Organizado por:

FUNDACION MARIE CURIE
Córdoba - Argentina

Congreso sobre Avances Integrados en Oncología, Radiocirugía y Física Médica: Innovación y Precisión en el tratamiento del cáncer

QUE HAY DE NUEVO EN EL TRATAMIENTO DEL ADENOCARCINOMA DE PULMON EGFR MUTADO

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Objetivos y Agenda

Revisión de mutaciones EGFR y Relevancia Clínica

Resumir terapias de 1L iniciales

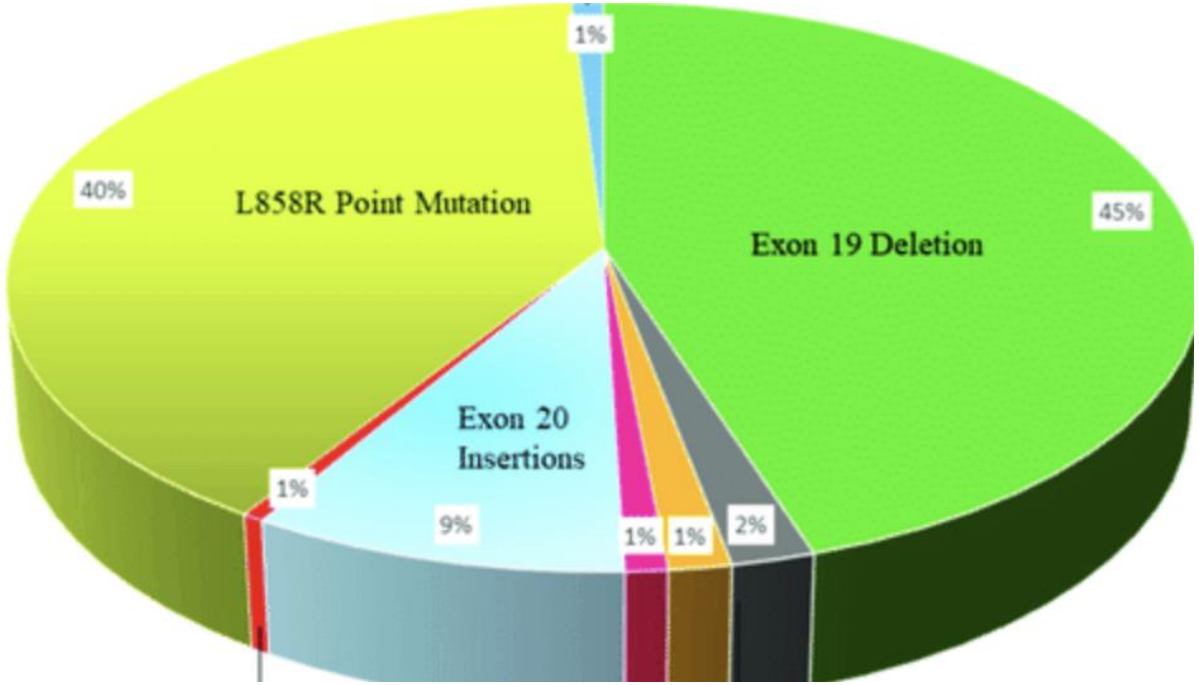
Describir mecanismos de Resistencia

Opciones terapéuticas tras progresión a Osimertinib en enfermedad avanzada

Nuevas evidencias en tratamientos de 1L

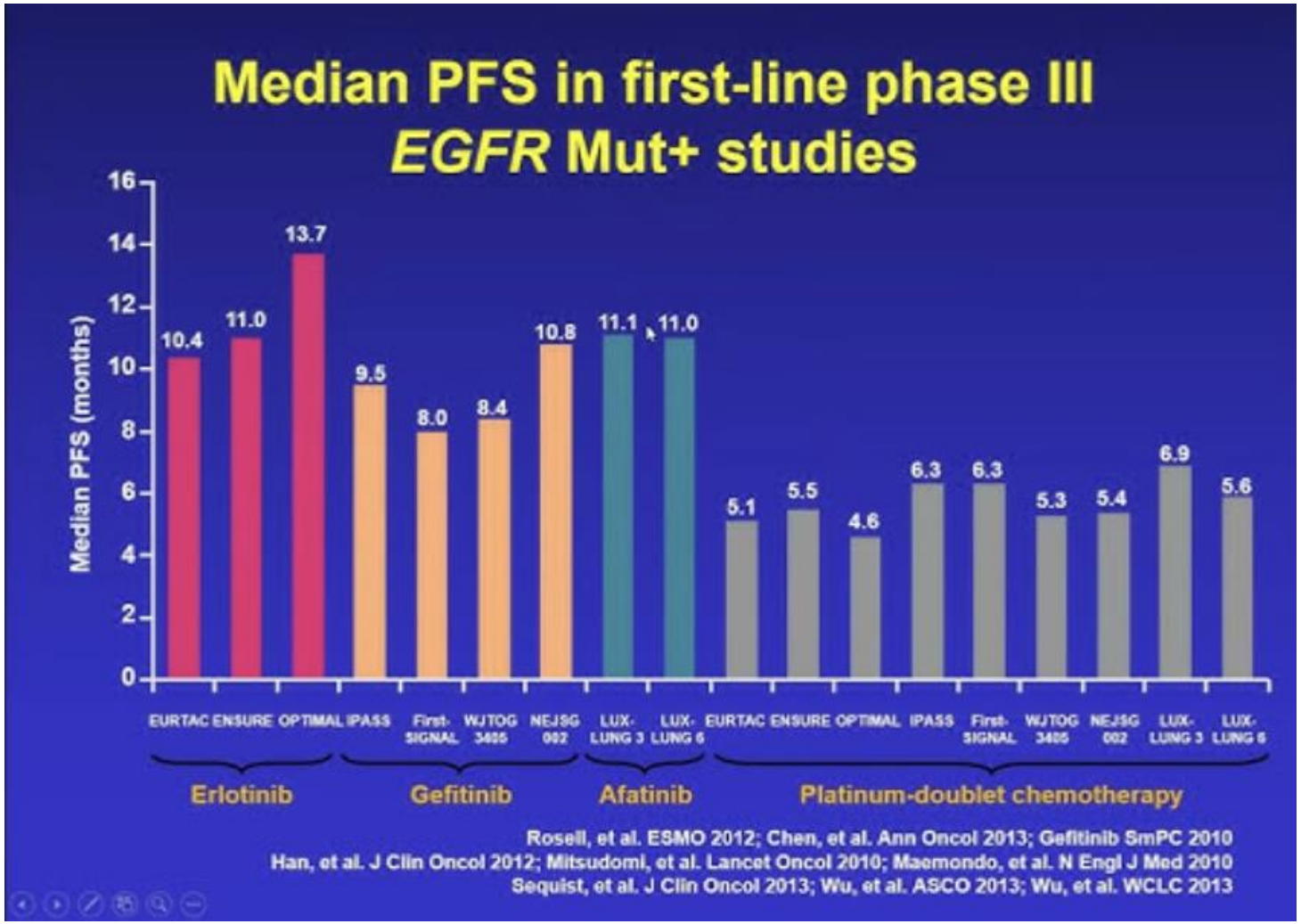
Mutaciones EGFR y relevancia Clínica

- Las mutaciones EGFR se presentan en 10-15% de los adenocarcinomas de pulmón en la población occidental siendo mas frecuentes en países asiáticos (40%)
- Las dos más comunes están representadas por deleciones en exón 19 (ex19Del) y sustitución en codon 858 de exón 21 (L858R)



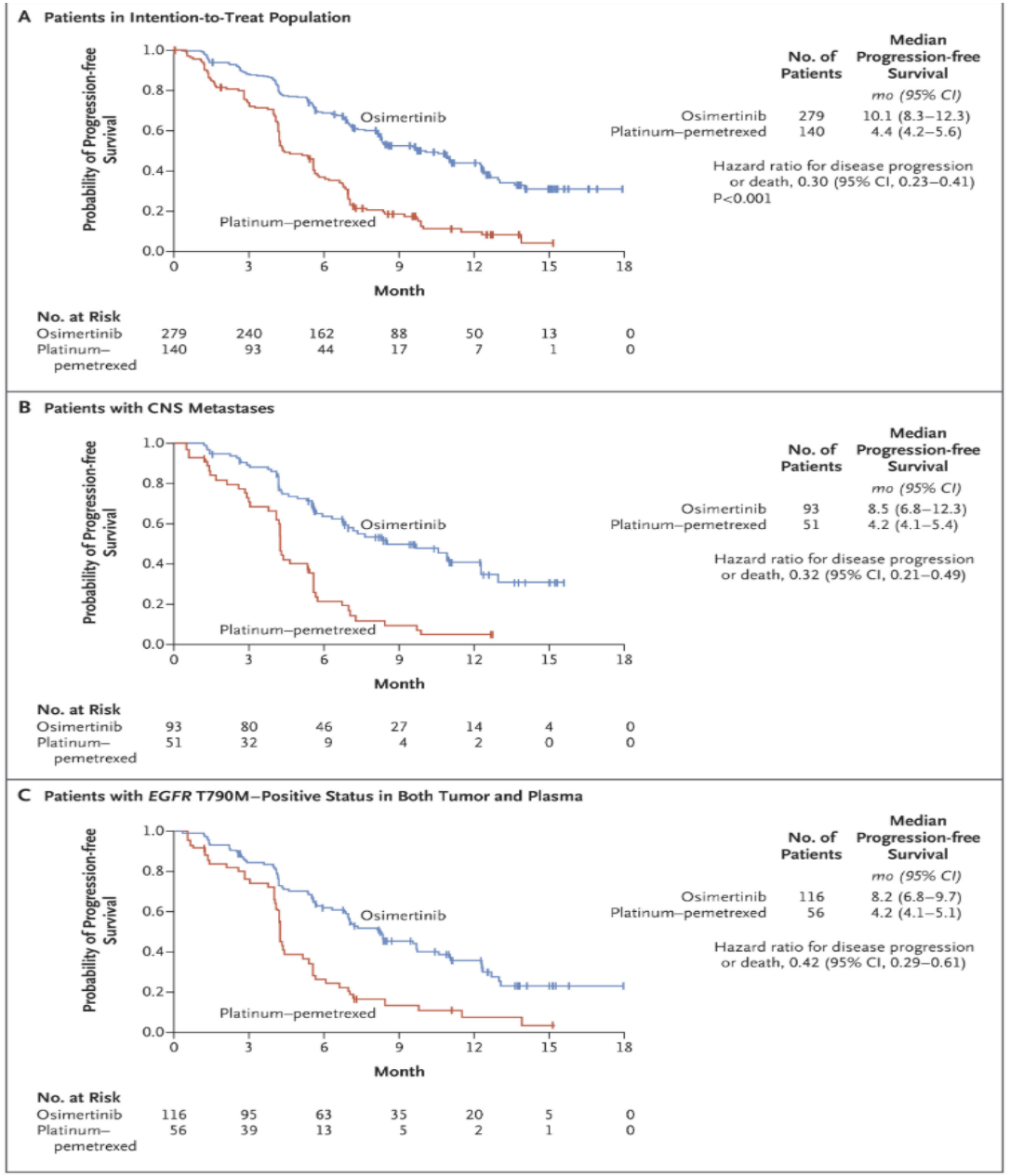
Mutaciones EGFR y relevancia Clínica

- Varios estudios Fase III demostraron la superioridad de TKIs de primera (Erolitinib-Gefitinib) y segunda generación (Afatinib) sobre la quimioterapia estándar en términos de ORR y PFS
- Lamentablemente los pacientes desarrollaran resistencia adquirida en el término medio de 9-15 meses



Mutaciones EGFR y relevancia Clínica

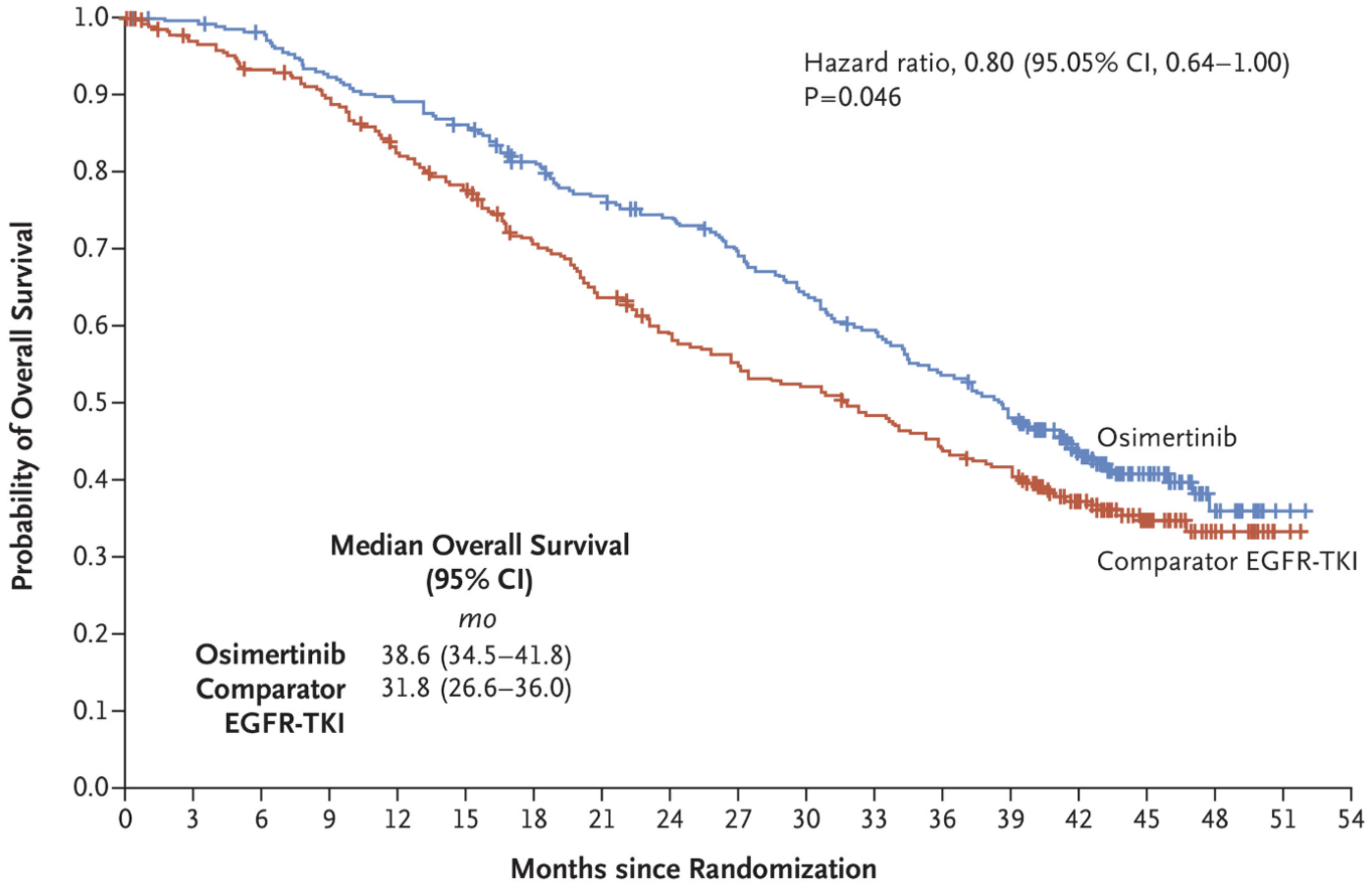
- Osimertinib (TKI de 3ª generación) demostró su eficacia en pacientes con resistencia adquirida producto de una mutación secundaria (T790M) incluso con actividad en SNC



N Engl J Med 2017 ; 376 : 629 - 640 DOI: 10.1056/NEJMoa1612674

Mutaciones EGFR y relevancia Clínica

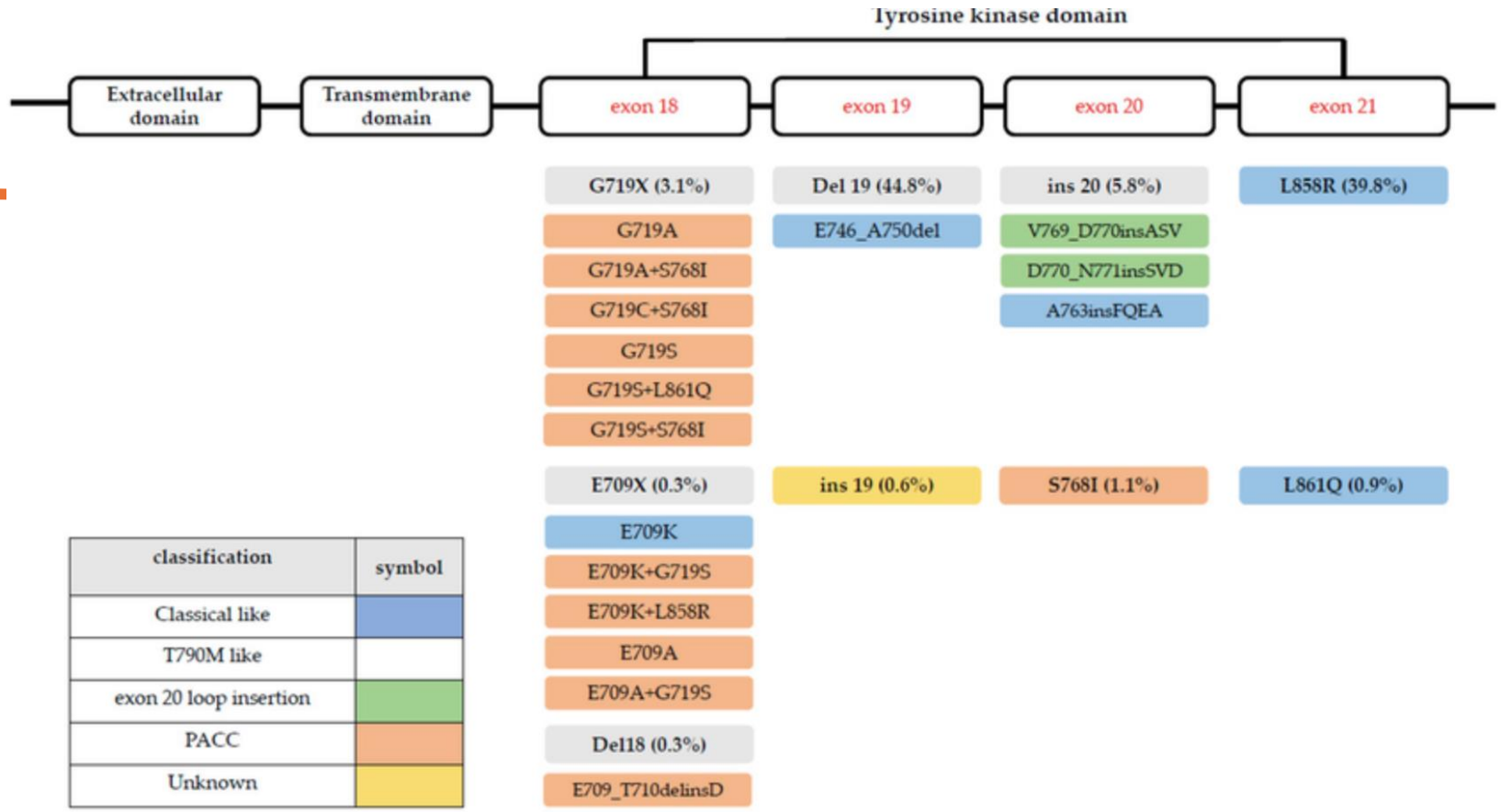
- Más recientemente en un ensayo fase III (FLAURA) osimertinib demostró mejor sobrevida global en primera línea en comparación con TKIs de 1ª generación en pacientes con mutaciones comunes.
- Osimertinib se impuso como la nueva terapia standard en 1L en pacientes con deleciones en exón 19 (ex19Del) y sustitución en codon 858 de exón 21 (L858R)



N Engl J Med 2020;382:41-50 DOI: 10.1056/NEJMoa1913662

Mutaciones EGFR y relevancia Clínica

- Existen otras mutaciones infrecuentes caracterizadas por una mayor agresividad y menor respuesta terapéutica



Resistencia Primaria a Osimertinib

- Definición: Demostración de pérdida de beneficio clínico y/o progresión de enfermedad dentro de los 6 meses desde el inicio del TKI
- Representan 20-30% de los pacientes y supone estar relacionada a alteraciones moleculares presentes previamente al inicio de la terapia
  - **Heterogenicidad molecular de mutaciones en EGFR**
  - **Alteraciones coexistentes en otros genes**

Heterogenicidad molecular de mutaciones en EGFR

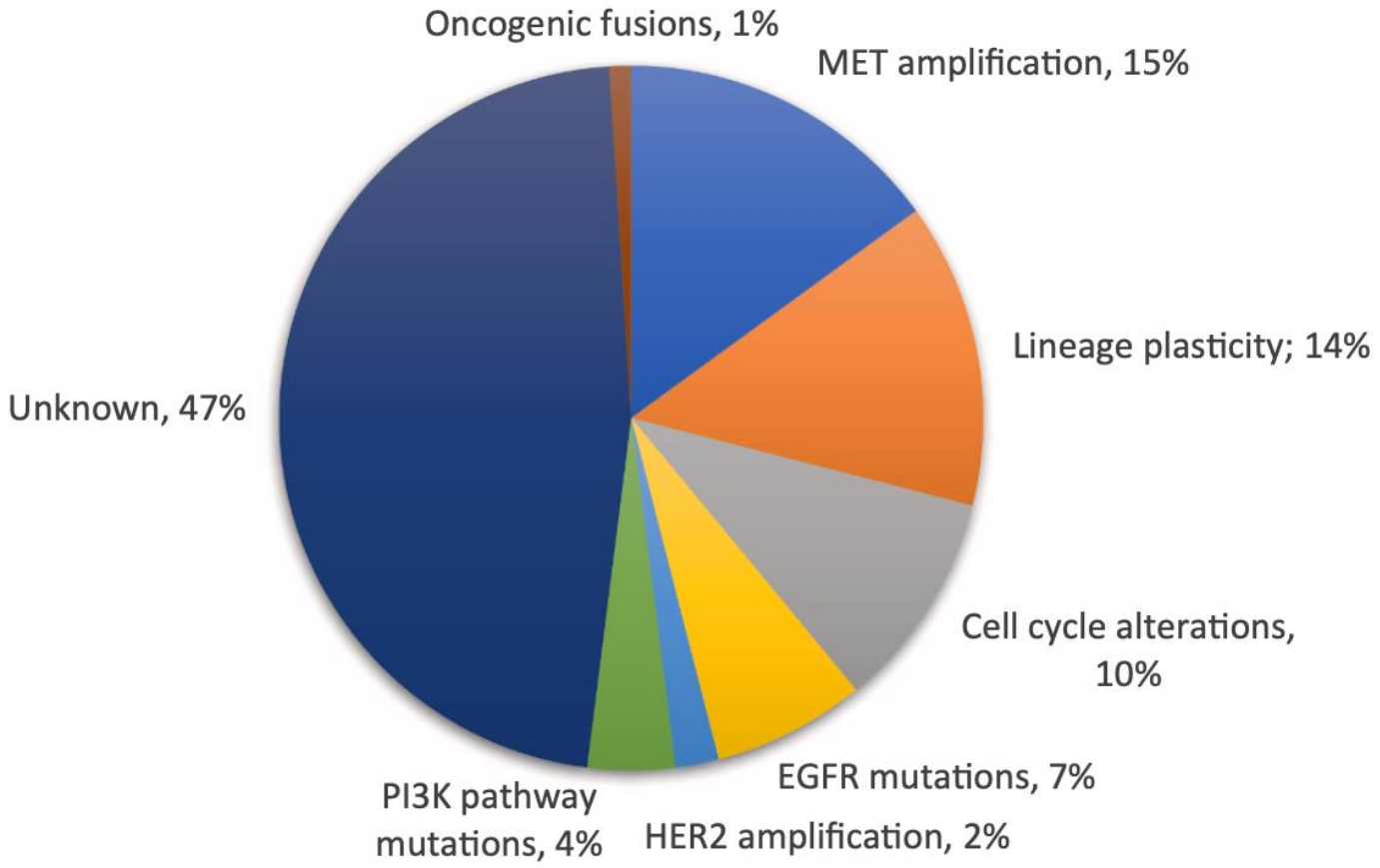
- Inserciones en sitios diferentes a Exón 20
  - G719X, S768I, L861Q
  - Favorable sensibilidad a TKIs de 2ª y 3ª especialmente Afatinib
- Inserciones de Exón 20
  - 50% de las mutaciones no comunes (10% del total de mEGFR)
  - Ausencia de eficacia de Osimertinib
  - Multiples TKIs en desarrollo
    - Poziotinib
    - Mobocertinib
    - Amivantamab

Alteraciones coexistentes en otros genes

- Por lejos menos frecuente que las inserciones previamente descriptas
  - TP53 (54.6–64.6%)
  - KRAS (6-35%)
  - RB1 (9.6–10.33%)
  - ERBB2 (8–11%)
  - CTNNB1 (5.3–9.6%)
  - PIK3CA (9–12.4%)
  - NKX2–1 (12.2–16.7%)
  - CDK4 (7–10%)
  - CDK6 and CCNE1

Resistencia Adquirida a Osimertinib 1L

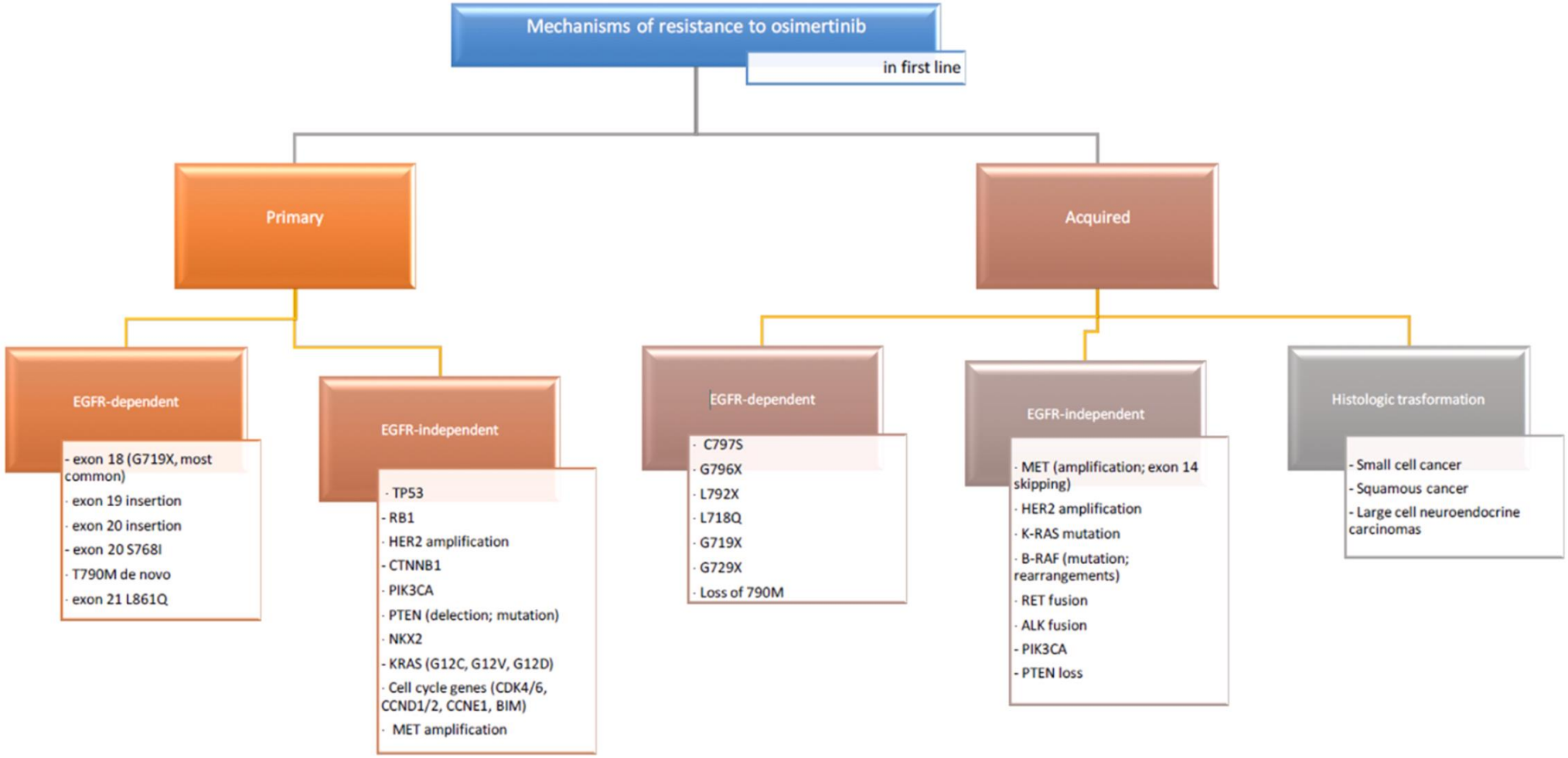
- La resistencia en el objetivo (On-Target) se debe a una mutación en EGFR que altera la unión de la proteína TKI o permite que EGFR funcione a pesar de la inhibición de TKI.
    - C797S (7%), G724 (1-4%), L718Q, G796S, S768I
- La resistencia fuera del objetivo (Off-target) es causada por la activación de una vía molecular alternativa capaz de alimentar la supervivencia y proliferación de las células cancerosas a pesar de la inhibición de EGFR.
- Transformación histológica o plasticidad linear.



La resistencia fuera del objetivo (Off-target) y Transformación histológica

- MET (7-15%)
- Amplificación HER2 (2-5%)
- Fusión de RET – ALK (raras)
- KRAS (3-4%)
- BRAF (V600E 3%)
- PIK3CA (3-10%)
- Transformación Histológica (3-15%)
  - SCLC más frecuente
  - Epidermoide y Neuroendócrino de células grandes

Resistencia a Osimertinib en Primera Línea



Estrategia Terapéutica ante Resistencia Adquirida a Osimertinib

- Oligoprogresión asintomática
- Progresión única en SNC
- Progresión sistémica y sintomática
  - Estrategia considerando selección molecular del paciente
  - Estrategia sin selección molecular del paciente

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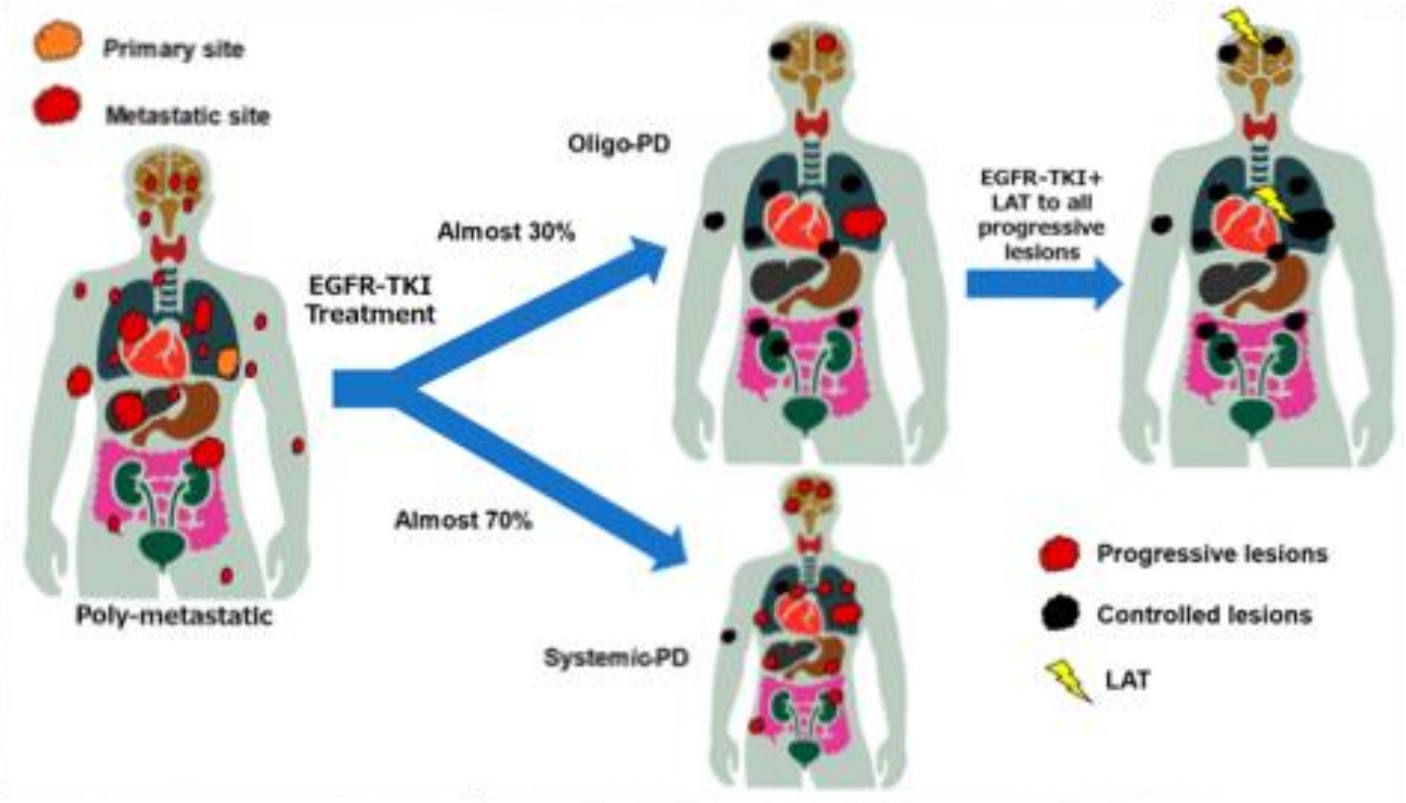

First-line continual EGFR-TKI plus local ablative therapy demonstrated survival benefit in EGFR-mutant NSCLC patients with oligoprogressive disease

Análisis retrospectivo de pacientes con NSCLC EGFR mutado con ≤5 metástasis tratados en 1L con TKIs

CRITERIOS DE INCLUSION:

- Estadio IV con mutaciones EGFR m (Deleción Exón 19 o mutación L858R Exón 21)
- Oligometástasis sincrónicas (1-5 Mts en múltiples órganos)
- PET e IRM cerebral

Gefitinib, erlotinib o icotinib hasta progresión sintomática o empeoramiento de PS

LCT (Cirugía, SBRT, RacioCx, XRT, ablación por radiofrecuencia en Mts hepáticas)

Objetivos: 1: PFS1, PFS2 y OS

2019; 10(2): 522-529. doi: 10.7150/jca.26494

First-line continual EGFR-TKI plus local ablative therapy demonstrated survival benefit in EGFR-mutant NSCLC patients with oligoprogressive disease

Characteristic	Patients (n)	(%)
Median age, y (range)	58 (28~83)	
<65	143	69.4
□≥□	63	30.6
Gender		
Male	97	41.7
Female	109	58.3
ECOG performance status		
0~1	153	74.3
2	53	25.7
Histology		
Adenocarcinoma	174	84.5
Squamous cell	2	0.9
Large cell	7	3.4
Adeno-squamous	14	6.8
NOS	9	4.4
Disease stage		
IIIB	39	18.9
IV	167	81.1
Smoking status		
Non-smoker	125	60.7
Present or former smoker	81	39.3
Metastases number		
1	79	38.3
2	25	12.1
3	31	15.1
4	42	20.4
5	29	14.1
EGFR mutation		
Exon 19 deletion	89	43.2
Exon 21 L858R	117	56.8
EGFR TKIs		
Gefitinib	107	51.9
Erlotinib	47	22.8
Icotinib	52	25.3
Response to first-line EGFR TKIs		
Partial or complete response	140	68.0
Stable disease	41	19.9
Disease progression	25	12.1
Oligoprogressive symptom		
Symptomatic	71	34.5
Asymptomatic	135	65.5
Second- or further-line treatment		
Chemotherapy	164	79.6
Osimertinib±chemotherapy	11	5.4
CTHM	31	15.0
Metastasis location		
Brain	124	60.2
Bone	86	41.7
Adrenal	35	17.0
Lung	40	19.4
Liver	18	8.7
Chest wall	10	4.9
Neck lymph nodes	9	4.4
Intestine	1	0.5
LAT for oligometastasis		
Brain	124	
Whole-brain irradiation	23	18.5
SRS	89	71.8
Surgery + whole-brain irradiation	12	9.7
Bone	86	
Surgery + EBRT (30 Gy)	4	4.7
EBRT (30-40 Gy)	82	95.3
Adrenal	35	
Surgery	10	28.6
SBRT	16	45.7
EBRT (45-50 Gy)	9	25.7
Lung	40	
SBRT	26	65.0
EBRT (55-63 Gy)	11	27.5
Surgery	3	7.5
Liver	18	
Radiofrequency ablation	16	88.9
Surgery	2	11.1
Chest wall	10	
EBRT (45-55Gy)	10	100.0
Neck lymph nodes	9	
EBRT (55-63Gy)	9	100.0
Intestine	1	
Surgery	1	100.0

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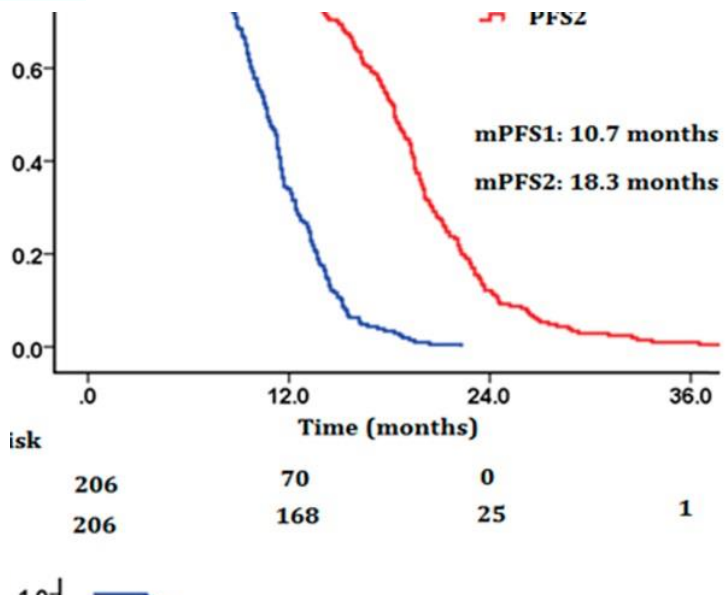
First-line continual EGFR-TKI plus local ablative therapy demonstrated survival benefit in EGFR-mutant NSCLC patients with oligoprogressive disease



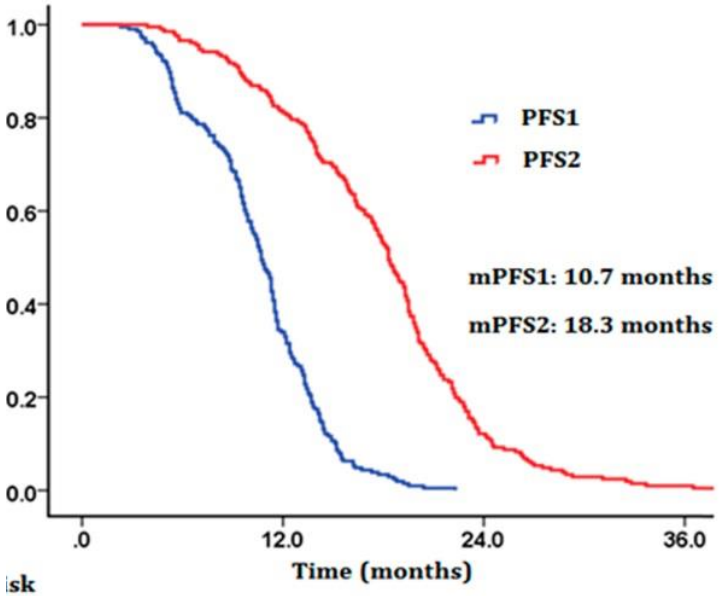
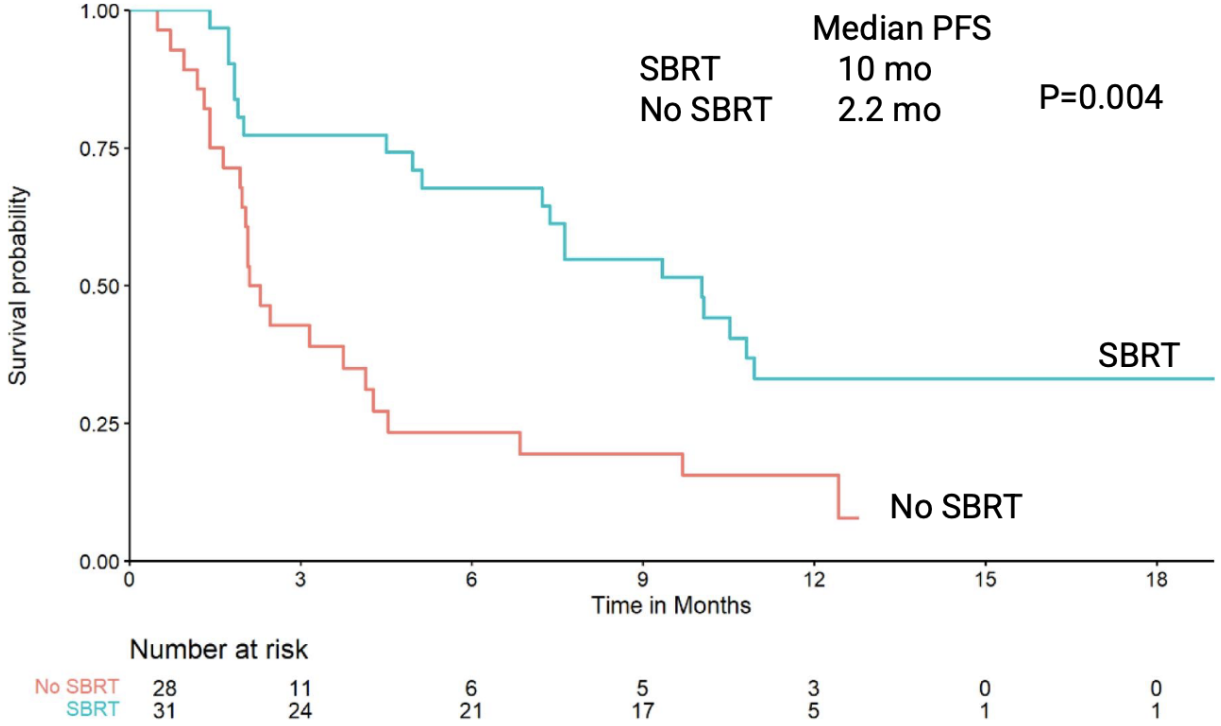


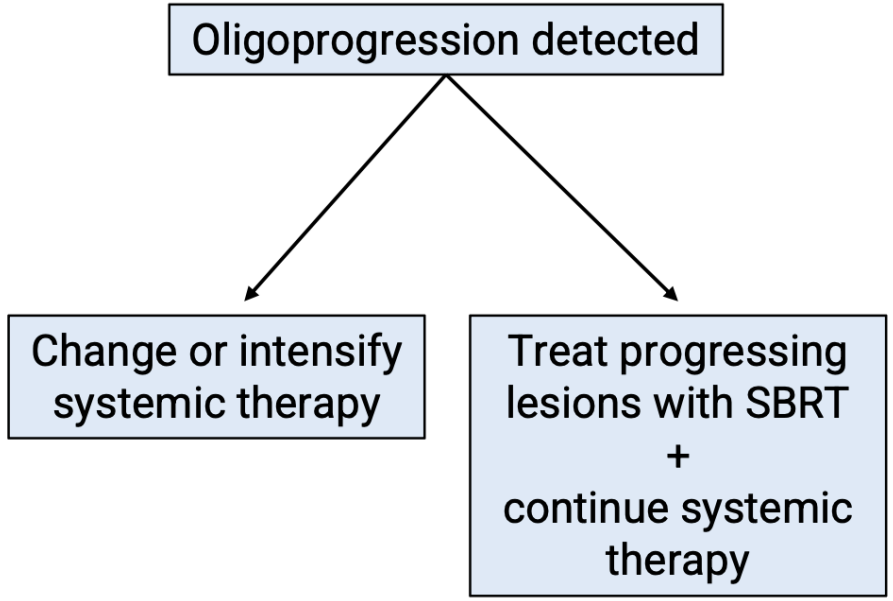
Table 3. Multivariable analysis of covariables associated with PFS and OS.

Variable	PFS1		PFS2		OS	
	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value	HR (95% CI)	*p* Value
Gender (male VS. female)	0.69 **(0.50-0.95)**	0.025	0.61 **(0.43-0.82)**	0.016	0.612 **(0.43-0.87)**	0.006
Histology (adenocarcinoma vs. nonadenocarcinoma)	1.27 **(0.83-1.94)**	0.281	0.85 **(0.55-1.30)**	0.445	1.70 **(1.10-2.62)**	0.016
Smoking status (non-smoker vs. present or former)	1.08 **(0.78-1.51)**	0.648	0.95 **(0.69-1.31)**	0.753	1.02 **(0.72-1.44)**	0.916
EGFR mutation (exon19 vs. exon 21)	4.06 **(2.86-5.76)**	<0.001	3.90 **(2.75-5.98)**	<0.001	4.68 **(3.19-6.87)**	<0.001
Metastases number (1 vs.>1)	1.64 **(1.19-2.16)**	0.002	0.642 **(0.48-0.86)**	0.003	1.76 **(1.28-2.40)**	<0.001
Response to first-line EGFR TKIs (Partial or complete response vs. Stable disease or disease progression)	2.92 **(1.37-2.69)**	<0.001	0.49 **(0.36-0.69)**	<0.001	1.93 **(1.38-2.70)**	<0.001

2019; 10(2): 522-529. doi: 10.7150/jca.26494

Standard-of-care systemic therapy with or without stereotactic body radiotherapy in patients with oligoprogressive breast cancer or non-small-cell lung cancer (Consolidative Use of Radiotherapy to Block [CURB] oligoprogression): an open-label, randomised, controlled, phase 2 study





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Estrategia Terapéutica ante Resistencia Adquirida a Osimertinib

- Oligoprogresión asintomática
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  - Estrategia considerando selección molecular del paciente
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Progresión sistémica y sintomática
Estrategia considerando selección molecular del paciente

- MET
  - Savolitinib
  - Tepotinib
  - Capmatinib
- Amplificación HER2
  - TDM1
- BRAF, ALK, RET
  - Crizotinib, Alectinib, Dabrafenib/Trametinib

2025 ASCO ANNUAL MEETING

Savolitinib combined with osimertinib versus chemotherapy in EGFR-mutant and MET-amplified advanced NSCLC after disease progression on EGFR tyrosine kinase inhibitor: results from a randomized phase 3 SACHI study

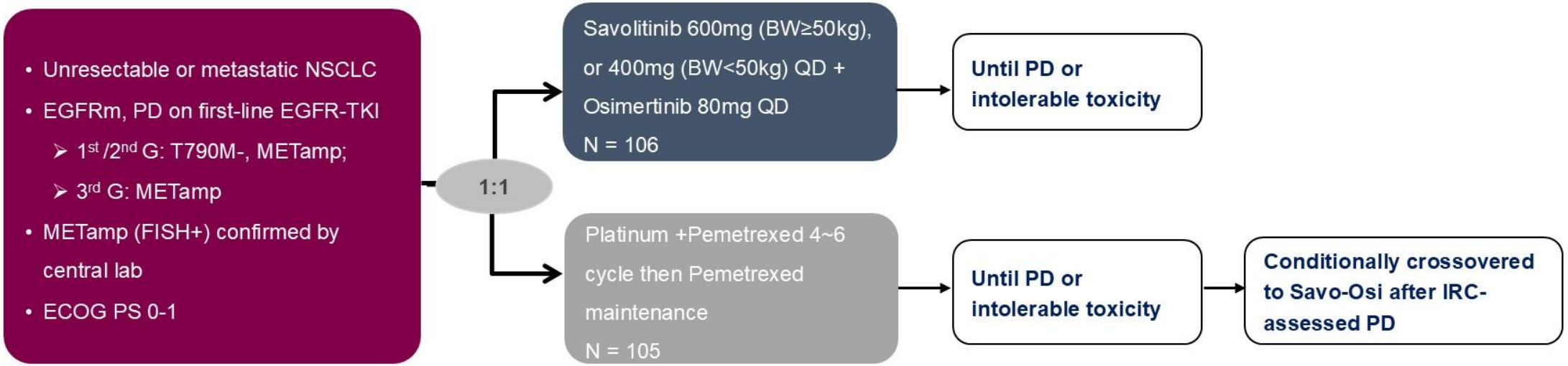
Shun Lu[1], Jie Wang[2], Nong Yang[3], Dongqing Lv[4], Lijuan Chen[5], Lin Wu[3], Xingya Li[6], Longhua Sun[7], Yongfeng Yu[1], Bo Jin[8], Lin Yang[9], Yubiao Guo[10], Haipeng Xu[11], Tienan Yi[12], Aiping Zeng[13], Xiaorong Dong[14], Jianhua Chen[3], Ziping Wang[15], Tony Mok[16], Weiguo Su[17]

1. Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; 2. Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China: 3. Hunan Cancer Hospital, Changsha, China; 4. Taizhou Hospital of Zhejiang Province, Taizhou, China; 5. Henan Cancer Hospital, Zhengzhou, China; 6. First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; 7. First Affiliated Hospital of Nanchang University, Nanchang, China; 8. The First Hospital of China Medical University, Shenyang, China; 9. Shenzhen People's Hospital, Shenzhen, China; 10. The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China; 11. Fujian Provincial Cancer Hospital, Fuzhou, China; 12. Xiangyang Central Hospital, Xiangyang, China; 13. The Cancer Hospital Affiliated to Guangxi Medical University, Nanning, China; 14. Union Hospital Tongji Medical College Huazhong University of Science and Technology, Wuhan, China; 15. Beijing Cancer Hospital, Beijing, China; 16. Department of Clinical Oncology, Faculty of Medicine, The Chinese University of Hong Kong, Hongkong, China; 17. HUTCHMED, Shanghai, China

PRESENTED BY: Shun Lu, MD, PhD

SACHI Phase 3 Study Design

Randomized, open-label, multi-center phase 3 study conducted across 68 centers in China.



METamp:

- **Post 1st /2nd G:** MET copy number ≥5 or MET/CEP7 ≥2
- **Post 3rd G:** MET copy number ≥ 10

Stratification factors:

- **Brain metastasis**: (yes or no)
- **Prior 3rd G EGFR-TKI**: (yes or no)
- **EGFR mutation**: (ex19del vs L858R vs others)

Primary endpoint: PFS by investigator

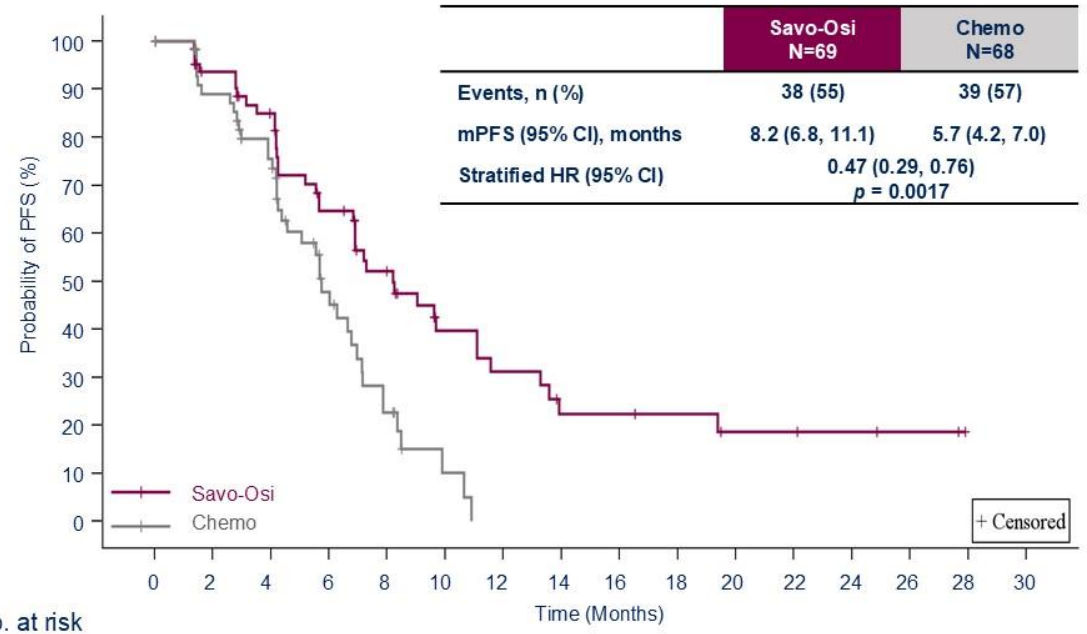
Secondary endpoints: PFS by IRC, ORR, DCR, DoR, TTR, OS, safety

PRESENTED BY: Shun Lu, MD, PhD

1st /2nd G: first or second generation; 3rd G: third generation; BW: body weight; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; EGFRm, EGFR mutant; FISH, fluorescence in situ hybridization; IRC, independent review committee; METamp, MET amplification; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progression disease; PFS, progression-free survival; QD, once daily; Savo-Osi, Savolitinib-Osimertinib; TKI, tyrosine kinase inhibitor; TTR, time to response.

Progression-free Survival: IRC

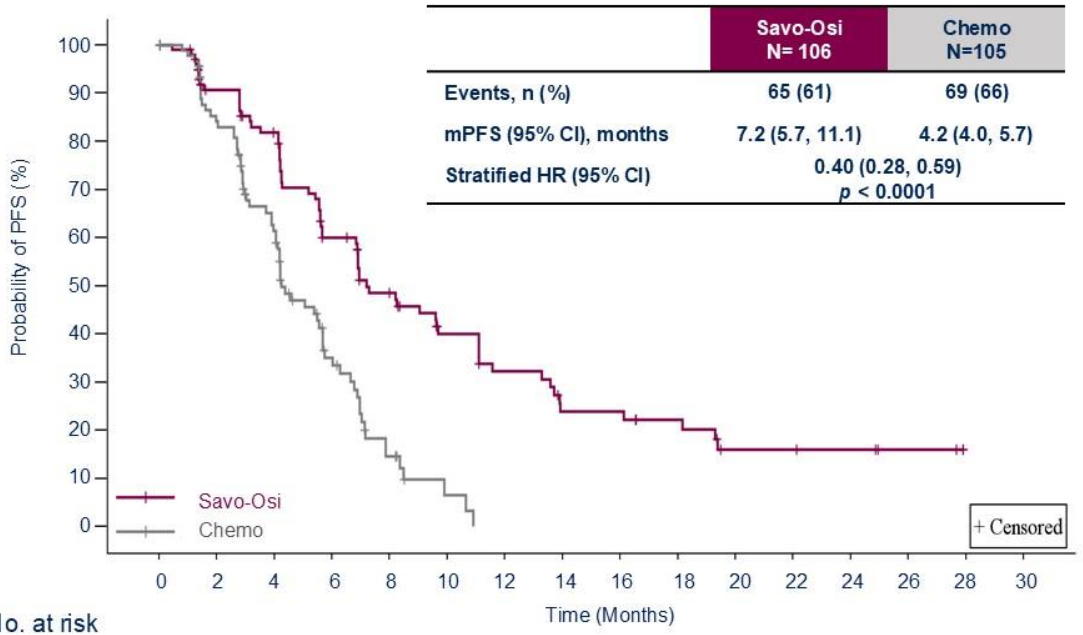
Prior 1st /2nd G EGFR-TKI-treated population



	Savo-Osi N=69	Chemo N=68
Events, n (%)	38 (55)	39 (57)
mPFS (95% CI), months	8.2 (6.8, 11.1)	5.7 (4.2, 7.0)
Stratified HR (95% CI)	0.47 (0.29, 0.76) $p = 0.0017$	

No. at risk														
Savo-Osi	69(0)	55(10)	47(13)	34(15)	23(20)	14(24)	11(24)	7(25)	7(25)	6(26)	4(27)	4(27)	3(28)	2(29)	0(31)
Chemo	68(0)	48(14)	37(18)	18(25)	8(26)	2(29)	0(29)								

ITT population



	Savo-Osi N= 106	Chemo N=105
Events, n (%)	65 (61)	69 (66)
mPFS (95% CI), months	7.2 (5.7, 11.1)	4.2 (4.0, 5.7)
Stratified HR (95% CI)	0.40 (0.28, 0.59) $p < 0.0001$	

No. at risk														
Savo-Osi	106(0)	83(14)	72(17)	50(20)	36(25)	26(29)	20(30)	14(31)	14(31)	11(33)	6(35)	6(35)	5(36)	3(38)	0(41)
Chemo	105(0)	73(18)	49(23)	22(31)	8(33)	2(36)	0(36)								

The PFS assessment according to IRC was consistent with investigator.

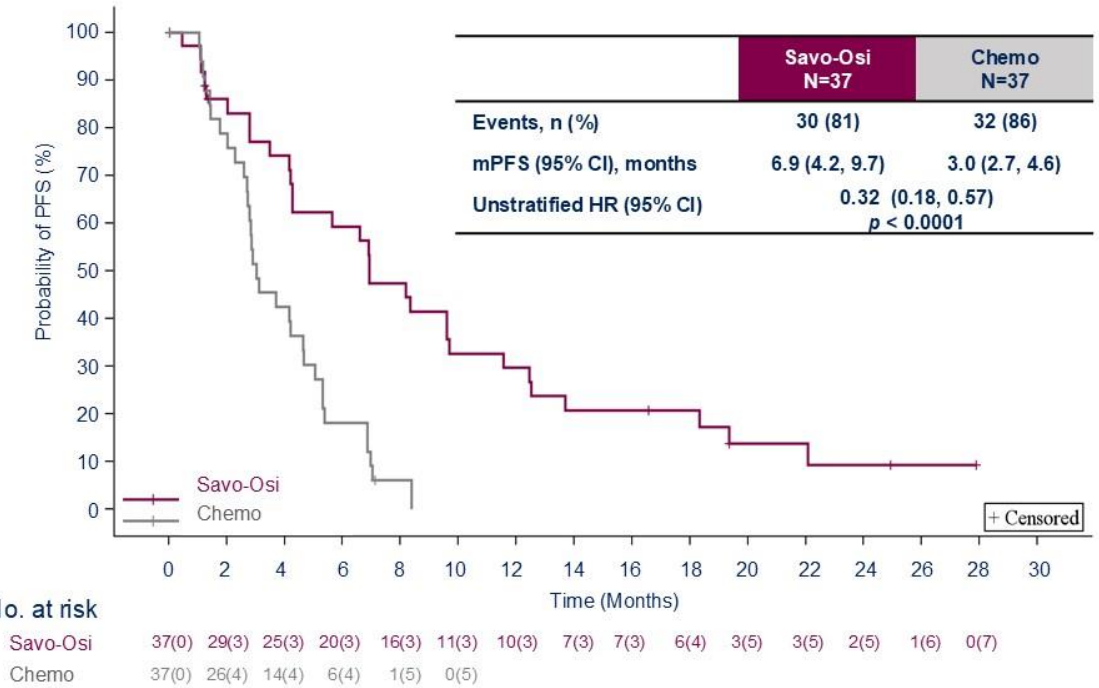
PRESENTED BY: Shun Lu, MD, PhD

Median duration of PFS follow-up: 8.5 months (95%CI: 6.9, 16.5) for prior 1st /2nd G EGFR-TKI-treated population, and 13.8 months (95%CI: 8.3, 19.4) for ITT population.
1st /2nd G: first or second generation; chemo, chemotherapy; CI, confidence interval; EGFR, epidermal growth factor receptor; HR: hazard ratio; ITT, intent to treat; (m)PFS, (median) progression-free survival; Savo-Osi, Savolitinib-Osimertinib; TKI, tyrosine kinase inhibitor.

Progression-free Survival

- Prior 3rd G EGFR-TKI treated subgroup

Investigator

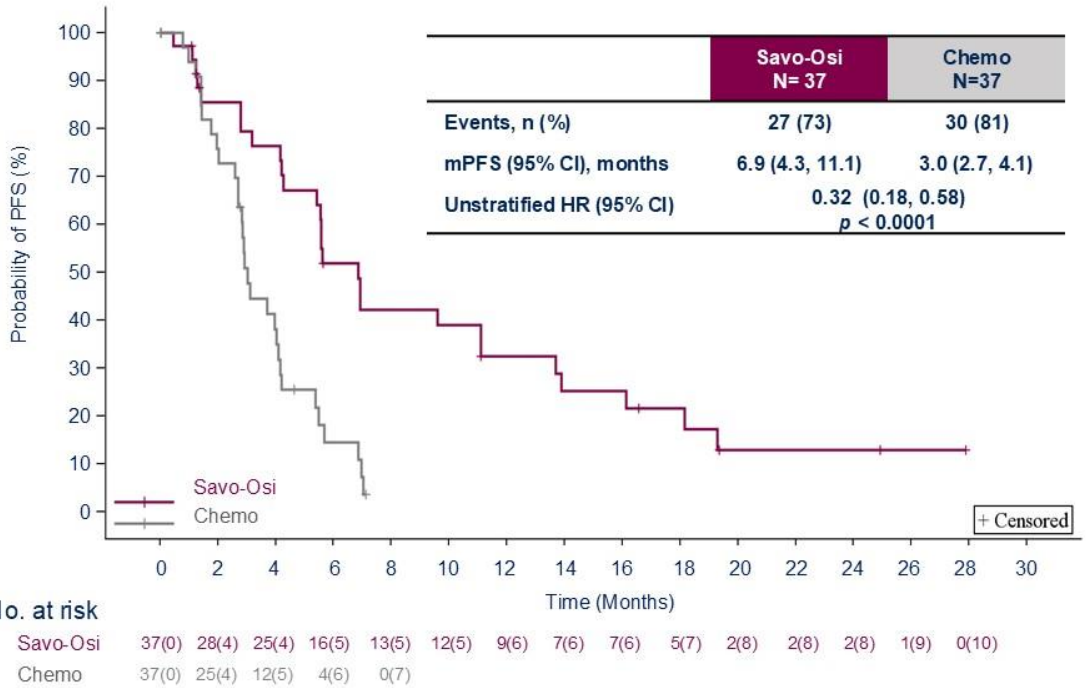


	Savo-Osi N=37	Chemo N=37
Events, n (%)	30 (81)	32 (86)
mPFS (95% CI), months	6.9 (4.2, 9.7)	3.0 (2.7, 4.6)
Unstratified HR (95% CI)	0.32 (0.18, 0.57) $p < 0.0001$	

No. at risk

Savo-Osi	37(0)	29(3)	25(3)	20(3)	16(3)	11(3)	10(3)	7(3)	7(3)	6(4)	3(5)	3(5)	2(5)	1(6)	0(7)
Chemo	37(0)	26(4)	14(4)	6(4)	1(5)	0(5)									

IRC



	Savo-Osi N= 37	Chemo N=37
Events, n (%)	27 (73)	30 (81)
mPFS (95% CI), months	6.9 (4.3, 11.1)	3.0 (2.7, 4.1)
Unstratified HR (95% CI)	0.32 (0.18, 0.58) $p < 0.0001$	

No. at risk

Savo-Osi	37(0)	28(4)	25(4)	16(5)	13(5)	12(5)	9(6)	7(6)	7(6)	5(7)	2(8)	2(8)	2(8)	1(9)	0(10)
Chemo	37(0)	25(4)	12(5)	4(6)	0(7)										

PFS benefits in the population progressing on prior 3rd G EGFR-TKI treatment were comparable to those in ITT and prior 1st /2nd G EGFR-TKI treated populations.

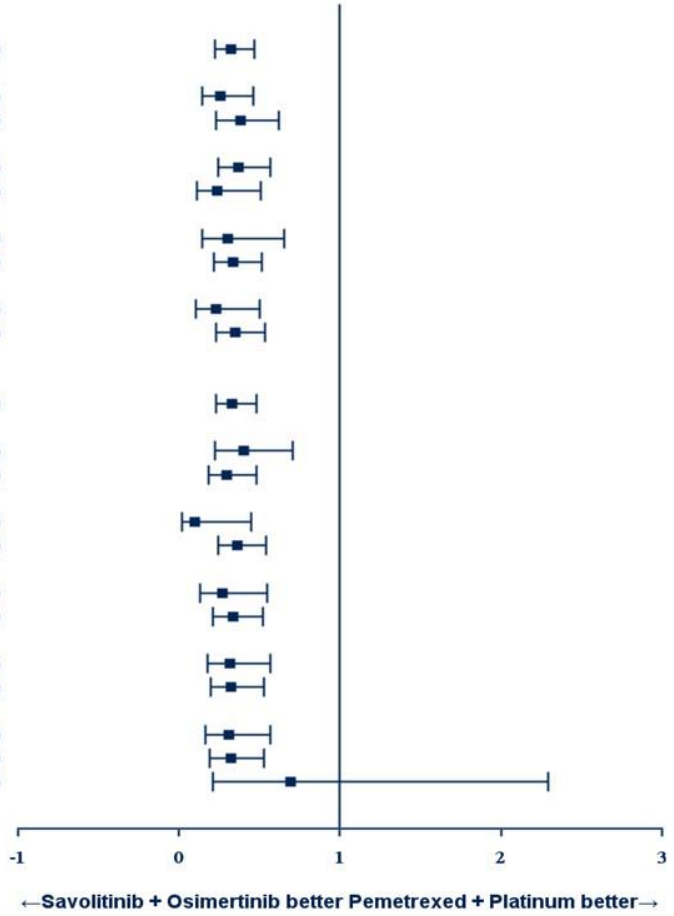
PRESENTED BY: Shun Lu, MD, PhD

Median duration of PFS follow-up: 24.9 months (95%CI: 6.6, NE) for investigator assessment, and 19.4 months (95%CI: 11.1, NE) for IRC assessment.
3rd G: third generation; chemo, chemotherapy; CI：confidence interval; EGFR, epidermal growth factor receptor; HR: hazard ratio; ITT, intent to treat; (m)PFS, (median) progression-free survival; Savo-Osi, Savolitinib-Osimertinib; TKI, tyrosine kinase inhibitor.

Progression-free Survival: Subgroups in ITT

Investigator

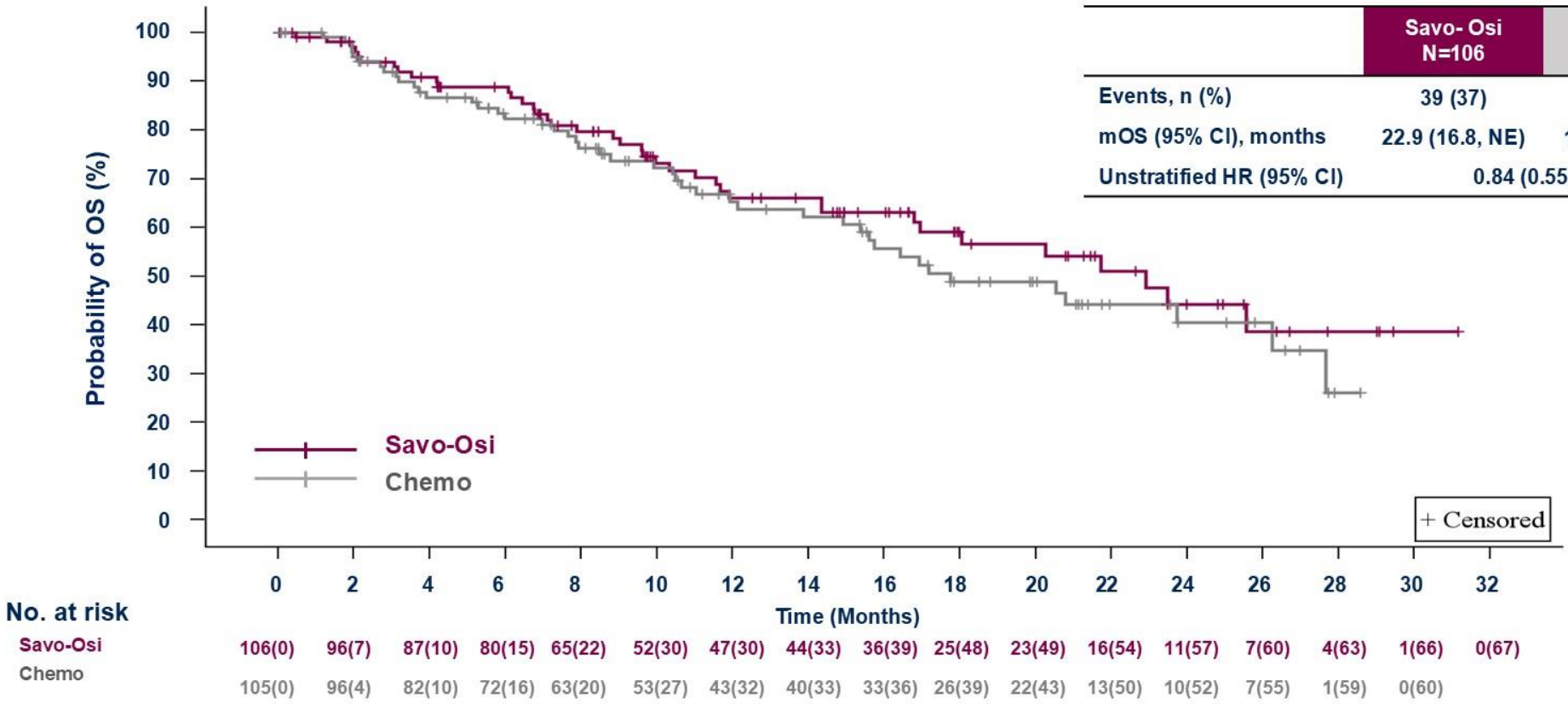
Subgroup	Savolitinib + Osimertinib Event/N	Pemetrexed + Platinum Event/N	HR (95%CI)
Overall	70/106	76/105	0.325 (0.224, 0.471)
Sex			
Male	26/44	39/50	0.259 (0.145, 0.463)
Female	44/62	37/55	0.379 (0.232, 0.618)
Age at randomization			
< 65	54/77	49/65	0.369 (0.240, 0.567)
>= 65	16/29	27/40	0.234 (0.108, 0.504)
Baseline ECOG performance status			
0	20/28	18/27	0.304 (0.142, 0.653)
1	50/78	58/78	0.333 (0.217, 0.511)
Smoking status			
Current/Previous smoker	17/28	21/27	0.230 (0.105, 0.504)
Nonsmoker (Never)	53/78	55/78	0.349 (0.228, 0.536)
Current tumor stage			
IIIB/IIIC	0/1	3/6	
IV/IVA/IVB	70/105	73/99	0.330 (0.228, 0.479)
Brain metastases			
Yes	28/38	31/39	0.399 (0.225, 0.707)
No	42/68	45/66	0.297 (0.183, 0.482)
Liver metastases			
Yes	9/11	13/15	0.097 (0.021, 0.449)
No	61/95	63/90	0.362 (0.244, 0.538)
Number of metastases sites			
< 3	19/35	24/31	0.269 (0.133, 0.545)
>= 3	51/70	49/68	0.333 (0.212, 0.524)
Previous use of 3rd generation EGFR-TKI			
Yes	30/37	32/37	0.316 (0.175, 0.569)
No	40/69	44/68	0.324 (0.199, 0.527)
Type of EGFR mutations			
Exon 19 Deletion	24/40	33/41	0.307 (0.166, 0.570)
L858R	38/54	37/52	0.319 (0.193, 0.528)
Other	8/12	6/12	0.694 (0.210, 2.291)



chemo, chemotherapy; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR: hazard ratio; IRC, independent review committee; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Overall Survival-ITT

- OS data were still evolving, with overall maturity of 40%. 55 (52%) patients in Chemo group received subsequent MET inhibitor treatment (including 45 patients receiving study crossover treatment and 10 patients receiving other MET inhibitors).



	Savo- Osi N=106	Chemo N=105
Events, n (%)	39 (37)	45 (43)
mOS (95% CI), months	22.9 (16.8, NE)	17.7 (14.9, 26.3)
Unstratified HR (95% CI)	0.84 (0.55, 1.29)	

PRESENTED BY: Shun Lu, MD, PhD

Median duration of OS follow-up: 17.7 months (95%CI: 15.3, 19.8) for ITT population.
chemo, chemotherapy; CI, confidence interval; HR: hazard ratio; ITT, intent to treat; (m)OS, (median) overall survival; NE, not estimable; Savo-Osi, Savolitinib-Osimertinib; TKI, tyrosine kinase inhibitor.

Progresión sistémica y sintomática
Estrategia SIN selección molecular del paciente

- Considerando la alta prevalencia de alteraciones en MET
  - Amivantamab/Lazertinib
    - MARIPOSA 2
    - PALOMA 3

- Considerando ausencia detectables de mecanismos de resistencia
  - TROP2
    - OptiTROP-Lung03 (
  - HER3
  - Antiangiogénicos? (IMPOWER 150) Inmunoterapia? (KN 789)

MADRID 2023 ESMO congress

The MARIPOSA-2 study

Amivantamab plus chemotherapy +/- lazertinib in EGFR-mutated advanced NSCLC after progression on osimertinib

A phase 3, global, randomized, controlled trial

2:2:1 Randomization (N=657)

Serial brain MRIs were required for all patients[a]

Key Eligibility Criteria

- Locally advanced or metastatic NSCLC
- Documented *EGFR* Ex19del or L858R
- *Progressed on or after osimertinib monotherapy (as most recent line)*
- ECOG PS 0 or 1
- Stable brain metastases were allowed; radiation/definitive therapy was not required (untreated)

Amivantamab-Lazertinib-Chemotherapy (n=263)

Chemotherapy (n=263)

Amivantamab-Chemotherapy (n=131)

Stratification Factors

- Osimertinib line of therapy (1st vs 2nd)
- Asian race (yes or no)
- History of brain metastases (yes or no)

Dosing (in 21-day cycles)

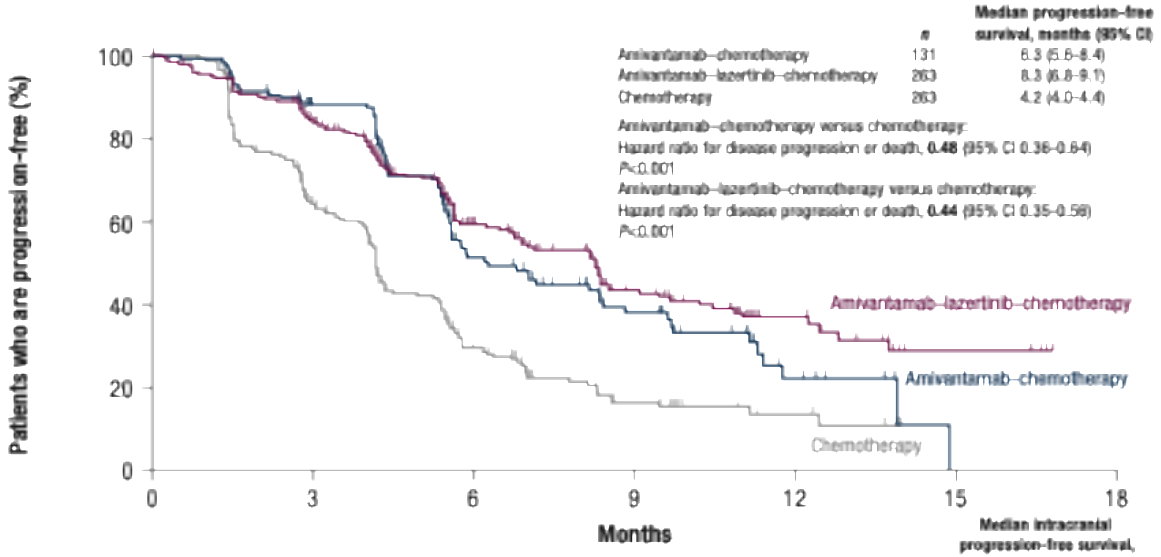
Amivantamab: 1400 mg (1750 mg if ≥80 kg) for the first 4 weeks, then 1750 mg (2100 mg if ≥80 kg) every 3 weeks starting at Cycle 3 (week 7)

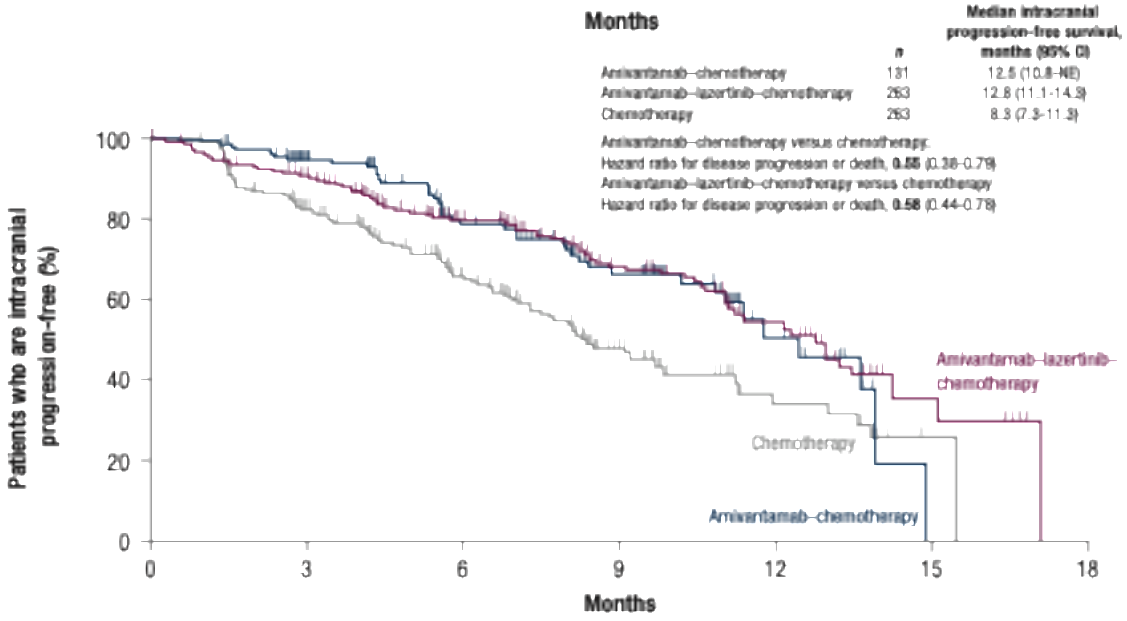
Lazertinib: 240 mg daily starting after completion of carboplatin[b]

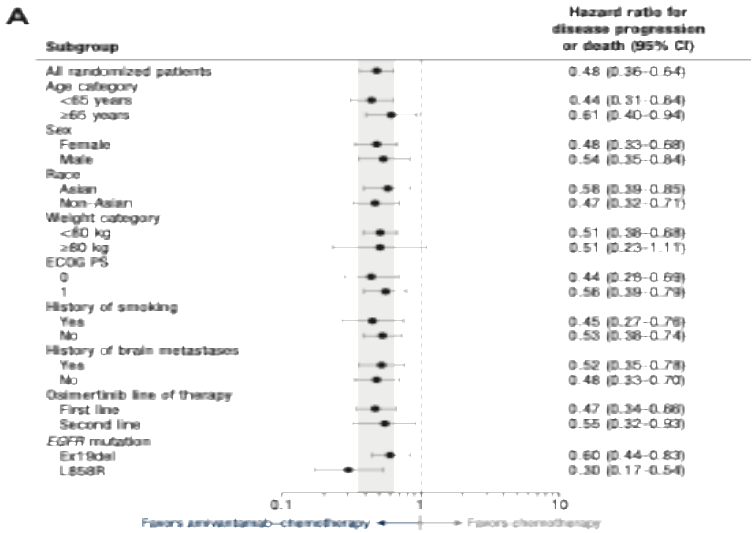
Chemotherapy administered at the beginning of every cycle:

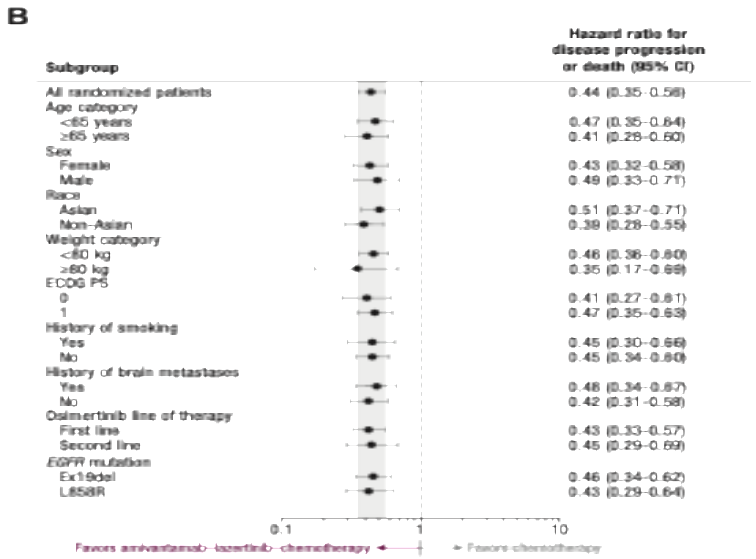
- **Carboplatin:** AUC5 for the first 4 cycles
- **Pemetrexed:** 500 mg/m² until disease progression

Amivantamab plus chemotherapy with and without lazertinib in *EGFR*-mutant advanced NSCLC after disease progression on osimertinib: primary results from the phase III MARIPOSA-2 study☆









https://doi.org/10.1016/j.annonc.2023.10.117

Amivantamab plus chemotherapy with and without lazertinib in *EGFR*-mutant advanced NSCLC after disease progression on osimertinib: primary results from the phase III MARIPOSA-2 study☆

Table 3. Treatment-emergent adverse events

Event, *n* (%)	Chemotherapy (*n* = 243)		Amivantamab–chemotherapy (*n* = 130)		Amivantamab–lazertinib–chemotherapy (*n* = 263)	
Adverse events[a]	All	Grade ≥3	All	Grade ≥3	All	Grade ≥3
Neutropenia[b]	101 (42)	52 (21)	74 (57)	59 (45)	181 (69)	144 (55)
Thrombocytopenia[b]	72 (30)	22 (9)	57 (44)	19 (15)	158 (60)	96 (37)
Infusion-related reaction	1 (0.4)	0	76 (58)	7 (5)	148 (56)	9 (3)
Anemia	97 (40)	23 (9)	51 (39)	15 (12)	141 (54)	48 (18)
Paronychia	1 (0.4)	0	48 (37)	3 (2)	133 (51)	11 (4)
Nausea	90 (37)	2 (1)	58 (45)	1 (1)	131 (50)	16 (6)
Rash	12 (5)	0	56 (43)	8 (6)	126 (48)	17 (6)
Stomatitis	21 (9)	0	41 (32)	1 (1)	120 (46)	24 (9)
Leukopenia	68 (28)	23 (9)	37 (28)	26 (20)	106 (40)	71 (27)
Adverse events of special interest	All	Grade ≥3	All	Grade ≥3	All	Grade ≥3
Rash[c]	30 (12)	0	92 (71)	13 (10)	197 (75)	40 (15)
Venous thromboembolism[d]	11 (5)	7 (3)	13 (10)	3 (2)	58 (22)	17 (6)
Interstitial lung disease[e]	0	0	2 (2)	1 (1)	7 (3)	5 (2)

https://doi.org/10.1016/j.annonc.2023.10.117

PALOMA-3: Phase 3 Study Design

Key eligibility criteria

- Locally advanced or metastatic NSCLC
- Disease had progressed on or after osimertinib and platinum-based chemotherapy, irrespective of order
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0–1

Stratification factors

- Brain metastases (yes or no)
- *EGFR* mutation type (Ex19del vs L858R)
- Race (Asian vs non-Asian)
- Type of last therapy (osimertinib vs chemotherapy)

1:1 randomization (N=418)

SC Amivantamab + Lazertinib (n=206)

IV Amivantamab + Lazertinib (n=212)

Dosing (in 28-day cycles)

SC Amivantamab[a,b] (co-formulated with rHuPH20 and administered by manual injection): 1600 mg (2240 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks thereafter

IV Amivantamab[b]: 1050 mg weekly (1400 mg if ≥80 kg) for the first 4 weeks, then every 2 weeks thereafter

Lazertinib: 240 mg PO daily

Prophylactic anticoagulation recommended for the first 4 months of treatment

Co-primary endpoints[c]**:**

- C_{trough} (noninferiority)[d]
- C2 AUC (noninferiority)[e]

Secondary endpoints:

- ORR (noninferiority)
- PFS (superiority)
- DoR
- Patient satisfaction[f]
- Safety

Exploratory endpoints:

- OS

PALOMA-3 (ClinicalTrials.gov Identifier: NCT05388669) enrollment period: August 2022 to October 2023; data cutoff: 03-Jan-2024.

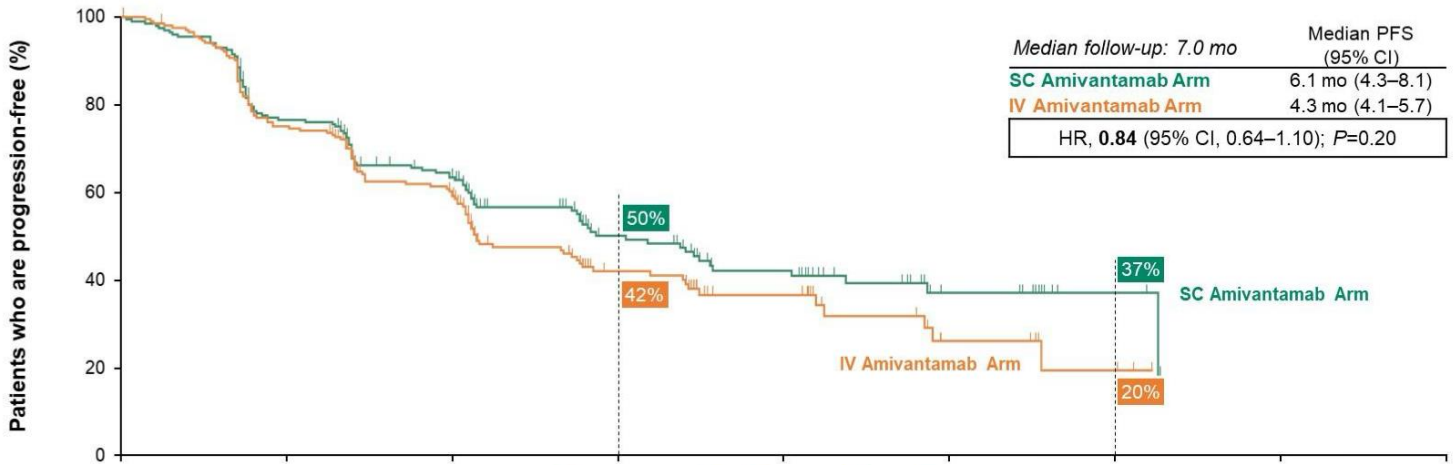
[a]SC amivantamab was co-formulated with rHuPH20 at a concentration of 160 mg/mL. [b]C1 for IV: Days 1 to 2 (Day 2 applies to IV split dose only [350 mg on Day 1 and the remainder on Day 2]), 8, 15, and 22; C1 for SC: Days 1, 8 , 15, and 22; after C1 for all: Days 1 and 15 (28-day cycles). [c]For calculating primary and key secondary outcomes, we estimated that a sample size of 400 patients would provide >95% power for a 1-sided alpha of 0.05 allocated to each of the co-primary endpoints and 80% power with a 1-sided alpha of 0.025 allocated to ORR. A hierarchical testing approach at a 2-sided alpha of 0.05 was used for the co-primary endpoints (noninferiority), followed by ORR (noninferiority) and PFS (superiority), with a combined 2-sided alpha of 0.05. [d]Two definitions of the same endpoint were used as per regional health authority guidance. [e]Measured between C2D1 and C2D15. [f]Assessed by modified TASQ.

AUC, area under the concentration-time curve; C, Cycle; C_{trough}, observed serum concentration of amivantamab at steady state; D, Day; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; rHuPH20, hyaluronidase; SC, subcutaneous; TASQ, Therapy Administration Satisfaction Questionnaire.

PRESENTED BY: Natasha B Leighl

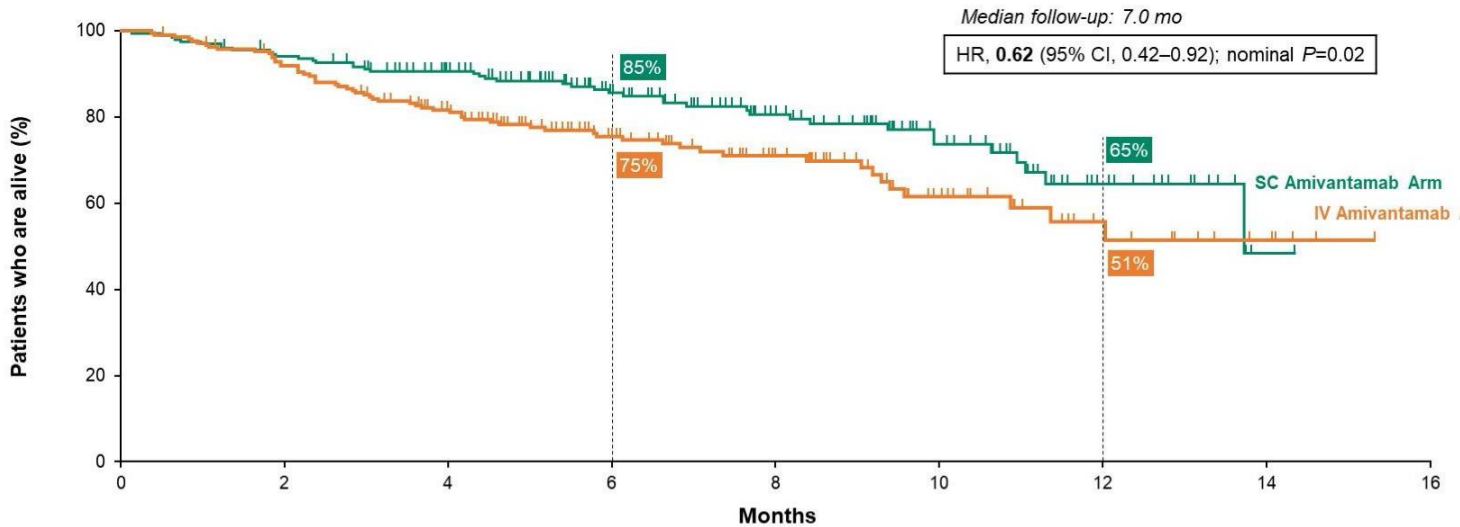
Progression-free Survival

PFS was numerically longer with SC vs IV amivantamab, with an HR of 0.84

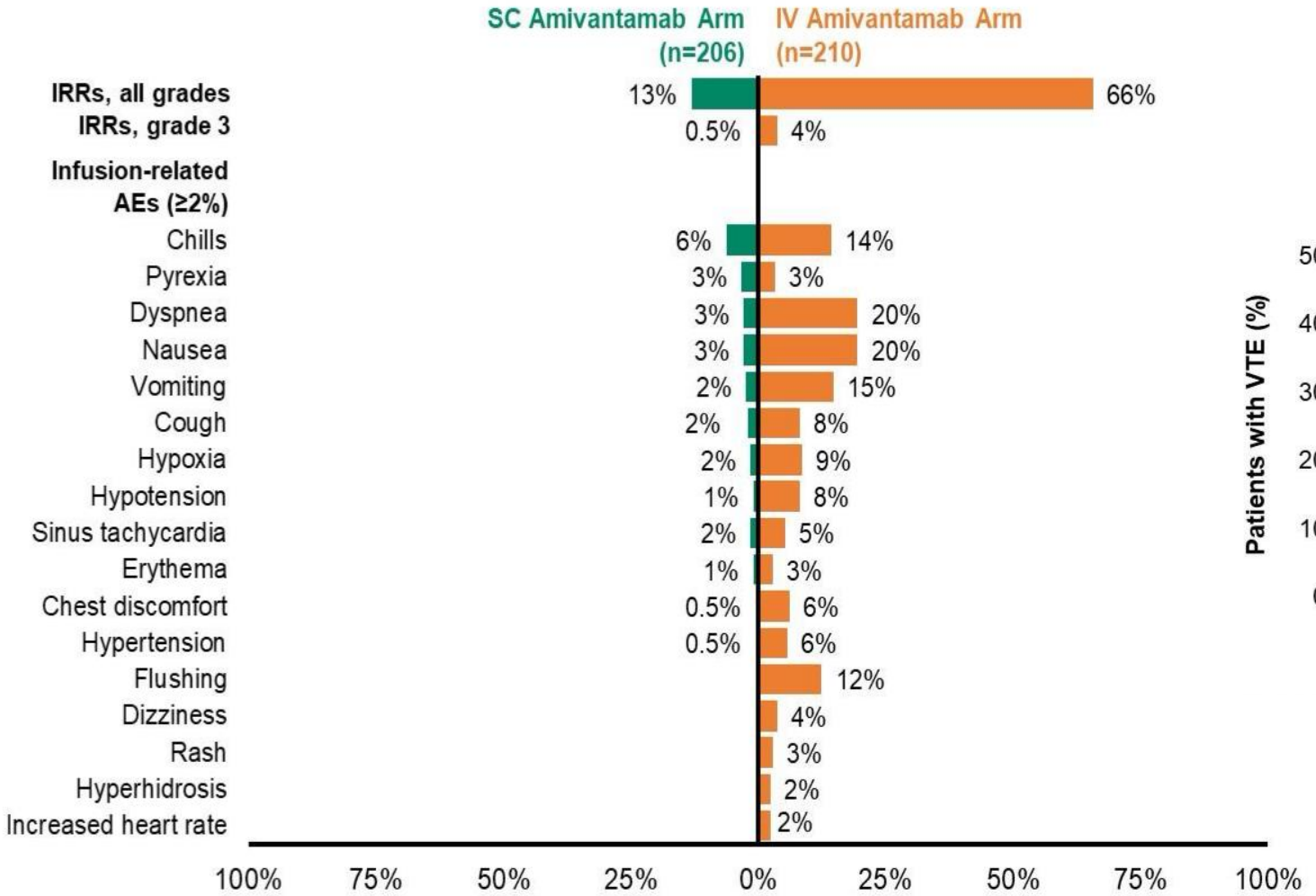


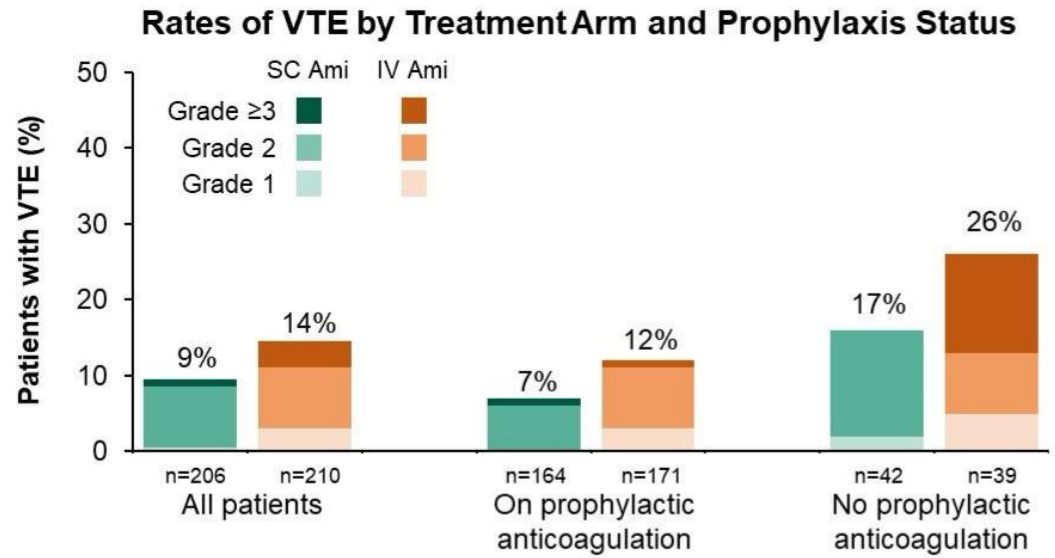
Overall Survival

There was an OS benefit associated with SC amivantamab, with an HR of 0.62 compared to the IV amivantamab arm[a]



Incidence of IRR-related Symptoms





OptiTROP-Lung03 Study Design

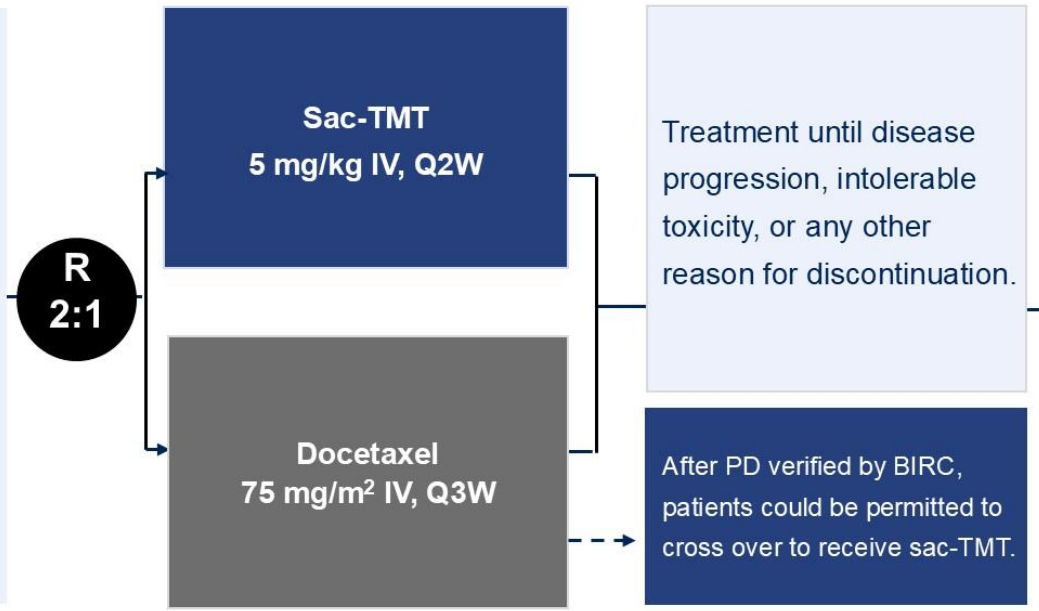
Open-label, randomized, multicenter, registrational trial (NCT05631262)

Key Eligibility

- ECOG score 0 or 1
- Nsq-NSCLC (stage IIIB/IIIC ineligible for surgery or radical radiotherapy or stage IV)
- EGFR-sensitizing mutations, including 19-Del and L858R
- Progression after prior combination or sequential treatment with EGFR-TKIs and platinum-based chemotherapy

Stratification factors:

- Brain metastases (present vs. absent)



Primary Endpoint[a]

- ORR* assessed by BIRC

Secondary endpoints[a]

- PFS
- OS
- ORR assessed by investigator
- DOR, DCR, TTR
- Safety

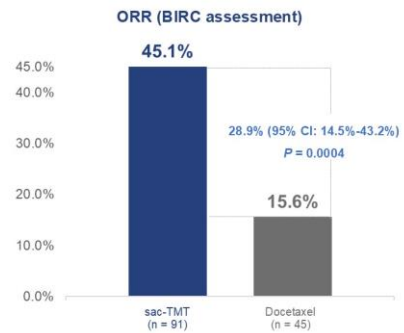
- Tumor assessments will be performed every 6 weeks (± 7 days) within 48 weeks after randomization
- After 48 weeks of randomization, tumor assessments will be performed every 12 weeks (± 7 days).

[a] Tumor response was assessed using RECIST version 1.1.
* Confirmed ORR;
BIRC, blinded independent review committee; IV, intravenous; PD, progressive disease; DOR, duration of response; DCR, disease control rate; TTR, time to response; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

Confirmed ORR by BIRC

Sac-TMT improved ORR with a statistically significant difference of 28.9% over docetaxel.

	Sac-TMT (n = 91)	Docetaxel (n = 45)
cORR, n (%) (95% CI)	41 (**45.1**) (34.6, 55.8)	7 (**15.6**) (6.5, 29.5)
Difference (95% CI)	**28.9 (14.5, 43.2)**	
One-sided P-value	0.0004	
DCR, n (%) (95% CI)	75 (82.4) (73.0, 89.6)	27 (60.0) (44.3, 74.3)
Difference (95% CI)	22.3 (6.0, 38.7)	
DOR, n (%)	26 (63.4)	6 (85.7)
Median DOR, months (95% CI)	**7.0** (5.4, 9.1)	**5.1** (3.1, NE)

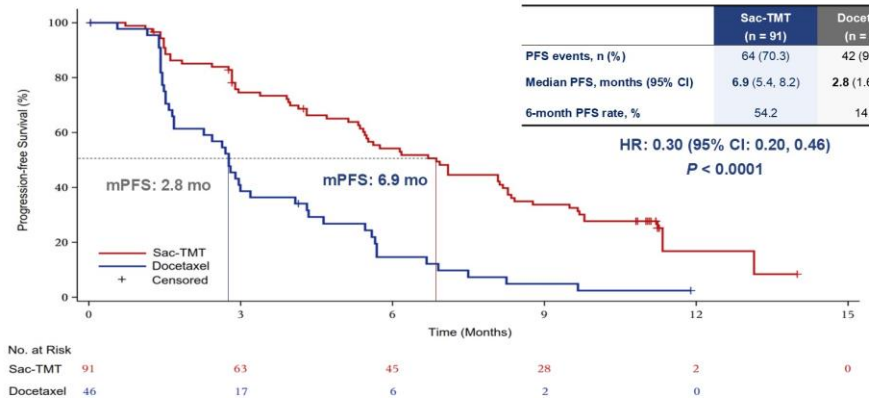


- **ORR benefit favoring patients with sac-TMT over docetaxel across all pre-specified subgroups, including brain metastases, EGFR mutation type, etc.**

Data cutoff date: Dec 31, 2024.

Progression-Free Survival by BIRC

Sac-TMT significantly improved PFS over docetaxel with 70% lower risk of disease progression or death.



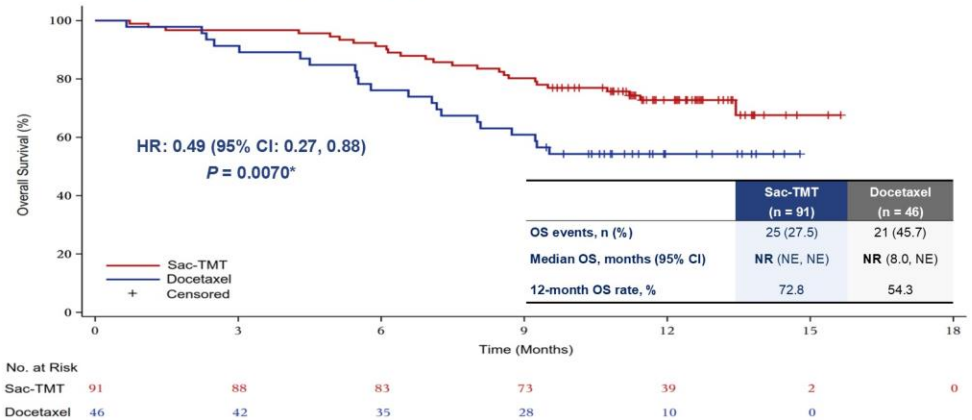
	Sac-TMT (n = 91)	Docetaxel (n = 46)
PFS events, n (%)	64 (70.3)	42 (91.3)
Median PFS, months (95% CI)	**6.9** (5.4, 8.2)	**2.8** (1.6, 4.1)
6-month PFS rate, %	54.2	14.6

HR: 0.30 (95% CI: 0.20, 0.46)
***P* < 0.0001**

Data cutoff date: Dec 31, 2024.

Overall Survival

At the interim analysis, Sac-TMT significantly improved OS over docetaxel with 51% lower risk of death.



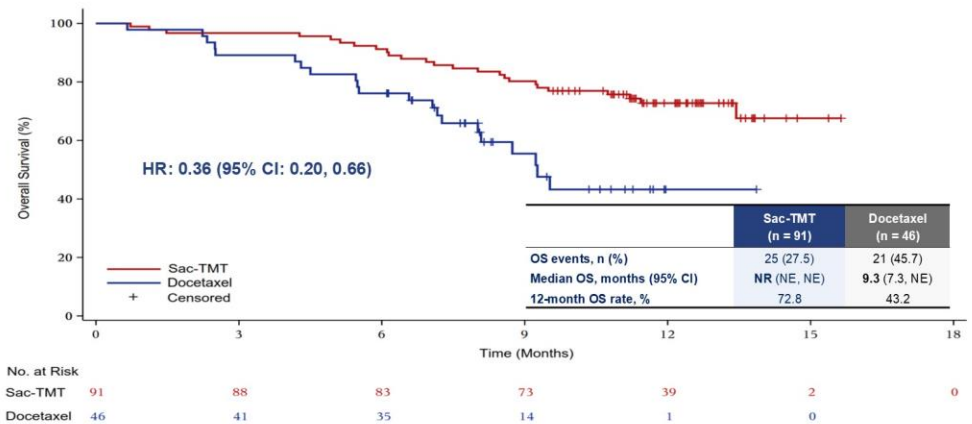
	Sac-TMT (n = 91)	Docetaxel (n = 46)
OS events, n (%)	25 (27.5)	21 (45.7)
Median OS, months (95% CI)	**NR** (NE, NE)	**NR** (8.0, NE)
12-month OS rate, %	72.8	54.3

Data cutoff date: Dec 31, 2024 **(pre-specified interim analysis; median follow-up 12.2 mo).**

* Based on OS interim analysis, one-sided *P* value was less than the pre-specified efficacy boundary to achieve statistically significant improvement (alpha level of 0.0123 determined by alpha spending function).
NE, not evaluable; NR, not reached.

Overall Survival Adjusted for Crossover

- **Of 44 patients who discontinued docetaxel, 36.4% crossed over to receive sac-TMT.**
- **After using RPSFT model adjusted for crossover, sac-TMT significantly improved OS over docetaxel with 64% lower risk of death.**



	Sac-TMT (n = 91)	Docetaxel (n = 46)
OS events, n (%)	25 (27.5)	21 (45.7)
Median OS, months (95% CI)	**NR** (NE, NE)	**9.3** (7.3, NE)
12-month OS rate, %	72.8	43.2

Data cutoff date: Dec 31, 2024 (median follow-up 12.2 mo).

Avances en Estrategia Terapéutica en Primera Línea

- Osimertinib + Quimioterapia vs Osimertinib
  - FLAURA 2
- Amivantamab + Lazertinib vs Osimertinib
  - MARIPOSA
  - PALOMA 2

- Sacituzumab Tirumotecan + Osimertinib
  - OptiTROP-Lung04

FLAURA2 phase III study[1]

Patients with untreated locally advanced / metastatic EGFRm NSCLC

Key inclusion criteria:

- Aged ≥18 years
- Pathologically confirmed non-squamous NSCLC
- Ex19del / L858R (local / central test)
- WHO PS 0 / 1
- Stable CNS metastases were allowed
- Brain scans at baseline (MRI / CT; mandatory)

N=557

R 1:1

Stratified by:

Race (Asian Chinese / Asian non-Chinese / non-Asian)

EGFRm test (local / central)

WHO PS (0 / 1)

Osimertinib 80 mg (QD) + pemetrexed 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² (Q3W for 4 cycles for platinum-based treatments)

Maintenance osimertinib 80 mg (QD) + pemetrexed 500 mg/m² (Q3W)

Treatment beyond PD allowed per investigator discretion

Osimertinib 80 mg (QD)

Follow-up:

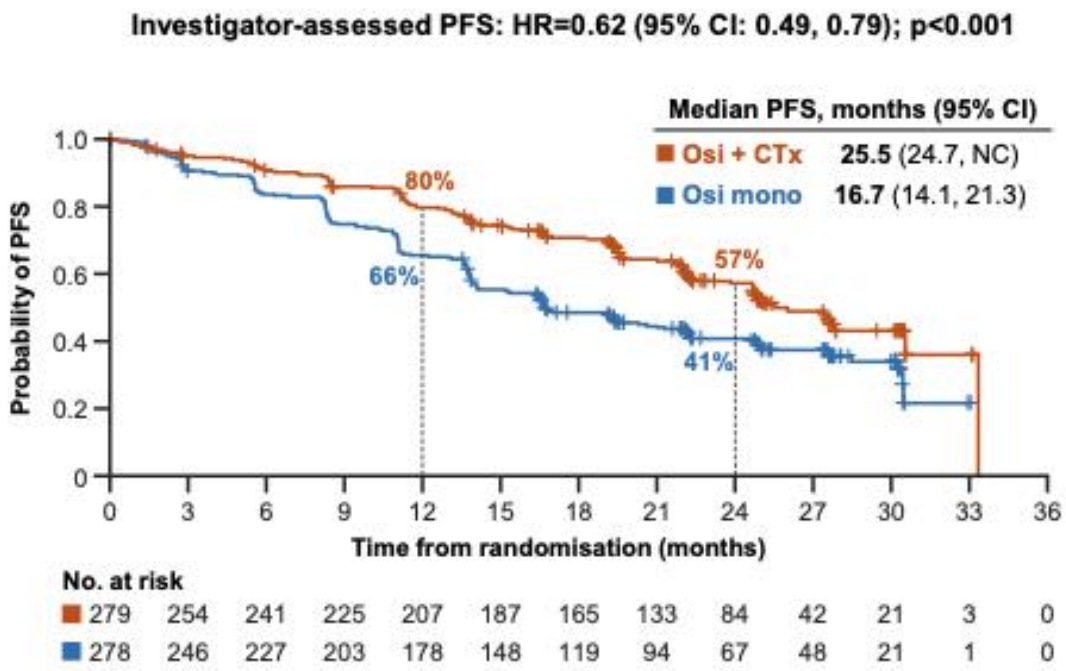
- RECIST v1.1 assessment at 6 and 12 weeks, then Q12W until RECIST v1.1-defined radiological PD
- Survival follow-up for Q12W until data cut-off for the planned final OS analysis

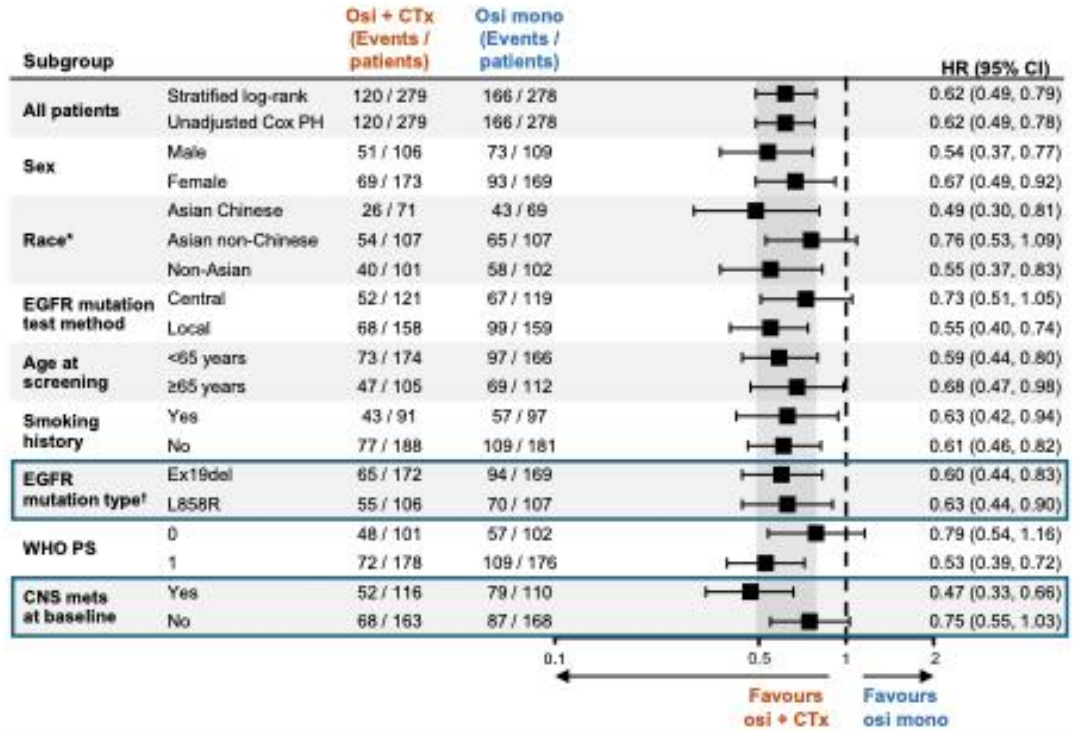
- **Primary endpoint:** Investigator-assessed PFS (RECIST v1.1)[1]
- **Secondary endpoints included:** OS, TFST, DoR, DCR, PFS2, TSST, HRQoL

OS was a key secondary endpoint*

Final OS analysis performed at 57% maturity

Primary analysis: Progression-free survival[1]



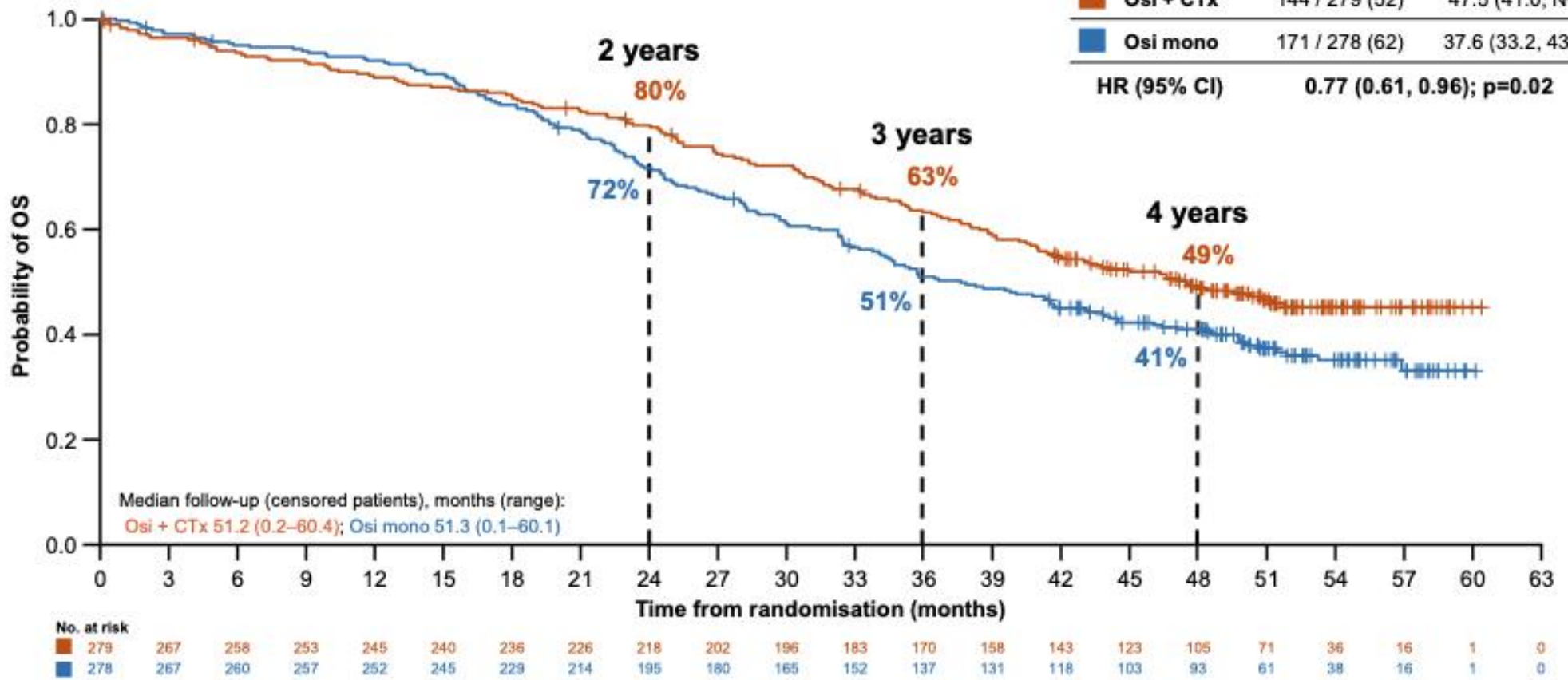


Osi + CTx showed a statistically significant and clinically meaningful improvement in PFS versus osi mono; PFS benefit was consistent across predefined subgroups

FLAURA2: Overall survival

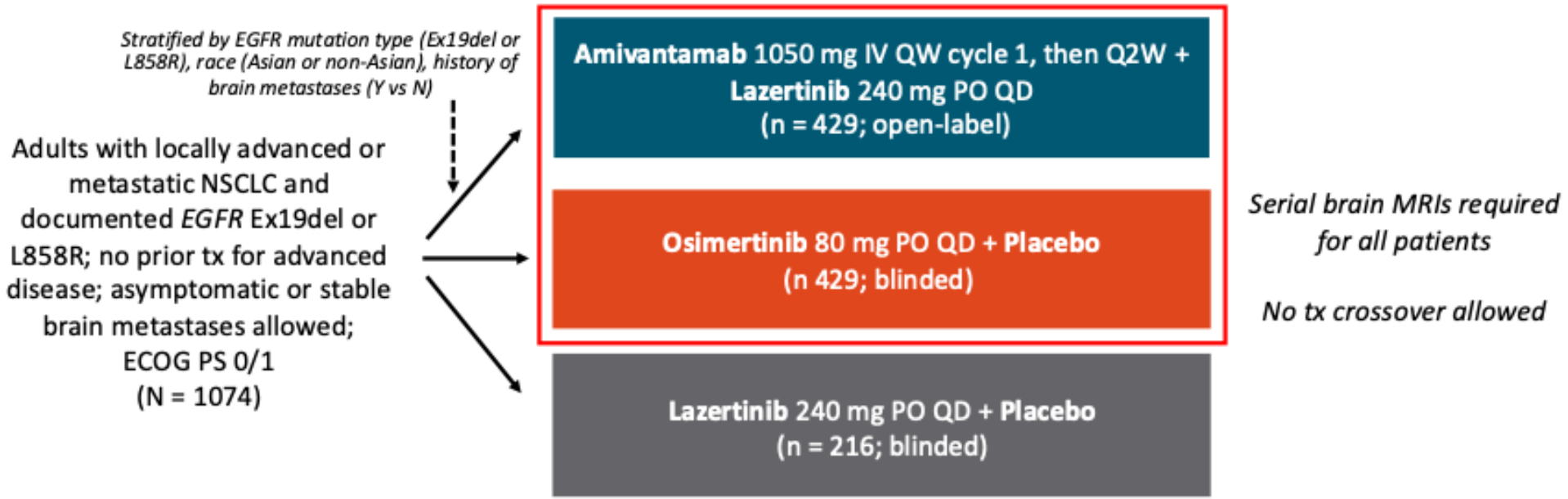
Median OS with osi + CTx was 47.5 months

	No. Events / no. patients (%)	Median OS, months (95% CI)
Osi + CTx	144 / 279 (52)	47.5 (41.0, NC)
Osi mono	171 / 278 (62)	37.6 (33.2, 43.2)
HR (95% CI)	0.77 (0.61, 0.96); p=0.02	



MARIPOSA: Study Design

- International, randomized phase III study



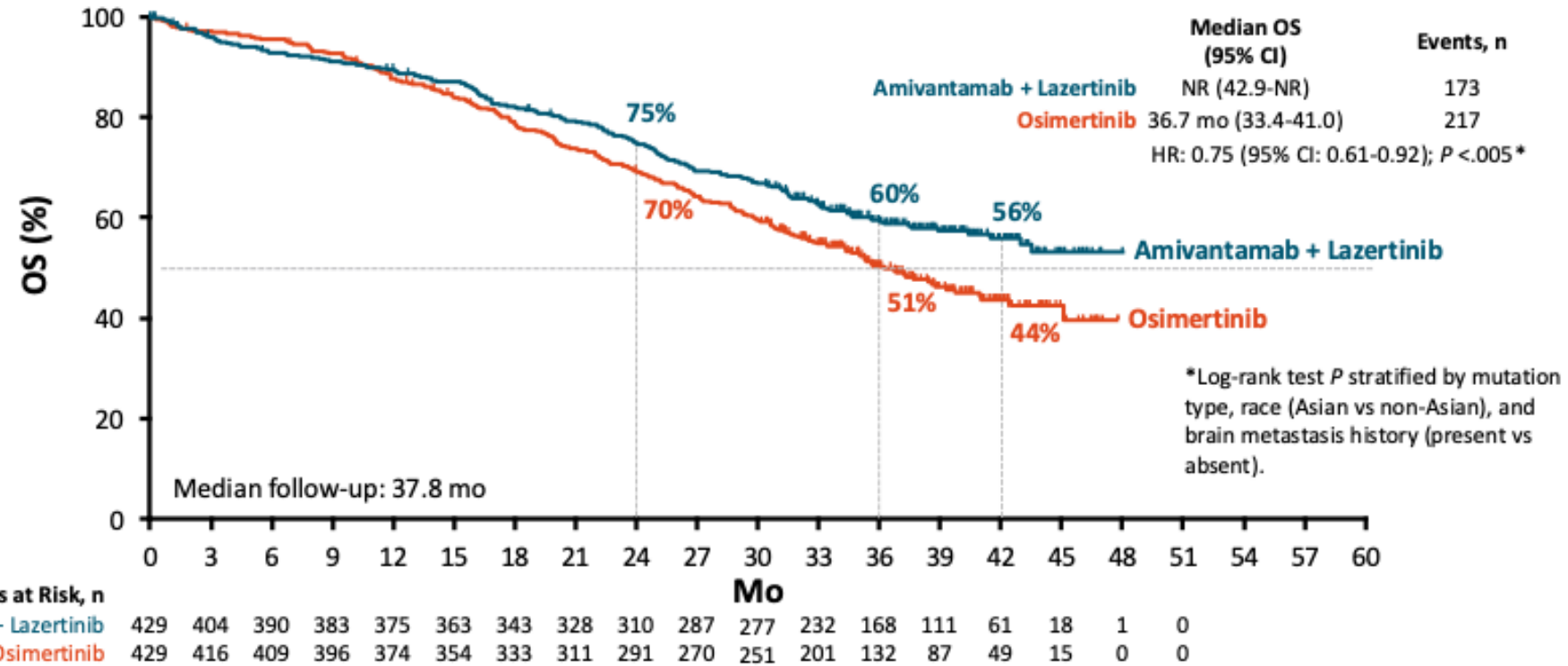
- **Primary endpoint**: PFS by BICR per RECIST v1.1
- **Key secondary endpoints**: OS,* icPFS, icORR, icDoR, TTSP, safety

*Prespecified interim OS analysis: 2-sided alpha of 0.005. Final OS: protocol specified ~390 deaths in amivantamab + lazertinib and osimertinib arms; evaluated at a 2-sided significance level of 0.0484.

Yang. ELCC 2025. Abstr 4O.

Slide credit: clinicaloptions.com

MARIPOSA: OS



- OS was significantly longer in amivantamab + lazertinib arm vs osimertinib arm
- OS curves continue to diverge with time; projected >1-yr median OS benefit†

†Based on exponential distribution assumption of OS in both arms.

Yang. ELCC 2025. Abstr 4O. Reproduced with permission.

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MARIPOSA: Prophylaxis for Early-Onset AEs

AE	Tx Regimen	Participants With AE on Tx Regimen, %	Participants With AE Without Tx Regimen/SoC, %
Dermatologic[1]	COCOON DM	Grade ≥2: 38.6 Grade 2: 34.3 Grade 3: 4.3	Grade ≥2: 76.5 Grade 2: 67.6 Grade 3: 8.8
IRR[2]	SKIPPirr Dexamethasone 8 mg IRR prophylaxis	22.5	67.4
VTE[3]	Prophylactic anticoagulation	11.4	20.0

- Early-onset AEs can be reduced using approaches that are simple, accessible, and preventative[4]

1. Girard. ELCC 2025. Abstr 10MO. 2. Spira. J Thorac Oncol. 2025:[Epub].
3. Lim. ASCO 2024. Abstr LBA8612. 4. Yang. ELCC 2025. Abstr 4O.

Slide credit: clinicaloptions.com

PALOMA-2 Cohort 5 Study Design

PALOMA-2 (MARIPOSA population)

Key eligibility criteria for Cohort 5 (N=77)

- Treatment-naïve, locally advanced or metastatic NSCLC
- Documented *EGFR* Ex19del or L858R mutations
- If brain metastases are present, they must be stable[a]
- ECOG PS score of 0 or 1

Amivantamab SC Q4W
+
lazertinib

Prophylactic anticoagulation *recommended* for the first 4 months of treatment

Dosing (in 28-day cycles)

Amivantamab SC[b]:
Subcutaneous abdominal injection with a Q4W dosing regimen of 1600 mg (2240 mg if ≥80 kg) weekly for the first 4 weeks, and 3520 mg (4640 mg if ≥80 kg) Q4W thereafter

Lazertinib: 240 mg orally daily

Primary endpoint:
- ORR by INV[c]

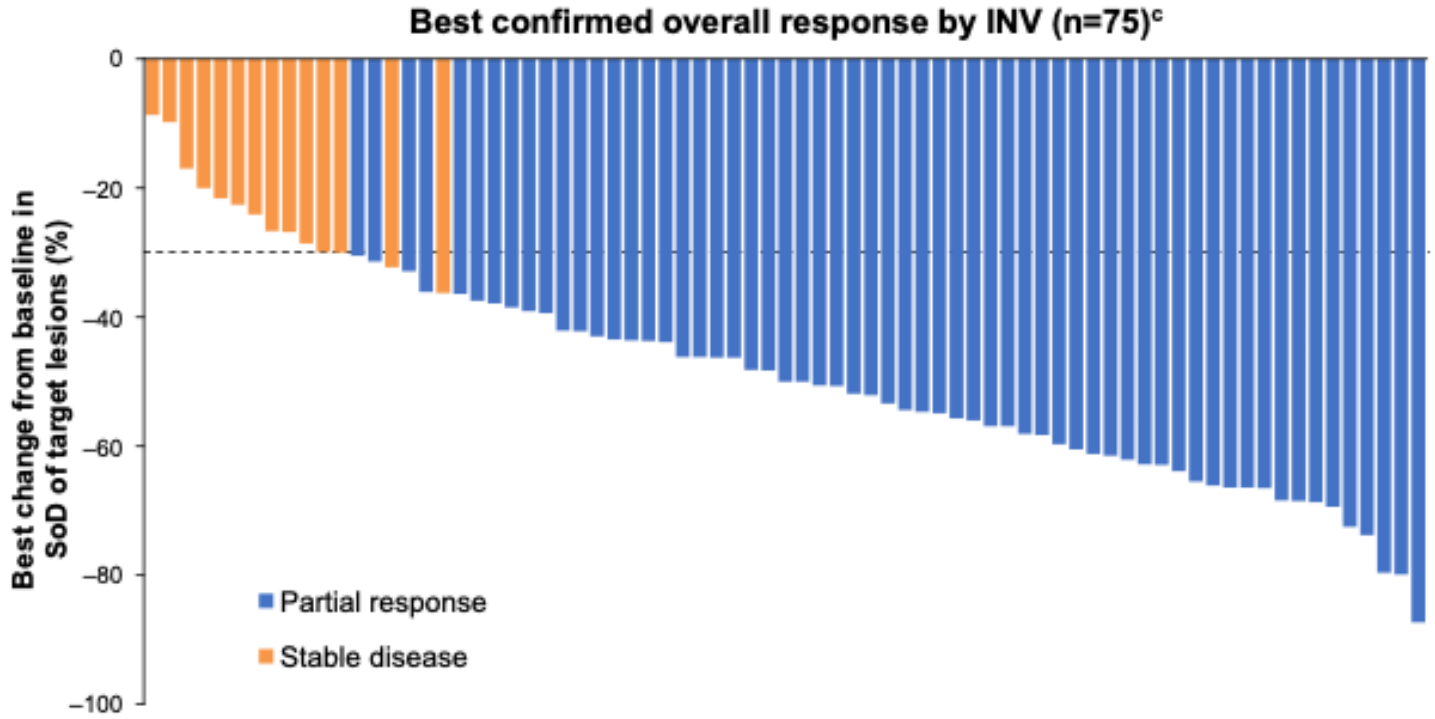
Secondary endpoints:
- ORR by ICR[c]
- Duration of response
- Time to response
- Clinical benefit rate[d]
- Progression-free survival
- Overall survival
- Safety
- PK

[a]Includes asymptomatic or previously treated participants with stable brain metastases. [b]Coformulated with recombinant human hyaluronidase PH20 [c]Tumor response was assessed according to RECIST v1.1. [d]Clinical benefit rate was defined as confirmed response or stable disease for ≥11 weeks.

ORR and Best Response

PALOMA-2 (MARIPOSA population)

- Among all participants, ORR was 82% (95% CI, 71–90) by INV[a] and 87% (95% CI, 77–94) by ICR
  - Results are consistent with the primary analysis of MARIPOSA, which demonstrated an ORR of 86% (95% CI, 83–89) by BICR with amivantamab IV Q2W + lazertinib[1]
- Confirmed ORR was 79% (95% CI, 69–88) by INV and 83% (95% CI, 73–91) by ICR[b]
- Confirmed CBR was 97% (95% CI, 91–100) by INV and 96% (95% CI, 89–99) by ICR



[a]The primary endpoint was met: the null hypothesis of ORR <50% by INV was rejected. [b]Confirmation of responses by repeat assessments were performed ≥4 weeks after the criteria for PR or CR were met. [c]Among participants with measurable disease at baseline.
CBR, clinical benefit rate (defined as confirmed response or stable disease for ≥11 weeks); SoD, sum of diameters.

1. Cho BC, et al. *N Engl J Med*. 2024;391(16):1486-1498.

Paloma-2 Cohorte 5 – Eventos adversos

Most common TEAEs (≥20%), n (%)	Cohort 5 (N=77)	
	All grades	Grade ≥3
Associated with EGFR inhibition		
Paronychia	56 (73)	4 (5)
Rash	45 (58)	9 (12)
Dermatitis acneiform	31 (40)	6 (8)
Stomatitis	29 (38)	3 (4)
Pruritus	26 (34)	1 (1)
Diarrhea	22 (29)	2 (3)
Associated with MET inhibition		
Hypoalbuminemia	49 (64)	4 (5)
Peripheral edema	28 (36)	0
Other		
Increased ALT	25 (32)	3 (4)
Increased AST	21 (27)	1 (1)
Dry skin	18 (23)	0

	Prophylactic anticoagulation (n=67)	No prophylactic anticoagulation (n=10)	Overall (N=77)
Any VTE, n (%)	7 (10)	3 (30)	10 (13)
Grade ≥3	0	0	0
Grade 5	0	0	0
Any VTE leading to any discontinuation, n (%)	0	0	0
Grade ≥3 bleeding, n (%)	1 (1)	0	1 (1)

OptiTROP-Lung04 Study Design

Randomized, multicenter, open-label, phase 3 trial (NCT05870319)

Key Eligibility

- ECOG score 0 or 1
- Nsq-NSCLC (stage IIIB/IIIC or stage IV)
- EGFR-sensitive mutations
- Progression after 3rd gen TKI therapy or progression after 1st or 2nd gen TKIs with negative T790M

R 1:1

- **Sac-TMT 5 mg/kg IV, Q2W**
- **Pemetrexed 500 mg/m^2 + Carboplatin AUC 5 or Cisplatin 75 mg/m^2 Q3W for up to 4 cycles**
- **Pemetrexed 500 mg/m^2 maintenance, Q3W**

Treatment until disease progression, intolerable toxicity, or patient request to discontinue treatment.

Primary endpoints*

- PFS assessed by BICR

Secondary endpoints*

- OS (key secondary endpoint)
- PFS assessed by investigator
- ORR, DCR, DOR, etc.
- Safety

Stratification factors:

1. Prior EGFR-TKI therapy
   (**3rd gen TKI in 1st line** *vs* **in 2nd line** *vs* **no 3rd gen TKI**)
2. Brain metastases (**yes** *vs* **no**)

Statistical considerations:

- Hierarchical testing was conducted for PFS by BICR and OS.
- Pre-specified interim analysis for OS:
  at approximately 50% maturity,
  or 24 months after the first patient randomized.

*Tumor response was assessed using RECIST version 1.1.

BICR, blinded independent central review; OS, overall survival; ORR, objective response rate; DOR, duration of response; DCR, disease control rate; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; IA, interim analysis; ECOG, Eastern Cooperative Oncology Group.

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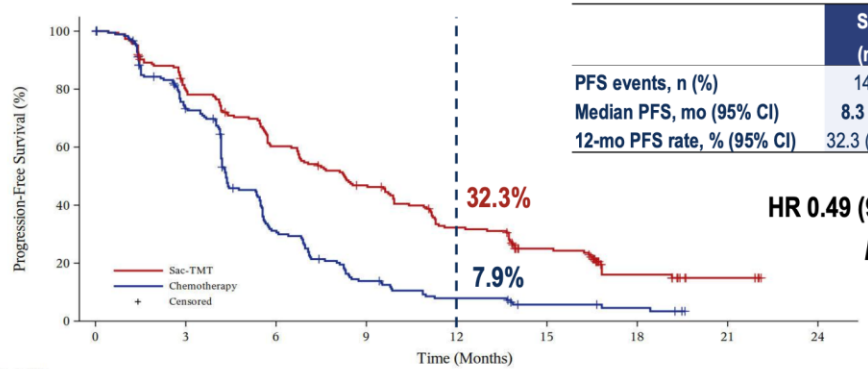
Progression-Free Survival by BICR

Sac-TMT significantly improved PFS over chemotherapy with 51% lower risk of disease progression or death.



	Sac-TMT (n = 188)	Chemotherapy (n = 188)
PFS events, n (%)	144 (76.6)	159 (84.6)
Median PFS, mo (95% CI)	**8.3** (6.7 - 9.9)	**4.3** (4.2 - 5.5)
12-mo PFS rate, % (95% CI)	32.3 (25.5 - 39.2)	7.9 (4.4 - 12.8)

HR 0.49 (95% CI: 0.39 - 0.62)

***P* < 0.0001**

No. at risk

Sac-TMT	188	144	108	82	55	35	14	5	0
Chemotherapy	188	125	51	22	12	6	4	0	

Data cutoff: July 06, 2025; the final analysis of PFS.

For pre-specified IA of PFS (data cutoff: July 11, 2024), HR was 0.47 (95% CI, 0.35-0.62) and *P*<0.0001 was less than the pre-specified efficacy boundary (two-sided alpha level of 0.0337 determined by the O'Brien-Fleming alpha spending function).

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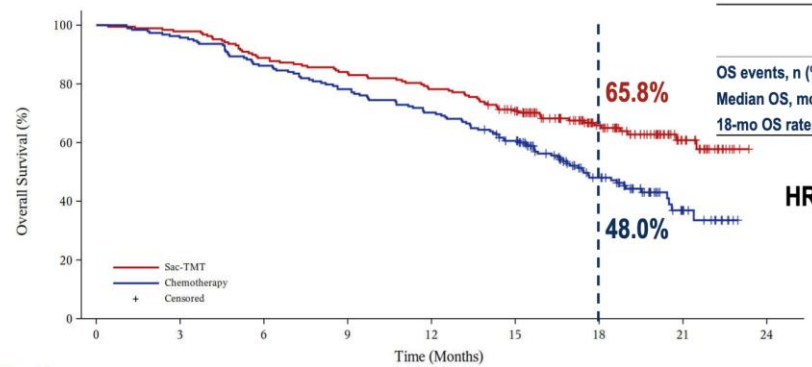
Overall Survival

At the interim analysis, sac-TMT significantly improved OS over chemotherapy with 40% lower risk of death.



	Sac-TMT (n = 188)	Chemotherapy (n = 188)
OS events, n (%)	67 (35.6)	101 (53.7)
Median OS, mo (95% CI)	**NR** (21.5 - NE)	**17.4** (15.7 - 20.4)
18-mo OS rate, % (95% CI)	65.8 (58.3 – 72.3)	48.0 (40.2 - 55.4)

HR 0.60 (95% CI: 0.44 - 0.82)

two-sided *P* = 0.001*

No. at risk

Sac-TMT	188	184	167	158	147	127	75	25	0
Chemotherapy	188	180	162	147	132	110	57	13	0

Data cutoff: July 06, 2025; **the pre-specified IA of OS.**

*Based on pre-specified OS IA, two-sided *P* value was less than the pre-specified efficacy boundary to achieve statistically significant improvement **(two-sided alpha level of 0.0124 determined by the O'Brien-Fleming alpha spending function).**

NE, not evaluable; NR, not reached.

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Conclusiones

Existen importantes avances en el conocimiento de la identificación molecular en adenocarcinoma de pulmón tanto en enfermedad virgen de tratamiento como en las previamente tratadas.

El desarrollo de nuevas moléculas a partir de este conocimiento ha demostrado beneficios que impactan en los resultados terapéuticos.

Es crucial considerar el testeo molecular al diagnóstico y, eventualmente a la progresión, teniendo en cuenta el uso de NGS o tejido tumoral de rebiopsia cuando sea posible.