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Newcastle University

Health Technology Briefing
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Trastuzumab duocarmazine for third-line treatment of HER2-positive unresectable metastatic breast cancer

Company/Developer	Medac GmbH

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 23938	NICE TSID: 11855	UKPS ID: 668833

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Trastuzumab duocarmazine is in clinical development for the treatment of human epidermal growth factor receptor 2 positive (HER2+) metastatic breast cancer in adult patients. Breast cancer is the most common cancer in the UK. Breast cancer is when abnormal cells in the breast begin to grow and divide in an uncontrolled way and eventually form a growth (tumour). HER2+ means that the cancer expresses a lot of HER2 protein and are likely to grow and spread faster than HER2- cancer. Metastatic breast cancer describes cancer that has spread beyond the breast to other parts of the body. Affected patients often experience disease progression after standard treatment.

Trastuzumab duocarmazine is a specifically targeted drug therapy against the HER2 protein. Upon administration, trastuzumab duocarmazine binds to the HER2 proteins which can be found on the tumour cell surface. This in turn causes the tumour cell to engulf the drug, which then releases its active ingredient – duocarmazine. Duocarmazine then binds to the DNA within the cell, destroying proteins within the DNA, ultimately causing tumour cell death. Trastuzumab duocarmazine is administered intravenously. If approved, trastuzumab duocarmazine would offer an effective additional treatment option for patients with HER2+ metastatic breast cancer, when other treatment options have been exhausted.

Proposed Indication

Treatment of adults with human epidermal growth factor receptor 2 positive (HER2+) metastatic breast cancer after at least two HER2-targeting treatment regimens or after (ado-)trastuzumab emtansine treatment.[1]

Technology

Description

[Vic]-trastuzumab duocarmazine (SYD985, Synthon) incorporates Byondis' distinctive, proprietary duocarmazine linker-drug (LD) technology ByonZine®.[2] The antibody drug conjugate (ADC) is comprised of the anti-HER2 monoclonal antibody trastuzumab and a cleavable linker-drug called valine-citrulline-seco-DUocarmycin-hydroxyBenzamide-Azaindole (vc-seco-DUBA). The antibody part of trastuzumab duocarmazine binds to HER2 on the surface of the cancer cell and the ADC is internalised by the cell. After proteolytic cleavage of the linker, the inactive cytotoxin is activated and DNA damage is induced, resulting in tumour cell death.[3]

Trastuzumab duocarmazine is in development for treatment of patients with HER2+ metastatic breast cancer. In the phase III clinical trial (TULIP; NCT03262935), patients will be administered (vic-) trastuzumab duocarmazine intravenously every 3 weeks.[1]

Key Innovation

HER2+ breast cancer presents a more aggressive from of the disease, greater likelihood of recurrence and poorer prognosis. Trastuzumab duocarmazine provides a much needed alternate for HER2+ breast cancer patients.[4] Trastuzumab duocarmazine improved progression-free survival for patients with pre-treated, metastatic HER2+ breast cancer when compared with physician's choice chemotherapy.[1,5] Trastuzumab duocarmazine novel mechanism-of-action, will provide an additional ADC option which is still efficacious when other ADC therapies have been exhausted.[4] In addition, trastuzumab duocarmazine is an ADC that is highly stable in circulation and carry an intricate, inactivated and potent cytotoxic drug that rapidly self-destructs if prematurely released, limiting damage to healthy tissue and improving the therapeutic window.[6]

If licensed, trastuzumab duocarmazine would offer an additional treatment option for patients with HER2+ metastatic breast cancer.

Regulatory & Development Status

Trastuzumab duocarmazine does not currently have marketing authorisation in the EU/UK for any indication.

Trastuzumab duocarmazine is also currently in phase II development for other indications including:[7]

Other metastatic breast cancer.
Metastatic endometrial carcinoma.
Ocular toxicity
Other solid tumours
Trastuzumab duocarmazine was granted FDA fast track designation for pre-treated HER2-positive metastatic breast cancer.[8]

Patient Group

Disease Area and Clinical Need

Breast cancer is the most common type of cancer in the UK. Most women diagnosed with breast cancer are over the age of 50 years, but younger women can also get breast cancer.[9] Breast cancer is when abnormal cells in the breast begin to grow and divide in an uncontrolled way and eventually form a growth (tumour). Breast cancer starts in the breast tissue, most commonly in the cells that line the milk ducts of the breast.[10] Risk factors known to affect your likelihood of developing breast cancer are: age, most common in women over 50 years. Family history - a patient with close relatives who have had breast cancer of may be at higher risk. Genetics; BReast CAncer gene (BRCA) 1 and BRCA2 can increase your risk of developing breast cancer.[11] HER2+ breast cancer means that the breast tumour expresses HER2 proteins. This type of cancer tends to be more aggressive than HER2-negative breast cancers.[12]

Breast cancer is the most common cancer in the UK, accounting for 15% of all new cancer cases (2016-2018).[13] In England, there were 46,109 registrations of newly diagnosed cases of malignant neoplasm of breast (ICD-10 code C50), and the directly age-standardised rates per 100,000 population were 166.7 among females and 1.3 among males.[14] In 2021-22, there were 205,082 finished consultant episodes (FCEs) for malignant neoplasm of breast (ICD-10 code C50), and 201,297 admissions resulting in 48,154 bed days and 174,668 day cases.[15] In England (2017) there were 9,569 deaths due to malignant neoplasm of the breast; the directly age-standardised rates per 100,000 population of registrations of death from malignant neoplasm of the breast were 33.3 and 0.3 for females and males respectively.[14] For adult women in England diagnosed with stage IV breast cancer between 2013 and 2017, the 1-year and 5-year age standardised survival rate was 66% and 26.2% respectively.[16]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends the following pharmacological therapies for the third line treatment of adult patients with HER2+ metastatic breast cancer:[17-20]

- Trastuzumab deruxtecan.
- Tucatinib with trastuzumab and capecitabine.
- Trastuzumab emtansine
- Erilbulin

Clinical Trial Information

Trial	TULIP; NCT03262935; A Multi-centre, Open-label, Randomized Clinical Trial Comparing the Efficacy and Safety of the Antibody-drug Conjugate SYD985 to Physician's Choice in Patients with HER2-positive Unrespectable Locally Advanced or Metastatic Breast Cancer. **Phase III** – Active, not recruiting. **Location(s):** UK, 7 EU countries, USA, Canada, and Singapore **Primary Completion Date:** July 2021.
Trial Design	Randomised, parallel assignment, open-label.
Population	N = 436 participants; 18 years and older, female, histologically confirmed, unresectable locally advanced or metastatic breast cancer, HER2-positive tumour

Intervention(s)	(vic-) trastuzumab duocarmazine, administered intravenously every 3 weeks.
Comparator(s)	Lapatinib Capecitabine Trastuzumab Vinorelbine Eribulin
Outcome(s)	Progression Free Survival [Time frame: Up to 2 years from baseline] See trial record for full list of other outcomes
Results (efficacy)	Preliminary results: The primary endpoint of centrally reviewed improved progression-free survival (PFS) was met, with a centrally reviewed median PFS of 7.0 months (95% CI, 5.4-7.2 months; *P* = .002) for patients on [vic] trastuzumab duocarmazine compared with 4.9 months (95% CI, 4.0-5.5 months) for physician's choice chemotherapy. Investigator-assessed PFS was also better with [vic]-trastuzumab duocarmazine, at 6.9 months (95% CI, 6.0-7.2 months) versus 4.6 months (95% CI, 4.0-5.6 months). Secondary endpoints included overall survival (OS), which was 20.4 months and 16.3 months, (HR, 0.83; 95% CI, 0.62-1.09; P = .153), which was not statistically significant. Overall response rate (ORR) and health-related quality of life (HRQoL) were also secondary endpoints, though there was no statistically significant difference between [vic]-trastuzumab duocarmazine and physician's choice chemotherapy observed in the study.[4]
Results (safety)	Preliminary results: the most frequently observed adverse events (AEs) for [vic] trastuzumab duocarmazine were conjunctivitis (38.2%), keratitis (38.2%), and fatigue (33.3%). Interstitial lung disease/pneumonitis occurred in 7.6% of patients on the drug, including 5.2% grade 1-2 events, and 2 grade 5 events. More than a third (35.4%) of patients discontinued treatment with [vic]-trastuzumab duocarmazine due to adverse events, most frequently citing eye disorders (20.8%) or respiratory disorders (6.3%).

Estimated Cost

The cost of trastuzumab duocarmazine is currently unknown.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Tucatinib with trastuzumab emtansine for treating HER2-positive unresectable or advanced breast cancer after a taxane, trastuzumab or both together [TA11110]. Expected publication date: TBC.
- NICE technology appraisal. Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies [TA786]. April 2022.
- NICE technology appraisal. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies [TA704]. May 2021.

- NICE technology appraisal. Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane [TA458]. July 2018. Last updated: November 2017.
- NICE technology appraisal. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens [TA423]. December 2016.
- NICE clinical guideline. Early and locally advanced breast cancer: diagnosis and treatment (NG101). July 2018.
- NICE clinical guideline. Advanced breast cancer: diagnosis and treatment (CG81). February 2009, updated August 2017.

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

- European Society of Medical Oncology (ESMO). ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. December 2021.[21]
- American Society of Clinical Oncology. Current and Future Management of HER2-Positive Metastatic Breast Cancer. October 2021.[22]
- National Comprehensive Cancer Network (NCCN). Breast Cancer, Version 2022, NCCN Guidelines for Patient; Metastatic Breast cancer. Dec 2021.[23]
- Journal of Clinical Oncology. Management of Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases: ASCO Guideline Update. May, 2022.[24]

Additional Information

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