

III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN
SEVILLA, 12 Y 13 DE FEBRERO DE 2026

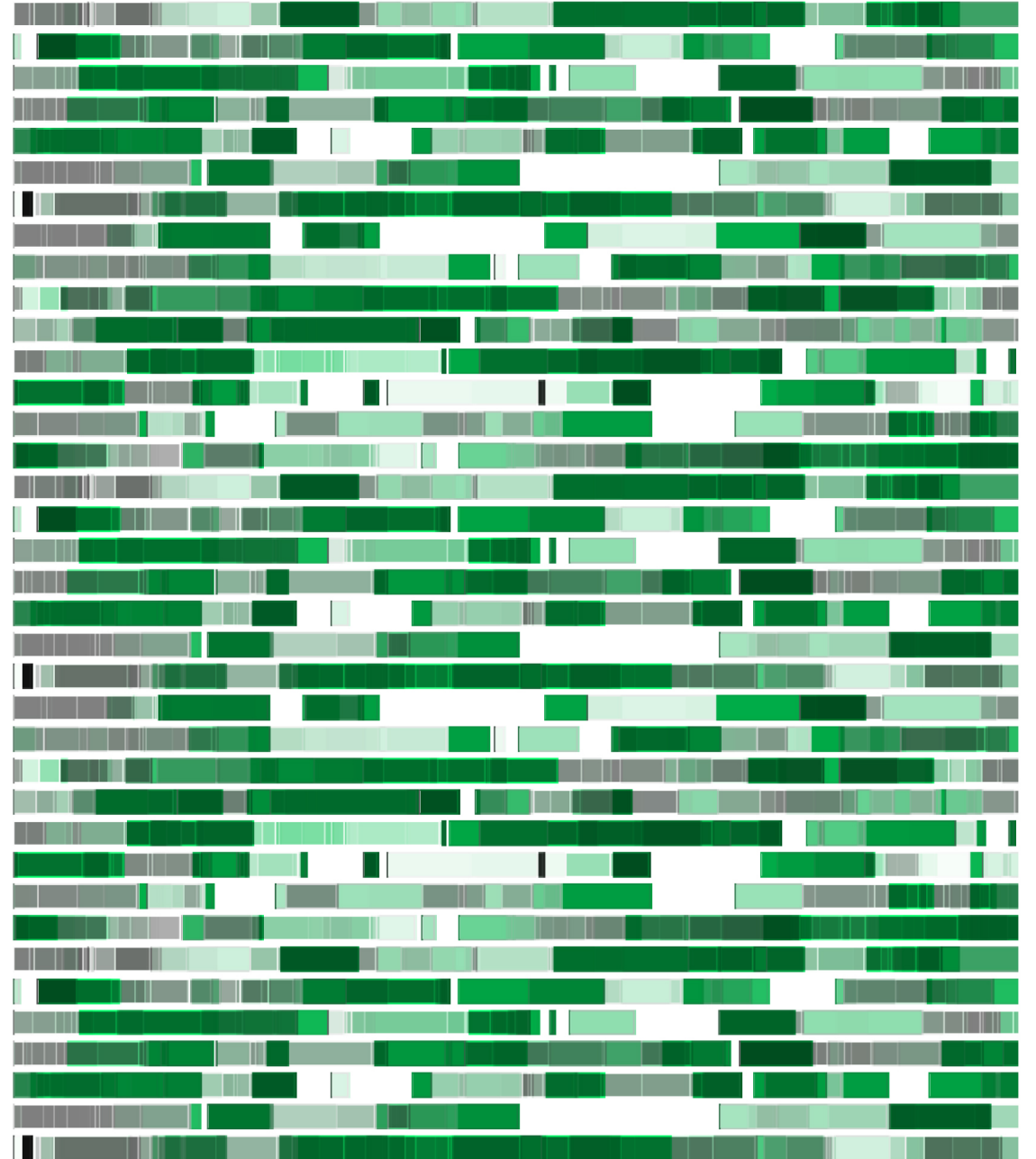
Importancia de las traslocaciones en el cáncer de pulmón

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Organizador por:

HENDERE HEALTHCARE





INTRODUCCION

TIERRAS RARAS... “conjunto de 17 elementos químicos (escandio, itrio y 15 lantánidos) **ESENCIALES PARA LA TECNOLOGIA MODERNA.** Aunque no son extremadamente escasos en la corteza terrestre, su extracción es difícil y costosa.”

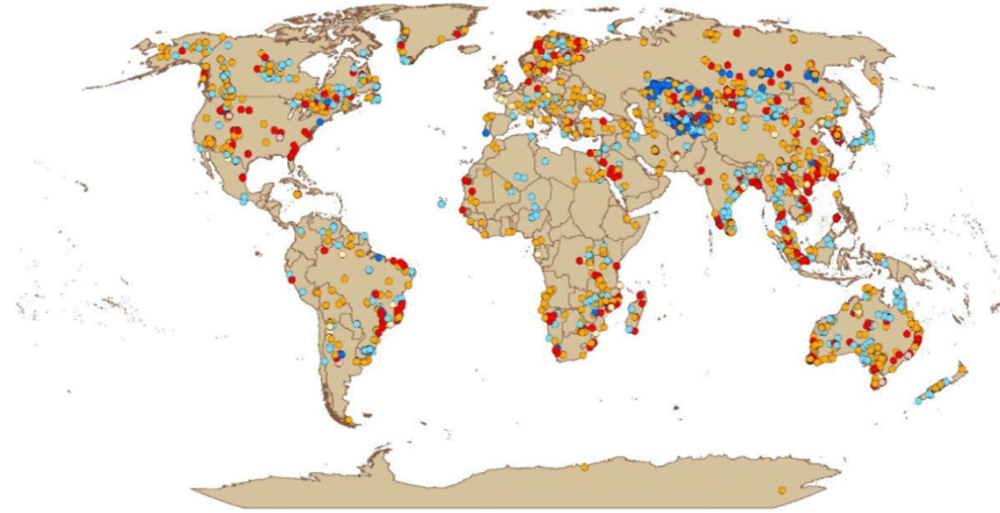


Tabla periódica de los elementos

grupo 1																	grupo 18							
1	2															10	11	12	13	14	15	16	17	18
1	H																	He						
2	Li	Be											B	C	N	O	F	Ne						
3	Na	Mg											Al	Si	P	S	Cl	Ar						
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr						
5	Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe						
6	Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn						
7	Fr	Ra	Lr	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Cn	Nh	Fl	Mc	Lv	Ts	Og						

masa atómica: número másico del isótopo más estable
 1°: energía de ionización en kJ/mol
 símbolo químico
 nombre
 configuración electrónica

número atómico
 electronegatividad
 estados de oxidación más comunes en los reactivos

metales alcalinos
 metales alcalinotérreos
 otros metales
 metales de transición
 lantánidos
 actínidos
 metaloides
 no metales
 halógenos
 gases nobles
 elementos desconocidos (datos de elementos adyacentes entre paréntesis)

Bloques de configuración electrónica
 s p d f

Notas
 * Lantano = 138,905 u
 † Actínido representado por un símbolo de elemento de la tabla periódica
 ‡ Los números de oxidación de los elementos 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 205, 210, 215, 220, 225, 230, 235, 240, 245, 250, 255, 260, 265, 270, 275, 280, 285, 290, 295, 300, 305, 310, 315, 320, 325, 330, 335, 340, 345, 350, 355, 360, 365, 370, 375, 380, 385, 390, 395, 400, 405, 410, 415, 420, 425, 430, 435, 440, 445, 450, 455, 460, 465, 470, 475, 480, 485, 490, 495, 500, 505, 510, 515, 520, 525, 530, 535, 540, 545, 550, 555, 560, 565, 570, 575, 580, 585, 590, 595, 600, 605, 610, 615, 620, 625, 630, 635, 640, 645, 650, 655, 660, 665, 670, 675, 680, 685, 690, 695, 700, 705, 710, 715, 720, 725, 730, 735, 740, 745, 750, 755, 760, 765, 770, 775, 780, 785, 790, 795, 800, 805, 810, 815, 820, 825, 830, 835, 840, 845, 850, 855, 860, 865, 870, 875, 880, 885, 890, 895, 900, 905, 910, 915, 920, 925, 930, 935, 940, 945, 950, 955, 960, 965, 970, 975, 980, 985, 990, 995, 1000, 1005, 1010, 1015, 1020, 1025, 1030, 1035, 1040, 1045, 1050, 1055, 1060, 1065, 1070, 1075, 1080, 1085, 1090, 1095, 1100, 1105, 1110, 1115, 1120, 1125, 1130, 1135, 1140, 1145, 1150, 1155, 1160, 1165, 1170, 1175, 1180, 1185, 1190, 1195, 1200, 1205, 1210, 1215, 1220, 1225, 1230, 1235, 1240, 1245, 1250, 1255, 1260, 1265, 1270, 1275, 1280, 1285, 1290, 1295, 1300, 1305, 1310, 1315, 1320, 1325, 1330, 1335, 1340, 1345, 1350, 1355, 1360, 1365, 1370, 1375, 1380, 1385, 1390, 1395, 1400, 1405, 1410, 1415, 1420, 1425, 1430, 1435, 1440, 1445, 1450, 1455, 1460, 1465, 1470, 1475, 1480, 1485, 1490, 1495, 1500, 1505, 1510, 1515, 1520, 1525, 1530, 1535, 1540, 1545, 1550, 1555, 1560, 1565, 1570, 1575, 1580, 1585, 1590, 1595, 1600, 1605, 1610, 1615, 1620, 1625, 1630, 1635, 1640, 1645, 1650, 1655, 1660, 1665, 1670, 1675, 1680, 1685, 1690, 1695, 1700, 1705, 1710, 1715, 1720, 1725, 1730, 1735, 1740, 1745, 1750, 1755, 1760, 1765, 1770, 1775, 1780, 1785, 1790, 1795, 1800, 1805, 1810, 1815, 1820, 1825, 1830, 1835, 1840, 1845, 1850, 1855, 1860, 1865, 1870, 1875, 1880, 1885, 1890, 1895, 1900, 1905, 1910, 1915, 1920, 1925, 1930, 1935, 1940, 1945, 1950, 1955, 1960, 1965, 1970, 1975, 1980, 1985, 1990, 1995, 2000, 2005, 2010, 2015, 2020, 2025, 2030, 2035, 2040, 2045, 2050, 2055, 2060, 2065, 2070, 2075, 2080, 2085, 2090, 2095, 2100, 2105, 2110, 2115, 2120, 2125, 2130, 2135, 2140, 2145, 2150, 2155, 2160, 2165, 2170, 2175, 2180, 2185, 2190, 2195, 2200, 2205, 2210, 2215, 2220, 2225, 2230, 2235, 2240, 2245, 2250, 2255, 2260, 2265, 2270, 2275, 2280, 2285, 2290, 2295, 2300, 2305, 2310, 2315, 2320, 2325, 2330, 2335, 2340, 2345, 2350, 2355, 2360, 2365, 2370, 2375, 2380, 2385, 2390, 2395, 2400, 2405, 2410, 2415, 2420, 2425, 2430, 2435, 2440, 2445, 2450, 2455, 2460, 2465, 2470, 2475, 2480, 2485, 2490, 2495, 2500, 2505, 2510, 2515, 2520, 2525, 2530, 2535, 2540, 2545, 2550, 2555, 2560, 2565, 2570, 2575, 2580, 2585, 2590, 2595, 2600, 2605, 2610, 2615, 2620, 2625, 2630, 2635, 2640, 2645, 2650, 2655, 2660, 2665, 2670, 2675, 2680, 2685, 2690, 2695, 2700, 2705, 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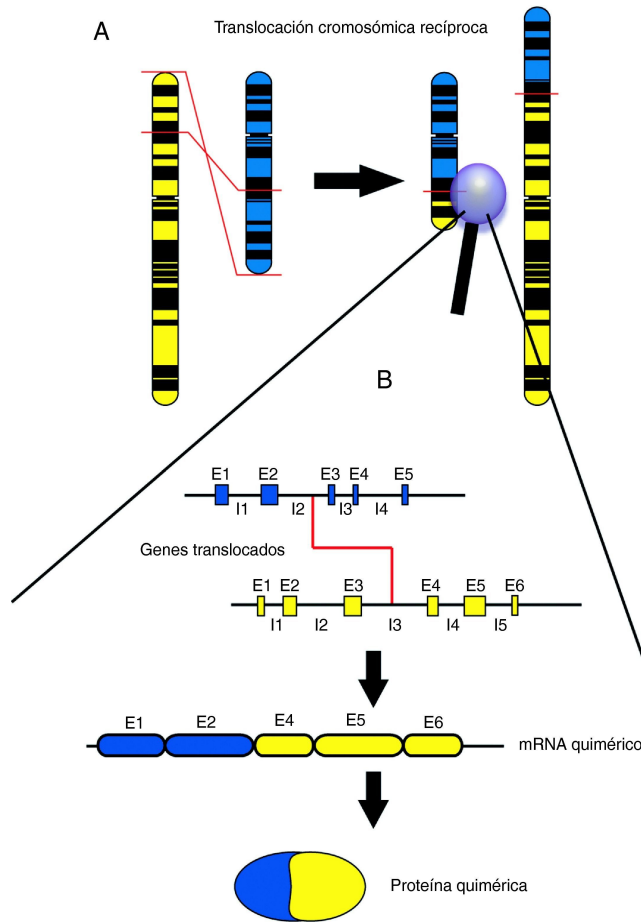
INTRODUCCION

Las traslocaciones en CPNM son como esas TIERRAS RARAS....

- ✓ SON POCO FRECUENTES (pero no tanto, en total pueden suponer en torno a un 10%)
- ✓ DIFICILES, COSTOSAS DE DETECTAR (relativamente, principal problema optimizar la habitualmente “escasa” muestra tumoral disponible)
- ✓ SON DE EXTRAORDINARIO VALOR, DADO QUE **ENCONTRAR UNA TRASLOCACION EN EL DIAGNOSTICO DE CANCER DE PULMON CAMBIARA LA VIDA DE NUESTRO PACIENTE**

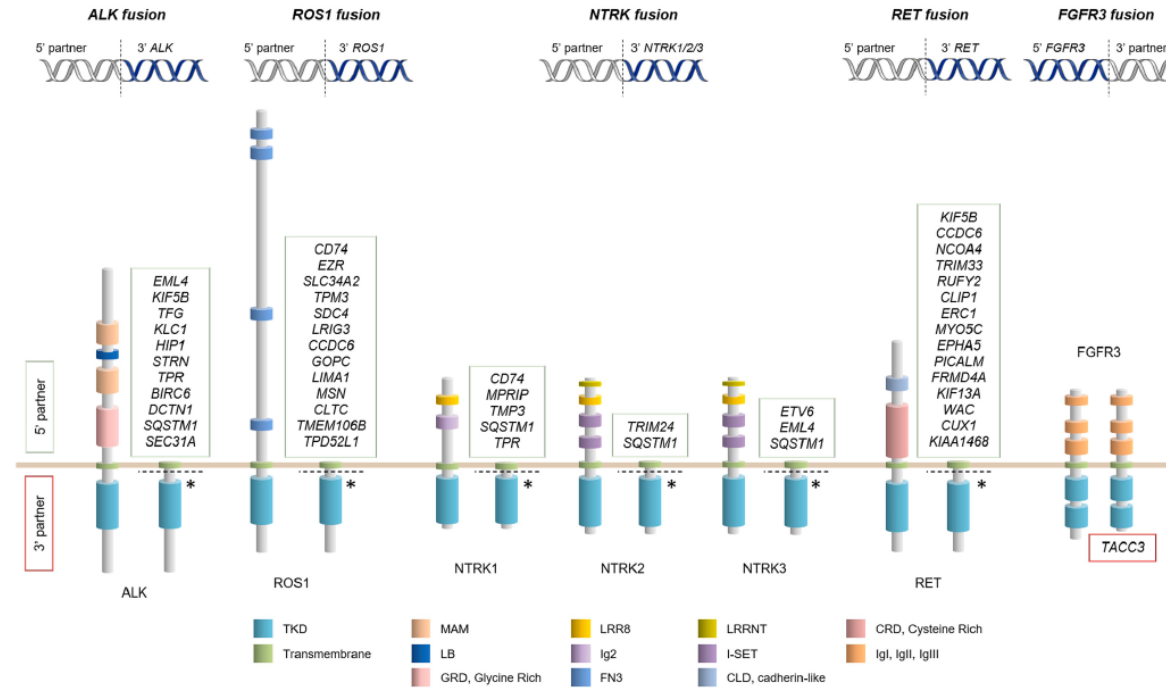


MECANISMO MOLECULAR TRASLOCACIONES



M. Saigí et al.

Cancer Treatment Reviews 109 (2022) 102430

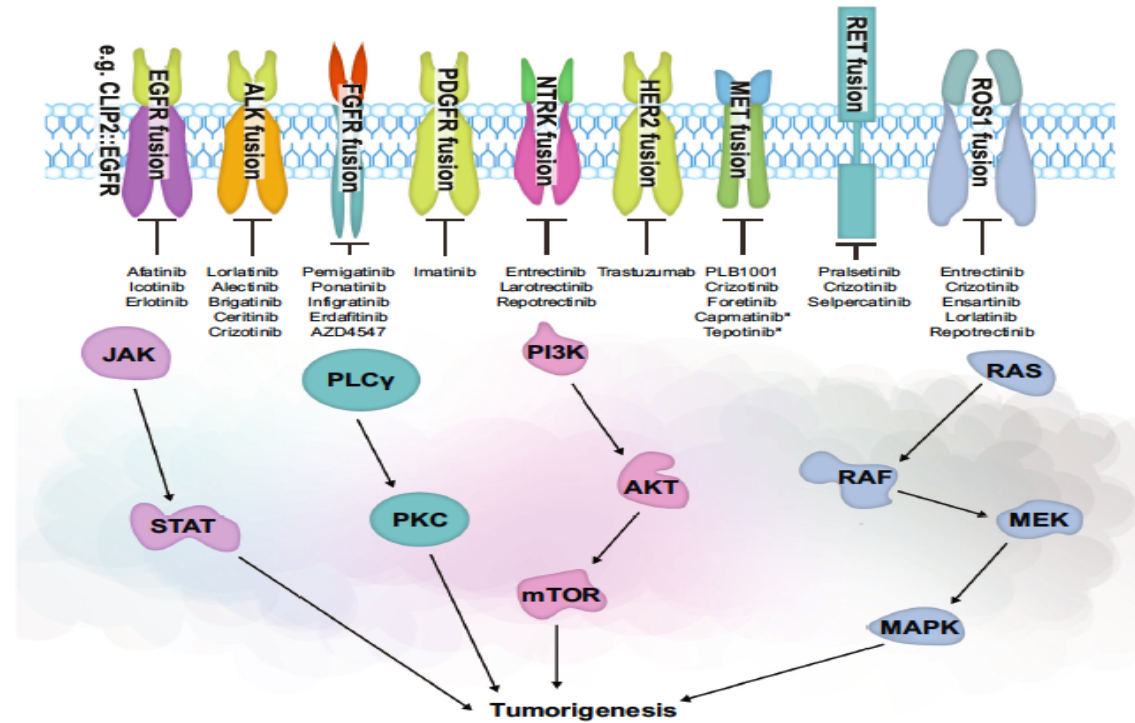
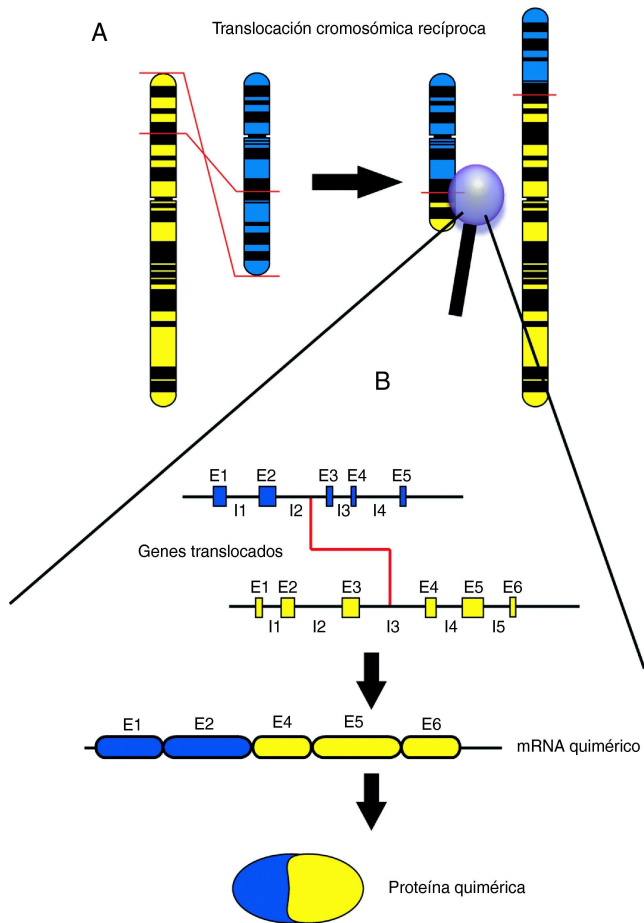


Intercambio genético entre cromosomas tras la ruptura de los mismos:
2 genes separados se yuxtaponen → genes de fusión

Translocación cromosómica (A) y genes traslocados (B)
→ ARN resultante → proteína quimérica.



MECANISMO MOLECULAR TRASLOCACIONES

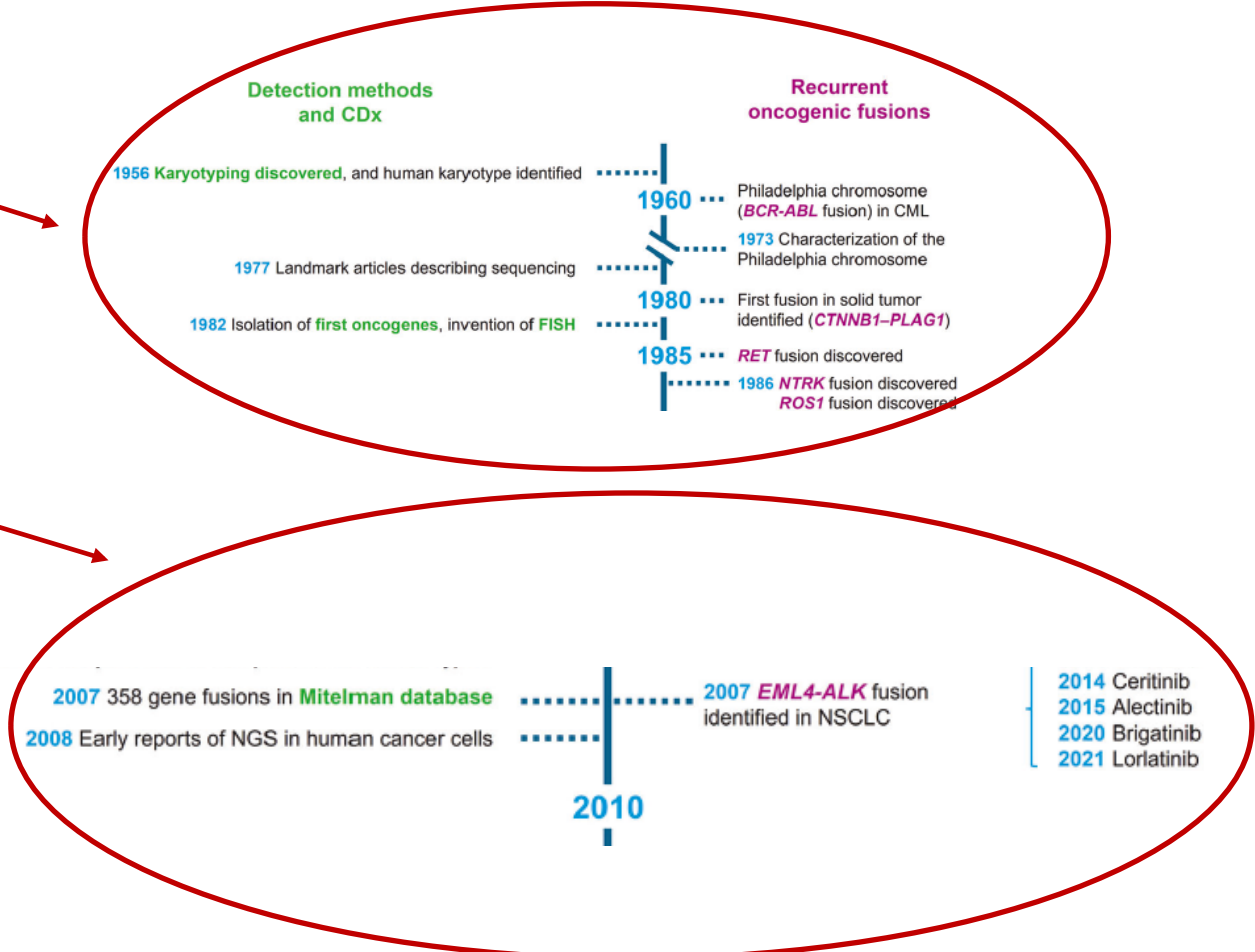
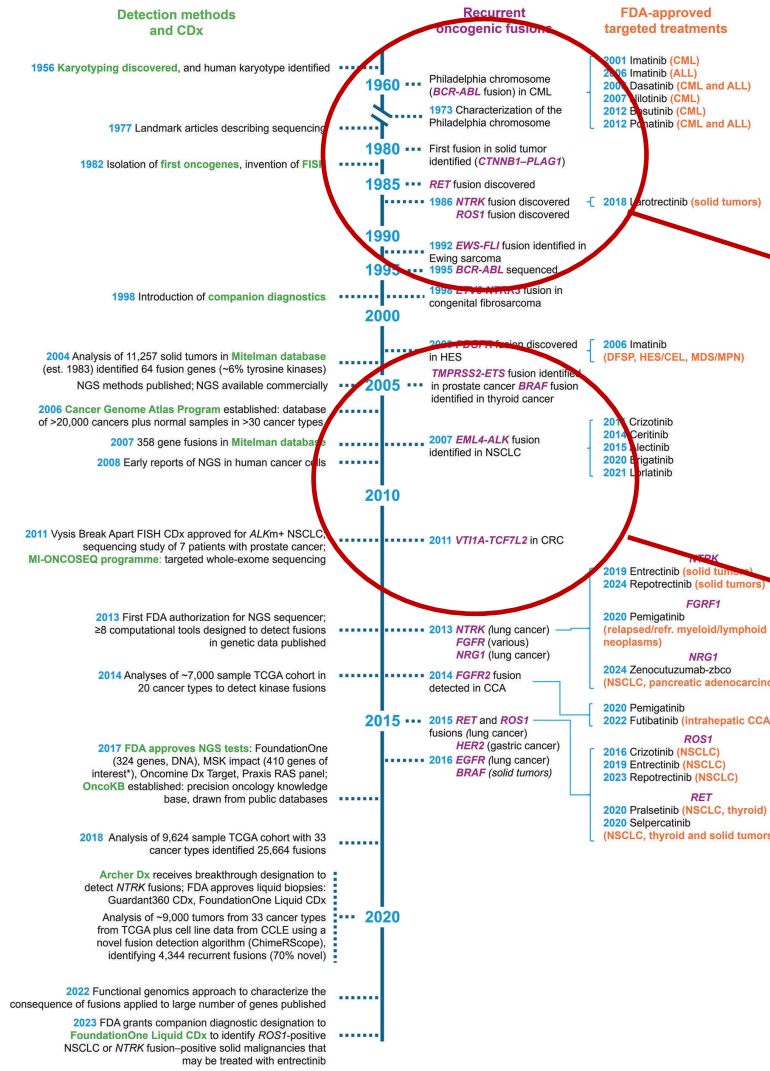


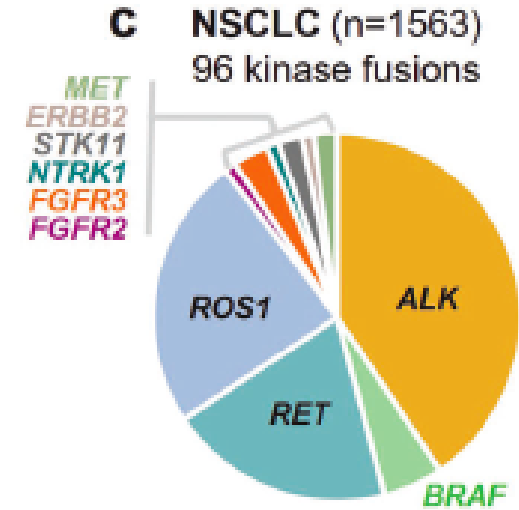
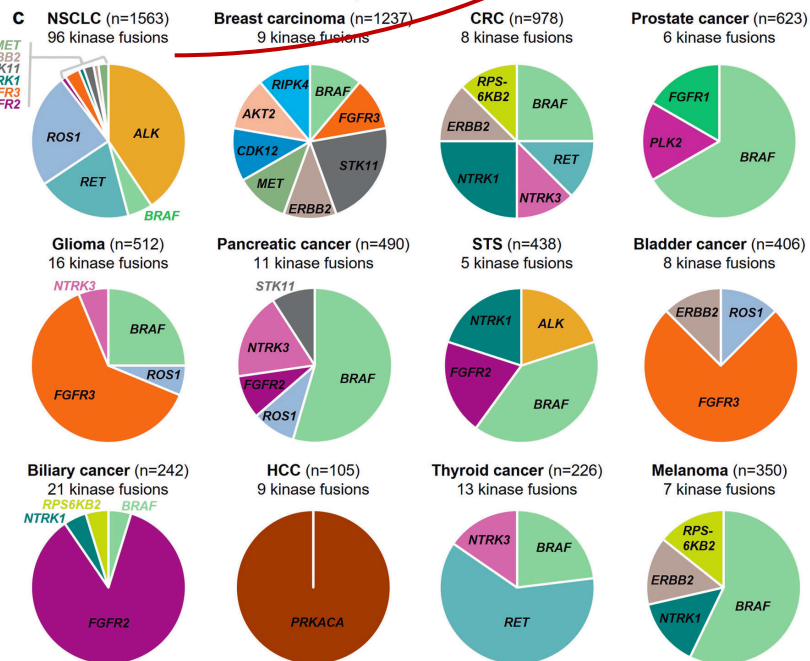
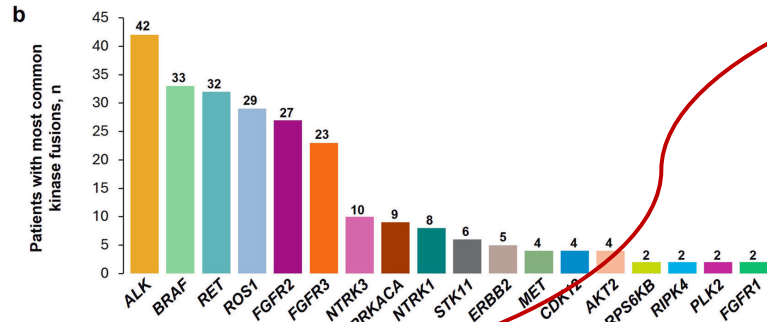
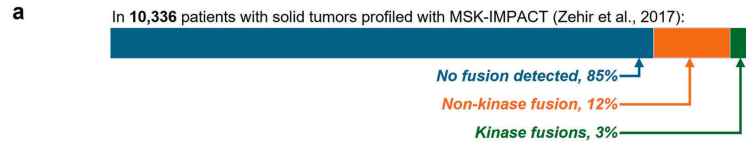
Los genes de fusión dan lugar a una proteína quimérica TK activada de forma constitutiva, lo que implica la puesta en marcha de vías de proliferación celular (JAK-STAT, PI3K-AKT-mTOR, RAS-MAPK)

Translocación cromosómica (A) y genes traslocados (B)
→ ARN resultante → proteína quimérica.



PRIMERA TRASLOCACION IDENTIFICADA (años 60): fusión BCR-ABL de LMC.

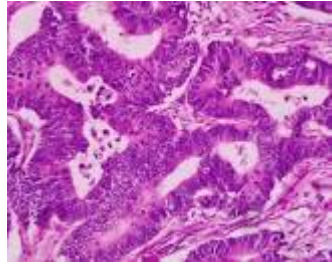




✓ La fusión más frecuente en CPNM es la fusión ALK (frecuencia del 5-8%), seguida de ROS1 y RET. El resto son mucho menos frecuentes.

✓ No todas disponen de terapia dirigida

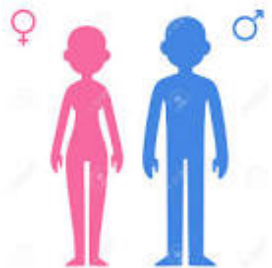
Liu et al. Signal Transduction and Targeted Therapy (2025).
Westphalen et al. Annals of Oncology (2024).



Adenocarcinoma: subtipos especiales (anillo de sello, desdiferenciado)



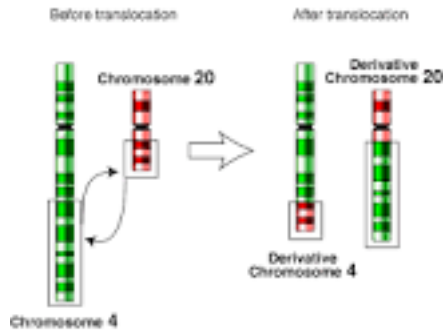
Edad media más joven



Predominio mujeres:
ALK, ROS 1

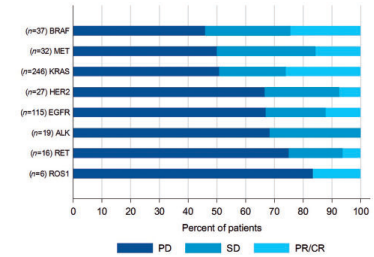


No fumadores

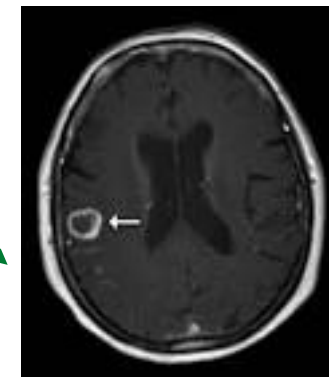


FUSIONES

Menor respuesta a
inmunoterapia



Riesgo aumentado
ETEVE: ALK (OR 2.1), ROS1
(OR 3.15)

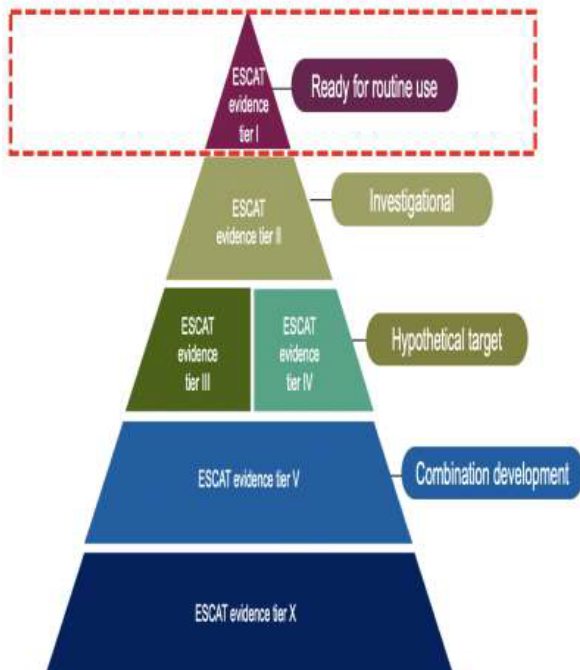


Afectación SNC
hasta 50% debut



CONSENSO SEOM-SEAP BIOMARCADORES EN CPNM

The ESMO Precision Medicine Working Group¹



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
ALK	Fusions (mutations as mechanism of resistance)	IA
MET	Mutations ex 14 skipping	IB
ESCAT TIER EVIDENCE II		
BRAP ⁶³⁰	Mutations	IB
ROS1	Fusions (mutations as mechanism of resistance)	IB
NTRK	Fusions	IC
RET	Fusions	IC
ESCAT TIER EVIDENCE III-IV		
KRAS ^{G12C}	Mutations	IIB
EGFR	Exon 20 insertion	IIB
ERBB2	Hotspot mutations and Amplifications	IIB
MET	Focal amplifications (acquired resistance on EGFR TKI)	IIB
ESCAT TIER EVIDENCE V		
BRCA 1/2	Mutations	IIIA
PIK3CA	Hotspot mutations	IIIA
NRG1	Fusions	IIIB

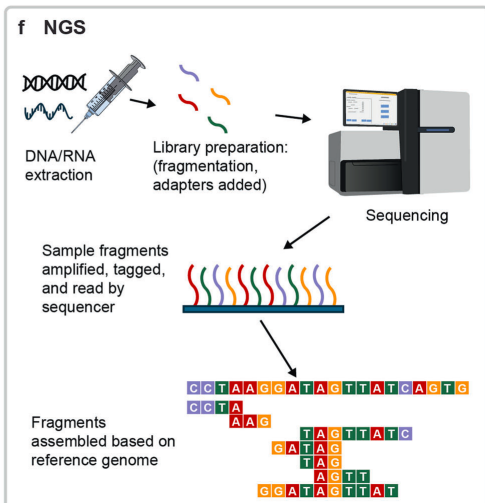
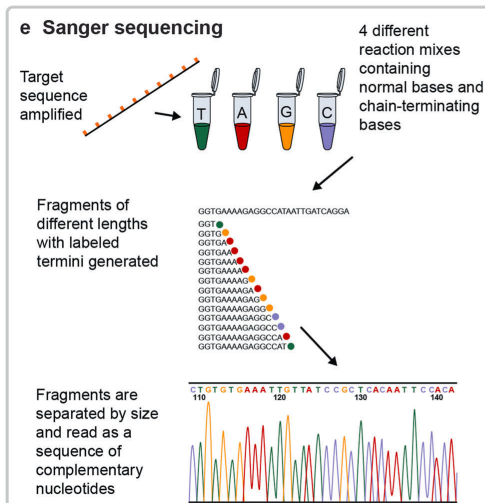
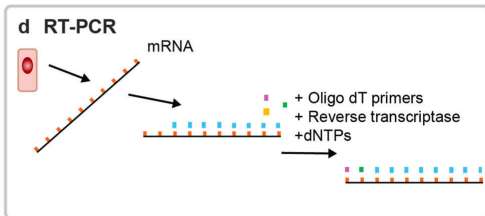
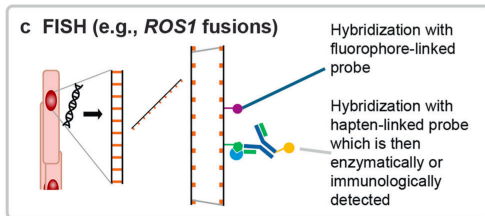
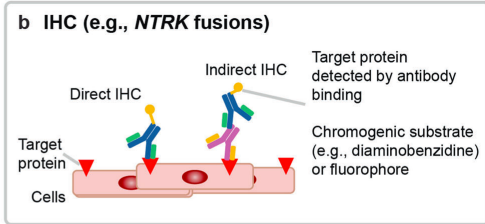
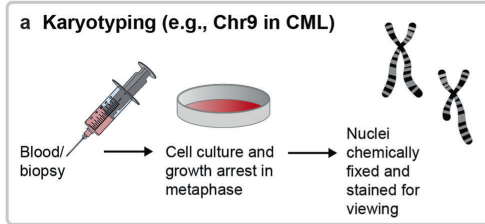
CONSENSO NACIONAL DE BIOMARCADORES ESENCIALES EN CPNM PARA TERAPIA 1ª LINEA

Gene/protein	Predictive alteration	Methodology
<i>EGFR</i>	Mutation	PCR: Sanger sequencing, real-time PCR and NGS
<i>ALK</i>	Rearrangement	IHC, FISH, real-time PCR and NGS
<i>ROS1</i>	Rearrangement	IHC (screening), FISH, real-time PCR and NGS
<i>BRAF V600</i>	Mutation	Real-time PCR and NGS
<i>PD-L1</i>	Overexpression	IHC
<i>NTRK</i>	Rearrangement	IHC (screening), real-time PCR and NGS
<i>RET</i>	Rearrangement	FISH, real-time PCR and NGS
<i>KRAS</i>	Mutation	PCR: Sanger sequencing, real-time PCR and NGS
<i>MET</i>	Mutation Amplification	NGS FISH, real-time PCR and NGS

ALK anaplastic lymphoma kinase, *BRAF* B-Raf proto-oncogene, *EGFR* epidermal growth factor receptor, *FISH* fluorescence in situ hybridisation, *IHC* immunohistochemistry, *KRAS* Kirsten rat sarcoma virus, *MET* mesenchymal epithelial transition factor, *NGS* next-generation sequencing, *NSCLC* non-small cell lung cancer, *NTRK* neurotrophic tyrosine receptor kinase, *PCR* polymerase chain reaction, *PD-L1* programmed death ligand-1, *RET* rearranged during transfection, *ROS1* c-ros oncogene 1

ESCAT (*ESMO Scale for Clinical Actionable of molecular Targets*): clasifica las alteraciones genómicas en función de su relevancia clínica como dianas terapéuticas en oncología.

DETECCION DE TRASLOCACIONES



404

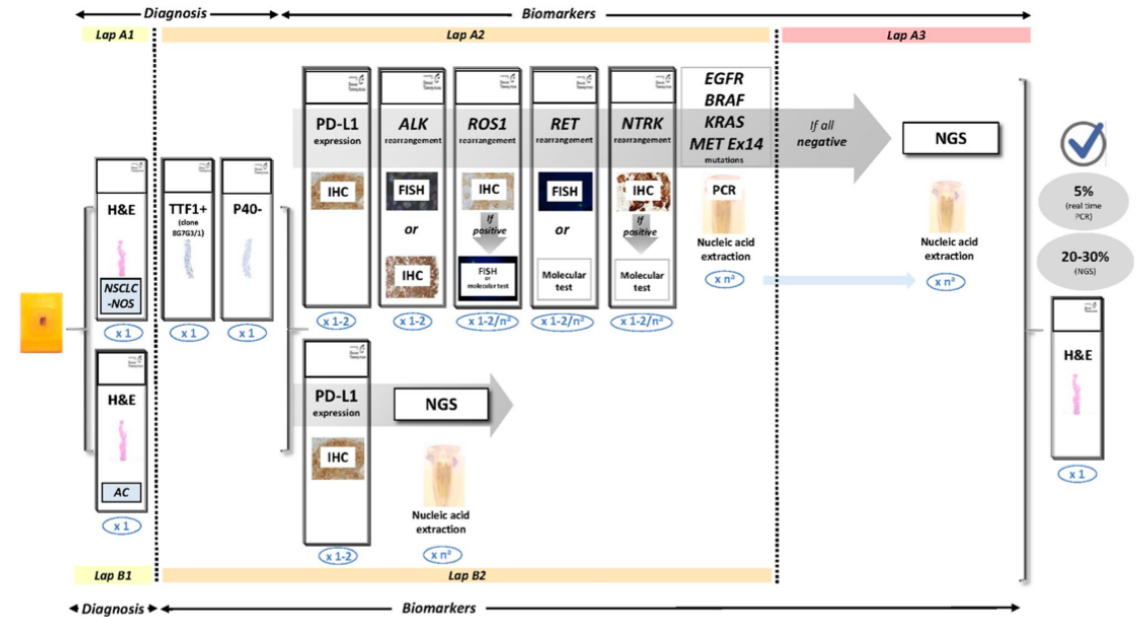
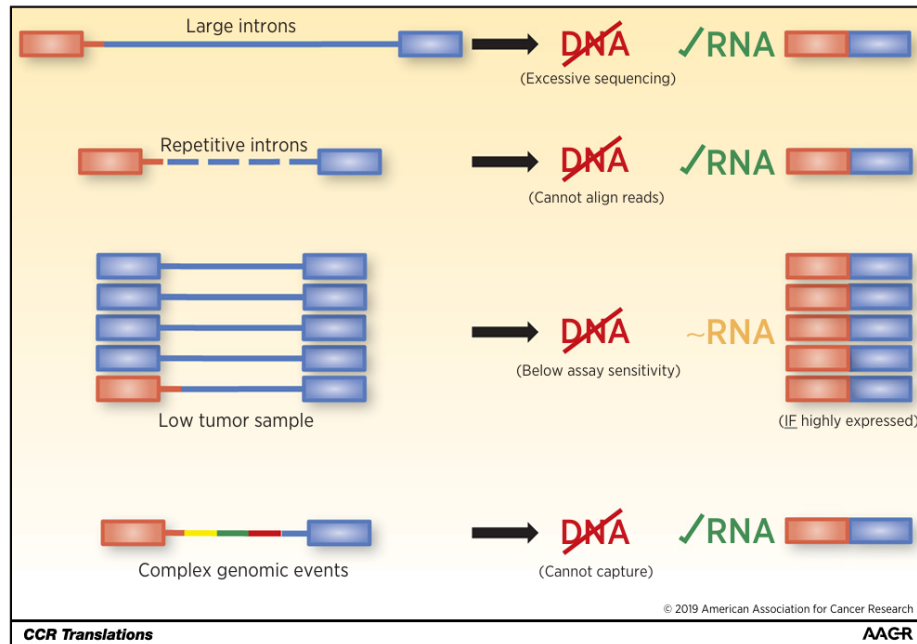
The Oncologist, 2023, Vol. 28, No. 5

Table 1. Differential features of molecular testing techniques (adapted from Belli et al.²⁴).

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	+++	+++	Yes	Expensive, requires high-quality RNA, may detect alterations of uncertain clinical significance and gene expression
NGS	+++	+++	Yes	Use of circulating tumor DNA requires shorter turnaround time and is less invasive than tissue/tumor testing
DNA-sequencing	++/+++	++	Yes	
NGS	++/+++	++	Yes	

^aYes if a specific fusion partner probe is used.
FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; RT-PCR, reverse transcription polymerase chain reaction; ++ indicates moderate; +++ indicates high.

La mejor técnica para detectar las fusiones es la NGS (en concreto RNA-Seq: es costosa, lleva tiempo y requiere muestra de alta calidad)

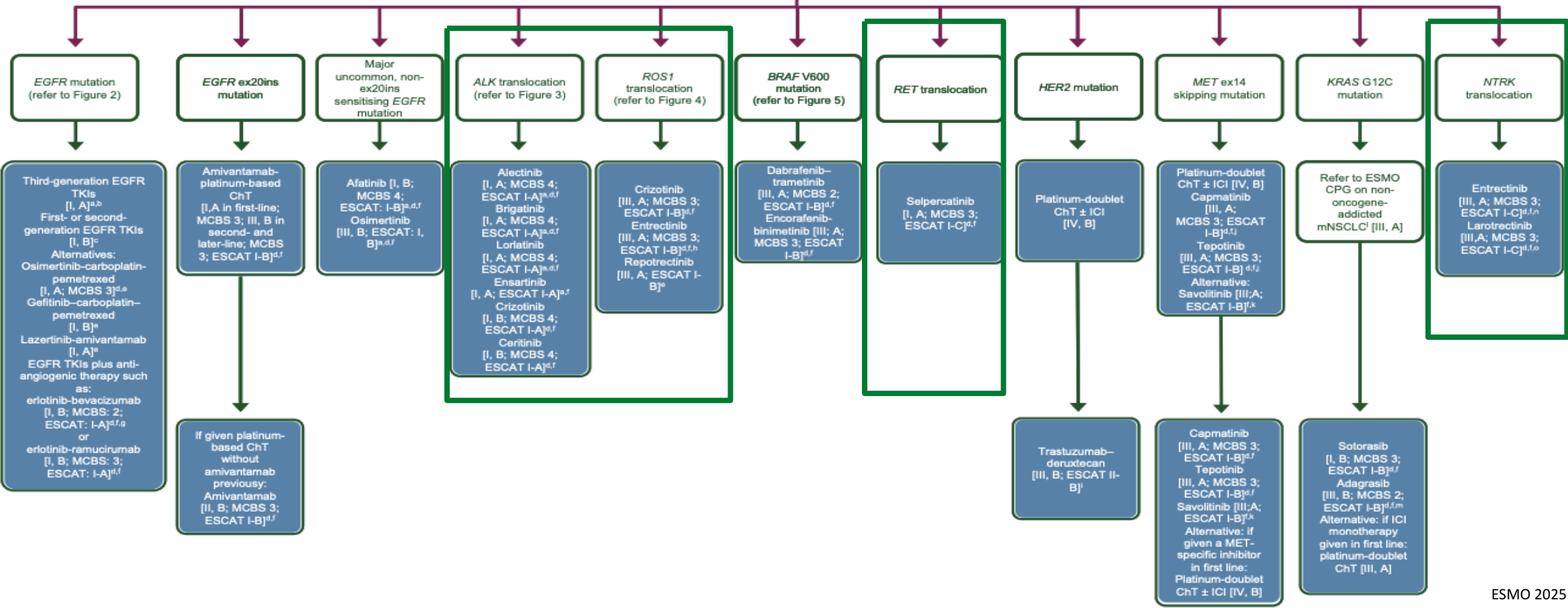


DETECCION DE FUSIONES POR DNaseq VS RNaseq.

- ✓ DNA Seq: ofrece alta S y E, así como posibilidad de detectar nuevos *partners*. La sensibilidad depende de cobertura del panel y breakpoints, por ejemplo, si región intrónica del dominio kinasa es muy larga o hay elementos repetitivos de intrones puede dar falsos negativos.
- ✓ RNA Seq: ofrece la ventaja de que no incluye intrones, y es una verificación directa de genes transcritos. Por el contrario, tiene la desventaja de la labilidad del RNA en la muestra



Stage IV mNSCLC, molecular tests positive (EGFR/ALK/ROS1/BRAF/RET/NTRK/MET/HER2/EGFRex20ins/KRAS G12C)

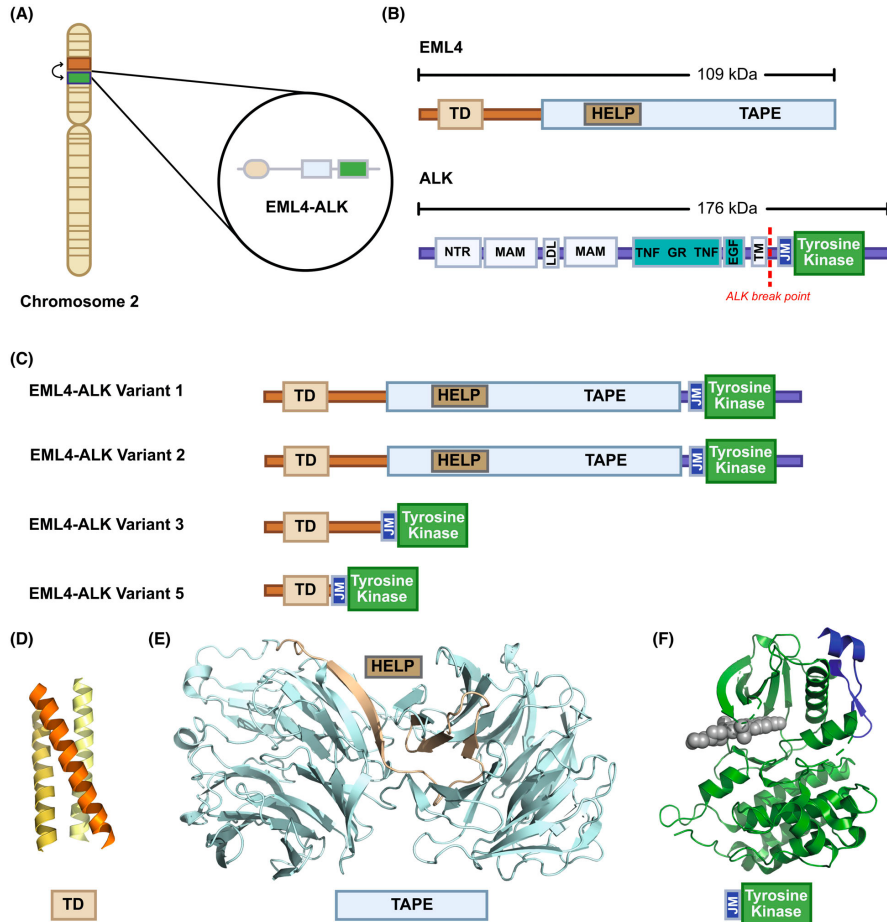


III JORNADA TRASLACIONAL
DE ONCOLOGÍA DE PRECISIÓN:

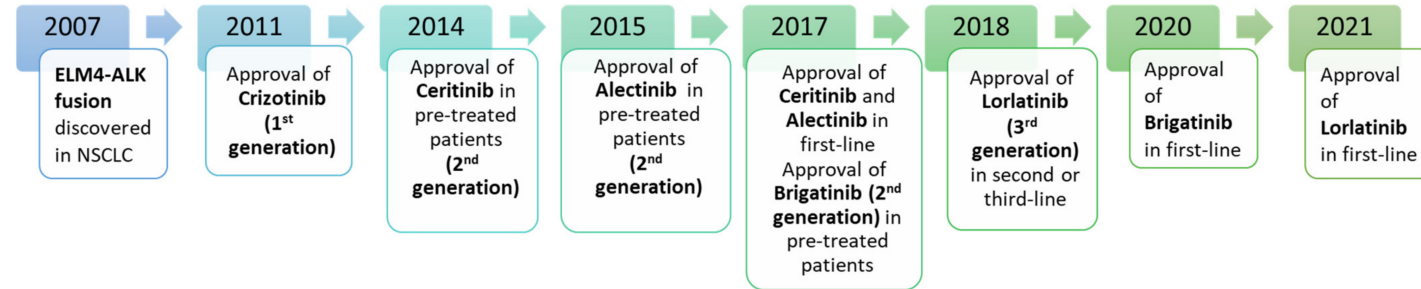
A TRAVÉS DE LAS VÍAS
DE SEÑALIZACIÓN
SEVILLA, 12 Y 13
DE FEBRERO DE 2026



TRASLOCACION ALK



ALK FUSIONES



DESARROLLO TEMPORAL DE INHIBIDORES ALK

Table 3. ALK tyrosine kinase inhibitors according to their generation.

TKI Generation	Name of Drugs
First-generation TKI	crizotinib
Second-generation TKI	ceritinib, alectinib, brigatinib, ensartinib
Third-generation TKI	lorlatinib

Incidencia 5 – 8 %, fusión más frecuente EML4-ALK. Variantes 1,3 más frecuentes; variantes cortas peor pronóstico



SLP CRIZOTINIB VS TKI 2ª GENERACION

ESTUDIO PROFILE 1014: Crizotinib como tratamiento de primera línea frente a quimioterapia en el cáncer de pulmón ALK positivo^{1,2}

Estudio fase 3, abierto, aleatorizado, multicéntrico que comparó crizotinib frente a pemetrexed + quimioterapia basada en platino en pacientes con CPNM avanzado ALK+, y sin tratamiento previo para analizar la eficacia, seguridad y calidad de vida.



OBJETIVOS

OBJETIVO PRINCIPAL: SLP evaluada por un comité revisor independiente

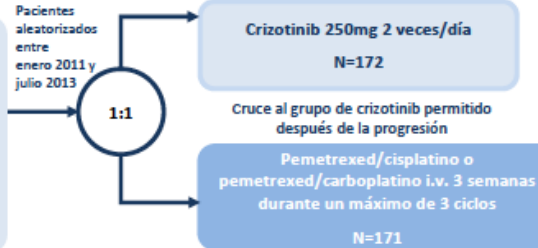
OBJETIVOS SECUNDARIOS: tasa de respuesta, SG, seguridad, calidad de vida



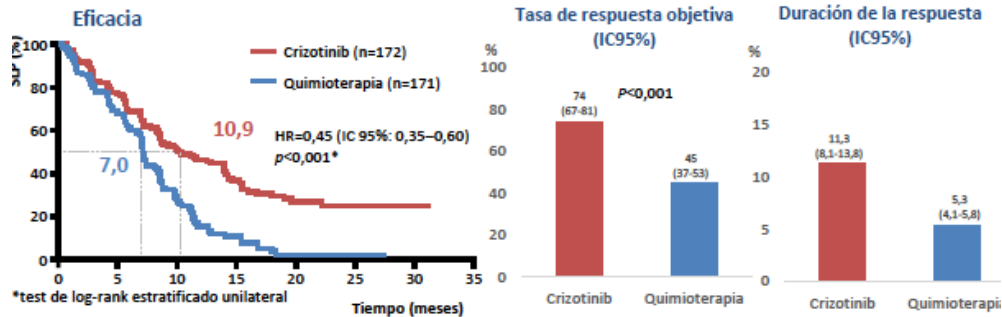
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DISEÑO DEL ESTUDIO

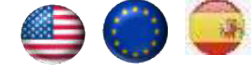
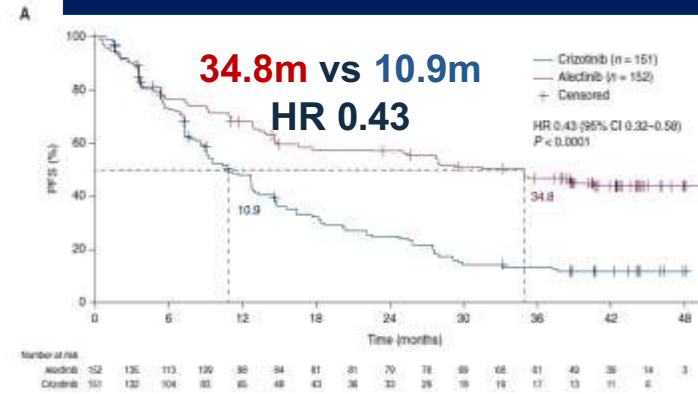
- Pacientes con CPNM ALK+.
- CPNM localmente avanzado o metastásico.
- Sin haber recibido tratamiento previo.
- Pacientes con metástasis cerebral tratada eran elegibles si ésta era estable al menos 2 semanas antes de la inclusión.
- ECOG: 0-2.



RESULTADOS

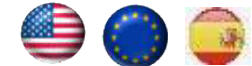
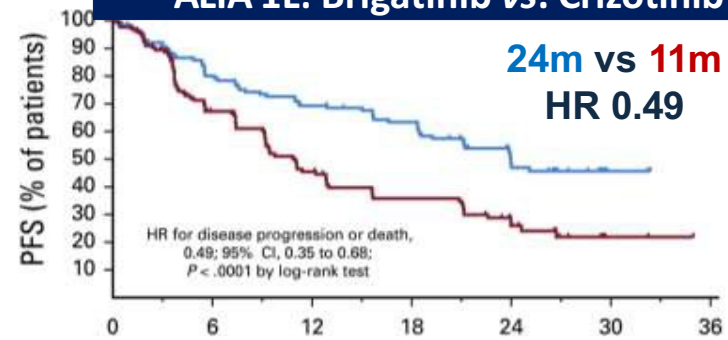


ALEX: Alectinib vs. Crizotinib



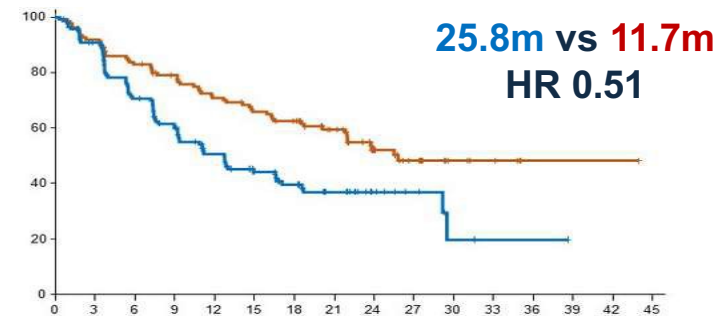
TROic 81%

ALTA 1L: Brigatinib vs. Crizotinib



TROic 78%

eXalt 3: Ensartinib vs. Crizotinib



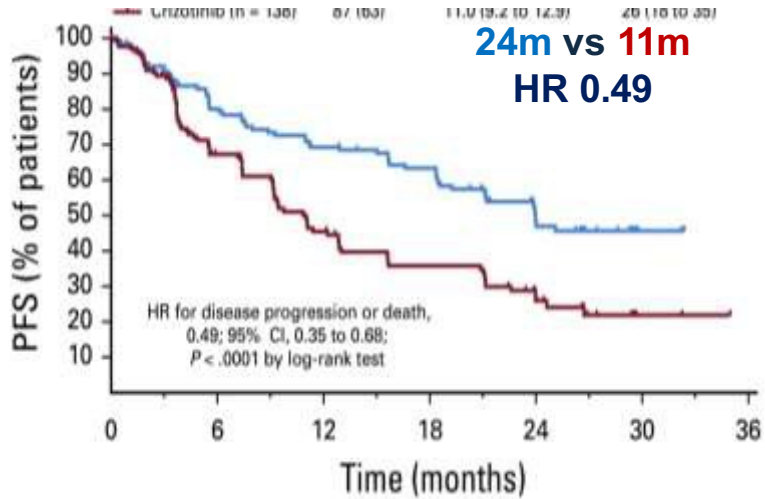
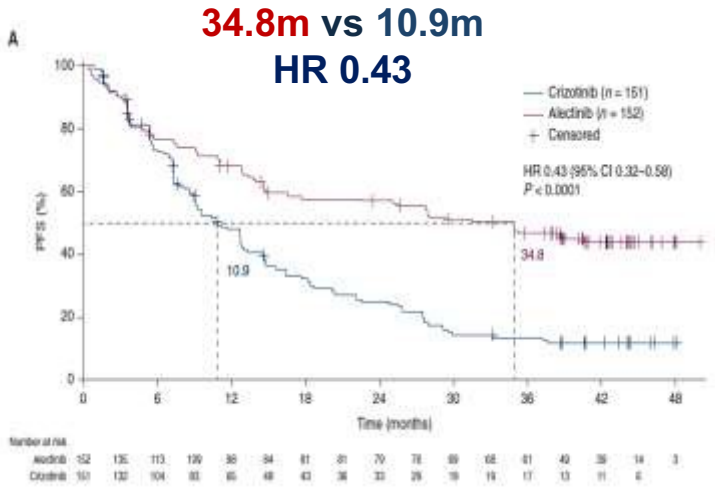
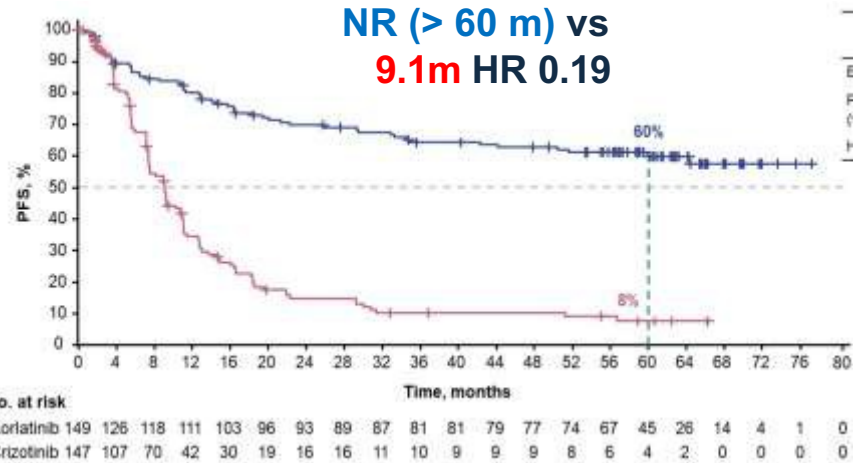
TROic 63%



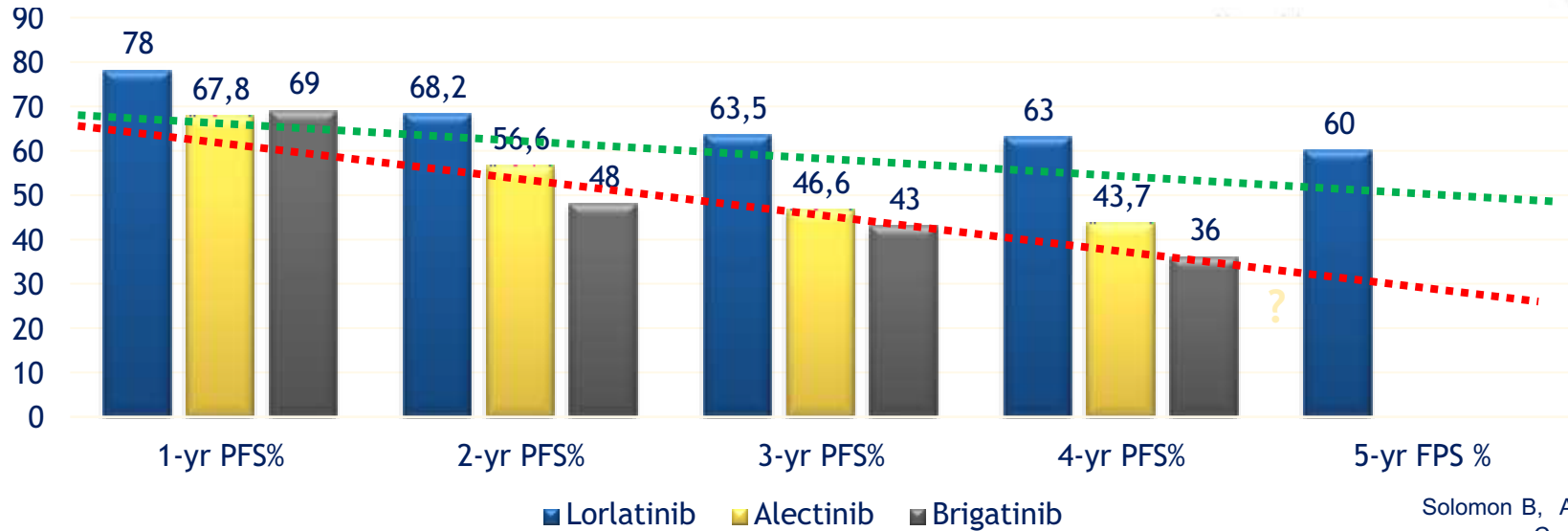
CROWN: Lorlatinib vs. crizotinib

ALEX: Alectinib vs. Crizotinib

ALTA 1L: Brigatinib vs. Crizotinib



TROic 82% con 71% de RC y reducción de riesgo de progresión ic 94%

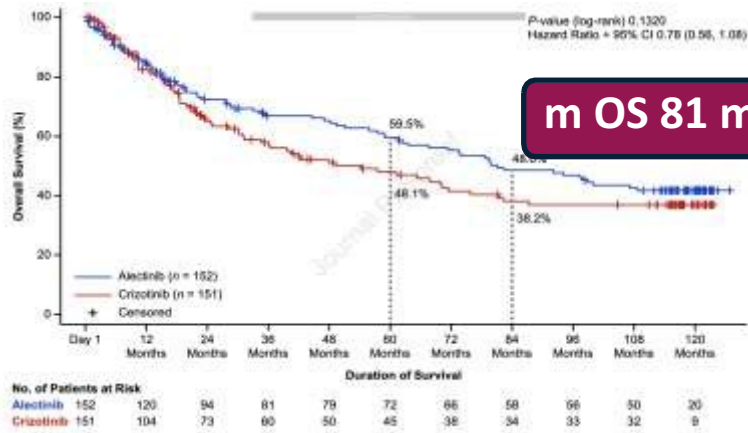




SG TKI 2ª VS TKI 3ª GENERACION

ALEX TRIAL

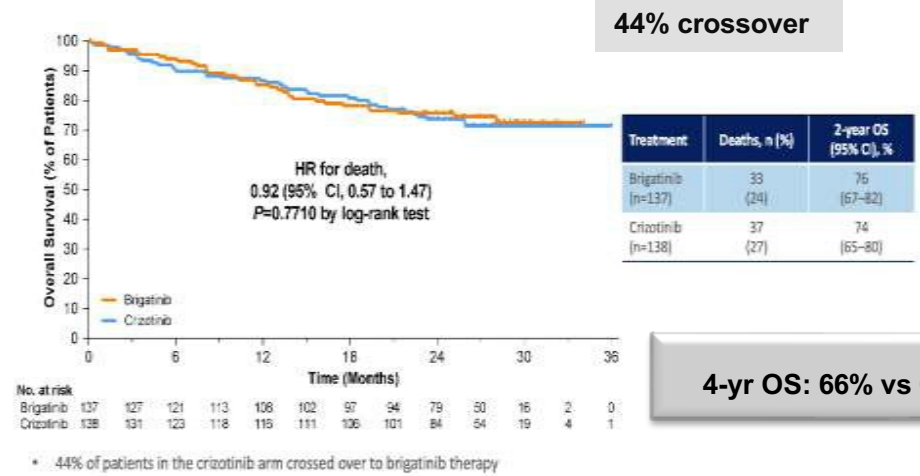
Alectinib vs Crizotinib



5-yr OS: 62% vs 45%
7y OS: 48% vs 38% HR 0.78; p0.13

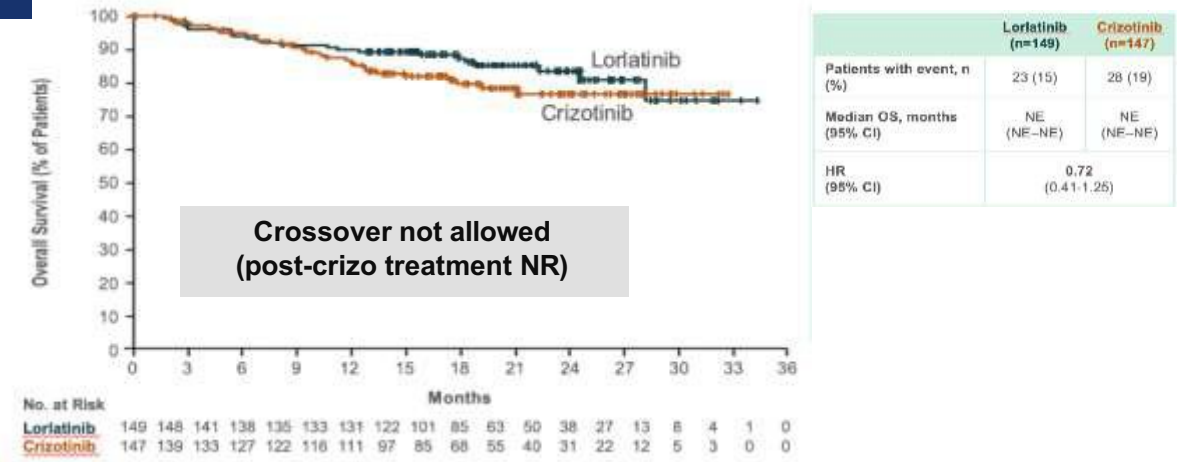
ALTA1L TRIAL

Brigatinib vs Crizotinib



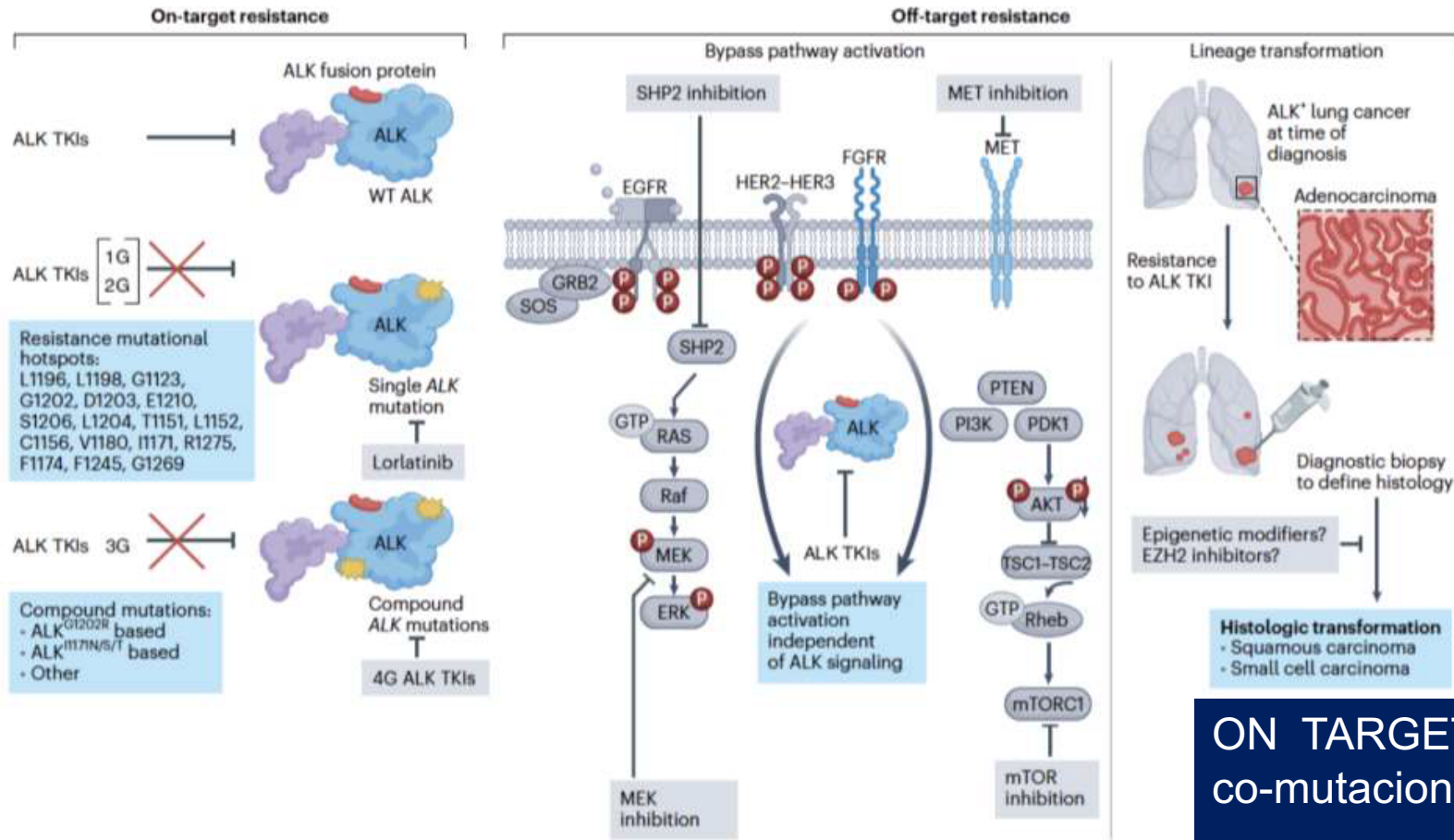
CROWN TRIAL

Lorlatinib vs Crizotinib





MECANISMOS DE RESISTENCIA A iALK

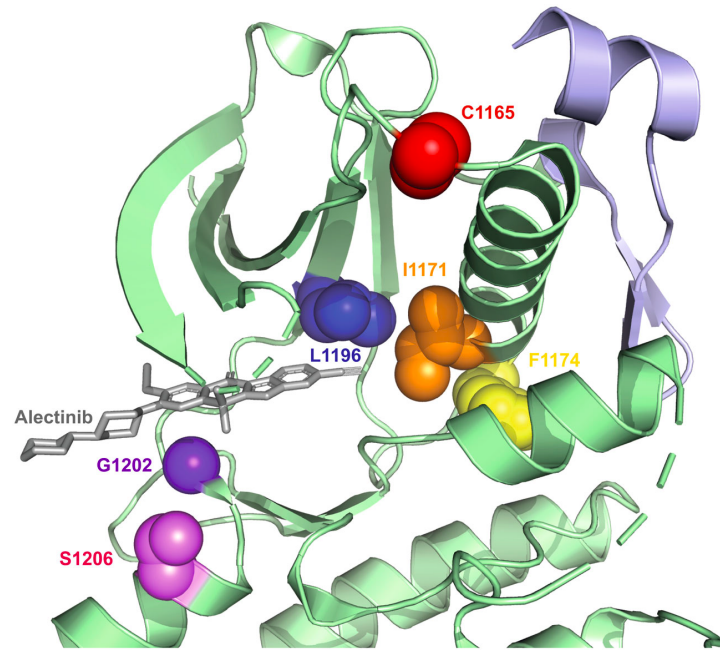


ON TARGET: mutaciones ALK (G1202), co-mutaciones

OFF TARGET: amp MET, SHP2, transformación AP



MECANISMOS DE RESISTENCIA A iALK



EML4-ALK drug resistance

M. Elshatlawy et al.

Table 3. Drug-Resistant mutations after ALK-TKIs treatment. (?) means the sensitivity of this mutation was not assessed against the given drug; (active) means mutation in that row is inhibited by the addressed drug. The differential colour coding highlights the key residues on the ALK kinase domain, as seen in Fig. 2.

EML4-ALK kinase inhibitors & drug-resistant mutations

Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
L1196M [46]	?	L1196M	?	?
G1269A [88]	?	?	?	?
C1156Y [45]	C1156Y/T	?	?	?
I1171T/N/S	Active	I1171T/N/S	?	?
S1206 C/Y [64]	Active	Active	S1206C	?
E1210K [45]	Active	Active	E1210K	?
L1152P/R [46]	L1152P/R	?	?	?
V1180L [88]	Active	V1180L	?	?
I1151T [46,88]	I1151T	?	?	?
F1174C [89]	F1174C/L	?	?	?
F1245C [90]	Active	?	?	?
G1202R [56]	G1202R	G1202R	G1202R	?
E1210K [53]	Active	Active	E1210K	?
D1203N [53]	Active	Active	D1203N	?
Active	?	?	?	L1198F [91]
?	?	Active	?	L1256F [92]
?	?	?	?	G1202R/S1206Y [32]



ALKove-1

Ongoing Global Phase 2 Investigation of NVL-655 for Patients with ALK+ NSCLC

Open and enrolling both **TKI-naïve** and **TKI pre-treated** patients

ALKOVE-1 PHASE 2 PATIENT POPULATION	PRIOR ALK TKI	PRIOR CHEMO/I-O	ALKOVE-1 PHASE 2 OBJECTIVES
ALK+ NSCLC	2-3 prior, any generation (<i>crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib</i> ^a)	0-2 lines	<ul style="list-style-type: none"> Primary: ORR by blinded, independent central review Secondary: Additional efficacy measures (DOR, TTR, CBR, PFS, OS), intracranial activity, overall safety and tolerability, confirmation of PK profile
	1 prior 2G (<i>ceritinib, alectinib, or brigatinib</i>)	0-2 lines	
	1 prior 3G (<i>lorlatinib</i>)	≤ 1	
	None (TKI-naïve)	≤ 1	
Other ALK+ Solid Tumors	Any (not eligible for other cohorts)	Any	
	≥ 1 prior ALK TKI or systemic therapy (or for whom no satisfactory standard therapy exists)	Any	

CBR, clinical benefit rate; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression free survival; PK, pharmacokinetics; TKI, tyrosine kinase inhibitor; TTR, time to response.

^a Excludes patients who received lorlatinib as the 1st prior ALK TKI.

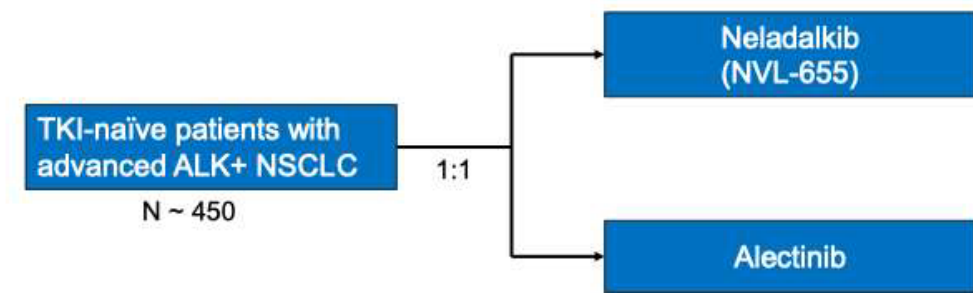
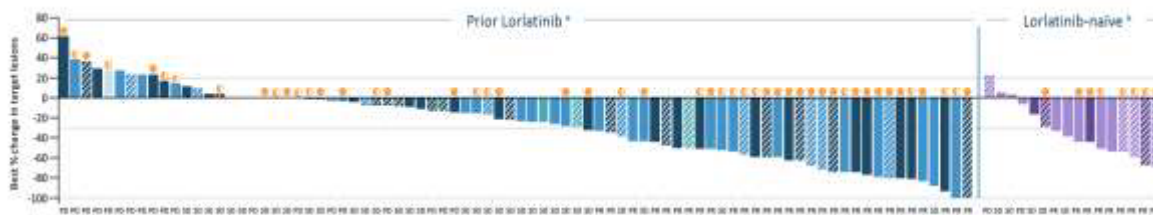
ALKove-1 Fase 2 NVL-655 con diferentes cohortes (naive, pretratados con 1 ó 2-3 iALK). TR naive lorlatinib 88%; TR post-lorlatinib 47%. Activa para mutacion ALK G1202

ALKAZAR FASE 3

On the Horizon: 4th Gen ALK TKI Neladalkib (NVL-655)

Preliminary Activity: Radiographic Tumor Responses Across Previously Treated Patients with ALK+ NSCLC

RECIST 1.1 ORR, % (n/N) ALK patients ± chemotherapy	NSCLC Response-Evaluable [Any Prior ALK TKI, range 1 – 5]			Prior Lorlatinib (≥2 ALK TKIs)			Lorlatinib-naïve (≤1 2G ± 1G)	
	All	Any ALK mutation	G1202R ^b	All	Any ALK mutation	Compound ALK mutation	All	Any ALK mutation
All Doses	38% (39/103)	52% (30/58)	69% (22/32) [#]	35% (30/85)	47% (23/49)	54% (15/28)	53% (9/17)	88% (7/8)
RP2D	38% (15/39)	55% (12/22)	71% (10/14)	35% (11/31)	50% (8/16)	64% (7/11)	57% (4/7)	80% (4/5)



Primary endpoint: PFS per BICR

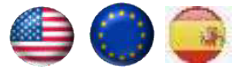
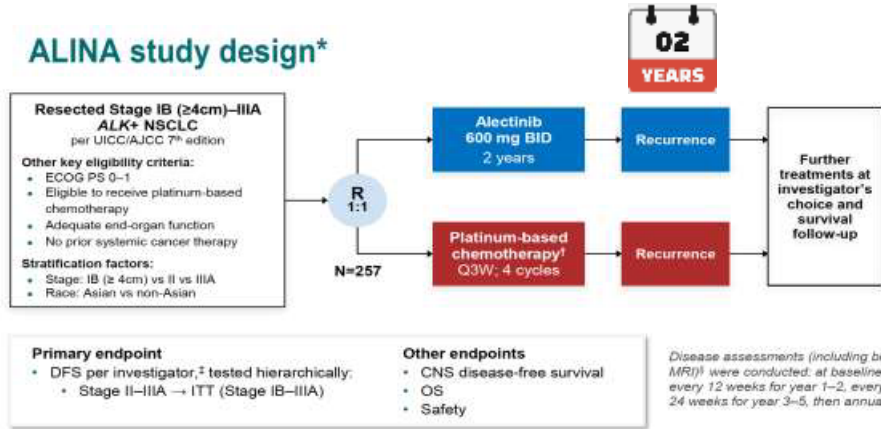
Secondary endpoints: PFS per investigator assessment, BICR-ORR, IC-ORR, OS, safety

Nuvalent press release

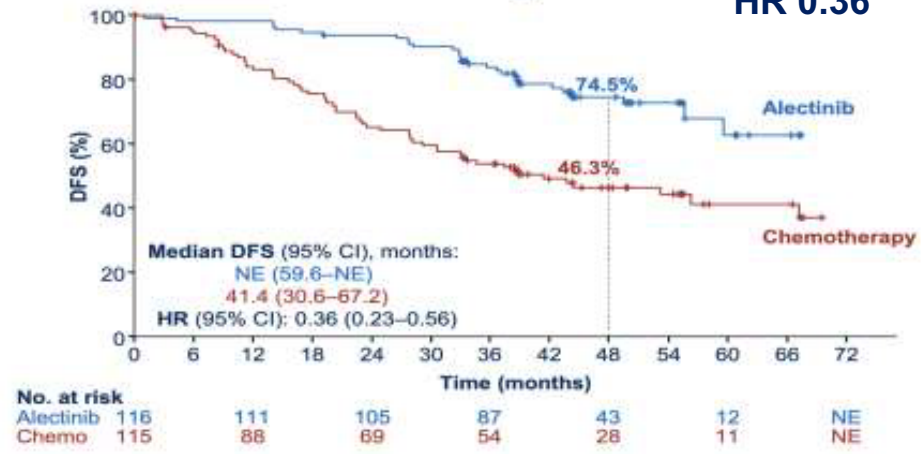


TKI-ALK ADYUVANTE 64-80 % reducción de riesgo de recurrencia en estadio II-IIIa

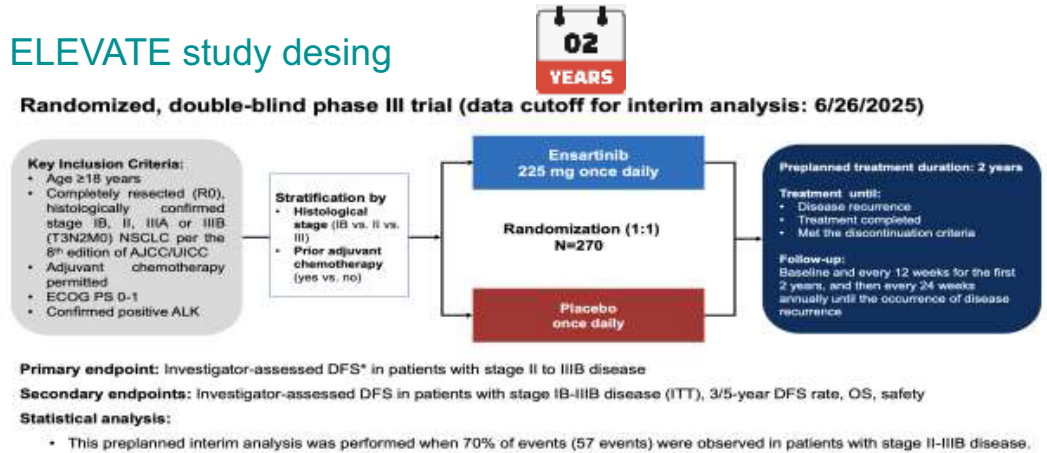
ALINA study design*



DFS in stage II-IIIa* **SLE NR vs 41.1 m**
HR 0.36

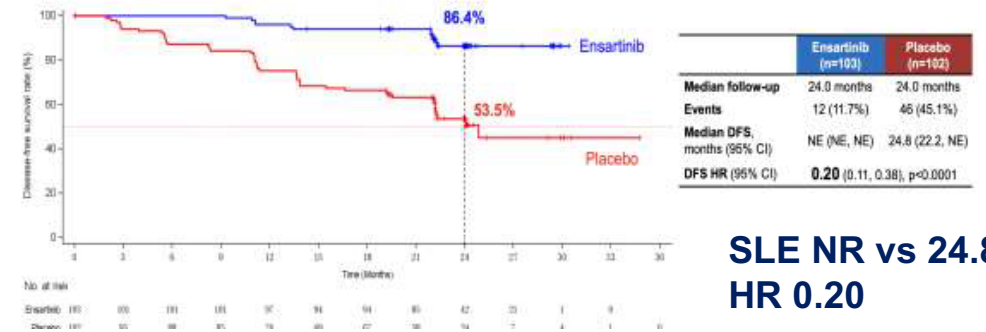


ELEVATE study desing



Ensartinib showed an improved DFS in patients with II-IIIB disease

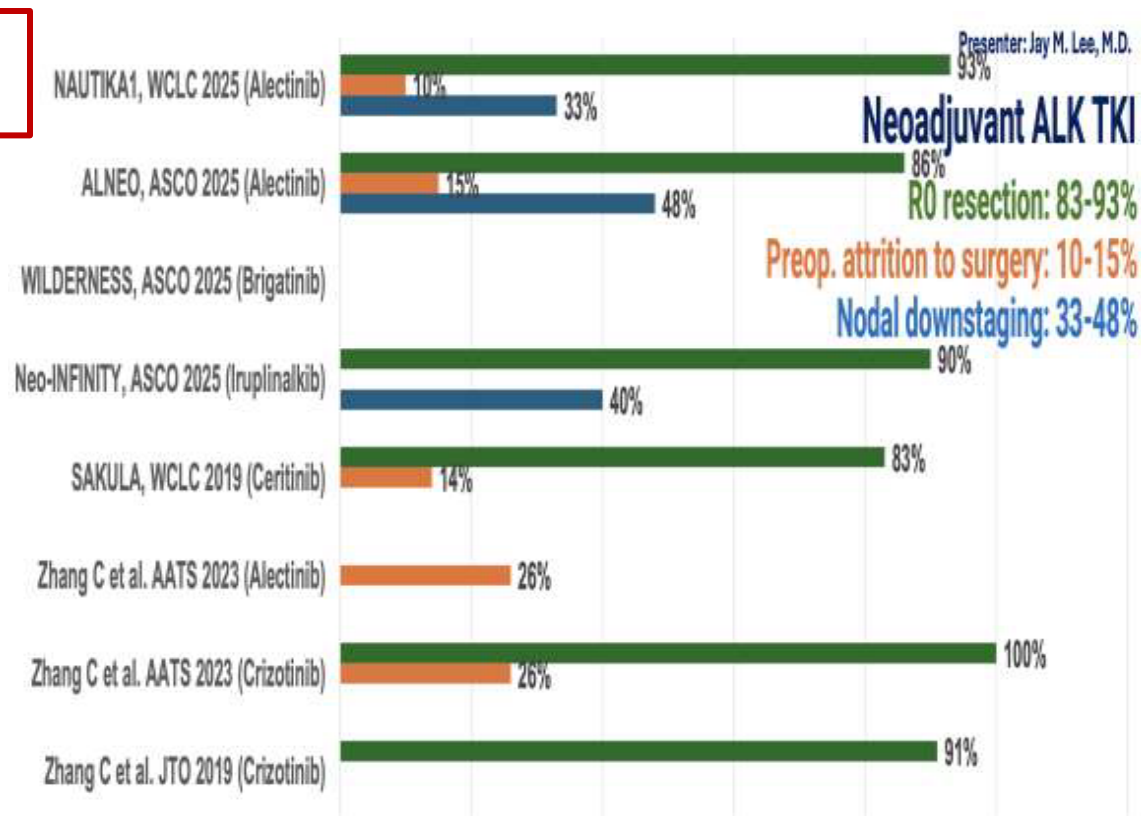
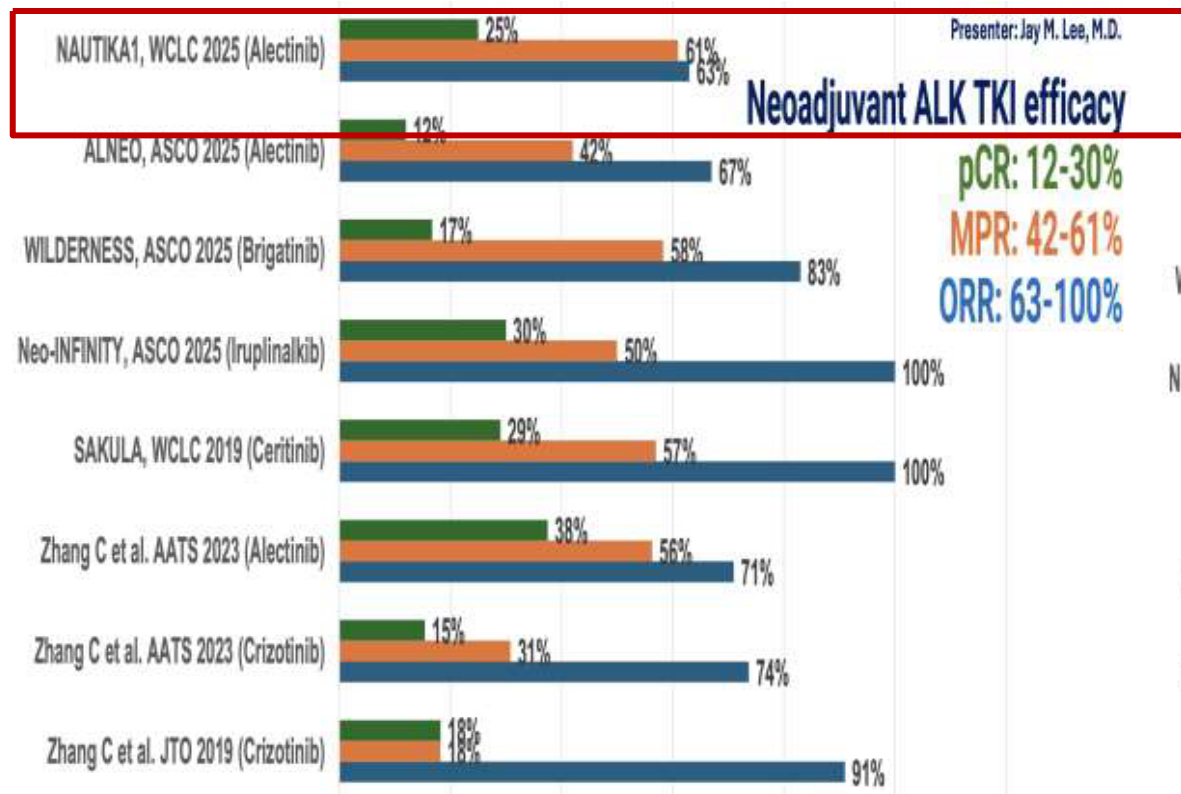
Investigator-assessed DFS



SLE NR vs 24.8 m
HR 0.20

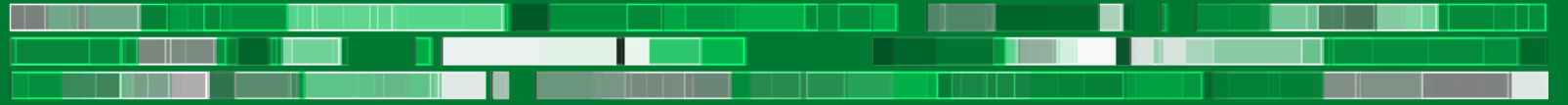


TKI-ALK NEOADYUVANTE... Ensayos fase 2 prometedores



III JORNADA TRASLACIONAL
DE ONCOLOGÍA DE PRECISIÓN:

A TRAVÉS DE LAS VÍAS
DE SEÑALIZACIÓN
SEVILLA, 12 Y 13
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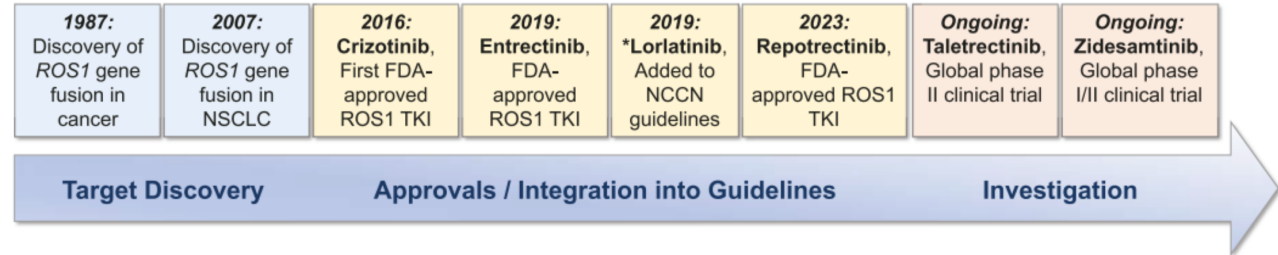
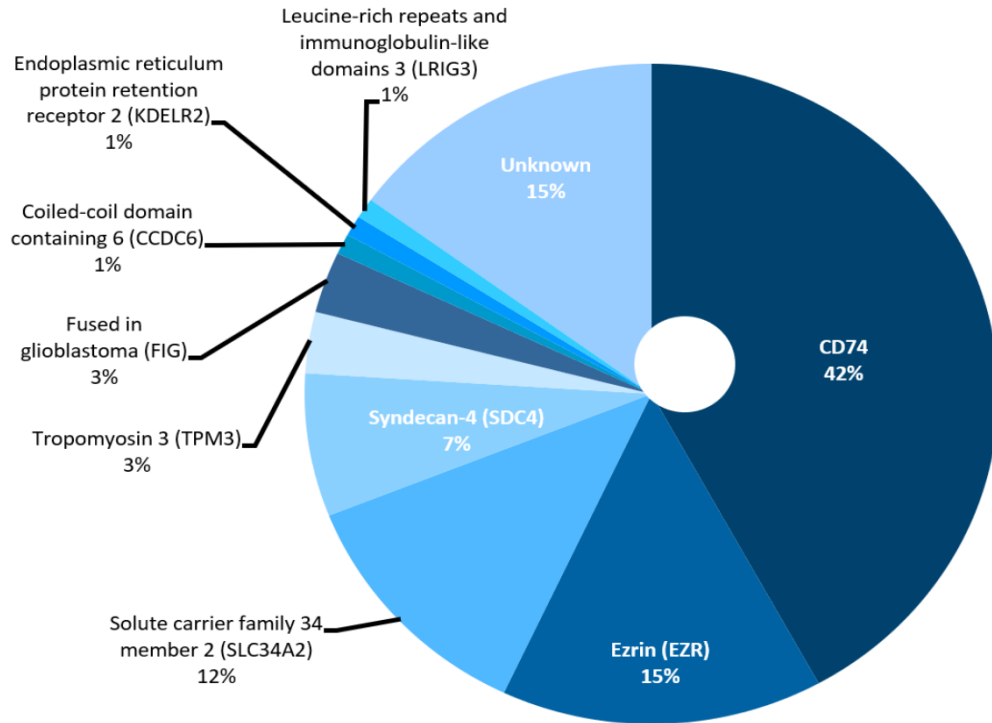


TRASLOCACION ROS 1



ROS1 FUSIONES

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











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.

DESARROLLO TEMPORAL DE INHIBIDORES ROS1

La fusión de ROS1 tiene una incidencia del 1-2% en adenocarcinoma de pulmón. La fusión más frecuente es CD74-ROS1 (42%)
 ROS1 comparte el 49% de la secuencia homóloga del dominio TK-ALK, por ello muchos iALK tienen actividad iROS1

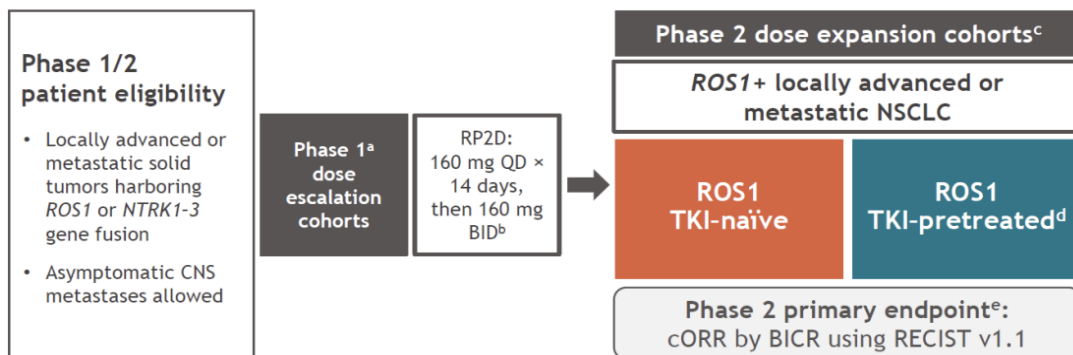


		iROS 1ª linea	ENSAYO	N	TRO	SLP	SG	TRO intracraneal
 		Crizotinib	EC PROFILE 1001 (fase 1)	53	72%	19.2 m	51.4 m	---
	 		Entrectinib (pool análisis)	ALKA372-001, STARTRK1, STARTRK2 (fase1-2)	168	68%	15.7 m	47.7m
 	Repotrectinib		TRIDENT-1 (fase 1-2)	121	79%	30.2 m	74.6 m	89%
		Taletrectinib	TRUST-1 (fase 1)	106	85.2%	44.6 m	NR	76.7%
		Zidesamtinib	ARROS-1 (fase 1)	25	89%	NR	NR	83%



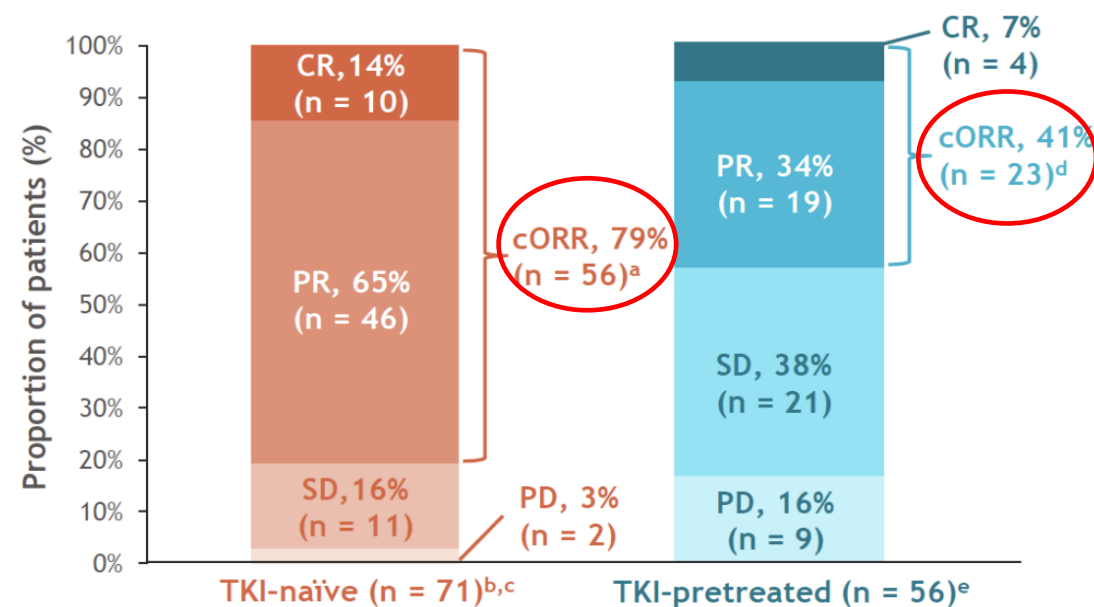
REPOTRECTINIB

UPDATE from TRIDENT-1: Phase 1/2 (WCLC 2025)



- Among patients with measurable brain metastases at baseline^f:
 - icORR was 89% in TKI-naïve patients (95% CI, 52-100; n/N = 8/9)^g; median icDOR was 43.2 months (95% CI, 11.1-NE)
 - icORR was 38% in TKI-pretreated patients (95% CI, 14-68; n/N = 5/13)^h; median icDOR was NE (95% CI, 3.0-NE)
- Among patients with the *ROS1* G2032R (solvent front) mutation across the 3 TKI-pretreated cohorts (n = 17), cORR was 59% (95% CI, 33-82)ⁱ

Response in the primary efficacy population



	TKI – naïve	TKI - pretreated
mPFS (months)	30.2	9.2
mOS (months)	74.6	20.5
	(N = 121)	(N = 107)



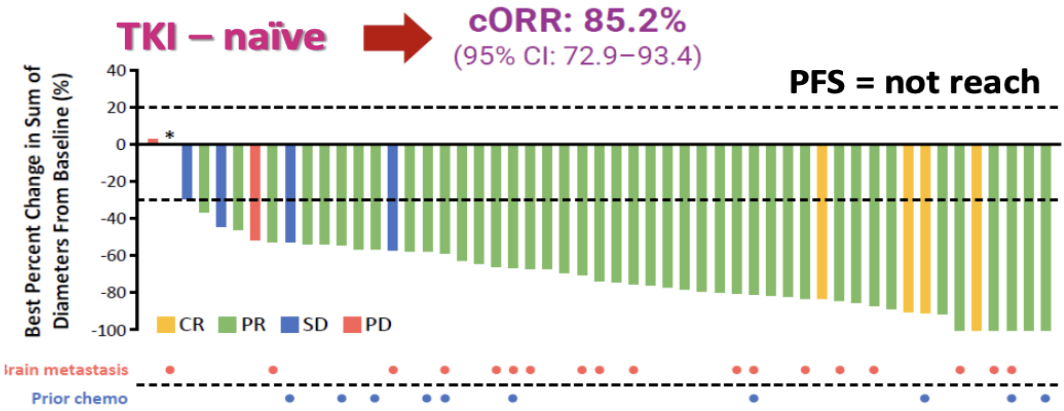
TALETRECTINIB

UPDATE from TRUST-II; Phase II (WCLC 2025)

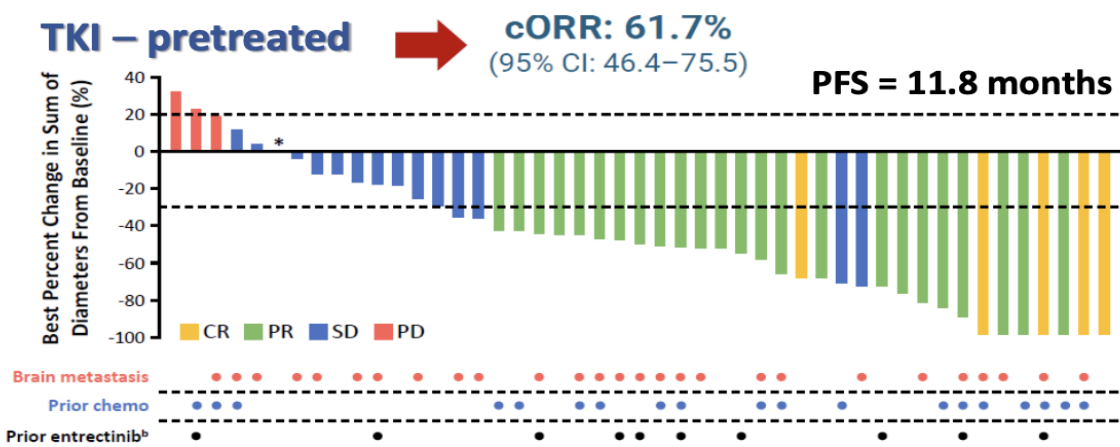
Key Eligibility Criteria
• Locally advanced or metastatic NSCLC with ROS1 fusion
• Age ≥18 years ^b
• ECOG PS 0-1



Endpoints		
Primary:		
• IRC-assessed cORR per RECIST v1.1		
Secondary:		
• DOR	• TTR	• OS
• IC-ORR ^d	• PFS	• Safety ^e



Efficacy	TKI-naïve (n=54)
cORR: prior chemo, yes / no, n/N (%)	9/10 (90.0) / 37/44 (84.1)
Median TTR, ^c mo (95% CI)	1.4 (1.3–1.4)
IC efficacy	(n=9) ^d
IC-ORR, % (95% CI)	66.7 (29.9–92.5)



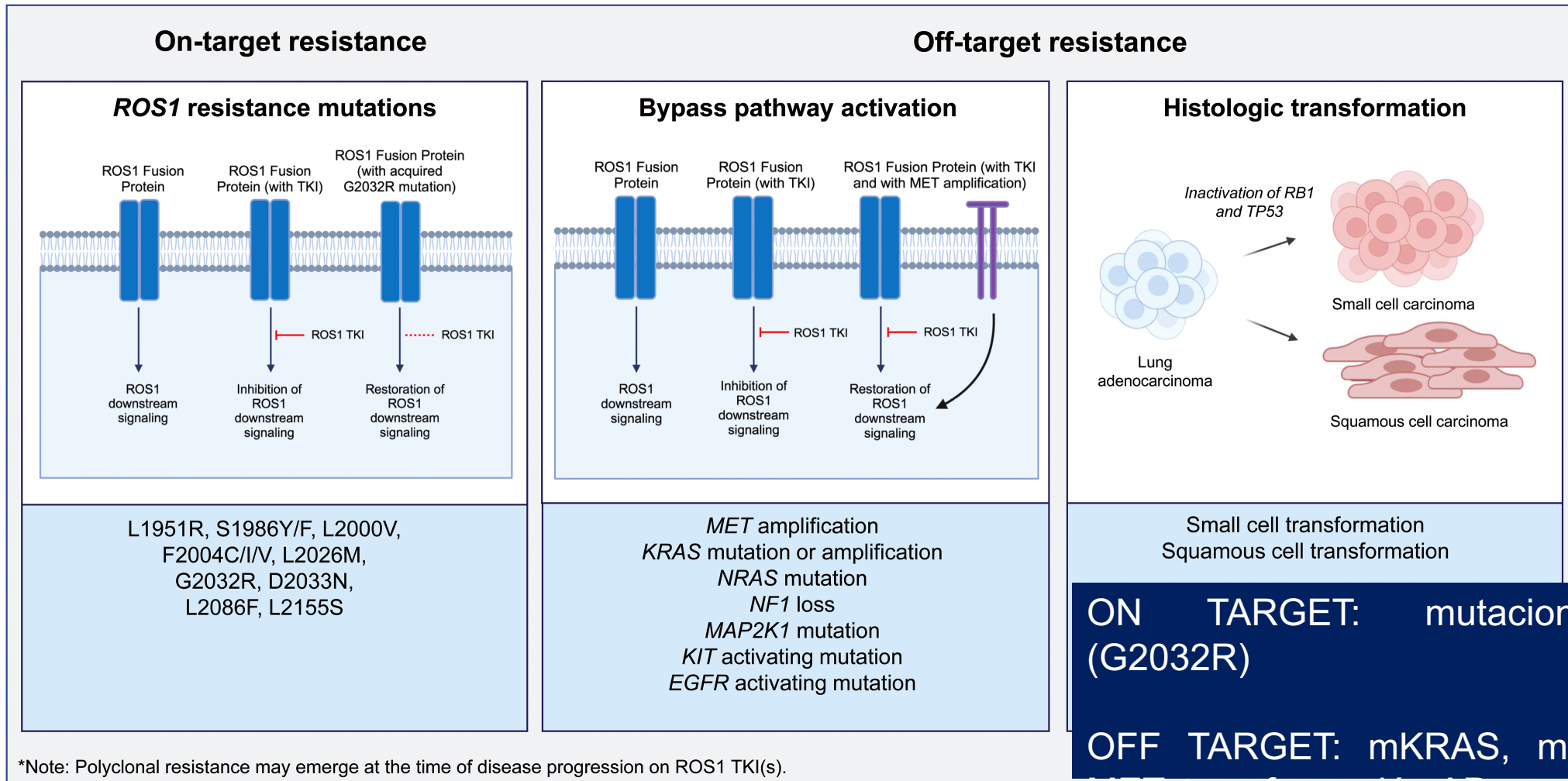
Efficacy	TKI-pretreated (n=47)
cORR: prior chemo, yes / no, n/N (%)	15/19 (78.9) / 14/28 (50.0)
Median TTR, ^c mo (95% CI)	1.4 (1.4–1.6)
IC efficacy	(n=16) ^d
IC-ORR, % (95% CI)	56.3 (29.9–80.3)

Co
Pr





MECANISMOS DE RESISTENCIA A iROS1



*Note: Polyclonal resistance may emerge at the time of disease progression on ROS1 TKI(s).



ZIDESAMTINIB

Advanced <i>ROS1</i> + NSCLC	PIVOTAL DATASET		Preliminary
	Any prior <i>ROS1</i> TKIs (range 1-4) ± chemotherapy	1 prior <i>ROS1</i> TKI (crizotinib or entrectinib) ± chemotherapy	<i>ROS1</i> TKI-naïve
ORR (BICR)	44%	51%	89%
% DOR ≥ 12 months	78%	93%	96%
% DOR ≥ 18 months	62%	93%	
% PFS ≥ 12 months	48%	68%	
% PFS ≥ 18 months	40%	68%	
Intracranial Activity	Any prior <i>ROS1</i> TKIs ± chemotherapy	Prior crizotinib only ± chemotherapy	<i>ROS1</i> TKI-naïve
IC-ORR (BICR)	48%	85%	83%
IC-DOR	71% ≥ 12 months	91% ≥ 12 months	No CNS progression among confirmed CNS responders

EC pivotal ARROS-1: tasa de respuestas en pacientes pre-tratados (44-51%) y con mutación de resistencia *ROS1* G2023R (54-85%)

<i>ROS1</i> G2032R Resistance Mutation		
Advanced <i>ROS1</i> + NSCLC Analysis by BICR	Any prior <i>ROS1</i> TKI ± chemotherapy	1 prior <i>ROS1</i> TKI (crizotinib or entrectinib) ± chemotherapy
ORR, % (n/N) [95% CI]	54% (14/26) [33, 73]	83% (5/6) [36, 100]
% DOR ≥ 6 months [95% CI] †	79% [47, 93]	80% † [20, 97]
% DOR ≥ 12 months [95% CI] †	60% [28, 81]	80% † [20, 97]

Responses were also observed in patients with:

- *ROS1* G2032R mutation following ≥2 prior *ROS1* TKIs ± chemotherapy, including lorlatinib or repotrectinib
- Other *ROS1* resistance mutations, including G1957A, L1982V, S1986F, F2004C/V, G2032K, and D2033N

† Patients received zidesamtinib as their first TKI designed with activity against *ROS1* G2032R.
† Analyses of DOR based on Kaplan-Meier estimates.
† One progression event among responders.

Measurable CNS lesions by BICR at baseline		
Advanced <i>ROS1</i> + NSCLC Analysis by BICR	Any prior <i>ROS1</i> TKI ± chemotherapy	Prior crizotinib only ± chemotherapy
IC-ORR, % (n/N) [95% CI]	48% (27/56) † [35, 62]	85% (11/13) [55, 98]
IC-CR, % (n/N)	20% (11/56)	54% (7/13)
% IC-DOR ≥ 6 months [95% CI] †	79% [56, 91]	91% † [51, 99]
% IC-DOR ≥ 12 months [95% CI] †	71% [46, 87]	91% † [51, 99]

• CNS responses also observed in patients who had received ≥1 prior brain-penetrant TKI, including prior entrectinib, lorlatinib, repotrectinib, or taletrectinib: IC-ORR: 37% (16/43) †, [95% CI 23, 53], including 4 IC-CRs

• No CNS progression was observed among patients who entered the study without brain metastases at baseline per BICR

† Includes 2 unconfirmed intracranial partial responses (PR).
† Analyses of DOR based on Kaplan-Meier estimates.
† One CNS progression event among CNS responders (n=11).



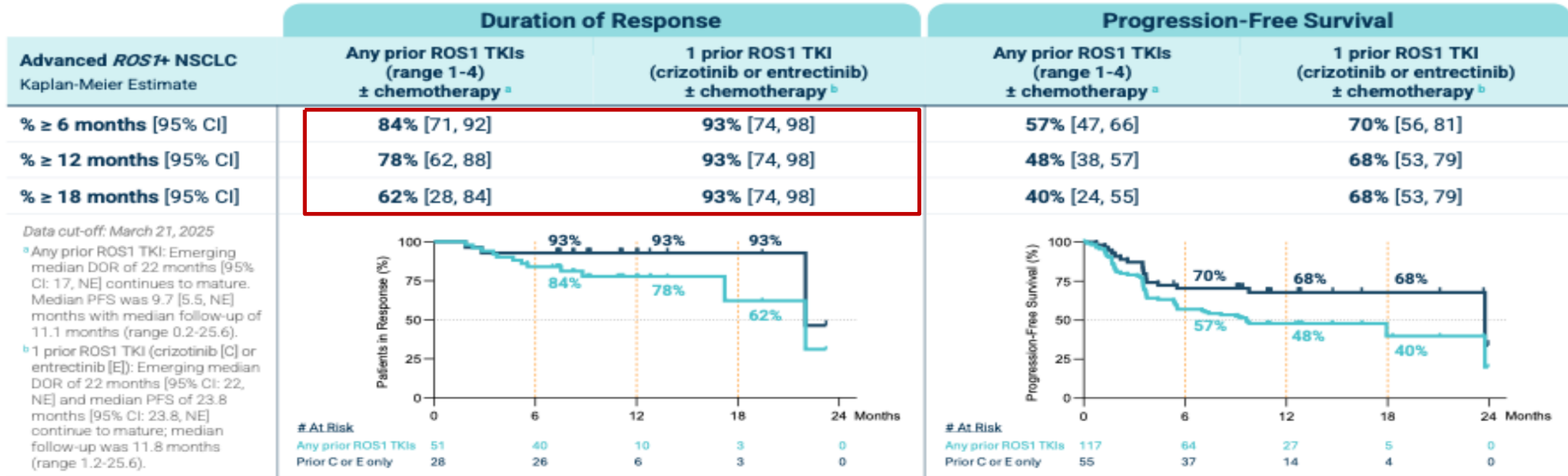
ZIDESAMTINIB

ROS1 rearrangements

Pivotal ARROS-1 Efficacy and Safety Data: Zidesamtinib in TKI Pretreated Patients with Advanced/Metastatic ROS1+ NSCLC

Duration of response

Progression Free Survival mSLP NR a los 24 meses



- In patients that received prior crizotinib only, there were no progression events among responders (DOR range: 7.3+ to 23.2+ months). PFS rate was 89% (95% CI: 70, 96) at 6, 12, and 18 months with median not reached.
- In patients that received ≥2 prior ROS1 TKIs ± chemotherapy, DOR rate was 71% (95% CI: 46, 86) at 6 months and 56% (95% CI: 29, 76) at 12 months.

III JORNADA TRASLACIONAL
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A TRAVÉS DE LAS VÍAS
DE SEÑALIZACIÓN
SEVILLA, 12 Y 13
DE FEBRERO DE 2026

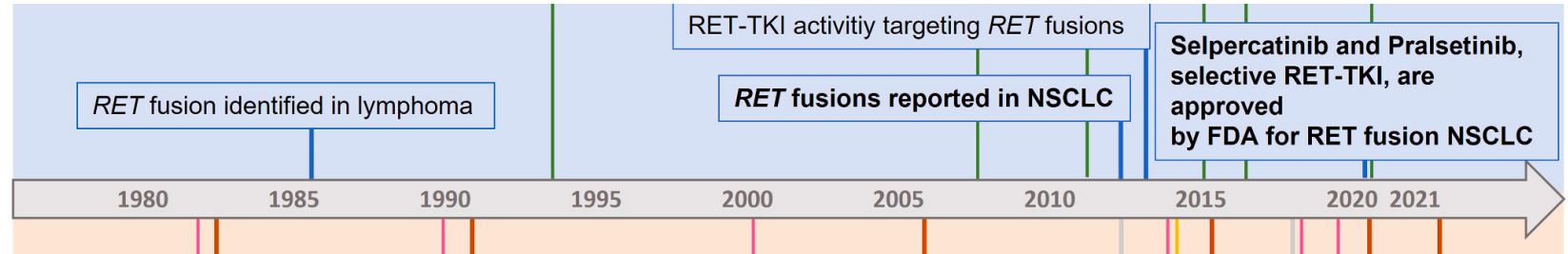
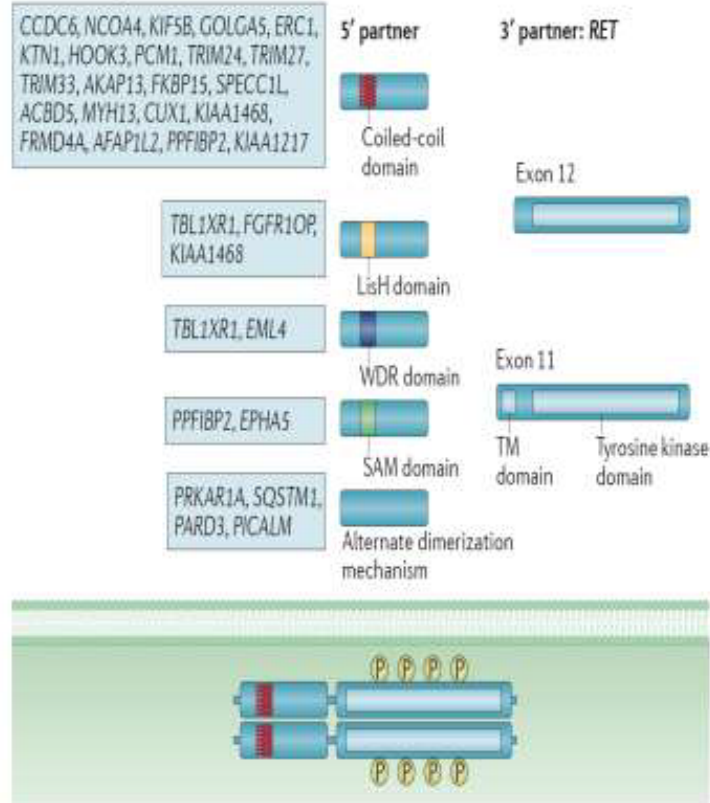


TRASLOCACION RET



RET FUSIONES

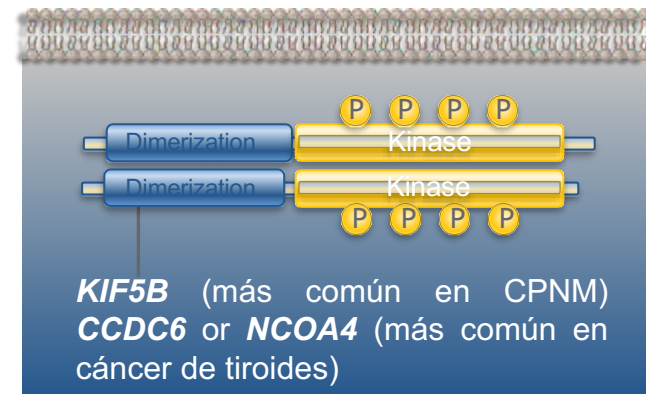
a RET fusion genes



DESARROLLO TEMPORAL DE INHIBIDORES RET

CPNM adenocarcinoma (1%-2%)

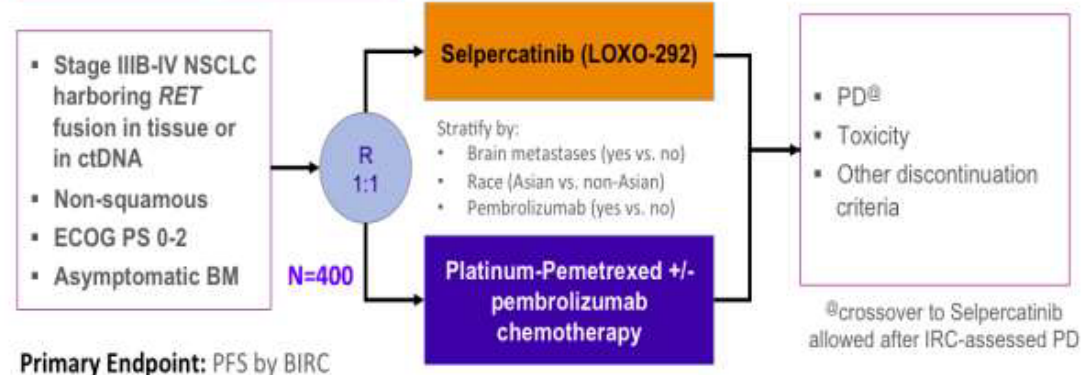
Hasta 45 diferentes *partners*. Más frecuente KIF5B (40-70%), seguida de CCDC6 (15-30%) y NCOA4. Con independencia del tratamiento parece que las fusiones CCDC6 tienen mejor pronóstico





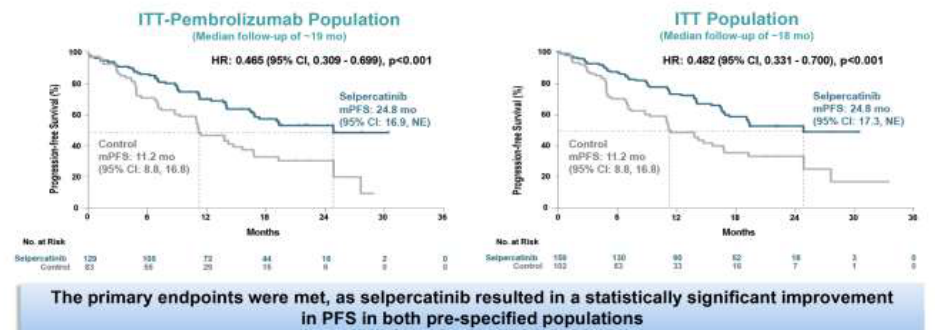
SELPERCATINIB

LIBRETTO-431 (NCT04194944)



Primary Endpoint: PFS by BIRC

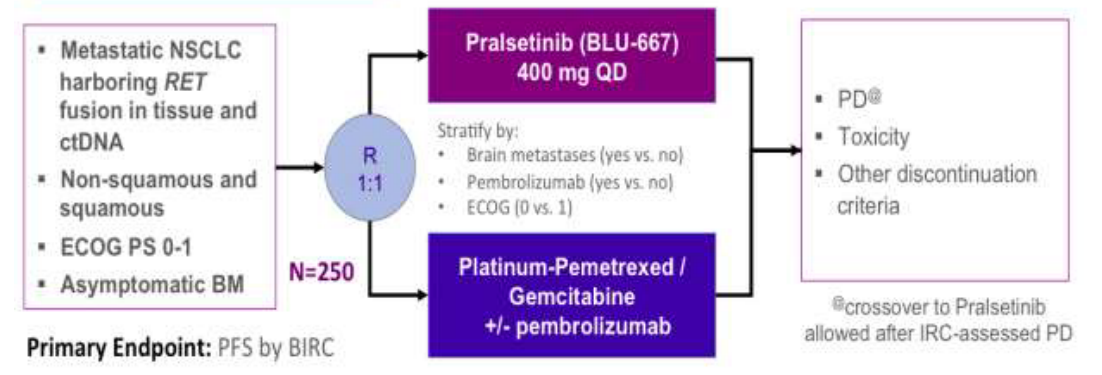
Progression-free survival (PFS) assessed by BICR



The primary endpoints were met, as selpercatinib resulted in a statistically significant improvement in PFS in both pre-specified populations

PRALSETINIB

ACCELE-RET (NCT04222972)



Primary Endpoint: PFS by BIRC

Retirada aprobación por EMA en 2024

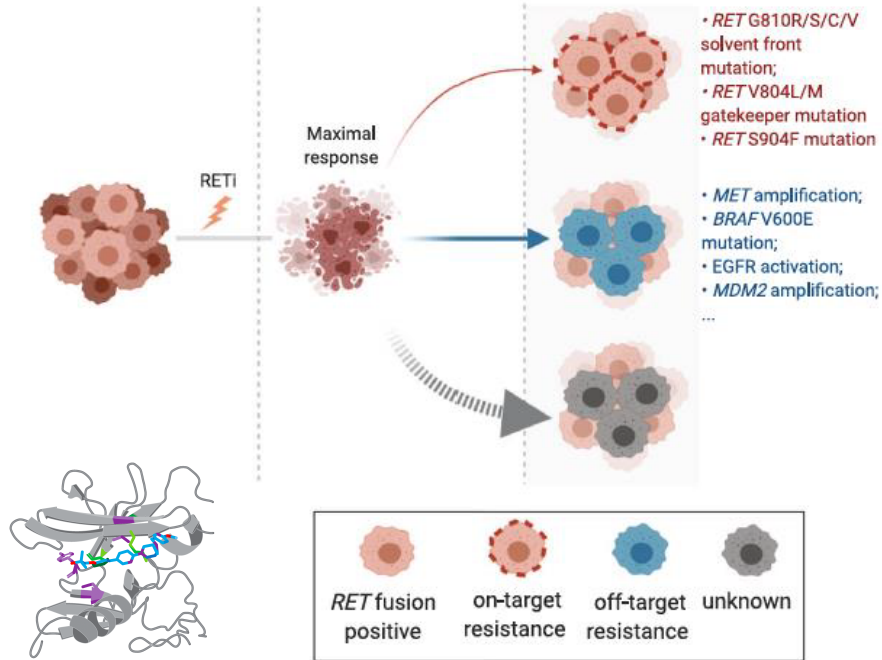
AcceleRET Lung: Pralsetinib versus SOC **CLOSED and end of recruitment (23 Jan 2025)**

LIBRETTO-001 fase 1-2:
TRO: 85%; icTRO: 82%
LIBRETTO-431:
TRO: 83.7% vs 65.1%
mSLP: 24.8 m vs 11.2m
mSG: Not reported

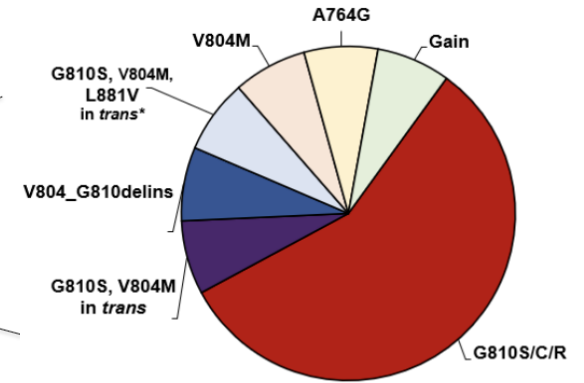
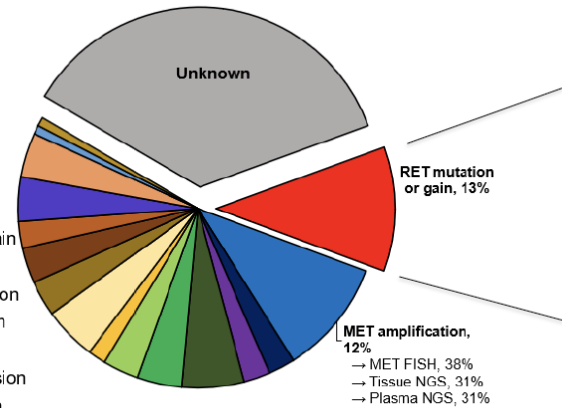
ARROW fase 1-2 pralsetinib:
TRO 79%
icTRO: 70%
mSLP 13 meses



MECANISMOS DE RESISTENCIA A iRET



- RET mutation or gain
- MET amp
- MET mut
- ATM mut
- Cell cycle gain
- CDKN2A/B loss
- PIK3CA mut
- PTEN loss
- MYC gain
- ERBB2 mut or gain
- EGFR gain
- BRAF mut or fusion
- KRAS mut or gain
- FGFR3 amp
- TPD52-ROS1 fusion
- EML4-ALK fusion
- Unknown



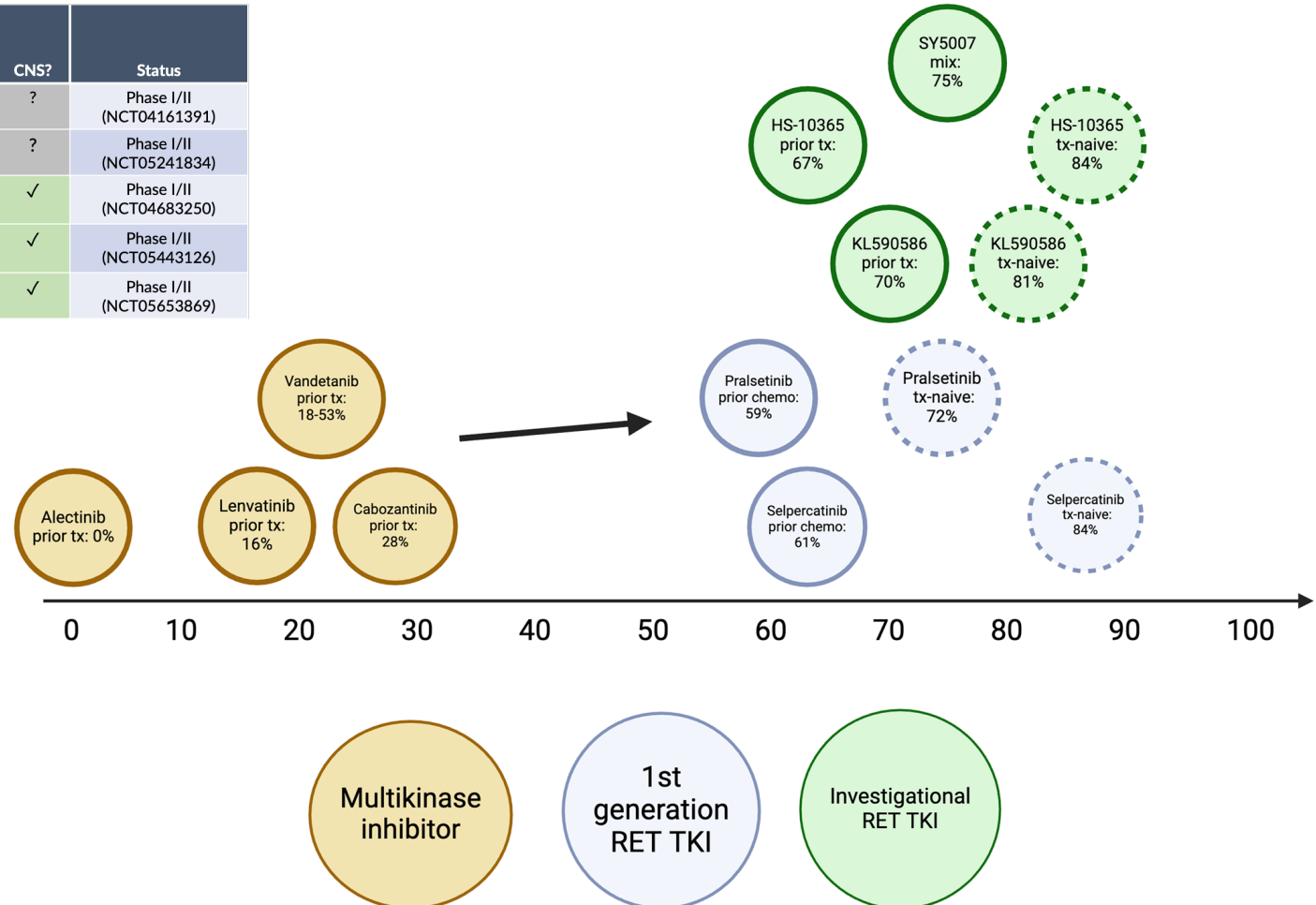
ON TARGET: mutaciones en RET (G810X, V804)

OFF TARGET: amp MET, transformación AP



MECANISMOS DE RESISTENCIA A iRET

Compound	RET Substitution Coverage			VEGFR2	Other Non-RET Kinases	CNS?	Status
	V804X Gatekeeper	G810X Solvent Front	Other RET Mutation				
TPX-0046 ¹	Less potent	✓	Y806N (hinge)	-	TRKA-C, SRC, FGFR1-2, FLT3, JAK2	?	Phase I/II (NCT04161391)
LOXO-260 ²	✓	✓	G810S+V804M	-	TRKC (40x selectivity)	?	Phase I/II (NCT05241834)
Vepafestib ^{3,4} (TAS0953/HM06)	✓	✓	Y806C/N	-		✓	Phase I/II (NCT04683250)
EP0031 ⁵ (A400/KL590586)	✓	✓		-	JAK1/2 (10-22x selectivity)	✓	Phase I/II (NCT05443126)
APS03118 ⁶	✓	✓	Y806H	-		✓	Phase I/II (NCT05653869)



Tasas de respuesta de iRET multikinasa, 1ª generación (selpercatinib, pralsetinib), nueva generación en investigación

III JORNADA TRASLACIONAL
DE ONCOLOGÍA DE PRECISIÓN:

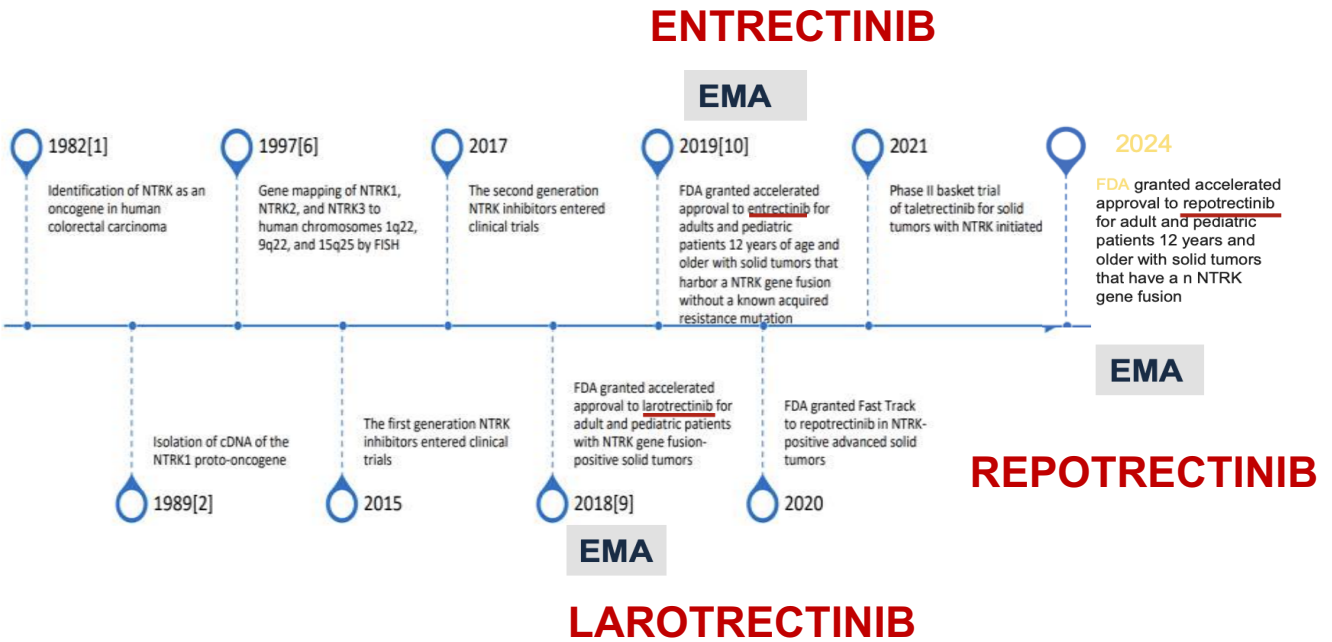
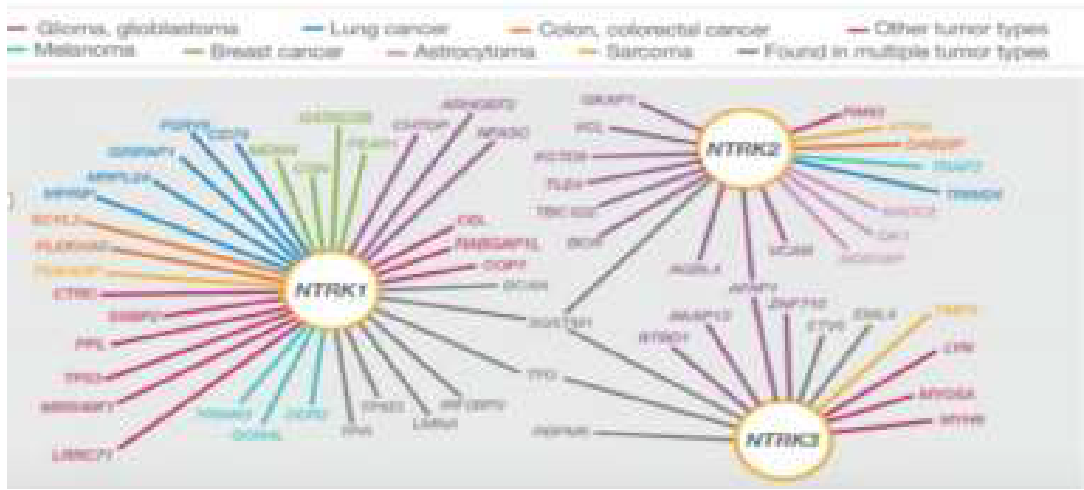
A TRAVÉS DE LAS VÍAS
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SEVILLA, 12 Y 13
DE FEBRERO DE 2026



TRASLOCACION NTRK



NTRK FUSIONES



DESARROLLO TEMPORAL DE INHIBIDORES NTRK

FUSION NTRK < 1% de incidencia en CPNM. NTRK1, 2 y 3. Más de 80 fusiones diferentes

La fusión NTRK3 es la más común, seguida de la fusión NTRK1, y las fusiones ETV6-NTRK3 y TPM3-NTRK1 son las parejas de fusión más comunes.

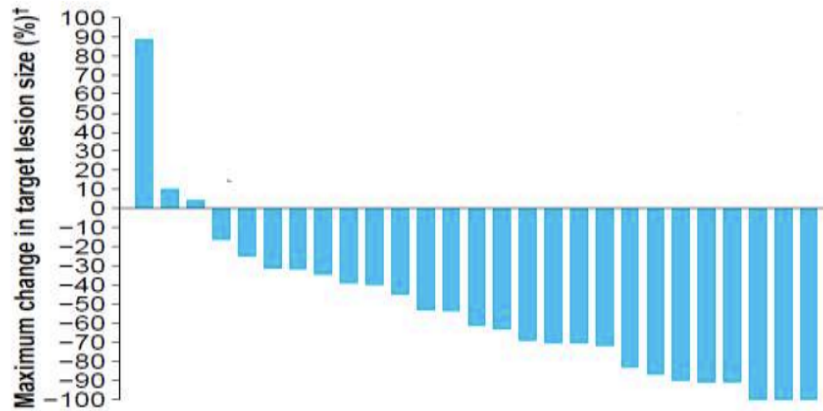


LAROTRECTINIB

Pooled analysis

→ LOXO-TRK, SCOUT, NAVIGATE

N=32 adults, 38% >3 lines, 38% BM

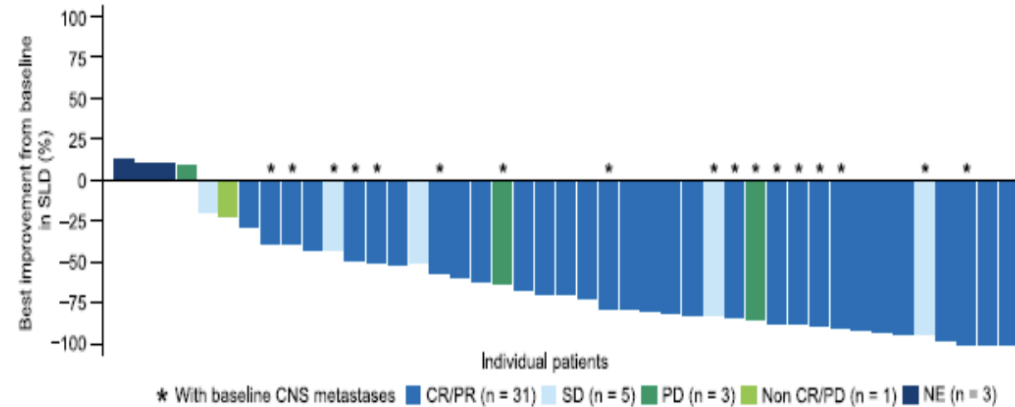


ENTRECTINIB

Pooled analysis

→ ALKA 372-001, STARTRK-1, STARTRK-2

N=51 adults, 40% >2 lines, 39% BM



* With baseline CNS metastases ■ CR/PR (n = 31) ■ SD (n = 5) ■ PD (n = 3) ■ Non CR/PD (n = 1) ■ NE (n = 3)

ORR 66%
mPFS 22m (95% CI 10-NE)
mOS 39m (95% CI 17-NE)

12p



icORR 67% (PR 100%)
mPFS 9.9m
mOS 19.4m

ORR 63% (w/o BM 78%, w BM 54%)
mPFS 28m (95% CI 15.8-30.4)
mOS 41.5m (95% C 30.9-NE)

20p



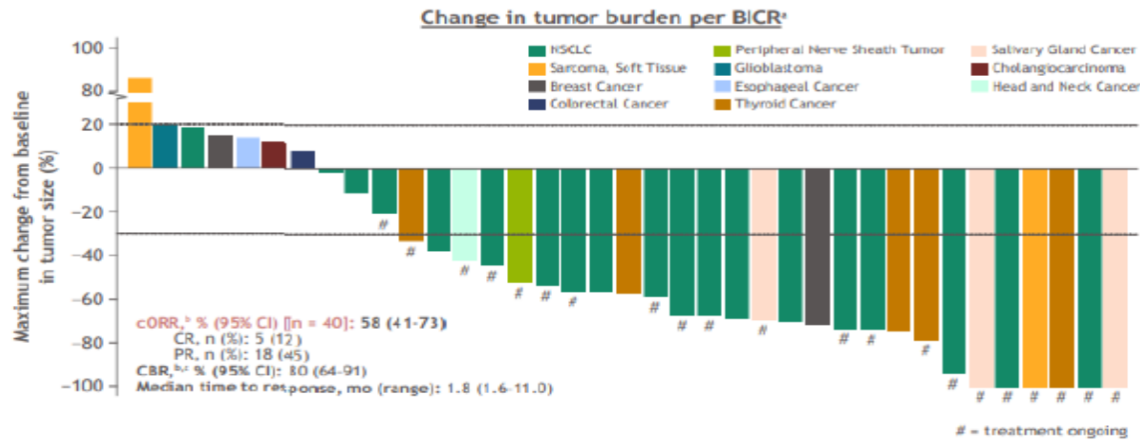
icORR 64% (CR 50%)
icDoR 55.7m
icPFS 32.7m



Repotrectinib in *NTRK*+

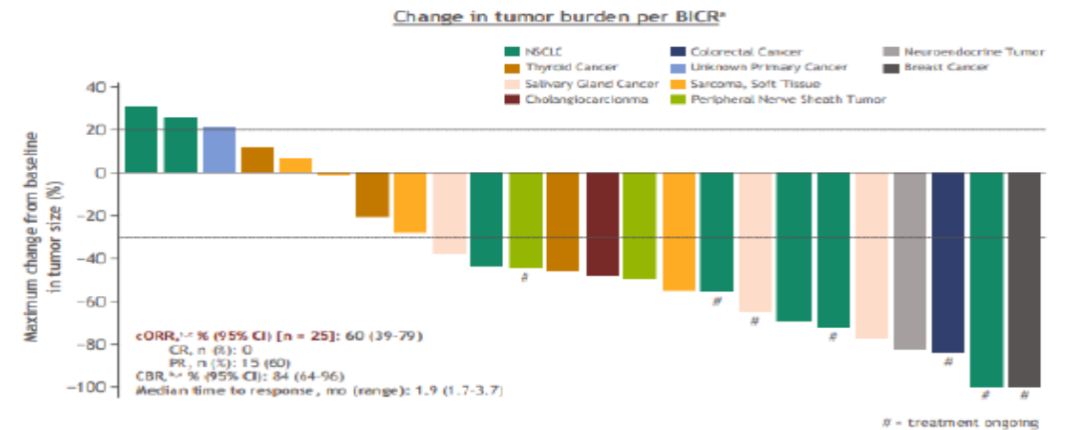
Phase 1/2 TRIDENT-1 trial tumor agnostic

NTRK TKI naive (N=40)



Median FU: 17.8 m
ORR 58% – mDoR NR
mPFS NR – mOS NR

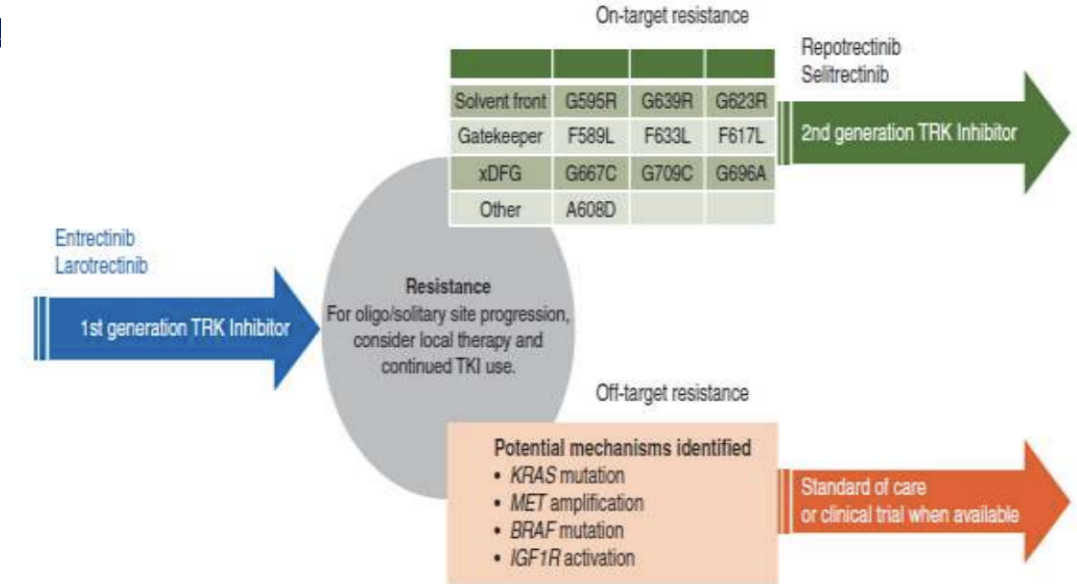
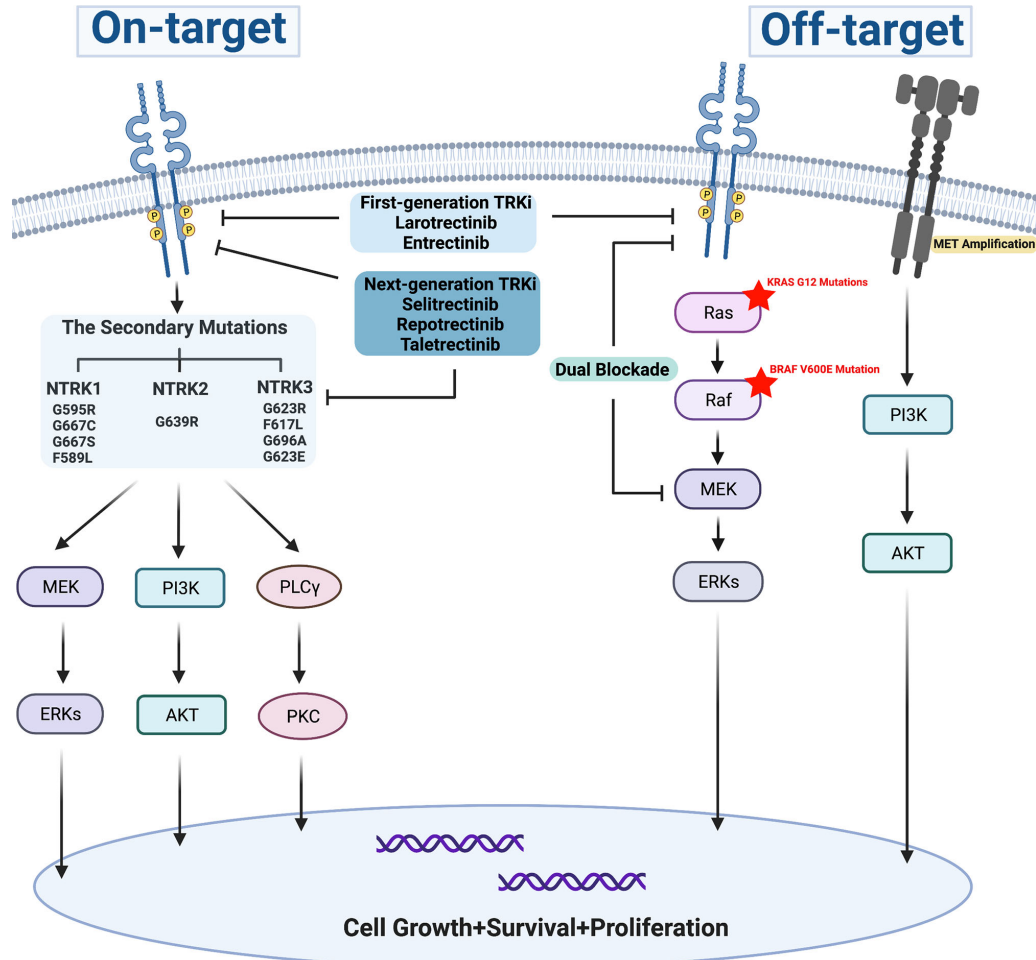
NTRK TKI pretreated (N=48)



Median FU: NA
ORR 60% – mDoR 7.4 m
mPFS 8.6 m – mOS NR



MECANISMOS DE RESISTENCIA A INTR



ZURLETRECTINIB

Cell lines/NTRK status	IC ₅₀ [nM]	Larotrectinib	Selitrectinib	Zurletrectinib	Repotrectinib
BaF3.LMNA-NTRK1	21.8	3.38	1.2	2.23	
BaF3.ETV6-NTRK2	53.6	9.1	5.61	5.94	
BaF3.ETV6-NTRK3-F589L	142	3.88	3.4	1.46	
BaF3.ETV6-NTRK3-F633L	514	46.9	40.3	4.45	
BaF3.ETV6-NTRK3-F617L	3119	119	163	11.9	
BaF3.ETV6-NTRK3-F617L	893	21.1	31.2	2.43	
BaF3.LMNA-NTRK3-G595R	3204	18.1	11	16.2	
BaF3.ETV6-NTRK3-G639R	3805	81.2	40	65.1	
BaF3.ETV6-NTRK3-G623R	962	6.7	6.45	11.6	
BaF3.ETV6-NTRK3-G623E	61.3	3.23	0.69	3.06	
BaF3.LMNA-NTRK3-G667A	118	21.1	5.27	6.48	
BaF3.LMNA-NTRK3-G667C	1368	183.6	38.8	68.1	
BaF3.LMNA-NTRK3-G667S	3195	537	193	139	
BaF3.ETV6-NTRK3-G709C	2788	323	72.6	116	
BaF3.ETV6-NTRK3-G696A	45.7	5.1	2.34	2.88	
BaF3.ETV6-NTRK3-G696C	780	51.6	15.5	32.2	
BaF3.LMNA-NTRK3-H573M	45.4	5.47	2.33	2.22	
BaF3.LMNA-NTRK3-A608D	19.7	3.16	1.18	2.12	
BaF3.ETV6-NTRK3-W689M	13.9	1.44	1.91	1.24	

▲ solvent front substitution ★ gate keeper substitution ⚙️ xDFG mutations

News | Article | May 2, 2023
Zurletrectinib Receives Priority Review from NMPA for NTRK Gene Fusion+ Advanced Solid Tumors
Author(s): Ashley Chan

Fase 1 tumores sólidos: TRO 90%, SG a los 24 meses 90%. Actividad frente a mutaciones NTRK (G595R).

Aprobación AGNÓSTICA en China (dic 2025)

III JORNADA TRASLACIONAL
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OTRAS TRASLOCACIONES

EMERGENTES EN CPNM

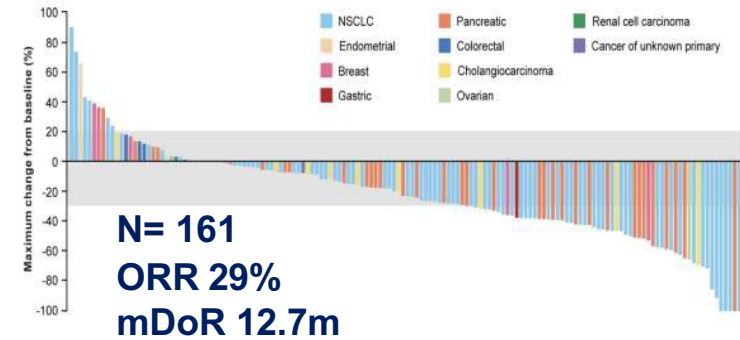


FUSION NRG-1 (Neuregulin-1)

Familia de factor de crecimiento con secuencia EGF-like → se une a ErbB3 y ErbB4 induciendo dimerización y activación. Incidencia global 0.2%.



ZENOCOTUZUMAB

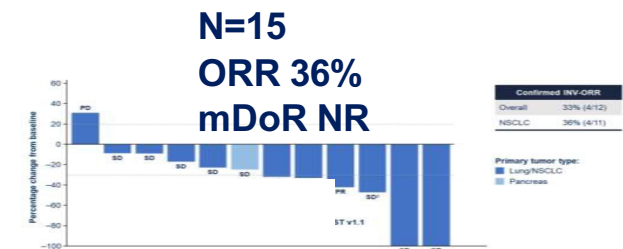


Discovery of Novel *RASGRF2* Fusions as a Therapeutic Target in Lung Adenocarcinoma of Never or Light Smokers

Yuki Terashima^{1,2} | Soohwan Park^{1,3} | Hiroshi Ikeuchi^{1,3} | Takuo Hayashi⁴ | Shinya Kojima¹ | Toshihide Ueno¹ | Masachika Ikegami¹ | Rina Kitada¹ | Yoshiyuki Suehara¹ | Shinya Tanaka^{2,5} | Kenji Suzuki³ | Hiroyuki Mano¹ | Kazuya Takamochi³ | Shinji Kohsaka¹

Pan-Cancer Analysis of Oncogenic MET Fusions Reveals Distinct Pathogenomic Subsets with Differential Sensitivity to MET-Targeted Therapy

SERIBANTUMAB



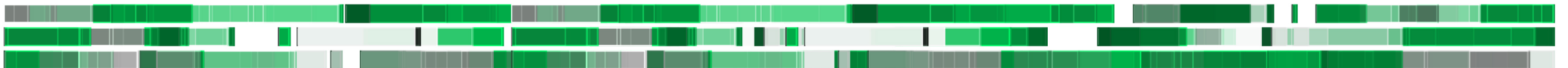


CONCLUSIONES

- ✓ Existen un porcentaje no despreciable de traslocaciones en CPNM, 4 de ellas cuentan con terapia dirigida aprobada en 1º línea (ALK, ROS1, RET, NTRK) por lo que es mandatorio su conocimiento antes de decidir la estrategia terapéutica de estos pacientes (SCAT ESMO tier I).
- ✓ NGS es la técnica GOLD ESTÁNDAR para su detección.
- ✓ Las terapias dirigidas para estas fusiones han demostrado ser altamente eficaces con medianas de SG nunca vistas en CPNM sin traslocaciones (mSG 81 m para ALK+ tratados con iALK 2º generación; mSG 74 m para ROS1 tratado con repotrectinib). **IMPORTANCIA DEL DIAGNOSTICO**
- ✓ La resistencia a estas terapias ha llevado al diseño de fármacos inhibidores de fusiones cada vez más potentes (sobre todo para ser activos sobre mutaciones añadidas). **IMPORTANCIA DE LA RE-BIOPSIA**
- ✓ Los buenos resultados en enfermedad metastásica de CPNM de estos fármacos ha llevado a su aplicación en enfermedad precoz / localmente avanzada (iALK adyuvante). **MUCHOS ENSAYOS EN MARCHA**

GRACIAS!

II JORNADA TRASLACIONAL
DE ONCOLOGÍA DE PRECISIÓN: A TRAVÉS DE LAS VÍAS
DE SEÑALIZACIÓN
SEVILLA, 6 Y 7
DE FEBRERO DE 2025





INTRODUCCION

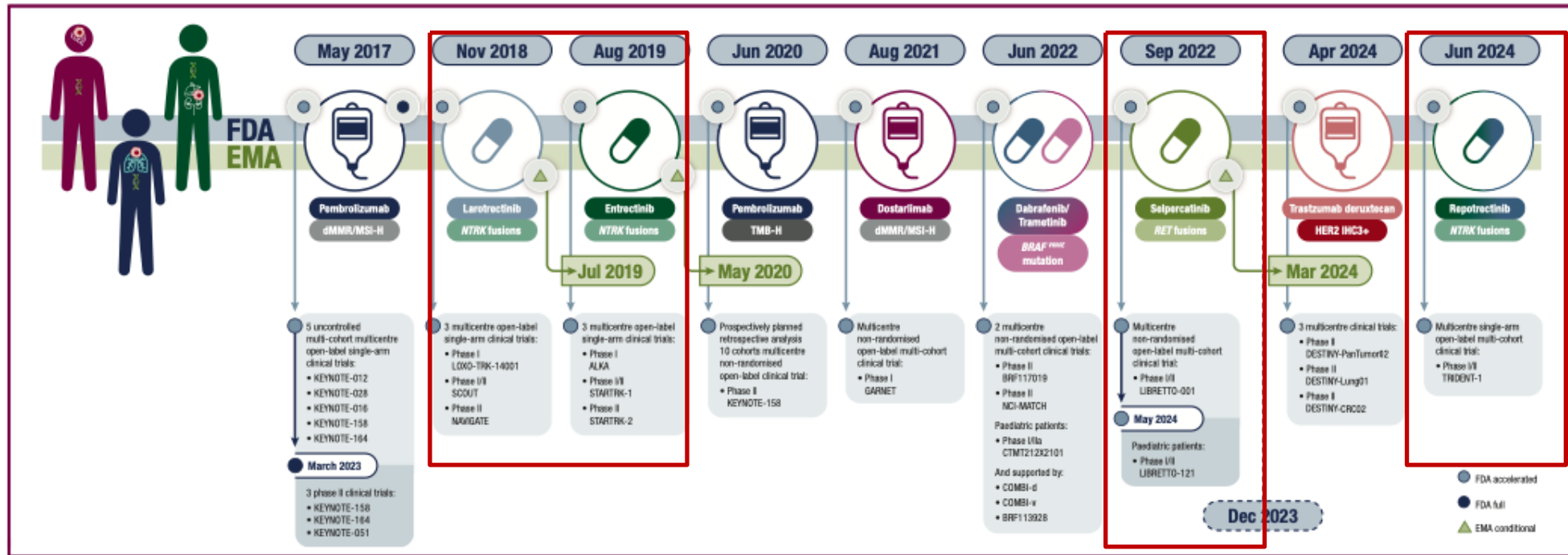


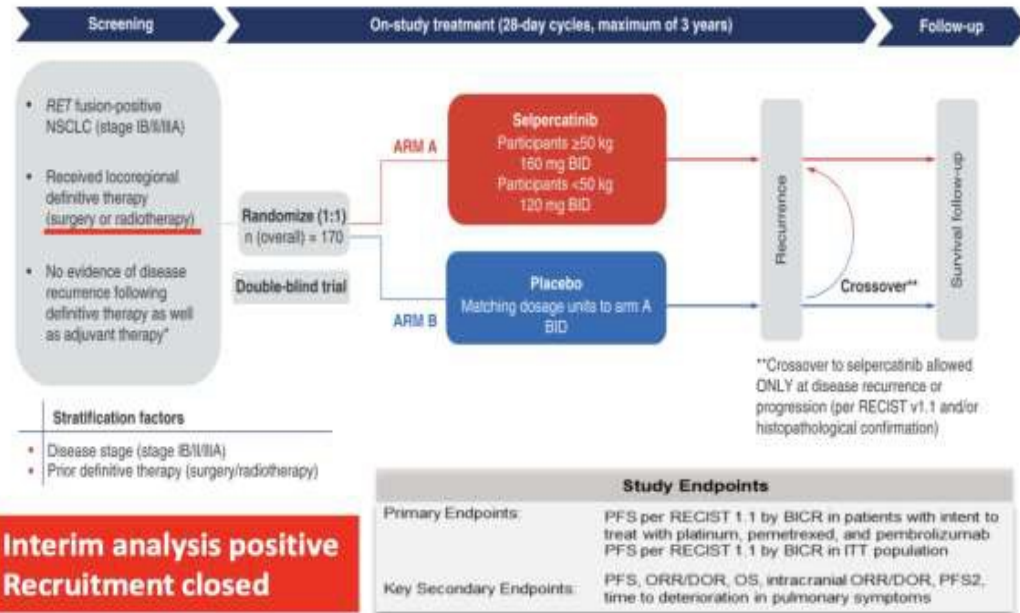
Figure 2. Landscape of the tumour-agnostic authorised indications by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as of 31 December 2023, and during the first half of 2024. Dates in blue: FDA-accelerated (light) and full (dark) approvals with the respective clinical trials which provided the supportive evidence for the decision; dates in green: EMA conditional approvals.

dMMR, mismatch repair deficiency; IHC, immunohistochemistry; HER2, human epidermal growth factor receptor 2; MSI-H, microsatellite instability-high; NTRK, neurotrophic tropomyosin receptor kinase genes; RET, rearranged during transfection genes; TMB-H, tumour mutational burden-high.

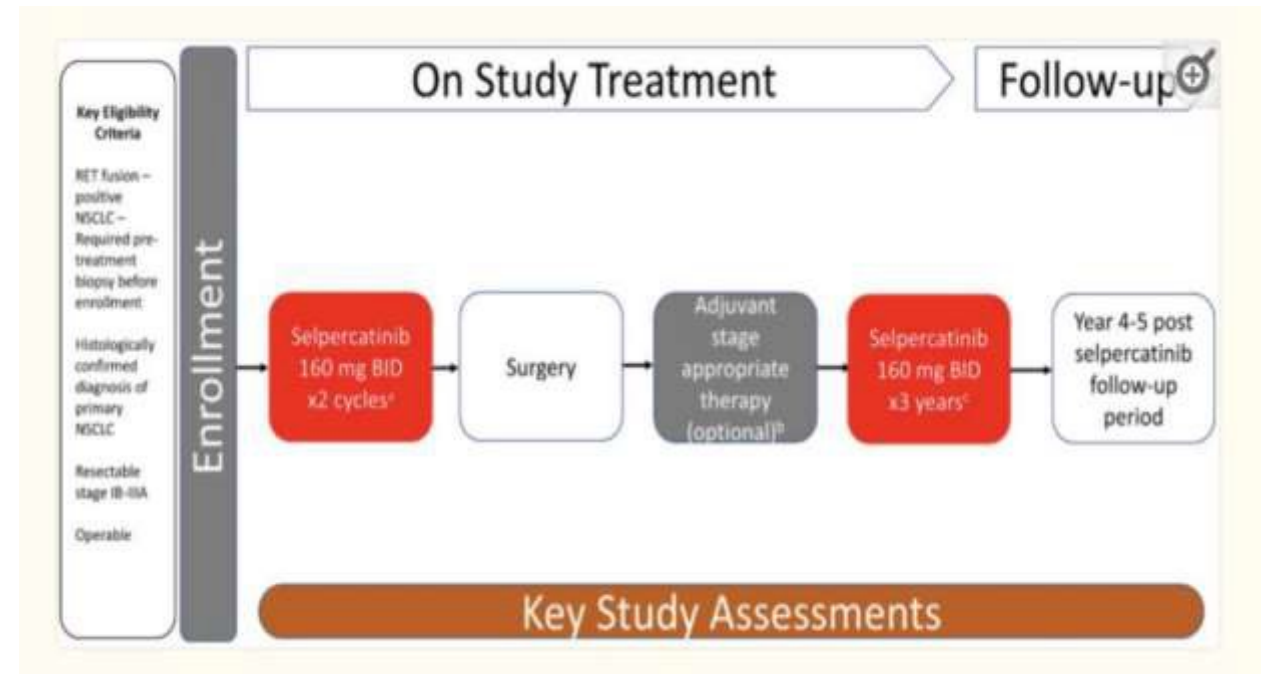


TKI-RET ADYUVANTE Y PERIOPERATORIO

LIBRETTO-432 (Adj, Phase III, RET+. NCT04819100)



Ph 2: LIBRETTO-001 (Periop Selpercatinib RET+. NCT03157128)



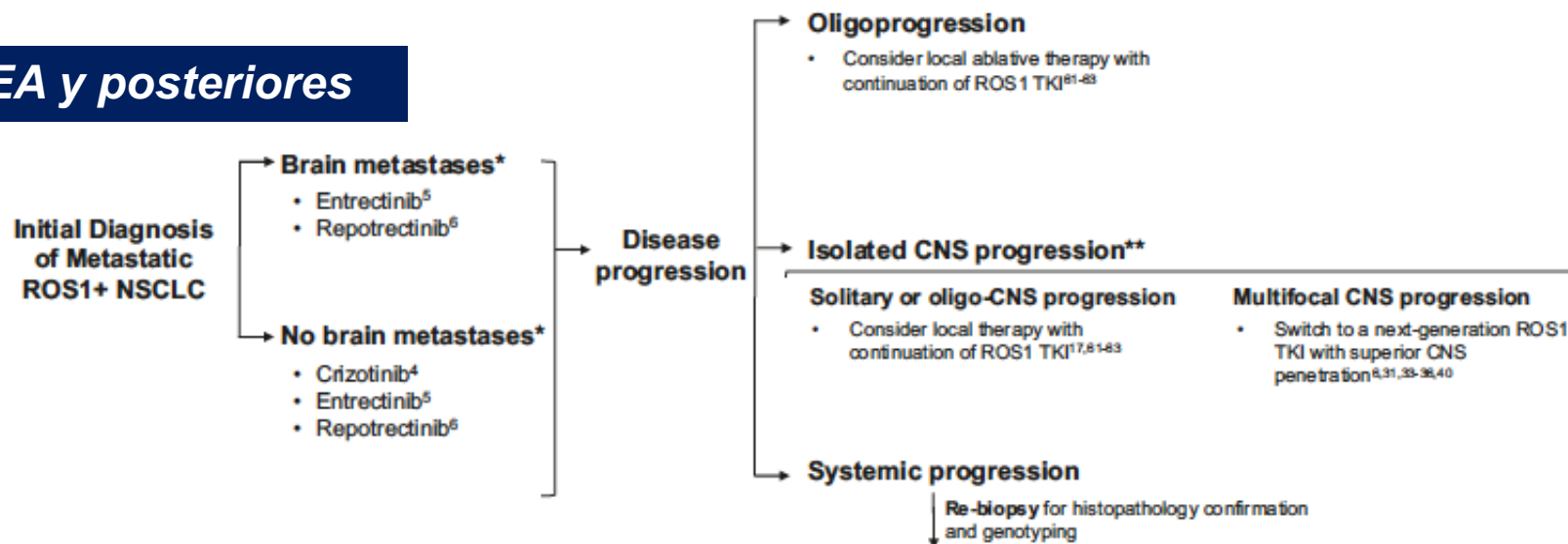
SELPERCATINIB EN ESTADIO I-IIIa TRAS TRATAMIENTO RADICAL (cirugía o RT)

SELPERCATINIB EN ESTADIO I-IIIa neoadyuvante



Drug	Number of patients ^a	ORR	PFS (months)	ORR in patients with known baseline ROS1 G2032R	Reference
Lorlatinib	40 (prior crizotinib)	35%	8.5	0% (0/6)	Global phase I/II ³¹
Repotrectinib ^b	56 (one previous TKI, no chemotherapy)	38%	9.0	59% (10/17)	TRIDENT-1 Global phase I/II ⁶
Taletrectinib ^c	67 (prior crizotinib)	51.5%	7.6	66.7% (8/12)	TRUST-I Chinese phase II ^{33,34}
Zidesamtinib ^c	21 (TKI-pretreated)	57.1%	Not reported	Not reported	TRUST-II Global phase II ³⁵
	21 (TKI-pretreated)	48% ^d	Not reported	78% (7/9)	ARROS-1 Global phase I/II ³⁶

iROS 2º LINEA y posteriores



ESTRATEGIAS DE 2º LINEA

ROS1-dependent resistance	ROS1-independent resistance	No known actionable resistance mechanism****
<ul style="list-style-type: none"> ROS1 G2032R or others <ul style="list-style-type: none"> Repotrectinib⁶ Investigational ROS1 TKI with G2032R or known ROS1 resistance mutation coverage (e.g., taletrectinib, zidesamtinib)³³⁻³⁶ ROS1 L2086F <ul style="list-style-type: none"> TKI-type switch (e.g. cabozantinib)^{7,78} 	<ul style="list-style-type: none"> Actionable bypass resistance driver <ul style="list-style-type: none"> Investigational combination strategy (e.g. ROS1 TKI + MET TKI for MET amplification)⁸⁰⁻⁸³ Histologic transformation <ul style="list-style-type: none"> Histology-specific chemotherapy^{***17,88} 	<ul style="list-style-type: none"> Chemotherapy¹⁷ <ul style="list-style-type: none"> Consider continuing CNS-penetrant ROS1 TKI⁹⁰ Clinical trials



ZIDESAMTINIB

ROS1 rearrangements

Pivotal ARROS-1 Efficacy and Safety Data: Zidesamtinib in TKI Pretreated Patients with Advanced/Metastatic ROS1 NSCLC

G2032R Resistance Mutation and CNS Subgroups

ROS1 G2032R Resistance Mutation		
Advanced ROS1+ NSCLC Analysis by BICR	Any prior ROS1 TKI ± chemotherapy	1 prior ROS1 TKI (crizotinib or entrectinib) ± chemotherapy ^a
ORR, % (n/N) [95% CI]	→ 54% (14/26) [33, 73]	→ 83% (5/6) [36, 100]
% DOR ≥ 6 months [95% CI] ^b	79% [47, 93]	80% ^c [20, 97]
% DOR ≥ 12 months [95% CI] ^b	60% [28, 81]	80% ^c [20, 97]

Responses were also observed in patients with:

- ROS1 G2032R mutation following ≥2 prior ROS1 TKIs ± chemotherapy, including lorlatinib or repotrectinib
- Other ROS1 resistance mutations, including G1957A, L1982V, S1986F, F2004C/V, G2032K, and D2033N

^a Patients received zidesamtinib as their first TKI designed with activity against ROS1 G2032R.

^b Analyses of DOR based on Kaplan-Meier estimates.

^c One progression event among responders.

Measurable CNS lesions by BICR at baseline		
Advanced ROS1+ NSCLC Analysis by BICR	Any prior ROS1 TKI ± chemotherapy	Prior crizotinib only ± chemotherapy
IC-ORR, % (n/N) [95% CI]	→ 48% (27/56) ^a [35, 62]	→ 85% (11/13) [55, 98]
IC-CR, % (n/N)	20% (11/56)	54% (7/13)
% IC-DOR ≥ 6 months [95% CI] ^b	79% [56, 91]	91% ^c [51, 99]
% IC-DOR ≥ 12 months [95% CI] ^b	71% [46, 87]	→ 91% ^c [51, 99]

- CNS responses also observed in patients who had received ≥1 prior brain-penetrant TKI, including prior entrectinib, lorlatinib, repotrectinib, or taletrectinib: IC-ORR: 37% (16/43 ^a; [95% CI 23, 53]), including 4 IC-CRs
- No CNS progression was observed among patients who entered the study without brain metastases at baseline per BICR

^a Includes 2 unconfirmed intracranial partial responses (PR).

^b Analyses of DOR based on Kaplan-Meier estimates.

^c One CNS progression event among CNS responders (n=11).





Lorlatinib after failure of first line ROS1: IFCT -2003 ALBATROS study

54 patients; 57% Brain Mts; 94% prior crizotinib

Efficacy of lorlatinib after failure of a first-line ROS1 tyrosine kinase inhibitor (ROS1 TKI) in patients (pts) with advanced ROS1-positive non-small cell lung cancer (ROS1+ NSCLC):

IFCT-2003 ALBATROS trial

NCT04621188 / EU CT 2024-512028-12-00

Single-arm, multicenter phase II trial

- ROS1-positive advanced NSCLC according to IHC and confirmed with FISH or NGS (local)
- Progression after a first-line therapy with ROS1 TKI
- PS 0, 1 or 2
- Stable and asymptomatic brain metastases allowed
- Measurable disease according to RECIST 1.1



- Lorlatinib 100 mg once daily
- Planned inclusion of 84 patients *
- Until progression or intolerable toxicity
- Required blood samples at time of progression

Primary endpoint: investigator-assessed confirmed Overall Response Rate (cORR)

Secondary endpoint: BICR cORR, DCR, PFS, DoR, OS, CNS ORR, safety

Results

- cORR of 30%
- median PFS 7.4 months
- median DoR 20.4 months
- median OS 42.3 months

Secondary endpoints: inv-assessed CNS ORR

	Investigator assessed N = 13 patients with measurable CNS disease
Complete Response	7 (53.8%) [26.7% ; 80.9%]
Partial Response	5 (38.5%) [12.0% ; 64.9%]
Objective Response	12 (92.3%) [77.8% ; 100.0%]
Stable Disease	1 (7.7%) [0.0% ; 22.2%]
Disease Control	13 (100.0%) [100.0% ; 100.0%]
Progressive Disease	0

Safety

TRAE grade ≥ 3 rate: 45%

Dose modification rate: 30%

TRAE permanent discontinuation rate: 1%

TRAEs with incidence ≥7.5%

