensus between studies, testing method, and cut-offs employed (gene copy number [GCN] vs ratio [*MET/CEN7*])[4]

MET exon 14 skipping mutation[1]



c-Met protein overexpression[3,4]

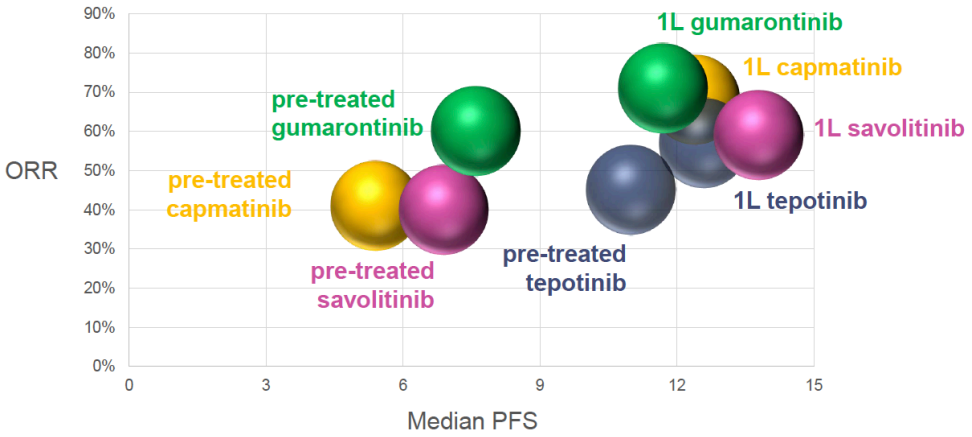


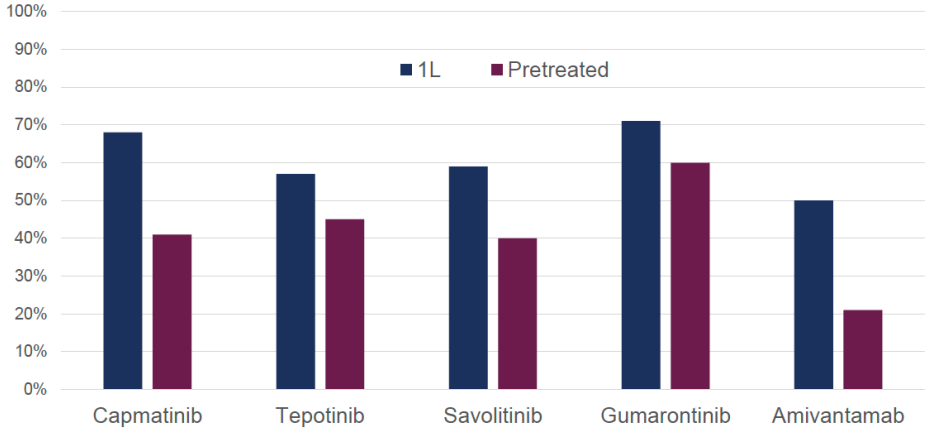
c-Met staining, scoring, and positivity cutoffs are not standardized[2]

c-Met protein expression can not be evaluated by NGS or FISH;
c-Met may be overexpressed in the absence of *MET* amplification / increased GCN or *MET* mutations

Orilon A, et al. J Thoras Oncol. 2017;12(1)15-26. 2. Boyle TA, et al. Appl ImmunohistochemMol Morphol. 2020;28(9):669-677. 3. Bubendorf L, et al. Lung Cancer. 2017;111:143-149. 4. Schubart C, et al. Cancers. 2021;13(19):5023.

Inhibidores MET: Mejores resultados en TR y SLP empleados en 1L





AUTHOR: Alexander Drilon. Refls: Lu et al, WCLC 2023; Lu et al, Lancet Resp Med 2021; Mazieres et al, JAMA Onc 2023; Wolf et al, NEJM 2020; Yu et al eClinical Medicine 2023; Leigh et al WCLC 2023

Resumen eficacia inhibidores MET (ITKs)

	CRIZOTINIB		CAPMATINIB		TEPOTINIB		SAVOLITINIB	
	PROFILE - 001		GEOMETRY-mono-1		VISION		NCT02897479	
Sample Size	1L 26	2L+43	1L 60	2L 100	1L 164	2L+ 241	1L 28	2L+ 42
Median Age	72		71	71	75	71	69	
ORR	25%	37%	67%	44%	56%	45%	46%	41%
mPFS (mo)	7.3		12.4	5.4	12.6	11	5.6	6.9
mOS (mo)	9.1		20.8	13.6	19.1	20	12.5	

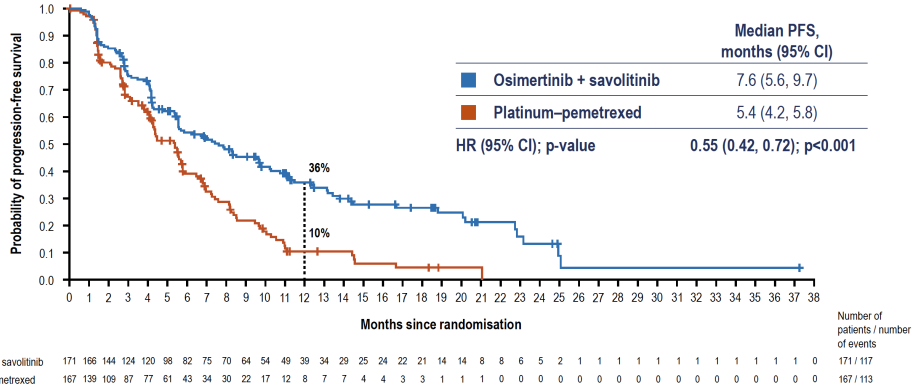


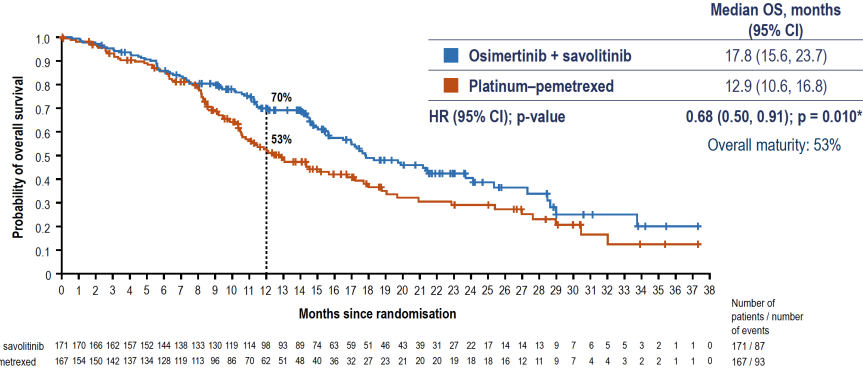
…¡En 2ª línea!

Drilon, Nat Med 2020 / Wolf NEJM 2020 / Paik NEJM 2020 / Paik WCLC 2020 / Lu Lancet Resp Med 2021 / Le IASLC Targeted Therapies 2022

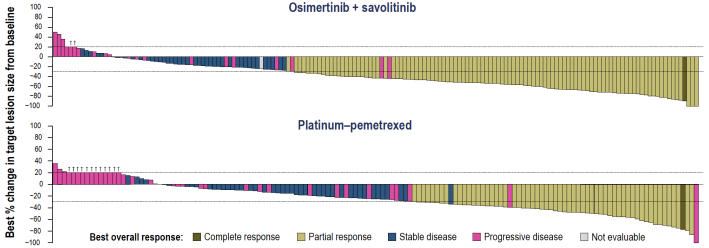
SAFFRON: Savolitinib + Osimertinib en 2L en CPNM EGFR+ tras PD a Osimertinib

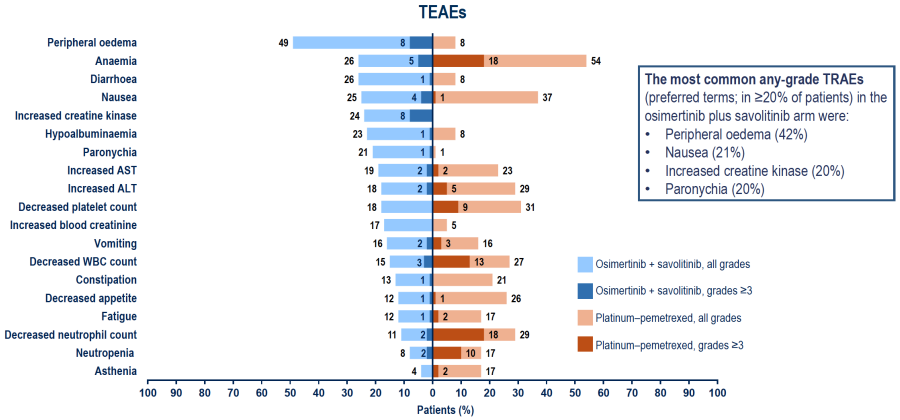
MET overexpression or amplification





	Osimertinib + savolitinib (n = 171)	Platinum–pemetrexed (n = 167)	Odds ratio (95% CI)
Patients with a confirmed objective response, n (%)	88 (51)	45 (27)	2.90 (1.85, 4.61)
Median DoR, months (95% CI)	9.7 (7.6, 12.5)	5.7 (4.4, 8.1)	
Median best percentage change in target lesion size, % (min, max)	−44 (−100, 50)	−25 (−100, 35)	
Patients with disease control,* n (%)	145 (85)	108 (65)	3.18 (1.88, 5.50)





The most common any-grade TRAEs (preferred terms; in ≥20% of patients) in the osimertinib plus savolitinib arm were:

- Peripheral oedema (42%)
- Nausea (21%)
- Increased creatine kinase (20%)
- Paronychia (20%)

Lu S et al. ESMO Congress 2026

BRAF V600

PHAROS: Encorafenib plus Binimetinib in patients with BRAF V600E mut, metastatic NSCLC

Encorafenib 450 mg QD + Binimetinib 45 mg BID

Treatment naive: median age was 68 years, 56% were women, 90% were White, and 31% had never smoked, 7% never smokers (naive)

Previously treated: median age was 71 years, 49% were women, 85% were White, and 28% had never smoked

PHAROS (NCT03915951): a single-arm, open-label, multicenter, phase 2 study[6,7]

Key eligibility criteria

- BRAF V600E-mutant mNSCLC[a]
- ECOG performance status 0 or 1
- No *EGFR* mutation, *ALK* fusion, or *ROS1* rearrangement
- No more than 1 prior line of treatment in the advanced setting
- No prior treatment with BRAF or MEK inhibitor
- No symptomatic brain metastases

Patients enrolled

- Treatment naive n=69
- Previously treated n=39

Encorafenib 450 mg QD + Binimetinib 45 mg BID

28-day cycles

Until progression or unacceptable toxicity[b]

Primary endpoint

- ORR[c] by IRR

Secondary endpoints

- ORR by investigator
- DOR, DCR, PFS, and TTR (all by IRR and investigator)
- Overall survival
- Safety

Baseline characteristics

	Treatment naive (n=69)	Previously treated (n=39)
Age, median (range), years	68 (47-83)	71 (53-86)
Sex, n (%)		
Female	33 (56)	19 (49)
Male	26 (44)	20 (51)
Race, n (%)		
White	53 (90)	33 (85)
Asian	3 (5)	4 (10)
Other or unknown	3 (5)	2 (5)
ECOG performance status, n (%)		
0	19 (32)	7 (18)
1	40 (68)	32 (82)

	Treatment naive (n=69)	Previously treated (n=39)
Smoking status, n (%)		
Current/former	41 (69)	28 (72)
Never	18 (31)	11 (28)
Brain metastases, n (%)		
No	55 (93)	35 (90)
Yes	4 (7)	4 (10)
Prior systemic treatment for metastatic disease, n (%)		
Immunotherapy	Not applicable	24 (62)[a]
Monotherapy	Not applicable	12 (31)
Combination therapy[a]	Not applicable	12 (31)
Chemotherapy	Not applicable	18 (46)

NAIVE

75% ORR by IRC

40m Median DoR

30.4m Median PFS

47.6m Median OS

PREVIOUSLY TREATED

49% ORR by IRC

16.7m Median DoR

9.3m Median PFS

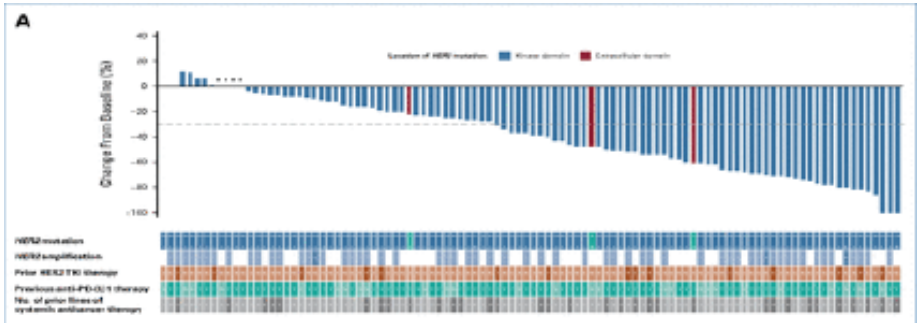
22.7 Median OS

Johnson M, et al ESMO 2025, Riely et al J Thorac Oncol 2025

Her2 mut

ADCs Her2 mut

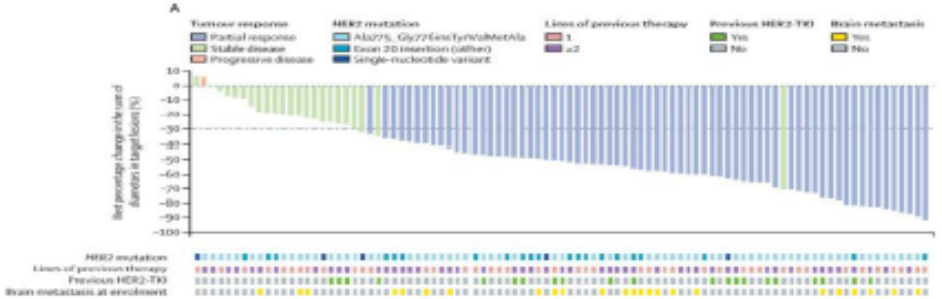
Trastuzumab deruxtecan



5.4mg/kg
ORR: 49.0%
mPFS 9.9m
mOS 19.5m

T-DXd was the first approved treatment in 2022 for pre-treated HER2-mutated NSCLC based on DL02, a single arm study

Trastuzumab Rezetecan



4.8mg/kg
ORR: 73.0%
mPFS 11.5m

China-only study, but efficacy parameters seem comparable with the limits of cross-trial comparisons

Salvatore Siena, ASCO 2020; Goto et al. JCO 2023

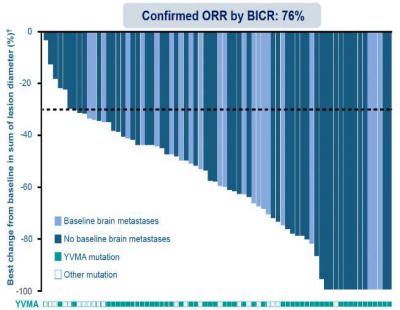
ITKs Her2 mut

Zongertinib

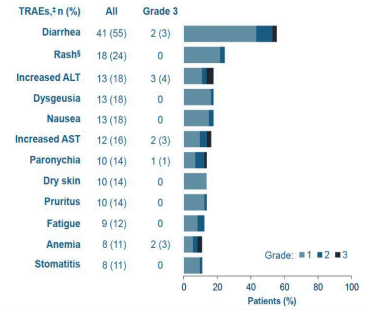
Zongertinib in 1L Treatment-Naïve Patients: Tumor Response

Confirmed response by BICR (RECIST v1.1)	Cohort 2: Treatment-naïve patients N = 74
ORR	**76%**
CR, n (%)	8 (11)
PR, n (%)	48 (65)
DCR	**96%**
SD, n (%)	15 (20)
PD, n (%)	1 (1)*

- Median time to objective response was 1.4 months (95% CI, 1.1 to 6.9)



1L zongertinib demonstrated clinical benefit in all patients, irrespective of *HER2* mutation type



Aprobación FDA 1L Feb26

Sevabertinib

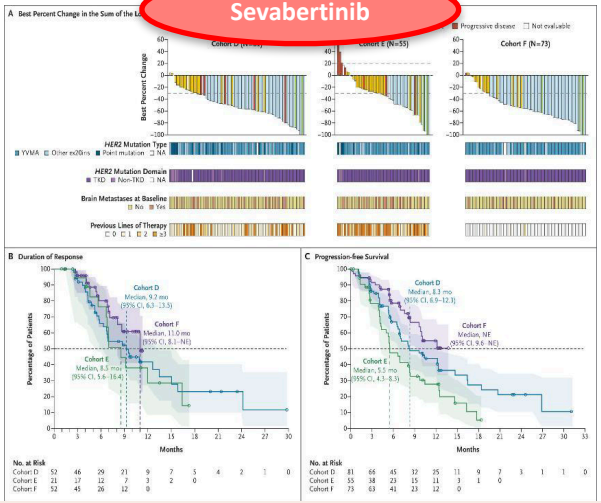


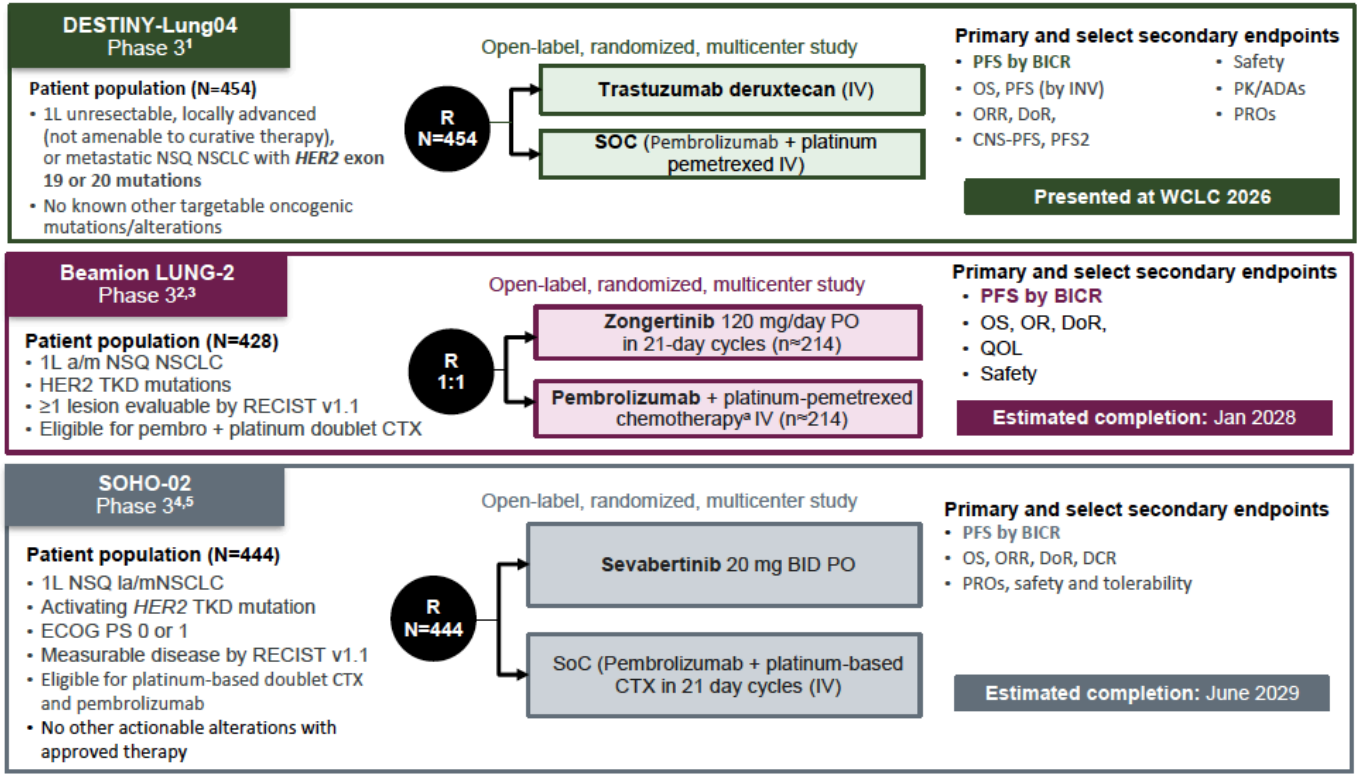
Table 3. Drug-Related Adverse Events among Patients Treated with Sevabertinib, 20 mg Twice Daily.☆

Event	Cohort D (N=81)	Cohort E (N=55)	Cohort F (N=73)
	number of patients (percent)		
Drug-related adverse event†			
Any grade	78 (96)	55 (100)	71 (97)
Grade 1	13 (16)	9 (16)	14 (19)
Grade 2	34 (42)	29 (53)	40 (55)
Grade 3	29 (36)	17 (31)	15 (21)
Grade 4	2 (2)‡	0	1 (1)§
Grade 5	0	0	1 (1)¶
Leading to dose reduction	21 (26)	19 (35)	18 (25)
Leading to dose interruption or delay	25 (31)	27 (49)	21 (29)
Leading to treatment discontinuation	4 (5)	2 (4)	1 (1)
Serious drug-related adverse event	12 (15)	5 (9)	6 (8)

Aprobación FDA 1L Sep26

Heymach ELCC 2026; Heymach et al NEJM 2026; Le et al. NEJM 2025

Desarrollo en 1L



Assuming all 3 trials show increased benefit (vs KN-189), how would we select treatment?

Factors to consider:

- Median PFS
- PFS HR vs SOC
- OS
- CNS efficacy
- Side effect profile
- Regulatory approval (before the others)

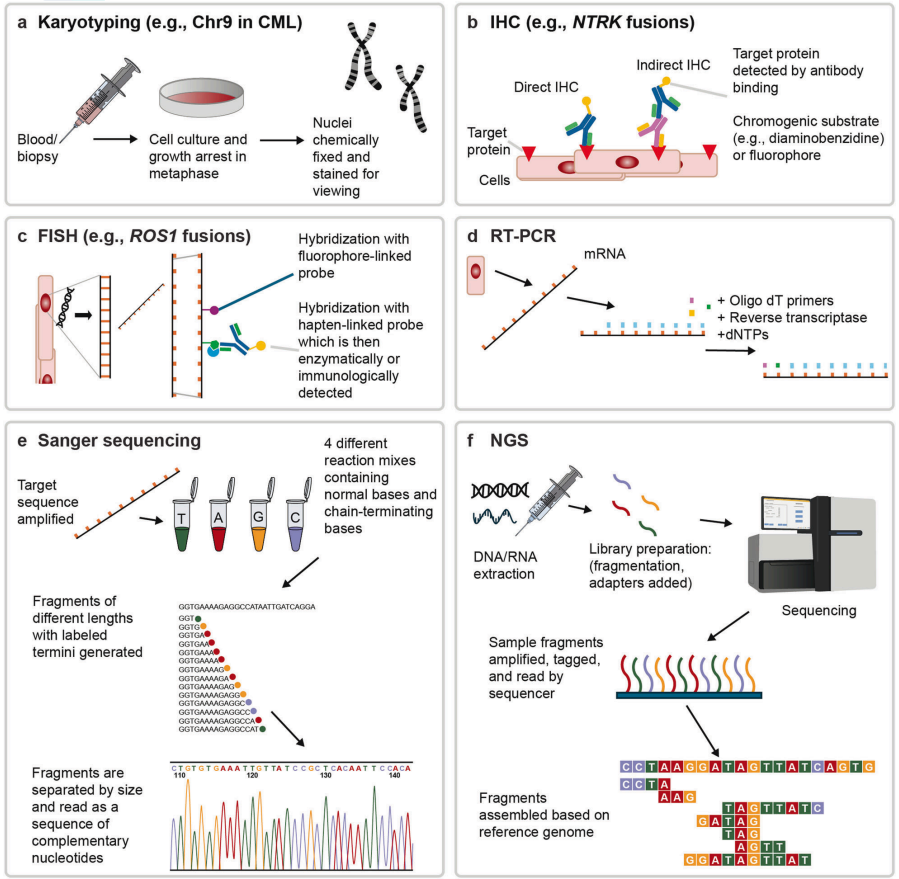
Potential to sequence options?

- More data are awaited to inform sequencing strategies

Adaptado de Saw. WCLC 2026

Fusiones

Cómo se diagnostican las fusiones

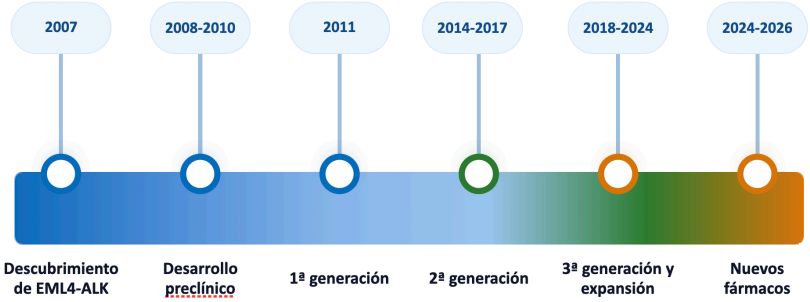


Technique	Specificity	Sensitivity	Detection of fusion partner?	Other advantages or disadvantages
IHC	++	++	No	Convenient but low sensitivity and specificity
Break apart FISH	+++	+++	No[a]	Rapid technique that requires little tissue
RT-PCR	+++	++/+++	Yes (known only)	Does not detect unknown fusion partners or those not preselected
RNA-sequencing NGS	+++	+++	Yes	Expensive, requires high-quality RNA, may detect alterations of uncertain clinical significance and gene expression
DNA-sequencing NGS	++/+++	++	Yes	Use of circulating tumor DNA requires shorter turnaround time and is less invasive than tissue/tumor testing

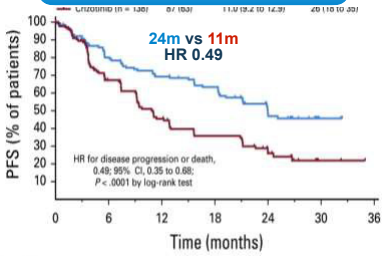
La mejor técnica para detectar las fusiones es la NGS, especialmente mediante RNA-Seq: es costosa, lleva tiempo y requiere una muestra de alta calidad

Liu SV, et al. Signal Transduct Target Ther. 2025; Novelo S, et al. Oncologist, 2023

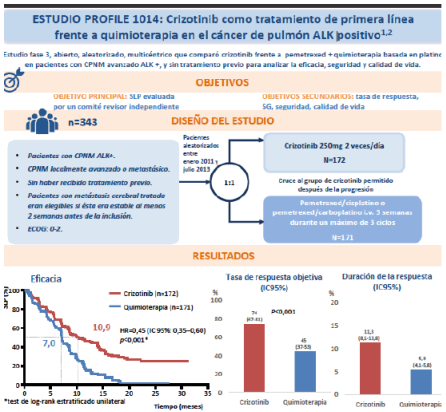
ALK: La fusión más común en CPNM



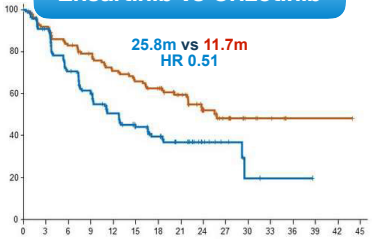
Brigatinib vs Crizotinib



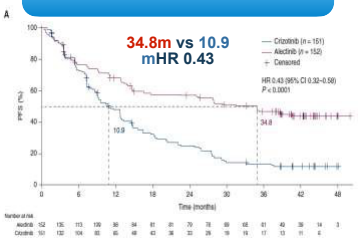
Crizotinib vs QT



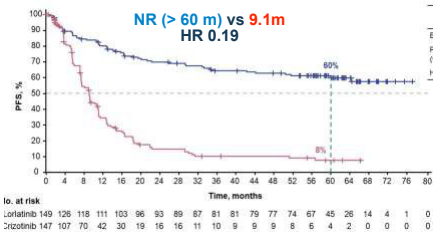
Ensartinib vs Crizotinib



Alectinib vs Crizotinib



Lorlatinib vs Crizotinib



Solomon BJ, et al. N Engl J Med, 2014; Mok Ann Oncol 2020; Camidge J Clin Oncol2022; Horn et al. JAMA Oncol 2021

ALK: La evidencia más robusta

Fármaco	Ensayo	Fase	TRO	TRO intracraneal	mSLP	HR SLP	HR SLP iC	mSG	HR para SG
Quimioterapia	Profile 1014	Fase III	45 %	-	7.0 meses	-	-	47.5 meses	-
Crizotinib	Profile 1014	Fase III	74 %	18 %	10.9 meses	0.45 (vs QT)	0.45 (NS)	No alcanzada (59.8m*)	0.760 (0.35*)
Ceritinib	ASCEND-4	Fase III	72.5 %	72.7%	16.6 meses	0.55 (vs QT)	0.54	No alcanzada (NR)	0.73 (vs QT)
Alectinib	ALEX	Fase III	82.9 %	81 %	34.8 meses	0.43 (vs Crizotinib)	0.16	81.1 meses	0.67 (vs Crizotinib)
Brigatinib	ALTA-1L	Fase III	74 %	78 %	29.4 meses	0.43 (vs Crizotinib)	0.42	No alcanzada (Tasa a 2 años: 76%)	0.92 (vs Crizotinib)
Ensartinib	EXALT3	Fase III	74 %	63.6%	25.8 meses	0.51 (vs Crizotinib)	0.32	No alcanzada (Tasa a 2 años: 78%)	0.91 (vs Crizotinib)
Lorlatinib	CROWN	Fase III	81 %	82 %	No alcanzada (5a: 60% sin PD)	0.19 (vs Crizotinib)	0.07	No alcanzada	-

… El comparador de base, la quimioterapia, mSLP 7m, TRO <50%

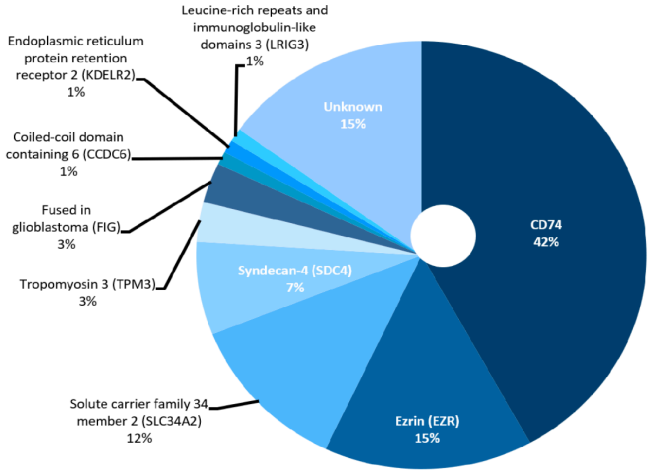
* Eliminando el sobrecruzamiento

Elaboración personal con datos extraídos de los ensayos clínicos citados en la tabla

ROS-1: Evidencia fase I y II

- Incidencia ~1-2% en ADC de pulmón.
- La fusión más frecuente es CD74-ROS1 (42%)
- ROS1 comparte el 49% de la secuencia homóloga del dominio TK de ALK, por ello muchos iALK también son iROS1

CD74-ROS1 is the most common ROS1 fusion in NSCLC patients



Timeline of ROS inhibitors development

1987: Discovery of *ROS1* gene fusion in cancer	*2007:* Discovery of *ROS1* gene fusion in NSCLC	*2016:* **Crizotinib**, First FDA-approved ROS1 TKI	*2019:* **Entrectinib**, FDA-approved ROS1 TKI	*2019:* ***Lorlatinib**, Added to NCCN guidelines	*2023:* **Repotrectinib**, FDA-approved ROS1 TKI	*Ongoing:* **Taletrectinib**, Global phase II clinical trial	*Ongoing:* **Zidesamtinib**, Global phase I/II clinical trial

Target Discovery → **Approvals / Integration into Guidelines** → **Investigation**

Crizotinib and entrectinib are also approved by EMA and globally. *Lorlatinib is not approved by the FDA for the treatment of patients with metastatic ROS1 fusion-positive NSCLC but is recommended as a subsequent treatment option by the NCCN guidelines and included in the ESMO guidelines.

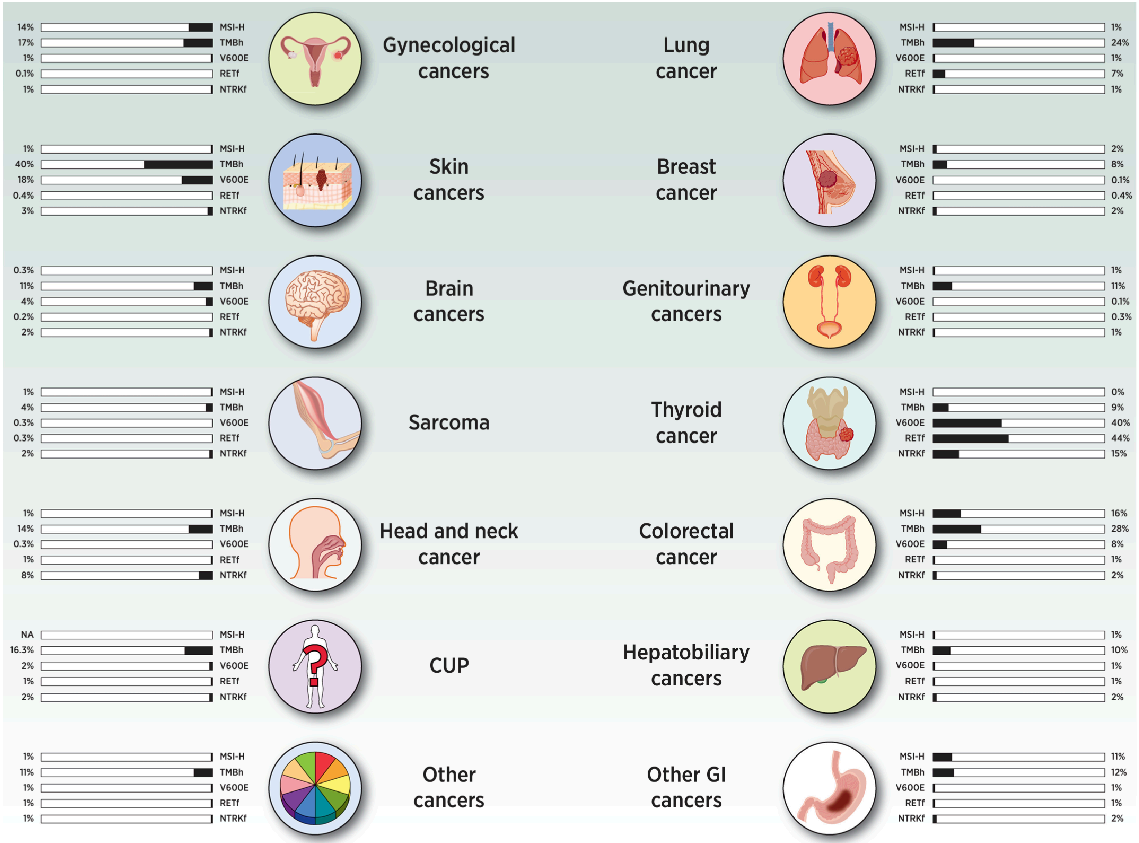
Gainor and SHAW . Oncologist 2013; Park et al, Path Res Pract, 2019

ROS-1: Evidencia fase I y II

Fármaco	Ensayo	Fase	n	TRO	TRO intracraneal	mSLP	mSG
Crizotinib	Profile 1001	Fase I	53	72 %	-	19.2 m	51.4 m
Entrectinib	ALKA 372-001 STARTRK-1 STARTRK-2	Fase I Fase II	168	68 %	80 %	15.7 m	47.7m
Repotrectinib	TRIDENT-1	Fase I-II	121	79 %	89 %	30.2 m	74.6 m
Taletrectinib	TRUST-1	Fase I	106	85.2%	76.7%	44.6 m	NR
Zidesamtinib	ARROS-1	Fase I	25	89 %	83 %	NR	NR

Elaboración personal con datos extraídos de los ensayos clínicos citados en la tabla

RET: Biomarcador transversal *(tumor-agnostic driver)*



Gouda M et al. Clin Cancer Res 2023

RET en CPNM: Evidencia Fase III

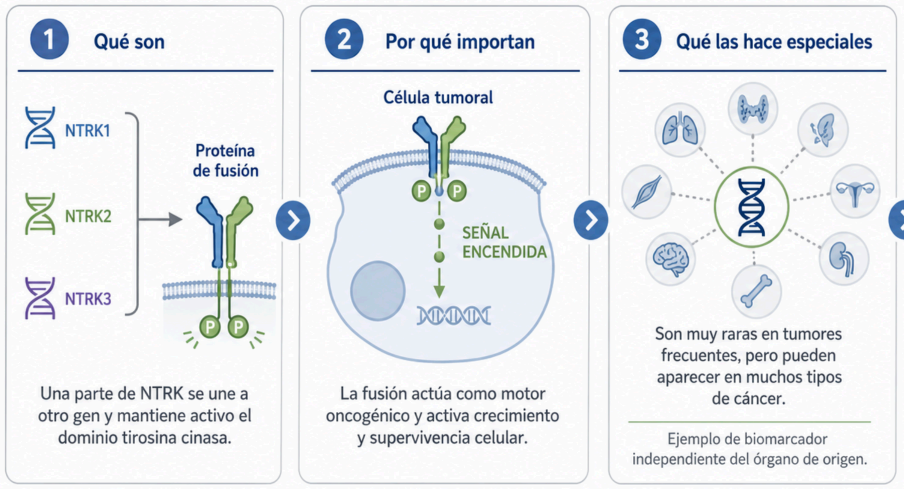
Fármaco	Ensayo	Fase	n	TRO	TRO intracraneal	mSLP	mSG
Selpercatinib	LIBRETTO-431	Fase III	129	83.7%	82.4%	24.8 m	NR*
Pralsetinib	ARROW	Fase I/II	281	63% 78% (näive)	53 %	13.1 m	44.3 m

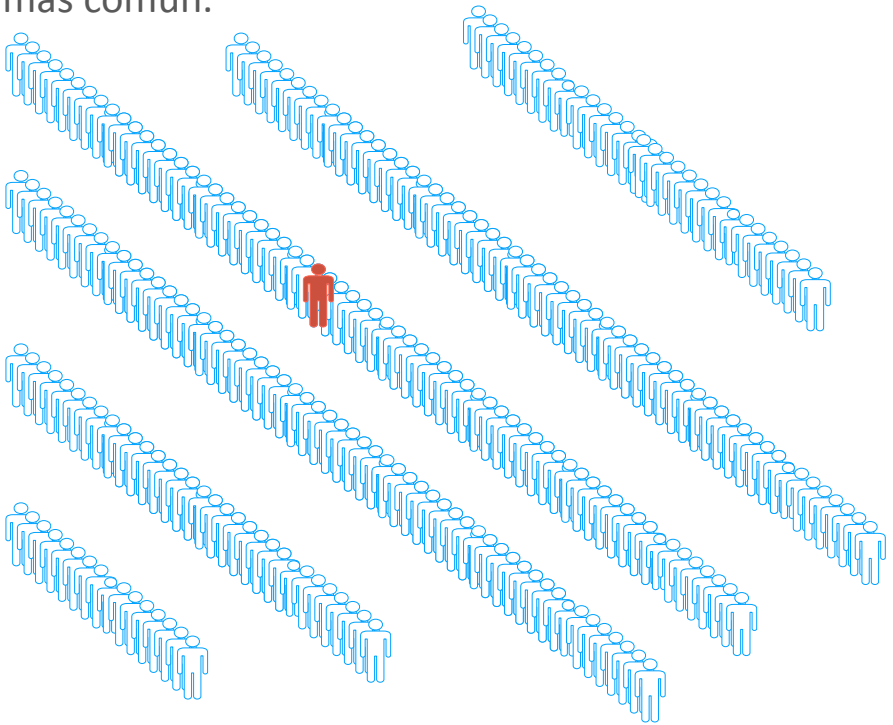
* mOS no alcanzada tampoco en Libretto-001, pero se reportaron 65.6% de pacientes vivos a 3a

Elaboración personal con datos extraídos de los ensayos clínicos citados en la tabla

NTRK: Fusión *agnóstica*

Fusión *MUY* rara (> 80 fusiones diferentes; NTRK3 la más común.



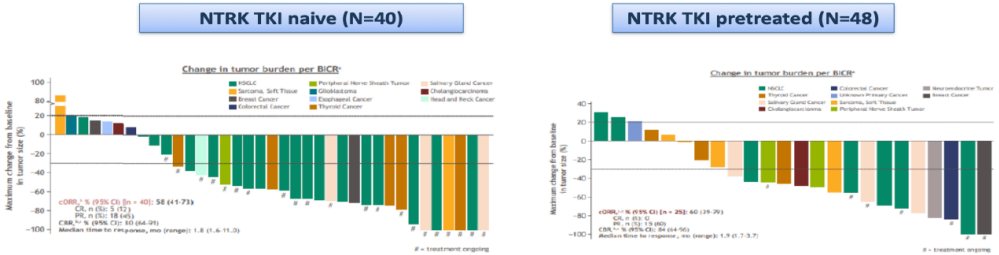


Hay que testar ~400 pacientes para encontrar un positivo

Elaboración personal

NTRK en CPNM: Evidencia fase I y II

Fármaco	Ensayo	Fase	n	TRO	TRO intracraneal	mSLP	mSG
Larotrectinib	LOXO-TRK SCOUT NAVIGATE	Fase I Fase I/II Fase II	32	66 %	67 %	22m	39m
Entrectinib	ALKA 372-001 STARTRK-1 STARTRK-1	Fase I Fase II	51	63 %	64 %	28m	41.5m
Repotrectinib	TRIDENT-1	Fase I/II	88	59 %	NR	8.6m - NR	NR



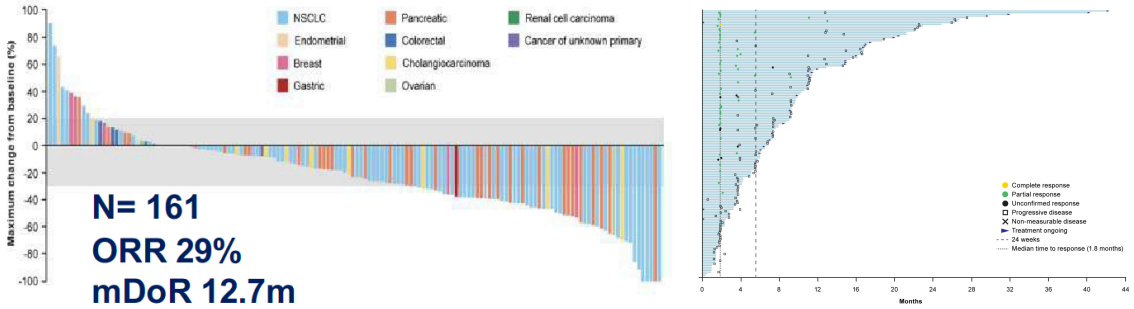
Elaboración personal con datos extraídos de los ensayos clínicos citados en la tabla; Solomon B. ESMO 2023

NRG-1: La ¿última? en llegar

- NEUREGULINA-1: Familia de factor de crecimiento con secuencia EGF-like
- Se une a ErbB3 y ErbB4 induciendo dimerización y activación.
- Incidencia global 0.2%.

Zenocutuzumab

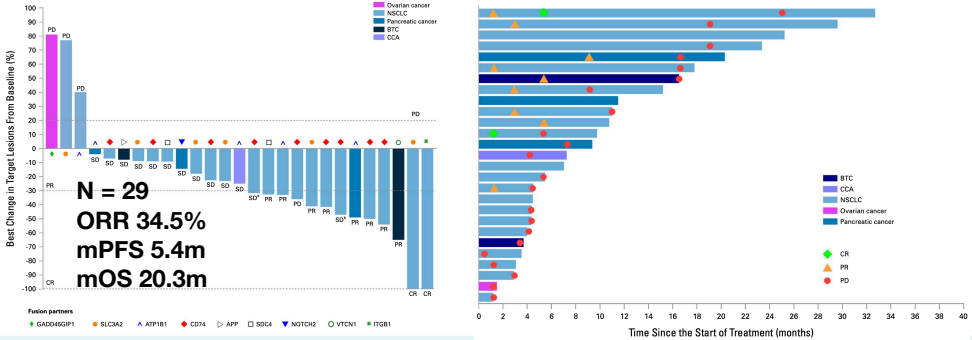
IgG1 biespecífico anti HER2 y HER3



Seribantumab es un anticuerpo anti-HER3 desarrollado para tumores con fusión NRG1; no inhibe una quinasa de fusión como ALK o ROS1, sino que bloquea la dependencia funcional HER3/HER2 inducida por NRG1

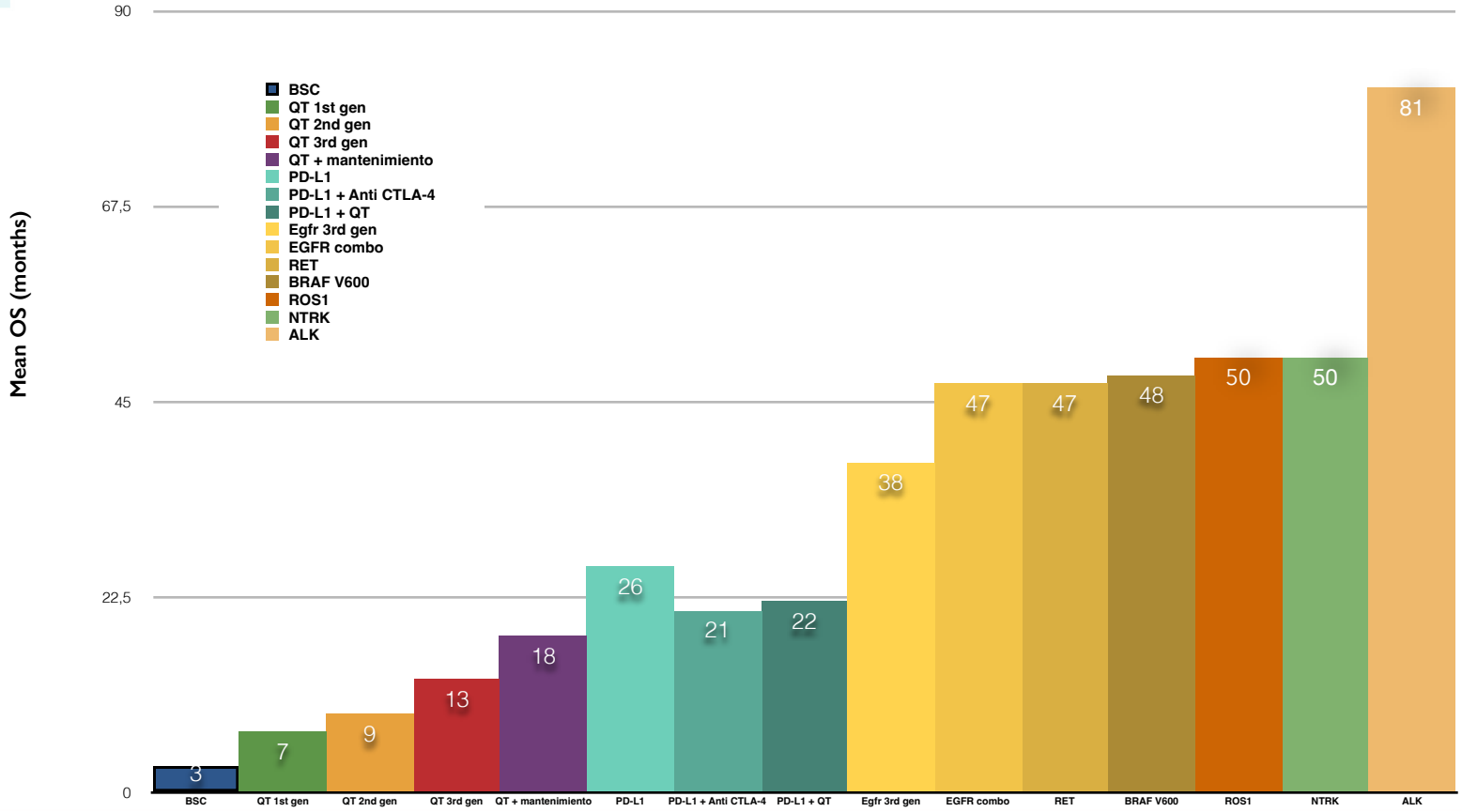
Seribantumab

IgG2 biespecífico anti HER2 y HER3



Schram A et al. N Engl J Med. 2025 Feb 6;392(6):566-576; Patil T et al. JCO Precis Oncol. 2025 Aug:9:e2500221.

Resultados de tratamiento: ADC avanzado, 1L



Elaboración personal

Para ir concluyendo

1. **Fragmentación oncogénica real:** El ~60% de los ADC tienen *driver* accionable; encontrarlos define supervivencia y anticipa santuarios clave como el SNC
2. **Diagnóstico eficiente = NGS inicial (DNA + RNA):** Supera el agotamiento tisular del abordaje monogénico, optimiza la detección de fusiones, ahorra costes globales y se complementa con la biopsia líquida
3. **Prioridad absoluta a la 1ª línea:** Tratar el *driver* desde el debut maximiza la tasa de respuestas y la supervivencia libre de progresión frente a otros esquemas
4. **Hacia la medicina de ultraprecisión:** La práctica clínica incorpora nuevas opciones con inhibidores de nueva generación con alta penetrancia en SNC, ADCs, biespecíficos, etc…, ampliando de forma continua las opciones en ESCAT Tier I

Muchas gracias por su amable atención

