



# **pan-Canadian Oncology Drug Review Final Economic Guidance Report**

## **Trastuzumab Emtansine (Kadcyla) Metastatic Breast Cancer**

September 19, 2014

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## **FUNDING**

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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# 1 ECONOMIC GUIDANCE IN BRIEF

## 1.1 Background

The main analysis submitted to pCODR by Hofmann-La Roche is a cost-utility and cost-effectiveness analysis that compared trastuzumab emtansine (Kadcyla) to lapatinib plus capecitabine as a second-line treatment for patients with HER2-positive, unresectable locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane. Trastuzumab emtansine (T-DM1) is administered intravenously and both lapatinib and capecitabine are administered orally. In addition, an indirect analysis was submitted and compared trastuzumab emtansine (Kadcyla) to capecitabine plus trastuzumab

**According to the pCODR Clinical Guidance Panel (CGP)**, this comparison is appropriate as lapatinib plus capecitabine is the standard of care in patients with HER2-positive, unresectable locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane. The comparator for the secondary analysis, capecitabine plus trastuzumab, is also considered appropriate.

**Patient advocacy group input** considered the following factors important in the review of trastuzumab emtansine, which are relevant to the economic analysis: adverse effects, and progression-free survival. A full summary of the patient advocacy group input is provided in the pCODR Clinical Guidance Report. These factors that were identified as important to patients were addressed in the economic analysis as follows:

- The submitter incorporated the occurrence of adverse effects by estimating utilities for the model based on their occurrence of observed adverse effects in the trial.
- The analysis took into account progression-free survival, extrapolating the data from that available from the clinical trial.

**The Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for trastuzumab emtansine, and which are relevant to the economic analysis: use of trastuzumab emtansine following pertuzumab, which pending a pERC recommendation may change the first line setting treatment; lapatinib plus capecitabine may not be appropriate for all jurisdictions as a second line treatment as uptake may be limited in some jurisdictions; and wastage. A full summary of the Provincial Advisory Group input is provided in the pCODR Clinical Guidance Report.

- As there is no clinical evidence of trastuzumab emtansine following pertuzumab, this was not addressed in the clinical model. The other factors that were identified as important by the PAG were addressed in the economic analysis as follows:
- A comparator of trastuzumab + capecitabine was considered as an indirect comparison, though this comparison was not based on randomized controlled trial data and the quality of the data limits the generalizability of the results. PAG indicated that uptake of 2<sup>nd</sup> line lapatinib + capecitabine may be limited and in some jurisdictions trastuzumab + chemotherapy is currently an alternative 2<sup>nd</sup> line treatment and considered it as a more relevant comparator.
- Wastage was not considered as part of the main analysis, but was considered in a modified analysis.

Trastuzumab emtansine costs \$2508 and \$4012.80 per 100mg and 160mg vial, respectively. At the recommended dose of 3.6 mg/kg, the average daily cost of trastuzumab emtansine is \$300.96 and the average cost per 28-day course is \$8426.88. The cost provided does not

take wastage of any excess trastuzumab emtansine into consideration. When wastage is taken into consideration, the average daily cost is \$310.51 and the average cost per 28-day course is \$8694.40. The manufacturer has also submitted a confidential price of \$ [REDACTED] per 100mg vial and \$ [REDACTED] for 160mg/vial for trastuzumab emtansine. Based on this confidential price the average cost per day in a course is \$ [REDACTED] and the average cost per 28 day course is \$ [REDACTED]. The cost of trastuzumab emtansine is based on a confidential price submitted by the manufacturer and cannot be disclosed to the public according to the *pCODR Disclosure of Information* guidelines.

## 1.2 Summary of Results

### A. Direct comparison: T-DM1 vs. Lapatinib plus Capecitabine (Direct Comparison)

The EGP's best estimate of the incremental cost-effectiveness ratio ( $\Delta C / \Delta E$ ) was revised to a lower estimate of a minimum of \$145,403 per quality-adjusted life year (QALY), but could be higher, when trastuzumab emtansine is compared with lapatinib plus capecitabine. It should be noted that the EGP's estimates could not account for structural limitations in the submitted model, and therefore no upper bound is placed on the estimate. The EGP revised the estimate based on comments from the manufacturer and further input from the Clinical Guidance Panel on the time horizon. As a time horizon of between 5 - 10 years is plausible for metastatic breast cancer, the EGP reverted to the submitter's time horizon of 7 years. The Economic Guidance Panel based these estimates on the model submitted by Hoffmann-La Roche and reanalyses conducted by the Panel.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost ( $\Delta C$ ) and the extra clinical effect ( $\Delta E$ ). The EGP's best estimate of the incremental cost-effectiveness ratio is based on key assumptions for resource use, clinical inputs and utilities as provided in the economic evaluation submission by Hoffmann-La Roche. Overall survival and progression-free survival estimates were informed, and extrapolated based on a phase-III randomized controlled trial. Resource use included the cost of administering the drugs, costs for supportive care in progression and progression-free health states, and the cost of adverse events for each treatment. Utility values were based on adverse events and an algorithm from a standard gamble utility study. The time horizon for the analysis was based on registry data for survival of metastatic breast cancer. The Economic Guidance Panel's best estimate assumed the price of trastuzumab emtansine to be the confidential price submitted to pCODR.

- the extra cost of trastuzumab emtansine is \$57,835 and is driven largely by the cost of the drugs.
- the extra clinical effect of trastuzumab emtansine is 0.398 QALYS ( $\Delta E$ ). The main drivers in effectiveness were overall survival, progression-free survival and the health utilities.

The Economic Guidance Panel made two changes to the submitted economic evaluation to derive the best estimate:

- The submitted analysis assumed no drug wastage for trastuzumab emtansine, though it is administered intravenously and is only available in two pre-specified sized vials. The Economic Guidance Panel reanalyses assumed that there would be wastage (planned dose) for trastuzumab emtansine as this was identified as being an important concern by the Provincial Advisory Group.

- In the submitted analysis, overall survival and progression-free survival were extrapolated (determined beyond what was actually measured) based on the follow-up data of the trial. This trial had a median patient follow-up of 13 months. In order to model the effect of trastuzumab emtansine, extended survival data was needed and was generated based on the actual data using different parametric distributions. The submitter used a gamma distribution for both the progression-free survival curve and the overall survival curve; however, the justification for the gamma distribution was not sufficient, as it was not the distribution that fit best. The Economic Guidance Panel reanalyses assumed the best fit for both curves.
- The submitted analysis provided a time horizon of 7 years based on registry data for metastatic breast cancer; however, given the median patient follow-up of 13 months in the trial, the pCODR CGP at first supported the Economic Guidance Panel's assumed time horizon of 5 years for a more conservative estimate. However, following comments from the manufacturer and based on previous decisions for other drugs in metastatic breast cancer, the EGP reverted to the submitter's time horizon of 7 years, which is within the clinically plausible range of 5 - 10 years. It should be noted that changing the time horizon from 7 years to 5 years increases the ICER from \$127,051 to \$144,627. It should also be noted that if a lifetime model is considered (based on the registry data of 7 years), all subsequent costs post-progression should be considered which the manufacturer did not consider. Though the manufacturer provided (after the checkpoint meeting) the proportion of patients on anti-HER2 and chemotherapy in each treatment arm, they did not detail specifically which treatments the patients were on, nor did they consider these costs in the model.

**The Economic Guidance Panel's estimates differed from the submitted estimates. Previously, the EGP identified that there was a strong possibility that up to 50% of the benefit of trastuzumab emtansine could be attributed to the post-progression state due to extrapolation. The submitter following this report provided information that states that the post-progression survival (HR 0.71; 95% CI, 0.52-0.98; p-value 0.0351) is very similar to pre-progression survival (0.68; 95% CI, 0.55 - 0.85; P<0.001). The CGP subsequently stated that there is limited data in determining post-progression survival. However, the EGP is still unable to modify this survival estimates and analyze their effect on the ICER. Therefore, the ICER provided remains a minimum, with no upper bound provided.**

According to the economic analysis that was submitted by Hofmann-La Roche when trastuzumab emtansine is compared with lapatinib plus capecitabine:

- the extra cost of trastuzumab emtansine is \$55,015. Costs considered in the analysis included the cost of the planned dose of the drugs excluding wastage, the cost of adverse events, the cost of administering the drugs, and supportive care costs.
- the extra clinical effect of trastuzumab emtansine is 0.433 quality-adjusted life years (QALY) or 0.617 life years (LY). The clinical effect considered in the analysis was based on extrapolation of overall survival and progression-free survival based on one phase-III clinical trial and utilities based on an algorithm that considered adverse events.

So, the Submitter estimated that the incremental cost-effectiveness ratio ( $\Delta C / \Delta E$ ) was \$127,052 per QALY or \$89,184 per LY gained. The manufacturer's estimates were based on a confidential price of T-DM1 submitter to pCODR.

## B. Indirect comparison: T-DM1 vs. Trastuzumab plus Capecitabine

The EGP's best estimate of the incremental cost-effectiveness ratio ( $\Delta C / \Delta E$ ) is \$90,540 per quality-adjusted life year (QALY), but could be higher, when trastuzumab emtansine is compared with trastuzumab plus capecitabine. The Economic Guidance Panel based these estimates on the model submitted by Hoffmann-La Roche and reanalyses conducted by the Panel.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost ( $\Delta C$ ) and the extra clinical effect ( $\Delta E$ ). The EGP's best estimate of the incremental cost-effectiveness ratio is based on key assumptions for resource use, clinical inputs and utilities as provided in the economic evaluation submission by Hoffmann-La Roche. Overall survival and progression-free survival estimates were informed, and extrapolated based on a systematic review that included three trials to inform the indirect comparison. The limited data in this area, and the lack of a direct comparator, contributed to uncertainty in the estimate. Resource use included the cost of administering the drugs, costs for supportive care in progression and progression-free health states, and the cost of adverse events for each treatment. Utility values were based on adverse events and an algorithm from a standard gamble utility study. The time horizon for the analysis was based on registry data for survival of metastatic breast cancer. The Economic Guidance Panel's best estimate assumed the price of trastuzumab emtansine as submitted to pCODR.

- the extra cost of trastuzumab emtansine is \$65,618 ( $\Delta C$ ) and is driven largely by the cost of the drugs.

the extra clinical effect of trastuzumab emtansine is 0.725 ( $\Delta E$ ). The main drivers in effectiveness were overall survival, progression-free survival and the health utilities.

The Economic Guidance Panel made two changes to the submitted economic evaluation to derive the best estimate:

- The submitted analysis assumed no drug wastage for trastuzumab emtansine, though it is administered intravenously and is only available in two pre-specified sized vials. The Economic Guidance Panel reanalyses assumed that there would be wastage (based on the planned dose) for trastuzumab emtansine as this was identified as being an important concern by the Provincial Advisory Group.
- In the submitted analysis, overall survival and progression-free survival were extrapolated (determined beyond what was actually measured) based on the follow-up data of the trial. This trial had a median patient follow-up of 13 months. In order to model the effect of trastuzumab emtansine, extended survival data was needed and was generated based on the actual data using different parametric distributions. The submitter used a gamma distribution for both the progression-free survival curve and the overall survival curve; however, the justification for the gamma distribution was not sufficient, as it was not the distribution that fit best. The Economic Guidance Panel reanalyses assumed the best fit for both curves.
- The submitted analysis provided a time horizon of 7 years; however, given the median patient follow-up of 13 months in the trial, the pCODR CGP at first supported the Economic Guidance Panel's assumed time horizon of 5 years for a more conservative estimate. However, following comments from the manufacturer and based on previous decisions for other drugs in metastatic breast cancer, the EGP, in consultation with the CGP, concluded that the submitter's time horizon of 7 years would be appropriate because it is within the clinically plausible range of 5 - 10 years.

The Economic Guidance Panel's estimates differed from the submitted estimates, and the upper bound cannot be determined due to structural limitations of the model and the uncertainty surrounding the hazard ratios for both progression-free and overall survival. Though the manufacturer reiterates in their feedback that they used the best available evidence, a sensitivity analysis using the 95% CI of the hazard ratios provides a large range for the ICER.

According to the economic analysis that was submitted by Hofmann-La Roche when trastuzumab emtansine is compared with trastuzumab plus capecitabine:

- the extra cost of trastuzumab emtansine is \$65,750. Costs considered in the analysis included the cost of the planned dose of the drugs excluding wastage, the cost of adverse events, the cost of administering the drugs, and supportive care costs.
- the extra clinical effect of trastuzumab emtansine is 0.762 quality-adjusted life years or 1.087 life years (LY). The clinical effect considered in the analysis was based on extrapolation of overall survival and progression-free survival based on one phase-III clinical trial and utilities based on an algorithm that considered adverse events.

So, the Submitter estimated that the incremental cost-effectiveness ratio ( $\Delta C / \Delta E$ ) was \$86,304 per QALY or \$60,478 per LY gained.

### 1.3 Summary of Economic Guidance Panel Evaluation

**If the EGP estimates of  $\Delta C$ ,  $\Delta E$  and the ICER differ from the Submitter's, what are the key reasons?**

The Economic Guidance Panel estimates differ from those provided by the submitter because of the consideration of drug wastage, the distribution chosen for the extrapolated overall survival and progression-free survival data and because the EGP was unable to modify survival estimates in the model. Wastage was identified as being an important concern of the Provincial Advisory Group. As the Economic Guidance Panel was not able to modify the survival estimates, the most appropriate estimate was to use the best fitting distribution.

In the indirect analysis, the Economic Guidance Panel estimates differ from those provided by the submitter because of the consideration of drug wastage, the distribution chosen for both the extrapolated overall survival and progression-free survival data, and the hazard ratios that were derived from the systematic review for the indirect comparison which had large confidence intervals. Wastage was identified as being an important concern of the Provincial Advisory Group.

**Were factors that are important to patients adequately addressed in the submitted economic analysis?**

Based on patient input, the two primary concerns are survival (both overall and progression-free) and the occurrence of adverse events. However, there is only one single clinical trial that has measured the effectiveness of trastuzumab emtansine, and the follow-up data is limited (13 months) in comparison to the submitters main analysis where they assumed benefits for up to 7 years. The occurrence of adverse events from the perspective of quality of life was considered within the model, however, not directly. The

trial did not directly measure the impact that trastuzumab emtansine would have on the quality of life of patients, and therefore estimated its effect using the occurrence of adverse events in both treatment arms. These estimates appear appropriate; however, they were not directly measured.

**Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?**

No, the design and structure were limited. In order to appropriately evaluate an economic model, full transparency is required. The Economic Guidance Panel were unable to adjust certain parameters, and certain elements were unclear. The EGP first assumed that the manufacturer made two large assumptions by using this model design: that a patient's risk of dying before progression is equal to their risk of dying after progression; and secondly, that the increased survival advantage of trastuzumab emtansine which is found in patients who have not yet progressed will continue after progression, despite having stopped treatment of trastuzumab emtansine. The manufacturer subsequently provided data that showed that the hazard ratios before and after progression are similar (HR=0.68 and HR=0.71, respectively). Though there is no clinical evidence to the contrary, the CGP could not conclude that post-progression survival is present. However, the EGP was still unable to modify the survival estimates given to ascertain the effect on the ICER. Probabilistic sensitivity analysis is unable to assess parameter uncertainty and not structural uncertainty within the model. As the manufacturer did not change the structure of the model, and only provided data that supports the lack of post-progression survival, the EGP revised their previous estimate that up to 50% of the benefit is seen in the post-progression state. The EGP maintains that there is benefit in the post-progression state, however, whether or not this is clinically plausible has not been tested, and cannot be confirmed nor refuted at this point. Therefore, the EGP is currently unable to estimate of the amount of benefit attributed to the post-progression state.

**For key variables in the economic model, what assumptions were made by the Submitter in their analysis that have an important effect on the results?**

In the submitted economic model, there was a structural assumption that a patient's risk of dying before progression is equal to a patient's dying after progression. The EGP requested evidence to support this assumption from the manufacturer at the outset of the review. Although the manufacturer provided some data to suggest similar hazard ratios for pre and post progression survival (HR=0.68 and HR=0.71, respectively) they deemed this information non-disclosable. It was only after the Initial Economic Guidance Report was completed and the pERC Initial Recommendation issued that the manufacturer made this information fully disclosable. Though there is no clinical evidence to the contrary, the CGP could not conclude that post-progression survival is present. Furthermore, the model does not allow the EGP to vary either progression-free survival or overall survival within the model, and is unable to assess post-progression survival independent of pre-progression survival. Further, though the manufacturer provided the proportion of patients on anti-HER2 and chemotherapy agents in each group, the exact proportion of patients who were on trastuzumab emtansine and go on to lapatinib post-progression was not provided, although the EGP had requested the manufacturer provide this breakdown. This could impact costs, as, without this breakdown, the EGP was unable to assess these post-progression costs in the model, introducing further uncertainty.

**Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the EGP would have chosen and were they adequate for answering the relevant question?**

Other than not considering the costs of drug wastage, the costing data was adequate and the EGP would have used similar data. The utility data was adequate; however, ideally a Canadian source would be preferred or measured directly from within the trial. Neither of these latter options are available. The estimates of clinical effect were not adequate as the estimates of long term survival gains had several limitations: they were based on only one source of data; the trial on which they were based on had a median follow-up of 13 months compared to a 7-year time horizon; and it was not possible to account for risks of death before and after tumor progression separately, which may affect the estimate of the ICER.

In addition to what was considered in the main analysis, that was maintained for the indirect comparison (costs, utility data, estimates of long term survival gain using extrapolation), the estimates of the clinical effect of trastuzumab emtansine versus capecitabine plus trastuzumab were based on only three trials, with varying levels of quality. The Economic Guidance Panel placed low confidence in the resulting hazard ratios, given the large confidence intervals, which have not changed following the feedback from the manufacturer.

## **1.4 Summary of Budget Impact Analysis Assessment**

**What factors most strongly influence the budget impact analysis estimates?**

A budget impact analysis (BIA) was submitted to determine the impact, from the public payers' perspective, should trastuzumab emtansine be introduced on the formulary over a three-year period. The BIA contains assumptions about the number of patients with metastatic breast cancer who could benefit from this therapy, current treatment patterns, costs associated with these treatments and market share (percentage each treatment

“owns” of the market). A chart audit conducted by a third party was used to determine the market share of trastuzumab emtansine and lapatinib plus capecitabine. Data from Statistics Canada and the literature informed the estimates on the number of patients who would be HER2-positive in a given year. Costs were consistent with those found in the economic model. The largest determinant for the BIA is the assumption around the market share.

**What are the key limitations in the submitted budget impact analysis?**

As in the main analysis, wastage was not considered in the main analysis of the submitters. Wastage was recognized by the Provincial Advisory Group as an important consideration. Further, there appears to be a structural limitation to the model: when wastage of trastuzumab emtansine as a second-line therapy is considered in the model, the cost decreases (despite more drug being used).

## **1.5 Future Research**

**What are ways in which the submitted economic evaluation could be improved?**

The economic evaluation could be improved by selecting a different design and structure that would separately model the risk of death in patients pre-progression and post-progression, as in a Markov model.

**Is there economic research that could be conducted in the future that would provide valuable information related to trastuzumab emtansine for metastatic breast cancer?**

Future research in this area could focus on collecting utilities within the clinical trial would greatly reduce the uncertainty around this parameter.

## 2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

### 3 ABOUT THIS DOCUMENT

This Final Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Breast Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of trastuzumab emtansine (Kadcyla) for metastatic breast cancer. A full assessment of the clinical evidence of trastuzumab emtansine (Kadcyla) for metastatic breast cancer is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website ([www.pcodr.ca](http://www.pcodr.ca)).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was redacted from this publicly available Guidance Report.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website ([www.pcodr.ca](http://www.pcodr.ca)). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

## REFERENCES

1. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. *British Journal of Cancer* 2006; 95: 683-90.
2. Verma S, Miles D, Gianni L, et al. Trastuzumab Emtansine for HER-2 positive advanced breast cancer. *N Engl J Med* 2012; 367: 1783-91.
3. Parkinson B, Pearson S-A, Viney R. Economic evaluations of trastuzumab in HER2-positive metastatic breast cancer: a systematic review and critique. *Eur J Health Econ* 2013; [Epub ahead of print].