Clinical Trial Protocol

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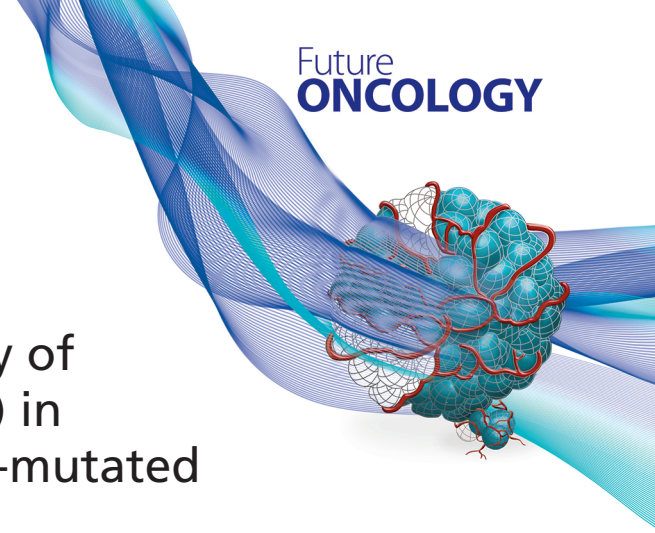

# HERTHENA-Lung01: a phase II study of patritumab deruxtecan (HER3-DXd) in previously treated metastatic *EGFR*-mutated NSCLC

Helena A Yu*[,1], James Chih-Hsin Yang[2], Hidetoshi Hayashi[3], Yasushi Goto[4], Enriqueta Felip [5], Martin Reck[6], Michele Vigliotti[7], Qian Dong[7], Frédérique Cantero[7], Pang-Dian Fan[7], Masayuki Kanai[7], David W Sternberg[7] & Pasi A Jänne[8]

[1]Department of Medicine, Medical Oncology, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
[2]Department of Oncology, National Taiwan University Hospital, Taipei City, 100, Taiwan
[3]Department of Medical Oncology, Kindai University, Osaka, 589-8511, Japan
[4]Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, 104-0045, Japan
[5]Medical Oncology Department, Vall d'Hebron University Hospital & Vall d'Hebron Institute of Oncology, 08035, Barcelona, Spain
[6]Department of Thoracic Oncology, LungenClinic, Airway Research Center North, German Center for Lung Research, 22927, Grosshansdorf, Germany
[7]Oncology Clinical Development, Daiichi Sankyo, Basking Ridge, NJ 07920, USA
[8]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA
*Author for correspondence: yuh@mskcc.org

Limited treatment options exist for *EGFR*-mutated NSCLC that has progressed after EGFR TKI and platinum-based chemotherapy. HER3 is highly expressed in *EGFR*-mutated NSCLC, and its expression is associated with poor prognosis in some patients. Patritumab deruxtecan (HER3-DXd) is an investigational, potential first-in-class, HER3-directed antibody–drug conjugate consisting of a HER3 antibody attached to a topoisomerase I inhibitor payload *via* a tetrapeptide-based cleavable linker. In an ongoing phase I study, HER3-DXd demonstrated promising antitumor activity and a tolerable safety profile in patients with *EGFR*-mutated NSCLC, with or without identified EGFR TKI resistance mechanisms, providing proof of concept of HER3-DXd. HERTHENA-Lung01 is a global, registrational, phase II trial further evaluating HER3-DXd in previously treated advanced *EGFR*-mutated NSCLC.

**Clinical Trial Registration**: NCT04619004 (ClinicalTrials.gov); 2020-000730-17 (EudraCT)

**Plain language summary – HERTHENA-Lung01: a phase II study of patritumab deruxtecan (HER3-DXd) in previously treated metastatic EGFR-mutated NSCLC:** This article describes a clinical trial of a new drug to treat non-small-cell lung cancer. About a third of patients with non-small-cell lung cancer have tumors with changes (mutations) in a gene called *EGFR*, which cause tumors to grow. These patients are treated with EGFR inhibitors and chemotherapy, both of which can stop the tumor from growing for a period of time. When these treatments stop working, new and effective treatments are needed. Most non-small-cell lung cancer tumors have a protein called HER3 on the surface of their cells. Patritumab deruxtecan (HER3-DXd) is a new drug candidate that uses HER3 to get chemotherapy inside tumor cells. In an earlier clinical trial for patients with lung cancer whose disease had grown after multiple treatments, HER3-DXd often shrank tumors or stopped them from growing. The side effects of HER3-DXd were tolerable. The clinical trial described in this publication, HERTHENA-Lung01 (NCT04619004), is testing HER3-DXd in a larger group of patients with non-small-cell lung cancer that has activating mutations in the *EGFR* gene and for whom previous treatments have stopped working. The results of this study will help doctors and regulators decide if HER3-DXd should be approved and used for patients with non-small-cell lung cancer with *EGFR* mutations.

First draft submitted: 12 December 2022; Accepted for publication: 10 May 2023; Published online: 22 May 2023

**Keywords:** antibody–drug conjugate • *EGFR* mutation • HER3-DXd • non-small-cell lung cancer • patritumab deruxtecan

## Background & rationale

### *Unmet need in non-small-cell lung cancer with EGFR-activating mutations*

Approximately 30% of patients with non-small-cell lung cancer (NSCLC) have activating mutations in the *EGFR* gene, and the most frequent (85%) comprise exon 19 deletion (ex19del) and the single amino acid substitution L858R in exon 21. These mutations confer tumor sensitivity to EGFR-directed tyrosine kinase inhibitors (TKI), but overall survival benefit of standard-of-care treatment with osimertinib in the first-line setting may differ among patients who harbor these alterations. Nonetheless, in the majority of patients, tumors eventually develop resistance and progress on EGFR TKI therapy [1–7]. Treatment after EGFR TKI therapy is not standardized, with typical treatment patterns consisting of successive rounds of other EGFR inhibitors, immunotherapy, and platinum-based chemotherapy, in combination or as monotherapy [6]. The lack of long-term effectiveness of these later-line therapies represents an urgent need for more efficacious therapies for these patients.

### *Current standard of care in EGFR-mutated NSCLC*

EGFR TKIs are the first-line treatment in *EGFR*-mutated (*EGFR*m) NSCLC as their use is associated with high response rates and extended clinical benefit [8–12]. Third-generation EGFR TKIs, such as osimertinib, were originally developed to overcome the *EGFR* T790M resistance mutation that commonly develops in patients who receive first- and second-generation EGFR TKIs [5]. Osimertinib, the current standard of care for first-line treatment of *EGFR*m NSCLC, is effective in treatment-naive *EGFR*m NSCLC as seen in the FLAURA trial (versus first-generation EGFR TKIs); median progression-free survival (PFS) was 18.9 versus 10.2 months (HR, 0.46; $p < .001$), and median overall survival (OS) was 38.6 versus 31.8 months (HR, 0.80; $p = .046$) [7,13]. Osimertinib is also effective as a second-line therapy following first- and second-generation EGFR TKIs as shown in the AURA3 trial (versus chemotherapy; median PFS, 10.1 vs 4.4 months; HR, 0.30; $p < .001$) [14]. However, many patients experience disease progression with osimertinib, and the resistance mechanisms associated with progression after first- or second-line treatment are heterogeneous [15,16]. Some of the known mechanisms of acquired resistance to osimertinib include *EGFR* mutations (C797X, L718Q, L792X, G724S, and others), amplifications in *MET, ERBB2*, and *PIK3CA*, other alterations that cause activation in the RAS-MAPK or PI3K pathway, alterations in cell cycle genes, and histological transformation [16]. Furthermore, therapeutic approaches that specifically target a genomic alteration are not available for many mechanisms of resistance.

There are no targeted therapies approved for use after osimertinib. Following progression on first-line osimertinib, patients typically receive platinum-based chemotherapy as the standard of care; however, responses are generally not durable. The median PFS in patients treated with platinum-based chemotherapy following EGFR TKI is approximately 5 months [14,17,18]. Immune checkpoint inhibitors (ICI) have been explored as a second-line treatment option but have not shown clear benefit compared with platinum-based chemotherapy [6,19,20]. Combination therapies (EGFR TKI-chemotherapy and EGFR TKI-ICI) have demonstrated similar results compared with chemotherapy alone, and EGFR TKI-ICI combinations have been shown to have an intolerable safety profile [6,21].

### *HER3 expression in EGFRm NSCLC*

HER3 expression has been observed in 83% of primary NSCLC tumors, including those with *EGFR* mutations [22–24]. Analysis of mRNA expression in patient tumor samples showed that *EGFR*m NSCLC tumors had increased levels of *ERBB3* mRNA compared with wild-type *EGFR* tumors [25]. In NSCLC, HER3 expression is associated with advanced-stage disease, shorter time to metastasis, and decreased survival rates [22,24,26,27]. Higher expression of HER3 has also been associated with resistance to EGFR TKIs [28]. Preclinical studies in *EGFR*m NSCLC showed that relative HER3 membrane protein expression was increased in xenograft mouse models of EGFR TKI resistance [29,30]. These findings were further supported in patients with *EGFR*m NSCLC who demonstrated increased HER3 tumor cell surface expression from baseline after disease progression while receiving treatment with an EGFR TKI [31]. Cell signaling analyses have also pointed to HER3 activation, mediated through the *EGFR*-independent mechanism of *MET* amplification, as playing a role in EGFR TKI resistance [32,33].

### *Patritumab Deruxtecan*

Patritumab deruxtecan (HER3-DXd) is a novel, first-in-class antibody–drug conjugate composed of a fully human anti-HER3 immunoglobulin G1 monoclonal antibody (patritumab) covalently linked to a potent topoisomerase I inhibitor payload via a tetrapeptide-based, tumor-selective, cleavable linker [34–37]. While the linker is stable in plasma, the circulating released payload has a short systemic half-life that helps to reduce the risk of systemic toxicity. HER3-DXd also has a high drug-to-antibody ratio of approximately 8 [34–37]. The proposed mechanism of action of HER3-DXd may be described in five key steps: (1) the monoclonal antibody component of HER3-DXd selectively binds to HER3 on the tumor cell surface [34]; (2) HER3-DXd is internalized by the tumor cell, and intracellular lysosomal enzymes (cathepsins), which are upregulated in tumor cells, cleave the tetrapeptide-based linker [30,34,38]; (3) the topoisomerase I inhibitor payload is released into the cytoplasm of the cell [36]; (4) the released payload enters the cell nucleus, which leads to damage of the tumor cell's DNA, resulting in tumor cell death [34,37,38] and (5) the topoisomerase I inhibitor payload is cell-membrane permeable, which enables a bystander antitumor effect resulting in elimination of both HER3-expressing and surrounding cells in the tumor microenvironment [36,37].

HER3-DXd has demonstrated antitumor activity in multiple murine cancer models, including patient-derived xenograft models of *EGFR*m NSCLC [29,39]. Based on these findings, U31402-A-U102, a phase I, open-label, dose-escalation and dose-expansion study assessing the efficacy and safety of HER3-DXd administered intravenously (IV) every 3 weeks (Q3W) in patients with NSCLC, was initiated [40]. In previous studies, unconjugated anti-HER3 antibodies that block ligand binding in combination with other agents have been explored; however, these treatment approaches demonstrated limited clinical efficacy. HER3-DXd has a unique mechanism of action, providing targeted delivery of a topoisomerase I inhibitor payload [28,41]. In the U31402-A-U102 study, HER3-DXd demonstrated durable antitumor activity in *EGFR*m NSCLC across an array of EGFR TKI resistance mechanisms, both known and unknown [40]. HER3-DXd has also demonstrated clinical efficacy in patients with NSCLC who do not harbor common *EGFR*-activating mutations [42].

In U31402-A-U102, a robust dose-selection process (compatible with the dose-finding paradigm established in the US FDA's Project Optimus) led to the recommended dose of HER3-DXd 5.6 mg/kg for patients with previously treated *EGFR*m NSCLC. The dose-selection strategy and selected dose for implementation in registrational studies, including the phase II HERTHENA-Lung01 trial, were aligned with the FDA through regulatory interactions.

Patients enrolled in dose-expansion cohort 1 of the U31402-A-U102 study had *EGFR*m NSCLC adenocarcinoma that had progressed on prior EGFR TKI therapy and platinum-based chemotherapy [40]. In this heavily pretreated patient population (patients pooled from the dose-escalation cohort who received HER3-DXd 5.6 mg/kg IV and dose-expansion cohort 1; n = 57), the objective response rate (ORR) was 39% (1 complete response and 21 partial responses), the median duration of response was 6.9 months, and the median PFS was 8.2 months. HER3 membrane expression was measured by immunohistochemistry in baseline biopsies available from 43 of 57 patients included in the pooled patient population. All tumor samples demonstrated HER3 expression; the levels of expression varied (the median membrane H-score was 180 [range, 2–280]), and clinical efficacy was observed across a wide range of baseline tumor HER3 membrane H-scores. The observation of HER3 expression in all tumor samples from patients previously treated with an EGFR TKI was consistent with data from prior studies showing an association between EGFR TKI resistance and HER3 expression [28–31]. This, along with the observation of antitumor activity of HER3-DXd across a wide range of HER3 expression, suggests that screening for HER3 was not necessary for this patient population.

While patient numbers were limited, the ORR was higher in patients with ex19del (42% [14/33]) than in those with L858R (25% [5/20]). In a subset of patients who had received prior osimertinib and platinum-based chemotherapy (n = 44), the ORR was 39% (1 complete response and 16 partial responses), the median duration of response was 7.0 months, and the median PFS was 8.2 months (Figure 1). Efficacy results were comparable to those in the pooled patient population.

HER3-DXd had a manageable safety profile; among patients treated with HER3-DXd 5.6 mg/kg IV (patients from dose escalation or cohort 1; n = 57), 6 (11%) had treatment-emergent adverse events (TEAE) associated with discontinuation, and there were no treatment-related TEAEs associated with death. The most common grade ≥3 TEAEs (in ≥10% of all patients) were thrombocytopenia (30%), neutropenia (19%) and fatigue (14%). Treatment-related interstitial lung disease (ILD) as determined by an independent adjudication committee was observed in four patients (7%; 3 grade 1/2 events, 1 grade 3 event) [40]. The potential pathophysiology of HER3-DXd–induced

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| Outcomes (BICR per RECIST 1.1)<br>Median follow-up, 10.2 mo (range, 5.2–19.9 mo)† | Pooled RDE (5.6 mg/kg)<br>All prior TKI ± PBC<br>(n = 57) | Pooled RDE (5.6 mg/kg)<br>Prior osimertinib and PBC<br>(n = 44) |
|---|---|---|
| Confirmed ORR (95% CI), % | 39 (26–52) | 39 (24–55) |
| Best overall response, n (%) | | |
| CR | 1 (2) | 1 (2) |
| PR | 21 (37) | 16 (36) |
| SD, non-CR/non-PD | 19 (33) | 13 (30) |
| PD | 9 (16) | 8 (18) |
| Not evaluable | 7 (12) | 6 (14) |
| Disease control rate (95% CI), %‡ | 72 (59–83) | 68 (52–81) |
| Time to response, median (range), mo | 2.6 (1.2–5.4) | 2.7 (1.2–5.4) |
| Duration of response, median (95% CI), mo | 6.9 (3.1–NE) | 7.0 (3.1–NE) |
| PFS, median (95% CI), mo | 8.2 (4.4–8.3) | 8.2 (4.0–NE) |
| OS, median (95% CI), mo | NE (9.4–NE) | NE (8.2–NE) |

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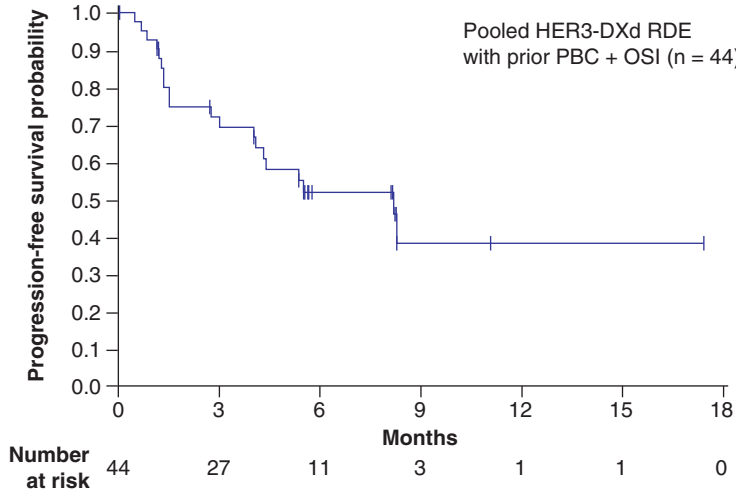


**Figure 1. Efficacy data for U31402-A-U102 dose-escalation (5.6 mg/kg) and dose-expansion cohort 1. (A)** Efficacy outcomes (by BICR per RECIST 1.1) and **(B)** Kaplan-Meieranalysis of progression-free survival.
†For patients treated with the RDE of HER3-DXd (n = 57).
‡Disease control rate is the number of patients who had a best overall response of confirmed CR, confirmed PR, or SD.
BICR: Blinded independent central review; CR: Complete response; KM: Kaplan–Meier; NE: Not evaluable; NSCLC: Non-small-cell lung cancer; ORR: Objective response rate; OS: Overall survival; OSI: Osimertinib; PBC: Platinum-based chemotherapy; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; RDE: Recommended dose for expansion; RECIST: Response Evaluation Criteria in Solid Tumors; SD: Stable disease; TKI: Tyrosine kinase inhibitor.
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ILD is currently unknown. The immunogenicity rate of HER3-DXd has been low; therefore, the pathogenetic association between immunogenicity and ILD occurrence to date is not evident.

The encouraging results from the U31402-A-U102 phase I trial thus provide a strong rationale to evaluate HER3-DXd in patients with *EGFR*m NSCLC that progressed with osimertinib and ≥1 platinum-based chemotherapy regimen. Here we present the study design of HERTHENA-Lung01, a phase II trial assessing the efficacy and safety of HER3-DXd 5.6 mg/kg IV Q3W in this patient population.

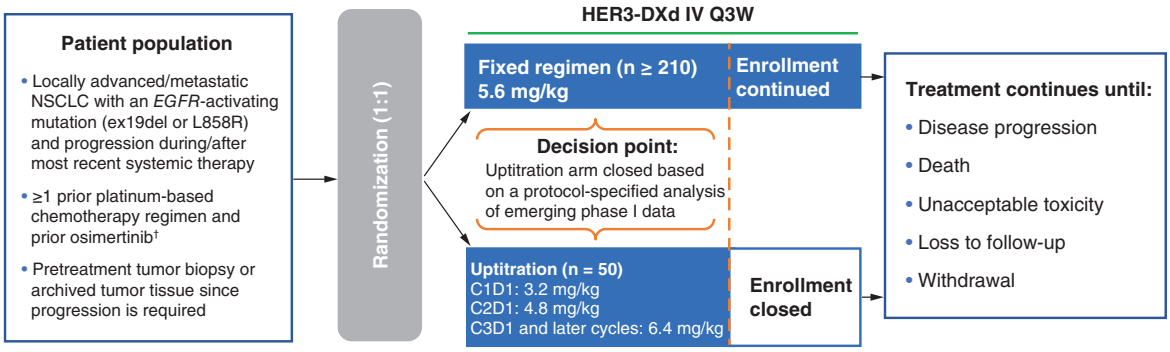


**Figure 2. HERTHENA-Lung01 study design.**
†In previous versions of the protocol, any prior EGFR TKI was allowed.
C: Cycle; D: Day; ex19del: Exon 19 deletion; IV: Intravenously; NSCLC: Non-small-cell lung cancer; TKI: Tyrosine kinase inhibitor; Q3W: Every 3 weeks.

## HERTHENA-Lung01 trial

### Study design

HERTHENA-Lung01 is a global, multicenter, open-label, phase II trial assessing the efficacy and safety of HER3-DXd in patients with metastatic or locally advanced NSCLC with *EGFR*-activating mutations (exon 19 deletion or L858R) whose disease has progressed on or after osimertinib, a third-generation EGFR TKI, and ≥1 platinum-based chemotherapy regimen (Figure 2).

The study began in February 2021, and the estimated study completion date is July 2024. The trial consists of three periods: a screening period, treatment period and follow-up period. During the 35-day screening period, patients provide a pretreatment tumor biopsy or archival tumor tissue after signing the informed consent form. An end-of-treatment visit occurs approximately 40 days after discontinuation of study treatment. Study sites are in Asia, Australia, Europe and the USA [31].

Eligible patients were randomly assigned in a 1:1 ratio to receive either a 5.6-mg/kg fixed-dose regimen (arm 1) or an uptitration dose regimen (arm 2; Figure 2) of HER3-DXd on day 1 of each 21-day cycle. The uptitration dosing schedule in arm 2 was used because it was hypothesized that a lower starting dose might be associated with a lower risk of AEs in early cycles and provide similar efficacy. Arm 2 has been closed based on a protocol-specified analysis of emerging phase I data. For all patients, treatment will continue until disease progression, death, loss to follow-up, or withdrawal of consent.

### Patient Population

Patients must be adults and have histologically or cytologically documented locally advanced or metastatic NSCLC with an *EGFR*-activating mutation (ex19del or L858R) and ≥1 measurable lesion confirmed by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. They must have received prior osimertinib and prior systemic therapy with ≥1 platinum-based chemotherapy regimen. In earlier versions of the protocol, any prior EGFR TKI therapy was permitted. This was amended to require prior osimertinib to ensure that approximately 80% of the enrolled patients will have received prior osimertinib based on recommendation from the FDA to align with the current standard of care for patients with *EGFR*m NSCLC. Patients with any history of ILD, current ILD, or suspected ILD are ineligible. Additional key inclusion and exclusion criteria are shown in Table 1.

### Study procedures

Treatment is administered on the first day of each 21-day treatment cycle. Patients are advised to receive premedication with antiemetics. The efficacy analysis set includes all patients who received ≥1 dose of HER3-DXd. Antitumor activity is evaluated by radiological tumor assessments (computed tomography or magnetic resonance imaging) taken at baseline during the screening period, every 6 weeks for the first 24 weeks, and then every 12 weeks until treatment ends (Figure 3). Response assessments are made by BICR and by the investigator per RECIST 1.1. Objective responses (complete or partial response) are confirmed ≥4 weeks after the initial response.

**Table 1. Key eligibility criteria.**

| Key inclusion criteria | Key exclusion criteria |
|---|---|
| • Age ≥18 years or the local age of consent<br>• ECOG PS 0-1<br>• Locally advanced or metastatic NSCLC with an *EGFR* mutation (ex19del or L858R) and ≥1 measurable lesion confirmed by BICR per RECIST version 1.1<br>• Documented radiological progression with or after most recent treatment regimen<br>• Must have received both[†]:<br>  • Osimertinib[‡]<br>  • ≥1 platinum-based chemotherapy regimen<br>• Must provide a pretreatment or archived tumor biopsy specimen (<3 months old)<br>• Patients with stable brain metastases are allowed | • Previous or current evidence of small cell or combined small cell/NSCLC<br>• Any history of ILD (including pulmonary fibrosis or radiation pneumonitis), current ILD, or suspected ILD at screening<br>• Uncontrolled or significant cardiovascular disease<br>• Prior treatment with:<br>  • Anti-HER3 antibody<br>  • Single-agent, unconjugated topoisomerase I inhibitor<br>  • ADC with any topoisomerase I inhibitor<br>• Current treatment with chronic systemic corticosteroids (>10 mg of prednisone or equivalent)<br>• Toxicities from prior cancer treatment, other than alopecia, not resolved to NCI CTCAE v5.0 grade ≤1 or baseline |

[†]Patients in South Korea with a clinically actionable genomic alteration in *ALK* or *ROS1* for which treatment is available must have also received prior treatment with ≥1 approved genotype-directed therapy.
[‡]In previous versions of the study protocol, any prior EGFR TKI therapy was permitted.
ADC: Antibody–drug conjugate; BICR: Blinded independent central review; ECOG PS: Eastern Cooperative Oncology Group performance status; ex19del: Exon 19 deletion; ILD: Interstitial lung disease; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC: Non-small-cell lung cancer; RECIST: Response Evaluation Criteria in Solid Tumors.

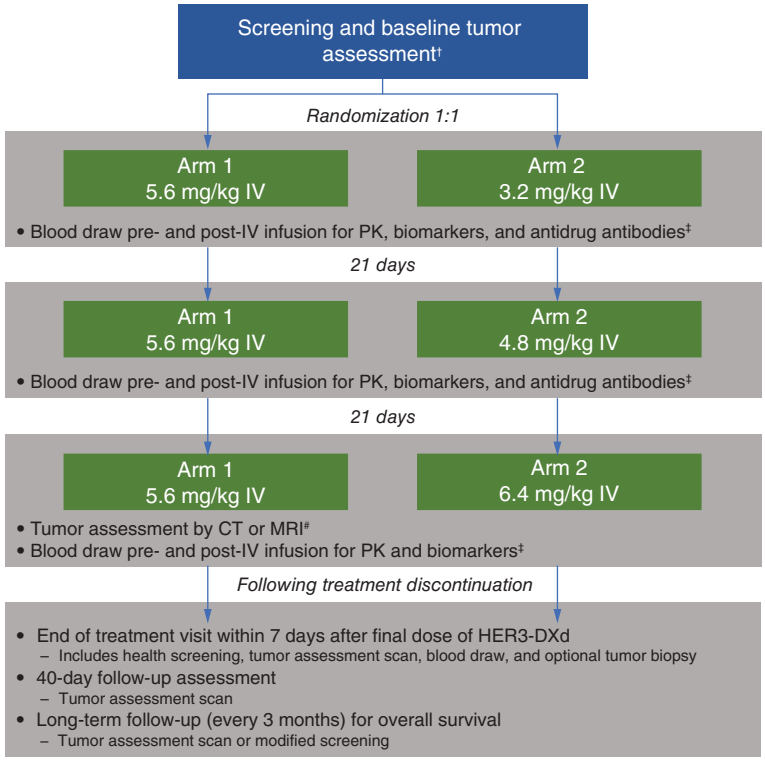


**Figure 3. HERTHENA-Lung01 assessment timeline.**
[†]Screening occurs within 35 days before cycle 1.
[‡]Blood draws for PK and biomarkers will be done in cycles 1–3. Blood draws for antidrug antibodies will be done in cycles 1 and 2.
[#]Tumor assessments will occur every 6 weeks from cycle 1 day 1 for the first 24 weeks (cycle 8), then every 12 weeks, independent of treatment cycle until documented disease progression by BICR per RECIST 1.1, death, loss to follow-up, or withdrawal of consent.
BICR: Blinded independent central review; IV: Intravenously; PK: Pharmacokinetics; RECIST: Response Evaluation Criteria in Solid Tumors.

Safety is assessed in all patients who received ≥1 dose of HER3-DXd by physical examinations, laboratory tests, vital signs, electrocardiograms, multigated acquisition scan or echocardiogram, Eastern Cooperative Oncology Group performance status, ophthalmologic assessment, and monitoring of AEs with grading according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5. Assessment of seriousness, severity, and causality is done by the investigator. An independent ILD adjudication committee reviews all cases of potential ILD. All events of ILD, regardless of severity or seriousness, will be followed up until resolution, including after drug discontinuation.

Pharmacokinetic analyses will evaluate serum concentrations of HER3-DXd, total anti-HER3 antibody, DXd payload, and immunogenicity. Biomarkers will also be evaluated.

**Table 2. Outcome measures.**

| Study end points | |
|---|---|
| Primary | Confirmed ORR by BICR per RECIST 1.1 |
| Secondary | • DOR by BICR and investigator per RECIST 1.1<br>• PFS by BICR and investigator per RECIST 1.1<br>• ORR by investigator per RECIST 1.1<br>• DCR per BICR and investigator per RECIST 1.1<br>• Time to response by BICR and investigator per RECIST 1.1<br>• Best percentage change in SOD by BICR and investigator<br>• OS<br>• Safety and tolerability<br>• Relationship between HER3 protein expression in the tumor and efficacy<br>• Immunogenicity |
| Exploratory | • Changes in HER3 expression and HER3 dynamics, correlated with efficacy<br>• Potential biomarkers associated with HER3-DXd sensitivity or resistance<br>• Pharmacokinetics<br>• Exposure/response for efficacy and safety end points |

BICR: Blinded independent central review; DCR: Disease control rate; DOR: Duration of response; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; RECIST: Response Evaluation Criteria in Solid Tumors; SOD: Sum of diameters.

## Outcome measures/end points

The objective of HERTHENA-Lung01 is to investigate the antitumor activity of HER3-DXd in patients with metastatic or locally advanced *EGFR*m NSCLC. The primary end point is confirmed ORR by BICR per RECIST 1.1. Secondary end points include PFS and duration of response by BICR and the investigator and OS. All study end points are shown in Table 2.

## Data collection, management & statistical analysis

An electronic case report form (eCRF) is completed for each patient who signs an informed consent form and undergoes any screening procedures. All data pertaining to that patient is logged in the individual eCRF. The patient is identified in the electronic database by a unique subject identification code. Data quality is ensured by the clinical research organization and regulatory authority inspectors through electronic and manual vetting of consistency, completeness, and any apparent discrepancies.

Hypothesis testing will be done with a two-sided significance level of 5%. The ORR will be presented with exact 95% CI using the Clopper–Pearson method. Distribution of time-to-event end points (duration of response, PFS and OS) will be estimated using the Kaplan–Meier method, and results will be presented graphically. Median event time with a two-sided 95% CI will be calculated using the Brookmeyer and Crowley method. Descriptive statistics for the best change from baseline in the sum of diameters (SOD) will be calculated. A waterfall plot of the best percentage change from baseline in the SOD for each patient will be presented. The data for each treatment arm will be summarized, and no formal comparisons between arms 1 and 2 are planned.

## Ethics & dissemination

This protocol has been approved by the institutional review board at each participating institution. This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation consolidated Guideline E6 for Good Clinical Practice, and applicable regulatory requirements. Informed consent is obtained from all patients before any study related procedures are performed and is documented in the patient's medical records.

All publications will adhere to the USA, European and Japanese policies for public disclosure and will follow the principles of 'Good Publication Practice (GPP) Guidelines for Company-Sponsored Biomedical Research: 2022 Update' and guidelines established by the International Council of Medical Journal Editors for sharing of the clinical study results.

# Conclusion

Most patients with *EGFR*m NSCLC have disease progression with EGFR TKI therapy and platinum-based chemotherapy. Preclinical studies show that HER3 expression is increased in *EGFR*m NSCLC tumors after treatment with EGFR TKIs; therefore, targeting HER3 could be an effective treatment strategy in these patients. Results from the phase I U31402-A-U102 study demonstrated that HER3-DXd had encouraging antitumor activity

across a broad range of HER3 expression and a manageable safety profile in patients with heavily pretreated *EGFR*m NSCLC that has progressed after EGFR TKI and platinum-based chemotherapy [40]. Based on the results from the phase I study, HER3-DXd has been granted a Breakthrough Therapy designation by the FDA, demonstrating its potential to advance the treatment landscape in *EGFR*m NSCLC.

The registrational phase II study, HERTHENA-Lung01 (NCT04619004), is designed to build on the results of the U31402-A-U102 phase I trial by assessing the efficacy and safety of HER3-DXd in patients with metastatic or locally advanced *EGFR*m NSCLC that has progressed with osimertinib and ≥1 platinum-based chemotherapy, the current standard-of-care. Results from the HERTHENA-Lung01 study will provide greater insight into the antitumor efficacy and safety profile of HER3-DXd in patients with *EGFR*m NSCLC. Given its antitumor activity across an array of EGFR TKI resistance mechanisms, HER3-DXd provides a new treatment strategy for this patient population and potentially for the broader population of patients with HER3 protein expressing tumors.

## Executive summary

**Background**

- Osimertinib, a third-generation EGFR tyrosine kinase inhibitor (TKI), is the standard-of-care for patients with non-small-cell lung cancer (NSCLC) with *EGFR*-activating mutations.
- Platinum-based chemotherapy is the standard second-line treatment option for patients whose disease progresses with osimertinib. Salvage therapies post-chemotherapy progression do not provide durable efficacy and generally have intolerable safety profiles.
- HER3 is expressed in *EGFR*-mutated NSCLC and is associated with poor treatment outcomes. HER3 expression is increased following progression with EGFR TKIs.

**Patritumab deruxtecan (HER3-DXd)**

- HER3-DXd is an investigative, first-in-class, antibody–drug conjugate composed of an anti-HER3 monoclonal antibody covalently linked to a topoisomerase I inhibitor payload via a tetrapeptide-based, tumor-selective, stable, cleavable linker.
- Higher HER3 expression is associated with EGFR TKI resistance.
- In the ongoing phase I U31402-A-U102 trial, HER3-DXd 5.6 mg/kg demonstrated promising antitumor efficacy across a broad range of HER3 expression and a tolerable safety profile in heavily pretreated patients with *EGFR*-mutated NSCLC (n = 57).

**HERTHENA-Lung01**

- HERTHENA-Lung01 (NCT04619004) is a global, open-label, registrational, phase II trial assessing the efficacy and safety of HER3-DXd in patients with metastatic or locally advanced *EGFR*-mutated NSCLC that has progressed with the current standard-of-care, including osimertinib and ≥1 platinum-based chemotherapy.
- The primary end point is objective response rate by blinded independent central review per Response Evaluation Criteria in Solid Tumors version 1.1 for all patients.
- Secondary end points include duration of response and progression-free survival by blinded independent central review and the investigator, overall survival, and safety.

**Conclusion**

- HERTHENA-Lung01 is assessing the antitumor efficacy and safety profile of HER3-DXd in patients with *EGFR*-mutated NSCLC that has progressed on osimertinib and platinum-based chemotherapy.
- Targeting HER3 could represent an effective treatment strategy for patients who experience progression with osimertinib and platinum-based chemotherapy.

### Author contributions

All authors contributed to the conception and drafting of the manuscript, participated in critical revisions that contributed to the intellectual content of the manuscript, and provided final approval of the draft to be published.

### Financial & competing interests disclosure

This study was funded by Daiichi Sankyo. HA Yu has received consulting fees from AstraZeneca, Daiichi Sankyo, Cullinan, Blueprint, Janssen, Black Diamond, and Takeda. J Chih-Hsin Yang has received a grant, personal fees, and advising/consulting institutional fees from AstraZeneca; personal fees and advising/consulting institutional fees from Amgen, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Merck KGaA, MSD, Novartis, Roche/Genentech, Takeda Oncology, and Yuhan Pharmaceuticals; advising/consulting institutional fees from Eli Lilly and Johnson & Johnson; advising/consulting fees from Ono Pharmaceuticals and Pfizer; and advising institutional fees from Puma Biotechnology, Gilead, and GSK. H Hayashi has received grants/contracts from AstraZeneca K.K., Astellas Pharma, MSD K.K., Ono Pharmaceutical, Nippon Boehringer Ingelheim, Novartis Pharma K.K., Pfizer

Japan, Bristol Myers Squibb, Eli Lilly Japan K.K., Chugai Pharmaceutical, Daiichi Sankyo, Merck Serono, Merck Biopharma, Takeda Pharmaceutical, Taiho Pharmaceutical, SymBio Pharmaceuticals, AbbVie, inVentiv Health Japan, ICON Japan K.K., Gritstone bio, Parexel International, Kissei Pharmaceutical, EPS Corporation, Syneos Health, Pfizer R&D Japan G.K., A2 Healthcare, Quintiles/IQVIA Services Japan K.K., EP-CRSU, Linical, Eisai, CMIC Shift Zero K.K., Kyowa Hakko Kirin, Bayer Yakuhin, EPS International, and Otsuka Pharmaceutical; payment/honoraria from Amgen K.K., AstraZeneca K.K., Boehringer Ingelheim Japan, Bristol Myers Squibb, Chugai Pharmaceutical, Daiichi Sankyo, Eli Lilly Japan K.K., Guardant Health, Kyorin Pharmaceutical, Merck Biopharma, MSD K.K., Novartis Pharma K.K., Ono Pharmaceutical, Shanghai Haihe Biopharma, Taiho Pharmaceutical, Pfizer, and Takeda Pharmaceutical outside the submitted work. Y Goto has received grants/contracts to their clinical trial group from AstraZeneca and Pfizer Japan; grants/contracts to their institution from AbbVie GK, Eli Lilly Japan K.K., Pfizer Japan, Bristol Myers Squibb K.K., Ono Pharmaceutical, Novartis Pharma K.K., Kyorin Pharmaceutical, Daiichi Sankyo, and Preferred Networks; payment/honoraria from Eli Lilly Japan K.K., Chugai Pharmaceutical, Taiho Pharmaceutical, Nippon Boehringer Ingelheim (Korea, Japan), Ono Pharmaceutical, Bristol Myers Squibb K.K., Pfizer Japan, MSD K.K., Novartis Pharma Japan, Merck (Germany, Japan), and Thermo Fisher; participation on a data safety monitoring board or advisory board for AstraZeneca, Chugai Pharmaceutical, Boehringer Ingelheim (Japan), Eli Lilly, Taiho Pharmaceutical, Pfizer Japan, Novartis (Switzerland Japan), Guardant Health, Illumina, Daiichi Sankyo, Ono Pharmaceutical, Bristol Myers Squibb, and MSD; and has a leadership or fiduciary role in a board, society, committee, or advocacy group, paid or unpaid, for Cancer Net Japan and Japan Association of Medical Translation for Cancer. E Felip has received institutional research funding grants/contracts from Grant for Oncology Innovation, Merck Healthcare KGaA, and Fundación Merck Salud; consulting fees from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, F. Hoffmann-La Roche, GSK, Ipsen, Janssen, Merck Serono, MSD, Novartis, Peptomyc, Pfizer, Sanofi, Takeda, and Turning Point Therapeutics; payment/honoraria from Amgen, AstraZeneca, Bristol Myers Squibb, Eli Lilly, F. Hoffmann-La Roche, Jansen, Medical Trends, Medscape, Merck Serono, MSD, PeerVoice, Pfizer, Sanofi, Takeda, and touchONCOLOGY; and other financial aid from Grifols as an independent member of the board. M Reck has received consulting fees from Amgen, AstraZeneca, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Merck, MSD, Mirati Therapeutics, Novartis, GSK, Pfizer, and Roche; payment/honoraria from Amgen, AstraZeneca, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Merck, MSD, Mirati Therapeutics, Novartis, GSK, Pfizer, and Roche; and support for attending meetings and/or travel from Amgen, AstraZeneca, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Merck, Mirati Therapeutics, Novartis, GSK, Pfizer, and Roche. M Vigliotti, Q Dong, F Cantero, P-D Fan, M Kanai, and DW Sternberg are employees of and have stock ownership in Daiichi Sankyo. PA Jänne has received royalties of licenses from Labcorp; consulting fees from AstraZeneca, Boehringer Ingelheim, Pfizer, Roche/Genentech, Chugai Pharmaceutical, Eli Lilly Pharmaceuticals, SFJ Pharmaceuticals, Voronoi, Daiichi Sankyo, Biocartis, Novartis, Sanofi, Takeda Oncology, Mirati Therapeutics, Transcenta, Silicon Therapeutics, Syndax, Nuvalent, Bayer, Eisai, Allorion Therapeutics, Accutar Biotech, and AbbVie; and has stock ownership in Gatekeeper Pharmaceuticals. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing and editorial support were provided by Erinn Gideons (ArticulateScience, LLC), and were funded by Daiichi Sankyo.

## Ethical conduct of research

The authors have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human experimental investigations. Written informed consent is required and has been obtained from the participants involved.

## Data sharing statement

The complete de-identified patient data set collected for the study will be made available to others. De-identified individual participant data (IPD) and applicable supporting clinical trial documents may be available upon request at https://vivli.org/. The data will be available after the primary study results have been accepted for publication. Supporting documents such as the analytic/statistical code and Informed consent form will also be available. Applicable clinical trial documents may be available upon request at https://vivli.org/ourmember/daiichi-sankyo/. The data will be available to researchers whose proposed use of the data has been approved and only for the specified purpose in the approved request. The data will be made available after approval of a research proposal and with a signed data use agreement.

## Open access

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