III JORNADA TRASLACIONAL
DE ONCOLOGÍA DE PRECISIÓN:
A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN
SEVILLA, 12 Y 13 DE FEBRERO DE 2026

ENFERMEDAD HER-2 EN CÁNCER DE PULMÓN

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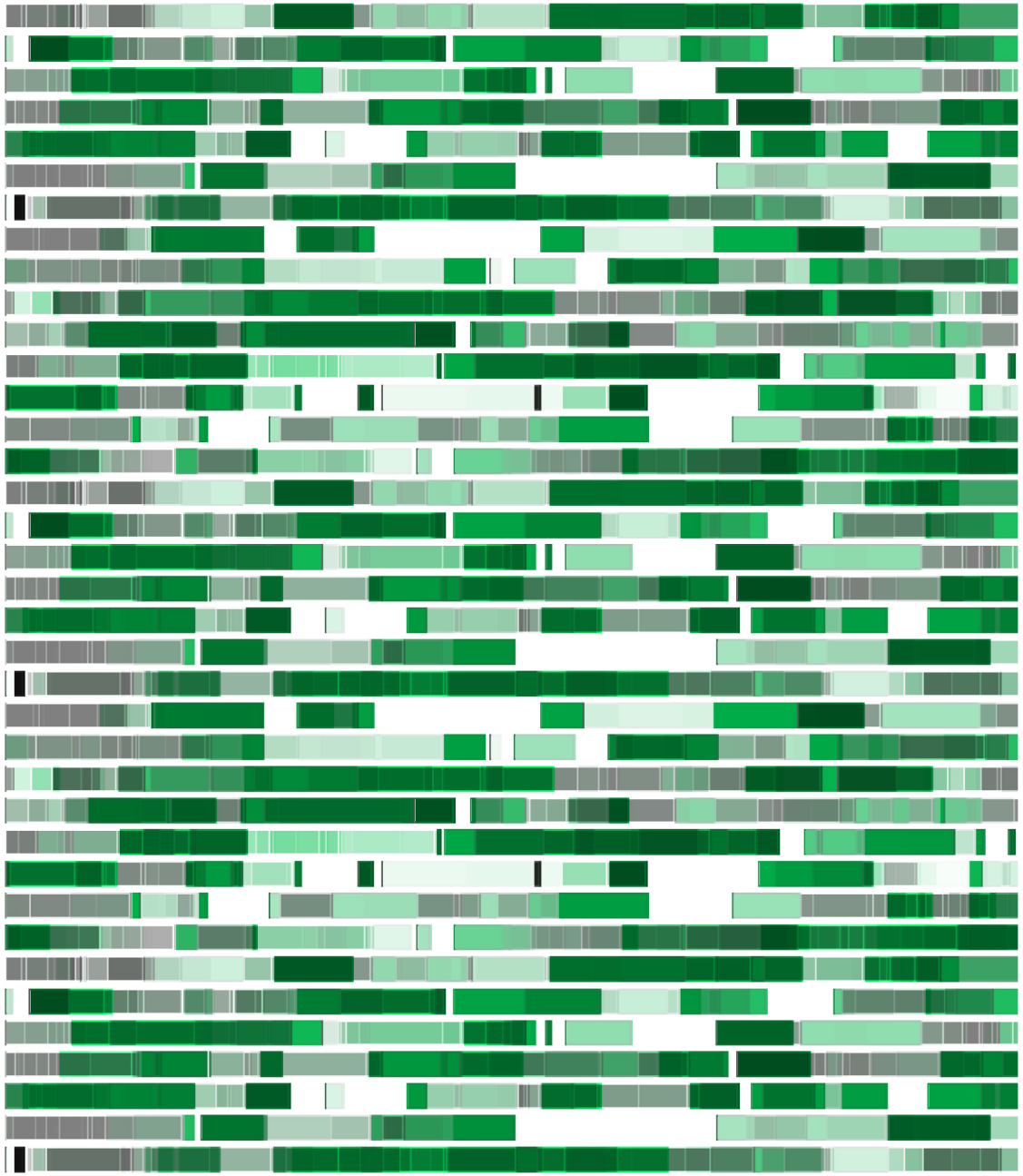

Organizador por:
HENDERE HEALTHCARE

DISCLOSURE

- **Employment:** H. Universitario Puerta de Hierro Majadahonda, Madrid
- **Consultant or Advisory Role:** Roche, AstraZeneca, MSD, BMS, Takeda, Regeneron, Pfizer, GSK, Boehringer Ingelheim, J&J, BeOne
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- **Research Funding:** Roche
- **Speaking:** Roche, AstraZeneca, MSD, BMS, Takeda, Regeneron, AMGEN, Pfizer, J&J, BeOne
- **Grant support:** none
- **Other:** none

OUTLINE

- Introduction
- NSCLC HER2
  - HER2 gene mutation
  - HER2 gene amplification
  - HER2 protein overexpression
- Treatment of HER2-altered NSCLC
  - Chemotherapy / Immunotherapy / Chemotherapy-Immunotherapy
  - Monoclonal antibody: Trastuzumab, Pertuzumab
  - ADCs: T-DM1, T-Dxd, T-Rezetecan
  - TKIs: Non-selective pan-HER TKIs, selective HER2 TKIs
- Conclusions

INTRODUCTION

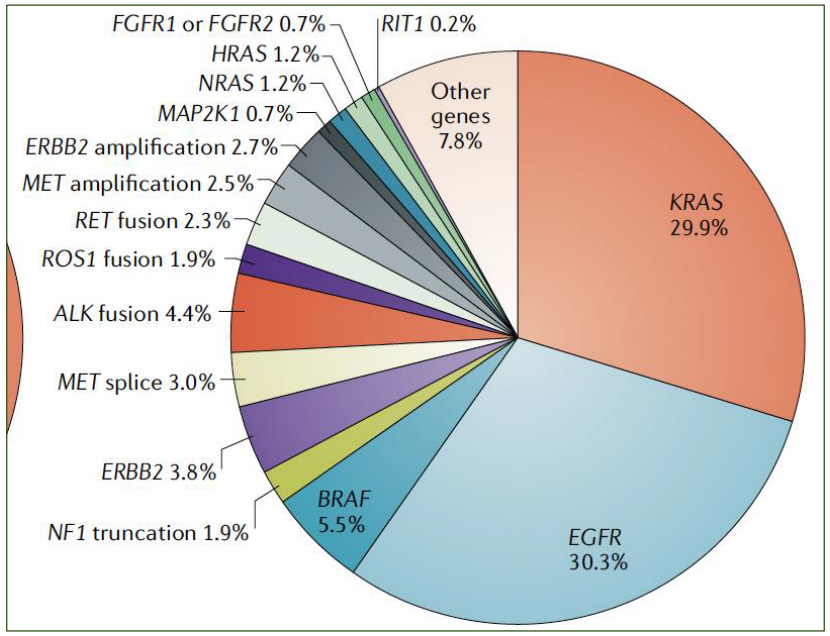
- HER2 is an ErbB receptor tyrosine-protein kinase (also known as ErbB2) encoded by the *ERBB2* gene located at chromosome 17q12
- *ERBB2* amplification and/or overexpression of HER2 promotes its homodimerization as well as heterodimerization with other ErbB proteins, resulting in the overactivation of downstream pathways that drives cellular transformation, survival, proliferation, invasion and, thus, tumor growth and dissemination

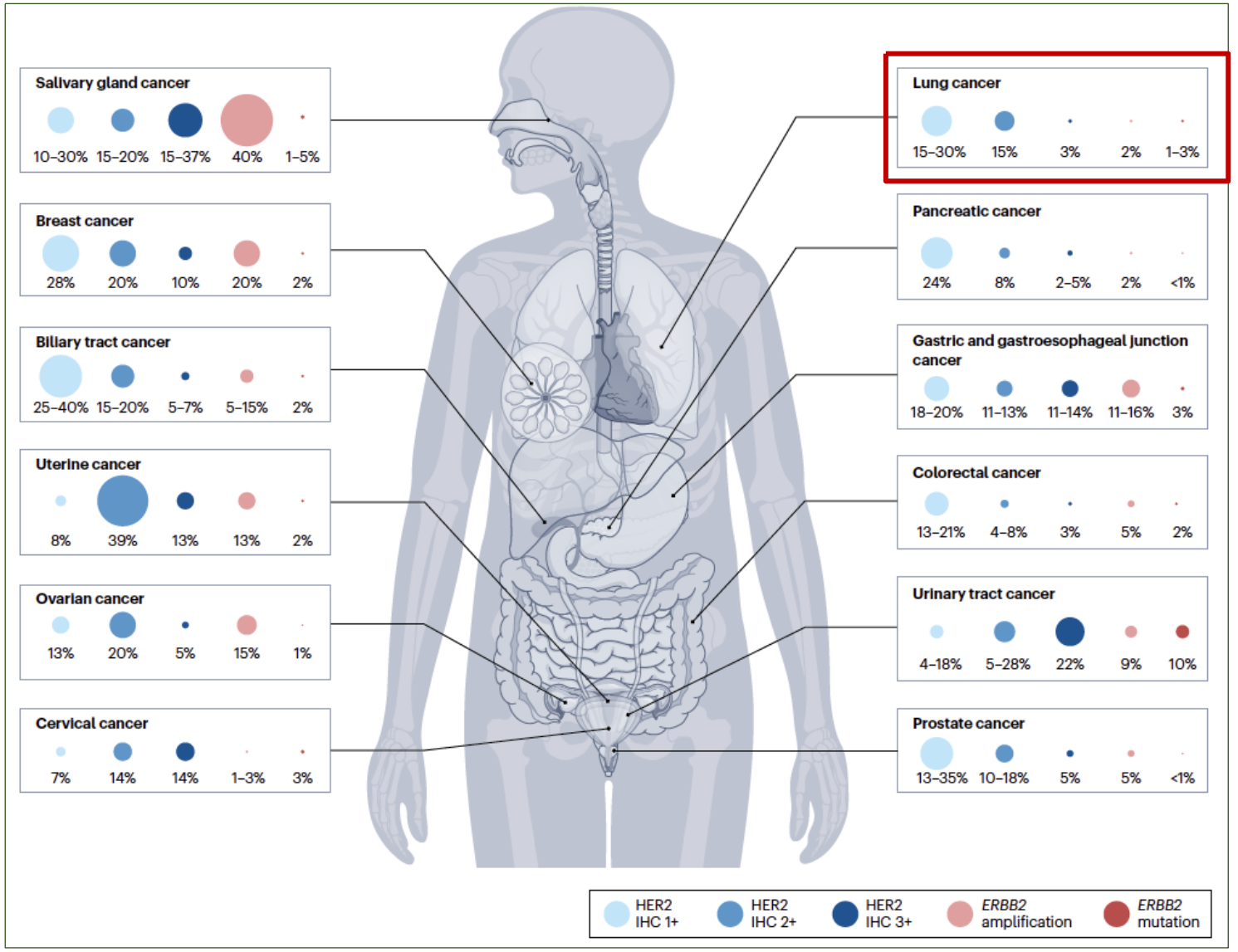
- HER2 (human epidermal growth factor receptor 2) is a therapeutic target with a long history in anticancer drug development, particularly for breast and gastric cancers

Popescu NC, et al. Genomics 1989;4:362-6; Gutierrez C, Schiff R. Arch Pathol Lab Med 2011;135:55-62

INTRODUCTION

- HER-2 is an emerging tumor agnostic in solid tumors

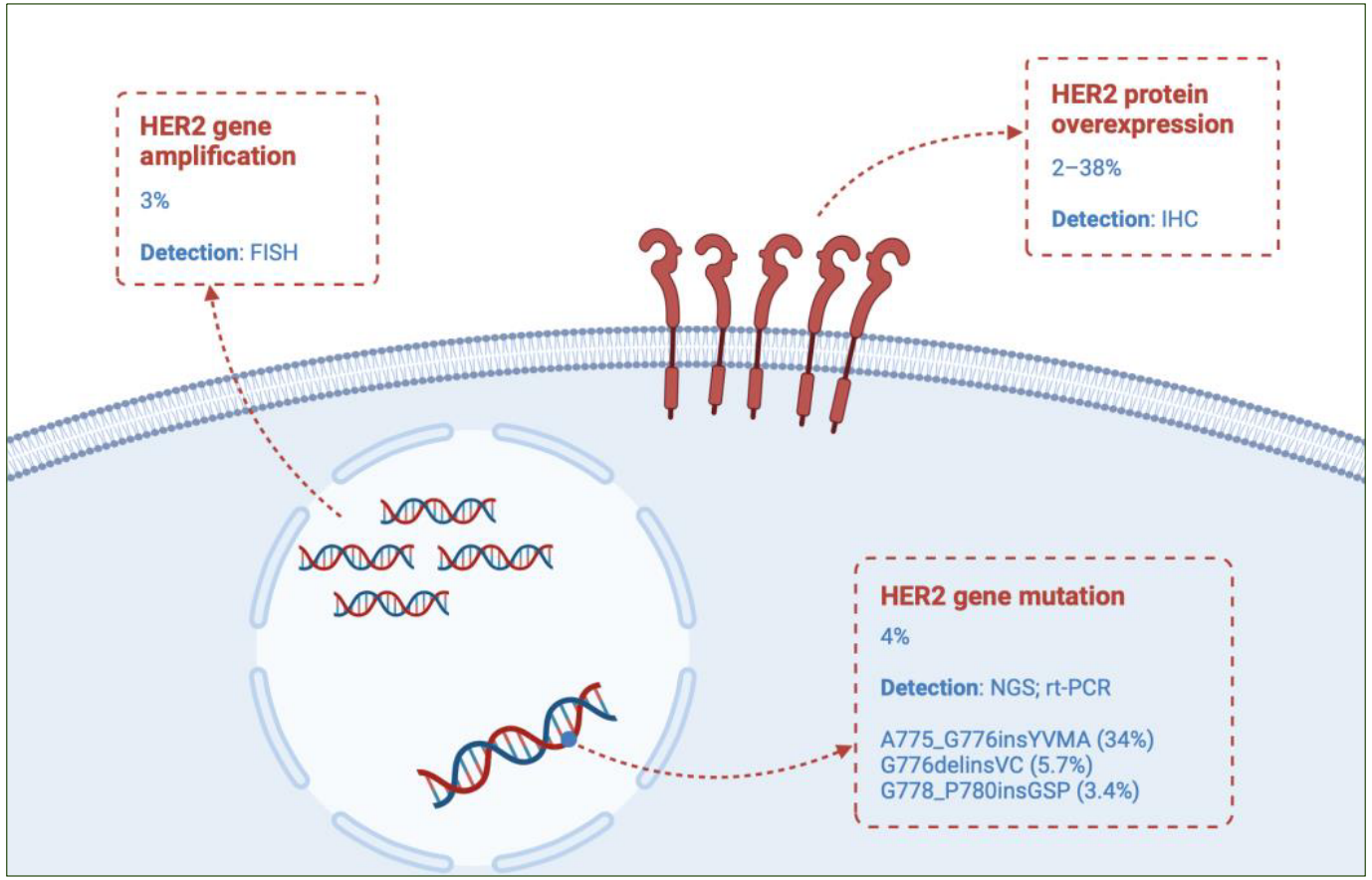




Yoon J, Oh DY. Nat Rev Clin Oncol. 2024;21(9):675-700; Skoulidis F, et al. Nat Rev Cancer. 2019;19(9):495-509.

NSCLC HER2

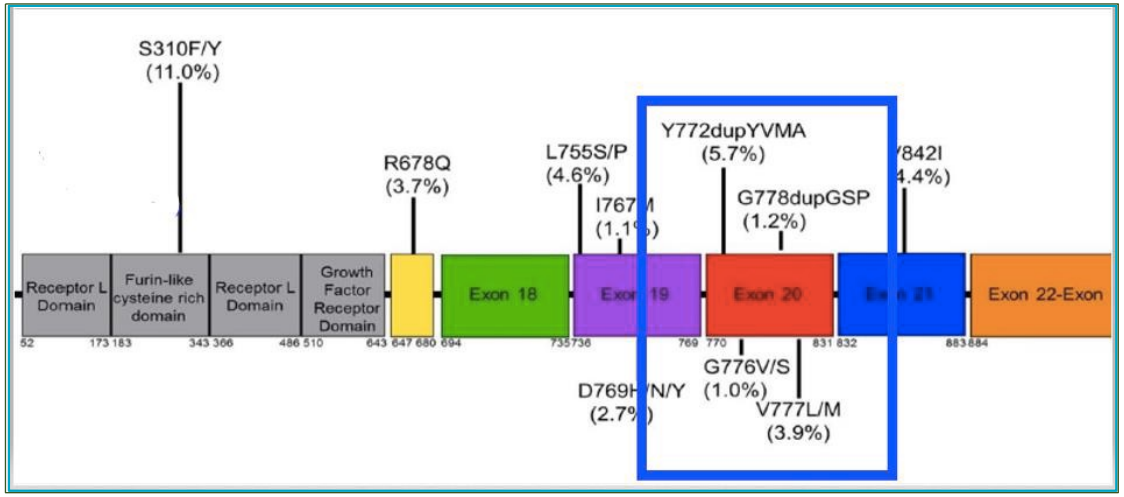
- Different types of HER2 alterations have been identified in NSCLC:
  - HER2 gene mutation: 4%
  - HER2 gene amplification: 3%
  - HER2 protein overexpression: 2-38%
- This alterations can be detected by distinct methods: NGS, rt-PCR; FISH; IHQ



Ferrari G, et al. Cancers (Basel). 2024 May 26;16(11):2018

NSCLC HER2: HER2 GENE MUTATION

- Incidence: 2-4% of NSCLC
- Adenocarcinoma (papillary growth), females, younger patients, never or light smokers
- High incidence of brain metastases



- Mutations of HER2, mostly represented by exon 20 insertions (85%) of all HER2 alterations. Y772_A775dupYVMA in over 50%
- Mutually exclusive with other drivers of genetic alterations: KRAS, EGFR and BRAF mutations

Nützinger J, et al. Lung Cancer. 2023;186:107385.

NSCLC HER2: HER2 GENE AMPLIFICATION

- Increase in the copy number of the HER2 gene, which can occur through focal amplification or polysomy of chromosome 17
- Incidence: 3% (2-5% of lung adenocarcinoma)
- Men, smokers, not exclusive of adenocarcinoma
- Predictive role in NSCLC remains unclear
- Detection by FISH or NGS in tumor biopsies and/or ctDNA
- Cutoff : HER2/CEP17 ratio ≥ 2 and/or HER2 copy number >6
    - True amplification very low incidence (4%)
    - HER2 polysomy (HER2/CEP17 ratio < 2 with HER2 copy number ≥ 6), wide range of positivity (1.6–53%)

Nützinger J, et al. Lung Cancer. 2023;186:107385; Reinhorn D, et al. Cancer. 2025;131 Suppl 1:e35780

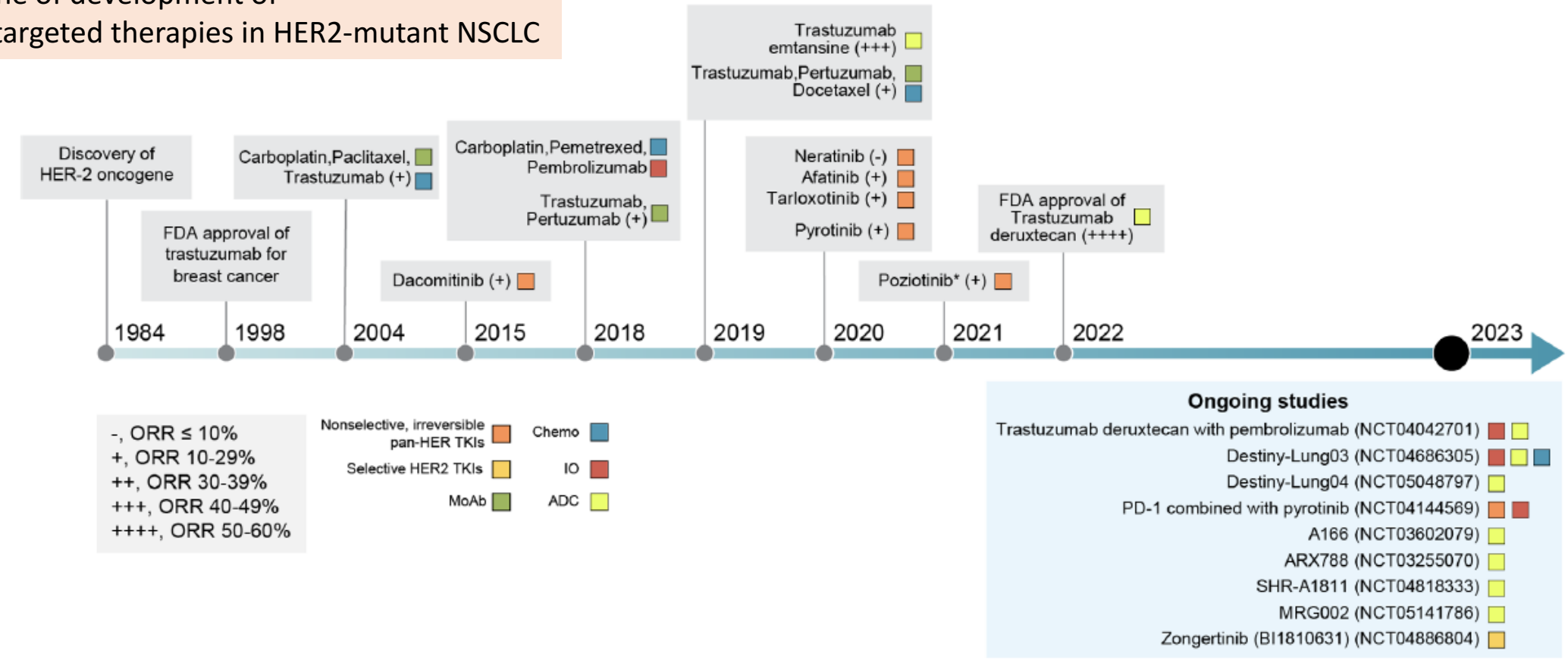
NSCLC HER2: HER2 GENE OVEREXPRESSION

- Incidence 2-30%, but levels of protein expression vary
- Men, smokers, not exclusive of adenocarcinoma
- Associated with poor prognostic and worse clinical outcomes
- Abnormally high amount of HER2 proteins on the surface of cancer cells
- Identified by IHC, but no standard definition in lung cancer
    - In T-DXd trials, HE adapted from HER2 gastric algorithm
- Different interpretation versus breast cancer: Positive 2+, 3+

Nützinger J, et al. Lung Cancer. 2023;186:107385; Reinhorn D, et al. Cancer. 2025;131 Suppl 1:e35780

TREATMENT OF HER2-ALTERED NSCLC

Timeline of development of
HER2 targeted therapies in HER2-mutant NSCLC

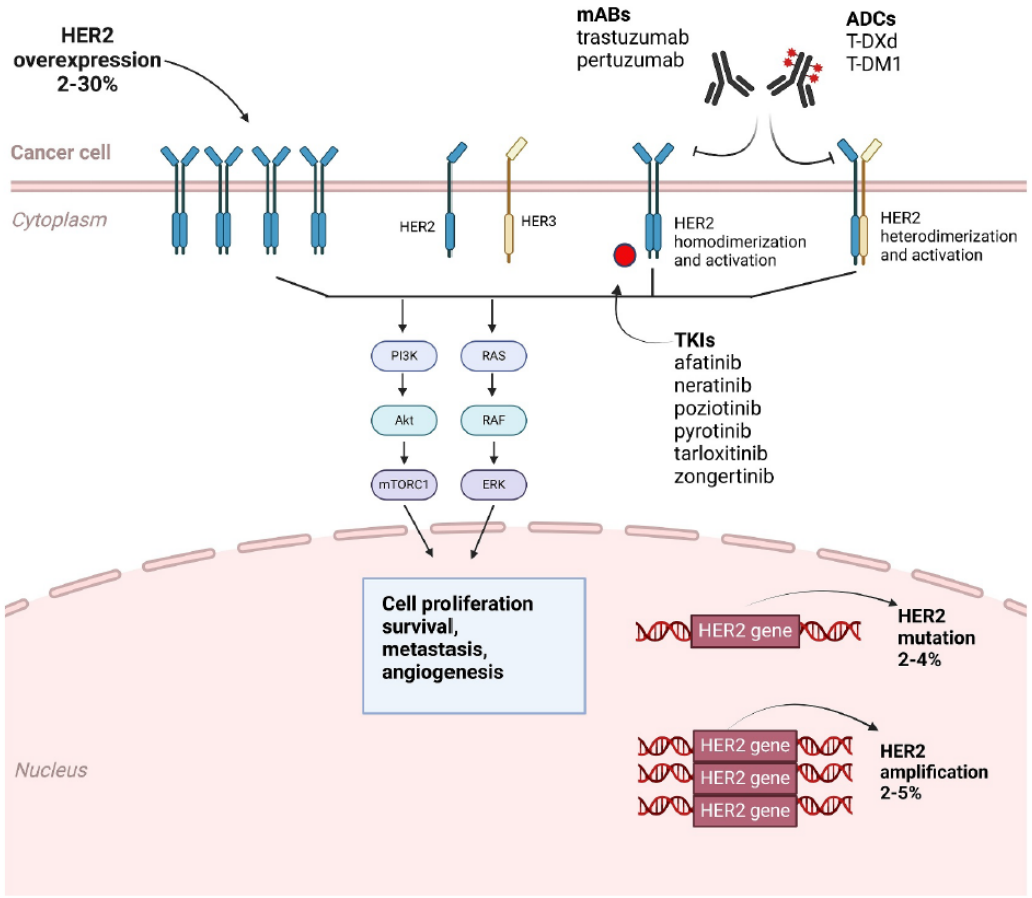


Nützinger J, et al. Lung Cancer. 2023;186:107385

TREATMENT OF HER2-ALTERED NSCLC

- The treatment of HER2-altered NSCLC has progressed in the last decade

- However, the current standard first-line therapy consists of platinum-based chemotherapy combined with ICIs



HER2 alterations in NSCLC and HER2-targeted therapy

Reinhorn D, et al. Cancer. 2025;131 Suppl 1:e35780

CHEMOTHERAPY

- Several retrospective studies have examined the efficacy of CT in HER2-altered NSCLC
- Response rates to CT in HER2m: 30-43%
- First line pemetrexed based chemotherapy (similar to the KRAS-mutant and EGFR-mutant group):
  - ORR: 36%
  - PFS: 5.1 months
- HER2 mutations variants: inferior PFS in A775_G776insYVMA vs other variants: PFS 4.2 vs 7.2 months, p=0.085

Mazéres J, et al. Ann Oncol 2016;27(2):281-6; Wang Y, et al. BMC Cancer 2018;18:326

IMMUNOTHERAPY

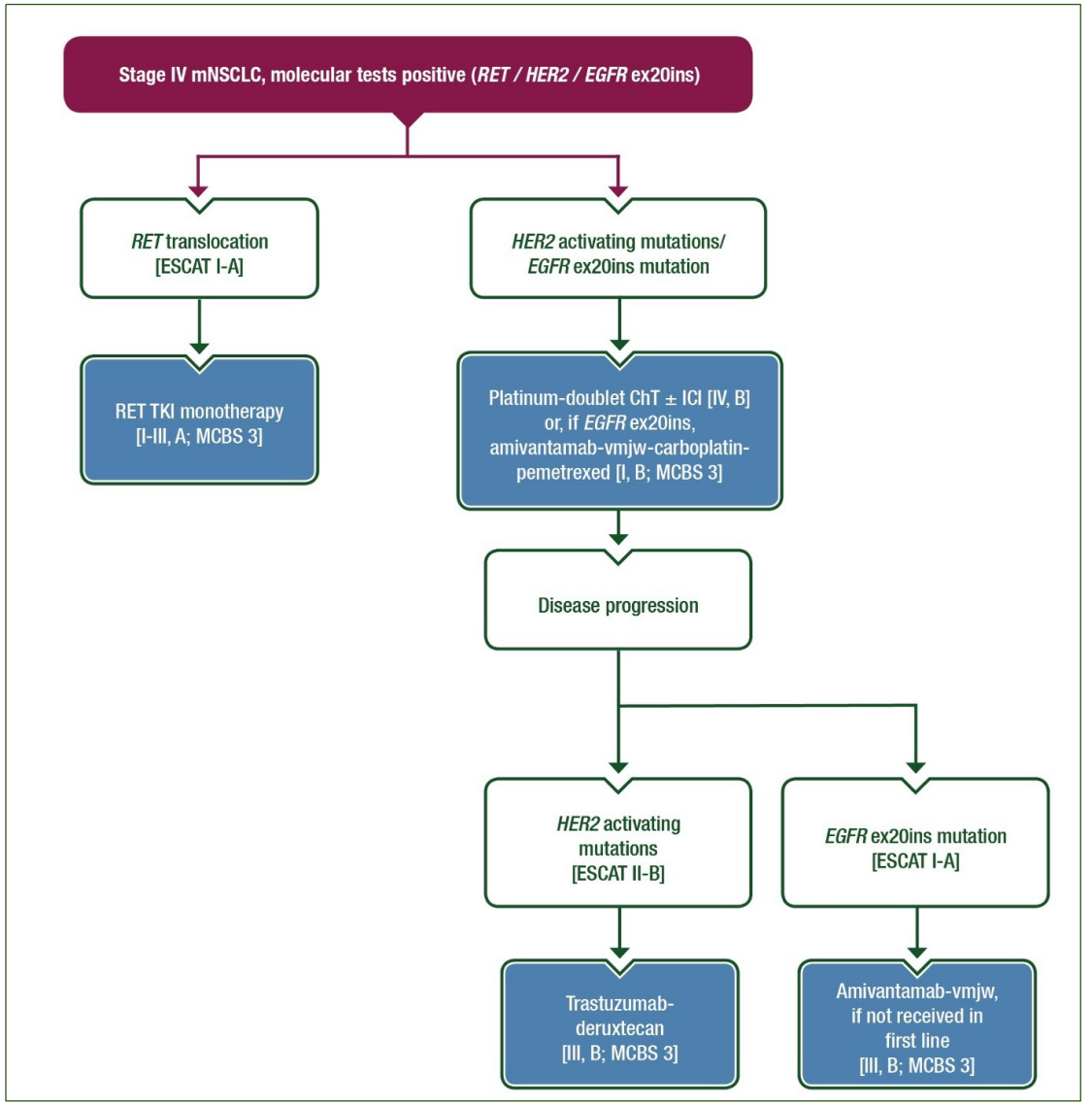
- NSCLC with HER2m:
  - LOW TUMOR MUTATION BURDEN (TMB)
  - LOW PD-L1 expression
- Retrospective analyses: low response rates to single agent ICI in HER2-altered:
  - ORR: 0-27.3%
  - PFS: 1.8-2.5 months

Treatment	Study type	Publication year	Study population (*n*)	ORR, %	mPFS, months	mOS, months
ICI	Retrospective	2018	HER2m (26)	12 (95% CI, 3%–30%)	1.9 (95% CI, 1.5–4.0)	10.4 (95% CI, 5.9–NR)
ICI	Retrospective	2018	HER2m (16)	6	1.8	17.1
ICI	Retrospective	2019	HER2m (29)	8	2.5 (95% CI, 1.8–3.5)	20.3 (95% CI, 3.8–28)
ICI	Retrospective	2020	HER2m (23)	27	2.2 (95% CI, 1.7–15.2)	20.4 (95% CI, 9.3–NR)
ICI	Retrospective	2021	HER2m (14)	29	3.6 (95% CI, 1.6–NR)	NA
ICI	Retrospective	2021	HER2m (28)[a]	NA	3	10.8
ICI + chemotherapy	Retrospective	2021	HER2m (13)	31	8 (95% CI, 5.2–NR)	NA
ICI ± chemotherapy	Retrospective	2021	HER2m first line monotherapy (5); combined with chemotherapy (22); subsequent line monotherapy (34)	52 (95% CI, 30%–74%, first line chemo immunotherapy); 20 (first line monotherapy); 16 (95% CI, 5%–34%, subsequent monotherapy)	6 (95% CI, 6–14, first line chemo immunotherapy); NR (first line monotherapy); 4 (95% CI, 4–6, subsequent monotherapy)	NR (first line); 10 (95% CI, 6· NR, subsequer monotherapy)
ICI + chemotherapy	Retrospective	2022	HER2m (78), HER2amp (5)	28.9	5.2 (95% CI, 3.64–6.76)	NR
ICI	Retrospective	2022	HER2amp (18)	0 (95% CI, 0%–19%)	2 (95% CI, 1–7)	11 (95% CI, 4–37)

Negrao MV, et al. J Immunother Cancer. 2021;9(8):e002891; Reinhorn D, et al. Cancer. 2025;131 Suppl 1:e35780

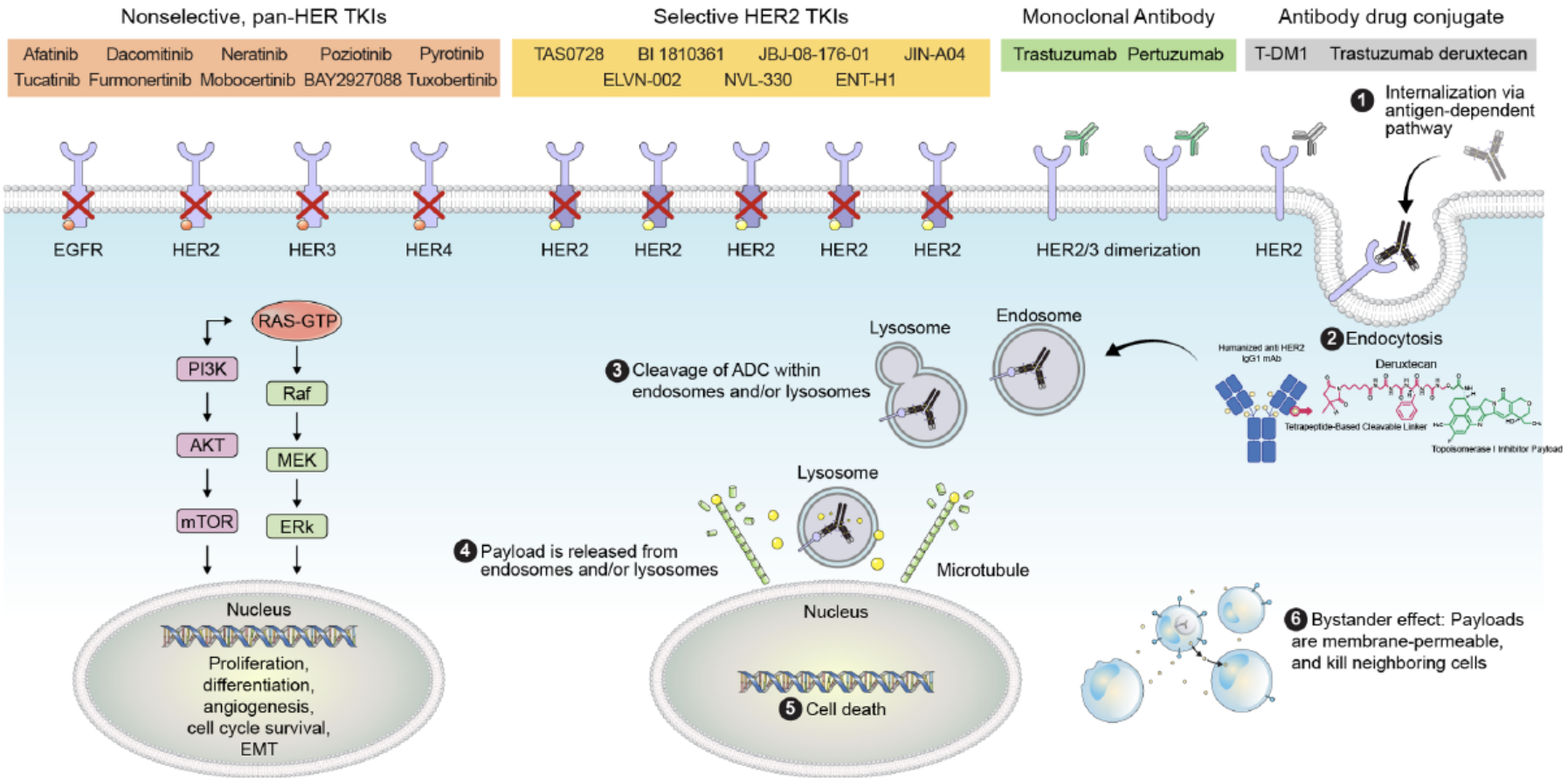
FIRST-LINE TREATMENT

- Retrospectives studies: ICI plus chemotherapy:
  - ORR: 52%
  - mPFS: 6 months

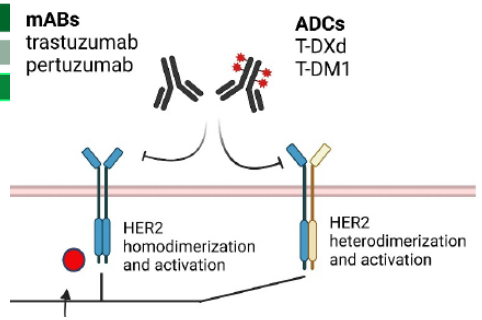


Saalfeld FC, et al. J Thorac Oncol 2021;16:1952-8; ESMO oncogene-addicted metastatic NSCLC living guideline, v1.2 January 2025

TREATMENT OF HER2-ALTERED NSCLC



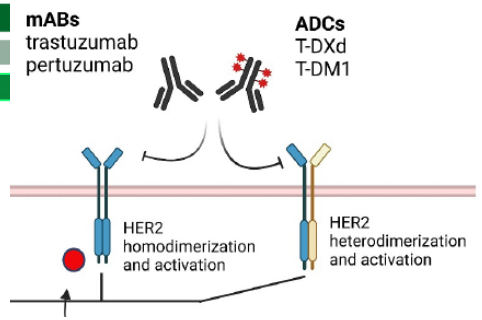
Nützinger J, et al. Lung Cancer. 2023;186:107385



MONOCLONAL ANTIBODIES

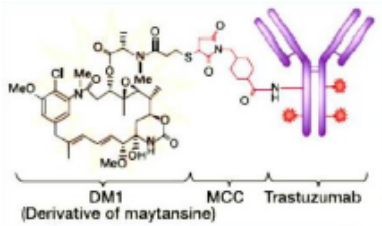
- TRASTUZUMAB
  - Focused on HER2 overexpressing NSCLC
  - Disappointing activity
  - HOT1303-B trial: ORR 0%; mPFS 5.2 months
  - Various phase II studies combining CT and Trastuzumab: ORR 23-38%; mPFS 3.3-8.5 months
- PERTUZUMAB
  - Phase II, combination Trastuzumab-Pertuzumab: N=24, ORR 8.3%
  - IFCT 1703-R2D2 trial, combination dual HER2 antibody blockade with CT: N=45, ORR 29%, mPFS 6.8 months

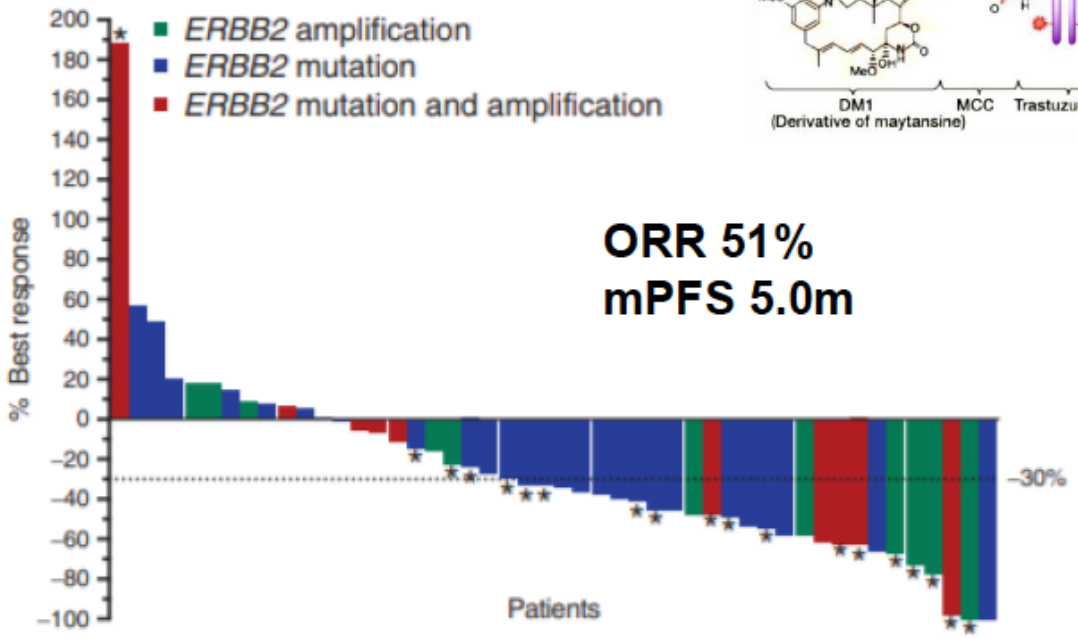
Kinoshita I, et al. Ann Oncol. 2018;29:viii540; Langer CJ, et al. J Clin Oncol 2004;22(7):1180-7; van Berge Henegouwen JM, et al. Eur J Cancer. 2022;171:114-123; Mazieres J, et al. J Clin Oncol. 2022;40:719-28



ANTIBODY-DRUG CONJUGATES: T-DM1

TRASTUZUMAB EMTANSINE (T-DM1)



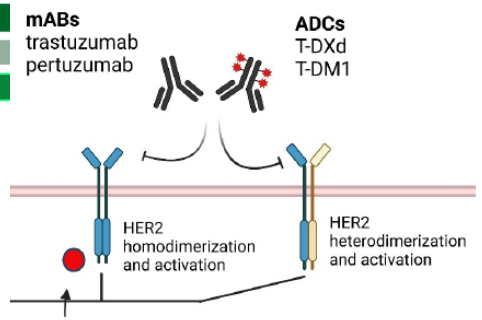


ORR 51%
mPFS 5.0m

Treatment	Study type	Publication year	Study population (*n*)	Line of therapy	ORR, %	mPFS, months	mOS, months
T-DM1	Phase 2	2018	HER2 overexpression (8), HER2m (7)	Advanced line	6.7 (95% CI, 0.3%–27.9%)	2 (95% CI, 1.4–4.0)	10.9 (95% CI, 4.4–12.0)
T-DM1	Phase 2	2018	HER2m (28), HER2amp (11), concurrent HER2m and HER2amp (10)	Advanced line	50 (95% CI, 31%–69%, HER2m); 55 (95% CI, 23%–83%, HER2amp); 50 (95% CI, 19%–81%, concurrent HER2m and HER2amp)	5 (95% CI, 3.5–5.9)	NA
T-DM1	Phase 2	2019	HER2 overexpression (29 IHC 2+, 20 IHC 3+)	Advanced line	0 (IHC +2); 20 (95% CI, 5.7%–43.7%, IHC +3)	2.6 (95% CI, 1.4–2.8, +2); 2.7 (95% CI, 1.4–8.3, +3)	12.2 (95% CI, 3.8–23.3, +2); 15.3 (95% CI, 4.1–NE, +3)
T-DM1	Phase 2	2022	HER2m (22)	Advanced line	38.1 (90% CI, 23.0%–55.9%)	2.8	8.1

- HER2 overexpression - disappointing results:
  - ORR: 7%, 0% (IHC 2+), 20% (IHC 3+)
  - mPFS: 2.6 months
- HER2m – promising efficacy:
  - ORR: 51%
  - mPFS: 5 months

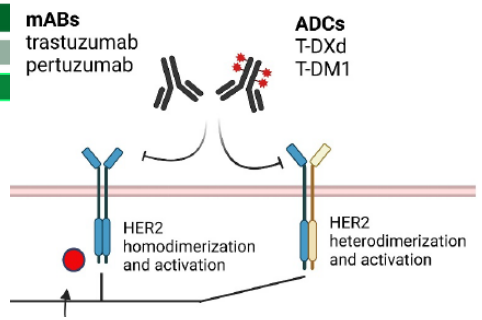
Hotta K, et al. J Thorac Oncol. 2018;13:273-9; Peters S, et al. Clin Cancer Res. 2019;25:64-72; Li BT, et al. J Clin Oncol. 2018; 36:2532-7; Iwana E, et al. Eur J Cancer2022;162:99-106



ANTIBODY-DRUG CONJUGATES

HER2-Directed ADCs		
ADC	**Status**	**Pivotal Trial(s)**
Trastuzumab deruxtecan (T-DXd)	FDA & EMA Approved	DESTINY-Lung01 & 02
	NSCLC indication(s): • *Previously treated unresectable or metastatic NSCLC with activating HER2 mutations.* • *Previously treated metastatic HER+ (IHC 3+) solid tumors*	
Trastuzumab rezetecan	Investigational	HORIZON-Lung

ANTIBODY-DRUG CONJUGATES: T-DXD



DESTINY-Lung01[a]

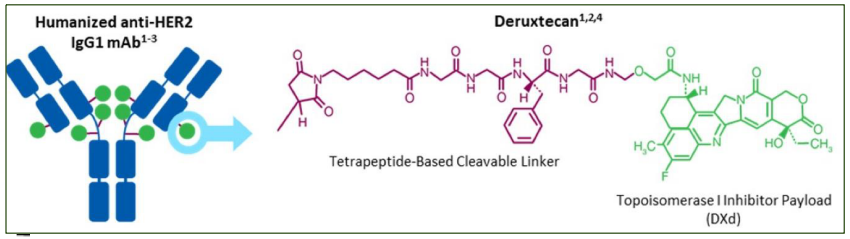
- Unresectable/metastatic nonsquamous NSCLC
- Relapsed from or is refractory to standard treatment
- Measurable disease by RECIST v1.1
- ECOG PS of 0 or 1
- Locally reported *HER2*m (Cohort 2)
- Asymptomatic BM allowed[c]

Cohort 1: HER2-OE (IHC 3+ or IHC 2+) T-DXd 6.4 mg/kg Q3W N = 49

Cohort 1a: HER2-OE (IHC 3+ or IHC 2+) T-DXd 5.4 mg/kg Q3W N = 41

Cohort 2: *HER2*m T-DXd 6.4 mg/kg Q3W N = 42

Cohort 2 expansion: *HER2*m T-DXd 6.4 mg/kg Q3W N = 49



TRASTUZUMAB-DERUXTECAN (T-Dxd) became the first treatment approved in HER2 mutated NSCLC

DESTINY-Lung02[b]

- Metastatic *HER2*m NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1
- Locally reported *HER2*m
- Asymptomatic BM allowed[c]

R 2:1

T-DXd 5.4 mg/kg Q3W n = 102

T-DXd 6.4 mg/kg Q3W n = 50

FDA and EMA approved

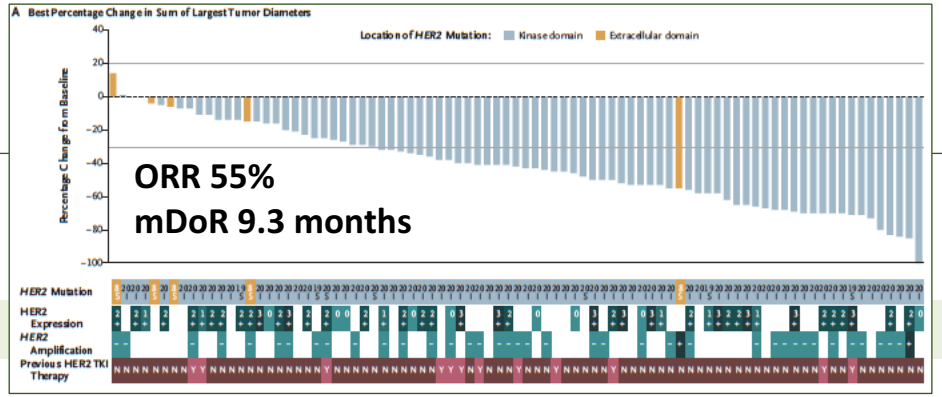
- T-DXd is a humanized anti-HER2 monoclonal antibody linked to a topoisomerase I inhibitor payload through a tetrapeptide-based cleavable linker

Li BT, et al. N Engl J Med. 2022;386:241-51; Goto K, et al. J Clin Oncol 2023;41:4852-63

ADCS: T-DXD

DESTINY-LUNG 01: phase 2

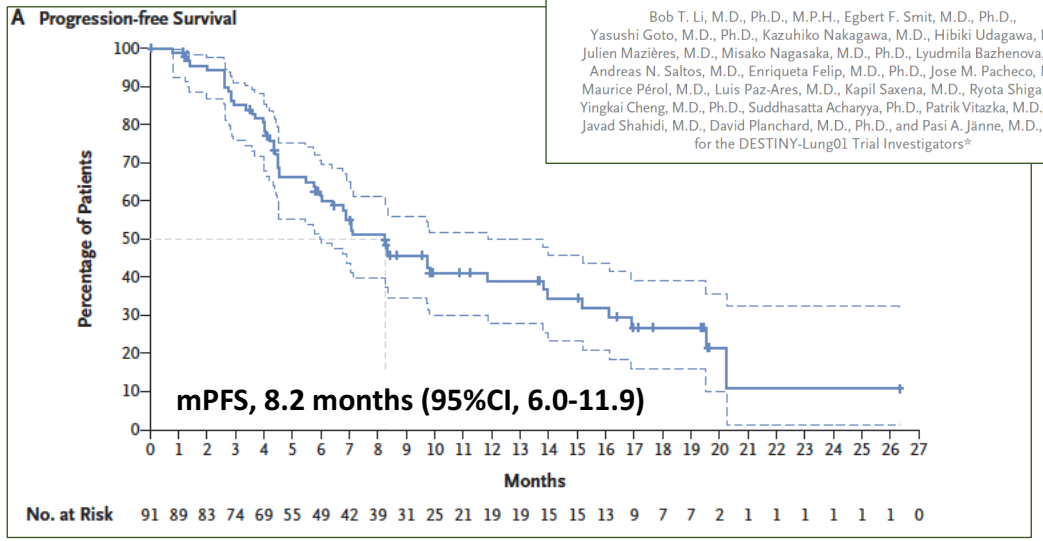
- N=91; ICI pretreated; T-Dxd 6.4 mg/kg
- ORR: 55%, mDoR 9.3 months
- mPFS 8.2 months, mOS 17.8 months
- 45% drug-related TRAEs G ≥ 3 (neutropenia 18%, anemia 10%)
- 25% discontinuation
- 34% dose reduction
- 26% ILD

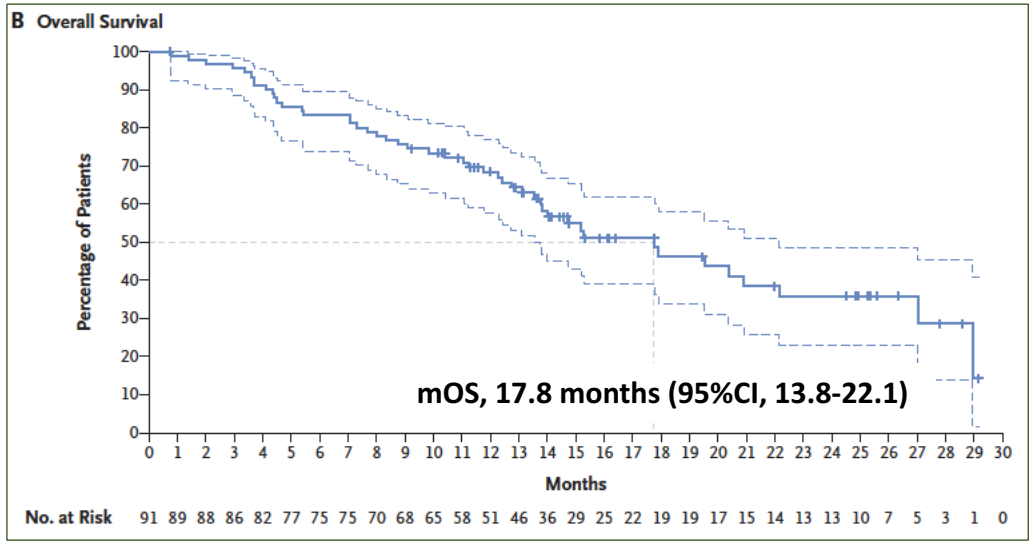


The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE

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

Bob T. Li, M.D., Ph.D., M.P.H., Egbert F. Smit, M.D., Ph.D., Yasushi Goto, M.D., Ph.D., Kazuhiko Nakagawa, M.D., Hibiki Udagawa, M.D., Julien Mazières, M.D., Misako Nagasaka, M.D., Ph.D., Lyudmila Bazhenova, M.D., Andreas N. Saltos, M.D., Enriqueta Felip, M.D., Ph.D., Jose M. Pacheco, M.D., Maurice Pérol, M.D., Luis Paz-Ares, M.D., Kapil Saxena, M.D., Ryota Shiga, B.Sc., Yingkai Cheng, M.D., Ph.D., Suddhasatta Acharyya, Ph.D., Patrik Vitazka, M.D., Ph.D., Javad Shahidi, M.D., David Planchard, M.D., Ph.D., and Pasi A. Jänne, M.D., Ph.D., for the DESTINY-Lung01 Trial Investigators*

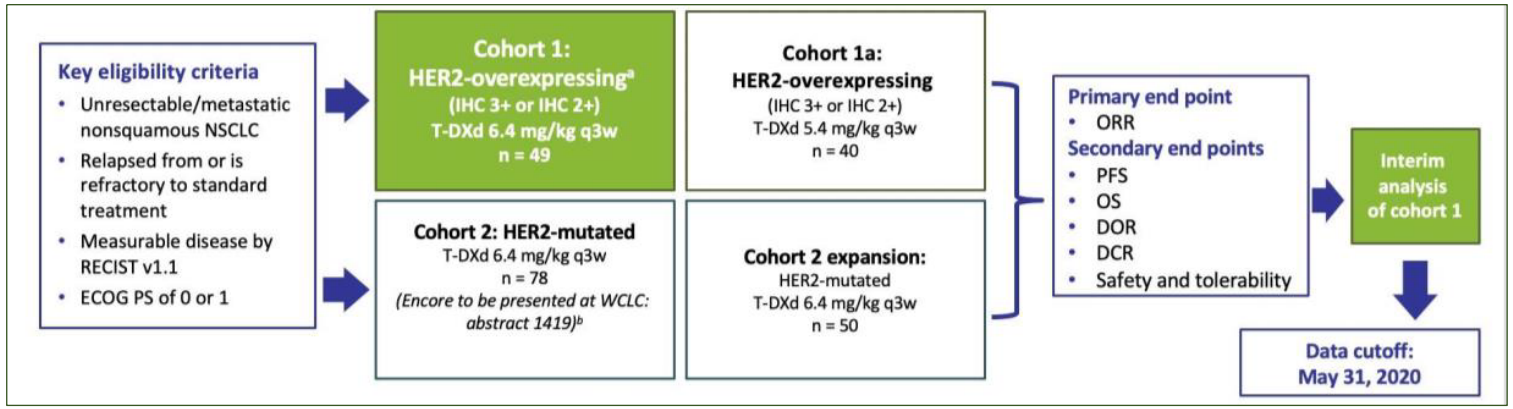




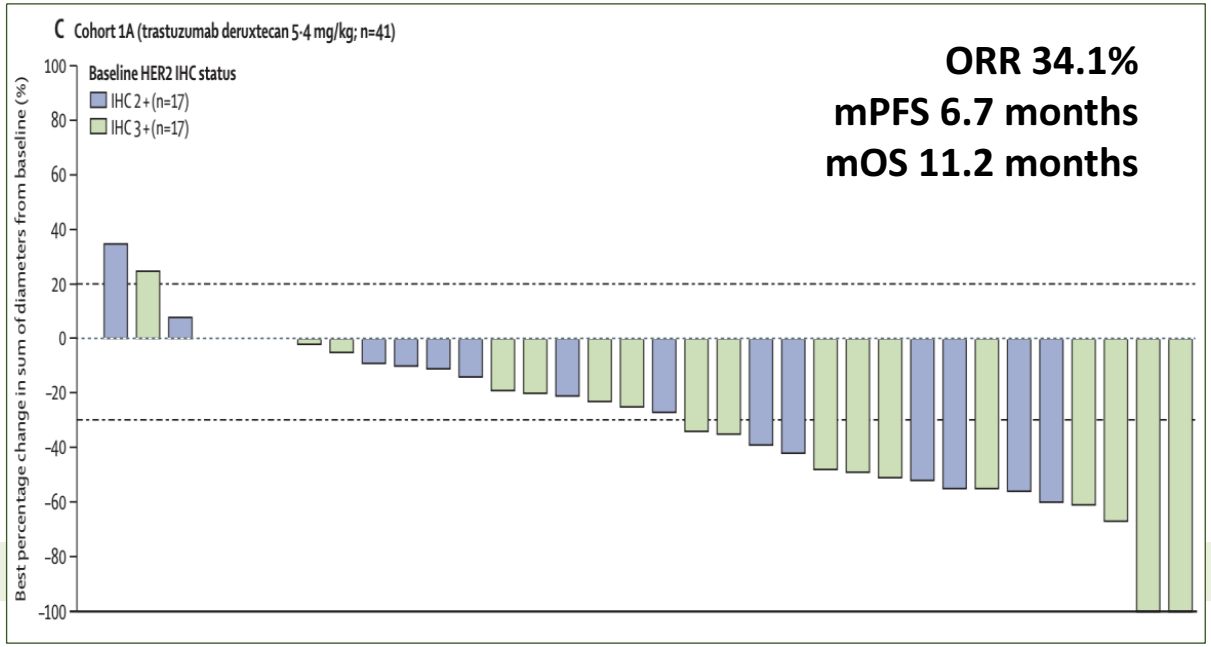
Li BT, et al. N Engl J Med. 2022;386:241-51

ADCS: T-DXD IN HER2 OVEREXPRESSION NSCLC

DESTINY-LUNG 01: phase 2



	6.4 mg/kg N: 49	5.4 mg/kg N: 41
Median treat duration (months)	4	5.5
IHC 3+/2+ (%)	20/80	41/59
ORR (%)	26	34
mDoR (months)	5.8	6.2
mPFS (months)	5.7	6.7
mOS (months)	12.4	11.2
TRAE G≥3 (%)	53	22
ILD (%)	20	5
ILD grade 5 (%)	6	2



Smit EF, et al. Lancet Oncol 2024;25:439-454

ADCS: T-DXD

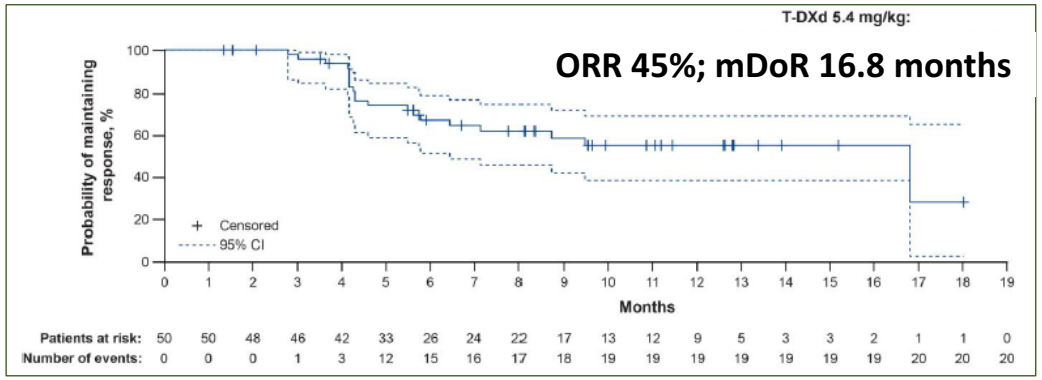
DESTINY-LUNG 02: phase 2

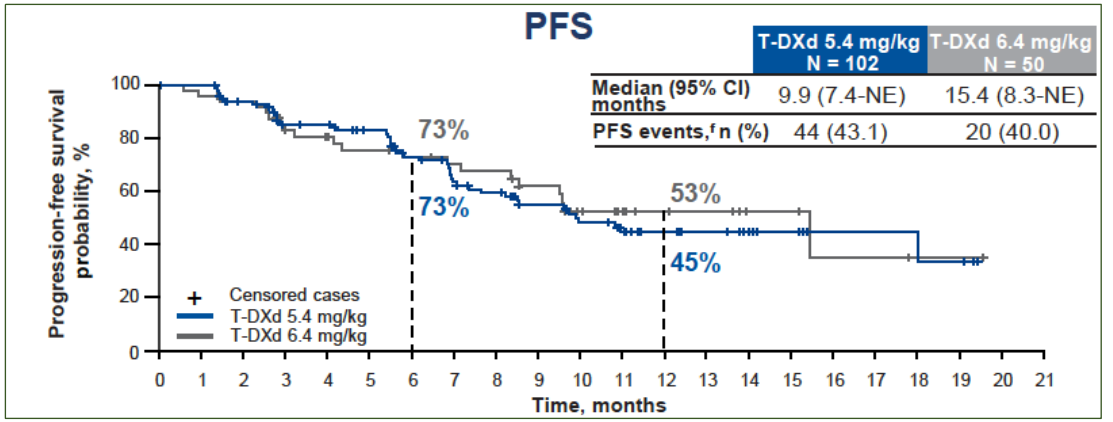
Trastuzumab Deruxtecan in Patients With *HER2*-Mutant Metastatic Non–Small-Cell Lung Cancer: Primary Results From the Randomized, Phase II DESTINY-Lung02 Trial

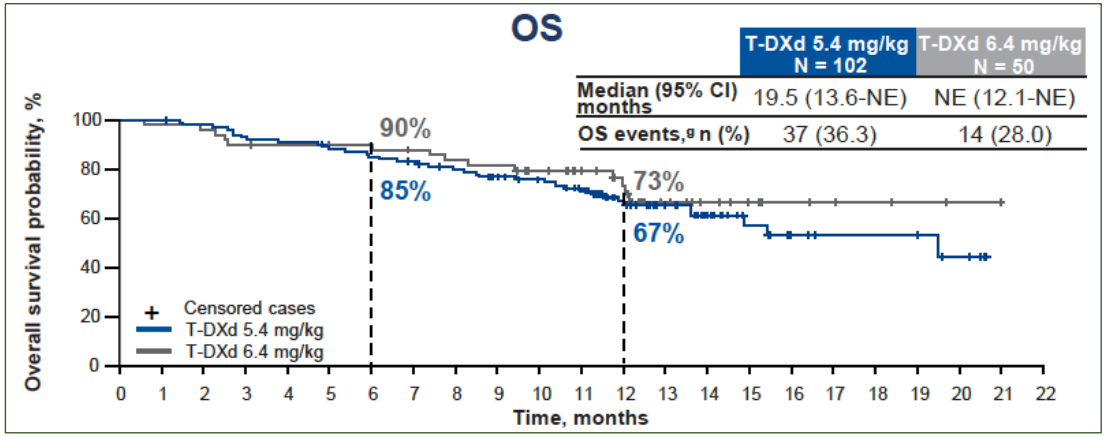
Koichi Goto, MD, PhD[1]; Yasushi Goto, MD, PhD[2]; Toshio Kubo, MD, PhD[3]; Kiichiro Ninomiya, MD, PhD[4]; Sang-We Kim, MD, PhD[5];

- N=102 (T-Dxd 5.4 mg/kg) and 50 patients (T-Dxd 6.4 mg/kg)

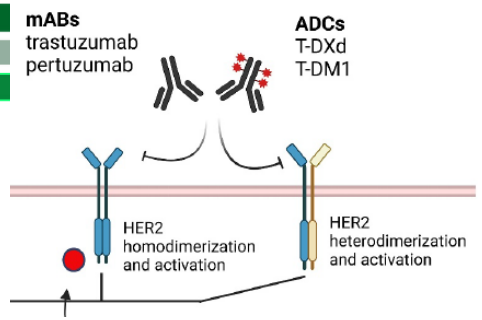
	T-Dxd 5.4mg/kg	T-Dxd 6.4mg/kg
ORR (%)	49% (95% CI 39-59)	56% (95% CI 41-70)
Median PFS	9.9m	15.4m
1y PFS rate (%)	45%	53%
G3-4 TRAEs (%)	39%	58%
Dose reduction/discont'	17% / 14%	32% / 20%
ILD (%)	13%	28%





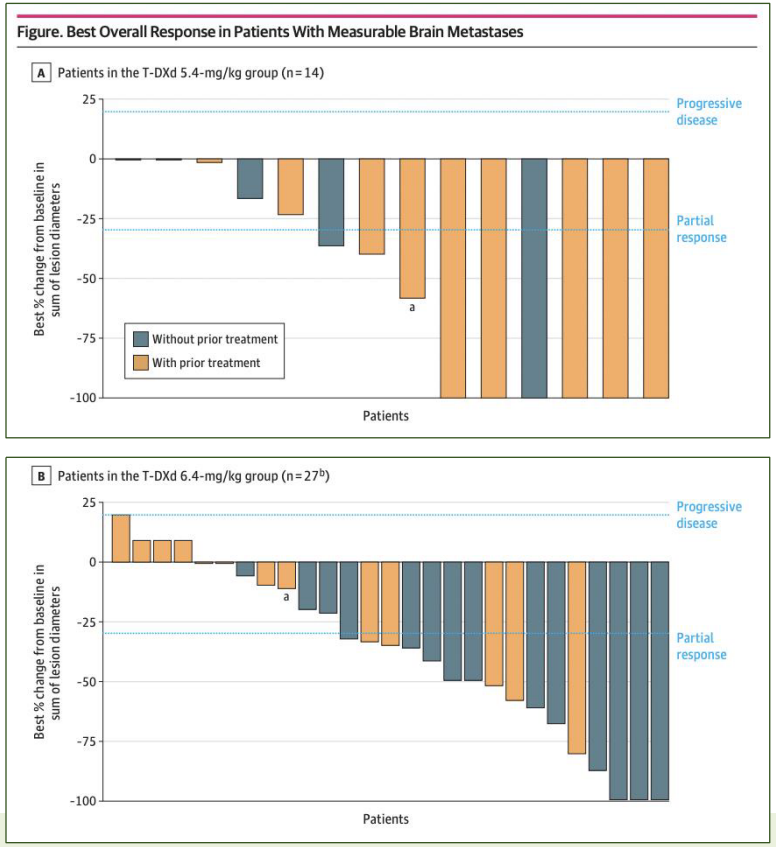


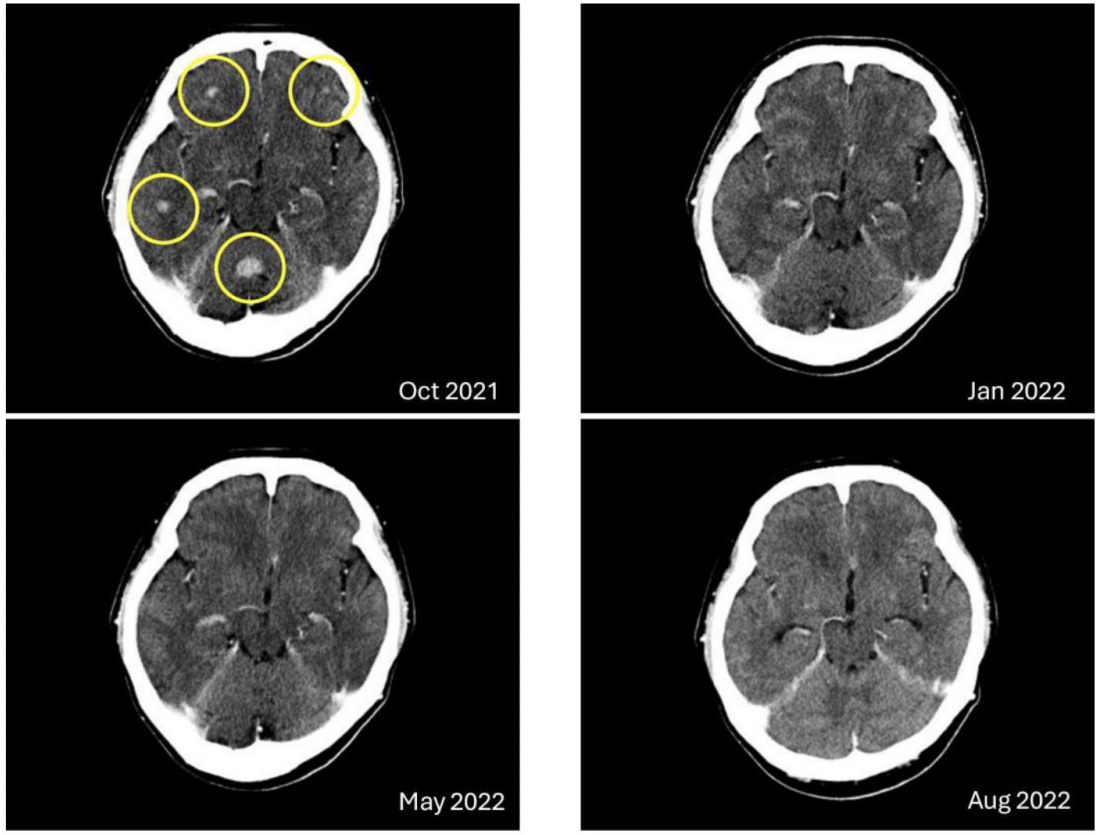
Goto K, et al. J Clin Oncol 2023;41:4852-63



ANTIBODY-DRUG CONJUGATES: T-DXD

- Posthoc analysis from DESTINY-Lung01 and DESTINY-Lung02: unexpected intracranial efficacy with T-Dxd in Her2 mutated NSCLC

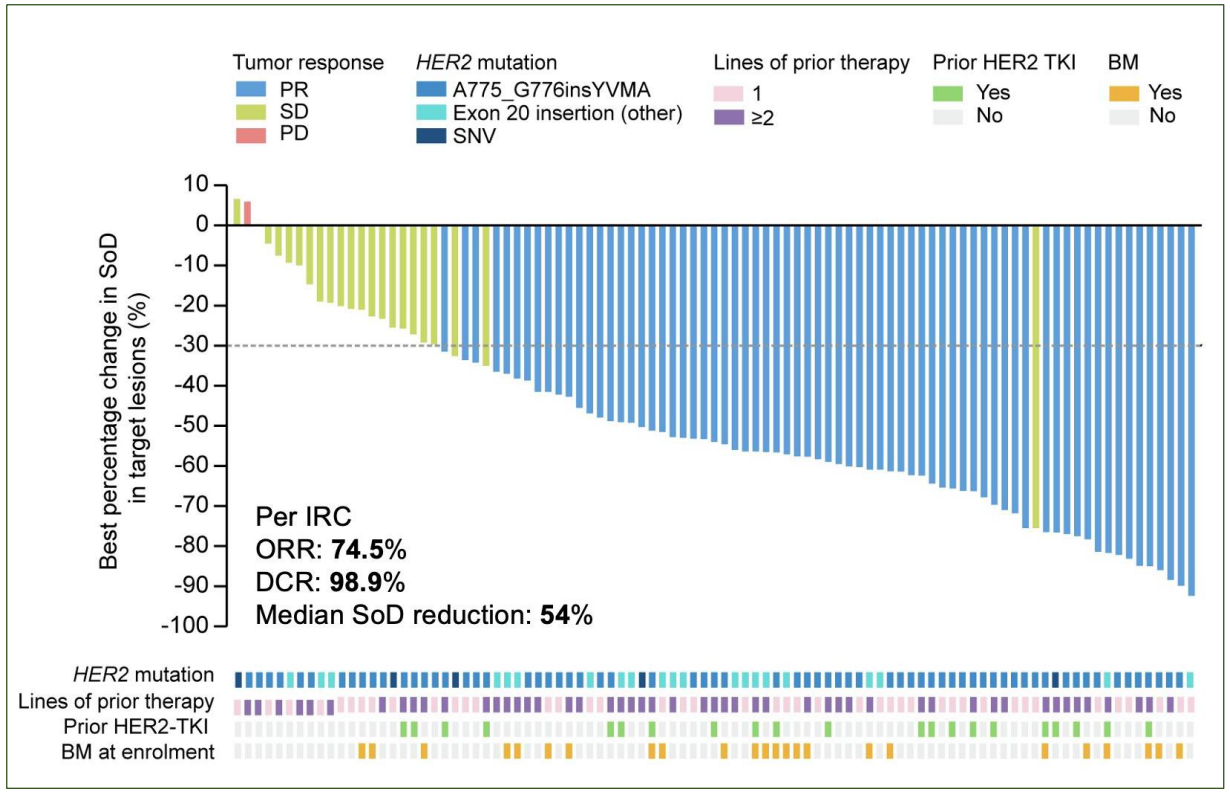


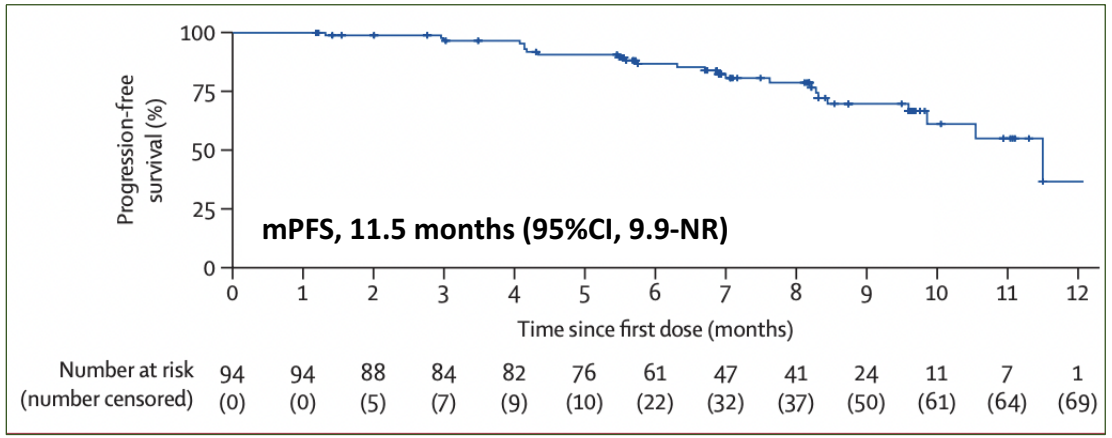


Jänne P, et al. JAMA Netw Open. 2025 Nov 3;8(11):e2543107

ANTIBODY-DRUG CONJUGATES: T-REZETECAN (SHR A1811)

- HORIZON LUNG: Phase I/II trial. N=94 Chinese patients.





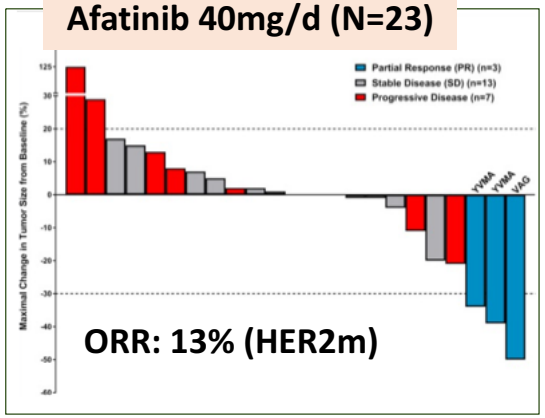
ILD	8 (8.5)
Grade 1-2	7 (7.4)
Grade 3	1 (1.1)

Li Z. AACR 2025; Li Z, et al. Lancet Oncol 2025; 26: 437-46

TYROSINE KINASE INHIBITORS (TKIS)

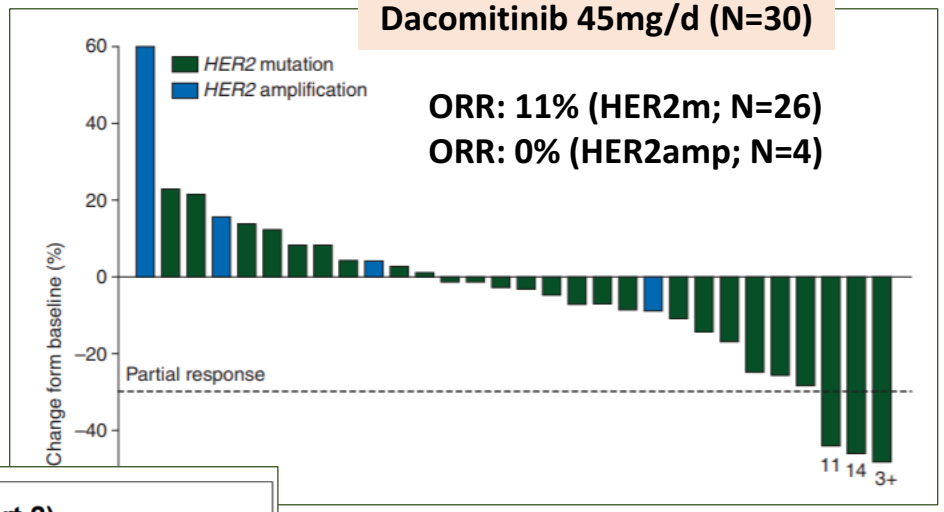
- **NON-SELECTIVE HER2 INHIBITORS** include the pan-HER TKIs: afatinib, dacomitinib, neratinib, poziotinib, pyrotinib, tucatinib, furmonertinib, mobocertinib, tarloxotinib and tuxobertinib

Afatinib 40mg/d (N=23)



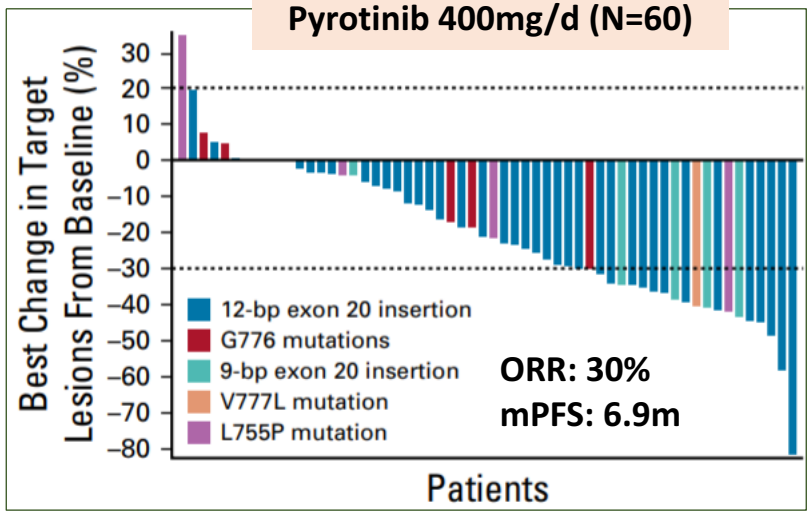
ORR: 13% (HER2m)

Dacomitinib 45mg/d (N=30)

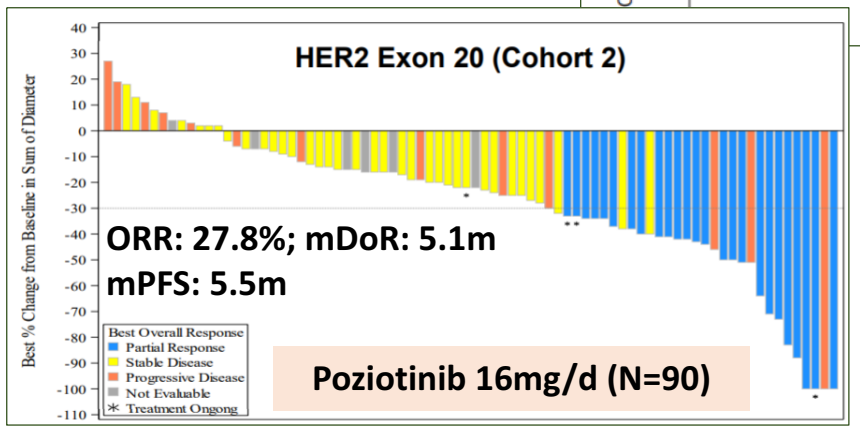


ORR: 11% (HER2m; N=26)
ORR: 0% (HER2amp; N=4)

Pyrotinib 400mg/d (N=60)



ORR: 30%
mPFS: 6.9m



ORR: 27.8%; mDoR: 5.1m
mPFS: 5.5m

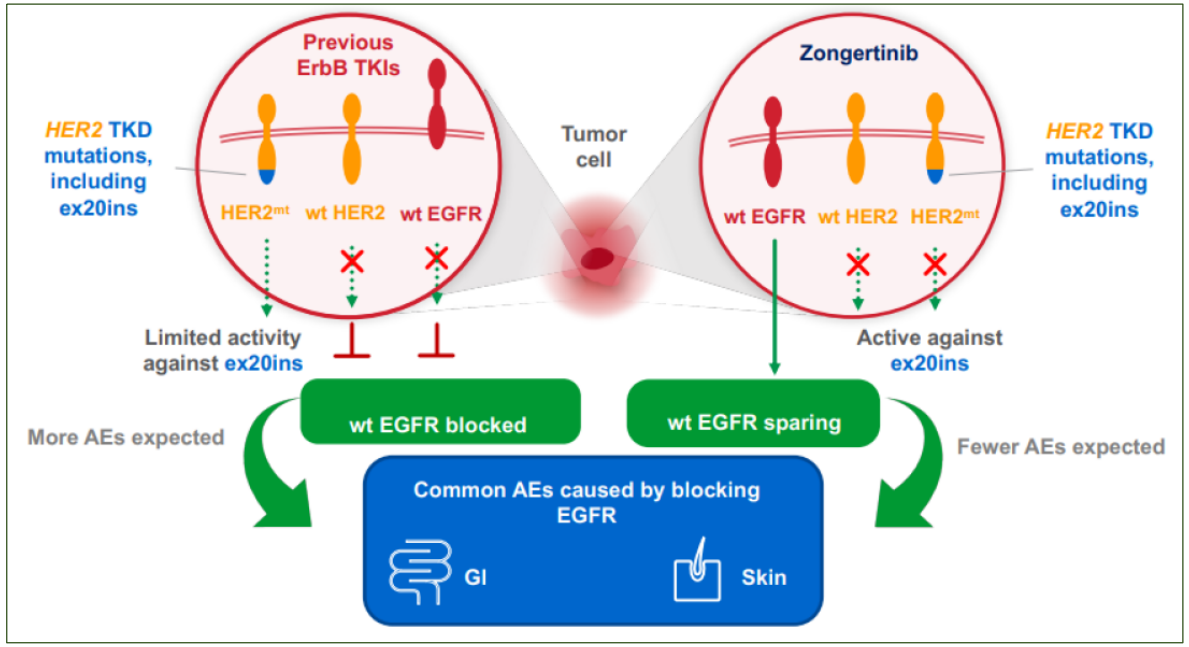
Poziotinib 16mg/d (N=90)

- Limited efficacy of pan-HER TKIs with significant skin and GI toxicities

Lai WV, et al. Eur J Cancer 2019;109:28-35; Kris MG, et al. Ann Oncol 2015;26:1421-7; Le X, et al. J Clin Oncol. 2022;40:710-8; Zhou C, et al. J Clin Oncol 2020;38:2753-61

TYROSINE KINASE INHIBITORS (TKIS)

- **SELECTIVE HER2 INHIBITORS:** novel HER2 TKIs, highly HER2 selective with EGFR sparing activity concurrently
  - ZONGERTINIB (BI 1810631)
  - SEVABERTINIB (BAY 2927088)



HER2-Directed TKIs		
TKI	**Status**	**Pivotal Trial(s)**
Zongertinib	FDA Approved	Beamion LUNG-1
	NSCLC indication: • *Previously treated unresectable or metastatic NSCLC with activating HER2 mutations.*	
Sevabertinib (BAY 2927088)	Investigational May 2025 - FDA granted priority review	SOHO-01
NVL-330	Investigational	HEROEX-1

TKIS: ZONGERTINIB

BEAMION LUNG-1: phase Ia/Ib

Phase Ia
(Dose Escalation)

HER2-altered advanced solid tumors

Patients received escalating doses of zongertinib either BID or QD in 3-week cycles to determine the RDE for Phase Ib

The MTD was not reached with either schedule

Two doses were taken to expansion for optimization[2]

Phase Ib (Dose Expansion)
Selected dose after interim futility analysis: zongertinib 120 mg QD

Current Analysis		Ongoing Analysis	
Previously treated patients with *HER2*-mutant advanced NSCLC		(data not yet available)	
Cohort 1	**Patients with TKD mutations***	**Cohort 2**	**Treatment-naïve with TKD mutations**
Cohort 5	**Patients with TKD mutations and prior HER2-directed ADC treatment**	**Cohort 4**	**TKD mutations and active brain metastases**
Cohort 3	**Patients with non-TKD mutations***		

Primary Endpoint:

Objective response (RECIST v1.1) by BICR (Cohorts 1 and 5) or investigator review (Cohort 3)

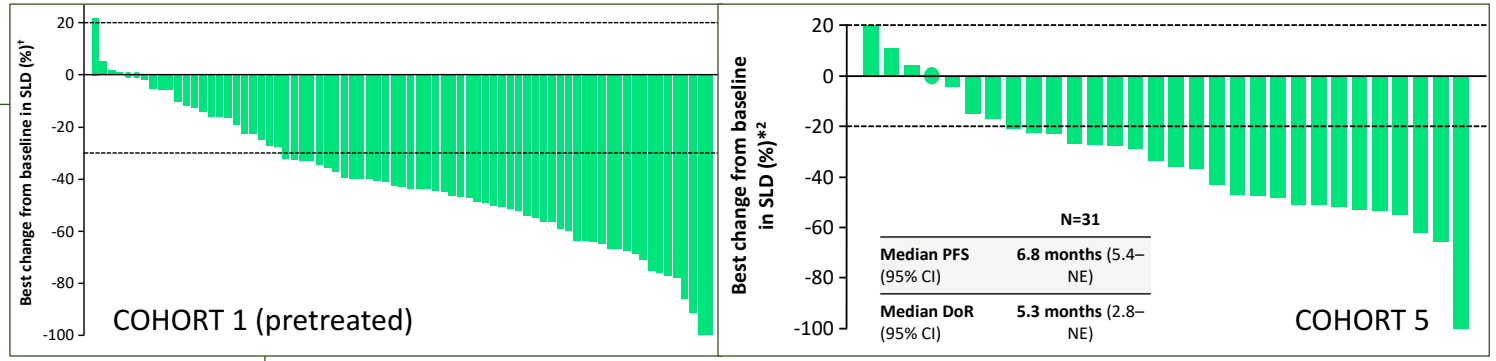
Secondary Endpoints:

DoR, DC, PFS (RECIST v1.1) in all patients, and objective response and DC (RANO-BM) in patients with CNS lesions at baseline, by BICR (Cohorts 1 and 5) or investigator review (Cohort 3)

Heymach JV, et al. N Engl J Med. 2025 Jun 19;392(23):2321-2333

TKIS: ZONGERTINIB

- COHORT 1 (N=75) – TKD mutations
  - ORR: 71%; mDoR: 14m; mPFS: 12.4m
  - Brain (N=27): IC ORR: 41%
- COHORT 5 (N=31) – TKD mutations and prior HER2-directed ADC treatment
  - ORR: 48%; mDoR: 5.3m; mPFS: 6.8m
  - Previous T-Dxd (N=22): ORR: 41%
- COHORT 3 (N=20) – non-TKD mutations
  - ORR: 30%



- 17% TRAE G ≥ 3 (AST, ALT)
- Diarrhea 56% G1-G2 (G3 1%)
- Rash 33% (no G3)
- Dose reduction: 7%
- Discontinuation: 3%
- No ILD

COHORT 1 (pretreated)

Heymach JV, et al. N Engl J Med. 2025 Jun 19;392(23):2321-2333

TKIS: ZONGERTINIB

In Cohort 4, the intracranial ORR by RANO-BM was 43% in patients with active brain metastases (N = 30)

In a pooled analysis of 58 patients with stable, asymptomatic or active brain metastases in Cohorts 1 and 4 (Cohort 1: 28, Cohort 4: 30),* the intracranial ORR by RANO-BM was 41%

	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

Zongertinib demonstrated encouraging intracranial efficacy by RANO-BM in patients with stable, asymptomatic or active brain metastases

Ruiter et al. WCLC 2025

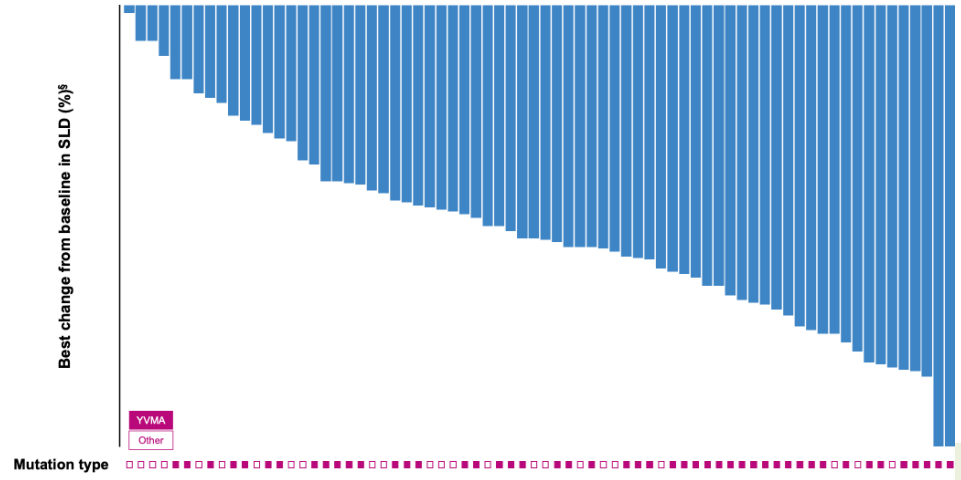
TKIS: ZONGERTINIB

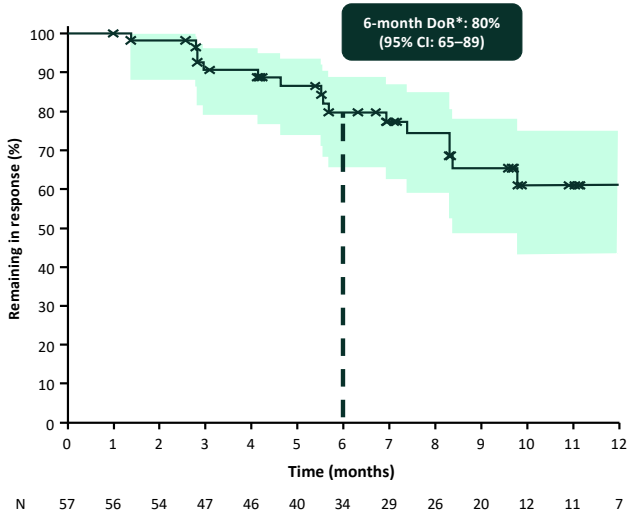
Cohort 2 — **Treatment-naïve patients with TKD mutations**

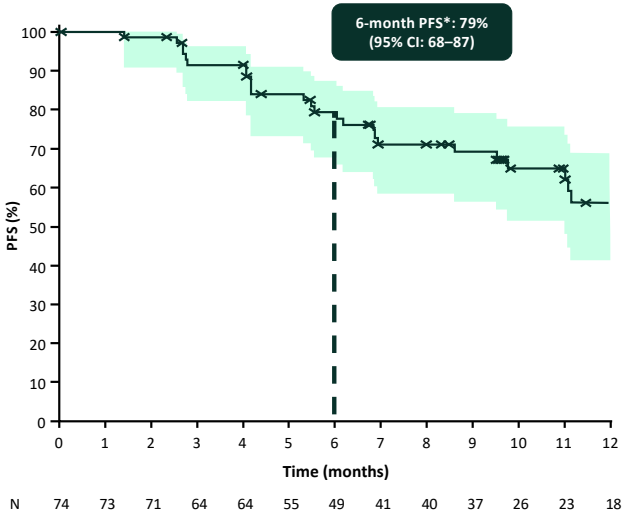
Primary endpoint: Objective response by BICR (RECIST v1.1)

Secondary endpoints: DC, DoR and PFS by BICR (RECIST v1.1)

Key inclusion criteria: aged ≥18 years, advanced/metastatic non-squamous *HER2*-mutant NSCLC (TKD mutation), ≥1 measurable non-CNS lesion (RECIST v1.1) and ECOG PS of 0/1. Patients with stable/asymptomatic brain metastases were eligible





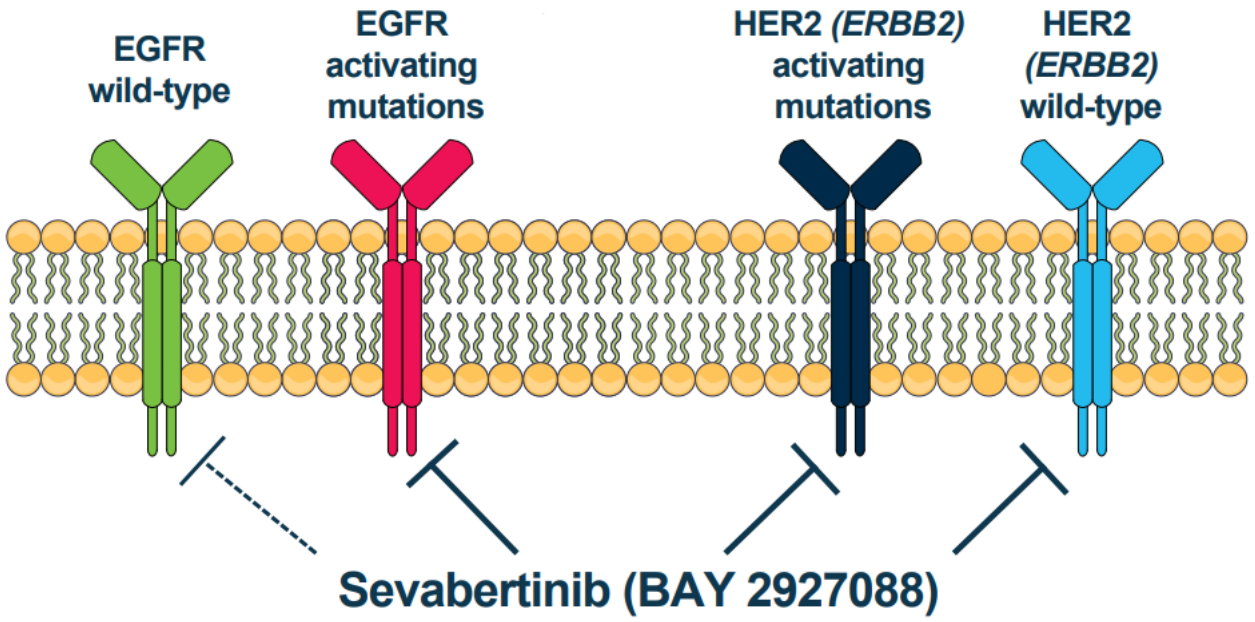


- G3 TRAEs in 13 (18%) patients
- There were no grade 4/5 TRAEs
- Dose reduction 15%; discontinuation 9%
- Two cases (3%) of ILD/pneumonitis (G2)

Popat et al. ESMO 2025

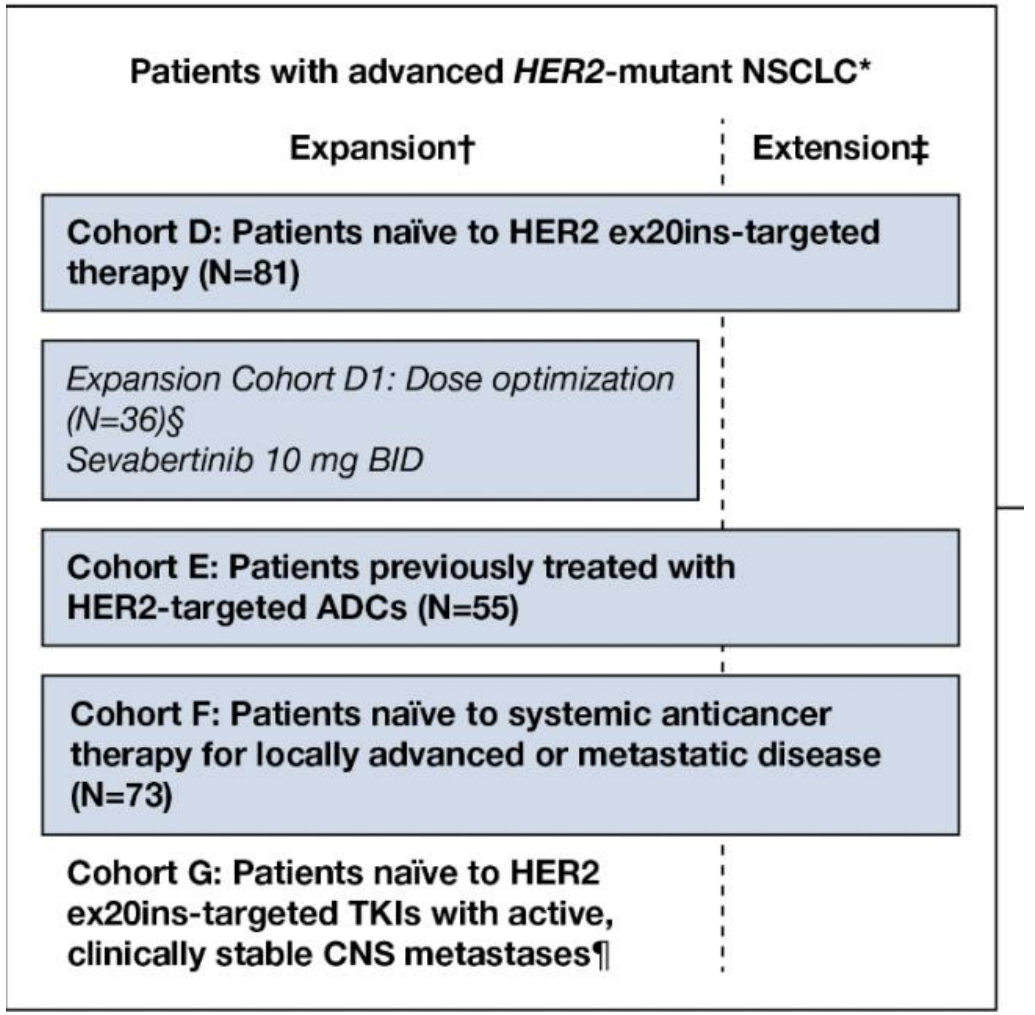
TKIS: SEVABERTINIB

SOHO-1: phase I/Ii



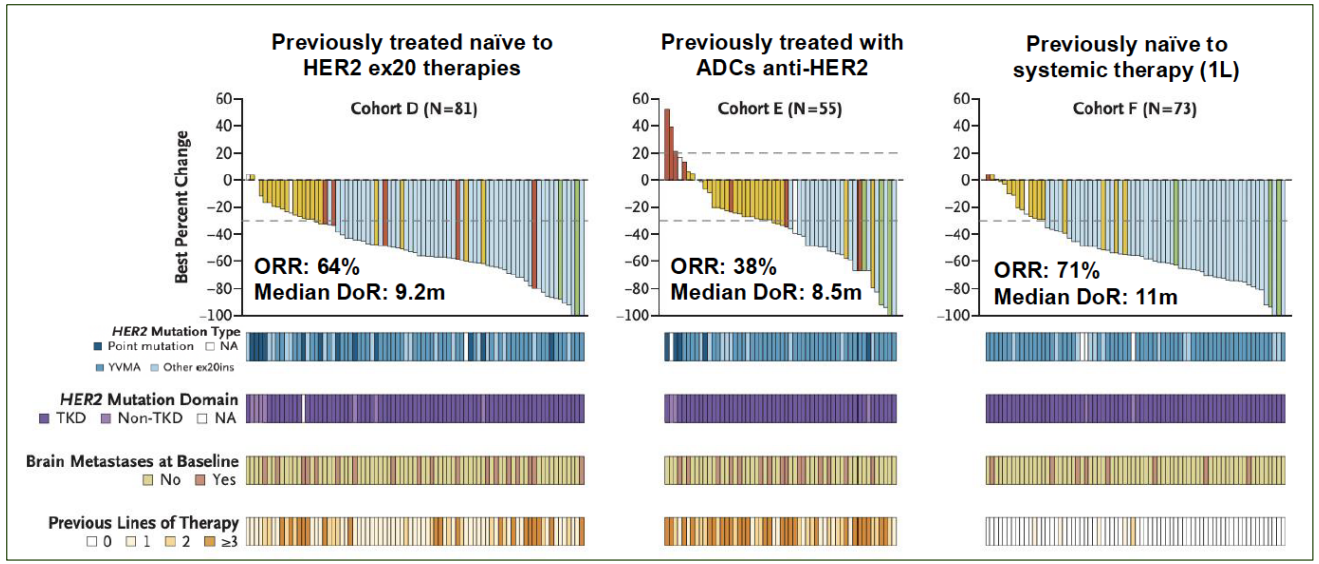
May 28, 2025 1:08 PM Eastern Daylight Time

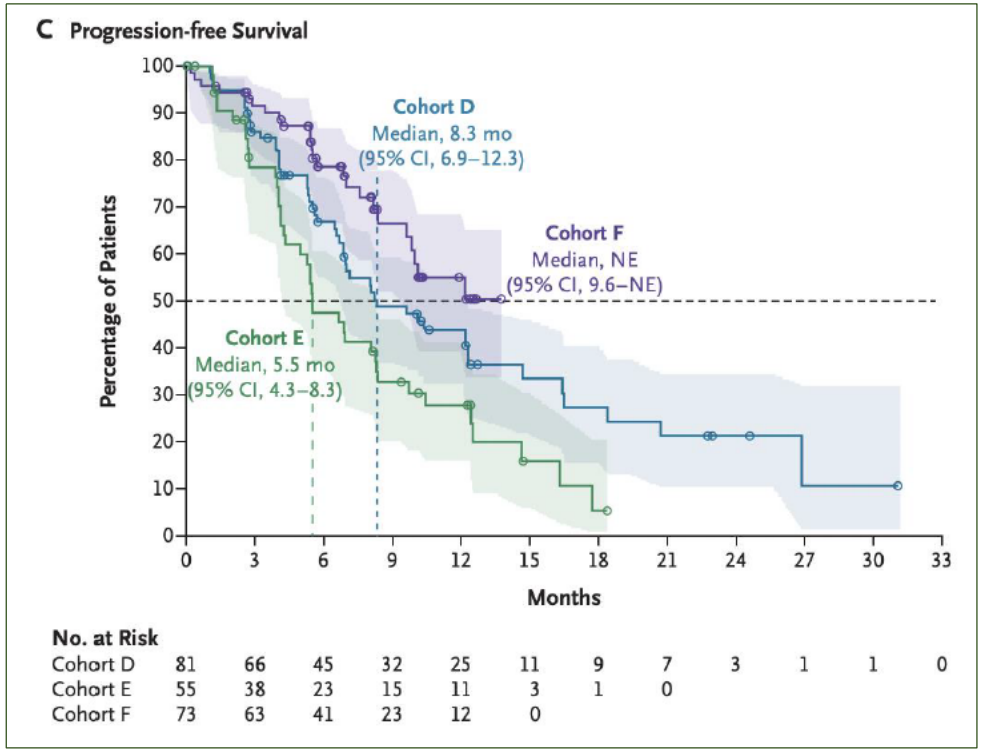
U.S. FDA Accepts New Drug Application Under Priority Review for sevabertinib (BAY 2927088) in HER2-Mutant Non-Small Cell Lung Cancer



Le X, et al. N Engl J Med. 2025 Nov 6;393(18):1819-1832

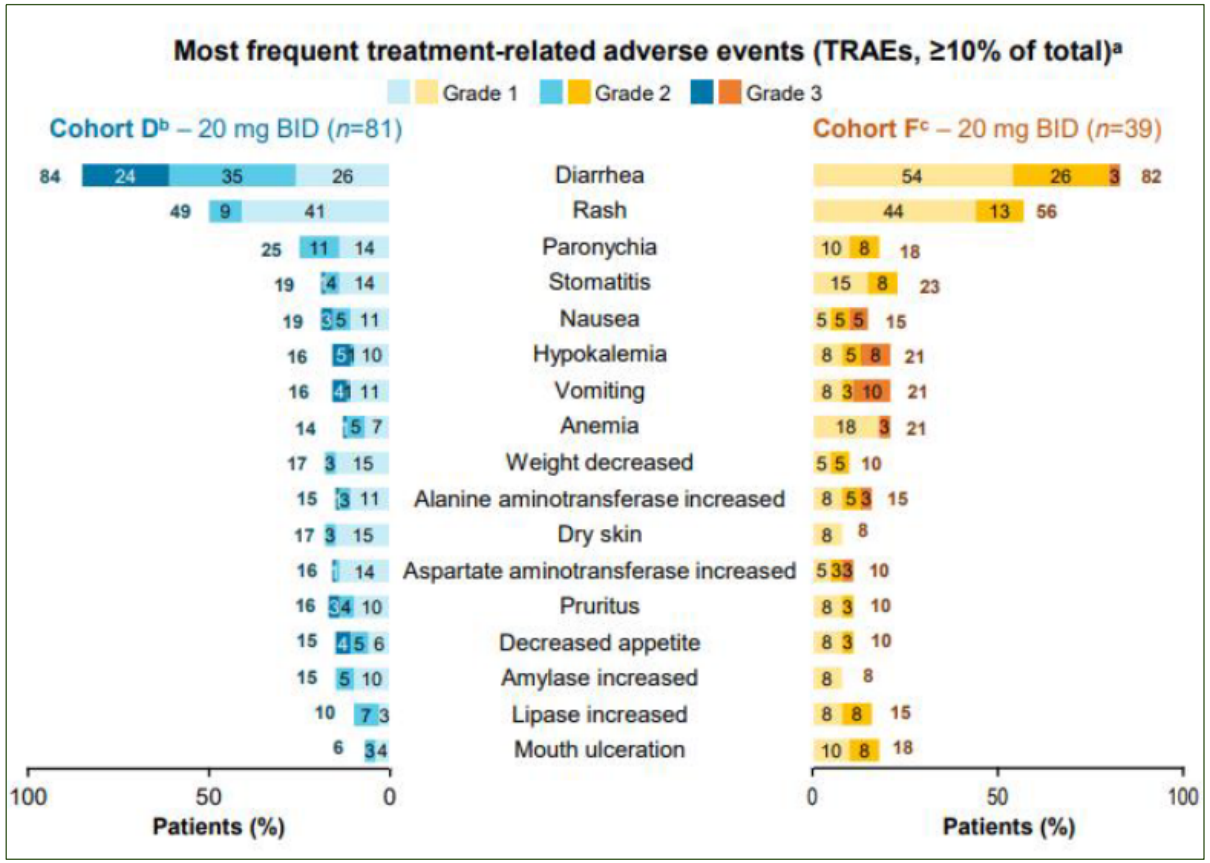
TKIS: SEVABERTINIB





Le X, et al. N Engl J Med. 2025 Nov 6;393(18):1819-1832

TKIS: SEVABERTINIB



EGFR-related AEs
-25% Gr3 diarrhea

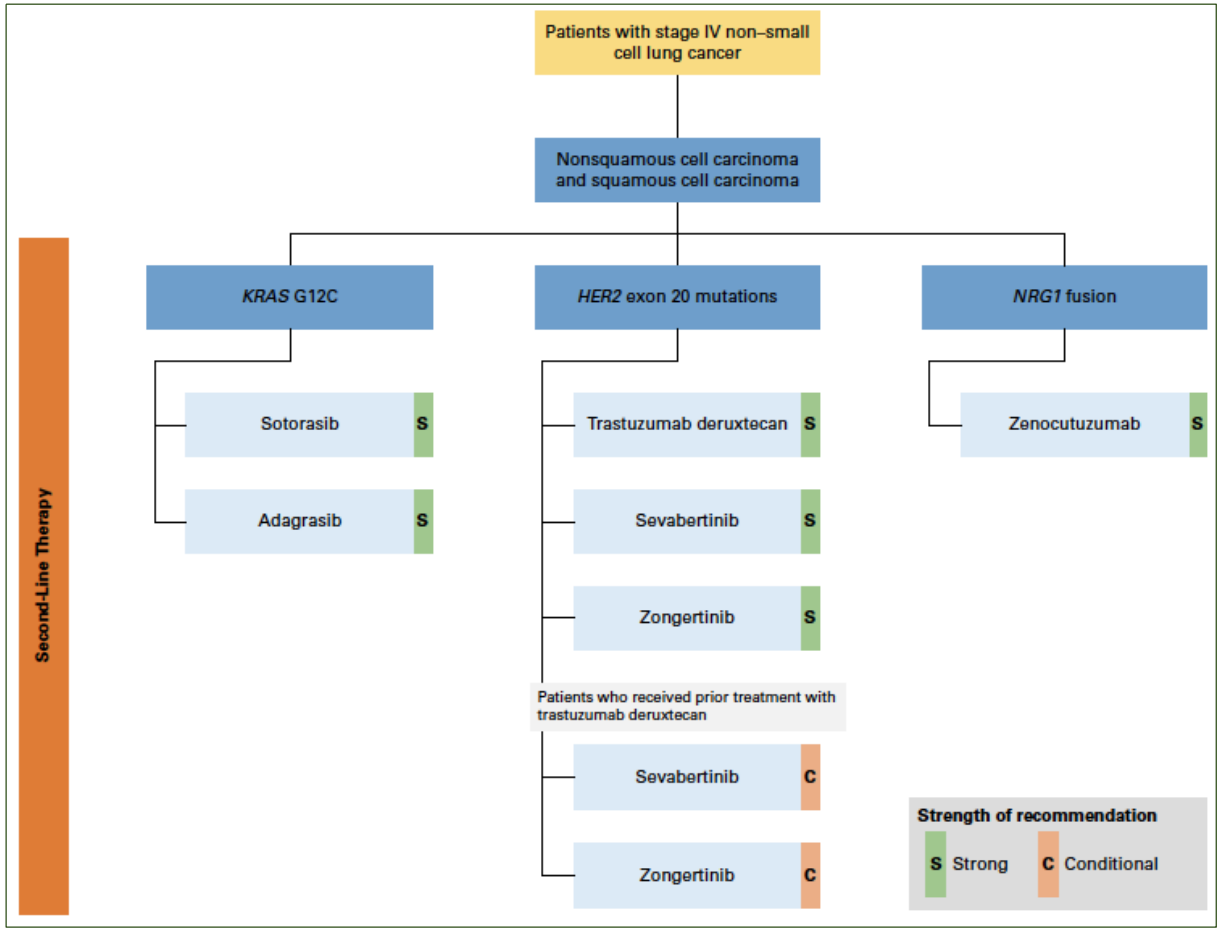
n (%)	All grades (*N*=44)	Grade ≥3 (*N*=44)
Any TRAE	42 (95.5)	19 (43.2)
Most common TRAEs occurring in ≥10% of patients		
Diarrhea	38 (86.4)	11 (25.0)
Rash	19 (43.2)	0
Paronychia	11 (25.0)	0
Nausea	11 (25.0)	1 (2.3)
Vomiting	9 (20.5)	2 (4.5)
Dermatitis acneiform	8 (18.2)	0
Stomatitis	8 (18.2)	1 (2.3)
Dry skin	7 (15.9)	0
Increased aspartate aminotransferase	6 (13.6)	1 (2.3)

Le X, et al. N Engl J Med. 2025 Nov 6;393(18):1819-1832

TREATMENT OF HER2-ALTERED NSCLC

Treatment	N	ORR	mPFS	AEs ≥ 3	Approval for HER2m NSCLC
Trastuzumab-deruxtecan	91	55%	8.2m	45%	FDA and EMA
Trastuzumab-rezetecan	94	74.5%	11.5m	62%	China
Zongertinib	75	71%	12.4m	17%	FDA*
Sevabertinib	81	64%	8.3m	31%	FDA*

(*) Accelerated approval



ASCO Living Guideline, 2026.3.0. J Clin Oncol. 2026

ONGOING PHASE III TRIALS IN 1L NSCLC HER2M

DESTINY-Lung04: Trastu-Dxd vs Chemo + ICI

Patient population (N≈264)

- Unresectable, locally advanced (not amenable to curative therapy), or metastatic nonsquamous NSCLC with *HER2* exon 19 or 20 mutations[a]
- Naive to systemic therapy in the locally advanced or metastatic setting
- No known other targetable oncogenic mutations/alterations

Randomization 1:1

- **Arm 1: T-DXd[b]**
- **Arm 2: Standard of care[b] platinum[c] (cisplatin or carboplatin) + pemetrexed + pembrolizumab**

[a] *HER2* mutations may be detected in tissue or ctDNA.
[b] Crossover is not permitted.
[c] Investigator's choice of cisplatin or carboplatin.

SHR-A1811-310: T-Rezetecan vs Chemo +ICI

300 participants in 2 patient groups

SHR-A1811
Experimental group
Treatment:
Drug: SHR-A1811

Standard of Care（Camrelizumab、Pemetrexed/ Paclitaxel、Carboplatin/ Cisplatin）
Active comparator group
Treatment:
Drug: Camrelizumab、Pemetrexed/ Paclitaxel、Carboplatin/ Cisplatin

Beamion LUNG-2: Zongertinib vs Chemo +ICI

N=416 (estimated)

Adults aged ≥18 years with:

- Advanced and/or metastatic non-squamous NSCLC
- Documented *HER2* mutation in the TKD as per local laboratory results
- No prior systemic treatment for locally advanced or metastatic disease
- ≥1 lesion evaluable by RECIST v1.1
- Eligible to receive cisplatin/pemetrexed or carboplatin/pemetrexed + pembrolizumab
- Life expectancy ≥12 weeks at start of treatment
- ECOG PS 0-1

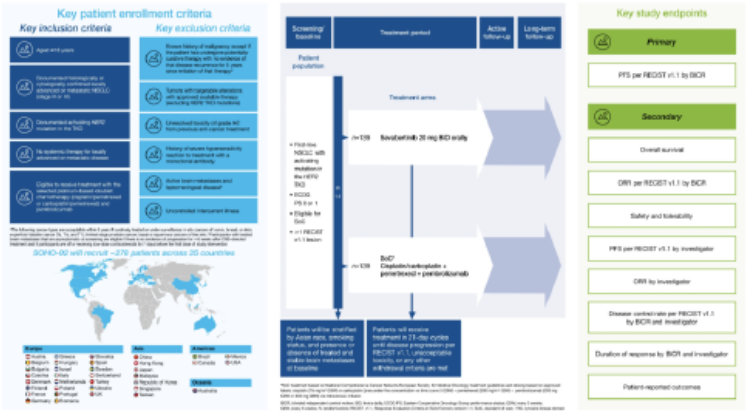
Phase III

Randomized 1:1, stratified on presence of A775_G776insYVMA mutation

- **120 mg zongertinib once daily orally in 21-day cycles (n≈208)**
- **Standard of care* (n≈208)**

*500 mg/m² platinum-pemetrexed IV chemotherapy plus 200 mg IV pembrolizumab followed by either 75 mg/m² cisplatin/carboplatin AUC 5 on Day 1 (determined by investigator prior to randomization), Q3W, for 4 21-day cycles, followed by maintenance therapy with 200 mg pembrolizumab plus pemetrexed 500 mg/m² Q3W for up to 35 cycles.

SOHO-02: Sevabertinib vs Chemo+ICI



CONCLUSIONS

- HER2 alterations are important oncogenic drivers in NSCLC
- Significant progress has been made
- Testing is key to identify HER2 mutations and effort should be made for standardizing IHC
- Trastuzumab-Deruxtecan was the first treatment approved for HER2 mutated (FDA and EMA) and for HER2 3+ overexpressed advanced NSCLC (FDA)
- New emerging ADCs and selective TKIs against HER2 (Zongertinib, Sevabertinib) have demonstrated clinically relevant efficacy in previously treated advanced NSCLC
- Challenges: CNS efficacy, best sequence, toxicity management
- Expectation clinical trials in the first-line setting

GRACIAS!

II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN: A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 6 Y 7 DE FEBRERO DE 2025