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CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Abemaciclib (Verzenio) for Metastatic Breast Cancer

July 5, 2019

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

Eli Lilly Canada Inc. submitted two economic analyses to pCODR. The first analysis compared the combination of abemaciclib (ABE) and non-steroidal aromatase inhibitors (NSAI) including anastrozole or letrozole, ribociclib (RIBO) and NSAI, palbociclib (PAL) and NSAI to NSAI for the treatment of advanced breast cancer (ABC) in patients with no prior therapy (hereafter referred to as Endocrine-naïve/Sensitive ABC Model as referred to as First-Line Systemic Therapy/Endocrine-Sensitive) over a time horizon of 15 years. Another analysis compared the combination of ABE and fulvestrant (ABE-FUL), exemestane (EXE) and everolimus (EVE; EXE-EVE), palbociclib (PAL) and FUL (PAL-FUL) to FUL for the treatment of breast cancer in patients with disease progression or after prior endocrine therapy (hereafter referred to as Endocrine-resistant ABC Model) over a time horizon of 5 years. Both analyses were conducted from the perspective of the Canadian healthcare system.

Table [1]. Submitted Economic Models

Endocrine-naïve/Sensitive ABC Model	
Funding Request/Patient Population Modelled	Align with funding request
Type of Analysis	*Cost-utility analysis and cost-effectiveness analysis*
Type of Model	*Markov cohort with a fixed pay-off to account for subsequent line of therapies*
Comparator	*ABE-NSAI, RIBO-NSAI, PAL-NSAI and NSAI*
Year of costs	*2018*
Time Horizon	*15 years*
Perspective	*Government*
Cost of abemaciclib	• $0.63 per mg (150 mg per tablet) • $190.40 per day • $5,331.20 per 28-day course
Cost of ribociclib Cost of palbociclib Cost of NSAI: letrozole Cost of NSAI: anastrozole ** Price Source: Quintiles IMS Delta PA accessed March 2018*	• $0.50 per mg (200 mg per tablet) • $223.20 per day • $6,249.60 per 28-day course • $2.03 per mg (125 mg per tablet) • $190.43 per day • $5,332.11 per 28-day course • $0.55 per mg (2.5 mg per tablet) • $1.33 per day • $38.58 per 28-day course • $1.27 per mg (1 mg per tablet) • $1.27 per day • $35.64 per 28-day course
Cost of abemaciclib + NSAI (letrozole)	• $1.19 per mg • $96.58 per day • $5,408.37 per 28-day course

Cost of abemaciclib +NSAI (anastrozole)	• $1.91 per mg • $96.47 per day • $5,402.48 per 28-day course
Model Structure	*A mathematical model with three health states including progression-free survival for the first-line, post-progression survival and death. Costs and outcomes following progression were attributed at the point of relapse based on the calculation of 'a fixed pay-off.' (Refer to Figure 1 in Section 2.1 of the Detailed Technical Report).*
Key Data Sources	• *MONARCH 3 trial (Data cut: 3 November 2017)* • *MONARCH 2 trial (Data cut: not specified)* • *Network Meta-Analysis (NMA) report from submitter*
Endocrine-resistant ABC Model	
Funding Request/Patient Population Modelled	Align with a funding request
Type of Analysis	*Cost-utility analysis and cost-effectiveness analysis*
Type of Model	*Partition-survival*
Comparator	*ABE-FUL, EXE-EVE, PAL-FUL, and FUL*
Year of costs	*2017*
Time Horizon	*5 years*
Perspective	*Government*
Cost of abemaciclib	• $0.63 per mg (150 mg per tablet) • $190.40 per day • $5,331.20 per 28-day course
Cost of exemestane Cost of everolimus Cost of palbociclib Cost of fulvestrant ** Price Source: : Quintiles IMS Delta PA accessed March 2018*	• $0.05 per mg (25 mg per tablet) • $1.33 per day • $37.24 Per 28-day course • $20.13 per mg (10 mg per tablet) • $201.25 per day • $5,635 per 28-day course • $2.03 per mg (125 mg per tablet) • $190.43 per day • $5,332.11 per 28-day course • $2.33 per mg (250 mg per ml) • $41.64 per day • $1,165.80 per 28-day course for cycle 2 onwards • Cost for cycle 1 (including loading dose) = = $2,331.60
Cost of abemaciclib + fulvestrant	• $2.97 per mg • $232.04 per day • $6,497.00 per 28-day course for cycle 2 onwards • Cost for cycle 1 (including fulvestrant loading dose) = $7,662.80

Model Structure	*A mathematical model with three health states including progression-free survival, post-progression survival and death (Refer to Figure 4 in Section 2.1 of the Detailed Technical Report).*
Key Data Sources	• *MONARCH 2 trial (data cut: 14th February 2017)* • *NMA report from the Submitter*

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison of abemaciclib – NSAI, ribociclib – NSAI, palbociclib – NSAI and NSAI is appropriate. The Submitter did include all relevant comparators in modifications to the main economic analysis.

The CGP concluded that there is a net overall clinical benefit to the addition of abemaciclib to NSAI for post-menopausal women with HR-positive, HER2 negative advanced breast cancer who had no prior systemic therapy in the advanced setting. Additionally, the CGP also concluded that there is a net clinical benefit to the addition of abemaciclib to fulvestrant for women with HR-positive, HER-2 negative ABC who had progressed while receiving neo-adjuvant or adjuvant endocrine therapy, < 12 months from the end of adjuvant ET, or while receiving first-line ET for metastatic disease (excluding patients previously treated with CDK inhibitors).

The conclusion is based on the MONARCH 3 and MONARCH 2 trials that demonstrated a clinically and statistically significant benefit in progression-free survival for abemaciclib in combination with NSAI or fulvestrant.

The CGP has no major concern regarding the effectiveness and toxicity of abemaciclib. The CGP assumed that abemaciclib had no detrimental effects on patient quality of life (QoL). This assumption was supported by an unpublished analysis of QoL data performed by the Submitter. The analysis showed no statistical difference in QoL between abemaciclib and control arms in both endocrine-naïve/sensitive and endocrine-resistant settings. The CGP also noted immature OS data obtained from MONARCH 2 and MONARCH 3 trials and the increased risk of myelosuppression with neutropenia, febrile neutropenia, and diarrhea among patients receiving abemaciclib. This concern was addressed in the submitted economic evaluations.

Summary of registered clinician input relevant to the economic analysis
The registered clinician considered abemaciclib as an alternative option for first-line therapy and for patients who are intolerant to palbociclib. Abemaciclib could also be preferred in patients with brain metastases, baseline cytopenias due to bone marrow involvement (by cancer) or residual effects of previous chemotherapy (for other cancers, or past adjuvant chemotherapy). Abemaciclib causes less myelosuppression and has a lower risk of significant neutropenia than palbociclib. *Side effects of abemaciclib and palbociclib flagged by the registered clinician were adequately considered in the economic analysis.*

Summary of patient input relevant to the economic analysis
Patients considered controlling disease progression and extending life expectancy as the most important outcomes for their breast cancer treatments. Patients who have been treated with abemaciclib had good experience with the treatment outcomes, but experienced manageable and tolerable diarrhea. Patients also reported other side effects of abemaciclib including lost of appetite, abdominal pain, nausea, gas and low blood counts. *The submitted economic analysis considered disease progression, life expectancy, quality of life, and important side effects of abemaciclib, such as diarrhea.*

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis

PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for abemaciclib which are relevant to the economic analysis:

- Additional healthcare resources that may be required to monitor toxicities and drug-drug interactions routinely. The high incidence of neutropenia and gastrointestinal-related toxicity may lead to more frequent visits to oncologists. *This factor was not considered in the submitted economic analysis. The EGP reanalysis showed that increased follow-up visits among patients receiving abemaciclib caused minimal impact on the cost-effectiveness results.*
- The increased tablets of abemaciclib compared to palbociclib and palbociclib may be less convenient for patients but a continuous daily schedule without day off treatment may be easier for the patient. The oral route of administration is also an enabler factor. *The economic analysis adequately considered this factor.*
- PAG was concerned about the impact of post-progression therapies, particularly the use of everolimus and exemestane after abemaciclib. *This concern was not addressed in the submitted economic analysis. The EGP reanalysis revealed that the combination of abemaciclib and non-steroidal aromatase inhibitor was less economically attractive if the proportion of patients receiving everolimus and exemestane after abemaciclib increased.*
- Fulvestrant is not publicly funded in any Canadian provinces. This may limit the uptake of the combination of abemaciclib and fulvestrant. *The submitted budget impact model did not account for this factor. The EGP reanalysis showed that if more patients were switched to abemaciclib from other treatments besides palbociclib, the budgetary impact of abemaciclib and fulvestrant would increase significantly.*

1.3 Submitted and EGP Reanalysis Estimates

Endocrine-naïve/Sensitive ABC

The EGP reanalysis focused on the comparison of ABE-NSAI and NSAI because the relative difference in efficacy of ABE and other CDK 4/6 inhibitors was unknown. The Submitter obtained the comparative efficacy of CDK 4/6 from an indirect comparison analysis which has poor methodological quality due to the substantial difference in patient characteristics enrolled in randomized control trials (RCTs) included in the analysis.

Table [2]. Submitted and EGP Reanalysis Estimates (ABE-NSAI vs. NSAI)

Estimates (range/point)	Submitted	EGP Reanalysis (Lower Bound, Upper Bound)
ΔE (LY)		
Progression-free	0.42	-0.14, 0.58
Post-progression	0.22	-0.17, 0.30
ΔE (QALY)		
Progression-free	0.340	-0.070, 0.440
Post-progression	0.111	-0.010, 0.150
ΔC ($)		
ICER estimate ($/QALY)	$331,023	$189,609, $2,125,957

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

- Given the large uncertainty in the results of indirect comparison for ABE-NSAI, RIBO-NSAI, and PAL-NSAI, the EGP performed an exploratory analysis and assumed comparable: a) time to progression and b) probability of death after the 1st line treatment for ABE-NSAI, RIBO-NSAI, and PAL-NSAI.

- The Submitter assumed the partial relationship between progression-free survival (PFS) and overall survival (OS). The EGP felt that the assumption was reasonable because a gain in PFS may not lead to a 100% gain in overall survival. However, there was high uncertainty in a calibration factor that used in the model to reduce the time spent in the post-progression survival. The Submitter did not provide any references for the calibration factor and the descriptions of how the factor was estimated.
- Long-term progression and survival data were predicted from an RCT with a short follow-up. The predicted long-term outcomes, especially for overall survival, were therefore highly uncertain given that the median overall survival from the MONARCH 3 trial has not been reached.
- The submitted model assumed no interruption to treatments and no change to drug dosage. The CGP and EGP believed that this assumption is unrealistic as patients might be asked to stop the treatment or reduce drug dosage due to adverse events (AEs). According to the MONARCH 3 trial, ABE dose was reduced due to adverse in 189 patients (42.9%) compared with three (1.3%) receiving placebo. Moreover, drug interruption due to AEs was found in 229 patients receiving ABE (51.9%) and in 26 patients (11.7%) receiving placebo.
- For each day a patient stayed in the hospital, the average cost was assumed to be $632.90 per day. The EGP was unable to verify the source of this unit cost and believed that the cost was underestimated given that the average hospital cost per day for patients with breast cancer in Ontario was $2,363.53.
- A health utility decrement of 0.113 was applied to ABC patients who received chemotherapies. This value was obtained from the published NICE report that cited a study conducted by Peasgood et al. (2010). The EGP reviewed the cited study but was unable to verify this value.

Endocrine-resistant ABC

The EGP reanalysis focused on the comparison of ABE-FUL and FUL because the relative difference in efficacy of ABE and other CDK 4/6 inhibitors questionable. The Submitter obtained the comparative efficacy of ABE-FUL and PAL-FUL from an indirect comparison analysis which has poor methodological quality due to the substantial difference in patient characteristics enrolled in RCTs included in the analysis.

Table [3]. Submitted and EGP Reanalysis Estimates (ABE-FUL vs. FUL)

Estimates (range/point)	Submitted	EGP Reanalysis (Lower Bound, Upper Bound)
ΔE (LY)		
Progression-free	0.80	0.57, 0.92
Post-progression	-0.68	-0.80, 0.22
ΔE (QALY)		
Progression-free	0.595	0.263, 0.825
Post-progression	-0.345	-0.449, -0.128
ΔC ($)		
ICER estimate ($/QALY)	$464,455	$430,659, $2,115,150

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

- The Submitter used a partition-survival model. Although this approach is appropriate, its key limitation is the assumption that survival functions are independent. This assumption may cause inaccurate and infeasible scenarios when extrapolating survival from within trial data. For instance, the predicted progression-free survival may be larger than the predicted overall survival that is considered unrealistic. The Submitter avoided unreasonable progression-free

survival estimates from the partition-survival model by forcing the model to select the minimum value of progression-free survival and overall survival.

- The Submitter obtained the comparative efficacy of ABE-FUL and FUL from the intention-to-treat population of the MONARCH 2 trial (data cut, 14 February 2017) but obtained the relative treatment effect of EXE-EVE, PAL-FUL, and FUL from the indirect comparison report. By using different data sources to inform treatment effect, the Submitter assumed that the characteristics of patients enrolled in the MONARCH 2 trial and in other RCTs included in the indirect comparison report were comparable and did not have any impact on the cost-effectiveness findings. The EGP felt that this assumption is unrealistic. To compare the cost-effectiveness of the four comparators (ABE-FUL, EXE-EVE, PAL-FUL, and FUL), the comparative efficacy of all treatments should come from the same data source, i.e. an indirect comparison report.
- In the base case model, a Weibull distribution was selected to extrapolate ABE-FUL and FUL OS data beyond the MONARCH 2 trial follow-up. Based on the parametric extrapolation curves and AIC/BIC statistics presented in the economic report, the EGP argue that a Gompertz distribution had the best fit with the observed trial data; this distribution, therefore, should be used in the base case. The EGP was also concerned about the use of data from the CONFIRM trial to append the overall survival data observed from the MONARCH 2 trial. The CONFIRM trial compared FUL 250 mg with FUL 500 mg in postmenopausal women with estrogen receptor–positive ABC. This approach may mislead the long-term overall survival data as it is unclear whether patients who enrolled in the CONFIRM and MONARCH 2 trials had similar baseline characteristics. The EGP was unable to compare the characteristics of patient enrolled in the two trials because the CONFIRM trial reported limited patient and disease characteristics.
- The Submitter used 28-month MONARCH 2 trial data to predict long-term clinical outcomes over 5 years. The overall survival prediction is highly uncertain given that the median overall survival from the MONARCH 2 trial has not been reached.
- The Submitter assumed a hospital cost of $612.19 per day. The EGP was unable to verify the source of this unit cost.

1.4 Detailed Highlights of the EGP Reanalysis

Endocrine-naïve/Sensitive ABC

Given the large uncertainty in the results of indirect comparison for ABE-NSAI, RIBO-NSAI, and PAL-NSAI, the EGP reanalyses focused on ABE-NSAI and NSAI. The EGP made the following changes to the economic model:

- As there is high uncertainty in the progression-free survival and overall survival data, the EGP shortened a model time horizon from a patient lifetime (15 years) to the trial follow-up period (37 months for MONARCH 3 trial and 28 months for MONARCH 2 trial).
- It is unclear the extent that the gain in progression-free survival may translate to the overall gain survival; the EGP, therefore, assessed the uncertainty in this parameter by varying the calibration factor from 13.75% to 55%. This range was chosen arbitrarily to reflect the change in the calibration factor by 50% from the base case value.
- The EGP accounted for the ratio of used to the planned dose intensity (relative dose intensity, RDI) reported in MONARCH 3, MONARCH 2 and other published RCTs in the reanalyses.
- The EGP addressed PAG's concern regarding the use of EXE-EVE as post-progression therapies by increasing the proportion of EXE-EVE use by 10% and 20%.
- PAG was concerned about additional follow-up visits due to abemaciclib. The EGP addressed this concern by arbitrarily varying the follow-up cost by 20%.

- The EGP replaced a hospital cost per day used in the submitted model with an alternative value of $2,363.53 obtained from patients with ABC residing in Ontario (1).
- The EGP varied a health utility decrement associated with chemotherapies by 20%. The range was chosen arbitrarily.
- PAG is interested in the comparative cost-effectiveness of CDK 4/6 inhibitors, the EGP conducted two exploratory analyses and assumed: a) the same efficacy and b) the same time-on-treatment across CDK 4/6 treatments.

Table [4]. EGP Reanalysis Estimates

One-way and multi-way sensitivity analyses					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
1.Used the relative efficacy data from the MONARCH 3 trial	$148,675	0.389	0.53	$382,342	$51,319
2. Shortened a time horizon from 15 years to the end of the follow-up of MONARCH 3 and MONARCH 2 trials	$76,555	-0.039	-0.08	-$1,962,949	-$2,293,972
3. Decreased the proportion of the gain in PFS to OS gain to 13.75%	$140,911	0.348	0.47	$404,342	$73,319
4. Increased the proportion of the gain in PFS to OS gain to 55%	$147,672	0.590	0.86	$250,402	-$80,621
5.Applied RDI observed in the primary RCT publications	$107,645	0.443	0.63	$242,732	-$88,291
6.Increased the proportion of patients with ABE-NSAI who received EXE-EVE as subsequent therapies by 10%	$147,226	0.445	0.61	$330,547	-$476
7.Increased the proportion of patients with ABE-NSAI who received EXE-EVE as subsequent therapies by 20%	$151,992	0.454	0.63	$334,961	$3,938
8. Decreased the cost of follow-up by 20%	$140,514	0.435	0.61	$323,351	$1,870
9. Increased the cost of follow-up by 20%	$147,649	0.432	0.61	$341,697	$10,674
10.Increased hospital cost per day to $2,363.53	$153,219	0.432	0.62	$354,281	$23,258
11.Decreased unit costs of increased ALT, increased AST and diarrhea	$142,962	0.432	0.61	$331,124	$101
12.Decreased health utility decrement due to chemotherapy by 20%	$143,724	0.432	0.62	$332,893	$1,870
13.Increased health utility decrement due to chemotherapy by 20%	$144,226	0.445	0.63	$324,304	-$6,719

EGP's Reanalysis for the Best Case Estimate					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR	Δ from baseline submitted ICER
Baseline (Submitter's best case)	143,906	0.435	0.62	$331,023	--
Best case estimates of above 7 parameters					
[LOWER BOUND]					
EGP's lower bound estimate combining the above reanalyses: 4, 5, 6, and 8*	$113,374	0.598	0.85	$189,609	-$141,414
[UPPER BOUND]					
EGP's upper bound estimate combining the above reanalyses: 1, 2, 3, 7, 9, 10, 11 and 12*	$80,543	0.038	-0.02	$2,125,957	$1,794,934

Note: *The EGP's lower bound combines scenarios with decreased ICUR from the base case, and the EGP's upper bound combines scenarios with increased ICUR from the base case.

Table [5]. EGP Exploratory Analysis Based on a Sequential Analysis

Description	Costs	ΔC	QALY	ΔE	ICUR
Submitter's Best Case					
NSAI	$120,719	Reference	2.476	Reference	Reference
PAL - NSAI	$227,578	$106,859	2.925	0.450	$237,662
RIBO - NSAI	$250,301	$237,662	2.903	-0.023	Dominated
ABE - NSAI	$264,625	$14,324	2.910	0.008	Dominated
Assuming the same efficacy across CDK 4/6 inhibitors					
NSAI	$120,511	Reference	2.478	Reference	Reference
PAL - NSAI	$227,678	$107,167	2.918	0.440	243,449
RIBO - NSAI	$250,709	$23,030	2.908	-0.011	Dominated
ABE - NSAI	$264,866	-$14,157	2.906	0.002	Dominated
Assuming the same TTD across CDK 4/6 inhibitors					
NSAI	$119,824	Reference	2.477	Reference	Reference
ABE - NSAI	$265,223	$145,400	2.928	0.451	$322,116
PAL - NSAI	$291,405	$26,182*	2.935	0.006*	$4,075,274*
RIBO - NSAI	$321,189	$29,784	2.912	-0.023	Dominated

Note: *compared to ABE-NSAI

Endocrine-resistant ABC

Given the large uncertainty in the results of indirect comparison for ABE-FUL and PAL-FUL, the EGP reanalyses focused on ABE-FUL and FUL. The EGP made the following changes to the economic model:

- The Submitter obtained the relative efficacy of ABE-FUL and FUL from the MONARCH 2 trial but obtained the relative efficacy of EVE-EXE, PAL-FUL, and FUL from the indirect comparison report. The EGP disagreed with this approach as it ignores the potential difference in study and patient characteristics between the MONARCH 2 trial and the RCTs included in the indirect comparison study. To compare the cost-effectiveness of the four comparators, the comparative efficacy of all treatments should come from the same data source, i.e. an indirect comparison report.

- In the base case, a Weibull distribution was used to extrapolate the ABE-FUL and FUL OS data beyond the MONARCH 2 trial follow-up period. The EGP performed a reanalysis by replacing the parametric survival distribution for overall survival data of ABE-FUL and FUL to a Gompertz distribution and removing the CONFIRM trial data from the model.
- The EGP assessed the uncertainty in the long-term progression-free survival and overall survival data by shortening a time horizon from a patient lifetime (5 years) to the MONARCH 2 trial follow-up period (28 months).
- The EGP believed that the hospital cost per day used in the submitted model was too low, leading to the underestimation of the total cost of ABE-FUL. The EGP used an alternative value of $2,310.38 obtained from patients with ABC in Ontario in a reanalysis (1).
- According to PAG, FUL will soon become generic, and its acquisition cost is therefore expected to decrease. The decreased cost of FUL led to a slight reduction in the estimated ICUR causing ABE-FUL more economically attractive.
- The EGP noted a minor error in the calculation of a standard error of hospital cost per day. The correction had a negligible impact of the cost-effectiveness results.
- PAG is interested in the comparative cost-effectiveness of CDK 4/6 inhibitors, the EGP conducted two exploratory analyses by assuming: a) the same efficacy and b) the same time-on-treatment across CDK 4/6 treatments.

Table [6]. EGP Reanalysis Estimates

One-way and multi-way sensitivity analyses					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
1. *Used the comparative efficacy of all treatments from the NMA*	$113,203	0.242	0.10	$467,162	$2,707
2. *Replaced the parametric survival model from a Weibull distribution with long-term data from the CONFIRM trial to a Gompertz distribution without the CONFIRM trial data*	$111,777	0.249	0.16	$448,508	-$15,947
3. *Shortened the analytical time horizon from 5 years to the end of the MONARCH 2 follow-up*	$88,255	0.122	0.05	$721,811	$257,356
4. *Did not adjust for interval censoring for PFS data and predicted long-term PFS using exponential distribution*	$114,139	0.237	0.11	$481,657	$17,202
5. *Did not adjust for interval censoring for PFS data and predicted long-term PFS using Gompertz distribution*	$112,103	0.220	0.11	$508,564	$44,109
6. *Increased hospital cost per day to $2,310.38*	$110,262	0.239	0.10	$461,235	-$3,220

7. *Decreased unit costs associated with increased gamma-glutamyltransferase and diarrhea*	$114,123	0.239	0.10	$476,602	$12,147
8. *Decreased the acquisition cost of FUL by 25%*	$111,743	0.243	0.10	$459,148	-$5,307
EGP's Reanalysis for the Best Case Estimate					
Description of Reanalysis	ΔC	ΔE		ICUR	Δ from baseline submitted ICER
Baseline (Submitter's best case)	$113,827	0.245	0.11	$464,455	--
[LOWER BOUND]					
EGP's lower bound estimate combining the above reanalyses: 2, 6 and 8*	$103,612	0.241	0.16	$430,659	-$33,796
Best case estimate of above 8 parameters					
[UPPER BOUND]					
EGP's upper bound estimate combining the above reanalyses: 1, 3, 5, and 7*	$87,442	0.041	0.12	$2,115,150	$1,650,695

Note: *The EGP's lower bound combines scenarios with decreased ICUR from the base case, and the EGP's upper bound combines scenarios with increased ICUR from the base case.

Table [7]. EGP Exploratory Analysis Based on a Sequential Analysis

Description	Costs	ΔC	QALY	ΔE	ICUR
Submitter's Best Case					
FUL	$57,001	Reference	1.784	Reference	Reference
EXE-EVE	$127,856	$70,855	1.898	0.114	Extended dominance
ABE-FUL	$170,828	$42,972	2.029	0.131	Extended dominance
PAL-FUL	$194,516	$137,515	2.089	0.305	$451,437
Assuming the same efficacy across CDK 4/6 inhibitors					
FUL	$57,047	Reference	1.787	Reference	Reference
EVE-EXE	$128,143	$71,097	1.902	0.115	Extended dominance
ABE-FUL	$170,654	$113,608	2.030	0.243	$467,659
PAL-FUL	$175,542	$4,888*	2.036	0.007*	$718,791*
Assuming the same TTD across CDK 4/6 inhibitors					
FUL	$57,046	Reference	1.784	Reference	Reference
EVE-EXE	$127,417	$70,370	1.896	0.112	Extended dominance
PAL-FUL	$171,153	$43,736	2.029	0.134	Extended dominance
ABE-FUL	$171,423	$114,377	2.099	0.315	$363,097

Note: * compared to ABE-FUL

1.5 Evaluation of Submitted Budget Impact Analysis

Endocrine-naïve/sensitive ABC

The factors that most influence the budget impact analysis include the number of treatment cycles, the ratio of used and planned dose intensity, and the variation in the uptake rate of ABE-NSAI. Replacing the number of treatment cycles by the mean progression survival decreased the budget impact. Assuming 100% of the ratio of used and planned dose intensity for all drugs increased budget impact due to increased drug

spending in all treatments. Varying the uptake rates of ABE-NSAI had minimal changes in the base case results. However, changes in the market shares of PAL-NSAI and RIBO-NSAI had a substantial impact on the 3-year budget due to their large acquisition costs. The larger market share of PAL-NSAI and RIBO-NSAI that ABE-NSAI can replace, the smaller budgetary impact of ABE-NSAI to the healthcare system.

Key limitations of the BIA model were:

- The budget impact analysis assumed that most of the market share of ABE-NSAI will come from PAL-NSAI. The EGP assessed the impact of this assumption by allocating the smaller proportion of the market share of PAL-NSAI to ABE-NSAI but increased the larger allocation (2%) of the market share of NSAI to ABE-NSAI. This EGP reanalysis increased the 3-year budgetary impact substantially by 479%.
- The Submitter assumed that patients are receiving each comparator for 16 cycles. This assumption would overestimate the total budgetary impact because 16 treatment cycles would suggest that patients received treatment for 14.7 months per year. The EGP was able to explore this limitation by restricting the number of treatment cycles to 12 months (13 cycles). Reducing the treatment cycles from 16 to 13 reduced the 3-year budgetary impact by 19%.
- The registered clinician consulted by pCODR suggested that ABE as monotherapy would be a valuable option as a second- or third-line therapy for selected patients given its significant activity after prior treatment with an aromatase inhibitor. If more patients are eligible for ABE, there would be a larger budgetary impact on the healthcare system.

Endocrine-resistant ABC

The factors that most influence the budget impact analysis include the number of treatment cycles, the ratio of used and planned dose intensity, and the variation in the uptake rate of ABE-FUL. Replacing the number of treatment cycles by the mean progression-free survival decreased the budgetary impact. Applying the ratio of used and planned dose intensity observed in each primary RCTs to the model decreased budget impact substantially. Varying the uptake rate of ABE-FUL had minimal impact on the base case results. However, changes in the market shares of PAL-FUL because of increased uptake of ABE-FUL had a substantial impact on the 3-year budgetary impact. The larger market share of PAL-FUL that ABE-FUL can replace, the smaller budgetary impact of ABE-FUL to the health care system.

Key limitations of the BIA model included:

- The model assumed that ABE-FUL was publicly funded for all eligible patients, and all market share of ABE-FUL will come from PAL-FUL. PAG advised that FUL is not publicly funded in any provinces for metastatic breast cancer. Increased market share of ABE-FUL may, therefore, come from the market shares of other publicly funded treatments. The EGP assessed the impact of this assumption by removing PAL-FUL from the list of comparators and assuming that the market share of ABE-FUL would come from EVE-EXE, EXE, and TMX. This EGP reanalysis changed the 3-year budget impact from cost-savings to a substantial cost-increase.
- In addition, the submitted model did not account for administration cost of FUL. PAG was concerned that FUL would require additional nursing resources to administer the intramuscular injection. EGP addressed this concern by adding the administration cost for FUL ($1,070.11 for loading dose and $222.93 for subsequent doses).
- PAG also noted that FUL would soon become generic. However, changes in the total cost of FUL did not affect the budgetary impact shown in the submitted base case because both ABE and PAL were used in combination with FUL.

1.6 Conclusions

For the endocrine-naïve/sensitive setting, the EGP's best estimate of ΔC and ΔE for the combination of abemaciclib and anastrozole/letrozole when compared to non-steroidal aromatase inhibitor is:

- Between $189,609/QALY and $2,125,957/QALY
- Within this range, the best estimate would likely be $382,342/QALY, corresponding to the scenario when the treatment effect was obtained from the MONARCH 3 trial.
- The extra cost of abemacliclib plus anastrozole/letrozole is between $80,543 and $113,374. The factor that has the greatest influence on cost is the time horizon used for the economic analysis.
- The extra clinical effect of abemacliclib plus anastrozole/letrozole is between 0.038 and 0.598 QALY. The factor that has the greatest influence on the QALY is the time horizon used for economic analysis.
- The exploratory sequential cost-effectiveness analysis conducted by the EGP showed that ABE-NSAI and RISO-NSAI were dominated by PAL-NSAI except when all CDK 4/6 inhibitors were assumed to have the same treatment duration. For this scenario, the ICUR of ABE-NSAI was $322,116 per QALY compared to NSAI, and the ICUR of PAL-NSAI was $4,075,274 per QALY compared to ABE-NSAI. Results of the sequential analysis should be interpreted with great caution due to the high clinical heterogeneity observed in the NMA of the comparative efficacy of ABE-NSAI, RIBO-NSAI and PAL-NSAI.

For the endocrine-resistant setting, the EGP's best estimate of ΔC and ΔE for the combination of abemaciclib and fulvestrant when compared to fulvestrant is:

- Between $430,659/QALY and $2,115,150/QALY,
- Within this range, the best estimate would likely be $448,508/QALY, corresponding to the scenario when a Gompertz model was used to predict long-term OS without leveraging data from the CONFIRM trial.
- The extra cost of abemacliclib plus fulvestrant is between $87,442 and $103,612. The factor that has the greatest influence on cost is the time horizon used for the economic analysis.
- The extra clinical effect of abemacliclib plus fulvestrant is between 0.241 and 0.245 QALY. The factor that has the greatest influence on the QALY is the time horizon used for the economic analysis. The exploratory sequential cost-effectiveness analysis conducted by the EGP showed that ABE-FUL was dominated by PAL-FUL except when all CDK 4/6 inhibitors were assumed to have the same treatment duration. For this scenario, EXE-EVE and PAL-FUL were dominated by ABE-FUL, and the ICUR of ABE-FUL was $363,097 per QALY compared to FUL. Results of the sequential analysis should be interpreted with great caution due to the high clinical heterogeneity observed in the NMA of the comparative efficacy of ABE-FUL, EXE-EVE and PAL-FUL.

Overall conclusions of the submitted model:

The model structures and assumptions are adequate and well-justified. Assumptions used for healthcare utilization and cost estimates are also well-described. However, the sequential cost-effectiveness analysis of abemaciclib in both endocrine-naïve/sensitive and endocrine-resistant settings are subject to important limitations concerning the poor methodological quality of indirect comparison of the efficacy and safety of CDK 4/6 inhibitors and the lack of longer-term clinical evidence of abemaciclib. In the absence of comparative studies comparing all CDK 4/6 inhibitors available in Canada, careful consideration must be taken when compared the cost-effectiveness of abemaciclib with other CDK 4/6 inhibitors.

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 Cancer 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 abemaciclib + NSAI or abemaciclib + fulvestrant for advanced or metastatic breast cancer. A full assessment of the clinical evidence of abemaciclib + NSAI or abemaciclib + fulvestrant for advanced or 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.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 non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

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.

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