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

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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; NF\(\kappa\)B = 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.

HER2 Mutations Also Feature at Varying Frequencies Across Tumor Types

ESMO = European Society for Medical Oncology; HER2 = human epidermal growth factor receptor 2.
**HER2 Mutations in NSCLC**

- **HER2 mutations occur in 1%–4% of NSCLC**
  - 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**

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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.

Role of Chemoimmunotherapy in HER2\textsuperscript{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\textsuperscript{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.

Numerous Therapeutic Strategies Targeting \( \text{HER2}^{\text{mt}} \) NSCLC Are in Development\(^1,2\)

**mAbs**
- Bind to the extracellular domain of HER2 to block homodimerization and heterodimerization\(^2\)

**ADCs**
- Utilize a mAb linked to a cytotoxic agent “payload” to direct the payload to cancer cells\(^2\)

**TKIs**
- Block phosphorylation of the tyrosine kinase residues, inhibiting cell proliferation\(^2\)

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mAbs Bind to the extracellular domain of HER2 to block homodimerization and heterodimerization\(^2\)

ADCs Utilize a mAb linked to a cytotoxic agent “payload” to direct the payload to cancer cells\(^2\)

TKIs Block phosphorylation of the tyrosine kinase residues, inhibiting cell proliferation\(^2\)

Novel HER2 TKIs

Non–EGFRwt-sparing\(^3\)

Pan-HER inhibitors

EGFRwt-sparing\(^3\)

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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\(^{\text{mt}}\) = human epidermal growth factor receptor 2-mutant; mAb = monoclonal antibody; NSCLC = non–small cell lung cancer; TKI = tyrosine kinase inhibitor; wt = wild type.

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

Efficacy in HER2\textsuperscript{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

ADC = antibody-drug conjugate; ESMO = European Society for Medical Oncology; HER2 = human epidermal growth factor receptor 2; HER2\textsuperscript{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.

T-DXd Is a HER2-targeting mAb Linked to a Chemotherapy “Payload”\(^1\textendash}^3

T-DXd payload: deruxtecan, a topoisomerase I inhibitor

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.
T-DXd Is a HER2-Targeting mAb Linked to a Chemotherapy “Payload”¹⁻³

1. T-DXd binds to HER2
2. Endocytosis
3. Cleavage of linker and payload release
4. DNA replication disruption
5. Induction of apoptosis
6. Bystander killing effect

Adapted from Lambert JM, Berkenblit A. 2018⁴ 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.

DESTINY-Lung02: A Phase 2 Trial of T-DXd in Metastatic HER2\textsuperscript{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

**Study Design**

**Randomization**

- T-DXd 5.4 mg/kg Q3W n=102
- T-DXd 6.4 mg/kg Q3W n = 50

**Ratio** 2:1

N=152

**Stratification Factor**

- Prior anti–PD-1/PD-L1 treatment

**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\textsuperscript{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.

DESTINY-Lung02 Primary Results: Antitumor Activity of T-DXd 5.4 mg/kg Q3W in HER2<sup>mt</sup> Metastatic NSCLC

**Best Percentage Change From Baseline**

<table>
<thead>
<tr>
<th></th>
<th>DESTINY-Lung02 (n = 152)</th>
<th>T-DXd 5.4 mg/kg Q3W (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, n (%)</td>
<td>50 (49.0)</td>
<td>(95% CI 39.0–59.1)</td>
</tr>
<tr>
<td></td>
<td>CR</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td></td>
<td>PR</td>
<td>49 (48.0)</td>
</tr>
<tr>
<td>Median DoR, mo</td>
<td>16.8</td>
<td>(95% CI 6.4–NE)</td>
</tr>
<tr>
<td></td>
<td>Median follow-up, mo</td>
<td>11.5</td>
</tr>
</tbody>
</table>

*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<sup>mt</sup> = 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.

DESTINY-Lung02 Primary Results: Antitumor Activity of T-DXd 6.4 mg/kg Q3W in HER2<sup>mt</sup> Metastatic NSCLC

Best Percentage Change From Baseline

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

*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<sup>mt</sup> = 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.

DESTINY-Lung02 Primary Results: OS

T-DXd Kaplan Meier Curves for OS

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.
HER2 ADCs: T-DXd

**DESTINY-Lung01**

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**

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)

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*Data cutoff: June 22, 2022. *1Median 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.
DESTINY-Lung01 Drug-Related AEs

<table>
<thead>
<tr>
<th>Event</th>
<th>Grades 1–2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-related AE</td>
<td>46 (51)</td>
<td>37 (41)</td>
<td>4 (4)</td>
<td>1 (1)a</td>
<td>88 (97)</td>
</tr>
<tr>
<td>Drug-related AEs with ≥20% incidence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>58 (64)</td>
<td>8 (9)</td>
<td>0</td>
<td>0</td>
<td>66 (73)</td>
</tr>
<tr>
<td>Fatigueb</td>
<td>42 (46)</td>
<td>6 (7)</td>
<td>0</td>
<td>0</td>
<td>48 (53)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>42 (46)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>42 (46)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>33 (36)</td>
<td>3 (3)</td>
<td>0</td>
<td>0</td>
<td>36 (40)</td>
</tr>
<tr>
<td>Neutropeniac</td>
<td>15 (16)</td>
<td>14 (15)</td>
<td>3 (3)</td>
<td>0</td>
<td>32 (35)</td>
</tr>
<tr>
<td>Anemiad</td>
<td>21 (23)</td>
<td>9 (10)</td>
<td>0</td>
<td>0</td>
<td>30 (33)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26 (29)</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>0</td>
<td>29 (32)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>27 (30)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>27 (30)</td>
</tr>
<tr>
<td>Leukopeniae</td>
<td>17 (19)</td>
<td>4 (4)</td>
<td>0</td>
<td>0</td>
<td>21 (23)</td>
</tr>
<tr>
<td>Constipation</td>
<td>20 (22)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>20 (22)</td>
</tr>
</tbody>
</table>

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

*a*One patient had grade 5 (i.e., 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.

DESTINY-Lung02 Primary Results: Overall Safety

- 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%)

*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.
Based on DESTINY-Lung02 Results, T-DXd Received FDA Accelerated Approval in August 2022

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


T-DXd SPC

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

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.
DESTINY-Lung04: A Phase 3 Trial of T-DXd as 1L Treatment in Metastatic HER2\textsuperscript{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\textsuperscript{a}
- Naive to systemic therapy in the locally advanced or metastatic setting
- No known other targetable oncogenic mutations/alterations

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\textsuperscript{a}HER2 mutations may be detected in tissue or ctDNA. \textsuperscript{b}Crossover is not permitted. \textsuperscript{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\textsuperscript{mt} = human epidermal growth factor receptor 2–mutant; NSCLC = non–small cell lung cancer; T-DXd = trastuzumab deruxtecan.

TKIs

TKI = tyrosine kinase inhibitor.
### Older EGFR/HER2 TKIs in HER2\textsuperscript{mt} NSCLC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target population</th>
<th>N</th>
<th>ORR</th>
<th>mPFS</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib\textsuperscript{1}</td>
<td>HER2\textsuperscript{mt}</td>
<td>13</td>
<td>8%</td>
<td>16 weeks</td>
<td>Diarrhea, vomiting, abdominal pain, skin rash, paronychia, fatigue, mucositis, dyspnea</td>
</tr>
<tr>
<td>Afatinib\textsuperscript{2}</td>
<td>HER2\textsuperscript{mt}</td>
<td>27</td>
<td>13%\textsuperscript{a}</td>
<td>3 mo</td>
<td>Diarrhea/GI toxicity, skin rash</td>
</tr>
<tr>
<td>Neratinib\textsuperscript{3}</td>
<td>HER2\textsuperscript{mt}</td>
<td>26</td>
<td>4%</td>
<td>5.5 mo</td>
<td>Diarrhea (74%), nausea (43%), vomiting (41%)</td>
</tr>
<tr>
<td>Dacomitinib\textsuperscript{4}</td>
<td>HER2\textsuperscript{mt}</td>
<td>26</td>
<td>12%</td>
<td>3 mo</td>
<td>Diarrhea (90%), rash (73%)</td>
</tr>
<tr>
<td>Mobocertinib\textsuperscript{5}</td>
<td>HER2\textsuperscript{mt}</td>
<td>136</td>
<td>0%, 22%</td>
<td>19%, 43%\textsuperscript{b}</td>
<td>10.2 mo</td>
</tr>
</tbody>
</table>

\textsuperscript{a}3/23 patients. \textsuperscript{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\textsuperscript{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.

Pyrotinib in the 1L Treatment of HER2mt NSCLC

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

**Tumor Response**

**ORR:**
- CF: 35.7%
- CU: 16.7%

**Brain metastases**
- Present
- Absent

**PFS**

**TRAEs Reported in ≥10% of Patients**

<table>
<thead>
<tr>
<th>TRAEs, n (%)</th>
<th>CF Cohort (n = 28)</th>
<th>CU Cohort (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grades 3/4</td>
</tr>
<tr>
<td>Any AEs</td>
<td>27 (96.4)</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24 (85.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rash</td>
<td>9 (32.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>AST increased</td>
<td>7 (25.0)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>6 (21.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Conjugated bilirubin increased</td>
<td>5 (17.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>5 (17.9)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Mouth ulcer</td>
<td>4 (14.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>4 (14.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>3 (10.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Serum uric acid increased</td>
<td>3 (10.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3 (10.7)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

**Notes:**
- 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; HER2mt = 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.
Poziotinib for HER2<sup>mt</sup> NSCLC: The ZENITH-20 Trial

- Poziotinib is an irreversible pan-ErbB family inhibitor

**ZENITH 20 Trial (NCT03318939): NSCLC patients with EGFR/HER2 exon 20 insertions**

**Key eligibility Criteria**
- NSCLC EGFR or HER2 exon20 insertions.
- Point mutations, including T790M, are not allowed.
- Stable brain metastases are allowed

**Osimertinib-resistant with EGFR mutations**

**Atypical EGFR or HER2 mutations**

**Cohort 1**
EGFR – previously treated

**Cohort 2**
HER2 – previously treated

**Cohort 3**
EGFR – treatment-naive

**Cohort 4**
HER2 – treatment-naive

**Cohort 5**
EGFR/HER2 exon 20 (n=180)

**Cohort 6**
EGFR osimertinib failure (n=30)

**Cohort 7**
Atypical EGFR / HER2 mutations (N=30)

**Oral daily dose of POZIOTINIB**
28-days cycle

- **Cohort 1**: 16mg QD with dose reduction
- **Cohort 2**: 8mg BID
- **Cohort 4**: 8mg BID

**Primary endpoint:**
- Response Rate by RECIST.

**Secondary endpoints:**
- Duration of response
- Disease control rate
- PFS (exploratory)
- Safety

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<sup>mt</sup> = 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.

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

### Clinical Response (RECIST v1.1 by BICR)

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

<sup>a</sup>The as-treated population was the primary analysis population and included all patients who received ≥1 dose of study medication. <sup>b</sup>The evaluable population excluded patients from the as-treated population who did not have a target lesion evaluable and/or did not have sufficient follow-up to evaluate tumor response. <sup>c</sup>CR/PR confirmation required ≥28 days after first observation of CR/PR. <sup>d</sup>CR/PR confirmation required ≥21 days after first observation of CR/PR.

Clinical Response (RECIST v1.1 by BICR)

#### Best % Change From Baseline

![Best % Change From Baseline](image)

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**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>As-treated population</th>
<th>Evaluable population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (N = 80)</td>
<td>16 mg QD (n = 47)</td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>31 (39)</td>
<td>21 (45)</td>
</tr>
<tr>
<td>95% CI</td>
<td>28–50</td>
<td>30–60</td>
</tr>
<tr>
<td>mDoR (mo)</td>
<td>5.7 (4.6–11.9)</td>
<td>NR</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mPFS (mo)</td>
<td>5.6 (5.4–7.3)</td>
<td>5.6</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>4.3–9.1</td>
</tr>
</tbody>
</table>

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.

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

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

aRash includes dermatitis acneform, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash generalized, rash maculopapular, and rash papular. bStomatitis 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.
Zongertinib (BI 181063) – Selective HER2 TKI

**Previous ErbB TKIs**
- HER2 TKD mutations, including ex20ins
- HER2\textsuperscript{mt} wt HER2 wt EGFR
- Limited activity against ex20ins
- Limited activity against HER2 TKD mutations, including ex20ins
- More AEs expected

**Zongertinib**
- HER2 TKD mutations, including ex20ins
- wt EGFR wt HER2 HER2\textsuperscript{mt}
- Active against ex20ins
- HER2 TKD mutations, including ex20ins
- Fewer AEs expected

**Common AEs caused by blocking EGFR**
- GI
- Skin

**wt EGFR blocked**

**wt EGFR sparing**

**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\textsuperscript{mt}** = human epidermal growth factor receptor 2–mutant; **TKD** = tyrosine kinase domain; **TKI** = tyrosine kinase inhibitor; **wt** = wild type.

Beamion LUNG-1
Phase 1 study of zongertinib in patients with advanced/metastatic solid tumors with HER2 aberrations, including HER2\textsuperscript{mt} NSCLC

*Overexpression, amplification, somatic mutation, or gene rearrangement involving HER2 or NRG1. 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\textsuperscript{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.

Beamion LUNG-1: Patient Characteristics

Baseline Characteristics (Total = 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 (%)\( ^a \):**
  - ≤2: 20 (40.0)
  - >2: 26 (52.0)
- **HER2 aberration, n/N tested (%):**
  - 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)

**Overall Tumor Types**

- NSCLC (65%)
- Other tumors (17%)
- Endometrial (4%)
- Colorectal cancer (6%)
- Lung cancer, unspecified (8%)

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.

**Beamion LUNG-1: Antitumor Response in Phase 1a**

**Best Percentage Change From Baseline**

<table>
<thead>
<tr>
<th></th>
<th>NSCLC (n = 34)</th>
<th>Overall (N = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best % Change</td>
<td>ORR: 50.0%</td>
<td>ORR: 41.3%</td>
</tr>
<tr>
<td></td>
<td>DCR: 97.1%</td>
<td>DCR: 91.3%</td>
</tr>
</tbody>
</table>

**Best Overall Treatment Response**

<table>
<thead>
<tr>
<th></th>
<th>Overall (N = 46)</th>
<th>NSCLC (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>19 (41.3%)</td>
<td>17 (50.0%)</td>
</tr>
<tr>
<td>CR</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>PR</td>
<td>19 (41.3%)</td>
<td>17 (50.0%)</td>
</tr>
<tr>
<td>SD</td>
<td>23 (50.0%)</td>
<td>16 (47.1%)</td>
</tr>
</tbody>
</table>

- **A775_G776 insYVMA (n = 11b)**
  - PR: 7/11 (63.6%)
  - SD: 3/11 (27.3%)
  - PD: 1/11 (9.1%)

Data cutoff: July 17, 2023.

- Patients with ≥1 postbaseline tumor assessment or discontinued before first assessment for any reason.
- 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.

Beamion LUNG-1: Treatment Response in Phase 1a

Zongertinib Treatment Response Over Time

Patients still on treatment as of July 17, 2023

62%

7.5 (1–24)
Median number of cycles (range)

PR
SD
PD
Ongoing

ESMO = European Society for Medical Oncology; PD = progressive disease; PR = partial response; SD = stable disease.
Beamion LUNG-1: Phase 1a Dose Escalation and Safety

<table>
<thead>
<tr>
<th>Phase 1a TRAEs (%) &lt;sup&gt;a&lt;/sup&gt;</th>
<th>Zongertinib BID (n = 17)</th>
<th>Zongertinib QD (n = 33)</th>
<th>Total (N = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any</td>
<td>Grade ≥3</td>
<td>Any</td>
</tr>
<tr>
<td>Any TRAE</td>
<td>76.5</td>
<td>5.9</td>
<td>84.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>47.1</td>
<td>—</td>
<td>36.4</td>
</tr>
<tr>
<td>AST increased</td>
<td>5.9</td>
<td>—</td>
<td>18.2</td>
</tr>
<tr>
<td>Rash &lt;sup&gt;b&lt;/sup&gt;</td>
<td>11.8</td>
<td>—</td>
<td>15.2</td>
</tr>
<tr>
<td>ALT increased</td>
<td>5.9</td>
<td>5.9</td>
<td>15.2</td>
</tr>
<tr>
<td>Paronychia</td>
<td>5.9</td>
<td>—</td>
<td>12.1</td>
</tr>
<tr>
<td>Dry skin</td>
<td>11.8</td>
<td>—</td>
<td>6.1</td>
</tr>
<tr>
<td>Anemia</td>
<td>11.8</td>
<td>—</td>
<td>6.1</td>
</tr>
</tbody>
</table>

<sup>a</sup> ≥8% of total patients. <sup>b</sup> 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.


Most TRAEs were grade 1 or 2

1. Patient with TRAE leading to treatment discontinuation (grade 3 ALT increased)
2. Patient with serious TRAEs (grade 3 ALT and AST increased)
3. Patients with DLTs during the on-treatment period
Beamion LUNG-1 (Phase 1b): Antitumor Activity in Previously Treated NSCLC With HER2 TKD Mutations

- ORR (95% CI): 73.9% (53.5%–87.5%)

Overall (N = 23)

- 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.

ELVN-002: Preclinical Activity

• ELVN-002 is a potent, irreversible inhibitor of HER2 with a >100-fold selectivity over EGFR

• ELVN-002 showed preclinical activity in xenograft models, including an intracranial model, driven by wt HER2 and HER2\textsuperscript{mt} and was well tolerated in all models tested.\textsuperscript{1} It is now being evaluated in a phase 1 study in HER2\textsuperscript{mt} solid tumors\textsuperscript{2}


ELVN-002 Antitumor Activity and Additive Activity With T-DXd\textsuperscript{3}

A. Beas2b HER2\textsuperscript{YVMA} Xenograft TGI

B. NCI-N87 HER2\textsuperscript{WT} Xenograft TGI: T-DXd Combination

C. Tucatinib vs ELVN-002 Brain Exposure

D. NCI-N87 HER2\textsuperscript{WT} Intracranial CNS Model

\textsuperscript{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).

\textsuperscript{b} 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\textsuperscript{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.

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 HER2mt NSCLC and HER2-overexpressed metastatic breast cancer.

*aSuccessive 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.

BID = twice daily; DL = dose level; ESMO = European Society for Medical Oncology; HER2 = human epidermal growth factor receptor 2; HER2mt = 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.

Summary and Conclusions

- **HER2 mutations occur in ≈1%–4% of NSCLC**
  - ex20ins are most common, but point mutations in the tyrosine kinase, transmembrane, and extracellular domain are also observed

- **T-DXd has accelerated FDA approval for HER2\(^{\text{mt}}\) NSCLC after prior systemic therapy**

- **The clinical development of EGFR/HER2 TKIs for HER2\(^{\text{mt}}\) NSCLC has been limited by significant toxicities (largely EGFR-related)**

- **Novel HER2-specific TKIs (zongertinib, ELVN-002) are now in clinical development**

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\(^{\text{mt}}\) = human epidermal growth factor receptor 2–mutant; NSCLC = non–small cell lung cancer; T-DXd = trastuzumab deruxtecan; TKI = tyrosine kinase inhibitor.