Ontario Health
Cancer Care Ontario

Evidence Building Program – Herceptin® (trastuzumab) Update

January 2022

Background

The 10-year anniversary of the establishment of the Evidence Building Program (EBP) was marked in 2021. The EBP was created to address an unmet need for cancer drugs in situations where the evidence supporting the treatment benefits is emerging but insufficient to make a fully informed funding decision. EBP provides funding for cancer drugs until real-world clinical effectiveness, safety and cost-effectiveness data are collected so that a final funding decision can be made by the Ontario Ministry of Health (MOH).

Adjuvant trastuzumab for the treatment of early-stage HER2-positive breast cancer following or in combination with chemotherapy for patients with **tumours greater than 1cm** has been funded through the New Drug Funding Program (NDFP) since 2005. In May 2011, Ontario Health – Cancer Care Ontario (OH (CCO)) announced funding of adjuvant trastuzumab with chemotherapy for the treatment of HER2-positive breast cancer patients with node negative **tumours less than or equal to 1cm in size** through the EBP. At the time, no direct evidence supporting the effectiveness of trastuzumab in patients with HER2-positive node-negative disease with **tumours less than or equal to 1cm in size** was available. In addition, a trial for such patients was considered unlikely. Therefore, in the absence of strong evidence supporting the use of trastuzumab in this patient population and based on the recommendations of a provincial expert group, MOH approved conditional funding for these patients with the expectation that real-world data would be collected to evaluate the clinical safety, effectiveness, and cost-effectiveness to inform a final funding decision. OH (CCO) established a process to obtain the evidence required to resolve existing uncertainty on treatment benefit, and data collection began in 2011.

During 2018-2021, OH (CCO) worked with provincial breast cancer experts, the OH (CCO) Data Analytics Team, and ICES to analyze all available data for patients receiving trastuzumab under EBP. These analysis findings were presented to a provincial expert committee for review and recommendations in summer 2021. Subsequently, overall findings from the trastuzumab data analysis and provincial expert committee recommendations were shared with the MOH for a final funding decision.

Evaluation Findings and Next Steps

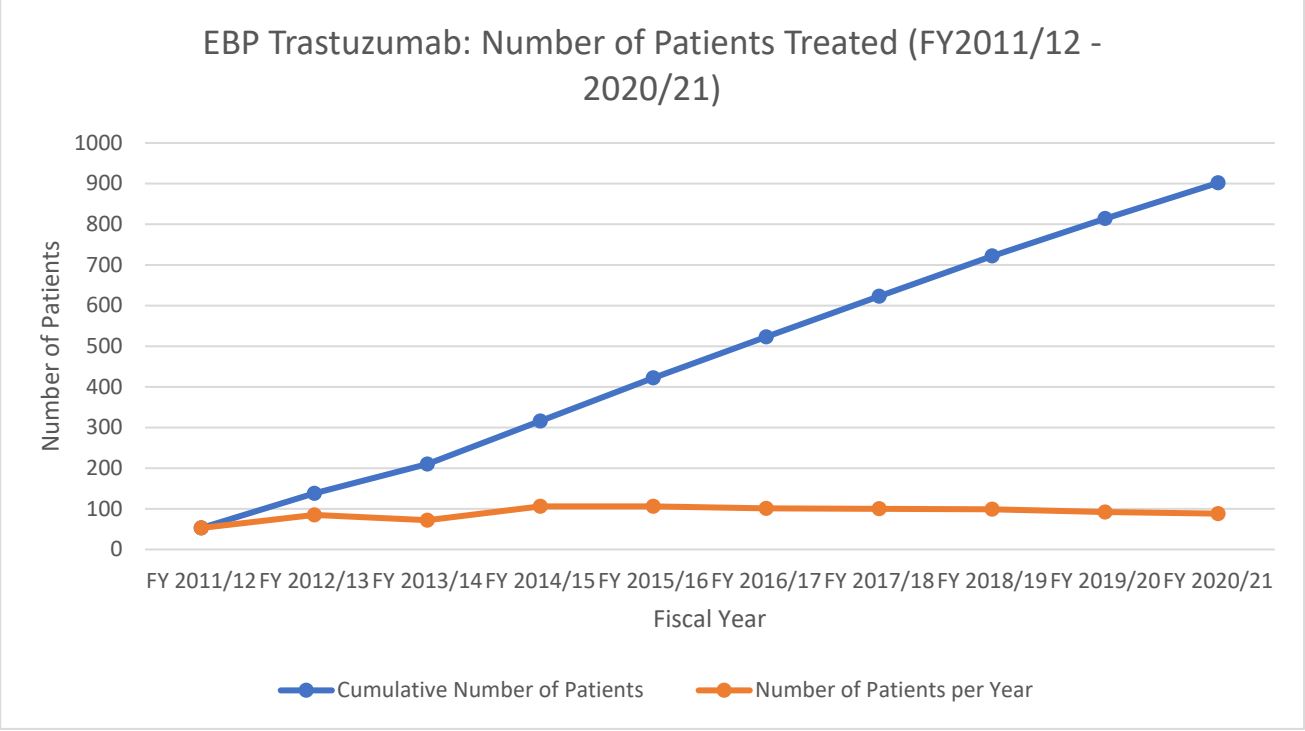
Presented below is a program summary of patients who received trastuzumab treatment through EBP along with key findings from the real-world data analysis, expert advice, and the final funding decision made by the MOH.

EBP Trastuzumab Eligibility Criteria:

- Breast cancer patients with node negative HER2-positive tumours ≤1cm (HER2-positive defined as either IHC3+ or FISH (or SISH) ≥2).
- The patient is a candidate for trastuzumab-based chemotherapy;
  - If age ≤ 50 years, LVEF ≥ 50% based on MUGA or ECHO
  - If age > 50 years, LVEF ≥ 55% based on MUGA or ECHO
  - No clinically significant cardiac disease
- Trastuzumab will be used in combination with, or sequentially after, adjuvant chemotherapy

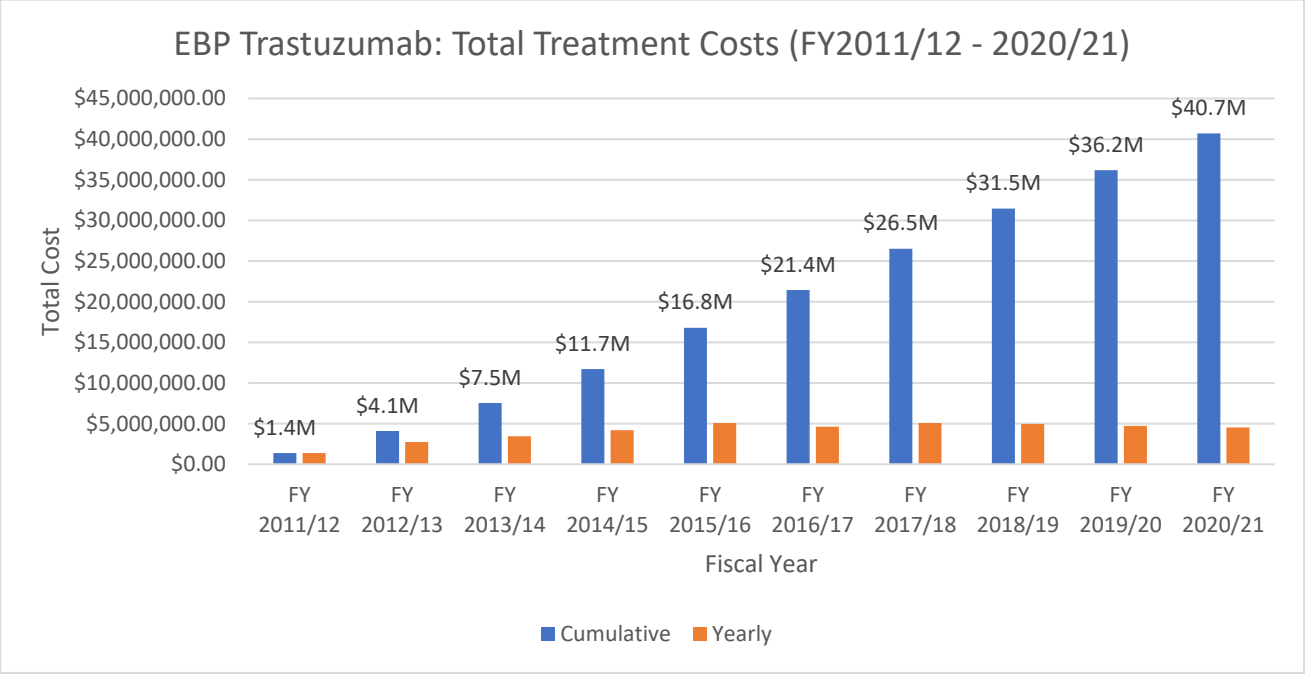
Patient Volumes

From fiscal year 2011/12 through 2020/21, a total of 902 patients received treatment funding through EBP, at an average rate of 90 patients per year.



Drug Expenditures

Over the course of 10 years, $40.7 million was spent to treat 902 patients under the EBP trastuzumab policy.



Real-world Data Analysis Findings

Approach:

The primary outcomes of interest for this analysis were: 1) safety based on incidence of cardiac toxicity and febrile neutropenia, 2) effectiveness in terms of survival. Two analyses were done using the data collected from the EBP: a matched retrospective cohort analysis and a retrospective, population-based cohort study. Both analyses compared EBP patients to breast cancer patients in the Ontario Cancer Registry (OCR) selected based on certain clinical criteria. Of note, prior to the establishment of EBP, HER2-positive breast cancer patients with node negative tumours less than or equal to 1cm in size did not receive trastuzumab and may not have received chemotherapy. Therefore, the safety analysis focused on adverse outcomes associated with both types of treatments.

Findings:

Safety

Use of trastuzumab with chemotherapy in the EBP was associated with an increased risk of congestive heart disease (CHD) and febrile neutropenia (FN). The expert committee felt that the analysis suggested an acceptable toxicity profile for the EBP trastuzumab indication. About 3.5% of patients experienced CHD

during treatment with trastuzumab through EBP. About 6% of patients receiving trastuzumab through EBP had an absolute reduction of left ventricular ejection fraction (LVEF) >10% or had reached LVEF <50%. Any elevated risk of CHD was accounted for by the use of anthracyclines; in an adjusted analysis of patients with HER2+ node negative tumours ≤1cm in size, risk of CHD was higher among older patients [hazard ratio (HR) 1.06 (1.03-1.08) per 1-year increase in age, p<0.0001] and for patients who received anthracyclines [HR 5.00 (1.71-14.7)], but not significantly increased among patients who received trastuzumab through the EBP compared to controls [HR 1.48 (0.77-2.85)]. In a matched analysis, the crude frequency of FN during treatment was 20% in patients who received trastuzumab through the EBP, compared to 3% over a similar timeframe among controls who did not receive chemotherapy or trastuzumab (p<0.001).

Effectiveness

The expert committee felt that the clinical data presented shows that use of trastuzumab in the study population led to improved outcomes. EBP patients had improved overall survival (OS) when compared to controls who received no chemotherapy or trastuzumab. The 3-year OS in the EBP population was 99.1 %, versus 96.9% in the controls (p=0.005) [adjusted HR 0.59 (95% CI 0.29-1.20)]. Patients receiving EBP trastuzumab had a significantly longer event-free survival than controls with or without chemotherapy [adjusted HR 0.54 (0.36-0.83), p=0.005] (manuscript in preparation).

Cost-Effectiveness

As part of the initial consideration, evidence from small tumours (e.g., 1-2cm) in the literature, along with clinical expert opinion was used to estimate the potential cost-effectiveness of trastuzumab for tumours ≤1cm in size. The incremental cost-effectiveness ratio (ICER) for adjuvant trastuzumab in HER2 positive primary breast cancer among small tumours was estimated to be approximately $70,000/quality-adjusted life year (QALY) gained ($25,000 - $270,000/QALY gained), with the assumptions that trastuzumab reduced risk of recurrence regardless of tumour size equally well, but absolute risk of recurrence was low in this population. After updating the initial analysis with the results of the EBP data analysis (recurrence, CHD, FN), the ICER was estimated conservatively to be $106,000/QALY gained, or $63,000/QALY gained ($43,000 - $95,000/QALY gained) using the trastuzumab biosimilar drug price. The committee felt that the treatment is likely to represent a cost-effective therapy, especially if funding is transitioned to biosimilars.

Expert Advice

In view of the analysis findings noted above, the advice from the provincial expert group was as follows:

1. Funding for trastuzumab for the adjuvant treatment of HER2-positive breast cancer patients with node negative tumours ≤1cm be transitioned to the NDFP.
2. Data collection for trastuzumab for the adjuvant treatment of HER2-positive breast cancer patients with node negative tumours ≤1cm be discontinued.

MOH Final Funding Decision

As of January 2022, the MOH has approved continued trastuzumab funding for the adjuvant treatment of HER2-positive breast cancer patients with node negative tumours less than or equal to 1cm in size via the NDFP. Of note, all new patients with this indication are only eligible for funding of a trastuzumab biosimilar, consistent with the other NDFP trastuzumab policies. The MOH has also approved the discontinuation of ongoing data collection through EBP.

OH (CCO) would like to thank provincial cancer centres and hospitals for their cooperation and support in the data collection which was essential for this real-world analysis.