

## Health Technology Briefing August 2024

### Trastuzumab deruxtecan for treating previously untreated locally advanced or metastatic non-small cell lung cancer with HER2 mutations

Company/Developer

Daiichi Sankyo UK Ltd

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 33825

NICE ID: Not Available

UKPS ID: 668898

#### Licensing and Market Availability Plans

Currently in phase III clinical trials.

#### Summary

Trastuzumab deruxtecan is in clinical development for treatment of previously untreated advanced or metastatic non-small cell lung cancer (NSCLC), with HER2 genetic mutations. Lung cancer is the third most common cancer in the UK and NSCLC accounts for approximately 85% of all lung cancer cases, with around 1-4% of these being caused by mutations in the HER2 gene. Lung cancer symptoms include a persistent cough, chest infections that keep coming back, coughing up blood, and pain when breathing. The survival rates following a lung cancer diagnosis are relatively low, meaning not many people survive for a long time following a diagnosis. Metastatic or advanced cancer means that it has spread from where the cancer started, this makes it harder to treat. There are currently limited HER2 specific options for initial treatment of advanced or metastatic NSCLC, this indicates that there remains an unmet need.

Trastuzumab deruxtecan is a HER2-targeted antibody-drug combination. The antibody is specific to HER2 and so binds to HER2 receptors expressed on the surface of certain tumour cells. After binding, the trastuzumab deruxtecan is taken into the cancer cells where the drug is released from the antibody and causes DNA damage within the cells to initiate cell death. Trastuzumab deruxtecan is administered via intravenous (IV) infusion. If licenced, trastuzumab deruxtecan would provide a HER2 specific treatment option for untreated locally advanced or metastatic NSCLC.

#### Proposed Indication

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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For the first-line treatment of unresectable, locally advanced or metastatic non-small cell lung cancer (NSCLC) with human epidermal growth factor (HER) 2 exon 19 or 20 mutations.<sup>1</sup>

## Technology

### Description

Trastuzumab deruxtecan (Enhertu) is a HER2-targeted antibody-drug conjugate. The antibody is a humanised anti-HER2 IgG1 attached to deruxtecan, a topoisomerase I inhibitor (DXd) bound by a tetrapeptide-based cleavable linker. The function of the antibody portion is to bind to HER2 expressed on the surface of certain tumour cells. After binding, the trastuzumab deruxtecan complex then undergoes internalisation and intracellular linker cleavage by lysosomal enzymes that are upregulated in cancer cells. Upon release, the membrane-permeable DXd causes DNA damage and apoptotic cell death. As the drug payload is cell membrane-permeable, it enables a 'bystander antitumour effect' resulting in elimination of both target and surrounding tumour cells.<sup>2</sup>

Trastuzumab deruxtecan is currently in clinical development for the first-line treatment of unresectable, locally advanced or metastatic NSCLC with HER2 exon 19 or 20 mutations. In the phase III clinical trial (DESTINY-Lung04, [NCT05048797](https://clinicaltrials.gov/ct2/show/study/NCT05048797)) participants are given trastuzumab deruxtecan via intravenous (IV) infusion.<sup>1</sup>

### Key Innovation

Recent progress in treating advanced NSCLC has been made using drugs targeting specific genetic mutations but so far HER2 mutations have not had specific treatments recommended by the National Institute for Health and Care Excellence (NICE).<sup>3,4</sup> Current first-line standard of care for patients with HER2 alterations includes chemotherapy or chemoradiotherapy, with no current standard of care treatments being specific to the underlying HER2 mutation(s).<sup>3,5</sup> HER2 mutant patients have been shown to respond less positively to general anti-tumour interventions than those patients without HER2 mutations.<sup>5</sup> Recent research has suggested that the survival rate of HER2 mutant patients is increased when treated with mutation specific interventions rather than generalised NSCLC treatments.<sup>6</sup> Some animal studies have found that HER2 amplifications are overrepresented in tumours that developed treatment resistance, suggesting that HER2 mutations be a potential cause for treatment resistance and therefore that mutation specific interventions may lead to less treatment resistance.<sup>7</sup> If licenced, drug trastuzumab deruxtecan will become the first HER2-targeted treatment available for patients with untreated advanced or metastatic NSCLC.

### Regulatory & Development Status

Trastuzumab deruxtecan has marketing authorisation in the EU/UK for the following indications:<sup>8</sup>

- HER2-positive breast cancer - following one or more prior anti-HER2-based regimens
- HER2-low breast cancer - following prior chemotherapy in the metastatic setting or if there is recurrence during or within 6 months of completing adjuvant chemotherapy
- NSCLC - in adult patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy
- Gastric cancer - in adult patients with advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen

Trastuzumab deruxtecan is also in phase II and/or III clinical development for:<sup>9</sup>

- Advanced solid tumours

- Brain cancers
- Oesophageal cancer
- Gastroesophageal cancer
- Biliary tract cancer
- Triple negative breast cancer

## Patient Group

### Disease Area and Clinical Need

Lung cancer is the third most common cancer in the UK with around 48,500 people diagnosed in the each year.<sup>10</sup> There are 2 main types of lung cancer, non-small cell and small cell lung cancer, with NSCLC accounting for approximately 85% of all lung cancer cases.<sup>6,10</sup> In around 1-4% of NSCLC cases, HER2 is found to be an oncogenic driver.<sup>7</sup> In locally advanced cancer cases the primary tumour site has not spread to another part of the body, whereas metastatic cancer occurs when cancerous cells break away from the primary tumour where the cancer first developed forming another tumour in a separate organ or tissue. There are usually no signs or symptoms of lung cancer in the early stages, however symptoms often develop as the condition progresses. The main symptoms of lung cancer include: a cough that does not go away after 3 weeks, chest infections that keep coming back, coughing up blood, an ache or pain when breathing or coughing, persistent breathlessness and persistent tiredness or lack of energy.<sup>11</sup> Smoking cigarettes is the single biggest risk factor for lung cancer, it is responsible for more than 7 out of 10 cases, other risk factors include occupational exposure to certain chemicals and substances and pollution.<sup>12</sup>

Lung cancer accounts for 13% of all new cancer cases (2017-2019).<sup>13</sup> The age standardised incidence rate of lung cancer in England is 86.8 and 67.0 per 100,000 amongst males and females respectively.<sup>14</sup> In England (2022-23) there were 122,866 finished consultant episodes (FCEs) and 104,232 admissions for malignant neoplasm of bronchus and lung (ICD-10 code C34), which resulted in 80,131 day cases and 217,569 FCE bed days.<sup>15</sup> With NSCLC accounting for around 85% of lung cancers, and approximately 4% of NSCLC cases involving HER2 mutations, it can be estimated that around 3,544 patients were admitted with HER2+ NSCLC, leading to 2,724 day cases and 7,397 FCE bed days. Estimates put the rate of metastatic disease between 30% to 40% during a diagnosis of NSCLC.<sup>16</sup> For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates were 37.1% and 13.8% respectively for men, and 44.5% and 19.0% respectively for women (includes data from patients with any stage of disease).<sup>17</sup>

### Recommended Treatment Options

The NHS recommends a combination of radiotherapy and chemotherapy for the first-line treatment of NSCLC, though dependent on several factors such as tumour size, tumour location and general physical health, other treatments include chemotherapy or radiotherapy on their own.<sup>18</sup>

NICE recommends the use of chemotherapy for use in the first-line treatment of advanced or metastatic NSCLC with HER2 mutations.

## Clinical Trial Information

<b>Trial</b>	<b>DESTINY-Lung04; <a href="#">NCT05048797</a></b> ; An Open-label, Randomized, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Trastuzumab Deruxtecan as First-line Treatment of Unresectable, Locally Advanced, or Metastatic NSCLC Harboring HER2 Exon 19 or 20 Mutations (DESTINY-Lung04) <b>Phase III: Recruiting</b> <b>Location(s):</b> 9 EU countries, USA, Canada, and other countries <b>Primary completion date:</b> June 2025
<b>Trial Design</b>	Randomized, parallel assignment, open label, active comparator controlled
<b>Population</b>	N= 450 (estimate); aged 18 years or older; locally advanced and unresectable NSCLC, not amenable to curative therapy, or metastatic disease with HER2 mutation in exons 19 or 20 by tissue NGS or ctDNA; treatment-naïve for palliative intent systemic therapy for locally advanced or metastatic disease.
<b>Intervention(s)</b>	Trastuzumab deruxtecan via intravenous (IV) infusion
<b>Comparator(s)</b>	Pembrolizumab and pemetrexed administered via IV infusion plus cisplatin or carboplatin via IV infusion (dependant on the investigator's choice of platinum chemotherapy)
<b>Outcome(s)</b>	Primary outcome measure: - Progression free survival (PFS) by blinded independent central review (BICR) up to approximately 12 months  See trial for full list of secondary outcomes
<b>Results (efficacy)</b>	-
<b>Results (safety)</b>	-

### Estimated Cost

The NHS indicative cost of trastuzumab deruxtecan (100mg, powder of concentrate for solution for infusion vials) costs £1,455.<sup>19</sup>

### Relevant Guidance

#### NICE Guidance

- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019 (Last updated March 2024).

#### NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. Clinical Commissioning Policy: Stereotactic Ablative Body Radiotherapy for Non-Small-Cell Lung Cancer (Adult). B01/P/a. April 2013.

#### Other Guidance

- National Comprehensive Cancer Network. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 2. 2021.<sup>20</sup>
- European Society for Medical Oncology (ESMO). Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2018.<sup>21</sup>
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.<sup>22</sup>

## Additional Information

## References

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