

ATLANTA
LUNG CANCER SYMPOSIUM

John V. Heymach MD, PhD
Chair, Thoracic Medical Oncology
Ruth Legett Jones Distinguished Chair
MD Anderson Cancer Center

HER-2 Mutated NSCLC: New First Line Therapy and Other Options

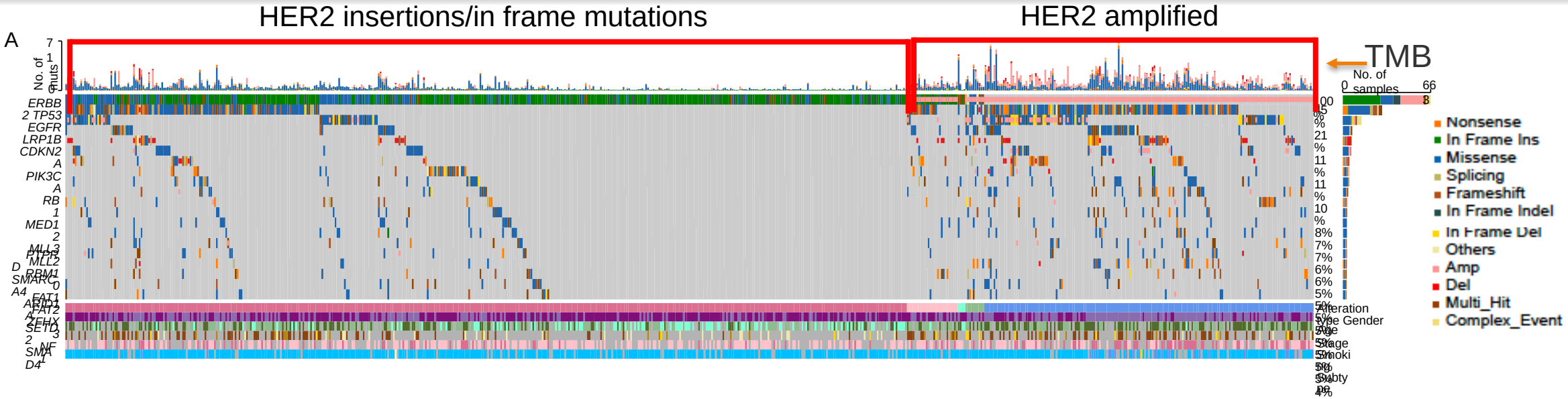
November 7, 2026

Partners for Advancing Clinical Education
Bio Ascend™

Disclosures

I have the following financial relationships to disclose:
Advisory Committees –AstraZeneca, Boehringer-Ingelheim, Catalyst, Genentech, GlaxoSmithKline, Guardant Health, Foundation medicine, Hengrui Therapeutics, Eli Lilly, Novartis, Spectrum, EMD Serono, Sanofi, Takeda, Mirati Therapeutics, BMS, BrightPath Biotherapeutics, Janssen Global Services, Nexus Health Systems, EMD Serono, Pneuma Respiratory, Kairos Venture Investments, Roche, Leads Biolabs
Research Support – AstraZeneca, GlaxoSmithKline, Spectrum
Royalties and Licensing fees – Spectrum for TKIs for exon 20 EGFR/HER2; patents pending regarding EGFR classification

HER2 mutant and HER2 amplified/overexpressing NSCLC are distinct and only the mutants appear to be drivers



HER2 mutants more likely than amplified to:

-be exclusive of other drivers

-occur in non-smokers

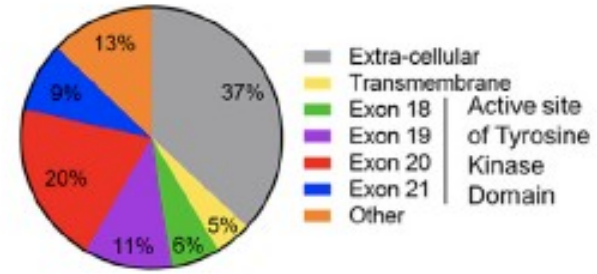
-have lower TMB and have fewer co-occurring alterations

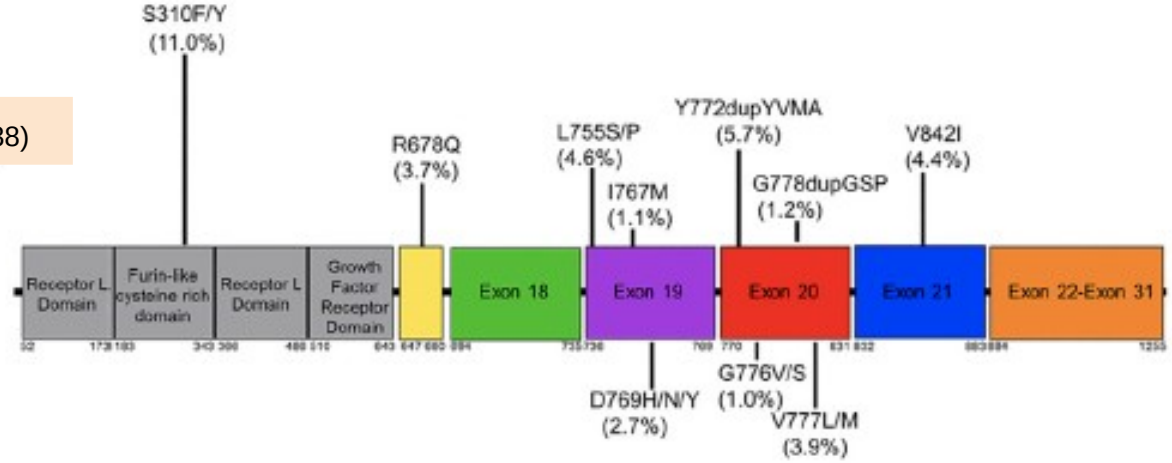
Cancer
UT MD Anderson

Hong (X. Le) et al, NPJ Presic Oncology, 2024

Across tumor types, most HER2 mutations occur in tyrosine kinase domains (TKD; exons 18-21) or ECD (S310F/Y). In NSCLC exon 20 insertions are most common

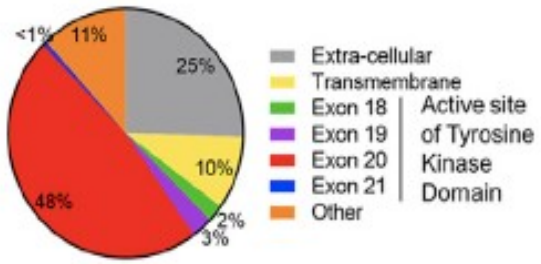
All cancers (N=2338)





NSCLC (N=177)

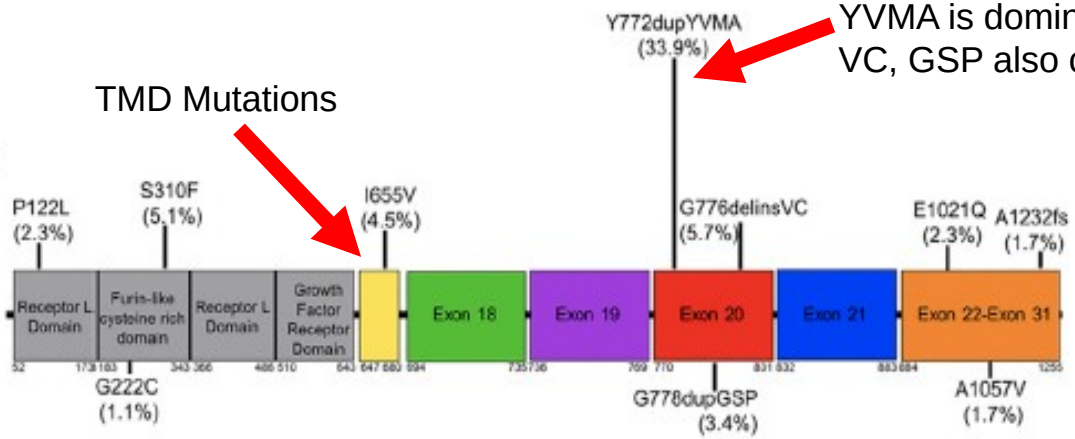
C



D

TMD Mutations

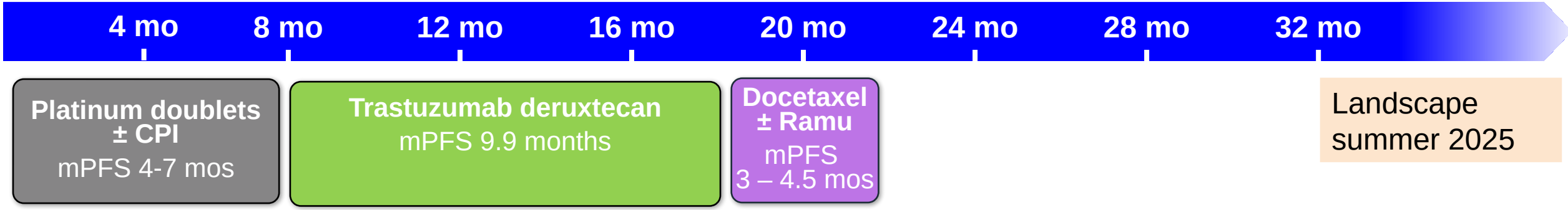
YVMA is dominant insertion
VC, GSP also common



Cancer
UT MD Anderson

Robichaux et al Cancer Cell 2019

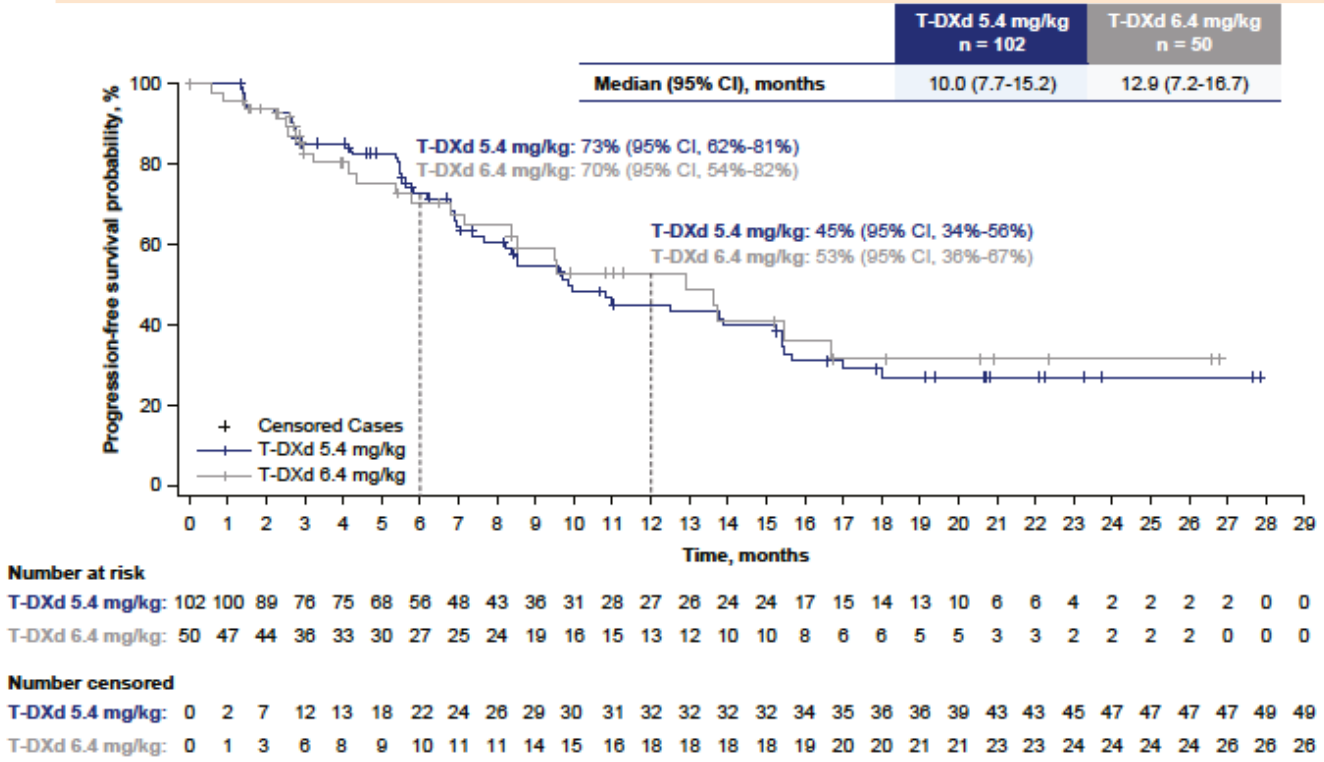
Evolution of the HER2 mutant NSCLC landscape



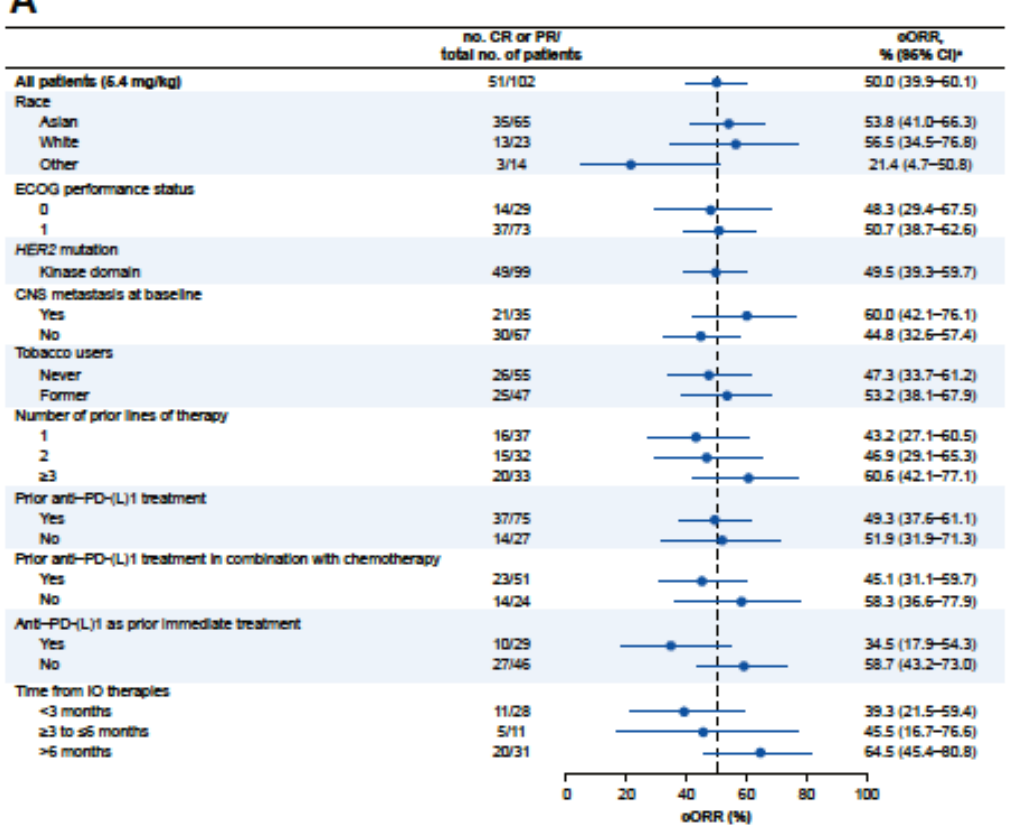
Cancer
UT MD Anderson

Final analysis from DESTINY-Lung02-A RP2 Study of Trastuzumab Deruxtecan in 2L+ HER2 mutant NSCLC

mPFS, 5.4 mg/kg: 10.0 (7.7-15.2)
Confirmed ORR: 50%



ORR by subgroups



Cancer
UT MD Anderson

Janne et al JTO 2025

Final analysis from DESTINY-Lung02-A RP2 Study of Trastuzumab Deruxtecan in 2L+ HER2 mutant NSCLC

ILD: 14.9% (all grade) at 5.4 mg/kg dose

Table 3. Adjudicated Drug-Related ILD[a]

Adjudicated Drug-Related ILD Variable	T-DXd 5.4 mg/kg n = 101[b]	T-DXd 6.4 mg/kg n = 50[b]
Any grade, n (%)	15 (14.9)	16 (32.0)
Grade 1	4 (4.0)	3 (6.0)
Grade 2	9 (8.9)	11 (22.0)
Grade 3	1 (1.0)	1 (2.0)
Grade 4	0	0
Grade 5	1 (1.0)[c]	1 (2.0)[c]
Grade ≥3	2 (2.0)	2 (4.0)
Outcome of ILD events,[d,e] n/N (%)		
Fatal	1/15 (6.7)	1/16 (6.3)
Not recovered/not resolved	3/15 (20.0)	6/16 (37.5)
Recovering/resolving	1/15 (6.7)	0
Recovered/resolved with sequelae	0	1/16 (6.3)
Recovered/resolved	10/15 (66.7)	8/16 (50.0)

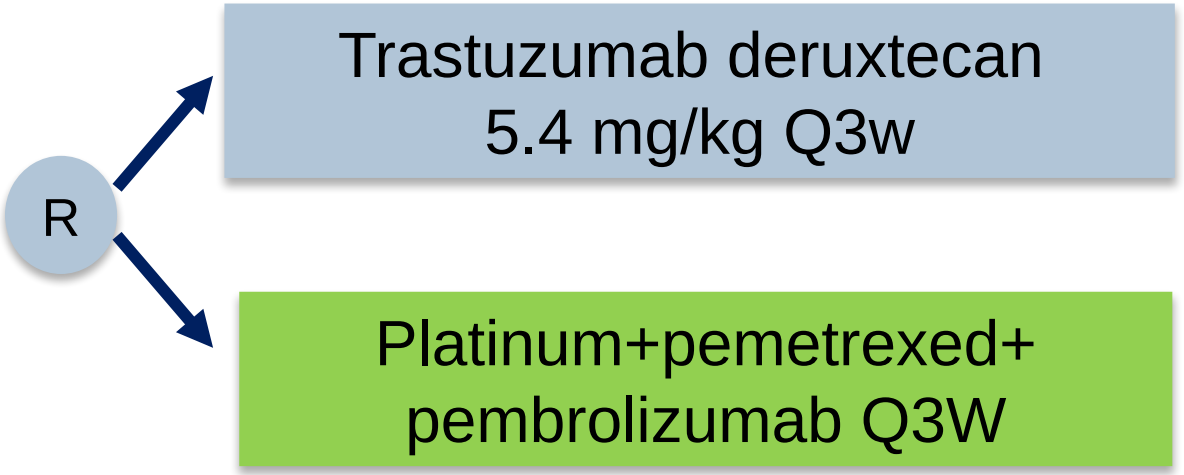
Cancer
UT MD Anderson

Janne et al JTO 2025

DESTINY-LUNG 04: Randomized phase III trial of trastuzumab deruxtecan chemotherapy/pembro as 1L for HER2 mutant NSCLC

- Locally advanced and unresectable nonsquamous NSCLC, not amenable to curative therapy, or metastatic disease
- Treatment-naïve for palliative intent systemic therapy for locally advanced or metastatic disease
- *HER2* mutation in exons 19 or 20

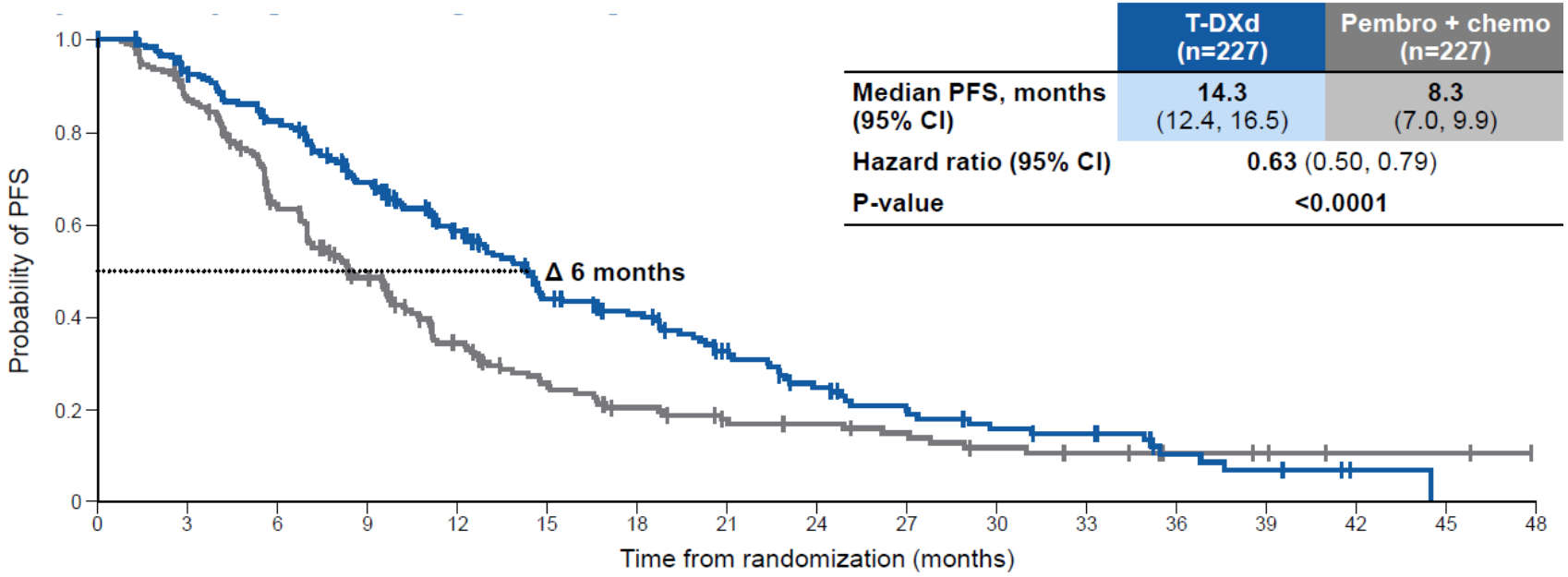
Primary endpoint: PFS



Cancer
UT MD Anderson

PFS results for DESTINY-LUNG 04: Randomized phase III trial of trastuzumab deruxtecan chemotherapy/pembro as 1L for HER2 mutant NSCLC

Median Progression-Free Survival: 14.3 vs 8.3 months



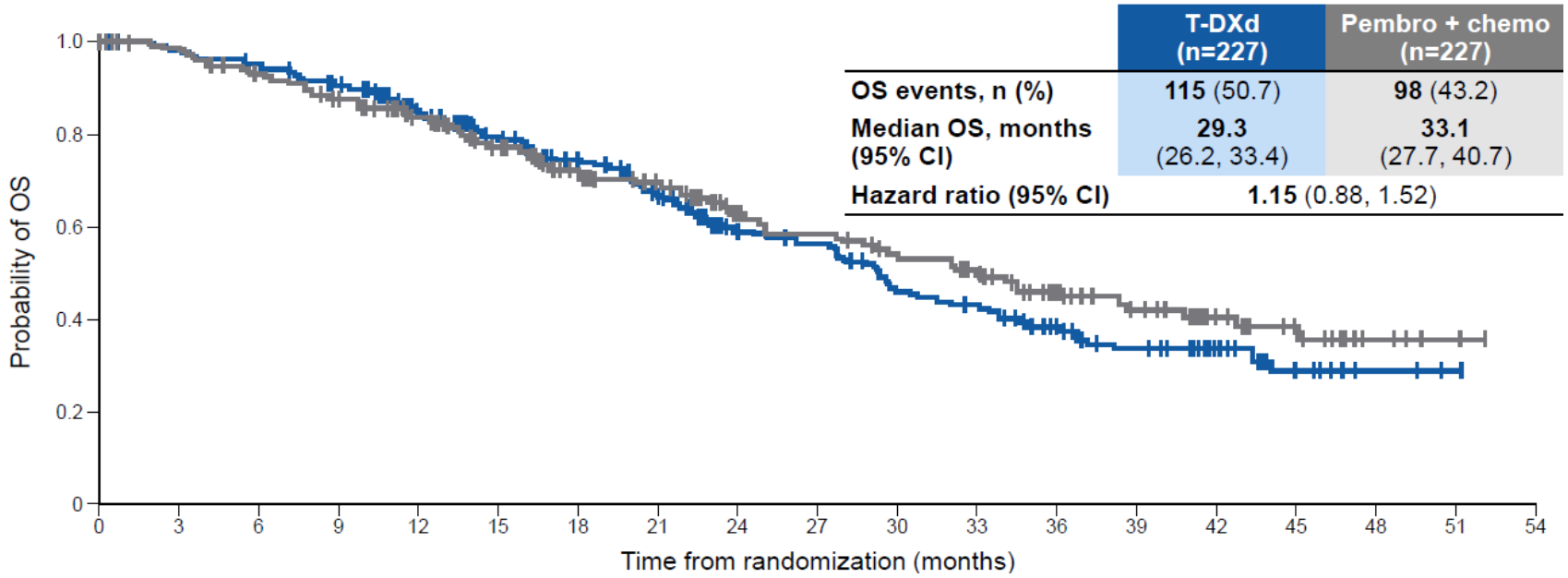
	T-DXd (n=227)	Pembro + chemo (n=227)
Median PFS, months (95% CI)	14.3 (12.4, 16.5)	8.3 (7.0, 9.9)
Hazard ratio (95% CI)	0.63 (0.50, 0.79)	
P-value	<0.0001	

Cancer
UT MD Anderson

J. Rotow et al, WCLC presentation, 2026

OS results for DESTINY-LUNG 04: Randomized phase III trial of trastuzumab deruxtecan chemotherapy/pembro as 1L for HER2 mutant NSCLC

Median OS: 29.3 vs 33.1 months, HR 1.15, P=NS



	T-DXd (n=227)	Pembro + chemo (n=227)
OS events, n (%)	**115** (50.7)	**98** (43.2)
Median OS, months (95% CI)	**29.3** (26.2, 33.4)	**33.1** (27.7, 40.7)
Hazard ratio (95% CI)	**1.15** (0.88, 1.52)	

ILD/pneumonitis

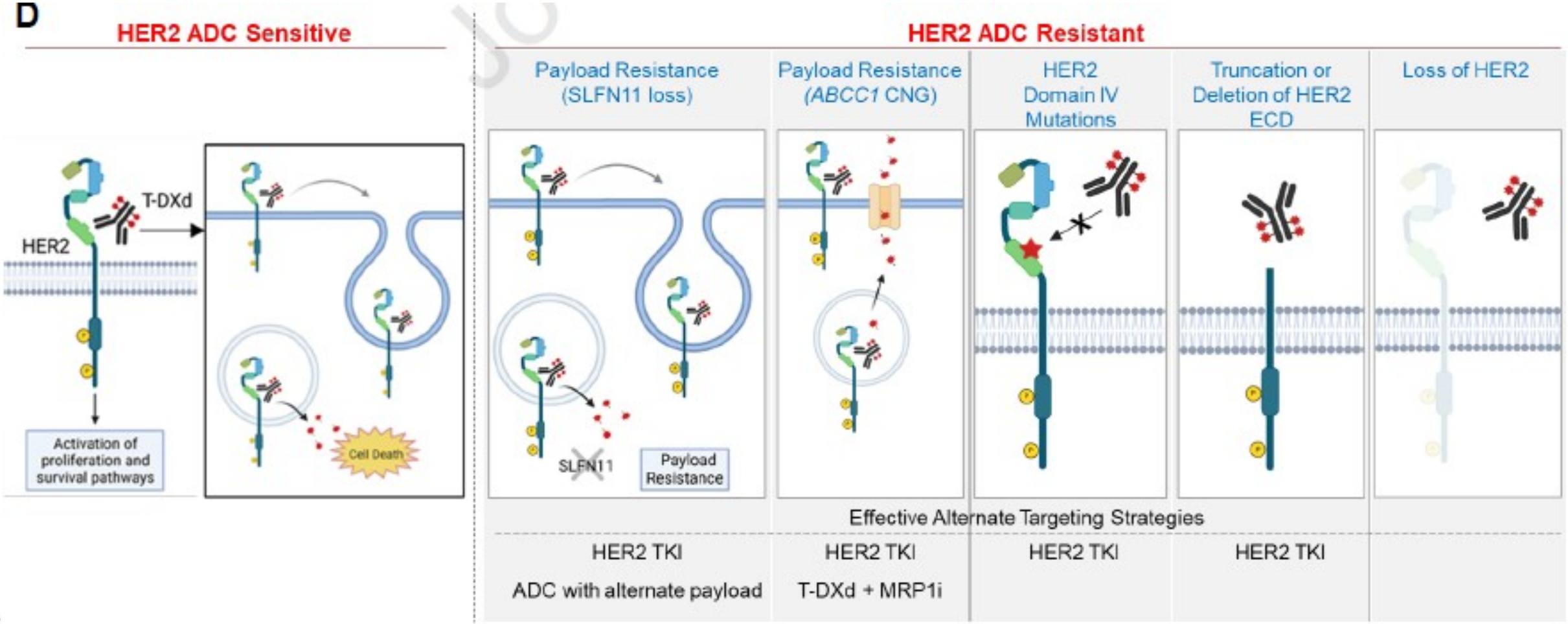
- Drug-related grade 3 AEs in 34% (both arms)
- Drug-related ILD/pneumonitis in 20.8% (vs 2% in control arm)

Subsequent therapies, primarily HER2-directed & immunotherapy-based, were imbalanced across treatment arms

Cancer UT MD Anderson

J. Rotow et al, WCLC presentation, 2026

Loss of payload sensitivity in T-DXd resistance



UT MD Anderson

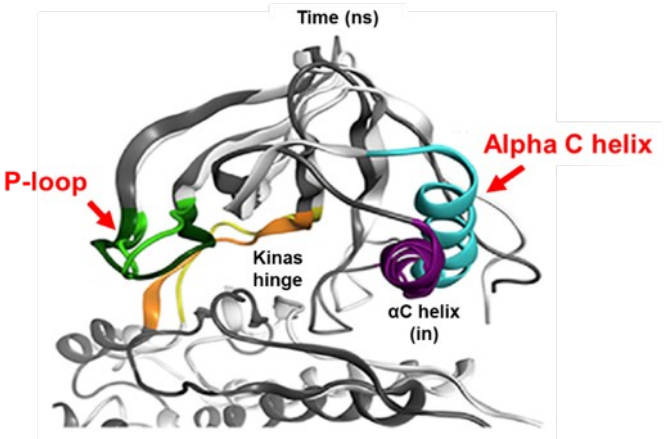
Nilsson et al, JTO 2026

The Challenge of Developing TKIs that Inhibit Mutant HER2 but Spare wild-type EGFR

Cancer
UT MD Anderson

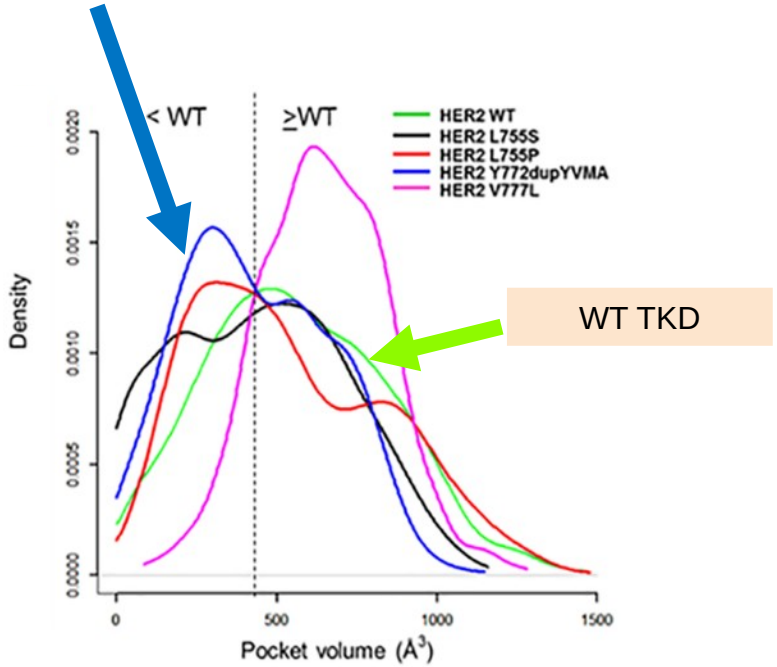
Challenge #1 for developing TKIs for HER2 mutant NSCLC: Exon 20 insertions impact the binding pocket compared with HER2 wild-type

HER2 binding pocket



Smaller binding pocket for ex20ins (YVMA) vs wt HER

YVMA insertion

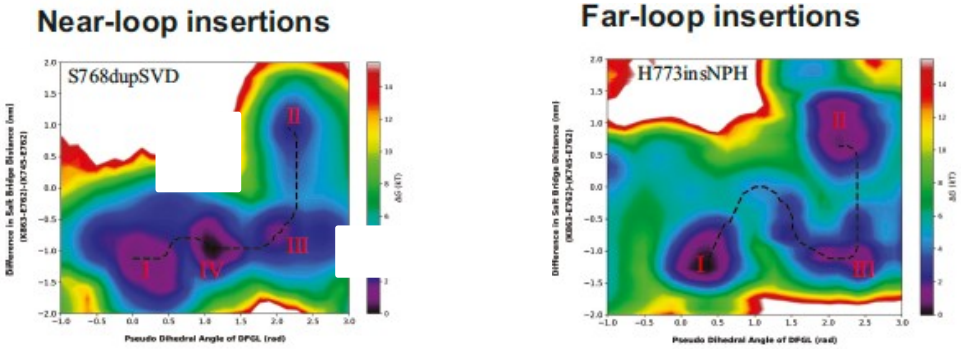


WT TKD

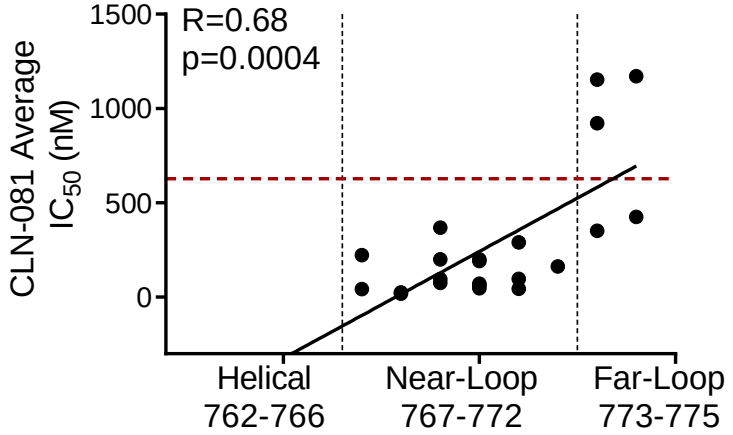
Small pocket

Larger pocket

Insertion location within exon20 can impact structure (MDS analysis EGFR ex20ins by Lawson et al)



Insertion location can impact TKI sensitivity



Cancer UT MD Anderson

Robichaux, … Heymach et al. ***Cancer Cell*** 2019; Hong…Heymach, Le et al, ***NPR Prec Oncol*** 2024; Le.. Lawson, Heymach et al ***Nat Comm*** 2025

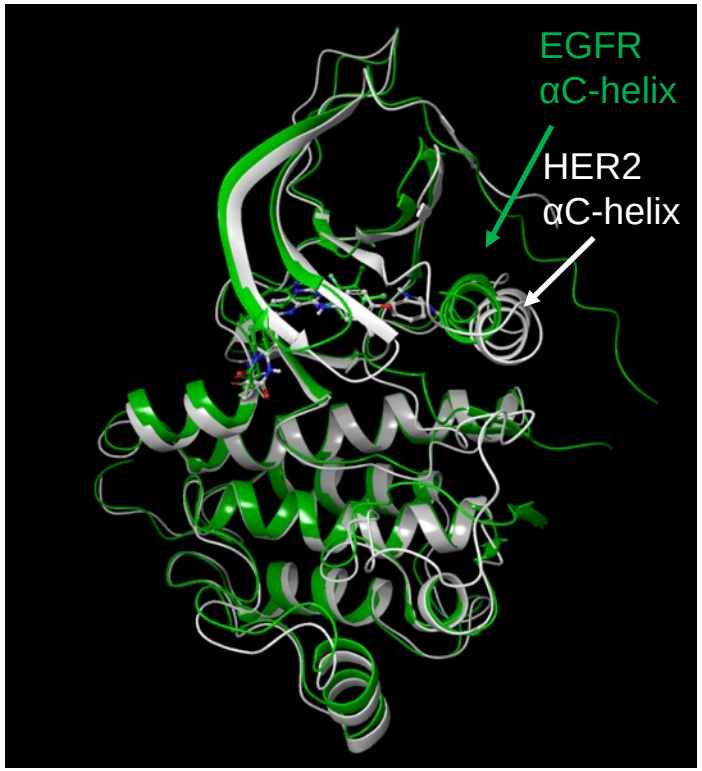
Challenge #2: EGFR and HER2 have very similar binding pockets, except for alpha C helix and S783

White

HER2
&
Zongertinib

Green

EGFR
&
Poziotinib



Cancer
UT MD Anderson

Prior HER2 TKIs for HER2 mutant NSCLC had modest activity with significant side effects related to off target inhibition of wild-type EGFR

TKIs	N	ORR (%)	Median PFS (months)	EGFR-related TRAEs (%)
Dacomitinib (NCT00818441)[1]	26	12	3.0	G≥3 rash: 14* G≥3 diarrhea: 8*
Neratinib (SUMMIT)[2]	26	4	5.5	G≥3 diarrhea: 22†
Afatinib[3]	18	0	2.8	G≥3 diarrhea: 17
Pyrotinib (NCT02834936)[4]	60	30	6.9	G≥3 diarrhea: 20
Poziotinib (ZENITH20-2)[5]	90	28	5.5	G≥3 rash: 49 G≥3 diarrhea: 26

There remains a clear unmet need for a potent TKI that selectively inhibits HER2 while sparing wild-type EGFR

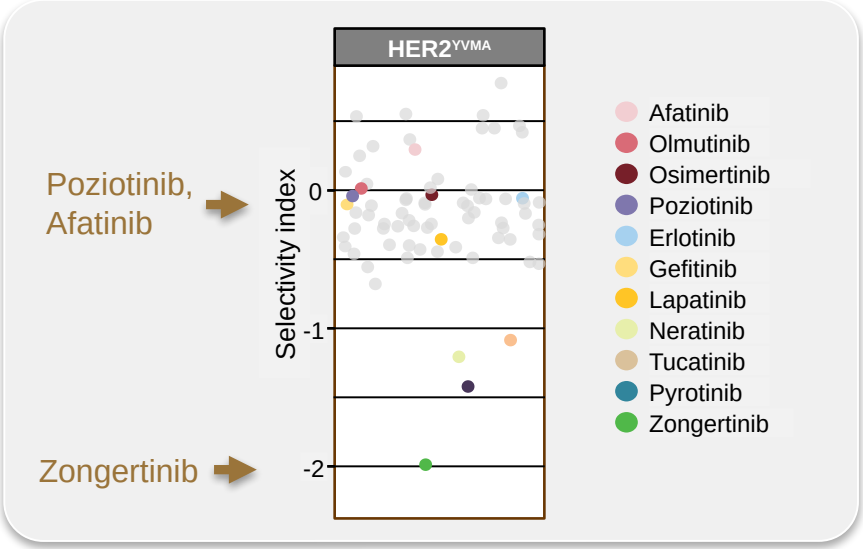
Cancer
UT MD Anderson

1. Kris MG et al. Ann Oncol. 2015;26:1421–7; 2. Hyman DM et al. Nature. 2018;554:189–94; 3. Fan Y et al. Lung Cancer. 2020;147:209–13;
4. Zhou C et al. J Clin Oncol. 2020;38:2753–61; 5. Le X et al. J Clin Oncol. 2022;40:710–8; 6. Li BT et al. J Clin Oncol. 2018;36:2532–7;
7. Goto K et al. J Clin Oncol. 2023;41:4852–63

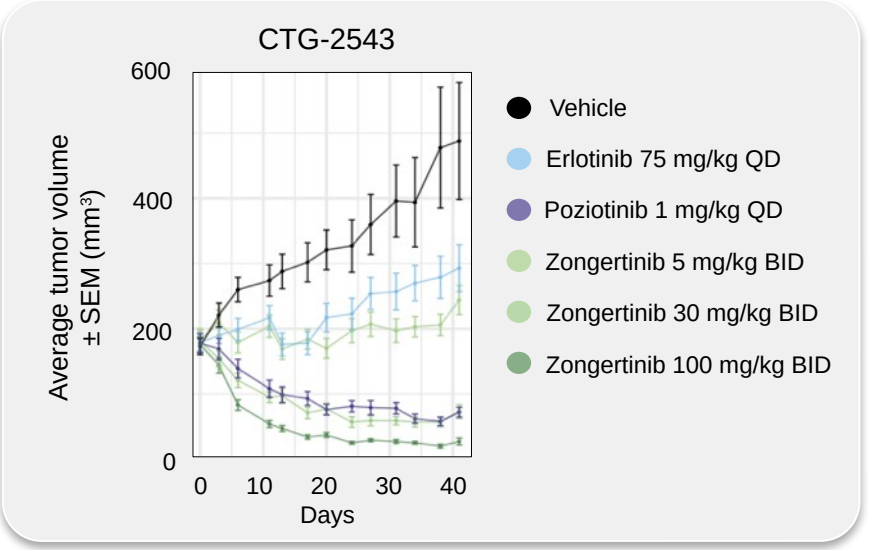
*Safety data from larger study in patients with *EGFR*-mutant NSCLC (n=227; Wu YL et al. Lancet. 2017,18:1454–66); †treatment-emergent diarrhea data from the entire basket study in patients with *HER2/3*-mutant cancers (n=141)

Zongertinib is an oral, HER2-specific, EGFR-sparing TKI

- Zongertinib is highly selective for mutant HER2 over EGFR wild-type[1]



- Zongertinib resulted in tumor regressions in a patient-derived NSCLC xenograft model carrying a *HER2* exon 20 insertion (HER2^{YVMA})[1]



Zongertinib is a potent, covalent TKI that selectively inhibits HER2 while sparing EGFR wild-type, thereby potentially limiting associated toxicities

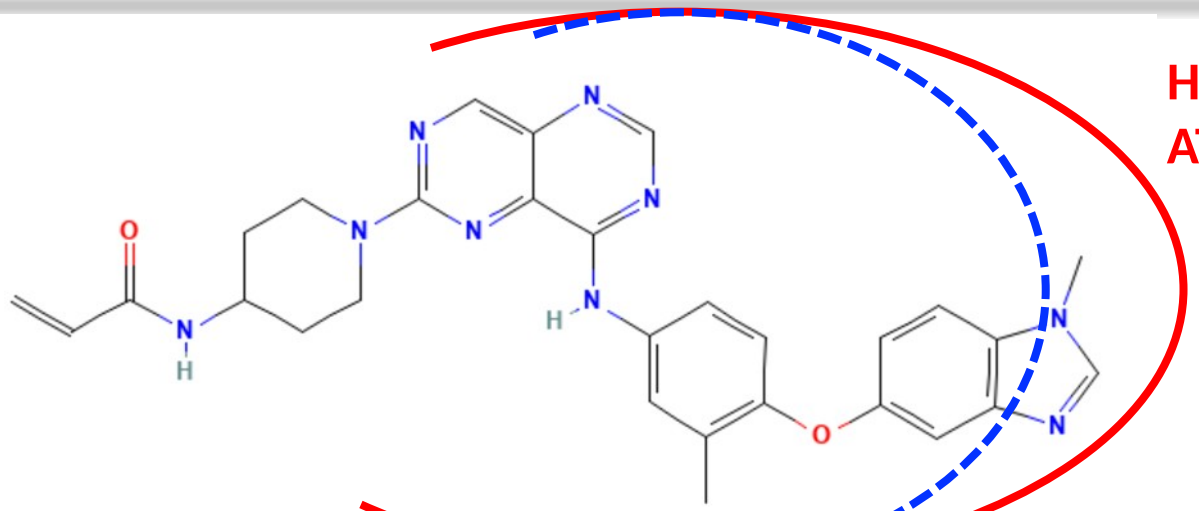
1. Wilding B et al. Cancer Discov. 2025;15:119–38

Plots by Wilding B et al. Cancer Discov. 2025; used under Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, with minor color amends

Cancer
UT MD Anderson

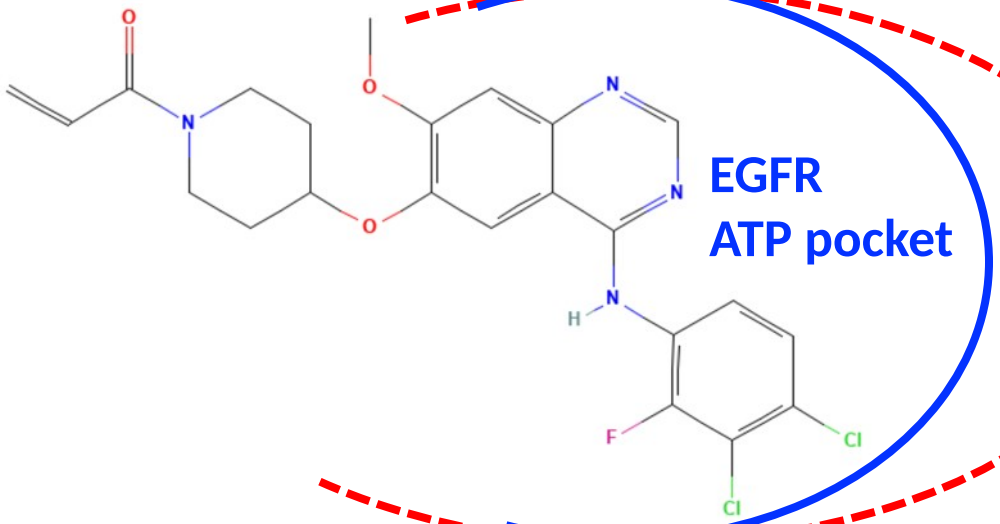
Zongertinib fits the more flexible and adaptive HER2 pocket, but is not accommodated in EGFR

Zongertinib



HER2
ATP pocket

Poziotinib



HER2
ATP pocket

EGFR
ATP pocket

Cancer
UT MD Anderson

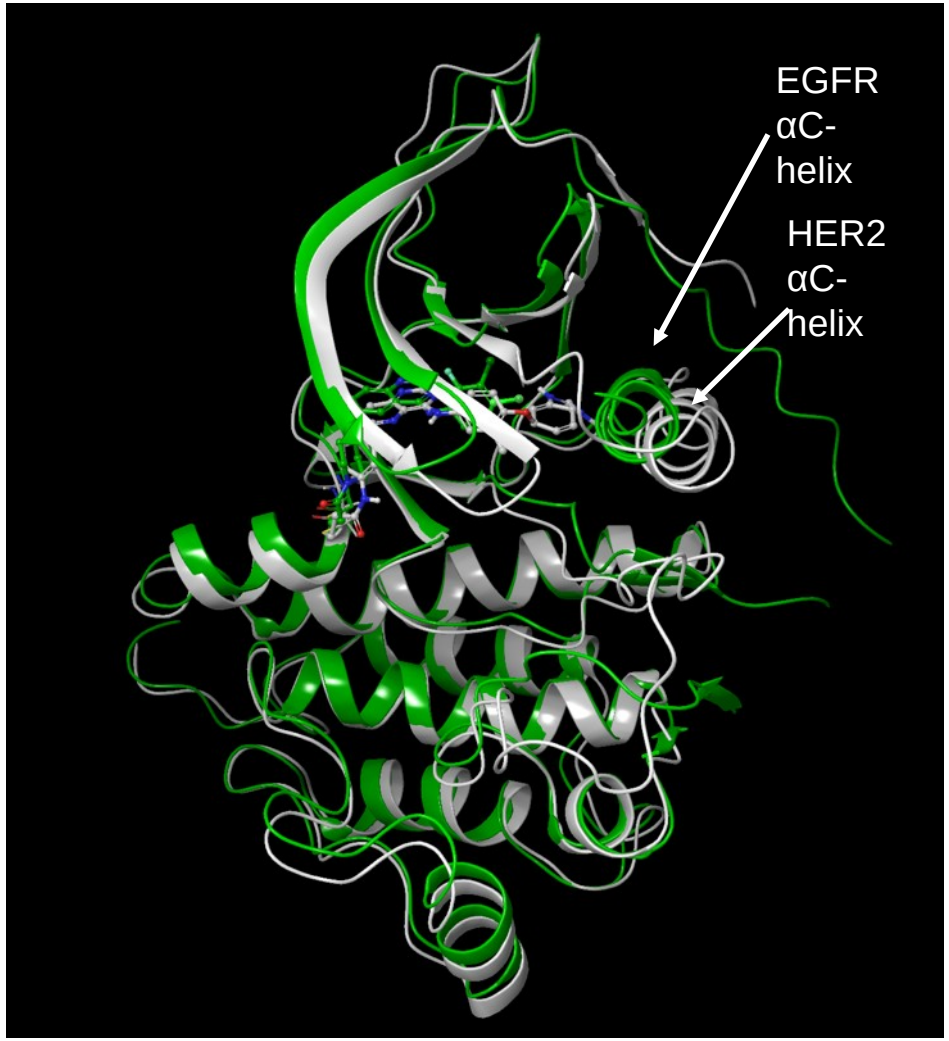
Zongertinib fits into a deeper pocket in HER2, but not into the tighter space in EGFR

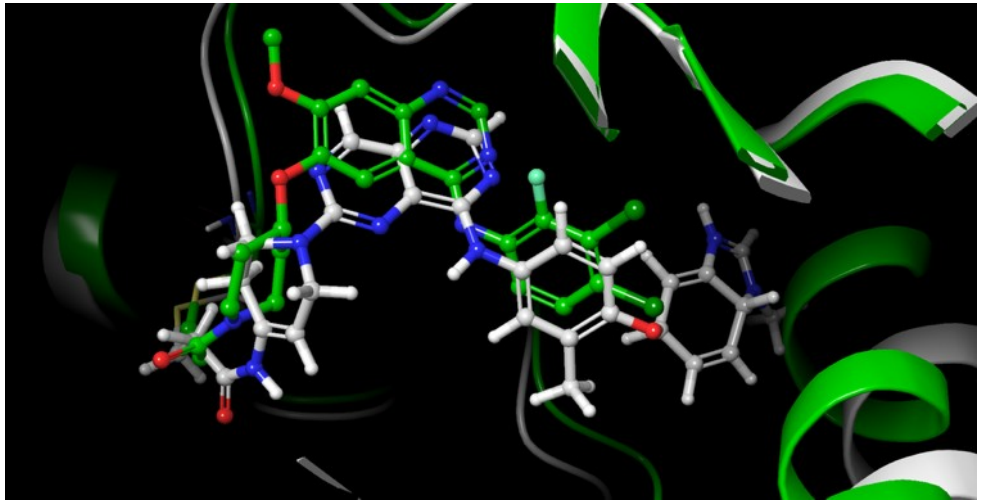
White

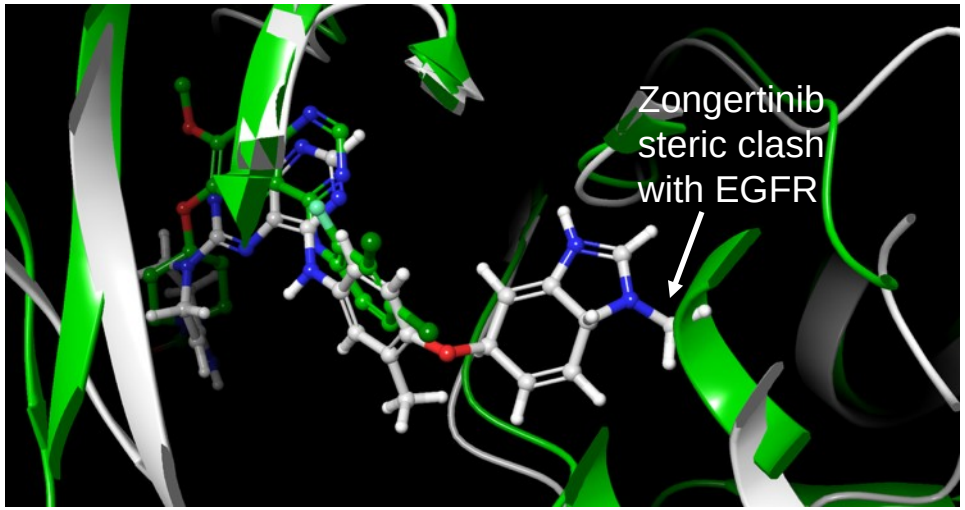
HER2 & Zongertinib

Green

EGFR & Poziotinib

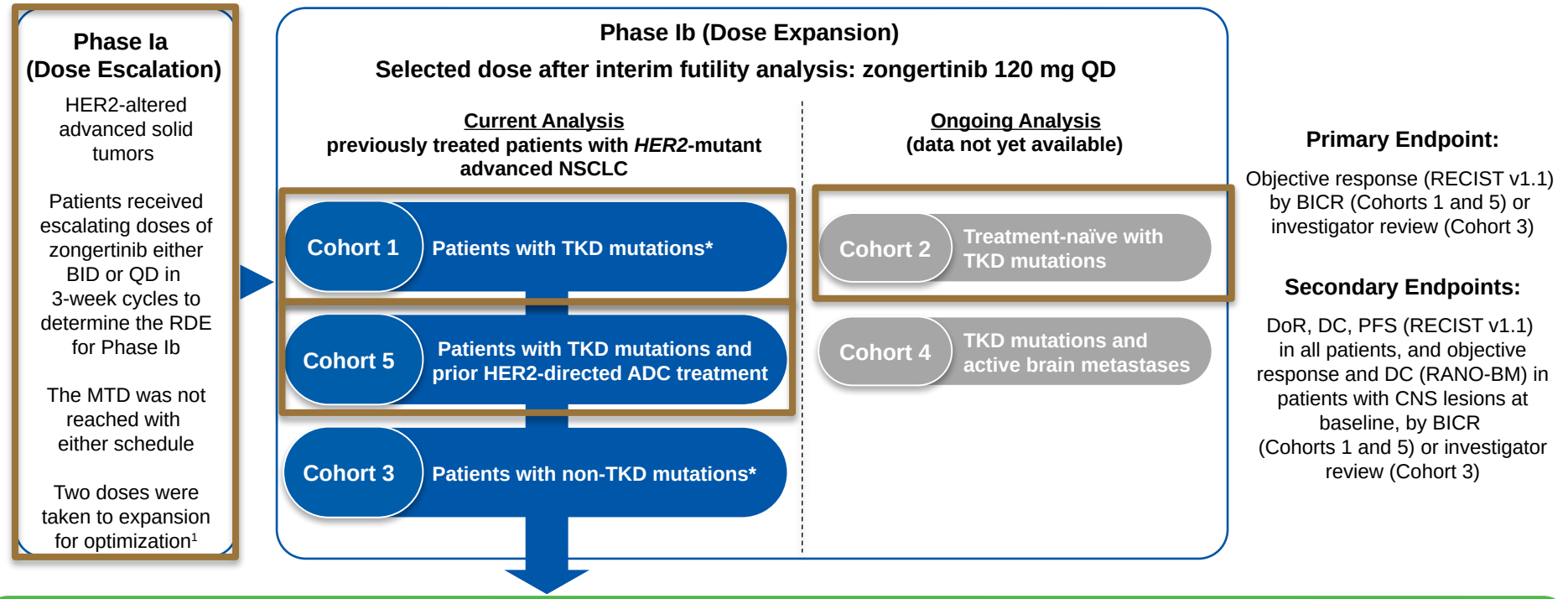






Cancer
UT MD Anderson

Beamion LUNG-1 study design

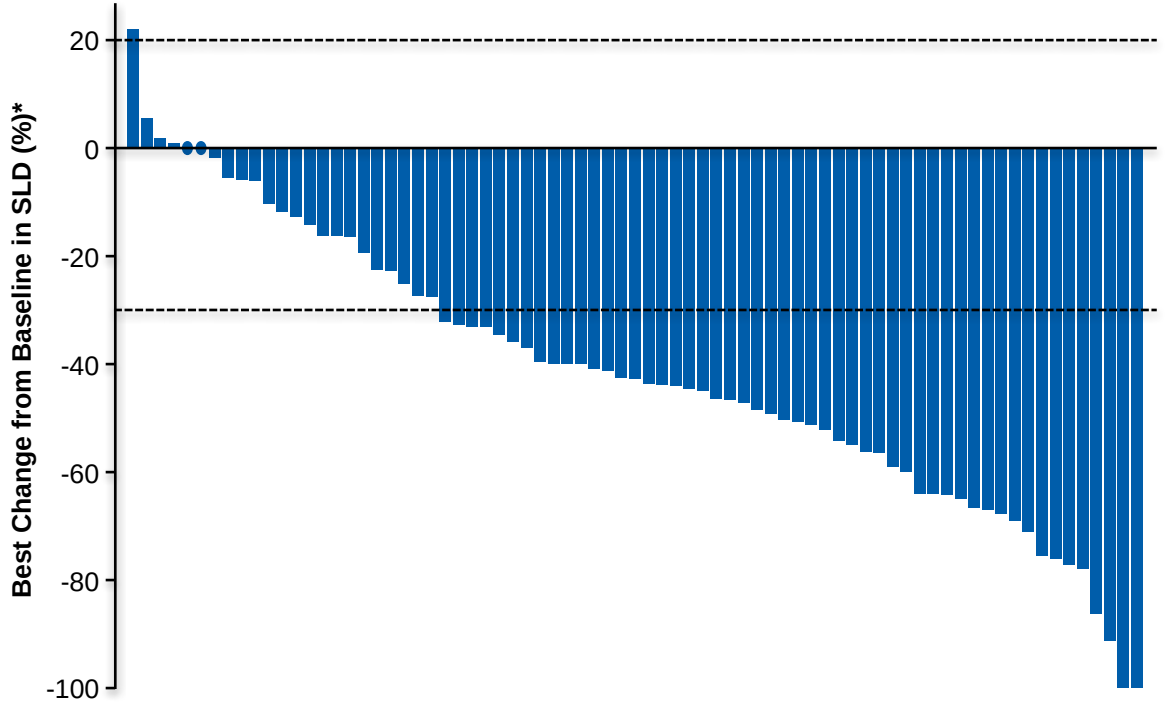


Here we present efficacy and safety data with zongertinib, including first mature time-to-event data from a data cut-off of November 29, 2024

Heymach et al. JCO. 2025;43:1337–47; Heymach et al NEJM 2025

Zongertinib in previously patients with TKD *HER2* mutations (cohort 1, 120 mg QD): tumor response

Confirmed response by BICR according to RECIST v1.1	Patients with TKD mutations N = 75
ORR	**71%**
95% CI	60–80
CR, %	7
PR, %	64
DCR	**96%**
95% CI	89–99
SD, %	25
PD, %	4



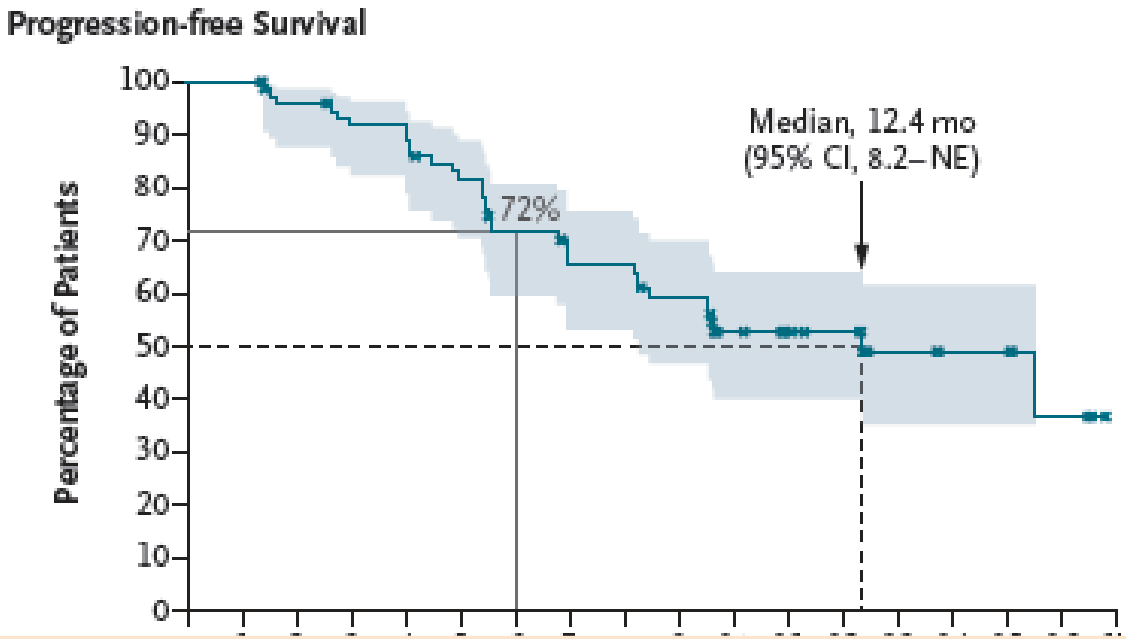
- The median best percentage change from baseline in target lesions was -43% (range, -100–22)*

Heymach et al. NEJM 2025; Heymach et al, Proc AACR 2025

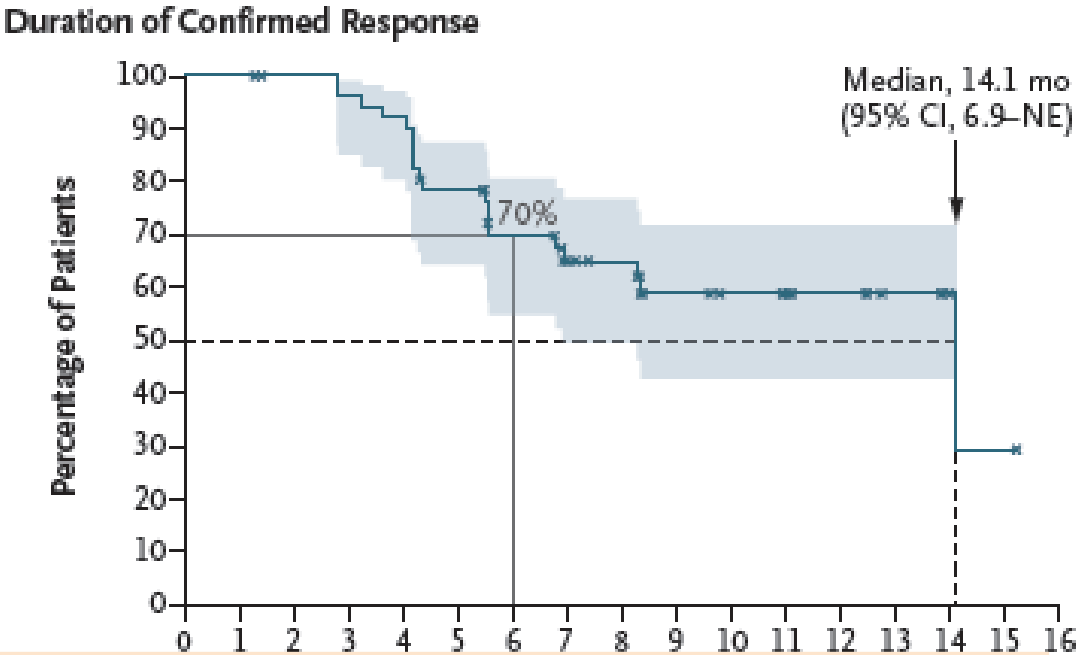
Median follow-up was 11.3 months (95% CI, 10.2–12.3)
*Due to the central review process, lesion measurements are only available for investigator assessment

Zongertinib in patients with TKD *HER2* mutations (Cohort 1, N=75): median PFS and mDoR

mPFS: 12.4 months (8.2–NE)



mDoR: 14.1 months (6.9-NE)



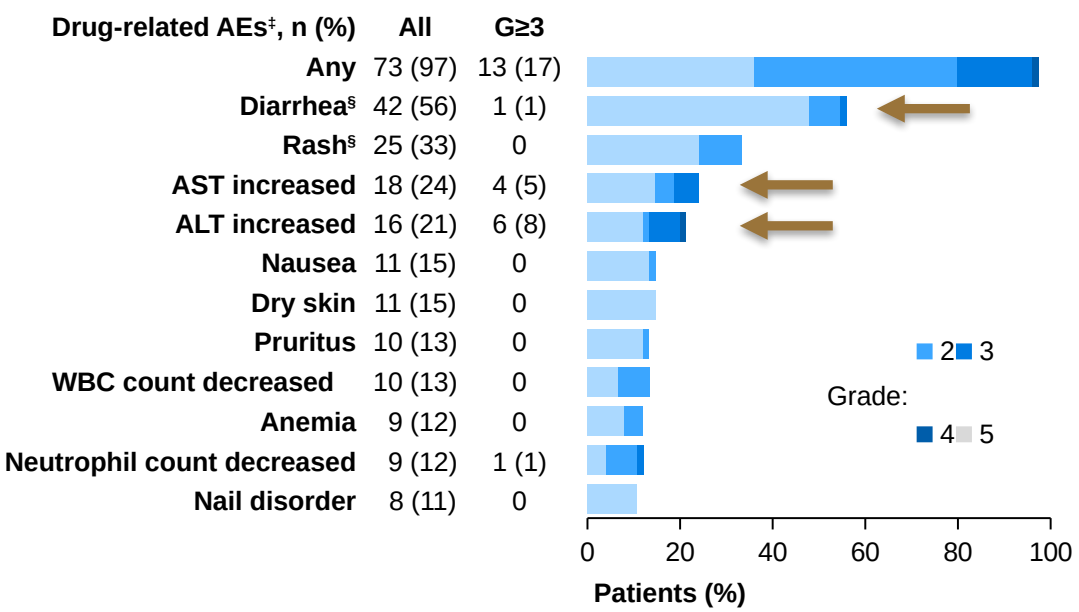
August 8, 2025: FDA grants accelerated approval to zongertinib for non-squamous NSCLC with HER2 TKD activating mutations

Heymach et al. NEJM 2025

Median follow-up was 11.3 months (95% CI, 10.2–12.3)

Zongertinib safety profile for Cohort 1

- In patients with TKD mutations (Cohort 1), most drug-related AEs were grade 1/2 and manageable
  - ➢ One patient had grade 3 drug-related diarrhea
  - ➢ Only 5 (7%) patients had AEs leading to **dose reduction***
  - ➢ Only 2 (3%) patients had AEs leading to **treatment discontinuation**†
- The safety profile of zongertinib was similar across the three cohorts, there were **no reported cases of drug-related ILD**



†AEs leading to treatment discontinuation: AST, ALT, GGT, or Alk phos increased, or pyrexia; ‡drug-related AEs as assessed by the investigator that occurred in ≥10% of patients are shown; §grouped terms

Zongertinib had a manageable safety profile with low incidence of Gr>drug related AeEs or dose reduction

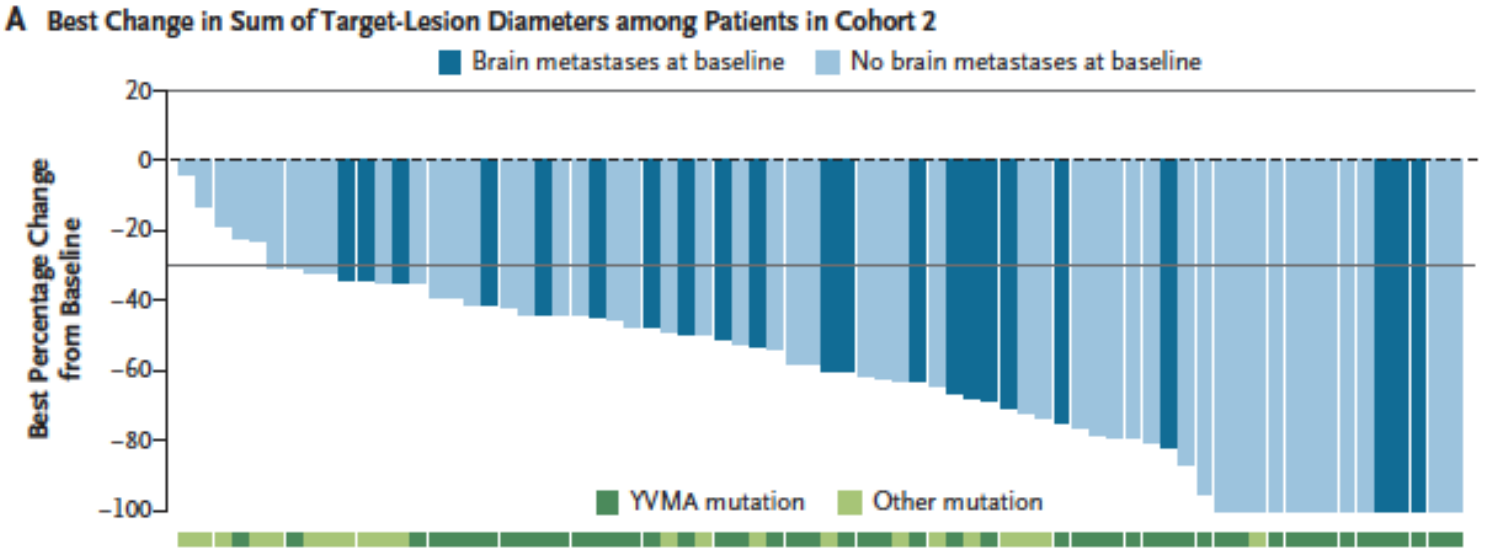
UT MD Anderson Cancer

Heymach et al NEJM 2025; Heymach et al, Proc AACR 2025

Zongertinib in 1L HER2 mutant NSCLC

ORR 76%

Confirmed response by BICR (RECIST v1.1)	Cohort 2: Treatment-naïve patients N = 74
ORR	**76%**
CR, n (%)	8 (11)
PR, n (%)	48 (65)
DCR	**96%**
SD, n (%)	15 (20)
PD, n (%)	1 (1)*



- Median time to objective response was 1.4 months (95% CI, 1.1 to 6.9)

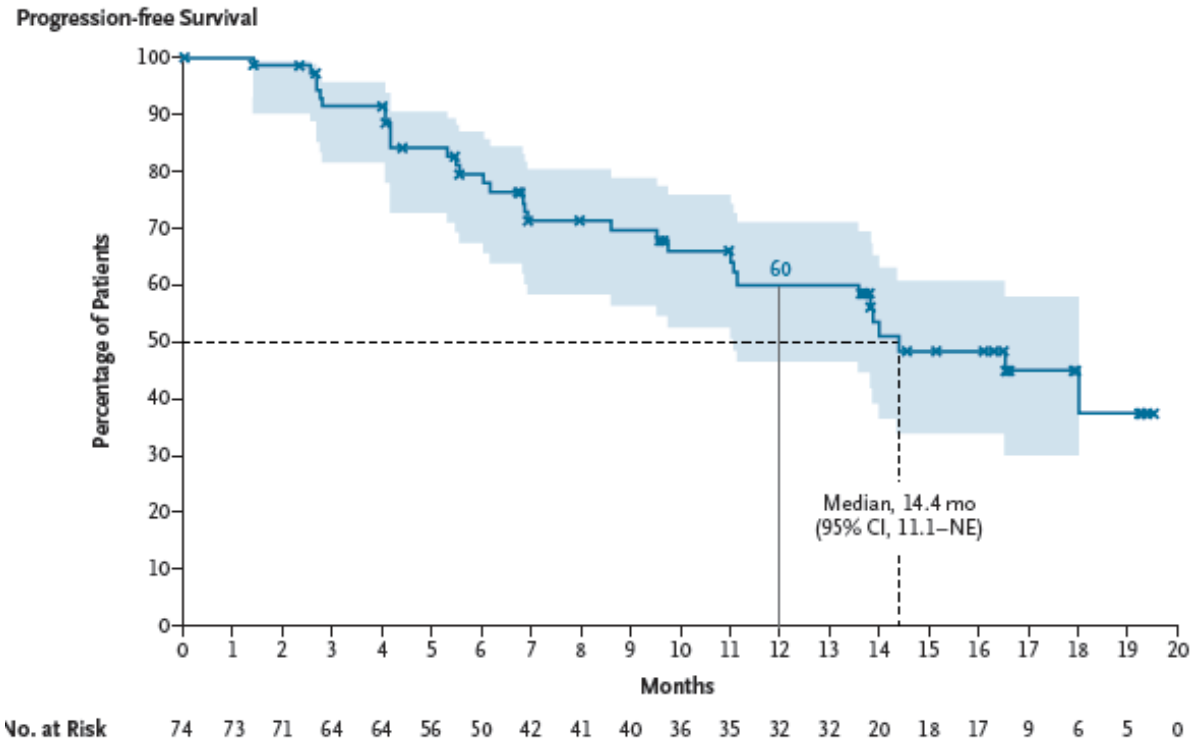
February 26, 2026: FDA granted accelerated approval to zongertinib as 1L for HER2 mutant NSCLC harboring HER2 (ERBB2) tyrosine kinase domain activating mutations.

UT MD Anderson Cancer

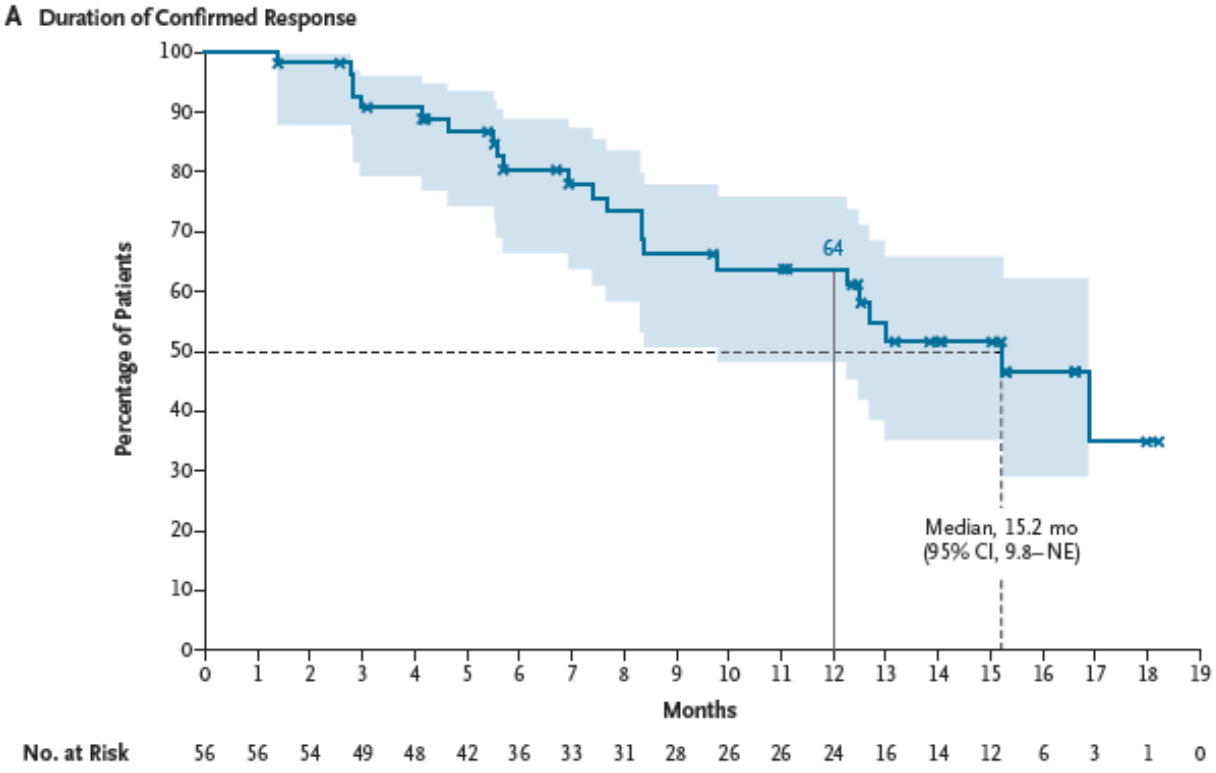
Heymach NEJM 2026; Heymach ELCC 2026

Zongertinib in 1L HER2 mutant NSCLC

mPFS 14.4 months



mDoR 15.2 months



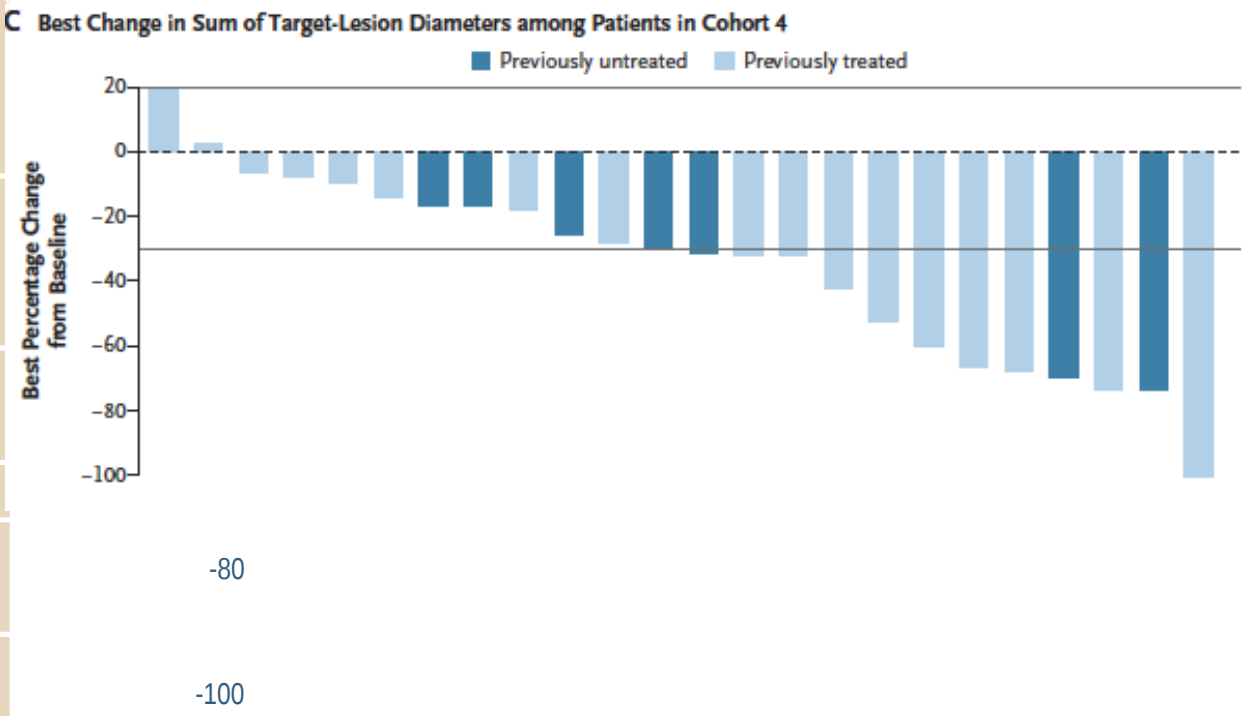
Cancer
UT MD Anderson

Heymach NEJM 2026; Heymach ELCC 2026

Zongertinib in 1L HER2 mutant NSCLC: Intracranial Tumor Response

ORR 47% (59% in those with no prior RT)

Confirmed intracranial response by BICR (RANO-BM)	Cohort 4: Active brain metastases	
	N = 30	No prior brain RT and confirmed measurable intracranial disease n = 17
ORR	**47%**	**59%**
CR, n (%)	2 (7)	1 (6)
PR, n (%)	12 (40)	9 (53)
DCR	**87%**	**94%**
SD, n (%)	12 (40)	6 (35)
NE, n (%)	4 (13)	1 (6)
Median DoR	**6.9 months**	**6.2 months**
95% CI	2.9–NE	2.7–NE
Median PFS	**8.2 months**	NE
95% CI	4.1–11.3	NE

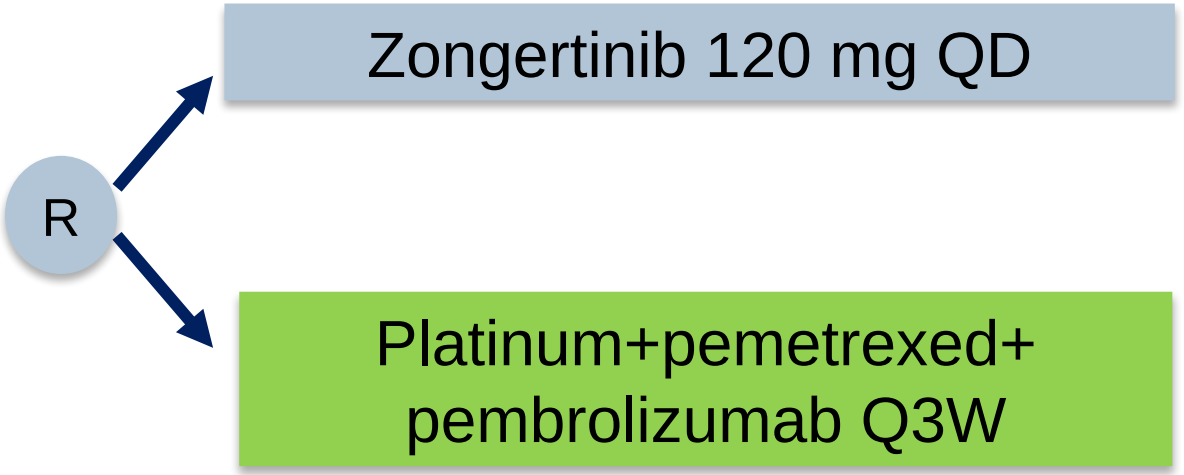


Heymach NEJM 2026; Heymach ELCC 2026

BEAMION-Lung 2: Randomized phase III trial of zongertinib vs chemotherapy+/-CPI as 1L for HER2 mutant NSCLC

Previously untreated locally advanced Her2 mutant NSCLC with TKD mutations
-stratified on YVMA mutation vs other mutations

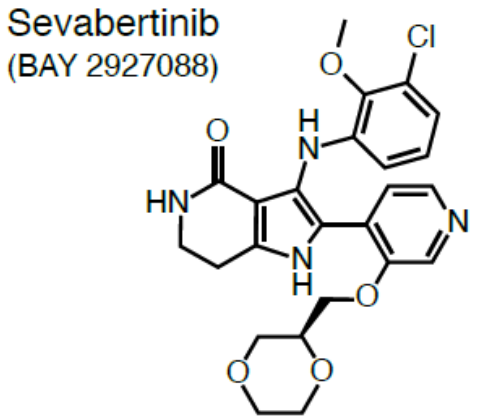
Primary endpoint: PFS
Secondary endpoints: ORR, OS, DoR, PRO, SAE

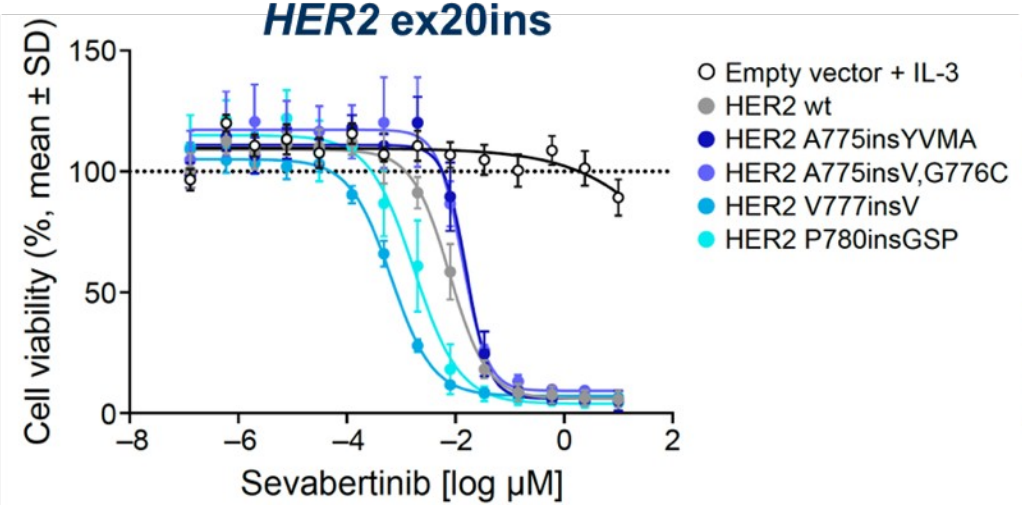


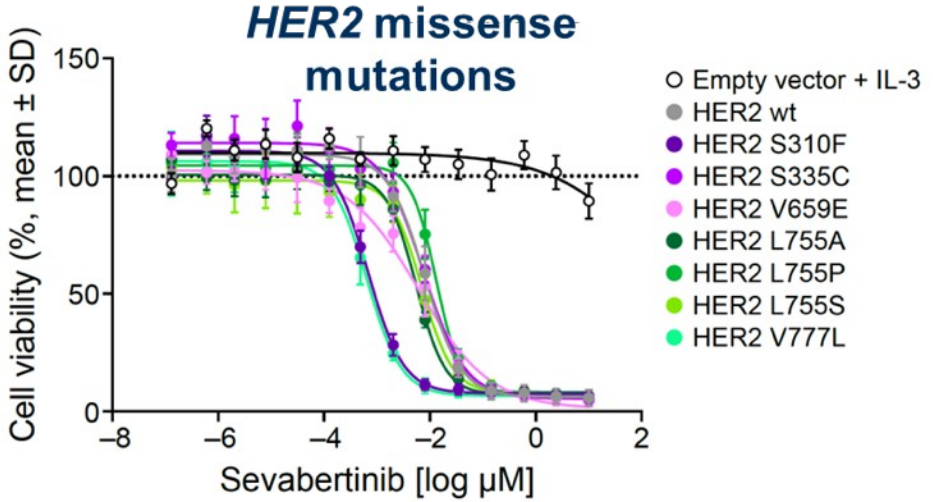
Cancer
UT MD Anderson

Sevabertinib is an oral, reversable HER2 TKI

- Sevabertinib is an oral, reversible TKI that potently inhibits activating *HER2* (*ERBB2*) mutations and has demonstrated efficacy against *HER2* insertions and missense mutations, secondary resistance including irreversible binding site mutation (C805S), and gatekeeper mutations (T798M/T798I)[1]
- Sevabertinib has anti-tumor activity and a manageable safety profile in patients with *HER2*-mutant NSCLC[2]
- In May 2025, the FDA granted NDA Priority Review for sevabertinib in patients with previously treated *HER2*-mutant NSCLC[3]





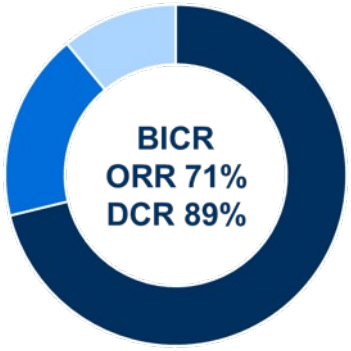


Cancer
UT MD Anderson

Le et al., ESMO 2025

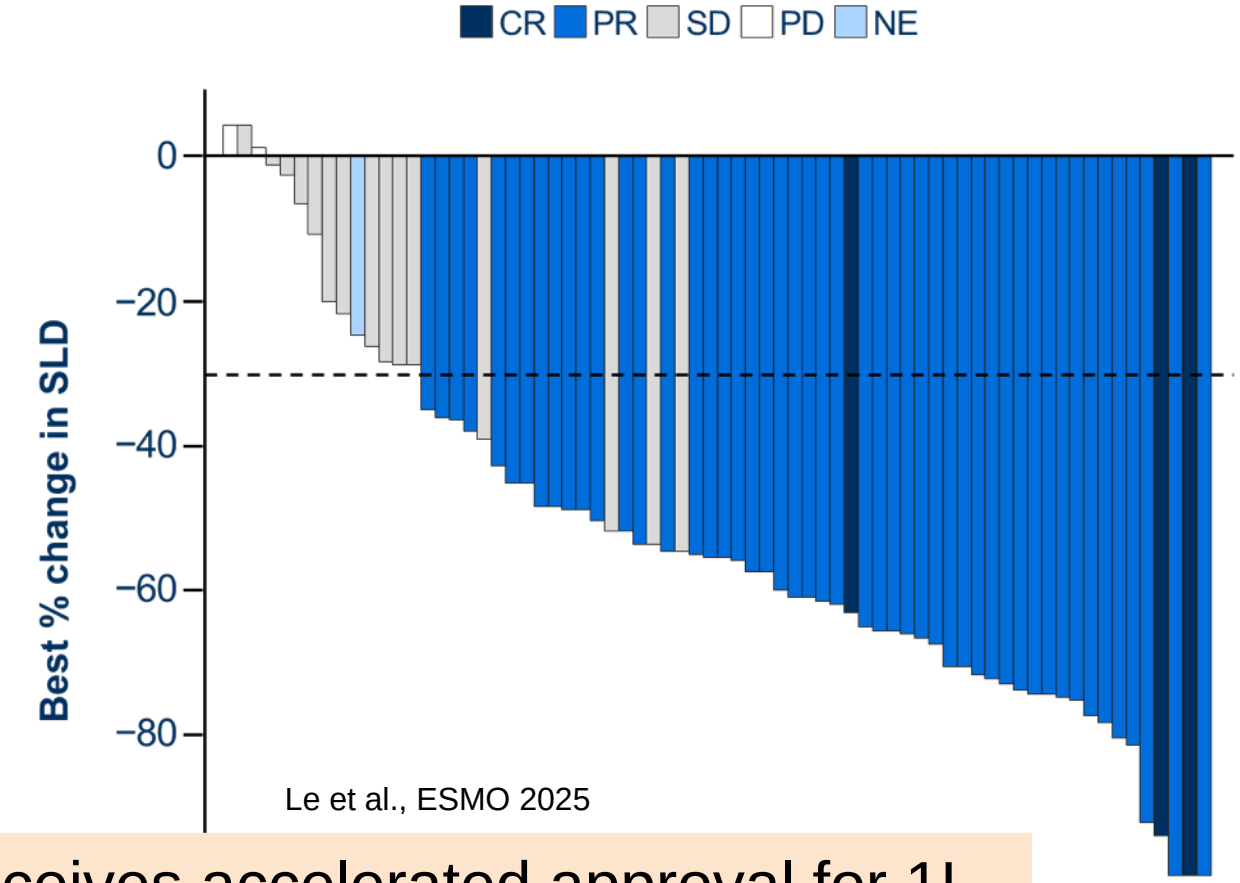
Cohort F (treatment-naïve, *n*=73): Objective response by BICR

Median follow-up: 9.9 months (range <1-15)



n (%)	
CR	3 (4)
PR	49 (67)
SD	16 (22)
PD	2 (3)
Not evaluable[a]	1 (1)
Not available[b]	2 (3)
ORR[c] [95% CI]	**52 (71)** [59, 81]
DCR[d] [95% CI]	**65 (89)** [80, 95]
DoR, median (months) [95% CI]	**11.0** [8.1, not estimable]
PFS, median (months) [95% CI]	Not estimable [9.6, not estimable]

ORR 71%



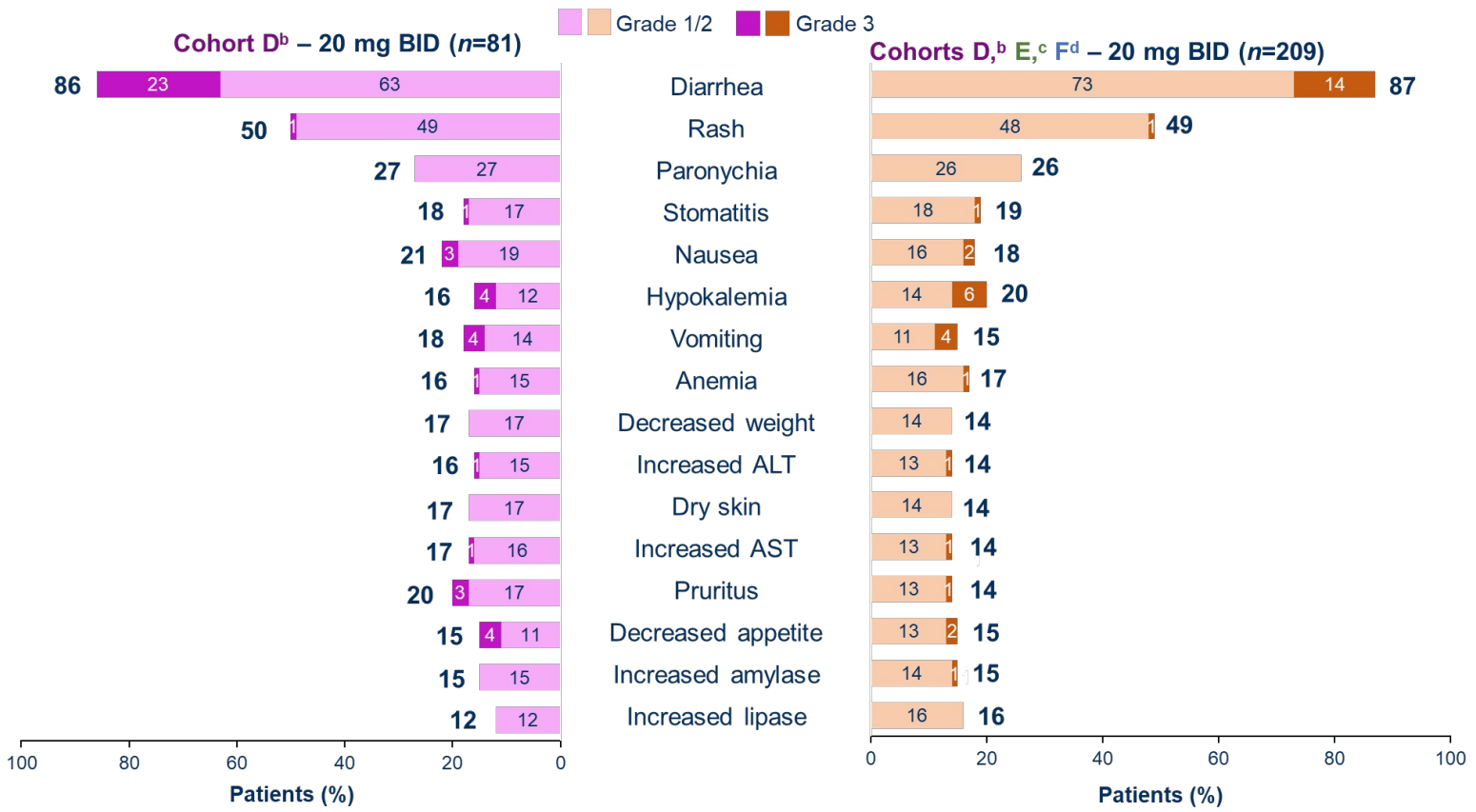
Le et al., ESMO 2025

Cancer
UT MD Anderson

Sept. 9, 2026: sevabertinib receives accelerated approval for 1L for HER2 TKD mutant NSCLC

Sevabertinib safety and tolerability

Most frequent treatment-related adverse events (≥10% of total)

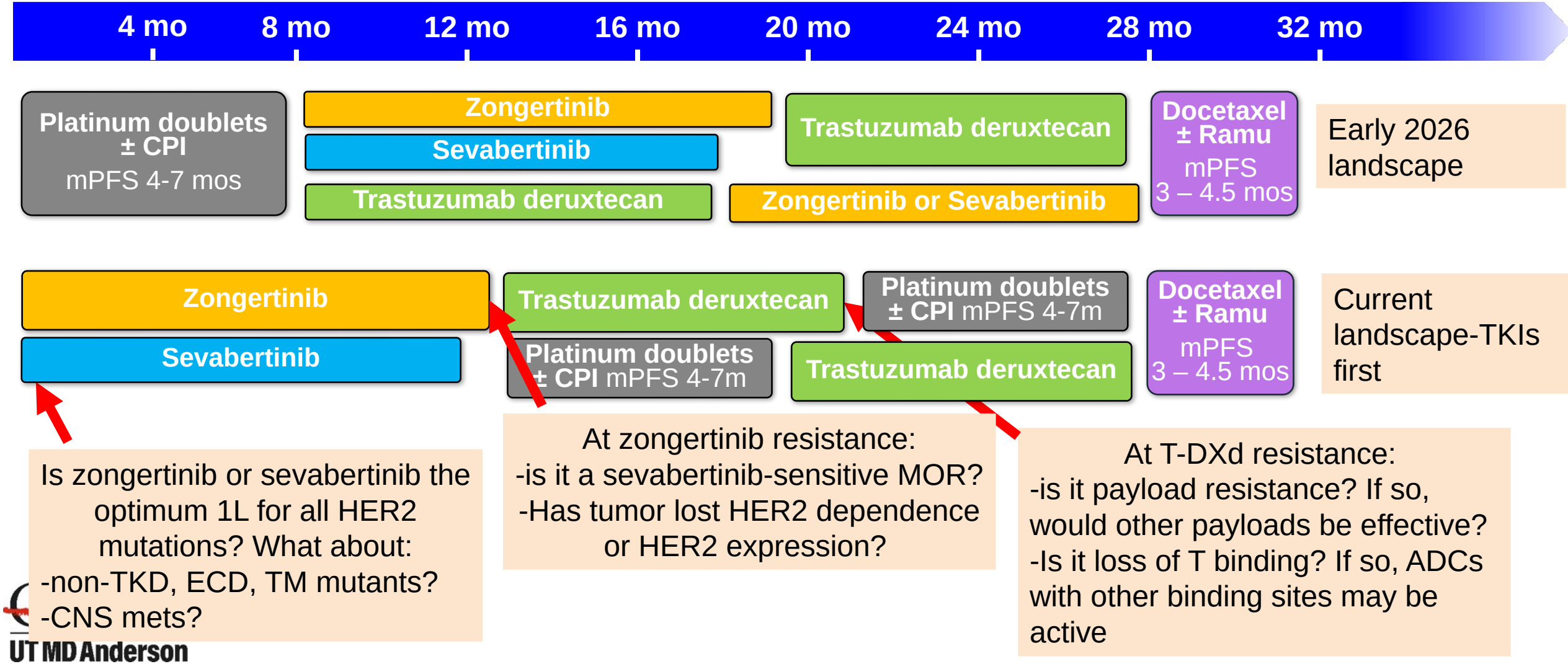


- Drug-related adverse events were reported in 96%, 100%, and 97% of patients in Cohorts D, E, and F, respectively
  - Grade 3 adverse events were reported in 29 (36%), 17 (31%), and 15 (21%) patients[e]
- Grade 3 diarrhea events were reported in 23% (D), 11% (E), and 5% (F) of patients
  - No grade 4 diarrhea
  - No treatment discontinuations due to diarrhea
- There were no cases of interstitial lung disease (ILD) or pneumonitis

Cancer
UT MD Anderson

Le et al., ESMO 2025

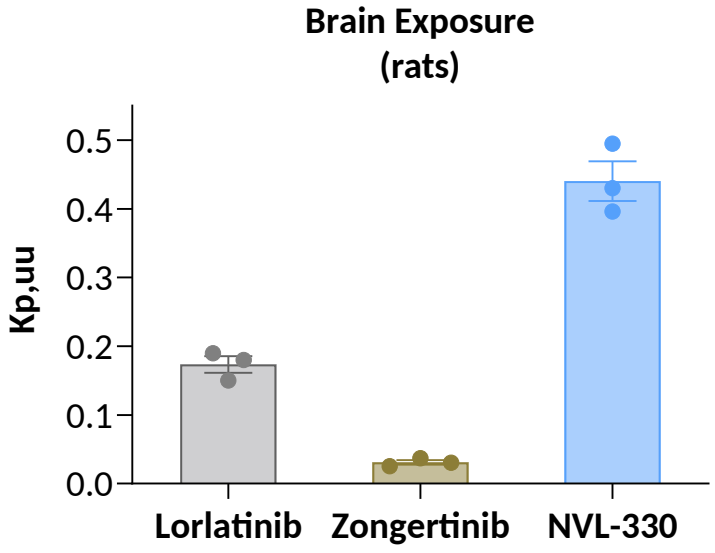
HER2 mutant NSCLC landscape and a roadmap to personalizing HER2 therapies



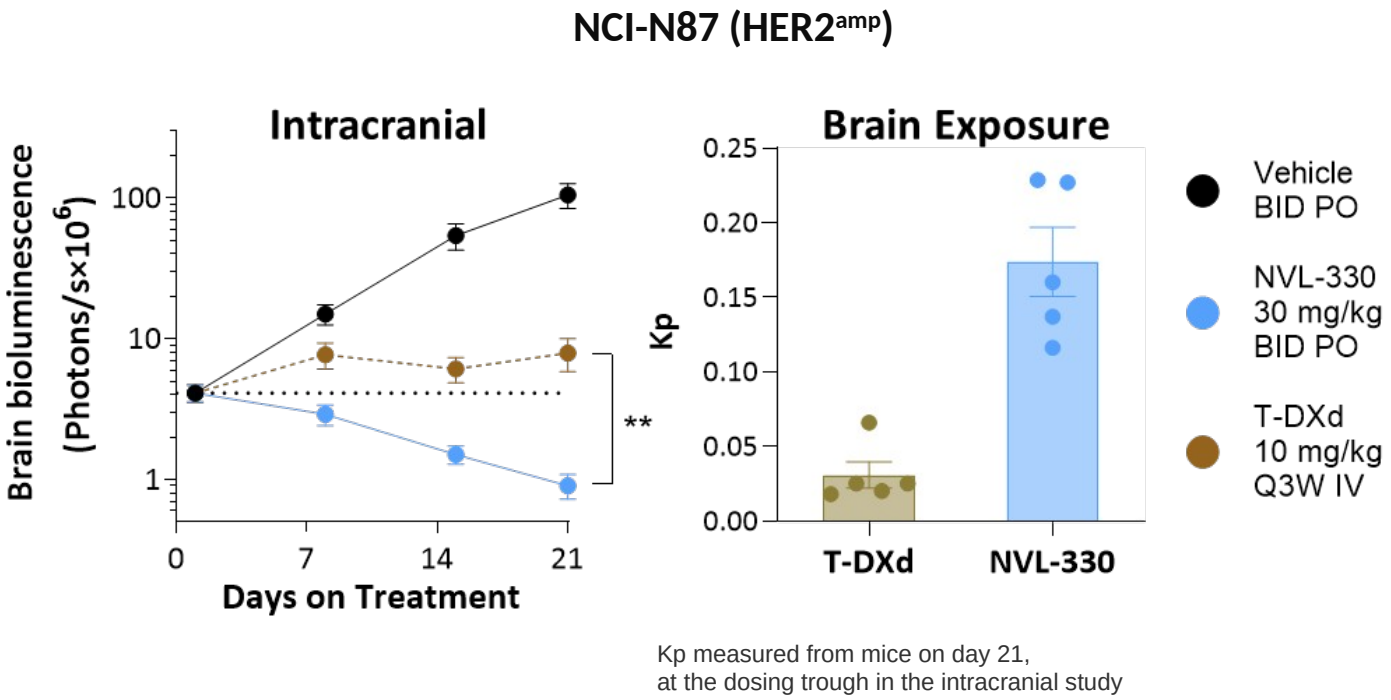
UT MD Anderson

NVL-330 has high CNS penetration vs other TKIs and improved intracranial activity vs T-DXd

- NVL-330 achieved deeper response and higher CNS penetrance in an intracranial tumor model at a clinically relevant concentration of TDXd



Wistar Han rats
10 mg/kg, single dose PO
1 hour timepoint



Kp measured from mice on day 21,
at the dosing trough in the intracranial study

Sun et al, Proc AACr-NCI-EORTC 2025; Mol Cancer Ther 2025;24(10 Suppl):Abstract nr B057; Nuvalent

31

IAM1363- phase I design

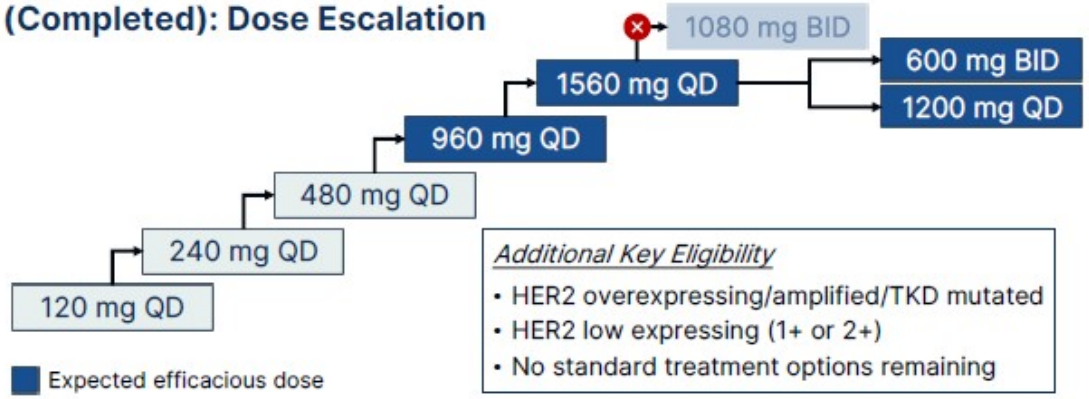
IAM1363-01 Study Design (Four Parts)

Key Eligibility Criteria (all parts)

- HER2-altered advanced cancers*
- Radiographically measurable disease by either/both of the following:
  - CNS disease: RANO-BM
  - Non-CNS disease: RECIST v1.1
- CNS metastases allowed†
- Measurable disease per modified RANO-BM: target lesions ≥5 mm
- Leptomeningeal and other non-measurable disease allowed

*Definition of HER2 alteration varies by study part
†Provided local therapy not indicated

Part 1 (Completed): Dose Escalation



Additional Key Eligibility
- HER2 overexpressing/amplified/TKD mutated
- HER2 low expressing (1+ or 2+)
- No standard treatment options remaining

Enrolling

Part 2: IAM1363 Monotherapy Dose Optimization

1:1 Ratio
- 960 mg QD
- 1200 mg QD

Additional Key Eligibility
- HER2+ per ASCO/CAP
- HER2 amplified per NGS
- HER2 TKD mutant
- Prior T-DXd allowed; no prior TKI in the metastatic setting*

*Participants with BC are allowed to have received prior tucatinib

Part 4: Combination Therapy Breast Cancer Cohorts

Cohort 4A
IAM1363 + Trastuzumab + Capecitabine

Cohort 4B
IAM1363 + Zanidatamab + Capecitabine

Additional Key Eligibility
- HER2+ per ASCO/CAP
- Prior T-DXd required; prior TKI in metastatic setting, including tucatinib, prohibited

Recommended Dose (Monotherapy)

Part 3 (Pending Recommended Dose): Monotherapy Expansion Basket Cohorts

Cohort A:
HER2 TKD mutant cancers; no prior TKI

Cohort B:
HER2+/amplified cancers, no prior TKI

Cohort C:
HER2 TKD mutant & HER2+/amplified cancers; prior TKI required

Cancer
UT MD Anderson

Chandana et al. ESMO 2025

Summary

- New HER2-specific TKIs are active in HER2 mutant NSCLC
  - Zongertinib is now approved for 1L, 2L NSCLC
  - Sevabertinib approved after platinum therapy
- Trastuzumab deruxtecan resistance is mediated, at least in part, via payload resistance mechanisms (e.g. SFLN11 loss, Top2 alterations)
- TKIs have distinct mechanisms of resistance which can help guide rational sequencing
- Emerging TKIs may improve selectivity and CNS penetration