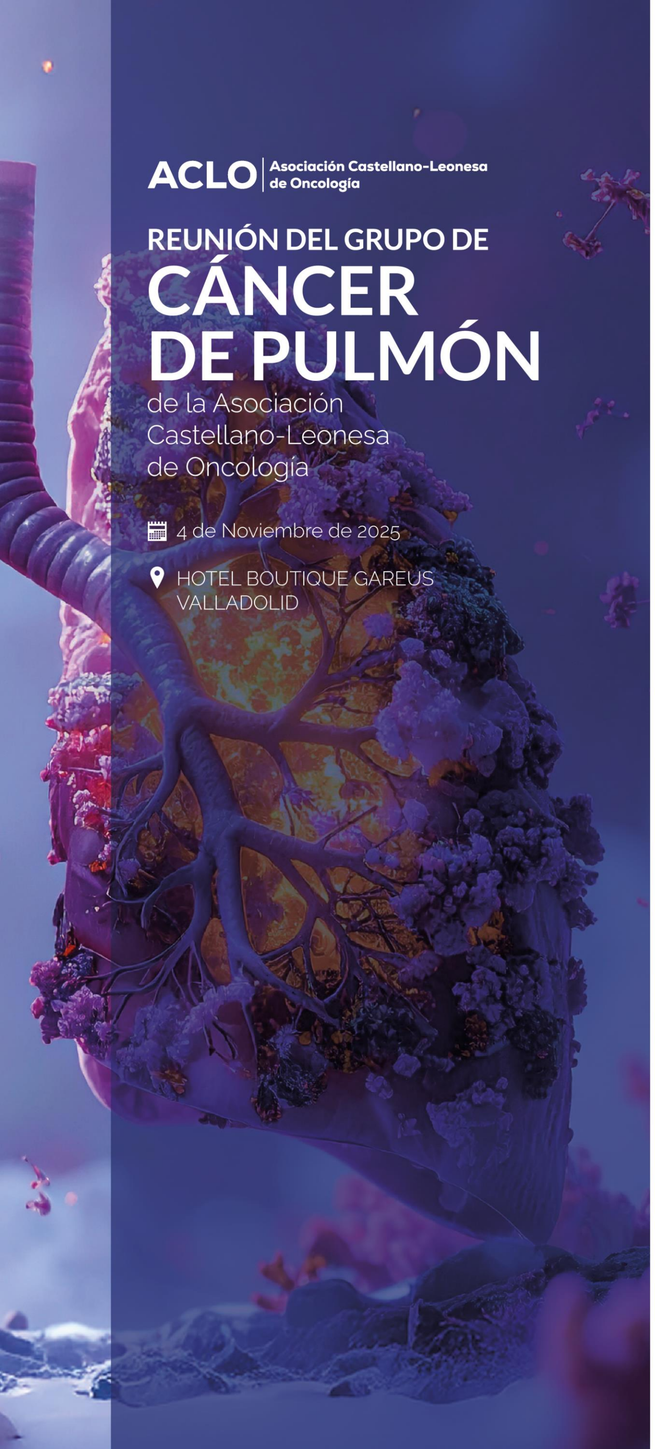
Cuarta mesa: Otras mutaciones

HER2 en CNMP

Asun Díaz Serrano
Complejo Asistencial de Zamora



Guión

Alteraciones de HER2 en CNMP

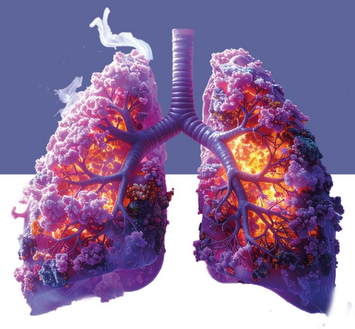
Perfil clínico

Estrategias de abordaje terapéutico

Guías clínicas

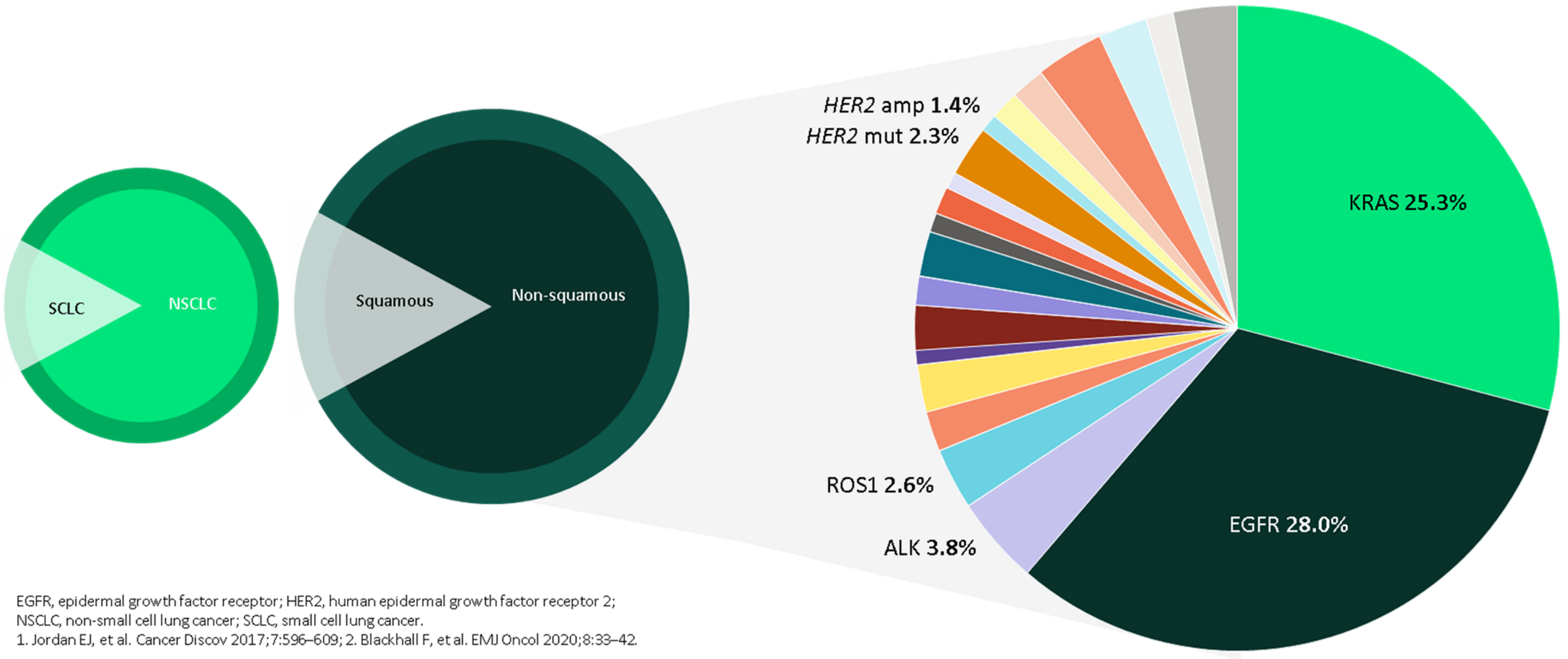
Conclusiones

Disclosures: Financiación de asistencia a congresos o de sesiones en reuniones científicas
Roche, Astrazeneca, Takeda, Pfizer, Merck, MSD, BMS, Novocure



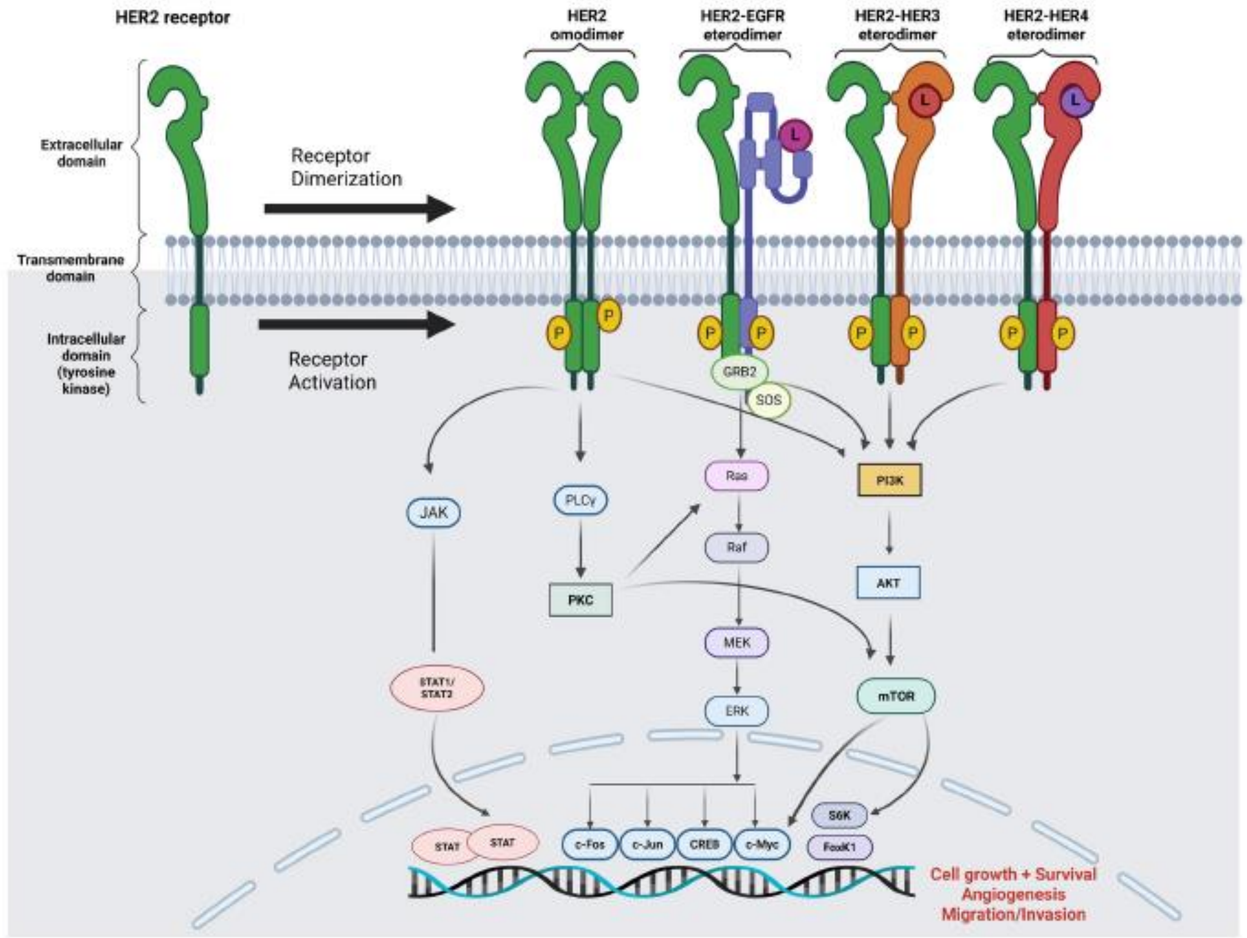
Él cáncer de pulmón como entidad múltiple

Alteraciones de HER2 en CNMP



EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.
1. Jordan EJ, et al. Cancer Discov 2017;7:596–609; 2. Blackhall F, et al. EMJ Oncol 2020;8:33–42.

Determinación de HER2: ¿gen o proteína?



Mutaciones activadoras (PCR o NGS) 1-4%

Mayor valor predictivo de respuesta a tratamientos dirigidos
Mutuamente excluyente con otras mutaciones drivers
Comutación más frecuente *p53*

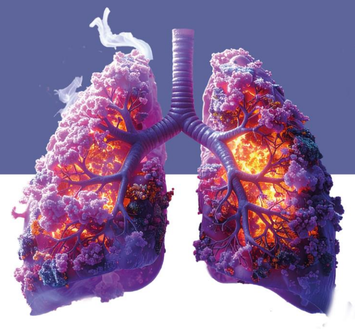
Amplificación génica (FISH o NGS) 2-20%

Verdadera amplificación 2-4%
Mecanismo de resistencia a TKIs, ej. EGFR-TKI 7-15%

Sobreexpresión proteica (IHQ 2+/3+) 2-35%

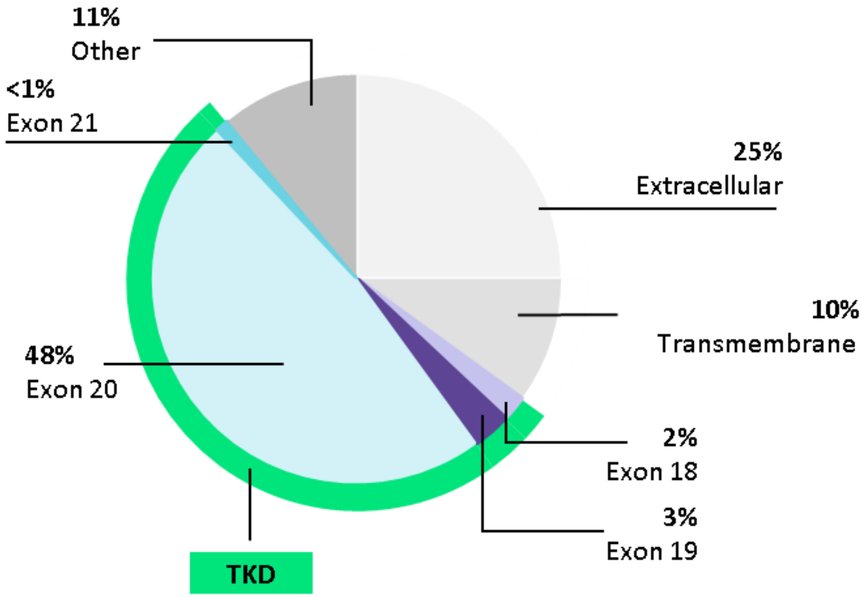
Heterogeneidad en la medición
Escasa correlación con amplificación génica

Trillo Aliaga P et al. Molecules 2025;30:2645
Ren S et al. ESMO Open 2022;7

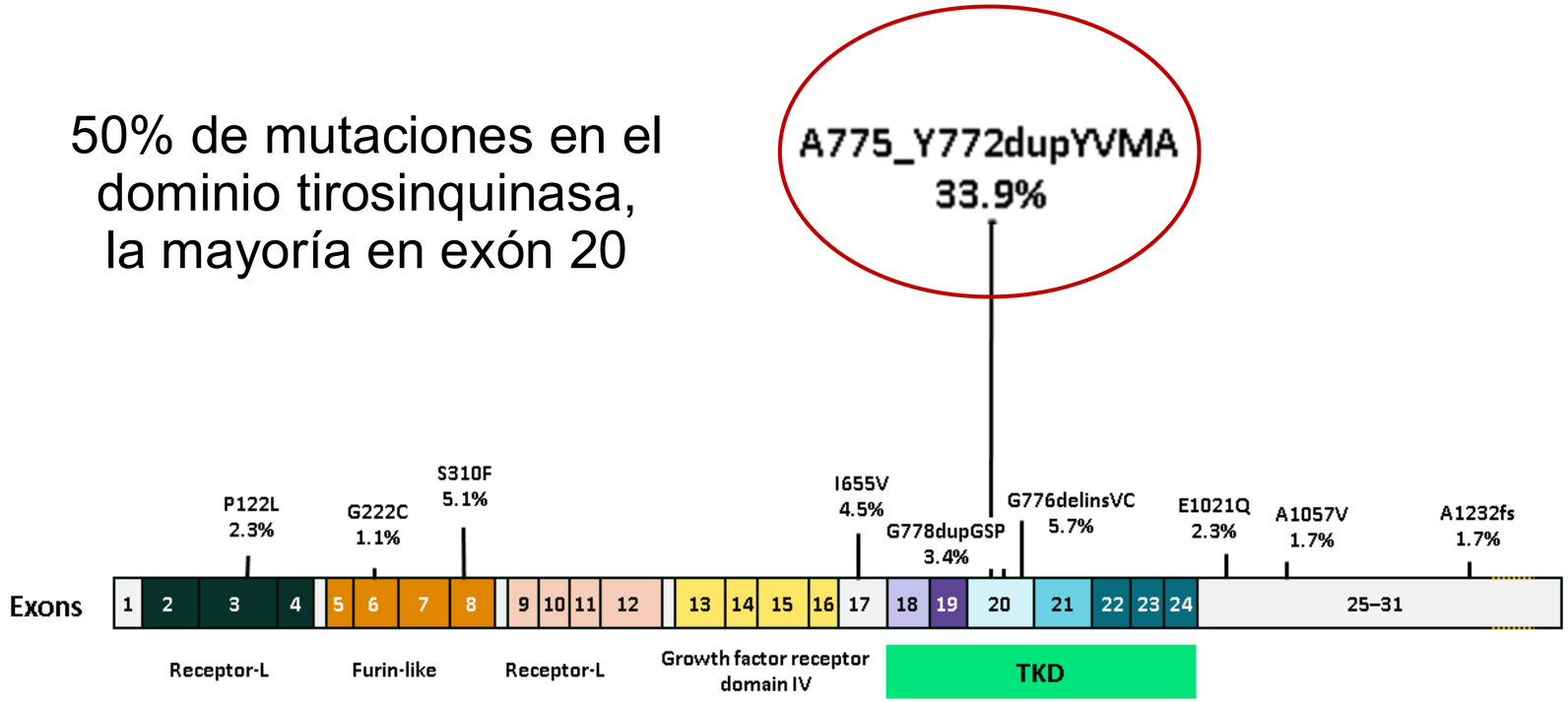


Mutaciones de HER2

1-4% de los pacientes con CNMP[1-3]



50% de mutaciones en el dominio tirosinquinasa, la mayoría en exón 20



Figures adapted from Hyman DM, et al. Nature 2018;554:189–194 and Robichaux JP, et al. Cancer Cell 2019;36:444–457.
HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; TKD, tyrosine kinase domain.

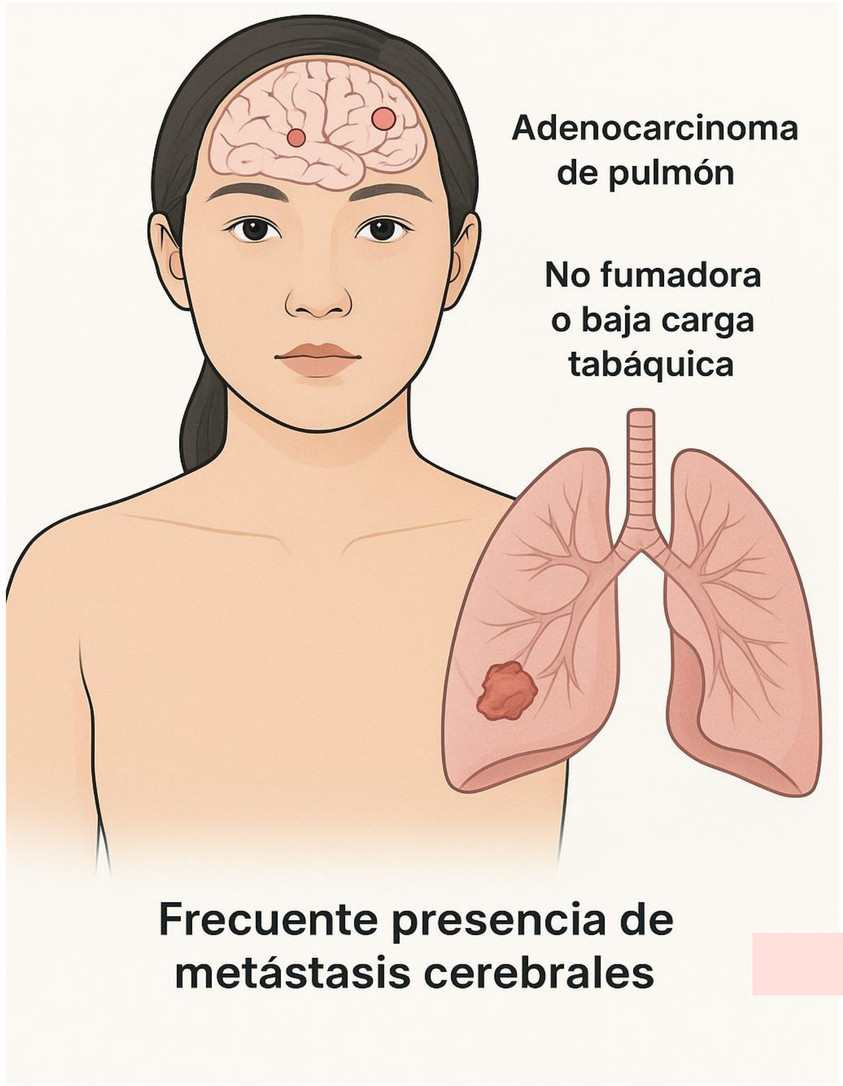
1.Trillo Aliaga P et al. Molecules 2025;30:2645
2.Ren S et al. ESMO Open 2022;7
3. Reinhorn et al. Cancer 2025:e35780

Mutaciones de HER2

Perfil clínico del paciente con mutación de HER2

≠

Perfil clínico del paciente con HER2 sobreexpresado o amplificado



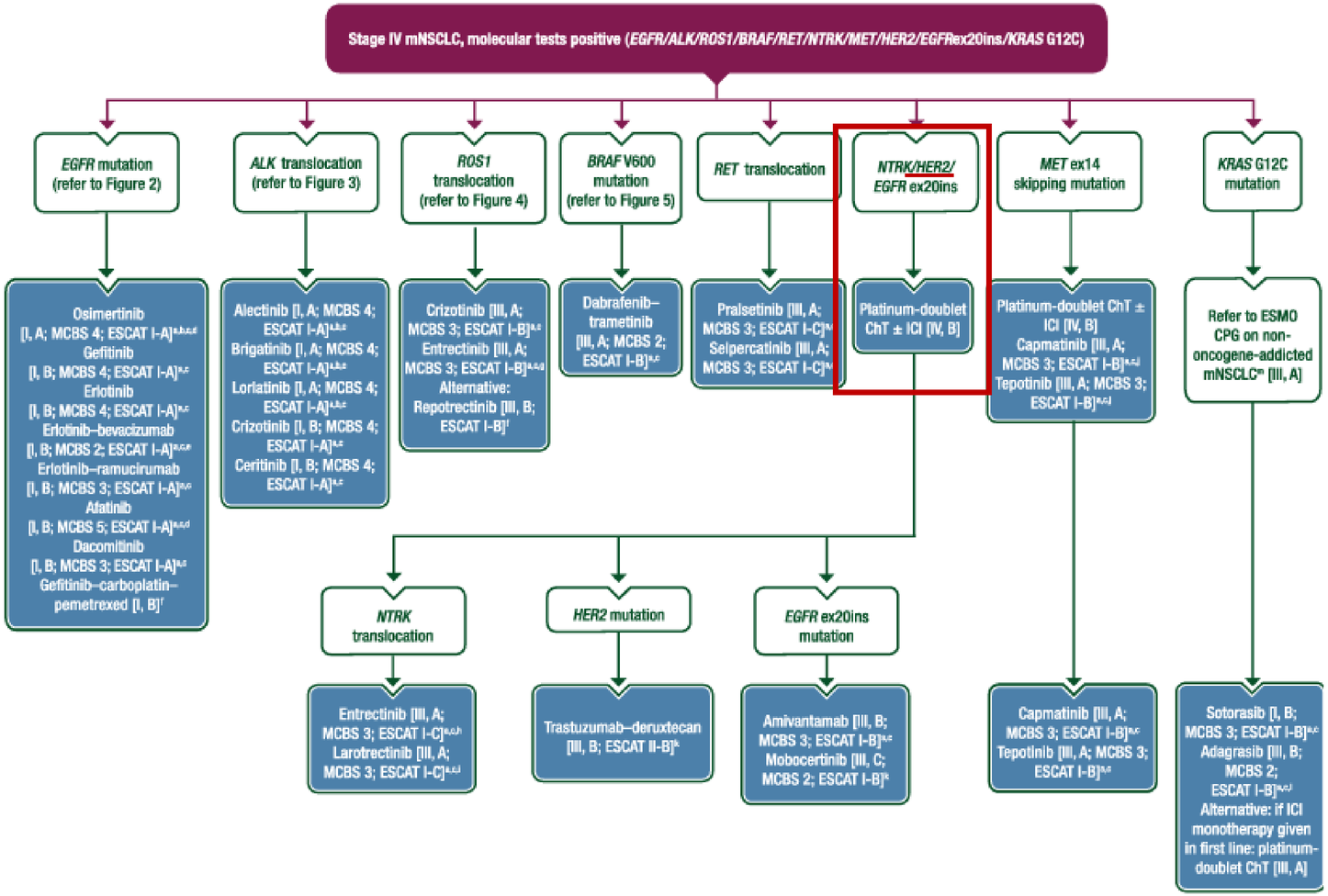
Peor pronóstico

20% al diagnóstico
50% en la evolución

Ren S et al. ESMO Open 2022;7
Reinhorn et al. Cancer 2025:e35780

Estrategias terapéuticas estándares

Necesidad de mejorar los resultados

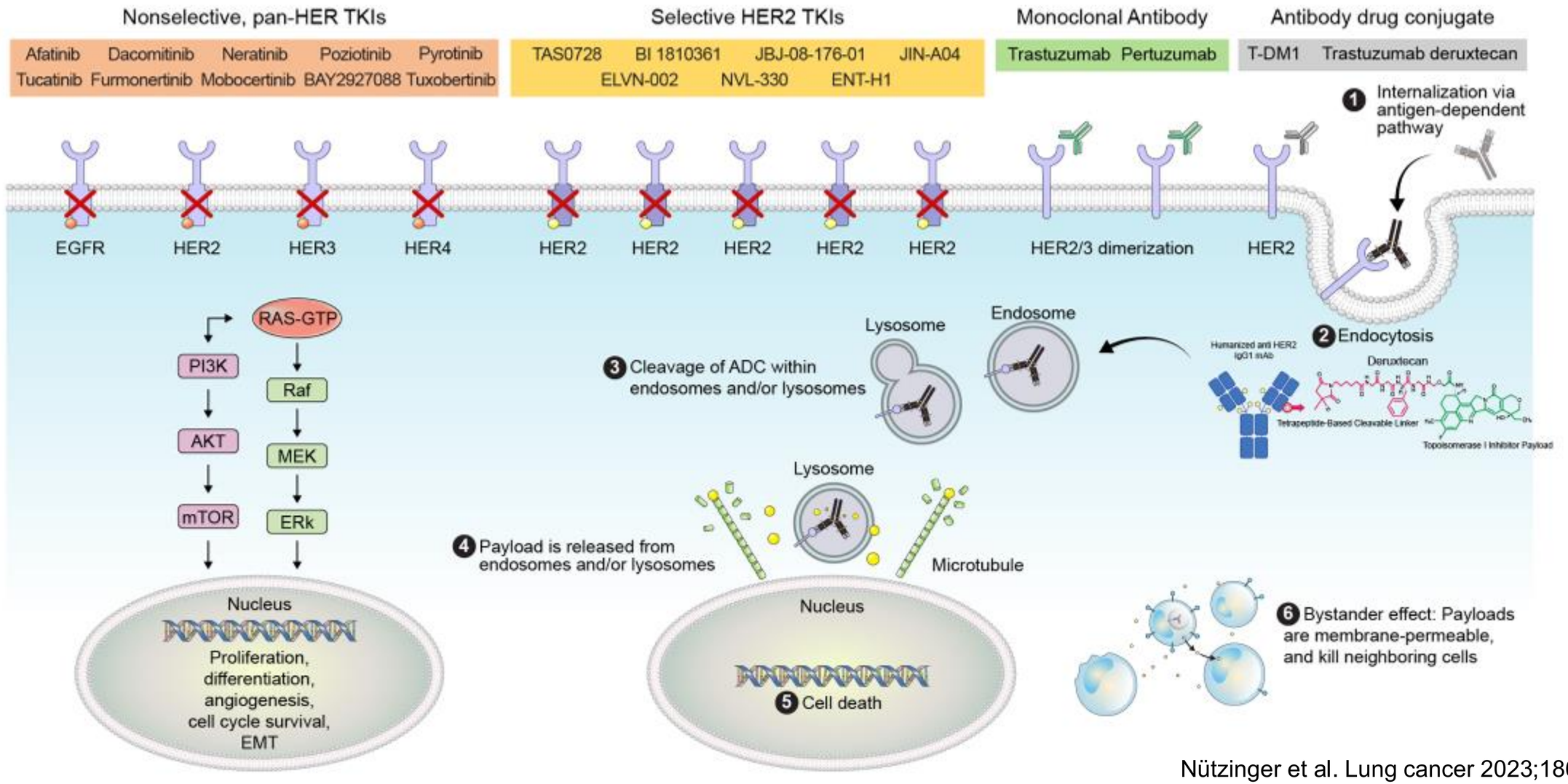


ORR en población HER2 (datos retrospectivos)

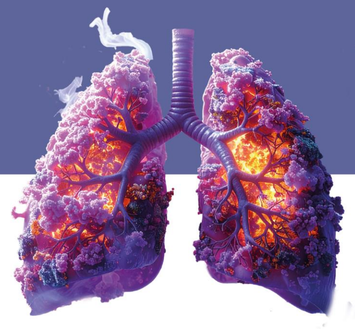
Platino	Inmunoterapia	Combo QT-ICI
ORR 30-40%	ORR 6-14%	ORR 29-55%
Comparable a poblaciones no seleccionadas	Baja TMB y expresión de PDL1	Comparable a poblaciones no seleccionadas

Reinhorn et al. Cancer 2025: e35780

Estrategias terapéuticas anti-HER2



Nützinger et al. Lung cancer 2023;186:107385



Estrategias terapéuticas anti-HER2

Anticuerpos conjugados con drogas (ADCs)

- **Trastuzumab deruxtecán**

Inhibidores tirosinquinasa (TKIs)

- Pan-HER
- EGFR/HER2
  - **Sevabertinib /BAY2927088**
- HER2 selectivos
  - **Zongertinib /HERNEXEOS®**

Otras estrategias

Trastuzumab deruxtecán

DESTINY-Lung 01

Fase 2

Patients

- Unresectable/metastatic nonsquamous NSCLC
- Relapsed/refractory to standard treatment
- HER2 expressing or HER2 activating mutation[a]
- No prior HER2 targeted therapy, except pan-HER TKIs

Cohort 1 (n = 42)
HER2 expressing (IHC3+ or IHC2+)

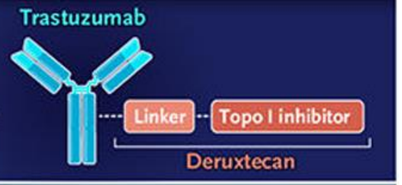
Cohort 2 (n = 42)
HER2 mutated

T-DXd 6.4 mg/kg q3w

Trastuzumab Deruxtecan in *HER2*-Mutant Non–Small-Cell Lung Cancer

MULTICENTER, INTERNATIONAL, PHASE 2 STUDY

91
Adults with metastatic *HER2*-mutant NSCLC refractory to standard treatment (median follow-up, 13 mo)



Confirmed objective response (assessed by independent central review)	55% (95% CI, 44–65)
Duration of response	9.3 mo
Progression-free survival	8.2 mo
Overall survival	17.8 mo

Grade 3 or higher drug-related adverse events occurred in 46% of patients.

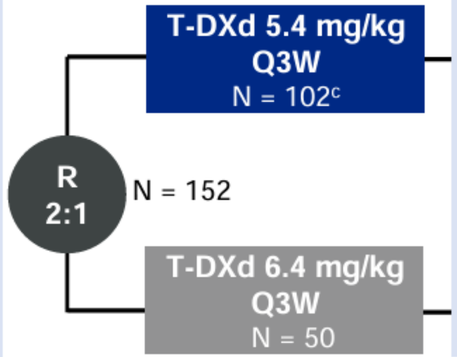
Trastuzumab deruxtecan showed durable anticancer activity.

DESTINY-Lung 02

Fase 2

Key Eligibility Criteria[a]
- Metastatic *HER2*m[b] NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1

Stratification Factor:
- Prior anti–PD-(L)1 treatment



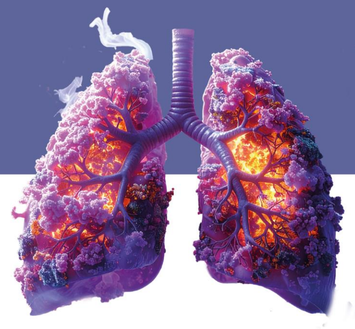
Primary Endpoint
- Confirmed ORR by BICR

Secondary Endpoints
- Confirmed ORR by INV
- DoR by BICR and INV
- DCR by BICR and INV
- PFS by BICR and INV
- OS
- Safety

Patients and investigators were blinded to the dose level

2 cohortes pero no diseñado para encontrar diferencias entre ambas

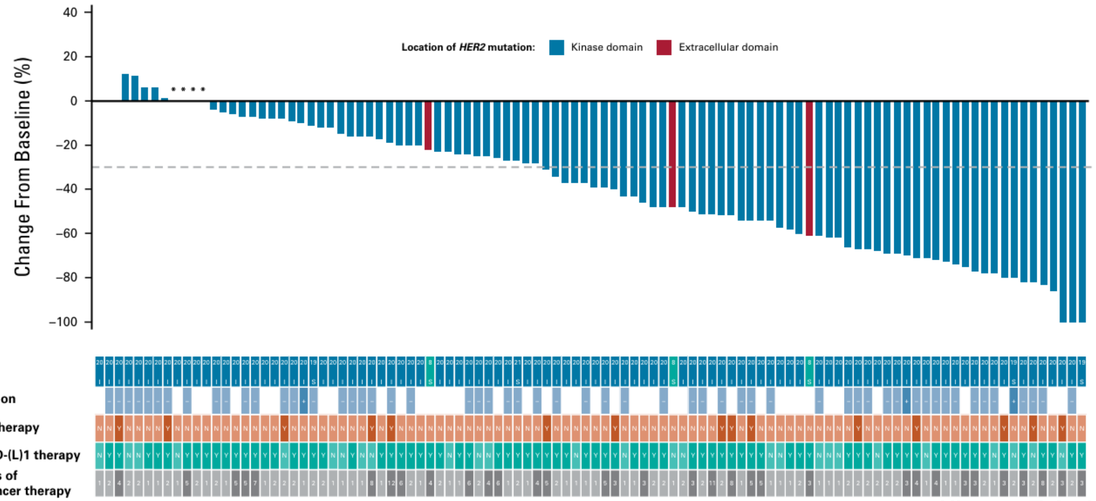
Li BT et al. N Engl J Med. 2022;386:241-251
Goto K et al. J of Clin Oncol. 2023;41:4852-63

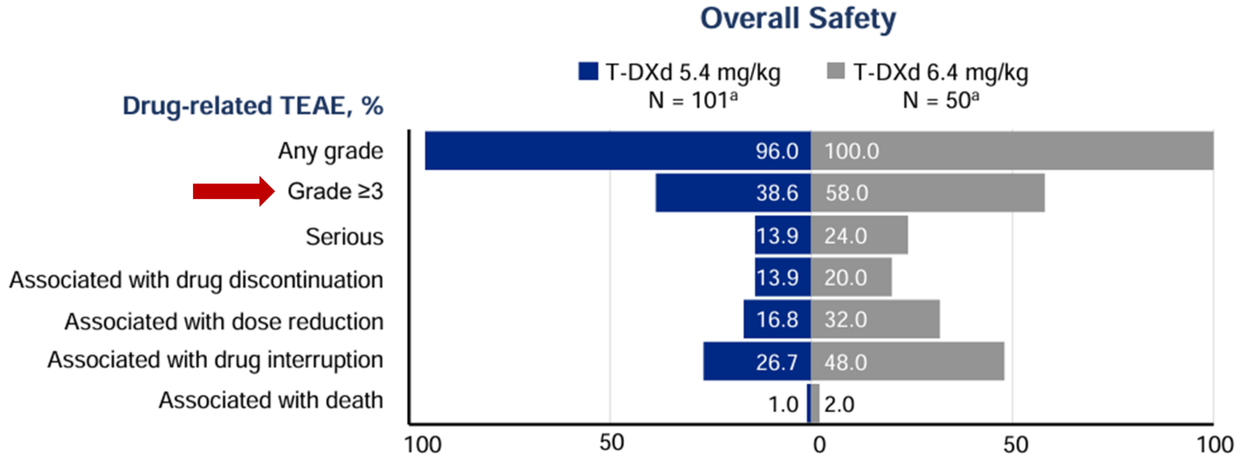


Trastuzumab deruxtecán

DESTINY-Lung 02: balance beneficio-toxicidad a favor de 5.4 mg/kg

Efficacy summary	T-DXd 5.4 mg/kg N = 102	T-DXd 6.4 mg/kg N = 50
Confirmed ORR,[a] n (%) [95% CI]	**50 (49.0)** [39.0-59.1]	**28 (56.0)** [41.3-70.0]
CR | PR	1 (1.0) | 49 (48.0)	2 (4.0) | 26 (52.0)
SD | PD	45 (44.1) | 4 (3.9)	18 (36.0) | 2 (4.0)
Non-evaluable[b]	3 (2.9)	2 (4.0)
DCR,[c] n (%) [95% CI]	95 (93.1) [86.4-97.2]	46 (92.0) [80.8-97.8]
Median DoR,[d,e] months (95% CI)	16.8 (6.4-NE)	NE (8.3-NE)
Median TTIR,[d] months (range)	1.8 (1.2-7.0)	1.6 (1.2-11.2)
Median follow-up, months (range)	11.5 (1.1-20.6)	11.8 (0.6-21.0)

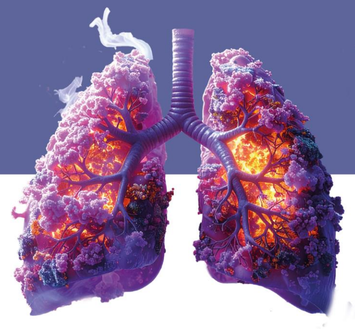




Adjudicated Drug-Related ILD

Adjudicated as drug-related ILD	T-DXd 5.4 mg/kg N = 101[a]	T-DXd 6.4 mg/kg N = 50[a]
Any grade, n (%)	**13 (12.9)**	**14 (28.0)**
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

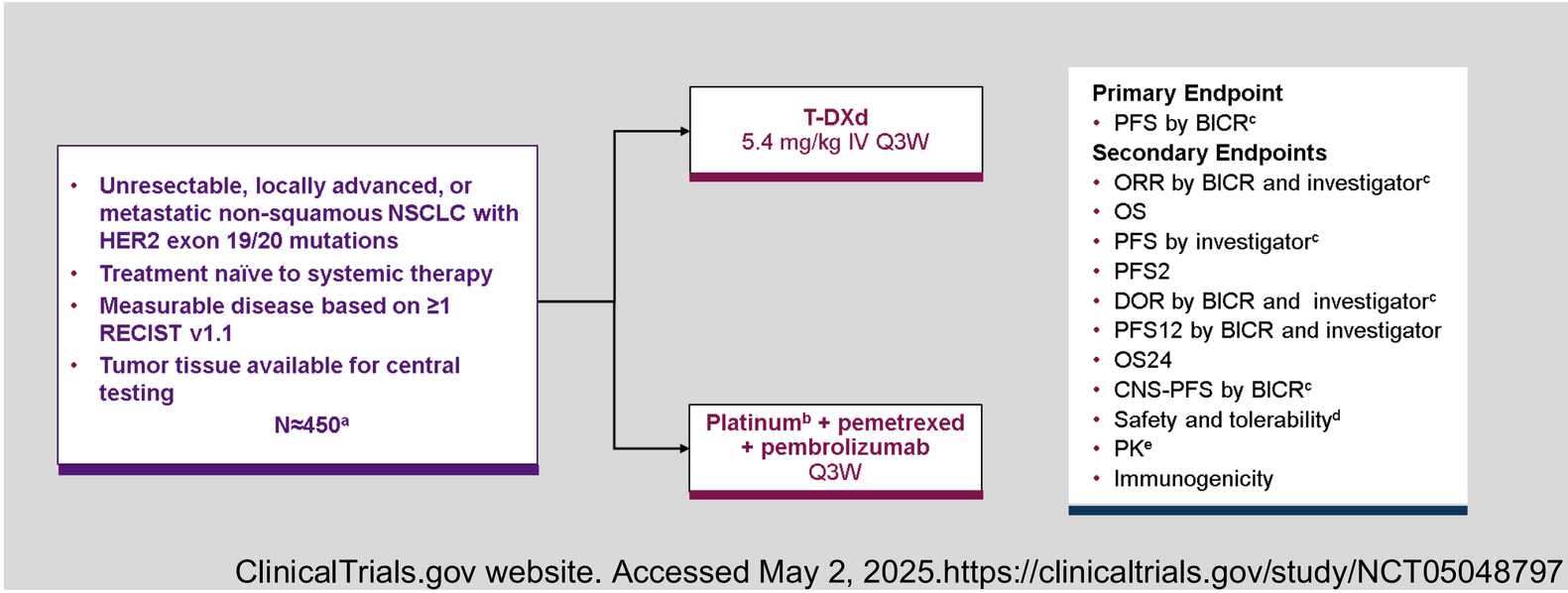
Jänne PA. WCLC 2023 Singapore 9-13 September. Goto K et al. J of Clin Oncol. 2023;41:4852-63



Trastuzumab deruxtecán

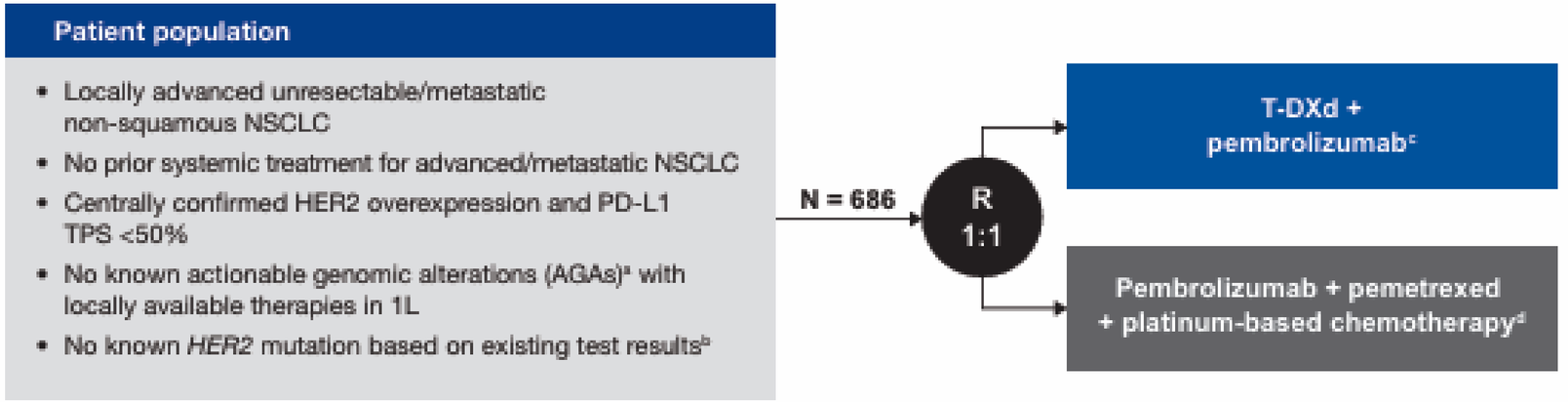
Fases 3 en marcha

DESTINY-Lung04
HER2 mutado (ex19-20)

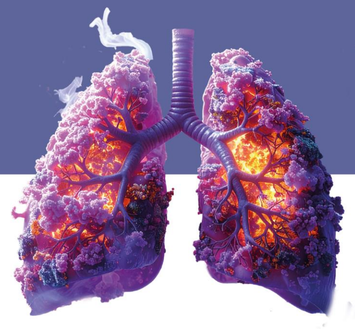


ClinicalTrials.gov website. Accessed May 2, 2025.https://clinicaltrials.gov/study/NCT05048797

DESTINY-Lung06
HER2 sobreexpresado (2/3+)
PDL1<50%

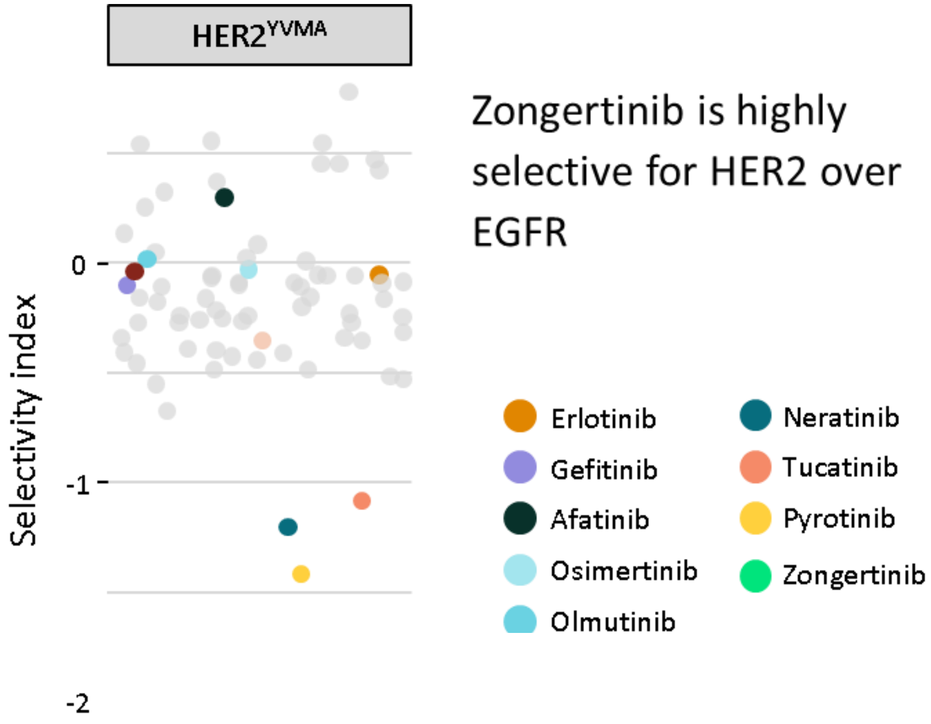


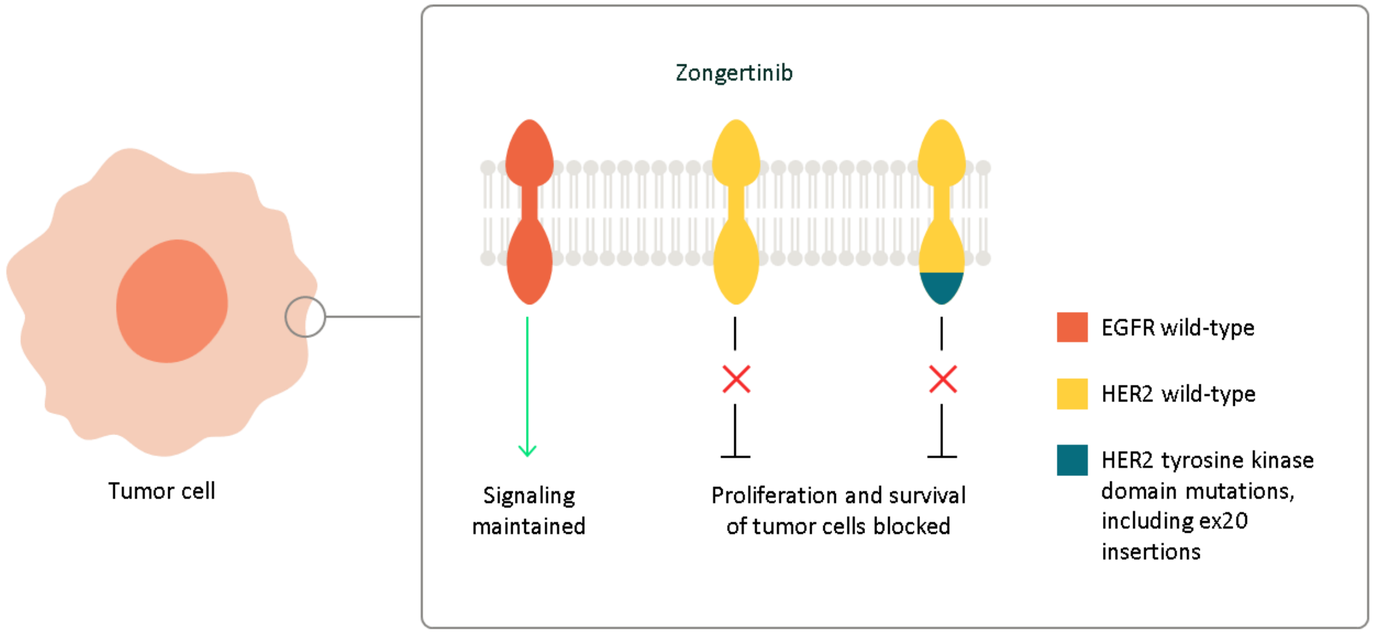
Extraído de Jänne PA. WCLC 2025, Poster P3.18.58



Zongertinib

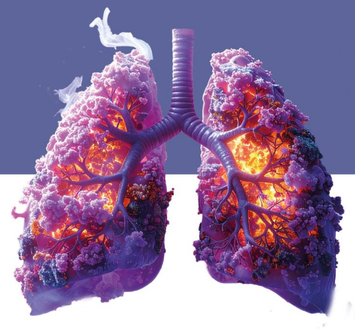
TKI irreversible, selectivo y potente de HER2





Neumüller R, et al. AACR-NCI-EORTC 2023 (Poster C140); Wilding, et al. Cancer Discov 2024; doi:10.1158/2159-8290.CD-24-0306.
CTG, CellTiter-Glo®; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; IC_{50}, half maximal inhibitory concentration; ins, insertion; KO, knockout; TKI, tyrosine kinase inhibitor.

HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; TKD, tyrosine kinase domain; TKI, tyrosine kinase inhibitor; wt, wild-type.
Heymach J et al. *Clin Lung Cancer* 2023;24:e65-68

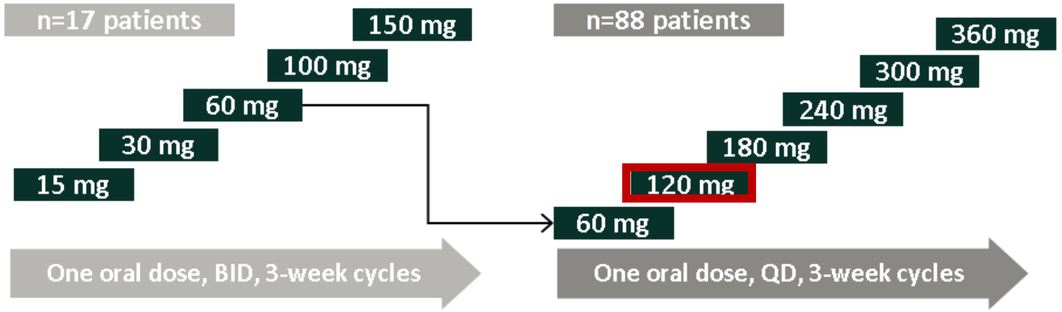


Zongertinib

Beamion LUNG-1: Phase Ia (dose escalation) and Phase Ib (dose expansion)

Phase Ia: dose escalation[1,2]

(zongertinib monotherapy in patients with advanced solid tumors with HER2 aberrations)



Ph Ia endpoints

Primary: MTD and DLTs
Further: preliminary efficacy (ORR)†

Key inclusion criteria

HER2 aberration: overexpression, amplification, somatic mutation, or gene rearrangement involving *HER2* or *NRG1*

Exhausted or not suitable for existing standard treatment options

Ph Ib primary endpoint

ORR†

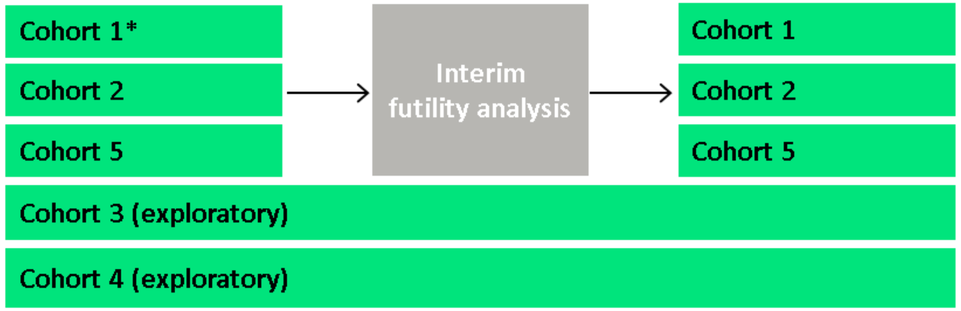
Key inclusion criteria

Patients with *HER2* mutation-positive NSCLC

Received ≥1 line of platinum-based combination chemotherapy (Cohorts 1, 3, 5)

Phase Ib: dose expansion[2,3]

(zongertinib monotherapy in patients with *HER2* mutation-positive NSCLC)



Cohort 1: Pre-treated NSCLC‡ with *HER2* TKD mutation

Cohort 2: Treatment-naive NSCLC with *HER2* TKD mutation

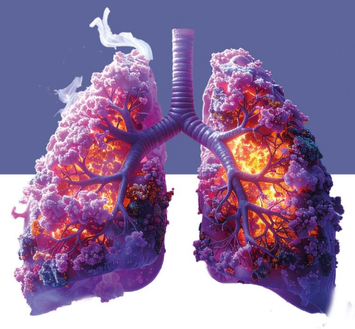
Cohort 3: NSCLC with a non-TKD *HER2* mutation or *HER2* TKD mutation-positive squamous NSCLC, pre-treated

Cohort 4: NSCLC with active brain metastases with a *HER2* TKD mutation

Cohort 5: NSCLC with a *HER2* TKD mutation and prior treatment with HER2 directed ADCs

* Randomized to receive either 240 mg or 120 mg QD. One dose will be selected at interim analysis; † RECIST v1.1; ‡ Excluding patients pre-treated with ADCs.
ADC, antibody-drug conjugate; BID, twice daily; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; QD, once daily; TKD, tyrosine kinase domain.
1. Heymach J, et al. J Clin Oncol 2025;43:1337–1347 (incl. suppl.); 2. Heymach J, et al. ASCO 2024. Oral presentation 8514; 3. Clinicaltrials.gov. Available at: https://clinicaltrials.gov/study/NCT04886804 [accessed March 2025].

Heymach JV et al. N Engl J Med. 2025;392;23:2321-33



Zongertinib

Características basales

		Cohort 1: Patients with TKD mutations N=75	Cohort 5: Patients with TKD mutations and prior HER2-directed ADC treatment N=31	Cohort 3: Patients with non-TKD mutations N=20
Median age, years (range)		62 (30–80)	61 (31–85)	65 (27–77)
Female, n (%)		51 (68)	21 (68)	9 (45)
Race, n (%)*	Asian	40 (53)	11 (35)	9 (45)
	Non-Asian	24 (32)	14 (45)	8 (40)
Lines of prior systemic anticancer treatment, n (%)†‡	1	46 (61)§	5 (16)	8 (40)
	≥2	29 (39)	26 (84)	12 (60)
ECOG PS, n (%)	0	28 (37)	7 (23)	4 (20)
	1	47 (63)	24 (77)	16 (80)
Brain metastases, n (%)		28 (37)	23 (74)	8 (40)
***HER2* TKD mutation type, n (%)**	A775_G776insYVMA	48 (64)	18 (58)	0
	P780_Y781insGSP	8 (11)	3 (10)	0
	Other	19 (25)	10 (32)	0

Data cut-off: November 29, 2024.

* Missing: Cohort 1, n=11; Cohort 5, n=6; Cohort 3, n=3; † Median lines of prior treatment: Cohort 1, n=1 (range, 1–10); Cohort 5, n=2 (range, 1–8); Cohort 3 (non-TKD only), n=2 (range, 1–4); ‡ 76% of patients in Cohort 1 received prior immunotherapy; § Three patients received prior treatment in the adjuvant setting only, but within 6 months of initiating zongertinib; therefore, these patients were considered as previously treated in the advanced/metastatic setting per protocol.

ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; ins, insertion; NSCLC, non-small cell lung cancer; TKD, tyrosine kinase domain.

Heymach J, et al. AACR 2025. Oral presentation CT050.

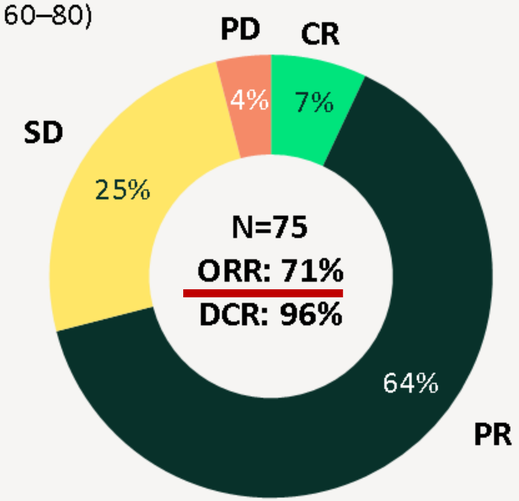
Heymach JV et al. N Engl J Med. 2025;392;23:2321-33

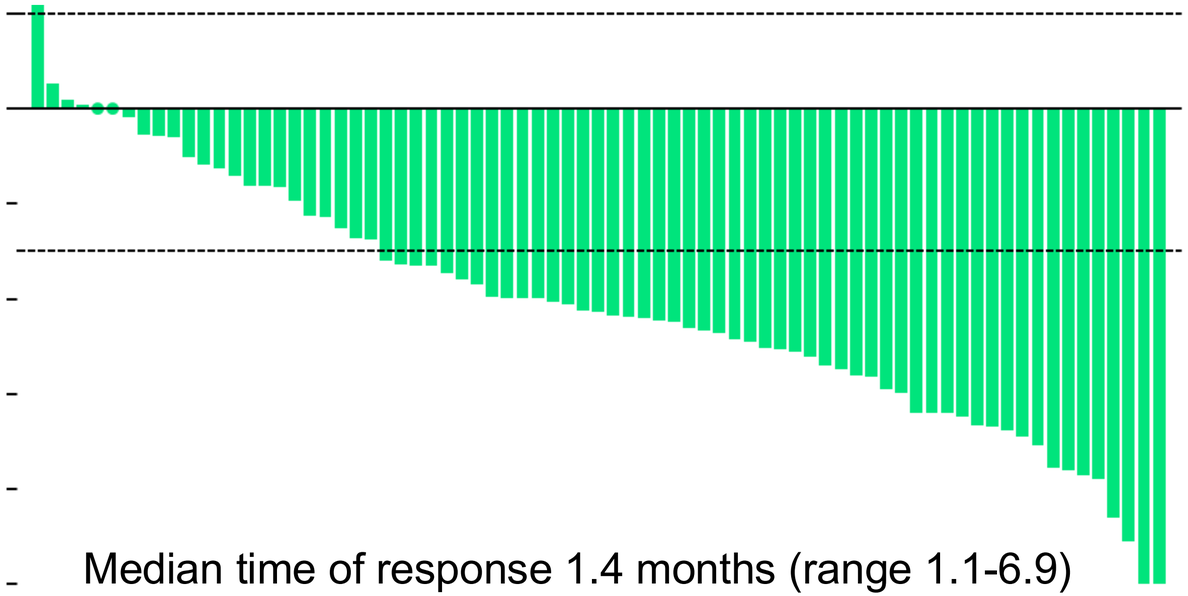
Zongertinib

Resultados cohorte 1: CNMP pretatado con mutaciones en TKD HER2

Confirmed response by BICR (RECIST v1.1):

71% (95% CI, 60–80)





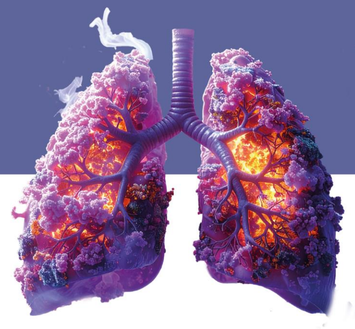
Median time of response 1.4 months (range 1.1-6.9)

The median best percentage change from baseline in target lesions was -43% (range, -100–22)*

Objective responses were observed in 71% of patients, including 7% with CR, and 96% of patients achieved DC with zongertinib

Data cut-off: November 29, 2024. Median follow-up was 11.3 months (95% CI, 10.2–12.3).
* Due to the central review process, lesion measurements are only available for investigator assessment.
BICR, blinded independent central review; CI, confidence interval; CR, complete response; DC, disease control; DCR, disease control rate; HER2, human epidermal growth factor receptor 2; ORR, objective response rate; PD, progressive disease; PR, partial response; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; SLD, sum of lesion diameters; TKD, tyrosine kinase domain.
Heymach J, et al. AACR 2025. Oral presentation CT050.

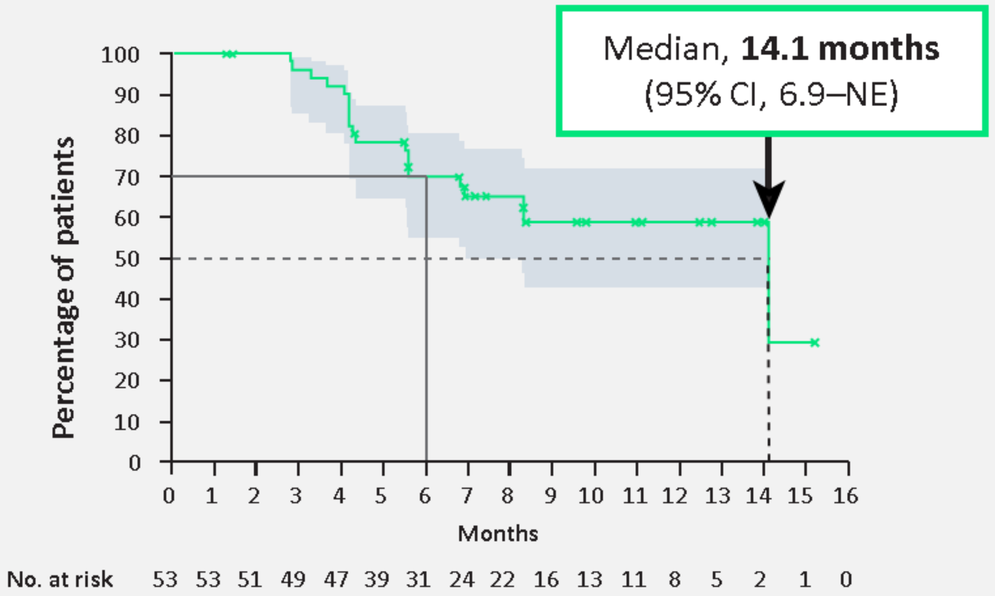
Heymach JV et al. N Engl J Med. 2025;392;23:2321-33



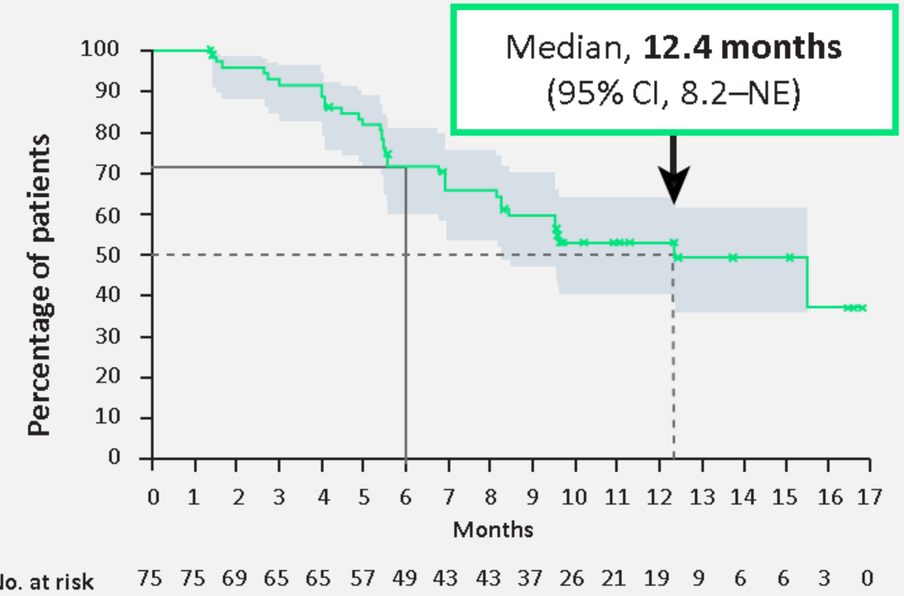
Zongertinib

Resultados cohorte 1: CNMP pretatado con mutaciones en TKD HER2

DoR



PFS



Figures reproduced with permission from Heymach JV, et al. N Engl J Med 2025;392:2321–33, Copyright Massachusetts Medical Society. *Cohort 1: Previously treated NSCLC with a *HER2* TKD mutation (excluding patients previously treated with ADCs). †In adults with unresectable or metastatic NSCLC whose tumors have HER2 TKD activating mutations and who have received prior systemic therapy. ADC, antibody–drug conjugate; CI, confidence interval; DoR, duration of response; HER2, human epidermal growth factor receptor 2; NE, not evaluable; NSCLC, non-small cell lung cancer; PFS, progression-free survival; QD, once daily; TKD, tyrosine kinase domain

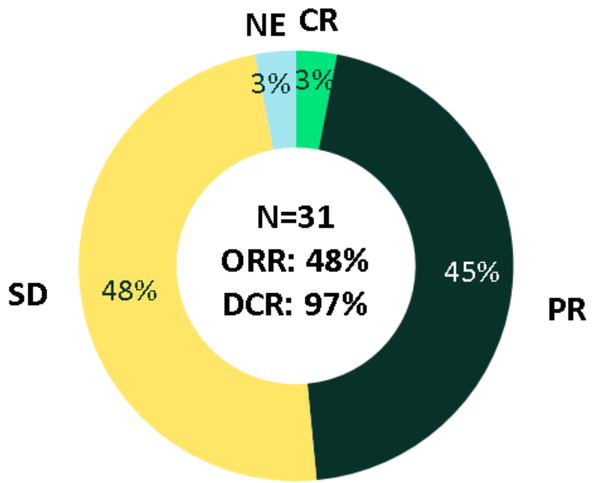
1. Heymach JV, et al. N Engl J Med 2025;392:2321–33; **2.** U.S. Food and Drug Administration. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-zongertinib-non-squamous-nsclc-her2-tkd-activating-mutations (Accessed: September 2025); **3.** Boehringer Ingelheim. https://www.boehringer-ingelheim.com/human-health/cancer/lung-cancer/hernexeos-approved-china-targeted-therapy-nsclc (Accessed: September 2025)

Heymach JV et al. N Engl J Med. 2025;392;23:2321-33

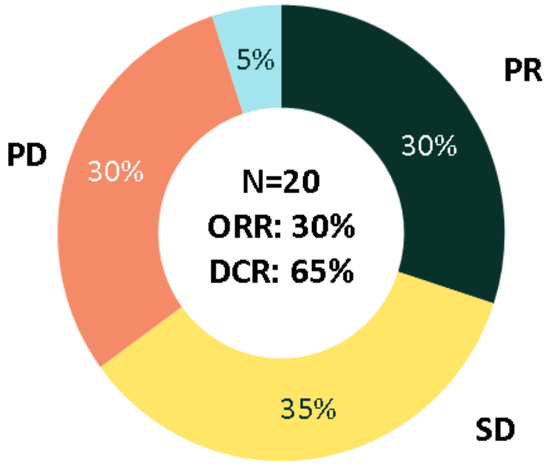
Zongertinib

Resultados cohortes 3 y 5

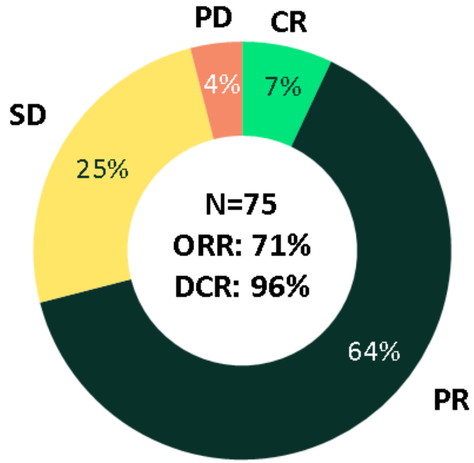
Cohorte 5: tratamiento previo con ADCs HER2



Cohorte 3: mutaciones HER2 fuera de TKD



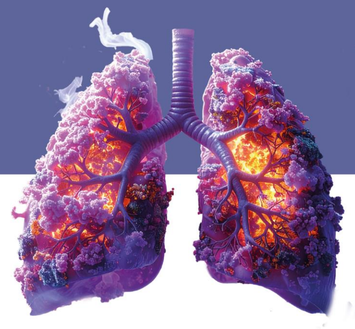
Cohorte 1: pretatados mutaciones TKD HER2



Data cut-off: November 29, 2024. Median follow-up was 6.8 months (95% CI, 5.5 to 8.5).
* Due to the central review process, lesion measurements are only available for investigator assessment.
ADC, antibody-drug conjugate; BICR, blinded independent central review; CI, confidence interval; CR, complete response; DCR, disease control rate; HER2, human epidermal growth factor receptor 2; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; SLD, sum of lesion diameters; T-DXd, trastuzumab deruxtecan; TKD, tyrosine kinase domain.

1. Heymach J, et al. AACR 2025. Oral presentation CT050; 2. Wilding B et al. Cancer Discov 2025;15:119–138; 3. Nilsson MB, et al. AACR 2024. Abstract 5857.

Heymach JV et al. N Engl J Med. 2025;392;23:2321-33



Zongertinib

Eficacia intracraneal en metástasis asintomáticas cohorte 1 o activas cohorte 4

Current analysis: patients with brain metastases at baseline

n=28

Cohort 1

Previously treated* patients with TKD mutations, including those with stable, asymptomatic brain metastases at baseline

Primary endpoint: Systemic OR by BICR (RECIST v1.1)

Secondary endpoints: CNS OR and DC by BICR (RANO-BM); systemic DC, DoR, and PFS by BICR (RECIST v1.1)

+

n=30

Cohort 4

Treatment-naïve or previously treated* patients with TKD mutations and active brain metastases at baseline

Primary endpoint: CNS OR by BICR (RANO-BM)

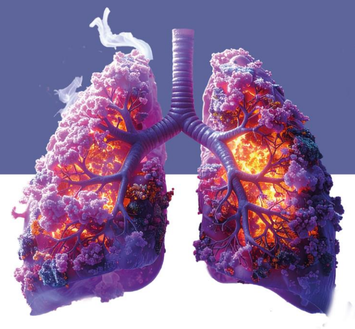
Secondary endpoints: CNS DC, DoR, and PFS by BICR (RANO-BM); systemic OR, DC, DoR, and PFS by BICR (RECIST v1.1)

	n=58
ORR	**41%**
CR	9%
PR	33%
DCR	**83%**
SD	41%
PD	7%
NE	10%

Median PFS	**8.2 months**
95% CI	4.5–12.3

Sin RT cerebral previa ORR 44%

Adapted from: Ruiter G, et al. IASLC 2025 World Conference on Lung Cancer, Barcelona, Spain, 2025. Poster presentation.

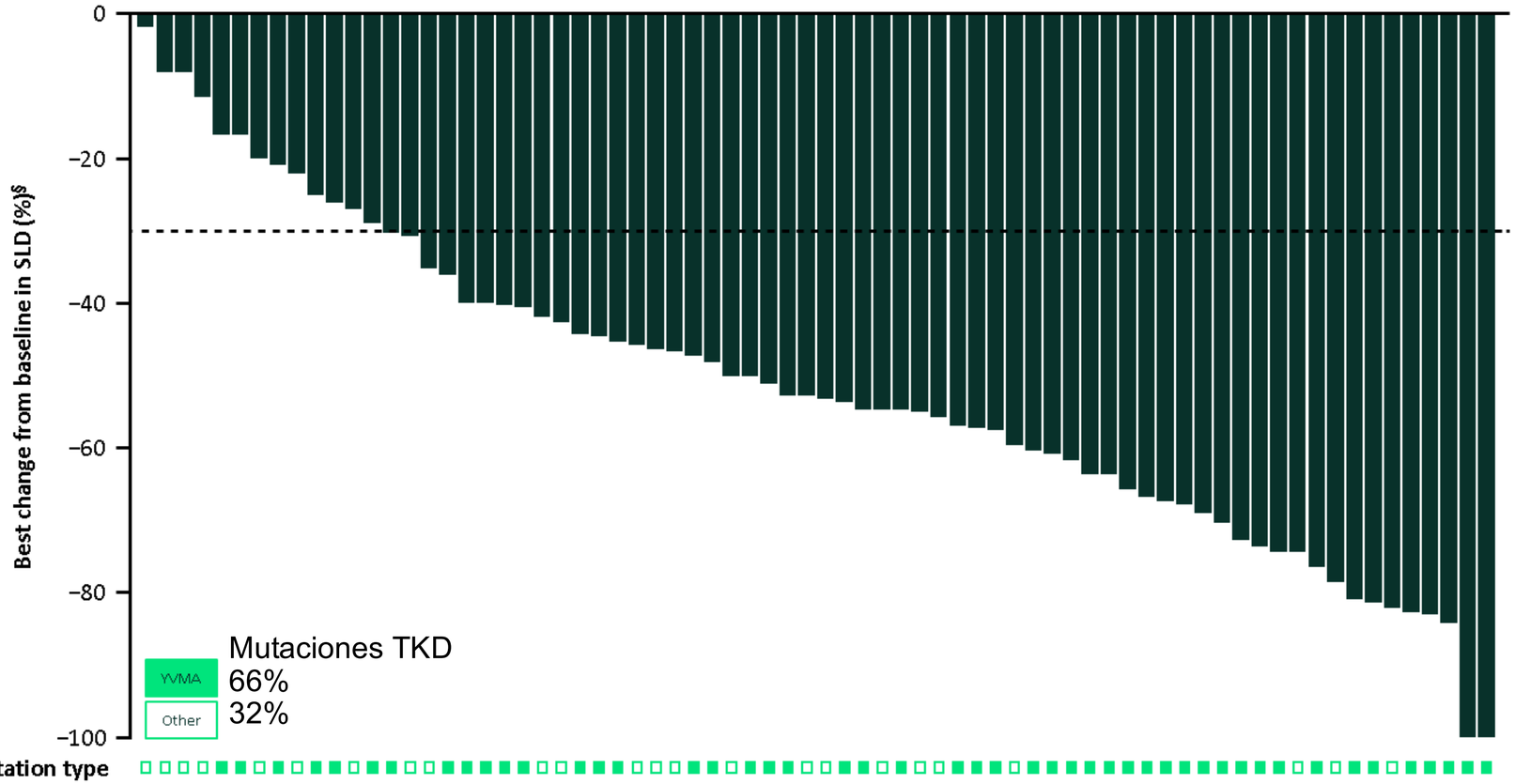


Zongertinib

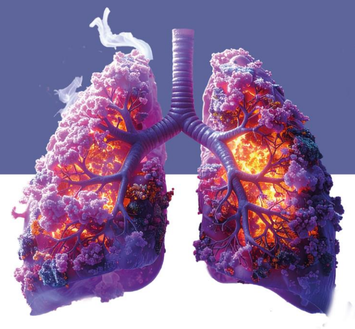
BERLIN 2025 ESMO congress

Resultados cohorte 2: 1ª línea mutaciones TKD

Confirmed response by BICR (RECIST v1.1)	N = 74*
ORR	**77%**
95% CI	66–85
p value†	<0.0001
CR, n (%)	6 (8)
PR, n (%)	51 (69)
DCR	**96%**
95% CI	89–99
SD, n (%)	14 (19)
PD, n (%)	1 (1)‡



Clinical benefit was observed with zongertinib in all patients, irrespective of *HER2* mutation type



Zongertinib

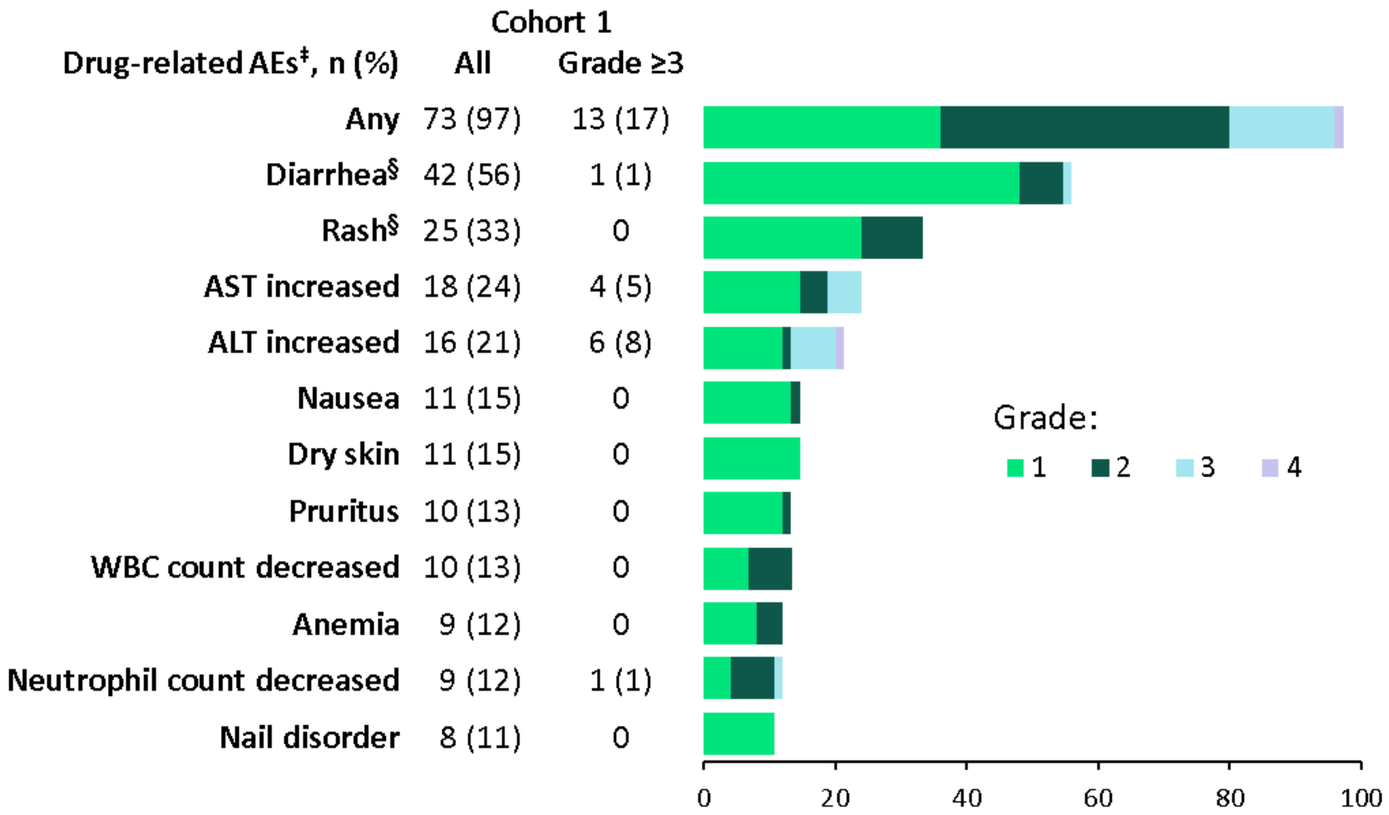
Seguridad y toxicidad

97% toxicidad de cualquier grado

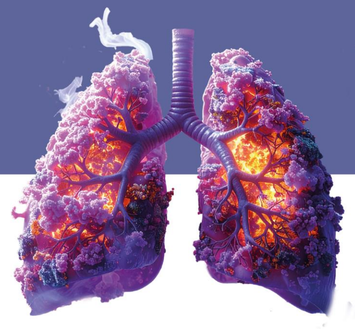
17% toxicidad grado 3 o superior

7% de AEs que condujeron a reducción de dosis y 3% discontinuaciones

No casos de enfermedad pulmonar intersticial



Data cut-off: November 29, 2024. * AEs leading to dose reduction: AST increased, ALT increased, blood creatinine phosphokinase increased, gamma-glutamyltransferase increased, hypertransaminasemia, neutrophil count decreased, and suspected drug-induced liver injury; † AEs leading to treatment discontinuation: AST increased, ALT increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, and pyrexia; ‡ Drug-related AEs as assessed by the investigator that occurred in ≥10% of patients are shown; § Grouped terms.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ILD, interstitial lung disease; TKD, tyrosine kinase domain; WBC, white blood cell.
Heymach J, et al. AACR 2025. Oral presentation CT050.



Zongertinib

Beamion LUNG-2: Confirmatory Phase III trial

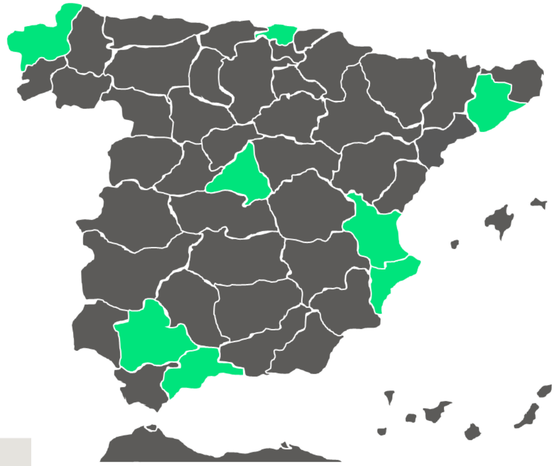
Beamion™ LUNG-2

N=416 patients with unresectable, locally advanced or metastatic NSCLC with *HER2* TKD mutations

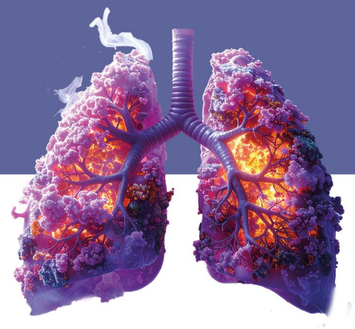
R

Zongertinib
(120mg)

SoC
(pembrolizumab + CT [cisplatin or carboplatin + pemetrexed])



- Hospital Universitario Vall d'Hebrón (Dra. Enriqueta Felip)
- ICO - Hospital Duran i Reynals (Dr. Ernest Nadal)
- Hospital de la Santa Creu i Sant Pau (Dr. Andrés Barba)
- Hospital Clínico Universitario Valencia (Dra. Amelia Insa)
- Hospital General Universitario de Alicante (Dr. Bartomeu Massuti)
- Hospital Universitario de Basurto (Dra. Mª Ángeles Sala)
- Complejo Hospitalario Universitario de La Coruña (Dra. Mª Rosario G. Campelo)
- Hospital Universitario 12 de Octubre (Dr. Jon Zugazagoitia)
- Hospital Universitario La Paz (Dr. Javier de Castro)
- Hospital Universitario Ramón y Cajal (Dra. Pilar Garrido)
- Hospital General Universitario Gregorio Marañón (Dr. Antonio Calles)
- Hospital Regional Universitario de Málaga (Dr. Manuel Cobo)
- Hospital Universitario Virgen del Rocío (Dra. Reyes Bernabé)



Sevabertinib/BAY2927088

BERLIN 2025 ESMO congress

TKI reversible de HER2/EGFR: SOHO-01

Ensayo fase 1-2, abierto internacional, multicohorte

DOSE ESCALATION AND BACKFILL

Patients with advanced NSCLC with *HER2* or *EGFR* mutations

Patients were treated with increasing oral doses of sevabertinib to identify the RDE (5 QD dose levels and 3 BID dose levels, from 10 mg QD to 40 mg BID)

20 mg BID

EXPANSION AND EXTENSION[a]
Cohorts of patients with *HER2* mutations[b]

To evaluate the safety, tolerability, and efficacy, and to characterize the pharmacokinetics, of sevabertinib at the RDE

- **D** Previously treated, naïve to HER2-targeted therapies
- **E** Previously treated with HER2-targeted ADCs
- **F** Naïve to systemic therapy for advanced disease

Cut-off date: June 27, 2025

Efficacy and safety from expansion / extension Cohorts D, E, and F

PRIMARY ENDPOINT (extension phase)

- ORR per RECIST v1.1 by BICR

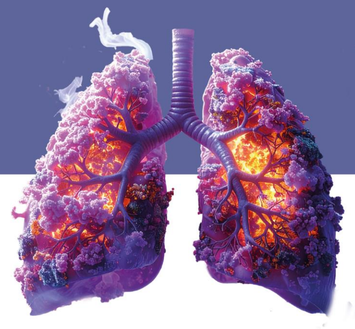
SECONDARY ENDPOINTS

- DoR, DCR, and PFS (per RECIST v1.1) by BICR and investigator assessment
- Safety and tolerability

[a]Patients from dose escalation / backfill treated with 20 mg BID and who met the same eligibility criteria were combined for statistical analysis; [b]Cohorts of patients with *EGFR* mutations are not shown

Le X, et al. Presented at the European Society for Medical Oncology (ESMO) Annual Meeting; 17–21 October, 2025; Berlin, Germany. Abstract LBA75.

Le X. Presented at ESMO Annual Meeting 17-21 October 2025
Le X et al. N Engl J Med. 2025, October 17



Sevabertinib/BAY2927088

Características basales

	Cohort D[a] (*n*=81)	Cohort E[b] (*n*=55)	Cohort F[c] (*n*=73)
Female, *n* (%)	50 (62)	36 (65)	46 (63)
Race, *n* (%)			
Asian	57 (70)	32 (58)	51 (70)
White	18 (22)	15 (27)	19 (26)
Black or African American	1 (1)	4 (7)	0
Not reported	5 (6)	4 (7)	3 (4)
Median age, years (range)	60 (29-82)	65 (35-91)	65 (31-82)
Baseline ECOG PS, *n* (%)			
0	31 (38)	15 (27)	18 (25)
1	50 (62)	40 (73)	54 (74)[d]
Smoking habits at informed consent, *n* (%)			
Never	50 (62)	35 (64)	57 (78)
Former or current	31 (38)	20 (36)	16 (22)
Adenocarcinoma histology[e]	77 (95)	55 (100)	71 (97)
Brain metastases at baseline, *n* (%)[f]	18 (22)	15 (27)	9 (12)

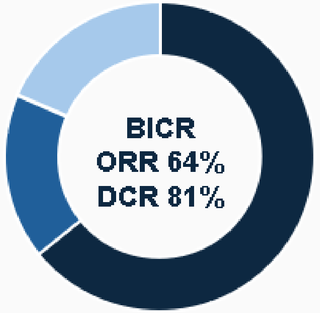
	Cohort D[a] (*n*=81)	Cohort E[b] (*n*=55)	Cohort F[c] (*n*=73)
Activating *HER2* mutations, *n* (%)			
Y772_A775dupYVMA	49 (60)	40 (73)	58 (79)
Other *HER2* ex20ins	19 (23)	9 (16)	11 (15)
HER2 point mutation	12 (15)	5 (9)	1 (1)
Not applicable[g]	1 (1)	1 (2)	3 (4)
***HER2* TKD mutation, *n* (%)**			
Yes	73 (90)	52 (95)	71 (97)
No	7 (9)	3 (5)	2 (3)
Not applicable[h]	1 (1)	0	0
Number of previous systemic anti-cancer therapies, *n* (%)			
0	0	0	67 (92)
1	46 (57)	12 (22)	4 (5)[i]
≥2	35 (43)	43 (78)	2 (3)[i]
Previous anti-cancer therapies, *n* (%)			
Chemotherapy	78 (96)	44 (80)	6 (8)
Platinum and no immunotherapy	20 (25)	12 (22)	3 (4)
Platinum and immunotherapy	56 (69)	31 (56)	3 (4)
Trastuzumab deruxtecan	2 (2)[j]	41 (75)	0

Le X. Presented at ESMO Annual Meeting 17-21 October 2025

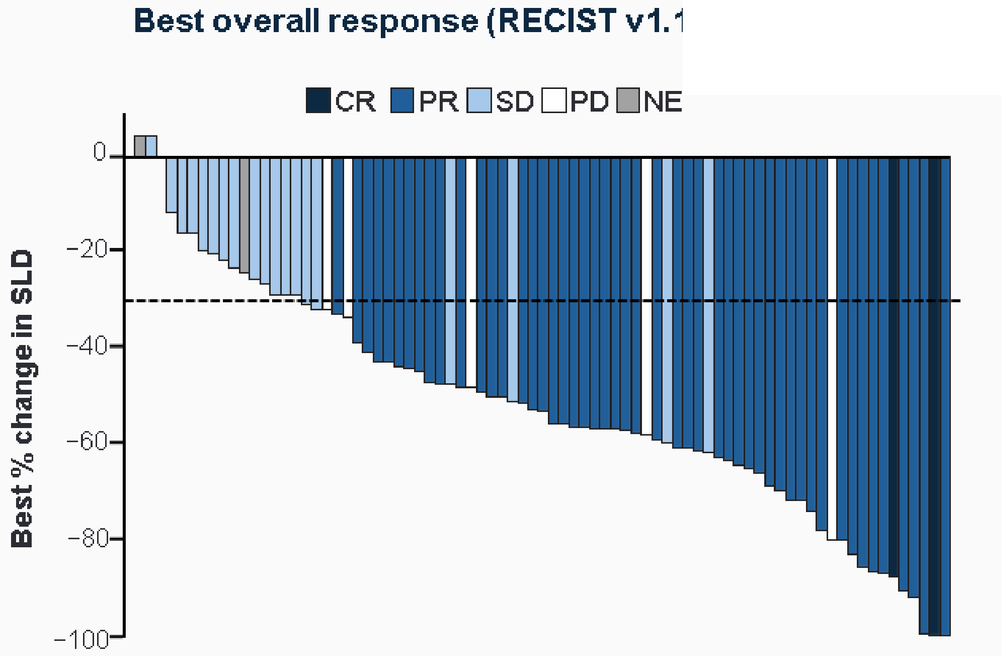
Sevabertinib/BAY2927088

Resultados cohorte D: previamente tratados, sin ADCs (n=81)

Median follow-up: 13.8 months (range 1–32)



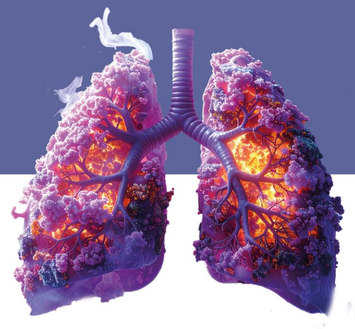
n (%)	
CR	2 (2)
PR	50 (62)
SD	20 (25)
PD	6 (7)
Not evaluable[a]	3 (4)
ORR[b] [95% CI]	**52 (64)** [53, 75]
DCR[c] [95% CI]	**66 (81)** [71, 89]
DoR, median months [95% CI]	**9.2** [6.3, 13.5]
PFS, median months [95% CI]	**8.3** [6.9, 12.3]



Mediana duración 9.2 meses
Mediana PFS 8.3 meses

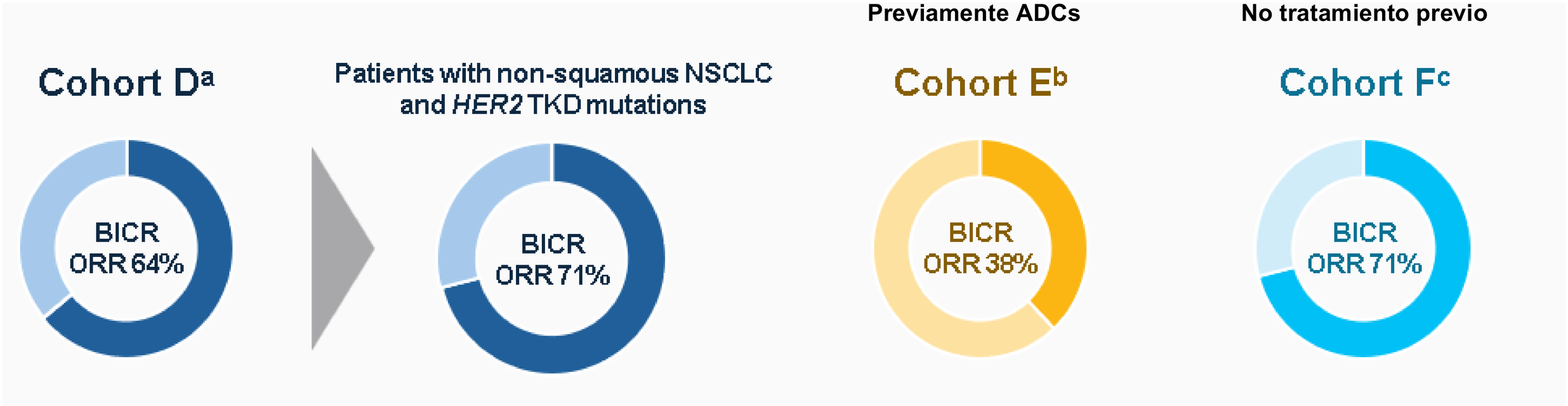
Analysis cut-off date was June 27, 2025. Data for patients without target lesion measurements are not shown in the waterfall plot
[a]Requirement for CR, PR, SD, or PD was not met; [b]Confirmed CR or confirmed PR; [c]Confirmed CR, confirmed PR, or SD for ≥12 weeks
Le X, et al. Presented at the European Society for Medical Oncology (ESMO) Annual Meeting; 17–21 October, 2025; Berlin, Germany. Abstract LBA75.

Le X. Presented at ESMO Annual Meeting 17-21 October 2025
Le X et al. N Engl J Med. 2025, October 17

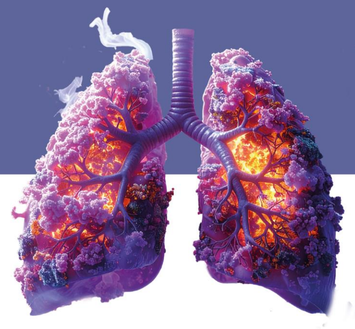


Sevabertinib/BAY2927088

Resultados de las diferentes cohortes



Le X. Presented at ESMO Annual Meeting 17-21 October 2025



Sevabertinib/BAY2927088

Eficacia según la presencia de metástasis cerebrales

	Cohort D[b]	Cohort E[c]	Cohort F[d]	Total
Brain metastases at baseline, *n/N* (%)[a]	18/81 (22)	15/55 (27)	9/73 (12)	42/209 (20)
ORR by BICR (RECIST v1.1), *n/N* (%)				
All patients	52/81 (64)	21/55 (38)	52/73 (71)	125/209 (60)
Brain metastases	11/18 (61)	4/15 (27)	7/9 (78)	22/42 (52)
No brain metastases	41/63 (65)	17/40 (43)	45/64 (70)	103/167 (62)

	Cohort D[b]	Cohort E[c]	Cohort F[d]	Total
Brain metastases at baseline, *n/N* (%)[a]	18/81 (22)	15/55 (27)	9/73 (12)	42/209 (20)
Post-baseline progression in brain	4/18 (22)	3/15 (20)	0/9 (0)	7/42 (17)
No brain metastases at baseline, *n/N* (%)	63/81 (78)	40/55 (73)	64/73 (88)	167/209 (80)
Post-baseline progression in brain	4/63 (6)	2/40 (5)	2/64 (3)	8/167 (5)

Le X. Presented at ESMO Annual Meeting 17-21 October 2025
Le X et al. N Engl J Med. 2025, October 17

Sevabertinib/BAY2927088

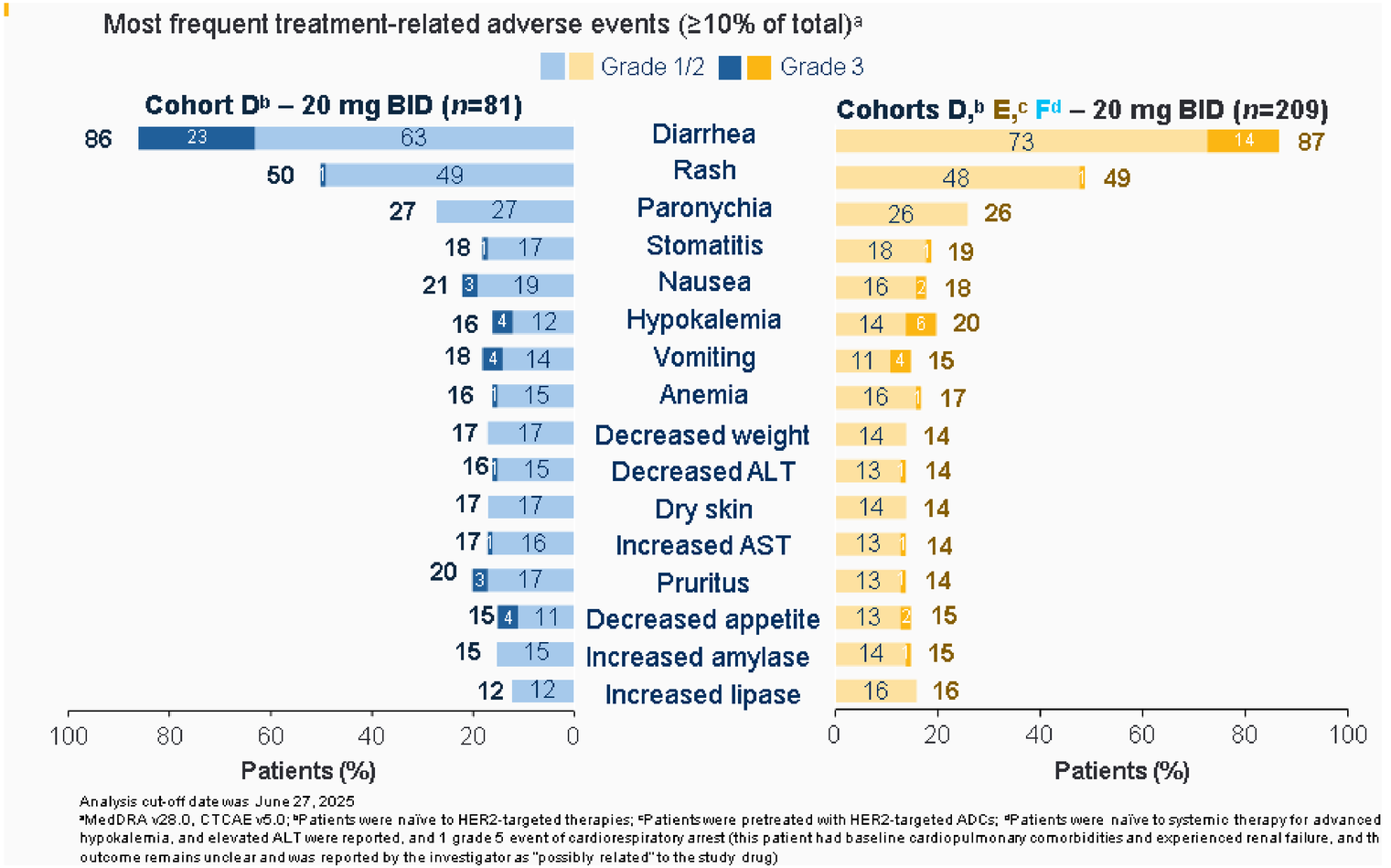
Seguridad y tolerabilidad

96% toxicidad de cualquier grado

36% toxicidad grado 3

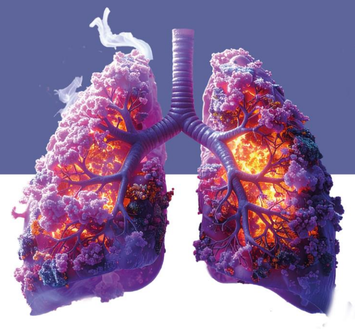
26% AEs que condujeron a reducciones de dosis y 5% de discontinuaciones

No descrita enfermedad pulmonar intersticial



Analysis cut-off date was June 27, 2025
[a]MedDRA v28.0, CTCAE v5.0; [b]Patients were naïve to HER2-targeted therapies; [c]Patients were pretreated with HER2-targeted ADCs; [d]Patients were naïve to systemic therapy for advanced
hypokalemia, and elevated ALT were reported, and 1 grade 5 event of cardiorespiratory arrest (this patient had baseline cardiopulmonary comorbidities and experienced renal failure, and th
outcome remains unclear and was reported by the investigator as "possibly related" to the study drug)

Le X. Presented at ESMO Annual Meeting 17-21 October 2025
Le X et al. N Engl J Med. 2025, October 17



Sevabertinib/BAY2927088

NOW ENROLLING: **SOHO-02:** A Phase 3 Open-label, Randomized, Active-controlled, Multicenter Trial to Evaluate the Efficacy and Safety of Orally Administered BAY 2927088 Compared With Standard of Care as a First-line Therapy in Patients With Locally Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC) With HER2-activating Mutations (NCT06452277)

Patient population:
18 Years and older

- 1L advanced NSCLC with activating mutation in the HER2 TKD
- ECOG PS 0-1
- Eligible for SoC
- ≥1 RECIST 1.1 lesion

N=278

R
1:1

Treatment arms

- BAY 2927088 20 mg BID oral (n=139)
- SoC (n=139) (platinum chemotherapy + pemetrexed + pembrolizumab)

PRIMARY ENDPOINT:

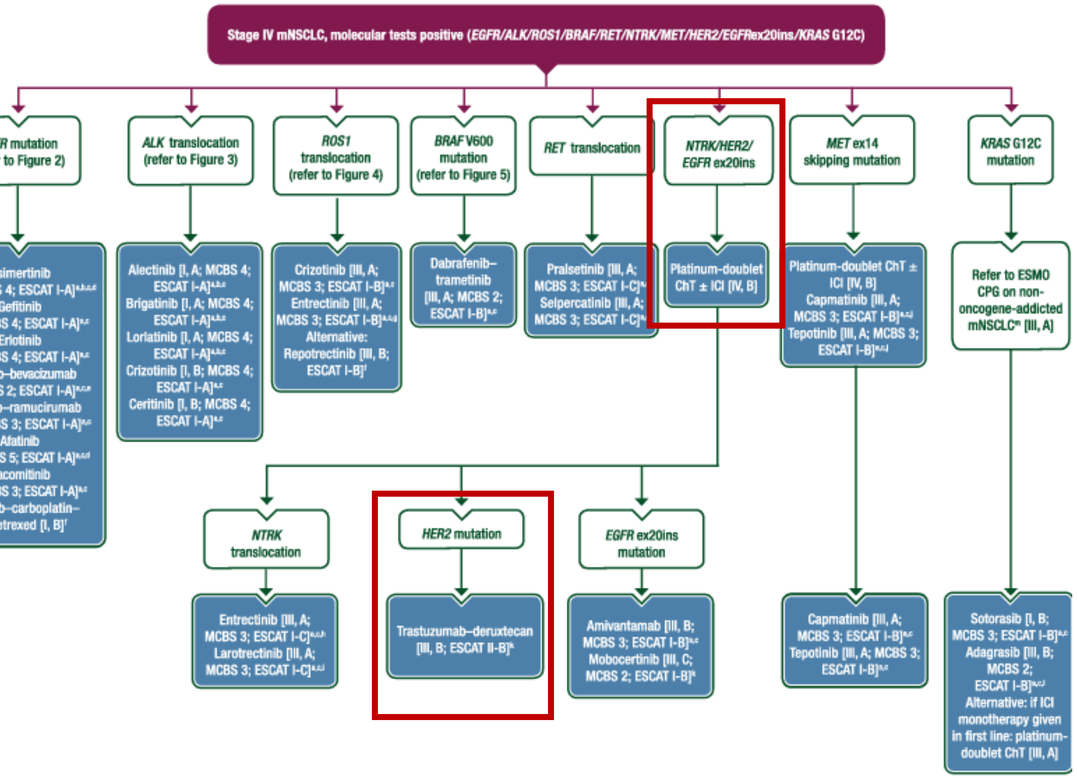
- PFS per RECIST 1.1 by BICR

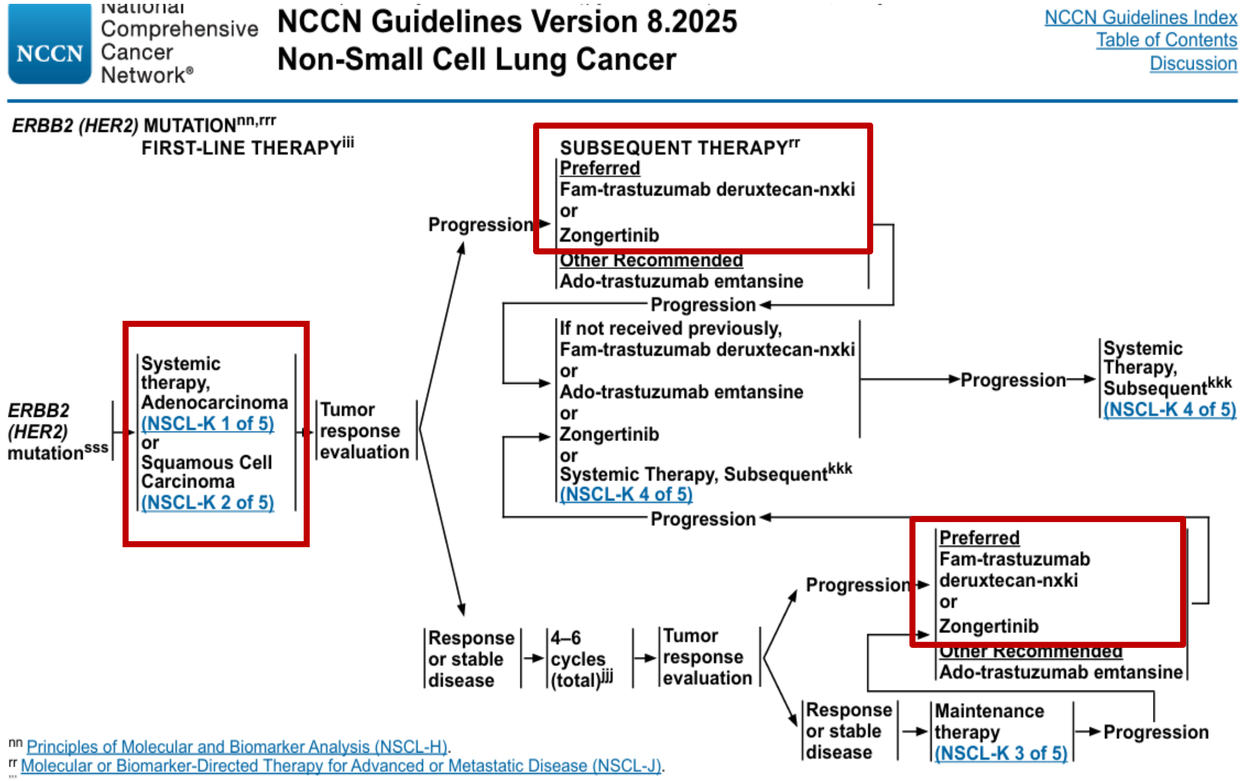
SECONDARY ENDPOINTS:

- OS
- ORR
- DOR
- Safety and tolerability, PK
- PRO

PFS, Progression free survival; BICR, blinded independent central review; RESIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SoC, Standard of care; ECOG PS, Eastern Cooperative Oncology Group performance status performance status; BID, Twice a day; OS, Overall survival; ORR, Objective response rate; DOR, Duration of response; TKD, tyrosine kinase domain; PRO, Patient reported outcomes; PK, Pharmacokinetics; CTCAE, Common terminology criteria for adverse events.

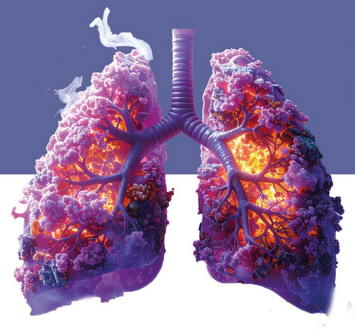
Guías clínicas





Hendricks et al. Ann Oncol.2023;34

www.nccn.org NSCLC version 8.2025



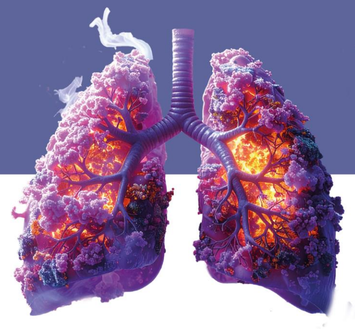
¿1ª línea?

Zongertinib
Beamion LUNG 2

Trastuzumab deruxtecán
DESTINY-Lung04

Sevabertinib
SOHO-02

Otros

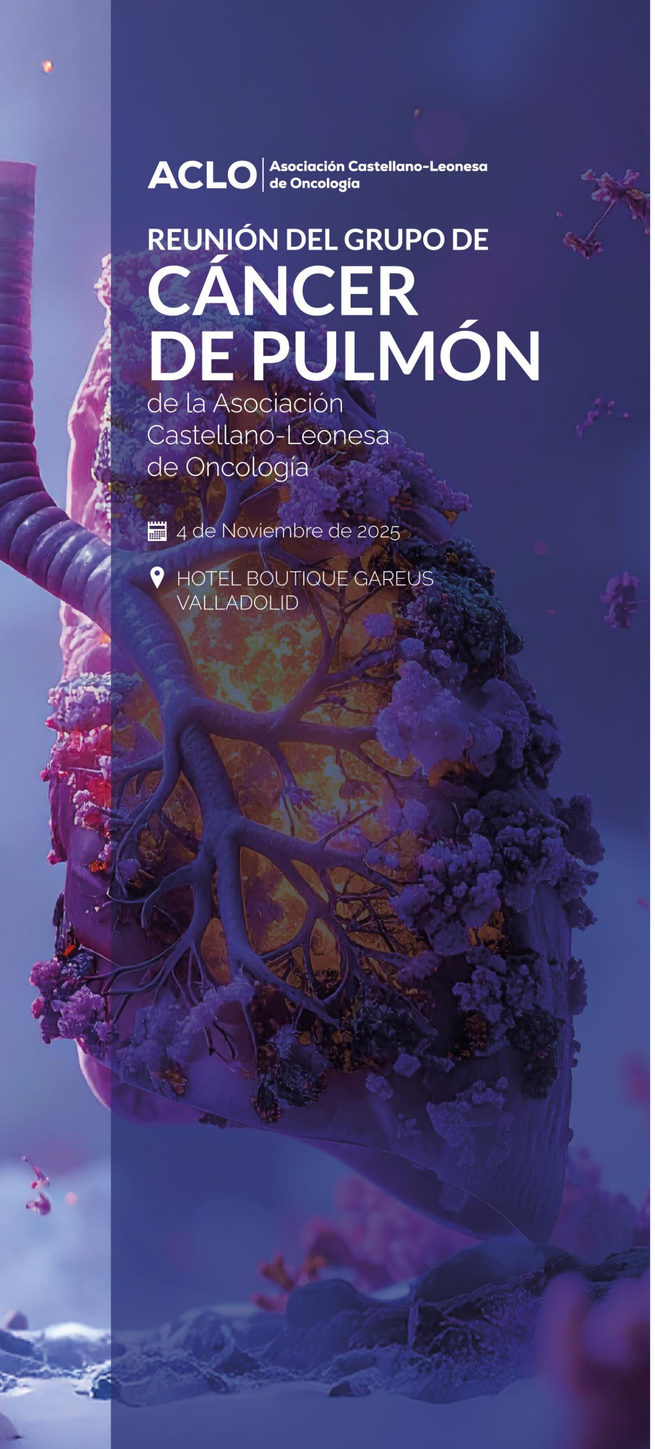


Conclusiones

- Existen diferentes alteraciones de HER2 (gen y proteína), cuyo denominador común es el pronóstico desfavorable.
- Las mutaciones de HER2, especialmente en el dominio TK, son las que presentan mayor respuesta al tratamiento dirigido, aunque debemos seguir investigando también otras alteraciones de HER2 como la sobrexpresión proteica.
- Las mutaciones de HER2 presentan una incidencia del 1-4% en CNMP, siendo el perfil clínico mujer no fumadora con histología no escamosa de edad más joven. Alta incidencia y prevalencia de metástasis cerebrales.
- En mutaciones de HER2 el abordaje clásico con quimio-inmunoterapia es subóptimo. Los estudios fase 1-2 con terapias dirigidas arrojan resultados muy prometedores que mejoran las respuestas objetivas y control de la enfermedad. Se encuentran en marcha los ensayos clínicos fase 3 randomizados que confirmen la superioridad frente a la terapia estándar en primera línea.

	Trastuzumab deruxtecán 5.4 mg/kg	Zongertinib	Sevabertinib
ORR (pretatados, TKD*)	49%	71%	71%
Eficacia en SNC	Por explorar	Sí	Sí
AEs G≥3	38%	17%	36%
Discontinuaciones	14%	3%	5%
Situación regulatoria	FDA, EMA, España no	FDA accelerated approval	FDA priority review designation

*En el estudio Destiny Lung 02 en la cohorte de 5.4 mg/kg el 97% eran mutaciones en el dominio TK



Muchas gracias