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HEALTH TECHNOLOGY BRIEFING
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Trastuzumab deruxtecan for HER2-positive gastric or gastroesophageal junction adenocarcinoma – third-line

NIHRIO ID	26878	**NICE ID**	10521
Developer/Company	Daiichi Sankyo Ltd	**UKPS ID**	659041

Licensing and market availability plans	Currently in phase II clinical trials.

SUMMARY

Trastuzumab deruxtecan is in development for HER2-positive gastric cancer. HER2 is a type of growth-promoting protein, which can increase cancer cell growth if present (HER2-positive). Gastric cancer originally develops in the stomach, whereas gastro-oesophageal junction cancer originates where the food pipe (oesophagus) joins the stomach. The initial stages of gastric or gastroesophageal cancer are often asymptomatic, with symptoms developing and worsening as the disease progresses.

Trastuzumab deruxtecan consists of an anti-HER2 therapy (trastuzumab) combined with a chemotherapy agent (deruxtecan). Trastuzumab specifically binds to cancer cells that are HER2-positive, which provides a targeted delivery of the deruxtecan inside cancer cells to kill them. This reduces "healthy" cells exposure to the chemotherapy with the potential to reduce negative side effects. If licensed, trastuzumab deruxtecan will offer an additional treatment option for patients whose disease progressed despite previous treatment with other anti-HER2 therapies.

PROPOSED INDICATION

Unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma in patients who have received two or more prior regimens, including an anti-HER2 therapy – third-line.[a]

TECHNOLOGY

DESCRIPTION

Trastuzumab deruxtecan (Enhertu; DS-8201a) is a novel, human epidermal growth factor receptor 2 (HER2)-targeted antibody-drug conjugate (ADC) with humanised anti-HER2 antibody, cleavable peptide-based linker and potent topoisomerase I inhibitor payload.[1] HER2 is a member of the epidermal growth factor transmembrane receptor family that is over expressed in gastric cancer and contributes to tumour cell proliferation, adhesion, migration, differentiation, and apoptosis.[1,2] ADCs are targeted cancer medicines that deliver cytotoxic agents to cancer cells via a linker attached to a monoclonal antibody that binds to a specific target expressed on cancer cells. Trastuzumab deruxtecan works as an ADC which targets and delivers the cytotoxic agents (deruxtecan) to the cancer cells via a linker attached to a monoclonal antibody (trastuzumab) that binds to a specific target HER2 expressed on cancer cells.[3]

Trastuzumab deruxtecan is currently at phase II clinical development (NCT03329690) for the treatment of patients with HER2-positive unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received two or more prior regimens, including an anti-HER2 therapy.[4] In the phase II clinical trial, participants receive an intravenous (IV) infusion of trastuzumab deruxtecan (6.4 mg per kilogram of body weight) every 3 weeks.[5]

INNOVATION AND/OR ADVANTAGES

The result from a pre-clinical trial suggested that trastuzumab deruxtecan was very potent in inhibiting tumour growth.[1] The novel feature of trastuzumab deruxtecan is that the released payload is highly membrane-permeable and able to exert anti-tumour activity on neighbouring cells including cells with no HER2 expression, through the bystander effect; this effect does not extend to distant sites.[6] This feature is designed for efficient delivery of the payload to tumour cells while reducing the potential for systemic toxicities.[1]

In the phase II, open-label, randomised clinical trial (NCT03329690) results show that trastuzumab deruxtecan led to significant improvement in response and overall survival, compared to standard therapies, among patients with HER2-positive gastric cancer.[5]

[a] Information provided by Daiichi Sankyo Ltd on UK PharmaScan

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

On December 10th 2020, the Committee for Medicinal Products for Human Use (CHMP) recommended granting a conditional marketing authorisation for trastuzumab deruxtecan for the treatment of metastatic HER2-positive breast cancer.[7]

Trastuzumab deruxtecan is currently at phase III clinical trials for the treatment of several different stages and forms of breast cancer. Trastuzumab deruxtecan is currently in phase II clinical trials for a number of different cancers including non-small cell lung cancer, osteosarcoma, breast cancers and HER2 expressing tumours.[8]

Trastuzumab deruxtecan has been granted Breakthrough Therapy Designation (BTD) by the US FDA in May 2020 for the treatment of gastric cancer.[9]

Trastuzumab deruxtecan has been granted Orphan Drug Designation (ODD) by the US FDA for the treatment of patients with gastric cancer in May 2020.[10]

PATIENT GROUP

DISEASE BACKGROUND

Gastric cancer is a malignant tumour originating in the cells of the stomach. There are several different types of stomach cancer. About 90-95% of stomach cancers develop in the cells of the stomach lining and are known as adenocarcinomas.[11,12] Most gastric cancers originate in the gland cells in the inner stomach lining.[12] While gastro-oesophageal junction cancer develops where the food pipe joins the stomach.[13] Gastric cancer begins in the stomach and can spread into the tissues around the stomach, either as locally advanced disease, or it can metastasise to other areas of the body such as the liver, lungs, lymph nodes, or the oesophagus (advanced or metastatic cancer). Advanced cancer cannot usually be cured, but treatment may control further growth of the disease, relieve symptoms and give the patient a good quality of life.[14] Gastric cancer begins with a mutation in the structure of the DNA in cells, which can affect how they grow. This means cells grow and reproduce uncontrollably, resulting in a tumour. It is not known what triggers the changes in DNA that lead to gastric cancer.[15] Gastric cancer can involve loss of the tumour suppressor gene, p53.[16]

Several factors which increase the risk of gastric cancer include ageing (55 years and older), male gender, smoking, severe chronic atrophic gastritis, peptic ulcers caused by Helicobacter pylori infection, diet, family history of gastric cancer, having another type of cancer, vitamin B12 deficiency, and history of stomach surgery.[15]

The initial diagnosis of gastric cancer is often delayed because up to 80% of patients are asymptomatic during the early stages of stomach cancer. Weight loss, abdominal pain, nausea and vomiting, early satiety, and peptic ulcer symptoms may accompany late-stage gastric cancer. Signs may include a palpably enlarged stomach, a primary mass (rare), an enlarged liver, Virchow's node, metastatic tumour felt on rectal examination, with growth in the rectouterine space.[17]

CLINICAL NEED AND BURDEN OF DISEASE

In 2017, gastric cancer was the 17th most common cancer in the UK. There were around 6,600 new cases of stomach cancer in the UK in 2015-2017. Around 1,300 cases of stomach cancer each year in England are linked with deprivation.[18]

More than 1 in 5 (21.6%) of people diagnosed with stomach cancer in England survive their disease for five years or more (2013-2017). It is predicted that more than 3 in 20 (16.7%) of people diagnosed with stomach cancer in England survive their disease for ten years or more (2013-2017).[19]

Stomach cancer patients with a known stage are most diagnosed at stage IV (46-57%). More patients with a known stage are diagnosed at a late stage (69-75% are diagnosed at stage III or IV), than an early stage (25-31% are diagnosed at stage I or II).[18] In the UK, 35% of stomach cancer cases are in females, and 65% are in males. According to 2010-2012 data in the UK, the largest proportion of gastric cancer cases (occur in the cardia next to the oesophagus).[18] In England, cancers of the gastro-oesophageal junction account for 40% of all cancers arising in the upper gastro-intestinal tract.[20]

In England, in 2019-20, there were 27,533 finished consultant episodes (FCE) and 22,055 admissions for malignant neoplasm of stomach (ICD-10 code C16), resulting in 16,097 day cases and 59,174 FCE bed days.[21] There were also 21,908 FCE and 17,965 admissions for malignant neoplasm of abdominal part of oesophagus and lower third of oesophagus (ICD-10 codes C15.2 and C15.5), resulting in 13,914 day cases and 41,393 FCE bed days.[21]

In England and Wales, in 2017, there were 3,772 deaths from malignant neoplasm of stomach (ICD-10 code C16).[22] Stomach cancer was the 14th most common cause of cancer death in the UK, accounting for 3% of all cancer deaths in 2017.[18] Latest published survival statistics estimate a 1-year net survival rate of 46.7% and a 5-year net survival rate of 20.6% (age-standardised) for patients diagnosed in 2018.[23]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment depends on where in the stomach the cancer is, how big it is, whether it has spread anywhere else in the body and general health of the patient. A team of health professional should discuss the best treatment and care for each individual patient.[24]

The most common treatments for stomach cancers are surgery, chemotherapy, targeted cancer drugs, and radiotherapy. The patient might have one of these treatments or a combination. Chemotherapy combined with radiotherapy is called chemoradiotherapy.[24]

Chemotherapy uses anti-cancer (cytotoxic) drugs to destroy cancer cells. Chemotherapy for advanced stomach cancer can relieve the symptoms. It can also control the cancer and improve the quality of life for a time. But it cannot cure the disease. There are different

chemotherapy drugs that patients might have for advanced stomach cancer. Usually the patients have a combination of 2 or 3 drugs.[25]

CURRENT TREATMENT OPTIONS

Lonsurf (trifluridine /tipiracil hydrochloride) is indicated as monotherapy for the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastroesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease.[26] Trifluridine–tipiracil is currently undergoing NICE technology appraisal for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more therapies.[27]

PLACE OF TECHNOLOGY

If licensed, trastuzumab deruxtecan will provide an additional treatment option for patients with unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma in patients who have received two or more prior regimens, including an anti-HER2 therapy.

CLINICAL TRIAL INFORMATION

Trial	**DESTINY-Gastric01; NCT03329690;** A Phase 2, Multicenter, Open-label Study of DS-8201a in Subjects With HER2-expressing Advanced Gastric or Gastroesophageal Junction Adenocarcinoma **Phase II –** Active, not recruiting **Location(s):** Japan and South Korea **Primary completion date:** Nov 2019
Trial design	Randomised, open label, parallel assignment
Population	N= 233; adults 20 years or older; locally advanced or metastatic adenocarcinoma of gastric or gastroesophageal junction; progression on and after at least 2 prior regimens
Intervention(s)	• Experimental: Parallel: Trastuzumab deruxtecan - Trastuzumab deruxtecan once every 3 weeks • HER2 IHC 2+/ISH- - Trastuzumab deruxtecan once every 3 weeks • Exploratory: Naïve HER2 IHC 1+ - Trastuzumab deruxtecan once every 3 weeks
Comparator(s)	Standard of care
Outcome(s)	• Percentage of Participants With Objective Response Rate Based on Independent Central Review Following Treatment With trastuzumab deruxtecan in Participants With HER2-Expressing Advanced Gastric or Gastroesophageal Junction Adenocarcinoma (Intent-to-Treat Analysis Set) [Time Frame: Baseline

	to date of first documented objective response (CR or PR), up to 25 months postdose] • Percentage of Participants With Best Overall Response Based on Independent Central Review Following Treatment With trastuzumab deruxtecan in Participants With HER2-Expressing Advanced Gastric or Gastroesophageal Junction Adenocarcinoma (Intent-to-Treat Analysis Set) [Time Frame: Baseline to date of first documented objective response, up to 25 months postdose] See trial record for a full list of other outcomes.
Results (efficacy)	An objective response was reported in 51% of the patients in the trastuzumab deruxtecan group, as compared with 14% of those in the physician's choice group (P<0.001). Overall survival was longer with trastuzumab deruxtecan than with chemotherapy (median, 12.5 vs. 8.4 months; hazard ratio for death, 0.59; 95% confidence interval, 0.39 to 0.88; P=0.01, which crossed the prespecified O'Brien–Fleming boundary [0.0202 on the basis of number of deaths]).[5]
Results (safety)	The most common adverse events of grade 3 or higher were a decreased neutrophil count (in 51% of the trastuzumab deruxtecan group and 24% of the physician's choice group), anemia (38% and 23%, respectively), and decreased white-cell count (21% and 11%). A total of 12 patients had trastuzumab deruxtecan–related interstitial lung disease or pneumonitis (grade 1 or 2 in 9 patients and grade 3 or 4 in 3), as adjudicated by an independent committee. One drug-related death (due to pneumonia) was noted in the trastuzumab deruxtecan group; no drug-related deaths occurred in the physician's choice group.[5]

ESTIMATED COST

The cost of trastuzumab deruxtecan is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Pembrolizumab for previously treated metastatic gastric or gastro-oesophageal junction cancer (ID1168). Expected publication date: TBC
- NICE technology appraisal in development. Trifluridine–tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after two or more therapies (ID1507). Expected publication date: Expected publication date: January 2021

- NICE technology appraisal. Capecitabine for the treatment of advanced gastric cancer (TA191). July 2010
- NICE guideline. Oesophago-gastric cancer: assessment and management in adults (NG83). January 2018

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Oesophageal and gastric (Adult). B11/S/a
- 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: Robotic assisted surgery for oesophagogastric cancers. 16006/P. July 2016

OTHER GUIDANCE

- National Comprehensive Cancer Network (NCCN). Gastric Cancer, Version 3. NCCN Clinical Practice Guidelines in Oncology. 2016[28]
- European Society for Medical Oncology (ESMO) Guidelines Committee. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2016[29]
- London Cancer Alliance (LCA). LCA Oesophageal and Gastric Cancer Clinical Guidelines. 2014[30]
- Britain and Ireland, the British Society of Gastroenterology and the British Association of Surgical Oncology. Guidelines for the management of oesophageal and gastric cancer. 2011[31]

ADDITIONAL INFORMATION

AstraZeneca is a collaborator for this technology.

REFERENCES

1 Shitara K, Iwata I, Takahashi S, Tamura K, Park H, Modi S. Tsurutani J, et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive gastric cancer: a dose-expansion, phase 1 study. *The Lancet Oncology*. 2019 Jun;20(6):827-36. Available from: https://doi.org/10.1016/S1470-2045(19)30088-9.

2 Doi T, Shitara K, Naito Y, Shimomura A, Fujiwara Y, Yonemori K, et al. Safety, pharmacokinetics, and antitumour activity of trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastro-oesophageal tumours: a phase 1 dose-escalation study. *The Lancet Oncology*. 2017 Nov;18(11):1512-22. Available from: https://doi.org/10.1016/s1470-2045(17)30604-6.

3 AstraZeneca. *Trastuzumab deruxtecan demonstrated clinically-meaningful response in patients with refractory HER2-positive metastatic breast cancer, a population with high unmet need.* 2019. Available from: https://www.astrazeneca.com/media-centre/press-releases/2019/trastuzumab-deruxtecan-demonstrated-clinically-meaningful-response-in-patients-with-refractory-her2-positive-metastatic-breast-cancer-a-population-with-high-unmet-need-08052019.html [Accessed 13 Dec 2020].

4 Clinicaltrials.gov. *DS-8201a in Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Gastric Cancer [DESTINY-Gastric01]. Trial ID: NCT03329690*. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT03329690 [Accessed 16 Dec 2020].

5 Shitara K, Bang Y-J, Iwasa S, Sugimoto N, Ryu M-H, Sakai D, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. *The New England Journal of Medicine*. 2020 Jun;382:2419-30. Available from: https://www.nejm.org/doi/10.1056/NEJMoa2004413.

6 Ogitani Y, Hagihara K, Oitate M, Naito H, Agatsuma T. Bystander killing effect of DS-8201a, a novel anti-human epidermal growth factor receptor 2 antibody-drug conjugate, in tumors with human epidermal growth factor receptor 2 heterogeneity. *Cancer Science*. 2016 Jun;107(7):1039-46. Available from: https://doi.org/10.1111/cas.12966.

7 European Medicines Agency (EMA). *Enhertu - Trastuzumab deruxtecan.* 2020. Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/enhertu [Accessed 16 Dec 2020].

8 Clinicaltrials.gov. *Trastuzumab deruxtecan clinical trials phase II and III.* 2020. Available from: https://clinicaltrials.gov/ct2/results?term=Trastuzumab+deruxtecan&age_v=&gndr=&type=&rslt=&phase=2&Search=Apply [Accessed 16 Dec 2020].

9 AstraZeneca. *Enhertu granted Breakthrough Therapy Designation in the US for HER2-positive metastatic gastric cancer.* 2020. Available from: https://www.astrazeneca.com/media-centre/press-releases/2020/enhertu-granted-breakthrough-therapy-designation-in-the-us-for-her2-positive-metastatic-gastric-cancer.html [Accessed 16 Dec 2020].

10 AstraZeneca. *Enhertu granted Orphan Drug Designation in the US for gastric cancer.* 2020. Available from: https://www.astrazeneca.com/media-centre/press-releases/2020/enhertu-granted-orphan-drug-designation-in-the-us-for-gastric-cancer.html [Accessed 16 Dec 2020].

11 American Cancer Society. *What is stomach cancer?* 2017. Available from: https://www.cancer.org/cancer/stomach-cancer/about/what-is-stomach-cancer.html [Accessed 13 Dec 2020].

12 Cancer Research UK. *What is stomach cancer?* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/stomach-cancer/about-stomach-cancer [Accessed 13 Dec 2020].

13 Cancer Research UK. *About gastro oesophageal junction cancer.* 2018. Available from: https://www.cancerresearchuk.org/about-cancer/gastro-oesophageal-junction-cancer/about [Accessed 13 Dec 2020].

14 Cancer Research UK. *What is advanced stomach cancer?* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/stomach-cancer/advanced-cancer/about-advanced-cancer [Accessed 13 Dec 2020].

15 NHS. *Stomach cancer - Causes.* 2019. Available from: https://www.nhs.uk/conditions/stomach-cancer/causes/ [Accessed 13 Dec 2020].

16 Zheng L, Wang L, Ajani J, Xie K. Molecular basis of gastric cancer development and progression. *Gastric Cancer*. 2004 Jun;7:61-77. Available from: https://doi.org/10.1007/s10120-004-0277-4.

17 Layke J, Lopez P. Gastric cancer: diagnosis and treatment options. *American Family Physician*. 2004 Mar;69(5):1133-41. Available from: https://www.aafp.org/afp/2004/0301/p1133.html.

18 Cancer Research UK. *Stomach cancer incidence.* 2020. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer#heading-Zero [Accessed 13 Dec 2020].

19 Cancer Research UK. *Stomach cancer survival.* 2020. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer#heading-Two [Accessed 13 Dec 2020].

20 National Cancer Intelligence Network. *Gastro-oesophageal junction cancers (ICD10 C15.2, C15.5, C16.0).* 2009. Available from: http://www.ncin.org.uk/view?rid=635 [Accessed 13 Dec 2020].
21 NHS Digital. *Hospital Episode Statistics for England. Admitted Patient Care statistics, 2019-20.* Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 [Accessed 16 Dec 2020].
22 Office for National Statistics (ONS). *Death registrations summary tables - England and Wales.* 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesenglandandwalesreferencetables [Accessed 13 Dec 2020].
23 Office for National Statistics (ONS). *Cancer survival in England - adults diagnosed between 2013-17.* Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed [Accessed 13 Dec 2020].
24 Cancer Research UK. *Stomach cancer - Treatment.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/stomach-cancer/treatment [Accessed 13 Dec 2020].
25 Cancer Research UK. *Chemotherapy for advanced cancer.* 2019. Available from: https://www.cancerresearchuk.org/about-cancer/stomach-cancer/treatment/advanced-treatment/advanced-chemotherapy [Accessed 13 Dec 2020].
26 Electronic Medicines Compendium (emc). *Lonsurf 15 mg/6.14 mg film-coated tablets - Therapeutic indications.* 2020. Available from: https://www.medicines.org.uk/emc/product/7309/smpc#INDICATIONS [Accessed 13 Dec 2020].
27 National Institute for Health and Care Excellence (NICE). *Trifluridine–tipiracil for treating metastatic gastric or gastro-oesophageal junction cancer after 2 or more therapies* (*GID-TA10456)*. Last Update Date: 05 Nov 2020. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10456 [Accessed 13 Dec 2020].
28 Ajani J, D'Amico T, Almhanna K, Bentrem D, Chao J, Das P, et al. Gastric Cancer, Version 3.2016, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network,*. 2016 Oct;14(10). Available from: https://doi.org/10.6004/jnccn.2016.0137.
29 Smyth E, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2016 Sep;27(supp. 5):v38-49. Available from: https://doi.org/10.1093/annonc/mdw350.
30 London Cancer Alliance. *LCA Oesophageal and Gastric Cancer Clinical Guidelines* 2014 Apr. Available from: https://rmpartners.nhs.uk/protocols-and-guidelines/ [Accessed 13 Dec 2020].
31 Allum W, Blazeby J, Griffin S, Cunningham D, Jankowski J, Wong R. Guidelines for the management of oesophageal and gastric cancer. *Gut*. 2011;60:1149-472. Available from: http://dx.doi.org/10.1136/gut.2010.228254.

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