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Zongertinib in Patients with Previously Treated *HER2*-mutant Advanced NSCLC: Beamion LUNG-1

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Disclosure Information

John V. Heymach, MD, PhD

I have the following relevant financial relationships to disclose:

- Advisory committees – AstraZeneca, Abbvie, Anheart, Boehringer Ingelheim, Bayer, BioAtla, BioNTech, Bristol Myers Squibb, Dizal, Ellipsis, EMD Serono, Genentech, GlaxoSmithKline, Hengrui Therapeutics, Janssen Global Services, Eli Lilly, ModeX Therapeutics, Novartis, Pfizer, Remunity, Sanofi, Spectrum, Takeda, Leads Biolabs, Regeneron
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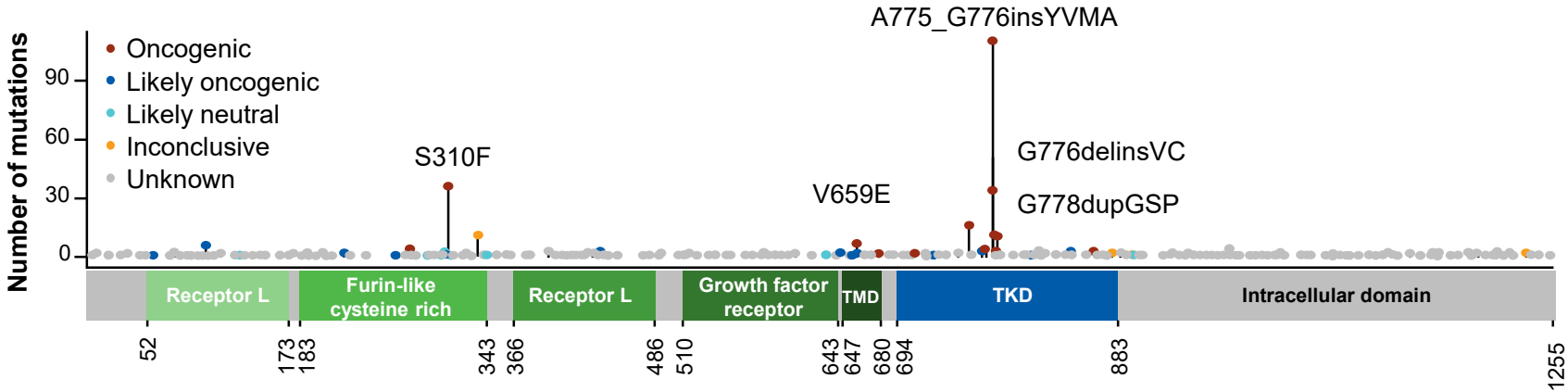
HER2 Mutations in NSCLC

- ~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

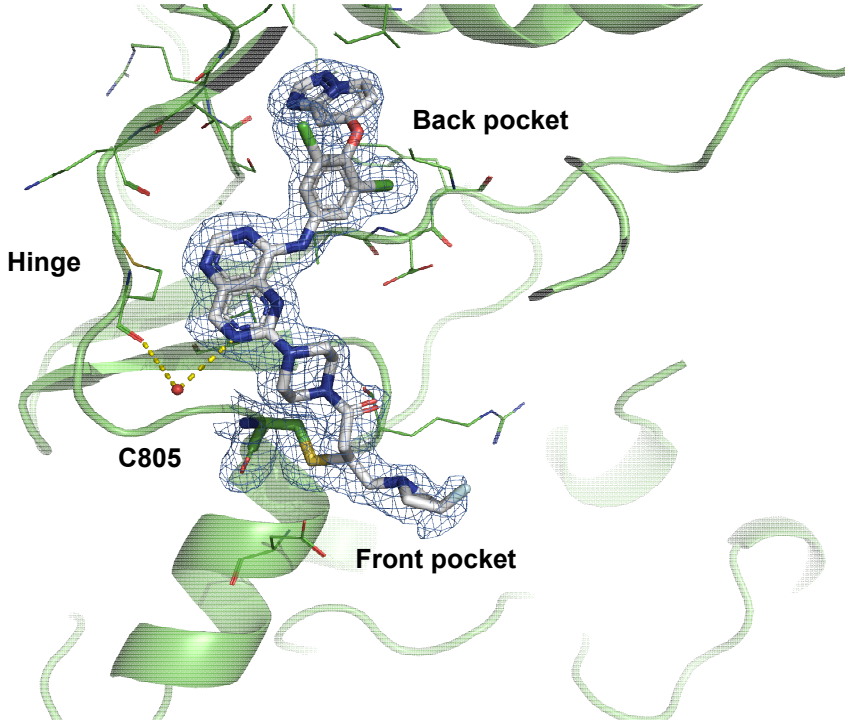
Mutational profile of *HER2* mutations in NSCLC[3]*



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
*Figure by Le X et al. ESMO. 2024. Poster 1298, used with permission from the authors, with minor amends

Historical Challenge in Targeting *HER2* Mutations in NSCLC

- *HER2* mutations (particularly exon 20 insertions) can change the size of the binding pocket, impacting drug sensitivity[1,2]
- EGFR and HER2 have structurally related kinases and historically many TKIs inhibiting *HER2* mutations also inhibited wild-type EGFR, leading to EGFR-related toxicities such as rash and diarrhea[2]
- Zongertinib was designed to address the need for a HER2-selective TKI that spares wild-type EGFR[2,3]



1. Robichaux JP et al. Cancer Cell. 2019;36:444–57; 2. Wilding B et al. Nat Cancer. 2022;3:821–83; 3. Wilding B et al. Cancer Discov. 2025;15:119–38
*Figure by Wilding B et al. Discovery of potent and selective HER2 inhibitors with efficacy against HER2 exon 20 insertion-driven tumors, which preserve wild-type EGFR signaling. Nat Cancer. 2022;3:821–36.

Clinical Limitations in Targeting *HER2* Mutations in NSCLC

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

	N	ORR (%)	Median PFS (months)	G≥3 TRAEs (%)	Drug-related ILD (%)
Antibody–drug conjugates					
T-DM1 (NCT02675829)[6]	18	44	5.0	NR	NR
T-DXd 5.4 mg/kg (DESTINY-Lung02)[7]	102	49	9.9	39	13

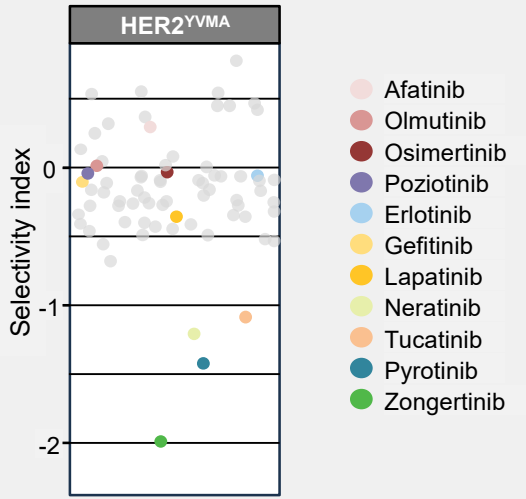
There remains a clear unmet need for a potent TKI that selectively inhibits HER2 while sparing wild-type EGFR

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

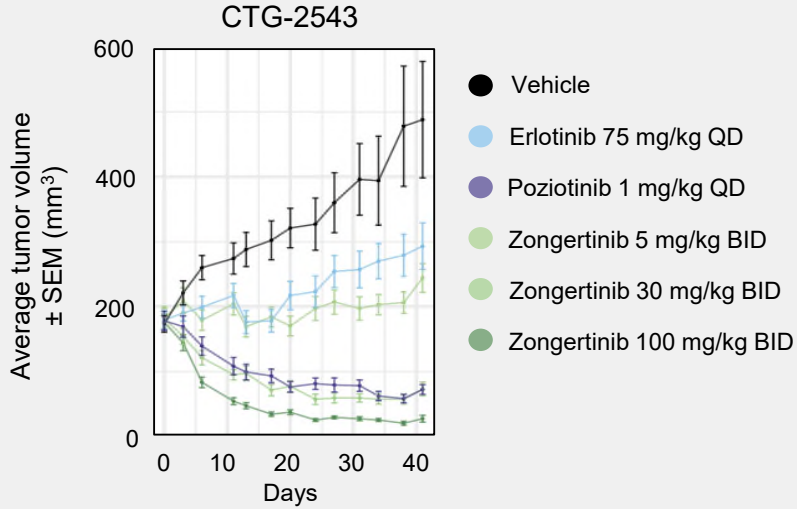
*Safety data from larger study in patients with *EGFR*-mutant NSCLC (n=227; Wu YL et al. Lancet. 2017,18:1454–66); †treatment-emergent diarrhea data from the entire basket study in patients with *HER2/3*-mutant cancers (n=141)

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 limiting associated toxicities

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

Beamion LUNG-1 Study Design

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[1]

Phase Ib (Dose Expansion)

Selected dose after interim futility analysis: zongertinib 120 mg QD

Current Analysis
previously treated patients with *HER2*-mutant 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*

Ongoing Analysis
(data not yet available)

- **Cohort 2** — Treatment-naïve with TKD mutations
- **Cohort 4** — TKD mutations and active brain metastases

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)

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

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

*Excluding those previously treated with a HER2-directed ADC

Baseline Characteristics

	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

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

Zongertinib in Patients with TKD *HER2* Mutations (Cohort 1, 120 mg QD): Tumor Response

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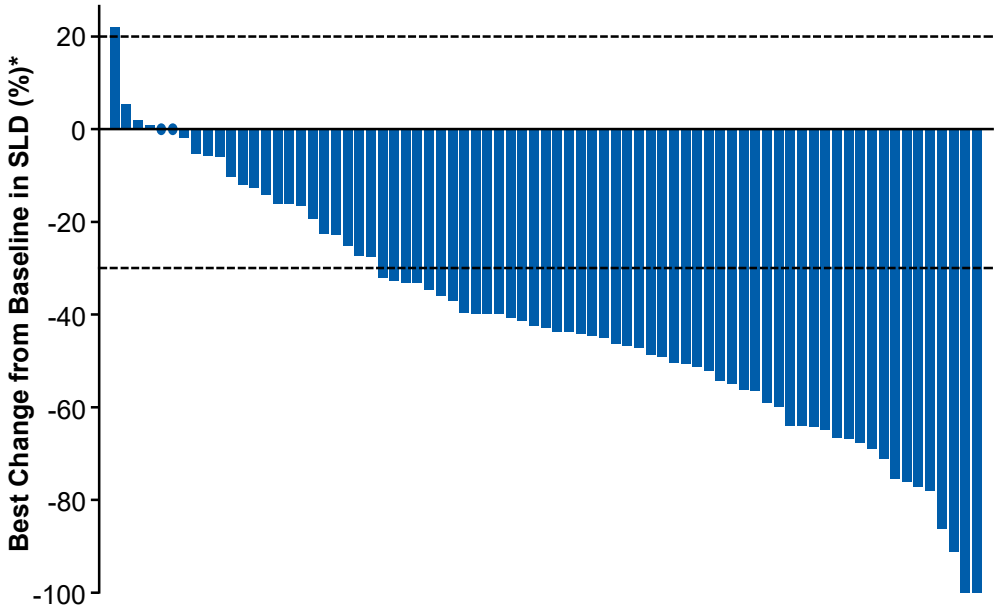
Confirmed response by BICR according to RECIST v1.1	Patients with TKD mutations N = 75
ORR	**71%**
95% CI	60–80
CR, %	7
PR, %	64
DCR	**96%**
95% CI	89–99
SD, %	25
PD, %	4



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

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 Patients with TKD *HER2* Mutations (Cohort 1): Tumor Response

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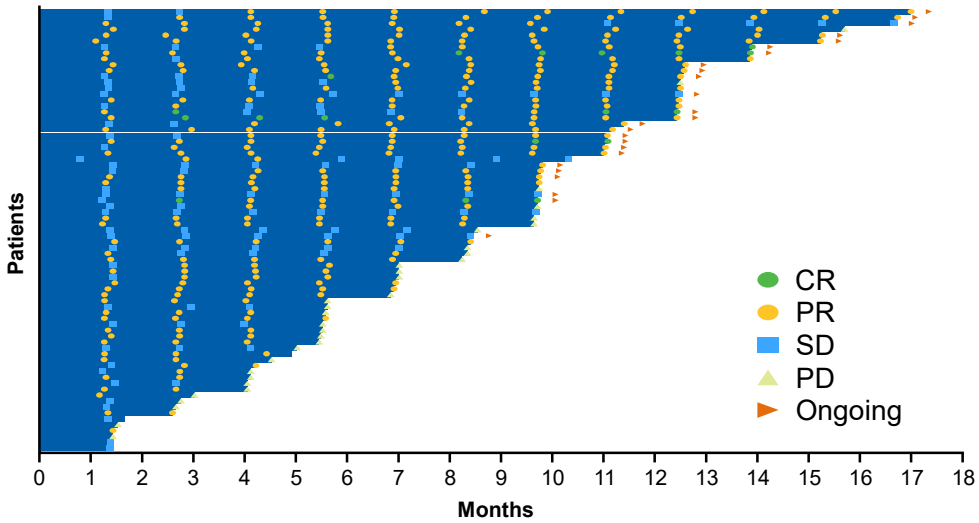
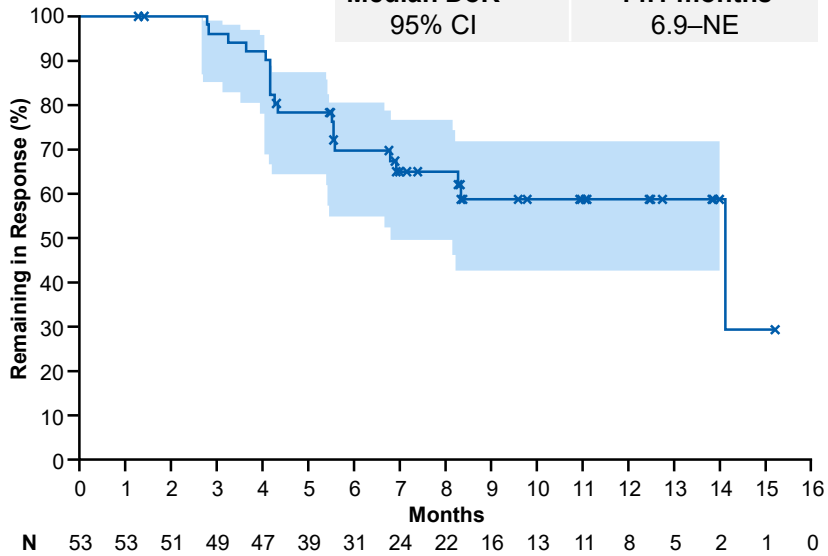
- At data cut-off, 44% of patients remained on treatment
- Median time to objective response was 1.4 months (range, 1.1–6.9)

	Patients with TKD mutations N = 75
Median DoR 95% CI	**14.1 months** 6.9–NE





Responses to zongertinib were durable, the majority were observed at the first assessment

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

Zongertinib in Patients with TKD *HER2* Mutations (Cohort 1): Median PFS

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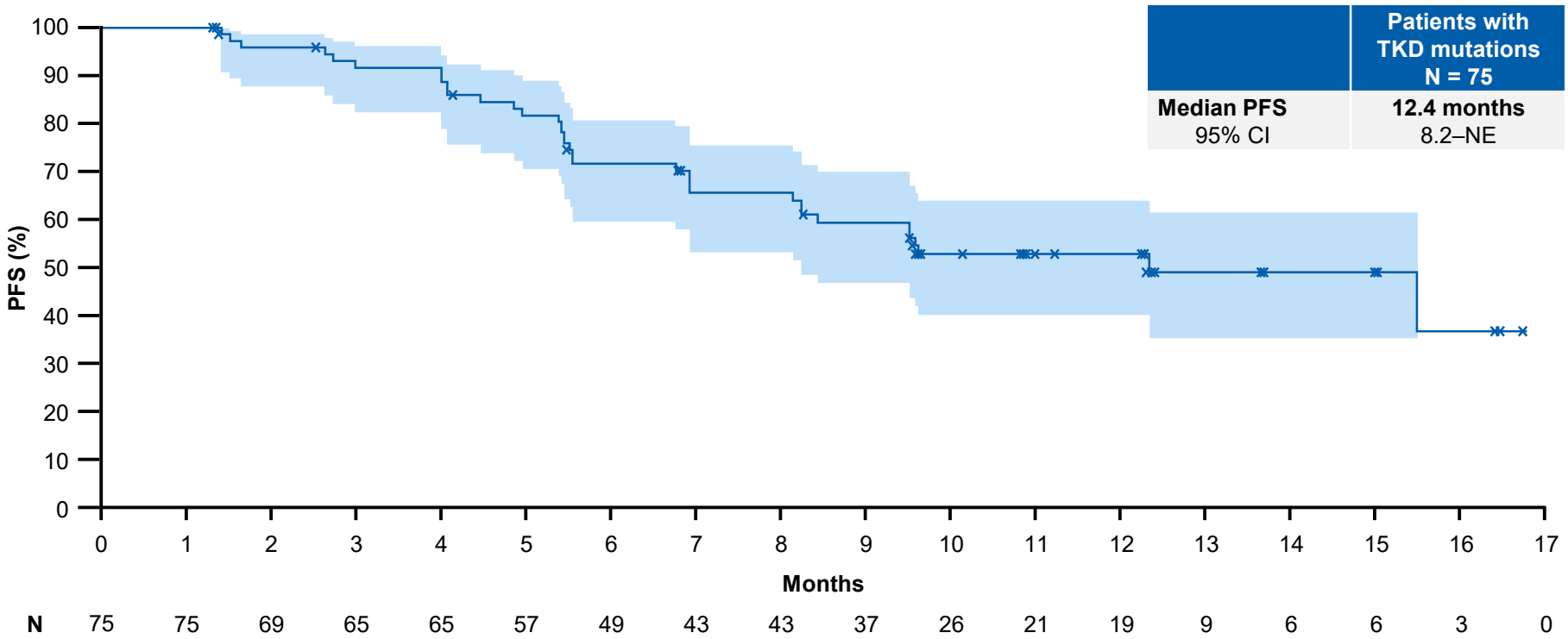

	Patients with TKD mutations N = 75
Median PFS 95% CI	**12.4 months** 8.2–NE

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

Intracranial Activity of Zongertinib in Patients with TKD *HER2* Mutations (Cohort 1)

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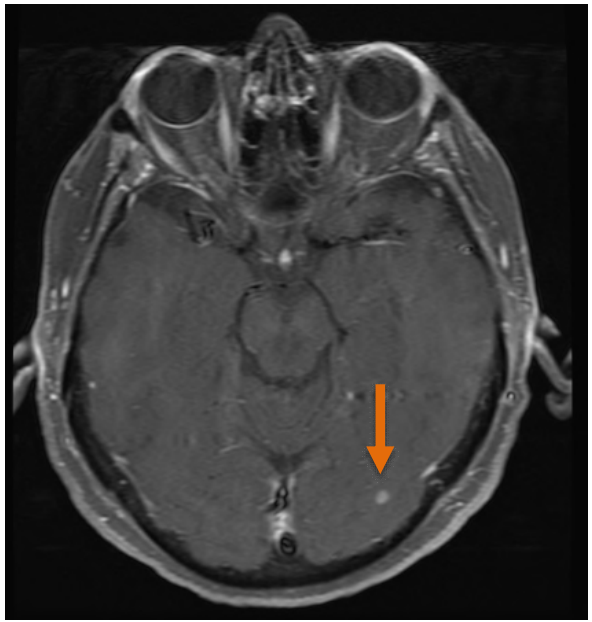
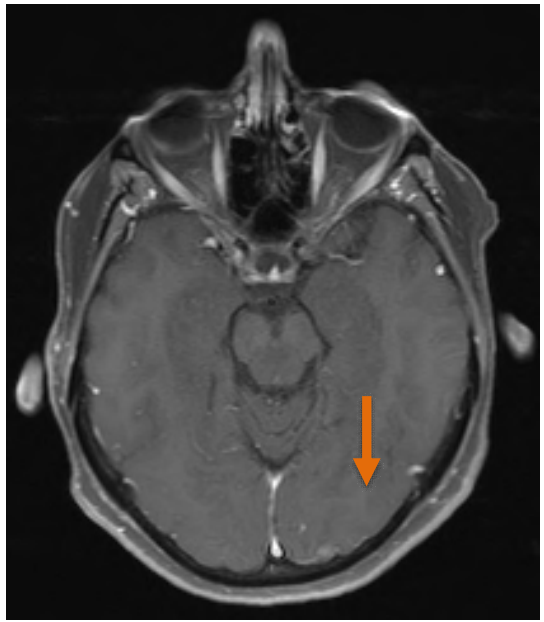
Confirmed intracranial response by BICR , RANO-BM	TKD mutations* N = 27
ORR	**41%**
95% CI	25–59
CR, %	15
PR, %	26
DCR	**81%**
95% CI	63–92
SD, %	41
PD, %	7
NE, %	11

Baseline



12 weeks

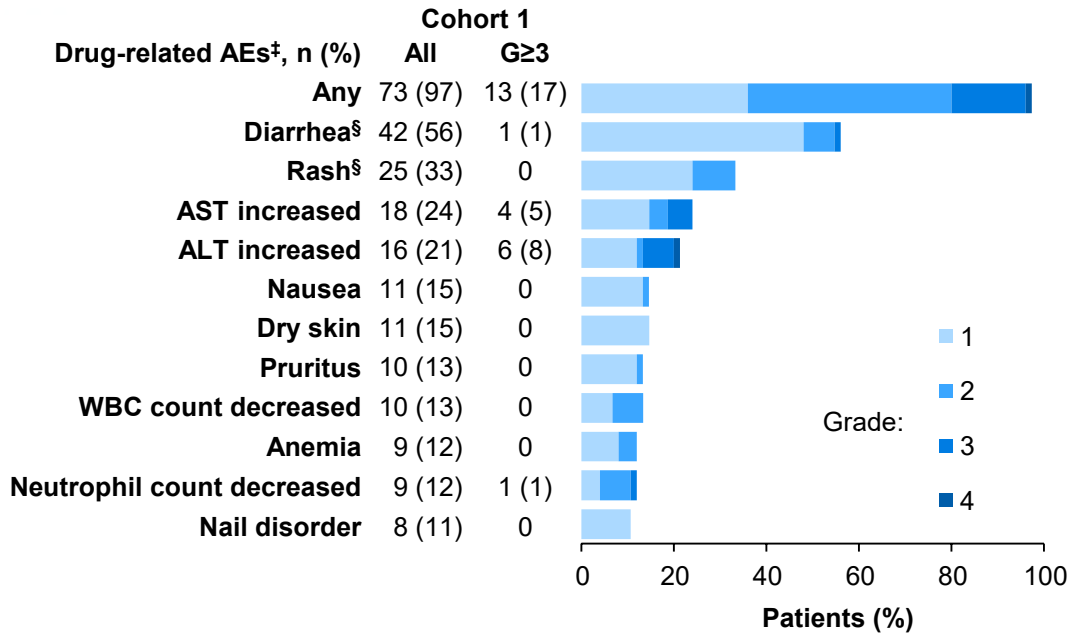


Zongertinib demonstrated intracranial activity in patients with brain metastases, 81% of patients achieved disease control

*Patients eligible for RANO-BM assessment only (patients where any target or non-target lesion was entered for RANO-BM assessment at baseline)

Zongertinib Safety Profile

- In patients with TKD mutations (Cohort 1), most drug-related AEs were grade 1/2 and manageable
  - ➢ Only 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**



Zongertinib had a manageable safety profile with notably low incidence of grade ≥3 drug-related AEs or dose reductions

*AEs leading to dose reduction: AST increased, ALT increased, blood creatinine phosphokinase increased, gamma-glutamyltransferase increased, hypertransaminasemia, neutrophil count decreased, and suspected drug-induced liver injury; †AEs leading to treatment discontinuation: AST increased, ALT increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, and pyrexia; ‡drug-related AEs as assessed by the investigator that occurred in ≥10% of patients are shown; §grouped terms

Zongertinib in Patients Previously Treated with HER2-directed ADC Treatment (Cohort 5): Tumor Response

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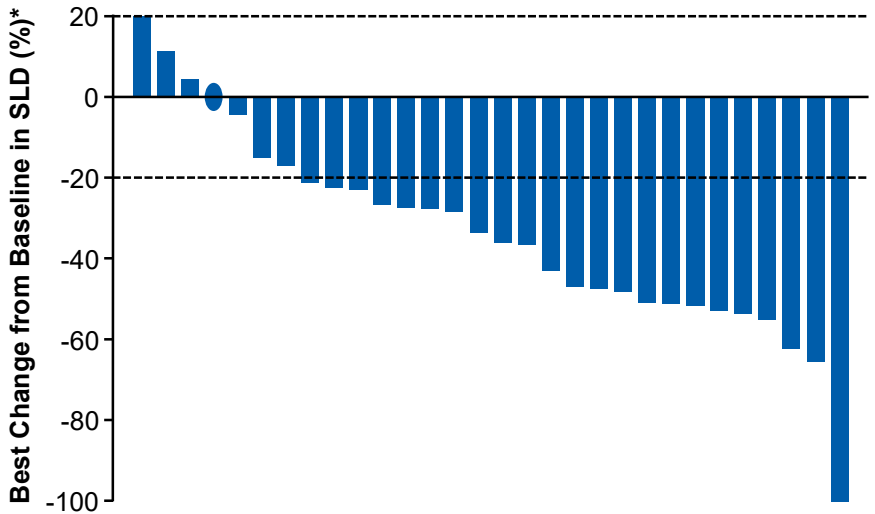
- In preclinical studies, zongertinib demonstrated activity in T-DXd resistant tumor models[1,2]
- In the 31 patients with TKD mutations and prior HER2-directed ADC treatment, the ORR was 48% (95% CI, 32–65)
- In the 22 patients who had received prior T-DXd treatment, the ORR was 41% (95% CI: 23–61)

Confirmed response by BICR (RECIST v1.1)	Patients with TKD mutations and prior HER2-directed ADC (N=31)
ORR	**48%**
95% CI	32–65
CR, %	3
PR, %	45
DCR	**97%**
95% CI	84–99
SD, %	48
PD, %	0
NE, %	3



Zongertinib demonstrated clinical activity in patients previously treated with HER2-directed ADCs

1. Wilding B et al. Cancer Discov. 2025;15:119–38; 2. Nilsson et al, Proceedings of the 115th AACR Annual Meeting, 2024, Abstract 5857

Median follow-up was 6.8 months (95% CI, 5.5 to 8.5); *Due to the central review process, lesion measurements are only available for investigator assessment

Zongertinib in Patients with Non-TKD *HER2* Mutations (Cohort 3): Tumor Response

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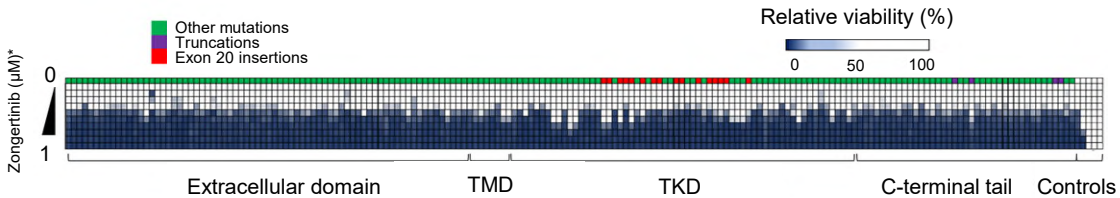
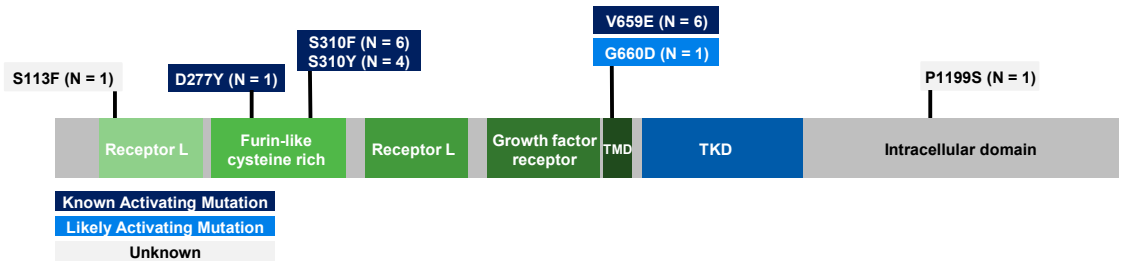
- Zongertinib is potent against both TKD and non-TKD *HER2* mutations in preclinical studies[1]





- Among the 20 non-TKD mutations, 17 were known activating mutations and 3 were of uncertain function[2]

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

Zongertinib demonstrated meaningful clinical activity with 65% of patients achieving disease control in the largest known dataset in this patient population

1. Wilding B et al. Cancer Discov. 2025;15:119–38 2. OncoKBTM. ERBB2. Available at www.oncokb.org/gene/ERBB2. Accessed on 7th April 2025

 Median follow up was 8.3 months (95% CI: 2.8–NE)

Conclusions and Future Directions

- Zongertinib provided clinically meaningful benefit in previously treated patients with advanced NSCLC with *HER2* mutations within and outside the TKD, including in patients with brain metastases
  - In patients with TKD mutations (Cohort 1), the ORR was 71% and median DoR and PFS were both over a year, 14.1 months and 12.4 months, respectively
- Zongertinib had a manageable safety profile which was consistent across all cohorts, with a notably low incidence of grade ≥3 drug-related AEs, including those related to EGFR
  - There were no reported cases of drug-related ILD across cohorts
- Zongertinib is currently under Priority Review by the FDA for patients with advanced, unresectable, or metastatic NSCLC whose tumors have activating *HER2* mutations and who have received prior systemic therapy
- Beamion LUNG-2 (NCT06151574), a Phase III randomized study evaluating first-line zongertinib versus standard of care in patients with unresectable, locally advanced or metastatic *HER2*-mutant NSCLC, is currently enrolling

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ORIGINAL ARTICLE

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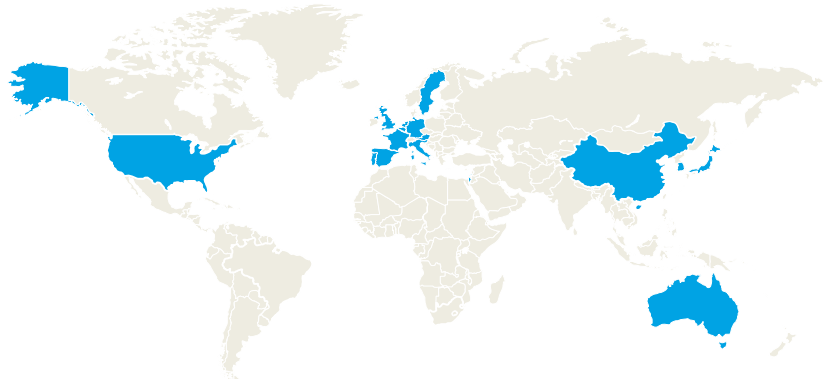
Beamion LUNG-1 Study Locations



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Abbreviations

ADC, antibody–drug conjugate
AE, adverse event
ALT, alanine aminotransferase
AST, aspartate aminotransferase
BICR, blinded independent central review
BID, twice daily
CI, confidence interval
CNS, central nervous system
CR, complete response
DC, disease control
DCR, disease control rate
DoR, median duration of response
ECD, extracellular domain
ECOG PS, Eastern Cooperative Oncology Group performance status
EGFR, epidermal growth factor receptor
FDA, Food and Drug Administration
G, grade
HER2, human epidermal growth factor receptor 2
ILD, interstitial lung disease
MTD, maximum tolerated dose
NE, not evaluable
NR, not reported
NSCLC, non-small cell lung cancer
ORR, objective response rate
PD, progressive disease
PFS, progression-free survival
PR, partial response
QD, once daily
RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases
RDE, recommended dose for expansion
RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1
SD, stable disease
SEM, standard error of the mean
SLD, sum of lesion diameters
T-DXd, trastuzumab deruxtecan
TKD, tyrosine kinase domain
TKI, tyrosine kinase inhibitor
TMD, transmembrane domain
WBC, white blood cell