Improving HER2 Targeting in NSCLC With Selective TKI

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Disclosures

- Consulting/Honoraria:
  - Blueprint Medicines, Daiichi Sankyo, Merck, Bayer, AstraZeneca, Janssen, Takeda, Eli Lilly, Boehringer Ingelheim

- Research Support (To Institution):
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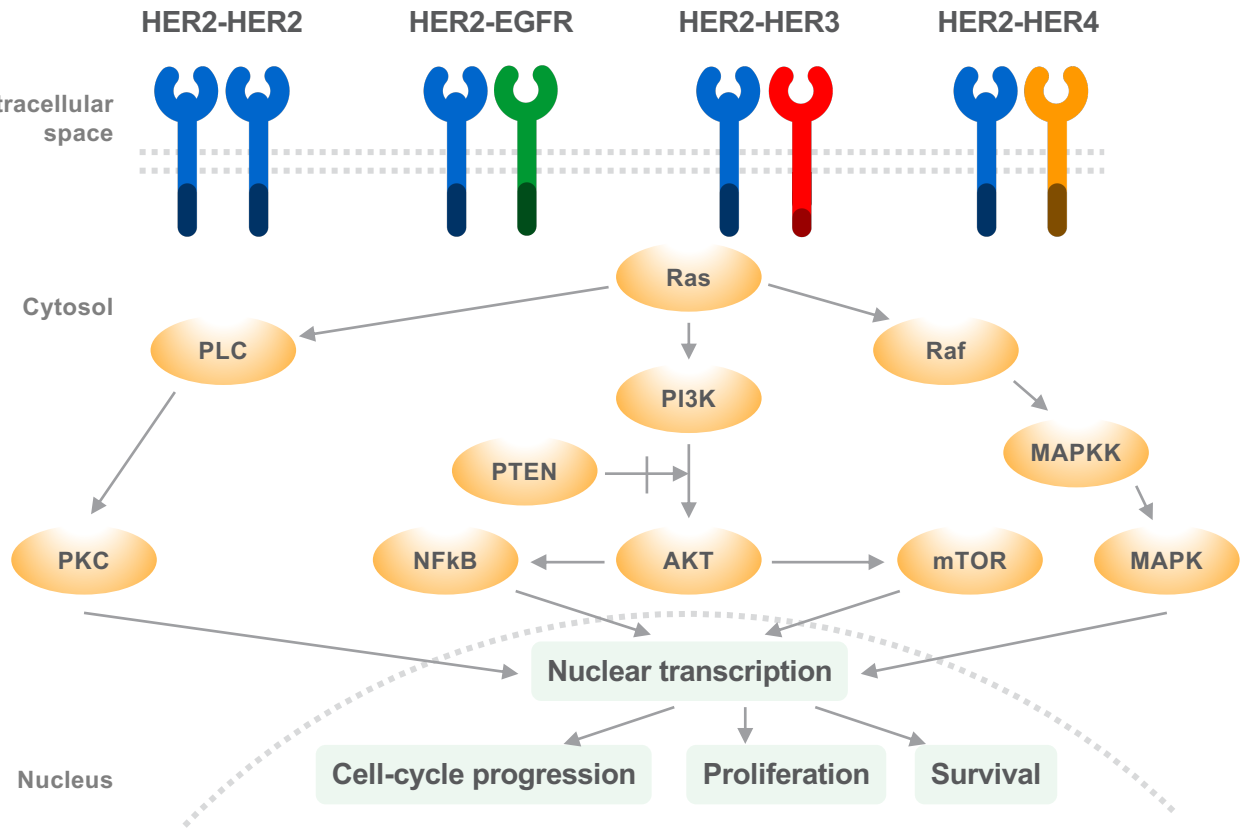
- Travel Support:
  - Janssen, AstraZeneca

ESMO = European Society for Medical Oncology.

HER2 Activation Drives Oncogenic Downstream Signaling, Promoting Tumor Proliferation and Survival

- **HER2 (ErbB2)** is one of the 4 members of the ErbB family of receptor tyrosine kinases, along with EGFR (ErbB1, HER1), HER3 (ErbB3), and HER4 (ErbB4)[1,2]
- **HER2 protein overexpression** and/or ***HER2* gene amplification** → up to 100-fold increase in cell-surface HER2 → increased formation of HER2-containing heterodimers → activation of several oncogenic signaling pathways, including MAPK, PI3K/AKT, PLC, PKC, and JAK-STAT[1,2]

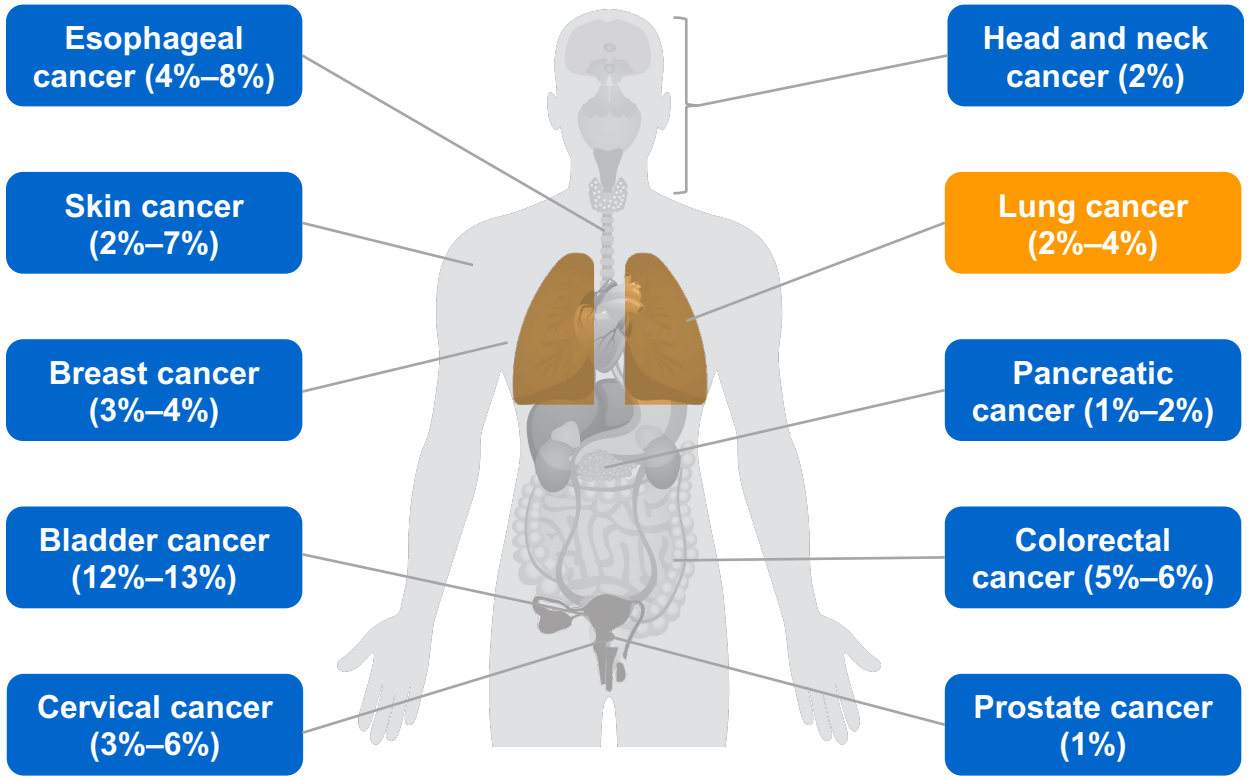


Adapted from Iqbal N, Iqbal N.[3]

AKT = protein kinase B; EGFR = epidermal growth factor receptor; ErbB = erythroblastic leukemia viral oncogene; ESMO = European Society for Medical Oncology; HER = human epidermal growth factor receptor; JAK = Janus kinase; MAPK = mitogen-activated protein kinase; MAPKK = mitogen-activated protein kinase leukaemia; NFκB = nuclear factor kappa B; mTOR = mammalian target of rapamycin; PI3K = phosphatidylinositol 3-kinase; PKC = protein kinase C; PLC = phospholipase-C; PTEN = phosphatase and tensin homolog; RAF = rapidly accelerated fibrosarcoma; Ras = Rat sarcoma virus; STAT = signal transducers and activators of transcription.

1. Vathiotis IA, et al. *Pharmaceuticals (Basel).* 2021;14(12):1300; 2. Ni J, Zhang L. *Onco Targets Ther.* 2021;14:4087–4098; 3. Iqbal N, Iqbal N. *Mol Biol Int*. 2014;2014:852748.

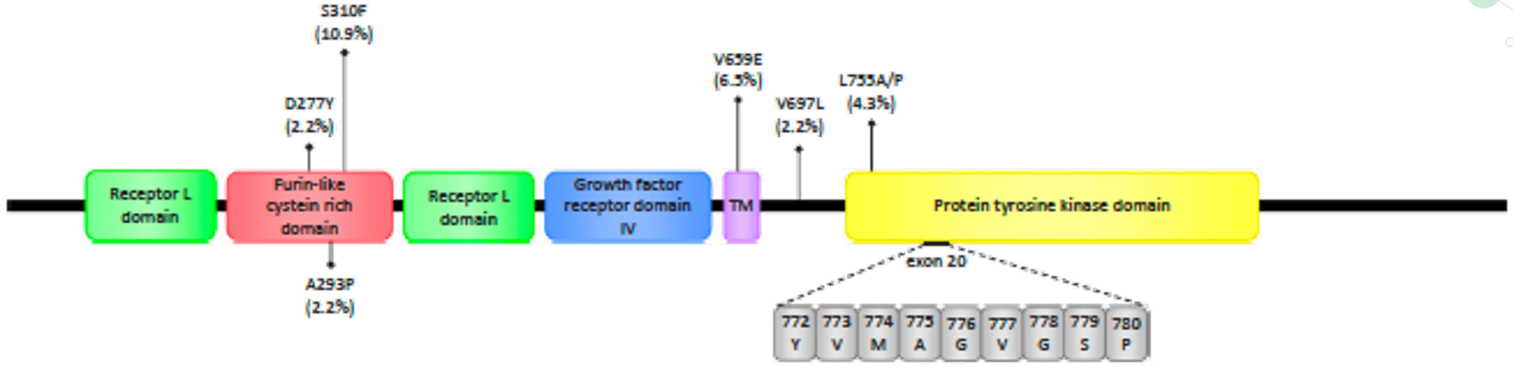
HER2 Mutations Also Feature at Varying Frequencies Across Tumor Types

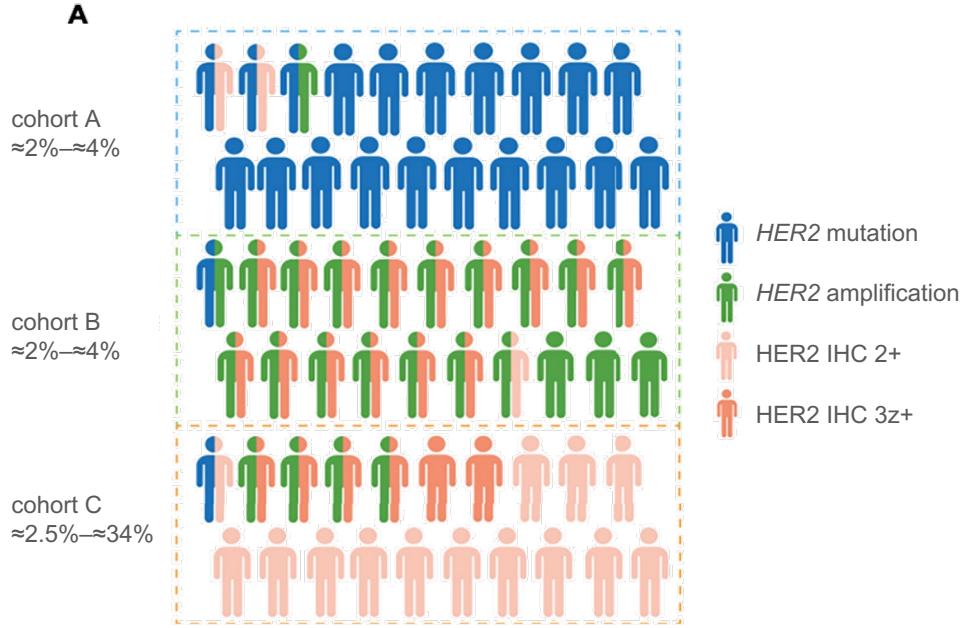


ESMO = European Society for Medical Oncology; *HER2* = human epidermal growth factor receptor 2.
Subramanian J, et al. *Oncologist*. 2019;24(12):e1303–e1314.

HER2 Mutations in NSCLC

- *HER2* mutations occur in 1%–4% of NSCLC[1–3]
  - Exon 20 insertions (YVMA variant ≈85%)
  - Point mutations in the tyrosine kinase, transmembrane, and extracellular domain
- *HER2* mutations have little overlap with gene amplification or protein expression





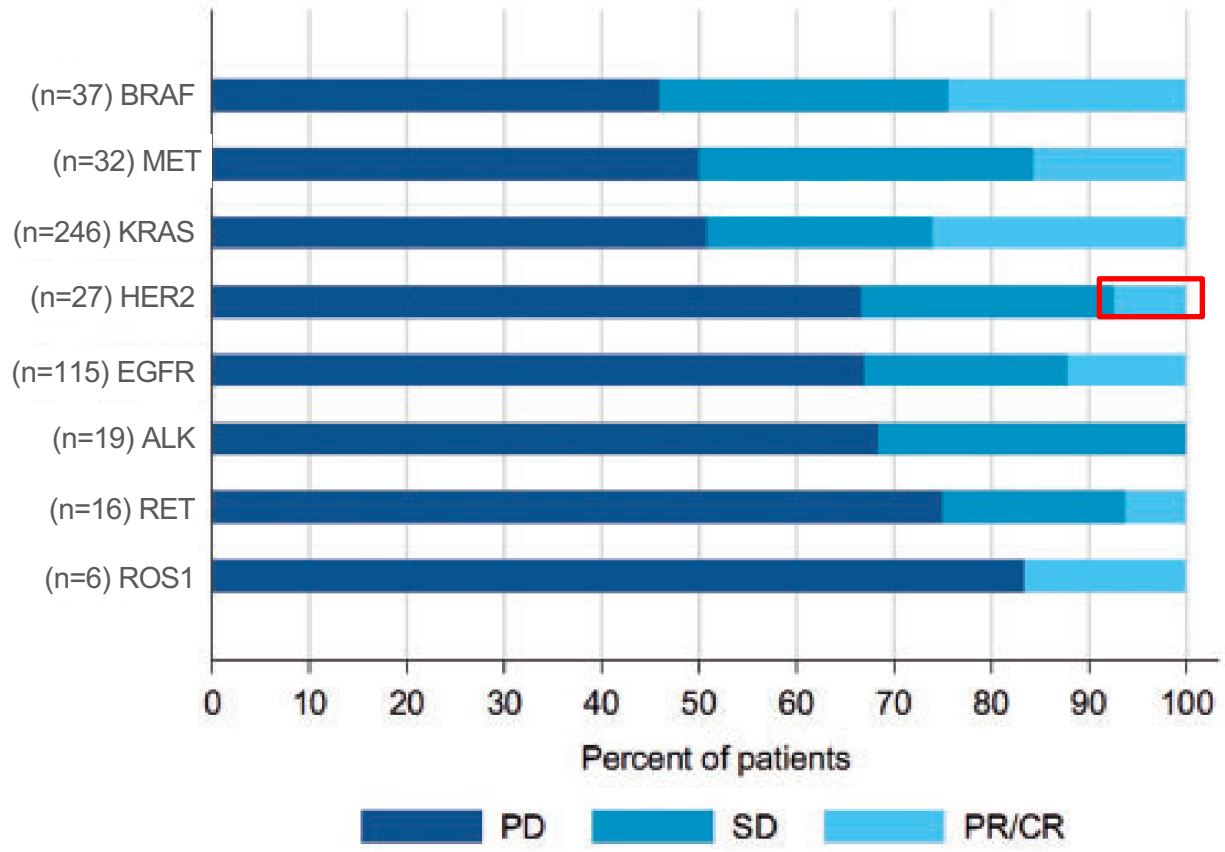
A = alanine; D = aspartic acid; E = glutamic acid; ESMO = European Society for Medical Oncology; F = phenylalanine; G = glycine; *HER2* = human epidermal growth factor receptor 2; IHC = immunohistochemistry; L = leucine; M = methionine; NSCLC = non–small cell lung cancer; P = proline; S = serine; TM = transmembrane domain; Y = tyrosine.

1. Jebbink M, et al. *Cancer Treat Rev.* 2020;86:101996; 2. Yu X, et al. *Front Oncol.* 2022;12:860313; 3. Arcila ME, et al. *Clin Cancer Res.* 2012;18:4910–4918.

Role of Chemoimmunotherapy in *HER2*^{mt} NSCLC

- As of today, chemotherapy ± immunotherapy remains the standard 1L therapy for *HER2*-mutant NSCLC
- Chemoimmunotherapy combinations are generally used
- However, *HER2*-mutant NSCLC has limited benefit from PD-1/PD-L1 inhibitors (IMMUNOTARGET)

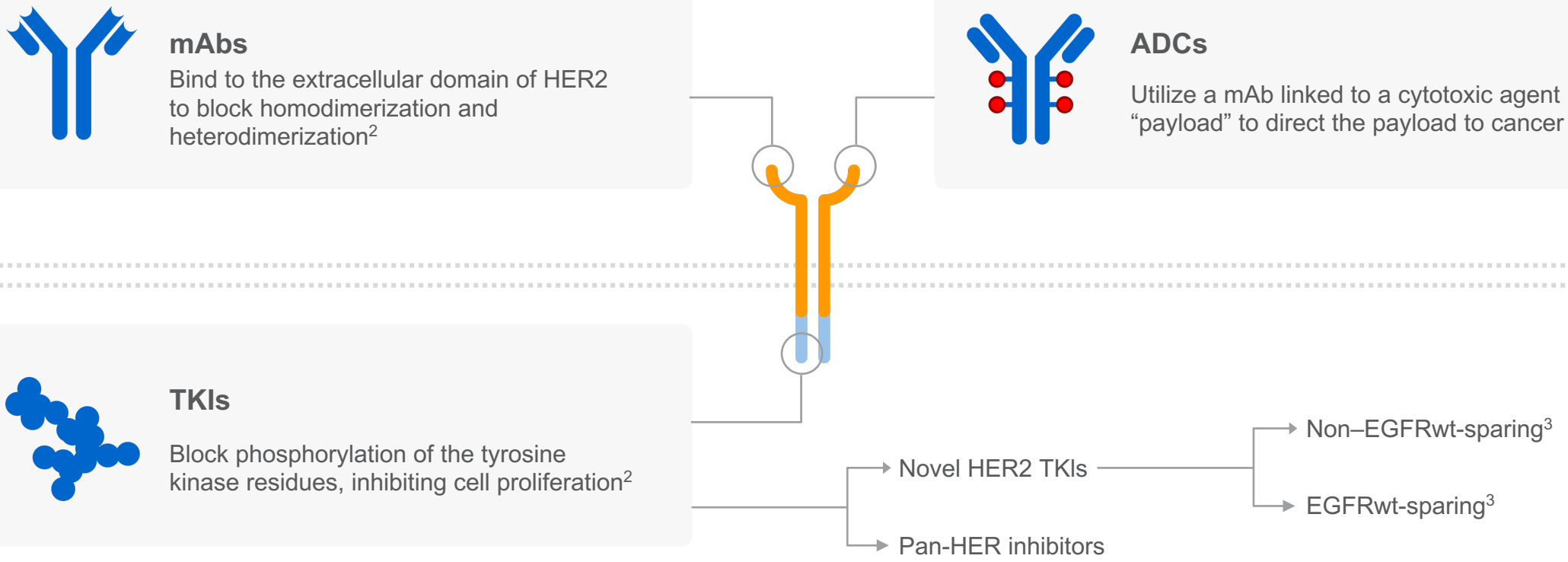
Best Response to PD-1/PD-L1 Inhibitors by Driver Mutation (IMMUNOTARGET Registry)



1L = first-line; ALK = anaplastic lymphoma kinase; BRAF = v-raf murine sarcoma viral oncogene homolog B1; CR = complete response; EGFR = epidermal growth factor receptor; ESMO = European Society for Medical Oncology; HER2 = human epidermal growth factor receptor 2; HER2^{mt} = human epidermal growth factor receptor 2–mutant; KRAS = Kirsten rat sarcoma viral oncogene homologue; MET = mesenchymal epithelial transition; NSCLC = non–small cell lung cancer; PD = progressive disease; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PR = partial response; RET = rearranged during transfection; ROS1 = rearrangement of c-ros oncogene 1; SD = stable disease.

Mazieres J, et al. *Ann Oncol.* 2019;30(8):1321–1328.

Numerous Therapeutic Strategies Targeting *HER2*^{mt} NSCLC Are in Development[1,2]



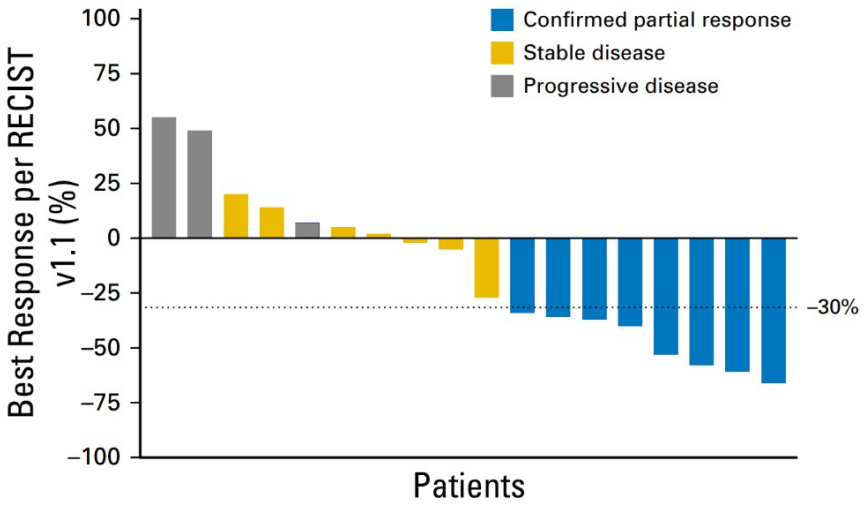
Adapted from Rolfo C, et al 2020[1] and Uy NF, et al 2022.[2]
ADC = antibody-drug conjugate; EGFR = epidermal growth factor receptor; ESMO = European Society for Medical Oncology; HER = human epidermal growth factor receptor; *HER2*^{mt} = human epidermal growth factor receptor 2-mutant; mAb = monoclonal antibody; NSCLC = non–small cell lung cancer; TKI = tyrosine kinase inhibitor; wt = wild type.
1. Rolfo C, Russo A. *Cancer Discov.* 2020;10(5):643–645; 2. Uy NF, et al. *Cancers (Basel).* 2022;14(17):4155; 3. Brazel D, et al. *BioDrugs.* 2022;36(6):717–729.

HER2 ADCs: Ado-trastuzumab Emtansine (T-DM1)

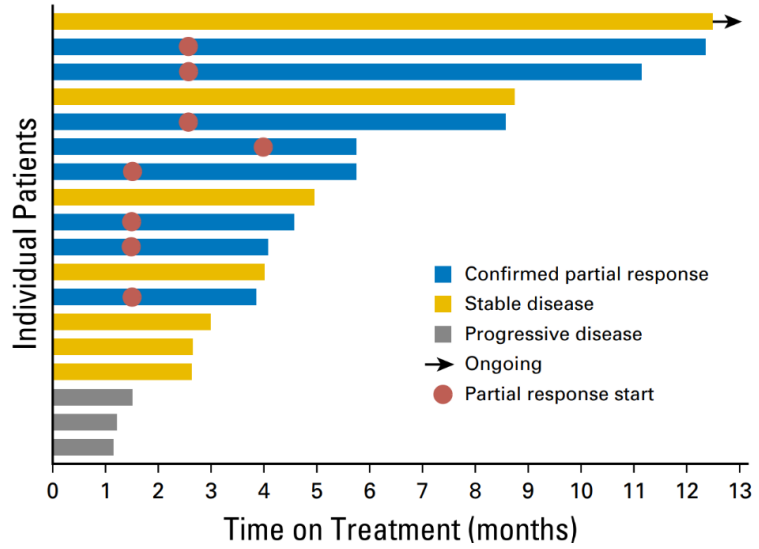
Efficacy in *HER2*^{mt} lung adenocarcinoma

- ORR, 8/18 (44%)
- mPFS, 5 mo (95% CI, 3–9)
- mDoR, 4 mo (range, 1−9 mo)
- Responses observed in:
  - *HER2* exon 20 insertions
  - TMD mutation
  - Furin-like domain mutations

Best Response



PFS



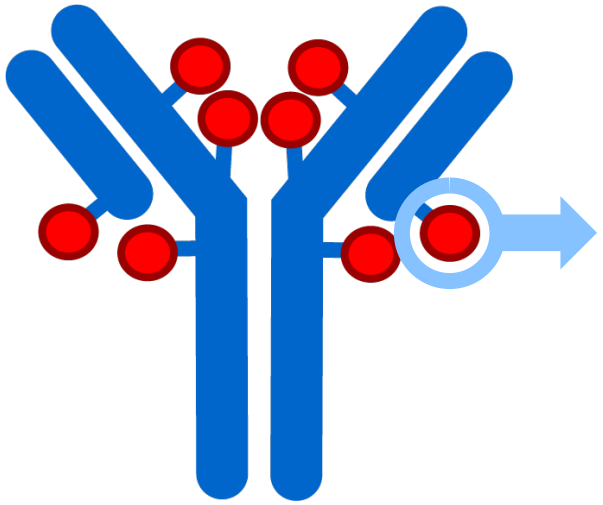
ADC = antibody-drug conjugate; ESMO = European Society for Medical Oncology; HER2 = human epidermal growth factor receptor 2; *HER2*^{mt} = human epidermal growth factor receptor 2-mutant; mDoR = median duration of response; mPFS = median progression-free survival; ORR = objective response rate; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; TMD = transmembrane domain.

Li BT, et al. *J Clin Oncol.* 2018;36(24):2532–2537.

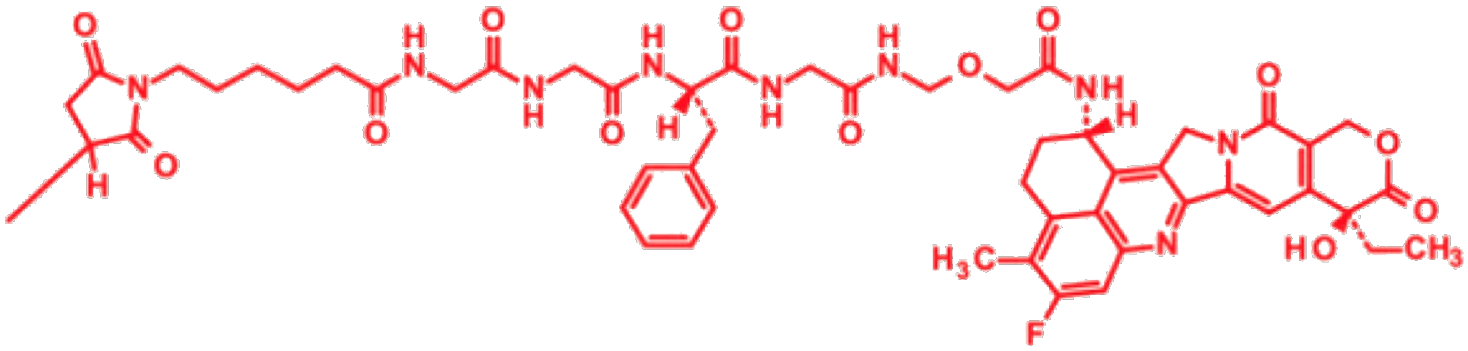
T-DXd Is a HER2-targeting mAb Linked to a Chemotherapy "Payload"[1–3]

T-DXd payload: deruxtecan, a topoisomerase I inhibitor

Humanized anti-HER2 IgG1 mAb



Deruxtecan



Cleavable tetrapeptide-based linker

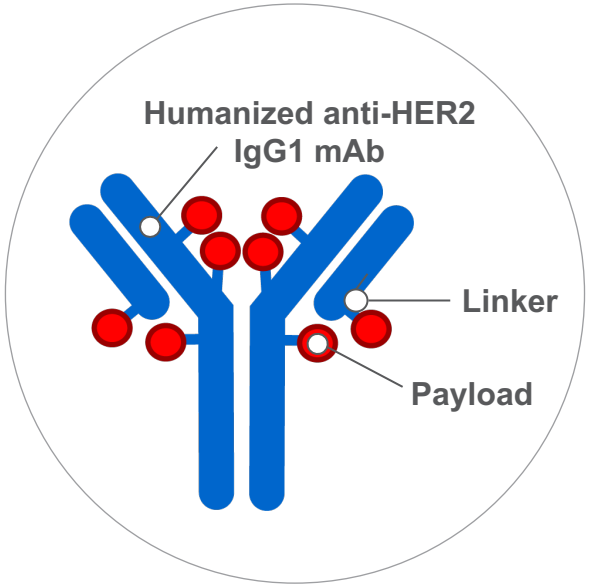
Topoisomerase I inhibitor payload

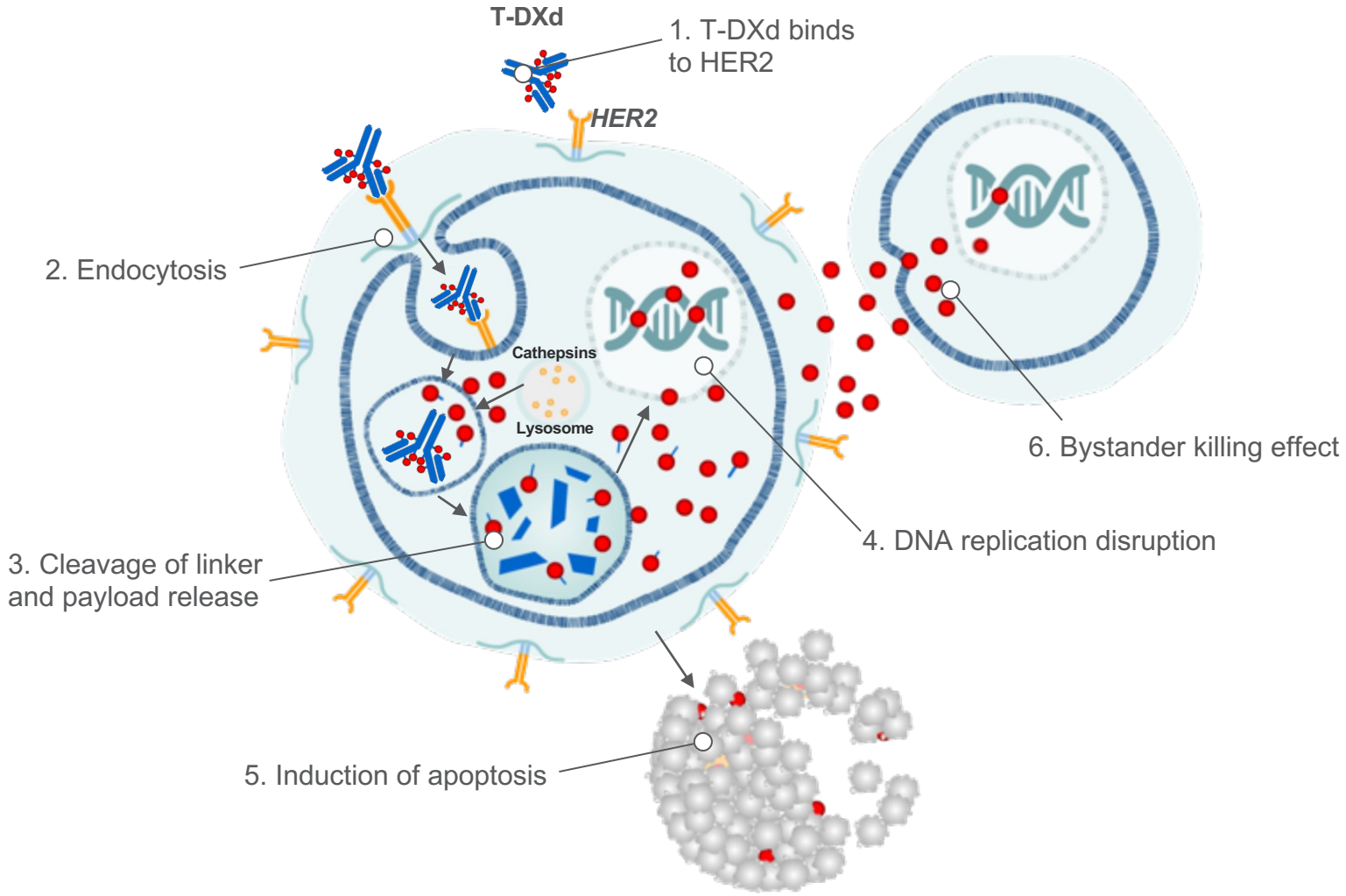
Adapted from Nakada T, et al. 2019.[3]

ESMO = European Society for Medical Oncology; HER2 = human epidermal growth factor receptor 2; IgG1 = immunoglobulin G1; mAb = monoclonal antibody; T-DXd = trastuzumab deruxtecan.

1. Li BT, et al. ASCO 2022. Poster TPS9137; 2. Azar I, et al. *Lung Cancer (Auckl).* 2021;12:103–114; 3. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173–185.

T-DXd Is a HER2-Targeting mAb Linked to a Chemotherapy "Payload"[1–3]





Adapted from Lambert JM, Berkenblit A. 2018[3] and Nakada T, et al. 2019.[4]

DNA = deoxyribonucleic acid; ESMO = European Society for Medical Oncology; HER2 = human epidermal growth factor receptor 2; IgG1 = immunoglobulin G1; mAb = monoclonal antibody; T-DXd = trastuzumab deruxtecan.

1. Li BT, et al. ASCO 2022. Poster TPS9137; 2. Azar I, et al. *Lung Cancer (Auckl).* 2021;12:103–114; 3. Lambert JM, Berkenblit A. *Annu Rev Med.* 2018;69:191–207; 4. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173–185.

DESTINY-Lung02: A Phase 2 Trial of T-DXd in Metastatic *HER2*^{mt} NSCLC Refractory to Standard Treatment

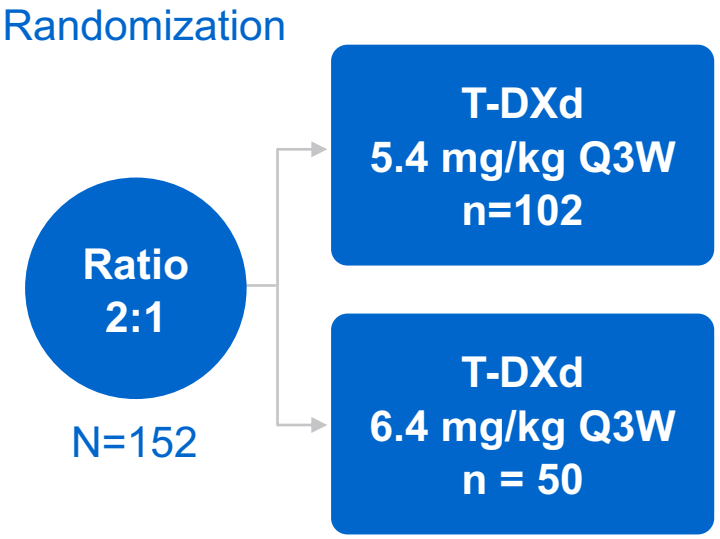
Key Eligibility Criteria

- Metastatic *HER2* mutation advanced NSCLC (ECOG PS 0–1)
- ≥1 prior therapy (platinum-based chemotherapy)
- Measurable disease per RECIST v1.1

Stratification Factor

- Prior anti–PD-1/PD-L1 treatment

Study Design



Primary Endpoint

- ORR by BICR

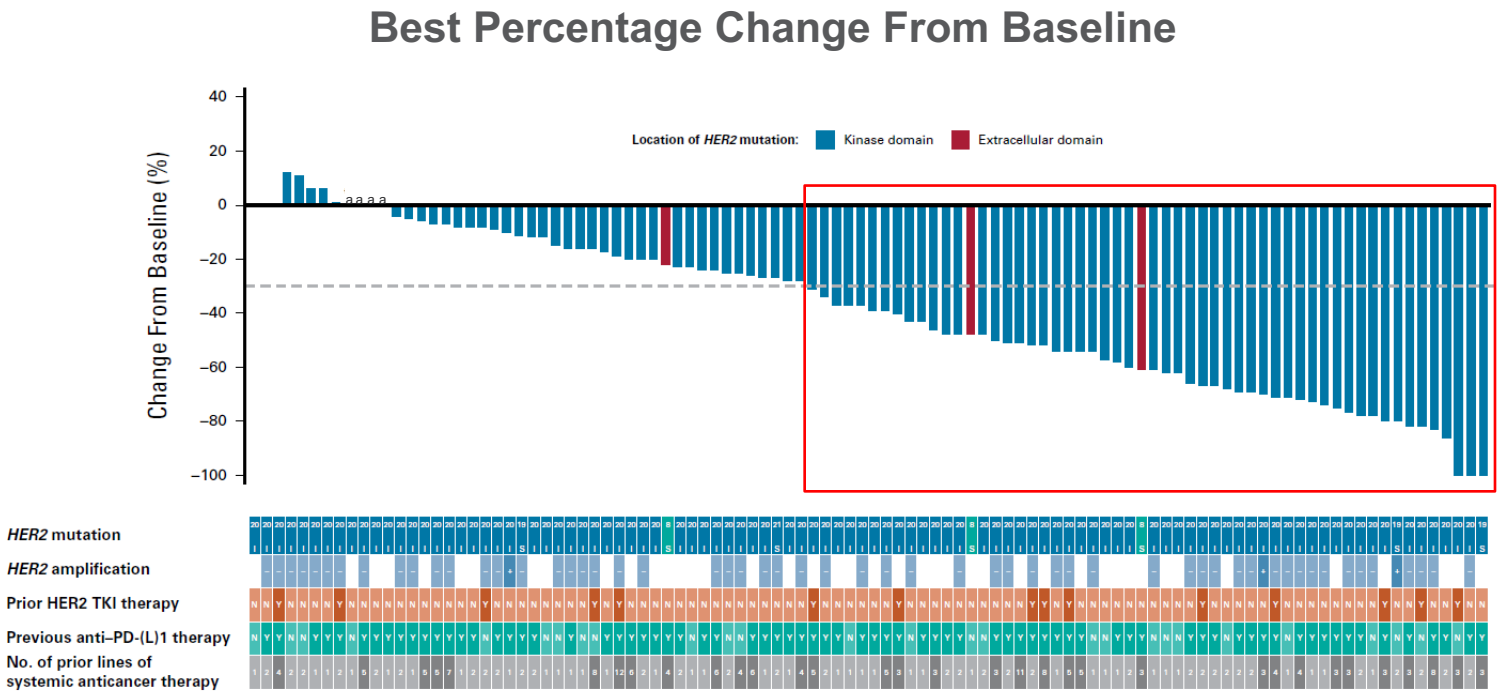
Secondary Endpoints

- Confirmed ORR by investigator
- DoR
- DCR
- PFS
- OS
- Safety

BICR = blinded independent central review; DCR = disease control rate; DoR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; ESMO = European Society for Medical Oncology; *HER2* = human epidermal growth factor receptor 2; *HER2*^{mt} = human epidermal growth factor receptor 2–mutant; NSCLC = non–small cell lung cancer; ORR = objective response rate; OS = overall survival; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; Q3W = every 3 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; T-DXd = trastuzumab deruxtecan.

Jänne P, et al. WCLC 2023. Mini oral presentation MA13.10.

DESTINY-Lung02 Primary Results: Antitumor Activity of T-DXd 5.4 mg/kg Q3W in *HER2*^{mt} Metastatic NSCLC

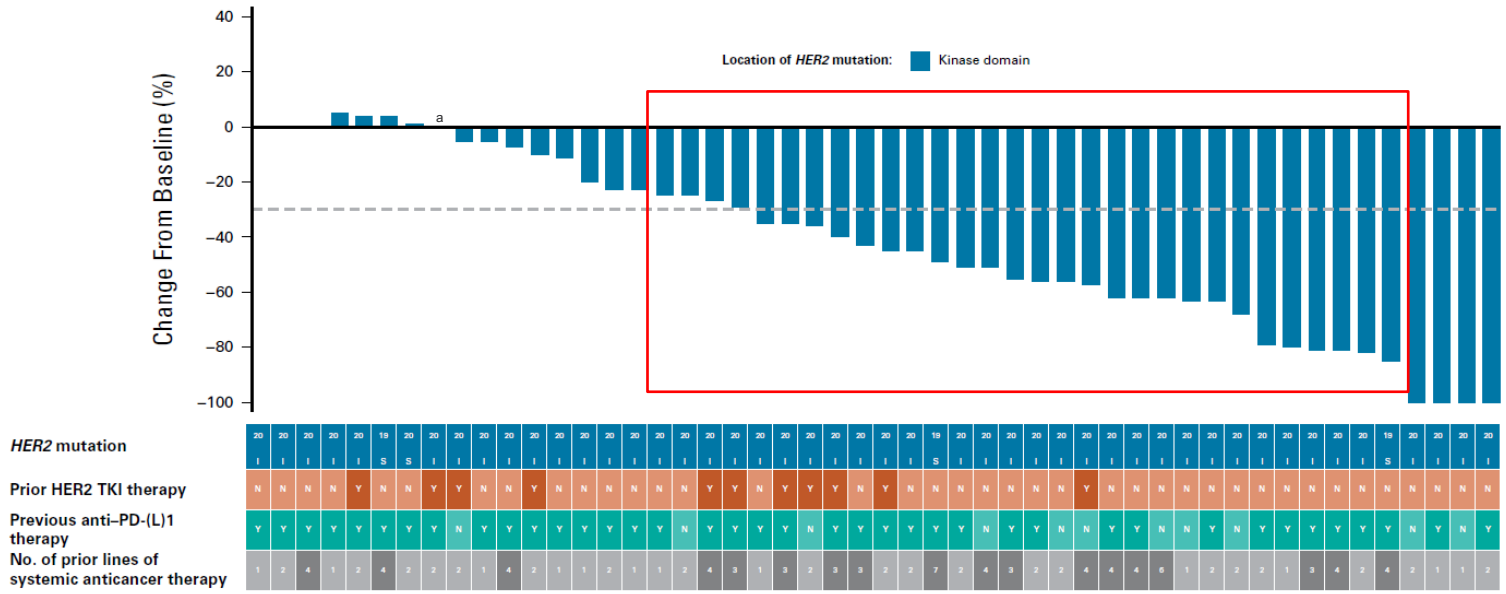


DESTINY-Lung02 (n = 152)	T-DXd 5.4 mg/kg Q3W (n = 102)
Confirmed ORR, n (%) (95% CI)	50 (49.0) (39.0–59.1)
CR	1 (1.0)
PR	49 (48.0)
Median DoR, mo (95% CI)	16.8 (6.4−NE)
Median follow-up, mo (range)	11.5 (1.1–20.6)

[a]Patients who had zero best percentage change from baseline in the sum of diameters for all target lesions.
CR = complete response; DoR = duration of response; ESMO = European Society for Medical Oncology; *HER2* = human epidermal growth factor receptor 2; *HER2*^{mt} = human epidermal growth factor receptor 2–mutant; mo = months; NE = not estimable; NSCLC = non–small cell lung cancer; ORR = objective response rate; PD-(L)1 = programmed cell death-(ligand)1; PR = partial response; Q3W = every 3 weeks; T-DXd = trastuzumab deruxtecan; TKI = tyrosine kinase inhibitor.
Goto K, et al. *J Clin Oncol.* 2023;JCO2301361.

DESTINY-Lung02 Primary Results: Antitumor Activity of T-DXd 6.4 mg/kg Q3W in *HER2*^{mt} Metastatic NSCLC

Best Percentage Change From Baseline

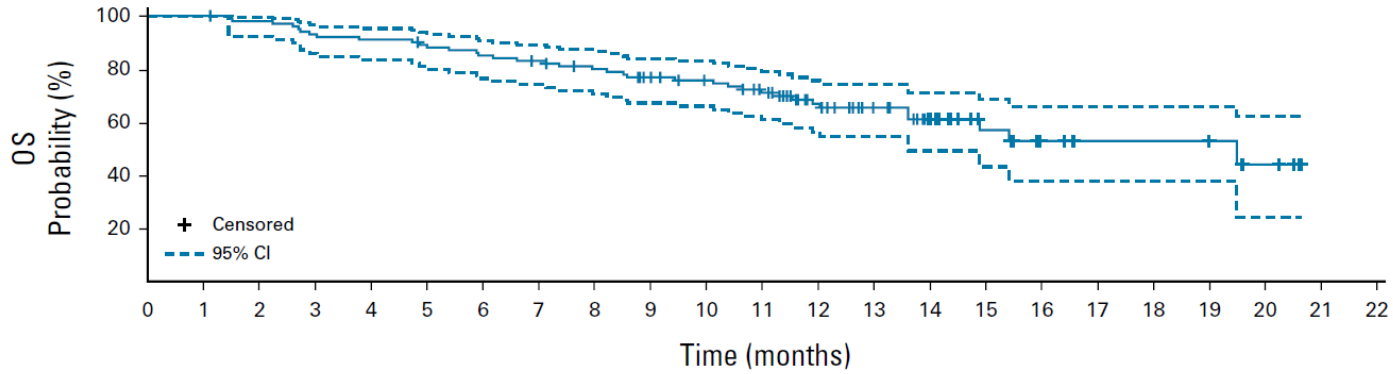


DESTINY-Lung02 (n = 152)	T-DXd 6.4 mg/kg Q3W (n = 50)
Confirmed ORR, n (%) (95% CI)	28, 56.0 (41.3–70.0)
CR, n (%)	2 (4.0)
PR, n (%)	26 (52.0)
Median DoR, mo (95% CI)	NE (8.3−NE)
Median follow-up, mo (range)	11.8 (0.6–21.0)

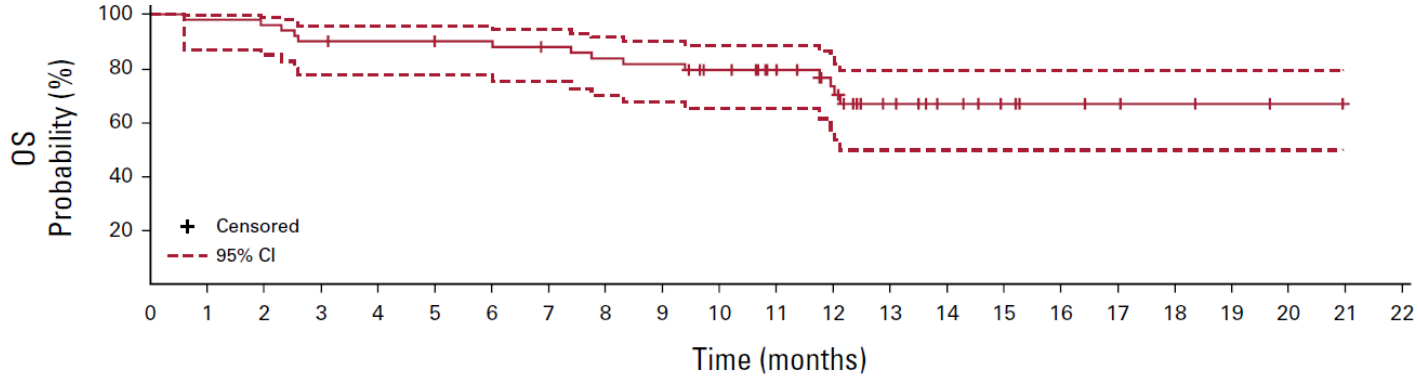
[a]Patients who had zero best percentage change from baseline in the sum of diameters for all target lesions.
CR = complete response; DoR = duration of response; ESMO = European Society for Medical Oncology; *HER2* = human epidermal growth factor receptor; *HER2*^{mt} = human epidermal growth factor receptor 2–mutant; NE = not estimable; NSCLC = non–small cell lung cancer; ORR = objective response rate; PD-(L)1 = programmed cell death-(ligand)1; PR = partial response; Q3W = every 3 weeks; T-DXd = trastuzumab deruxtecan; TKI = tyrosine kinase inhibitor.
Goto K, et al. *J Clin Oncol.* 2023;JCO2301361.

DESTINY-Lung02 Primary Results: OS

T-DXd Kaplan Meier Curves for OS



No. at risk:																						
Patients	102	102	99	94	92	88	85	82	77	71	66	59	45	33	22	14	9	7	7	6	4	0
Events	0	0	2	7	9	12	15	17	20	23	24	28	31	32	34	35	36	36	36	36	37	37



No. at risk:																						
Patients	50	49	48	45	44	43	43	41	39	38	34	29	23	15	10	7	5	4	3	2	1	0
Events	0	1	2	5	5	5	5	6	8	9	10	10	12	14	14	14	14	14	14	14	14	14

Median OS of T-DXd 5.4 mg/kg Q3W
19.5 mo (95% CI, 13.6−NE)

Median OS of T-DXd 6.4 mg/kg Q3W
NE (95% CI, 12.1–NE)

ESMO = European Society for Medical Oncology; NE = not estimable; OS = overall survival; Q3W = every 3 weeks; T-DXd = trastuzumab deruxtecan.

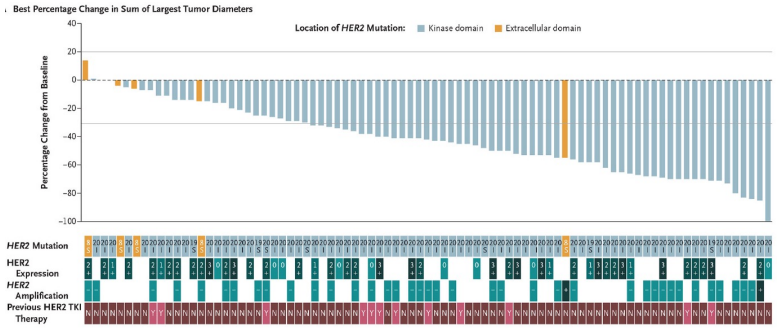
Goto K, et al. *J Clin Oncol.* 2023;JCO2301361.

HER2 ADCs: T-DXd

DESTINY-Lung01[1]

HER2-mutated NSCLC

- OR, 55% (95% CI, 44%–65%)
- mPFS, 8.2 mo (95% CI, 6.0–11.9 mo)
- mOS, 17.8 mo (95% CI, 13.8–22.1 mo)

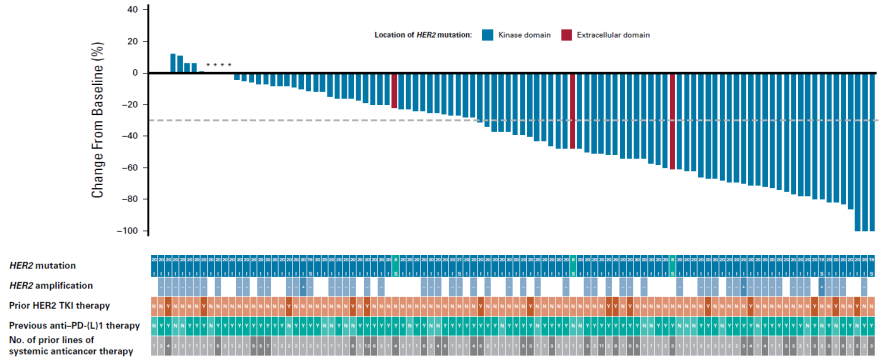


DESTINY-Lung02[2]

HER2-mutated nonsquamous NSCLC with disease progression after 1 prior systemic therapy

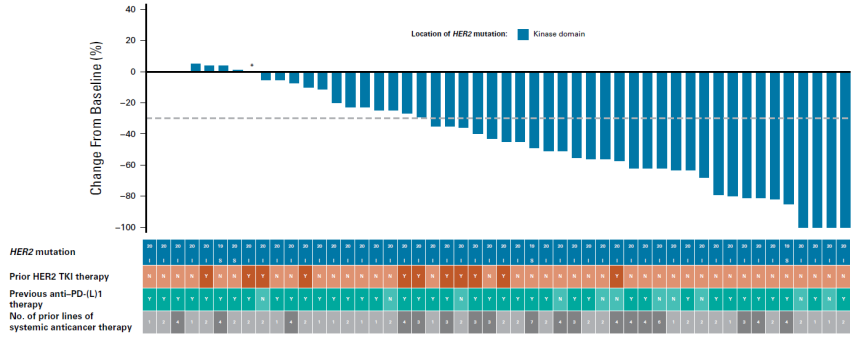
5.4 mg/kg Q3W

- OR, 49% (95% CI, 39.0%–59.1%)
- mPFS, 9.9 mo (95% CI, 7.4–NE)
- mOS,19.5 mo (95% CI, 13.6–NE)



6.4 mg/kg Q3W

- OR, 56% (95% CI, 41.3%–70.0%)
- mPFS,15.4 mo (95% CI, 8.3–NE)
- mOS, NE (95% CI, 12.1–NE)



[a]Data cutoff: June 22, 2022. [b]Median DoR based on Kaplan-Meier estimate.
ADC = antibody-drug conjugate; CI = confidence interval; DoR = duration of response; ESMO = European Society for Medical Oncology; *HER2* = human epidermal growth factor receptor 2; mOS = median overall survival; mPFS = median progression-free survival; NE = not estimable; NSCLC = non–small cell lung cancer; OR = objective response; PD-(L)1 = programmed death-ligand; Q3W = every 3 weeks; T-DXd = trastuzumab deruxtecan; TKI = tyrosine kinase inhibitor.

1. Li BT, et al. *N Engl J Med*. 2022;386(3):241–251; 2. Goto K, et al. *J Clin Oncol.* 2023;JCO2301361.

DESTINY-Lung01 Drug-Related AEs

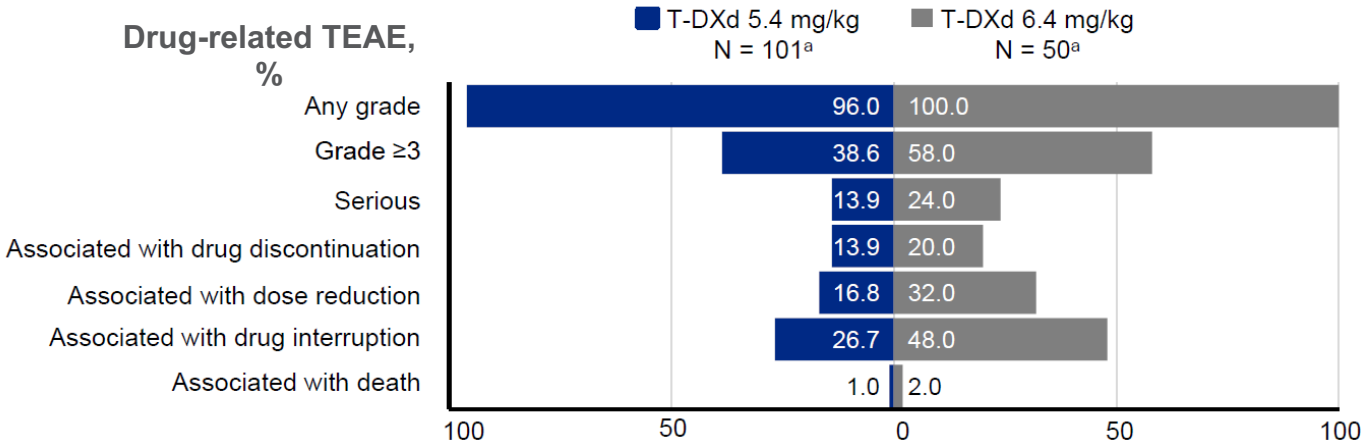
Event	Grades 1–2	Grade 3	Grade 4	Grade 5	Overall
			Number of patients (%)		
Drug-related AE	46 (51)	37 (41)	4 (4)	1 (1)[a]	88 (97)
Drug-related AEs with ≥20% incidence					
Nausea	58 (64)	8 (9)	0	0	66 (73)
Fatigue[b]	42 (46)	6 (7)	0	0	48 (53)
Alopecia	42 (46)	0	0	0	42 (46)
Vomiting	33 (36)	3 (3)	0	0	36 (40)
Neutropenia[c]	15 (16)	14 (15)	3 (3)	0	32 (35)
Anemia[d]	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[e]	17 (19)	4 (4)	0	0	21 (23)
Constipation	20 (22)	0	0	0	20 (22)

- Adjudicated drug-related ILD occurred in 24/91 patients (26%) at 6.4 mg/kg

[a]One patient had grade 5 (ie, fatal) pneumonitis that was assessed as drug-related by the investigator (subsequently adjudicated as ILD). Another patient had grade 3 ILD, as reported by the investigator, and died; the reported ILD was subsequently adjudicated as grade 5 by the ILD adjudication committee. [b]This category includes the preferred terms fatigue, asthenia, and malaise. [c]This category includes the preferred terms neutrophil count decreased and neutropenia. [d]This category includes the preferred terms hemoglobin decreased, red cell count decreased, anemia, and hematocrit decreased. [e]This category includes the preferred terms white cell count decreased and leukopenia.
AE = adverse event; ESMO = European Society for Medical Oncology; ILD = interstitial lung disease.
Li BT, et al. *N Engl J Med.* 2022;386(3):241–251.

DESTINY-Lung02 Primary Results: Overall Safety

Overall Safety



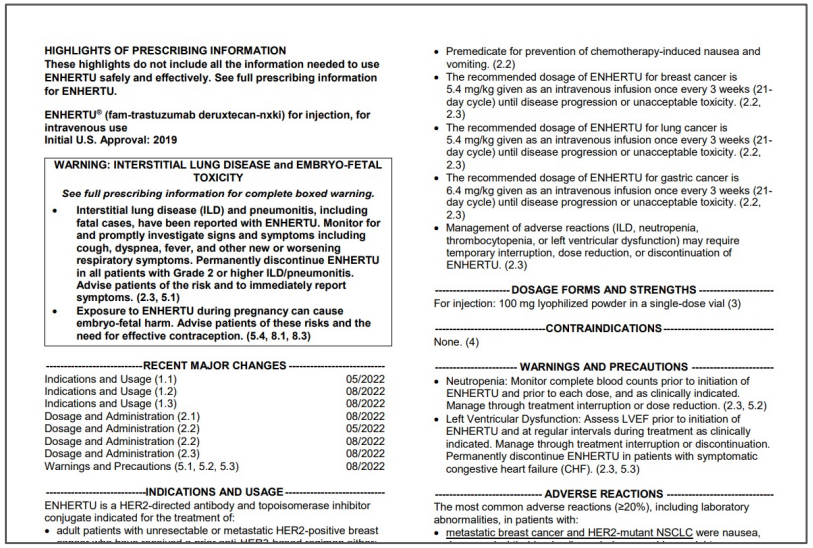
Adjudicated Drug-Related ILD

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

- Median treatment duration was 7.7 months (range, 0.7−20.8) with T-DXd 5.4 mg/kg and 8.3 months (range, 0.7−20.3) with T-DXd 6.4 mg/kg
- The most common any-grade TEAEs in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms included nausea (67.3% and 82.0%), neutropenia (42.6% and 56.0%), and fatigue (44.6% and 50.0%)
- The most common grade ≥3 TEAEs in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms included neutropenia (18.8% and 36.0%) and anemia (10.9% and 16.0%)

[a]Includes all randomly assigned patients who received ≥1 dose of T-DXd.
ILD = interstitial lung disease; T-DXd = trastuzumab deruxtecan; TEAE = treatment-emergent adverse event.
Jänne P, et al. WCLC 2023. Mini oral presentation MA13.10.

Based on DESTINY-Lung02 Results, T-DXd Received FDA Accelerated Approval in August 2022[1]



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Initial U.S. Approval: 2019

WARNING: INTERSTITIAL LUNG DISEASE and EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- **Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with ENHERTU. Monitor for and promptly investigate signs and symptoms including cough, dyspnea, fever, and other new or worsening respiratory symptoms. Permanently discontinue ENHERTU in all patients with Grade 2 or higher ILD/pneumonitis. Advise patients of the risk and to immediately report symptoms. (2.3, 5.1)**
- **Exposure to ENHERTU during pregnancy can cause embryo-fetal harm. Advise patients of these risks and the need for effective contraception. (5.4, 8.1, 8.3)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.1)	05/2022
Indications and Usage (1.2)	08/2022
Indications and Usage (1.3)	08/2022
Dosage and Administration (2.1)	08/2022
Dosage and Administration (2.2)	05/2022
Dosage and Administration (2.2)	08/2022
Dosage and Administration (2.3)	08/2022
Warnings and Precautions (5.1, 5.2, 5.3)	08/2022

----------INDICATIONS AND USAGE----------

ENHERTU is a HER2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of:

- adult patients with unresectable or metastatic HER2-positive breast

- Premedicate for prevention of chemotherapy-induced nausea and vomiting. (2.2)
- The recommended dosage of ENHERTU for breast cancer is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. (2.2, 2.3)
- The recommended dosage of ENHERTU for lung cancer is 5.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. (2.2, 2.3)
- The recommended dosage of ENHERTU for gastric cancer is 6.4 mg/kg given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. (2.2, 2.3)
- Management of adverse reactions (ILD, neutropenia, thrombocytopenia, or left ventricular dysfunction) may require temporary interruption, dose reduction, or discontinuation of ENHERTU. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 100 mg lyophilized powder in a single-dose vial (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Neutropenia: Monitor complete blood counts prior to initiation of ENHERTU and prior to each dose, and as clinically indicated. Manage through treatment interruption or dose reduction. (2.3, 5.2)
- Left Ventricular Dysfunction: Assess LVEF prior to initiation of ENHERTU and at regular intervals during treatment as clinically indicated. Manage through treatment interruption or discontinuation. Permanently discontinue ENHERTU in patients with symptomatic congestive heart failure (CHF). (2.3, 5.3)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥20%), including laboratory abnormalities, in patients with:

- metastatic breast cancer and HER2-mutant NSCLC were nausea,

T-DXd SPC

- Approved for adult patients with unresectable or metastatic NSCLC with *HER2* mutations **who have received prior systemic therapy**[2]
- This indication is approved under accelerated approval based on improvements observed in the DESTINY-Lung02 trial[1]
- The approved recommended dose is **5.4 mg/kg** given IV Q3W, based on results of DESTINY-Lung02[1,2]

T-DXd is currently being evaluated as 1L therapy in HER2-mutated NSCLC in DESTINY-Lung04[3]

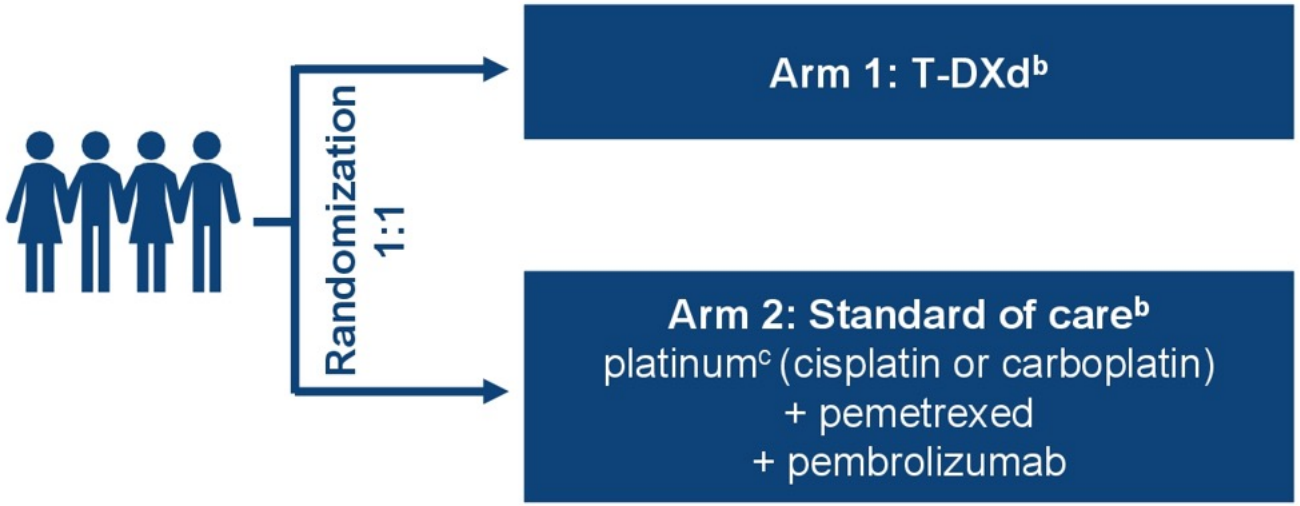
1L = first-line; ESMO = European Society for Medical Oncology; FDA = US Food and Drug Administration; HER2 = human epidermal growth factor receptor 2; IV = intravenously; NSCLC = non–small cell lung cancer; Q3W = every 3 weeks; SPC = summary of product characteristics; T-DXd = trastuzumab deruxtecan.

1. Enhertu Approved. *AstraZeneca*:2022. https://www.astrazeneca.com/media-centre/press-releases/2022/enhertu-approved-in-us-for-her2-mutant-nsclc.html. Accessed September 2023; 2. Enhertu Prescribing Information. November 2022; 3. ClinicalTrials.gov. https://www.clinicaltrials.gov/study/NCT05048797. Accessed September 2023.

DESTINY-Lung04: A Phase 3 Trial of T-DXd as 1L Treatment in Metastatic *HER2*^{mt} NSCLC

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.
1L = first-line; ESMO = European Society for Medical Oncology; *HER2* = human epidermal growth factor receptor 2; *HER2*^{mt} = human epidermal growth factor receptor 2–mutant; NSCLC = non–small cell lung cancer; T-DXd = trastuzumab deruxtecan.
Li BT, et al. ASCO 2022. Poster TPS9137.

TKIs

TKI = tyrosine kinase inhibitor.

Older EGFR/HER2 TKIs in *HER2*^{mt} NSCLC

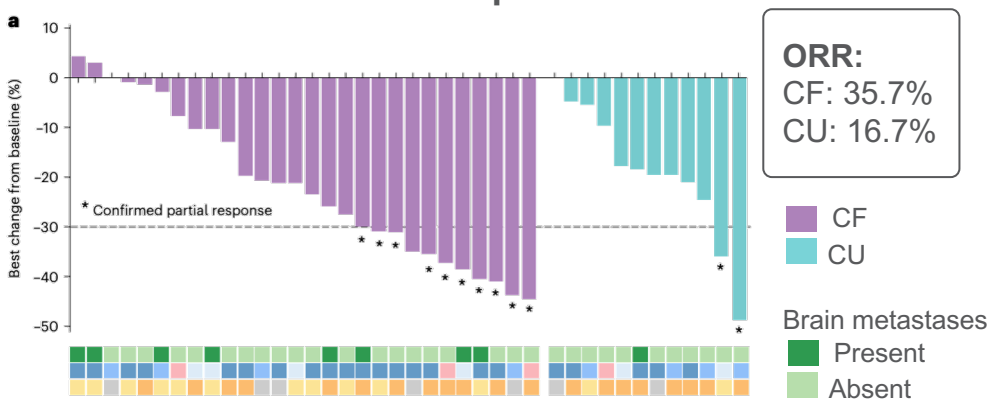
Drug	Target population	N	ORR	mPFS	Toxicities
Afatinib[1]	*HER2*^{mt}	13	8%	16 weeks	Diarrhea, vomiting, abdominal pain, skin rash, paronychia, fatigue, mucositis, dyspnea
Afatinib[2]	*HER2*^{mt}	27	13%[a]	3 mo	Diarrhea/GI toxicity, skin rash
Neratinib[3]	*HER2*^{mt}	26	4%	5.5 mo	Diarrhea (74%), nausea (43%), vomiting (41%)
Dacomitinib[4]	*HER2*^{mt}	26	12%	3 mo	Diarrhea (90%), rash (73%)
Mobocertinib[5]	*HER2*^{mt}	136	0%, 22% 19%, 43%[b]	10.2 mo	Diarrhea (83%), nausea (43%), rash (33%), vomiting (26%)

[a]3/23 patients. [b]At increasing doses of mobocertinib 5−40 mg/d, 80 mg/d total daily dose, 120 mg/d, and 160 mg/d in 70 patients with previously treated NSCLC and *EGFR* ex20ins mutations.
EGFR = epidermal growth factor receptor; ESMO = European Society for Medical Oncology; ex20ins = exon 20 insertion; GI = gastrointestinal; HER2 = human epidermal growth factor receptor 2; *HER2*^{mt} = human epidermal growth factor receptor 2–mutant; ORR = objective response rate; mPFS = median progression-free survival; NSCLC = non–small cell lung cancer; TKI = tyrosine kinase inhibitor.
1. Dziadziuszko R, et al. *J Thorac Oncol.* 2019;14:1086–1094; 2. Lai WV, et al. *Eur J Cancer.* 2019;109:28–35; 3. Hyman DM, et al. *Nature*. 2018;554(7691):189−194; 4. Kris MG, et al. *Ann Oncol.* 2015;26:1421–1427; 5. Riely GJ, et al. *Cancer Discov*. 2021;11(7):1688−1699.

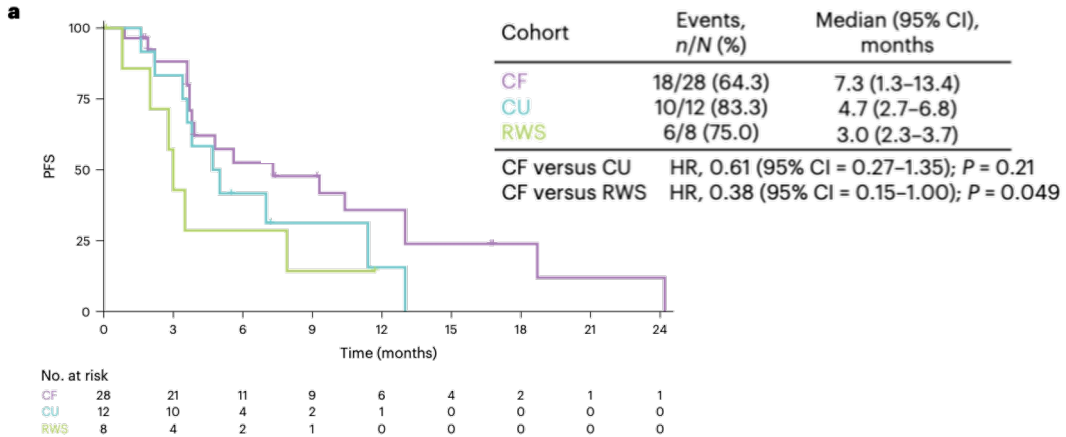
Pyrotinib in the 1L Treatment of *HER2*^{mt} NSCLC

- Pyrotinib is an oral, irreversible pan-ErbB family inhibitor

Tumor Response



PFS



Cohort	Events, *n/N* (%)	Median (95% CI), months
CF	18/28 (64.3)	7.3 (1.3–13.4)
CU	10/12 (83.3)	4.7 (2.7–6.8)
RWS	6/8 (75.0)	3.0 (2.3–3.7)
CF versus CU	HR, 0.61 (95% CI = 0.27–1.35); *P* = 0.21	
CF versus RWS	HR, 0.38 (95% CI = 0.15–1.00); *P* = 0.049	

TRAEs Reported in ≥10% of Patients

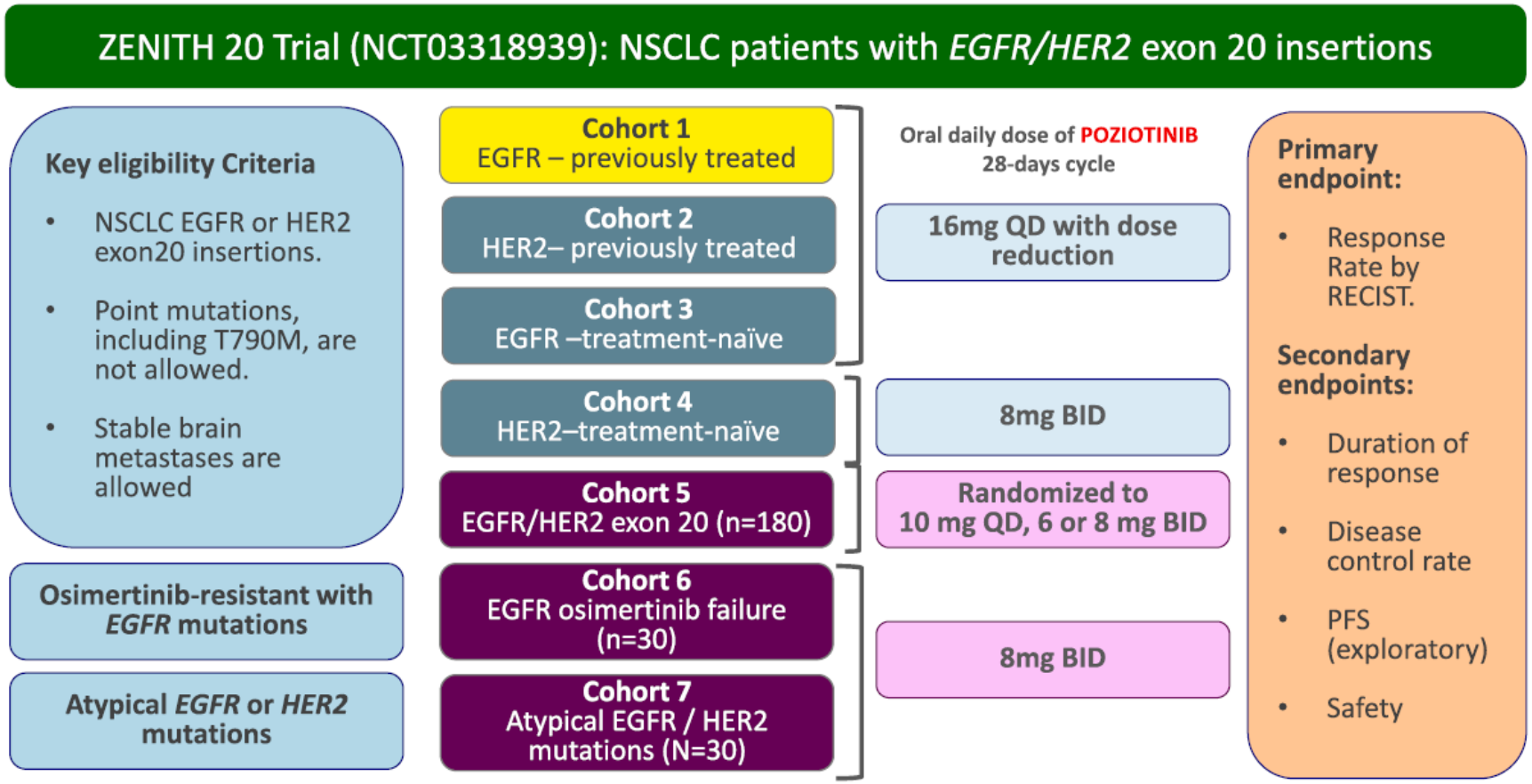
TRAEs, n (%)	CF Cohort (n = 28)		CU Cohort (n = 12)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Any AEs	27 (96.4)	3 (10.7)	11 (91.7)	4 (33.3)
Diarrhea	24 (85.7)	0 (0)	11 (91.7)	2 (16.7)
Rash	9 (32.1)	0 (0)	5 (41.7)	0 (0)
AST increased	7 (25.0)	1 (3.6)	1 (8.3)	0 (0)
Creatinine increased	6 (21.4)	0 (0)	2 (16.7)	0 (0)
Conjugated bilirubin increased	5 (17.9)	0 (0)	3 (25.0)	0 (0)
ALT increased	5 (17.9)	1 (3.6)	1 (8.3)	0 (0)
Mouth ulcer	4 (14.3)	0 (0)	2 (16.7)	0 (0)
Lymphocyte count decreased	4 (14.3)	0 (0)	2 (16.7)	0 (0)
Bilirubin increased	3 (10.7)	0 (0)	1 (8.3)	0 (0)
Serum uric acid increased	3 (10.7)	0 (0)	0 (0)	0 (0)
Pruritus	3 (10.7)	0 (0)	0 (0)	0 (0)

1L = first-line; AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CF = criteria fulfilled; CU = compassionate use; ErbB = erythroblastic leukemia viral oncogene; ESMO = European Society for Medical Oncology; *HER2*^{mt} = human epidermal growth factor receptor 2–mutant; HR = hazard ratio; NSCLC = non–small cell lung cancer; ORR = objective response rate; PFS = progression-free survival; RWS = real-world study; TRAE = treatment-related adverse event.

Liu SM, et al. *Nat Med.* 2023;29(8):2079–2086.

Poziotinib for *HER2*^{mt} NSCLC: The ZENITH-20 Trial

- Poziotinib is an irreversible pan-ErbB family inhibitor



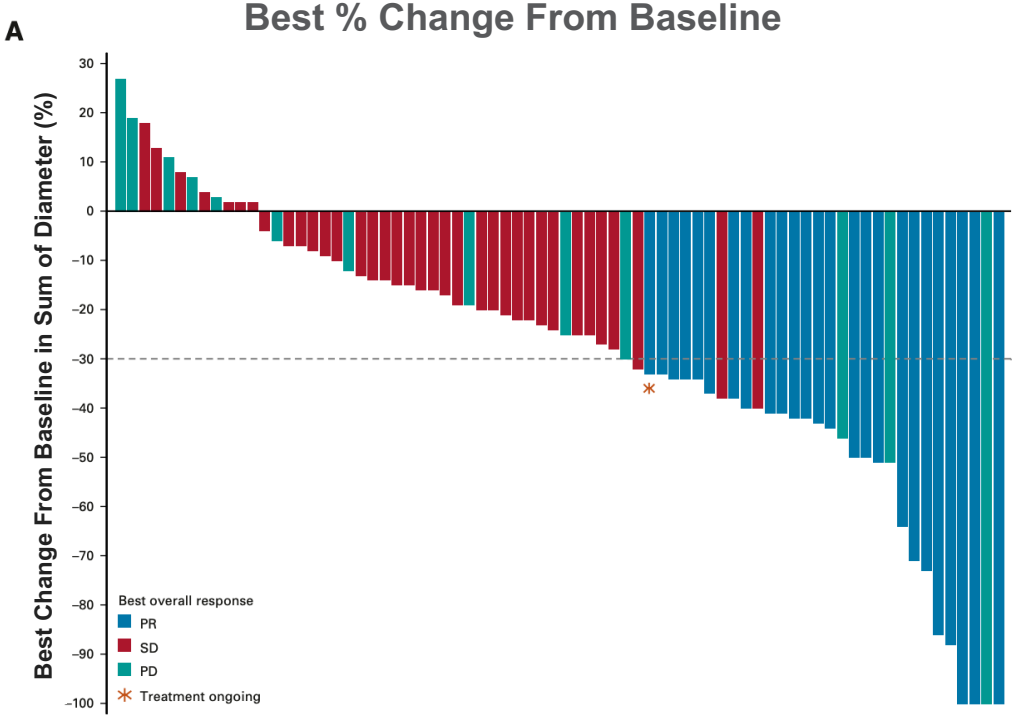
BID = twice daily; EGFR = epidermal growth factor receptor; ErbB = erythroblastic leukemia viral oncogene; ESMO = European Society for Medical Oncology; HER2 = human epidermal growth factor receptor 2; *HER2*^{mt} = human epidermal growth factor receptor 2–mutant; NSCLC = non–small cell lung cancer; PFS = progression-free survival; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors.

Remon J, et al. *Cancer Treat Rev.* 2020;90:102105.

Poziotinib in the Treatment of Previously Treated NSCLC With *HER2* ex20ins Mutations

- ZENITH20-2 trial, cohort 2 (n = 90), previously treated patients; all patients treated at 16 mg QD

Best % Change From Baseline



Clinical Response (RECIST v1.1 by BICR)

Parameter	As-treated[a] (n = 90)	Evaluable[b] (n = 74)
ORR, n (%) 95% CI	25 (27.8)[c] 18.9–38.2	26 (35.1)[d] 24.4–47.1
Best overall response, no. (%)		
CR	0 (0)	0 (0)
PR	25 (27.8)[c]	26 (35.1)[d]
SD	38 (42.2)	35 (47.3)
PD	13 (14.4)	13 (17.6)
NE	14 (15.6)	0 (0)
DCR, n (%) 95% CI	63 (70.0) 59.4–79.2	61 (82.4) 71.8–90.3
DoR, mo, median (range) 95% CI	5.1 (1–14.1) 4.2–5.5	5.1 (0.9–14.1) 4.2–5.5
PFS, mo, median (range) 95% CI	5.5 (0.0–17.6) 3.9–5.8	5.5 (0.6–17.6) 3.9–6.2

[a]The as-treated population was the primary analysis population and included all patients who received ≥1 dose of study medication. [b]The evaluable population excluded patients from the as-treated population who did not have a target lesion at baseline and/or did not have sufficient follow-up to evaluate tumor response. [c]CR/PR confirmation required ≥28 days after first observation of CR/PR. [d]CR/PR confirmation required ≥21 days after first observation of CR/PR.
BICR = blinded independent central reviews; CR = complete response; DCR = disease control rate; DoR = duration of response; ErbB = erythroblastic leukemia viral oncogene; ESMO = European Society for Medical Oncology; ex20ins = exon 20 insertion; *HER2* = human epidermal growth factor 2; NSCLC = non–small cell lung cancer; NE = not estimable; ORR = objective response rate; PD = progressive disease; PFS = progression-free survival; PR = partial response; QD = once daily; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SD = stable disease.

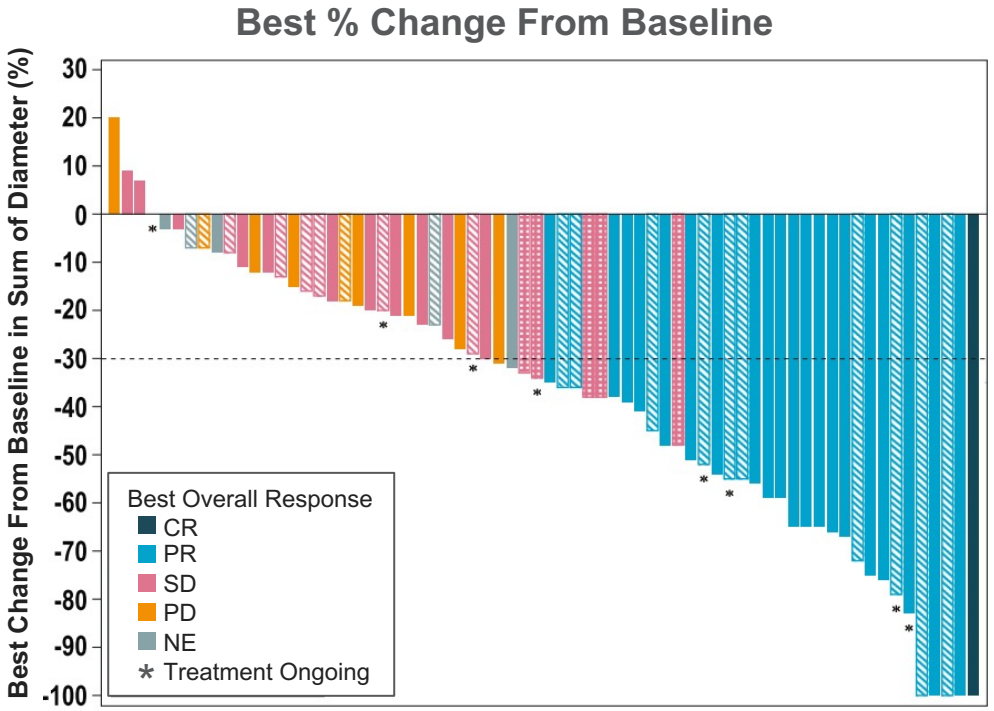
Le X, et al. *J Clin Oncol.* 2022;40(7):710–718.

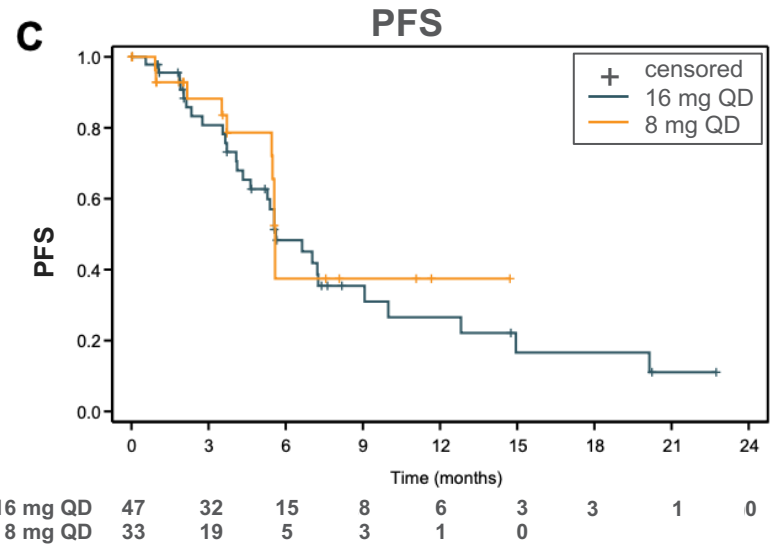
Poziotinib in the 1L Treatment of NSCLC With *HER2* ex20ins Mutations

- ZENITH20 trial, cohort 4 (n = 80)
  - Treated at 16 mg QD and 8 mg BID

Antitumor Activity by ICR

Parameter	As-treated population			Evaluable population		
Outcomes	Total (N = 80)	16 mg QD (n = 47)	8 mg BID (n = 33)	Total (N = 63)	16 mg QD (n = 41)	8 mg BID (n = 22)
ORR, n (%) 95% CI	31 (39) 28–50	21 (45) 30–60	10 (30) 16–49	31 (49) 36–62	21 (51) 35–67	10 (46) 24–68
mDoR (mo) 95% CI	5.7 4.6–11.9	5.7 4.6–11.9	NR	5.7 4.6–11.9	5.7 4.6–11.9	NR
mPFS (mo) 95% CI	5.6 5.4–7.3	5.6 4.3–9.1	5.6 5.5–NR	5.6 5.3–7.2	5.6 4.1–7.3	5.6 5.5–NR





1L = first-line; BID = twice daily; CR = complete response; ESMO = European Society for Medical Oncology; ex20ins = exon 20 insertion; *HER2* = human epidermal growth factor 2; ICR = independent central review; mDoR = median duration of response; mPFS = median progression-free survival; NE = not estimable; NR = not reached; NSCLC = non–small cell lung cancer; ORR = objective response rate; PD = progressive disease; PFS = progression-free survival; PR = partial response; QD = once daily; SD = stable disease.

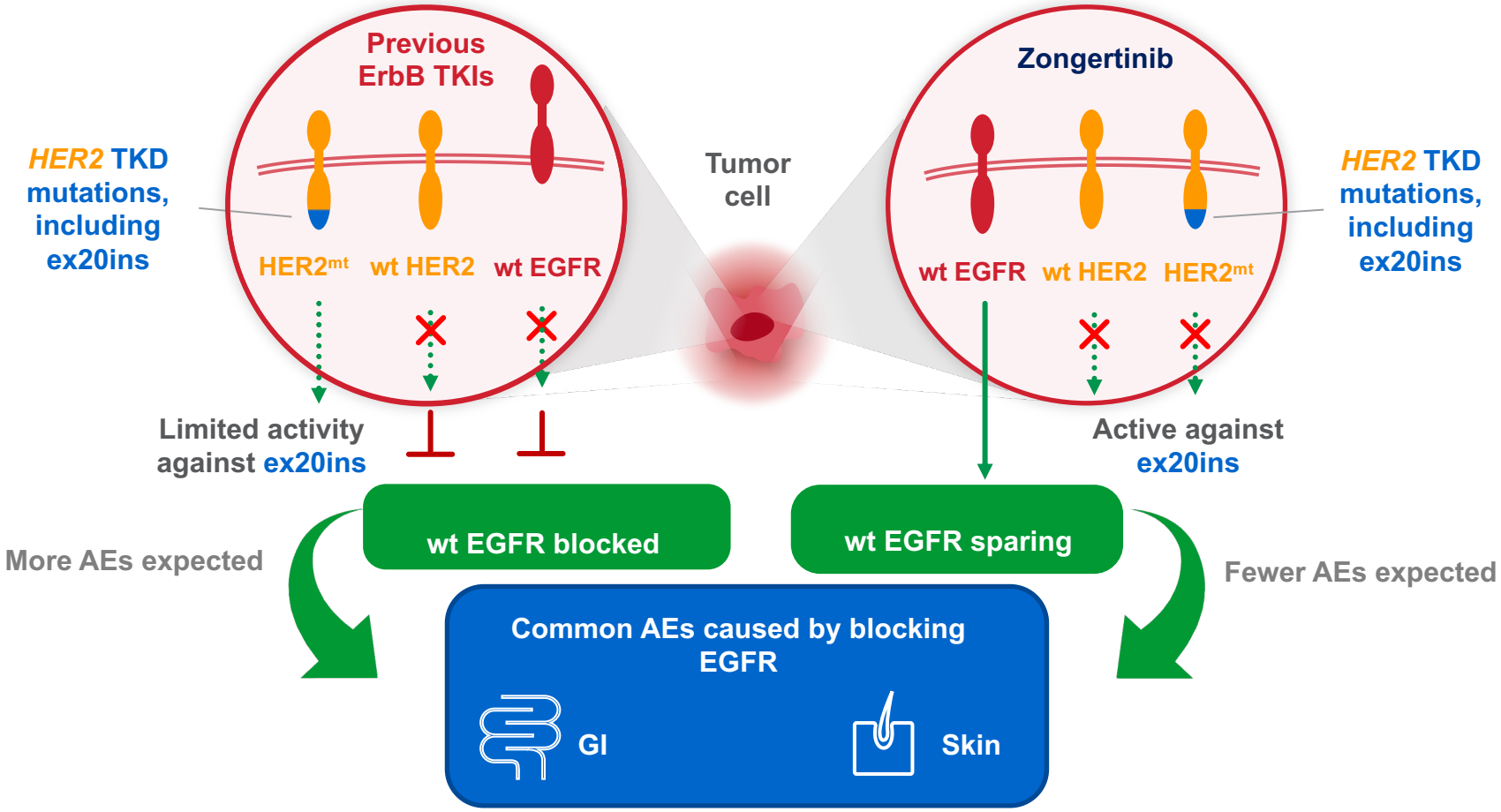
Cornelissen R, et al. *J Thorac Oncol.* 2023;18(8):1031–1041.

Poziotinib: Safety Profile in Patients With Treatment-Naïve NSCLC With *HER2* ex20ins Mutations

	Poziotinib 16 mg QD, n (%) (n = 47)			Poziotinib 8 mg BID, n (%) (n = 33)		
AEs (preferred term)	Any Grade	Grade 3	Grade 4/5	Any Grade	Grade 3	Grade 4/5
Patients with ≥1 event	47 (100)	33 (70)	0/1 (2)	32 (97)	24 (73)	2 (6)/0
Rash (multiple terms)[a]	46 (98)	21 (45)	0	27 (82)	13 (39)	0
Diarrhea	39 (83)	7 (15)	0	28 (85)	7 (21)	0
Stomatitis (multiple terms)[b]	38 (81)	10 (21)	0	24 (73)	5 (15)	0
Paronychia	23 (49)	5 (11)	0	18 (55)	4 (12)	0
Alopecia	16 (34)	0	0	13 (39)	0	0
Dry skin	16 (34)	1 (2)	0	10 (30)	1 (3)	0
Decreased appetite	15 (32)	0	0	13 (39)	1 (3)	0
Nausea	13 (28)	0	0	10 (30)	0	0
Weight decreased	12 (26)	1 (2)	0	8 (24)	0	0
Dysgeusia	9 (19)	0	0	10 (30)	1 (3)	0
Pruritus	9 (19)	3 (6)	0	9 (27)	0	0
Skin fissures	9 (19)	1 (2)	0	8 (24)	1 (3)	0
Fatigue	8 (17)	2 (4)	0	11 (33)	1 (3)	0
Vomiting	7 (15)	1 (2)	0	7 (21)	1 (3)	0
Dry mouth	7 (15)	0	0	6 (18)	0	0
Hypokalemia	6 (13)	3 (6)	0	6 (18)	2 (6)	2 (6)/0
Dizziness	5 (11)	0	0	2 (6)	0	0
Pneumonitis	2 (4)	0	0/1 (2)	1 (3)	1 (3)	0

[a]Rash includes dermatitis acneiform, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash generalized, rash maculopapular, and rash popular. [b]Stomatitis includes mucosal inflammation and stomatitis.
AE = adverse event; BID = twice daily; ESMO = European Society for Medical Oncology; ex20ins = exon 20 insertion; *HER2* = human epidermal growth factor 2; NSCLC = non–small cell lung cancer; QD = once daily.
Cornelissen R, et al. *J Thorac Oncol.* 2023;18(8):1031–1041.

Zongertinib (BI 181063) – Selective HER2 TKI

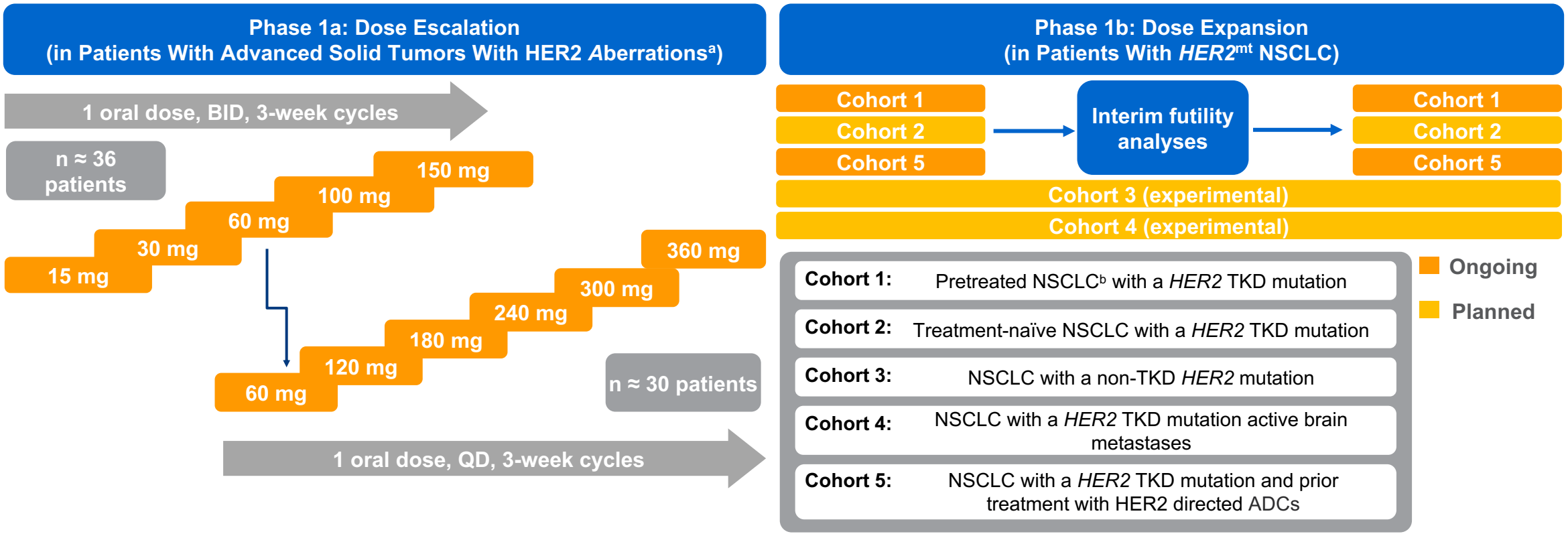


AE = adverse event; EGFR = epidermal growth factor receptor; ErbB = erythroblastic leukemia viral oncogene; ESMO = European Society for Medical Oncology; ex20ins = exon 20 insertion; GI = gastrointestinal; HER2 = human epidermal growth factor receptor 2; HER2^{mt} = human epidermal growth factor receptor 2–mutant; TKD = tyrosine kinase domain; TKI = tyrosine kinase inhibitor; wt = wild type.

Heymach J, et al. ASCO 2023. Abstract 8545.

Beamion LUNG-1

Phase 1 study of zongertinib in patients with advanced/metastatic solid tumors with HER2 aberrations, including *HER2*^{mt} NSCLC

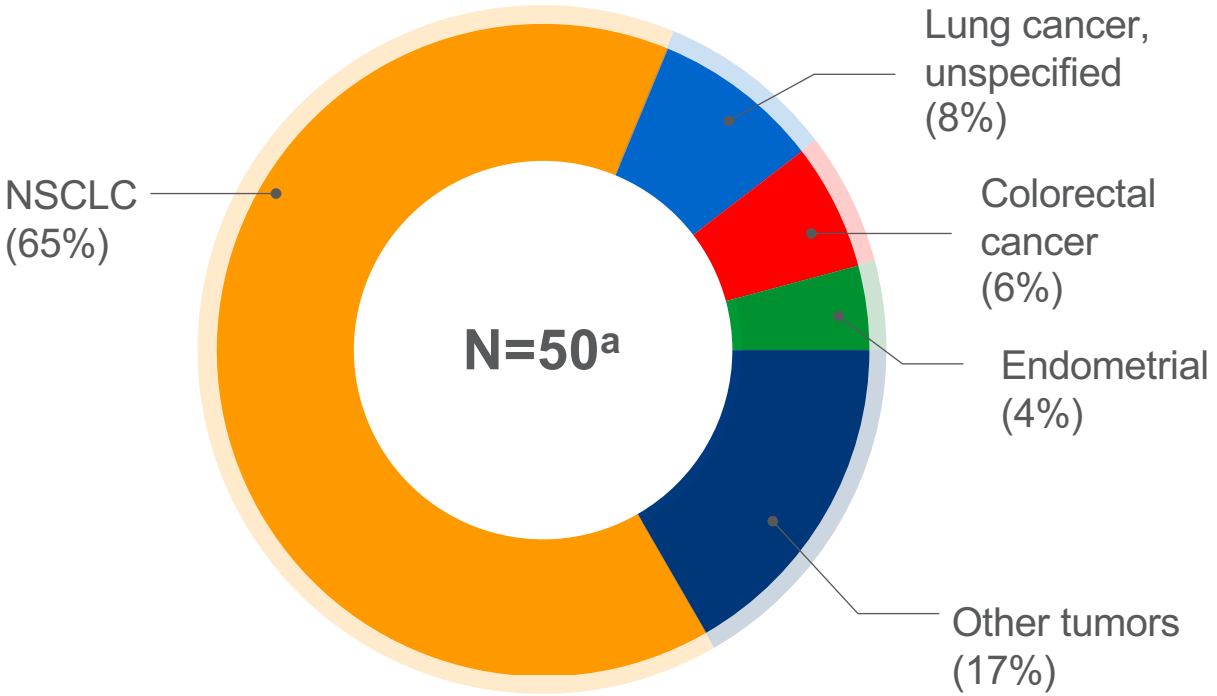


[a]Overexpression, amplification, somatic mutation, or gene rearrangement involving HER2 or NRG1. [b]Excluding patients treated with ADCs. Phase 1a primary endpoint: MTD and DLTs (MTD evaluation period); Phase 1b primary endpoint: objective response, according to RECIST v1.1.

ADC = antibody-drug conjugate; BID = twice daily; DLTs = dose-limiting toxicities; ESMO = European Society for Medical Oncology; *HER2* = human epidermal growth factor receptor 2; *HER2*^{mt} = human epidermal growth factor receptor 2–mutant; MTD = maximum tolerated dose; NRG1 = neuregulin 1; NSCLC = non–small cell lung cancer; QD = once daily; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; TKD = tyrosine kinase domain.

Yamamoto N, et al. WCLC 2023. Mini Oral Presentation MA13.08.

Beamion LUNG-1: Patient Characteristics



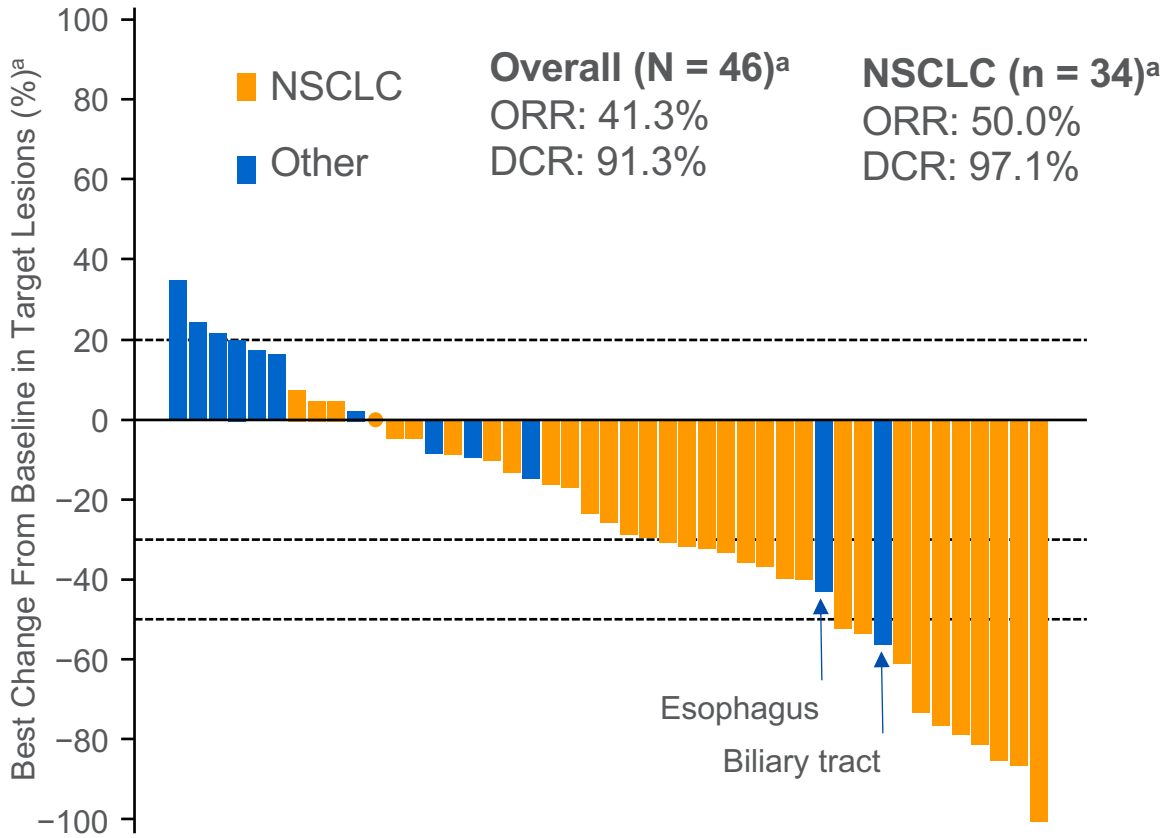
Baseline Characteristics	Total (N = 50)
Median age, y (range)	60.5 (31–79)
Gender, n (%)	
Male	26 (52.0)
Race, n (%)	
White	17 (34.0)
Asian	32 (64.0)
ECOG PS, n (%)	
0	17 (34.0)
1	33 (66.0)
Prior lines of therapy, n (%)[a]	15 (34.9)
≤2	20 (40.0)
>2	26 (52.0)
HER2 aberration, n/N tested (%)[b]	
Mutation	28/48 (58.3)
Amplification	4/5 (80.0)
Overexpression[c]	9/12 (75.0)
Rearrangement involving *HER2* or *NRG1*	10/48 (21.0)

Data cutoff: July 17, 2023.

[a]4 patient (8.0%) had missing data. [b]2 patients (4.0%) had missing data. [c]1+, 2+, or 3+ on immunohistochemistry.
ECOG PS = Eastern Cooperative Oncology Group performance status; ESMO = European Society for Medical Oncology; HER2 = human epidermal growth factor receptor 2; *NRG1* = neuregulin 1; NSCLC = non–small cell lung cancer.
Yamamoto N, et al. WCLC 2023. Mini Oral Presentation MA13.08.

Beamion LUNG-1: Antitumor Response in Phase 1a

Best Percentage Change From Baseline



Best Overall Treatment Response

n (%)	Overall (N = 46)[a]	NSCLC (n = 34)[a]
ORR	19 (41.3)	17 (50.0)
CR	0 (0)	0 (0)
PR	19 (41.3)	17 (50.0)
SD	23 (50.0)	16 (47.1)

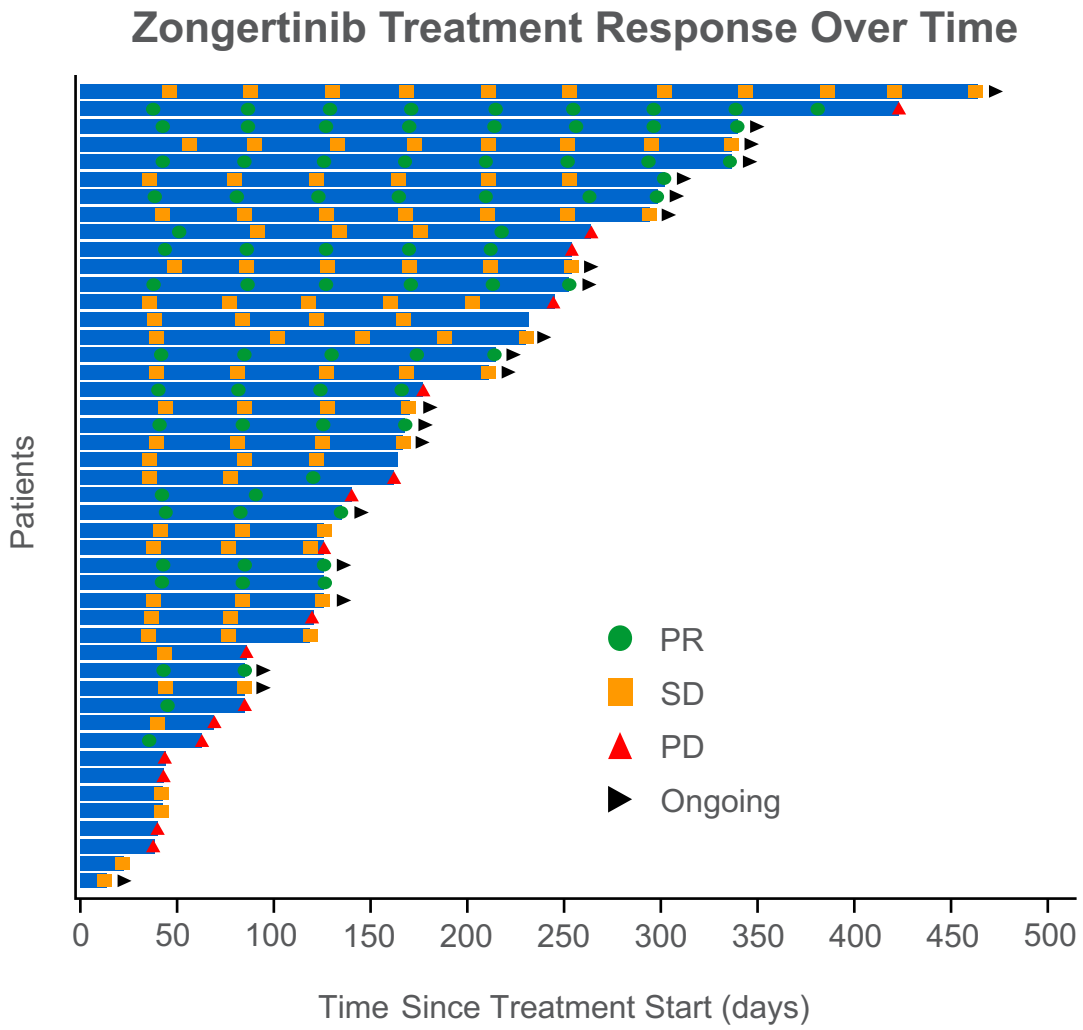
A775_G776 insYVMA (n = 11[b])

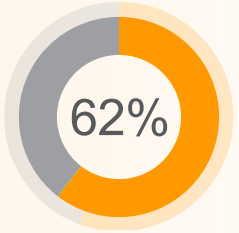
- PR: 7/11 (63.6%)
- SD: 3/11 (27.3%)
- PD: 1/11 (9.1%)

Data cutoff: July 17, 2023.

[a]Patients with ≥1 postbaseline tumor assessment or discontinued before first assessment for any reason. [b]Patients where mutation information was provided by the sites (which was optional in Phase 1a).
CR = complete response; DCR = disease control rate; ESMO = European Society for Medical Oncology; insYVMA = YVMA insertion; NE = not estimable; NSCLC = non–small cell lung cancer; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.
Yamamoto N, et al. WCLC 2023. Mini Oral Presentation MA13.08.

Beamion LUNG-1: Treatment Response in Phase 1a





Patients still on treatment as of July 17, 2023

7.5 (1–24)

Median number of cycles (range)

ESMO = European Society for Medical Oncology; PD = progressive disease; PR = partial response; SD = stable disease.
Yamamoto N, et al. WCLC 2023. Mini Oral Presentation MA13.08.

Beamion LUNG-1: Phase 1a Dose Escalation and Safety

Phase 1a TRAEs (%)[a]	Zongertinib BID (n = 17)		Zongertinib QD (n = 33)		Total (N = 50)	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Any TRAE	**76.5**	**5.9**	**84.8**	**12.1**	**82.0**	**10.0**
Diarrhea	47.1	—	36.4	—	40.0	—
AST increased	5.9	—	18.2	3.0	14.0	2.0
Rash[b]	11.8	—	15.2	—	14.0	—
ALT increased	5.9	5.9	15.2	6.1	12.0	6.0
Paronychia	5.9	—	12.1	—	10.0	—
Dry skin	11.8	—	6.1	—	8.0	—
Anemia	11.8	—	6.1	—	8.0	—

Most TRAEs were grade 1 or 2

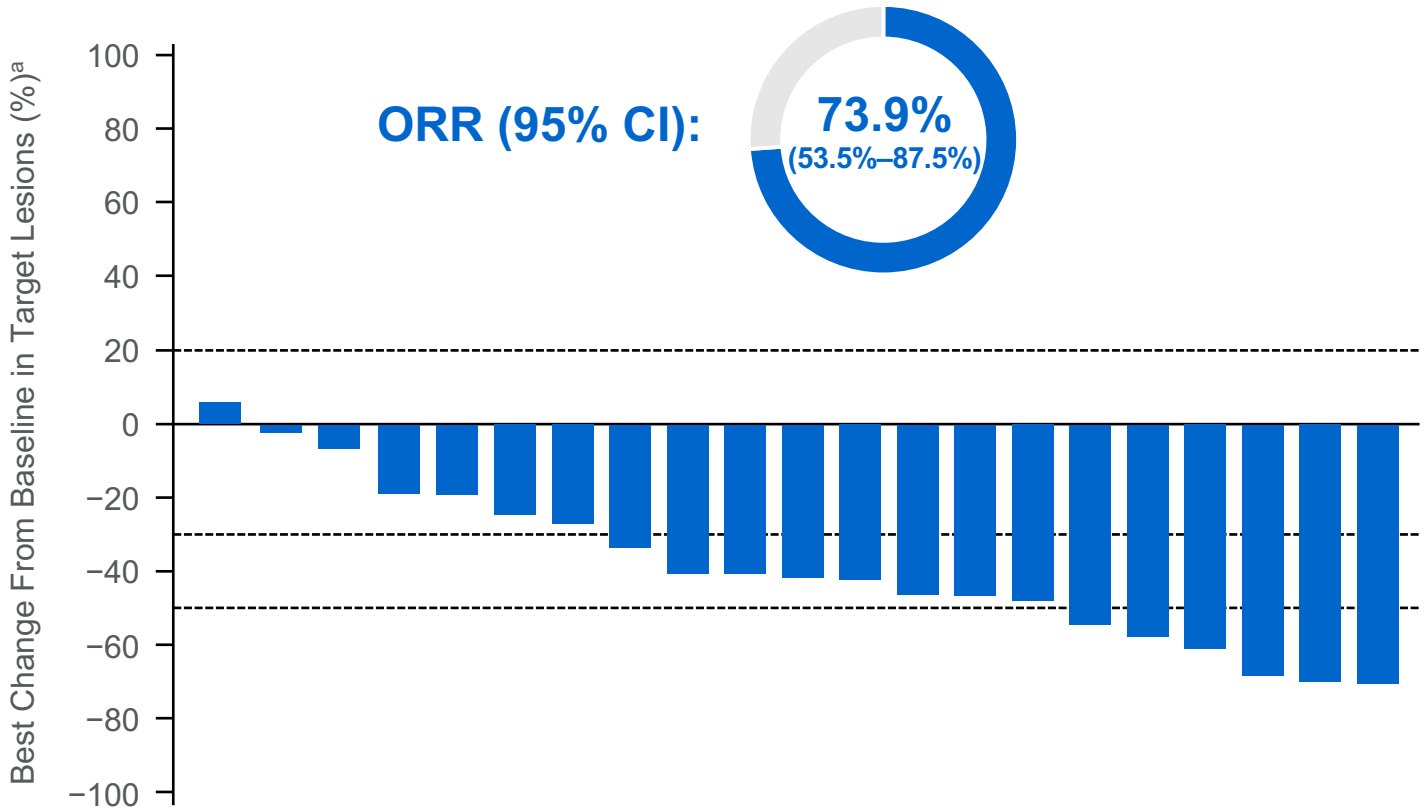
3 Patients with DLTs during the on-treatment period

1 Patient with TRAE leading to treatment discontinuation (grade 3 ALT increased)

1 Patient with serious TRAEs (grade 3 ALT and AST increased)

[a]≥8% of total patients. [b]Combined term, includes rash, rash maculopapular, and dermatitis acneiform.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; DLTs = dose-limiting toxicities; ESMO = European Society for Medical Oncology; QD = once daily; TRAEs = treatment-related adverse event.
Yamamoto N, et al. WCLC 2023. Mini Oral Presentation MA13.08.

Beamion LUNG-1 (Phase 1b): Antitumor Activity in Previously Treated NSCLC With *HER2* TKD Mutations



Overall (N = 23)[b]

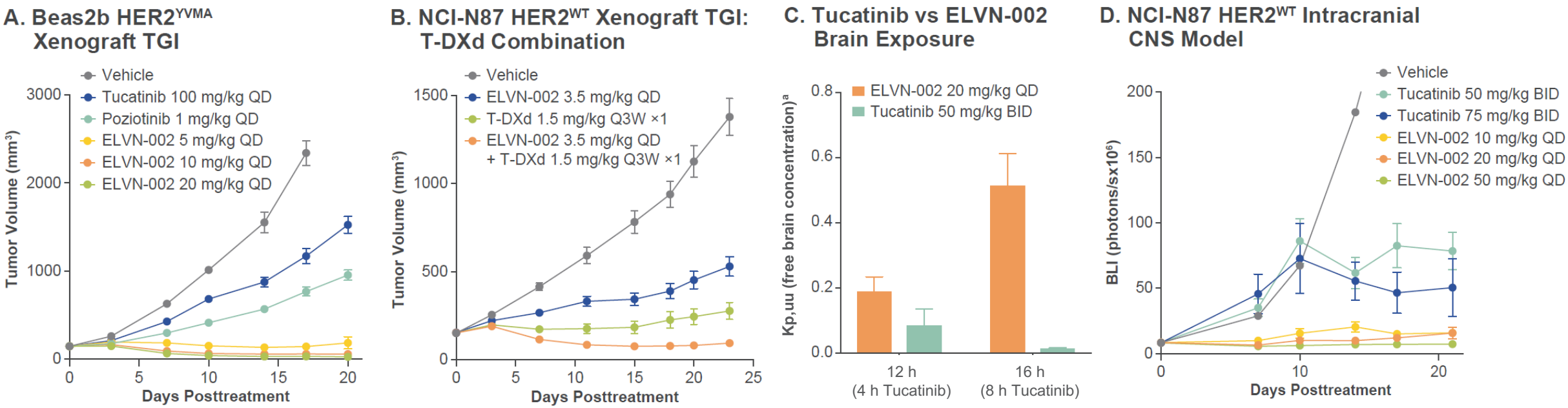
- Patients included had between 2 and 5 cycles of treatment at cutoff
- DCR: 91.3%
- Median best percentage change from baseline in target lesions: −41.2%

[a]Patients who started treatment ≥7 weeks prior to the snapshot date with baseline and postbaseline tumor assessments. [b]Patients who started treatment ≥7 weeks prior to the snapshot date.
CI = confidence interval; DCR = disease control rate; ESMO = European Society for Medical Oncology; *HER2* = human epidermal growth factor receptor 2; NSCLC = non–small cell lung cancer; ORR = objective response rate; TKD = tyrosine kinase domain.
Yamamoto N, et al. WCLC 2023. Mini Oral Presentation MA13.08.

ELVN-002: Preclinical Activity

- ELVN-002 is a potent, irreversible inhibitor of HER2 with a >100-fold selectivity over EGFR[1]
- ELVN-002 showed preclinical activity in xenograft models, including an intracranial model, driven by wt *HER2* and *HER2*^{mt} and was well tolerated in all models tested.[1] It is now being evaluated in a phase 1 study in *HER2*^{mt} solid tumors[2]

ELVN-002 Antitumor Activity and Additive Activity With T-DXd[3]



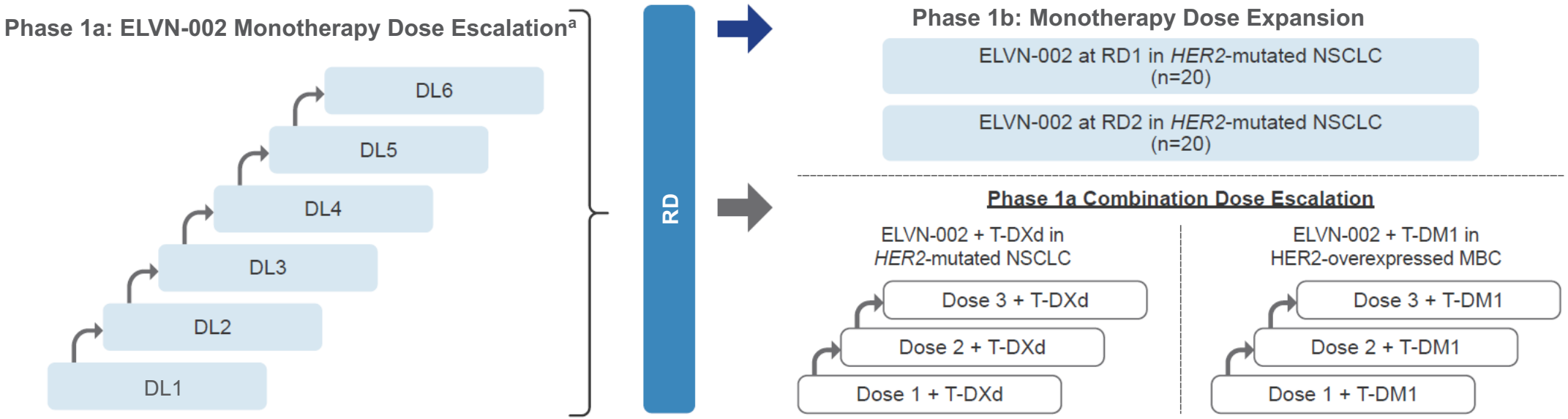
[a]Kp,uu is the unbound brain to plasma partition coefficient, which is used to define the unbound drug concentration in the brain relative to blood with a reference. Kp,uu = Free brain concentration (total brain concentration adjusted for brain tissue binding)/Free plasma concentration (total plasma concentration adjusted for protein binding).

BID = twice daily; CNS = central nervous system; EGFR = epidermal growth factor receptor; ESMO = European Society for Medical Oncology; HER2 = human epidermal growth factor receptor; *HER2*^{mt} = human epidermal growth factor receptor 2–mutant; Q3W = every 3 weeks; QD = once DAILY; T-DXd = trastuzumab deruxtecan; TGI = tumor growth inhibition; wt = wild type.

1. Aujay M, et al. *Cancer Res.* 2023;83(7_suppl):4019; 2. ClinicalTrials.gov. https://www.clinicaltrials.gov/study/NCT05650879. Accessed September 2023; 3. Bowyer S, et al. WCLC 2023. Poster P2.09.

ELVN-002: Phase 1 Study in Solid Tumors With *HER2* Mutations, Amplification, or Overexpression

ELVN-002-001 is a first-in-human, Phase 1, open-label, multicenter, dose-escalation and -expansion study to evaluate the safety, tolerability, PK, and preliminary antitumor activity of ELVN-002 monotherapy and in combination with T-DXd or T-DM1 in patients with solid tumors with HER2 alterations, including *HER2*^{mt} NSCLC and HER2-overexpressed metastatic breast cancer



[a]Successive cohorts will receive escalating doses of QD ELVN-002. Dose escalation decisions will follow a Bayesian design. Dosing will be continuous in 21-day cycles until disease progression or unacceptable toxicity. Dose escalation may continue until the maximum tolerated dose is identified. 2 RDs for phase 1b monotherapy expansion will be chosen. Evaluation of BID regimen and intermediate dose levels may occur upon approval of the Safety Review Committee. Dose exploration may consist of up to 30 patients who may be enrolled at ≥1 dose level to further evaluate the safety, tolerability, PK, and clinical activity. A maximum of 10 patients may be enrolled at any given dose level. [b]Single-patient cohort.

BID = twice daily; DL = dose level; ESMO = European Society for Medical Oncology; HER2 = human epidermal growth factor receptor 2; *HER2*^{mt} = human epidermal growth factor receptor 2–mutant; NSCLC = non–small cell lung cancer; PK = pharmacokinetics; QD = once daily; RD = recommended dose; T-DM1 = ado-trastuzumab emtansine; T-DXd = trastuzumab deruxtecan.

Bowyer S, et al. WCLC 2023. Poster P2.09.

Summary and Conclusions

- *HER2* mutations occur in ≈1%–4% of NSCLC[1–3]
  - ex20ins are most common, but point mutations in the tyrosine kinase, transmembrane, and extracellular domain are also observed[1–3]
- T-DXd has accelerated FDA approval for *HER2*^{mt} NSCLC after prior systemic therapy[4]
- The clinical development of EGFR/HER2 TKIs for *HER2*^{mt} NSCLC has been limited by significant toxicities (largely EGFR-related)[5–9]
- Novel HER2-specific TKIs (zongertinib, ELVN-002) are now in clinical development[10–13]

EGFR = epidermal growth factor receptor; ESMO = European Society for Medical Oncology; ex20ins = exon 20 insertions; FDA = US Food and Drug Administration; *HER2* = human epidermal growth factor receptor 2; *HER2*^{mt} = human epidermal growth factor receptor 2–mutant; NSCLC = non–small cell lung cancer; T-DXd = trastuzumab deruxtecan; TKI = tyrosine kinase inhibitor.

1. Jebbink M, et al. *Cancer Treat Rev.* 2020;86:101996; 2. Yu X, et al. *Front Oncol.* 2022;12:860313; 3. Arcila ME, et al. *Clin Cancer Res.* 2012;18:4910–4918; 4. Enhertu Approved. *AstraZeneca*:2022. Accessed September 2023; 5. Dziadziuszko R, et al. *J Thorac Oncol.* 2019;14:1086–1094; 6. Lai WV, et al. *Eur J Cancer.* 2019;109:28–35; 7. Hyman DM, et al. *Nature.* 2018;554(7691):189−194; 8. Kris MG, et al. *Ann Oncol.* 2015;26:1421–1427; 9. Son J, et al. *Cancer Res.* 2022;82(8):1633–1645; 10. Heymach J, et al. ASCO 2023. Abstract 8545; 11. Seymour C. *OncLive* 2023. https://www.onclive.com/view/zongertinib-proves-clinically-active-with-low-rate-of-egfr-mediated-aes-in-her2-mutant-solid-tumors. Accessed September 2023; 12. ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT05650879. Accessed September 2023; 13. Aujay M, et al. AACR 2023, Poster 4019.