

# Committee to Evaluate Drugs (CED)

## Recommendations and Reasons

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### Trastuzumab emtansine

**Product:** trastuzumab emtansine (T-DM1; Kadcycla®)

**Class of Drugs:** anti-HER2 monoclonal antibody-drug conjugate

**Reason for Use:** HER2-positive, unresectable locally advanced or metastatic breast cancer

**Manufacturer:** Hoffmann-La Roche Ltd.

**Date of Review:** January 15, 2014

### CED Recommendation

The CED noted that trastuzumab emtansine (T-DM1; Kadcycla®) has been shown to improve overall survival and progression-free survival when used as a second-line treatment for locally advanced or metastatic breast cancer. Due to concerns with cost-effectiveness, the CED recommended T-DM1 not be funded. This recommendation is aligned with the pan-Canadian Oncology Review recommendation.

### Executive Officer Decision\*

Based on the CED's recommendation and an agreement with the manufacturer to help address concerns raised by the CED, the Executive Officer decided to fund trastuzumab emtansine (T-DM1; Kadcycla®) for the treatment of locally advanced or metastatic breast cancer according to specific criteria.

### Funding Status\*

Funded through Cancer Care Ontario's New Drug Funding Program according to specific criteria.

*\* This information is current as of the posting date of the document. For the most up-to-date information on Executive Officer decision and funding status, see: [www.health.gov.on.ca/en/pro/programs/drugs/status\\_single\\_source\\_subm.aspx](http://www.health.gov.on.ca/en/pro/programs/drugs/status_single_source_subm.aspx).*

## Highlights of Recommendation:

- The EMILIA study showed that trastuzumab emtansine (T-DM1), compared with lapatinib plus capecitabine (an alternative treatment regimen) improved overall survival and progression-free survival in the second-line treatment of locally advanced or metastatic breast cancer.
- The study also showed that T-DM1 increased the length of time before a patient's quality of life deteriorated.
- The side-effect profile of T-DM1 appears favourable when compared to combination treatment with lapatinib and capecitabine.
- At the recommended dose, the average cost per 28-day course of T-DM1 is \$6,720. Based on economic analyses conducted by the pan-Oncology Drug Review, T-DM1 was not considered to be cost-effective.

## Background:

Breast cancer is the most commonly diagnosed cancer in Canadian women. Approximately 15-20% of all breast cancers are positive for human epidermal growth factor receptor 2 (HER2). Trastuzumab (Herceptin<sup>®</sup>) was the first agent developed to target the HER2 pathway, and trastuzumab in combination with a taxane is now recommended as initial (i.e. first-line) therapy for women with HER2-positive metastatic breast cancer (mBC). Despite the use of trastuzumab, the majority of patients with mBC experience disease progression.

Trastuzumab emtansine (abbreviated as T-DM1) is a combined antibody-drug product whereby trastuzumab is linked to the cytotoxic agent DM1.

## Detailed Discussions:

- For this evaluation, the CED considered:
  - Findings from the pan-Canadian Oncology Drug Review (pCODR) and the recommendation of the pCODR Expert Review Committee;
  - Information in the manufacturer's submission;
  - Patient group submissions received by Ontario and by pCODR.
  - Feedback from Cancer Care Ontario's Breast Disease Site Group.
- The CED evaluated one open-label, randomized controlled superiority trial, EMILIA, comparing T-DM1 to lapatinib plus capecitabine as second-line treatment for locally advanced or metastatic breast cancer (mBC).
- The EMILIA study had two co-primary efficacy endpoints, progression-free survival (PFS) and overall survival (OS). Statistically significant differences in OS (median 30.9 months versus 25.1 months; HR: 0.68, 95% CI: 0.55-0.85) and in PFS (median 9.6 months versus 6.4 months; HR: 0.65, 95% CI: 0.55-0.77) were demonstrated in favour of T-DM1 compared to lapatinib plus capecitabine. These benefits were considered to be clinically meaningful.
- The study evaluated the time before there was a deterioration in the patient's quality of life (QOL). The median time to a decline in QOL was longer in the T-DM1 group compared to

the lapatinib plus capecitabine group (7.1 months vs. 4.6 months; HR: 0.80, 95% CI: 0.67-0.95, p=0.012).

- There were no unexpected safety concerns seen with T-DM1. Its tolerability was considered acceptable relative to other cancer treatments, and appeared favourable when compared to the combination of lapatinib plus capecitabine.
- The CED also discussed the use of T-DM1 as a third-line therapy for mBC. A large subgroup of patients in the EMELIA study received T-DM1 as a third-line therapy or beyond. A pre-specified analysis in this subgroup demonstrated that there was a statistically significant difference in investigator-assessed PFS in favour of T-DM1 compared to lapatinib plus capecitabine (HR 0.69, 95% CI 0.55 to 0.86). In addition, an interim analysis from TH3RESA, a randomized controlled trial comparing T-DM1 to treatment of physician's choice for patients with HER2-positive mBC who have received at least two lines of prior HER-2 targeted therapy, showed that third-line patients receiving T-DM1 had improved PFS compared to physician's treatment of choice. Although the OS data from the TH3RESA study is not yet mature, a trend towards improved OS with T-DM1 was seen. The CED noted that T-DM1 could provide clinical benefit in the third-line setting or beyond.
- At the submitted price, T-DM1 costs \$2,000 per 100 mg vial and \$3,200 for 160 mg vial. At the recommended dose of 3.6 mg/kg every 21 days, the average cost per 28-day course is \$6,720. Based on analyses conducted by pCODR, T-DM1 was not considered to be cost-effective when compared to lapatinib plus capecitabine as a second-line treatment.
- The CED reviewed patient groups submissions received by Ontario and by pCODR. The submissions highlighted the burden of illness associated with metastatic breast cancer. Patients expressed concerns regarding the high drug costs and emphasized the importance of access to funding.
- Overall, the EMELIA study demonstrated that there were statistically and clinically significant improvements in both overall survival and progression-free survival for T-DM1 when compared to lapatinib plus capecitabine in the second-line treatment setting of metastatic breast cancer. The drug was not cost-effective.

### **Committee to Evaluate Drugs (CED)**

The Committee to Evaluate Drugs (CED) is comprised of practicing physicians, pharmacists, health economists, and patient representatives. In conducting its review, the CED considers data contained in the drug manufacturer's submission, input provided by patient groups, findings from the national Common Drug Review and the pan-Canadian Oncology Drug Review, and other scientific information as necessary.

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