VII SIMPOSIO NACIONAL
de ONCOLOGÍA de PRECISIÓN
Vigo, 20 y 21 de febrero de 2025

Anticuerpos biespecíficos: Papel en el cáncer de pulmón

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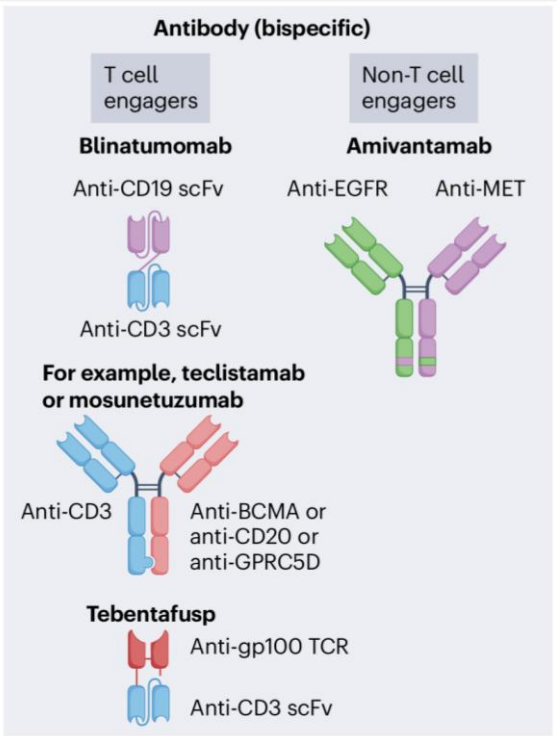
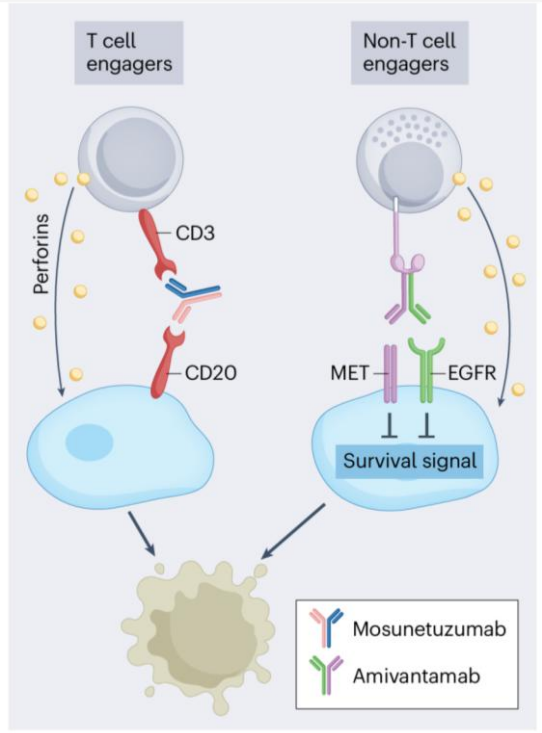
Conflictos de interés

- Advisory role: Boehringer, MSD, BMS, Takeda, Merck, GSK
- Speaker: AstraZeneca, BMS, Boehringer, Merck, Bayer, Eisai, MSD
- Travel grant: MSD, AstraZeneca, BMS, Regeneron, MSD

Anticuerpos biespecíficos: Mecanismo de acción



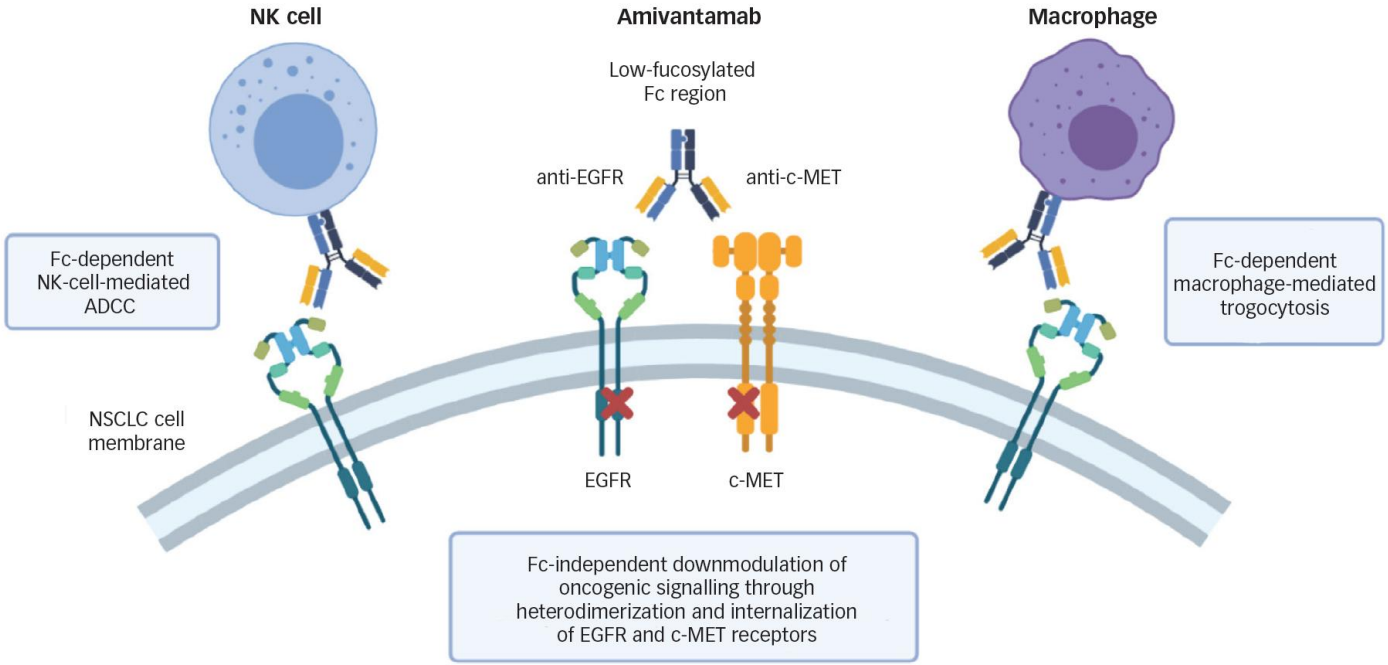


Paul S et al. Nature Reviews Cancer 2024;24:399-426

Anticuerpos biespecíficos en cáncer de pulmón

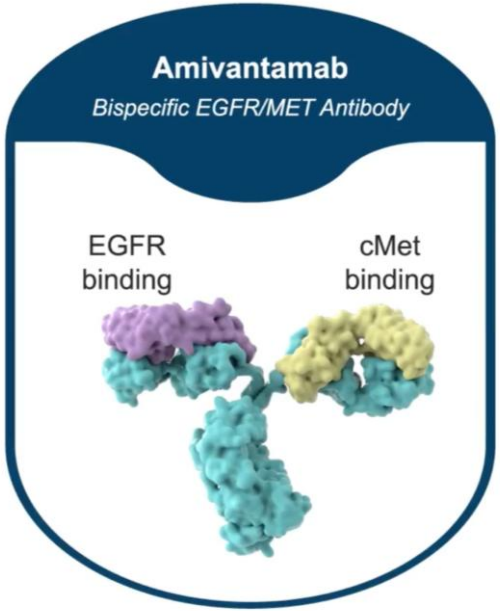
- Amivantamab: EGFR-MET
- Tarlatamab: DLL3-CD3
- Ivonescimab: PD1-VEGF
- Zenocutuzumab: HER2-HER3

Amivantamab mechanisms of action



Amivantamab targets EGFR-*mutated NSCLC tumour cells through Fc-dependent immune cell-mediated ADCC and trogocytosis, as well as Fc-independent dual EGFR/c-MET signalling downmodulation.*
Figure created by author Matthew Z Guo using BioRender.com subscription.
ADCC = antibody-dependent cellular cytotoxicity; EGFR = epidermal growth factor receptor; NK = natural killer; NSCLC = non-small cell lung cancer.

Amivantamab y *EGFR*



- *EGFR* exon 20 insertions
- *EGFR* mutaciones comunes (exon 19 del and L858R)

CHRYSALIS Phase I: Efficacy in *EGFR* exon 20 insertions

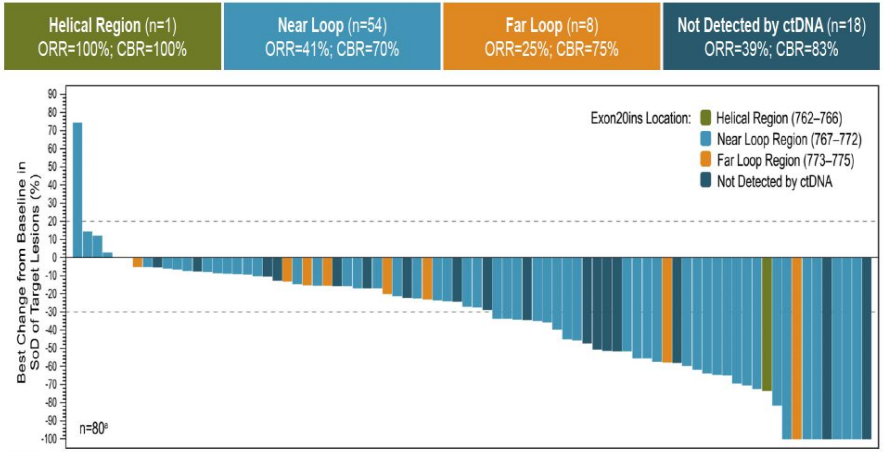
Amivantamab: Efficacy by BICR

BICR-assessed Response	Efficacy Population (n=81)
Overall response rate	**40%** (95% CI, 29–51)
Median duration of response	**11.1 months** (95% CI, 6.9–NR)
Best response, n (%)	
Complete response	3 (4)
Partial response	29 (36)
Stable disease	39 (48)
Progressive disease	8 (10)
Not evaluable	1 (1)
Clinical benefit rate[a]	74% (95% CI, 63–83)

Median follow-up: 9.7 months (range, 1.1–29.3)

Antitumor activity across insertion regions of EGFR Exon 20

Best ORR by Insertion Region of Exon 20 (detected by ctDNA)

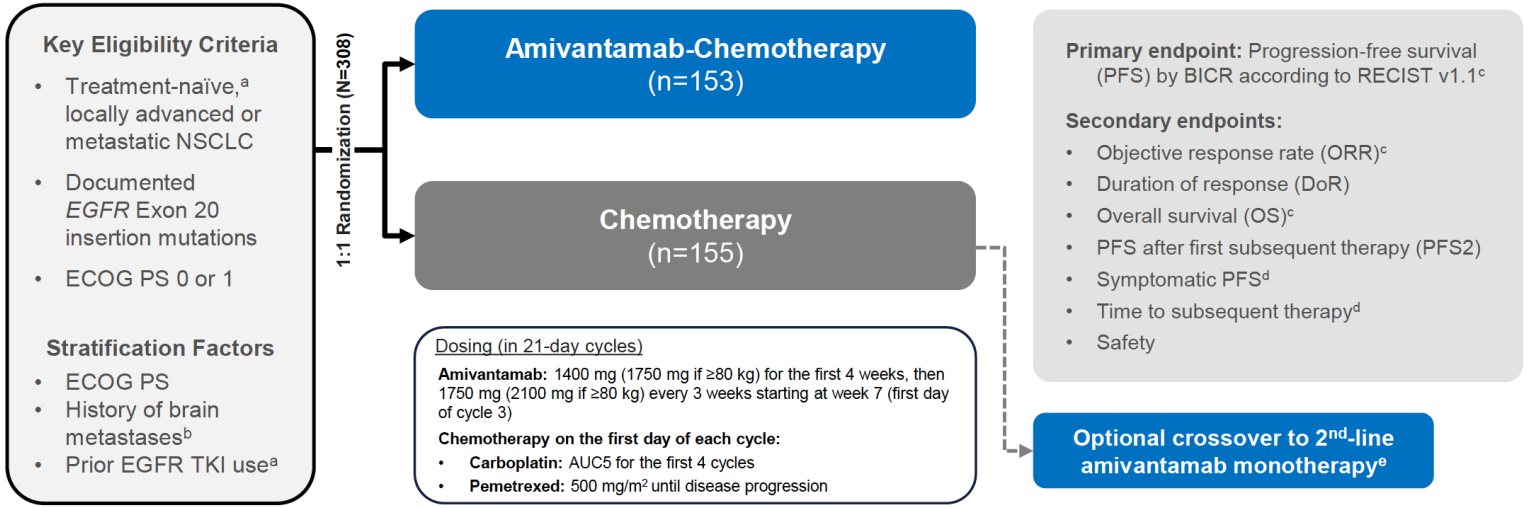


25 distinct Exon20ins variants identified by NGS of ctDNA (Guardant360®) from 63 evaluable patient samples

Park K et al. J Clin Oncol 2021; Sabari JK et al. WCLC 2020

Amivantamab plus Chemotherapy vs Chemotherapy as first-line treatment in *EGFR* Exon 20 Insertion–mutated advanced NSCLC

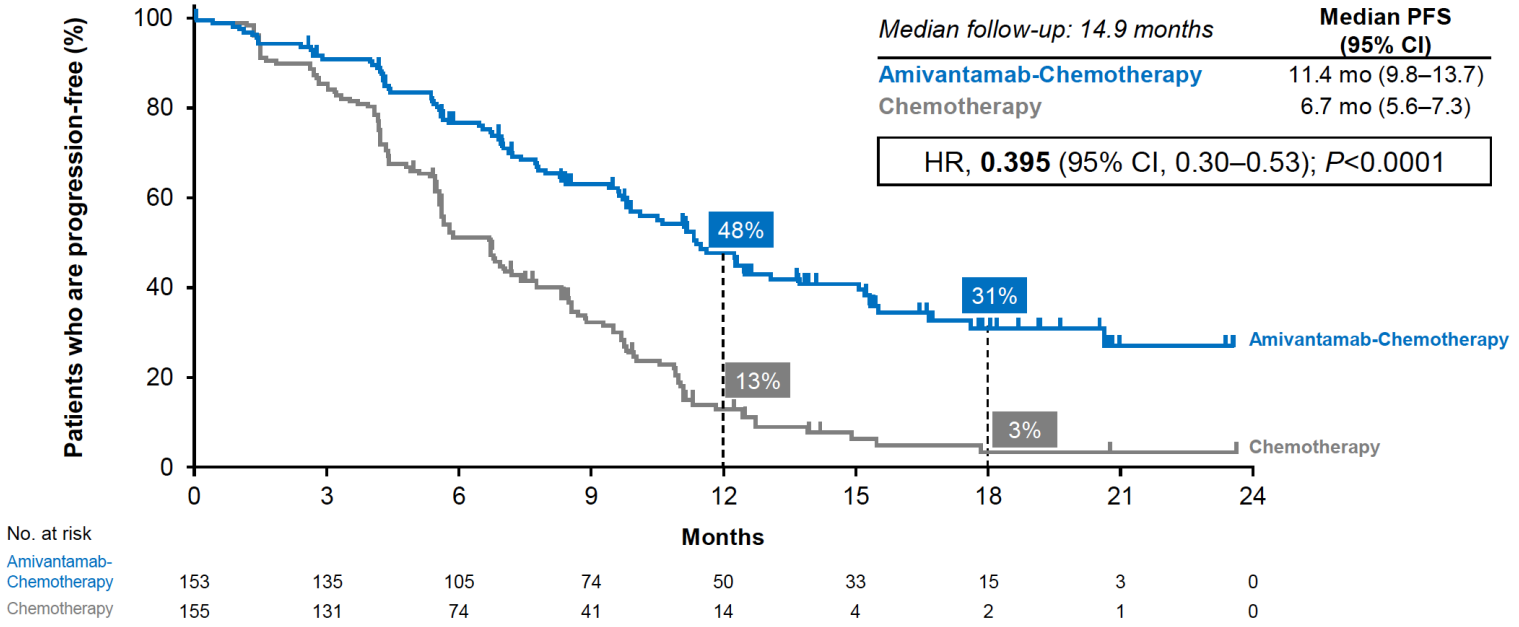
PAPILLON: Phase 3 Study Design



Girard N et al. ESMO 2023: Zhou C et al. N Engl J Med 2023; 389:2039-2051

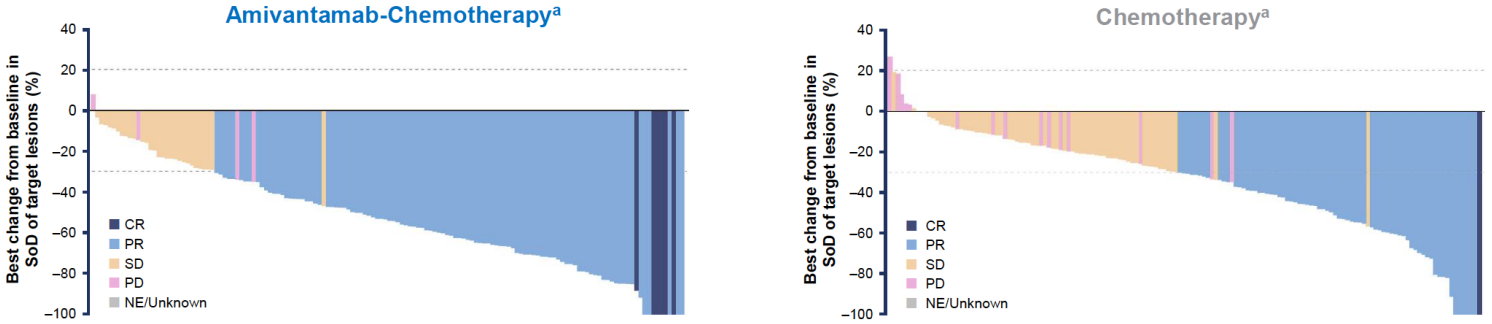
Primary endpoint: Progression-free survival by BICR

Amivantamab-chemotherapy reduced risk of progression or death by 60%



Girard N et al. ESMO 2023: Zhou C et al. N Engl J Med 2023; 389:2039-2051

Best response and ORR by BICR



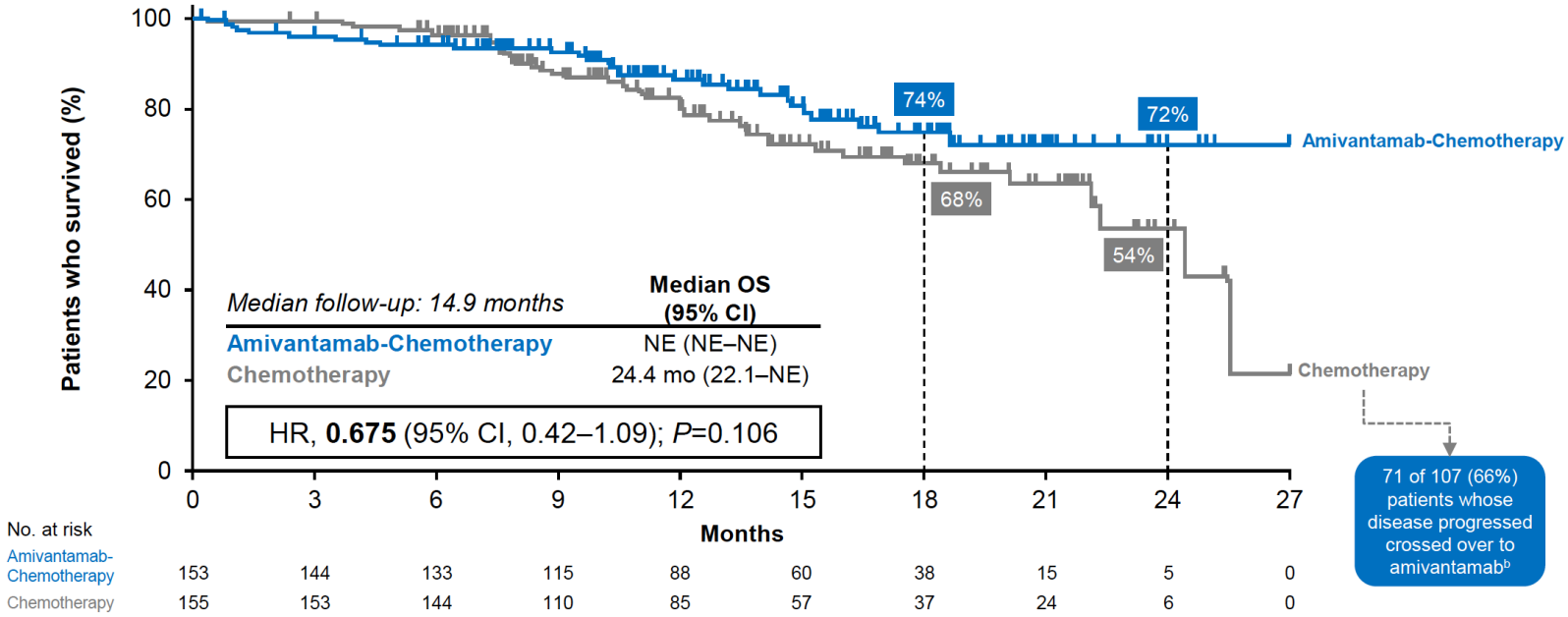
BICR-assessed response[b]	Amivantamab-Chemotherapy (n=153)	Chemotherapy (n=155)
Mean percent change of SoD	-53%[c]	-34%
ORR	73% (95% CI, 65–80)	47% (95% CI, 39–56)
Odds ratio	3.0 (95% CI, 1.8–4.8); *P*<0.0001	
Best response, n (%)		
Complete response	6 (4)	1 (1)
Partial response	105 (69)	71 (47)
Stable disease	29 (19)	62 (41)
Progressive disease	4 (3)	16 (11)
NE/Unknown	8 (5)	2 (1)
Median time to response	6.7 wk (range, 5.1–72.5)	11.4 wk (range, 5.1–60.2)

Consistent results with investigator assessment: ORR of 66% vs 43% (OR, 2.6; *P*<0.0001)

Girard N et al. ESMO 2023: Zhou C et al. N Engl J Med 2023; 389:2039-2051

Interim overall survival

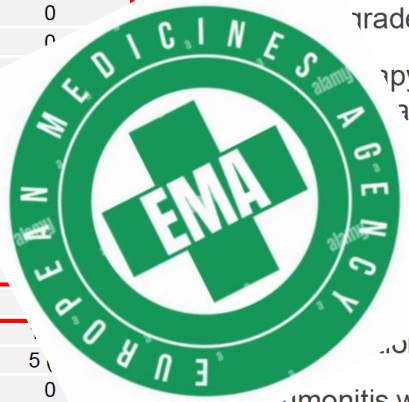
Amivantamab-chemotherapy shows trend in reducing risk of death by over 30%



Girard N et al. ESMO 2023: Zhou C et al. N Engl J Med 2023; 389:2039-2051

Safety profile

Most common AEs of any cause by preferred term (≥20%), n (%)	Amivantamab-Chemotherapy (n=151)		Chemotherapy (n=155)	
	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition				
Paronychia		10 (7)	0	0
Rash		17 (11)	12 (8)	0
Dermatitis acneiform		6 (4)	5 (3)	0
Stomatitis		2 (1)	9 (6)	
Diarrhea		5 (3)	20 (13)	
Associated w				
Hypoalbuminen		(4)	15 (10)	
Peripheral edema		(1)	16 (10)	
Other				
Neutropenia			70 (45)	
Anemia			85 (55)	
Infusion-related reactio			2 (1)	
Constipation		0	47 (30)	
Leukopenia		17 (11)	50 (32)	5
Nausea		1 (1)	65 (42)	0
Thrombocytopenia	(36)	15 (10)	46 (30)	16 (10,
Decreased appetite	54 (36)	4 (3)	43 (28)	2 (1)
Alanine aminotransferase increas d	50 (33)	6 (4)	56 (36)	2 (1)
Aspartate aminotransferase increased	47 (31)	1 (1)	51 (33)	1 (1)
COVID-19	36 (24)	3 (2)	21 (14)	1 (1)
Hypokalemia	32 (21)	13 (9)	13 (8)	2 (1)
Vomiting	32 (21)	5 (3)	29 (19)	1 (1)



- EGFR- and MET-related AEs
  creased with
  amab-chemotherapy,
  rade 1-2
- py-associated
  nd GI toxicities
  ble except for
- ransient;
  ere not
  ates of
  ons
- umonitis was reported in 4 (3%) patients in the amivantamab-chemotherapy arm

Girard N et al. ESMO 2023: Zhou C et al. N Engl J Med 2023; 389:2039-2051

Amivantamab en mutaciones comunes de *EGFR* (exon 19 del and L858R)

- **Primera línea: MARIPOSA**
- **Segunda línea: MARIPOSA-2**

MARIPOSA: Phase 3 study design

Key Eligibility Criteria

- Locally advanced or metastatic NSCLC
- Treatment-naïve for advanced disease
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0 or 1

Stratification Factors

- *EGFR* mutation type (Ex19del or L858R)
- Asian race (yes or no)
- History of brain metastases[a] (yes or no)

2:2:1 Randomization (N=1074)

Serial brain MRIs were required for all patients[a]

Amivantamab + Lazertinib
(n=429; open-label)

Osimertinib
(n=429; blinded)

Lazertinib
(n=216; blinded)

Dosing (in 28-day cycles)
Amivantamab: 1050 mg (1400 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks
Lazertinib: 240 mg daily
Osimertinib: 80 mg daily

Primary endpoint of progression-free survival (PFS)[b] by BICR per RECIST v1.1:

- **Amivantamab + lazertinib** vs **osimertinib**

Secondary endpoints of amivantamab + lazertinib vs osimertinib:

- Overall survival (OS)[b]
- Objective response rate (ORR)
- Duration of response (DoR)
- PFS after first subsequent therapy (PFS2)
- Symptomatic PFS[c]
- Intracranial PFS[c]
- Safety

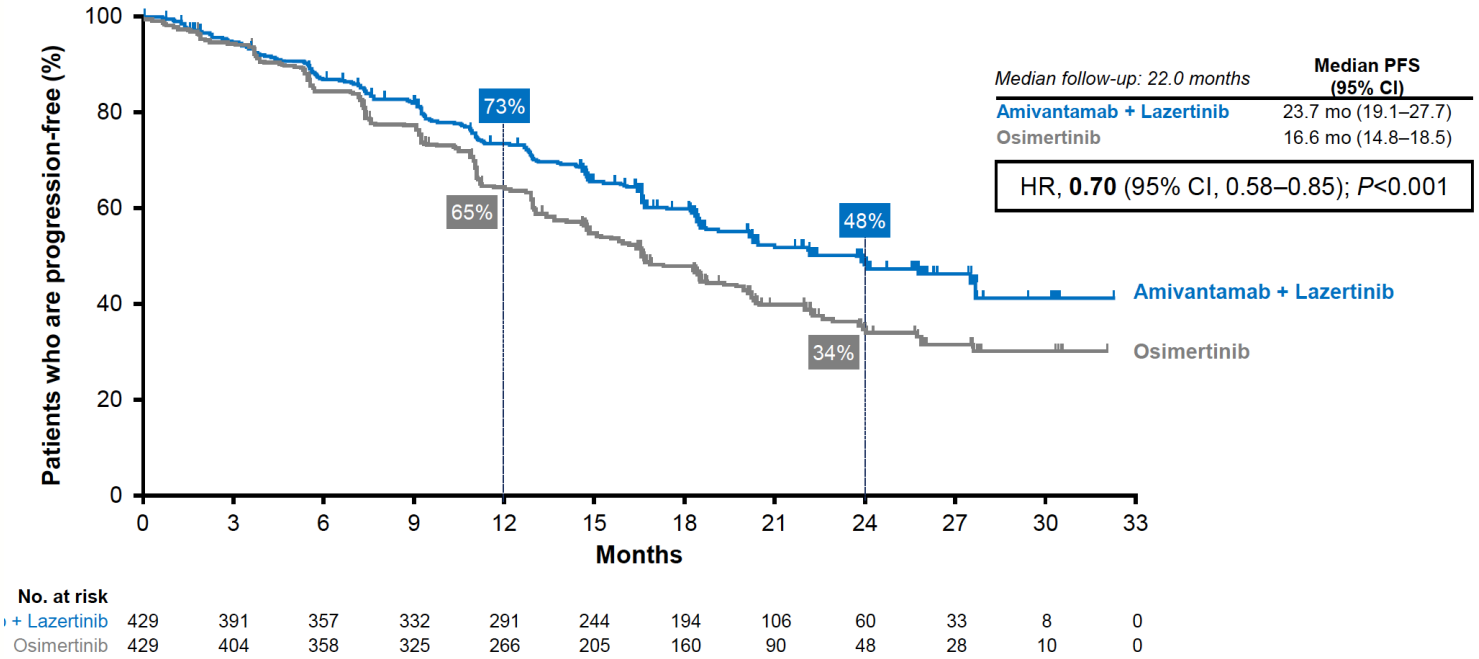
Lazertinib monotherapy arm was included to assess the contribution of components

MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080) enrollment period: November 2020 to May 2022; data cut-off: 11-Aug-2023.

Cho BC et al. ESMO 2023; Cho BC et al. N Engl J Med 2024;391:1486-1498

Primary endpoint: Progression-free survival by BICR

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



Cho BC et al. ESMO 2023; Cho BC et al. N Engl J Med 2024;391:1486-1498

Interim overall survival

Johnson&Johnson

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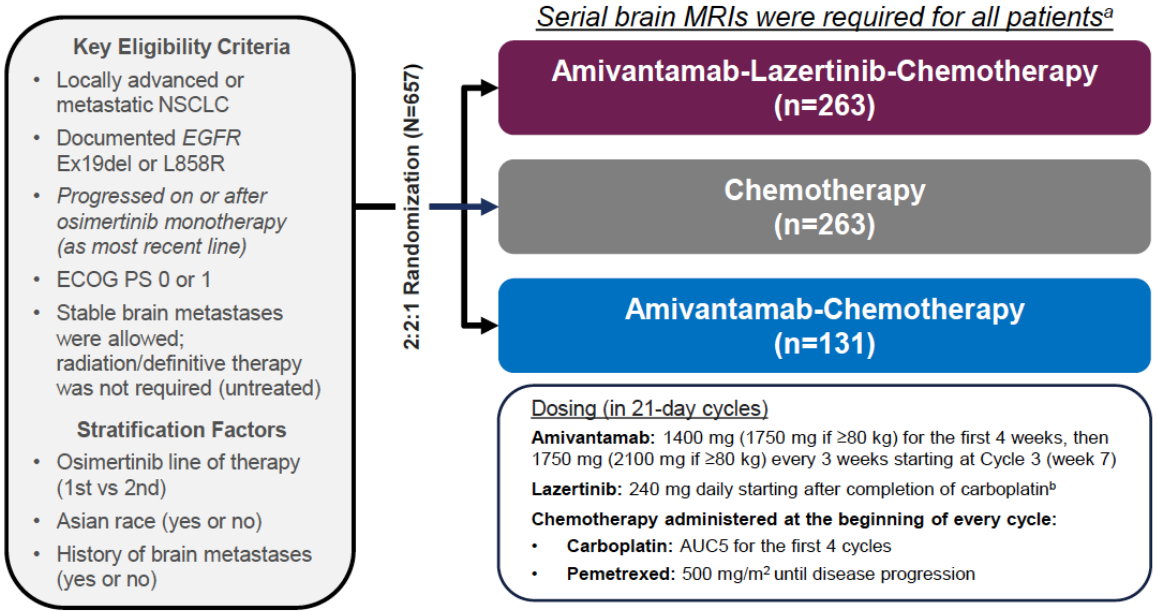
RARITAN, N.J., January 7, 2025 – Johnson & Johnson (NYSE:JNJ) today announced positive topline results for the gold standard endpoint in cancer treatment of overall survival (OS) from the Phase 3 MARIPOSA study, evaluating RYBREVANT® (amivantamab-vmjw) plus LAZCLUZE™ (lazertinib) as a first-line therapy for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions (ex19del) or L858R substitution mutations. The chemotherapy-free combination regimen met the final pre-specified secondary endpoint of OS and demonstrated clinically meaningful and statistically significant improvement in OS versus the current standard of care osimertinib. Improvement in median OS is expected to exceed one year.

Cho BC et al. ESMO 2023; Cho BC et al. N Engl J Med 2024;391:1486-1498

MARIPOSA-2: Phase 3 study design



Dual primary endpoint of PFS[c] by BICR per RECIST v1.1:

- **Amivantamab-Lazertinib-Chemotherapy** vs **Chemotherapy**
- **Amivantamab-Chemotherapy** vs **Chemotherapy**

Secondary endpoints:

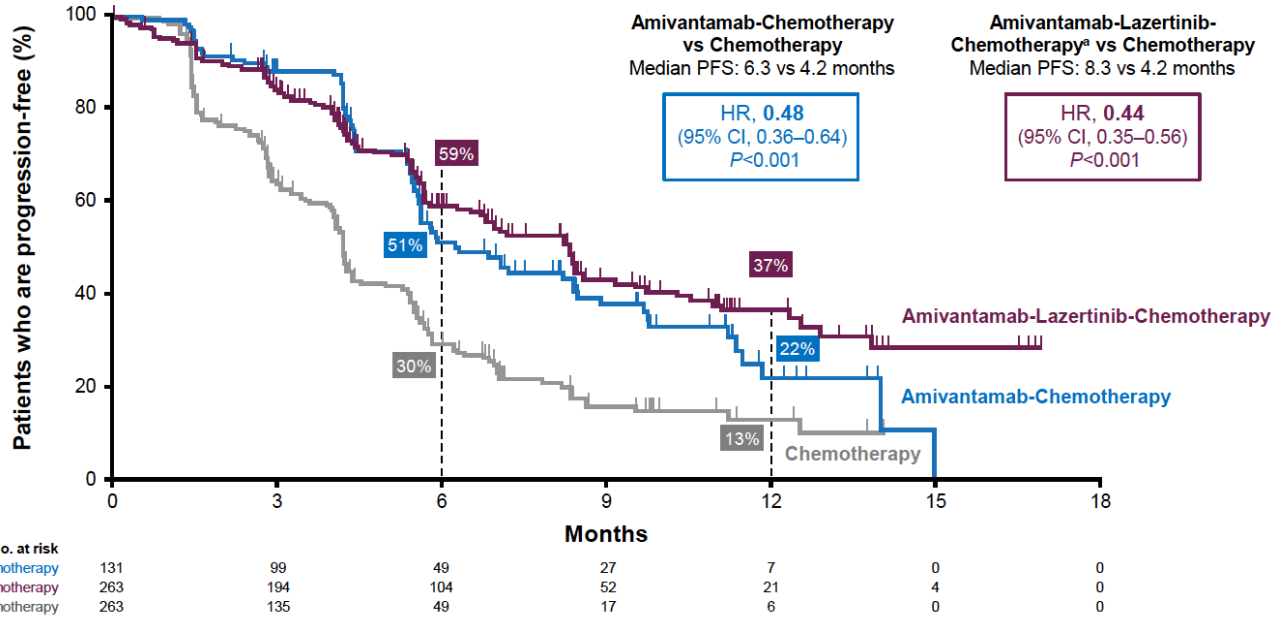
- Objective response rate (ORR)[c]
- Duration of response (DoR)
- Overall survival (OS)[c]
- Intracranial PFS
- Time to subsequent therapy[d]
- PFS after first subsequent therapy (PFS2)[d]
- Symptomatic PFS[d]
- Safety

MARIPOSA-2 (ClinicalTrials.gov Identifier: NCT04988295) enrollment period: December 2021 to April 2023; data cut-off: 10-Jul-2023

Passaro A et al. ESMO 2023; Passaro A et al. Ann Oncol 2024;35:77-90

Primary endpoint: Progression-free survival by BICR

At a median follow-up of 8.7 months, amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy reduced the risk of progression or death by 52% and 56%, respectively

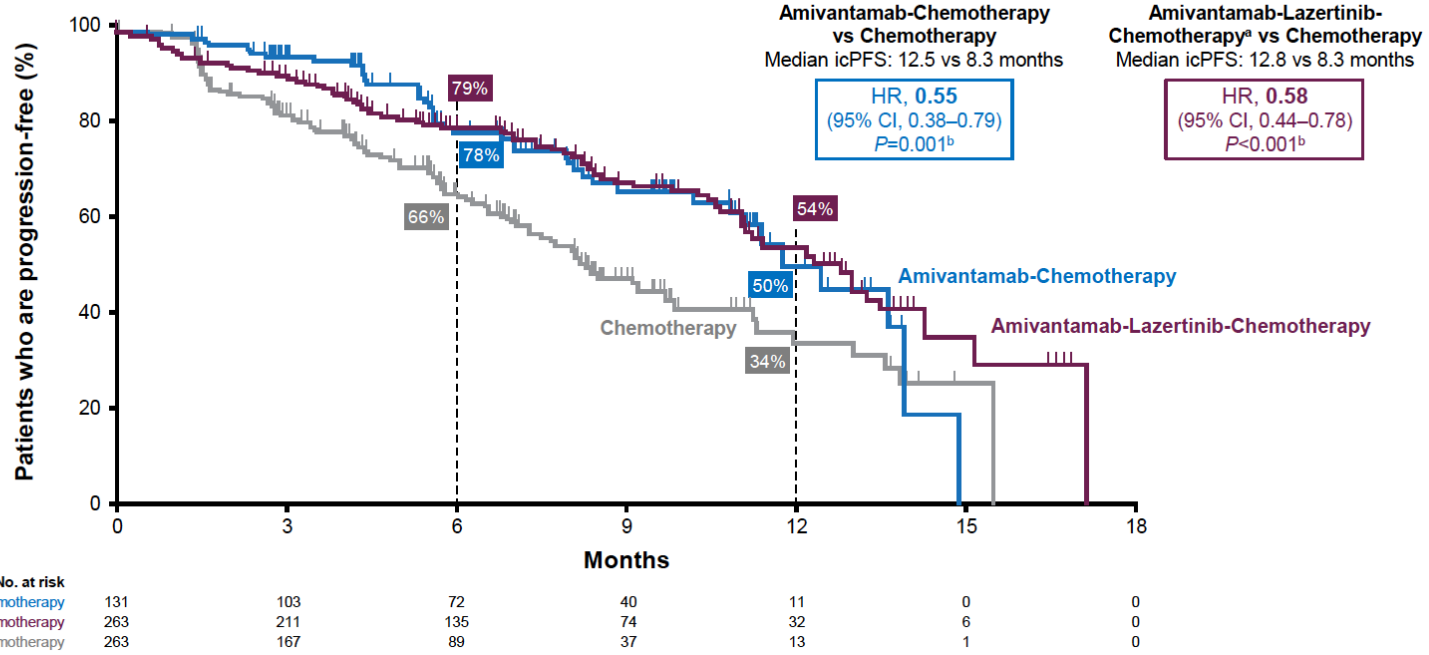


Consistent PFS benefit by investigator: HR, 0.41 (8.2 vs 4.2 mo; *P*<0.001[b]) & HR, 0.38 (8.3 vs 4.2 mo; *P*<0.001[b])

Passaro A et al. ESMO 2023; Passaro A et al. Ann Oncol 2024;35:77-90

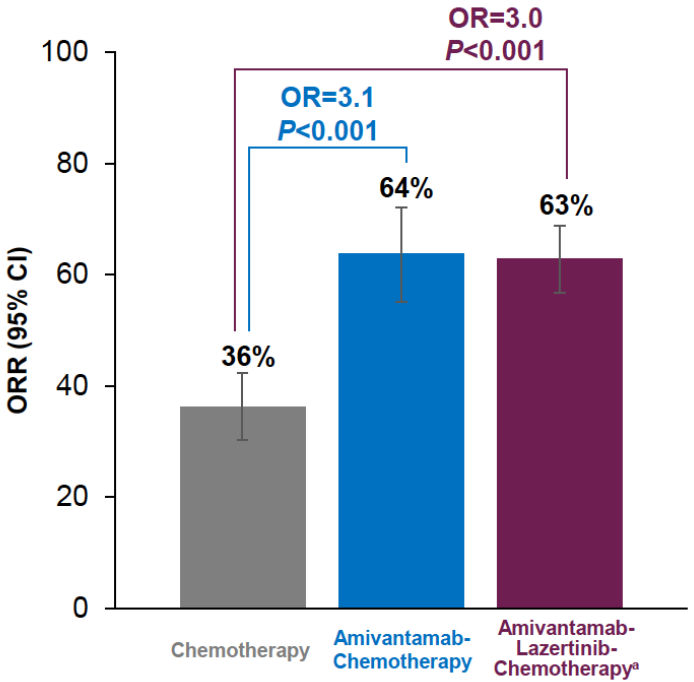
Intracranial progression-free survival by BICR

Amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy reduced the risk of intracranial progression or death by 45% and 42%, respectively



Passaro A et al. ESMO 2023; Passaro A et al. Ann Oncol 2024;35:77-90

ORR and DoR by BICR

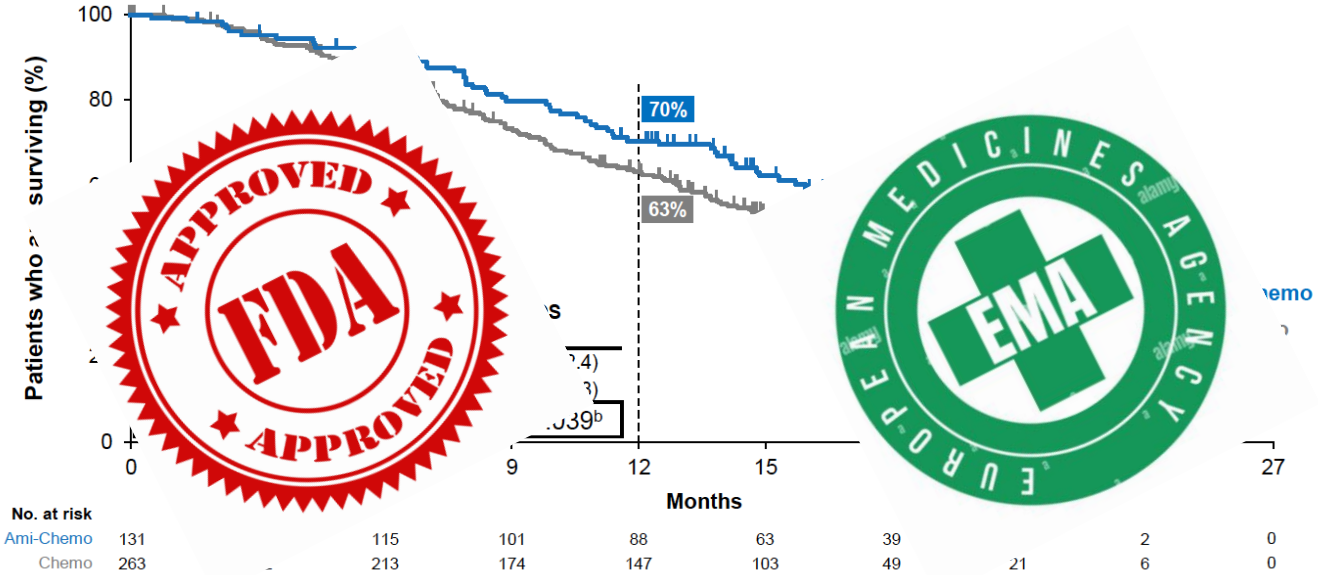


BICR-assessed Response, n (%)[b]	Chemotherapy (n=263)	Amivantamab-Chemotherapy (n=131)	Amivantamab-Lazertinib-Chemotherapy (n=263)
Best Response			
CR	1 (0.4)	2 (2)	6 (2)
PR	93 (36)	81 (62)	157 (61)
SD	82 (32)	30 (23)	61 (24)
PD	52 (20)	10 (8)	14 (5)
NE/UNK	32 (12)	7 (5)	21 (8)
Median DoR[c]	5.6 mo (95% CI, 4.2–9.6)	6.9 mo (95% CI, 5.5–NE)	9.4 mo (95% CI, 6.9–NE)

Passaro A et al. ESMO 2023; Passaro A et al. Ann Oncol 2024;35:77-90

Updated overall survival

Amivantamab-chemotherapy continues to demonstrate a clear and improving OS trend vs chemotherapy[a]



18-month landmark for OS was 50% for amivantamab-chemotherapy vs 40% for chemotherapy

[a]OS benefit of amivantamab-chemotherapy vs chemotherapy was generally consistent among pre-defined subgroups. [b]P-value is from a log-rank test stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes or no), and Asian race (yes vs no). OS was evaluated at a 2-sided alpha of 0.0142.

Popat S et al. ESMO 2024

Subcutaneous vs intravenous Amivantamab: PALOMA-3

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

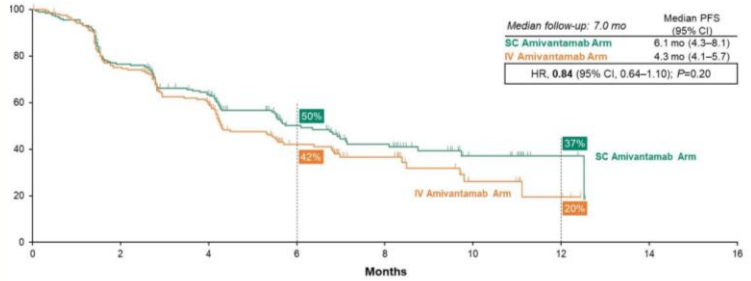
Co-primary endpoints[c]:
- C_{trough} (noninferiority)[d]
- C2 AUC (noninferiority)[e]

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

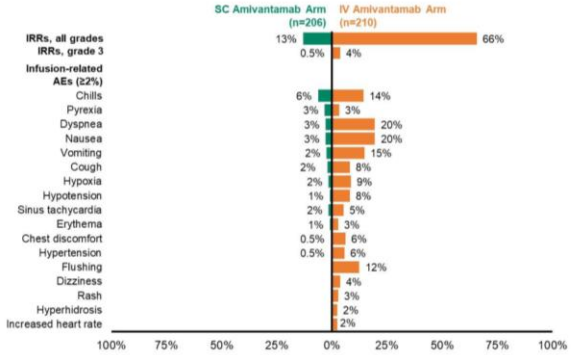
Exploratory endpoints:
- OS

Progression-free Survival

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



Incidence of IRR-related Symptoms

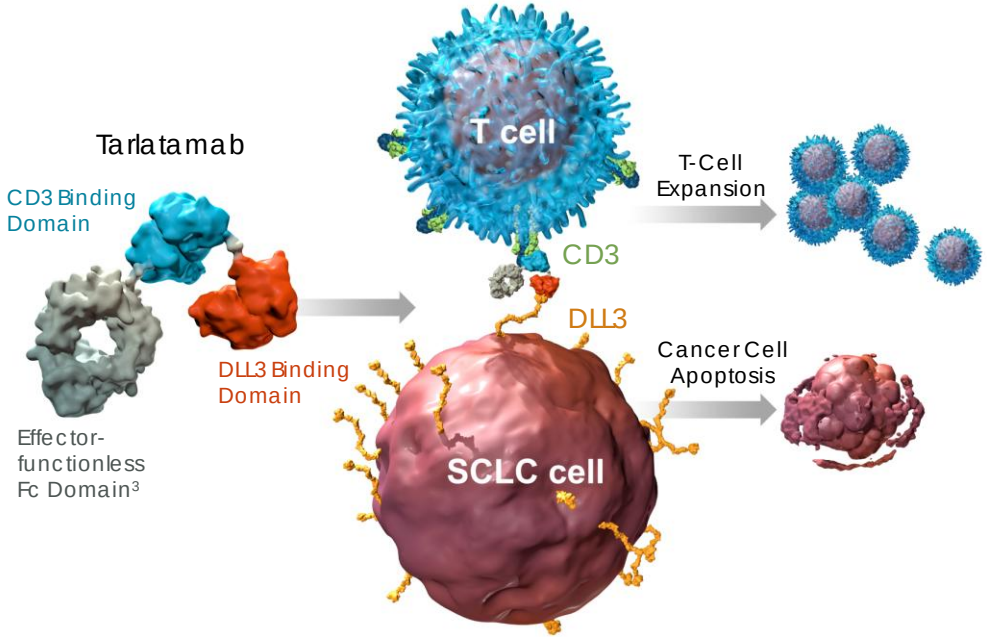


- IRRs were observed in 13% of patients in the SC arm vs 66% in the IV arm, representing a 5-fold reduction
  - There were no grade 4 or 5 IRRs
  - Most IRRs occurred during Cycle 1
- IRRs leading to hospitalization were not observed in the SC arm vs 2 events in the IV arm
- No IRR-related discontinuations occurred in the SC arm vs 4 events in the IV arm

Leighl N et al. J Clin Oncol 2024;42:3593-3605; Leghl et al. ASCO 2024

Tarlatamab is a BiTE® (Bispecific T-Cell Engager) immunotherapy that directs cytotoxic T Cells to DLL3-expressing cancer cells

- Tarlatamab binds both DLL3 on cancer cells and CD3 on T cells, leading to T-cell mediated cancer cell lysis[1]
- Binding creates a cytolytic synapse between T cells and cancer cells, and can activate T cells without relying on MHC I[2,3]



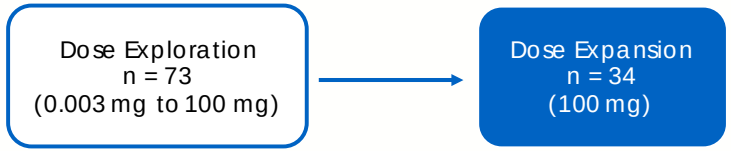
Tarlatamab Mechanism of Action[1]

1. Owen DH, et al. J Hematol Oncol. 2019;12:61. 2. Nagorsen D, et al. Exp. Cell Res. 2011; 317:1255-1260.
3. Giffin MJ, et al. Clin Cancer Res. 2021;27:1526-1537

DeLLphi-300: Phase 1 dose exploration/expansion study of Tarlatamab in relapsed/refractory SCLC

Inclusion Criteria

- Histologically or cytologically confirmed SCLC
- Progressed or recurred following ≥ 1 platinum-based chemotherapy (including PD-L1 inhibitor if SOC)
- ≥ 2 measurable lesions
- ECOG performance status: 0–2
- If present, clinically/radiologically stable brain metastases following treatment

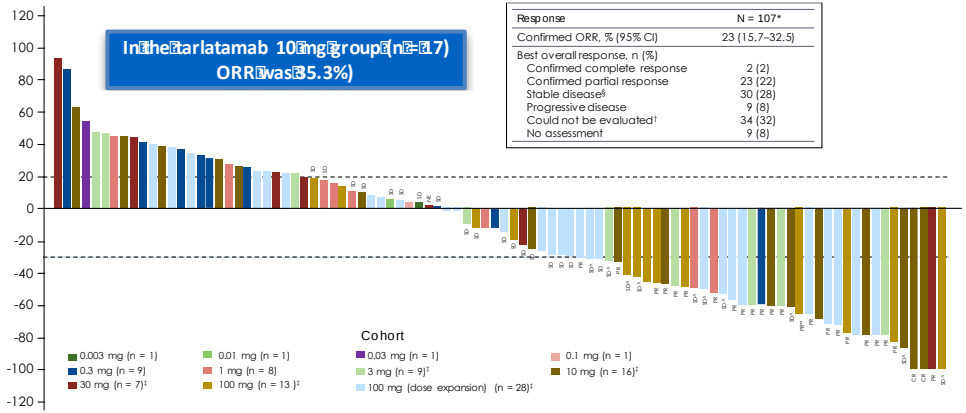


- Tarlatamab administered by IV infusion Q2W
- Step-dosing starting with the 3 mg cohort (1 mg run-in dose followed by target dose on day 8, day 15, and Q2W thereafter)

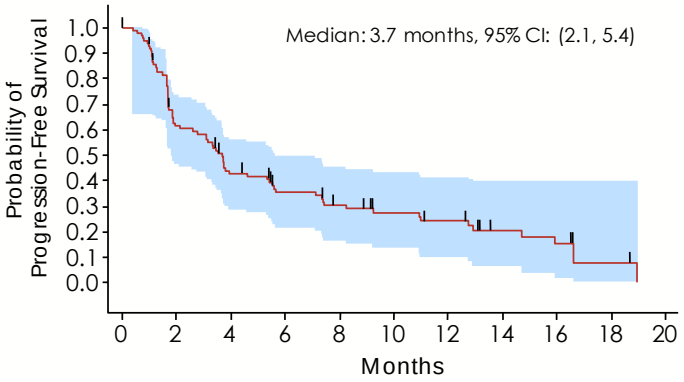
Primary Endpoint	▪ Safety, including DLTs, TEAEs, TRAEs
Secondary Endpoints	▪ ORR*, DOR, TTR, PFS, OS, and PK

Paz-Ares L et al. J Clin Oncol 2023;41:2893-2903

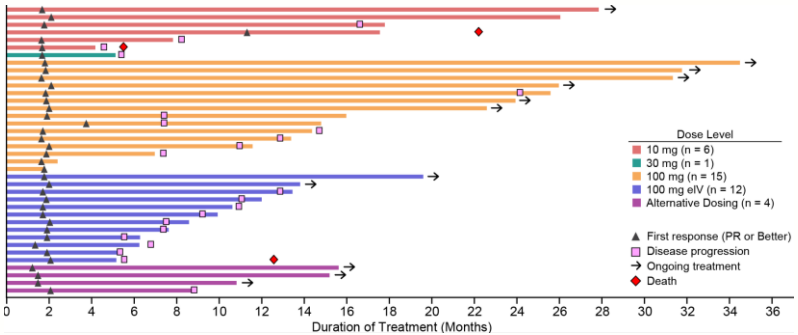
DeLLphi-300: Updated results and long-term outcomes



Progression-Free Survival

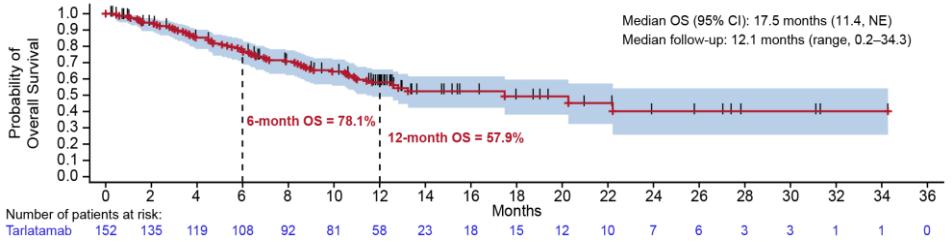


Time to response and duration of response among 38 responders (4 CR, 34 PR)



Pts with tarlatamab 10 mg (n = 17) — **Median DOR: 14.9 months**

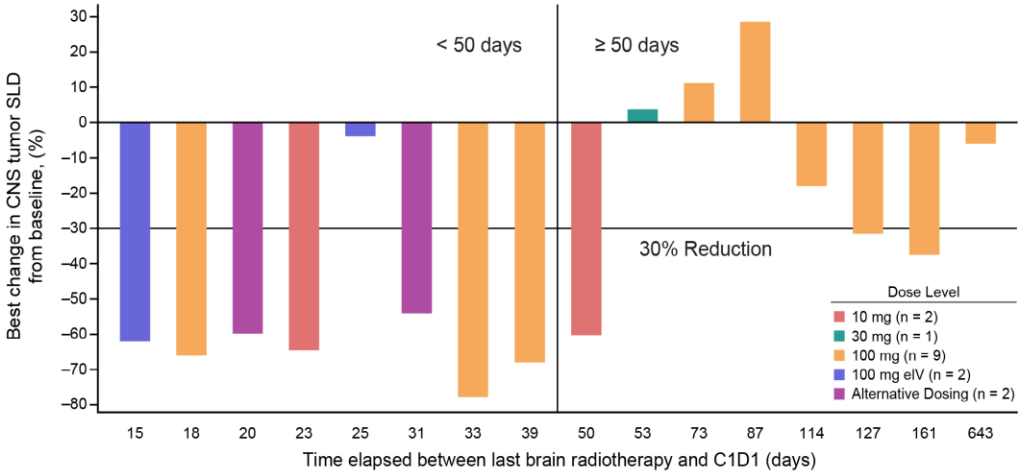
Overall Survival



Among 17 patients receiving the tarlatamab 10 mg dose, median OS was 20.3 months (95% CI, 5.1–NE)

Paz-Ares L et al. J Clin Oncol 2023;41:2893-2903; Dowlati A et al. J Clin Oncol 2024;42:3392-3399

DeLLphi-300: Intracranial activity



- mRANO BM* analyses (n = 16†)
  - CNS tumor shrinkage of ≥ 30% in 10 of 16 patients (62.5%) with baseline lesion of ≥ 10 mm
  - Intracranial disease control: 87.5% of patients
  - Median duration of intracranial disease control: 7.4 months (95% CI, 2.8 to NE)
- CNS disease progression occurred in 9 of 112 patients (8.0%)

Dowlati A et al. J Clin Oncol 2024;42:3392-3399

DeLLphi-300: AEs and cytokine release syndrome (CRS)

Treatment Related AEs*

Treatment-Related AEs†	Patients (N = 107) All Grades, n (%)	Grade ≥ 3, n (%)‡
Any treatment-related AE	97 (91)	33 (31)
Treatment-related AEs in > 15% of patients		
CRS	56 (52)	1 (1)
Pyrexia	40 (37)	2 (2)
Dysgeusia	24 (22)	0
Fatigue	23 (22)	3 (3)
Nausea	21 (20)	0

- 3.7% (n=4/107) of patients discontinued due to treatment-related AEs, including:
  - Encephalopathy (n=1)
  - ICANS (n=1)
  - Pneumonitis (n=2)
- One grade 5 due to disease progression and pneumonitis
  - 70-year-old man with prior carboplatin/etoposide chemotherapy§
  - Onset: C1D18 after the second 0.3 mg dose of tarlatamab
  - Clinically significant disease progression at the time of pneumonitis

Cytokine Release Syndrome

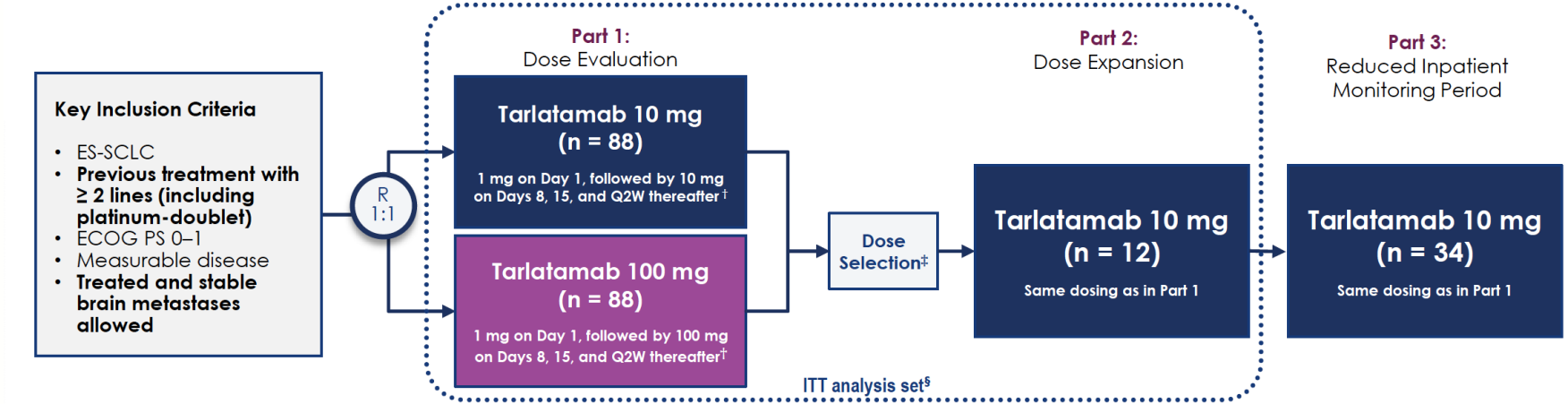
Patients (N=107)	All grades	Grade 1–2	Grade 3	Grade 4	Grade 5
CRS*, n (%)	56 (52)	55 (51)	1 (1)	0	0

- Median duration of CRS was 3 days (IQR 2–4 days)
- **Most CRS events were grade 1–2, resolved, and occurred in the first cycle**
- CRS events were generally manageable with supportive care, such as antipyretics, IV fluids, and corticosteroids
  - Tocilizumab was administered to eight patients

CRS, expected based on tarlatamab's MOA, were primarily grade 1-2, largely confined to the first cycle, and manageable and transient

Paz-Ares L et al. J Clin Oncol 2023;41:2893-2903

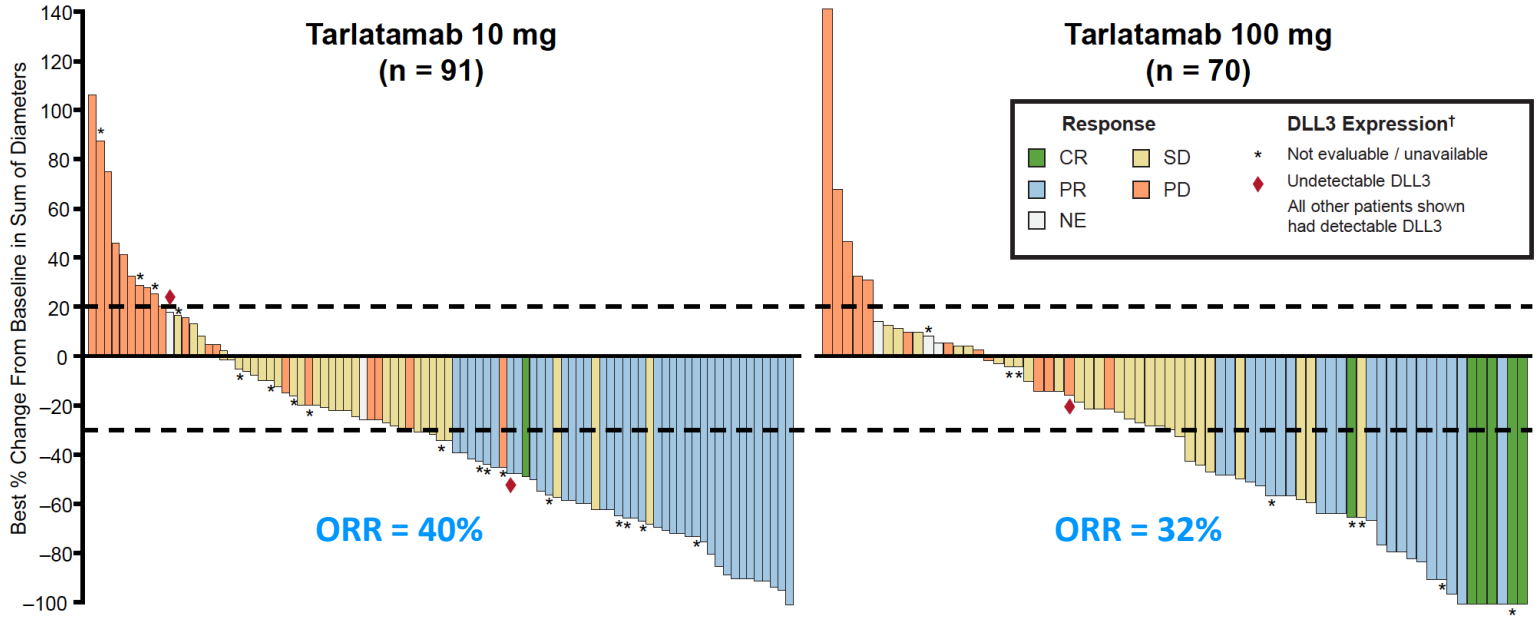
DeLLphi-301: Phase 2 study of Tarlatamab for patients with previously treated SCLC



Primary Endpoint: ORR per RECIST v1.1 by BICR
Secondary Endpoints Included: DOR, DCR, PFS per RECIST v1.1 by BICR, OS, TEAEs, tarlatamab serum concentrations

Ahn MJ, et al. N Engl J Med 2023;389:2063-2075

DeLLphi-301: overall response rate

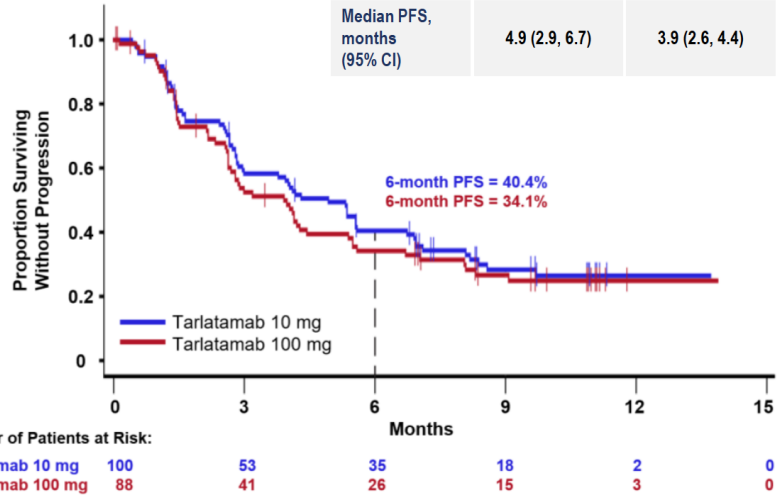


Responses were observed regardless of DLL3 expression, as well as in patients without evaluable tumor tissue

Ahn MJ, et al. N Engl J Med 2023;389:2063-2075

DeLLphi-301: PFS and OS

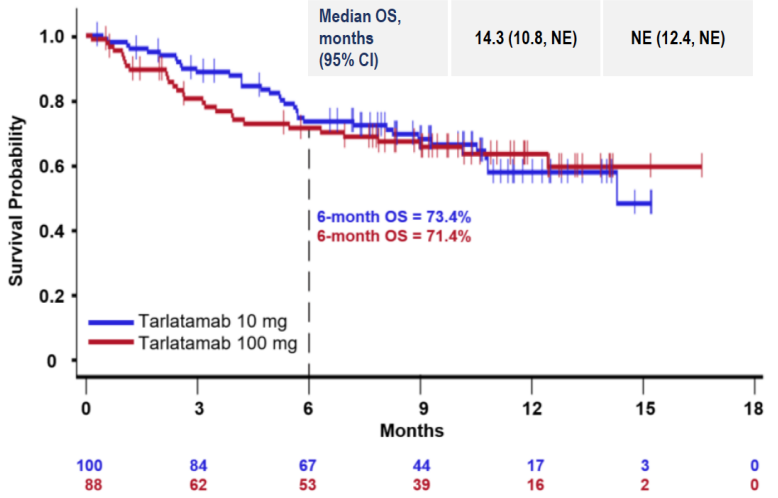
Outcome	Tarlatamab 10 mg (n = 100)	Tarlatamab 100 mg (n = 88)
Median PFS, months (95% CI)	4.9 (2.9, 6.7)	3.9 (2.6, 4.4)



Number of Patients at Risk:

Tarlatamab 10 mg	100	53	35	18	2	0
Tarlatamab 100 mg	88	41	26	15	3	0

Outcome	Tarlatamab 10 mg (n = 100)	Tarlatamab 100 mg (n = 88)
Median OS, months (95% CI)	14.3 (10.8, NE)	NE (12.4, NE)

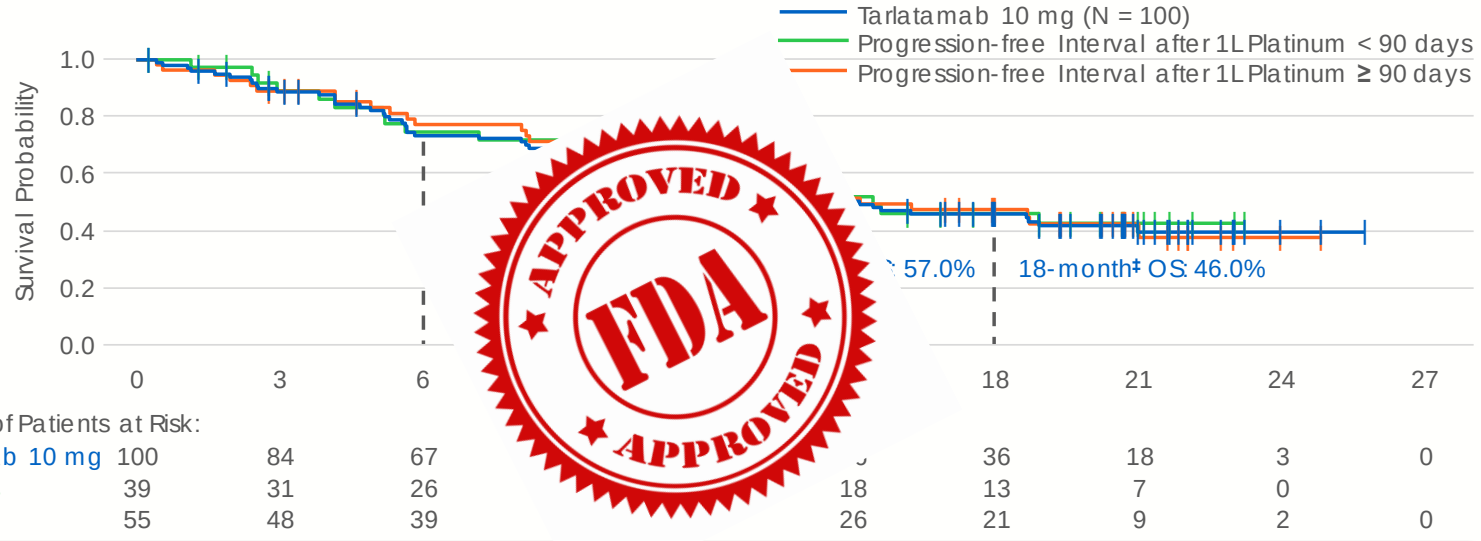


Tarlatamab 10 mg	100	84	67	44	17	3	0
Tarlatamab 100 mg	88	62	53	39	16	2	0

OS data is not yet mature; at the last follow-up, 57% of patients in the tarlatamab 10 mg group and 51% of patients in the tarlatamab 100 mg group were still alive

Ahn MJ, et al. N Engl J Med 2023;389:2063-2075

DeLLphi-301: Updated results for the 10 mg cohort



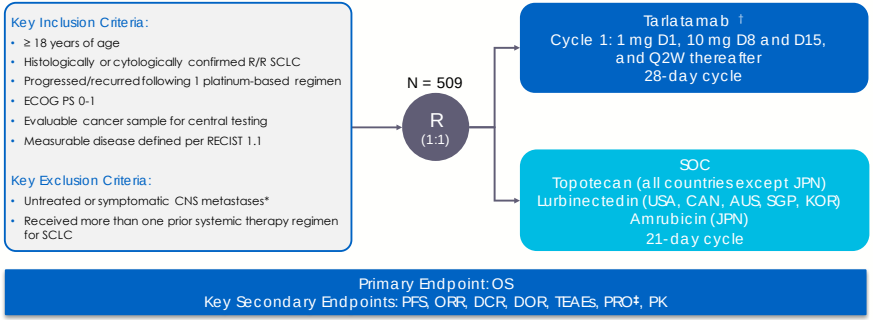
OS was similar regardless of progression-free interval after 1L platinum treatment (< 90 d vs ≥ 90 d)

Median OS was 15.2 months (95% CI, 10.8–NE)

Sands J et al. WCLC 2024 Annual Meeting

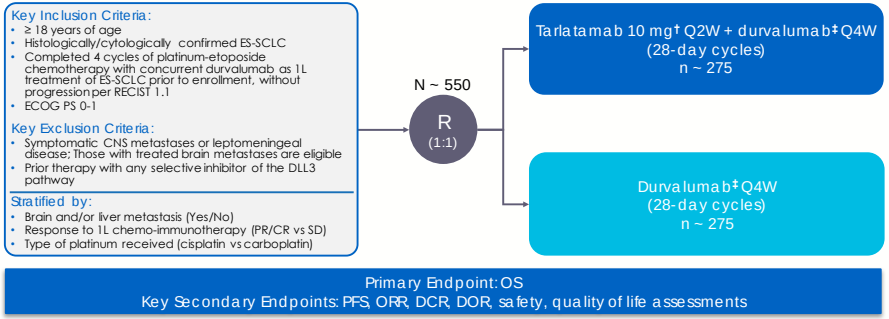
Tarlatamab phase III trials in SCLC

DeLLphi-304: A Randomized, Open-label, Phase 3 Study of Tarlatamab Compared With Standard of Care in Relapsed SCLC[1,2]



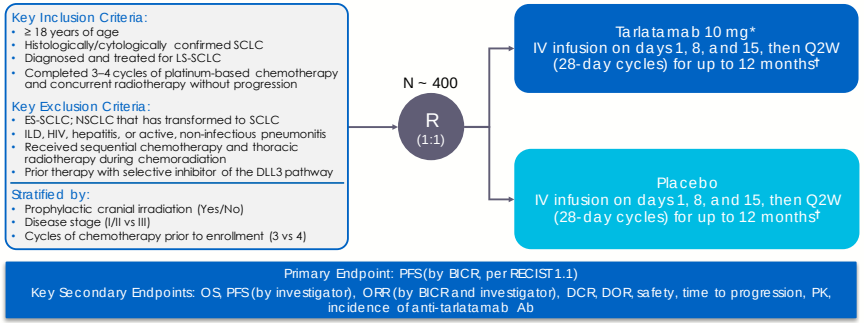
1. https://clinicaltrials.gov/ct2/show/NCT0574056.
2. 2. Paz-Ares et al. ASCO 2023 Poster TPS8611

DeLLphi-305: A Randomized, Open-label, Phase 3 Study of Tarlatamab Plus Durvalumab vs Durvalumab Alone as 1L Maintenance in Patients With ES-SCLC[1,2,*]



1. https://clinicaltrials.gov/study/NCT06211036. 2. Perol M et al. WCLC 2024 Poster P1.13A.02

DeLLphi-306: A Randomized, Double-Blind, Phase 3 Study of Tarlatamab After Concurrent Chemoradiotherapy in LS-SCLC[1,2]



1. https://clinicaltrials.gov/study/NCT06117774. 2. Dowlati A et al. WCLC) 2024 Poster P1.13A.01.

Ivonescimab: Mecanismo de acción

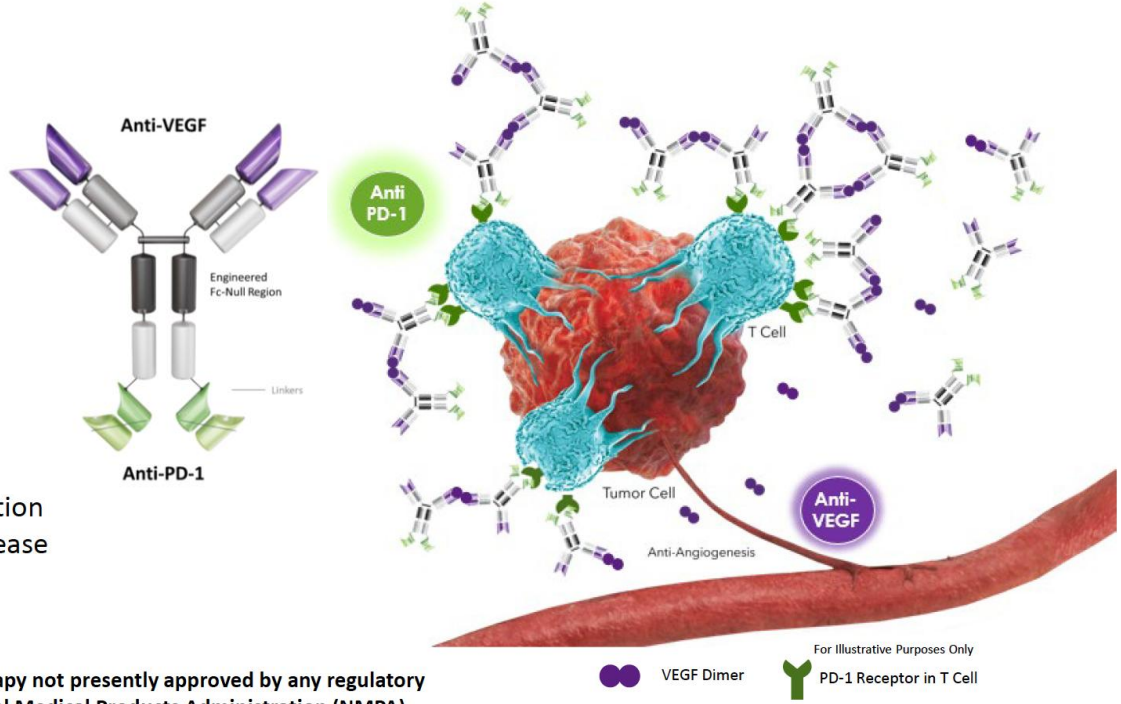
Simultaneous blocking of PD-1 & VEGF[1-3]

Increased Avidity in TME

VEGF increases affinity to **PD-1 by >18X**[3]
PD-1 increases affinity to **VEGF by >4X**[3]
(*in vitro*)

Enhanced Activity of T Cells

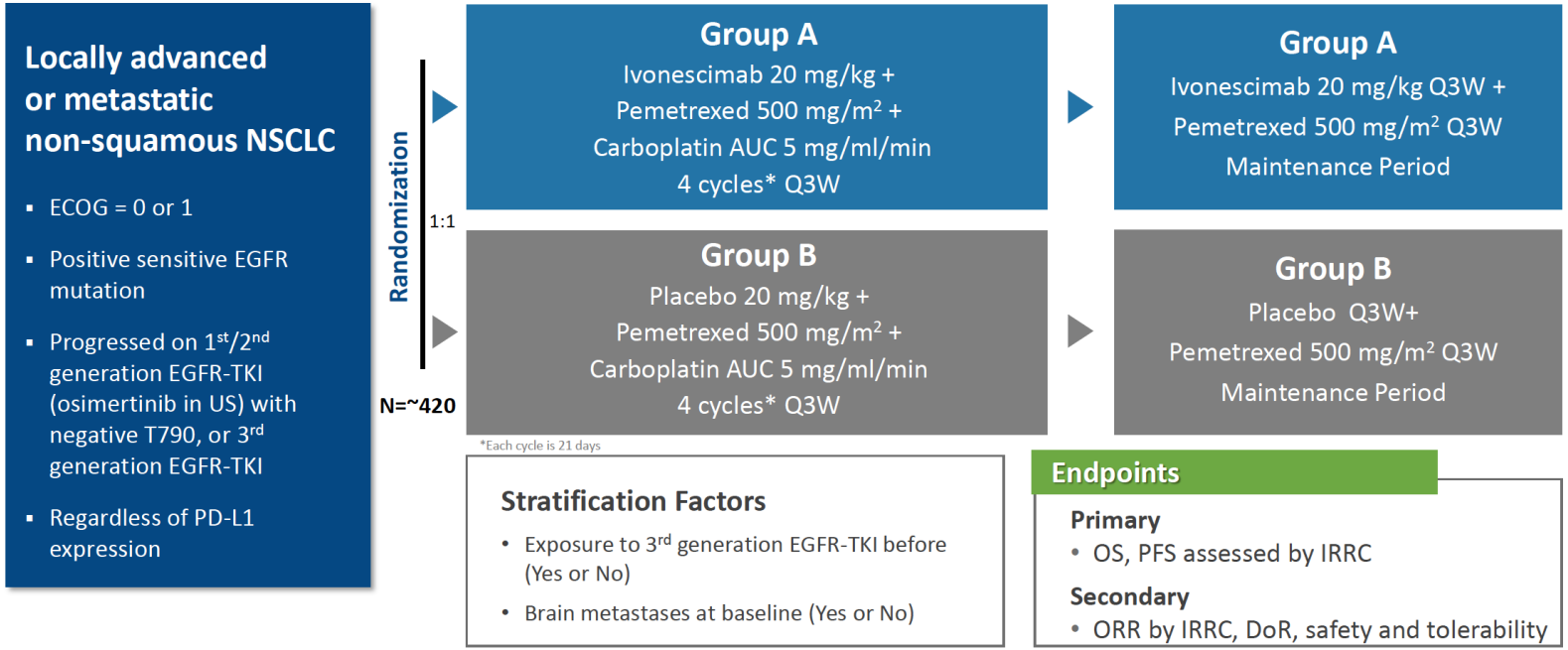
VEGF dimer leads to potential interconnection of ivonescimab molecules, which may increase activity of T cells[3]
(*in vitro*)



Ivonescimab is an investigational therapy not presently approved by any regulatory authority other than China's National Medical Products Administration (NMPA)

1. Zhao Y. et al., eClinicalMedicine. 2023; 3(62): 102106; 2. Wang L, et al. J Thorac Oncol. 2024 Mar;19(3):465-475;
3. Zhong T, et al. AACR-NCI-EORTC International Conference 2023.Poster #B123,Abstract #35333, Boston, MA, USA.

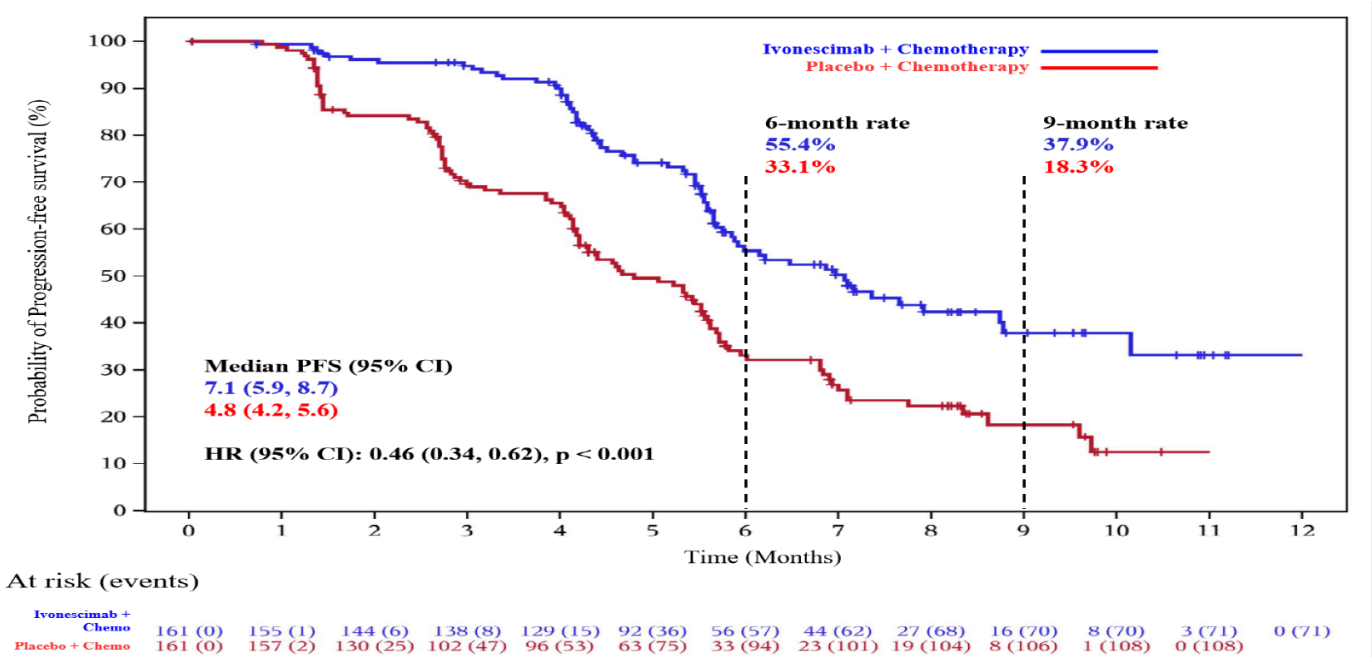
HARMONi-A: Phase 3 study in patients with *EGFR*+ advanced NSCLC progressed after EGFR-TKI



Fang W et al. JAMA 2024;332:561-570, Zhang Li et al. ASCO 2024, abstract 8508

HARMONi-A: Efficacy data

Primary Endpoint of PFS per IRRC



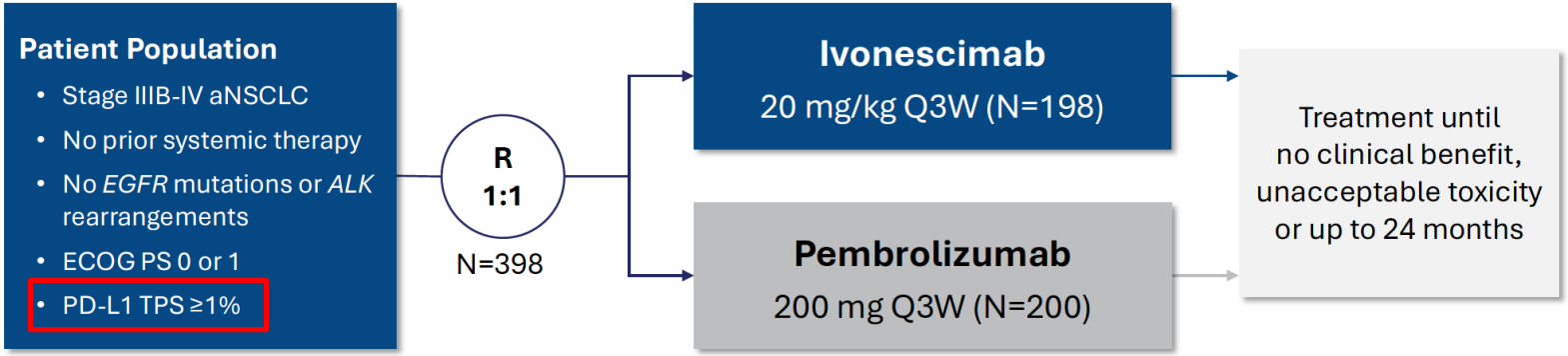
Data cutoff: Mar 10, 2023. Median (IQR) follow-up: 7.1 (5.4-9.0) months for ivonescimab and 8.2 (5.5-9.5) months for placebo.
HR and P-value were stratified by previous 3rd Gen EGFR-TKI use (yes vs. no) and presence of brain metastases (yes vs. no), and were calculated with stratified Cox model and log rank test. The two-sided P-value boundary is 0.024 as calculated using Lan-Demets spending function with O'Brien-Fleming approximation.

Fang W et al. JAMA 2024;332:561-570, Zhang Li et al. ASCO 2024, abstract 8508

HARMONi-2: Study design

Randomized, double-blind, phase 3 study[a]

Akeso-sponsored trial



[a] Patients were randomized from November 2022 to August 2023. Data cut off: January 29, 2024.

Stratification

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

Endpoints

Primary:
- PFS by blind IRRC per RECIST v1.1

Secondary:
- OS, PFS assessed by INVs, ORR, DoR, TTR and safety

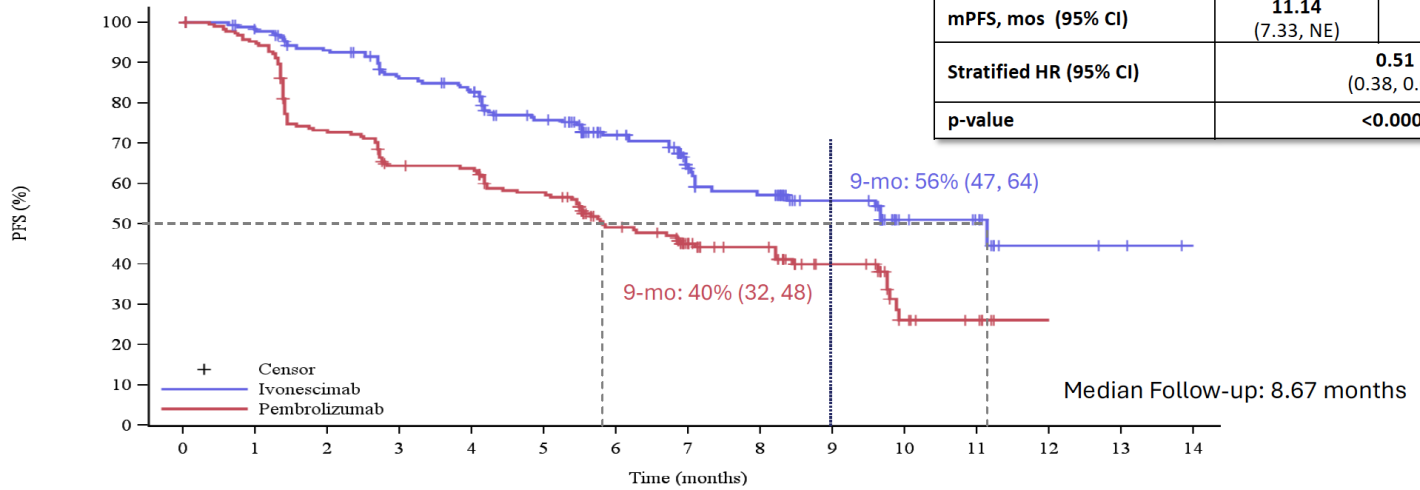
Exploratory:
- QoL

Zhou C et al. WCLC 2024 PL02.04

HARMONi-2: Efficacy data

Primary Endpoint—PFS per IRRC

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



Number at risk (Events)

Ivonescimab	198(0)	189(3)	175(13)	156(26)	148(32)	128(44)	99(50)	68(60)	59(67)	38(68)	14(71)	11(71)	3(72)	2(72)	0(72)
Pembrolizumab	200(0)	187(9)	141(52)	121(69)	119(70)	103(81)	74(95)	53(101)	45(102)	25(106)	9(112)	5(112)	0(112)		

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

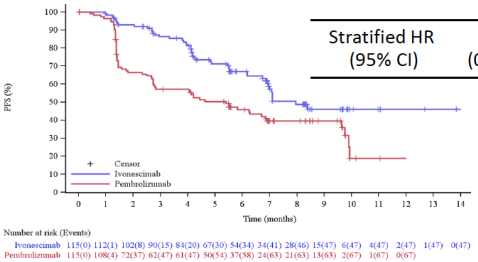
Zhou C et al. WCLC 2024 PL02.04

HARMONi-2: Efficacy data

Key PFS Subgroup Analyses

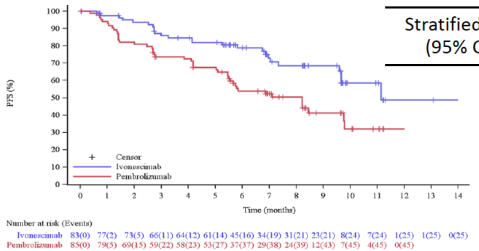
PD-L1 expression

PD-L1 Low (TPS 1-49%)



Stratified HR (95% CI): 0.54 (0.37, 0.79)

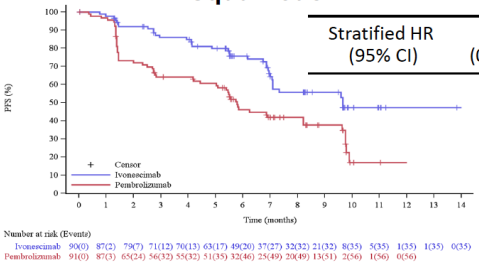
PD-L1 High (TPS ≥50%)



Stratified HR (95% CI): 0.46 (0.28, 0.75)

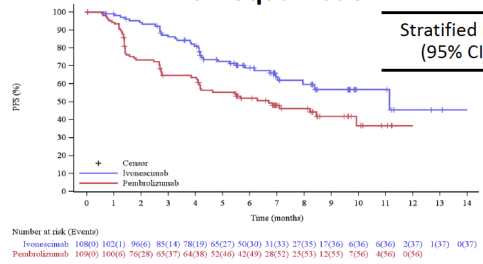
NSCLC Histology

Squamous



Stratified HR (95% CI): 0.48 (0.31, 0.74)

Non-Squamous



Stratified HR (95% CI): 0.54 (0.36, 0.82)

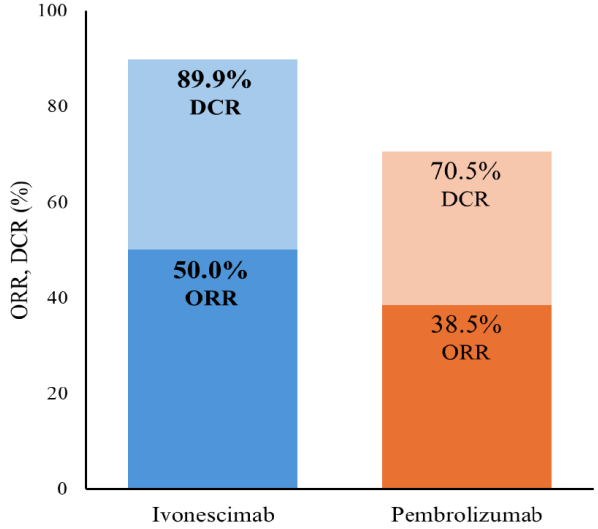
Ivonescimab showed meaningful improvement in PFS vs. pembrolizumab in patients with both low and high PD-L1, with squamous or non-squamous advanced NSCLC.

Ivonescimab is an investigational therapy not presently approved by any regulatory authority other than China's National Medical Products Administration (NMPA)

Zhou C et al. WCLC 2024 PL02.04

HARMONi-2: Efficacy data

Secondary Endpoint—ORR, DCR and DoR per IRRC



Data cut off: January 29, 2024.

	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)
Median DoR, mos (95% CI)	**NR** (NE, NE)	NR (8.28, NE)

ORR and DCR were higher with ivonescimab vs. pembrolizumab

Zhou C et al. WCLC 2024 PL02.04

HARMONi-2: Safety data

Immune-Related and Possible VEGF-Related AEs

Safety Summary, n (%)	Ivonescimab (n = 197[a])	Pembrolizumab (n = 199[a])
irAEs (all grades)	59 (29.9)	56 (28.1)
Grade≥3	14 (7.1)	16 (8.0)
Serious irAEs	11 (5.6)	22 (11.1)
Leading to discontinuation	0	5 (2.5)
Leading to death	0	0

[a] Patients who received ≥1 dose of study treatment.

Ivonescimab exhibited similar irAEs to that of pembrolizumab

Safety Summary, n (%)	Ivonescimab (n = 197[a])	Pembrolizumab (n = 199[a])
Possible VEGF-Related AEs (all grades)	94 (47.7)	42 (21.1)
Grade ≥3	20 (10.2)	2 (1.0)

Safety Summary by Classification, n (%)	Ivonescimab (n = 197[a])		Pembrolizumab (n = 199[a])	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Proteinuria	62 (31.5)	6 (3.1)	20 (10.1)	0
Hypertension	31 (15.7)	10 (5.1)	5 (2.5)	1 (0.5)
Hemorrhage	29 (14.7)	2 (1.0)	22 (11.1)	1 (0.5)
Arterial thromboembolism	2 (1.0)	2 (1.0)	1 (0.5)	0
Venous thromboembolism	0	0	1 (0.5)	0

[a] Patients who received ≥1 dose of study treatment.

Ivonescimab is an investigational therapy not presently approved by any regulatory authority other than China's National Medical Products Administration (NMPA)

- All VEGF-related AEs were Grades 1-3 in both arms
- Grade 3 hemorrhage was observed in two patients with non-SQ and was not reported in SQ patients in the ivonescimab arm

Zhou C et al. WCLC 2024 PL02.04

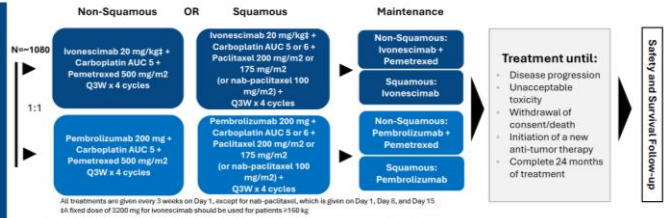
Ongoing studies with Ivonescimab

HARMONi-3: Phase 3 Study in 1L Metastatic NSCLC (NCT05899608)

HARMONi-3

Key Inclusion
- First-line Stage IV squamous and non-squamous NSCLC

Key Exclusion:
- Known actionable mutations for which 1L approved agents are available
- Symptomatic CNS metastases
- Major blood vessel or organ invasion
- History of bleeding tendencies or coagulopathy or clinically significant bleeding symptoms or risk (including GI bleeding, hemoptysis, etc.)
- Active autoimmune disease



Stratification Factors:
- Squamous vs. non-squamous histology
- TPS Score: PD-L1 ≥1% or <1%
- Sex (female vs male)
- Age (<65 vs ≥65 years)
- Geographical region: East Asia vs ROW
- Liver or brain metastases at study entry (present vs absent)
- Prior treatment with PD-1/L1 inhibitor containing therapy (yes vs no)

Endpoints

Primary
- OS, PFS by investigator assessment

Secondary
- ORR, DCR, DOR by investigator assessment, safety, PK, immunogenicity

HARMONi-7

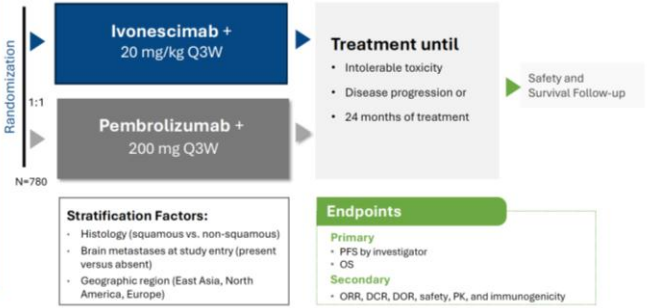
HARMONi-7

Phase 3 Study in 1L Metastatic NSCLC (TPS ≥50%)

Overall Study Design

Key Inclusion
- Untreated Stage IV NSCLC with high tumor PD-L1 expression (TPS ≥50%) and without activating mutations
- Histologically or cytologically confirmed squamous or non-squamous NSCLC

Key Exclusion
- Any prior therapy for NSCLC in the metastatic setting
- Symptomatic CNS metastases
- Tumor major blood vessel or organ invasion
- History of bleeding tendencies or coagulopathy or clinically significant bleeding symptoms or risk within 4 weeks prior to randomization, including GI bleeding, hemoptysis, etc.
- Active autoimmune disease



Stratification Factors:
- Histology (squamous vs. non-squamous)
- Brain metastases at study entry (present versus absent)
- Geographic region (East Asia, North America, Europe)

Endpoints

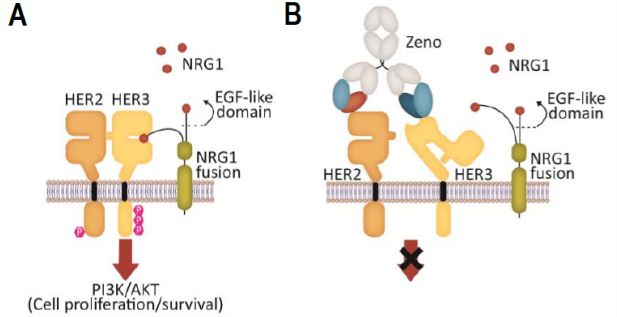
Primary
- PFS by investigator
- OS

Secondary
- ORR, DCR, DOR, safety, PK, and immunogenicity

Zenocutuzumab is a novel HER2 - HER3 bispecific antibody targeting NRG1

- Neuregulin 1 (NRG1) is a ligand that binds to HER3, promoting HER2/HER3 heterodimerization and oncogenesis, leading to tumor growth[1,2]
- Chromosomal rearrangements involving *NRG1* are rare oncogenic drivers in a broad range of solid tumors (NRG1+ cancer), including NSCLC (in <1% of patients)[3,4,5,6]
- *NRG1* fusions may be associated with poor prognosis, including lower response rates to standard therapy, and shorter overall survival in NSCLC[7,8]

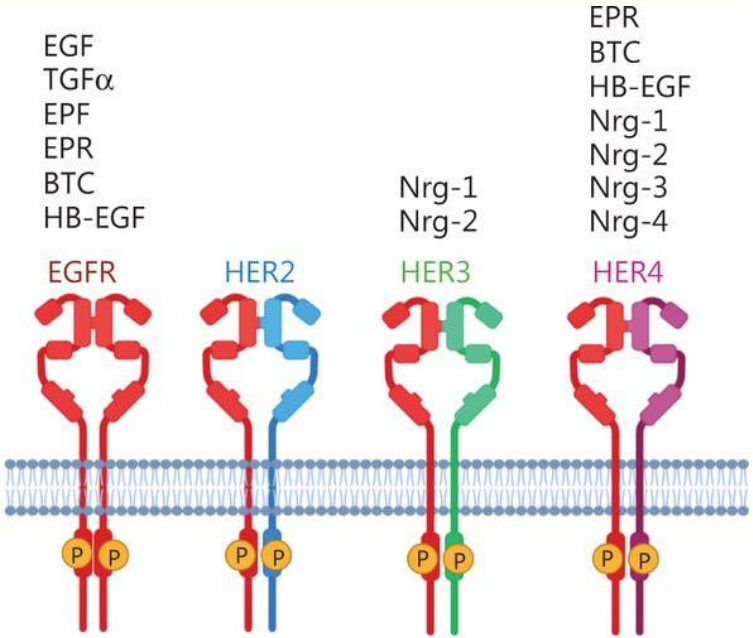
***NRG1* Fusion Signaling and Zenocutuzumab Mechanism of Action**

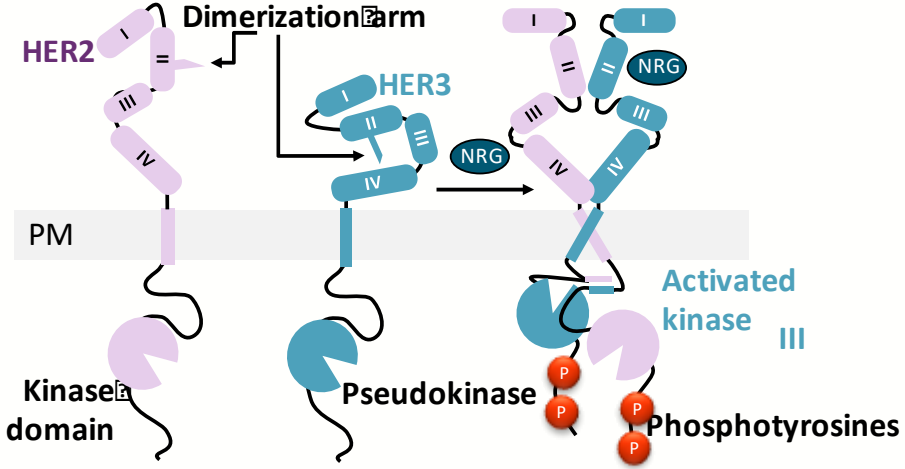


- Zenocutuzumab is a bispecific antibody that binds to the extracellular domains of HER2 and HER3
  - Preclinical data demonstrate anticancer activity is due to blocking NRG1:HER3 binding and HER2:HER3 dimerization, suppressing tumor cell proliferation and survival via the PI3K-AKT-mTOR oncogenic signaling pathway[9,10]
  - *In vitro,* zenocutuzumab also mediates antibody-dependent cellular cytotoxicity (ADCC), eliminating tumor cells[9,10]
- Zenocutuzumab was recently granted Breakthrough Therapy Designations for NRG1+ NSCLC and NRG1+ pancreatic cancer

Schram AM et al. ESMO 2023; Schram AM et al. N Engl J Med 2025;392:566-576

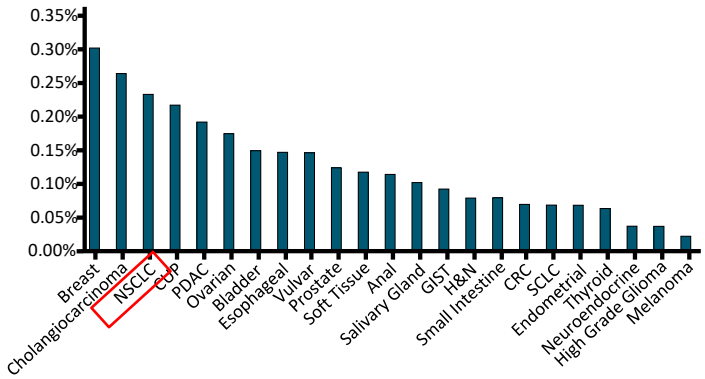
Role of HER3 in the HER/ERRB Family



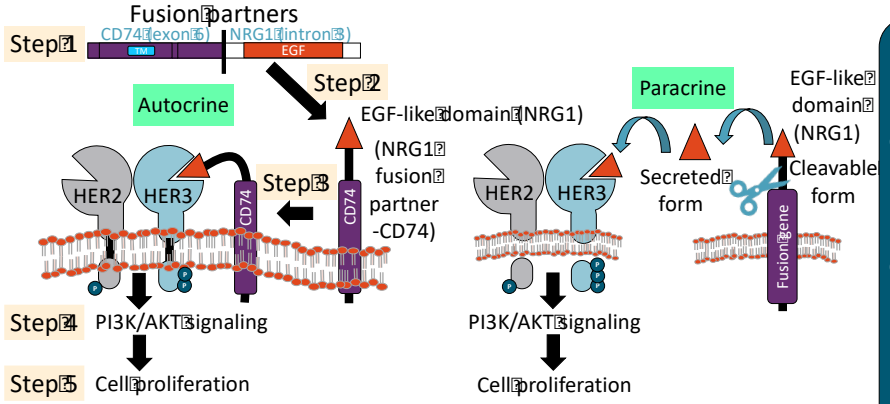


NRG1 Fusions

***NRG1* fusion prevalence by cancer type**



NRG1 fusion proteins: Mechanisms of action



Fusion genes

Genes with a transmembrane domain: UBXN8, CD74, SLC3A2, CD9, TMEM66, TNFRSF10B

Genes without a transmembrane domain GATA5, BRE DDHD2, PCM1, ZCCHC7, IKBKB, FUT10, KCTD9, CCAR2, BIN3, ERO1L

Gupta et al. ASCO 2023 Abstract 3132

Global, multicenter Zenocutuzumab NRG1+ cancer development program

Ongoing phase 1/2 global, open-label clinical trial (eNRGy) + Early Access Program (EAP)

NSCLC, PDAC[a], and other solid tumors

Inclusion Criteria

- Locally advanced unresectable or metastatic solid tumor
- NRG1+ cancer
- Previously treated with or unable to receive standard therapy
- ≥ 18 years of age
- ECOG PS ≤ 2

Treatment Plan

- Zenocutuzumab 750 mg IV Q2W until PD
- Tumor assessment Q8W

Follow-up

Survival follow-up: up to 2 years

Endpoints and Population

Primary endpoint
Overall response rate (ORR)[b] using RECIST v1.1 per investigator assessment

Secondary endpoints
Duration of response (DOR)[c], ORR per central review, safety[d]

Primary analysis population
≥ 1 dose of zenocutuzumab, opportunity for ≥ 24 weeks follow-up at the data cutoff date, and met criteria for primary efficacy population

Enrollment and Analysis

Data cutoff date
July 31, 2023

Enrollment
105 patients with NRG1+ NSCLC

NSCLC primary analysis population
79 patients

87 patients with ≥ 24 weeks follow-up[e]; of them, 8 patients were excluded[f]

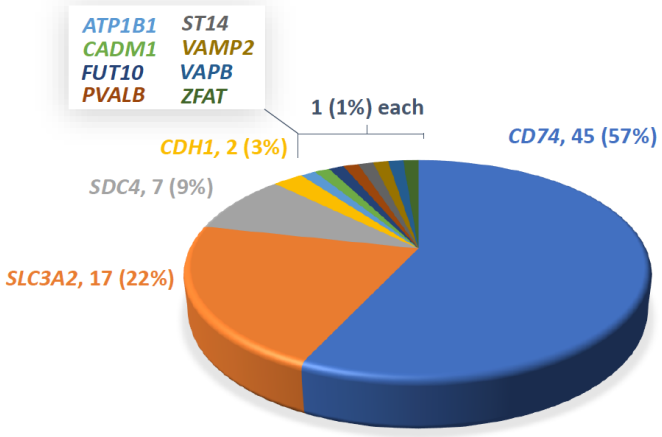
- 2 patients discontinued early for reasons not related to PD
- 2 patients with prior anti-HER3 inhibitor
- 2 patients with other genetic driver mutation
- 1 patient with concomitant anti-cancer medication use
- 1 patient with baseline scan > 5 weeks before first dose

Schram AM et al. ESMO 2023; Schram AM et al. N Engl J Med 2025;392:566-576

NRG1+ patient characteristics

Demographics and Prior Therapy N = 79	
Age, years, median (range)	64 (32-88)
Male / female, n (%)	30 (38) / 49 (62)
ECOG PS 0 / 1 / 2 / Missing, n (%)	24 (30) / 50 (63) / 3 (4) / 2 (3)
Race, Asian / White / Other[a], n (%)	40 (51) / 30 (38) / 9 (11)
Prior lines of systemic therapy, median (range)	1 (0-6)
Platinum pre-treated, n (%)	57 (72)
Prior afatinib, n (%)	9 (11)
Treatment naïve, n (%)	12 (15)
Patient disposition, n (%)	
Treatment ongoing	20 (25)
Discontinued due to PD[b] / other reason[c]	58 (73) / 1 (1)
Number of metastatic sites, median (range)[d]	2 (0-8)
Histology, n (%)	
Adenocarcinoma	66 (84)
Invasive mucinous adenocarcinoma	11 (14)
Squamous cell carcinoma	1 (1)
Poorly differentiated carcinoma	1 (1)

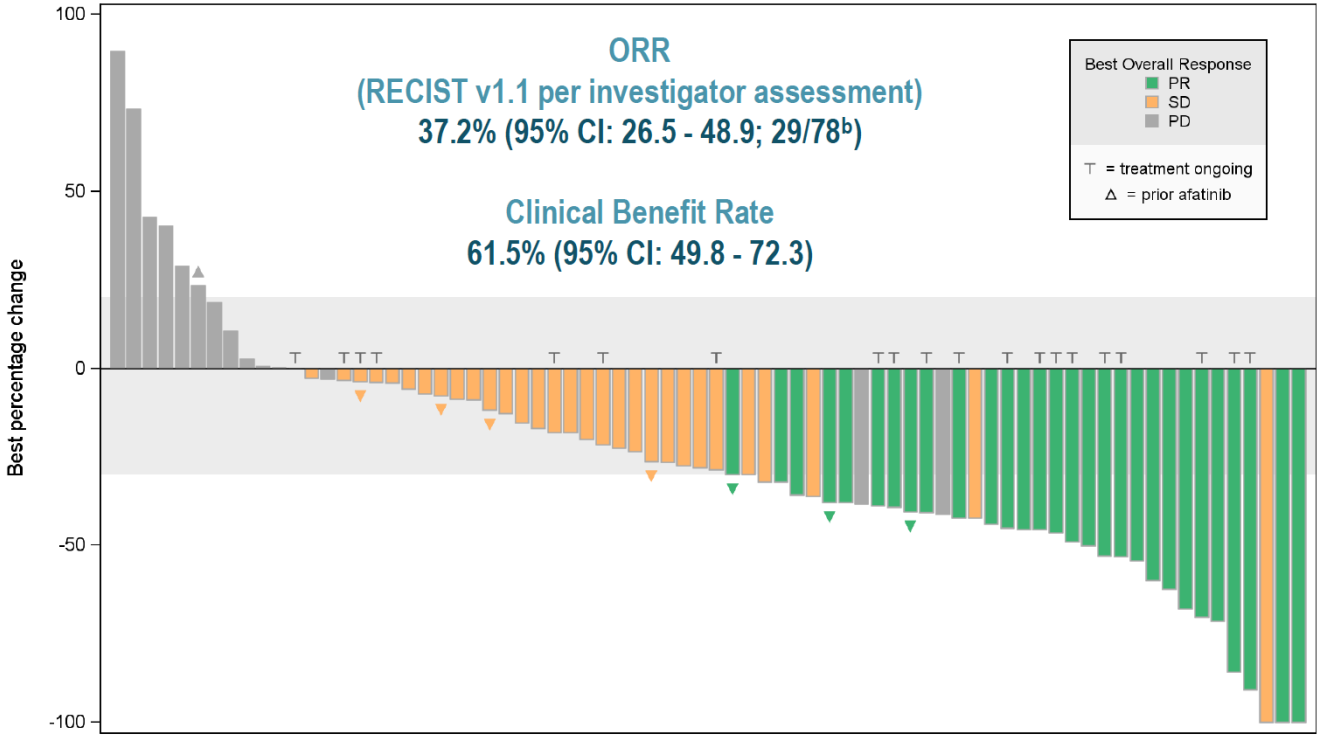
NRG1 Fusion Partners N = 79



NRG1 identification technology, n (%)	
RNAseq	64 (81)
DNAseq	11 (14)
Nanostring	1 (1)
Missing	3 (4)

Schram AM et al. ESMO 2023; Schram AM et al. N Engl J Med 2025;392:566-576

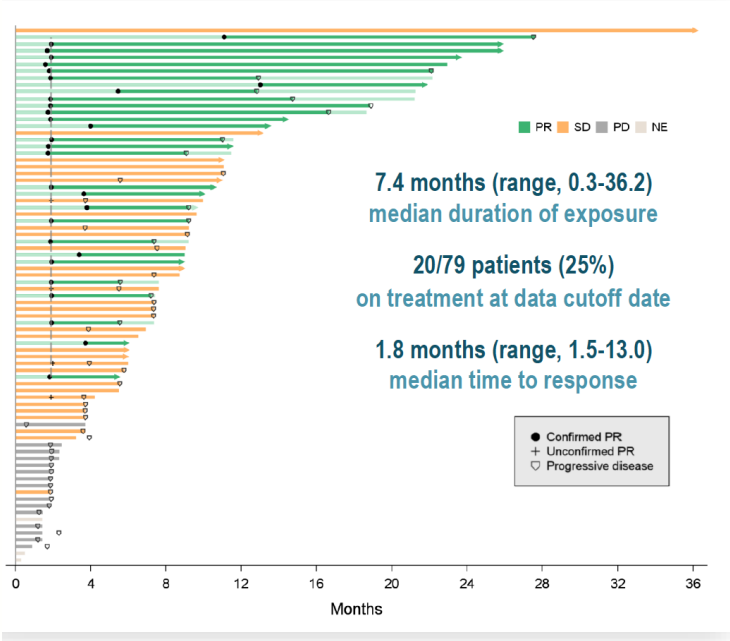
Zenocutuzumab ativity in NRG1+ NSCLC

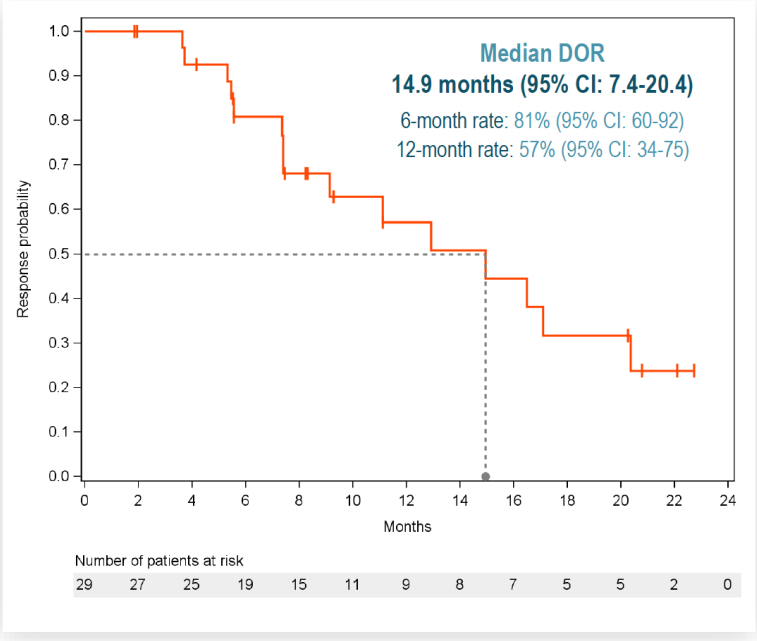


Schram AM et al. ESMO 2023; Schram AM et al. N Engl J Med 2025;392:566-576

Zenocutuzumab ativity in NRG1+ NSCLC

Time on Therapy[a] and Duration of Response





Schram AM et al. ESMO 2023; Schram AM et al. N Engl J Med 2025;392:566-576

Zenocutuzumab safety profile

Safety Profile in NRG1+ Cancer

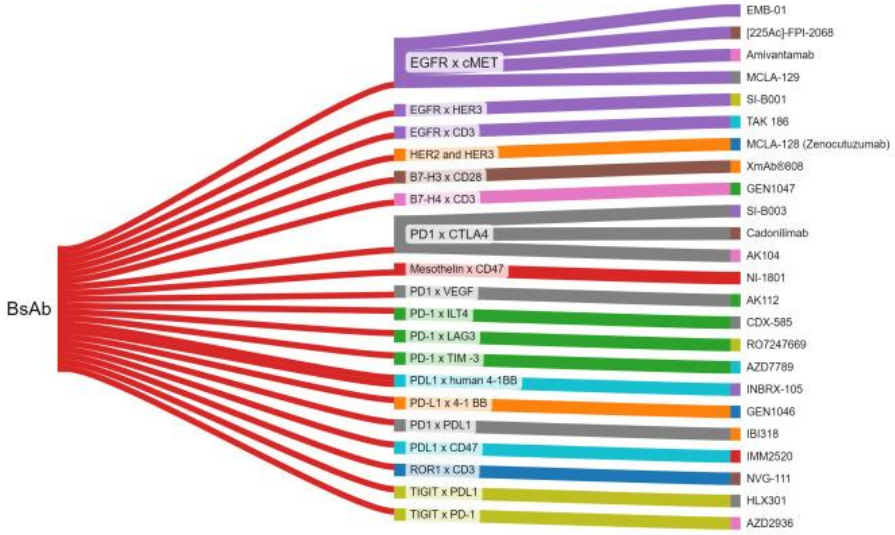
- 189 NRG1+ cancer patients treated with zenocutuzumab 750 mg Q2W monotherapy[a]
- Low incidence of grade 3 or 4 treatment-related TEAEs
- No patient discontinued treatment due to treatment-related TEAEs
- No grade 5 treatment-related TEAEs
- Infusion-related reactions[b] in 23 of 189 (12%) patients, with no grade 3 or greater events

[a] 189 patients enrolled in the eNRGy trial or EAP, including 105 patients with NSCLC.
[b] Composite term covering preferred terms considered by the investigator to be infusion-related reactions occurring within 24 hours of infusion start.

	Related TEAEs (≥10% patients and all Grade 3-4) n (%)		TEAEs Irrespective of Causality (≥10% patients and all Grade 3-4) n (%)	
	grades	Grades 3-4	All grades	Grades 3-4
≥1 TEAE	(61)	11 (6)	166 (88)	66 (35)
Diarrhea	17)	3 (2)	53 (28)	4 (2)
In		0	23 (12)	0
		0	30 (16)	4 (2)
		2 (1)	30 (16)	3 (2)
		1 (1)	21 (11)	1 (1)
		1 (1)	29 (15)	7 (4)
		0	24 (13)	0
		1 (1)	18 (10)	5 (3)
A		2 (1)	14 (7)	5 (3)
De		1 (1)	16 (8)	2 (1)
Abdo	2)	1 (1)	21 (11)	4 (2)
Dyspne	2 (1)	0	24 (13)	6 (3)
GGT inci	2 (1)	1 (1)	13 (6)	6 (3)
Platelet co decreased	2 (1)	1 (1)	4 (2)	1 (1)
Hyperuricemia	2 (1)	1 (1)	3 (2)	1 (1)
Bacteremia	1 (1)	1 (1)	2 (1)	2 (1)
Hypertransaminasemia	1 (1)	1 (1)	1 (1)	1 (1)

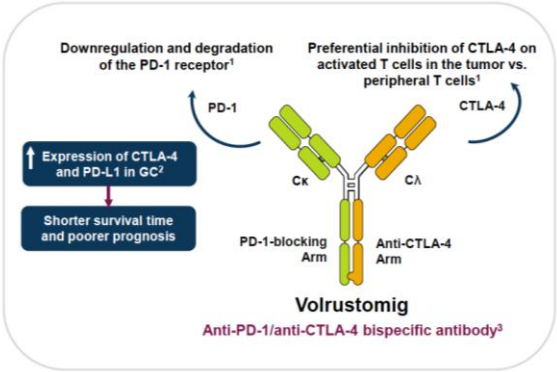
Schram AM et al. ESMO 2023; Schram AM et al. N Engl J Med 2025;392:566-576

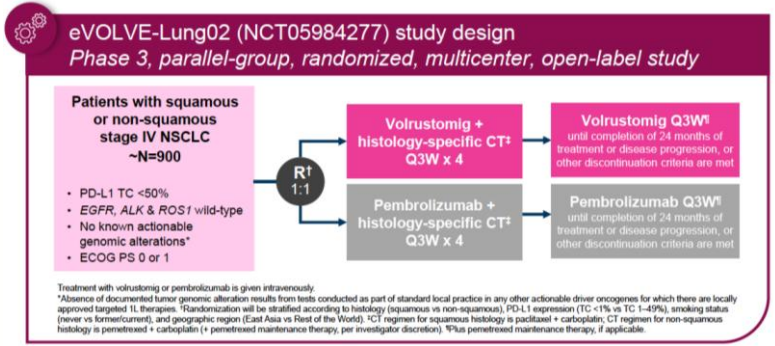
Bispecific antibodies are an emerging class of checkpoints modifiers in NSCLC



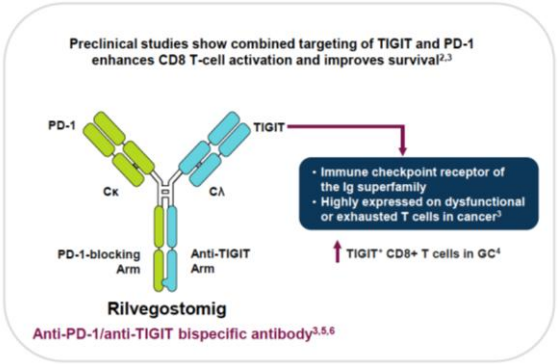
Trial	Phase	Molecule	Target		Population	Previous treatment
NCT05499390	III	**Ivonescimab**	**PD-1**	**VEGF**	PD-L1-positive LA or mNSCLC	Frontline
NCT04995523	III	**Rilvegostomig**	**PD-1**	**TIGIT**	PD-L1-positive unresectable advanced or mNSCLC	+/- prior IO treatment
NCT06129864	III	**Volrustomig**	**PD-1**	**CTLA4**	Advanced NSCLC	Previously treated
NCT04931654	II	**Sabestomig**	**PD-1**	**TIM3**	Advanced NSCLC	Previously treated
NCT05645692	II	**Tobemstomig**	**PD-1**	**LAG3**	With chemo vs chemo/pembro	Frontline
NCT05918107 NCT05844150 NCT05756972	III	**PM8002**	**PD-L1**	**VEGF A**	With chemo in SCLC and MPM	Frontline
NCT03917381	I / II	**BNT311/ GEN1046**	**PD-L1**	**4-1BB**	Solid tumors	Previously treated
NCT04083599	I / II	**BNT312/ GEN1042**	**CD40**	**4-1BB**	Solid tumors	Previously treated
NCT04857138	I	**RG6189**	**CD40**	**FAP**	Solid tumors with atezolizumab	Previously treated
NCT05571839	I	**SGN-BB228**	**CD228**	**4-1BB**	Mel, NSCLC, CRC, PDAC, meso	Previously treated

Volrustomig (MEDI5752)

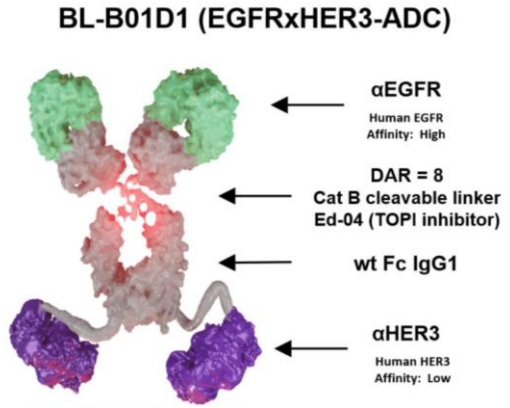




Rilvegostomig (AZD2936)



Izalontamab brengitecan: ADC targeting EGFR-HER3



Conclusiones

- Amivantamab: inserciones exón 20 y mutaciones comunes del *EGFR*
- Tarlatamab: SCLC tras quimioterapia con platino-etopósido
- Ivonescimab: primea línea NSCLC vs pembrolizumab
- Zenocutuzumab: fusiones de NRG1
- Muchos fármacos en ensayo

Bispecific antibodies are an emerging class of checkpoints modifiers in NSCLC


Thank
you