Trastuzumab emtansine

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.2. Targeted therapies

ATC codes: L01FD03

Indication	Carcinoma of breast, specialised type ICD11 code: 2C60
INN	Trastuzumab emtansine
Medicine type	Biological agent
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 100 mg in vial powder for injection ; 160 mg in vial powder for injection
EML status history	Application rejected in 2017 (TRS 1006) Application rejected in 2019 (TRS 1021)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Trastuzumab emtansine
DrugBank	Trastuzumab emtansine

Expert Committee recommendation

The Committee endorsed the recommendations of the EML Cancer Medicine Working Group with regard to the proposed threshold of four to six months of overall survival benefit as a guiding principle for prioritizing cancer medicines for inclusion on the EML, and applied this principle to the consideration of trastuzumab emtansine. The Committee acknowledged that for second-line treatment of metastatic breast cancer, trastuzumab emtansine was associated with a relevant survival benefit, within the range of the established threshold. However, the Committee noted that survival benefits did not meet the four to six month threshold when trastuzumab emtansine was used as first-line treatment in the metastatic setting, or in early stage breast cancer. Existing EML-listed options are available for metastatic disease and may be suitable alternatives (e.g., trastuzumab, taxanes, etc.). However, the Committee noted the current challenges in achieving full access to trastuzumab in many settings. Taking this into account, trastuzumab emtansine for secondline treatment of metastatic disease (i.e. late in the care pathway) was considered to be a lower priority for EML inclusion at this time. Compared to the 2017 application, the Committee noted that few new clinical data were included in the current application and that the request was not based on a comprehensive review encompassing additional breast cancer medicines, compared with the standard of care, which would allow countries to understand the additional value of adding each option to national EMLs. The Expert Committee therefore did not recommend the addition of trastuzumab emtansine to the complementary list of the

EML for the treatment of unresectable, locally advanced and metastatic HER2-positive breast cancer.

Background

The application requested the addition of trastuzumab emtansine (T-DM1) to the complementary list of the EML for the treatment of unresectable, locally advanced and metastatic human epidermal growth factor receptor 2 (HER2)- positive breast cancer. Trastuzumab emtansine (T-DM1), as a single agent, is indicated for the treatment of adult patients with human epidermal growth factor receptor 2 (HER2)- positive, unresectable locally advanced or metastatic breast cancer (MBC) who had previously received trastuzumab and a taxane, separately or in combination. Both trastuzumab and taxanes are already included in the WHO Model List. T-DM1 was considered for inclusion on the EML by the Expert Committee in 2017 and was not recommended. At that time the Committee acknowledged the significant public health burden of breast cancer and noted the availability of other medicines for this condition (e.g. pertuzumab, lapatinib), which have never been proposed for evaluation for inclusion on the EML. The Committee considered that it would have been preferable to consider T-DM1 as part of a comprehensive review encompassing additional medicines, compared with the standard of care, better understanding the additional value and implications of adding them to national EMLs. Trastuzumab is currently included on the EML for treatment of metastatic HER2-positive breast cancer. EML-listed cytotoxic medicines for metastatic breast cancer include capecitabine, cyclophosphamide, docetaxel, doxorubicin, paclitaxel and vinorelbine. EML-listed hormonal therapies for MBC include anastrozole and tamoxifen.

Public health relevance

Breast cancer is the leading cause of cancer death among women globally, responsible for 15% of all cancer deaths. In 2018, the global cancer burden increased to 18.1 million cases, causing 9.6 million deaths (1). Changes in lifestyle, life expectancy and reproductive factors are responsible in many lowand middle-income countries (LMICs) for a sharp increase in the incidence of breast cancer, and the number of deaths as a percentage of incident cases is greater than that seen in high-income countries. For example, in 2008, this figure was 24% in high-income countries, 38% in high-middle-income countries, 40% in low-middle-income and 48% in low-income (2). The HER2 receptor has emerged as one of the most important targets for the treatment of breast cancer. HER2 is involved in regulating cell growth, survival, and differentiation (3). Amplification and/or overexpression of HER2 occurs in approximately 18%–22% of breast cancers (4, 5). HER2 amplification/overexpression (HER2-positivity) is associated with increased tumour aggressiveness, higher rates of recurrence, and increased mortality (5– 10). The median age of patients presenting with HER2-positive breast cancer is in the mid-50s, approximately five years younger than the general breast cancer population (11). At the early stage, breast cancer is usually operable and can be treated with curative intent. However, approximately 20%–35% of patients experience relapse (12) and those with metastatic or unresectable disease are generally incurable. Such tumours often continue to express high levels of HER2 (13). Patients with metastatic disease have a 5-year life expectancy of approximately 18% in Europe (14).

Benefits

Locally advanced and metastatic breast cancer The efficacy of single-agent T-DM1 at a dose of 3.6 mg/kg every three weeks has been investigated in Phase II and III trials in HER2-positive advanced breast cancer. The pivotal Phase III EMILIA trial was a randomized, multicentre, international, two-arm, open-label clinical trial that evaluated the efficacy and safety of treatment with T-DM1 was compared with the efficacy and safety of treatment with lapatinib plus capecitabine in 991 patients with HER2-positive, unresectable, locally advanced or metastatic breast cancer who had been previously treated with trastuzumab and a taxane (15, 16). The primary efficacy endpoints were overall survival (OS) and independent review committeeassessed progression-free survival (PFS). The study demonstrated a statistically significant improvement in both PFS (9.6 months vs 6.4 months, HR 0.65, 95%CI 0.59 to 0.77) and OS (30.9 months vs 25.1 months, HR 0.68, 95%CI 0.55 to 0.85) for T-DM1 compared with lapatinib plus capecitabine. The final OS analysis was scheduled to be conducted after the occurrence of 632 deaths. At the data cut-off date for this analysis (December 2014), median OS was prolonged in patients treated with T-DM1 (29.9 months) when compared with patients treated with capecitabine plus lapatinib (25.9 months; HR

0.75, 95%CI 0.64 to 0.88) (16). The comparator regimen of lapatinib plus capecitabine used in the EMILIA trial has not been considered for inclusion on the Model List. The Phase III TH3RESA trial was a randomized, open-label, multicentre trial that compared T-DM1 with treatment of physician's choice in 602 patients with progressive HER2-positive advanced breast cancer, previously treated with at least two HER2-directed regimens (17, 18). The study demonstrated a statistically significant improvement in both PFS (6.2 months vs 3.3 months, HR 0.53, 95%CI 0.42 to 0.66) and OS (median not reached at that time vs 14.9, HR 0.55, 95%CI 0.37 to 0.83) for T-DM1 compared with treatment of physician's choice (17). At the data cut-off date for final OS analysis (February 2015), median OS was prolonged in patients treated with T-DM1 compared with treatment of physician's choice (22.7 months vs 15.8 months; HR 0.68, 95%CI 0.54 to 0.85) (18). Early breast cancer The Phase III KRISTINE study evaluated neoadjuvant T-DM1 plus pertuzumab compared with docetaxel, carboplatin and trastuzumab plus pertuzumab in 444 patients with HER2-positive early breast cancer (19). The study found that total pathological complete response rates (a surrogate outcome for survival) were higher in patients receiving trastuzumab emtansine plus pertuzumab or docetaxel, carboplatin, than trastuzumab plus pertuzumab. However, OS was not significantly different between treatment groups (HR 1.21, 95%CI 0.37 to 3.96). Event-free survival significantly favoured trastuzumab-containing regimens, without T-DM1 (HR 2.61, 95%CI 1.36 to 4.98) (20). In the KATHERINE study, adjuvant T-DM1 significantly improved Invasive disease–free survival rates compared to trastuzumab group in 1486 patients with residual disease following neoadjuvant chemotherapy plus trastuzumab-based anti-HER2 treatment (HR for invasive disease or death 0.50, 95%CI 0.39 to 0.64) (21). OS did not significantly differ (HR 0.70, 95%CI 0.47 to 1.05). These results are based on an early interim analysis based on few events.

Harms

The safety profile of T-DM1 in MBC is based on pooled data from 1871 patients receiving single-agent T-DM1 treatment at 3.6 mg/kg every three weeks (Studies TDM3569g, TDM4258g, TDM4374g, TDM4688g, TDM4450g/BO21976, TDM4370g/BO21977, TDM4788g/BO22589, TDM4997g/BO25734 and TDM4529g/BO25430). The most common adverse events (AEs) for singleagent T-DM1 (AEs in ≥25% of patients) were nausea, fatigue and headache (22). The Phase III EMILIA study compared T-DM1 with lapatinib plus capecitabine treatment, in patients with HER2-positive locally-advanced or metastatic breast cancer (15). In accordance with the differing mechanisms of action, the safety profile of T-DM1 was different from that of lapatinib plus capecitabine, as shown by differences in incidence of common AEs. In the T-DM1 arm, the most common events (occurring in at least 25% of patients) were nausea, fatigue, thrombocytopenia, headache, constipation, diarrhoea and increased aspartate aminotransferase, whereas the most common events associated with lapatinib plus capecitabine treatment were diarrhoea, palmarplantar erythrodysesthesia syndrome, nausea, vomiting, fatigue and rash (Roche, data on file). Fewer patients were reported with AEs of Grade 3 or higher, and serious adverse events (SAEs) in the T-DM1 arm than in the lapatinib plus capecitabine arm. In the Phase III TH3RESA study, fewer patients receiving T-DM1 than those receiving treatment of physician's choice had AEs of Grade 3 or higher. Grade 3 or higher thrombocytopenia was reported more frequently in patients receiving T-DM1 (≥2% more patients than in the TPC arm), whereas patients receiving TPC reported more Grade ≥3 neutropenia, leukopenia, febrile neutropenia and diarrhoea (17). Cardiac safety of T-DM1 in patients with early breast cancer was evaluated in the Phase II study TDM4874g/BO22857 (23). There were no events of symptomatic heart failure. One patient discontinued T-DM1 treatment as a result of an asymptomatic left ventricular ejection fraction (LVEF) decline. The most common AEs while receiving T-DM1 (in at least 20% of patients) were nausea, headache, epistaxis, asthenia, pyrexia, fatigue, arthralgia, thrombocytopenia and myalgia. The most common Grade 3 or higher AEs (>2%) reported while receiving T-DM1 were thrombocytopenia, alanine transaminase (ALT) increase, aspartate aminotransferase (AST) increase, neutropenia, and hypertension; all of which occurred in less than 10% of patients. In the neoadjuvant KRISTINE (BO28408) study, safety was better in the T-DM1 + pertuzumab arm compared with trastuzumab, pertuzumab plus chemotherapy, with a lower incidence of, Grade 3 or higher: 13.0% in the T-DM1 + pertuzumab arm vs 64.4% in the trastuzumab, pertuzumab plus chemotherapy arm; serious AEs: 4.9% in T-DM1 + pertuzumab arm vs 28.8% in trastuzumab, pertuzumab plus chemotherapy arm; and AEs leading to treatment discontinuation: 3.1% in the T-DM1 + pertuzumab arm vs 8.7% in the trastuzumab, pertuzumab plus chemotherapy arm. The most common Grade 3–4 adverse events in the docetaxel, carboplatin, and trastuzumab plus pertuzumab group were

neutropenia (55 [25%] of 219 vs one [<1%] of 223 with T-DM1 plus pertuzumab), diarrhoea (33 [15%] vs 2 [<1%]), and febrile neutropenia (33 [15%] vs 0). No deaths were reported during neoadjuvant treatment (19). The overall safety profile of the T-DM1 arm in the adjuvant KATHERINE (BO27938) study was consistent with the known safety profile of T-DM1 (21). Any-grade AEs were more common in the T-DM1 arm (98.8% vs 93.3%). Adverse events leading to randomized treatment discontinuation occurred in 133 (18.0%) T-DM1–treated patients and 15 (2.1%) trastuzumab-treated patients. The most common adverse events leading to discontinuation in the T-DM1 arm were laboratory abnormalities (platelet count decreased (4.2%), blood bilirubin increased (2.6%), aspartate aminotransferase increased (1.6%), alanine aminotransferase increased (1.5%)), peripheral sensory neuropathy (1.5%), and ejection fraction decreased (1.2%). The most common Grade 3 or higher adverse events were decreased platelet count (5.7%) and hypertension (2.0%) in the T-DM1 group. Serious adverse events occurred in 94 patients (12.7%) receiving T-DM1. One fatal adverse event of intracranial haemorrhage after subject fall occurred in the T-DM1 arm. Adjudicated cardiac events occurred in four patients (0.6%) in the trastuzumab arm and in one patient in the T-DM1 arm (0.1%).

Additional evidence

The following is a summary of additional evidence presented as part of the 2017 Expert Committee consideration of T-DM1 in 2017 (24). A 2016 meta-analysis of nine studies evaluated the safety and efficacy of T-DM1 in advanced HER2-positive breast cancer. The overall hazard ratios for PFS and OS were calculated by meta-analysing, respectively, three (EMILIA (15), TH3RESA (17), BO21976 (25)) and two (EMILIA, TH3RESA,) controlled trials. Median PFS significantly favoured T-DM1; difference ranged from 2.9 months to 5 months (total HR 0.60; 95%CI 0.53 to 0.69). Cumulative OS was associated with an improved survival for T-DM1 compared with treatment physician's choice (odds ratio (OR) 0.60; 95%CI 0.48 to 0.75). Heterogeneity was low in both analyses. The National Institute for Health and Care Excellence (NICE) published its technology appraisal for T-DM1, assessing efficacy and cost–effectiveness (26–28). As part of the process, NICE reviewed evidence submitted by Roche, clinical experts and other stakeholders; clinical evidence came primarily from EMILIA and TH3RESA clinical trials. Because head-to-head treatment comparisons were available only for lapatinib in combination with capecitabine (LC), the company conducted a Bayesian network meta-analysis using a fixedeffect model involving five clinical trials (EMILIA, CEREBEL, EGF100151, NCT00777101 and GBG26). NICE's Evidence Review Group (ERG), reviewing Roche's submission, repeated the network meta-analysis using a random-effects model. From the ERG's model, compared with LC, T-DM1 was associated with a 32% decrease in hazard of death (HR 0.68, 95% credible Interval (CrI) 0.37 to 1.25) and a 35% reduction in the hazard of tumour progression or death (HR 0.65, 95%CrI 0.35 to 1.20). However, the authors report that CrI values "do not rule out the possibility that T-DM1 is less efficacious than comparators" (28). After analysing the technology appraisal, NICE concluded that T-DM1 was clinically effective for treatment for HER2-positive, unresectable, locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane, but ultimately did not find it to be cost effective at the price that Roche was offering at the time (27). Comparison with trastuzumab Trastuzumab is associated with relevant benefits in HER2-positive breast cancer patients. In a systematic review of eight studies, total 11 991 patients, the combined HRs for OS and disease-free survival (DFS) significantly favoured trastuzumab-containing regimens (HR 0.66, 95%CI 0.57 to 0.77; p<0.00001; and HR 0.60, 95%CI 0.50 to 0.71; p<0.00001, respectively) (29). Currently, a combination of trastuzumab with a taxane is considered to be the standard of care (i.e. first-line) in metastatic breast cancer. Medicines in this regimen are included on the WHO EML. The Phase III MARIANNE randomized controlled trial studied untreated HER2-positive metastatic breast cancer patients receiving T-DM1 plus pertuzumab, T-DM1 plus placebo, or a combination of trastuzumab with a taxane (paclitaxel or docetaxel) (30, 31). At the cut-off date of May 2016, therapies containing T-DM1 were non-inferior to trastuzumab and taxane treatments for PFS. However, OS curves essentially overlapped (trastuzumab + taxane vs trastuzumab emtansine + placebo, HR 0.93, 95%CI 0.73 to 1.20; trastuzumab + taxane vs trastuzumab emtansine + pertuzumab HR 0.86, 95%CI 0.67 to 1.11) with survival medians approaching one another (trastuzumab + taxane 50.86 months, trastuzumab emtansine + placebo 53.68, trastuzumab emtansine + pertuzumab 51.78) (32). T-DM1 was better tolerated, contributing to better quality of life secondary endpoints and less treatment discontinuation related to adverse events (31).

Cost / cost effectiveness

A Canadian study demonstrated that the use of T-DM1 for the management of HER2-positive metastatic breast cancer results in substantial savings to the public health care system when the costs of treatment related AEs are taken into account, due to less toxicity compared with lapatinib plus capecitabine (33). The findings were confirmed in sensitivity analyses in which the number and costs of AEs were changed, however, the magnitude of cost savings varied. Whether the same findings would be realized in other countries and health care systems is not known. T-DM1 has been accepted as a cost-effective treatment option in eligible patients with HER2-positive metastatic breast cancer in the United Kingdom (34), Canada (35), Australia (36), Scotland (37), Ireland (38), France (39), and Sweden (40).

WHO guidelines

None available.

Availability

T-DM1 was first granted marketing approval in United States on February 2013, followed by the European Union (EU) and Japan in the same year. As of 15 November 2018, T-DM1 has been approved in more than 100 countries worldwide.

Other considerations

Based on results of the EMILIA study (15, 41), T-DM1 received a score of 4 on the ESMO-MCBS v1.1 for use in the metastatic breast cancer setting as secondline therapy after trastuzumab failure (42). The U.S. National Comprehensive Cancer Network (NCCN) v3, 25 October 2018 clinical guidelines and compendium recommend use of T-DM1 as a first-line treatment option for patients with HER2-positive MBC in patients not eligible for pertuzumab-trastuzumab plus a taxane. Based on the trial data from Study BO22589/TDM4788g that demonstrated T-DM1 is noninferior with better quality of life compared with trastuzumab plus taxane, and possibly better tolerated for some patients, the NCCN panel included T-DM1 as one of the first-line options for the treatment of patients with HER2-positive MBC. Pertuzumab, trastuzumab, and a taxane, however, remain the preferred firstline regimen for HER2-positive metastatic disease based on data demonstrating improved overall survival compared with trastuzumab and a taxane. T-DM1 as first-line therapy should be considered only in patients not suitable for the preferred treatment (43). The American Society of Clinical Oncology (ASCO) clinical practice guideline recommends the use of T-DM1 for the treatment of HER2-positive advanced breast cancer that has progressed during or after first-line HER2- targeted therapy (Evidence quality: High; Strength of recommendation: Strong) (44). The same guideline also recommends the use of T-DM1 in patients whose HER2-positive breast cancer has progressed during or after second-line or greater HER2-targeted therapy if they have not previously been treated with T-DM1 (44). Updated European Society for Medical Oncology (ESMO) guidelines recommend T-DM1 in patients who have progressed through at least one line of trastuzumab-based therapy based on its OS benefit (Category IA) (45). Comments on the application were received from the WHO Department of Management of NCDs, Disability, Violence and Injury Prevention. The technical unit advised that it did not support inclusion of trastuzumab emtansine on the EML at this time, though noting recent studies demonstrating its utility as second-line therapy in metastatic and non-metastatic settings. At the current time, given the narrow gain in overall survival and small benefit on disease control, the technical unit considered that trastuzumab did not currently meet criteria as a priority medicine for breast cancer.

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