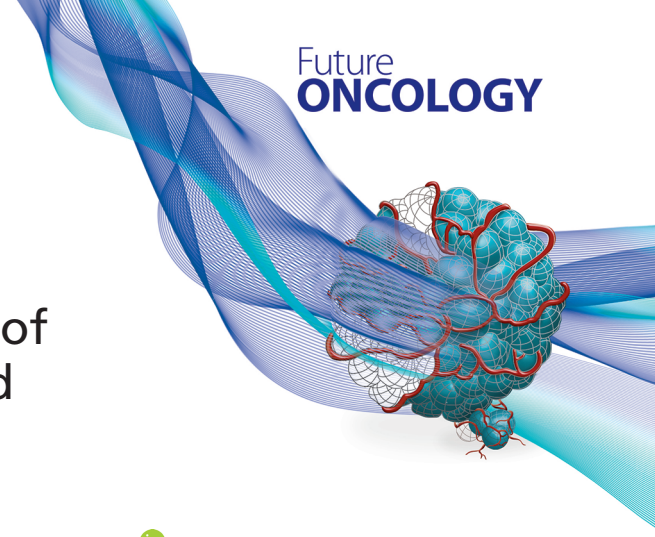
Clinical Trial Protocol

Future ONCOLOGY



HERTHENA-Lung02: phase III study of patritumab deruxtecan in advanced *EGFR*-mutated NSCLC after a third-generation EGFR TKI

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After disease progression on EGFR tyrosine kinase inhibitor (TKI) therapy, patients with *EGFR*-mutated NSCLC who are then treated with platinum-based chemotherapy (PBC) obtain only limited clinical benefit with transient responses. Therapies with greater efficacy and tolerable safety profiles are needed in this setting. The receptor tyrosine kinase HER3 is widely expressed in NSCLC, and increased expression is associated with poor treatment outcomes. In the U31402-A-U102 phase I trial, HER3-DXd showed promising antitumor activity with manageable safety in heavily pre-treated patients with *EGFR*-mutated NSCLC across a range of tumor HER3 expression levels and EGFR TKI resistance mechanisms. HERTHENA-Lung02 is the first phase III trial to evaluate the safety and efficacy of HER3-DXd versus PBC in patients with progression on a third-generation EGFR TKI.

Clinical Trial Registration: NCT05338970 (clinicaltrials.gov); 2021-005879-40 (EudraCT Number).

Plain language summary: In some patients with non-small-cell lung cancer, changes (or mutations) in the DNA sequence can alter a protein called EGFR and allow tumors to grow and survive. Drugs called EGFR tyrosine kinase inhibitors (EGFR TKIs for short) are used to treat these tumors by interfering with the abnormal EGFR protein. Treatment with these drugs can work well at first, but some tumors never respond, and for tumors that do respond, the cancer eventually becomes resistant to the EGFR TKI and the drug stops working. Platinum-based chemotherapy is often prescribed after an EGFR TKI stops working; however, platinum-based chemotherapy can provide only temporary control of the tumor growth. Most patients with non-small-cell lung cancer have a protein called HER3 on the surface of their tumor cells. A new drug candidate called patritumab deruxtecan (HER3-DXd) finds tumor cells and attaches to the HER3 protein on their surface. HER3-DXd then moves inside the cancer cells, where a novel antitumor payload is released and kills the tumor cells. This article describes the phase III clinical trial HERTHENA-Lung02 (NCT05338970) that compares the benefit of HER3-DXd to platinum-based chemotherapy for patients who have non-small-cell lung cancer with the abnormal EGFR protein and whose disease stopped responding or never responded to EGFR TKI therapy.

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

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HERTHENA-Lung02 Trial

HERTHENA-Lung02 is a global, multicenter, open-label, phase III trial evaluating the efficacy and safety of patritumab deruxtecan (HER3-DXd) versus platinum-based chemotherapy (PBC) in patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) with *EGFR*-activating mutations (exon 19 deletion or L858R substitution) after progression on treatment with EGFR tyrosine kinase inhibitor (TKI) therapy, including a third-generation EGFR TKI.

Background & rationale

Current treatment landscape for EGFR-mutated NSCLC

The discovery of EGFR TKIs revolutionized the treatment landscape for *EGFR*-mutated lung cancer. Patients with NSCLC harboring exon 19 deletions and exon 21 L858R point mutations demonstrate high response rates; however, progression on treatment with early-generation EGFR TKIs is frequent, occurring after a median of 8–16 months, due to acquired resistance most commonly driven by the *EGFR* T790M mutation [1–6].

Osimertinib is an EGFR inhibitor that has demonstrated clinical efficacy in tumors with both EGFR TKI-sensitizing mutations and the T790M resistance mutation. It is the only third-generation EGFR TKI to receive US FDA approval for the treatment of *EGFR*-mutated NSCLC and has demonstrated superiority over earlier generations of EGFR TKIs [7,8]. Results from the pivotal phase III FLAURA trial established osimertinib as the standard of care in treatment-naive patients with metastatic *EGFR*-mutated NSCLC [7,8]. Treatment with osimertinib demonstrated a 54% reduction in the risk of progression and a 20% reduction in the risk of death compared with treatment with the first-generation EGFR TKIs erlotinib or gefitinib (median progression-free survival, 18.9 vs 10.2 months; median overall survival, 38.6 vs 31.8 months) [7,8]. More recently, results from the phase III FLAURA2 trial have suggested patients may derive increased treatment benefit from first-line osimertinib in combination with PBC compared with single-agent osimertinib (median progression-free survival, 25.5 vs 16.7 months); however, overall survival results remain immature and currently show no difference in outcomes. Of note, preliminary findings suggest the combination regimen may be an important treatment option for certain subgroups, particularly patients with metastasis in the central nervous system [9]. Other third-generation EGFR TKIs, including abivertinib (NCT03856697), alflutinib (NCT03787992), aumolertinib (NCT04923906), lazertinib (NCT04248829) and rezivertinib (NCT03866499), are being evaluated in phase III trials in *EGFR*-mutated NSCLC.

Despite their improved efficacy over first-generation EGFR TKIs [8,10], development of resistance to third-generation EGFR TKIs is typical and subsequent standard therapy with PBC has shown modest and transient efficacy (median progression-free survival, ≈5 months) [11–13]. Combination treatment regimens that include chemotherapy plus the immune checkpoint inhibitors nivolumab or pembrolizumab have been evaluated against PBC in the KEYNOTE-789 and CheckMate 722 clinical trials, but results from these studies have shown no statistical difference in survival outcomes between regimens in patients who experienced treatment failure with EGFR TKIs [14,15]. An interim analysis from the ORIENT-31 trial has shown that bevacizumab, a humanized anti-VEGF monoclonal antibody, in combination with immunotherapy and chemotherapy may provide treatment benefit for patients with previously treated *EGFR*-mutated NSCLC; however, these data are immature, and the study design is limited to treatment centers across China [16]. Furthermore, final results from the IMpower151 trial showed no statistically significant treatment benefit from the addition of bevacizumab to chemotherapy plus immunotherapy combination regimens in patients with NSCLC, including those with *EGFR* mutations (median PFS, 9.5 vs 7.1 months; hazard ratio, 0.84) [17].

Disease progression on third-generation EGFR TKIs is associated with different acquired genomic alterations, including *EGFR* mutations, amplification of *MET* and *ERBB2*, *PIK3CA*-activating mutations, and alterations in cell cycle-related genes [18]. Several therapies that target these genomic alterations, including *MET* amplification and the *EGFR* C797S mutation, are currently in different stages of clinical development [19–21]. While the *EGFR* C797S mutation typically arises after the T790M mutation, together with *MET* amplification, they represent the most common on- and off-target mechanisms of resistance to third-generation EGFR TKIs, respectively. However, both genomic alterations represent a minority (<30%) of cases of acquired resistance [21,22]. Multiple mechanisms associated with EGFR TKI resistance have been revealed, but they are heterogenous, and many have yet to be

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identified [23,24]. Developing a treatment approach that can address diverse mechanisms of resistance is an urgent need for patients who have disease progression after treatment with a third-generation EGFR TKI.

HER3-DXd: promising treatment for EGFR-mutated NSCLC

Protein expression of HER3 has been observed in 83% of primary NSCLC tumors and is associated with metastatic progression and reduced survival [25–27]. Additionally, *in vitro* and translational studies have suggested that activation of HER3 signaling is associated with acquired resistance to *EGFR*-targeted therapies, and HER3 expression in patient tumor samples is increased after progression with first-line EGFR TKIs [28,29]. Given the sum of these findings, HER3 presents as an attractive target for therapeutic development within this treatment landscape.

HER3-DXd is an investigational, first-in-class, antibody–drug conjugate (ADC) composed of a fully human anti-HER3 immunoglobulin G1 monoclonal antibody, patritumab, covalently linked to a topoisomerase I inhibitor payload via a tetrapeptide-based, tumor-selective, stable, cleavable linker [30–33]. The covalent linker molecule is stable while in plasma, and when the payload is released, it has a short systemic half-life; both of these attributes contribute to reduced risk of systemic toxicity [30,31,33,34]. HER3-DXd leverages the clinically validated and highly potent deruxtecan technology and has a high drug-to-antibody ratio of approximately 8 [30,31,33,34]. The proposed mechanism of action begins with HER3-DXd selectively binding to HER3 on the tumor cell surface where it is internalized by the tumor cell and trafficked to the lysosome. The linker is then cleaved by lysosomal enzymes upregulated in tumor cells, allowing the released topoisomerase I inhibitor payload to then enter the cell nucleus and cause DNA damage and eventually tumor cell death. The payload is cell-membrane permeable, enabling a bystander antitumor effect resulting in the death of both HER3-expressing and surrounding cells within the tumor microenvironment [30,32–35].

In the phase I, open-label, multicohort, dose-escalation and dose-expansion study U31402-A-U102, the efficacy and safety of HER3-DXd was evaluated in patients with *EGFR*-mutated NSCLC [36]. HER3-DXd demonstrated durable antitumor activity in this heavily pretreated population (median of four prior lines of systemic therapy in the metastatic setting), and efficacy was observed across a wide range of tumor HER3 expression levels and diverse mechanisms of EGFR TKI resistance [36]. In a subgroup of 44 patients who experienced disease progression after osimertinib and PBC, HER3-DXd 5.6 mg/kg demonstrated a confirmed objective response rate of 39%, with one complete response and 16 partial responses [36]. The median duration of response in this subset was 7.0 months (95% CI, 3.1 months-not estimable), and the median progression-free survival was 8.2 months (95% CI: 4.0 months-not estimable) [36]. HER3-DXd demonstrated a manageable safety profile; in patients treated with HER3-DXd 5.6 mg/kg iv. (patients from dose escalation or cohort 1; N = 57), 11% had treatment-emergent adverse events (TEAE) associated with discontinuation, and no deaths were associated with treatment-related TEAEs. The most common grade ≥3 TEAEs (observed in ≥10% of all patients) were thrombocytopenia (30%), neutropenia (19%) and fatigue (14%). Centrally adjudicated treatment-related interstitial lung disease (ILD) was observed in four patients, and most cases were of lower-grade severity (7%; 3 grade 1/2, 1 grade 3) [36].

These promising results from the U31402-A-U102 phase I trial have prompted further evaluation of HER3-DXd in the phase II HERTHENA-Lung01 trial evaluating HER3-DXd in patients with *EGFR*-mutated NSCLC after progression on an EGFR TKI and PBC. Initial results from this trial demonstrated HER3-DXd to have evidence of efficacy with durable responses [37,38]. These observations have also supported initiation of the phase III HERTHENA-Lung02 trial described here in patients with advanced *EGFR*-mutated NSCLC after failure of a third-generation EGFR TKI but prior to receiving chemotherapy. This study aims to evaluate the safety and efficacy of HER3-DXd 5.6 mg/kg iv. every 3 weeks (Q3W) compared with PBC in patients with *EGFR*-activating mutations who have received 1 or 2 lines of EGFR TKI treatment, including a third-generation EGFR TKI, and experienced progression on or following treatment with a third-generation EGFR TKI.

HERTHENA-Lung02 trial

Study design

HERTHENA-Lung02 (NCT05338970) is a global, randomized, open-label, phase III trial evaluating the efficacy and safety of HER3-DXd versus PBC in patients with metastatic or locally advanced NSCLC with a common *EGFR*-activating mutation (exon 19 deletion or L858R mutation) following progression on a third-generation EGFR TKI (Figure 1); patients may have received an earlier-generation EGFR TKI prior to the third-generation inhibitor. Patients are enrolled from approximately 179 clinical sites in 21 countries spanning North America, Europe, Australia and the Asia Pacific region (Figure 2). Enrollment began in August 2022, with the first patient

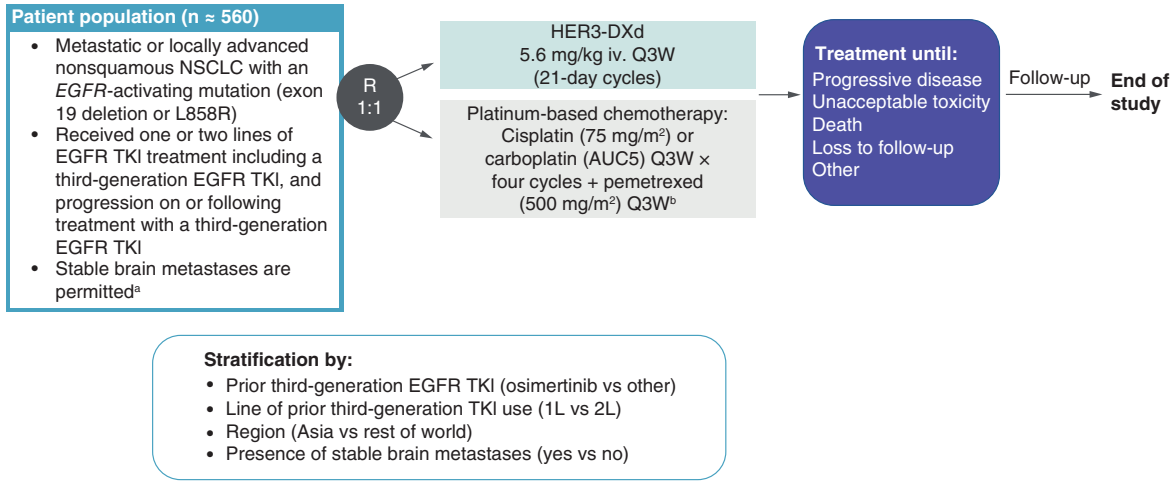

Figure 1. HERTHENA-Lung02 study design.
[a]Presence of brain metastases includes any history of brain metastasis or current stable brain metastasis.
[b]Patients without disease progression after four cycles of platinum-based chemotherapy plus pemetrexed may continue treatment with maintenance pemetrexed (500 mg/m^2 Q3W), with no restriction on the number of cycles.
1L: First-line; 2L: Second-line; AUC: Area under the curve; iv.: Intravenous; NSCLC: Non-small-cell lung cancer; Q3W: Every 3 weeks; R: Randomization; TKI: Tyrosine kinase inhibitor.

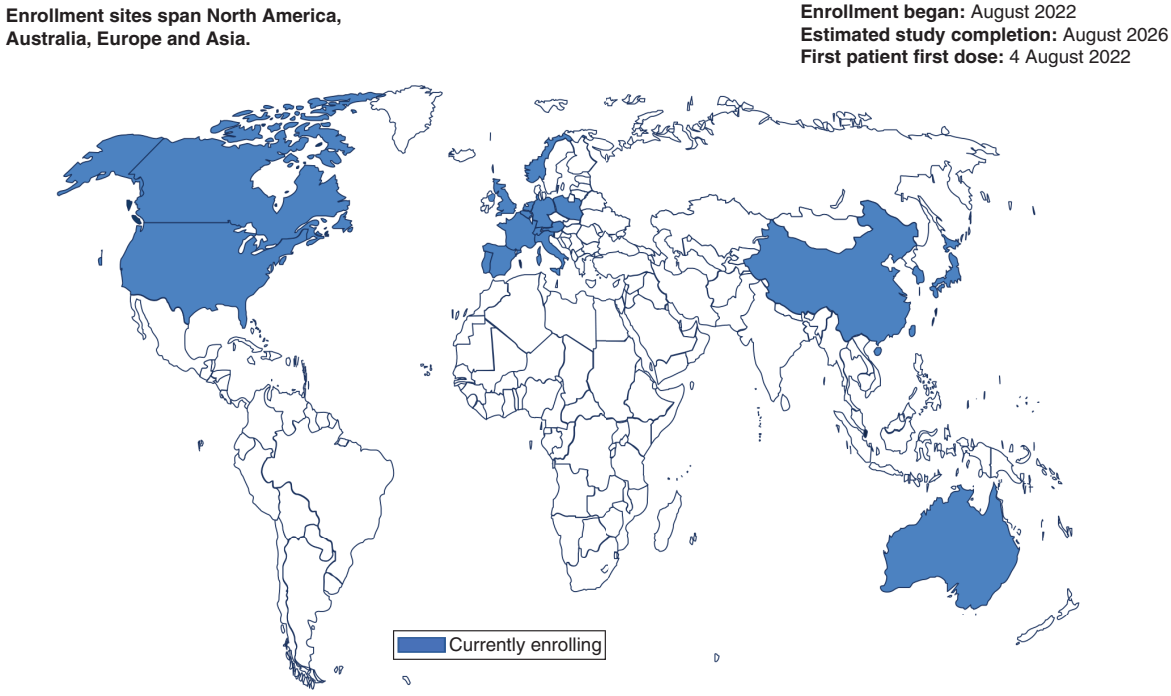

Figure 2. Map of clinical sites fully enrolled or currently enrolling.

receiving the first dose on 4 August 2022; the study is estimated to be completed in August 2026.

During the screening period, patients provide a pretreatment tumor biopsy or archival tumor tissue for biomarker analyses. The treatment period begins after randomization, and patients continue treatment until disease progression, unacceptable toxicity, withdrawal of consent, or other reasons. An end-of-treatment visit will occur when treatment is completed. A safety follow-up visit happens approximately 40 days after treatment is completed, and survival status is monitored every 3 months.

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Table 1. Key eligibility criteria.

Key inclusion criteria
• Age ≥18 years (or local age of consent)
• Locally advanced or metastatic nonsquamous NSCLC not amenable to curative surgery or radiation, with documentation of an *EGFR*-activating mutation (exon 19 deletion or L858R) with one or more measurable lesions per RECIST 1.1 by investigator assessment
• Received one or two prior lines of an approved EGFR TKI in the locally advanced or metastatic setting, which must have included a third-generation EGFR TKI, and progression on or following treatment with a third-generation EGFR TKI
• ECOG PS 0 or 1
• Pretreatment tumor biopsy or archived tumor tissue since progression
• May have received (neo)adjuvant therapy if progression to locally advanced or metastatic disease occurred ≥12 months after the last dose of (neo)adjuvant therapy and subsequently experienced progression on or after a third-generation EGFR TKI in the advanced setting
• Has not received any other prior systemic therapies (including chemotherapy and immunotherapy)
• Has adequate bone marrow reserve and hepatic function based on local laboratory data within 14 days prior to randomization
Key exclusion criteria
• Prior treatment with any systemic therapies in the advanced setting, including chemotherapy or systemic therapies combined with an EGFR TKI
• Prior treatment with any agent, including ADCs, containing a chemotherapeutic agent that targets topoisomerase I, or with any agent containing an anti-HER3 antibody
• History of ILD (including pulmonary fibrosis or radiation pneumonitis), current ILD, or suspected ILD by imaging during screening
• Clinically severe respiratory compromise (based on investigator's assessment) resulting from intercurrent pulmonary illnesses including underlying pulmonary disorder, restrictive lung disease, pleural effusion, autoimmune or inflammatory disorders with pulmonary involvement, or prior complete pneumonectomy
• Uncontrolled or significant cardiovascular disease
• Any history of or evidence of current leptomeningeal disease
• Clinically active spinal cord compression or brain metastases (untreated and symptomatic) or requiring treatment with corticosteroids or anticonvulsants
• Immunosuppressive therapy including chronic systemic corticosteroids dosed at >10 mg of prednisone
• Clinically significant corneal disease

ADC: Antibody–drug conjugate; ECOG PS: Eastern Cooperative Oncology Group performance status; ILD: Interstitial lung disease; NSCLC: Non-small-cell lung cancer; RECIST: Response Evaluation Criteria in Solid Tumors; TKI: Tyrosine kinase inhibitor.

Interventions & randomization

Approximately 560 patients are randomized 1:1 to receive HER3-DXd 5.6 mg mg/kg iv. Q3W or four cycles of PBC containing cisplatin (75 mg/m^2) or carboplatin (AUC5) Q3W in combination with pemetrexed (500 mg/m^2) Q3W. Patients without disease progression after four cycles of platinum plus pemetrexed therapy may continue treatment with maintenance pemetrexed, with no restriction on the number of cycles. Patients assigned to PBC are not permitted to cross over to the HER3-DXd treatment arm. Randomization is performed using an Interactive Response Technology platform and stratified by prior use of a third-generation EGFR TKI (osimertinib vs other), line of prior third-generation EGFR TKI use (first-line vs second-line), region (Asia vs rest of the world), and presence of brain metastases (yes vs no).

Patient population

Patients must be ≥18 years of age with locally advanced or metastatic nonsquamous NSCLC with an *EGFR*-activating mutation, including an exon 19 deletion or the L858R point mutation, and one or more measurable lesions per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by investigator assessment. Prior treatment with one or two lines of an approved EGFR TKI treatment in the locally advanced or metastatic setting is required and must include a third-generation EGFR TKI as the most recent therapy. Patients with any history of interstitial lung disease (ILD) or who are suspected to have ILD by clinical or radiological assessment are ineligible for the study. Additional key inclusion and exclusion criteria are shown in Table 1.

Objectives & end points

The primary objective of this study is to compare the efficacy of HER3 DXd versus PBC measured by the primary end point of progression-free survival according to blinded independent central review (BICR) based on RECIST 1.1. The key secondary end point is overall survival. All study end points, including additional secondary end points for efficacy, safety and biomarkers, are summarized in Table 2. While no known predictive biomarkers have been identified in the setting of HER3-directed therapies to date, this study is conducting biomarker analyses

Table 2. Study end points.

Study end points	
Primary	Progression-free survival by BICR per RECIST 1.1
Key secondary	Overall survival
Secondary	• Progression-free survival assessed by investigator per RECIST 1.1 • Progression-free survival 2 by local standard clinical practice • Objective response rate† • Duration of response† • Clinical benefit rate† • Disease control rate† • Time to response† • Safety • Patient-reported outcomes • Biomarkers • Immunogenicity
Exploratory	• Patient-reported outcomes • Pharmacokinetics • Population pharmacokinetics

†As assessed by BICR and investigator per RECIST 1.1.
BICR: Blinded independent central review; RECIST: Response Evaluation Criteria in Solid Tumors.

(e.g., genomic alterations in tumor and/or blood, gene expression, and HER3 protein expression) in all patients to explore potential associations with clinical outcome measures.

Study procedures

The treatment period begins after randomization for both the HER3-DXd and PBC arms, starting on day 1 of cycle 1 for each 21-day cycle until the end of treatment (Figure 3). Patients are recommended to receive an antiemetic combination regimen of two to three agents, including dexamethasone with either a 5-HT3 or an NK-1 receptor antagonist as well as other indicated drugs, prior to HER3-DXd administration. Choice of agents is based on the discretion of the treating physician per local and institutional guidelines. Efficacy is assessed in the full analysis set of all patients who have been randomized and assigned study treatment. Baseline tumor assessments must be performed within 28 days before randomization. Radiographic tumor assessments are performed every 6 weeks for the first 48 weeks, and then every 12 weeks until the time of disease progression, death, loss to follow-up, or withdrawal of consent. Patients who discontinue study treatment for any other reason will continue to undergo tumor assessments until the time of radiographic disease progression or until the patient discontinues from the study.

Safety is assessed in all patients who have received one or more doses of the study drug through physical examinations, clinical laboratory tests, vital signs, cardiac assessments, Eastern Cooperative Oncology Group performance status and ophthalmologic assessments. Adverse event monitoring and grading is in accordance with the National Cancer Institute Common Terminology for Adverse Events version 5. An independent ILD adjudication committee reviews all potential cases of ILD, and all cases of ILD will be monitored until resolution, regardless of severity.

Pharmacokinetic analyses are performed in all patients who have received one or more doses of HER3-DXd and had one or more pharmacokinetic samples to assess serum concentrations of HER3-DXd, total anti-HER3 antibody, released payload, and the presence of neutralizing antidrug antibodies. Exploratory biomarkers are also being assessed in all patients using blood samples collected at multiple time points, and tissues samples acquired prior to treatment and, optionally, at the end of treatment.

Patient-reported outcomes (PRO) are directly reported by the patient on-site during screening and electronically at home thereafter for patient convenience.

Data collection, management & statistical analysis

An electronic case report form is created for any patient who signs an informed consent form and undergoes a screening procedure that is reviewed by the investigator. Data are vetted to ensure quality; all adverse events are coded using Medical Dictionary for Regulatory Activities (MedDRA), and all concomitant medications and prior cancer therapies are coded using the World Health Organization Drug Reference (WHODRUG) Dictionary.

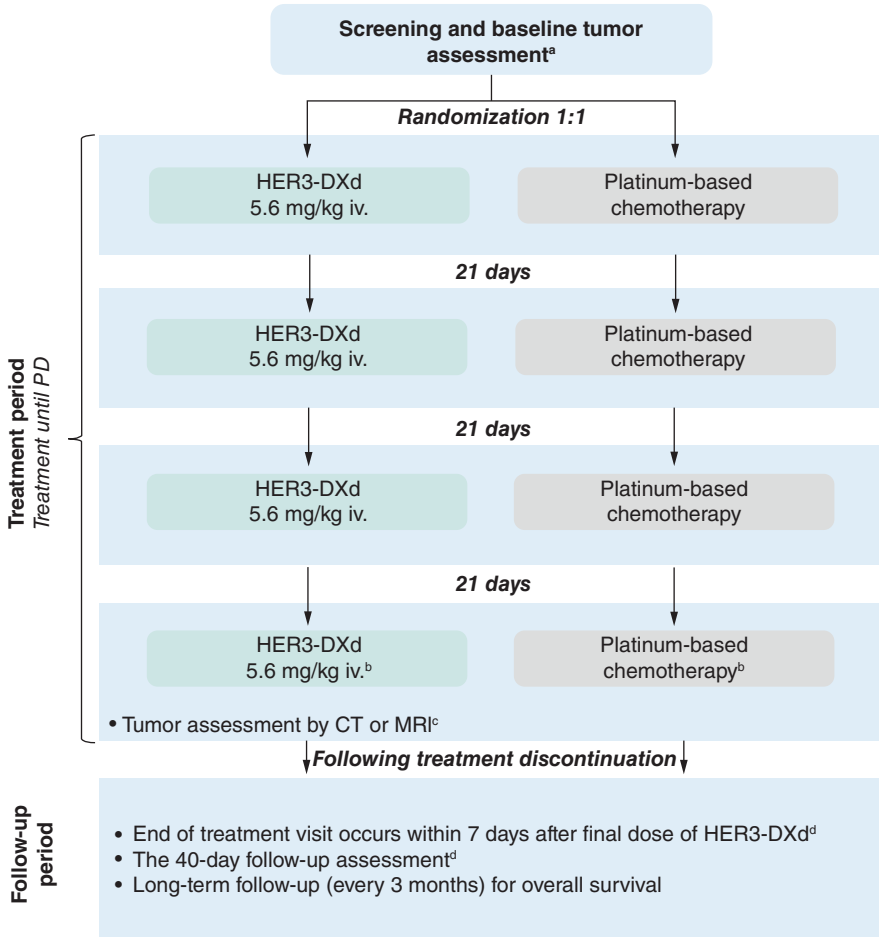

Figure 3. Timeline for tumor assessments.
[a]Screening period will be a maximum of 35 days prior to randomization, and dosing must begin within 3 days of randomization; baseline tumor assessments must occur within 28 days prior to randomization.
[b]Treatment with cycles of HER3-DXd 5.6 mg/kg will continue until treatment discontinuation. Patients without disease progression after four cycles of platinum-based chemotherapy plus pemetrexed may continue treatment with maintenance pemetrexed (500 mg/m^2 Q3W), with no restriction on the number of cycles.
[c]Tumor assessments will occur every 6 weeks from randomization for the first 48 weeks, then every 12 weeks during the follow-up period, independent of treatment cycle until documented disease progression by both BICR and investigator per RECIST 1.1 or the patient discontinues treatment.
[d]Or before starting new anticancer treatment, whichever comes first.
BICR: Blinded independent central review; iv.: Intravenous; PD: Progressive disease; Q3W: Every 3 weeks; RECIST: Response Evaluation Criteria in Solid Tumors.

The primary hypothesis is that HER3-DXd is superior to PBC in terms of progression-free survival as assessed by BICR, and the key secondary hypothesis is that HER3-DXd is superior to PBC in terms of overall survival. The primary and key secondary efficacy analyses will be the comparison of the distribution of progression-free survival and overall survival between the two treatment groups using stratified log-rank tests at two-sided 5% levels of significance. The survival distribution of progression-free survival and overall survival will be estimated using the Kaplan–Meier method. The hazard ratios of progression-free survival and overall survival in the treatment arm versus control arm and the two-sided 95% CI will be estimated using the stratified Cox proportional hazards regression model with the assigned treatment as the only model factor. The stratification factors will use values as recorded during randomization.

Other efficacy measures will be compared between treatment arms using Clopper-Pearson confidence intervals (objective response rate, disease control rate and clinical benefit rate), or analyzed using Kaplan–Meier methodology and compared between treatment groups with a stratified log-rank test. All safety and quality-of-life measures will

be assessed using descriptive statistics by treatment arm, analyzed using the Kaplan–Meier methodology for time-to-event parameters, and with a linear mixed-effect model for longitudinal analysis.

Data monitoring, dissemination & ethics

An independent data monitoring committee (IDMC) will continually monitor the safety of patients enrolled in the clinical trial. The IDMC is composed of qualified physicians and scientists who are not investigators in the study and not otherwise directly associated with the sponsor.

This protocol is approved by the institutional review board at each participating institution. This study is being conducted in compliance with the protocol, the ethical principles of the Declaration of Helsinki, the International Council for Harmonization for Good Clinical Practice, and local regulatory requirements. Regular inspections of facilities and various study records are performed to ensure protocol adherence. Informed consent is obtained from all patients and is documented in the patient's electronic medical records and all adverse events are reported in the electronic case report form. Reporting of events include the investigator's assessment of seriousness, severity and causality attributed to either treatment.

Conclusion

Although third-generation EGFR TKIs have significantly improved treatment outcomes for patients with advanced or metastatic NSCLC with *EGFR*-activating mutations, patients are likely to develop resistance, and salvage therapies are limited [7,8,12,23,24]. Treatment with standard PBC after progression on or after EGFR TKI therapy has shown modest, yet transient, efficacy. Combination regimens with immune checkpoint blockade have failed to demonstrate superiority over platinum-based treatments in the pivotal phase III KEYNOTE-789 and CheckMate722 trials [11–15]. Results from ongoing studies evaluating VEGF inhibitor regimens are compelling, but a recent randomized phase III study conducted in China (Impower151) did not show statistically significant benefit [16,17]. In a phase I study, HER3-DXd has demonstrated antitumor activity across a broad range of baseline tumor HER3 expression and diverse mechanisms of EGFR TKI resistance; early, durable antitumor activity was observed in patients previously treated with a third-generation EGFR TKI and PBC [36]. These data support the ongoing clinical development of HER3-DXd in *EGFR*-mutated NSCLC, beginning with the phase II HERTHENA-Lung01 trial (NCT04619004) in patients previously treated with one or more EGFR TKIs and one or more lines of PBC. This phase III HERTHENA-Lung02 trial (NCT05338970) aims to further confirm the efficacy and safety of HER3-DXd while investigating its potential treatment benefit compared with the standard of care in patients who experienced disease progression on a third-generation EGFR TKI. In addition, the phase I U31402-A-U103 (NCT04676477) dose-escalation and -expansion study is underway, evaluating HER3-DXd in combination with osimertinib for patients with *EGFR*-mutated NSCLC in the first- and second-line settings to help better understand the role of HER3-DXd in potential treatment strategies.

Executive summary

Background

- EGFR tyrosine kinase inhibitor (TKI) therapy shows initial efficacy in the majority of patients with *EGFR*-mutated non-small-cell lung cancer (NSCLC); however, treatment resistance typically emerges.
- Osimertinib is a third-generation EGFR TKI that is the current standard of care for patients with NSCLC with *EGFR*-activating mutations.
- For patients whose disease progresses with osimertinib, platinum-based chemotherapy (PBC) is the standard subsequent therapy and has demonstrated transient clinical benefit. Salvage treatments after progression on chemotherapy generally have intolerable safety profiles and do not provide durable efficacy.
- HER3 is expressed in *EGFR*-mutated NSCLC, particularly after progression on EGFR TKIs, and increased expression is associated with poor clinical outcomes.

Patritumab deruxtecan (HER3-DXd)

- HER3-DXd is a potential 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.
- In the phase I U31402-A-U102 trial, HER3-DXd 5.6 mg/kg demonstrated antitumor efficacy across a broad range of HER3 expression and diverse mechanisms of EGFR TKI resistance. HER3-DXd also showed tolerable safety outcomes in heavily pretreated patients with *EGFR*-mutated NSCLC.

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HERTHENA-Lung02

- HERTHENA-Lung02 (NCT05338970) is a global, randomized, open-label, phase III trial evaluating HER3-DXd versus PBC in patients with metastatic or locally advanced NSCLC with the *EGFR*-activating exon 19 deletion or L858R mutation following treatment with one or two lines of EGFR TKI therapy, including progression with a third-generation EGFR TKI.
- The primary end point is progression-free survival by blinded independent central review per Response Evaluation Criteria in Solid Tumors version 1.1, and the key secondary end point is overall survival.

Conclusion

- HERTHENA-Lung02 is assessing the safety and efficacy of HER3-DXd 5.6 mg/kg compared with PBC in patients with *EGFR*-activating mutations after progression on one or two lines of EGFR TKI treatment, including a third-generation EGFR TKI.
- This trial aims to further confirm the efficacy and safety of HER3-DXd while evaluating its potential to improve treatment outcomes in this patient population compared with standard therapies.
- Targeting HER3 could represent an effective treatment strategy in an otherwise limited treatment landscape for patients with *EGFR*-mutated NSCLC that progressed on treatment with a third-generation EGFR TKI.

Supplementary data

An infographic accompanies this paper. To view or download this infographic in your browser please click here: https://www.futuremedicine.com/doi/suppl/10.2217/fon-2023-0602

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.

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The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, stock ownership or options and expert testimony.

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Ethical conduct of research

The investigators have obtained appropriate institutional review board approval and 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

After the primary study results have been accepted for publication, complete de-identified individual participant data (IPD) and applicable supporting clinical trial documents may be available upon request at https://vivli.org/ to researchers whose proposed use of the data has been approved (intended use of the data must be specified in the request). Applicable clinical trial documents, such as analytic/statistical codes and informed consent forms, may be available upon request at https://vivli.org/ourmember/daiichi-sankyo/.

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