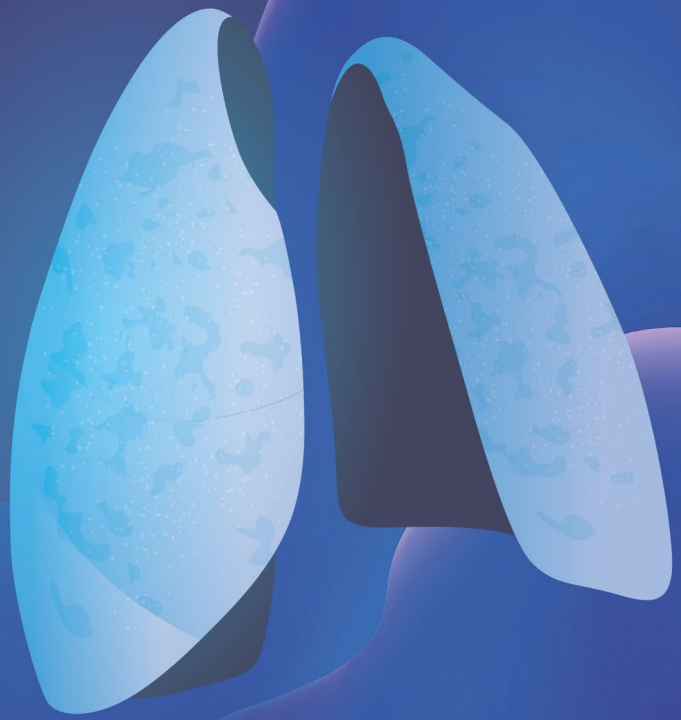

Novedades & Claves en CÁNCER de PULMÓN 2024

Enfermedad metastásica (incluyendo inmunoterapia)

Noelia Vilariño

ICO Hospital Duran i Reynals
Hospitalet de Llobregat, Barcelona

Organizado por:

GECP lung cancer research

Patrocinado por:

Bristol Myers Squibb™

Johnson&Johnson

Agenda

Advanced NSCLC

Without driver alteration

1L setting

- ***Interim Analysis of NVALT trial***
- ***Primary Analysis of Phase III trial HARMONi-2***

2L setting

- ***Primary results from the phase 3 EVOKE-01 study***
- ***Final OS from TROPION-Lung01 trial***
- ***New Biomarker predictive of outcome in TROPION-Lung 01 trial***

With driver alterations

EGFR

- ***Primary results from PALOMA-3 trial***
- ***A secondary analysis from the phase 3 MARIPOSA study***
- ***Results from CHRYSALIS-2 trial***

ALK

- ***5-year progression-free survival and safety from the CROWN study***
- ***Phase 1/2 ALKOVE-1 study***

KRAS G12C

- ***Primary results from KRYSTAL-12 trial***

Organizado por:

GECP lung cancer research

Agenda

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Without driver alteration

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KRAS G12C

- ***Primary results from KRYSTAL-12 trial***

Organizado por:

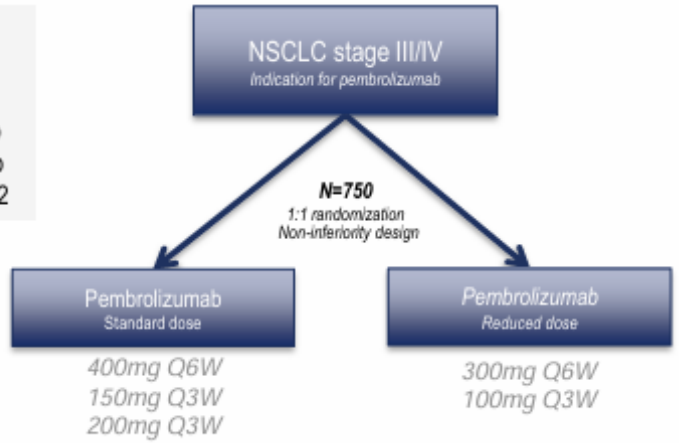
GECP lung cancer research

1258MO - Low dose versus standard dose pembrolizumab for treatment of stage IV stage non-small cell lung carcinoma: Results of the pre-planned interim analysis of the NVALT-30 clinical trial

Design

DEDICATION-1 trial (NVALT-30)

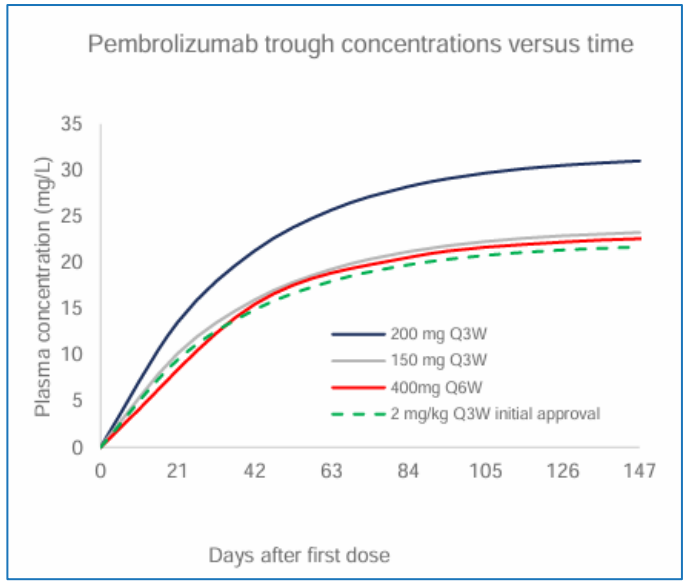
Stratification factors:
- Type of treatment:
  - Pembrolizumab
  - Pemetrexed / platinum / pembrolizumab
  - Carboplatin / paclitaxel / pembrolizumab
- Smoking, PDL1 status, Gender, PS 0/1 vs 2



Primary objective:

To investigate the non-inferiority of reduced dose pembrolizumab vs. standard dose for treatment of advanced stage NSCLC in terms of overall survival

Secondary objectives:
- DCR, PFS, OS, 1yr-DCR, ORR
- To develop, assess, and validate immune checkpoint inhibitor response biomarkers



Interim analysis:
was preplanned after the first 250 patients were included and followed for a year
A difference of 10% between arms in one-year overall survival (OS) was considered clinically relevant and set as stopping criterion for the interim analysis

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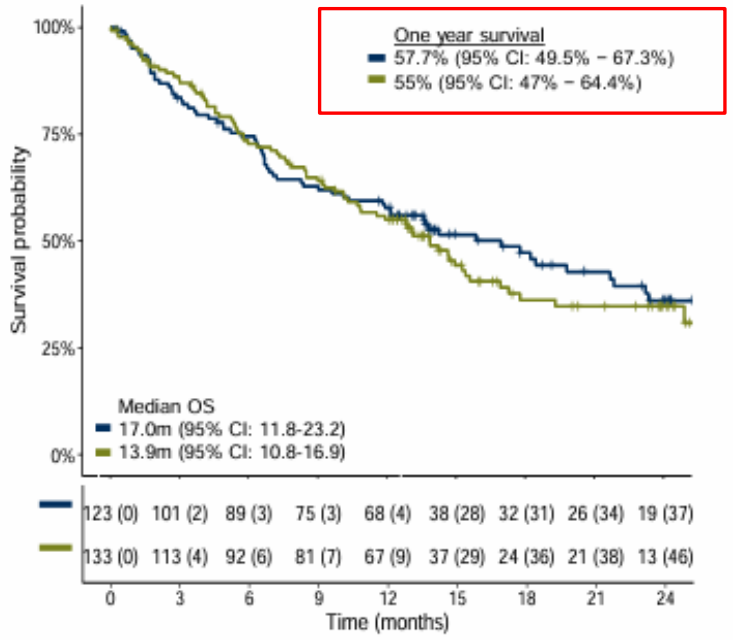
Advanced NSCLC without driver alteration

NVALT-30 TRIAL

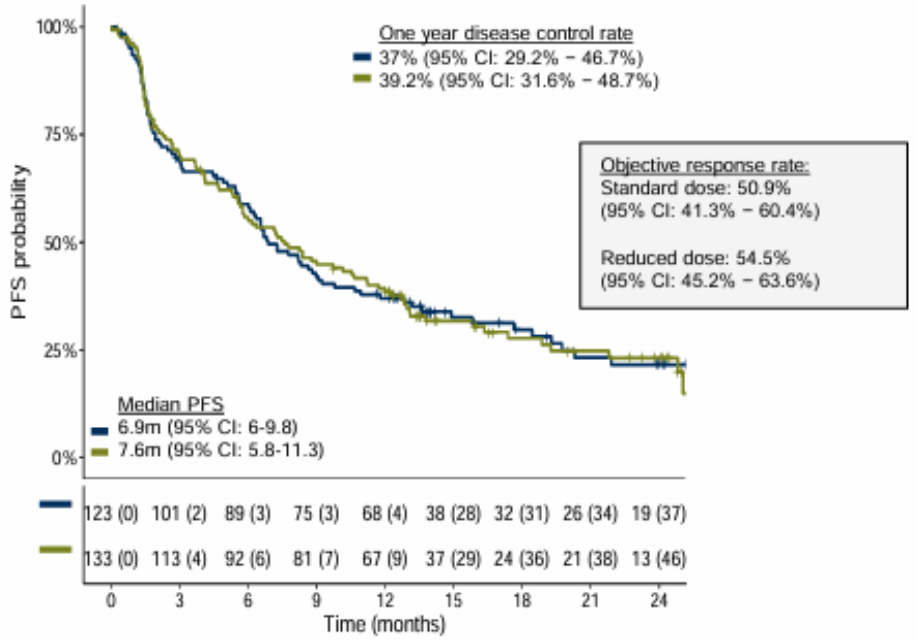
Survival analysis

DEDICATION-1 trial (NVALT-30)

Overall survival



Progression free survival



Standard dose Reduced dose

Estudio que reporta una diferencia de un 2.7% en la tasa de SG al año y cumple el objetivo preespecificado
Reclutamiento ongoing
Estudio clínicamente relevante

organizado por: GECP lung cancer research

M. van den Heuvel, et al. ESMO 2024

PL02.04: Phase 3 Study of Ivonescimab (AK112) vs. Pembrolizumab as First-line Treatment for PD-L1-positive Advanced NSCLC: Primary Analysis of HARMONi-2

HARMONi-2 Study Design

Key patient inclusion criteria
- Stage IIIB–IV NSCLC
- No EGFRm or ALK rearrangements
- No prior systemic therapy
- PD-L1 TPS ≥1%
- ECOG PS 0–1

(n=398)

R 1:1

Ivonescimab 20 mg/kg q3w (n=198)

Pembrolizumab 200 mg q3w (n=200)

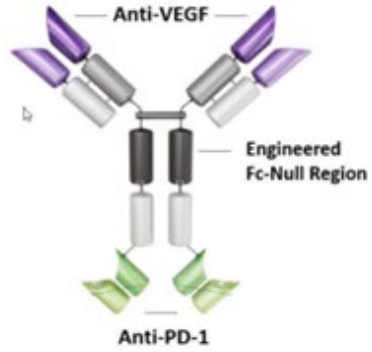
Stratification
- Clinical stage (IIIB/C vs. IV)
- Histology (SQ vs. NSQ)
- PD-L1 TPS (≥50% vs. 1–49%)

PD/toxicity/up to 24 months

Primary endpoint
- PFS (BIRC, RECIST v1.1)

Secondary endpoints
- OS, ORR, DoR, TTR, QoL, safety

Bispecific antibody



Advanced NSCLC without driver alteration

HARMONi-2

Asian Population Chinese Trial

Characteristics, n (%)		Ivonescimab (n = 198[a])	Pembrolizumab (n = 200[a])	Total (n = 398[a])
Age (years)	<65	97 (49.0)	85 (42.5)	182 (45.7)
	≥65	101 (51.0)	115 (57.5)	216 (54.3)
Sex	Male	164 (82.8)	169 (84.5)	333 (83.7)
	Female	34 (17.2)	31 (15.5)	65 (16.3)
ECOG PS	0	25 (12.6)	26 (13.0)	51 (12.8)
	1	173 (87.4)	174 (87.0)	347 (87.2)
Smoker	Never	39 (19.7)	38 (19.0)	77 (19.3)
	Current	39 (19.7)	42 (21.0)	81 (20.4)
	Former	120 (60.6)	120 (60.0)	240 (60.3)
Clinical stage	IIIB/C	15 (7.6)	16 (8.0)	31 (7.8)
	IV	183 (92.4)	184 (92.0)	367 (92.2)
Pathology	SQ	90 (45.5)	91 (45.5)	181 (45.5)
	Tumor centrally located[b]	65 (72.2)	57 (62.6)	122 (67.4)
	Tumor with cavitation/necrosis[b]	9 (10.0)	7 (7.7)	16 (8.8)
	Tumor encasing large blood vessel[b]	6 (6.7)	1 (1.1)	7 (3.9)
	Non-SQ	108 (54.5)	109 (54.5)	217 (54.5)
PD-L1 TPS	≥50%	83 (41.9)	85 (42.5)	168 (42.2)
	1-49%	115 (58.1)	115 (57.5)	230 (57.8)
Liver metastases	Yes	25 (12.6)	28 (14.0)	53 (13.3)
	No	173 (87.4)	172 (86.0)	345 (86.7)
Brain metastases	Yes	33 (16.7)	39 (19.5)	72 (18.1)
	No	165 (83.3)	161 (80.5)	326 (81.9)

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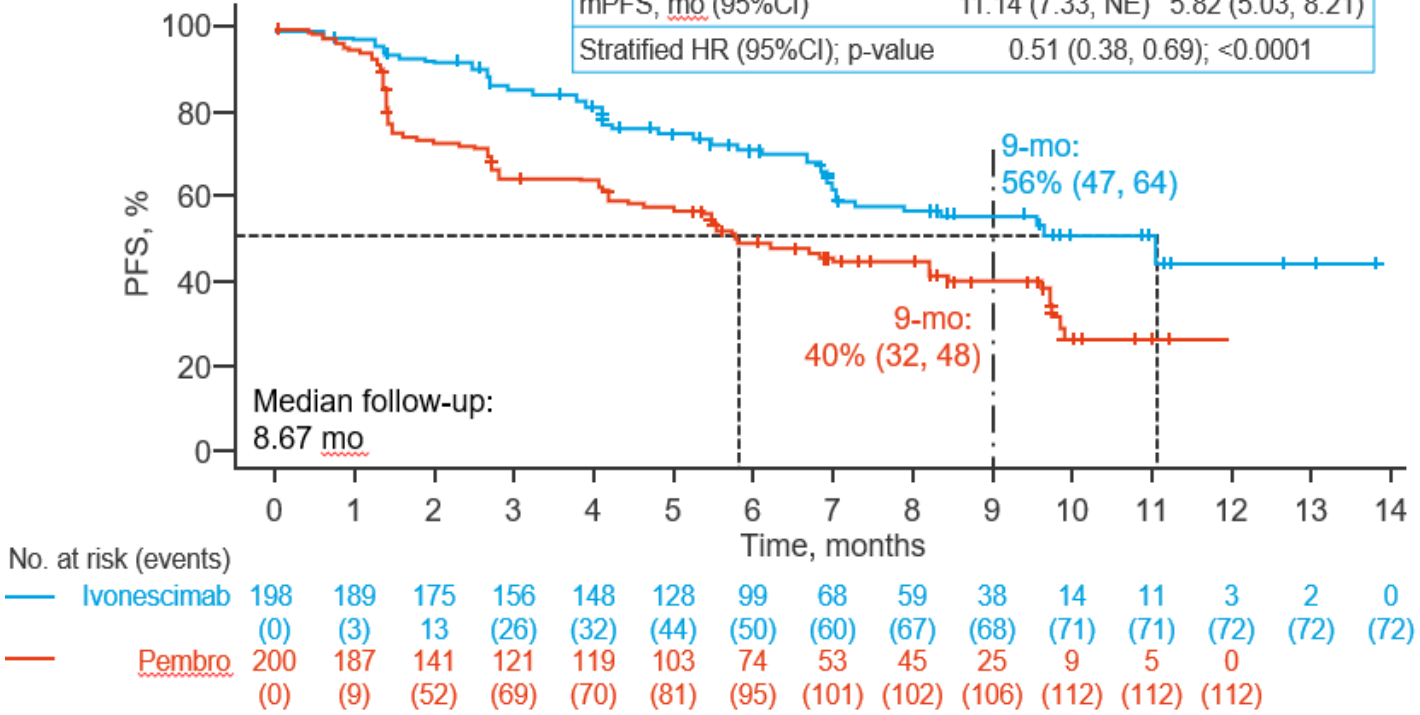
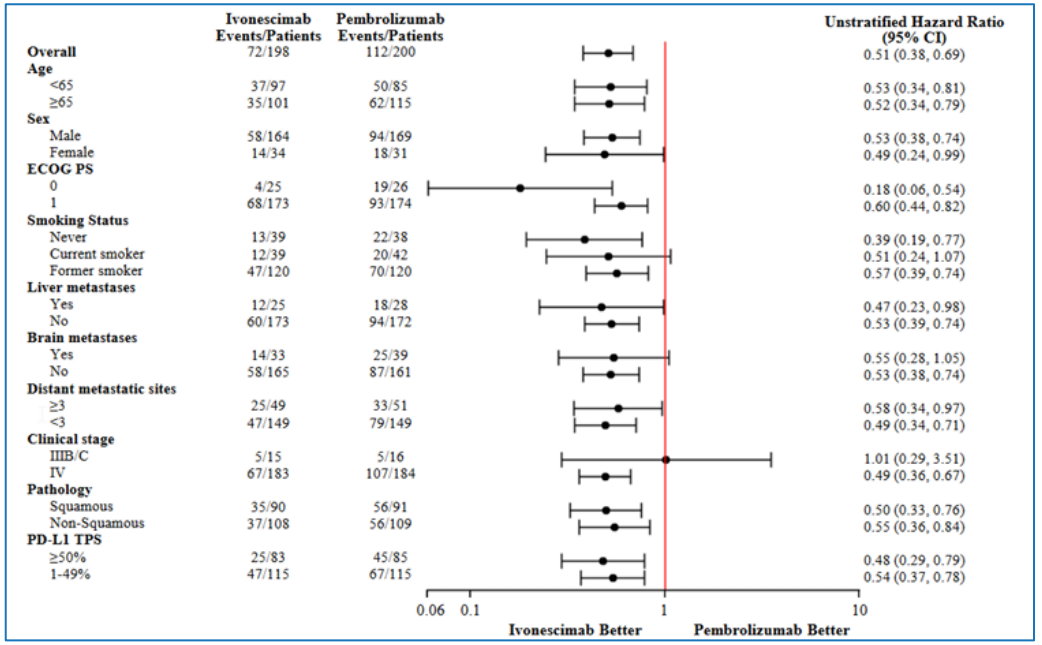
Advanced NSCLC without driver alteration

HARMONi-2

Progression-free survival (BIRC)

	Ivonescimab (n=198)	Pembrolizumab (n=200)
mPFS, mo (95%CI)	11.14 (7.33, NE)	5.82 (5.03, 8.21)
Stratified HR (95%CI); p-value	0.51 (0.38, 0.69); <0.0001	





Outcomes	Ivonescimab (n=198)	Pembrolizumab (n=200)
ORR, % (95%CI)	50.0 (42.8, 57.2)	38.5 (31.7, 45.6)
DCR, % (95% CI)	89.9 (84.8, 93.7)	70.5 (63.7, 76.7)
mDoR, mo (95%CI)	NR (NE, NE)	NR (8.3, NE)

Ivonescimab demonstrated a statistically significant improvement in PFS vs. pembrolizumab with HR = 0.51, and a 5.3 months improvement in mPFS.

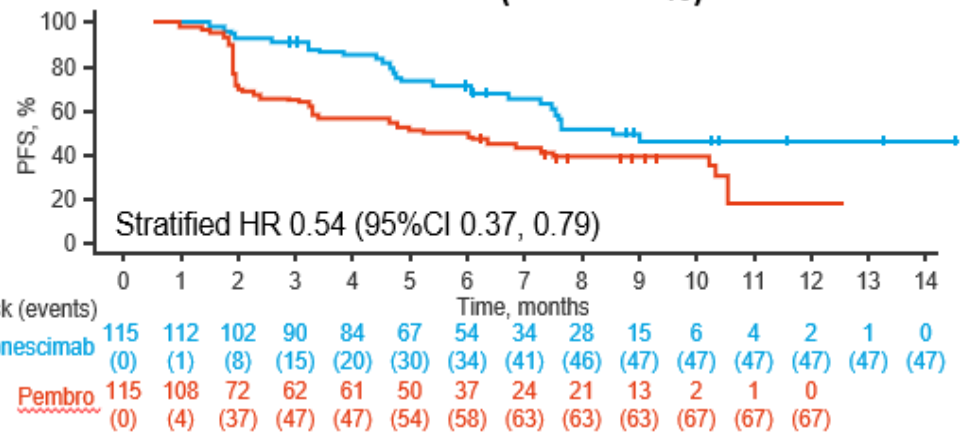
Advanced NSCLC without driver alteration

HARMONi-2

Progression-free survival by PD-L1 expression and NSCLC histology

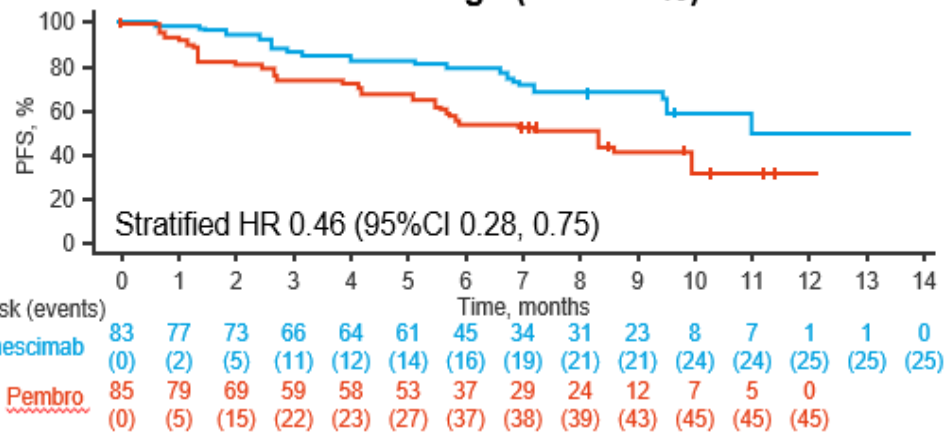
PD-L1 expression

PD-L1 low (TPS 1–49%)



No. at risk (events)															
Ivonescimab	115 (0)	112 (1)	102 (8)	90 (15)	84 (20)	67 (30)	54 (34)	34 (41)	28 (46)	15 (47)	6 (47)	4 (47)	2 (47)	1 (47)	0 (47)
Pembro	115 (0)	108 (4)	72 (37)	62 (47)	61 (47)	50 (54)	37 (58)	24 (63)	21 (63)	13 (63)	2 (67)	1 (67)	0 (67)		

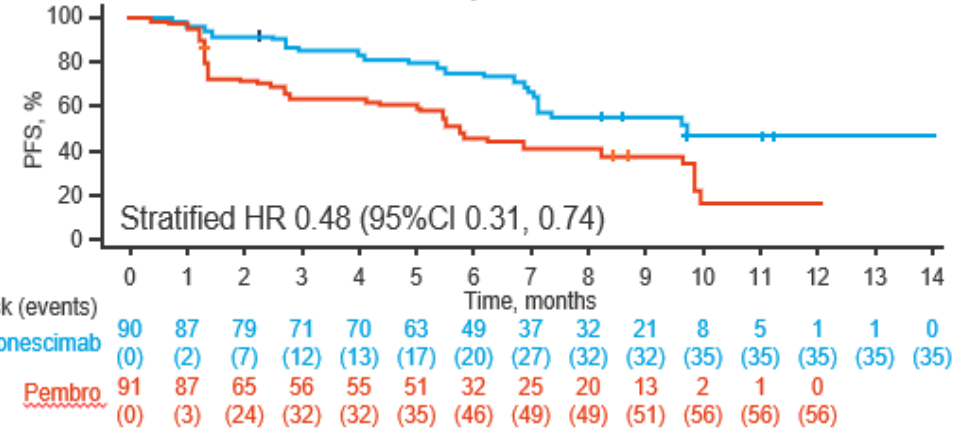
PD-L1 high (TPS ≥50%)



No. at risk (events)															
Ivonescimab	83 (0)	77 (2)	73 (5)	66 (11)	64 (12)	61 (14)	45 (16)	34 (19)	31 (21)	23 (21)	8 (24)	7 (24)	1 (25)	1 (25)	0 (25)
Pembro	85 (0)	79 (5)	69 (15)	59 (22)	58 (23)	53 (27)	37 (37)	29 (38)	24 (39)	12 (43)	7 (45)	5 (45)	0 (45)		

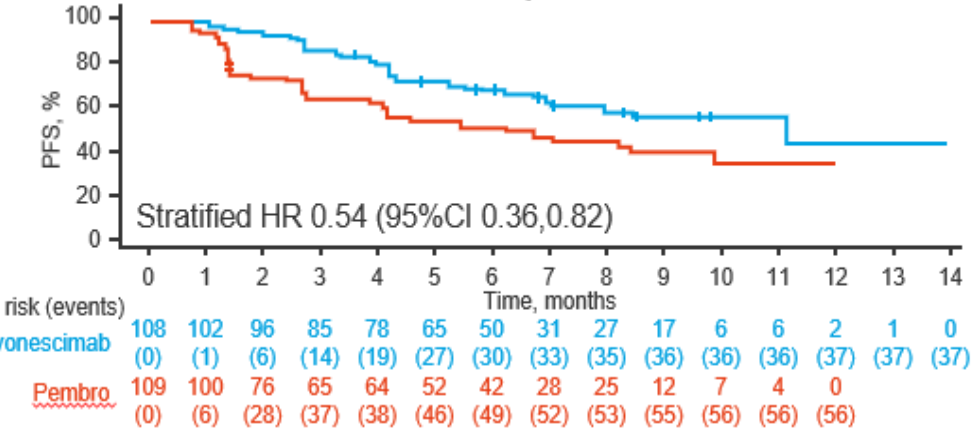
NSCLC histology

Squamous



No. at risk (events)															
Ivonescimab	90 (0)	87 (2)	79 (7)	71 (12)	70 (13)	63 (17)	49 (20)	37 (27)	32 (32)	21 (32)	8 (35)	5 (35)	1 (35)	1 (35)	0 (35)
Pembro	91 (0)	87 (3)	65 (24)	56 (32)	55 (32)	51 (35)	32 (46)	25 (49)	20 (49)	13 (51)	2 (56)	1 (56)	0 (56)		

Non-squamous



No. at risk (events)															
Ivonescimab	108 (0)	102 (1)	96 (6)	85 (14)	78 (19)	65 (27)	50 (30)	31 (33)	27 (35)	17 (36)	6 (36)	6 (36)	2 (37)	1 (37)	0 (37)
Pembro	109 (0)	100 (6)	76 (28)	65 (37)	64 (38)	52 (46)	42 (49)	28 (52)	25 (53)	12 (55)	7 (56)	4 (56)	0 (56)		

Organizado por: GECP lung cancer research

Advanced NSCLC without driver alteration

HARMONi-2

TRAEs, n (%)	Ivonescimab (n=197)	Pembrolizumab (n=199)
Any	177 (89.8)	163 (81.9)
Grade ≥3	58 (29.4)	31 (15.6)
Serious	41 (20.8)	32 (16.1)
Led to discontinuation	3 (1.5)	6 (3.0)
Led to death	1 (0.5)	2 (1.0)

irAEs, n (%)	Ivonescimab (n=197)	Pembrolizumab (n=199)
Any	59 (29.9)	56 (28.1)
Grade ≥3	14 (7.1)	16 (8.0)
Serious	11 (5.6)	22 (11.1)
Led to discontinuation	0	5 (2.5)

VEGR-related AEs, n (%)	Ivonescimab (n=197)	Pembrolizumab (n=199)
Any	94 (47.7)	42 (21.1)
Grade ≥3	20 (10.2)	5 (1.0)
Proteinuria	6 (3.1)	0
Hypertension	10 (5.1)	1 (0.5)
Hemorrhage	2 (1.0)	1 (0.5)
Arterial thromboembolism	2 (1.0)	0
Venous thromboembolism	0	0

Estudio con resultados muy prometedores en relación a la SLP
El comparador, pembrolizumab, no sería el estándar en población con TPS 1-49%
Necesidad de confirmar eficacia en OS y en población no asiática

Organizado por: GECP lung cancer research

LBA8500: Sacituzumab govitecan (SG) vs docetaxel (doc) in patients (pts) with metastatic non-small cell lung cancer (mNSCLC) previously treated with platinum (PT)-based chemotherapy (chemo) and PD(L)-1 inhibitors (IO): Primary results from the phase 3 EVOKE-01 study

EVOKE-01: Global, Randomized, Open-Label, Phase 3 Study

Key eligibility criteria

- Measurable stage IV NSCLC
- ECOG PS 0–1
- Radiographic progression after platinum-based and anti-PD-(L)1–containing regimen[a]
- In addition, patients with known AGAs must have received ≥ 1 approved TKI[b]
  - *EGFR/ALK* test required. Testing of other AGAs recommended[c]
- Previously treated stable brain metastases were included
- No prior treatment with Topo-1 inhibitors, Trop-2–targeted therapies, or docetaxel

N = 603

R 1:1

Sacituzumab govitecan
10 mg/kg on Days 1 and 8 of 21-day cycles[d]

Docetaxel
75 mg/m² on Day 1 of 21-day cycles[d]

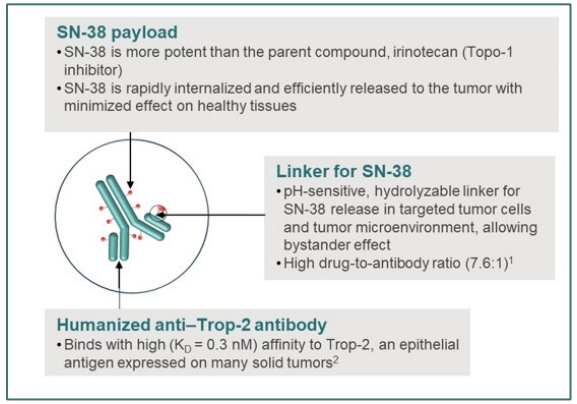
End points

Primary
- OS

Secondary
- PFS, ORR, DOR, and DCR by INV per RECIST v1.1
- Safety and tolerability
- QoL using NSCLC-SAQ

Stratified by
- **Histology** (squamous vs nonsquamous)
- **Response to last anti-PD-(L)1–containing regimen** (responsive [best response CR/PR] vs nonresponsive [PD/SD])
- **Received prior targeted therapy for AGA** (yes vs no)

At data cutoff (29 November 2023), the study median follow-up was 12.7 months (range, 6.0–24.0)



Organizado por: GECP lung cancer research

Patient Baseline Characteristics (ITT)

Characteristic	SG (n = 299)	Docetaxel (n = 304)
Median age (range), years	66 (31–84)	64 (32–83)
Male, %	64.9	71.1
Race, %		
Asian	5.7	8.6
Black	2.0	2.3
White	76.6	71.1
Other[a]	15.7	18.1
ECOG PS,[b] %		
0	33.8	29.3
1	66.2	69.7
Disease stage at diagnosis,[c] %		
Stage I-III	25.4	33.6
Stage IV	73.2	66.4
Prior lines of therapy, %		
1	55.9	54.9
2	34.4	33.2
≥ 3	9.7	11.8
History of brain metastasis, %	11.7	12.8

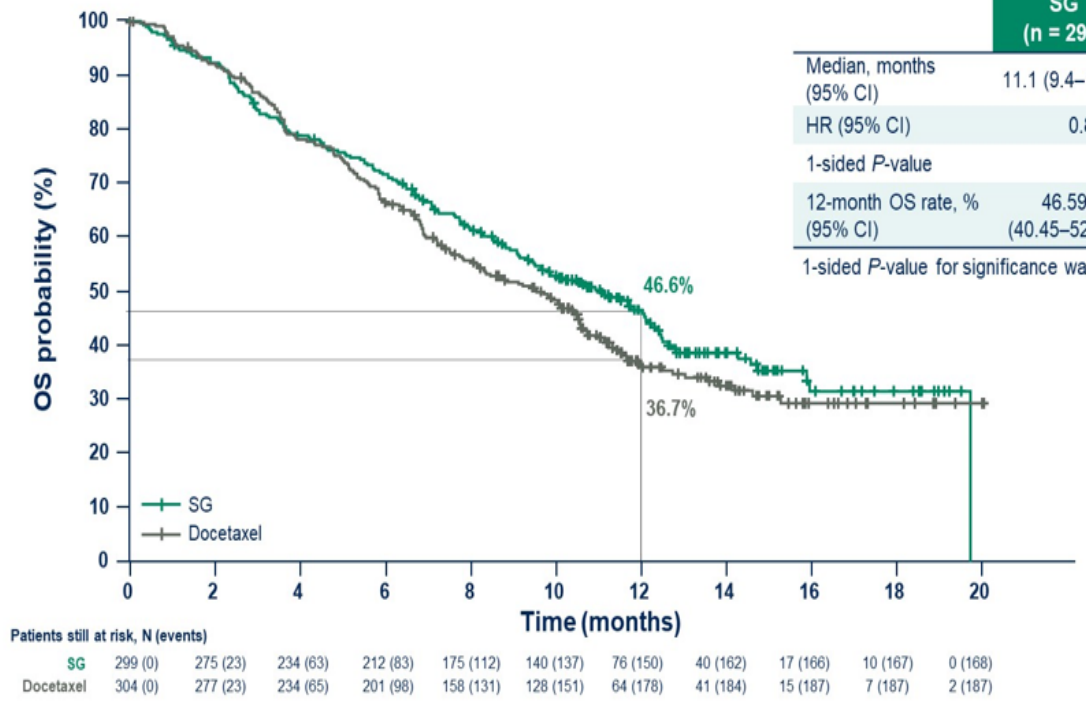
Characteristic	SG (n = 299)	Docetaxel (n = 304)
Histology,[d] %		
Nonsquamous[e]	71.9	73.7
Squamous	28.1	26.3
Best response to last anti-PD-(L)1–containing regimen,[d] %		
Responsive (CR/PR)	35.5	37.2
Nonresponsive (PD/SD)	64.2	62.8
Not available	0.3	0
Prior therapy for AGA,[d] %		
No	93.6	91.8
Yes[f]	6.4	8.2
EGFR	2.0	4.3
ALK	0.3	0.3
Other[g]	5.7	4.9

Organizado por: GECP lung cancer research

Advanced NSCLC without driver alteration

EVOKE-01 TRIAL

Primary End Point: Overall Survival (ITT)

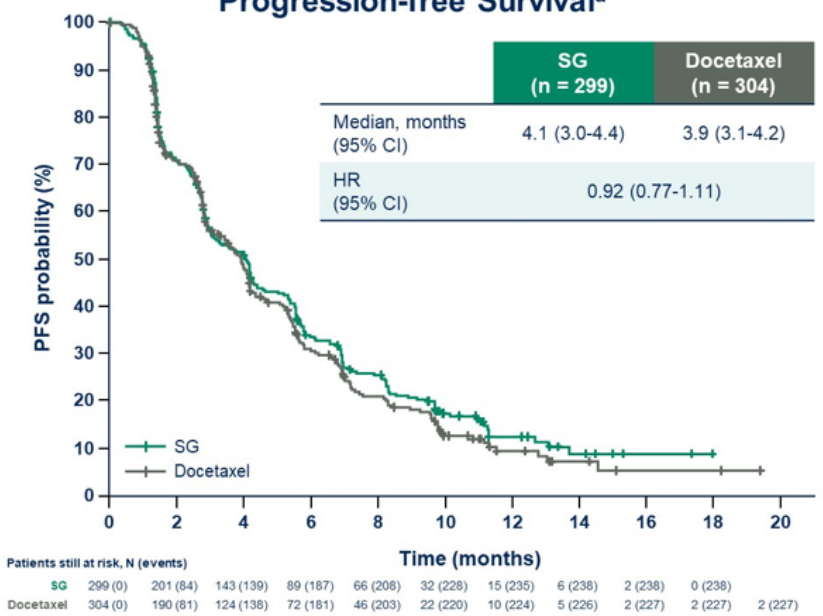


	SG (n = 299)	Docetaxel (n = 304)
Median, months (95% CI)	11.1 (9.4–12.3)	9.8 (8.1–10.6)
HR (95% CI)	0.84 (0.68–1.04)	
1-sided *P*-value	0.0534	
12-month OS rate, % (95% CI)	46.59 (40.45–52.50)	36.72 (30.88–42.57)

1-sided *P*-value for significance was $P \leq 0.0223$

Secondary End Points (ITT)

Progression-free Survival[a]



	SG (n = 299)	Docetaxel (n = 304)
Median, months (95% CI)	4.1 (3.0-4.4)	3.9 (3.1-4.2)
HR (95% CI)	0.92 (0.77-1.11)	

Objective Response Rate[a]

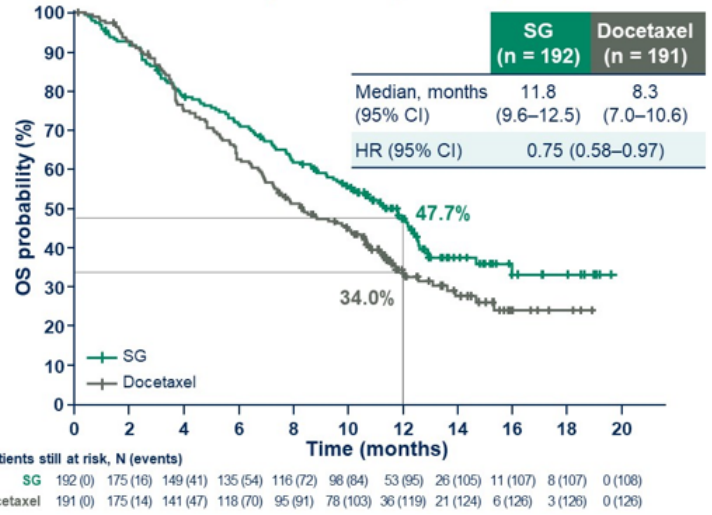
	SG (n = 299)	Docetaxel (n = 304)
ORR, % (95% CI)	13.7 (10.0–18.1)	18.1 (13.9–22.9)
DCR, % (95% CI)	67.6 (61.9–72.8)	67.1 (61.5–72.4)
Median DOR, months (95% CI)	6.7 (4.4–9.8)	5.8 (4.1–8.3)
DOR rate at 6 months, % (95% CI)	52.5 (35.6–66.9)	46.5 (31.9–59.8)

EVOKE-01 TRIAL

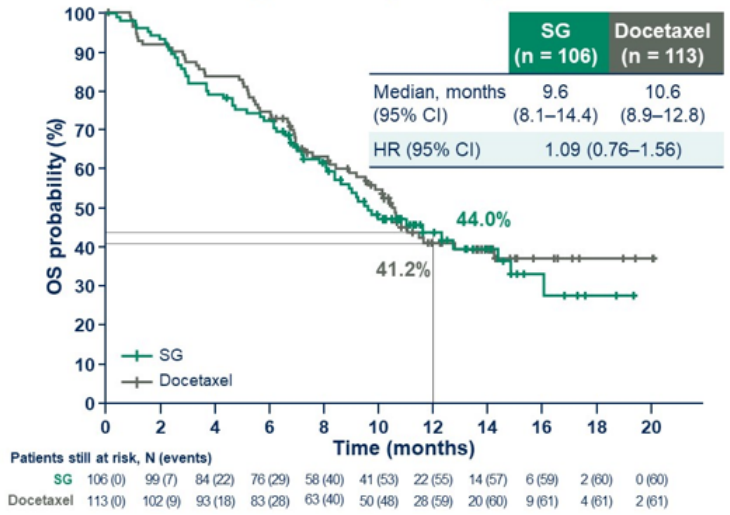
Overall Survival: Best Response to Last Anti-PD-(L)1–Containing Regimen

SG had a 3.5-month median OS improvement over docetaxel among subgroups with nonresponsive (SD/PD) disease

Nonresponsive (SD/PD)

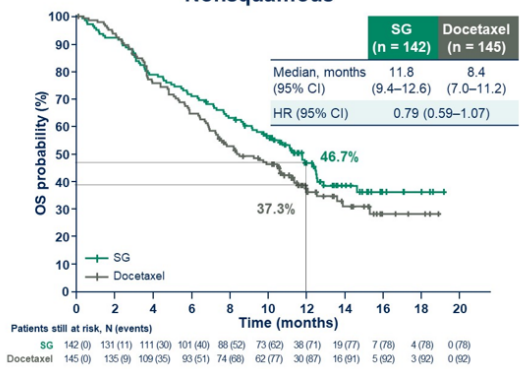


Responsive (CR/PR)

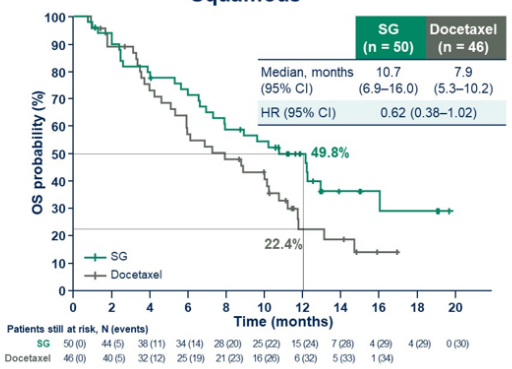


SG had similar OS benefit over docetaxel in both squamous and nonsquamous histology

Nonsquamous



Squamous



Organizado por: GECP lung cancer research

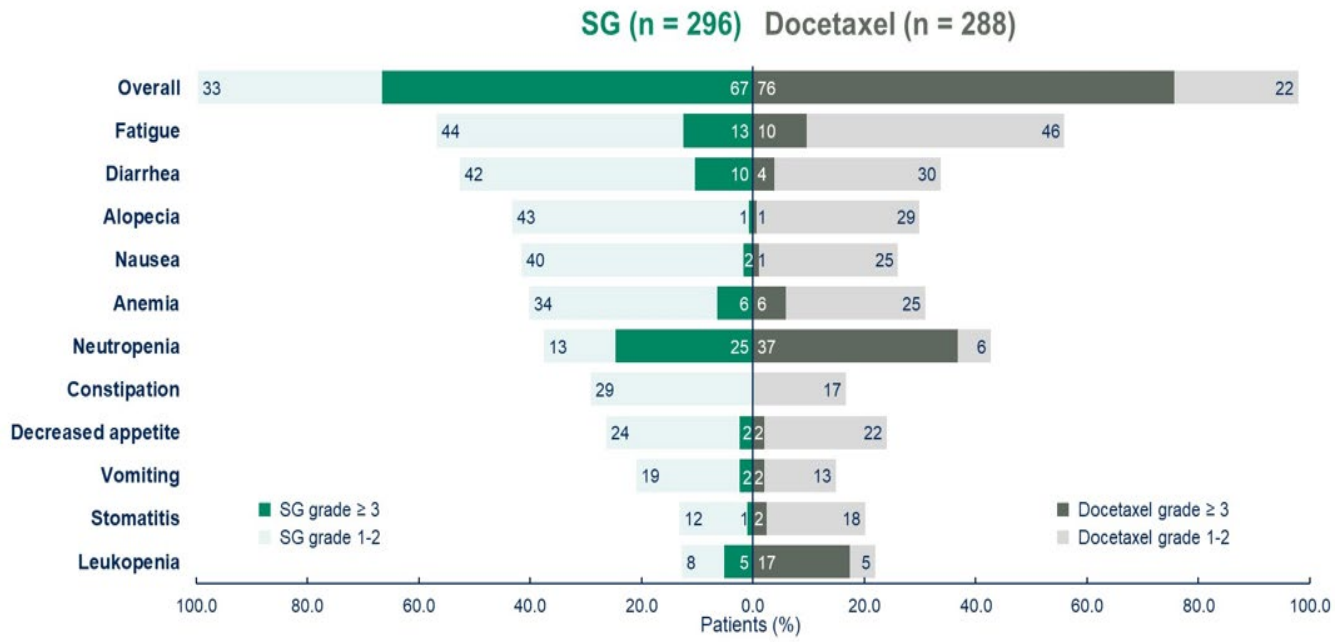
Advanced NSCLC without driver alteration

EVOKE-01 TRIAL

Overall Safety Summary

Safety-evaluable patients, n (%)	SG (n = 296)	Docetaxel (n = 288)
	TEAE	TEAE
Any grade	295 (99.7)	282 (97.9)
Grade ≥ 3	197 (66.6)	218 (75.7)
Serious	137 (46.3)	124 (43.1)
Leading to discontinuation	29 (9.8)	48 (16.7)
Leading to dose reduction	87 (29.4)	112 (38.9)
Leading to death[a]	10 (3.4)	13 (4.5)

In ≥ 20% of patients receiving SG or docetaxel



Estudio negativo con un beneficio modesto (numérico) en la OS
Se evalúa el rol de este fármaco en primera línea en combinación con IT

Organizado por: GECP lung cancer research

OA08.03: Datopotamab Deruxtecan Vs Docetaxel in Patients with Non-Small Cell Lung Cancer: Final Overall Survival from TROPION-Lung01

Study Design

TROPION-Lung01

Randomized, Phase 3, Open-Label, Global Study (NCT04656652)

Key eligibility criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0–1
- No prior docetaxel

Without actionable genomic alterations

- One to two prior lines, including platinum-based CT and anti–PD-(L)1 mAb therapy

With actionable genomic alterations

- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
- One to two prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

1:1

- **Dato-DXd** 6 mg/kg Q3W (N=299)
- **Docetaxel** 75 mg/m² Q3W (N=305)

Dual primary endpoints

- PFS by BICR[a]
- OS

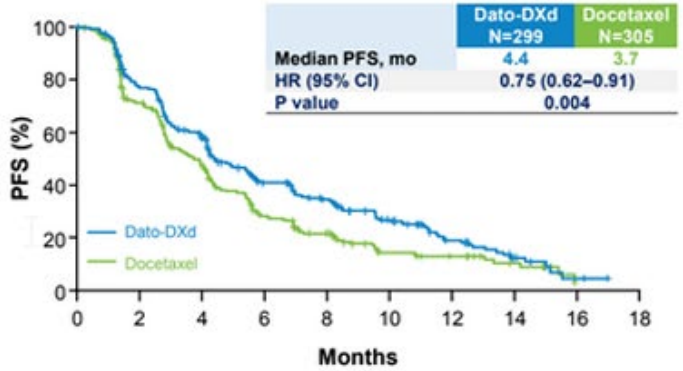
Secondary endpoints

- ORR[a]
- DOR[a]
- Safety and tolerability

Stratified by histology (nonsquamous vs squamous), actionable genomic alteration status,[b] anti–PD-(L)1 mAb included in most recent prior therapy, and geography[c]

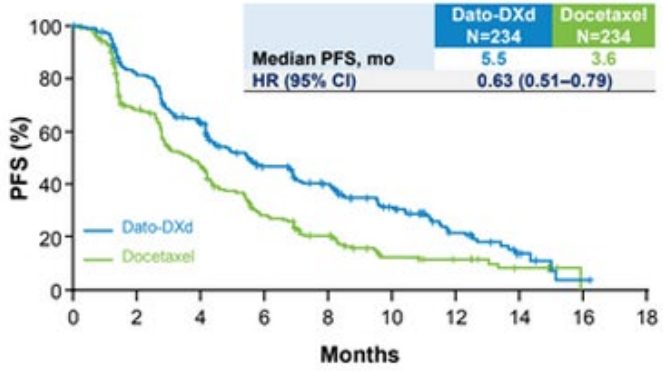
Statistical considerations: Study deemed positive if either of the dual primary endpoints (PFS by BICR or OS) were statistically significant; the pre-specified P-value boundary for the OS analysis was α=0.045

ITT



	Dato-DXd N=299	Docetaxel N=305
Median PFS, mo	4.4	3.7
HR (95% CI)	0.75 (0.62–0.91)	
P value	0.004	

NSQ



	Dato-DXd N=234	Docetaxel N=234
Median PFS, mo	5.5	3.6
HR (95% CI)	0.63 (0.51–0.79)	

	Dato-DXd N=234	Docetaxel N=234
Median DOR, mo	7.7	5.6

- Differential PFS outcomes by histology for Dato-DXd have been independently reported in two other NSCLC trials[5,6]

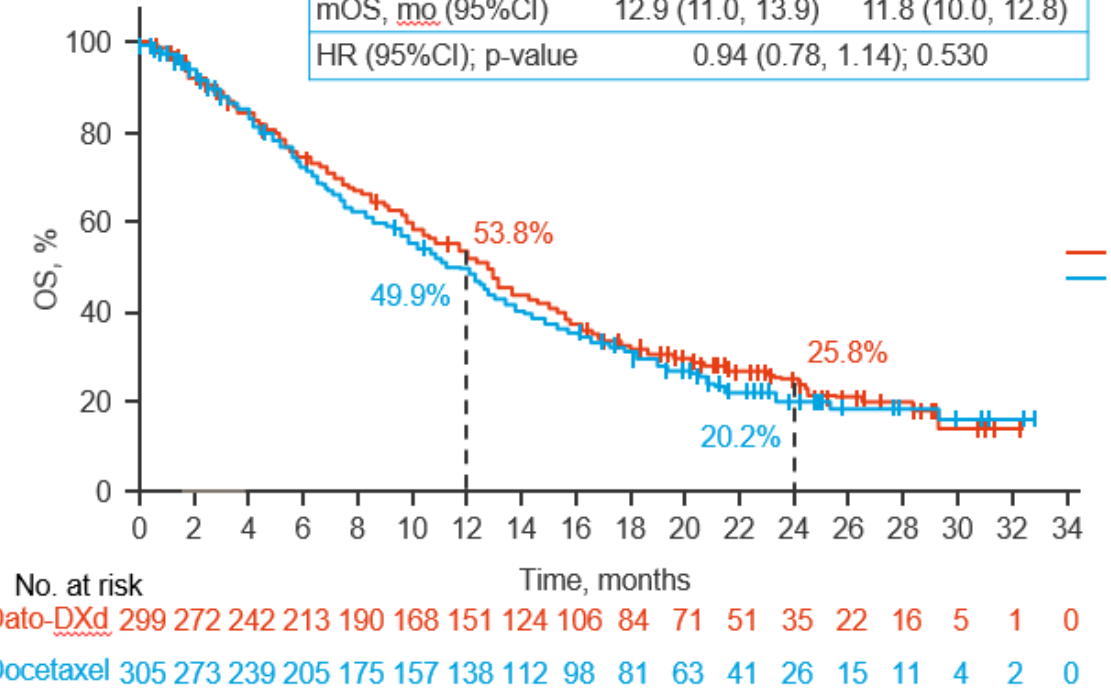
Organizado por: GECP lung cancer research

Advanced NSCLC without driver alteration

TROPION-LUNG01 TRIAL

Overall survival

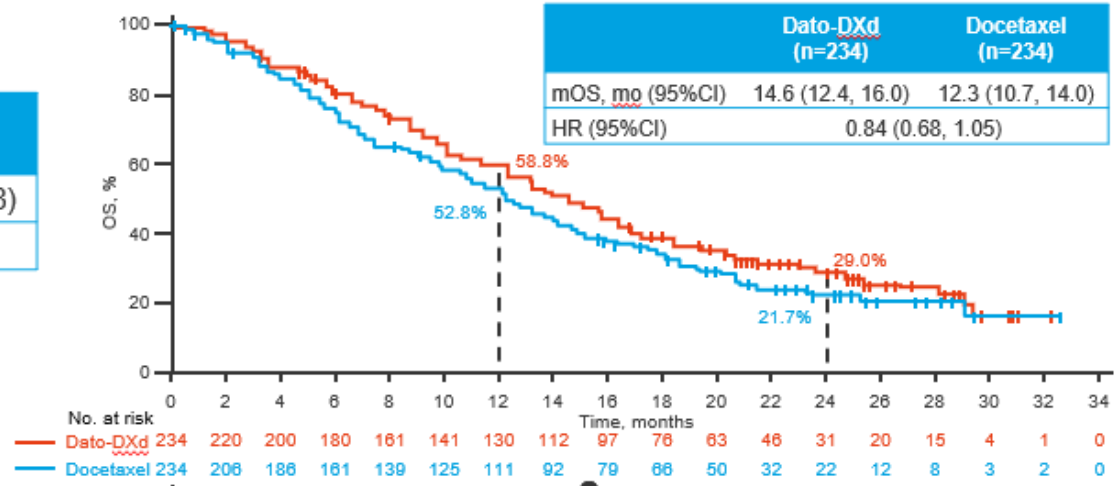
	Dato-DXd (n=299)	Docetaxel (n=305)
mOS, mo (95%CI)	12.9 (11.0, 13.9)	11.8 (10.0, 12.8)
HR (95%CI); p-value	0.94 (0.78, 1.14); 0.530	



[a]Median (95% CI) OS follow-up was 23.1 (22.0, 24.8) months for Dato-DXd and 23.1 (21.7, 24.2) months for docetaxel. [b]At primary OS analysis (data cutoff: March 1, 2024). 433 OS events (IF) were observed.
IF, information fraction.

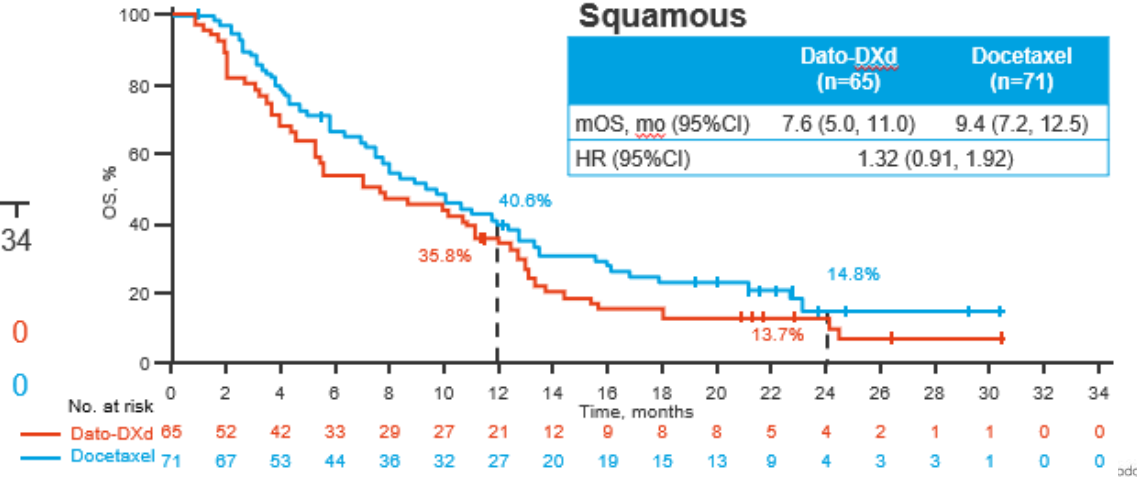
Nonsquamous

	Dato-DXd (n=234)	Docetaxel (n=234)
mOS, mo (95%CI)	14.6 (12.4, 16.0)	12.3 (10.7, 14.0)
HR (95%CI)	0.84 (0.68, 1.05)	



Squamous

	Dato-DXd (n=65)	Docetaxel (n=71)
mOS, mo (95%CI)	7.6 (5.0, 11.0)	9.4 (7.2, 12.5)
HR (95%CI)	1.32 (0.91, 1.92)	

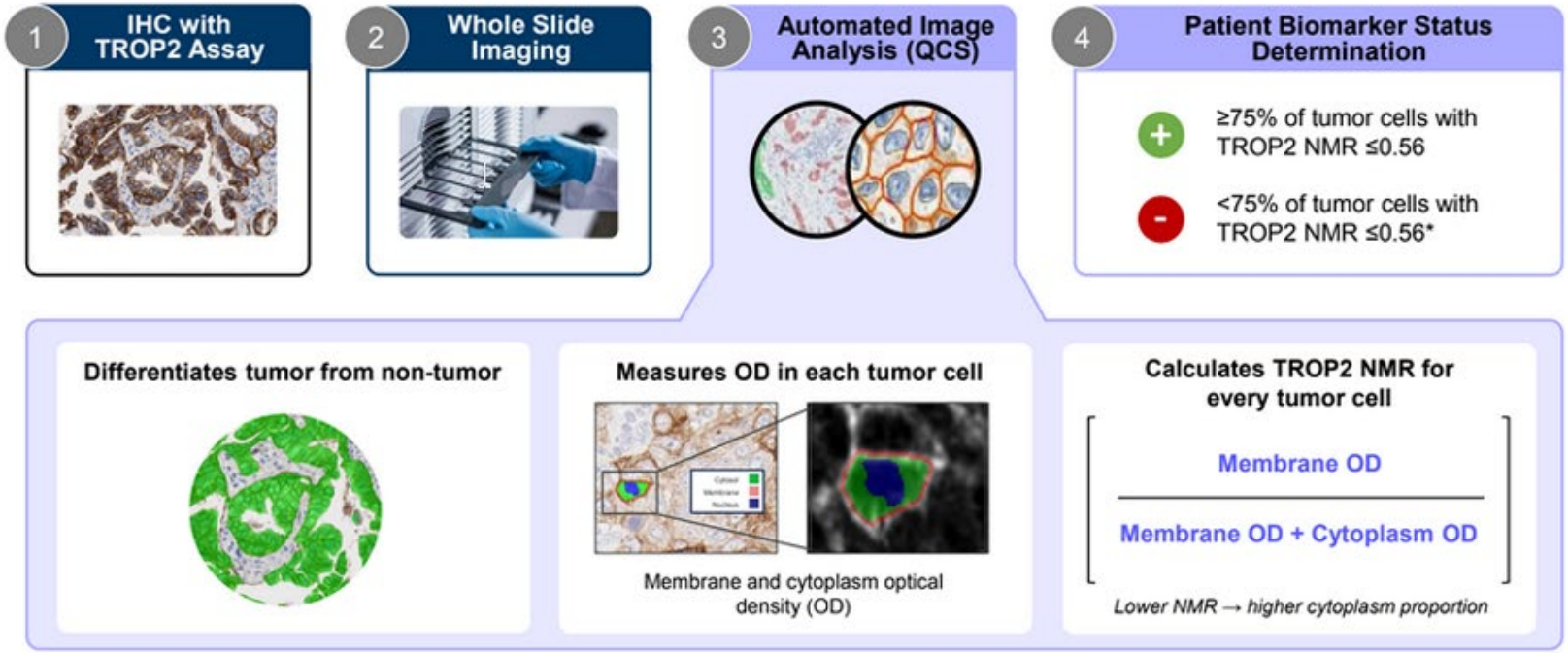


La mejora en PFS no se traslada en una mejora en la OS
OS numéricamente mayor en la rama de Dato-Dxt en población no escamosa

PL02.11: Normalized Membrane Ratio of TROP2 by Quantitative Continuous Scoring is predictive of Clinical Outcomes in TROPION-Lung 01

TROP2 Normalized Membrane Ratio (NMR) measured by Quantitative Continuous Scoring (QCS)

QCS is a novel, fully-supervised computational pathology approach that precisely quantifies and locates targets like TROP2



Prevalence

Histology subgroup	Prevalence of TROP2 QCS-NMR+, % (n)
Biomarker-evaluable population, n=352	
NSQ	66% (179/272)
NSQ/non-AGA	63% (140/221)
NSQ/AGA	76% (39/51)
SQ	44% (35/80)

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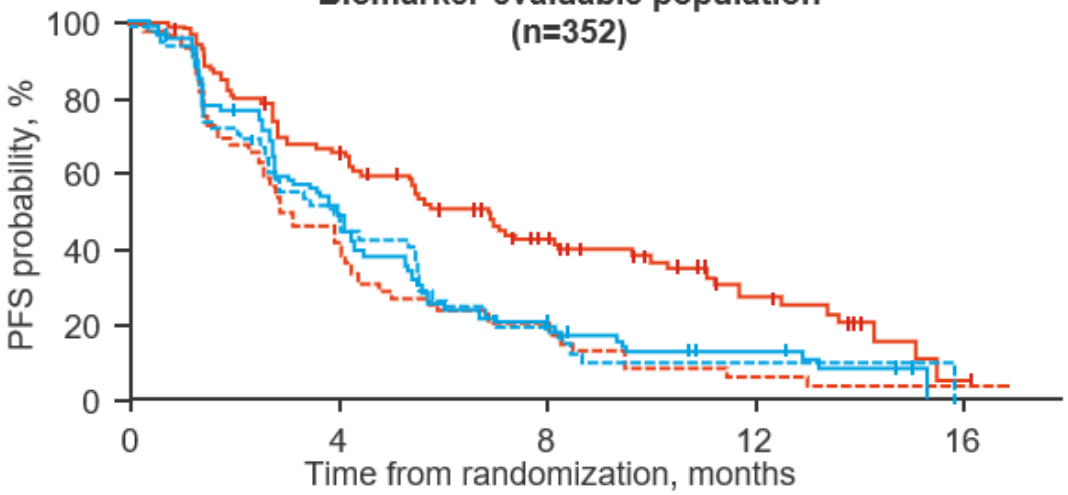
Advanced NSCLC without driver alteration

TROPION-LUNG01 TRIAL

- **Key results**

Progression-free survival

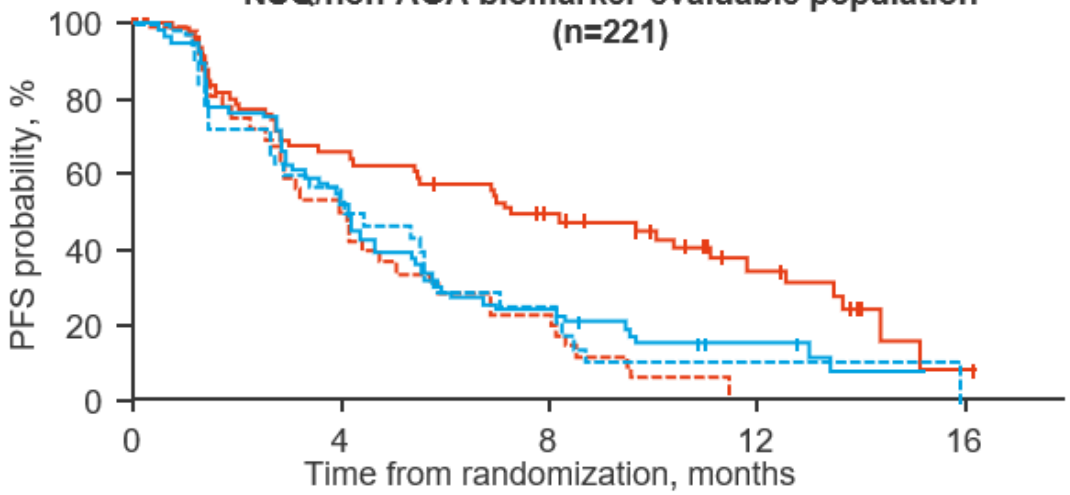
Biomarker-evaluable population (n=352)



	TROP2 QCS-NMR+		TROP2 QCS-NMR-	
	Dato-DXd (n=107)	Docetaxel (n=107)	Dato-DXd (n=65)	Docetaxel (n=73)
ORR, %	32.7	10.3	16.9	15.1
mPFS, mo	6.9	4.1	2.9	4.0
HR (95%CI)	0.57 (0.41, 0.79)		1.16 (0.79, 1.70)	

Treatment by biomarker status interaction: p=0.0063

NSQ/non-AGA biomarker-evaluable population (n=221)



	TROP2 QCS-NMR+		TROP2 QCS-NMR-	
	Dato-DXd (n=68)	Docetaxel (n=72)	Dato-DXd (n=40)	Docetaxel (n=41)
ORR, %	36.8	15.3	22.5	12.2
mPFS, mo	7.2	4.1	4.0	4.4
HR (95%CI)	0.52 (0.35, 0.78)		1.22 (0.74, 2.00)	

Treatment by biomarker status interaction: p=0.0098

Dato-DXd, QCS-NMR+ | Dato-DXd, QCS-NMR- | Docetaxel, QCS-NMR+ | Docetaxel, QCS-NMR-

organizado por: GECP lung cancer research

Advanced NSCLC without driver alteration

TROPION-LUNG01 TRIAL

Safety by TROP2 QCS-NMR status, n (%)		TROP2 QCS-NMR+		TROP2 QCS-NMR-	
		Dato-TXd (n=106)	Docetaxel (n=102)	Dato-TXd (n=65)	Docetaxel (n=71)
TRAEs	Any	92 (87)	94 (92)	56 (86)	58 (82)
	Grade ≥3	31 (29)	47 (46)	14 (22)	19 (27)
AESIs					
Stomatitis	All grades	57 (54)	23 (23)	29 (45)	10 (14)
	Grade ≥3	7 (7)	3 (3)	2 (3)	-
Ocular surface events	All grades	27 (25)	6 (6)	7 (11)	6 (8)
	Grade ≥3	3 (3)	-	1 (2)	-
Adjudicated ILD	All grades	8 (8)	3 (3)	4 (6)	1 (1)
	Grade ≥3	3 (3)	1 (1)	1 (2)	1

TROP2 QCS-NMR es predicitivo de la eficacia de Dato-Dxt
Su valor se está evaluando en otros estudios en 1L

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Agenda

Advanced NSCLC

Without driver alteration

1L setting

- *Interim Analysis of NVALT trial*
- *Primary Analysis of Phase III trial HARMONi-2*

2L setting

- *Primary results from the phase 3 EVOKE-01 study*
- *Final OS from TROPION-Lung01 trial*
- *New Biomarker predictive of outcome in TROPION-Lung 01 trial*

With driver alterations

EGFR

- ***Primary results from PALOMA-3 trial***
- ***A secondary analysis from the phase 3 MARIPOSA study***
- ***Results from CHRYSALIS-2 trial***

ALK

- ***5-year progression-free survival and safety from the CROWN study***
- ***Phase 1/2 ALKOVE-1 study***

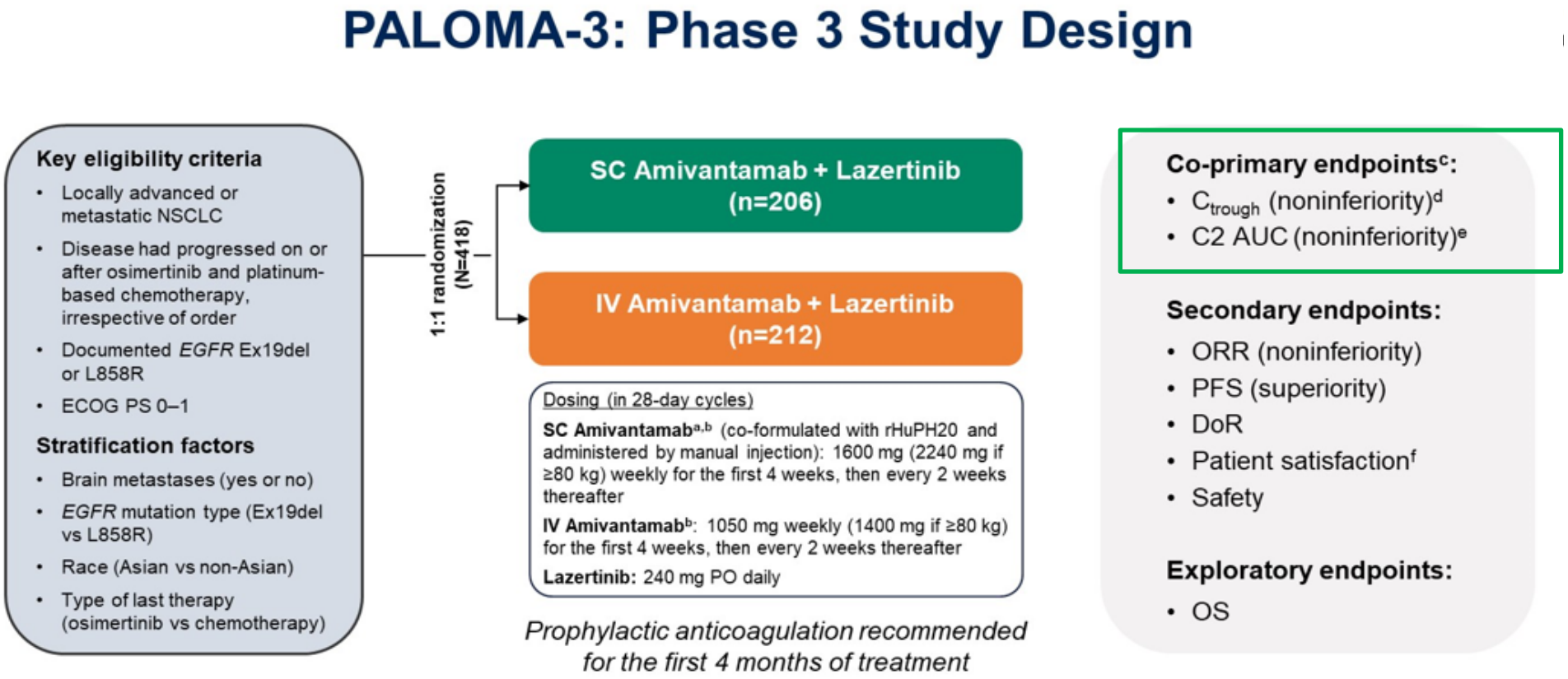
KRAS G12C

- ***Primary results from KRYSTAL-12 trial***

Organizado por:

GECP lung cancer research

LBA8505: Subcutaneous amivantamab vs intravenous amivantamab, both in combination with lazertinib, in refractory EGFR-mutated, advanced non-small cell lung cancer (NSCLC): Primary results, including overall survival (OS), from the global, phase 3, randomized controlled PALOMA-3 trial



Organizado por: GECP lung cancer research

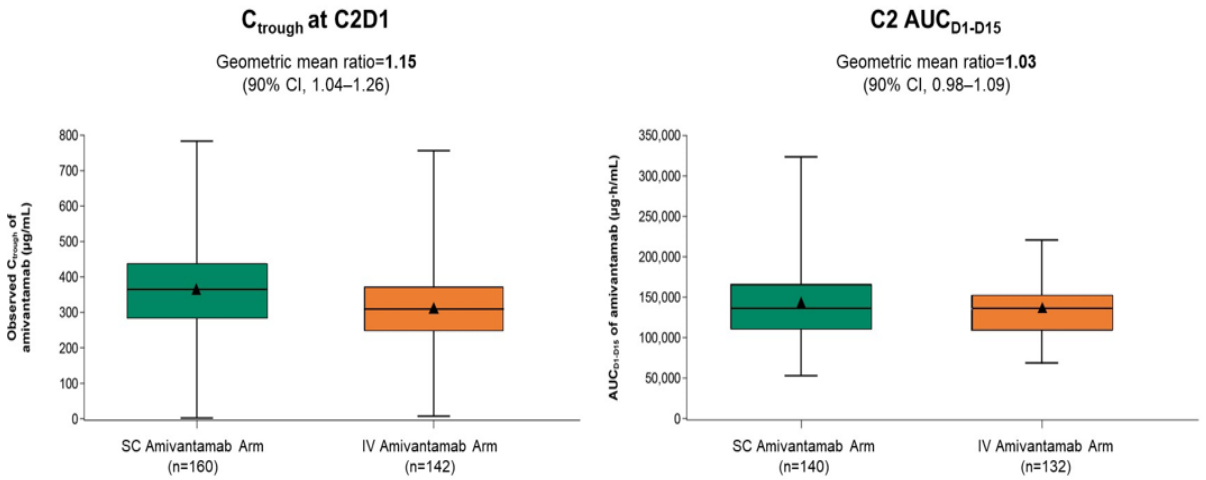
Paloma-3 Trial

Baseline Demographics

Demographics and baseline disease characteristics were well balanced between treatment groups

Characteristic, n (%)	SC Amivantamab Arm (n=206)	IV Amivantamab Arm (n=212)
Median age, years (range)	61 (35–82)	62 (29–81)
Male/female	68 (33) / 138 (67)	71 (33) / 141 (67)
Body weight: <80 kg/≥80 kg	184 (89) / 22 (11)	184 (87) / 28 (13)
Race		
Asian	126 (61)	129 (61)
White	78 (38)	77 (36)
Other[a]	2 (1)	6 (3)
Median prior lines of therapy (range)	**2 (1–5)**	**2 (1–4)**
ECOG PS		
0	58 (28)	61 (29)
1	148 (72)	151 (71)
EGFR mutation type at randomization		
Ex19del	135 (66)	138 (65)
L858R	71 (34)	74 (35)
History of brain metastases	**70 (34)**	**72 (34)**
History of smoking	65 (32)	67 (32)
Last therapy before randomization		
Osimertinib	91 (44)	96 (45)
Chemotherapy	115 (56)	116 (55)
Adenocarcinoma histology	204 (99)	207 (98)

Co-primary PK Endpoints Met Noninferiority Criteria



- Geometric mean ratio for C_{trough} at steady state (C4D1) was 1.43 (90% CI, 1.27–1.61)

Pharmacokinetic samples were available from 414 patients

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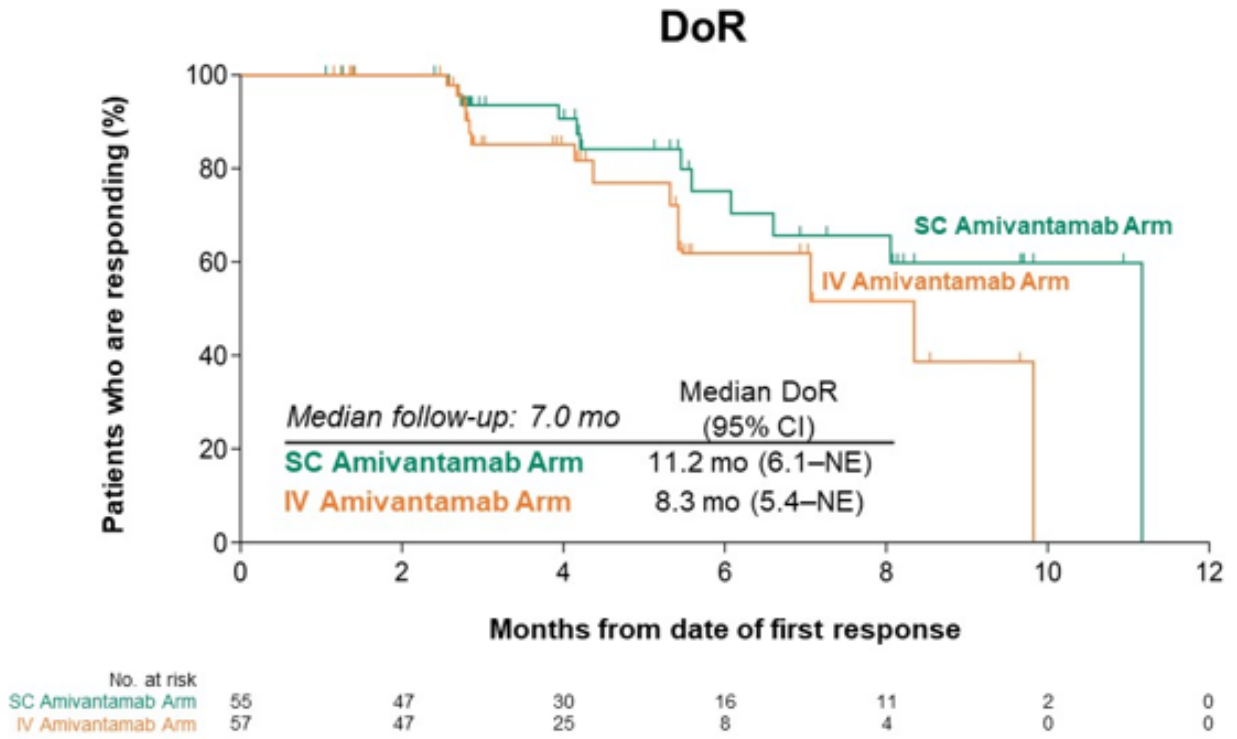
Paloma-3 Trial

ORR and DoR

	SC Amivantamab Arm (n=206)	IV Amivantamab Arm (n=212)
ORR, % (95% CI)[a]		
All responders	**30 (24–37)**	**33 (26–39)**
	Relative risk, 0.92 (95% CI, 0.70–1.23); *P*=0.001	
Confirmed responders	**27 (21–33)**	**27 (21–33)**
	Relative risk, 0.99 (95% CI, 0.72–1.36); *P*<0.001	
Best response, n (%)		
CR	1 (0.5)	1 (0.5)
PR	61 (30)	68 (32)
SD	93 (45)	81 (38)
PD	37 (18)	42 (20)
Not evaluable	14 (7)	20 (9)
DCR, % (95% CI)[b]	**75 (69–81)**	**71 (64–77)**
Median time to response (range), mo	**1.5 (1.2–6.9)**	**1.5 (1.2–9.9)**



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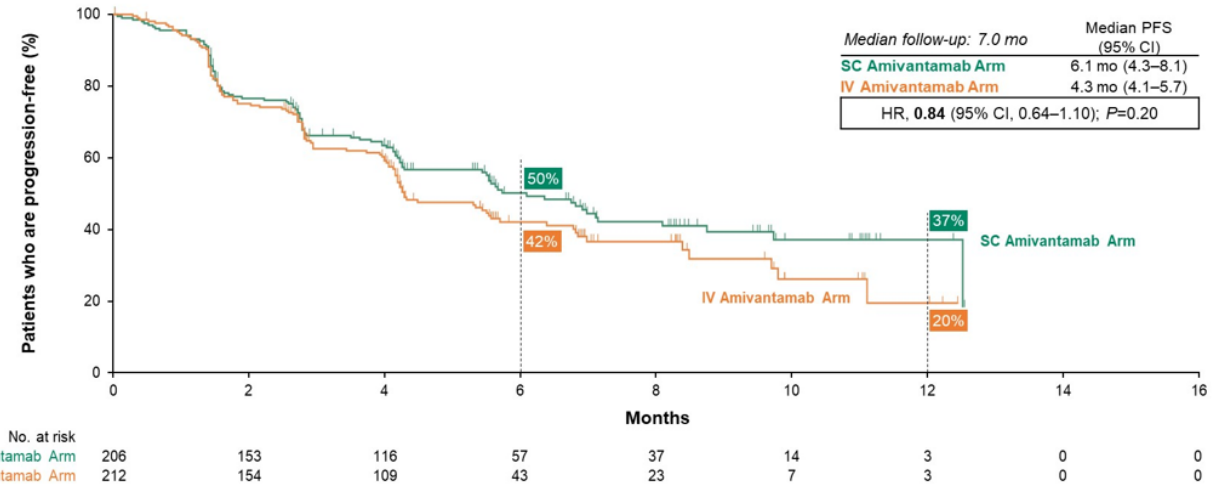
Advanced NSCLC with driver alteration

Paloma-3 Trial

Progression-free Survival

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

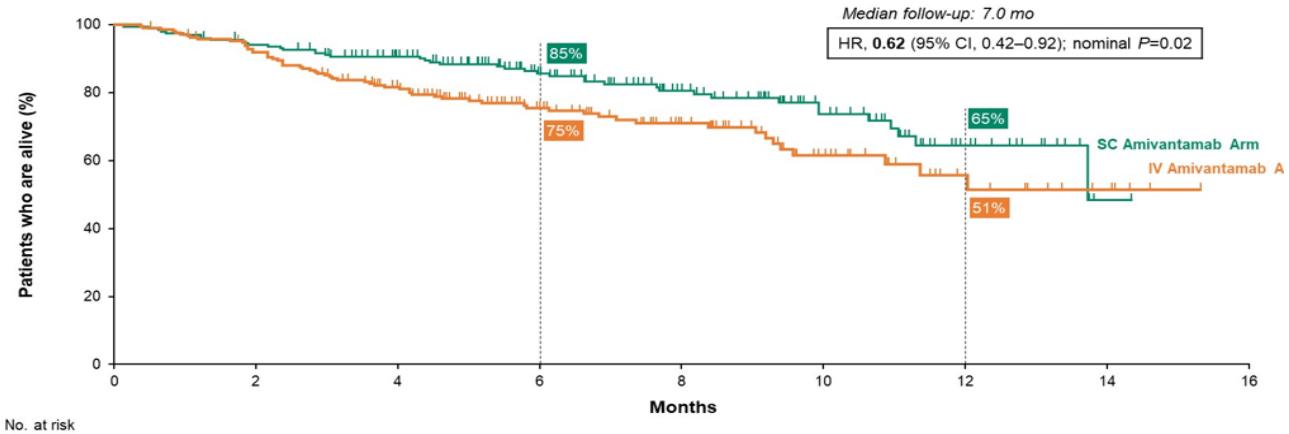


No. at risk

SC Amivantamab Arm	206	153	116	57	37	14	3	0	0
IV Amivantamab Arm	212	154	109	43	23	7	3	0	0

Overall Survival

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



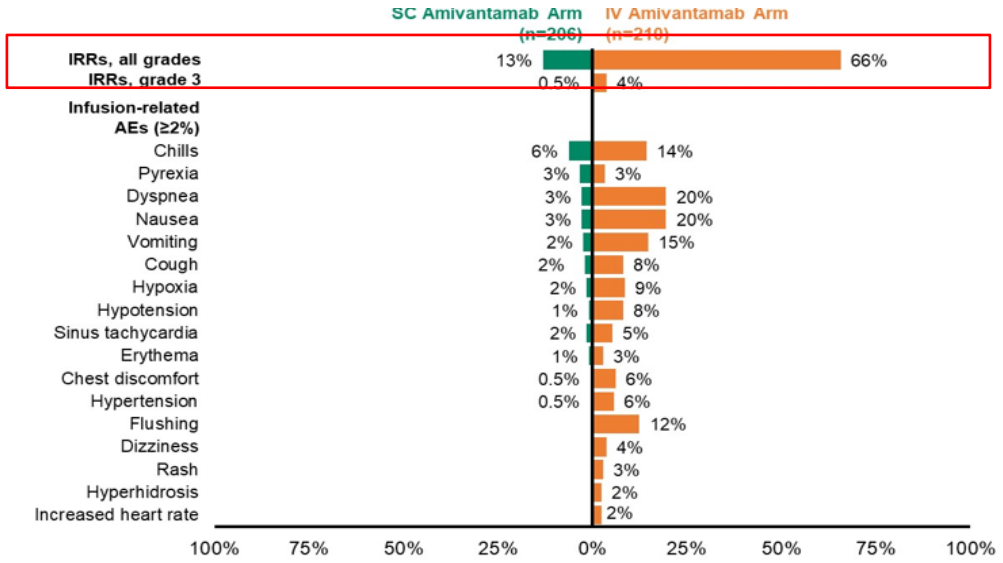
No. at risk

SC Amivantamab Arm	206	192	163	109	71	36	10	0	0
IV Amivantamab Arm	212	191	144	92	51	24	10	1	0

Organizado por:
GECP lung cancer research

Paloma-3 Trial

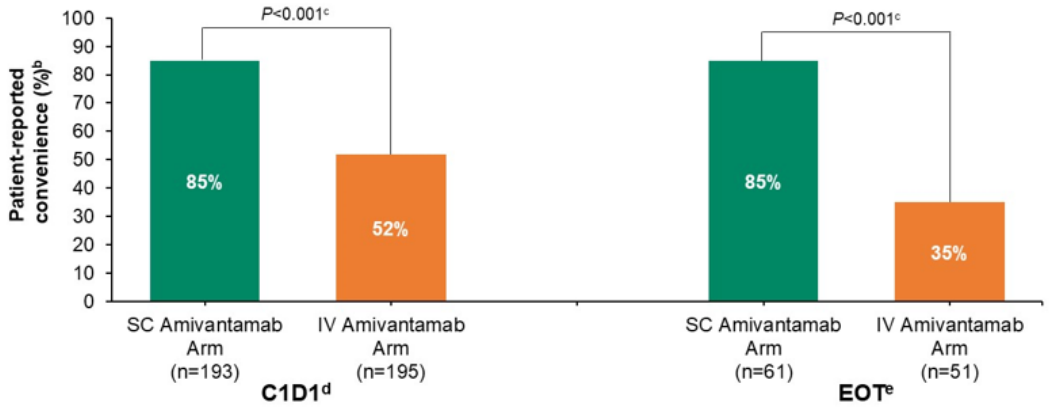
Incidence of IRR-related Symptoms



Treatment Administration Time and Convenience

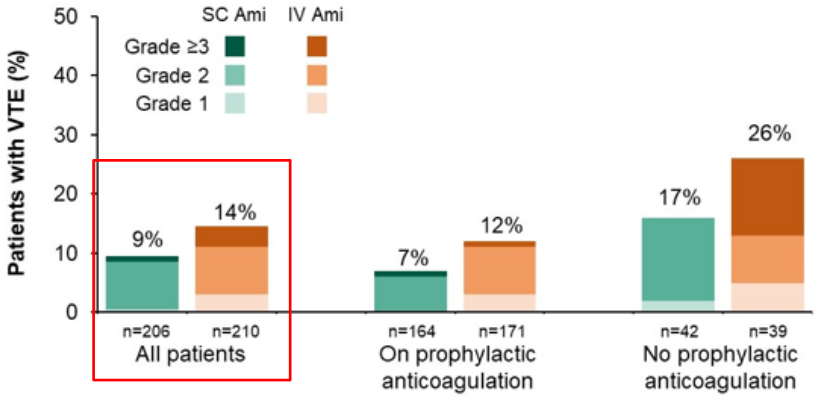
- Treatment administration time was reduced to less than 5 minutes for SC amivantamab from 5 hours for the first infusion (2 hours for subsequent infusions) for IV amivantamab

Frequency of Patient-reported Convenience per Modified TASQ[a]



Adverse Event of Special Interest: VTE[a]

Rates of VTE by Treatment Arm and Prophylaxis Status



Estudio que demuestra la no inferioridad de amivantamab sc vs iv
Muy relevante la reducción en la prevalencia de IRRs (19% vs 66%) y VTE (9% vs 14%)
Más pacientes consideraron amivantamab sc más cómodo

8504: Amivantamab plus lazertinib vs osimertinib in first-line EGFR-mutant advanced non-small cell lung cancer (NSCLC) with biomarkers of high-risk disease: A secondary analysis from the phase 3 MARIPOSA study

MARIPOSA Study Design and Methods

- Amivantamab is an EGFR-MET bispecific antibody with immune cell–directing activity[1-3]
- Lazertinib is a CNS-penetrant, 3rd-generation EGFR TKI[4,5]

Key eligibility criteria
- Locally advanced or metastatic NSCLC
- Treatment naïve for advanced disease
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0 or 1
- Asymptomatic brain metastases did not require definitive treatment

2:2:1 randomization (N=1074)

Focus of this presentation

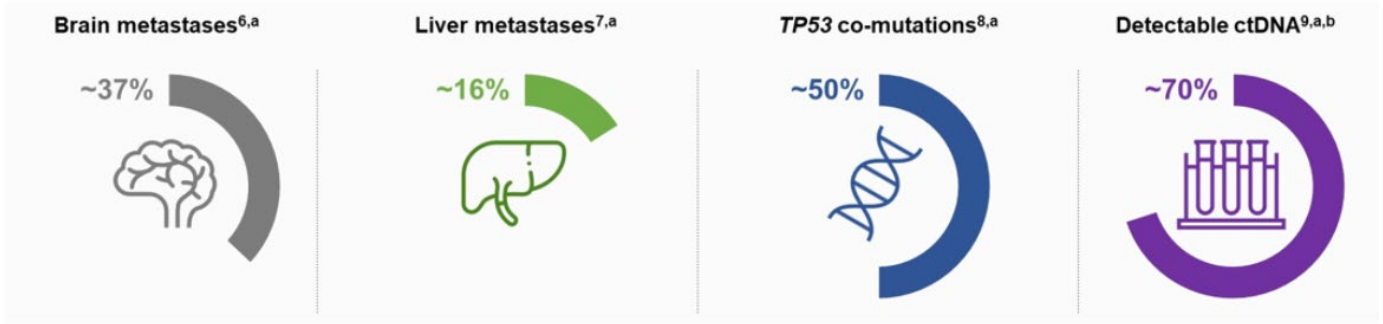
- **Amivantamab + Lazertinib** (n=429; open label)
- **Osimertinib** (n=429; blinded)
- **Lazertinib** (n=216; blinded)

Primary endpoint of PFS[a] by BICR per RECIST v1.1:
- Amivantamab + Lazertinib vs Osimertinib

High-risk subgroups analyzed:
- Brain metastases
- Liver metastases
- *TP53* co-mutation
- Detectable *EGFR*m ctDNA at baseline
- Without *EGFR*m ctDNA clearance at Week 9 (C3D1)

Diagnostic tests:
- ctDNA NGS[b]: baseline co-mutations
- ctDNA ddPCR[c]: detection and clearance of Ex19del and L858R

Stratification factors:
- EGFR mutation type (Ex19del or L858R)
- Asian race (yes or no)
- History of brain metastases (yes or no)



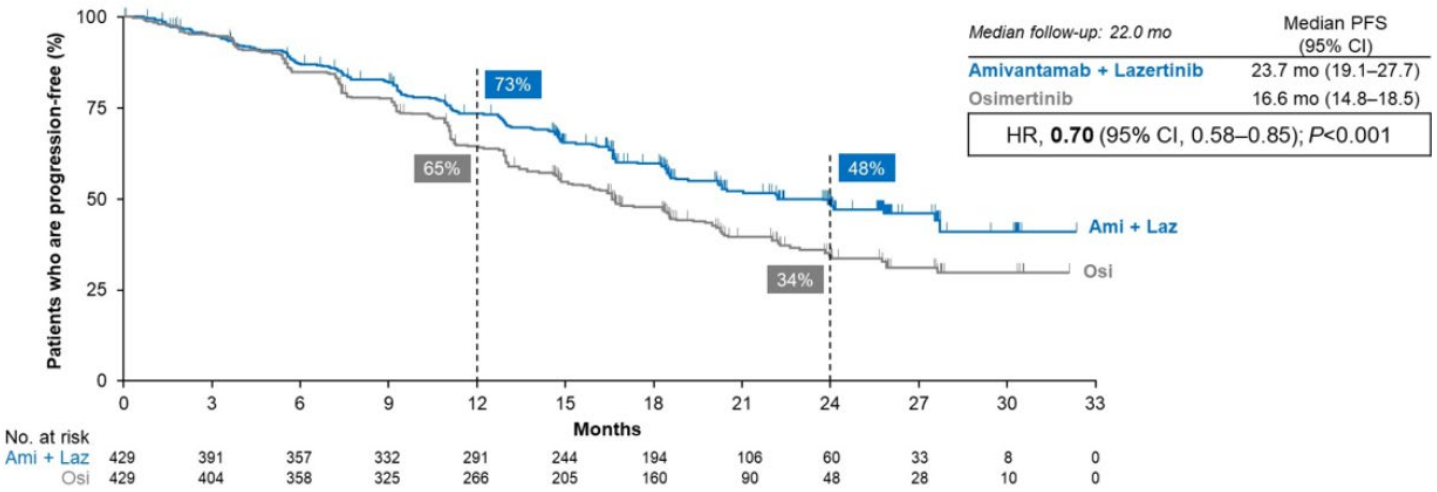
Organizado por: GECP lung cancer research

Advanced NSCLC without driver alteration

MARIPOSA TRIAL

Primary Endpoint: PFS by BICR

Amivantamab + lazertinib reduced the risk of progression or death by 30% and improved median PFS by 7.1 months



Median follow-up: 22.0 mo	Median PFS (95% CI)
Amivantamab + Lazertinib	23.7 mo (19.1–27.7)
Osimertinib	16.6 mo (14.8–18.5)

HR, **0.70** (95% CI, 0.58–0.85); *P*<0.001

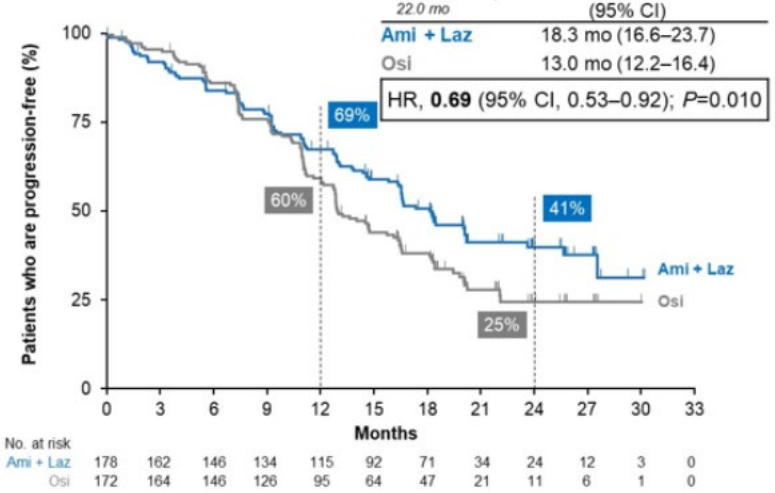
PFS by Baseline Brain Metastases

- In the amivantamab + lazertinib arm, 41% of patients had a history of brain metastases vs 40% in the osimertinib arm

With History of Brain Metastases

Median follow-up: 22.0 mo	Median PFS (95% CI)
Ami + Laz	18.3 mo (16.6–23.7)
Osi	13.0 mo (12.2–16.4)

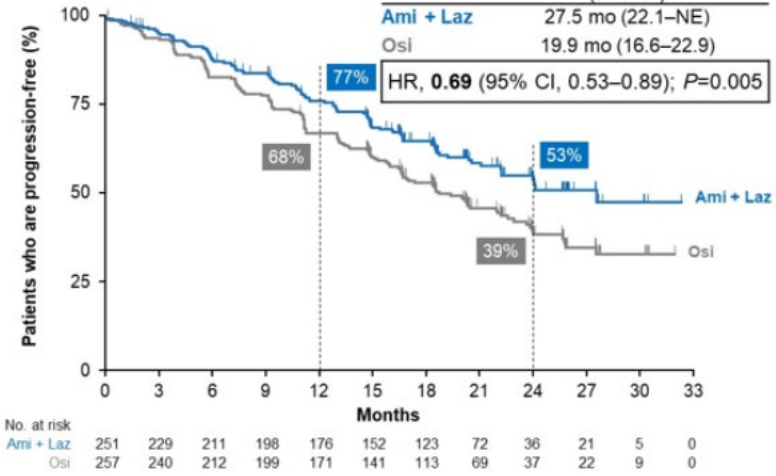
HR, **0.69** (95% CI, 0.53–0.92); *P*=0.010



Without History of Brain Metastases

Median follow-up: 22.0 mo	Median PFS (95% CI)
Ami + Laz	27.5 mo (22.1–NE)
Osi	19.9 mo (16.6–22.9)

HR, **0.69** (95% CI, 0.53–0.89); *P*=0.005



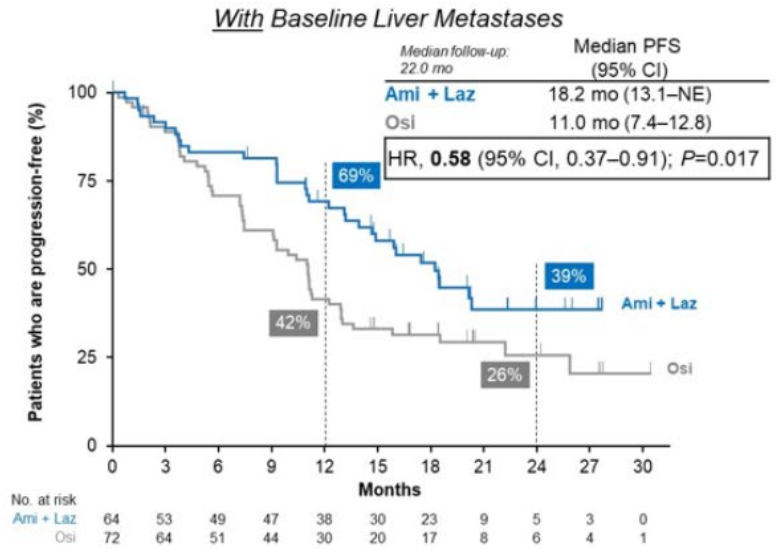
Organizado por:

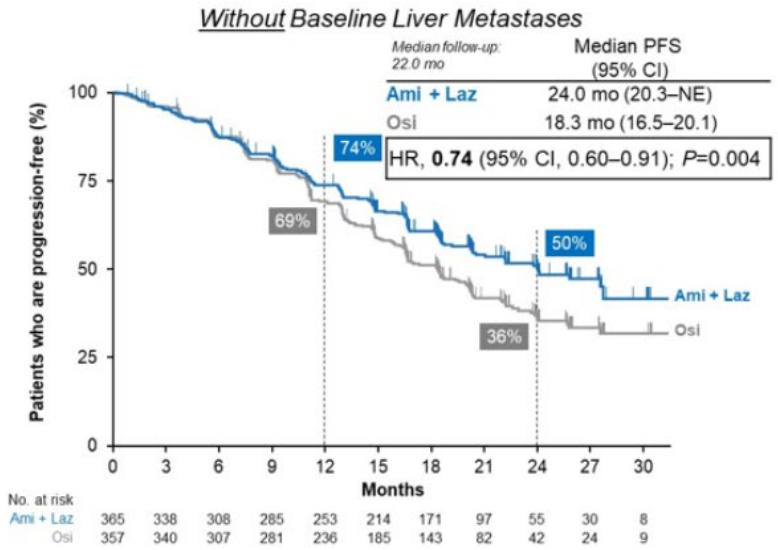
GECP lung cancer research

Advanced NSCLC without driver alteration

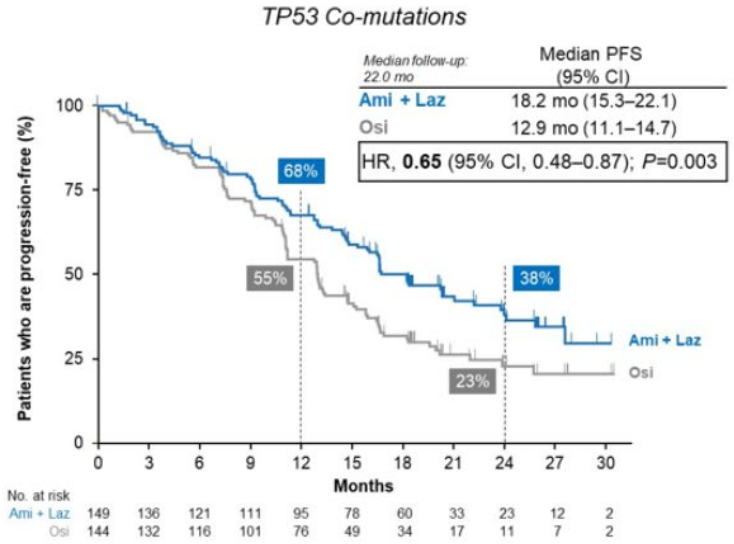
MARIPOSA TRIAL

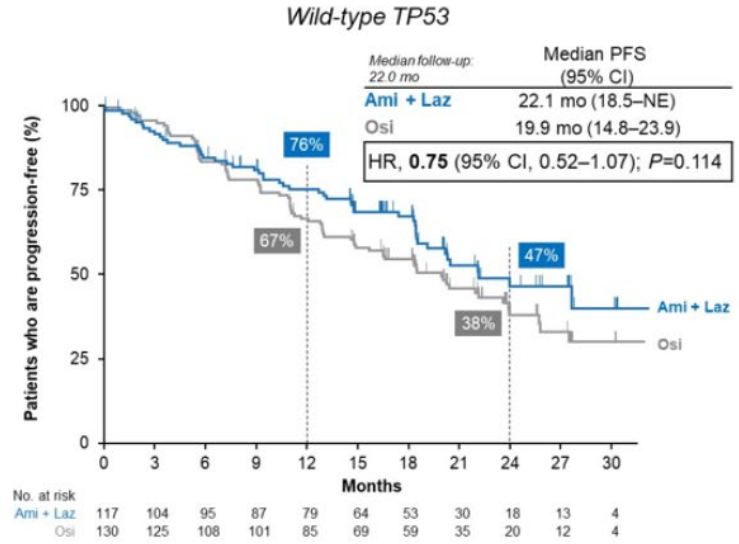
Liver Metastases





TP53 mutation





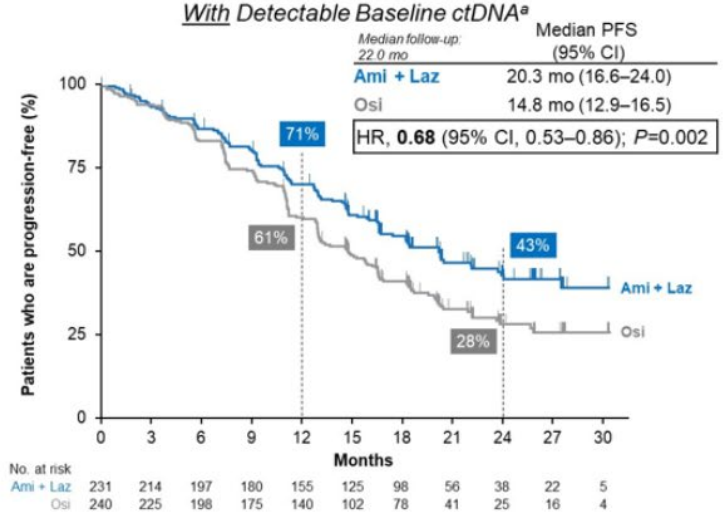
Organizado por: GECP lung cancer research

Advanced NSCLC without driver alteration

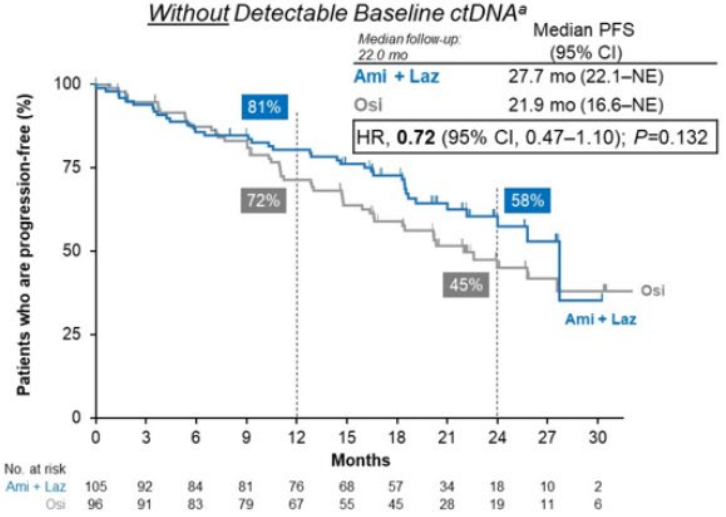
MARIPOSA TRIAL

Detectable EGFRm ctDNA baseline

With Detectable Baseline ctDNA[a]

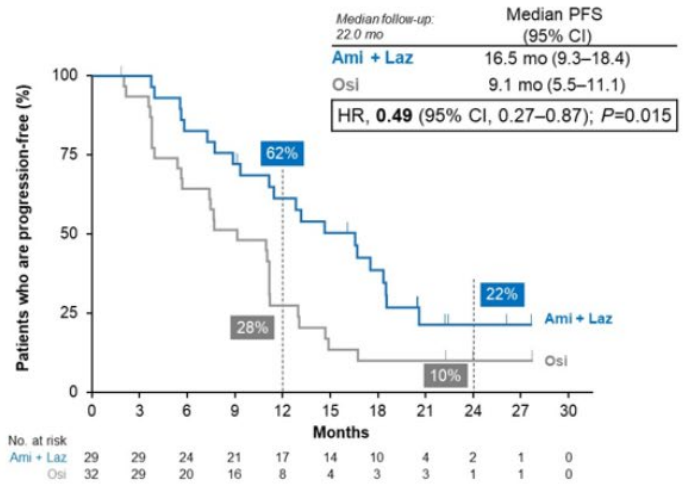


Without Detectable Baseline ctDNA[a]

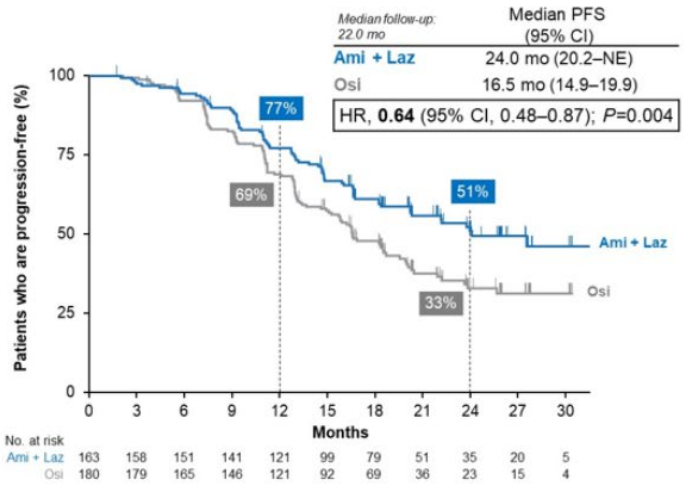


Without EGFRm ctDNA at week 9

Without Cleared EGFRm ctDNA[a] at Week 9



With Cleared EGFRm ctDNA[a] at Week 9



Todos los subgrupos de pacientes de mal pronóstico analizados se benefician de la combinación

Organizado por: GECP lung cancer research

8516: Amivantamab plus lazertinib in atypical EGFR-mutated advanced non-small cell lung cancer (NSCLC): Results from CHRYSALIS-2

CHRYSALIS-2 Study Design

CHRYSALIS-2
Ami + Laz in
Atypical *EGFR*+
NSCLC

Dose escalation phase

RP2CD was identified:
Amivantamab 1050 mg (1400 mg if ≥80 kg) IV
plus
Lazertinib 240 mg PO

Dose expansion cohorts

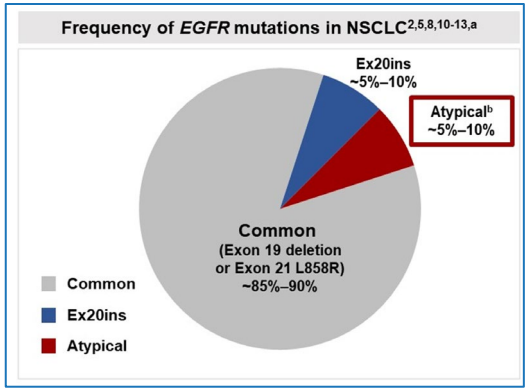
- **Cohort A:** *EGFR* Ex19del or L858R[a] (post-osimertinib/post-platinum)
- **Cohort B:** *EGFR* Ex20ins[a] (post-SOC/post-platinum)
- **Cohort C: Atypical *EGFR* mutations (treatment naïve or post-TKI/chemo)**
- **Cohort D:** *EGFR* Ex19del or L858R[a] (post-osimertinib; biomarker validation)
- **Cohort E:** *EGFR* Ex19del or L858R (post-osimertinib; IHC biomarker validation)
- **Cohort F[b]:** *EGFR* Ex19del or L858R (post-osimertinib; IHC biomarker validation)

Primary endpoint:
- ORR by investigator per RECIST v1.1

Secondary endpoints:
- DoR
- CBR[c]
- PFS
- OS
- Safety (AEs)

Focus of this presentation

- Cohort C included patients with atypical *EGFR* mutations who were treatment naïve or had ≤2 prior lines (excluding 3rd-gen EGFR TKIs)
- Patients with **Ex20ins and Ex19del/L858R co-mutations were excluded**
- Baseline ctDNA NGS analyses were performed using Guardant Health G360[d]



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Demographic and Baseline Disease Characteristics

CHRYSALIS-2
Ami + Laz in
Atypical *EGFR*+
NSCLC

- As of January 12, 2024, 105 patients received amivantamab + lazertinib, with a median follow-up of 16.1 months (range, 0.1–31.5)

Characteristic, n (%)	Cohort C (n=105)
Median age, years (range)	64 (30–85)
Male / female	53 (50) / 52 (50)
Race	
White	31 (30)
Asian	71 (68)
Black or African American	1 (1)
Not reported	2 (2)
Brain metastases at baseline	33 (31)
Prior therapies in metastatic setting	
Treatment naïve	49 (47)
Prior afatinib	34 (32)
Prior 1st-/2nd-gen EGFR TKI (other than afatinib)[a]	9 (9)
Prior platinum chemotherapy	7 (7)
Prior afatinib + prior platinum chemotherapy	6 (6)

Characteristic, n (%)	Cohort C (n=105)
ECOG PS	
0	33 (31)
1	72 (69)
Type of *EGFR* mutation[b]	
Exon 18 G719X	60 (57)[c]
Exon 21 L861X	27 (26)[d]
Exon 20 S768X	25 (24)[e]
Exon 18 E709K	2 (2)
Exon 20 E709A	2 (2)
L833V	2 (2)
R776C	2 (2)
R776H	1 (1)
R831H	1 (1)
V744M	1 (1)
V769L	1 (1)
V774M	1 (1)
Other	10 (10)

[a]1st-/2nd-generation EGFR TKIs other than afatinib included gefitinib, dacomitinib, erlotinib, and icotinib. [b]Patients may be counted in ≥1 category. [c]G719X included G719A, G719S, and G719C. [d]L861X included L861Q, L861R, and L861G. [e]S768X included S768I and S768L.
ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; gen, generation; TKI, tyrosine kinase inhibitor.

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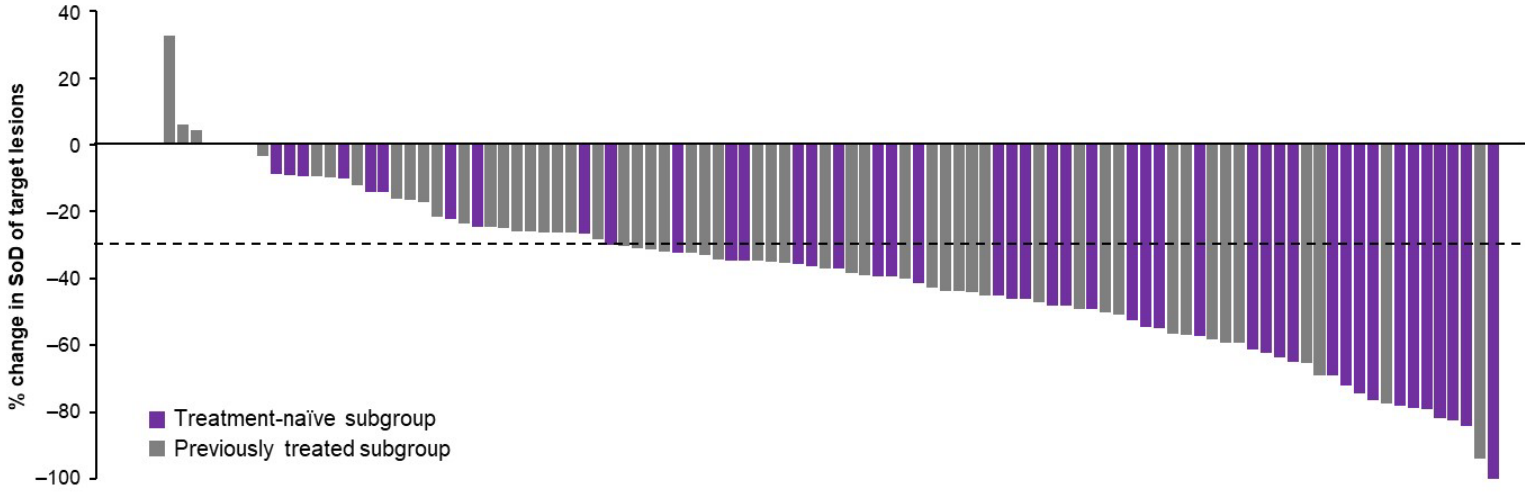
Chrysalis-2 Trial

Efficacy Outcomes of Amivantamab + Lazertinib Among All Patients in Cohort C

CHRYSALIS-
Ami + Laz in
Atypical *EGFR*+
NSCLC

Investigator-assessed response (n=105)	
Median follow-up	16.1 mo (range, 0.1–31.5)
ORR	52% (95% CI, 42–62)
Median DoR	14.1 mo (95% CI, 9.5–26.2)
DoR ≥6 mo, n (%)[a]	38 (69)
Best response, n (%)	
CR	0
PR	55 (52)
SD	37 (35)
PD	8 (8)
Not evaluable/UNK	5 (5)
CBR[b]	79% (95% CI, 70–86)
Median PFS	11.1 mo (95% CI, 7.8–17.8)
Median OS	NE (95% CI, 22.8–NE)



- In a heterogeneous population, the **median PFS was 11.1 months** and **median OS was NE**

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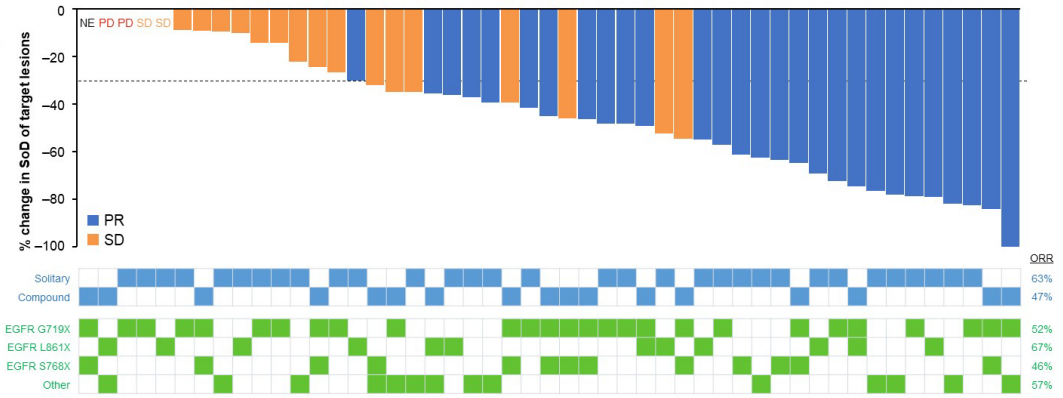
Advanced NSCLC with driver alteration

Chrysalis-2 Trial

1st LINE

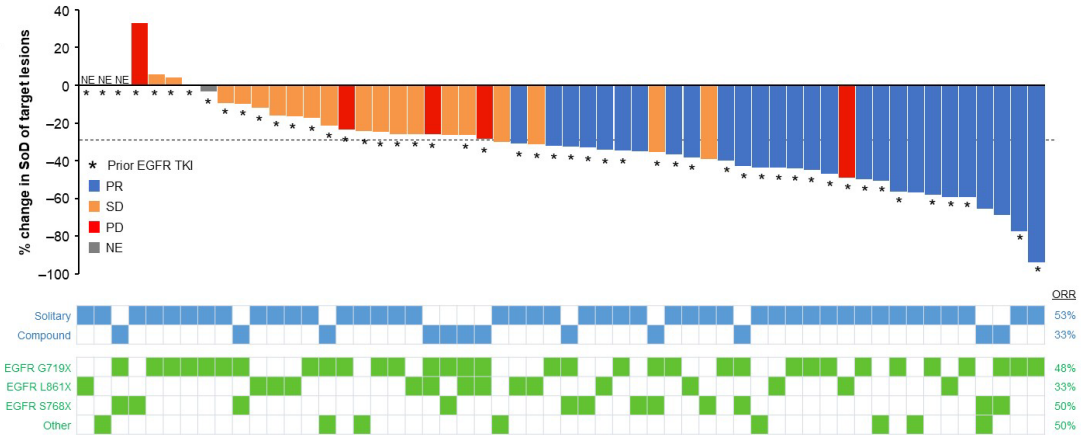
Investigator-assessed response (n=49)	
Median follow-up	17.3 mo (range, 0.1–31.5)
ORR	57% (95% CI, 42–71)
Median DoR	20.7 mo (95% CI, 9.9–NE)
DoR ≥6 mo, n (%)[a]	21 (75)
CBR[b]	84% (95% CI, 70–93)
Median PFS	19.5 mo (95% CI, 11.2–NE)
Median OS	NE (95% CI, 26.3–NE)



- The presence of *TP53* co-mutation and other pathogenic alterations were not associated with a lower response rate
- At a median follow-up of 17.3 months, the **median PFS was 19.5 months** and **median OS was NE**

2nd/3rd LINE

Investigator-assessed response (n=56)	
Median follow-up	15.4 mo (range, 0.3–30.8)
ORR	48% (95% CI, 35–62)
Median DoR	11.0 mo (95% CI, 4.5–NE)
DoR ≥6 mo, n (%)[a]	17 (63)
CBR[b]	75% (95% CI, 62–86)
Median PFS	7.8 mo (95% CI, 5.4–11.1)
Median OS	22.8 mo (95% CI, 16.9–NE)



- 88% of patients received a prior EGFR TKI
- The presence of *TP53* co-mutation and other pathogenic alterations were not associated with a lower response rate
- At a median follow-up of 15.4 months, the **median PFS was 7.8 months** and **median OS was 22.8 months**

Resultados clínicamente muy relevantes de la combinación en pacientes con mutaciones atípicas de EGFR

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LBA8503: Lorlatinib vs crizotinib in treatment-naïve patients with advanced ALK+ non-small cell lung cancer: 5-year progression-free survival and safety from the CROWN study

Current Post Hoc Analyses at 5 Years

Endpoint evaluation by BICR stopped after the 3-year analysis

Key eligibility criteria

- Stage IIIB/IV *ALK*+ NSCLC
- No prior systemic treatment for metastatic disease
- ECOG PS 0-2
- Asymptomatic treated or untreated CNS metastases were permitted
- ≥1 extracranial measurable target lesion (RECIST 1.1) with no prior radiation required

Randomized 1:1 N=296

Stratified by:

- Presence of brain metastases (yes vs no)
- Ethnicity (Asian vs non-Asian)

Lorlatinib 100 mg once daily n=149

Crizotinib 250 mg twice daily n=147

No crossover between treatment arms was permitted

Current analyses

Data cutoff: October 31, 2023

- **Investigator Assessed**
  - PFS[a]
  - ORR and IC ORR
  - DOR and IC DOR
  - IC TTP
- Safety
- Biomarker analyses

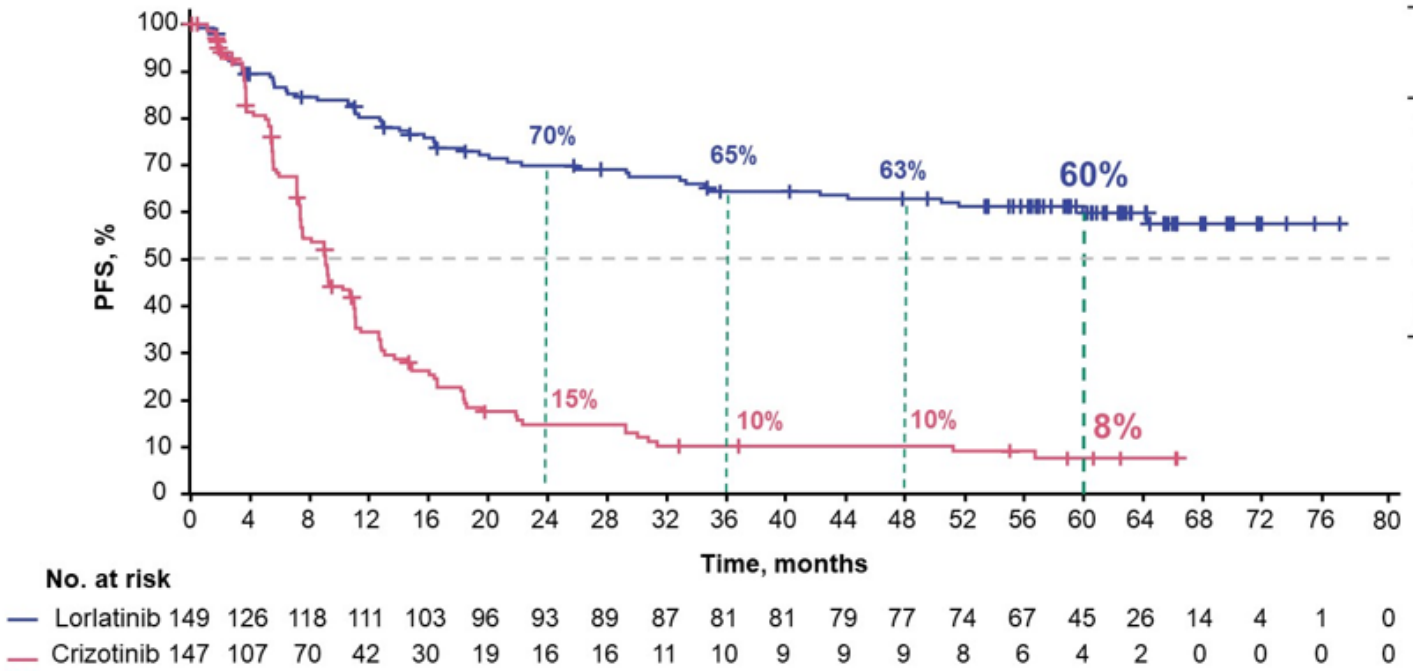
Primary Objective:
- PFS by BICR

- The median duration of follow-up for PFS was 60.2 months (95% CI, 57.4-61.6) in the lorlatinib arm and 55.1 months (95% CI, 36.8-62.5) in the crizotinib arm

Organizado por: GECP lung cancer research

Crown Study

At 60.2 Months of Median Follow-Up, Median PFS by Investigator Was Still Not Reached With Lorlatinib



	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	55	115
PFS, median (95% CI), months	NR (64.3-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.27)**	

At the time of this analysis, the required number of OS events for a protocol-specified second interim analysis **has not been reached**. OS follow up is ongoing

HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

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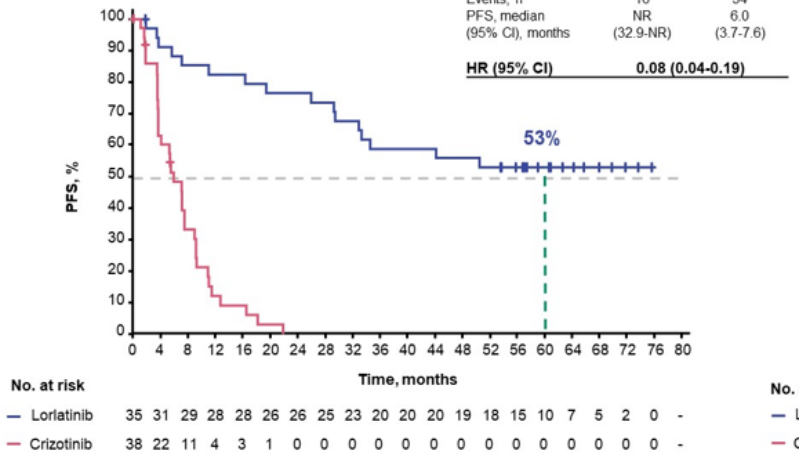
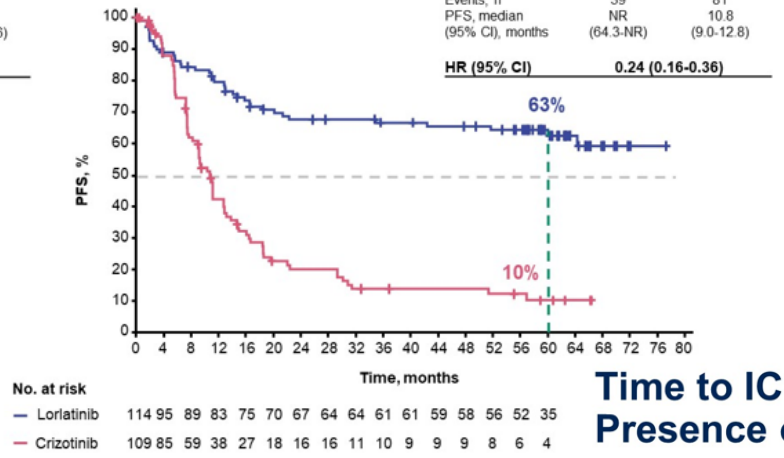
Crown Study

Lorlatinib Showed Superior PFS Benefit Irrespective of Presence or Absence of Baseline Brain Metastases

With Baseline Brain Metastases

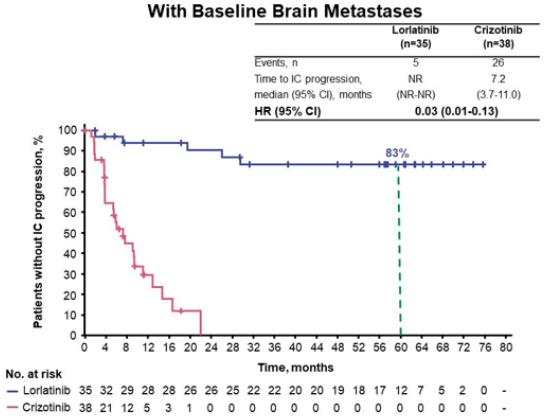


Without Baseline Brain Metastases

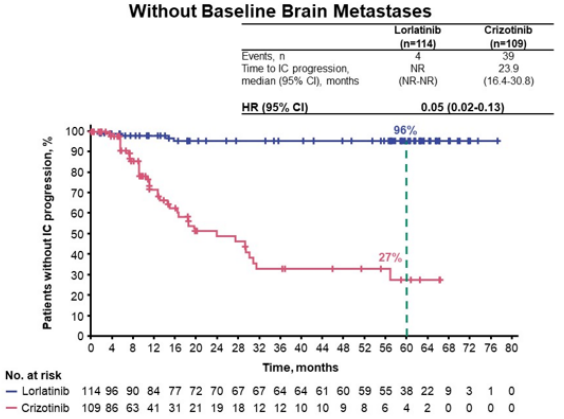


Time to IC Progression Was Longer With Lorlatinib in Presence or Absence of Baseline Brain Metastases

With Baseline Brain Metastases

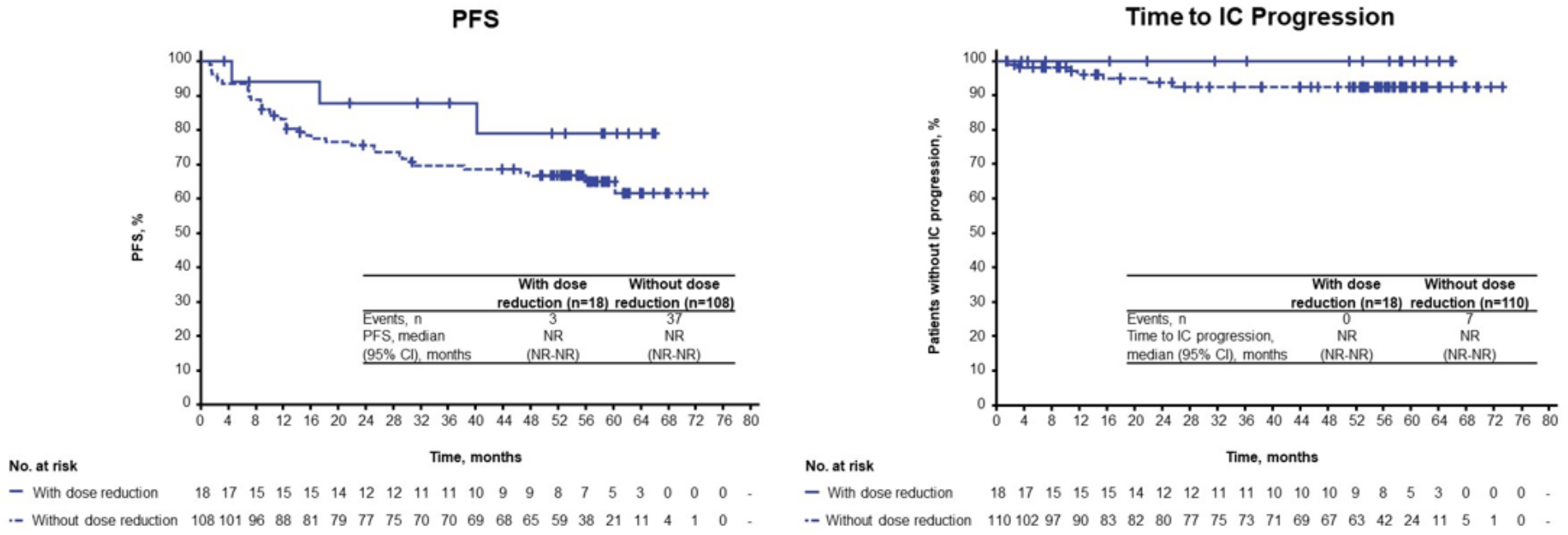


Without Baseline Brain Metastases



Crown Study

Dose Reduction Did Not Impact Efficacy of Lorlatinib in Patients Who Had Dose Reduction in the First 16 Weeks



Tras 5 años de seguimiento, la SLP en la rama de lorlatinib no se alcanza pero in 60% de los pacientes están libres de progression
Probabilidad de estar libre de PE a nivel de intracraneal 92%
Se confirma su role como estandar de tratamiento en 1L

Organizado por: GECP lung cancer research

Solomon BJ, et al ASCO 2024.

1253O: Phase 1/2 ALKOVE-1 study of NVL-655 in ALK-positive (ALK+) solid tumors

ALKove-1

A Global First-in-Human Phase 1/2 Clinical Trial of NVL-655 in Advanced ALK-Positive NSCLC and Other Solid Tumors (NCT05384626)

PATIENT POPULATION

- Advanced solid tumors harboring an ALK fusion or activating mutation (by local testing)
- Patients with NSCLC: ≥ 1 prior 2G or 3G ALK TKI
- ≤ 2 prior chemotherapies/immunotherapies
- Excluded: concurrent oncogenic drivers (e.g., EGFR/ROS1/MET/RET/BRAF alterations) [a]
- Evaluable but non-measurable disease allowed [a]

PHASE 1 OBJECTIVES

- Primary: Selection of RP2D and, if applicable, MTD
- Overall safety and tolerability
- PK characterization
- Preliminary antitumor activity
- Intracranial activity

PHASE 1 DOSE-ESCALATION COMPLETED, FOLLOW-UP CONTINUES

Enrollment June 2022 to February 2024 (Data cut-off: 15 June 2024)

NVL-655 Phase 1	All Doses	15 mg QD	25 mg QD	50 mg QD	100 mg QD	RP2D 150 mg QD	200 mg QD
All-Treated Population	N = 133	3	12	12	32	52	22
NSCLC Response-Evaluable Population	N = 103	3	7	10	27	39	17

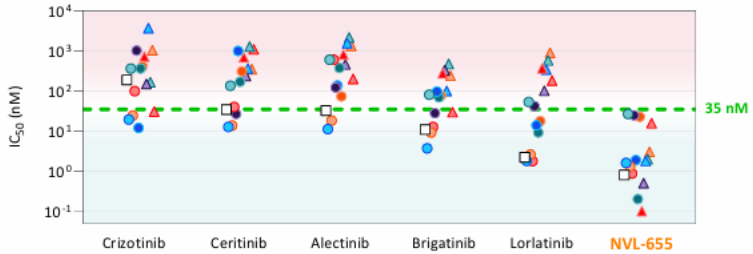
2G, 2nd generation ALK TKI (i.e., ceritinib, alectinib, or brigatinib); **3G**, 3rd generation ALK TKI (i.e., lorlatinib); **MTD**, maximum tolerated dose; **NSCLC**, non-small cell lung cancer; **PK**, pharmacokinetics; **QD**, once daily; **RP2D**, recommended phase 2 dose; **TKI**, tyrosine kinase inhibitor

[a] Response evaluable population prospectively defined as all NSCLC patients with measurable disease, without concurrent oncogenic driver, and who undergo ≥1 post-baseline response assessment (or discontinue treatment due to clinical progression/death prior to the first response assessment). Patients unevaluable for response: no measurable disease at baseline (n = 18); tumor with alternate oncogenic driver (MET amplification [n = 4], BRAF G469A [n = 2], BRAF fusion [n = 1], NTRK fusion [n = 1]); no post-baseline scan and discontinued treatment for reasons other than progressive disease (n = 2); other solid tumor (n = 2).

NVL-655:

ALK Fusion and ALK Single/Compound Mutation Activity

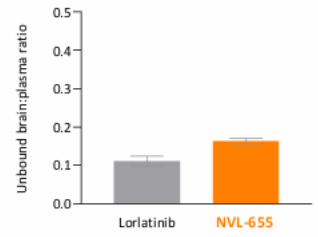
Potent activity (IC_{50} = 0.1 – 30 nM) against ALK-driven cell lines, including ALK single and compound mutants



Cell lines harboring EML4-ALK fusion
3-day cell viability assay

Brain Penetrance

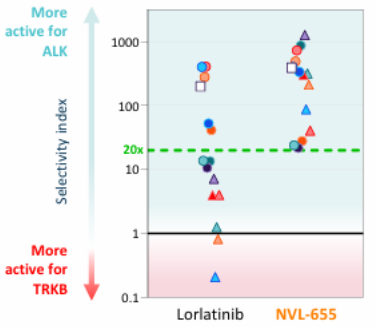
Preclinical pharmacokinetic data similar to lorlatinib



Wistar Han rats
10 mg/kg, single dose PO
1-hour timepoint

Avoidance of TRK Inhibition

Selective inhibition of ALK and ALK mutants over TRK



$$\text{Selectivity index} = \frac{IC_{50}\ (\text{pTRKB})}{IC_{50}\ (\text{Ba/F3 EML4-ALK})}$$

Alkove phase 1 study

Patient Population:
Heavily Pretreated ALK-Positive Solid Tumors

Patient Characteristic	All Treated (N = 133)	RP2D (N=52)
Age, median (range)	57 (24, 83)	59 (24, 83)
Female	84 (63%)	35 (67%)
ECOG PS		
0	60 (45%)	24 (46%)
1	73 (55%)	28 (54%)
Non-smoker	95 (71%)	36 (69%)
Tumor Type		
NSCLC	131 (98%)	52 (100%)
Pancreatic adenocarcinoma	1 (1%)	0
Atypical carcinoid, lung	1 (1%)	0
History of CNS metastases [a]	**75 (56%)**	**31 (60%)**
ALK Fusion	133 (100%)	52 (100%)
Secondary ALK mutation [b]	68 (51%)	28 (54%)
Single ALK mutation	34 (26%)	15 (29%)
Compound (i.e., ≥2) ALK mutations [c]	**34 (26%)**	**13 (25%)**
ALK G1202R (single or compound)	35 (26%)	15 (29%)

Treatment History	All Treated (N = 133)	RP2D (N=52)
Prior lines of anticancer treatment		
1	13 (10%)	4 (8%)
2	32 (24%)	13 (25%)
≥3	88 (66%)	35 (67%)
Median (range)	**3 (1, 9)**	**4 (1, 8)**
Prior treatments		
1 ALK TKI	18 (14%)	6 (12%)
2 ALK TKIs	54 (41%)	20 (39%)
≥3 ALK TKIs	61 (46%)	26 (50%)
Chemotherapy	74 (56%)	30 (58%)
ALK TKIs received [d]		
1G (crizotinib)	57 (43%)	24 (46%)
2G	127 (96%)	49 (94%)
alectinib	120 (90%)	46 (89%)
brigatinib	29 (22%)	12 (23%)
ceritinib	17 (13%)	8 (15%)
3G (lorlatinib)	**111 (84%)**	**44 (85%)**
Any 2G or lorlatinib	133 (100%)	52 (100%)
≥2 ALK TKIs, including 2G and lorlatinib	105 (79%)	41 (79%)
≥3 ALK TKIs, including 2G and lorlatinib	**58 (44%)**	**24 (46%)**

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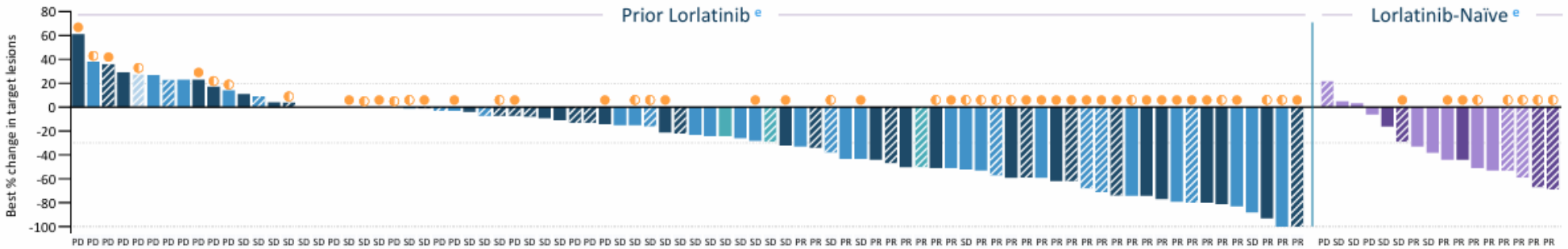
Alkove phase 1 study

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

RECIST 1.1 ORR, % (n/N) *All patients ± chemotherapy*	NSCLC Response-Evaluable (Any Prior ALK TKI, range 1 – 5)			Prior Lorlatinib (≥2 ALK TKIs)			Lorlatinib-naive (≥1 2G ± 1G)	
	All	Any ALK mutation [a]	G1202R [b]	All	Any ALK mutation	Compound ALK mutation [c]	All	Any ALK mutation
All Doses	**38%** (39/103)	**52%** (30/58)	**69%** (22/32) [d]	**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)



Data cut-off: 15 June 2024. Response-evaluable patients with NSCLC. All responses were confirmed.

NSCLC, non-small cell lung cancer; **ORR**, objective response rate; **PD**, progressive disease; **PR**, partial response; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours version 1.1; **RP2D**, Recommended Phase 2 dose (150 mg QD); **SD**, stable disease; **TKI**, tyrosine kinase inhibitor.

[a] Includes all patients with ≥1 identified ALK resistance mutation as per local or central testing of blood (ctDNA) or tissue. Responses observed in patients with ALK I1171N/S, V1180L, L1196Q, L1198F, D1203N, or E1210K mutations, including where multiple mutations co-occur, in addition to those with G1202R.

[b] Includes patients with G1202R single and compound (≥2) mutations.

[c] Cis-allelic configuration has not been confirmed for all patients with compound (≥2) ALK resistance mutations.

[d] **ORR = 67% (20/30) for G1202R patients with prior lorlatinib, and ORR= 100% (2/2) for lorlatinib-naïve G1202R patients.**

[e] Five response-evaluable patients (4 with no known ALK mutations and 1 with single ALK mutation) not shown due to incomplete or missing post-baseline tumor assessments in the setting of PD or symptomatic deterioration.

KEY: PATIENT DETAILS

Lorlatinib Pre-treated:
- ≥ 3 prior ALK TKIs
- 2 prior, 2G + lorlatinib
- 2 prior, 1G + lorlatinib
- 1 prior (lorlatinib only)

Lorlatinib-naïve:
- ≥ 2 prior ALK TKIs
- 1 prior, alectinib

Patient treated at RP2D

- **ALK single resistance mutation**
- **ALK compound (≥2) resistance mutation**

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6

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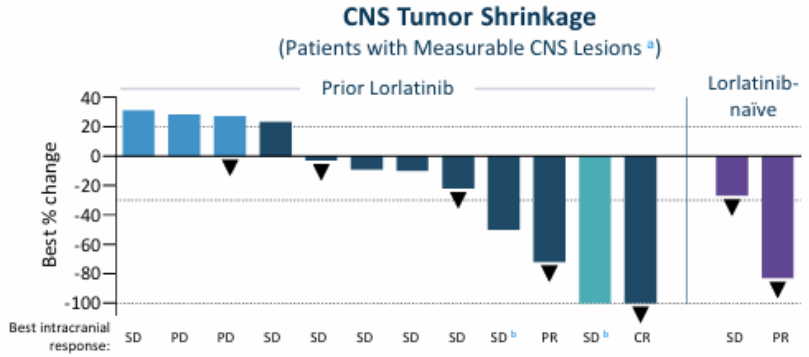
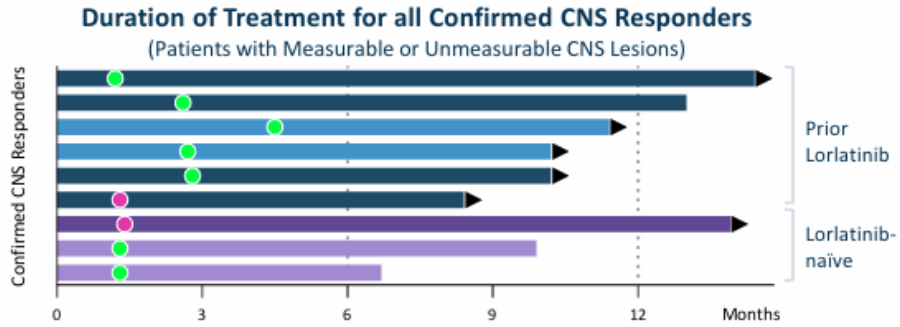
Alkove phase 1 study

CNS Activity: Durable Intracranial Responses in Lorlatinib-naïve and Lorlatinib Pre-treated Patients with ALK+ NSCLC

- **IC-ORR** (patients with measurable CNS lesions):
  - **Lorlatinib-naïve**: 50% (1/2)
  - **Prior lorlatinib:** 15% (2/13)
    - 31% (4/13) including 2 CNS uPRs not confirmed due to discontinuation of treatment in absence of CNS progression
- **No CNS progression among confirmed CNS responders, including in patients who previously received the brain-penetrant TKI lorlatinib** (measurable or unmeasurable CNS lesions)
  - Treatment duration: 6.7 - 14.4+ months





Data cut-off: 15 June 2024.

1G, 1st generation ALK TKI (i.e., crizotinib); **2G**, 2nd generation ALK TKI (i.e., ceritinib, alectinib, or brigatinib); **CNS**, central nervous system; **CR**, complete response; **IC-ORR**, intracranial ORR for patients with measurable CNS lesions; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease; **uPR**, unconfirmed partial response.

[a] Figure excludes one lorlatinib-pretreated patient with measurable CNS metastases at baseline who discontinued due to symptomatic deterioration without follow-up brain imaging.

[b] Single-timepoint PR not confirmed due to discontinuation of treatment in absence of CNS PD.

KEY: PATIENT DETAILS

Lorlatinib Pre-treated:
- ≥ 3 prior ALK TKIs
- 2 prior, 2G + lorlatinib
- 2 prior, 1G + lorlatinib

Lorlatinib-naïve:
- ≥ 2 prior ALK TKIs
- 1 prior, alectinib

Treatment Ongoing
- 1st CNS CR
- 1st CNS PR

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Alkove phase 1 study

Preliminary Safety Profile: Favorable and Consistent with ALK-Selective, TRK-Sparing Design of NVL-655

- Discontinuation due to TRAE: 2% (3/133) [a]
- Dose reduction due to TRAE: 15% (20/133) [b]
- Preliminary overall safety profile consistent with avoiding TRK-related neurotoxicities

Treatment-Related Adverse Events (TRAEs) in ≥ 10% of Patients
All Treated (N = 133)

Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)
ALT increased	21 (16%)	6 (5%)	17 (13%)	1 (1%)	45 (34%)
AST increased	21 (16%)	7 (5%)	12 (9%)	-	40 (30%)
Constipation	15 (11%)	6 (5%)	-	-	21 (16%)
Dysgeusia	15 (11%)	2 (2%)	-	-	17 (13%)
Nausea	15 (11%)	1 (1%)	-	-	16 (12%)

RP2D selected as 150 mg QD

- MTD not reached through 200 mg QD
- No clear dose-toxicity relationship through 150 mg QD dose level
- 150 mg QD maintained steady state plasma levels at or above the target efficacy thresholds

(ALK fusions + ALK single/compound mutations in periphery and in the CNS)

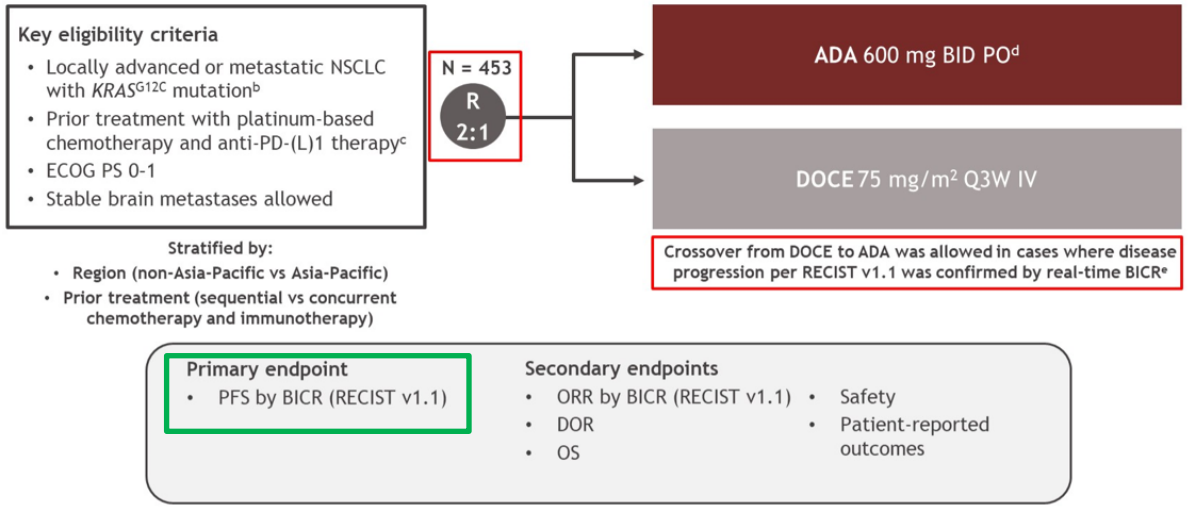
NVL-655 fármaco muy prometedor , altas tasas de respuesta incluso en pacientes pretratados con lorlarinib
Muy interesante el perfil de toxicidad
Necesidad de más estudios para confirmar dosificación y eficacia

Organizado por: GECP lung cancer research

Drilon AE, et al. ESMO 2024

LBA8509: KRYSTAL-12: Phase 3 study of adagrasib versus docetaxel in patients with previously treated advanced/metastatic non-small cell lung cancer (NSCLC) harboring a KRASG12C mutation

KRYSTAL-12[a] study design



Baseline patient characteristics

	ADA (n = 301)	DOCE (n = 152)
Median age, years (range)	64 (34-83)	65 (45-80)
Age category, %		
< 65 years	53	49
≥ 65 years	47	51
Male, %	64	72
Region, %		
Non-Asia-Pacific	74	74
Asia-Pacific	26	26
ECOG PS, %[a]		
0	32	31
1	68	68
Disease stage, %		
Locally advanced	6	5
Metastatic	94	95
Histology, %		
Adenocarcinoma	94	97
Other[b]	6	3

	ADA (n = 301)	DOCE (n = 152)
Smoking status, %[a]		
Current	19	20
Former	76	74
Never	6	6
Metastases at baseline, %[c]		
Brain	17	18
Liver	15	12
Bone	23	26
Tumor PD-L1 expression, %		
< 1%	20	22
1-49%	42	45
≥ 50%	24	19
Not evaluated	14	13
Prior chemo-immunotherapy, %		
Sequential	27	27
Concurrent	73	73

Percentages may not total 100 due to rounding. [a]Data missing for 1 patient in DOCE arm. [b]Other histologies in ADA/DOCE arms, respectively, were large-cell (n = 4/n = 1), unclassified or undifferentiated (n = 6/n = 1), squamous (n = 6/n = 0) and other (n = 2/n = 3). [c]In accordance with RECIST v1.1 per BICR.

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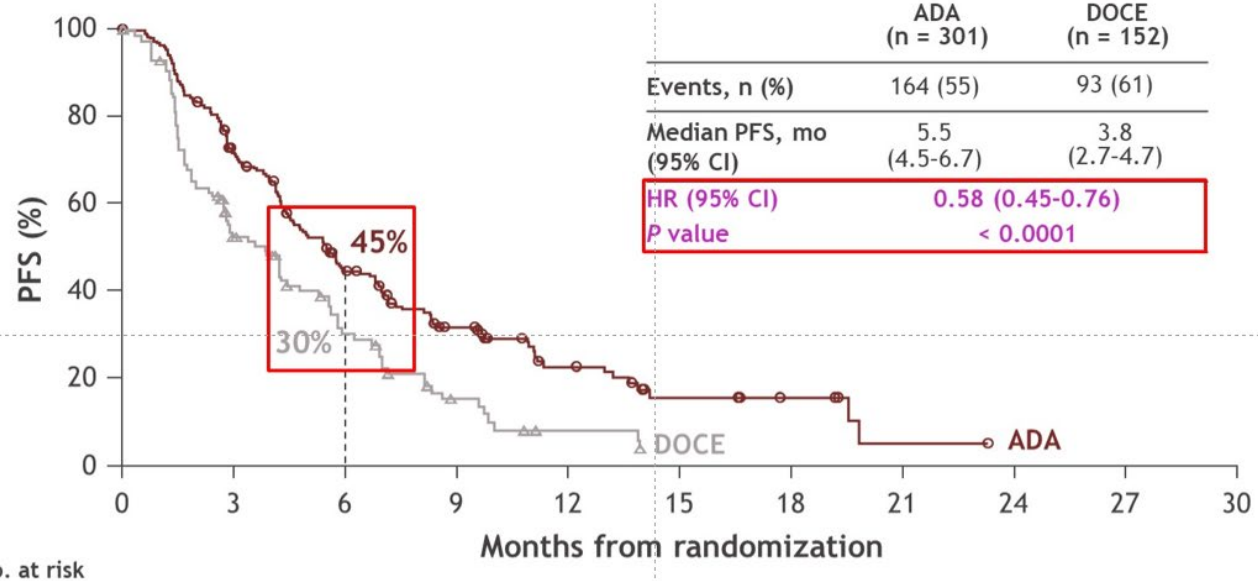
Primary endpoint: PFS[a] per BICR



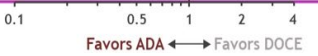
	ADA (n = 301)	DOCE (n = 152)
Events, n (%)	164 (55)	93 (61)
Median PFS, mo (95% CI)	5.5 (4.5-6.7)	3.8 (2.7-4.7)
HR (95% CI)	0.58 (0.45-0.76)	
P value	< 0.0001	

Median follow-up: 7.2 months.

[a]Time from randomization to the date of disease progression per BICR or death due to any cause, whichever occurs first. For patients who started a subsequent anticancer therapy prior to disease progression or death, PFS was censored at the date of the last tumor assessment prior to the start of the new therapy.

PFS subgroup analysis per BICR

	Median PFS, mo		Unstratified HR (95% CI)	Unstratified HR
	ADA (n = 301)	DOCE (n = 152)		
Overall (N = 453)	5.5	3.8		0.58
< 65 years (n = 234)	5.4	2.9		0.56
≥ 65 years (n = 219)	5.9	4.2		0.60
Male (n = 303)	5.4	2.9		0.55
Female (n = 150)	5.6	5.6		0.64
Non-Asia-Pacific (n = 335)	5.7	3.4		0.55
Asia-Pacific (n = 118)	5.4	3.9		0.66
ECOG PS 0 (n = 143)	11.1	5.8		0.44
ECOG PS 1 (n = 309)	4.6	2.8		0.61
Current smoker (n = 86)	4.2	4.4		0.89
Former smoker (n = 340)	5.8	3.6		0.51
Never smoker (n = 26)	5.5	6.2		0.70
Brain metastases at baseline (n = 80)[a]	4.1	4.2		0.71
No brain metastases at baseline (n = 373)[a]	5.8	3.6		0.55
Liver metastases at baseline (n = 64)[a]	4.5	1.4		0.43
No liver metastases at baseline (n = 389)[a]	5.6	4.2		0.59
Bone metastases at baseline (n = 107)[a]	4.4	2.8		0.56
No bone metastases at baseline (n = 346)[a]	5.8	4.2		0.58
PD-L1 < 1% (n = 95)	5.8	2.8		0.44
PD-L1 1-49% (n = 195)	5.9	3.6		0.56
PD-L1 ≥ 50% (n = 100)	5.0	3.9		0.62
Sequential chemo-immunotherapy (n = 121)	5.8	2.9		0.53
Concurrent chemo-immunotherapy (n = 332)	5.4	3.9		0.60



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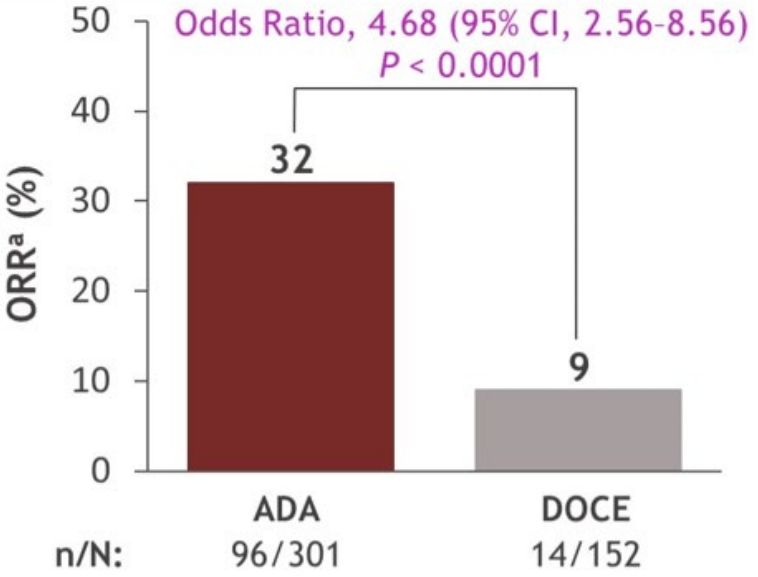
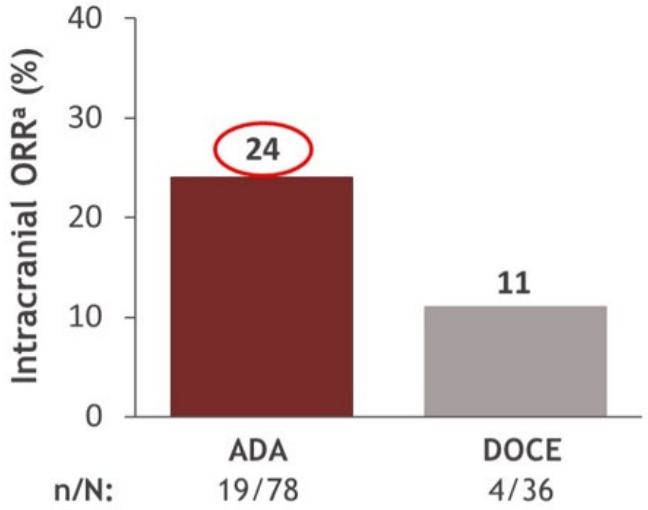
Tumor response per BICR



Tumor response	ADA (n = 301)	DOCE (n = 152)
DCR,[b] n (%)	236 (78)	89 (59)
Median DOR,[c] mo (95% CI)	8.3 (6.1-10.4)	5.4 (2.9-8.5)
Remaining in response at 6 mo, %	64	39

Intracranial response per BICR[a]

All patients with baseline CNS metastases[a]



Intracranial response[a]	ADA (n = 78)	DOCE (n = 36)
Intracranial DCR, n (%)	64 (82)	20 (56)

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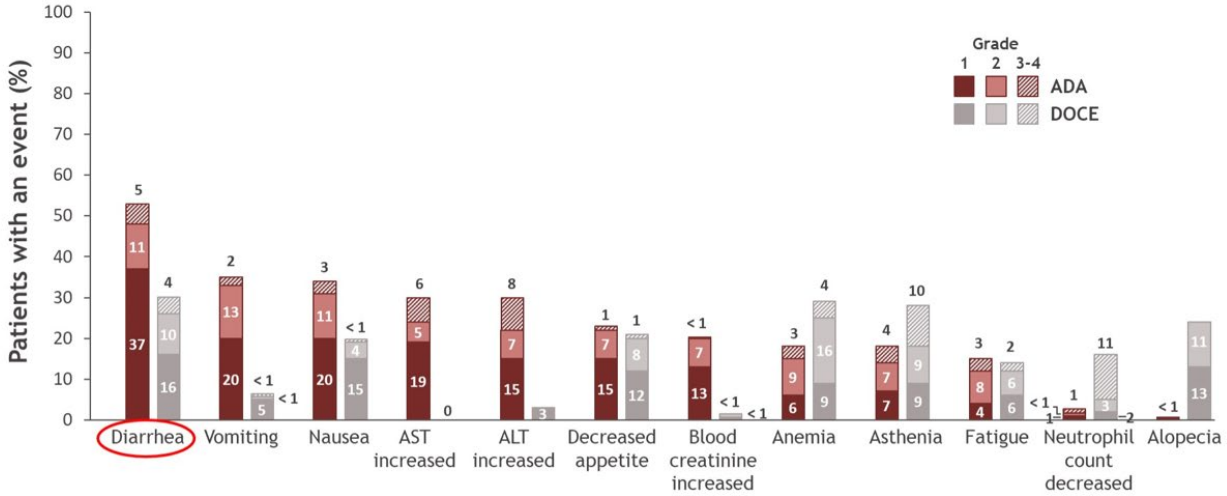
Safety summary[a]

Patients, %	ADA (n = 298)	DOCE (n = 140)
TRAEs	94	86
Grade ≥ 3 TRAEs	47	46
TRAEs leading to discontinuation[b]	8	14
TRAEs leading to dose reduction	48	24
TRAEs leading to dose interruption	59	19
Treatment-related SAEs	21	16
Treatment-related deaths[c]	1	< 1

Most frequent TRAEs (> 15% in either treatment arm[a])



Estudio positive en el que se confirma la mejora en SLP, ORR y mejor perfil de seguridad de adagrasib frente a docetaxel

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Muchas gracias

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