CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Pertuzumab-Trastuzumab for Early Breast Cancer

November 29, 2018

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by **Hoffmann-La Roche** compared pertuzumab in combination with trastuzumab and chemotherapy to trastuzumab and chemotherapy for the adjuvant treatment of patients with HER-2 positive early breast cancer at high risk of recurrence, defined as either node-positive or hormone receptor-negative disease in the adjuvant setting.

Table 1. Submitted Economic Model

Requested reimbursement criteria	Pertuzumab in combination with trastuzumab and chemotherapy for 18 cycles of treatment of HER2-positive early breast cancer patients at high risk of recurrence (node-positive or hormone receptor negative).
Type of Analysis	CUA / CEA
Type of Model	Markov
Comparator	Trastuzumab plus chemotherapy
Year of costs	2017
Time Horizon	52 years; monthly cycle length
Perspective	Government
Cost of pertuzumab*	Pertuzumab costs $7.93 per mg • At the recommended dose of 840 mg (loading dose) administered as a 60-minute intravenous infusion, followed every 3 weeks thereafter by a dose of 420 mg (maintenance dose) administered over a period of 30 to 60 minutes pertuzumab costs: ○ $ 6,657.10 (loading dose) ○ $3,328.55 (maintenance dose)
Cost of trastuzumab*	Trastuzumab costs $6.43 per mg • At the recommended dose of 8 mg/kg (loading dose) administered as an IV infusion, followed every 3 weeks thereafter by a dose of 6 mg/kg (maintenance dose) trastuzumab costs: ○ $ 3,466.55 (loading dose) ○ $ 2,599.92 (maintenance dose)
Cost of Chemotherapy Cost of 5-fluorouracil*	5-Fluorouracil costs $0.03 per mg. • At the recommended dose of 600mg/m^2 IV every 3 weeks for 3 cycles 5-fluorouracil costs: ○ $33.16 per treatment cycle

Cost of epirubicin *	Epirubicin costs $4.01 per mg (small vial) and $3.9 per mg (large vial) • At the recommended dose of 120mg/m^2 IV every 3 weeks for 3 cycles epirubicin costs: o $803.25 per treatment cycle
Cost of doxorubicin* Note: recommended dose for • FAC regimen: 50 mg/m^2; • AC regimen: 60 mg/m^2.	Doxorubicin costs $5.05 per mg (small vial) and $4.87 per mg (large vial) • At the recommended dose of 50mg/m^2 IV every 3 weeks for 3 cycles doxorubicin costs: o $417.75 per treatment cycle • At the recommended dose of 60mg/m2 IV every 3 weeks for 3 cycles doxorubicin costs: o $501.30 per treatment cycle
Cost of cyclophosphamide*	Cyclophosphamide costs $0.14 per mg (small vial) and $0.09 per mg (large vial) • At the recommended dose of 600 mg/m^2 IV every 3 weeks for 3 cycles cyclophosphamide costs: o $88.19 per treatment cycle
Cost of paclitaxel*	Paclitaxel costs $10.00 per mg (small vial) and $10.95 per mg (large vial) • At the recommended dose of 80 mg/m^2 once weekly for 12 weeks paclitaxel costs: o $1,373.89 per treatment cycle
Cost of docetaxel* Note: recommended dose for • TH regimen: 100 mg/m^2; • TCH regimen: 75mg/m^2.	Docetaxel costs $11.42 per mg (small vial) and $11.56 per mg (large vial) • At the recommended dose of 100 mg/m2 IV every 3 weeks for 4 cycles docetaxel costs: o $1,961.83 per treatment cycle • At the recommended dose of 75 mg/m2 IV every 3 weeks for 4 cycles docetaxel costs: o $1,471.37 per treatment cycle
Cost of carboplatin*	Carboplatin costs $1.4 per mg (small vial) and $1.4 per mg (large vial) • At the recommended dose of AUC 6 every 3 weeks carboplatin costs: o $ 909.84 per treatment cycle
Model Structure	The model structure consists of six health states (Figure 1): invasive disease-free survival (IDFS) (on/off adjuvant treatment), non-metastatic recurrence, remission, first-line metastatic breast cancer, subsequent lines of treatment in

	metastatic breast cancer and death.
Key Data Sources	Phase III APHINITY trial[1]
** Price Source: Ontario wholesale prices obtained from the IQVIA Delta PA database; accessed January 2018. The vial prices of PERJETA and HERCEPTIN were provided by Roche Canada. All calculations are based on 67.4 kg and BSA = 1.72m^2* *AC = Adriamycin and Cytoxan; EC = epirubicin, Cytoxan; FAC Fluorouracil, Adriamycin and Cytoxan; FEC = 5 fluorouracil, epirubicin and cyclophosphamide; TCH = Taxotere (docetaxel), carboplatin and Herceptin (trastuzumab); TH = Taxotere (paclitaxel), Herceptin (trastuzumab).*	

Figure 1. Model structure, as copied from pCODR submission

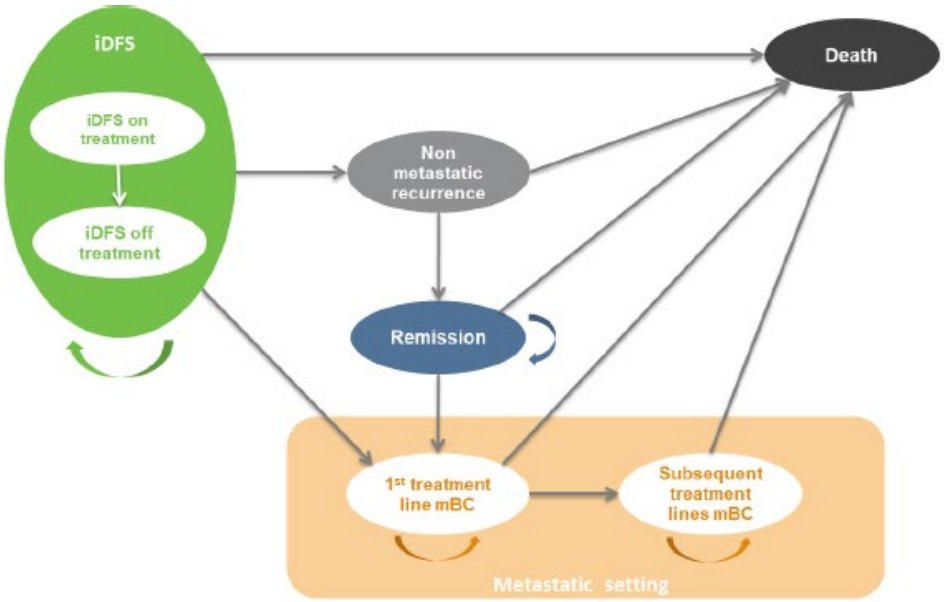
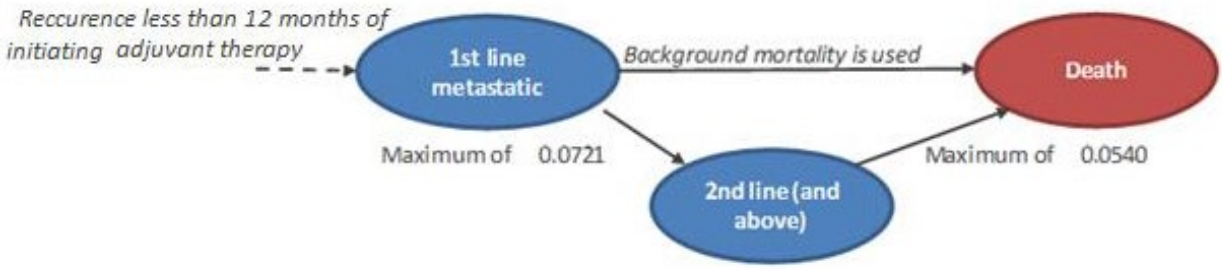


Figure 2. Summary of monthly transition probabilities in the metastatic setting in case of an early recurrence event



1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate as current treatment for adjuvant treatment of early breast cancer is trastuzumab with chemotherapy. Relevant issues identified included:

1) Lymph-node positive subgroup

- There is ***likely*** a small yet clinically meaningful net clinical benefit of pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy.
- Pre-defined subgroup analysis from the APHINITY clinical trial[1] demonstrated a significant improvement in IDFS among patients diagnosed with node positive disease.
- Toxicity profile of pertuzumab/trastuzumab seemed tolerable. The higher risk for primary cardiac events speaks to the need for monitoring and possible intervention during therapy.
- Node positive disease has been traditionally considered at higher risk for disease recurrence, due to the higher stage of disease (i.e. tumour burden) at presentation.
- More effective and less toxic therapies which improve survival rates are urgently required in this population.

In their feedback on the initial recommendation one PAG member noted that their tumour group disagreed with pERC's initial recommendation. The tumour group suggested that pertuzumab, trastuzumab, and chemotherapy could benefit a high risk group (3+ nodes and locally advanced population [Stage III]) treated with a neoadjuvant approach. It was also noted that treating a high-risk group would reduce the number needed to treat and could prevent distant recurrences which would save money on the treatment of metastatic breast cancer. The EGP felt that they could not comment on the tumour group's feedback given that the models submitted for this review were for the hormone-receptor negative and node-positive subgroups, both of which are inherently "high risk" already, and that it is not possible to tease out results for those patients with 3 or more positive lymph nodes (who may or may not be "higher risk" than the populations analyzed).

2) Hormone-receptor negative subgroup

- There is ***not*** a net clinical benefit to pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy
- Pre-defined subgroup analysis from the APHINITY clinical trial[1] demonstrated a treatment effect that favored pertuzumab-trastuzumab, however, the difference in IDFS was not statically significant.
- Observed treatment effect could be the result of an interaction with lymph-node status as the majority of patients in the hormone-receptor negative subgroup also had lymph-node positive disease.
- It has not been established whether the definition of high risk HER2 positive breast cancers includes all patients with hormone receptor negative tumours, as the main biological driver of risk in this population is considered to be HER2 overexpression.

Generalizability issues included:

- The trial limited inclusion to patients with ECOG performance status of 0 and 1.

Summary of registered clinician input relevant to the economic analysis

Two registered clinician inputs were provided for the drug under review. In terms of the clinical benefit, it was noted in the joint input that the improvement demonstrated in the node-positive patients was minimal in the APHINITY trial and that there was no real advantage in node-negative patients. While the clinicians acknowledged the benefit of pertuzumab and trastuzumab, when compared with placebo and trastuzumab for IDFS in the APHINITY trial[1], they were unsure if the observed benefit is clinically meaningful given the lack of a significant difference in overall survival. In addition, the clinicians providing the joint input did not believe this treatment fills an unmet need because there are effective treatments available already, and the trial only demonstrated a modest improvement. It was noted by

the individual clinician providing input that overall the trial results in the adjuvant setting were disappointing, however, selective use of this therapy could benefit higher risk populations including node positive patients. For clinical use, pertuzumab would be added in combination with trastuzumab and not sequentially. Companion diagnostic testing would include HER2 positive testing, which is already done as routine standard of practice

Summary of patient input relevant to the economic analysis
Patients considered the following important:

- Effectiveness of the treatment,
- Reducing the risk of disease recurrence,
- Maintaining quality of life and mobility,
- Maintain productivity
- Minimal side effects

Overall, the following factors were shown to affect patients' choice of treatment options (in order of importance): effectiveness of the treatment, reducing the risk of disease recurrence, maintaining quality of life and maintaining mobility, maintain productivity, minimal side effects, minimal medical appointments and ability to continue childcare duties. Patients who have experience with pertuzumab in combination with trastuzumab and chemotherapy reported that it was difficult for them to determine if the side effects experienced were from the chemotherapy or from the combination therapy. Relative to the experienced side effects, participants had an overall positive attitude towards the combination treatment, reporting gratitude at having access to this treatment and expressed that more women should have access to this treatment. IDFS, overall survival (OS), quality of life (QoL) and adverse events were incorporated into the economic model. The economic model took the perspective of the health care provider and not the societal perspective and hence did not account for changes in patients' economic productivity.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG noted that pertuzumab is an add-on drug to the current treatment with trastuzumab plus chemotherapy, followed by trastuzumab alone for up to 18 cycles.
The following factors are important to consider if implementing a funding recommendation for pertuzumab in combination with trastuzumab and chemotherapy which are relevant to the economic analysis:

<u>Barriers</u>

- For the requested indication, pertuzumab is only available in a package that includes both pertuzumab and trastuzumab (Perjeta-Herceptin Combo Pack). Although pertuzumab is administered at a fixed dose, trastuzumab is administered based on weight. While it is possible that excess trastuzumab can be used for other patients, the burden on inventory management resources would be substantial.

<u>Enablers</u>

- No drug wastage for pertuzumab as the 420 mg flat dose is available as one vial in the combo pack.

The EGP explored various scenario analyses around actual and planned doses with and without vial sharing.

1.3 Submitted and EGP Reanalysis Estimates

A. HR-negative sub-population

Table 2. Submitted and EGP Reanalysis Estimates- HR-negative population

Estimates (range/point)	Submitted	EGP Reanalysis
ΔE (LY)	0.67	0.59
IDFS	0.91	0.73
Non-metastatic recurrence	-0.01	-0.01
Remission	-0.07	-0.06
Metastatic	-0.08	-0.03
Metastatic progressed	-0.09	-0.04
ΔE (QALY)	0.53	0.46
IDFS	0.70	0.56
Non-metastatic recurrence	-0.01	-0.01
Remission	-0.06	-0.05
Metastatic	-0.06	-0.02
Metastatic progressed	-0.05	-0.02
ΔC ($)	$43,136	$52,207
ICER estimate ($/QALY)	$81,279	$112,487

B. Node-positive sub-population

Table 3. Submitted and EGP Reanalysis Estimates- node-positive population

Estimates (range/point)	Submitted	EGP Reanalysis
ΔE (LY)	1.09	0.81
IDFS	1.51	0.98
Non-metastatic recurrence	-0.01	-0.01
Remission	-0.10	-0.07
Metastatic	-0.14	-0.04
Metastatic progressed	-0.16	-0.05
ΔE (QALY)	0.87	0.64
IDFS	1.15	0.75
Non-metastatic recurrence	-0.01	-0.01
Remission	-0.08	-0.05
Metastatic	-0.10	-0.03
Metastatic progressed	-0.09	-0.03
ΔC ($)	$28,122	$48,169
ICER estimate ($/QALY)	$32,202	$75,904

The main assumptions and limitations with the submitted economic evaluation were:

- Time horizon: The submitted base case assumed a time horizon of 52 years. In the previous pCODR review for pertuzumab-trastuzumab in the neoadjuvant setting, the time horizon used was 28 years, given the more aggressive nature of the disease. For this population, a time horizon that is 24 years longer than that used in the neoadjuvant setting is not realistic. Further, the median age of women presenting with HER2+ breast cancer is usually in the mid-50s. A time horizon of 52 years for this age of patient is not realistic even in a healthy Canadian population.
- Inclusion of a non-metastatic recurrent state in the model: In the submitted model structure patients in IDFS could transition to either non-metastatic recurrence or directly to 1st line treatment for metastatic breast cancer. Following non-metastatic recurrence, the model

assumes that all patients automatically transition to remission. The CGP disagreed with the submitted model structure. The CGP identified that it was not clinically plausible to have non-metastatic recurrences. The CGP indicated that almost all patients with disease progression from the IDFS state will be treated as a metastatic recurrence as it is difficult to distinguish from metastatic versus non-metastatic recurrences.

- Metastatic recurrence: In the submitted base case, it was assumed that all "early metastatic recurrences" are all recurrences occurring less than 12 months after initiating adjuvant therapy. The CGP disagreed with this assumption and felt that less than 18 months was more reflective of clinical practice; as they felt that recurrences less than 18 months would have similar poor prognosis as recurrences less than 12 months.

  In their feedback on the initial recommendation the submitter clarified that their base case assumed that early metastatic recurrences, which have poorer prognosis and thus are modelled differently than other metastatic recurrences, should be defined as all recurrences within 12-months of initiating adjuvant therapy. The CGP reiterate that they would define early metastatic recurrences as all recurrences < 18 months, as the CGP believe that recurrences <18 months would have similar poor prognosis as recurrences < 12 months. Therefore the EGP made no changes to the initial reanalyses.

- Clinical inputs for metastatic setting: The data used to inform the metastatic setting in the economic model was not taken from the APHINITY trial[1], but was taken from the EMILIA clinical trial[2] as according to the submitter, the EMILIA[2] survival data had more mature long-term survival relative to APHINITY[1]. The population of the EMILIA trial[2] and the APHINITY trial[1] are not equivalent. Patients in the EMILIA trial[2] received trastuzumab alone and not pertuzumab in combination with trastuzumab.
- Treatment mix metastatic setting: In the submitted base case, the treatment mix in the metastatic setting was informed by expert opinion. This expert opinion assumed that 80% of patients in the first-line metastatic setting would receive the pertuzumab combination and that alternative treatment with chemotherapy would not be used. The CGP disagreed with this assumption. They felt the treatment mix from the APHINITY trial[1] (which includes a much higher proportion of chemotherapy) was more relevant in the metastatic setting. The CGP felt that re-challenging with pertuzumab-trastuzumab would be more relevant for patients beyond 18 months and would be available to those patients that had a long disease-free interval. Treatment mix in the metastatic setting is an important driver in the model because survival in the metastatic setting is dependent on treatment mix. In the submitted base case, survival is modeled based on the assumption that 80% of patients will receive pertuzumab-trastuzumab, which is not what was used in the APHINITY trial[1]. When using the treatment mix from the APHINITY trial[1] (higher proportion of chemotherapy), the modeled survival aligns with that of the APHINITY trial[1].
- Utilities in the metastatic setting: The utilities used in the metastatic state were taken from the literature and were derived using standard gamble techniques. In this methodology, the utility is estimated by eliciting the preferences from a healthy population for the disease (states) of interest. It is not the gold standard of utility measurement. It should be noted that utility values were not collected in the post-progression health state in APHINITY[1].
- Duration of treatment effect: In the submitted base case, the submitter assumed that the time point at which the incremental treatment effect began to wane was 7 years, and the time point when incremental treatment effect ceased was 10 years. The chosen duration of treatment effect was not well justified. The submitter based their choice on the previous duration of treatment effective of pertuzumab in the neo-adjuvant setting and the assumption that there is a longer duration of treatment effect to reflect the benefit of receiving 18 cycles of pertuzumab. The EGP explored alternative duration of treatment effects, however, in the absence of alternative data, elected to shorten the duration of treatment effect to align with

the clinical trial, notable a treatment effect maintained for 4 years (median duration of follow-up for APHINITY[1]), and waning until 7 years.

1.4 Detailed Highlights of the EGP Reanalysis

A. HR-negative sub-population

The EGP made the following changes to the submitted economic model:

- Time horizon: In the submitted base case, the submitter chose a time horizon of 52 years. Given the age at diagnosis, this time horizon is highly unlikely for this patient population. The CGP supported a time horizon of 40 years.
- IDFS parametric distribution: The EGP chose to use the best fitting distribution (exponential), and not the distribution chosen in the submitted base case (log-logistic). There was no justification provided by the submitter for choosing the log-logistic distribution.
- Duration of treatment effect: In the submitted base case, the submitter made the assumption that the treatment effect was maintained for 7 years, and then waned until 10 years where it ceased. The submitter did not provide a strong justification for this assumption. The EGP disagreed with the submitted treatment duration assumptions and chose to have the treatment effect maintained for 4 years (equivalent to median follow-up in the clinical trial), and then wane until 7 years.
- Metastatic recurrence: In the submitted base case, it was assumed that all "early metastatic recurrences" are all recurrences occurring less than 12 months after initiating adjuvant therapy. The CGP disagreed with this assumption and felt that less than 18 months was more reflective of clinical practice; as they felt that recurrences less than 18 months would have similar poor prognosis as recurrences less than 12 months.

  In their feedback on the initial recommendation the submitter clarified that their base case assumed that early metastatic recurrences, which have poorer prognosis and thus are modelled differently than other metastatic recurrences, should be defined as all recurrences within 12-months of initiating adjuvant therapy. The CGP reiterate that they would define early metastatic recurrences as all recurrences < 18 months, as the CGP believe that recurrences <18 months would have similar poor prognosis as recurrences < 12 months. Therefore the EGP made no changes to the initial reanalyses.

- Treatment mix in metastatic setting: In the submitted base case, the submitter used expert opinion to determine the treatment mix in the metastatic setting. They had determined that 80% of patients would receive a re-challenge with pertuzumab, trastuzumab and chemotherapy, 15% would receive trastuzumab and chemotherapy and 5% would receive no treatment. The CGP disagreed with this assumption. They felt that the treatment mix from the APHINITY trial[1] (defined as 18.3% pertuzumab combination, 17.0% trastuzumab and chemotherapy and 64.7% chemotherapy) was more relevant in the metastatic setting. The CGP felt that the treatment mix of the pertuzumab combination would be more relevant for patients with disease recurrence beyond 18 months of completing adjuvant therapy. Further, as treatment mix is used to determine overall survival in the economic model, when using the treatment mix from the APHINITY trial[1], the modelled OS fits the KM data better than the predicted survival when using the treatment mix based on expert opinion.

Table 4. EGP Reanalysis Estimates- HR-negative population

Baseline (Submitter's best	$43,136	0.53	0.67	$81,279	--

case)					
Description of Reanalysis	ΔC (95% CrI)	ΔE QALYs (95% CrI)	ΔE LYs (95% CrI)	ICUR (QALY)	Δ from submitted ICER
Time horizon 40 years	$43,187	0.51	0.63	$84,760	$3,481
IDFS parametric extrapolation - exponential	$42,404	0.56	0.69	$76,439	-$4,840
Duration of treatment effect maintained for 4 years, ceases at 7 years	$46,853	0.43	0.54	$108,434	$27,155
All early recurrences within 18 months of initiating adjuvant therapy are metastatic	$43,692	0.54	0.67	$81,728	$449
Treatment mix in metastatic setting from APHINITY[1]	$50,545	0.58	0.74	$87,098	$5,819
Best estimate of above 5 parameters	$52,207 ($49,197, $54,769)	0.46 (0.39, 0.52)	0.59 (0.50, 0.66)	$112,487	$31,208

B. Node-positive sub-population

The EGP made the following changes to the economic model:

- Time horizon: In the submitted base case, the submitter chose a time horizon of 52 years. Given the age at diagnosis, this time horizon is highly unlikely for this patient population. The CGP supported a time horizon of 40 years.
- Duration of treatment effect: In the submitted base case, the submitter made the assumption that the treatment effect was maintained for 7 years, and then waned until 10 years where it ceased. The submitter did not provide a strong justification for this assumption. The EGP disagreed with the submitted treatment duration assumptions and chose to have the treatment effect maintained for 4 years (equivalent to median follow-up in the clinical trial), and then wane until 7 years.
- Metastatic recurrence: In the submitted base case, it was assumed that all "early metastatic recurrences" are all recurrences occurring less than 12 months after initiating adjuvant therapy. The CGP disagreed with this assumption and felt that less than 18 months was more reflective of clinical practice; as they felt that recurrences less than 18 months would have similar poor prognosis as recurrences less than 12 months.

  In their feedback on the initial recommendation the submitter clarified that their base case assumed that early metastatic recurrences, which have poorer prognosis and thus are modelled differently than other metastatic recurrences, should be defined as all recurrences within 12-months of initiating adjuvant therapy. The CGP reiterate that they would define early metastatic recurrences as all recurrences < 18 months, as the CGP believe that recurrences <18 months would have similar poor prognosis as recurrences < 12 months. Therefore the EGP made no changes to the initial reanalyses.

- Treatment mix in metastatic setting: In the submitted base case, the submitter used expert opinion to determine the treatment mix in the metastatic setting. They had determined that 80% of patients would receive the pertuzumab combination, 15% would receive trastuzumab and chemotherapy and 5% would receive no treatment. The CGP disagreed with this assumption. They felt that the treatment mix from the APHINITY trial[1] (defined as 18.3%

pertuzumab combination, 17.0% trastuzumab and chemotherapy and 64.7% chemotherapy) was more relevant in the metastatic setting. The CGP felt that the treatment mix of the pertuzumab combination would be more relevant for patients with disease recurrence beyond 18 months of completing adjuvant therapy. Further, as treatment mix is used to determine overall survival in the economic model, when using the treatment mix from the APHINITY trial[1], the modelled OS fits the KM data better than the predicted survival when using the treatment mix based on expert opinion.

Table 5. EGP Reanalysis Estimates- node-positive population

Baseline (Submitter's best case)	$28,122	0.87	1.09	$32,202	--
Description of Reanalysis	ΔC (95% CrI)	ΔE QALYs (95% CrI)	ΔE LYs (95% CrI)	ICUR (QALY)	Δ from submitted ICER
Time horizon 40 years	$28,214	0.84	1.04	$33,743	$1,541
Duration of treatment effect maintained for 4 years, ceases at 7 years	$38,509	0.59	0.74	$64,877	$32,675
All early recurrences within 18 months of initiating adjuvant therapy are metastatic	$28,719	0.87	1.10	$32,851	$649
Treatment mix in metastatic setting from APHINITY[1]	$42,997	0.97	1.25	$44,254	$12,052
Best estimate of above 4 parameters	$48,169	0.64	0.81	$75,904	$43,702
Notes: CrI = Credible interval					

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include:

- The market share. Increasing the market share to 50%, 64% and 75% in years 1, 2 and 3 for pertuzumab update increases the total 3-year budget impact by 14% (regardless of patient population.
- The proportion of patients receiving adjuvant treatment. Increasing the proportion of patients for whom treatment is initiated adjuvantly by 10% from the submitted base case, increases the total 3-year budget impact by 12.5% (regardless of patient population).

Key limitations of the BIA model include the underestimation of the market share. There is little contraindication to adding pertuzumab in the adjuvant setting, given the low toxicity. The submitted base case estimates for market share are therefore not plausible. Another limitation is not including the prevalent patient population. It is difficult to estimate the impact on the budget if patients were to add pertuzumab part way through their treatment. Finally, estimates are for provincial populations only with Ontario as the reference case.

1.6 Conclusions

A. Hormone-receptor negative population

The EGP's best estimate of ΔC and ΔE for pertuzumab-trastuzumab when compared to trastuzumab is:

- $112,487/QALY
- The extra cost of pertuzumab is $52,207 (95% CrI: $49,197, $54,769) (ΔC). The main factors that influence ΔC in the submitted base case include the treatment mix in the metastatic setting and the duration of treatment effect.
- The extra clinical effect of pertuzumab is 0.46 (95% CrI: 0.39, 0.52) (ΔE). The main factors that influence ΔE in the submitted base case include the duration of treatment effect and not adjusting the utilities for age.

  In their feedback on the Initial Recommendation, the submitter suggested that the main factors that influence the incremental effect in the submitted base case were the duration of effect and the treatment mix. The EGP maintains that according to the one-way scenario analyses performed for the hormone-receptor negative subgroup (Table 27, pages 31,32) removing the adjustment for age for the utilities from the submitted base case has a larger impact on the incremental effectiveness than changing assumptions around treatment mix.

B. Node-positive population

The EGP's best estimate of ΔC and ΔE for pertuzumab-trastuzumab when compared to trastuzumab is:

- $75,904/QALY
- The extra cost of pertuzumab is $48,169 (95% CrI: $44,613, $51,386(ΔC). The main factors that influence ΔC in the submitted base case include the treatment mix in the metastatic setting and the duration of treatment effect.
- The extra clinical effect of pertuzumab is 0.64 (95% CrI: 0.55, 0.73) (ΔE). The main factors that influence ΔE in the submitted base case include the duration of treatment effect and the treatment mix in the metastatic setting.

Overall conclusions of the submitted model:

- *Mature survival data is not available for this intervention, in this population.*
- *The CGP noted that regardless of the magnitude of the ICER, an adjuvant treatment with an intent to cure (such as this submission) should demonstrate more accrued QALYs.*

In their feedback on the initial recommendation the submitter disagreed with pERC's assessment that ICERs could not be determined, and that it was not possible to draw a conclusion on cost-effectiveness as pERC was not satisfied that there is a clinically meaningful net clinical benefit with pertuzumab, trastuzumab, and chemotherapy compared with trastuzumab and chemotherapy. Specifically the submitter argued that:

(1) ICERs can be estimated, as the EGP produced two best case ICERs; one for each subgroup and did not conclude that ICERs cannot be calculated.
(2) There is a clinically meaningful net clinical benefit, based on the results of APHINITY and the conclusions of the CGP.

In response to the submitter's feedback the EGP reviewed pERC's rationale, noting that pERC agreed that the estimates of incremental effect in the economic analysis are largely based on a key clinical assumption that differences in the rate of IDFS can lead to improvement in OS. Further, given the Committee's lack of confidence in the clinical effect estimates for IDFS derived from the subgroup analyses and the uncertainty whether IDFS is a reliable surrogate outcome for OS, pERC was not satisfied that there is a clinically meaningful net clinical benefit of pertuzumab and trastuzumab. Therefore, pERC could not draw a conclusion on the cost-effectiveness and could not determine the ICER.

The EGP agreed with pERC that the subgroup analyses were pre-specified but exploratory and, therefore, the trial was not designed to detect treatment effect differences based on subgroups. The EGP noted that there was a lack of evidence regarding a difference in treatment effect in each subgroup, which may impact the interpretation of the magnitude of incremental effectiveness, and the resulting ICER. In addition, the EGP stated that, if IDFS is not accepted as a meaningful surrogate for OS in this patient population by pERC, the results of the economic model are difficult to interpret as the model is dependent on the acceptance of this outcome.

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 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 pertuzumab and trastuzumab for the adjuvant treatment of early breast cancer. A full assessment of the clinical evidence of pertuzumab and trastuzumab for the adjuvant treatment of early 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.cadth.ca/pcodr).

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*. There was no information 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. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

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.cadth.ca/pcodr). 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) von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer.[Erratum appears in N Engl J Med. 2017 Aug 17;377(7):702; PMID: 28700263]. *N Engl J Med.* 2017;377(2):122-131.

2) Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012;367(19):1783-1791.

3) Hamilton SN, et al. Second malignancies after adjuvant radiation therapy for early stage breast cancer: is there increased risk with addition of regional radation to local radiation? Int J Radiat Oncol Biol Phys. 2015;91(5):977-985.

4) Swain ea. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015;372(8):724-734.

5) Marty ea. Randomized Phase II Trial of Efficacy and Safety of Trastuzumab Combined With Docetaxel in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer Administered as First Line Treatment: The M77001 Study Group. Journal of Clinical Oncology. 2005;23(19):4265-4274.

6) Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. British Journal of Cancer. 2006;95:683-690.

7) Ara R, Brazier J. Using Health State Utility Values from the General Population to Approximate Baselines in Decision Analytic Models when Condition-Specific Data are Not Available. Value in Health. 2011;14:539-545.

8) Canadian Agency for Drugs and Technologies in Health (CADTH). pan-Canadian Oncology Drug Review Final Economic Guidance Report Carfilzomib (Kyprolis) for Multiple Myeloma. Toronto, Ontario2016: https://www.cadth.ca/sites/default/files/pcodr/pcodr_carfilzomib_kyprolis_mm_fn_egr.pdf.

9) de Oliveira C, Pataky R, Bremner KE, et al. Phase-specific and lifetime costs of cancer in Ontario, Canada. BMC Cancer. 2016;16(806).

10) Ontario Case Costing Costing Analysis Tool. Health Data Branch; 2016. https://stage.hsim.health.gov.on.ca/hdbportal/?destination=front_page. Accessed December 20, 2017.

11) Cancer Care Ontario. AC-DOCE; AC-DOCE+TRAS Provider Monograph. 2018; https://www.cancercareontario.ca/en/drugformulary/regimens/monograph/46071.

12) Cancer Care Ontario. CRBPDOCETRAS Provider Monograph. 2018; https://www.cancercareontario.ca/en/drugformulary/regimens/monograph/45506.

13) Cancer Care Ontario. FEC-D; FEC-D+Tras Provider Monograph. 2018; https://www.cancercareontario.ca/en/drugformulary/regimens/monograph/46066. Accessed January 10, 2018.

14) Beauchemin C, Letarte N, Mathurin K, Yelle L, Lachaine J. A global economic model to assess the cost-effectiveness of new treatments for advanced breast cancer in Canada. *J Med Econ.* 2016;19(6):619-629.

15) Lidgren ea. Health related quality of life in different states of breast cancer. *Qual Life Res.* 2007;16(6):1073-1081.

16) Hedden L, O'Reilly S, Lohrisch C, et al. Assessing the real-world cost-effectiveness of adjuvant trastuzumab in HER-2/neu positive breast cancer. *Oncologist*. 2012;17(2):164-171.

17) Paracha N, Thuresson P, Ray J. Assessing the Contribution of Patients' Proximity to Death in Economic Evaluations in Patients with HER2+ Metastatic Breast Cancer: An Event Based Analysis. Paper presented at: Society for Medical Decision Making2016.