

## HEALTH TECHNOLOGY BRIEFING JANUARY 2021

### Trastuzumab deruxtecan for HER2 mutant unresectable and/or metastatic non-squamous non-small cell lung cancer – second line

NIHRIO ID	26877	NICE ID	10520
Developer/Company	Daiichi Sankto Ltd	UKPS ID	659042

Licensing and market availability plans	Currently in phase II clinical trials
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### SUMMARY

Trastuzumab deruxtecan is in clinical development as a second-line treatment for advanced, HER-2 mutant, non-squamous non-small cell lung cancer (NSCLC). NSCLC makes up the majority of lung cancers in the UK and at the metastatic stage (stage IV), the disease has already spread from the lungs to other sites. Symptoms of lung cancer include a persistent cough, shortness of breath, coughing up blood, aches and pains in the chest or shoulder, loss of appetite, weight loss and fatigue. Most patients with NSCLC are diagnosed at the advanced/metastatic stage where curative treatment with surgery is unsuitable. While current treatments exist for advanced NSCLC, significant unmet medical need remains for human epidermal growth factor receptor 2 (HER-2) mutant specific treatments.

Trastuzumab deruxtecan is a humanised monoclonal antibody directed at HER-2 that is present on cancer cells. Activation of HER2 has been linked to cell transformation and oncogenesis. Trastuzumab deruxtecan binds to HER2 and induces cell death. If licensed, trastuzumab deruxtecan (given as an intravenous infusion) may offer a second-line treatment option for patients with advanced HER2 mutant NSCLC.

*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.*

## PROPOSED INDICATION

Adult patients with HER2 mutant unresectable and/or metastatic non-squamous NSCLC whose disease has progressed following one or more systemic therapies.<sup>a</sup>

## TECHNOLOGY

### DESCRIPTION

Trastuzumab deruxtecan (Enhertu; DS8201; DS-8201a; TDxd) is a human epidermal growth factor receptor 2 (HER2) targeting antibody drug conjugate (ADC), structurally composed of a humanised anti-human HER2 (anti-hHER2) antibody, an enzymatically cleavable peptidelinker and a topoisomerase I inhibitor, exatecan derivative.<sup>1</sup> Trastuzumab deruxtecan, which was designed to improve on the critical attributes of currently available antibody-drug conjugates, has a higher drug-to-antibody ratio than trastuzumab emtansine (approximately 8 vs. 3 to 4) while retaining a favorable pharmacokinetic profile.<sup>2</sup> The proprietary tetrapeptide-based linker is stable in plasma and is selectively cleaved by cathepsins that are up-regulated in tumor cells. Unlike trastuzumab emtansine, trastuzumab deruxtecan has a released payload that easily crosses the cell membrane, which potentially allows for a potent cytotoxic effect on neighboring tumor cells regardless of target expression.<sup>3</sup> In addition, the released payload has a short half-life, which is designed to minimise systemic exposure.<sup>1</sup>

In a phase II clinical trial (NCT03505710), participants received either 5.4mg/kg (HER2 overexpressing group) or 6.4mg/kg trastuzumab deruxtecan (HER2 overexpressing or HER2 mutated groups) by intravenous infusion.<sup>4</sup>

### INNOVATION AND/OR ADVANTAGES

Currently no HER2 specific directed therapies are approved for second-line treatment of HER2 mutated NSCLC.<sup>5</sup>

In a phase I trial, trastuzumab deruxtecan showed promising antitumour activity in HER2 mutant NSCLC.<sup>6</sup> The safety profile was also shown to be generally acceptable.

### DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Trastuzumab deruxtecan does not currently have Marketing Authorisation for any indication in the UK/EU. However, the Committee for Medicinal Products for Human Use (CHMP) recommended the granting of a conditional Market Authorisation.<sup>7</sup>

Trastuzumab deruxtecan was awarded US Breakthrough Therapy Designation in 2020.<sup>8</sup>

Trastuzumab deruxtecan is in phase II/III clinical development for the treatment of several cancers such as bladder cancer, biliary tract cancer, cervical cancer, endometrial cancer, ovarian cancer, pancreatic cancer, osteosarcoma, recurrent osteosarcoma and colorectal neoplasm.<sup>9</sup>

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<sup>a</sup> Information provided by Daiichi Sankyo Ltd on UK PharmaScan

### DISEASE BACKGROUND

Lung cancer is classified into two main types: small-cell lung cancer (SCLC) or NSCLC. NSCLC comprises approximately 80 to 85% of lung cancers in the UK. There are three common types of NSCLC; adenocarcinoma (the most common type which starts in the mucus making glands in the lining of the airways), squamous cell cancer (develops in the flat cells that cover the surface of the airways and tends to grow near the centre of the lung) and large cell carcinoma (cancer cells which appear large and round under the microscope).<sup>10</sup> In stage IV the cancer has spread, either to both lungs, the chest or beyond.<sup>11</sup>

Tobacco smoking remains the main cause of lung cancer and the geographical and temporal patterns of the disease largely reflect tobacco consumption during previous decades.<sup>12</sup> Several other factors have been described as lung cancer risk factors including; exposure to radiation, certain chemicals (e.g. asbestos, silica and diesel engine exhaust fumes) and previous lung disease (e.g. tuberculosis and COPD). Other factors include family history of lung cancer and certain genetic mutations.<sup>13</sup>

Symptoms of lung cancer include a persistent cough (which may be more painful, have a different sound or bring up coloured mucus), shortness of breath, coughing up blood, aches and pains in the chest or shoulder, loss of appetite, weight loss and fatigue.<sup>14,15</sup>

Human Epidermal growth factor Receptor 2 (HER2) is a protein that can affect the growth of some cancer cells which is found on the surface of normal lung cells. HER2 regulates cell growth, survival, and differentiation via multiple signal transduction pathways and participate in cellular proliferation and differentiation.<sup>16</sup>

### CLINICAL NEED AND BURDEN OF DISEASE

Primary lung cancer remains the most common malignancy after non-melanocytic skin cancer, and deaths from lung cancer exceed those from any other malignancy worldwide.<sup>12</sup>

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases in 2017. There are around 48,000 new lung cancer cases in the UK yearly. Incidence rates for lung cancer in the UK are highest in people aged 85 to 89 (2015-2017). Incidence rates for lung cancer are projected to fall by 7% in the UK between 2014 and 2035, to 88 cases per 100,000 people by 2035.<sup>17</sup>

In 2019/20 there were 111,188 hospital admissions with primary diagnosis malignant neoplasm of bronchus and lung (ICD-10 code C34), and 132,969 finished consultant episodes (FCEs), resulting in 243,883 FCE bed days.<sup>18</sup> According to the National Cancer Registration and Analysis Service (NCRAS), there were 18,213 diagnosed cases of stage IV lung cancer in 2017, this represents 47% of the overall number of lung cancer cases diagnosed for that year.<sup>19</sup> In the UK it is estimated that up to 85% of lung cancer cases are NSCLC, applying this figure to the number of stage IV lung cancer cases diagnosed in 2017, it can be estimated that approximately 15,481 cases diagnosed with stage IV in 2017 were NSCLC.<sup>10</sup>

Survival rates for lung cancer depend on at which stage of disease the cancer is identified.<sup>17</sup> In England between 2013 and 2017, the age-standardised net lung cancer survival for stage IV was 19.3% at one year and 2.9% at five years.<sup>20</sup> There are around 35,300 lung cancer deaths in the UK every year (based on data from 2015-2017). Mortality rates for lung cancer are projected to fall by 21% in the UK between 2014 and 2035.<sup>17</sup> In England and Wales in 2019

there were 29,463 deaths with malignant neoplasm of bronchus and lung (ICD-10 codes C34) recorded as the underlying cause.<sup>21</sup>

In NSCLC, activating mutations in HER2 occur in ~2%–4% of cases, most commonly in adenocarcinoma histology and never smokers. The most common mutation consists of a 12 basepair insertion in exon 20 resulting in an YVMA insertion. Also in NSCLC, oncogenic amplification of HER2 occurs in around 3% of cases without prior Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitor (TKI) treatment and even higher, around 10% of cases, in EGFR TKI resistance. HER2 amplification and mutations do not usually occur together. A third mechanism of HER2 activation in lung cancer is protein overexpression, reported to occur in 2%–20% of cases depending on level of overexpression (IHC 2+ or 3+) and demonstrated to have a poor prognostic role.<sup>22</sup>

## PATIENT TREATMENT PATHWAY

### TREATMENT PATHWAY

Treatment of NSCLC depends on the stage of the cancer and the general health of the patient. At stage IV NSCLC, treatment aims to control the cancer for as long as possible and help with symptoms. Treatment generally include chemotherapy, targeted drugs, radiotherapy and symptom control treatment.<sup>23</sup>

### CURRENT TREATMENT OPTIONS

Atezolizumab plus bevacizumab, carboplatin and paclitaxel is recommended as an option for metastatic non-squamous NSCLC in adults who have not had treatment for their metastatic NSCLC before and whose PD-L1 tumour proportion score is between 0% and 49% or when targeted therapy for EGFR-positive or ALK-positive NSCLC has failed.<sup>5</sup>

### PLACE OF TECHNOLOGY

If licensed, trastuzumab deruxtecan would provide an additional second-line treatment for advanced, HER2 mutated, non-squamous, NSCLC.

## CLINICAL TRIAL INFORMATION

<b>Trial</b>	<b>DESTINY-Lung01; <a href="#">NCT03505710</a>, <a href="#">2017-004781-94</a>; A Phase 2, Multicenter, Open-Label, 2-Cohort Study of Trastuzumab Deruxtecan (DS-8201a), an Anti-HER2 Antibody Drug Conjugate (ADC), for HER2-Over-Expressing or -Mutated, Unresectable and/or Metastatic Non Small Cell Lung Cancer (NSCLC) (DESTINY-Lung01) <b>Phase II</b> – Active, not recruiting <b>Location(s):</b> US, Japan and EU (not incl. UK) <b>Primary completion date:</b> February 2021</b>
<b>Trial design</b>	Non-randomised, parallel assignment, open label
<b>Population</b>	N = 170; 20 years and older in Japan, 18 years and older elsewhere; pathologically documented unresectable and/or metastatic non-squamous NSCLC; has relapsed from or is

	refractory to standard treatment or for which no standard treatment is available
<b>Intervention(s)</b>	Either 5.4mg/kg (HER2 overexpressing group) or 6.4mg/kg trastuzumab deruxtecan (HER2 overexpressing or HER2 mutated groups) by intravenous infusion
<b>Comparator(s)</b>	No comparator
<b>Outcome(s)</b>	Overall response rate (ORR) of trastuzumab deruxtecan (DS-8201a) assessed by independent central review (ICR) [Time frame: within 30 months]  See trial record for full list of other outcomes
<b>Results (efficacy)</b>	Confirmed ORR by ICR among the 42 patients was 61.9% (95% CI, 45.6%-76.4%); median duration of response (DOR) was not reached at data cutoff; 16 of 26 responders remained on treatment at data cutoff; disease control rate (DCR) was 90.5% (95% CI, 77.4%-97.3%); estimated median progression-free survival was 14.0 mo (95% CI, 6.4-14.0 mo) <sup>24</sup>
<b>Results (safety)</b>	<ul style="list-style-type: none"> <li>All patients (42/42) had treatment-emergent adverse events (TEAEs); 64.3% were grade ≥ 3 (52.4% drug-related), including decreased neutrophil count (26.2%) and anemia (16.7%).</li> <li>There were 5 cases (11.9%) of drug-related interstitial lung disease (ILD) as adjudicated by an independent committee (all grade 2, no grade ≥ 3) and 1 case of grade 1 ILD is pending adjudication.</li> <li>TEAEs led to dose interruption in 25 pts (59.5%), dose reduction in 16 pts (38.1%), and treatment discontinuation in 10 pts (23.8%).<sup>24</sup></li> </ul>

## ESTIMATED COST

The cost of trastuzumab deruxtecan is not yet known.

## RELEVANT GUIDANCE

### NICE GUIDANCE

- NICE technology appraisal. Durvalumab for treating locally advanced unresectable non-small-cell lung cancer after platinum-based chemoradiation. (TA578). May 2019.
- NICE technology appraisal. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy (TA520). May 2018.
- NICE technology appraisal. Nivolumab for previously treated non-squamous non-small-cell lung cancer. (TA484). November 2017.
- NICE technology appraisal. Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (TA347). July 2015.
- NICE guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). March 2019.

### 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.

## OTHER GUIDANCE

- National Comprehensive Cancer Network (NCCN). Non-Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.<sup>25</sup>
- European Society for Medical Oncology. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016.<sup>26</sup>
- European Society for Medical Oncology. ESMO Consensus Guidelines: Non-small-cell lung cancer first-line/second and further lines in advanced disease. 2014.<sup>27</sup>
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.<sup>28</sup>

## ADDITIONAL INFORMATION

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**NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.**