16th CONGRESS Lung ON CANCER

BARCELONA 27 / 28 NOVEMBER 2025

GECP lung cancer research

HER2: A new frontier in precision oncology

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/Salut ICO Institut Català d'Oncologia

Universitat de Barcelona

IDIBELL Oncobell program

CONFLICTO DE INTERESES

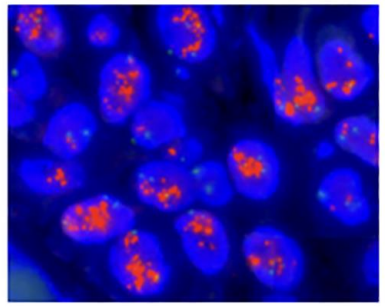
Research funding: Roche, Pfizer, Merck-Serono, Bristol Myers Squibb

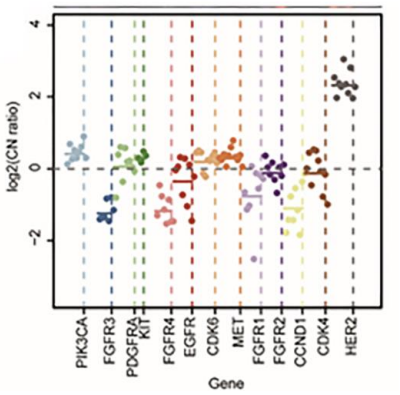
Advisory board or lectures: Amgen, Apollomics, AstraZeneca, BeOne, Bristol Myers Squibb, Boehringer-Ingelheim, Daiichi-Sankyo, Genmab, Glaxo Smith Kline, Illumina, Johnson & Johnson, Lilly, Merck Sharp & Dohme, Merck-Serono, Pfizer, PharmaMar, Pierre Fabre, Qiagen, Regeneron, Roche, Sanofi and Takeda

Travel support: Roche, Takeda, J&J, and MSD.

Views expressed in the session are mine, and/or are based on unbiased, peer reviewed and published literature.

HER2 is an actionable driver gene that can be activated in lung cancer through distinct mechanisms & detected by distinct methods





HER2 gene amplification

3%

Detection: FISH; NGS

Weak staining

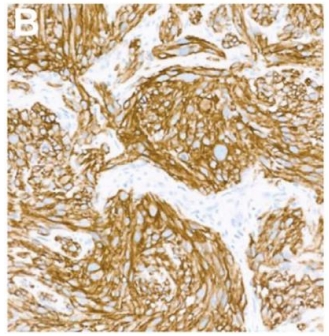
Moderate staining

Strong staining

HER2 protein overexpression

2–38%

Detection: IHC

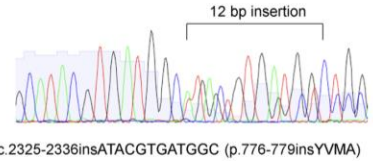


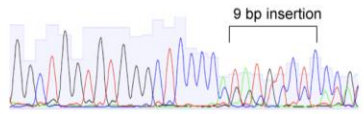
HER2 gene mutation

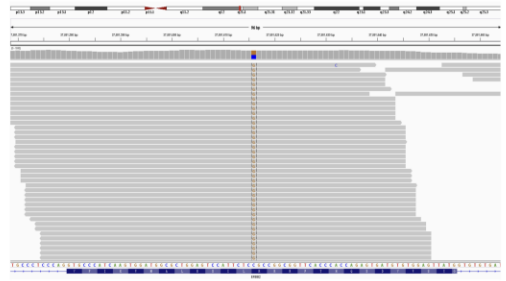
4%

Detection: NGS; rt-PCR

A775_G776insYVMA (34%)
G776delinsVC (5.7%)
G778_P780insGSP (3.4%)







Modified from Ferrari G et al. Cancers 2024

Importance of reporting HER2 alterations in NSCLC

Specimens collection

Whether the patient is medically fit for invasive tissue sampling and whether adequate tissue are available?

Yes

No

Tissue specimens

Plasma ctDNA

IHC

FISH

NGS/PCR

IHC 0

IHC 1+

IHC 2+

IHC 3+

HER2-negative

HER2 overexpression

HER2 amplification

HER2 mutation

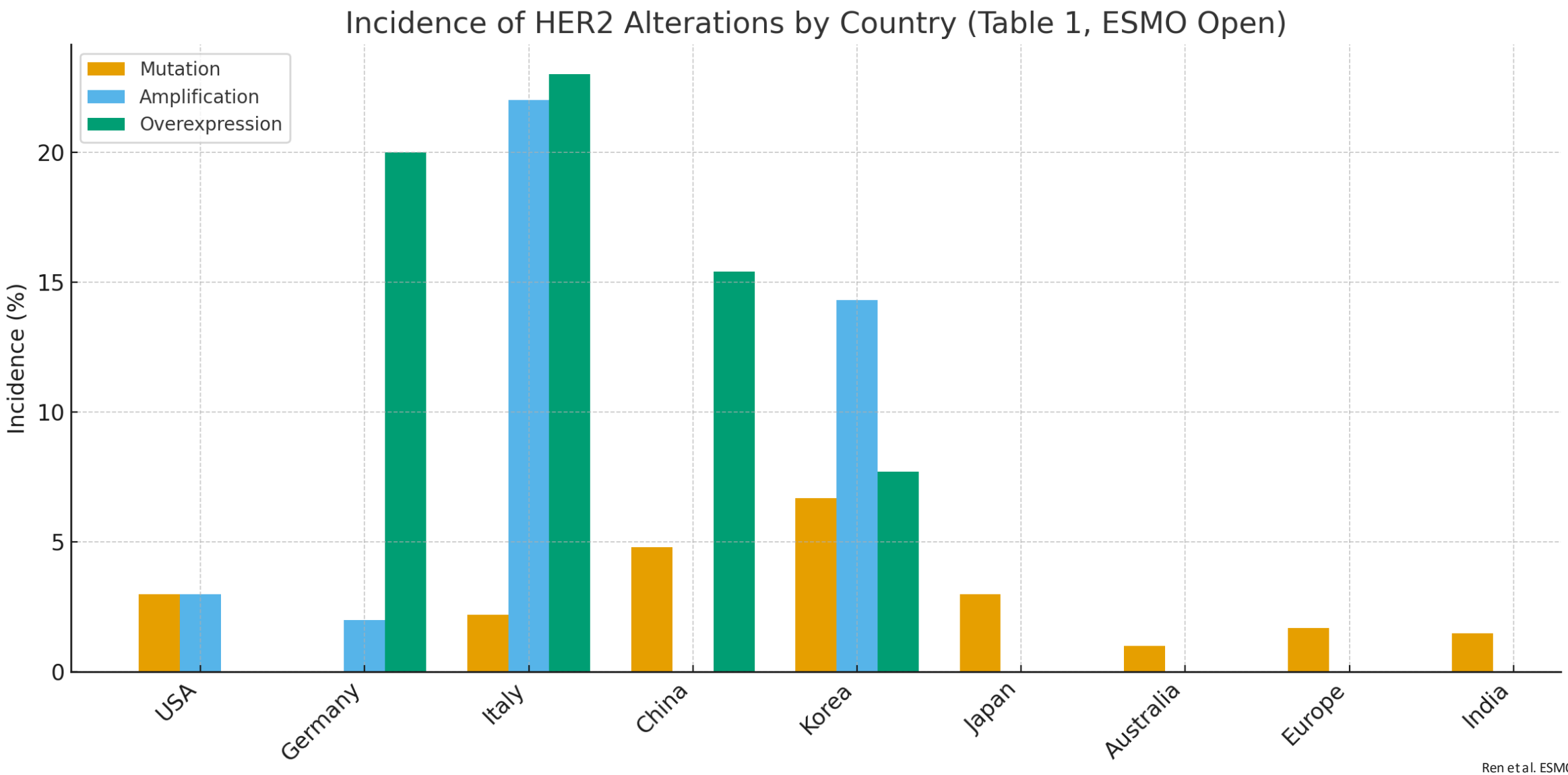
HER2 alterations testing results reported

Test repeated when any one of following is presented:
(i) results are inconclusive
(ii) initial sample quality is low
(iii) plasma testing is negative
(iv) close to a cut-off limit
(v) a novel mutation is found

Caution: Germline HER2 mutations have been found in families with aggregation for lung cancer

Ren et al. ESMO Open 2022; Yamamoto et al. JNCI 2013

Limited information about HER2 alterations in NSCLC in Spain

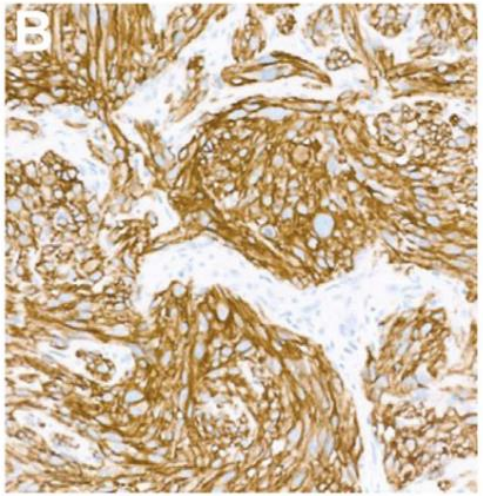


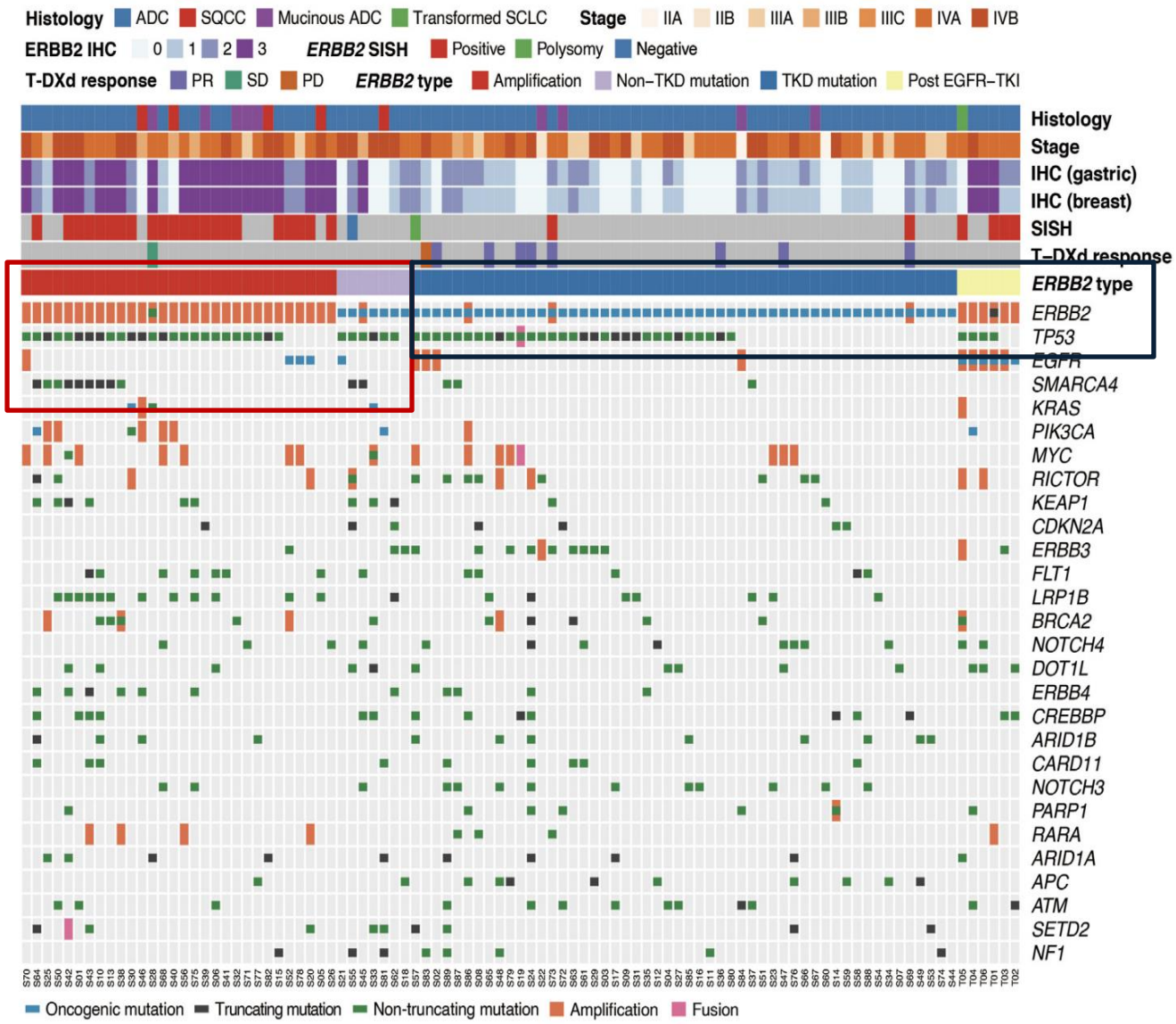
Ren et al. ESMO Open 2022

HER2 alterations are diverse and can coexist in NSCLC

HER2 amplified tumors and non-TKD mutations are enriched for other driver alterations (EGFR, KRAS, SMARCA4)

More common in smokers and can be found in lung SCC
More likely to have HER2 overexpression





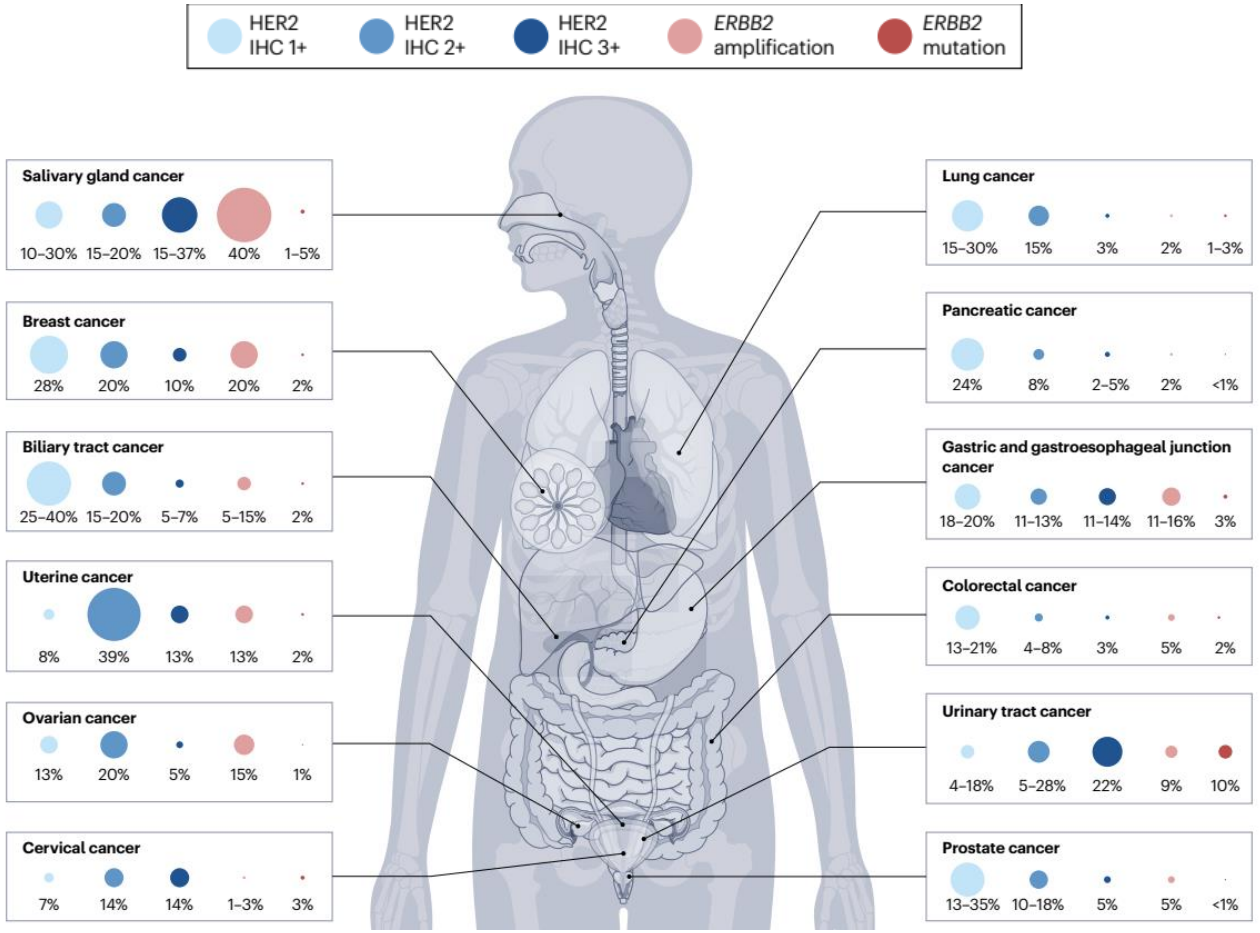
HER2 TKD mutations
Mutually exclusive with other oncogenic drivers

More likely in women, nonsmokers and lung AD

Less likely to have HER2 overexpression

Lee et al. Mod Pathol 2024

HER2 is an emerging tumor agnostic target in solid tumors



Drug/medicine	Target	Tumor-agnostic indication (all in r/r solid tumors)	Biomarker testing
Larotrectinib	TRK	NTRK gene fusion (first indication)	Tissue/NGS
Entrectinib	TRK	NTRK gene fusion (first indication)	Tissue/NGS
Pembrolizumab	PD-1	MSI-H or dMMR	Tissue/NGS (MSI-H)
			Tissue/IHC (dMMR)
		TMB-H ≥10 mut/Mb	Tissue/NGS
Dostarlimab	PD-1	dMMR	Tissue/IHC
Dabrafenib and trametinib	BRAF	BRAF V600E mutation	Tissue/NGS
Selpercatinib	RET	RET gene fusion	Tissue/NGS
Trastuzumab deruxtecan	Her2	Her2/neu	Tissue/IHC

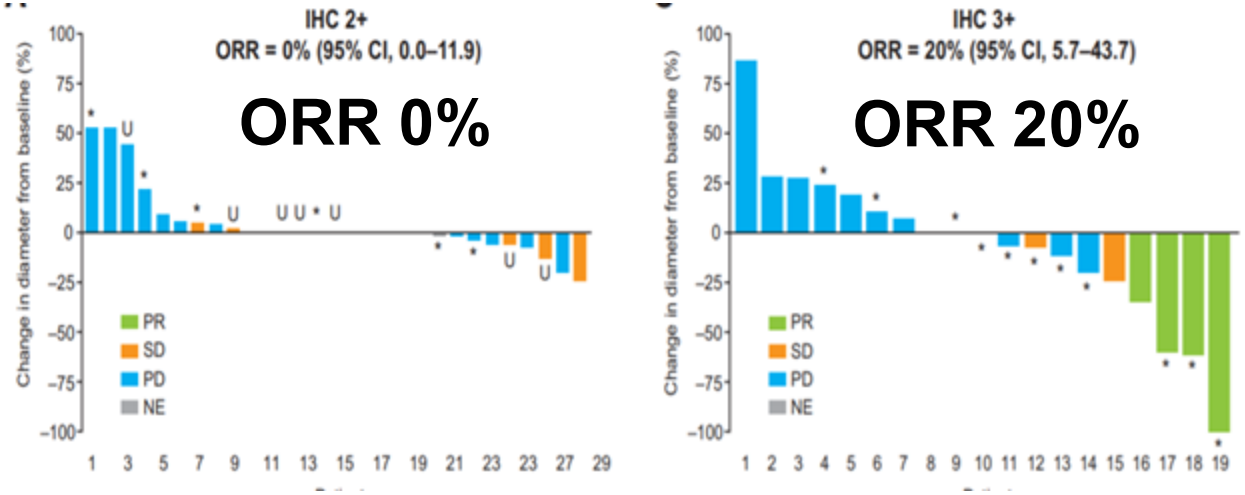
FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive solid tumors

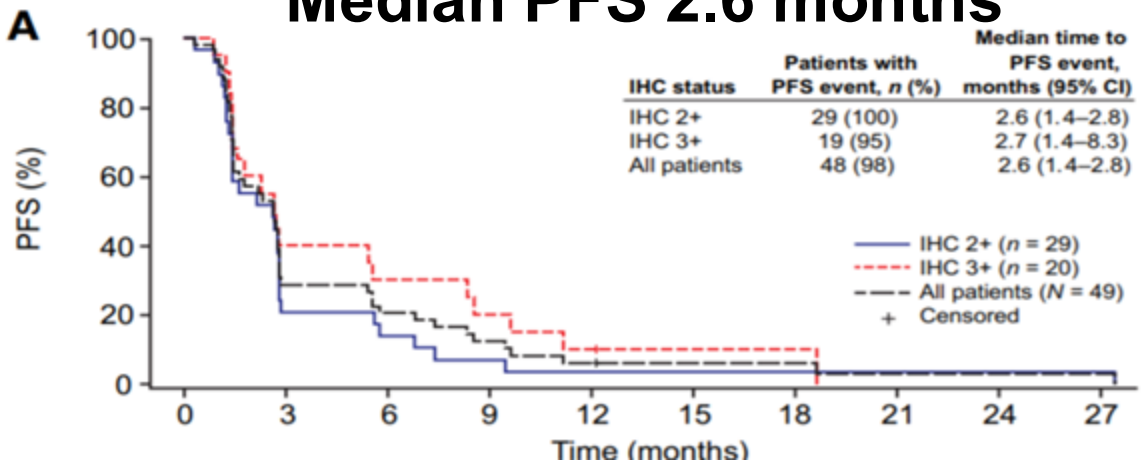
Abril 2024

Yoon, J., Oh, DY. *Nat Rev Clin Oncol* 2024; *Subbiah et al. CA Cancer J Clin. 2024;74:433–45*

Proof of concept of HER2 ADCs (T-DM1 and T-Dxd) in NSCLC with HER2 overexpression

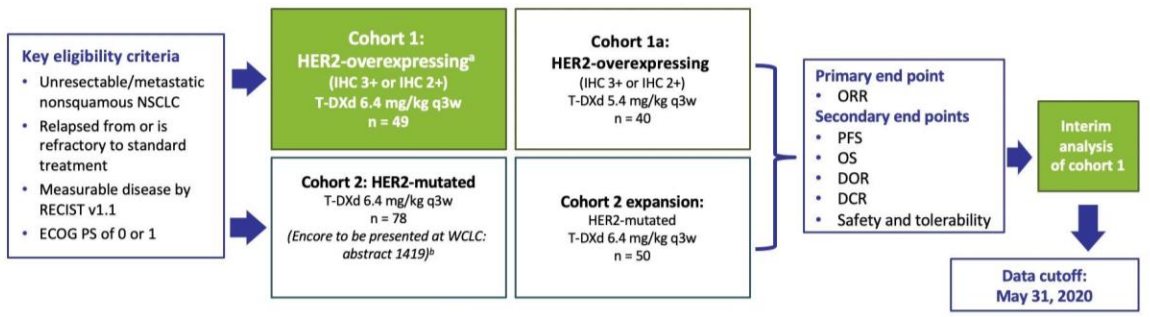
Phase 2 study of T-DM1 (HER2 2+/3+) - N = 49

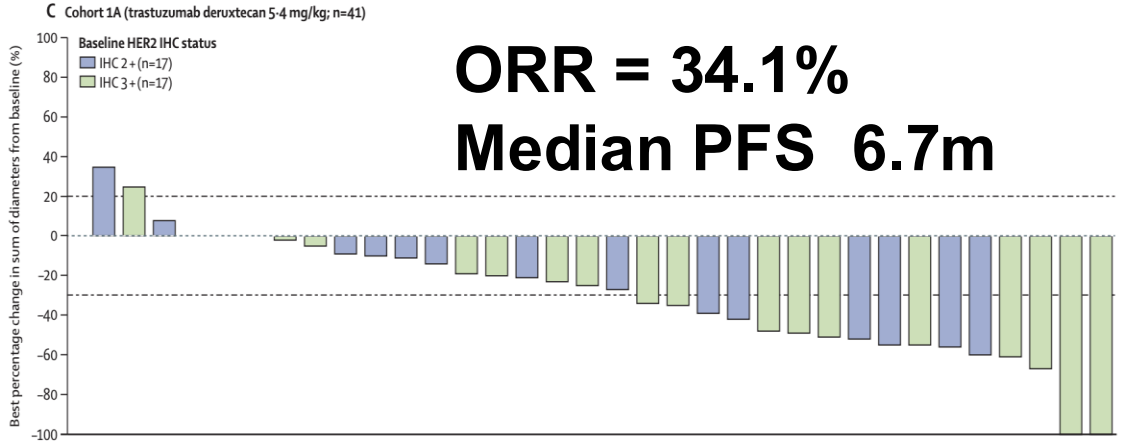




IHC status	Patients with PFS event, *n* (%)	Median time to PFS event, months (95% CI)
IHC 2+	29 (100)	2.6 (1.4–2.8)
IHC 3+	19 (95)	2.7 (1.4–8.3)
All patients	48 (98)	2.6 (1.4–2.8)

DESTINY-Lung 01 - Cohort 1 T-Dxd (HER2 2+/3+) - N = 49





ORR = 34.1%
Median PFS 6.7m

Peters S, et al. Clin Cancer Res 2019;25:64–72; Smit et al. Lancet Oncol 2024;

What is the efficacy of T-DXd in NSCLC overexpressing HER2?

DESTINY-Lung 03 - Part 1 (HER2 2+/3+) - N= 36

Patient population

- Aged ≥18 years
- Centrally assessed HER2-OE (IHC 3+/2+)* unresectable, locally advanced or metastatic nonsquamous NSCLC
- Measurable disease per RECIST v1.1
- WHO/ECOG performance status 0–1
- Patients in Part 1 had one or two prior lines of therapy; those with therapy-targetable alterations must have had prior appropriate targeted therapy

Part 1: dose escalation† (enrollment complete)

Arm 1A: T-DXd + durvalumab + cisplatin
Arm 1B: T-DXd + durvalumab + carboplatin

Part 1: T-DXd monotherapy (enrollment complete)

Arm 1D: T-DXd 5.4 mg/kg IV Q3W (N=36)

Part 3: dose confirmation and expansion (currently recruiting)

T-DXd + volrustomig ± carboplatin

Part 4: safety run-in and expansion (currently recruiting)

T-DXd + rilvegostomig ± carboplatin

Key endpoints: T-DXd monotherapy (arm 1D)

Secondary:

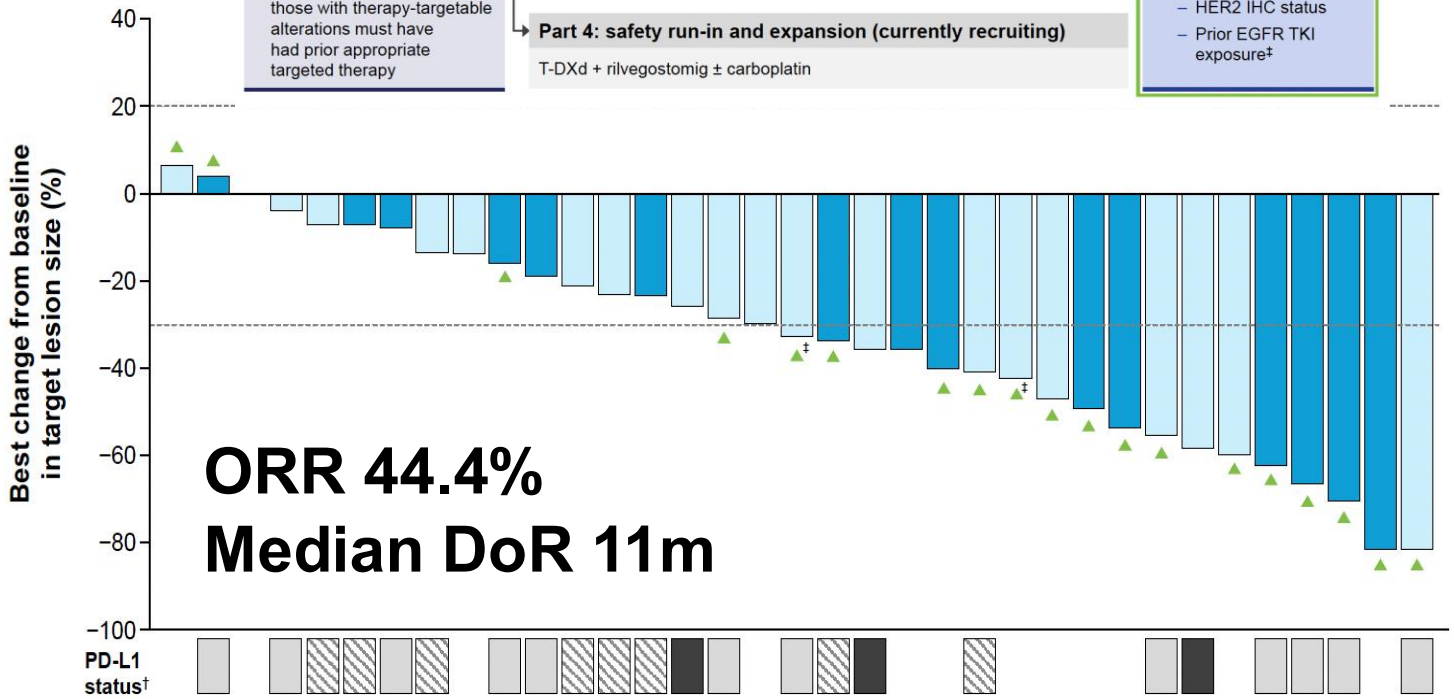
- ORR
- DOR
- DCR
- PFS

(Investigator assessed)

- OS
- Safety and tolerability

Exploratory:

- Efficacy outcomes by:
  - HER2 IHC status
  - Prior EGFR TKI exposure‡



Smit et al. Lancet Oncol 2024; 25: 439–54 ; Planchard et al. WCLC 2024

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- DOR
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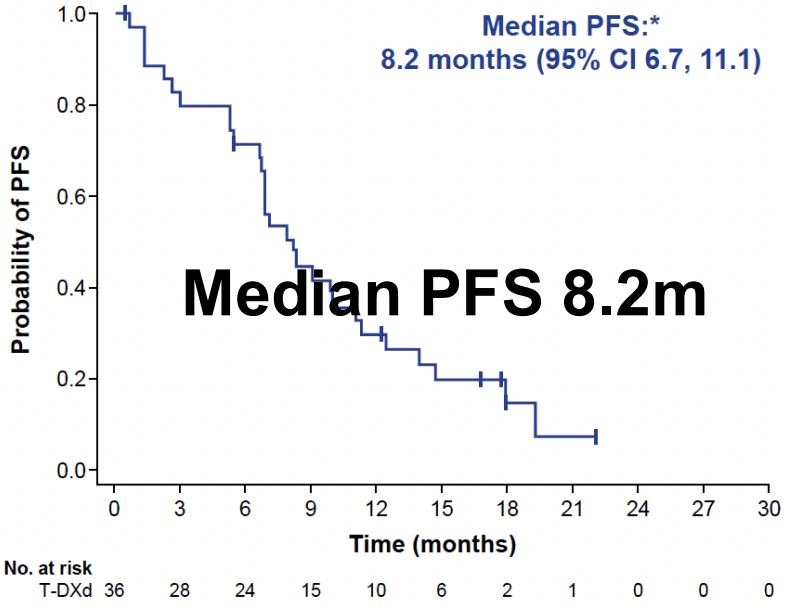
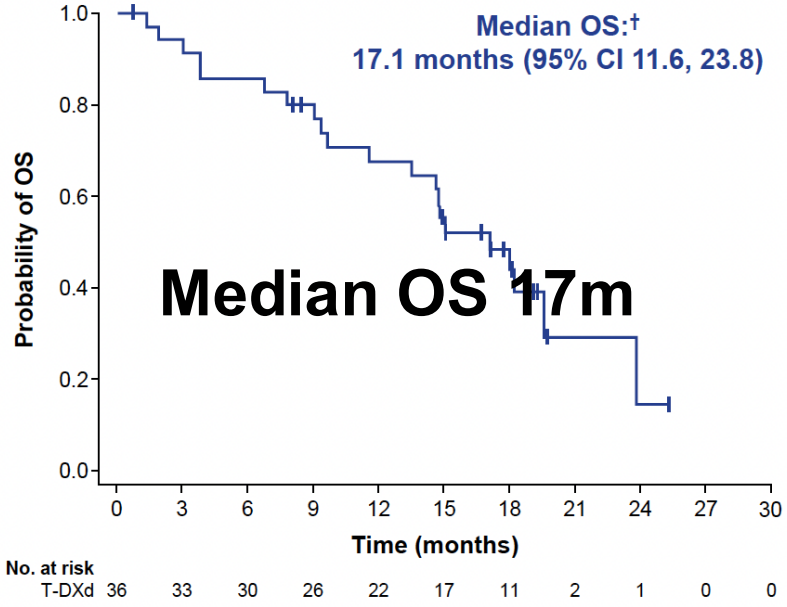
(Investigator assessed)
- OS
- Safety and tolerability

Exploratory:
- Efficacy outcomes by:
  - HER2 IHC status
  - Prior EGFR TKI exposure‡

Part 1: T-DXd monotherapy (arm 1D)	HER2 IHC 3+ (n=16)	HER2 IHC 2+ (n=20)
Confirmed ORR, % (n)*† 95% CI	56.3 (9) 29.9, 80.3	35.0 (7) 15.4, 59.2
DCR at 12 weeks, % (95% CI)*‡	81.3 (54.4, 96.0)	75.0 (50.9, 91.3)
Median DOR, months (95% CI)*§	12.5 (5.5, NE)	6.6 (4.5, 11.0)
Median PFS, months (95% CI)*¶	6.9 (5.3, 17.9)	8.2 (5.4, 10.0)
Median OS, months (95% CI)‖	16.4 (6.8, NE)	17.1 (9.4, 23.8)





Smit et al. Lancet Oncol 2024; 25: 439–54 ; Planchard et al. WCLC 2024

NCCN guidelines recommend to test for HER2 in NSCLC (SCC and non SCC)

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2026
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

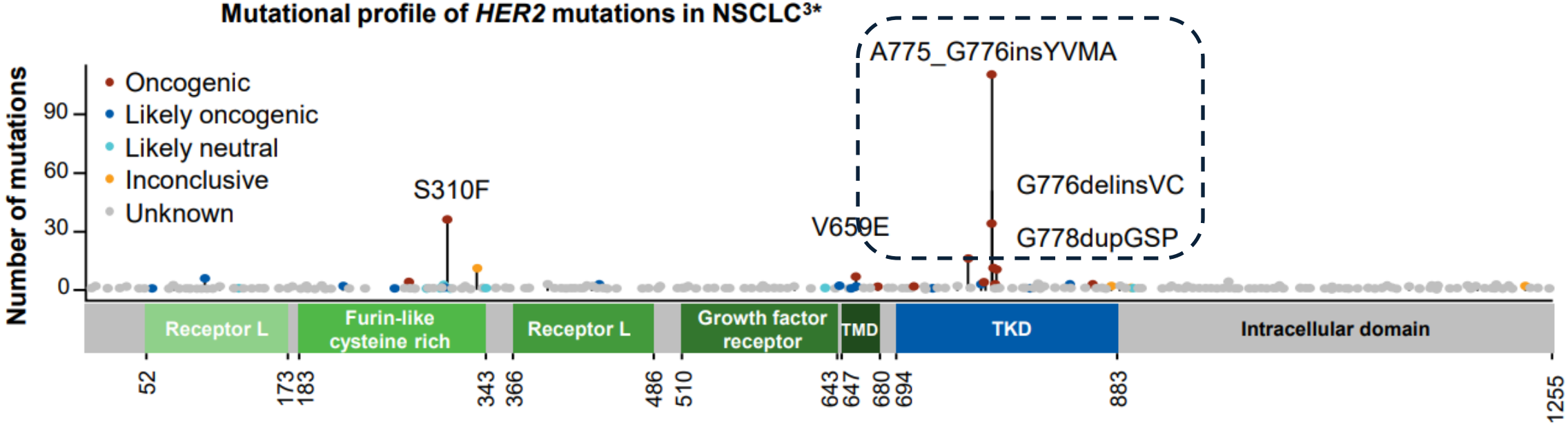
PRINCIPLES OF SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – SUBSEQUENT

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–2)	SQUAMOUS CELL CARCINOMA (PS 0–2)
Preferred (no previous IO) Systemic ICIs • Nivolumab (category 1) • Pembrolizumab[k] (category 1) • Atezolizumab (category 1) Preferred (*EGFR* mutations[l]) • Datopotamab deruxtecan-dlnk Other Recommended (*EGFR* exon 19 deletion or L858R mutation) • Lazertinib + Amivantamab-vmjw[m,n] Other Recommended (no previous immuno-oncology [IO] or previous IO)[n] • Docetaxel • Pemetrexed • Gemcitabine • Docetaxel + Ramucirumab • Albumin-bound Paclitaxel • Fam-trastuzumab deruxtecan-nxki (HER2 IHC 3+) FDA APPROVED • Telisotuzumab vedotin-tllv (HGFR [*MET*] ≥50% IHC 3+ and *EGFR* wild-type)	Preferred (no previous IO) Systemic ICIs • Nivolumab (category 1) • Pembrolizumab[k] (category 1) • Atezolizumab (category 1) Other Recommended (no previous IO or previous IO)[n] • Docetaxel • Gemcitabine • Docetaxel + Ramucirumab • Albumin-bound Paclitaxel • Fam-trastuzumab deruxtecan-nxki (HER2 IHC 3+) FDA APPROVED

ERBB2 (HER2) mutations in NSCLC

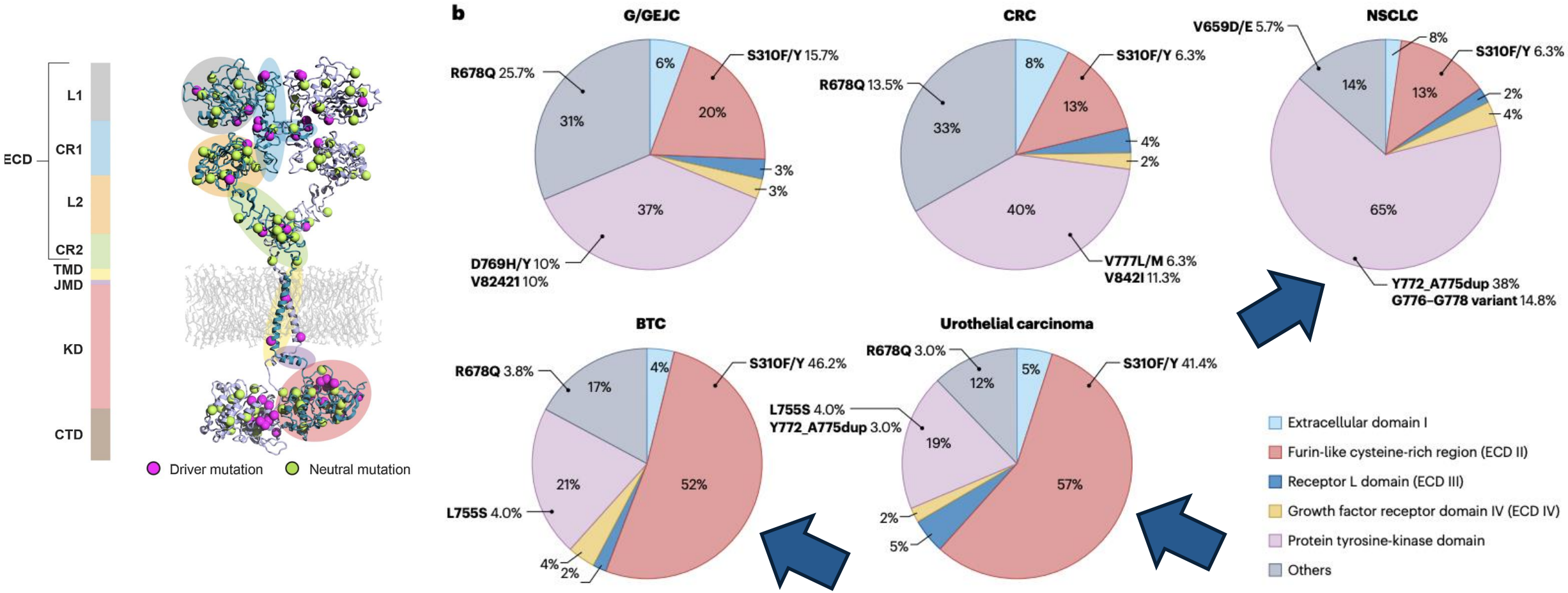
- ~2–4% of NSCLC harbor *HER2* (ErbB2) mutations leading to constitutive activation of downstream signaling pathways and oncogenesis[1]
- Associated with a poor prognosis and higher incidence of brain metastases[1]
- The most common activating mutations in NSCLC are tyrosine kinase domain (TKD) mutations, particularly exon 20 insertions,[1,2] although non-TKD mutations also occur

Mutational profile of *HER2* mutations in NSCLC[3]*



1. Nützinger J et al. Lung Cancer. 2023;186:107385; 2. Robichaux JP et al. Cancer Cell. 2019;36:444–57; 3. Le X et al. ESMO. 2024. Poster 1298

HER2 mutations patterns are different across distinct solid tumors



Yoon, J., Oh, DY. *Nat Rev Clin Oncol* **21**, 675–700 (2024).

Landscape of treatments investigated in advanced HER2 mutated NSCLC

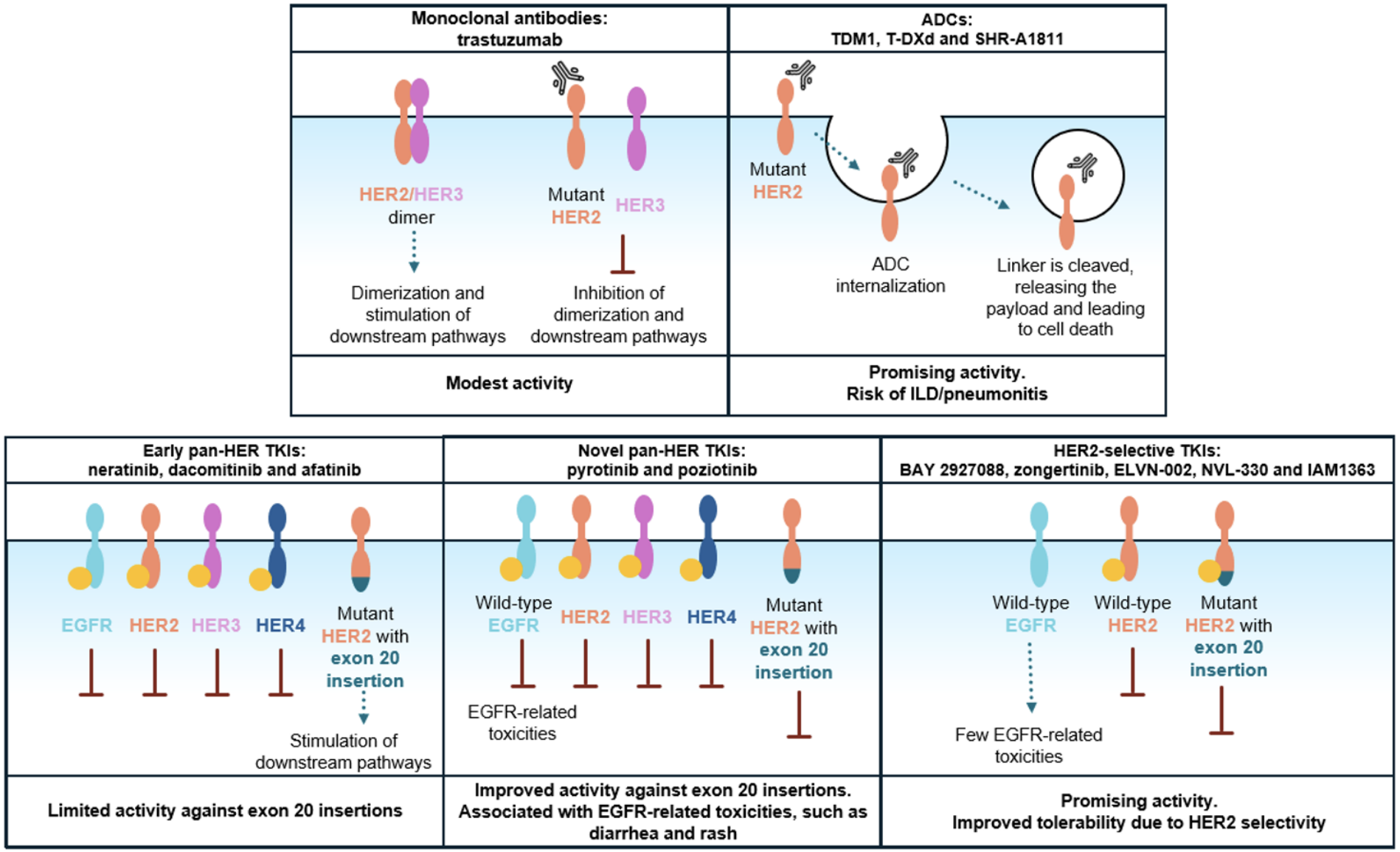
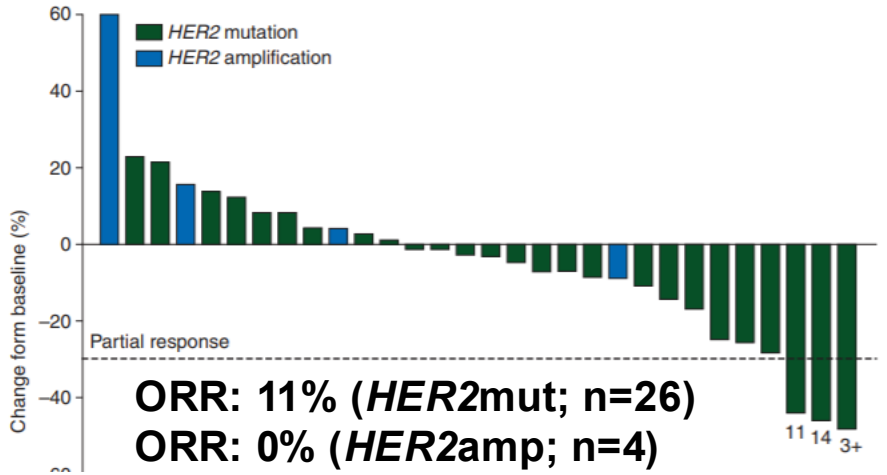


Figure from a manuscript in preparation

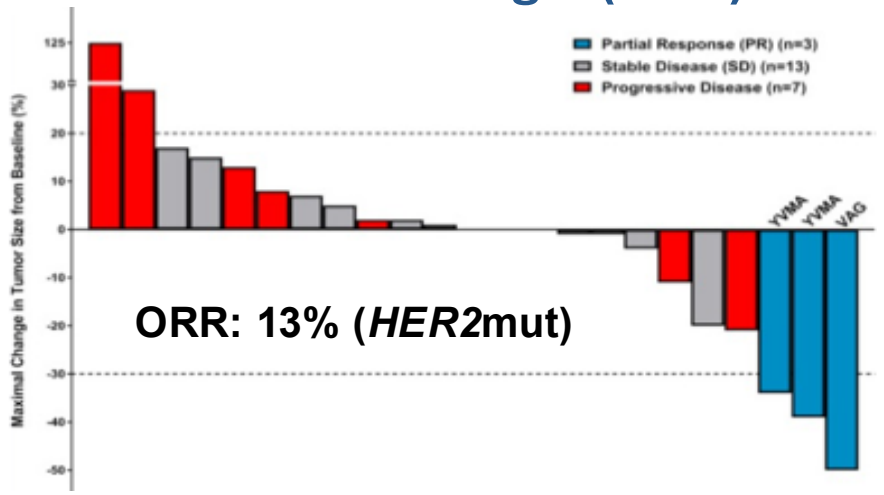
Limited efficacy of pan-HER TKIs with significant skin & GI toxicities

Dacomitinib 45mg/d (n=30)



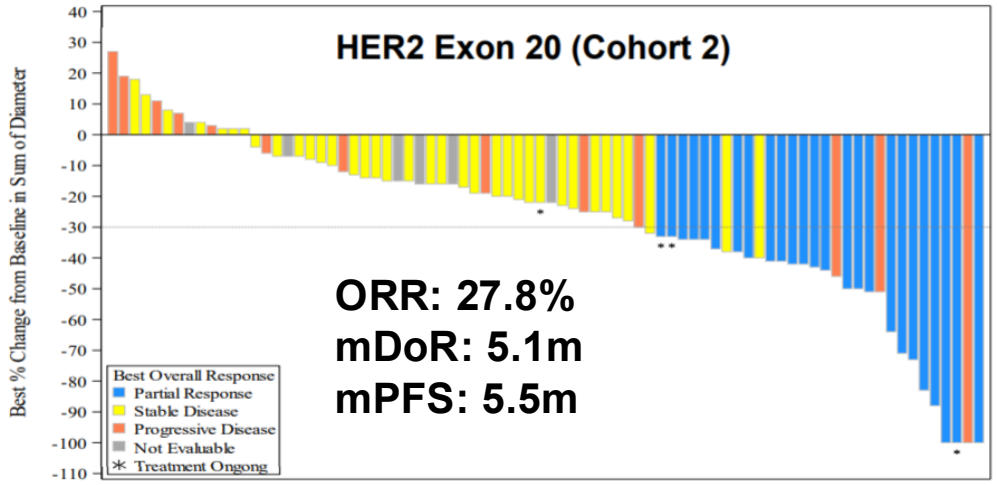
ORR: 11% (*HER2*mut; n=26)
ORR: 0% (*HER2*amp; n=4)

Afatinib 40mg/d (n=23)



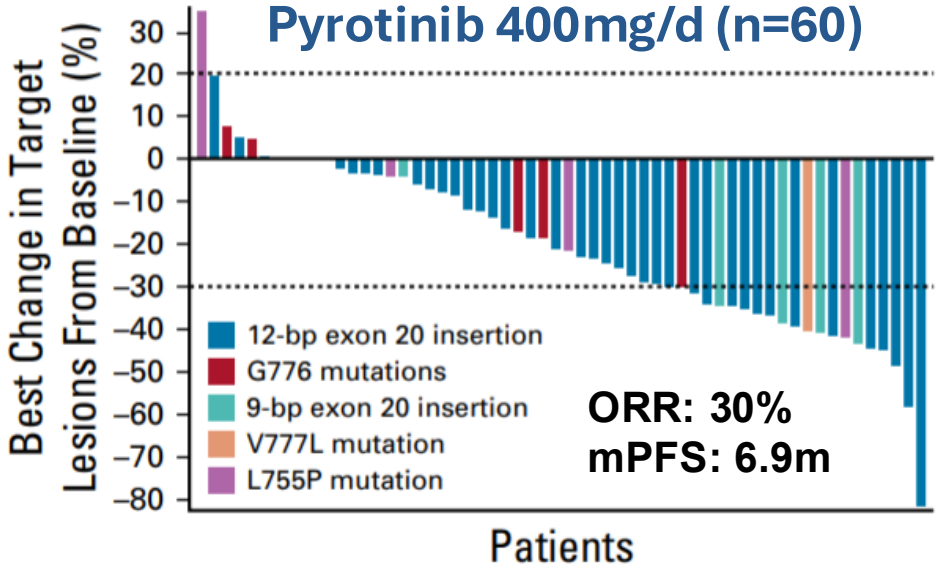
ORR: 13% (*HER2*mut)

ZENITH20: Poziotinib 16mg/d (n=90)



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

Pyrotinib 400mg/d (n=60)

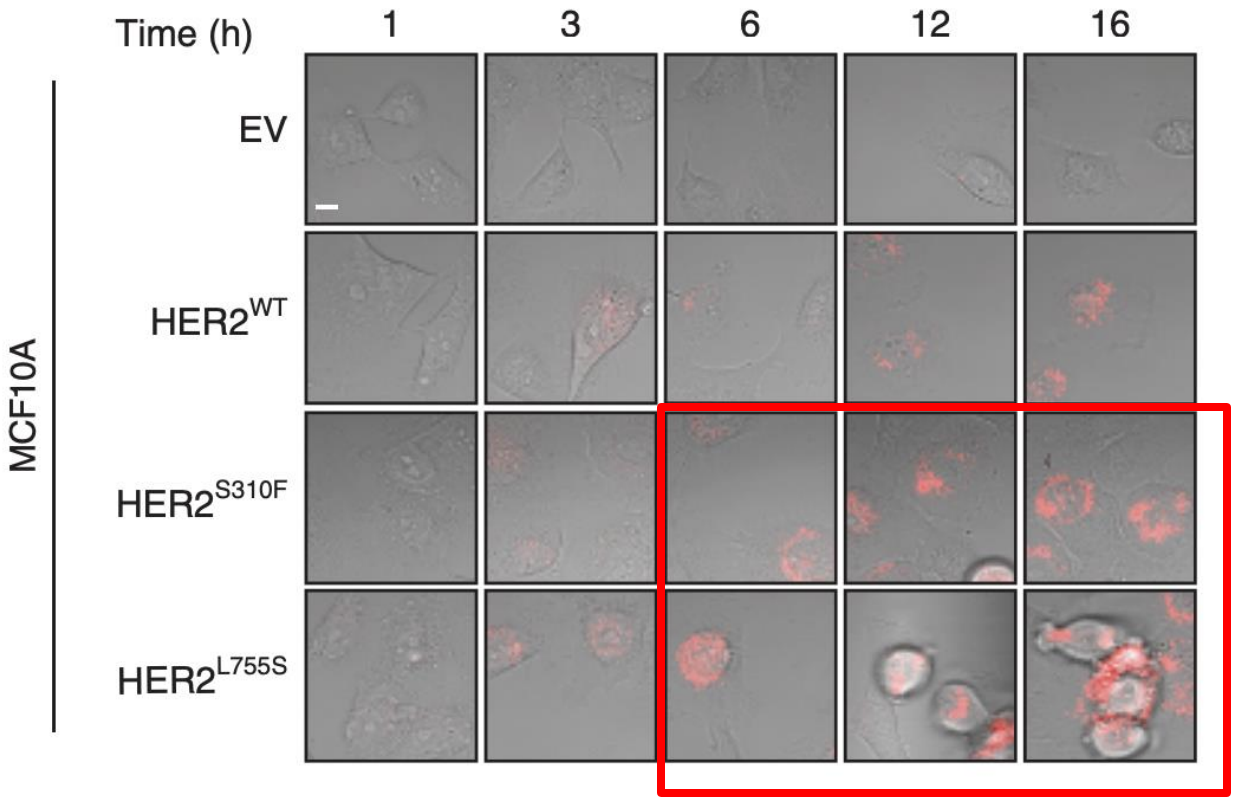


ORR: 30%
mPFS: 6.9m

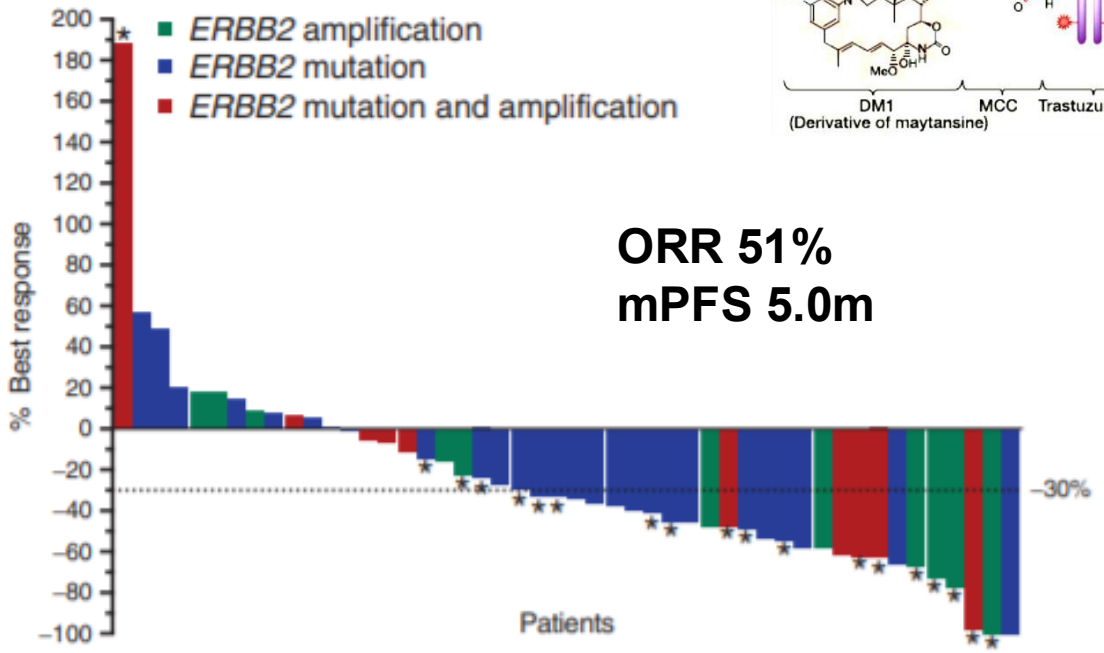
Kris MG, et al. Ann Oncol 2015;26:1421–7; Lai WV, et al. Eur J Cancer 2019;109:28–35; Socinski MA, et al. Presented at: IASLC WCLC 2020; Zhou C, et al. J Clin Oncol 2020;38:2753–61

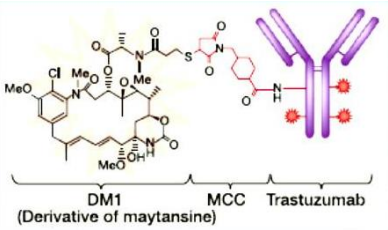
ERBB2 mutations increase the HER2 internalization which partly explains efficacy of ADCs targeting HER2 like T-DM1

HER2 internalization in MCF10 cells



Trastuzumab Emtansine (T-DM1; n=49)





ORR 51%
mPFS 5.0m

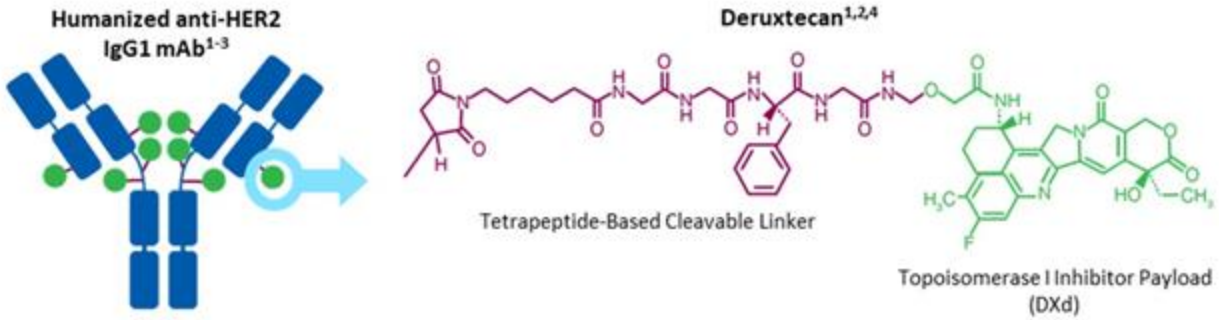
Li BT, et al. Cancer Discov 2020;10:674-87

Overview of Key HER2-Directed Therapies in NSCLC

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

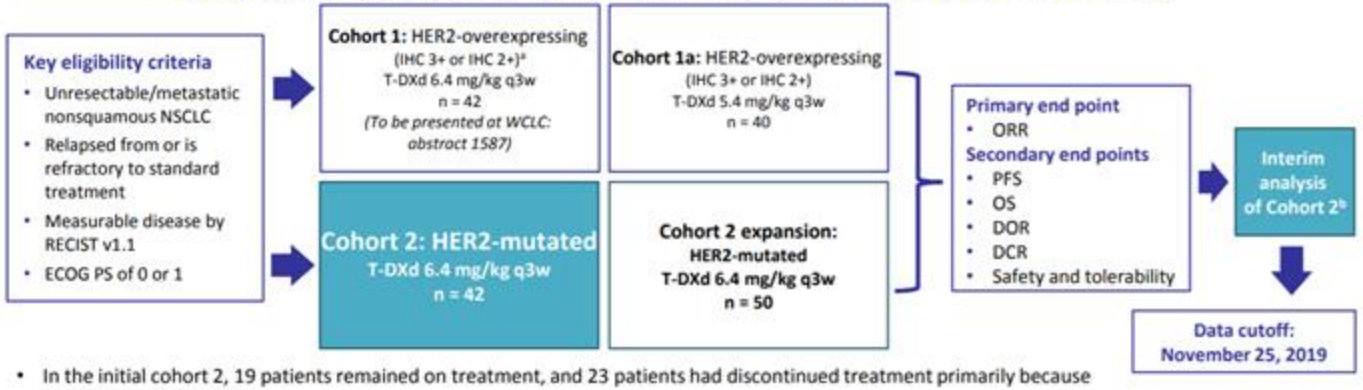
HER2-Directed TKIs		
TKI	**Status**	**Pivotal Trial(s)**
Zongertinib	FDA Approved	Beamion LUNG-1
	NSCLC indication: • *Previously treated unresectable or metastatic NSCLC with activating HER2 mutations.*	
Sevabertinib (BAY 2927088)	Investigational May 2025 – FDA granted priority review	SOHO-01
NVL-330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

HER2 ADCs: Trastuzumab-deruxtecan (T-Dxd) became the first treatment approved in HER2 mutated NSCLC



Destiny-Lung01

Phase 2 study of trastuzumab deruxtecan (T-DXd), a novel antibody-drug conjugate, in patients with HER2-overexpressing or HER2-mutated metastatic NSCLC (NCT03505710)

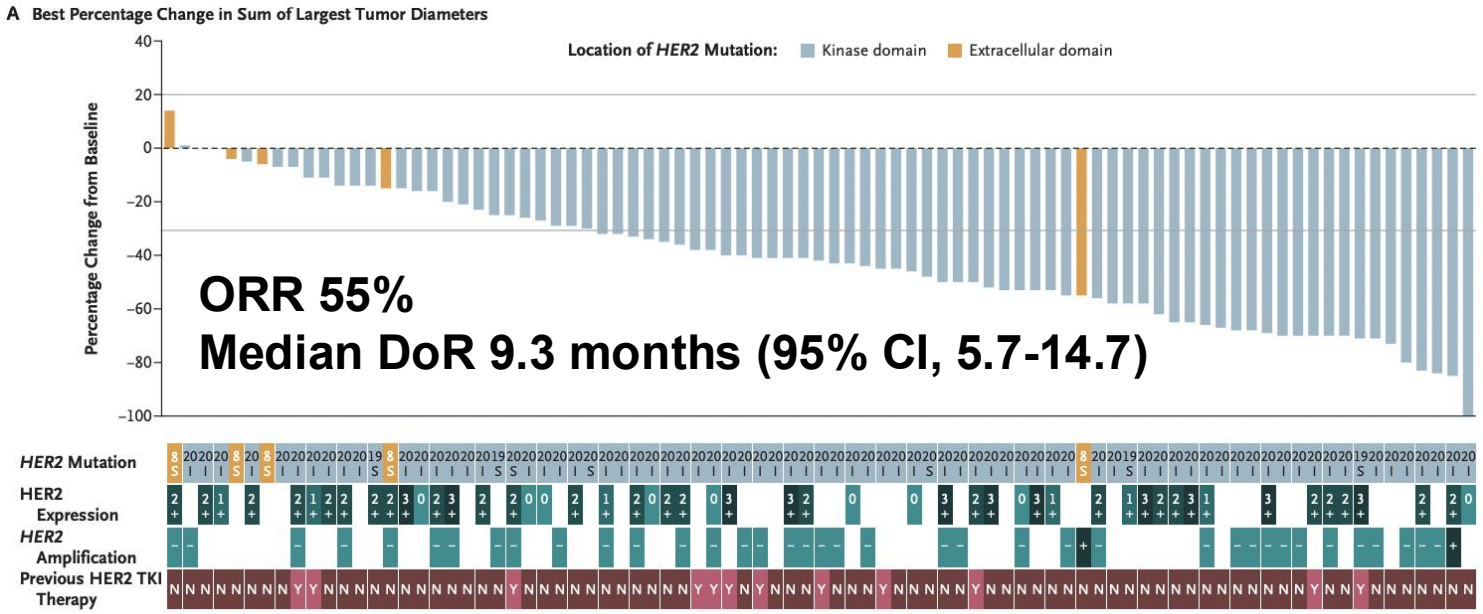


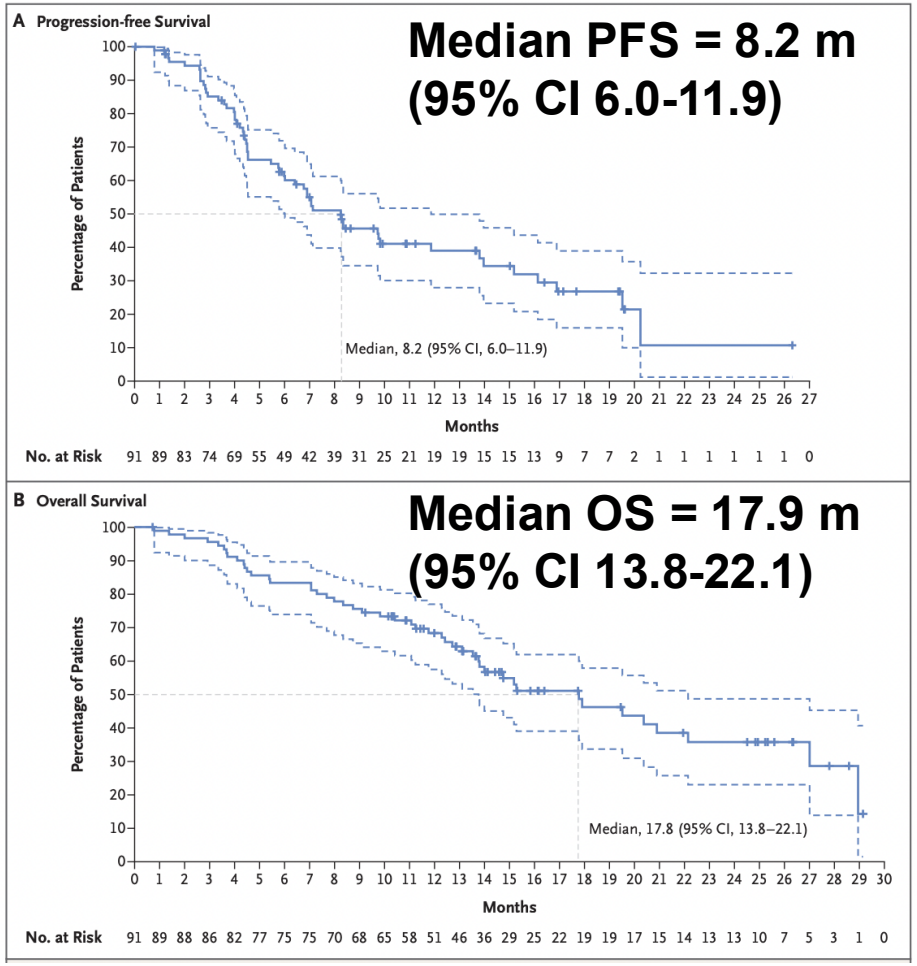
- In the initial cohort 2, 19 patients remained on treatment, and 23 patients had discontinued treatment primarily because of PD or AEs (n = 9 each)[c]

Characteristic	Patients (N = 91)
Median age (range) — yr	60 (29–88)
Female sex — no. (%)	60 (66)
Race — no. (%)†	
Asian	31 (34)
White	40 (44)
Black	1 (1)
Other	19 (21)
Geographic region — no. (%)	
Asia	23 (25)
North America	35 (38)
Europe	33 (36)
ECOG performance-status score — no. (%)‡	
0	23 (25)
1	68 (75)
Location of *HER2* mutations — no. (%)	
Kinase domain	85 (93)
Extracellular domain	6 (7)
Previous cancer therapy — no. (%)	90 (99)§
No. of lines of previous cancer therapy — median (range)	2 (0–7)
Previous cancer therapy — no. (%)	
Platinum-based therapy	86 (95)
Docetaxel	18 (20)
Anti–PD-1 or anti–PD-L1 treatment	60 (66)
HER2 TKI	13 (14)

Li BT, et al. N Engl J Med 2022; DOI: 10.1056/NEJMoa2112431

T-Dxd demostrated clinically relevant efficacy in this clinical setting, regardless of the type of mutation, Her2 expression / amplification





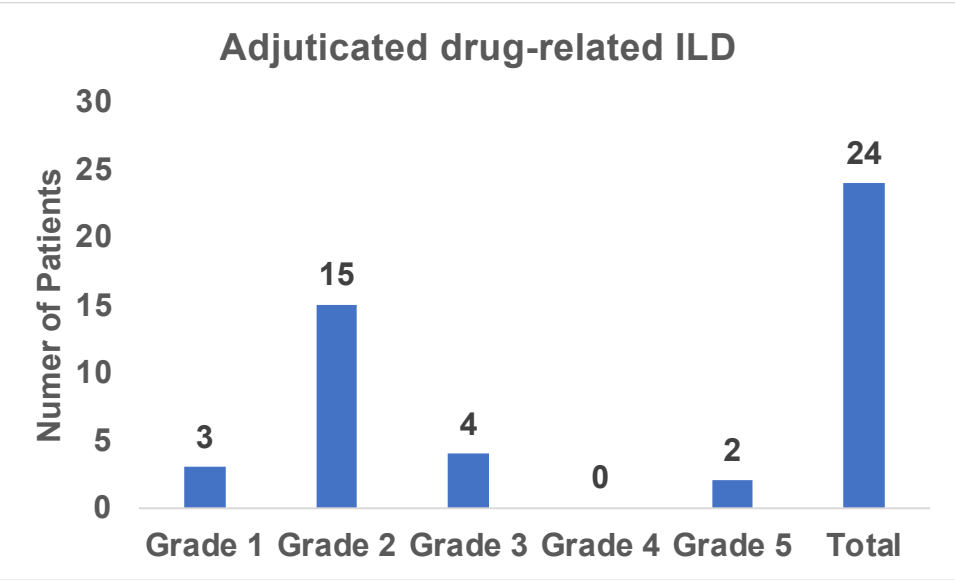
Li BT, et al. N Engl J Med 2022; DOI: 10.1056/NEJMoa2112431

The rate of G3-4 treatment-related AEs was 45% with 26% of drug-related lung toxicity (any grade)

Table 3. Most Common Investigator-Reported Drug-Related Adverse Events in the Study Population (91 Patients).

Event	Grade 1–2	Grade 3	Grade 4	Grade 5	Overall
			number of patients (percent)		
Drug-related adverse event	46 (51)	37 (41)	4 (4)	1 (1)*	88 (97)
Drug-related adverse events with ≥20% incidence					
Nausea	58 (64)	8 (9)	0	0	66 (73)
Fatigue†	42 (46)	6 (7)	0	0	48 (53)
Alopecia	42 (46)	0	0	0	42 (46)
Vomiting	33 (36)	3 (3)	0	0	36 (40)
Neutropenia‡	15 (16)	14 (15)	3 (3)	0	32 (35)
Anemia§	21 (23)	9 (10)	0	0	30 (33)
Diarrhea	26 (29)	2 (2)	1 (1)	0	29 (32)
Decreased appetite	27 (30)	0	0	0	27 (30)
Leukopenia¶	17 (19)	4 (4)	0	0	21 (23)
Constipation	20 (22)	0	0	0	20 (22)

* One patient had grade 5 (i.e., fatal) pneumonitis that was assessed as drug-related by the investigator (subsequently adjudicated as interstitial lung disease). Another patient had grade 3 interstitial lung disease, as reported by the investigator, and died; the reported interstitial lung disease was subsequently adjudicated as grade 5 by the interstitial lung disease adjudication committee. All adjudicated events of drug-related interstitial lung disease are reported in Table S5.



Of the 24 patients with adjudicated drug-related ILD, 21 received at least one dose of glucocorticoids.

Li BT, et al. N Engl J Med 2022; DOI: 10.1056/NEJMoa2112431

T-Dxd 5.4mg/kg was considered the optimal dose for future studies

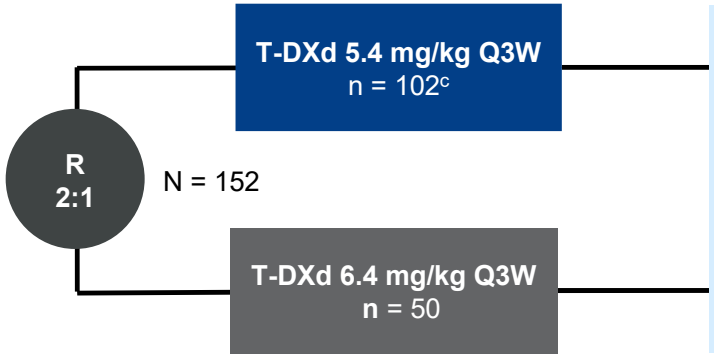
DESTINY-Lung02

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

Study Design



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

The study was not powered to statistically compare the 5.4 mg/kg and 6.4 mg/kg doses of T-DXd

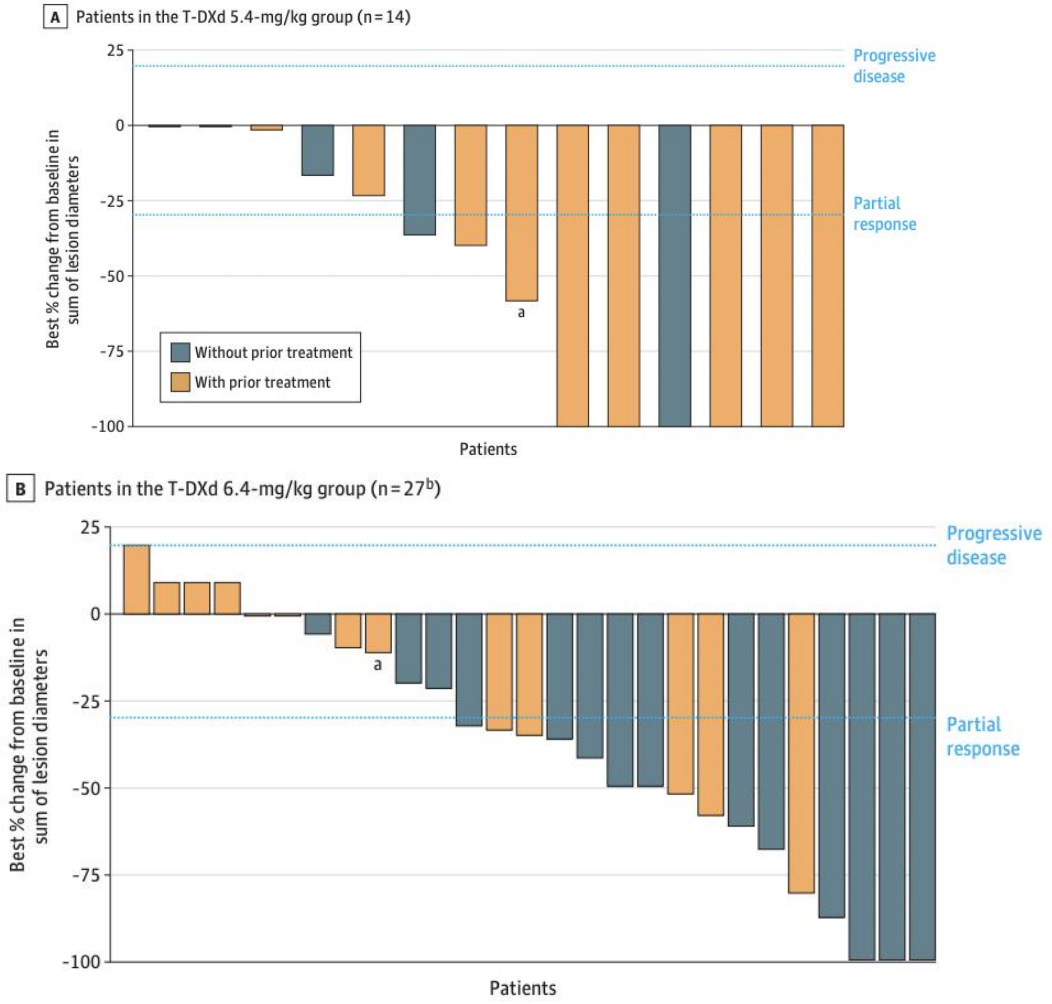
	T-Dxd 5.4mg/kg	T-Dxd 6.4mg/kg
ORR (%)	49% (95% CI 39-59)	56% (95% CI 41-70)
Median PFS	9.9m	15.4m
1y PFS rate (%)	45%	53%
G3-4 TRAEs (%)	39%	58%
Dose reduction/discont'	17% / 14%	32% / 20%
ILD (%)	13%	28%

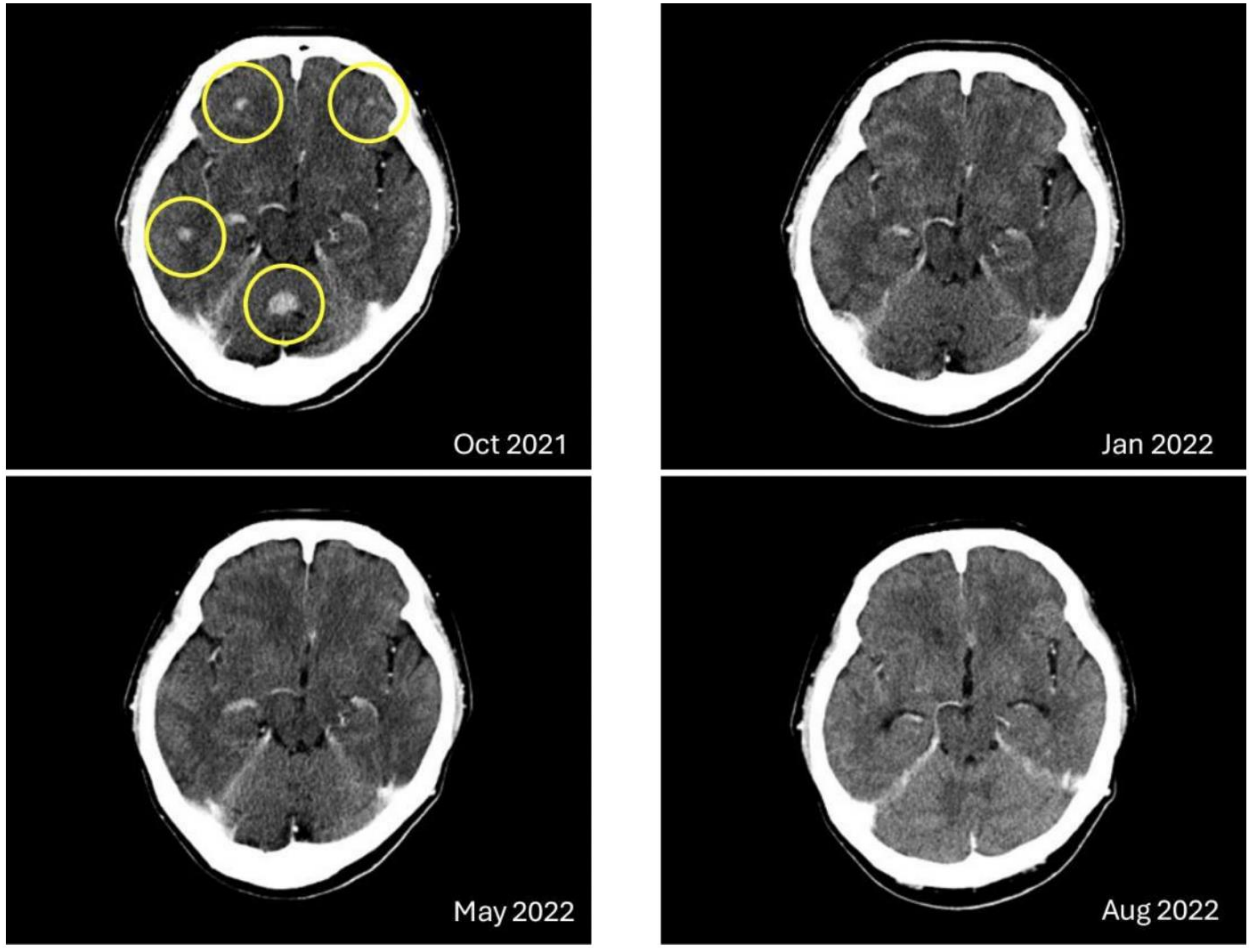
Goto K et al. *J Clin Oncol*. 2023;41:4852-4863 2. Goto K et al. *J Clin Oncol*. 2023;41:4852-4863

Unexpected intracranial efficacy with T-Dxd in HER2 mutated NSCLC

Posthoc analysis from DESTINY-Lung01 + 02

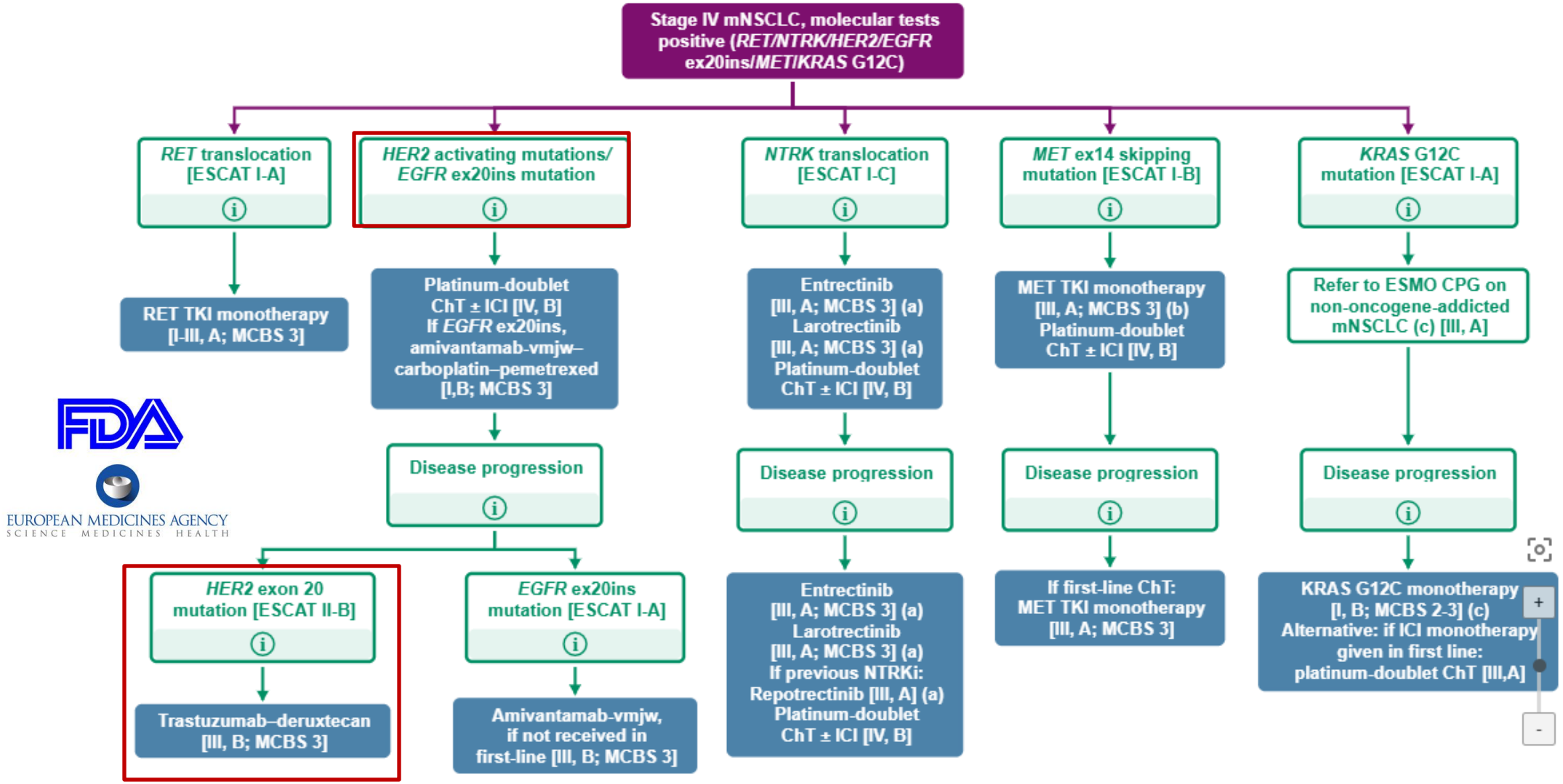
Figure. Best Overall Response in Patients With Measurable Brain Metastases





Jänne et al. JAMA Network Open. 2025;8(11):e2543107

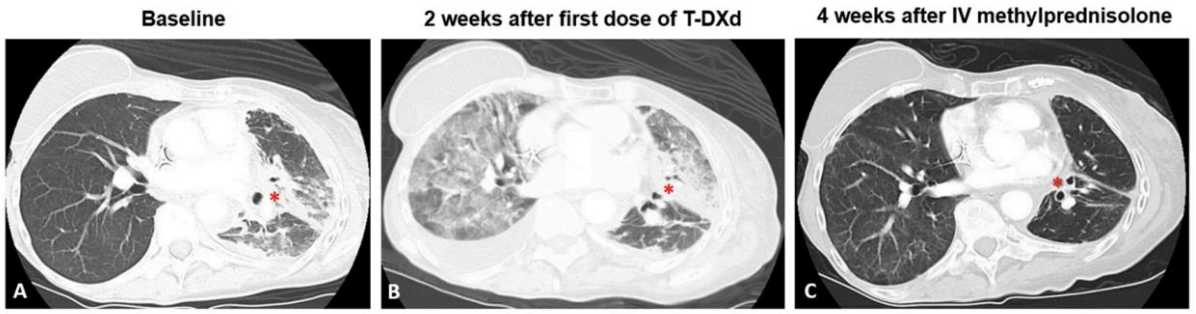
ESMO Guidelines: T-Dxd is considered the standard of care in 2L in HER2 exon 20 mutated NSCLC



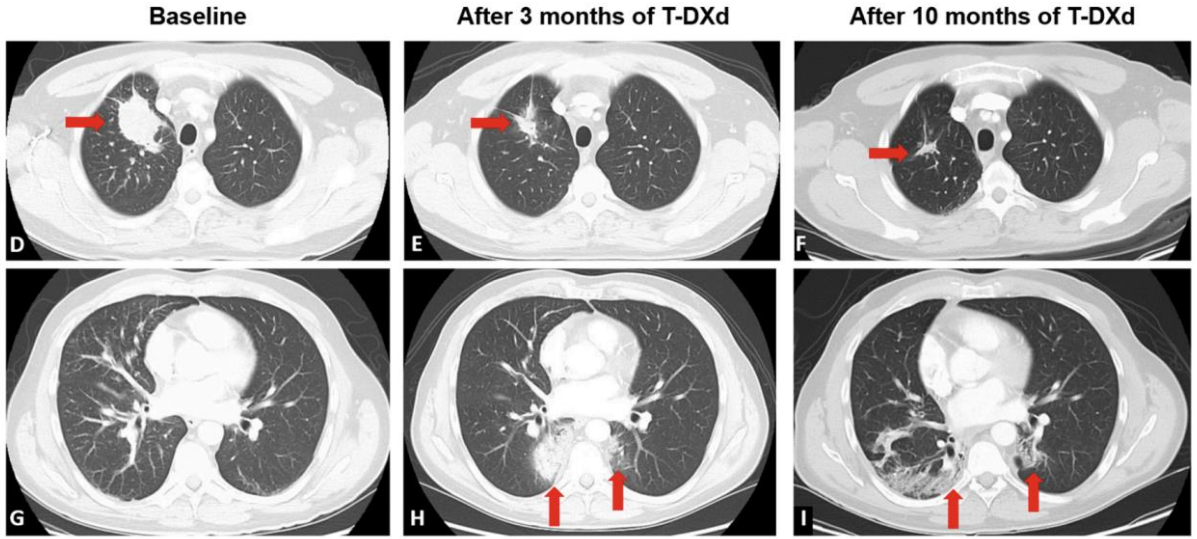
ESMO Living Guidelines. Oncogene-Addicted Metastatic NSCLC (v1.2 2025)

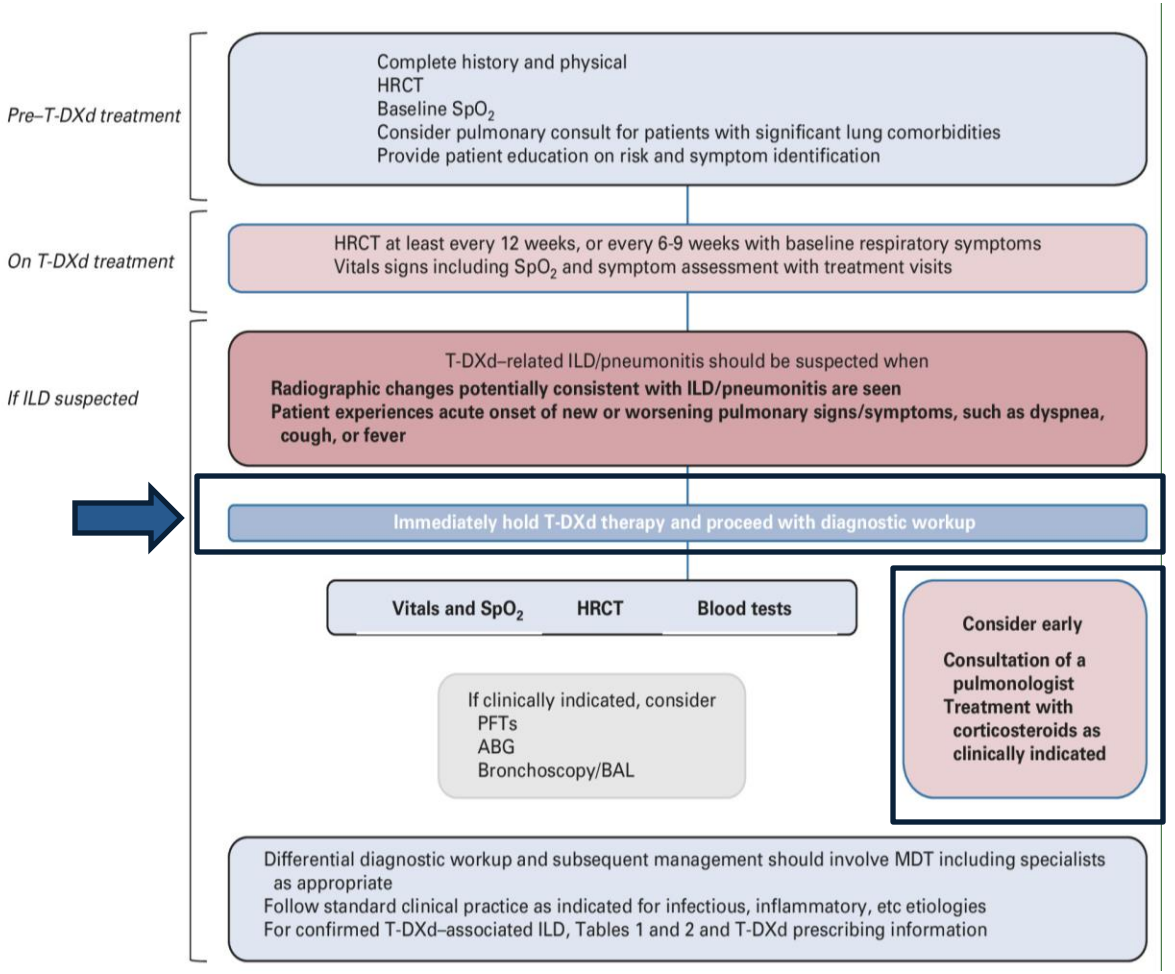
Importance of having a low suspition threshold for lung toxicity

Patient 1



Patient 2

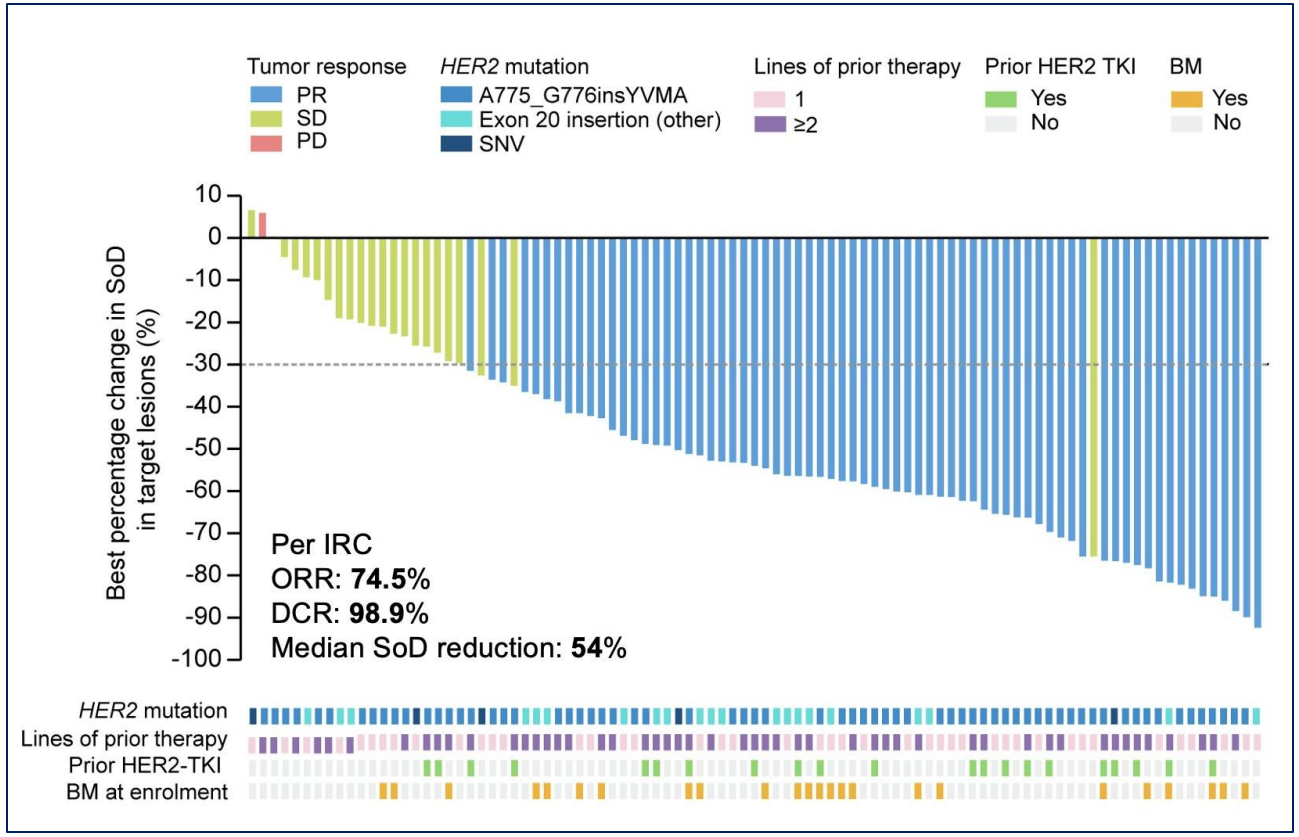


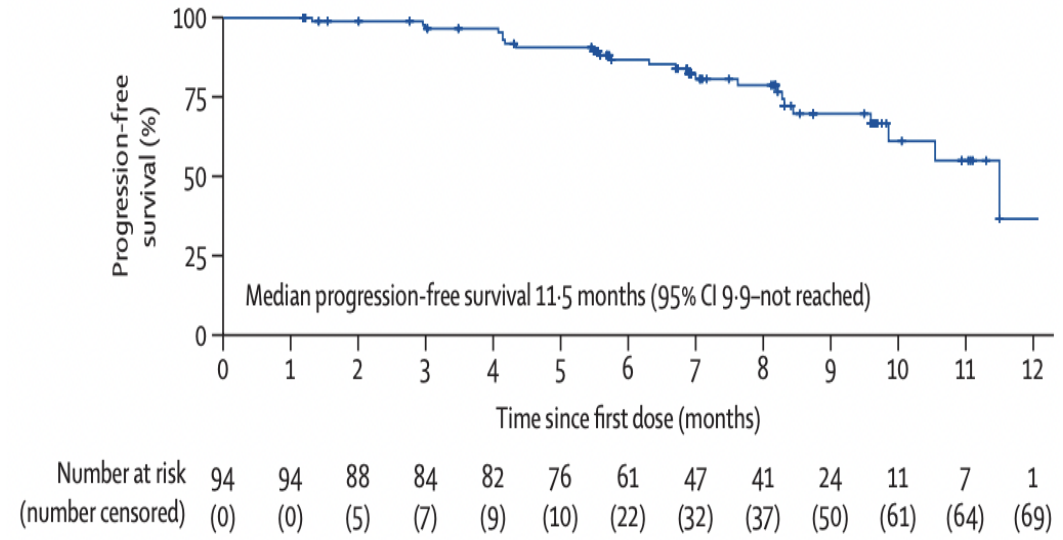


Swain et al. Cancer Treatment Reviwws 2022; Rugo et al. JCO Oncology Practice 2023

Other emerging ADCs targeting Her2: Trastuzumab-Rezetecan (SHR-A1811)

HORIZON-Lung: Phase 2 of T-Rezetecan in Her2 mutated NSCLC



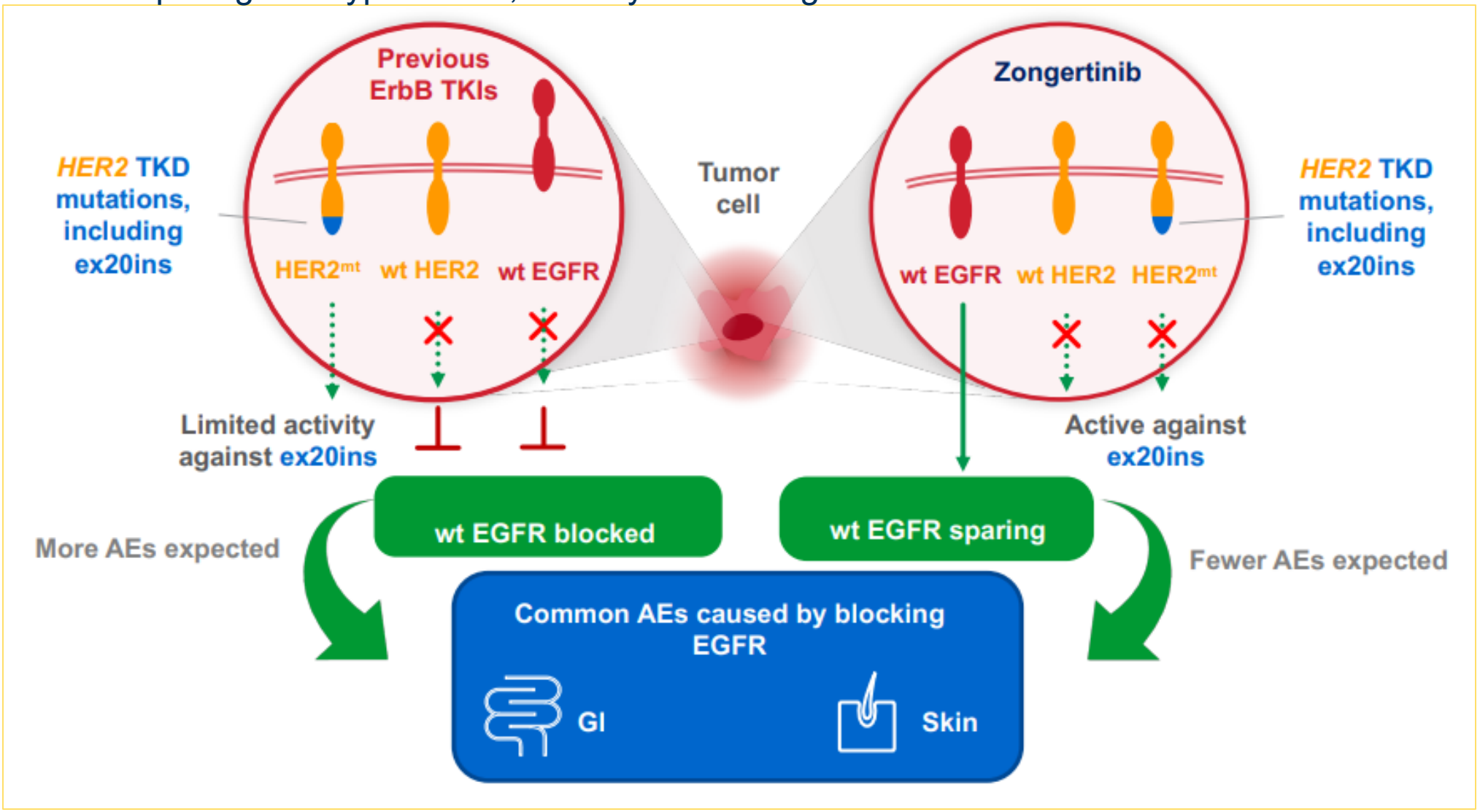


ILD	8 (8.5)
Grade 1-2	7 (7.4)
Grade 3	1 (1.1)

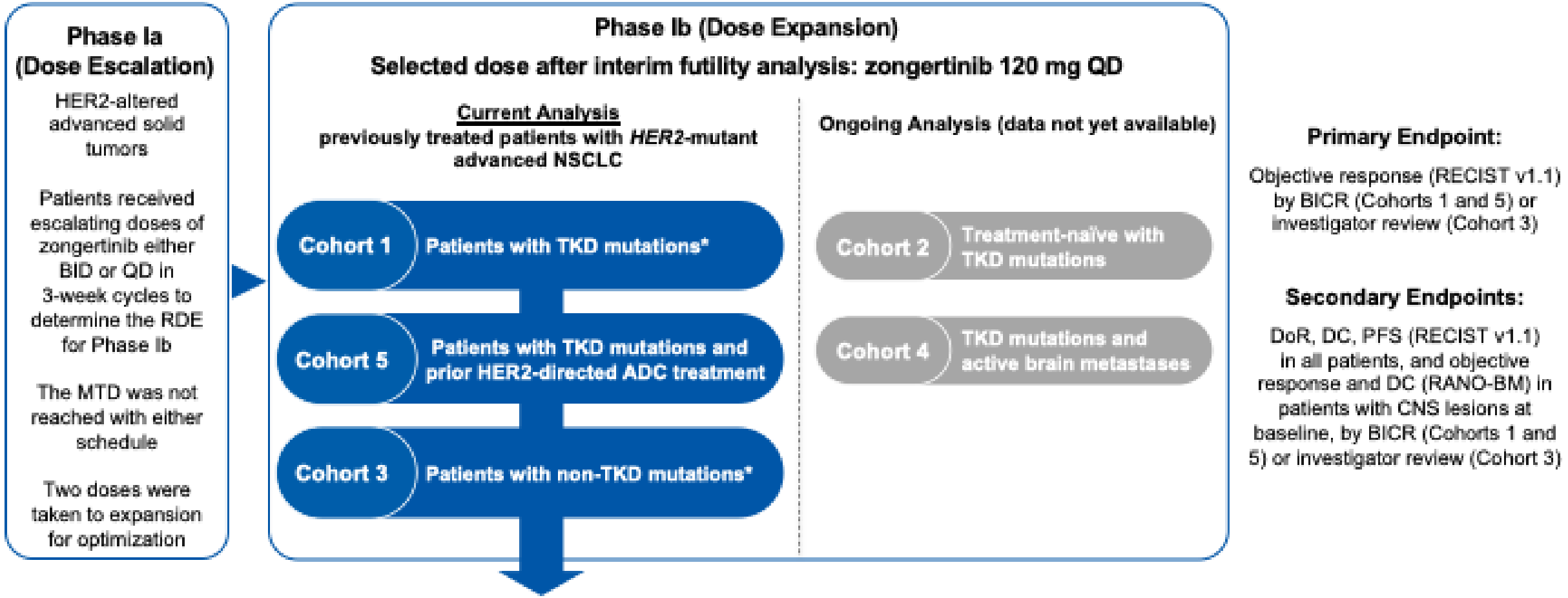
Li et al. Lancet Oncol 2025; 26: 437-46

Selective HER2 TKIs: Zongertinib mechanism of action

Zongertinib is an orally administered, irreversible TKI that selectively inhibits HER2 while sparing wild-type EGFR, thereby minimizing associated toxicities



BEAMION LUNG-1: Phase 1 clinical trial in HER2 mutated advanced NSCLC



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 et al. N Engl J Med 2025; DOI: 10.1056/NEJMoa2503704

BEAMION LUNG-1: Phase 1 clinical trial in HER2 mutated advanced NSCLC

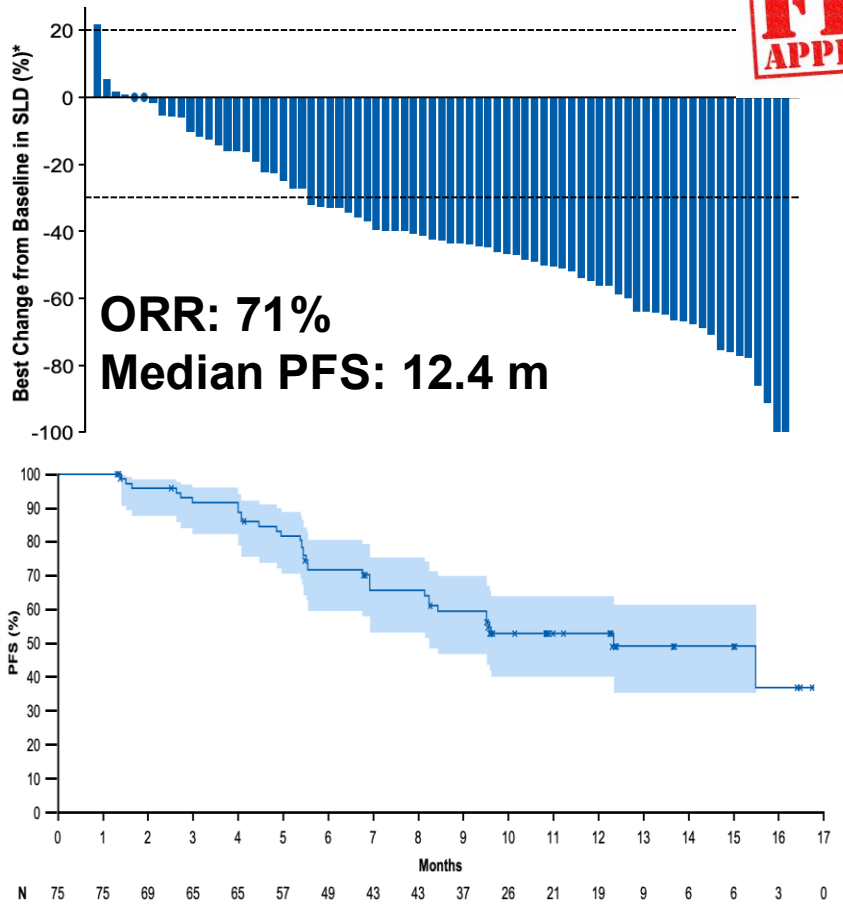
	Cohort 1: Patients with TKD mutations	Cohort 5: Patients with TKD mutations and prior HER2-directed ADC treatment	Cohort 3: Patients with non-TKD mutations
	N = 75	**N = 31**	**N = 20**
Median age, years (range)	62 (30–80)	61 (31–85)	65 (27–77)
Female, n (%)	51 (68)	21 (68)	9 (45)
Race, n (%)*			
Asian	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

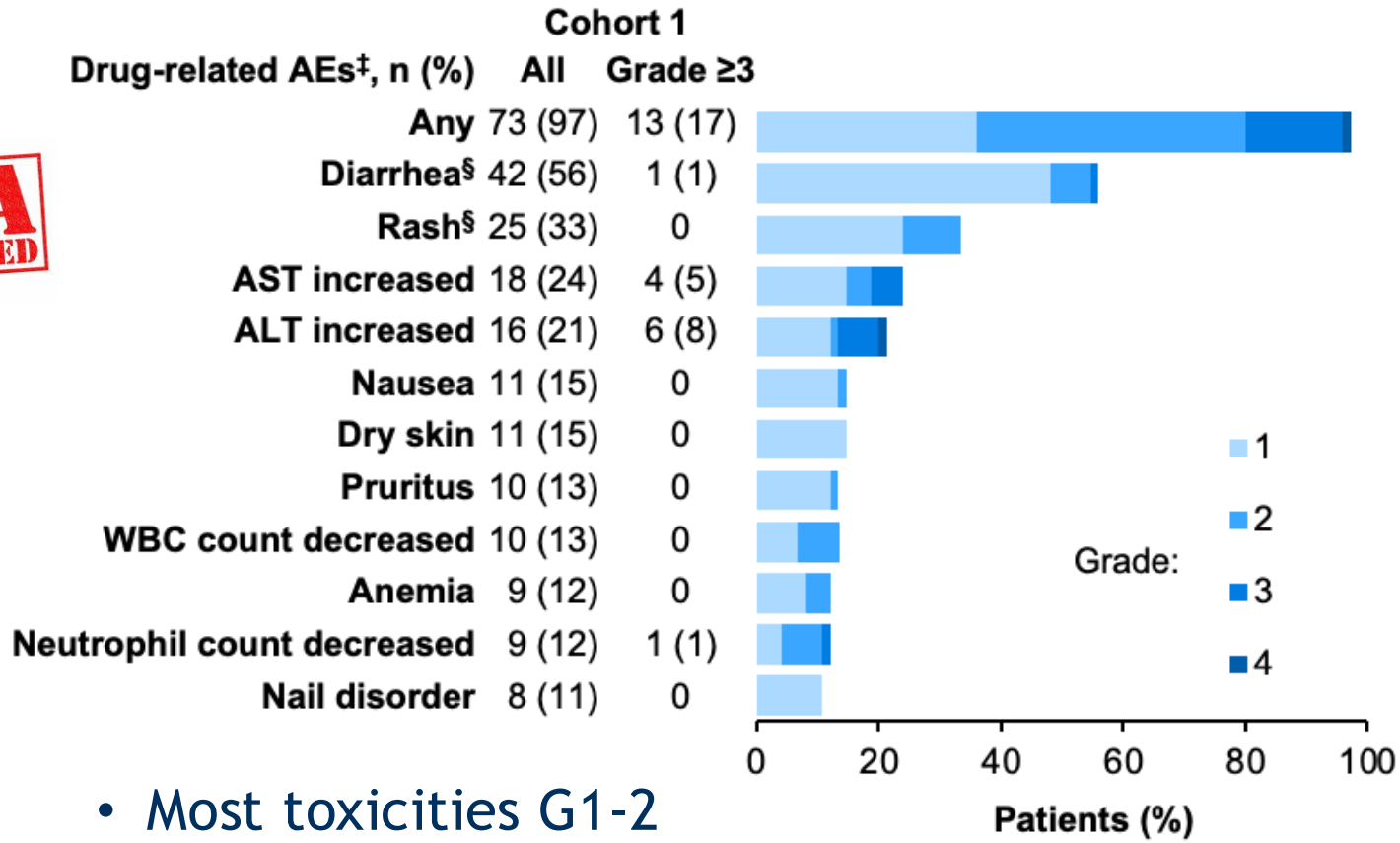
Heymach et al. N Engl J Med 2025; DOI: 10.1056/NEJMoa2503704

BEAMION LUNG-1: Efficacy of Zongertinib in patients with HER2 TKD mutant NSCLC who were previously treated

Cohort 1 Patients with TKD mutations*

FDA APPROVED



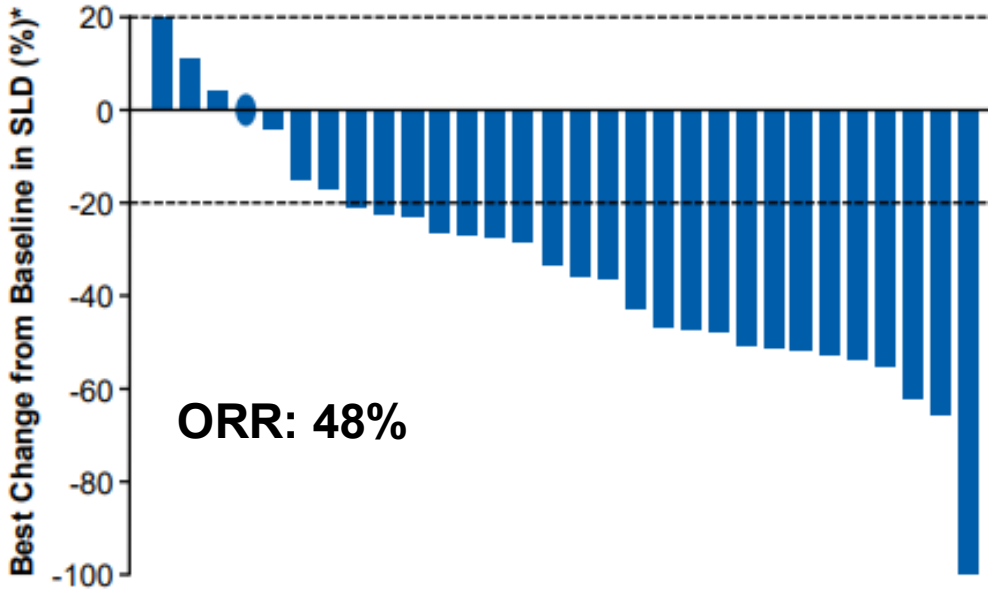


- Most toxicities G1-2
- G3 Diarrhea in only 1 patient
- Dose reduction 7%; discontinuation 3%
- No cases of ILD/pneumonitis

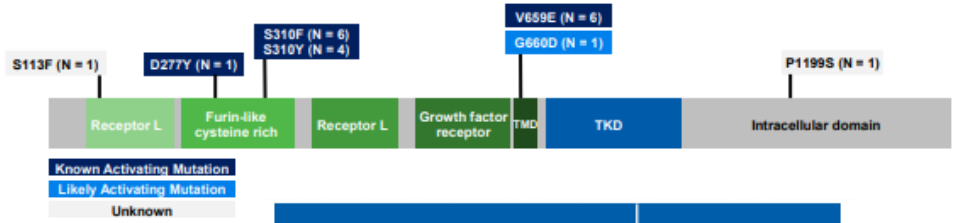
Heymach et al. N Engl J Med 2025; DOI: 10.1056/NEJMoa2503704

BEAMION LUNG-1: Efficacy of Zongertinib in patients HER2 TKD mutations NSCLC who received prior ADCs or with nonTKD mutations

Cohort 5 Patients with TKD mutations and prior HER2-directed ADC treatment



Cohort 3 Patients with non-TKD mutations*



Confirmed response by investigator review according to RECIST v1.1	Patients with non-TKD mutations N = 20
ORR	**30%**
95% CI	15–52
CR, %	0
PR, %	30
DCR	**65%**
95% CI	43–82
SD, %	35
PD, %	30
NE, %	5

Heymach et al. N Engl J Med 2025; DOI: 10.1056/NEJMoa2503704

BEAMION LUNG-1: Intracranial efficacy of Zongertinib (Cohort 4)

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

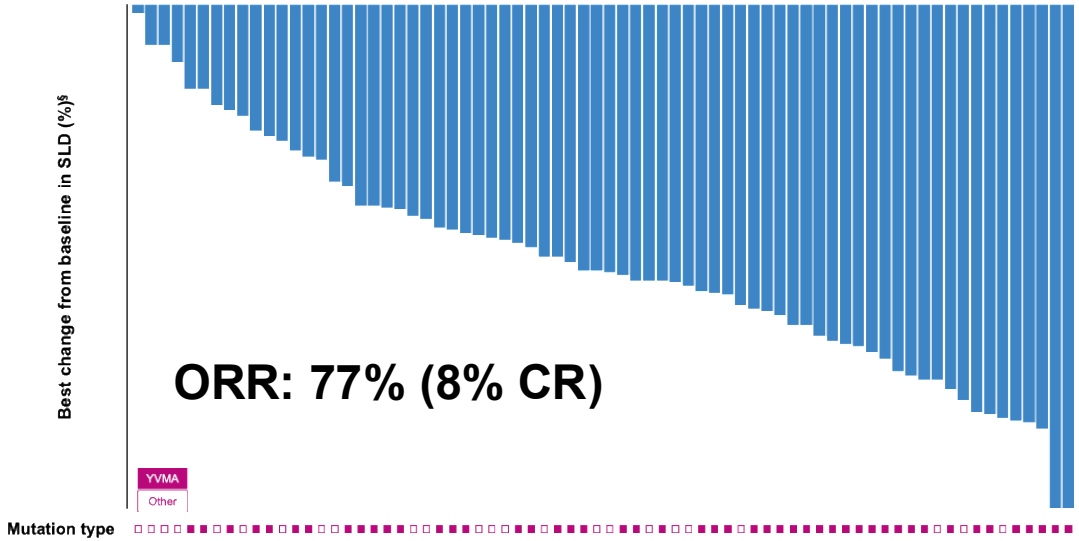
BEAMION LUNG-1: Efficacy of Zongertinib in patients HER2 TKD mutations NSCLC who were treatment nave (1L)

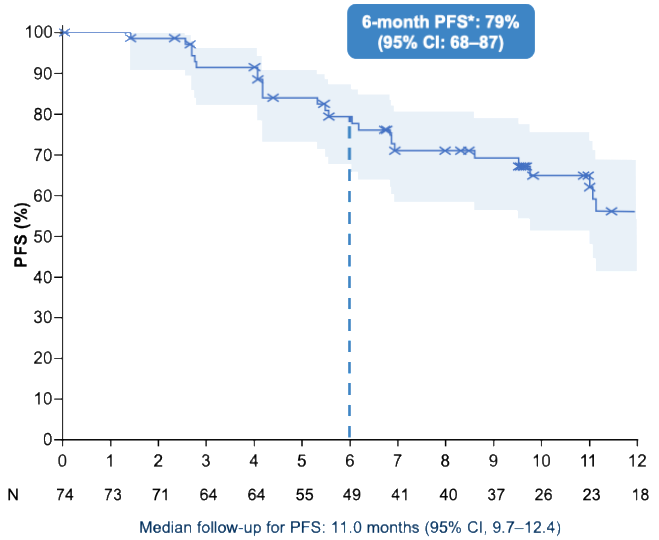
Cohort 2 **Treatment-naïve patients with TKD mutations**

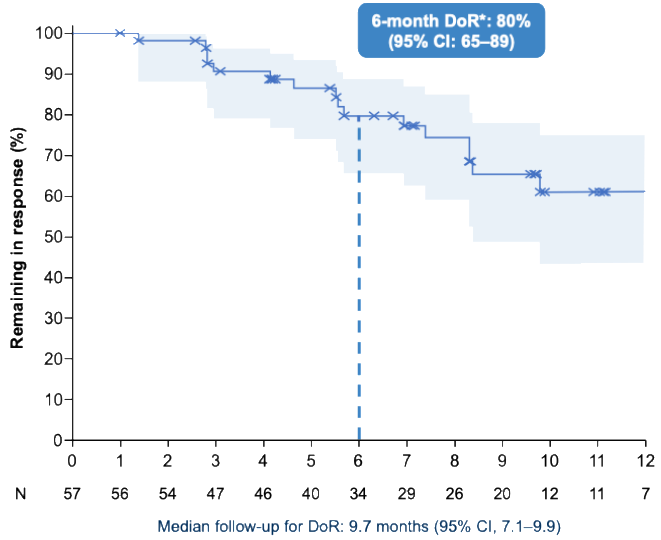
Primary endpoint: Objective response by BICR (RECIST v1.1)

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



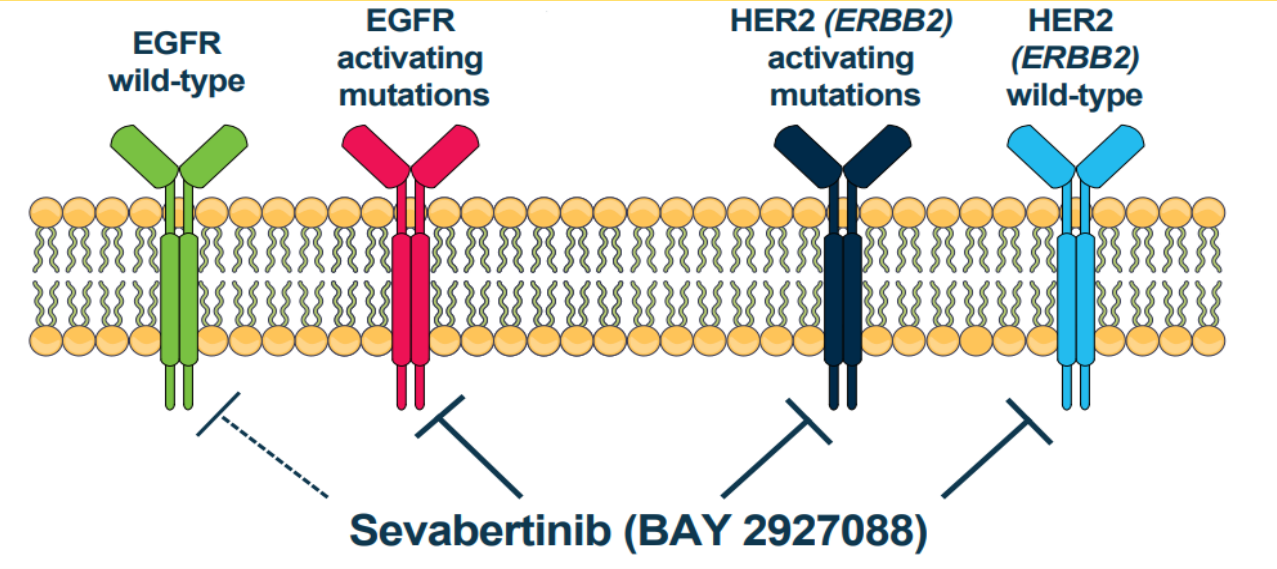




- G3 TRAEs in 13 (18%) patients
- There were no grade 4/5 TRAEs
- Dose reduction 15%; discontinuation 9%
- Two cases (3%) of ILD/pneumonitis (G2)

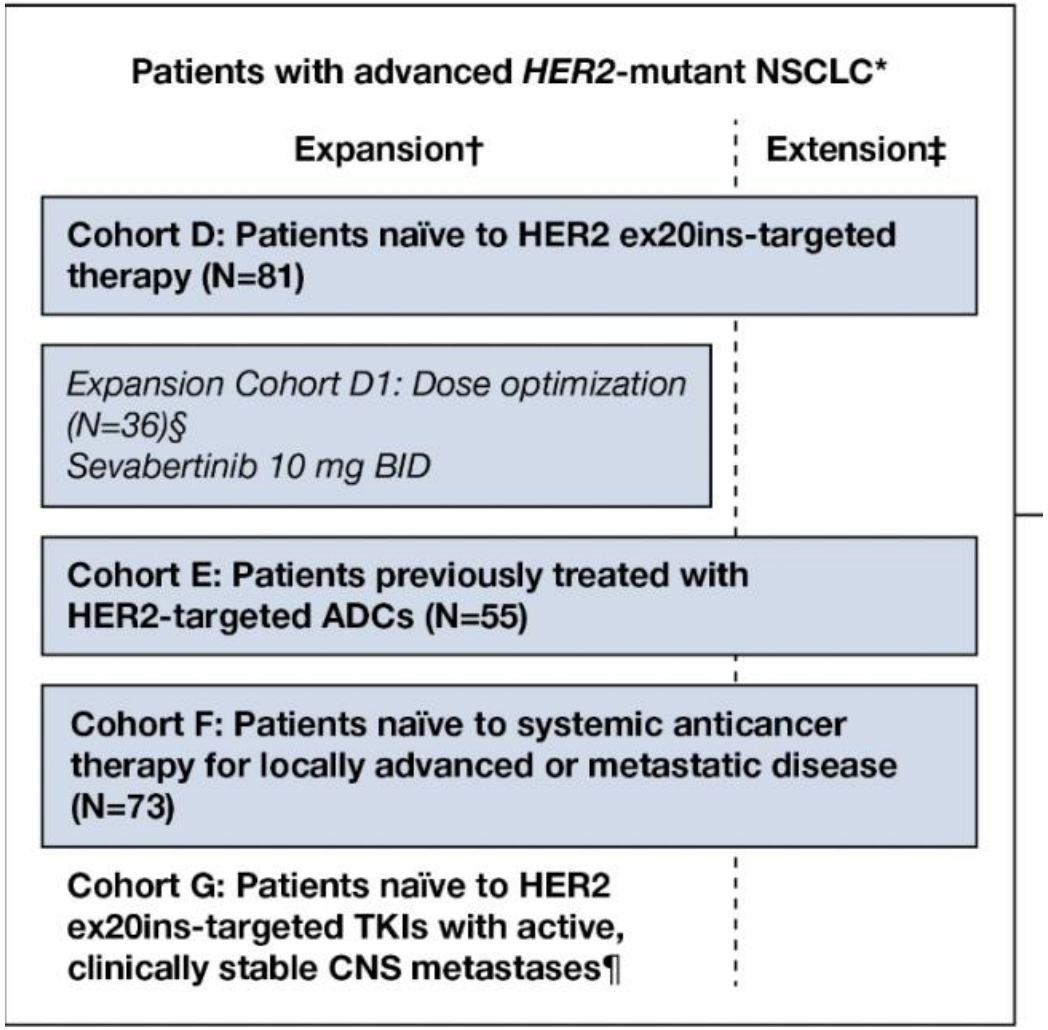
Popat et al. ESMO 2025

Sevabertinib. Mechanism of Action and SOHO-1 clinical trial (Ph1/2)



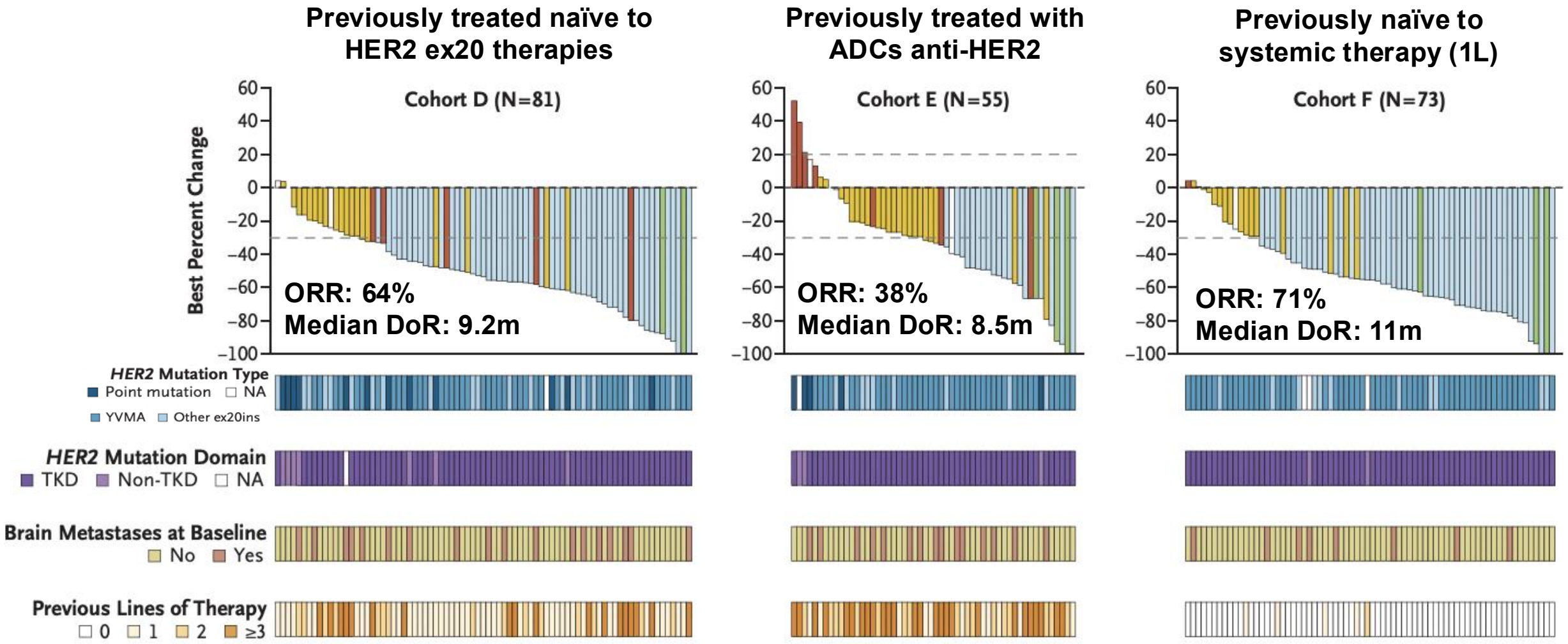
May 28, 2025 1:08 PM Eastern Daylight Time

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



Le et al. N Engl J Med 2025

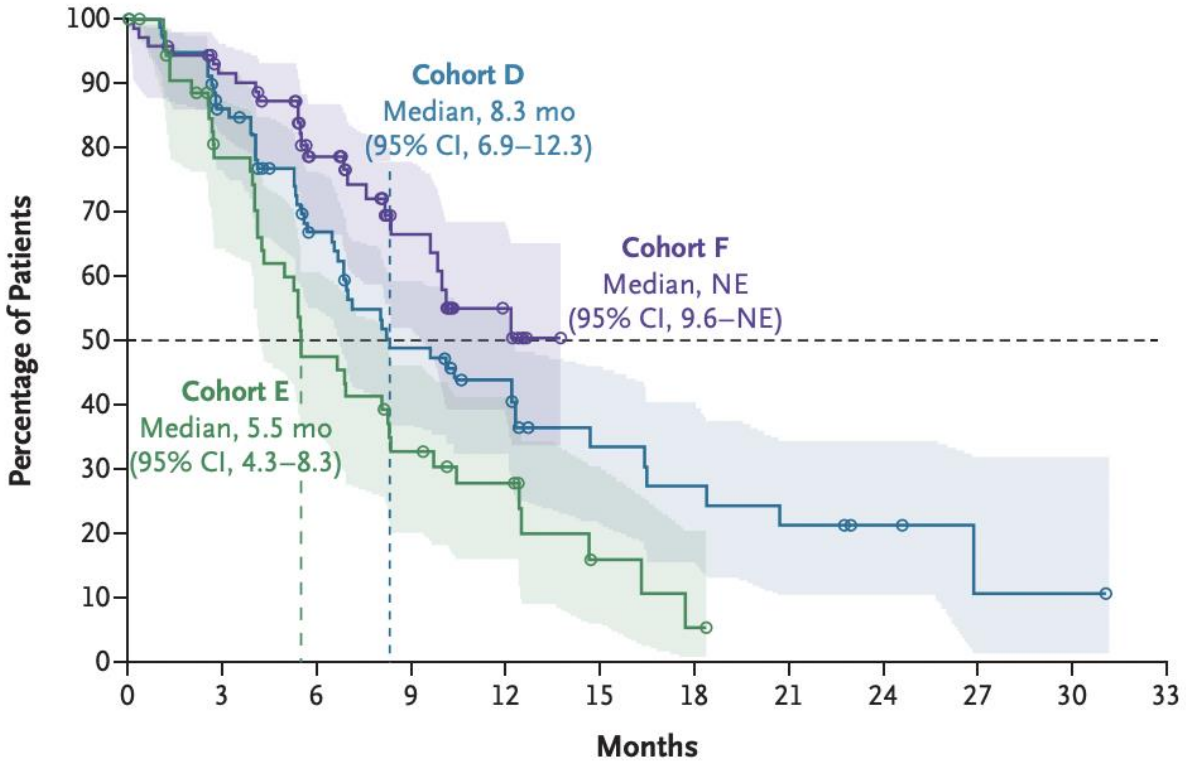
SOHO-1 – Sevabertinib Efficacy Results



Le et al. N Engl J Med 2025

SOHO-1 – Sevabertinib Efficacy Results

C Progression-free Survival

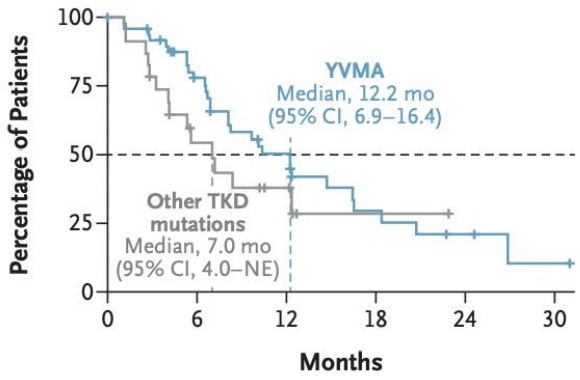


No. at Risk

Cohort D	81	66	45	32	25	11	9	7	3	1	1	0
Cohort E	55	38	23	15	11	3	1	0				
Cohort F	73	63	41	23	12	0						

Cohort D

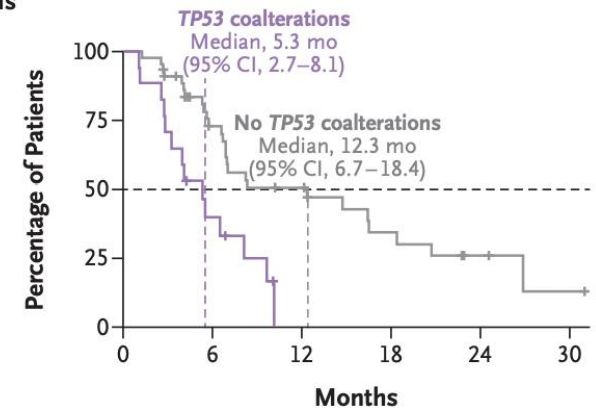
Progression-free Survival According to *HER2* YVMA Mutation Status



No. at Risk

YVMA mutation	49	32	19	7	3	1
Other TKD mutations	23	10	5	1	0	0

Progression-free Survival According to *TP53* Mutation Status

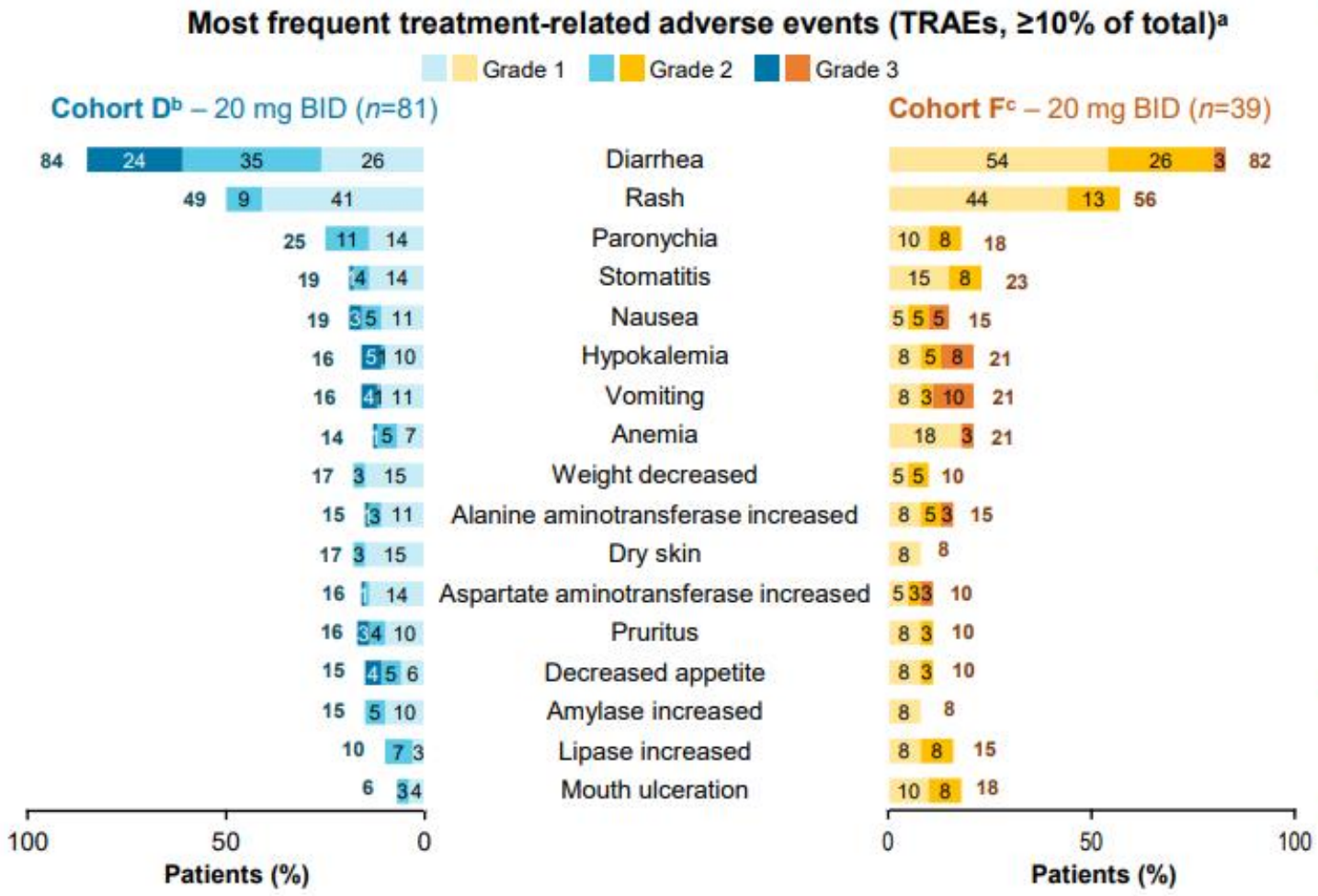


No. at Risk

No *TP53* co-alterations	44	26	17	8	3	1
TP53 coalter-ations	17	6	0	0	0	0

Le et al. N Engl J Med 2025

SOHO-1 – Sevabertinib Safety Results



- **In pretreated patients (Cohort D), the safety profile was consistent with previous reports**
  - Grade 3 treatment-related diarrhea occurred in 24% of patients
  - Exploratory analysis showed a median of 1 episode (IQR 1, 1) and a median time to onset of 1.3 months (IQR 0.5, 3.6)
- **In first-line patients (Cohort F), treatment-related grade 3 diarrhea was reported in only 1 patient (3%)**
- **Overall, there were no cases of grade 4 diarrhea**
- **There were no reported cases of interstitial lung disease or pneumonitis**
- **4 patients (4.9%) in Cohort D and 1 patient (2.6%) in Cohort F had TRAEs leading to treatment discontinuation[d]**

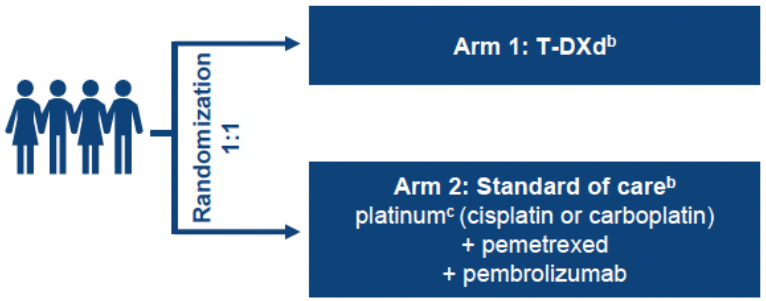
Loong HH, et al. ASCO 2025. Oral Abstract 8504

Which is the best treatment in the frontline?

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



[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

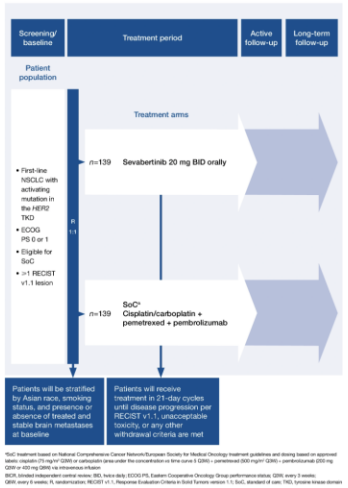
Phase III

Randomized 1:1, stratified on presence of A775_G776insYVMA mutation

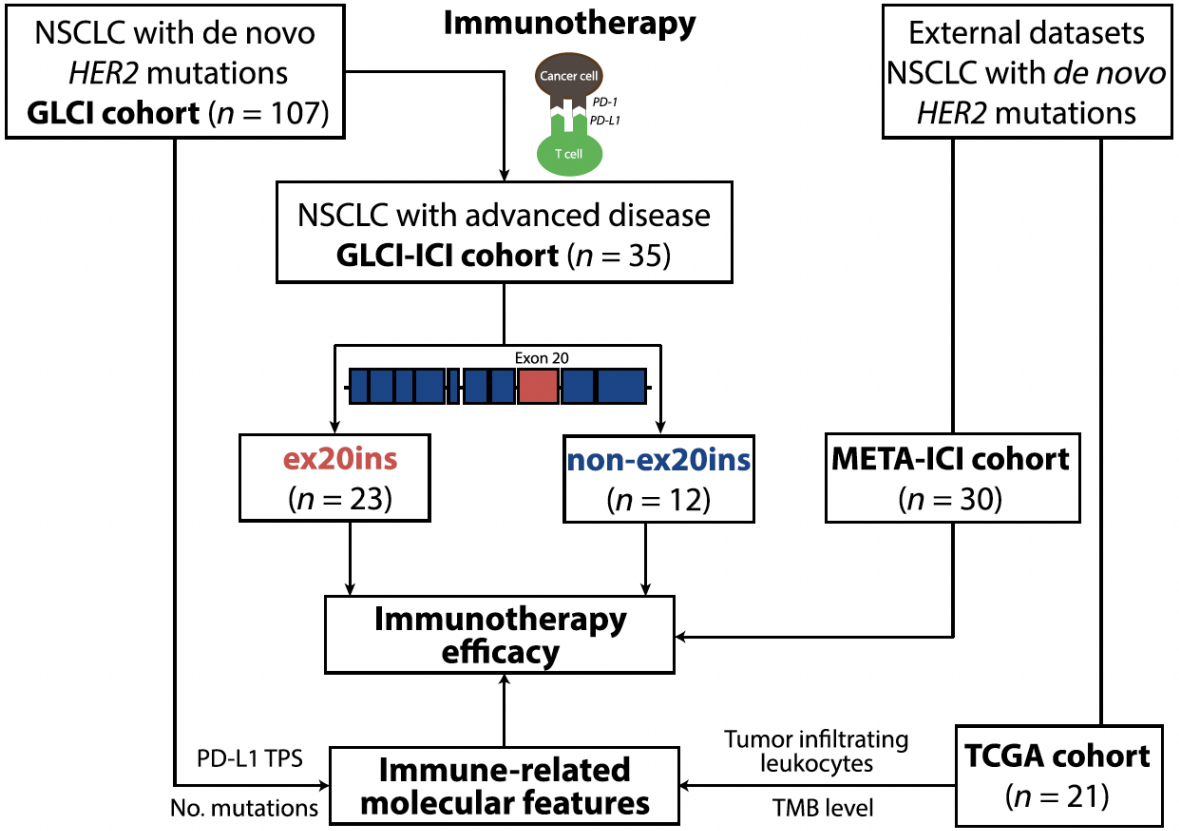
- **120 mg zongertinib once daily orally in 21-day cycles (n≈208)**
- **Standard of care* (n≈208)**

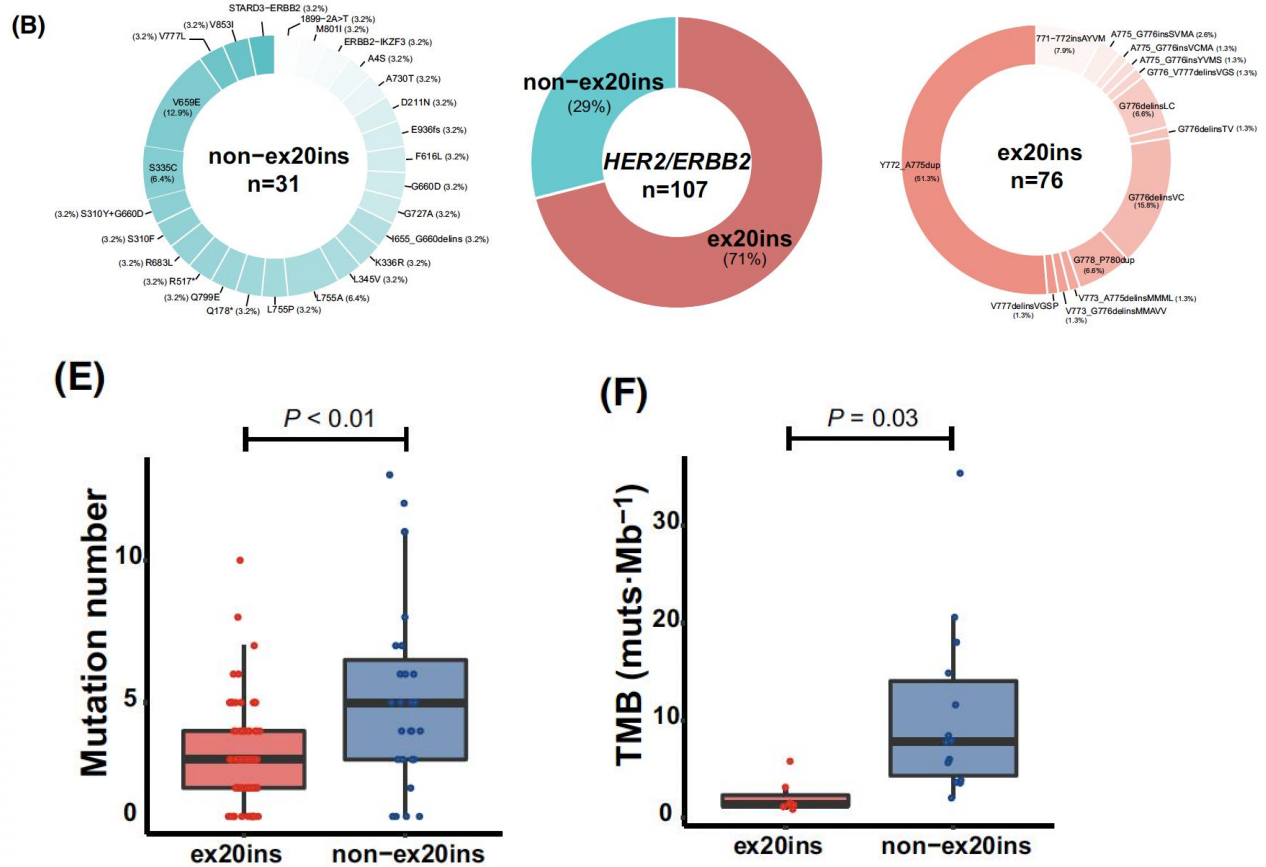
*500 mg/m² platinum-pemetrexed IV chemotherapy plus 200 mg IV pembrolizumab followed by either 75 mg/m² cisplatin/carboplatin AUC 5 on Day 1 (determined by investigator prior to randomization), Q3W, for 4 21-day cycles, followed by maintenance therapy with 200 mg pembrolizumab plus pemetrexed 500 mg/m²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

SOHO-02: Sevabertinib vs Chemo+ICI



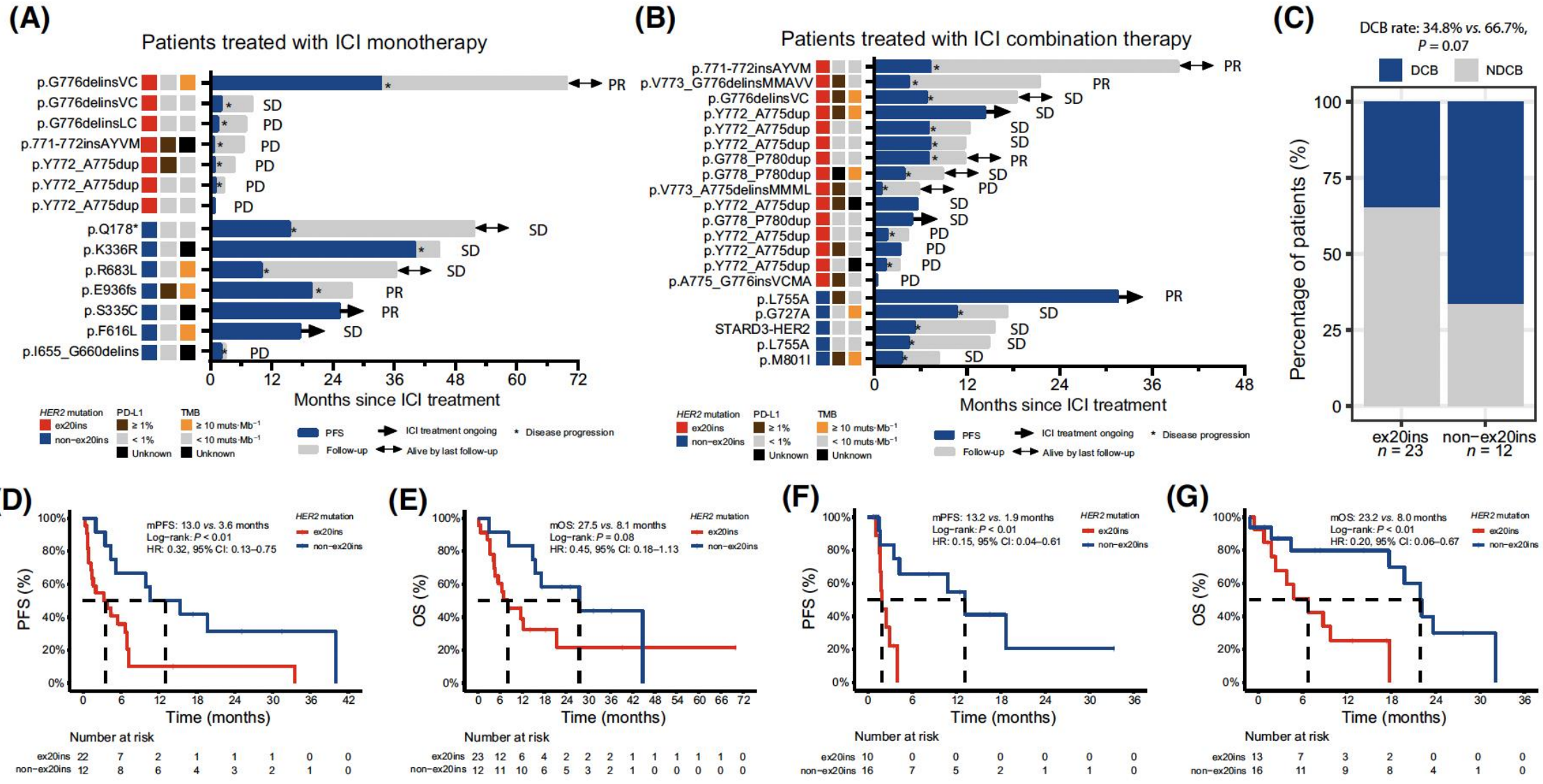
Do HER2 mutant tumors benefit from immunotherapy?





Tu et al. Mol Oncol 2023

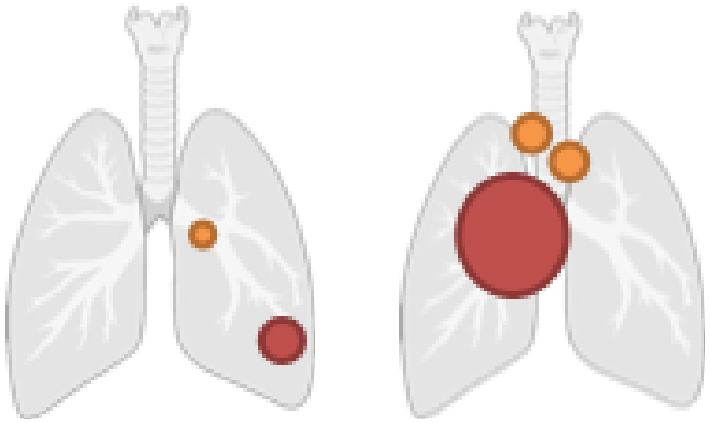
Do HER2 mutant tumors benefit from immunotherapy?



Tu et al. Mol Oncol 2023

Open Questions and Challenges Ahead

Optimal Sequence:
ADCs or TKIs first?



Personalized HER2 therapy in the curative setting

Mechanisms of Resistance
Role of comutations
Value of ctDNA

Take Home Messages

- HER2 mutations represents a novel actionable target in NSCLC
- Trastuzumab Deruxtecan was the 1st treatment approved for HER2 mutated (FDA & EMA) and for HER2 3+ overexpressed advanced NSCLC (FDA)
- New emerging ADCs and selective TKIs against HER2 have demonstrated clinically relevant efficacy in previously treated advanced NSCLC:

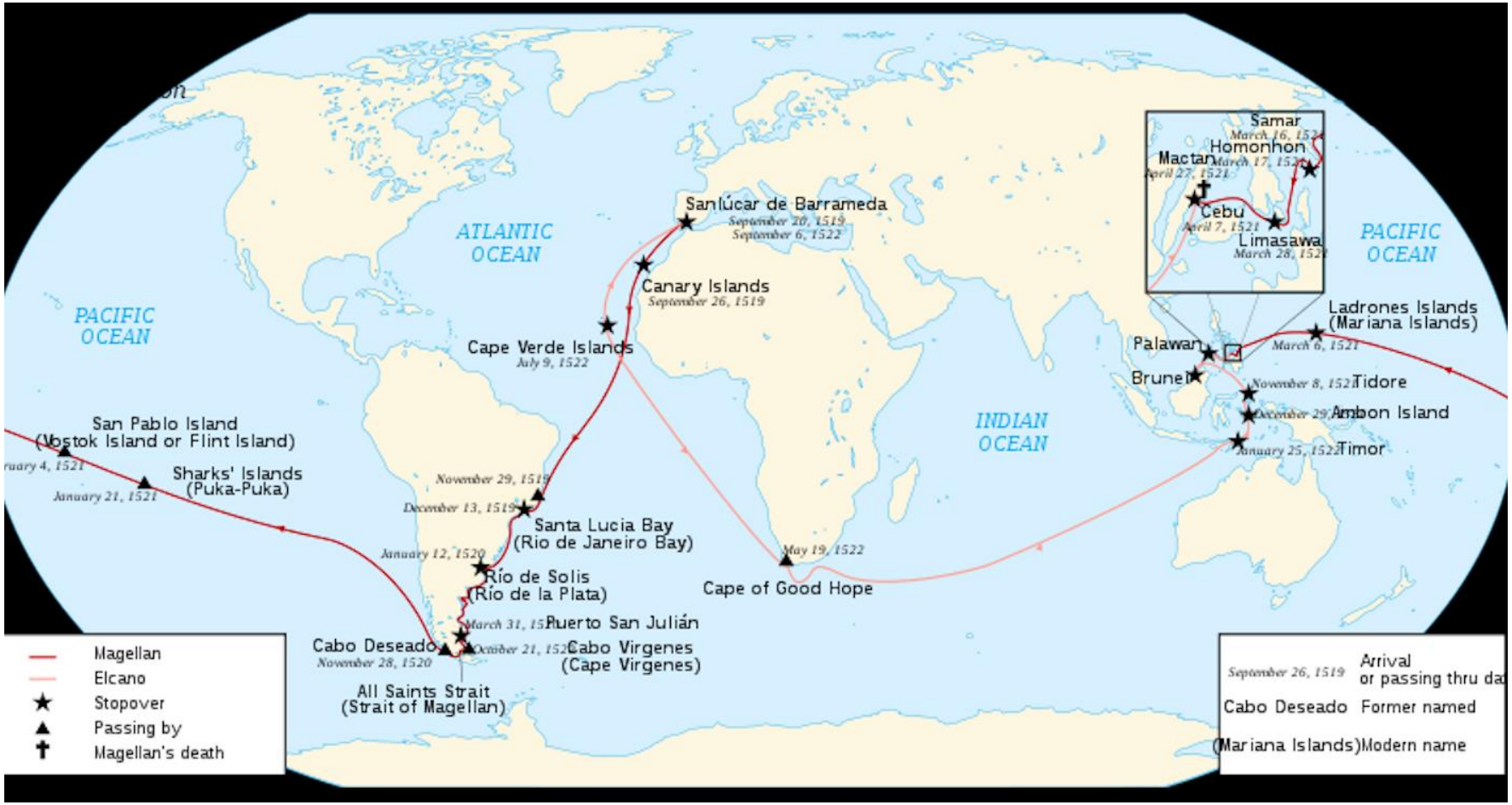
Treatment	N	ORR	PFS	≥G3 AEs	Approval for HER2 mutant NSCLC
Trastuzumab-deruxtecan	91	55%	8.2m	46%	FDA and EMA
Trastuzumab-rezetecan	94	74.5%	11.5m	62%	China
Zongertinib	75	71%	12.4m	17%	FDA (*)
Sevabertinib	81	64%	8.3m	31%	FDA (*)

(*) Accelerated approval

Li BT, et al. N Engl J Med 2022; Li et al. Lancet Oncol 2025; Heymach et al. N Engl J Med 2025; Loong HH, et al. ASCO 2025. Oral Abstract 8504

HER2 is a new frontier in Precision Medicine in NSCLC:

"The church says the earth is flat, but I know that it is round, for I have seen the shadow on the moon." — Frequently attributed to Magellan, though likely apocryphal



16th CONGRESS Lung ON CANCER

BARCELONA 27 / 28 NOVEMBER 2025

THANK YOU

/Salut

ICO Institut Català d'Oncologia

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IDIBELL Oncobell program

GECP lung cancer research