Novedades y Claves en Cáncer de Pulmón 2021

Enfermedad metastásica

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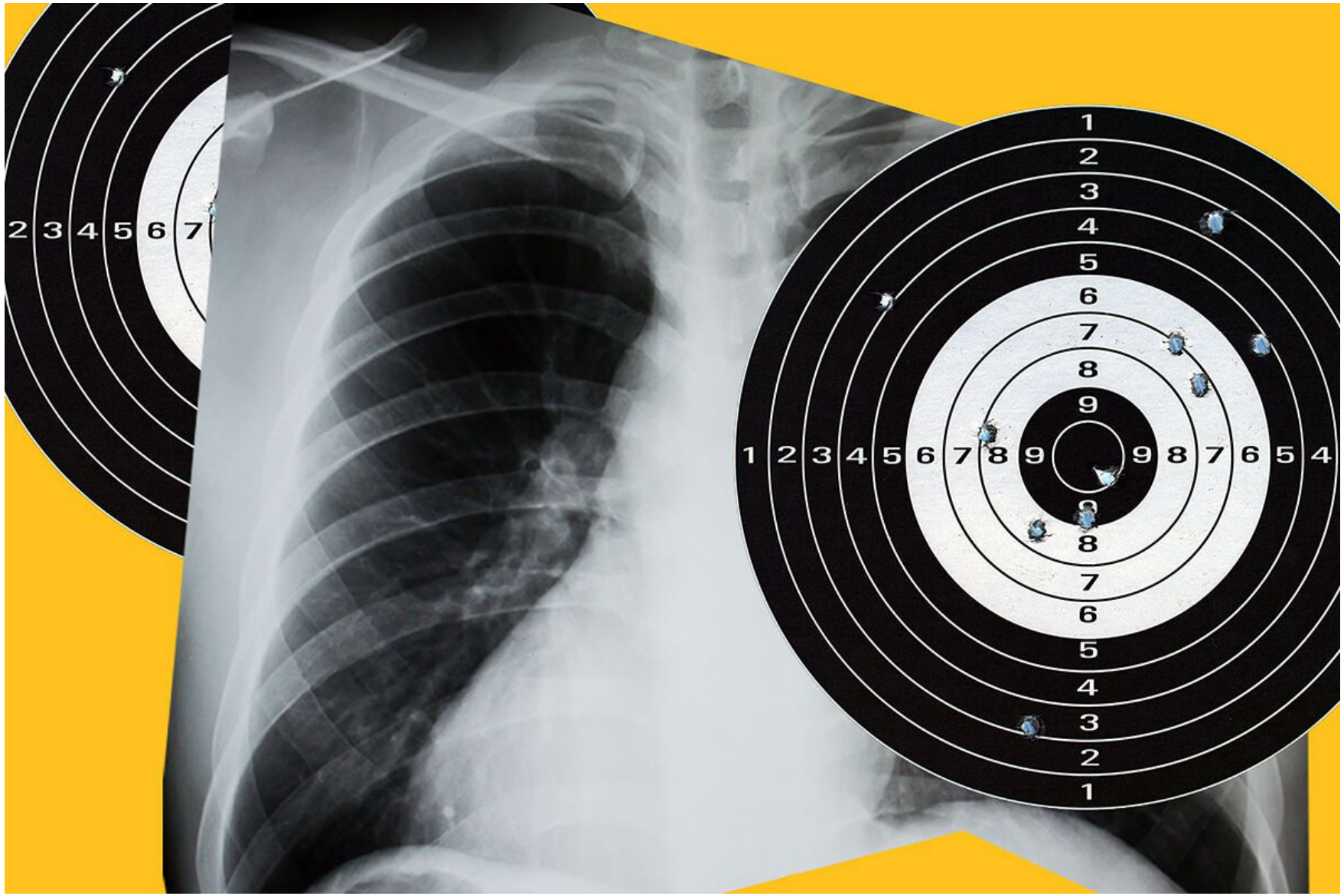
Organizado por:

GECP lung cancer research

Terapias diana. EGFR



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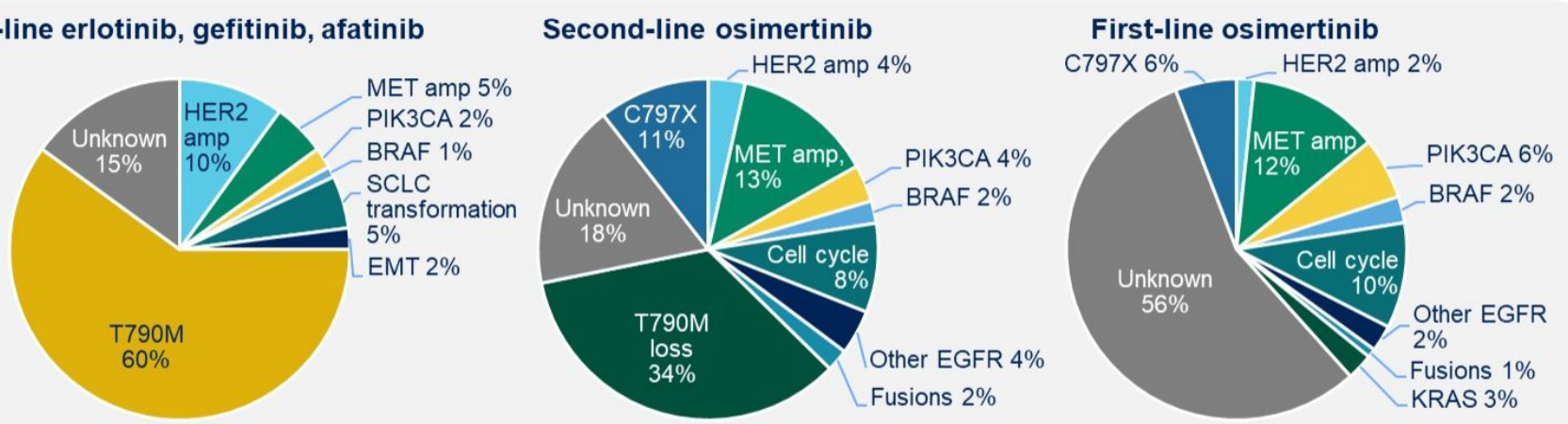
Broad Range of Resistance Mechanisms in *EGFR*m NSCLC Following the Failure of EGFR Tyrosine Kinase Inhibitor (TKI) Therapy

- Efficacy of EGFR TKI in *EGFR*m NSCLC has been established; however, the development of various resistance mechanisms commonly leads to disease progression[1-2]
- Platinum-based chemotherapy following EGFR TKI failure has limited efficacy (ORR, 25%–44%; PFS, 2.7–6.4 months)[3]
- Salvage therapies after EGFR TKI and platinum-based chemotherapy have not been effective (PFS, 2.8–3.2 months)[4]

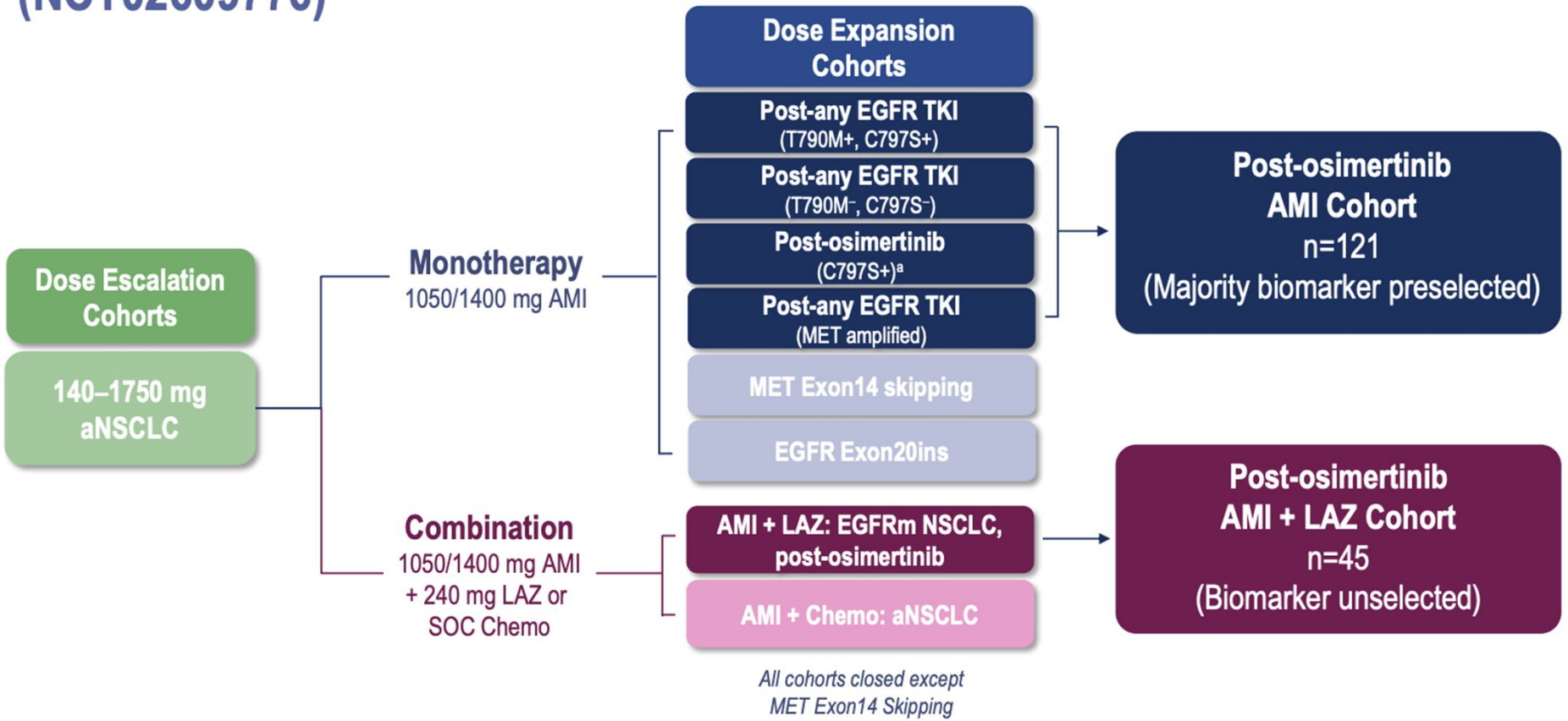
Wide variety of genomic alterations associated with EGFR TKI resistance[1,2]



1. Engelman JA, et al. *Science*. 2007;316:1039-1043. 2. Schoenfeld AJ, Yu HA. *J Thorac Oncol*. 2020;15:18-21. 3. Han B, et al. *Onco Targets Ther*. 2018;11:2121-9. 4. Yang CJ, et al. *BMC Pharmacol Toxicol*. 2017;18(1).

CHRYSALIS Study Design Fase 1

(NCT02609776)



All cohorts closed except MET Exon14 Skipping

Amivantamab (am-e-van-tuh-mab)

- Fully human bispecific antibody that targets EGFR and MET
- Fc portion has immune cell-directing activity[1]
- Demonstrated clinical activity across diverse EGFRm NSCLC[2-4]
- Granted Breakthrough Therapy Designation for EGFRm Exon20ins NSCLC post-chemotherapy in US and China

Lazertinib (la-zer-tin-ib)

- Potent 3rd-gen TKI with efficacy in activating EGFR mutations, T790M, and CNS disease[5-6]
- Low rates of EGFR-related toxicity such as rash and diarrhea[5]
- Low cardiovascular safety risk[7]
- Safety profile that supports combination with other anti-EGFR molecules

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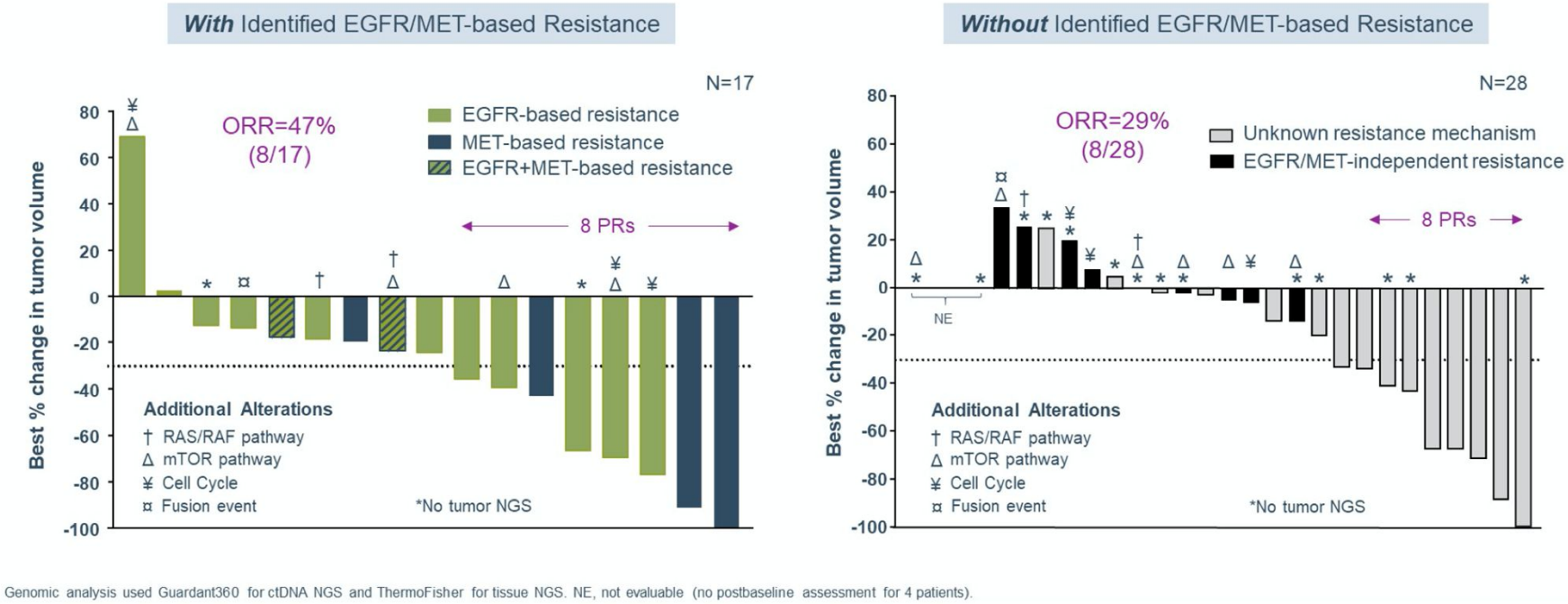
ASCO 2021
Combinación

	Total (N=45)
Previously reported brain metastases, n (%)	13 (29)
Median prior lines, n (range)	2 (1–4)
Prior 1st or 2nd-gen TKI, n (%)	33 (73)
Prior 3rd-gen TKI, n (%)	45 (100)
EGFR primary mutation, n (%)	
Exon 19 deletion	30 (67)
Exon 21 L858R	14 (31)
Unknown[a]	1 (2)



Genomic analysis used Guardant360 for ctDNA NGS and ThermoFisher for tissue NGS. NE, not evaluable (no postbaseline assessment for 4 patients).

- Hasta 1/3 de los pacientes responden independientemente del mecanismo de resistencia a osimertinib
- ORR 47% cuando la resistencia esta mediada por EGFR/MET y ausencia de respuestas en mecanismos de resistencia independientes de estos.
- ORR 75% relacionado con MET

Investigator-assessed Response (N=45) *mF/U: 11.0 months (range, 1.0–15.0)* *mDOT: 5.6 months (range, 0.5–14.8)*	
ORR	36% (95% CI, 22–51)
mDOR, months	9.6 (95% CI, 5.3–NR)
DOR ≥6 months	69%
CBR	64% (95% CI, 49–78)
mPFS, months	4.9 (95% CI, 3.7–9.5)

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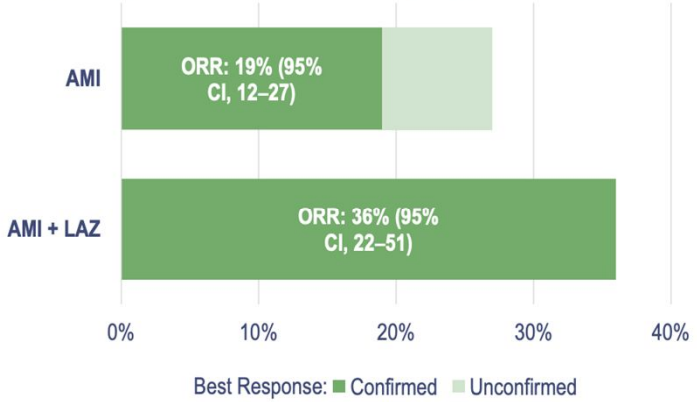
ESMO 2021

Efficacy: AMI Monotherapy and AMI + LAZ

(descriptive cross-cohort analysis)



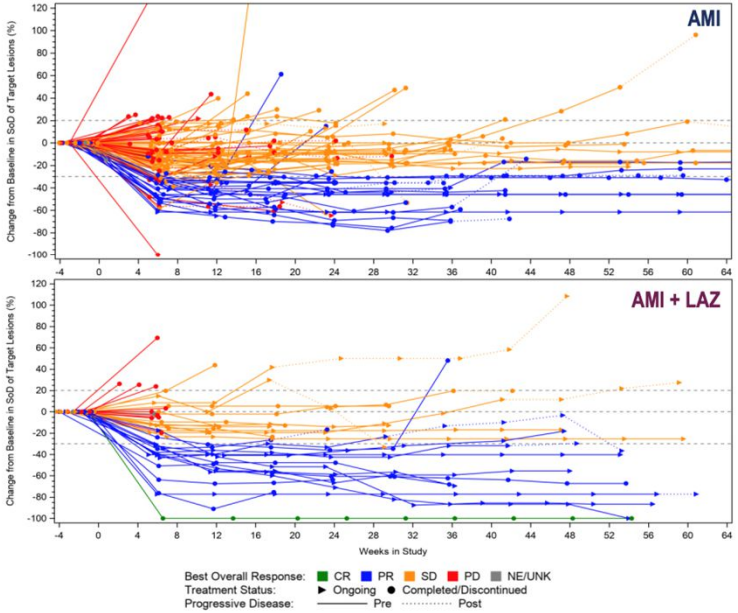
	AMI (n=121)	AMI + LAZ (n=45)
Best response[a]	27%	36%
Confirmed ORR* (95% CI)	**19%** (12–27)	**36%** (22–51)
CR	0	1 (2%)
PR	23 (19%)	15 (33%)
SD	53 (44%)	14 (31%)
PD	39 (32%)	11 (24%)
NE	6 (5%)	4 (9%)
mDOR (95% CI)	**5.9 mo** (4.2–12.6)	**9.6 mo** (5.3–NR)
CBR (95% CI)	48% (39–57)	64% (49–78)
mPFS (95% CI)	4.2 mo (3.2–5.3)	4.9 mo (3.7–9.5)
mF/U (range)	6.9 mo (0.7–38.6)	11.1 mo (1.0–15.0)

*ORR among patients with identified EGFR/MET-based osimertinib resistance was 18% for AMI and 47% for AMI + LAZ[1]

Addition of lazertinib to amivantamab was associated with numerically higher objective response rate and longer duration of response after progression on osimertinib

Responses over Time for AMI Monotherapy and AMI + LAZ

(descriptive cross-cohort analysis)



AMI (n=121):

- Median time on treatment = 3.7 mo (range, 0.03–32.2)
  - Among responders = 8.3 mo (range, 2.8–32.2)
- 39% had responses ≥6 months
- CNS progression[a] was documented among 17% of patients with 13% being new CNS lesions

AMI + LAZ (n=45):

- Median time on treatment = 5.6 mo (range, 0.5–14.8)
  - Among responders = 12.0 mo (range, 4.1–14.6)
- 69% had responses ≥6 months
- CNS progression[a] was documented among 7% of patients with 4% being new CNS lesions

- Tasas de respuesta del 36% vs 19%
- Mediana de duración de 9.6 combinación vs 5.9 meses monoterapia
- Mantenían respuesta ≥ 6meses el 69% vs 39%
- Efecto protector SNC

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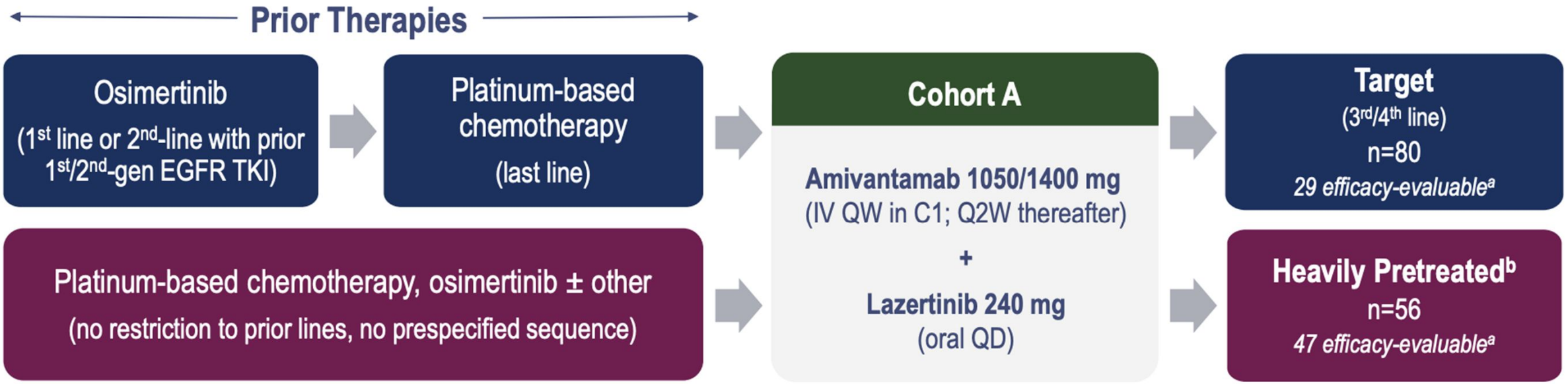
Conclusions

- The combination of amivantamab + lazertinib after osimertinib appears to have higher activity and response durability compared to the amivantamab monotherapy experience, with potentially improved CNS protection, supporting the simultaneous targeting of extracellular and catalytic domains of EGFR
  - AMI + LAZ ORR = 36% (95% CI, 22–51), mDOR = 9.6 months (95% CI, 5.3–NR)
  - AMI monotherapy ORR = 19% (95% CI, 12–27), mDOR = 5.9 months (95% CI, 4.2–12.6)
  - Documented CNS progression was low with both AMI monotherapy and AMI + LAZ (17% and 7%, respectively)
- The safety profile for both monotherapy and combination therapy was consistent with previously reported experience, with no new safety signals identified

- NGS identificó un subgrupo con mayores probabilidades de responder (resistencia basada en EGFR/MET)
  - ✓ La mitad de los respondedores no se identificaron usando este criterio
- El análisis por IHC sugiere que la alta expresión de EGFR y MET puede ser un enfoque alternativo para identificar posibles respondedores

CHRYSALIS-2 Study Design: Cohort A (NCT04077463)

FASE 1/1b



Key Eligibility Criteria

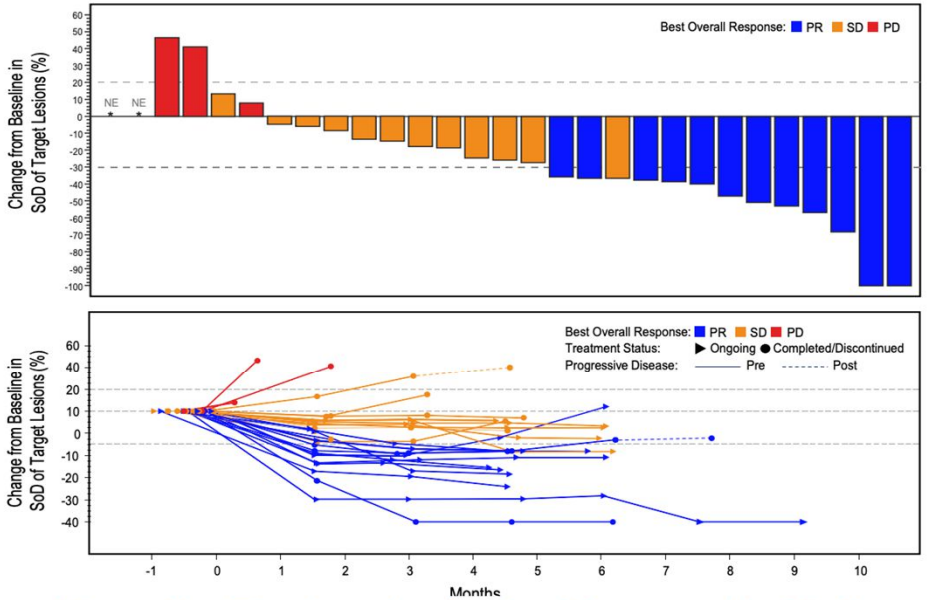
- Metastatic advanced NSCLC
- EGFR Exon19del or L858R

Endpoints

- Overall response rate (Primary)
- Clinical benefit rate
- Duration of response
- Progression-free survival
- Overall survival
- Adverse events

lung cancer research

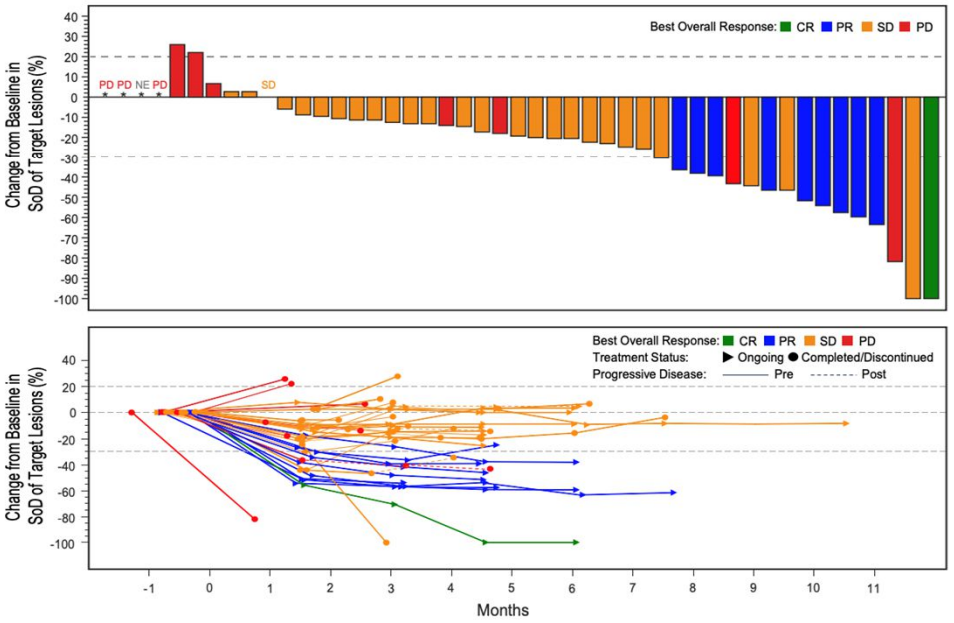
Target Population: Antitumor Activity of Amivantamab + Lazertinib



Among 29 efficacy-evaluable[a] patients at a median follow-up of 4.6 mo (range, 0.4–9.6):

- ORR = 41% (95% CI, 24–61)
- CBR = 69% (95% CI, 49–85)
- Median time on treatment = 4.2 mo (range, 0.03–8.4)
- Responses observed early
  - mTTR = 1.4 mo (range, 1.4–4.4)
- 8/12 patients who responded are progression-free and remain on treatment
- 5/12 patients with stable disease remain on treatment (longest at 6.9+ mo)

Heavily Pretreated: Antitumor Activity of Amivantamab + Lazertinib



Among 47 efficacy-evaluable[a] patients at a median follow-up of 4.5 mo (range, 0.3–9.7):

- ORR = 21% (95% CI, 11–36)
- CBR = 51% (95% CI, 36–66)
- Median time on treatment = 3.7 mo (range, 0.03–9.7)
- Responses observed early
  - mTTR = 1.5 mo (range, 1.3–4.2)
- 10/10 patients who responded are progression-free and remain on treatment
- 10/26 patients with stable disease remain on treatment (longest at 9.6+ mo)

- Actividad post quimioterapia muy parecida a lo reportado en Chrysalis(parece que la quimioterapia no impacta en la actividad)

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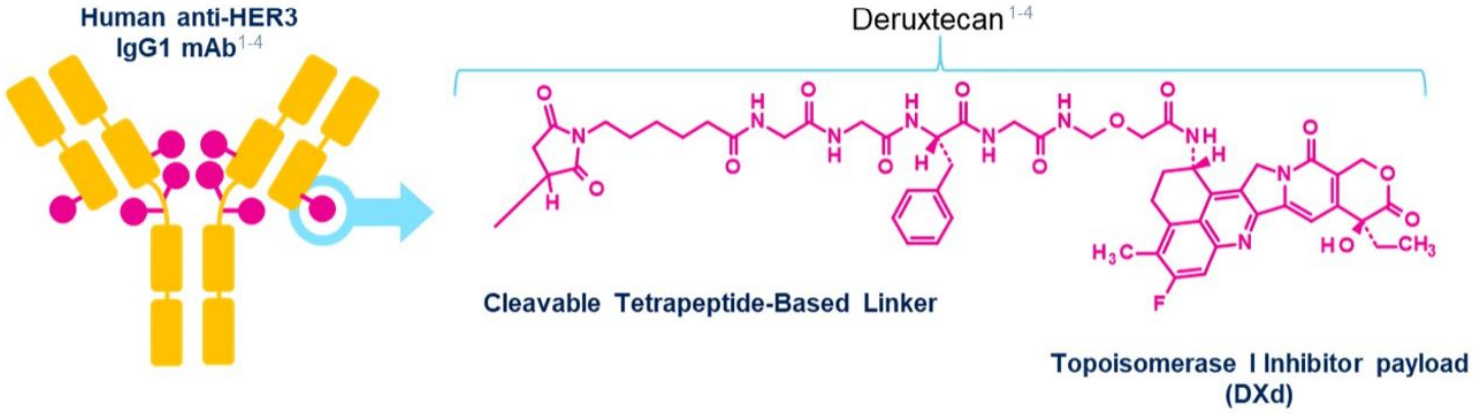
Patritumab Deruxtecan (HER3-DXd)—Targeting HER3 May Address Multiple EGFR TKI Resistance Mechanisms

- HER3-DXd is an ADC with 3 components:[1-6]
  - A fully human anti-HER3 IgG1 mAb (patritumab), covalently linked to:
  - A topoisomerase I inhibitor payload, an exatecan derivative, via
  - A tetrapeptide-based cleavable linker
- HER3-DXd is in clinical evaluation for NSCLC, metastatic breast cancer, and colorectal cancer

HER3 is expressed in 83% of NSCLC tumors[7,a]

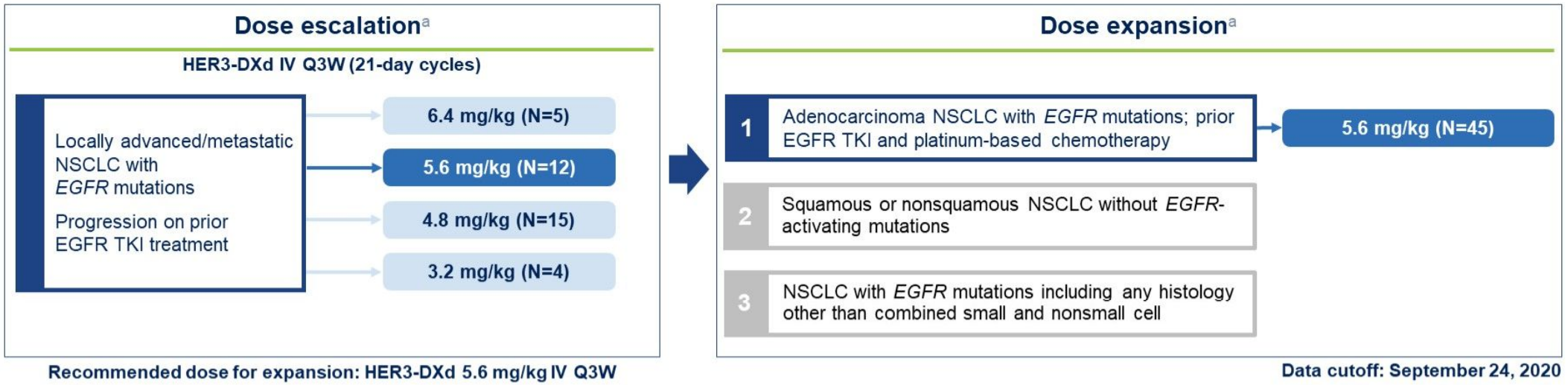
HER3 alterations are not known to be a mechanism of resistance to EGFR TKI in *EGFR*m NSCLC



[a] HER3 overexpression is associated with metastatic progression and decreased relapse-free survival in patients with NSCLC.

1. Hashimoto Y, et al. *Clin Cancer Res.* 2019;25:7151-7161. 2. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. 3. Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097-5108. 4. Koganemaru S, et al. *Mol Cancer Ther.* 2019;18:2043-2050. 5. Haratani K, et al. *J Clin Invest.* 2020;130(1):374-388. 6. Ogitani Y, et al. *Cancer Sci.* 2016;107(7):1039-1046. 7. Scharpenseel H et al, *Sci Rep* 2019;9(1):7406.

U31402-A-U102 is a Phase 1 Dose Escalation and Dose Expansion Study in Patients With NSCLC



Recommended dose for expansion: HER3-DXd 5.6 mg/kg IV Q3W

Data cutoff: September 24, 2020

57 patients with EGFR TKI–resistant, *EGFR*m NSCLC were treated with HER3-DXd 5.6 mg/kg in dose escalation (N=12) and dose expansion Cohort 1 (N=45)

- **Efficacy** evaluation in pooled patients with *EGFR*m NSCLC treated with HER3-DXd 5.6 mg/kg (**N=57**)
  (Median Follow Up: 10.2 mo; range, 5.2-19.9 mo)
- **Safety** evaluation in all patients in dose escalation and dose expansion Cohort 1 (**N=81**)

Clinicaltrials.gov, NCT03260491; EudraCT, 2017-000543-41; JapicCTI, 194868.
[a] Patients with stable brain metastases were permitted to enroll; A tumor biopsy was required prior to study entry but patients were not selected for inclusion based on measurement of HER3.

Patients with *EGFR*m NSCLC were Heavily Pre-treated with Majority Receiving Prior Platinum-based Chemotherapy

Patient Characteristics and Treatment History	HER3-DXd 5.6 mg/kg (N=57)	HER3-DXd All Doses (N=81)
Age, median (range), years	65 (40-80)	64 (40-80)
Female, n (%)	36 (63)	52 (64)
ECOG performance status 0/1, n (%)	23 (40) / 34 (60)	34 (42) / 47 (58)
Sum of diameters at baseline,[a] median (range), mm	54 (13-195)	51.5 (10-195)
History of CNS metastases, n (%)	27 (47)	43 (53)
Prior lines of systemic therapy, median (range)[b]	4 (1-9)	4 (1-9)
Prior cancer regimens		
Prior EGFR TKI therapy, n (%)	57 (100)	81 (100)
Prior osimertinib, n (%)	49 (86)	72 (89)
Prior platinum-based chemotherapy, n (%)	52 (91)	65 (80)
Prior immunotherapy, n (%)	23 (40)	28 (35)

Data cutoff: September 24, 2020.
[a] By blinded independent central review per RECIST 1.1. [b] In the locally advanced or metastatic setting

HER3-DXd Demonstrated Durable Antitumor Activity After Failure of EGFR TKI and Platinum-based Chemotherapy (PBC)

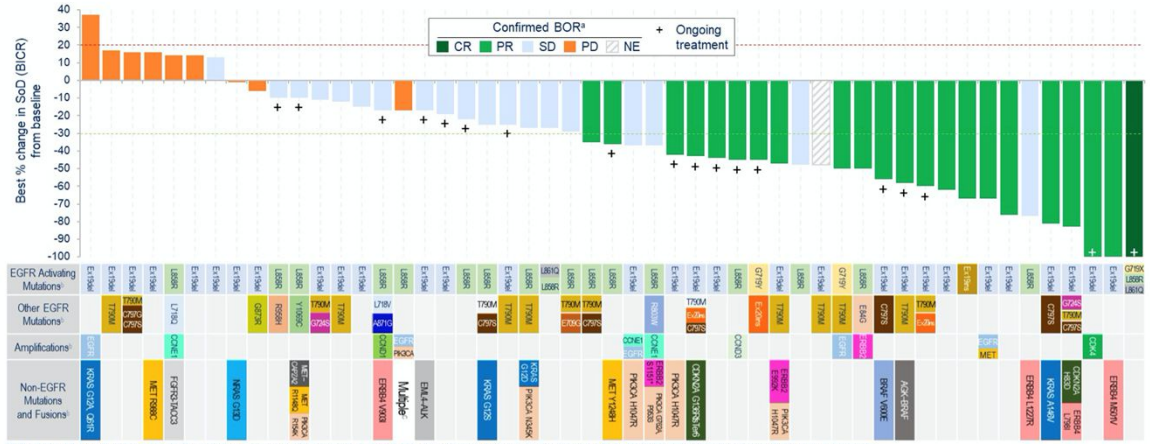
Outcomes (BICR per RECIST 1.1) Median Follow Up: 10.2 (range, 5.2-19.9) mo[a]	HER3-DXd 5.6 mg/kg Prior TKI, ± PBC (N=57)	HER3-DXd 5.6 mg/kg Prior OSI, PBC (N=44)
Confirmed ORR, % (95% CI)	39 (26-52)	39 (24-55)
Best overall response, n (%)		
CR	1 (2)	1 (2)
PR	21 (37)	16 (36)
SD, Non-CR/Non-PD	19 (33)	13 (30)
PD	9 (16)	8 (18)
Not evaluable	7 (12)	6 (14)
Disease control rate, % (95% CI)	72 (59-83)	68 (52-81)
Time to response, median (range), mo	2.6 (1.2-5.4)	2.7 (1.2-5.4)
Duration of response, median (95% CI), mo	6.9 (3.1-NE)	7.0 (3.1-NE)
PFS, median (95% CI), mo	8.2 (4.4-8.3)	8.2 (4.0-NE)

BICR, blinded independent central review; CR, complete response; NE, not evaluable; ORR, objective response rate; OSI, osimertinib; PBC, platinum-based chemotherapy; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
Data cutoff: September 24, 2020.
[a] For patients treated with the recommended dose for expansion of HER3-DXd (N=57)

The subgroup of patients treated with prior **osimertinib (OSI)** and **platinum-based chemotherapy** demonstrated similar efficacy to the overall efficacy population

HER3-DXd Demonstrated Activity in Patients With Diverse Mechanisms of EGFR TKI Resistance

Patritumab Deruxtecan
U31402-A-U102



BICR, blinded independent central review; BOR, best overall response; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD stable disease; SoD, sum of diameters.
Data cutoff: September 24, 2020.
[a] Six patients had BORs of NE due to no adequate post-baseline tumor assessment and are not shown; 1 had BOR of NE due to SD too early (< 5 weeks) and is shown with hatched markings [b] Genomic alterations known to be associated with EGFR TKI resistance identified in assays of tumor tissue/ctDNA in blood, collected prior to treatment with HER3-DXd. [c] CDKN2A A143V, PIK3CA E542K, E545K, E726K, ERBB2 K200N, ERBB3 Q847*, Q849*.

- ORR 39%
- Tasa de control de la enfermedad 72-68%
- Mediana de duración de respuesta 7 meses
- PFS 8.2 meses
- Independiente del mecanismo de resistencia

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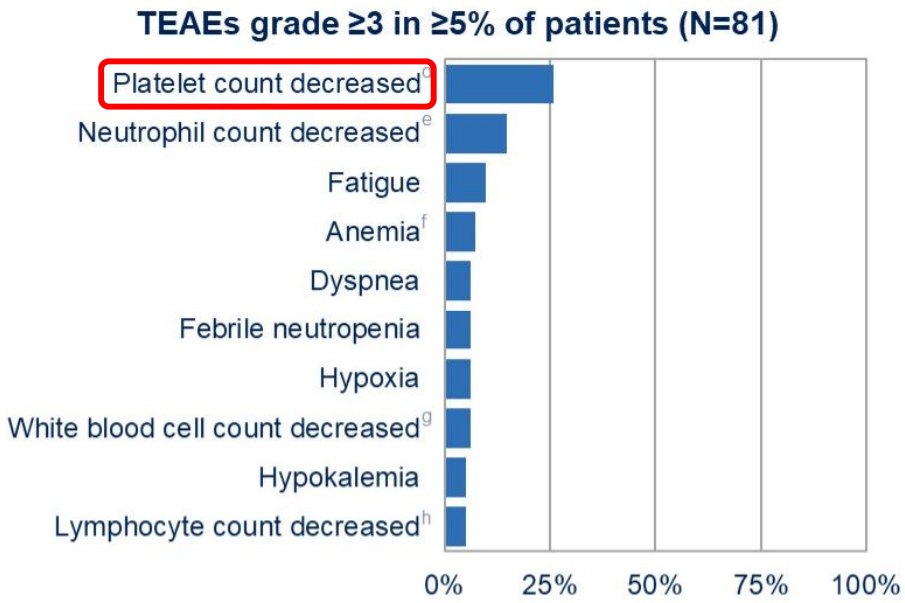
HER3-DXd Was Associated With a Manageable Safety Profile and a Low Rate of Discontinuations Due to Adverse Events

TEAEs, n (%) Median treatment duration: 5.7 (range, 0.7-28.3) mo	5.6 mg/kg (N=57)	All Doses (N=81)
Any TEAE	57(100)	81 (100)
Associated with treatment discontinuation[a]	6 (11)	7 (9)
Associated with treatment dose reduction	12 (21)	18 (22)
Associated with treatment dose interruption	21 (37)	30 (37)
Associated with death[b]	4 (7)	5 (6)
Grade ≥3 TEAE	42 (74)	52 (64)
Treatment-related TEAE:	55 (96)	78 (96)
Associated with death	0	0
Grade ≥3	31 (54)	38 (47)
Serious TEAE	12 (21)	15 (19)
Interstitial lung disease[c]	4 (7)	4 (5)
Grade 1	2 (4)	2 (2)
Grade 2	1 (2)	1 (1)
Grade 3	1 (2)	1 (1)
Grade 4/5	0	0



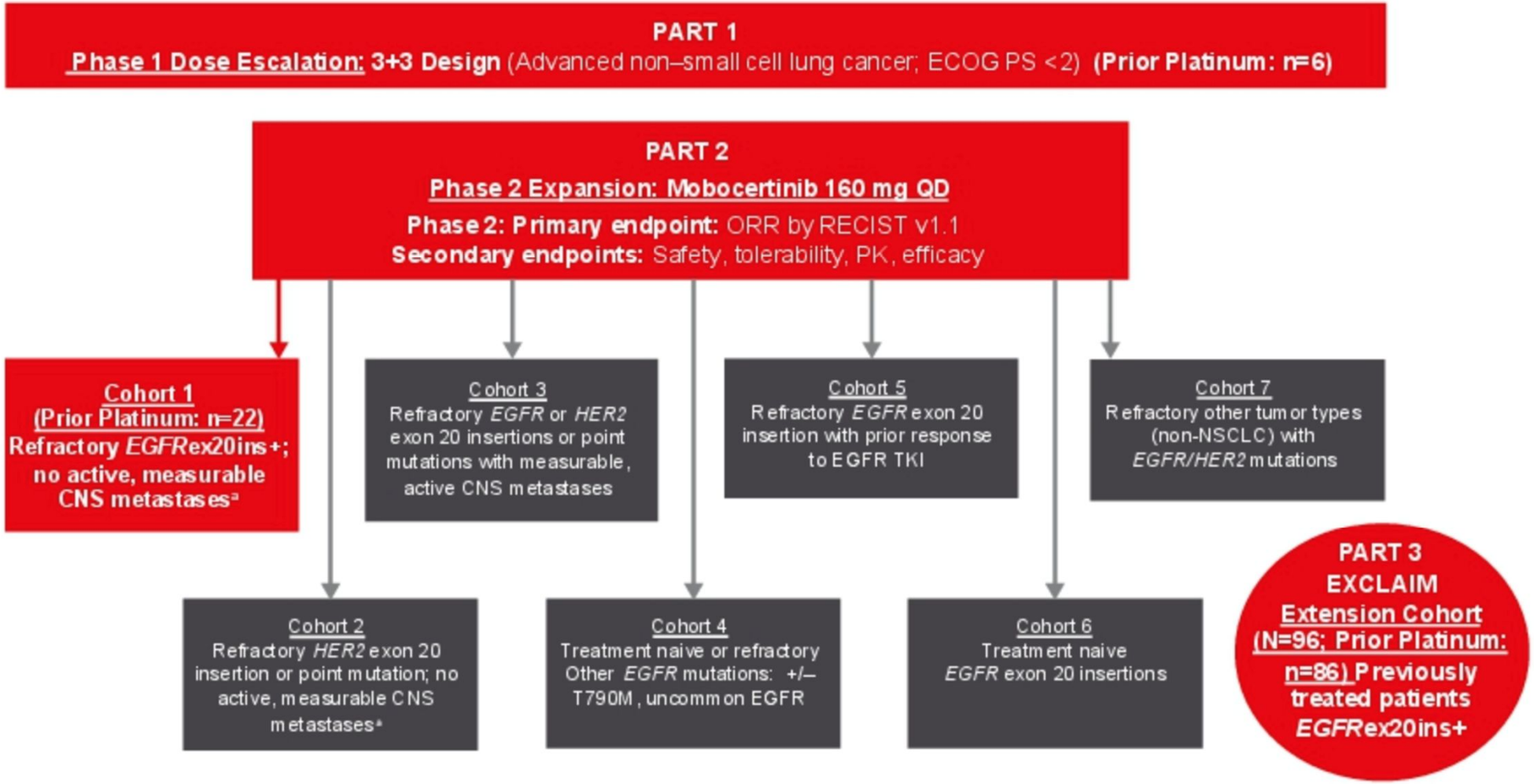
- The rate of adjudicated treatment-related interstitial lung disease was 5%; none were grade 4/5
- Median time to adjudicated onset of treatment-related interstitial lung disease was 53 (range, 13-130) days

Data cutoff: September 24, 2020.

[a] TEAEs associated with treatment discontinuation were fatigue (2); nausea, decreased appetite, interstitial lung disease, neutrophil count decreased, pneumonitis, and upper respiratory tract infection; none were for thrombocytopenia (1 each). [b] TEAEs associated with death were: disease progression (2), respiratory failure (2), and shock (1). [c] One additional occurrence of Grade 5 ILD was determined by adjudication to be unrelated to study treatment. [d] Includes thrombocytopenia. [e] Includes neutropenia. [f] Includes hemoglobin decreased. [g] Includes leukopenia. [h] Includes lymphopenia.

Mobocertinib (TAK-788) in EGFR exon 20 insertion (ex20ins)+ metastatic NSCLC (mNSCLC): Additional results from platinum-pretreated patients (pts) and EXCLAIM cohort of phase 1/2 study.

Suresh S. Ramalingam et al. J Clin Oncol 39, 2021 (suppl 15; abstr 9014)



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Efficacy

Table 2. Mobocertinib Clinical Activity in Previously Treated *EGFR*ex20ins+ mNSCLC

	PPP Cohort n=114	EXCLAIM Cohort n=96
IRC assessments		
Confirmed ORR (95% CI)	28% (20%–37%)	25% (17%–35%)
CR, %	0%	0%
PR, %	28%	25%
Median DoR (95% CI)[a]	17.5 months (7.4–20.3)	NE (5.6–NE)
Confirmed DCR (95% CI)[b]	78% (69%–85%)	76% (66%–84%)
Investigator assessments		
Confirmed ORR, % (95% CI)	35% (26%–45%)	32% (23%–43%)
CR, %	<1%	1%
PR, %	34%	31%
Median DoR, months (95% CI)[a]	11.2 months (5.6–NE)	11.2 months (7.0–NE)
Confirmed DCR (95% CI)[b]	78% (69%–85%)	75% (65%–83%)

Data cutoff date: November 1, 2020

[a]DoR per Kaplan-Meier estimates; [b]DCR defined as confirmed CR or PR, or best response of stable disease for at least 6 weeks after initiation of study drug

Median ORR 25-28%
Median PFS 7.3 months
Median DoR 17.5 months
Median OS 24 months

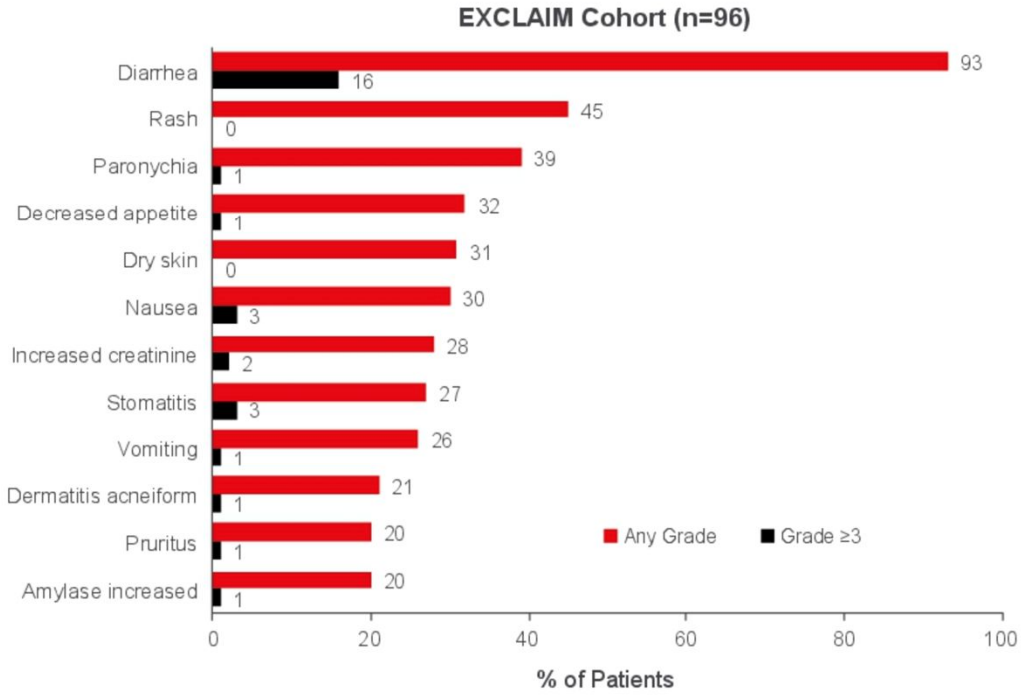
-CNS was common site of PD on study
-Mobocertinib effective against all types of EGFR ex20ins
-Dose reduction in 22-25% due to AE
-Study drug discontinuation in 10-17% due to AE

Safety

Table 4. Overview of Adverse Events (AEs)

	PPP Cohort (n=114)		EXCLAIM Cohort (n=96)	
n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE	114 (100)	79 (69)	96 (100)	63 (66)
Any treatment-related AE	113 (99)	54 (47)	95 (99)	40 (42)
Serious AE	56 (49)	52 (46)	45 (47)	42 (44)
AE leading to dose reduction	29 (25)	—	21 (22)	—
AE leading to treatment discontinuation	19 (17)	—	10 (10)	—

Data cutoff date: November 1, 2020



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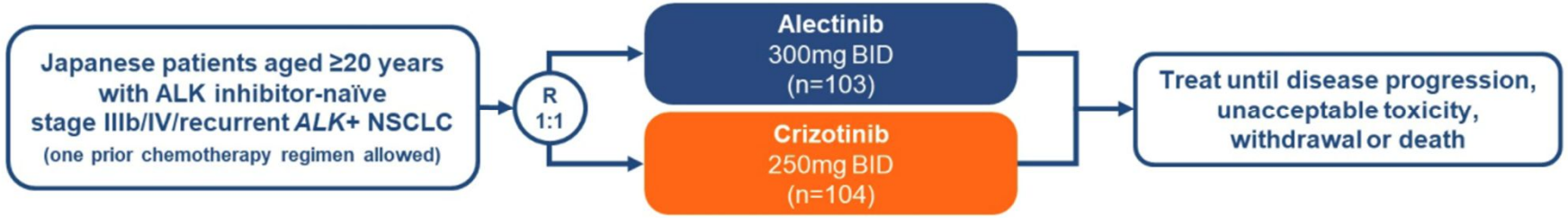
ALK

Yoshioka H, et al.

Abstract number #9022

Final OS analysis from the phase III J-ALEX study of alectinib (ALC) vs. crizotinib (CRZ) in Japanese ALK-inhibitor naïve *ALK*-positive non-small cell lung cancer (*ALK*+ NSCLC)



Primary endpoint: IRF-assessed PFS

Secondary endpoints: OS, ORR, DoR, time to response, CNS PFS, HRQoL, safety and PK

Objective of this analysis: To report the final OS analysis from J-ALEX after a minimum of 5 years of follow up

Median duration of OS follow-up:
68.6 months alectinib vs 68.0 months crizotinib

	ITT population (N=207)[1]	
Baseline demographics	**Alectinib (n=103)**	**Crizotinib (n=104)**
Median age, years (range)	61.0 (27–85)	59.5 (25–84)
Female / Male, %	60.2 / 39.8	60.6 / 39.4
ECOG PS 0 / 1 / 2, %	52.4 / 45.6 / 1.9	46.2 / 51.9 / 1.9
First / second treatment line, %	64.1 / 35.9	64.4 / 35.6
Stage IIIB / Stage IV / recurrent, %	2.9 / 73.8 / 23.3	2.9 / 72.1 / 25.0
Brain metastases by IRF, %	13.6	27.9

Mature PFS data from J-ALEX was previously reported; alectinib demonstrated superiority in IRF-assessed PFS vs crizotinib (HR 0.37, 95% CI 0.26–0.52; median PFS 34.1 vs 10.2 months)[2]

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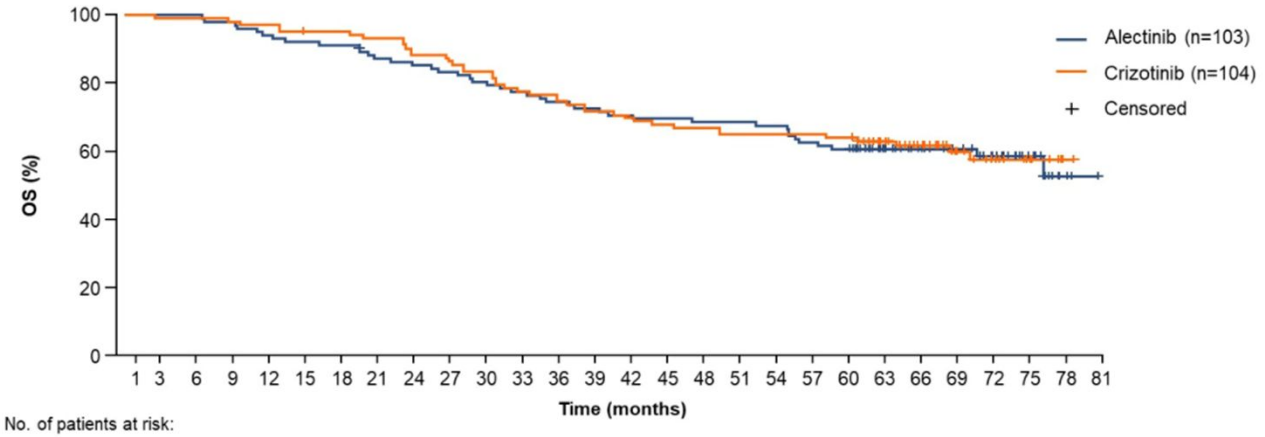
OS in the ITT population



No. of patients at risk:

Crizotinib	104	103	103	102	101	98	98	96	91	88	86	80	77	74	72	70	69	67	67	67	66	54	42	27	20	10	2
Alectinib	103	103	103	101	97	95	94	89	87	85	82	79	76	74	72	71	70	70	69	64	62	48	40	31	23	13	3

- In total, 83 death events occurred, 42 (40.8%) in the alectinib arm and 41 (39.4%) in the crizotinib arm
- Superiority in OS was not demonstrated at the final analysis (HR 1.03, 95.0405% CI 0.67–1.58)
- Median OS was not reached in either treatment arm; alectinib NE (95% CI 70.6–NE) and crizotinib NE (95% CI 68.3–NE)

Median duration of follow up: alectinib 68.6 months (range 6–81); crizotinib 68.0 months (range 2 –79). NE, not estimable

n (%)	Alectinib (n=103)	Crizotinib (n=104)
Patients with at least one treatment	48 (46.6)	95 (91.3)
ALK inhibitors	26 (25.2)	86 (82.7)
Alectinib	0	82 (78.8)
Crizotinib	11 (10.7)	0
Brigatinib	6 (5.8)	1 (1.0)
Lorlatinib	4 (3.9)	3 (2.9)
Ceritinib	5 (4.9)	0
Chemotherapy	18 (17.5)	7 (6.7)
Pemetrexed	13 (12.6)	5 (4.8)
VEGF inhibitor	4 (3.9)	1 (1.0)
Cancer immunotherapy	2 (1.9)	0
RANKL inhibitor[a]	2 (1.9)	2 (1.9)

CrossOver

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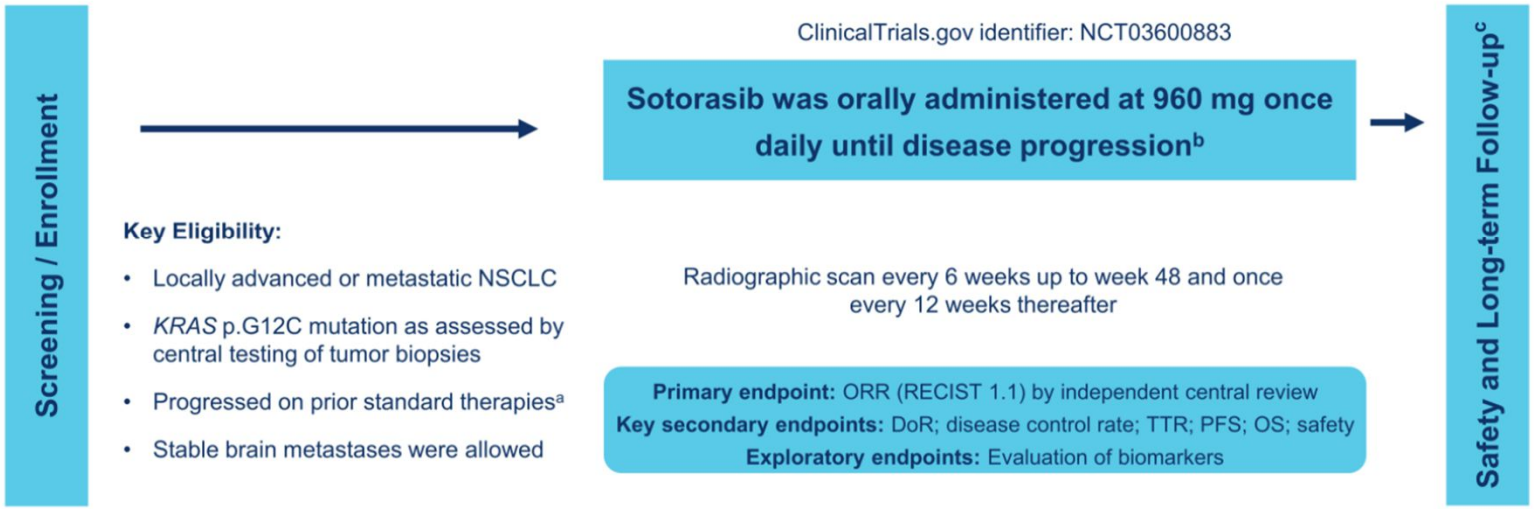
KRAS (OS y análisis de subgrupos)

Seguimiento
15 meses

Phase 2 CodeBreaK100 Trial Design



Baseline Characteristics	Sotorasib 960mg, QD N = 126
Median age – years (range)	63.5 (37–80)
ECOG performance status – n (%)	
0	38 (30.2)
1	88 (69.8)
Smoking history – n (%)	
Never	6 (4.8)
Current or former	117 (92.9)
Prior lines of systemic anticancer therapy – n (%)	
1	54 (42.9)
2	44 (34.9)
3	28 (22.2)
Types of prior anticancer therapy – n (%)	
Platinum-based chemotherapy	113 (89.7)
PD-1 or PD-L1 inhibitors	115 (91.3)
Platinum-based chemotherapy and PD-1/PD-L1 inhibitors	102 (81.0)

a: no more than 3 prior lines of therapies were allowed; b: treatment beyond disease progression was allowed if certain criteria were met; c: safety follow-up occurs 30 (+7) days after the last dose of sotorasib; long-term follow-up occurs every 12 (±2) weeks for up to 3 years. NSCLC: non-small cell lung cancer; ORR: objective response rate; DoR: duration of response; TTR: time to response; PFS: progression-free survival; OS: overall survival; RECIST: Response Evaluation Criteria in Solid Tumors.

Tumor Response

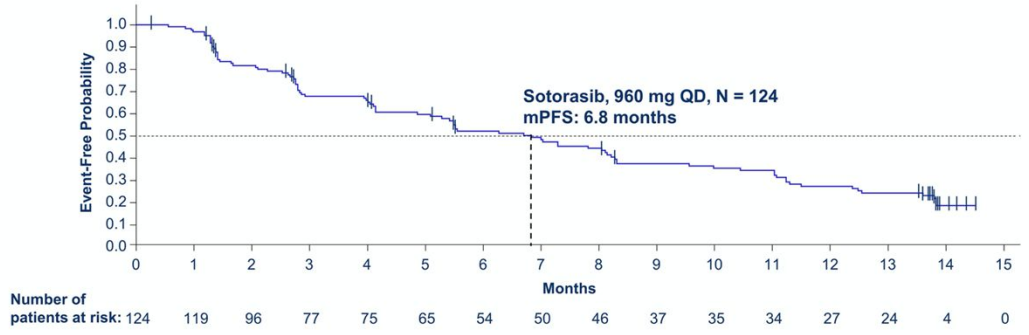
	Sotorasib 960mg, QD N = 124[a]
Objective Response Rate – % (95% CI)	37.1 (28.6, 46.2)
Best Overall Response – n (%)	
Complete response	4 (3.2)
Partial response	42 (33.9)
Stable disease	54 (43.5)
Progressive disease	20 (16.1)
Not evaluable or missing scan[b]	4 (3.2)
Disease Control Rate – % (95% CI)	80.6 (72.6, 87.2)
Duration of Response – months	
Median (95% CI)	11.1 (6.9, NE)
Time to Response – months	
Median (min, max)	1.35 (1.2, 10.1)

a: according to central review, 2 patients did not have measurable lesions at baseline per RECIST 1.1 and were excluded from response assessment; b: 2 patients stopped treatment without postbaseline scans and were deemed as "missing scan"; 2 patients had 1 postbaseline scan and were assessed as "not evaluable" by central review.
CI: confidence interval; NE: not evaluable; QD: once a day; RECIST: Response Evaluation Criteria in Solid Tumors.

- ORR 37,1%
- Tasa de control de la enfermedad 80.6%
- Duración media respuesta 11.1 meses
- mPFS 6.8 meses
- OS 12.5 meses (17.7 meses en los que habían recibido solo 1 línea)

Over 80% of patients achieved disease control with sotorasib, including 4 complete responses and 42 partial responses

Progression-Free Survival



QD: once a day; mPFS: median progression-free survival; CI: confidence interval.

Median progression-free survival was 6.8 months (95% CI: 5.1, 8.2)

Overall Survival

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QD: once a day; mOS: median overall survival; CI: confidence interval.

Median overall survival was 12.5 months (95% CI: 10.0, not evaluable)

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Safety

Treatment-Related Adverse Events (TRAEs) Occurring in > 5%	Any Grade N = 126 n (%)	Grade 3 N = 126 n (%)
Any TRAEs	88 (69.8)	25 (19.8)
Diarrhea	40 (31.7)	5 (4.0)
Nausea	24 (19.0)	0
ALT increase	19 (15.1)	8 (6.3)
AST increase	19 (15.1)	7 (5.6)
Fatigue	14 (11.1)	0
Vomiting	10 (7.9)	0
Blood alkaline phosphatase increase	9 (7.1)	1 (0.8)
Maculopapular rash	7 (5.6)	0

One patient (0.8%) reported grade 4 TRAEs (pneumonitis and dyspnea)

- **No fatal TRAEs occurred**
- **TRAEs led to dose modifications in 28 patients (22.2%)**
- **TRAEs led to treatment discontinuation in 9 patients (7.1%)**
  - Drug-induced liver injury (n=3, 2.4%)
  - LFT increase (n=1, 0.8%)
  - ALT increase (n= 2, 1.6%)
  - AST increase (n=2, 1.6%)
  - Blood alkaline phosphatase increase (n=1, 0.8%)
  - Transaminases increase (n=1, 0.8%)
  - Pneumonitis (n=2, 1.6%)
  - Dyspnea (n=1, 0.8%)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; LFT: liver function test.

Treatment-related adverse events were mostly grade 1 or 2 and were generally manageable

HER 2

DESTINY-Lung01 Study Design

Trastuzumab deruxtecan

Multicenter, international, 2-cohort phase 2 trial (NCT03505710)

Key eligibility criteria

- Unresectable/metastatic nonsquamous NSCLC
- Relapsed from or is refractory to standard treatment
- Measurable disease by RECIST v1.1
- Asymptomatic CNS metastases at baseline[a]
- ECOG PS of 0 or 1
- Locally reported *HER2* mutation (for Cohort 2)[b]

Cohort 1: HER2-overexpressing[c] (IHC 3+ or IHC 2+)
T-DXd 6.4 mg/kg q3w
N = 49

Cohort 1a: HER2-overexpressing[c] (IHC 3+ or IHC 2+)
T-DXd 5.4 mg/kg q3w
N = 41

Cohort 2:
***HER2*-mutated**
T-DXd 6.4 mg/kg q3w
N = 42

Cohort 2 expansion:
***HER2*-mutated**
T-DXd 6.4 mg/kg q3w
N = 49

Primary end point
- Confirmed ORR by ICR[d]

Secondary end points
- DOR
- PFS
- OS
- DCR
- Safety

Exploratory end point
- Biomarkers of response

Data cutoff: May 3, 2021

- 91 patients with *HER2*m NSCLC were enrolled and treated with T-DXd
- 15 patients (16.5%) remain on treatment to date
- 76 patients (83.5%) discontinued, primarily for progressive disease (37.4%) and adverse events (29.7%)

Prior Therapies

	Patients (N = 91)
History of any prior systemic cancer therapy, n (%)	**90 (98.9)**
Prior lines of treatment, median (range)	2 (0-7)[a]
Prior treatment, n (%)	
Platinum-based therapy	86 (94.5)
Anti–PD-(L)1 therapy	60 (65.9)
Platinum-based and anti–PD-(L)1 therapy[b]	57 (62.6)
Docetaxel	18 (19.8)
HER2 TKI[c]	13 (14.3)

[a]One patient was enrolled without receiving prior cancer therapy
[b]Given separately or in combination
[c]Patients previously treated with a HER2 antibody or an antibody-drug conjugate were ineligible, but those who previously received a HER2 TKI such as afatinib, pyrotinib, or poziotinib were allowed

Demographics and Baseline Characteristics

	T-DXd (N = 91)
Age, median (range), years	60.0 (29.0-88.0)
Female, %	65.9
Race, %	
Asian	34.1
White	44.0
Black	1.1
Other	20.9
Region, %	
Asia	25.3
Europe	36.3
North America	38.5
ECOG PS, %	
0 | 1	25.3 | 74.7
***HER2* mutation, %**	
Kinase domain	93.4
Extracellular domain	6.6
Asymptomatic CNS metastases at baseline, %	36.3
Smoking status, %	
Never | Former | Current	57.1 | 40.7 | 2.2
History of prior lung resection, %	22.0

Confirmed ORR, Best Overall Response, and DoR

	Patients (N = 91)
Confirmed ORR[a], n (%)	**50 (54.9)** (95% CI, 44.2-65.4)
Best overall response, n (%)	
CR	**1 (1.1)**
PR	**49 (53.8)**
SD	**34 (37.4)**
PD	**3 (3.3)**
Not evaluable	**4 (4.4)**
DCR, n (%)	84 (92.3) (95% CI, 84.8-96.9)
Median DoR, months	9.3 (95% CI, 5.7-14.7)
Median follow up, months	13.1 (range, 0.7-29.1)

[a]Primary endpoint

- Tasa de respuesta objetiva del 54.9%
- Tasa control de la enfermedad de 92.3%
- Mediana de duración de respuesta 9.3 meses

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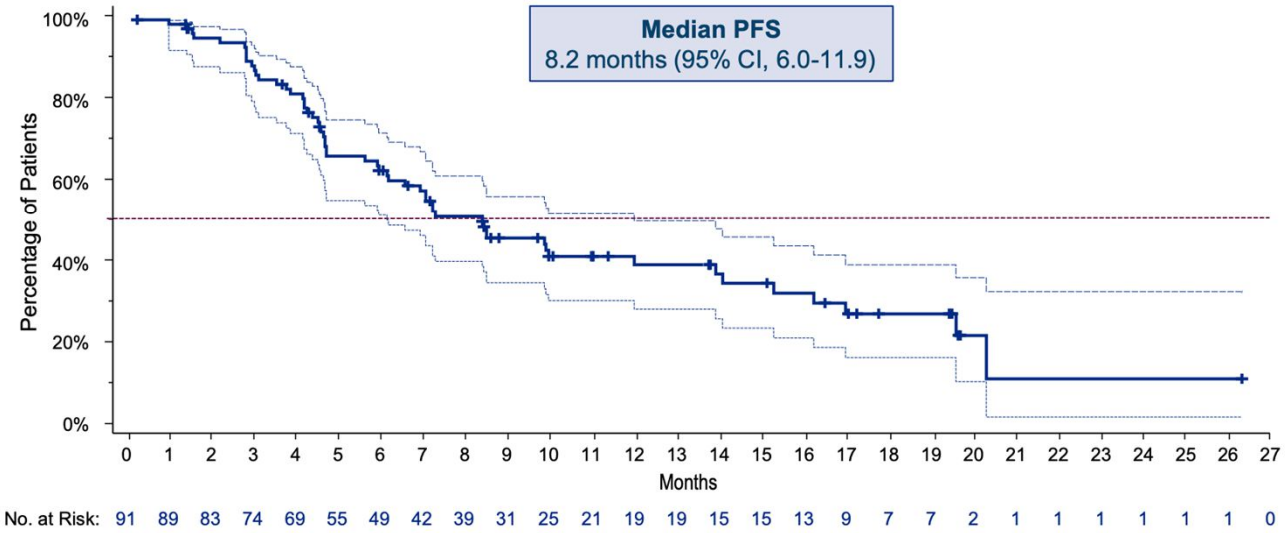
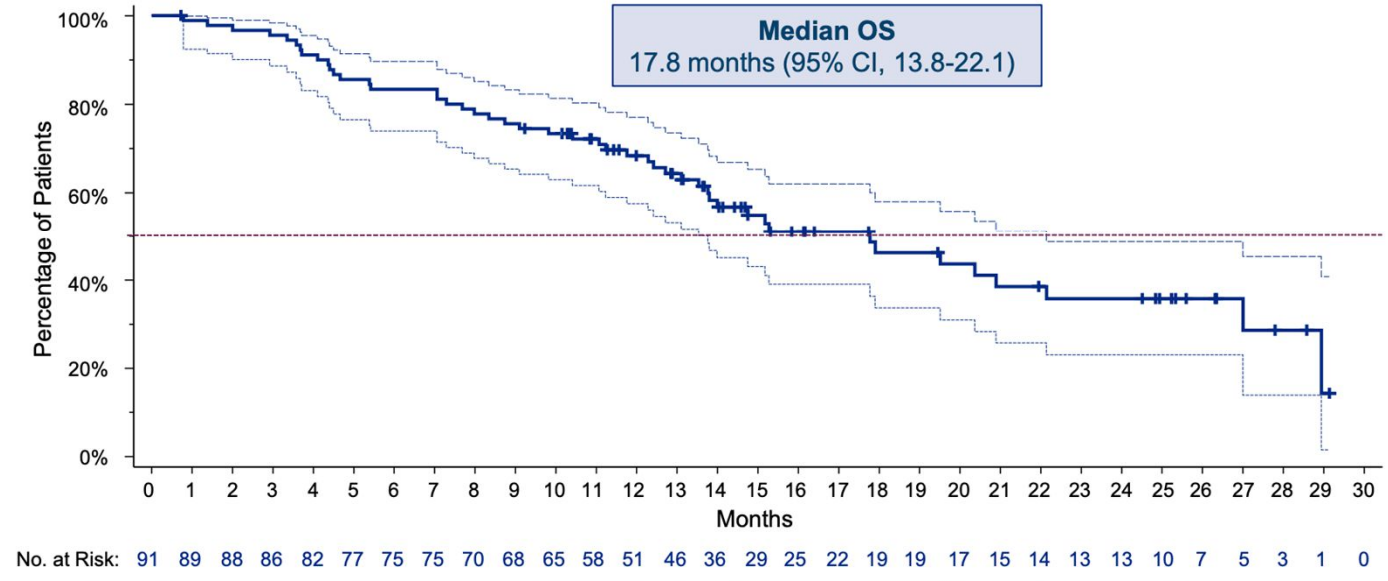
Progression-free Survival



Overall Survival



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Overall Safety Summary

n (%)	Patients (N = 91)
Any drug-related TEAE	88 (96.7)
Drug-related TEAE Grade ≥3	42 (46.2)
Serious drug-related TEAE	18 (19.8)
Drug-related TEAE associated with discontinuation[a]	23 (25.3)
Drug-related TEAE associated with dose reduction	31 (34.1)
Drug-related TEAE associated with an outcome of death	2 (2.2)[c]

- Median treatment duration was 6.9 months (range, 0.7-26.4 months)
- The most common drug-related TEAEs associated with treatment discontinuation were investigator-reported pneumonitis (13.2%) and ILD (5.5%)
- The most common drug-related TEAEs associated with dose reduction were nausea (11.0%) and fatigue (8.8%)

Conclusions

- T-DXd demonstrated **robust and durable anticancer activity** in patients with previously-treated *HER2*m NSCLC
  - Efficacy was consistently observed across subgroups, including in those patients with stable CNS metastases
  - Exploratory analyses demonstrated anticancer activity across different *HER2* mutation subtypes, as well as in patients with no detectable HER2 expression or *HER2* gene amplification
- Overall, the **safety profile** was **consistent** with previously reported studies
  - Most adjudicated drug-related ILD/pneumonitis cases were of low grade
  - ILD/pneumonitis remains an important identified risk. Effective early detection and management are critical in preventing high-grade ILD/pneumonitis
- The 5.4 mg/kg dose is being explored in future studies to evaluate the optimal dosing regimen in patients with *HER2*m NSCLC (DESTINY-Lung02; NCT04644237)
- DESTINY-Lung01 provides **compelling evidence of positive benefit/risk balance** with T-DXd in the 2L+ setting and supports its establishment as a **potential new treatment standard**

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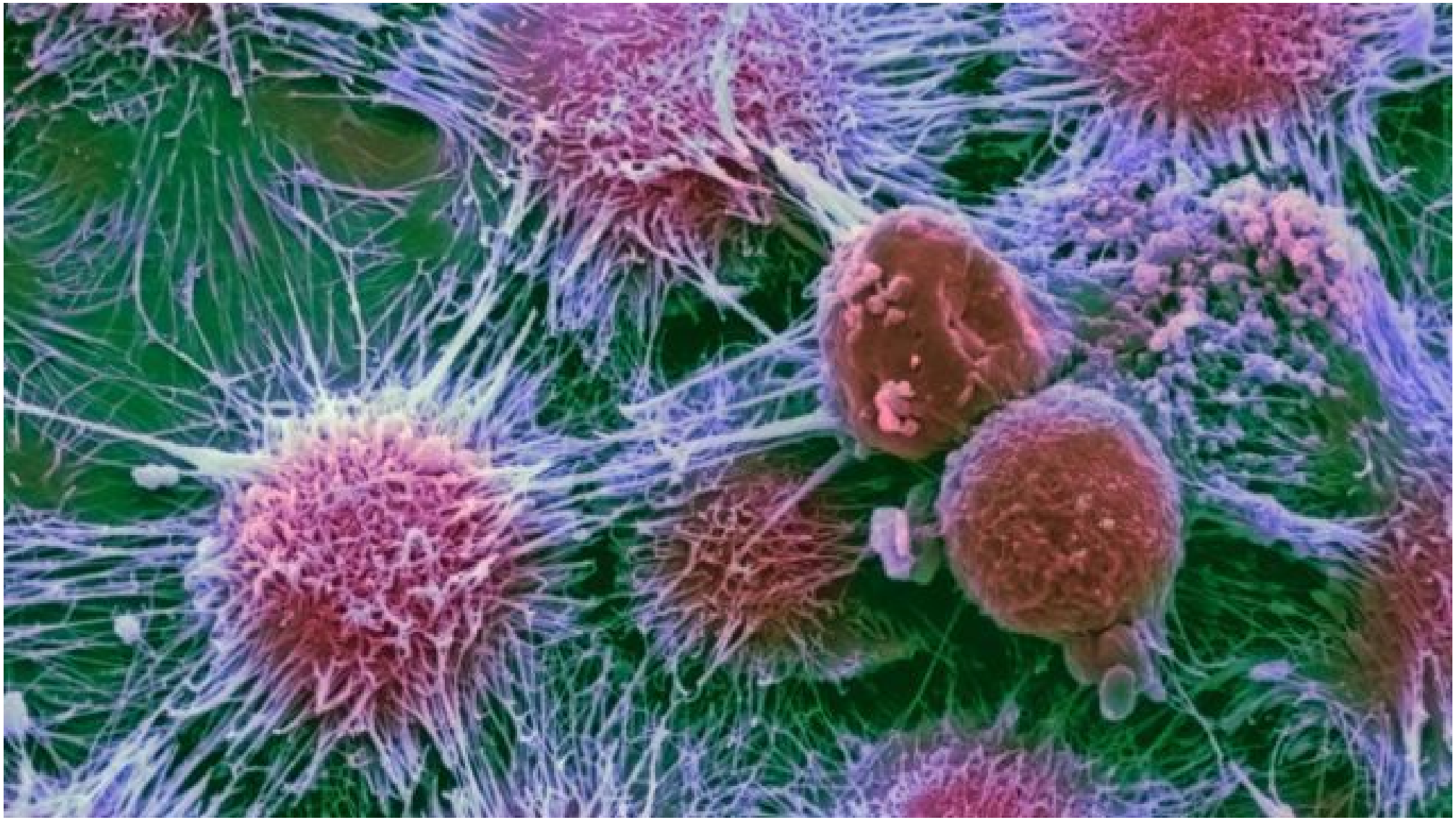
Inmunoterapia



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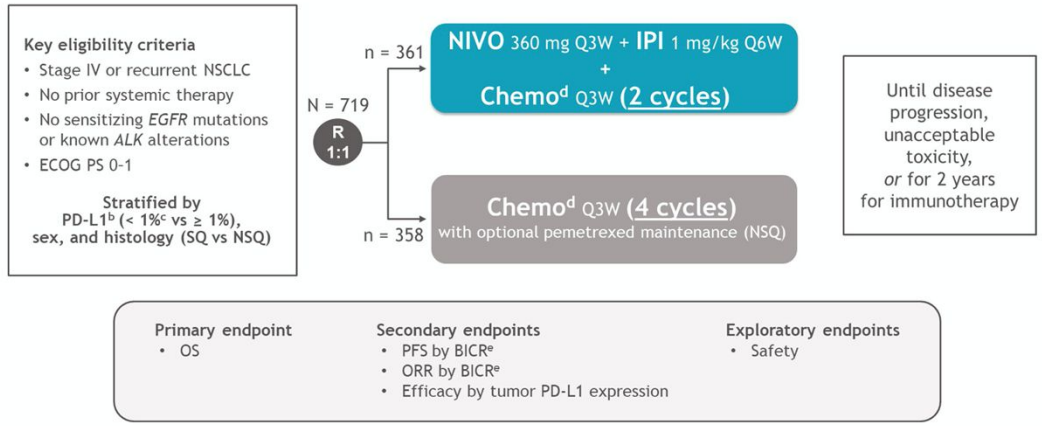
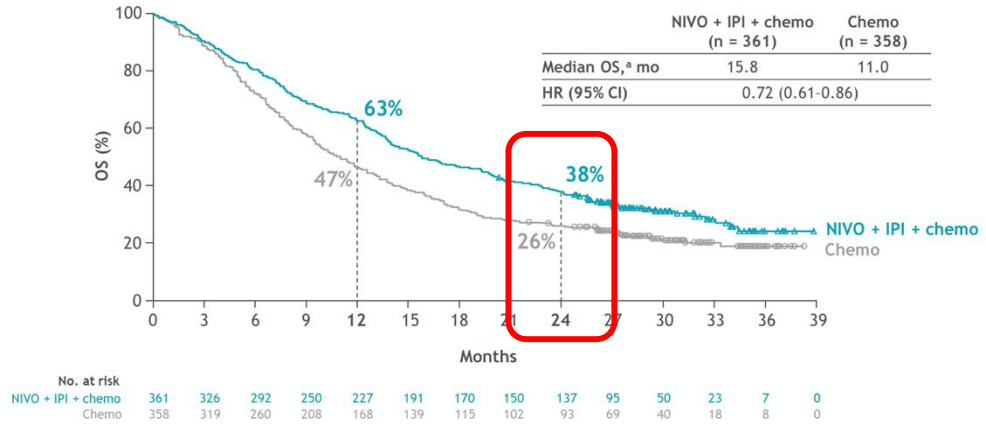
CheckMate 9LA

2 años de seguimiento y análisis de eficacia post hoc en pacientes que suspendieron por efectos adversos

CheckMate 9LA study design[a]

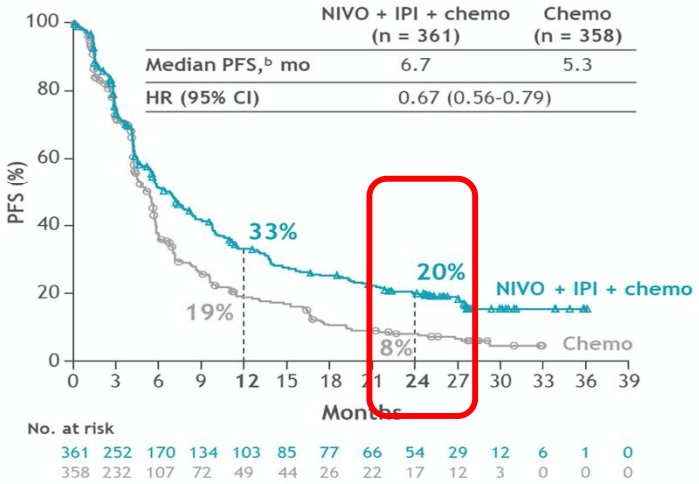


2-Year update: OS in all randomized patients

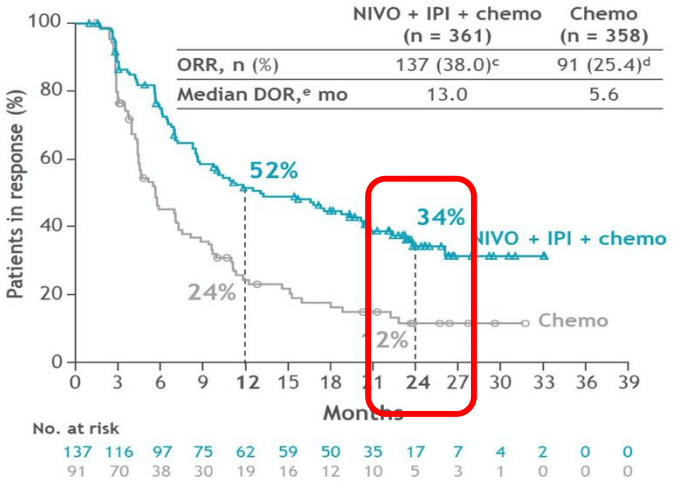


2-Year update: PFS and DOR

PFS[a]



DOR[a]



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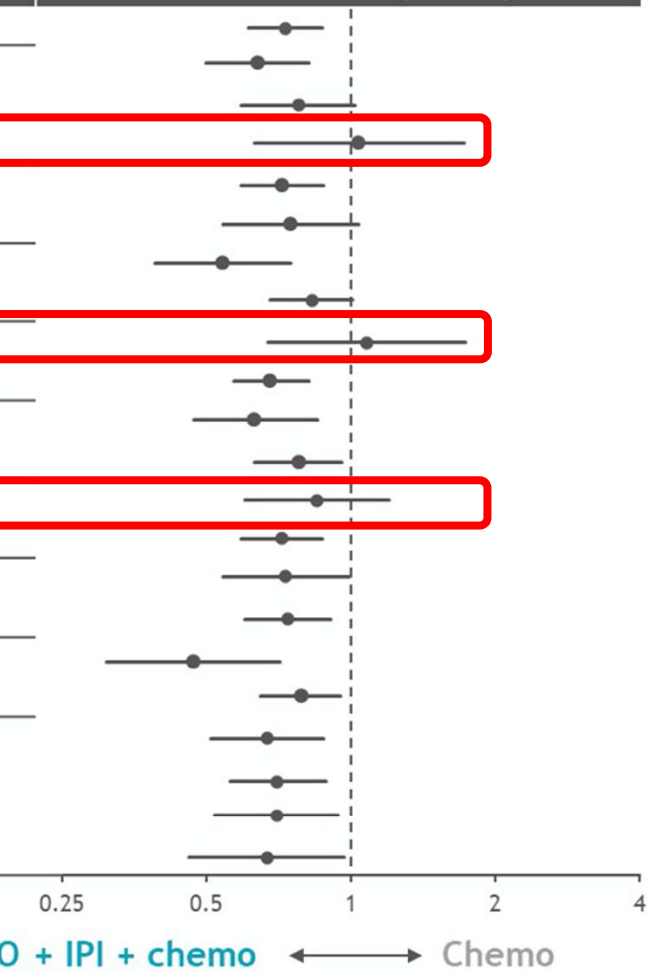
2-Year update: OS subgroup analysis

Subgroup	Median OS, mo		Unstratified HR	Unstratified HR (95% CI)
	NIVO + IPI + chemo n = 361	Chemo n = 358		
All randomized (N = 719)	15.8	11.0	0.73	
< 65 years (n = 354)	15.9	10.7	0.64	
≥ 65 to < 75 years (n = 295)	19.0	11.9	0.78	
≥ 75 years (n = 70)	8.5	11.5	1.04	
Male (n = 504)	14.2	9.8	0.72	
Female (n = 215)	22.2	15.9	0.75	
ECOG PS 0 (n = 225)	27.1	14.1	0.54	
ECOG PS 1 (n = 492)	13.6	9.7	0.83	
Never smoker (n = 98)	14.1	14.4	1.08	
Smoker (n = 621)	16.2	10.4	0.68	
SQ (n = 227)	14.5	9.1	0.63	
NSQ (n = 492)	17.8	12.0	0.78	
Liver metastases (n = 154)	10.2	8.1	0.85	
No liver metastases (n = 565)	19.3	12.4	0.72	
Bone metastases (n = 207)	11.9	8.3	0.73	
No bone metastases (n = 512)	19.7	12.4	0.74	
CNS metastases (n = 123)	19.9	7.9	0.47	
No CNS metastases (n = 596)	15.6	11.8	0.79	
PD-L1 < 1% (n = 264)	17.7	9.8	0.67	
PD-L1 ≥ 1% (n = 407)	15.8	10.9	0.70	
PD-L1 1-49% (n = 233)	15.2	10.4	0.70	
PD-L1 ≥ 50% (n = 174)	18.9	12.9	0.67	

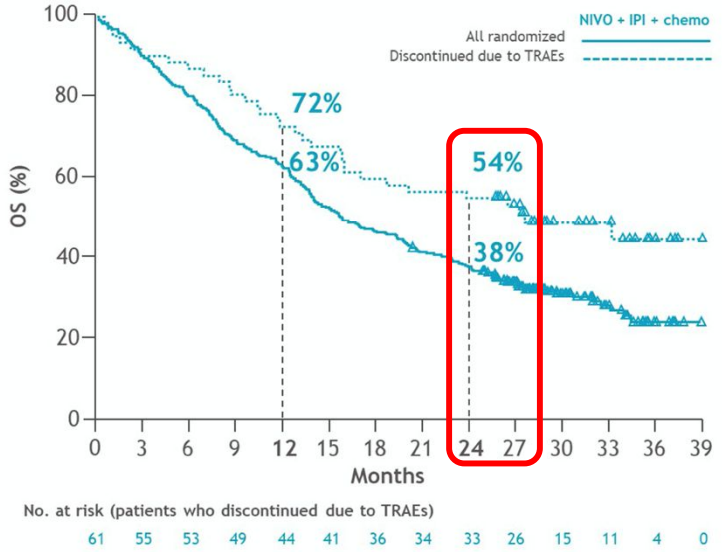


2-Year update: safety and exposure summary

TRAE,[a] %	NIVO + IPI + chemo (n = 358)		Chemo (n = 349)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any TRAE	92	48	88	38
TRAEs leading to discontinuation of any component of the regimen	22	18	8	5
TRAEs leading to discontinuation of all components of the regimen	17	14	6	3
Serious TRAEs	30	26	18	15
Treatment-related deaths[b]	2		2	

- Median (range) duration of therapy: 6.1 (0-24.4) months with NIVO + IPI + chemo; 2.5 (0-34.5) months with chemo
- In the NIVO + IPI + chemo arm, patients received a median (range) of 9.0 (1-36) doses of NIVO and 4.0 (1-18) doses of IPI; 93% of patients received 2 cycles of chemo
- Incidence of exposure-adjusted TRAEs per 100 patient-years: 714.8 (NIVO + IPI + chemo); 880.0 (chemo)

Efficacy in patients who discontinued NIVO + IPI + chemo due to TRAEs[a]



Patients who discontinued all components of NIVO + IPI + chemo due to TRAEs

	NIVO + IPI + chemo (n = 61)
Median OS,[b] mo	27.5
2-year OS rate, %	54
ORR, n (%)	31 (51)
Median DOR after discontinuation,[c] mo	14.5
Ongoing response for ≥ 1 year after discontinuation,[c] %	56

Among patients who discontinued all components of NIVO + IPI + chemo due to TRAEs:
- Median (range) number of doses was 7 (1–33) for NIVO and 3 (1–17) for IPI
- Median (range) duration of treatment was 4.4 (0–23.3) months

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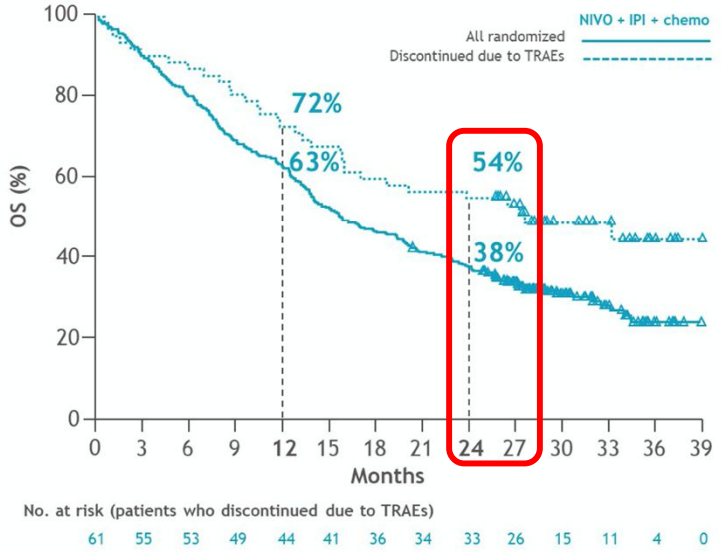
These updated results continue to support NIVO + IPI + 2 cycles of chemo as an efficacious 1L treatment option for patients with advanced NSCLC



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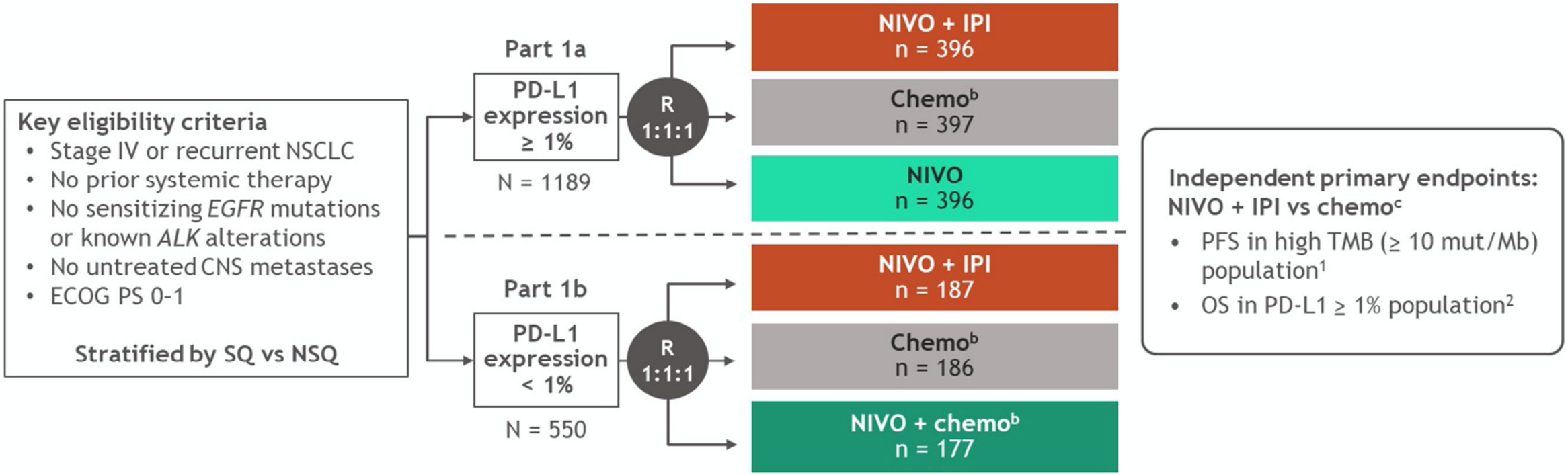
Nivolumab + ipilimumab vs chemotherapy as first-line treatment for advanced non-small cell lung cancer: 4-year update from CheckMate 227[a]



- Here we present updated 4-year efficacy and safety results for CheckMate 227 Part 1, and a post hoc efficacy analysis in patients who discontinued NIVO + IPI due to TRAEs

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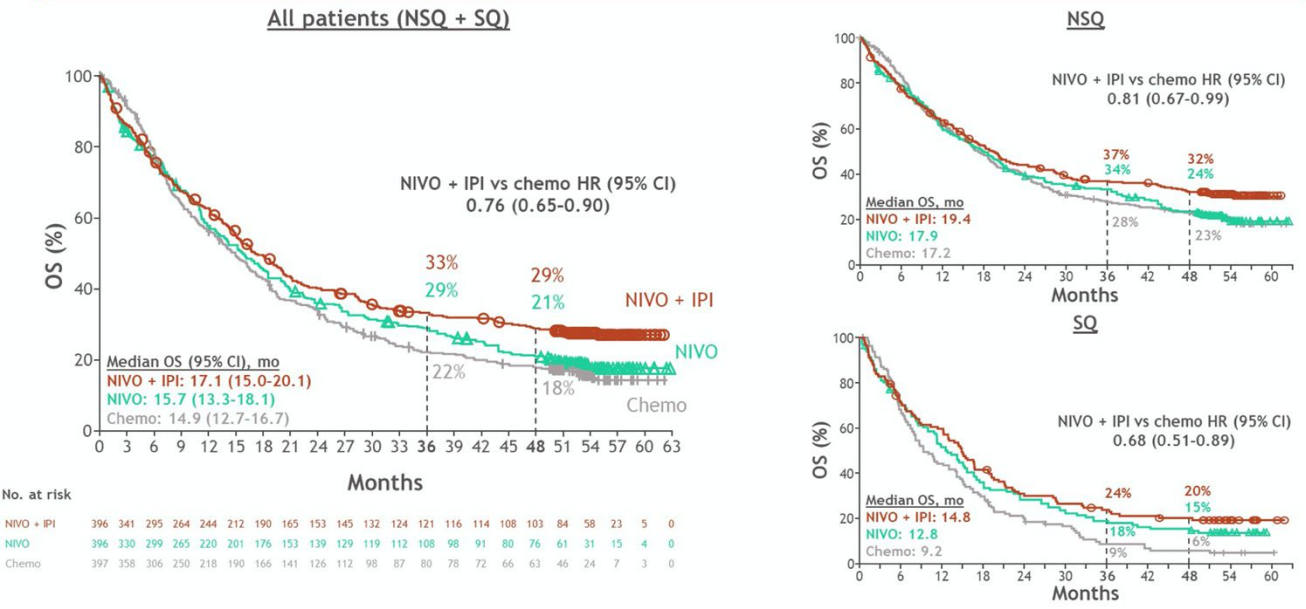
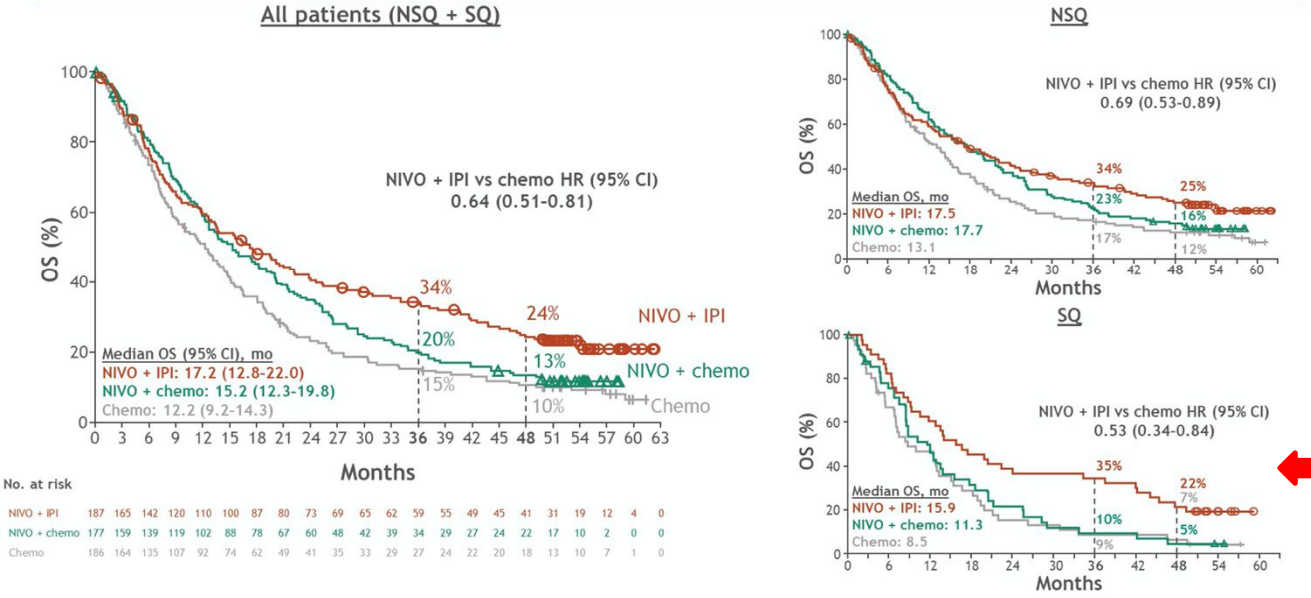
4-year OS in patients with PD-L1 ≥ 1%

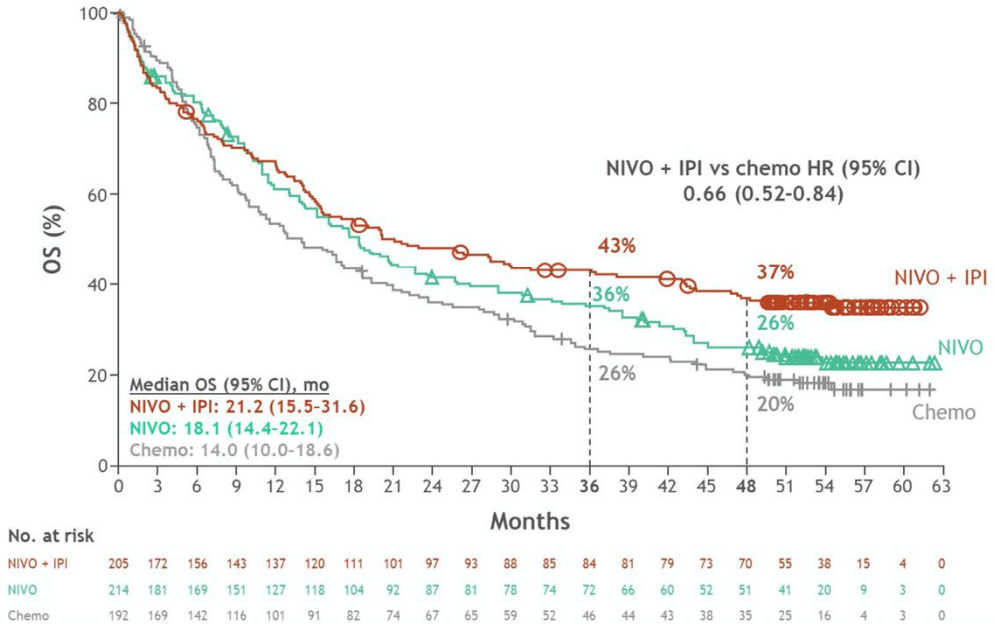


In all patients with PD-L1 ≥ 1% (NSQ + SQ) with a PFS event (per BICR), subsequent systemic therapy was received by 34% in the NIVO + IPI arm, 46% in the NIVO arm, and 49% in the chemo arm; subsequent immunotherapies by 7%, 9%, and 40%; and subsequent chemo by 32%, 45%, and 25%, respectively.

4-year OS in patients with PD-L1 < 1%



4-year OS in patients with PD-L1 ≥ 50%



- Se benefician todos los subgrupos independientemente de nivel PDL1 e histología
- Mayor beneficio en escamoso PDL1 negativo

HR 0.53

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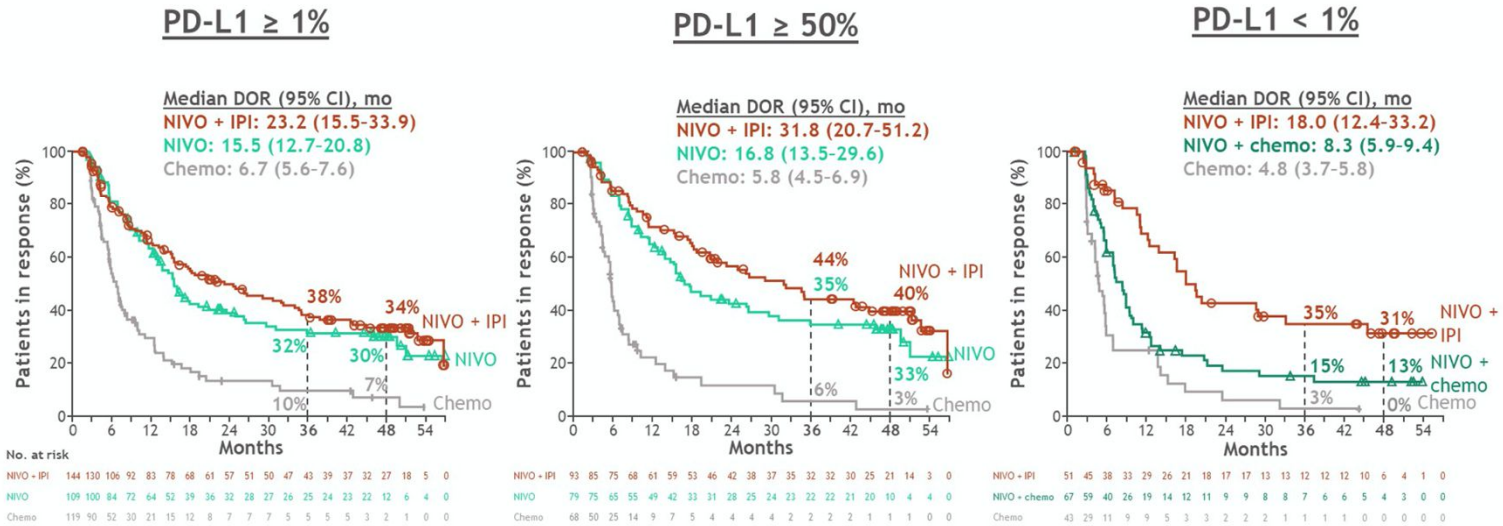
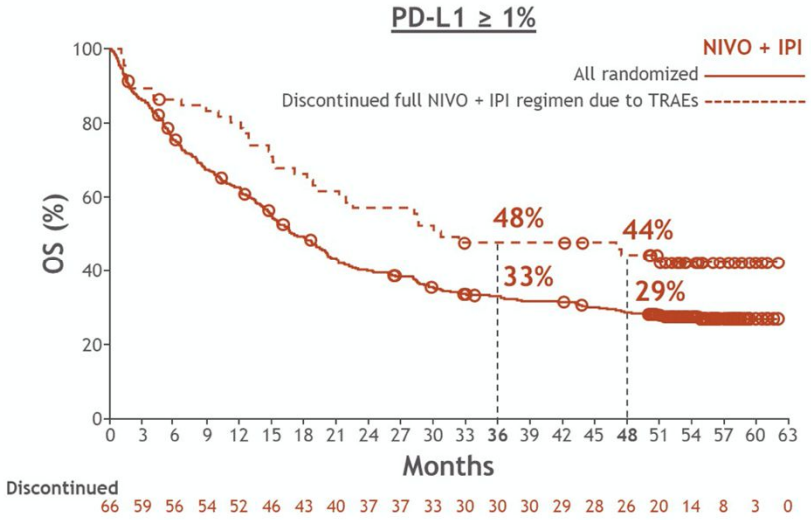
GECP lung cancer research

4-year update: DOR



- Mayor duración de la respuesta con combinación sobre todo en pacientes PDL1 mas del 50% con una media de 31.8 meses

Post hoc analysis: efficacy in patients who discontinued NIVO + IPI due to TRAEs[a]



	PD-L1 ≥ 1% (n = 66)	PD-L1 ≥ 1% and < 1% (n = 97)
Median OS, mo[b]	30.6	41.5
4-year OS rate, %	44	44
ORR, n (%)	35 (53)	50 (52)
Median DOR after discontinuation, mo[c]	52.6	34.2
Ongoing response for ≥ 3 years after discontinuation, %[c]	53	48

- 66 patients with PD-L1 ≥ 1% (17%) and 97 patients with PD-L1 ≥ 1% and < 1% (17%) treated with NIVO + IPI had TRAEs that led to discontinuation of all components of the regimen

- 44% de los pacientes que discontinuaron por toxicidad mantienen beneficio a 4 años

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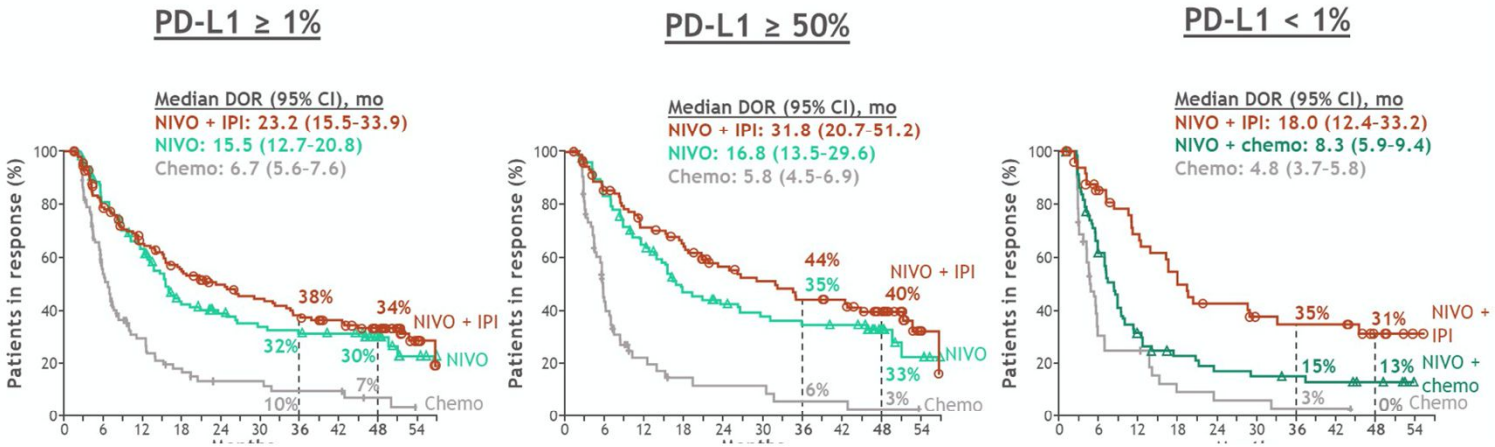
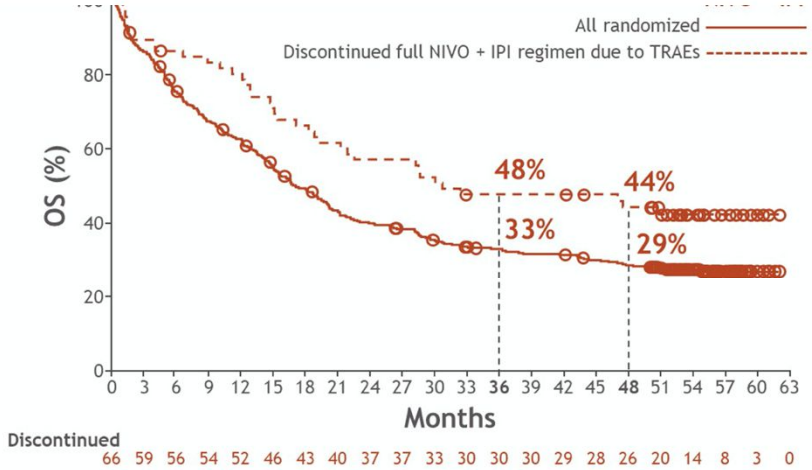
4-year update: DOR



Taken together, these updated results from CheckMate 227 continue to reinforce the positive benefit-risk profile of dual immunotherapy at 2 years after treatment discontinuation and support the use of NIVO + IPI as 1L treatment of patients with advanced NSCLC



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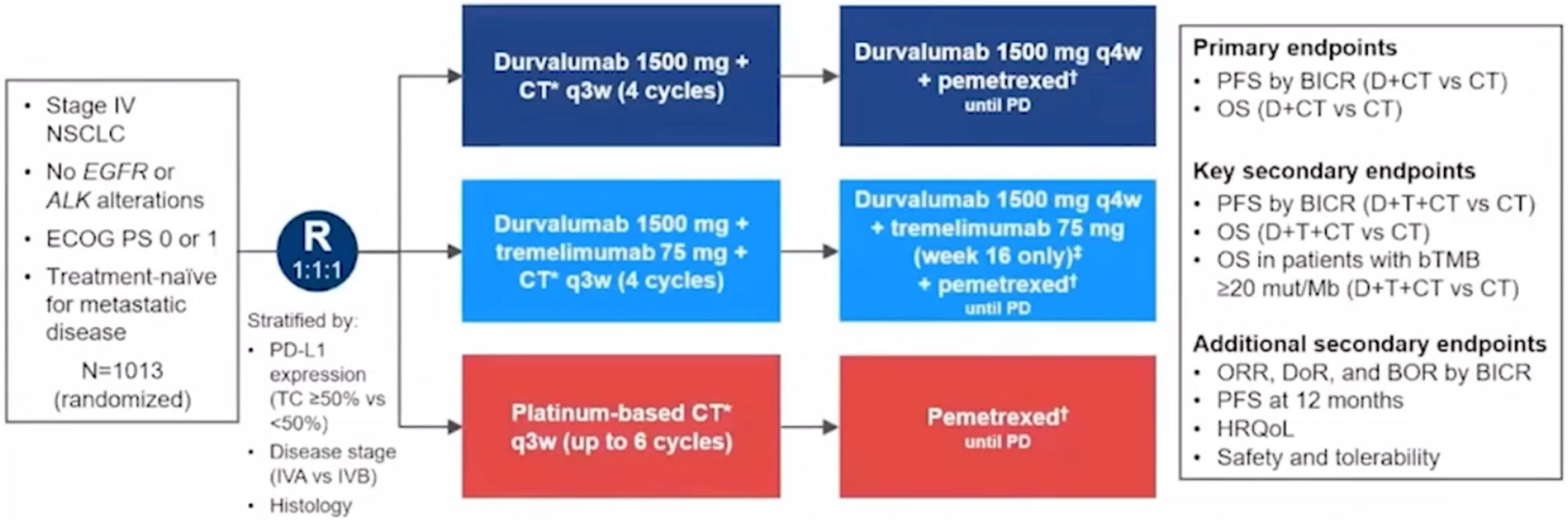
Durvalumab ± Tremelimumab + Chemotherapy as First-line Treatment for mNSCLC: Results from the Phase 3 POSEIDON Study

POSEIDON Study Design

Phase 3, global, randomized, open-label, multicenter study

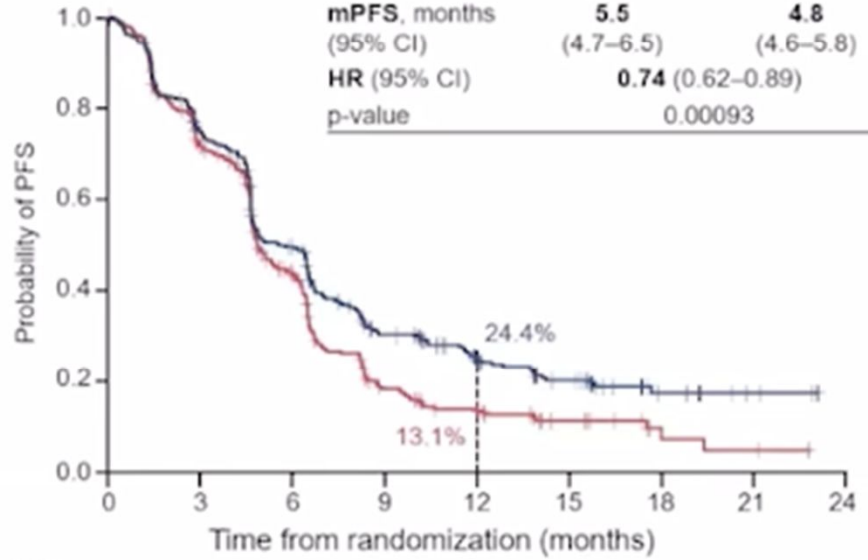


*CT options: gemcitabine + carboplatin/cisplatin (squamous), pemetrexed + carboplatin/cisplatin (non-squamous), or nab-paclitaxel + carboplatin (either histology); †Patients with non-squamous histology who initially received pemetrexed during first-line treatment only (if eligible); ‡Patients received an additional dose of tremelimumab post CT (5th dose)

Durvalumab + CT vs CT: PFS and OS

PFS

	D+CT	CT
Events, n/N (%)	253/338 (74.9)	258/337 (76.6)
mPFS, months (95% CI)	**5.5** (4.7–6.5)	**4.8** (4.6–5.8)
HR (95% CI)	**0.74** (0.62–0.89)	
p-value	0.00093	



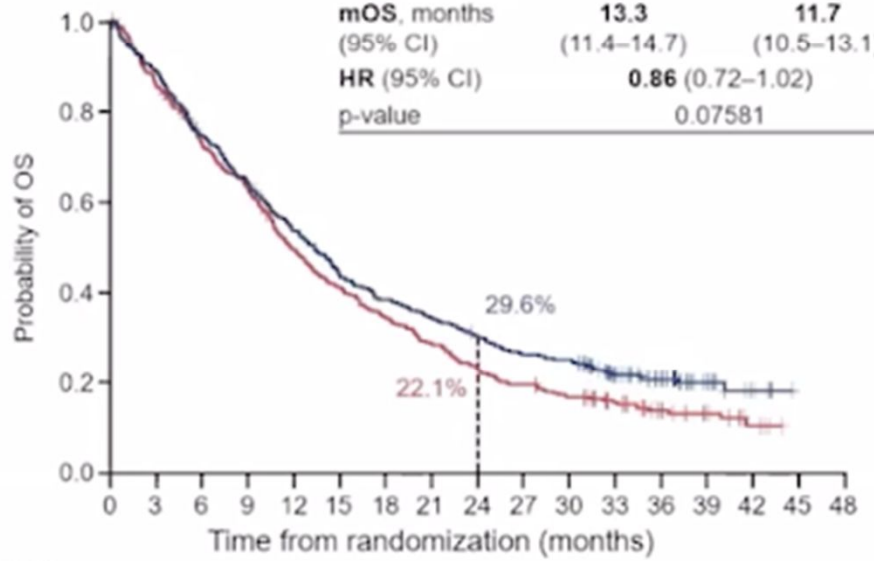
No. at risk

D+CT	338	246	158	88	53	35	11	4	0
CT	337	219	121	43	23	12	3	2	0

- Median follow-up in censored patients at DCO: 10.3 months (range 0–23.1)

OS

	D+CT	CT
Events, n/N (%)	264/338 (78.1)	285/337 (84.6)
mOS, months (95% CI)	**13.3** (11.4–14.7)	**11.7** (10.5–13.1)
HR (95% CI)	**0.86** (0.72–1.02)	
p-value	0.07581	



No. at risk

D+CT	338	296	247	212	176	142	126	112	97	85	81	51	33	15	5	0	0
CT	337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0	0

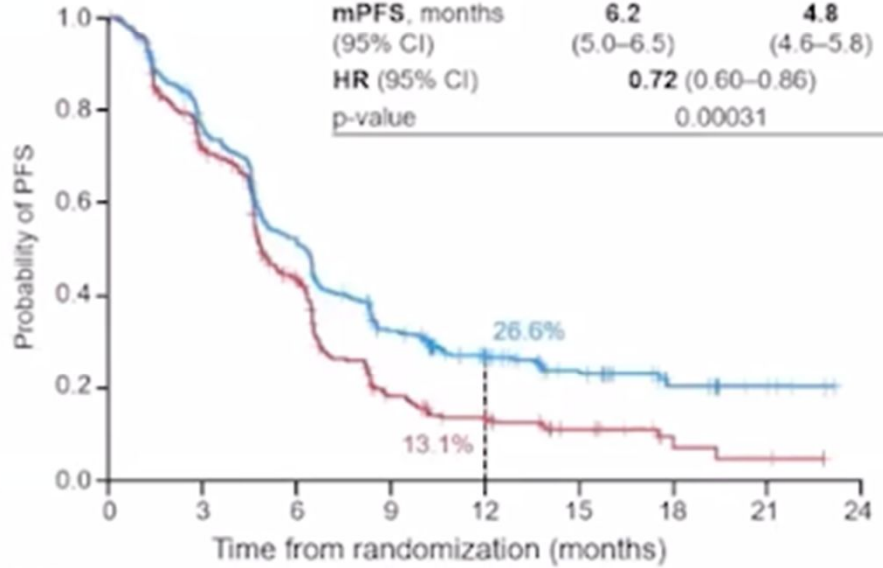
- Median follow-up in censored patients at DCO: 34.9 months (range 0–44.5)

- Beneficio en PFS al añadir Durvalumab a la Qt (HR 0.74)
- Mejoría no estadísticamente significativa de SG: HR 0.86
  - 33% de los pacientes del brazo control recibieron IO en líneas sucesivas

Durvalumab + Tremelimumab + CT vs CT: PFS and OS

PFS

	D+T+CT	CT
Events, n/N (%)	238/338 (70.4)	258/337 (76.6)
mPFS, months (95% CI)	**6.2** (5.0–6.5)	**4.8** (4.6–5.8)
HR (95% CI)	**0.72** (0.60–0.86)	
p-value	0.00031	



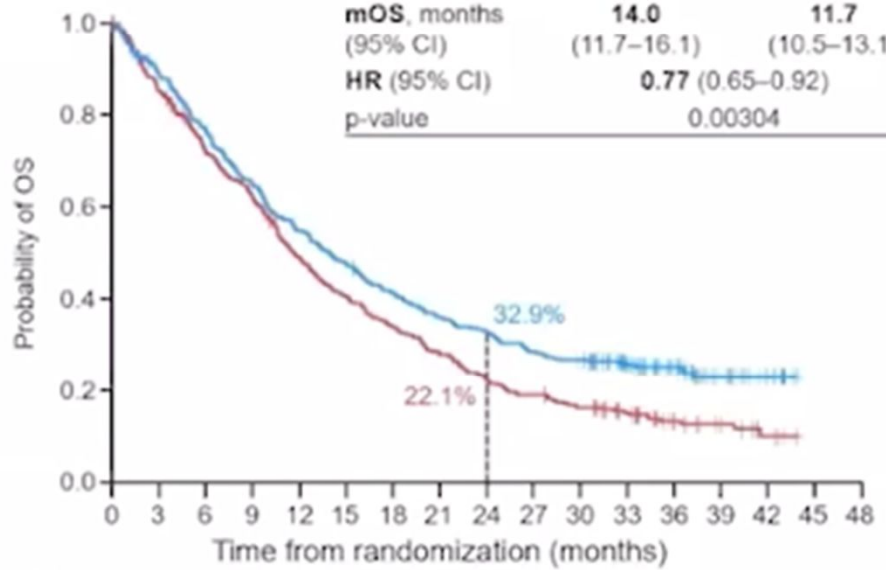
No. at risk

D+T+CT	338	243	161	94	56	32	13	5	0
CT	337	219	121	43	23	12	3	2	0

- Median follow-up in censored patients at DCO: 10.3 months (range 0–23.1)

OS

	D+T+CT	CT
Events, n/N (%)	251/338 (74.3)	285/337 (84.6)
mOS, months (95% CI)	**14.0** (11.7–16.1)	**11.7** (10.5–13.1)
HR (95% CI)	**0.77** (0.65–0.92)	
p-value	0.00304	



No. at risk

D+T+CT	338	298	256	217	183	159	137	120	109	95	88	64	41	20	9	0	0
CT	337	284	236	204	160	132	111	91	72	62	52	38	21	13	6	0	0

- Median follow-up in censored patients at DCO: 34.9 months (range 0–44.5)

- Beneficio en PFS al añadir Durvalumab + Tremelimumab a la Qt (HR: 0.72)
- Mejor SG (HR 0.77)

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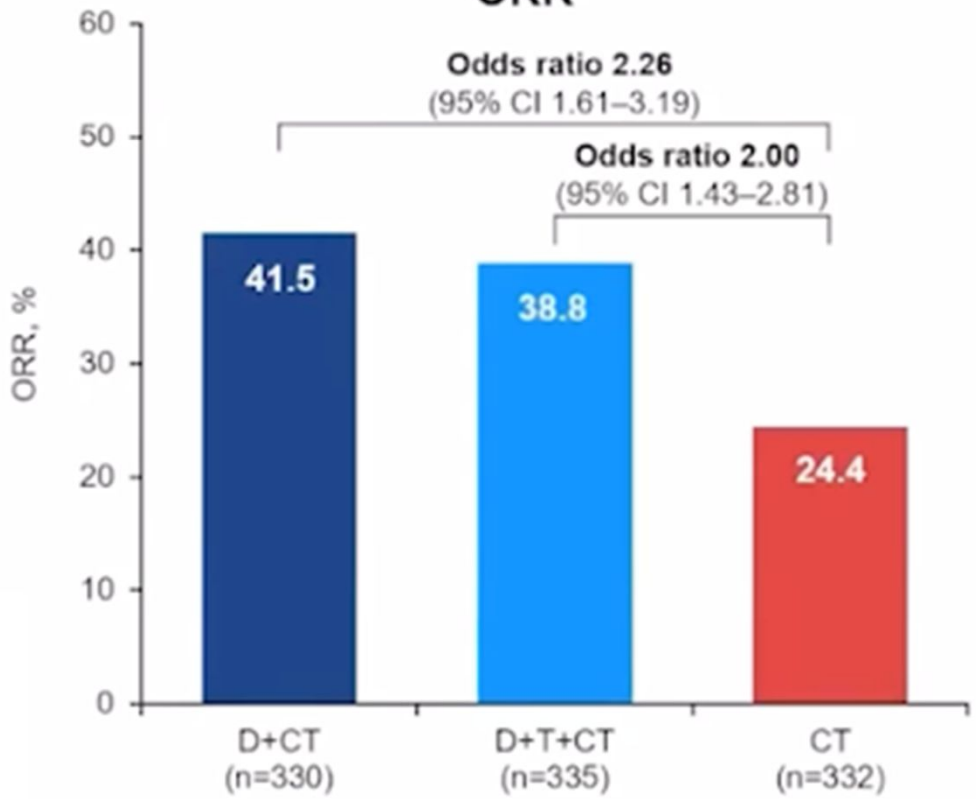
Confirmed Objective Response Rate and Duration of Response

ORR*



Duration of Response

	D+CT	D+T+CT	CT
Responders*, n	137	130	81
Median DoR, months (95% CI)	**7.0** (5.7–9.9)	**9.5** (7.2–NE)	**5.1** (4.4–6.0)
Remaining in response at 12 months, %	**38.9**	**49.7**	**21.4**

- Mejor tasa de respuesta en ambos brazos experimentales
- Mayor duración de la respuesta en brazos experimentales

Organizado por:
GECP
lung cancer research

Immune-Mediated Adverse Events (Grouped Terms)

	D+CT (n=334)		D+T+CT (n=330)		CT (n=333)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any imAE*, n (%)	64 (19.2)	23 (6.9)	111 (33.6)	33 (10.0)	17 (5.1)	5 (1.5)
Hypothyroid events	20 (6.0)	0	27 (8.2)	0	3 (0.9)	0
Pneumonitis	10 (3.0)	4 (1.2)	12 (3.6)	3 (0.9)	2 (0.6)	2 (0.6)
Rash	5 (1.5)	2 (0.6)	13 (3.9)	3 (0.9)	6 (1.8)	2 (0.6)
Hepatic events	11 (3.3)	8 (2.4)	12 (3.6)	7 (2.1)	0	0
Dermatitis	4 (1.2)	1 (0.3)	14 (4.2)	1 (0.3)	1 (0.3)	0
Colitis	4 (1.2)	1 (0.3)	13 (3.9)	5 (1.5)	0	0
Hyperthyroid events	4 (1.2)	1 (0.3)	9 (2.7)	0	1 (0.3)	0
Adrenal insufficiency	4 (1.2)	1 (0.3)	8 (2.4)	2 (0.6)	0	0
Rare/miscellaneous	1 (0.3)	1 (0.3)	11 (3.3)	3 (0.9)	2 (0.6)	1 (0.3)

imAEs leading to death occurred in 1 patient receiving D+CT (myocarditis) and in 2 patients receiving D+T+CT (pneumonitis in 1 patient; and hepatic, renal, and pancreatic events and myocarditis in 1 patient)

EMPOWER-Lung 3 (Part 2) Study Design (NCT03409614)

Background: Cemiplimab (a high-affinity, fully human anti–PD-1) is approved as first-line monotherapy for advanced NSCLC with PD-L1 ≥50% (EMPOWER-Lung 1 Study[1])

Key eligibility criteria
- Treatment-naive advanced NSCLC (non-squamous and squamous histology; Stage IIIb/c†, IV)
- Any PD-L1 expression
- No *EGFR*, *ALK*, or *ROS1* mutations
- ECOG PS 0 or 1
- Treated, clinically stable CNS metastases‡

Stratification factors
- PD-L1 expression: <1% vs 1–49% vs ≥50%
- Histology: non-squamous vs squamous

Endpoints
- Primary: OS
- Key secondary: PFS and ORR
- Additional secondary: DOR, BOR, safety, and PRO

R 2:1

Arm A
Cemiplimab 350 mg Q3W + investigator's choice platinum-doublet chemo Q3W for 4 cycles§

Arm B
Placebo Q3W + investigator's choice platinum-doublet chemo Q3W for 4 cycles§

PD or 108 weeks

PD or 108 weeks

Follow-up

N=466

Two interim analyses were prespecified per protocol
Second interim analysis (14 June 2021) presented here

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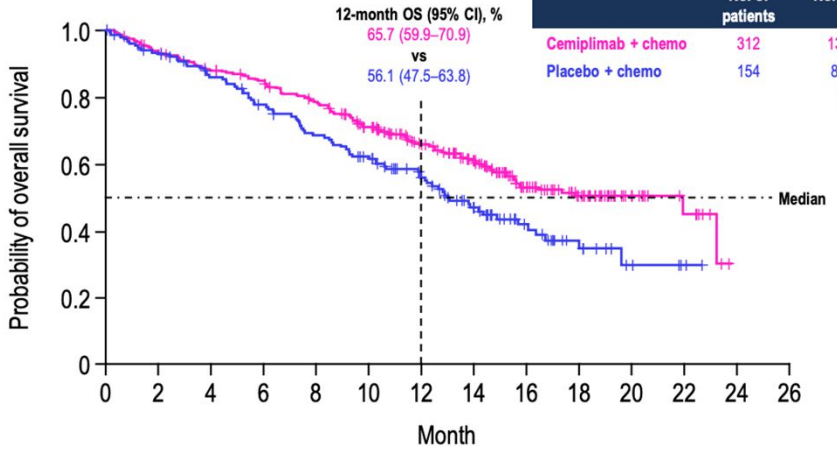
Overall Survival

Median duration of follow-up (range): 16.4 (8.5–24.0) months

	No. of patients	No. of events, n (%)	OS, median (95% CI), months
Cemiplimab + chemo	312	132 (42.3)	21.9 (15.5–NE)
Placebo + chemo	154	82 (53.2)	13.0 (11.9–16.1)

HR (95% CI) = 0.71 (0.53–0.93); *P*=0.014



No. at risk:

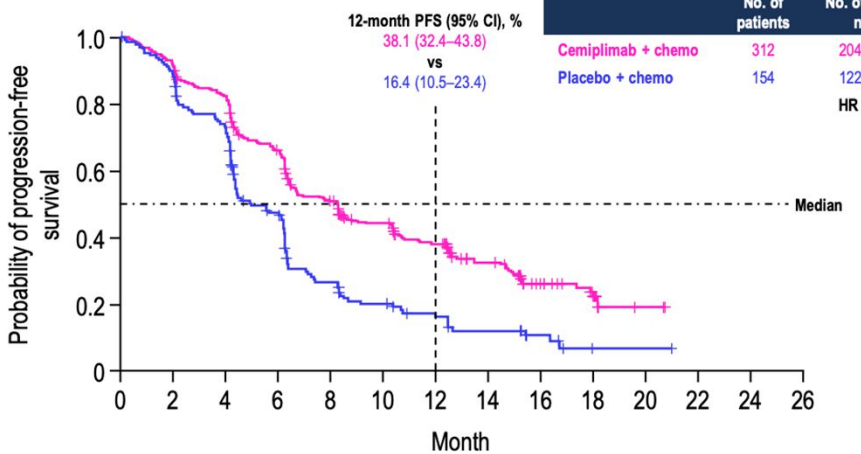
Cemiplimab + chemo	312	289	269	256	233	199	162	131	86	52	18	8	0	0
Placebo + chemo	154	141	126	112	98	85	65	46	26	14	5	2	0	0

Progression-Free Survival

Median duration of follow-up (range): 16.4 (8.5–24.0) months

	No. of patients	No. of events, n (%)	PFS, median (95% CI), months
Cemiplimab + chemo	312	204 (65.4)	8.2 (6.4–9.3)
Placebo + chemo	154	122 (79.2)	5.0 (4.3–6.2)

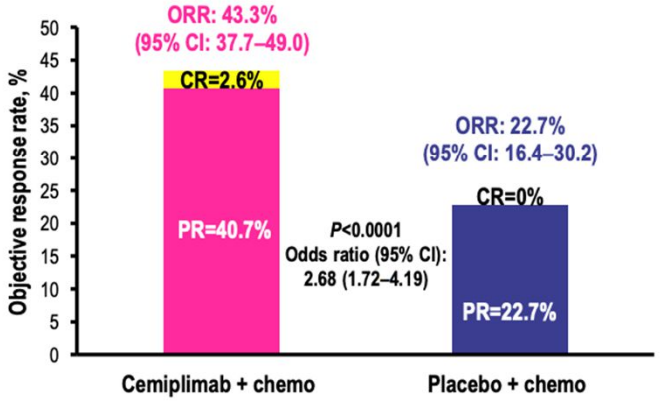
HR (95% CI) = 0.56 (0.44–0.70); *P*<0.0001



No. at risk:

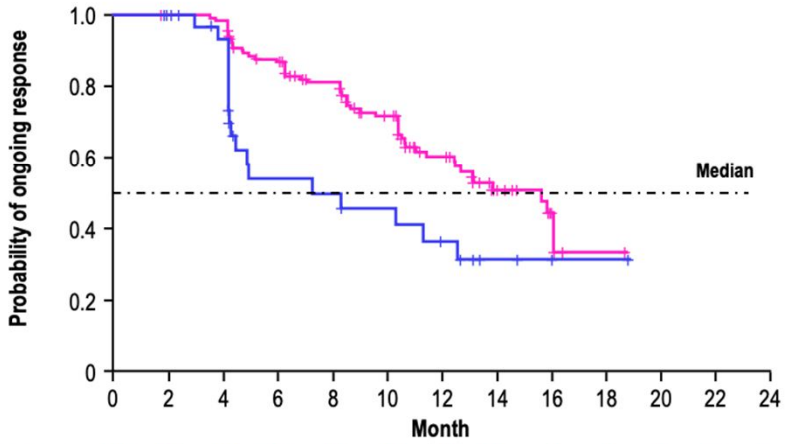
Cemiplimab + chemo	312	280	248	194	145	113	90	57	27	15	2	0	0	0
Placebo + chemo	154	133	106	64	34	24	16	11	6	1	1	0	0	0

Tumour Response and DOR



Among patients with objective response

	No. of patients	No. of events, n (%)	DOR, median (95% CI), months
Cemiplimab + chemo	135	53 (39.3)	15.6 (12.4–NE)
Placebo + chemo	35	18 (51.4)	7.3 (4.3–12.6)



No. at risk:

Cemiplimab + chemo	135	134	131	110	93	71	43	21	4	1	0	0	0
Placebo + chemo	35	33	28	13	12	10	7	3	2	1	0	0	0

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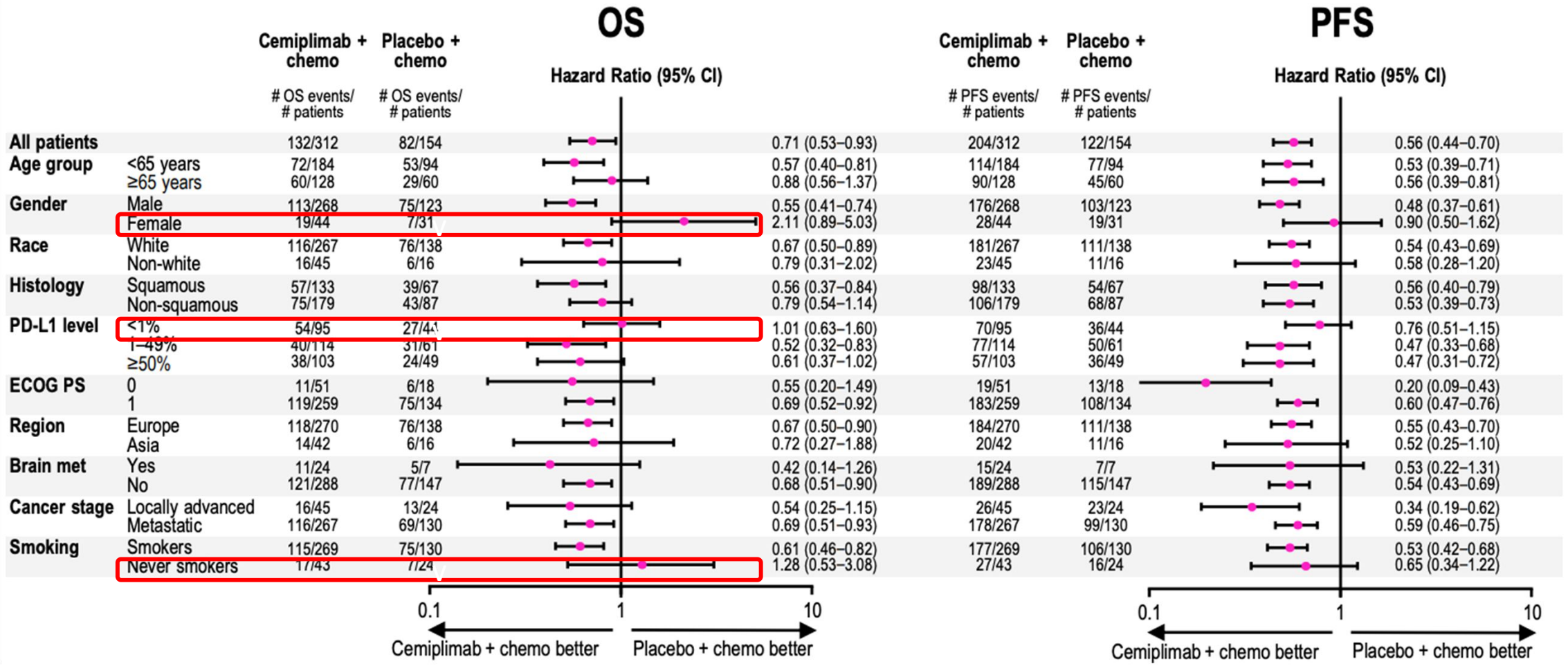
OS and PFS by Subgroup



Safety Summary

n (%), unless stated	Cemiplimab + chemo (n=312)		Placebo + chemo (n=153)	
Duration of exposure, median (range), weeks	38.5 (1.4–102.6)		21.3 (0.6–95.0)	
Treatment-emergent AEs, regardless of attribution	**Any grade**	**Grade 3–5**	**Any grade**	**Grade 3–5**
Overall	299 (96)	136 (44)	144 (94)	48 (31)
Led to discontinuation	16 (5)	13 (4)	4 (3)	4 (3)
Led to death	19 (6)	19 (6)	12 (8)	12 (8)
Treatment-related AEs				
Overall	275 (88)	90 (29)	129 (84)	28 (18)
Led to discontinuation	10 (3)	7 (2)	1 (1)	1 (1)
Led to death	4 (1)	4 (1)	1 (1)	1 (1)
Immune-related AEs†				
Overall	59 (19)	9 (3)	–	–
Led to discontinuation	3 (1)	3 (1)	–	–
Led to death	1 (0.3)	1 (0.3)	–	–

PRO Summary

- **Delay** in the time to definitive clinically meaningful deterioration in GHS/QoL [HR, 0.78 (95% CI, 0.51–1.19); *P*=0.248] and pain symptoms [HR, 0.39 (95% CI, 0.26–0.60); *P*<0.0001].
- **Improvement** in overall change from baseline in GHS/QoL [0.61 (95% CI, -2.23, 3.45) *P*=0.673] and pain symptoms [-4.98 (95% CI, -8.36, -1.60); *P*=0.004].

Treatment-emergent AEs in ≥10% of patients in either arm, n (%)	Cemiplimab + chemo (n=312)		Placebo + chemo (n=153)	
	Any grade	**Grade 3–5**	**Any grade**	**Grade 3–5**
Overall	299 (96)	136 (44)	144 (94)	48 (31)
Anaemia	136 (44)	31 (10)	61 (40)	10 (7)
Decreased appetite	53 (17)	3 (1)	18 (12)	0
Fatigue	38 (12)	7 (2)	11 (7)	1 (1)
Constipation	43 (14)	1 (0)	17 (11)	0
Nausea	78 (25)	0	25 (16)	0
Vomiting	38 (12)	0	15 (10)	0
Thrombocytopaenia	41 (13)	8 (3)	19 (12)	2 (1)
Neutropaenia	48 (15)	18 (6)	19 (12)	9 (6)
Alopecia	115 (37)	0	66 (43)	0
Hyperglycaemia	55 (18)	6 (2)	18 (12)	0
Alanine aminotransferase increased	51 (16)	7 (2)	22 (14)	3 (2)
Arthralgia	48 (15)	2 (1)	20 (13)	0
Aspartate aminotransferase increased	46 (15)	1 (0)	18 (12)	3 (2)
Dyspnoea	39 (13)	7 (2)	10 (7)	1 (1)
Asthenia	38 (12)	6 (2)	18 (12)	2 (1)
Decreased weight	35 (11)	4 (1)	13 (8)	0
Insomnia	34 (11)	0	11 (7)	0
Diarrhoea	33 (11)	4 (1)	10 (7)	0
Hypoalbuminaemia	32 (10)	2 (1)	9 (6)	0

GECP lung cancer research

ATEZO-BRAIN Trial Design

Single arm phase II clinical trial

Key Elegibility Criteria:
Stage IV non-squamous NSCLC
Untreated brain metastases
Treatment naïve
EGFR/ALK negative, any PD-L1
ECOG PS 0-1
Anticonvulsivants and dexamethasone ≤ 4 mg qd allowed
Measurable systemic and brain lesion/s

Carboplatin (5 AUCs) + Pemetrexed 500mg/m² + Atezolizumab 1200mg Q3W for 4-6 cycles → **Pemetrexed 500mg/m2 + Atezolizumab 1200mg Q3W until tumor progression (*), unacceptable toxicity or 2 years**

Tumor evaluation by body CT scan and brain MRI Q6W until the 12th week and thereafter Q9W until PD

(*) If exclusive CNS PD, patients could continue on study after brain RT

Co-primary endpoints:
- Safety
- Investigator-based PFS by RECIST v1.1 & RANO-BM

Secondary endpoints:
- Response rate, DoR
- Overall Survival
- QoL, neurocognitive function
- Time to brain radiotherapy

Exploratory endpoints:
- To identify neuroimaging (MRI) and blood biomarkers predicting response or resistance

- Metástasis cerebrales asintomáticas (NO TRATADAS), máximo 4 mg dexametasona
- N=40

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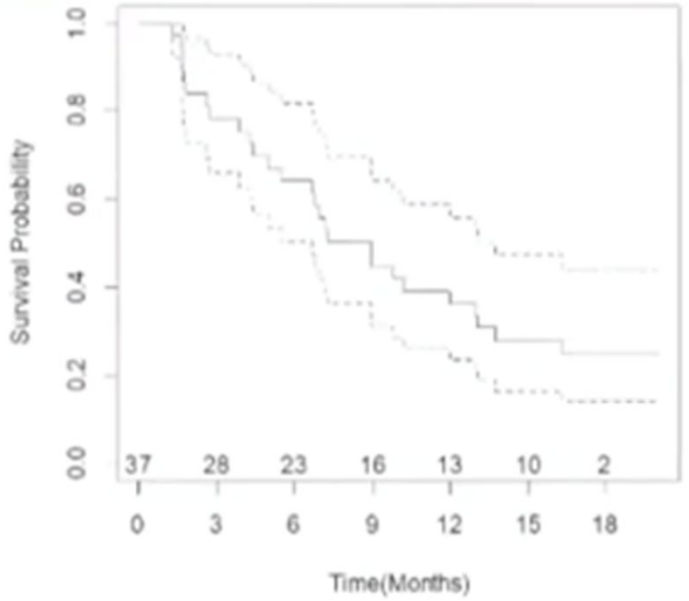
Primary Endpoint: Systemic and Intracranial PFS

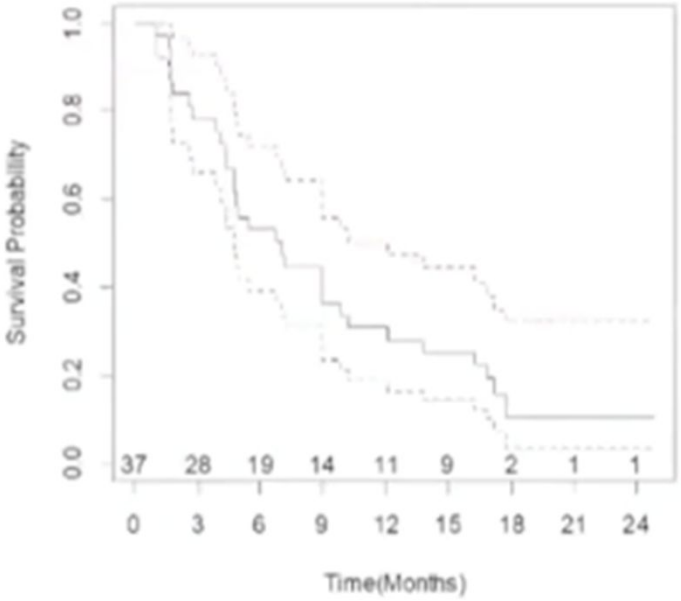
Median follow-up
17.3 months

Systemic PFS by RECIST v1.1



Median systemic PFS = 8.9 months (95% CI 6.7- 13.8)
18 month PFS rate = 24.9%

Intracranial PFS by RANO-BM



Median icPFS = 6.9 months (95% CI 4.7 – 12.1)
18 month icPFS rate = 10.4%

- PFS sistémica 8.9 meses
- PFS intracraneal 6.9 meses

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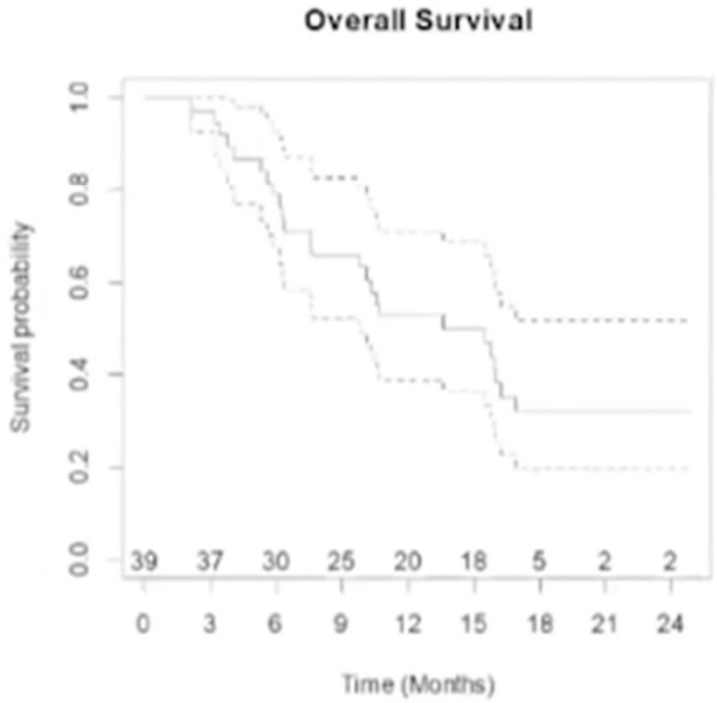
Secondary Endpoints: Response Rate and Overall Survival

	Best Intracranial Response (RANO-BM)	Best Systemic Response (RECIST v1.1)
CR	4 (10%)	0
PR	12 (30%)	19 (47.5%)
SD	19 (47.5%)	16 (40%)
PD	4 (10%)	3 (7.5%)
NE	1 (2.5%)	2 (5%)
ORR	**16 (40%)**	**19 (47.5%)**

Only 4 patients had discordance among systemic and CNS response:

- 2 with PD in body and SD in brain
- 2 with PD in brain and PR in body



Median OS = 13.6 months (95% CI 9.7 – NR)
2y OS rate = 32%

- ORR intracraneal 40% (similar a lo reportado en subanálisis 9LA con M1 tratadas)
- SG 13.6 meses
- Tasa de supervivencia a 2 años del 32%

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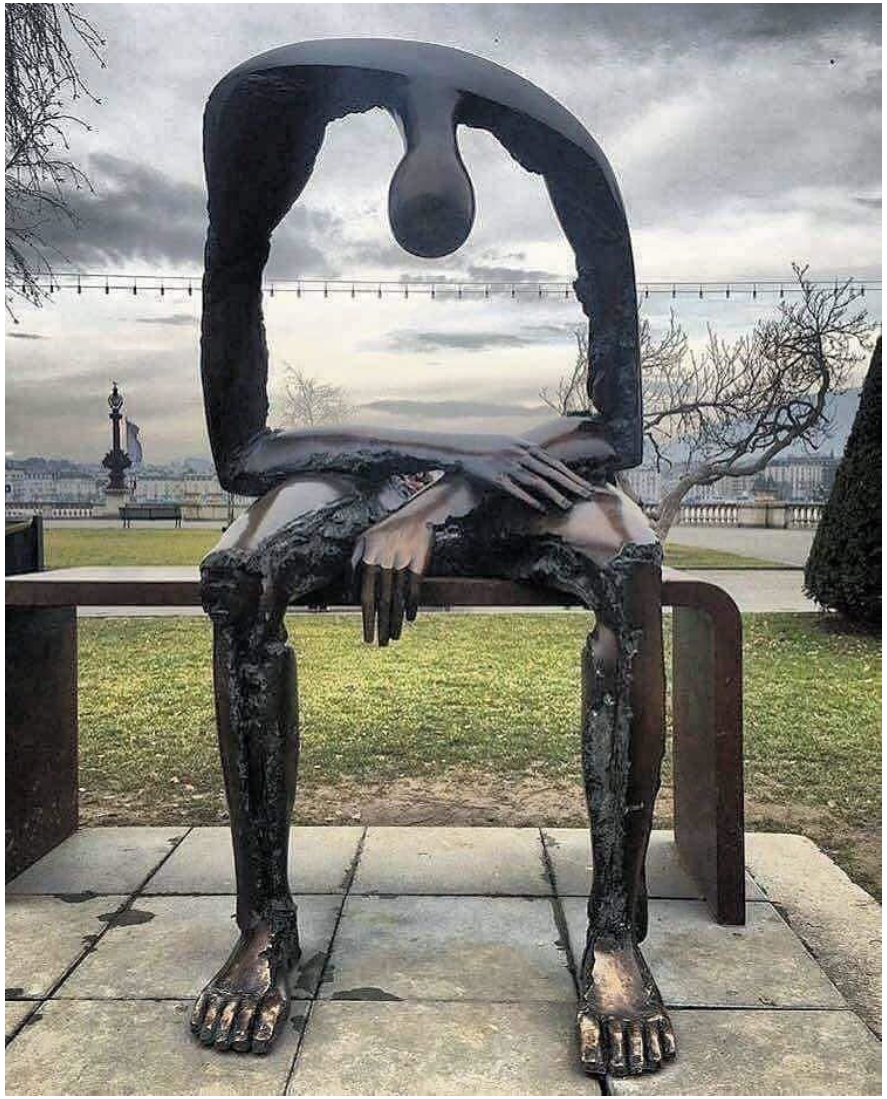
2das LINEAS Y POSTERIORES



Albert Gyorgy

Atalante-1 Study Design: NSCLC After Failure to Chemo – IO

FASE III

- Advanced/metastatic NSCLC
- EGFRwt, ALK-negative, all PD-L1 status
- HLA-A2+ (blood)
- Failure to platinum-based CT and IO, combined or sequenced
- IO last line with primary or secondary resistance*
- Brain metastases allowed if asymptomatic & treated
- ECOG PS 0 to 1

R 2:1

Arm A: OSE2101 Q3W for 6 subcutaneous injections, then Q8W up to Year 1, then Q12W until progression or toxicity

Arm B: SoC (docetaxel or pemetrexed) Q3W until progression or toxicity

Primary endpoint: OS

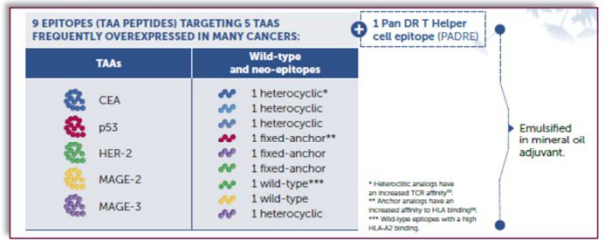
Stratification:
- Histology
- Best response to 1st line
- Line rank of prior IO

*Primary resistance: failure within 12 weeks of IO, secondary resistance: failure after minimum 12 weeks of IO; Kluger et al. 2020

OSE2101 Mechanism of Action and Rationale

OSE2101 (Tedopi®) is an anticancer vaccine of neoepitopes restricted to HLA-A2+ targeting 5 TAAs frequently expressed in lung cancer[1]

Previous phase 2 study in pretreated NSCLC patients showed promising survival (OS) which correlated with T cell immune response[2,3,4]



Low	0-1 epitope: 406 ± 58 days of survival
Medium	2-3 epitopes: 778 ± 72 days of survival
High	4-6 epitopes: 875 ± 67 days of survival

- OSE 2101: Vacuna antitumoral
- Dirigido a 5 antígenos: CEA, p53, HER 2, MAGE 2 y MAGE 3

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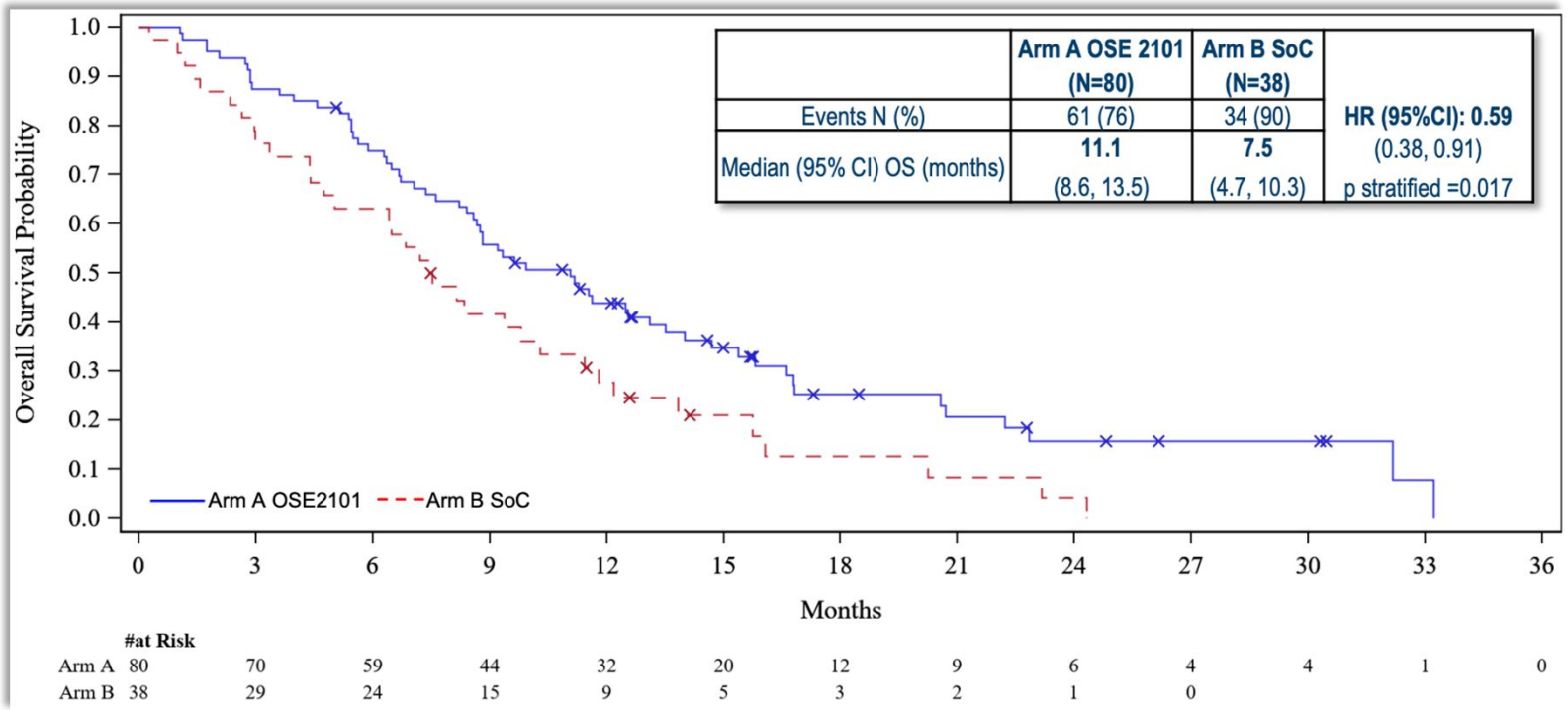
- OS in population of interest (PoI): patients with IO secondary resistance after sequential IO
- Median follow-up 25 months

Overall Survival in PoI



	Arm A OSE 2101 (N=80)	Arm B SoC (N=38)	
Events N (%)	61 (76)	34 (90)	**HR (95%CI): 0.59** (0.38, 0.91) p stratified =0.017
Median (95% CI) OS (months)	**11.1** (8.6, 13.5)	**7.5** (4.7, 10.3)	

Cut-off 15JAN2021; median follow-up 25 months

PoI=Population of interest; SoC=Standard of care; OS=Overall survival; HR=Hazard ratio; CI=Confidence interval

- Población de interés: Al menos 12 semanas de IO y resistencia secundaria

- SG 11.1 meses vs 7.5 meses
- HR 0.59

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Disease Control Rate, Objective Response and PFS in PoI

DCR at 6 months similar between arms despite a longer PFS and OR favoring SoC

PoI	Arm A OSE2101 (N= 80)	Arm B SoC (N=38)	
Patients with measurable lesions at baseline	78	38	
Disease Control Rate at 6 months; N (%)	19 (25)	9 (24)	Odds ratio (95%CI): 1.09 (0.43, 2.75) p=0.87
Objective Response; N (%)	6 (8)	7 (18)	Odds ratio (95%CI): 0.33 (0.10, 1.11) p=0.07
Median (95%CI) PFS (months)	2.7 (1.6; 2.8)	3.2 (2.6; 4.7)	Hazard ratio (95%CI): 1.20 (0.8, 1.8) p=0.40

- Tasa de control de la enfermedad a 6 meses similar en ambos brazos
- PFS y respuesta objetivas favorecían al brazo quimioterapia

Reason of Permanent Treatment Discontinuation in Pol

	Arm A OSE2101 (N=80)	Arm B SoC (N=38)
Not treated (N, %)	1 (1)	1 (3)
Reason of permanent treatment discontinuation (N, %)	77 (96)	37 (97)
Adverse Event	**8 (10)**	**7 (18)**
Death	**2 (3)**	**3 (8)**
Withdrawal of Consent	0 (0)	0 (0)
Disease Progression	63 (79)	24 (63)
Other	1 (1)	1 (3)

In Arm B Standard of Care (SoC): docetaxel (n=30); pemetrexed (n=7); in Arm A OSE2101: treatment ongoing in 2 patients

- Mayor toxicidad g3-4 el brazo de la Qt

Most frequent >10% Drug-Related AEs in Pol

	Arm A OSE2101 (N=79)		Arm B SoC (N=37)	
	All grade N (%)	Severe G3-4 N (%)	All grade N (%)	Severe G3-4 N (%)
All Drug-Related AEs	60 (76)	9 (11)*	29 (78)	13 (35)*
Drug-related AEs in > 10% of patients by preferred term				
Administration site reaction**	31 (39)	1 (1)	-	-
Pyrexia	15 (19)	2 (3)	3 (8)	-
Arthralgia	9 (11)	-	1 (3)	-
Asthenia	13 (17)	-	15 (41)	6 (16)
Alopecia	-	-	8 (22)	1 (3)
Diarrhea	3 (4)	-	8 (22)	1 (3)
Neutropenia	-	-	6 (16)	6 (16)
Fatigue	6 (8)	-	5 (14)	-
Anemia	1 (1)	-	5 (14)	-
Nausea	5 (6)	-	5 (14)	-
Vomiting	5 (6)	1 (1)	5 (14)	1 (3)
Decrease appetite	4 (5)	-	4 (11)	-

Cytokine release syndrome was reported in 6 (8%) patients including 1 (1%) severe G3 in OSE2101 arm

CONCLUSION

In the population of patient with secondary resistance to sequential CT-IO, OS was statistically improved in OSE2101 arm with HR of 0.59 and a meaningful gain of median OS of 3.6 months over SoC (docetaxel/pemetrexed). HR for OS in the overall population at final analysis was of 0.86 (ns)

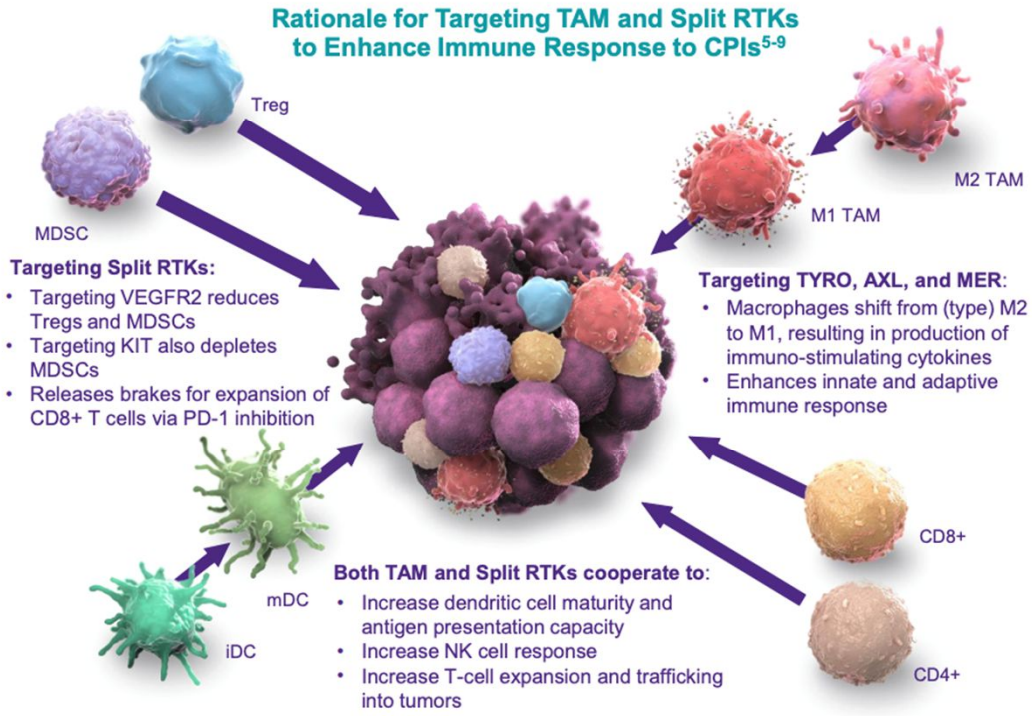
The cancer vaccine OSE2101 demonstrated efficacy as stand alone compared to an active comparator

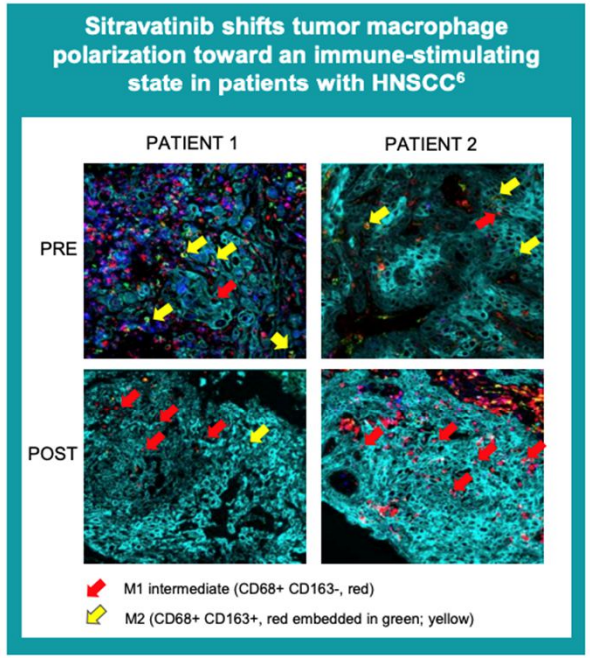
OSE2101 was well tolerated with significantly less severe adverse events; QoL and good ECOG PS 0/1 were statistically better for OSE2101

Overall, OSE2101 had a favorable benefit/risk versus SoC in advanced HLA-A2+ NSCLC patients with secondary resistance to sequential CT-IO without therapeutic alternatives

MRTX-500: Phase 2, Open-Label Study of Sitravatinib + Nivolumab in Patients With Nonsquamous NSCLC With Prior Clinical Benefit From Checkpoint Inhibitor Therapy

Sitravatinib Is a TKI That Targets TAM Receptors (TYRO3, AXL, MERTK) and Split-Family Receptors (eg, VEGFR2)





Presented at the European Society for Medical Oncology (ESMO) Congress, 18 September 2021

- Progresiones a IO por diferentes mecanismos entre los que se encuentra un microambiente tumoral inmunosupresor
- Sitravatinib es un TKI dirigido a los receptores TAM y al factor de crecimiento del endotelio vascular tipo 2 lo que puede modular el microambiente inmunosupresor

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MRTX-500: Phase 2, Open-Label Study of Sitravatinib + Nivolumab in Patients With Nonsquamous NSCLC With Prior Clinical Benefit From Checkpoint Inhibitor Therapy

Key Eligibility Criteria
(n=68)

- Advanced/metastatic nonsquamous NSCLC[a]
- No actionable driver mutations
- Anti–PD-1/L1 must be the most recent line of therapy
- Prior Clinical Benefit (PCB) to CPI: CR, PR, or SD ≥12 weeks from prior CPI therapy
- No uncontrolled brain metastases
- ECOG PS 0-2

→ **Sitravatinib** 120 mg QD + nivolumab

Primary Endpoint:

- Objective Response Rate[b] (ORR), as defined by RECIST 1.1

Secondary Endpoints:

- Safety and tolerability
- DOR
- CBR
- PFS
- OS
- 1-year survival rate

Here we report updated efficacy and safety with sitravatinib + nivolumab in the 2L or 3L setting in patients with nonsquamous NSCLC who have experienced clinical benefit on a prior CPI and subsequent disease progression

Data as of 1 June 2021

[a] Additional cohorts included a CPI-experienced cohort that did not receive prior clinical benefit from CPI therapy (radiographic progression of disease ≤12 weeks after initiation of treatment with CPI) and a CPI-naive cohort in patients that were previously treated with platinum-based chemotherapy. [b]Objective response rate based on investigator assessment. Dosing: sitravatinib free base formulation; nivolumab, 240 mg Q2W or 480 mg Q4W. Treatment discontinuation could be due to (but is not limited to) disease progression, global health deterioration, AEs, protocol violation, lost to follow-up, refusal of further treatment, study termination, or death.

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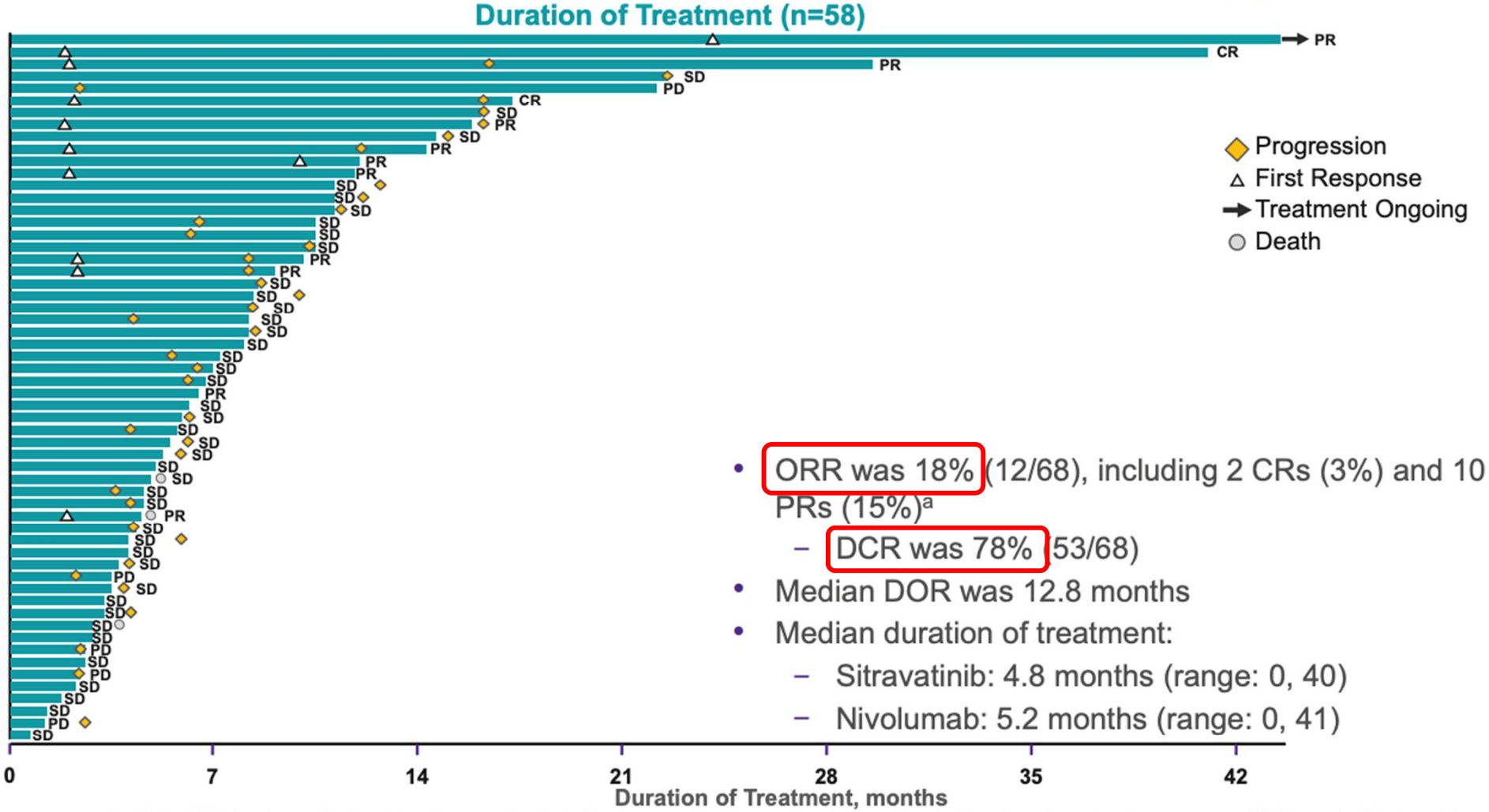
Duration of Treatment With Sitravatinib + Nivolumab in Patients With Nonsquamous NSCLC With Prior Clinical Benefit From CPI Therapy



- ORR was 18% (12/68), including 2 CRs (3%) and 10 PRs (15%)[a]
  - DCR was 78% (53/68)
- Median DOR was 12.8 months
- Median duration of treatment:
  - Sitravatinib: 4.8 months (range: 0, 40)
  - Nivolumab: 5.2 months (range: 0, 41)

[a]10 (14.7%) patients were not evaluable for ORR: 8 patients without post-baseline scan, 1 patient without measurable disease at baseline, and 1 patient for whom all post-baseline scans were NE. The study did not meet the primary endpoint of ORR.
Median follow-up in the PCB cohort was 33.6 months. Data as of 1 June 2021

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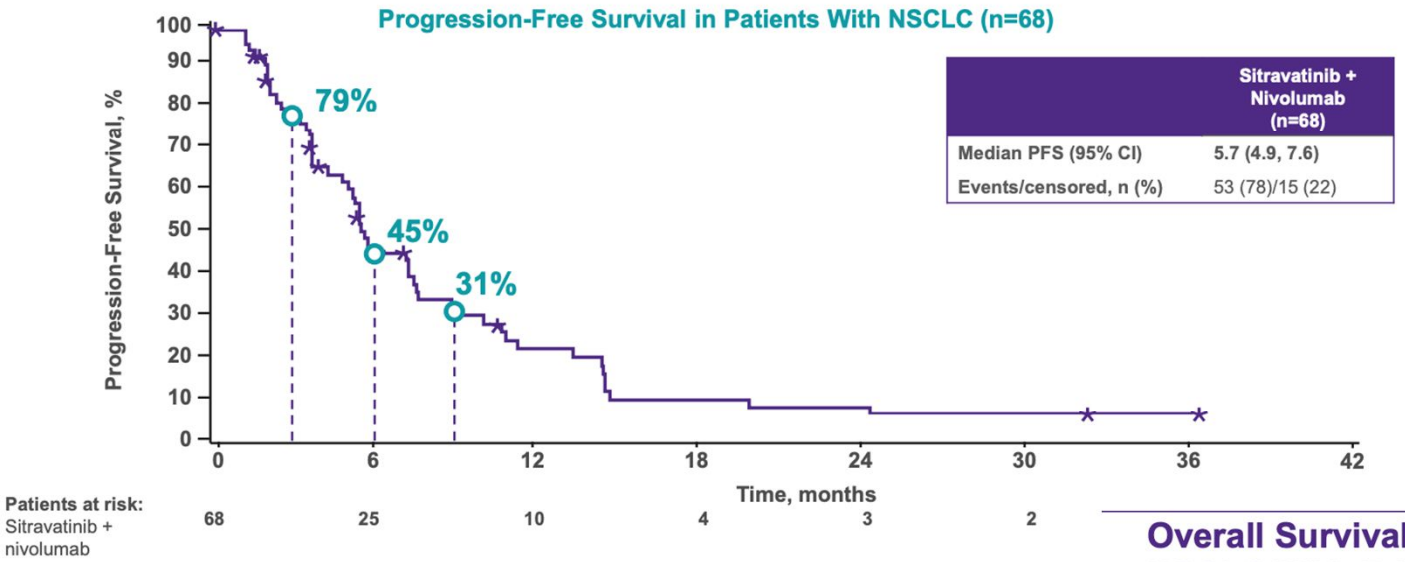
Progression-Free Survival With Sitravatinib + Nivolumab in Patients With Nonsquamous NSCLC With Prior Clinical Benefit From CPI Therapy



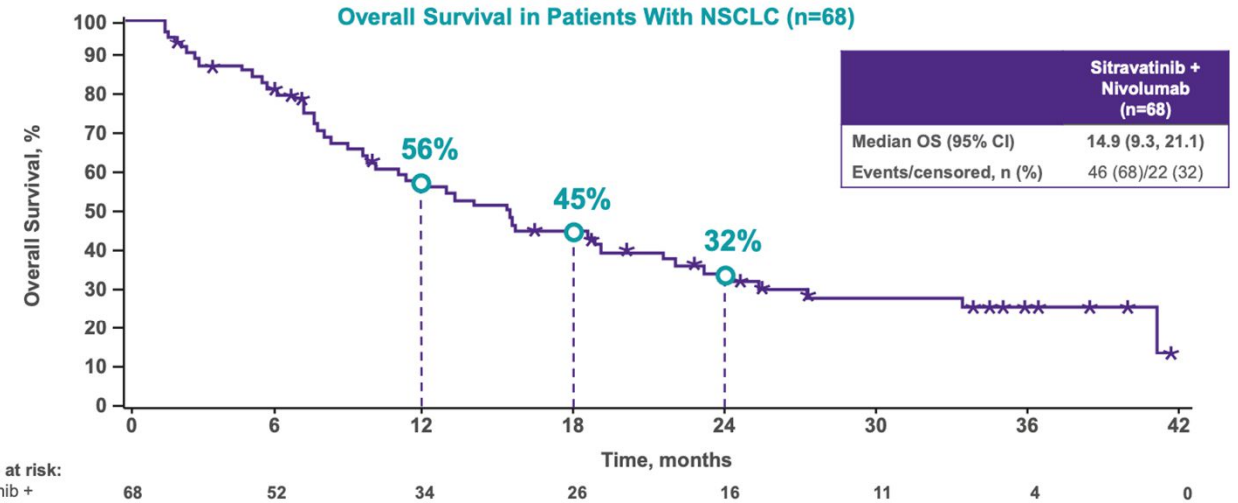
	Sitravatinib + Nivolumab (n=68)
Median PFS (95% CI)	5.7 (4.9, 7.6)
Events/censored, n (%)	53 (78)/15 (22)

Median follow-up in PCB cohort: 33.6 months.
Data as of 1 June 2021.

Presented at the European Society for Med

- Mediana de PFS 5.7 meses
- 45% de pacientes libres de progresión a 6 meses
- Mediana SG 14.9 meses
- OS:
  - 1 año 56%
  - 2 años 32%

Overall Survival With Sitravatinib + Nivolumab in Patients With Nonsquamous NSCLC With Prior Clinical Benefit From CPI Therapy



	Sitravatinib + Nivolumab (n=68)
Median OS (95% CI)	14.9 (9.3, 21.1)
Events/censored, n (%)	46 (68)/22 (32)

Median follow-up in PCB cohort: 33.6 months.
Data as of 1 June 2021.

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Incidence of Treatment-Related Adverse Events

Most Frequent (≥15%) TRAEs (n=68)	2L/3L Sitra + Nivo	
TRAEs	**Any Grade**	**Grade 3-4**
Any TRAEs	93%	66%
Most frequent TRAEs, %		
Diarrhea	62%	16%
Fatigue	52%	4%
Nausea	44%	2%
Hypertension	40%	22%
Decreased appetite	35%	0%
Weight decreased	31%	9%
Vomiting	31%	0%
Hypothyroidism	22%	0%
Dysphonia	19%	0%
ALT increase	18%	2%
AST increase	16%	0%
Stomatitis	15%	2%
PPE syndrome	15%	3%
Dehydration	15%	3%

- The most frequent immune-related TRAES included hypothyroidism, diarrhea, ALT increase, AST increase, TSH increase maculopapular rash, and pancreatitis[a]
- No grade 5 events occurred in the CPI-experienced cohort[b]

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Summary

- Sitravatinib is a spectrum-selective TKI targeting TAM (TYRO3, AXL, MERTK) receptors and VEGFR2 that can potentially overcome an immunosuppressive TME[5]
- Sitravatinib + nivolumab demonstrated antitumor activity, encouraging OS, and durable responses in patients with nonsquamous NSCLC with prior clinical benefit from a CPI
  - Median DOR was 12.8 months; ORR was 18% (12/68)
  - 1- and 2-year OS were 56% and 32%, respectively
- No unexpected safety signals with the combination were observed, and AEs were manageable
- These results support the ongoing Phase 3 SAPPHIRE study (NCT03906071), evaluating sitravatinib + nivolumab in patients with nonsquamous NSCLC who received clinical benefit from and subsequently experienced progressive disease on a prior CPI

Gracias al grupo español de cáncer de pulmón por la invitación

Gracias a todos por escucharme y compartir esta experiencia conmigo

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