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Newcastle University

Health Technology Briefing
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Trastuzumab deruxtecan for treating locally advanced, unresectable, or metastatic HER2+ solid tumours

Company/Developer	Daiichi Sankyo UK Ltd.

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 30328	NICE ID: Not available	UKPS ID: 672066

Licensing and Market Availability Plans

Currently in phase II clinical development.

Summary

Trastuzumab deruxtecan is in clinical development for treatment of unresectable (unable to be removed with surgery), locally advanced or metastatic (i.e., the cancer has spread to other tissues or organs) HER2+ solid tumours which have not responded to a prior treatment. HER2+ means that, due to a genetic mutation, the cancer cells produce a protein called HER2 in large quantities on their surface, making the tumour grow rapidly. Normally HER2 receptors are involved in controlled cell growth but in some cases, due to genetic mutations, these receptors can become overactive. HER2 overexpression is present in a relatively low percentage of solid tumours, but its presence has been linked with a more aggressive cancer development, a reduced response to generalised anticancer treatments and an increase in mortality. There are currently limited types of cancers with solid tumours that have approved treatments that target the HER2 mutations, indicating that there remains to be an unmet need for targeted therapies in other cancer types.

Trastuzumab deruxtecan is a HER2-targeted antibody-drug combination. The antibody (a type of protein) is specific to HER2 and so binds to HER2 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 unresectable, locally advanced or metastatic HER2+ solid tumours.

Proposed Indication

For the treatment of selected locally advanced, unresectable, or metastatic HER2 expressing solid tumours.[1]

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. In vitro studies indicate that the antibody portion of trastuzumab deruxtecan, which has the same amino acid sequence as trastuzumab, also binds to Fcγ RIIIa and complement C1q. The antibody mediates antibody-dependent cellular cytotoxicity in tumour cells that overexpress HER2.[2]

Trastuzumab deruxtecan is in clinical development for the treatment of unresectable, locally advanced or metastatic solid tumours with HER2 mutations. In the phase II clinical trial (DESTINY-PanTumor02, NCT04482309) participants are given 5.4 mg/kg of trastuzumab deruxtecan via intravenous (IV) infusion once every 3 weeks.[1,3]

Key Innovation

Human epidermal growth factor receptor 2 (HER2) is a transmembrane tyrosine kinase receptor involved in the stimulation of cell proliferation, differentiation, and survival. HER2 overexpression can occur in a range of solid tumours, including breast, gastric, biliary tract, bladder, pancreatic, and gynaecological tumours. HER2 overexpression is associated with a biologically aggressive tumour phenotype, poor prognosis, increased risk of disease recurrence, and limited benefit from chemotherapy.[3] HER2 targeting therapies are the standard of care for several HER2+ cancers (including breast cancers, gastric cancers, colorectal and gastroesophageal junction adenocarcinomas), however, many other HER2+ cancers with solid tumours are treated with standard therapies of chemoradiotherapy which have poor prognosis and limited alternatives.[3] The recent phase II trial, (DESTINY-PanTumour02), has reported results suggesting that trastuzumab deruxtecan may improve survival outcomes in HER2+ solid tumour cases.[3]

If licenced, trastuzumab deruxtecan would provide a HER2 specific treatment option for unresectable, locally advanced or metastatic HER2 IHC3+ solid tumours.

Regulatory & Development Status

Trastuzumab deruxtecan as a monotherapy has Marketing Authorisation in the EU/UK for the following indications:[2]

- The treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens
- The treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy
- The treatment of adult patients with advanced non-small cell lung cancer whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based

chemotherapy with or without immunotherapy
- The treatment of 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 the treatment of several cancer indications including:[4]
- Brain cancers
- Oesophageal cancer
- Gastroesophageal cancer
- Biliary tract cancer
- Early breast cancer
- Triple negative breast cancer
- Non-small cell lung cancer

Patient Group

Disease Area and Clinical Need

Solid tumours are abnormal masses of tissue that do not contain cysts or liquid areas, when these masses are caused by cancerous cells the tumour is considered to be malignant. These tumours may arise in most areas of the body, including epithelial neoplasms (e.g. lung carcinoma, prostate carcinoma, breast carcinoma, colon carcinoma), and neoplasms of the soft tissues and bones (e.g. leiomyosarcoma, liposarcoma, chondrosarcoma, osteosarcoma).[5] The symptoms of cancer can vary widely depending on where tumours have grown and the stage of disease. Common symptoms include coughing, chest pain, breathlessness, changes in bowel habits, swelling or lumps, unexplained weight loss and general fatigue or feeling unwell.[6] HER, including HER2 are a class of membrane bound protein receptors that activate several intracellular pathways leading to cell growth, development and division. HER2 overexpression has been linked with poor prognosis, with more aggressive cancer development and an increased lethality.[7] Unresectable tumours are tumours that are unable to be removed via surgery.[8] A locally advanced cancer means that cancerous cells have begun to spread from where they originated and begun to grow in nearby tissues; metastatic cancers occur when the cancerous cells spread through the blood or the lymphatic system, from the original site of the tumour to tissues or organs further away in the body.[9,10]

Several studies and meta analyses have suggested that HER2 amplification or overexpression are linked with poorer responses to non-targeted treatments and a decrease in survival rates.[11,12] Between 2017 and 2019 there were over 385,000 new cancer cases each year in the UK. Based on worldwide data it can be estimated that more than 90% of new cancer cases are solid cancers, including breast, lung, colorectal, and prostate cancer.[13,14]

Recommended Treatment Options

There are multiple treatment options currently available for solid tumours including:
surgery, chemotherapy, radiotherapy, hormone therapy, immunotherapies and targeted cancer drugs. The
treatment provided will vary according to type of cancer, how big the cancer it, how it has spread and according to the patients' general health.[15]

The National Institute for Health and Care Excellence (NICE) currently do not recommend any HER2 targeted treatment for the solid tumour types listed in the Clinical Trial Information table (population

section) below at this time.[16]

Clinical Trial Information	
Trial	DESTINY-PanTumor02, NCT04482309, EudraCT 2020-001574-29; A Phase 2 Study of T-DXd in Patients With Selected HER2 Expressing Tumors (DPT02) **Phase II**: Recruiting **Location(s)**: 6 EU countries, UK, USA, Canada and other countries **Primary completion date**: July 2027
Trial Design	Non-randomized, parallel assignment, open label
Population	N=468 (estimated); adults aged 18 years or older. The study consists of two parts, part 1 includes patients with a diagnosis of any of the following locally advanced, unresectable, or metastatic cancers based on most recent imaging: • biliary tract cancer • bladder cancer • cervical cancer • endometrial cancer • epithelial ovarian cancer • pancreatic cancer • rare tumours (classified here as patients with tumours that express HER2, excluding the tumours mentioned above, and breast, non-small cell lung cancer, gastric cancer, and colorectal cancer) Part 2 includes patients with metastatic or advanced solid tumours that are: • HER2 IHC 3+ • HER2 IHC 2+/ISH+ any tumour • solid endometrial cancer tumour(s) that is HER2 IHC 2+ or 1+ • ovarian cancer tumour(s) that is HER2 IHC 2+ or 1+ • solid cervical cancer tumour(s) that is HER2 IHC 2+ or 1+ Patients must have progressed following prior treatment or who have no satisfactory alternative treatment option
Intervention(s)	5.4 mg/kg of trastuzumab deruxtecan via IV infusion once every 3 weeks[3]
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: Objective response rate (ORR) (Time frame: an average of approximately 6 months) See trial for full list of other outcomes
Results (efficacy)	In all patients, the ORR was 37.1% (n = 99) with responses in all cohorts; the median duration of response (DOR) was 11.3 months; the median progression-free survival (PFS) was 6.9 months, and the median overall survival (OS) was 13.4 months.

	In patients with central HER2 IHC 3+ expression (n = 75), the ORR was 61.3%, the median DOR was 22.1 months, the median PFS was 11.9 months, and the median OS was 21.1 months.[3]
Results (safety)	Grade ≥3 drug-related adverse events were observed in 40.8% of patients; 10.5% experienced adjudicated drug-related interstitial lung disease, with three deaths.[3]

Estimated Cost

The NHS indicative cost of trastuzumab deruxtecan (100mg, powder of concentrate for solution for infusion vials) costs £1,455.[17]

Relevant Guidance

NICE Guidance

- NICE quality standard. Suspected cancer (QS124). June 2016.

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

No relevant guidance identified.

Additional Information

References

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