CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Palbociclib (Ibrance) with Fulvestrant for Metastatic Breast Cancer

May 3, 2019

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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.
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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Pfizer Canada Inc,** compared Palbociclib + fulvestrant with fulvestrant alone, for the treatment of patients with hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2 negative) locally advanced or metastatic breast cancer (aBC or mBC) who have progressed on prior endocrine therapy.

- Palbociclib + letrozole (an aromatase inhibitor (AI)) is currently approved and reimbursed for the initial treatment of patients in this population.
- Palbociclib in combination with fulvestrant received Health Canada approval for the following indication in May 2017.
- For the treatment of women with HR+/HER2- locally ABC or mBC whose disease progressed after prior endocrine therapy. Pre or perimenopausal women treated with palbociclib must also be treated with a luteinizing hormone releasing hormone (LHRH) agonist.
- Palbociclib is also approved in Canada in the following indication:
- In combination with letrozole for the treatment of postmenopausal women with ER+, HER2- ABC as initial endocrine based therapy for their metastatic disease.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	**Pfizer Canada Inc** is requesting Palbociclib + fulvestrant to be listed for the treatment of patients with HR+/HER2- locally ABC/mBC who have progressed on prior endocrine therapy This aligns with the patient population that the economic model is built on.
Type of Analysis	Cost effectiveness and cost utility analysis
Type of Model	*Partitioned-survival model*
Comparator	*<u>Reference case:</u>* *Fulvestrant (500 mg)* *<u>Secondary analyses:</u>* *Everolimus (10 mg) + Exemestane (25 mg)* *Exemestane (25 mg)* *Anastrozole (1 mg)* *Letrozole (2.5 mg)*
Year of costs	*2018*
Time Horizon	*15 years*
Perspective	*Government*
Cost of Palbociclib	Available as 125 mg capsule. Recommended dose of 125 mg once daily for 21 consecutive days, followed by 7 days off treatment Per dosage form and amount • $253.9123 per unit • $5,332.16 per cycle
Cost of Fulvestrant	Available as 250 mg/ 5 ml injection. Recommended dose of 500 mg on days 0, 14, 28 and every 28 days thereafter. • $ 582.90 per unit • 1st cycle cost: $2,331.60 • Subsequent cycles cost: $1,165.80

Cost of Exemestane	Available as 25 mg; recommended dose of 25 mg; • $1.3263 per dosage form • $37.14 per 28-day course
Cost of everolimus	Available as 10 mg; recommended dose 10 mg; • $201.25 per dosage form • $5,634.87 per 28-day course
Model Structure	*The model was comprised of 3 health states: pre-progression, progression (or post-progression), and death. Transitions between these health states were driven by the PALOMA-3 trial progression-free survival (PFS) and overall survival (OS) data. A NMA was conducted to inform comparisons between palbociclib + fulvestrant and other relevant comparators.*
Key Data Sources	*The efficacy and safety parameters were based on the PALOMA-3 trial. Various statistical methods for extrapolating survival beyond the trial period were considered.*

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison of palbociclib plus fulvestrant to fulvestrant plus placebo is not appropriate to the Canadian setting as fulvestrant monotherapy is not widely used in Canada. The Submitter did include a comparison to Canadian treatment options in modifications to the main economic analysis.

Relevant issues identified included:

- *The comparison regimen, fulvestrant (with placebo) is not currently funded in most Canadian provinces and is not widely used. However, a NMA considered to be methodologically sound, did provide comparisons with other commonly used endocrine therapies. PFS/TTP were superior for palbociclib + fulvestrant compared with endocrine monotherapies, but similar to the combination of everolimus + exemestane.*
- *Although through indirect comparison between palbociclib + fulvestrant versus everolimus + exemestane in the NMA it was not possible to determine a difference in efficacy based on PFS/OS, registered clinician input suggests that the side-effect profile of the former regimen is more favorable. Everolimus + exemestane is often poorly tolerated due to mucositis, nausea, diarrhea and rash. Thus, the CGP considered that there is net clinical benefit for palbociclib + fulvestrant, and this regimen may be preferred by treating clinicians.*
- *The CGP agreed with the Methods team that it was reasonable to exclude chemotherapy regimens from the NMA, as usual clinical practice is to try all possible endocrine options before considering chemotherapy, unless there is clear evidence of complete endocrine resistance, or the presence of rapidly progressive/life-threatening disease. Furthermore, while there was no direct or indirect comparison of palbociclib plus fulvestrant with tamoxifen, the CGP felt confident that there was sufficient body evidence to confirm that AI's are more effective than tamoxifen. The CGP therefore agreed that as the PALOMA-3 results were consistent with the palbociclib combination having improved efficacy in comparison to aromatase inhibitors that are known to be more effective than tamoxifen, palbociclib + fulvestrant is likely to have superior efficacy to tamoxifen monotherapy, and may be the preferred option.*
- *The trial was stopped early for efficacy benefit (although after full recruitment) and this could lead to a substantial over-estimate of benefit in a trial with fewer than 500 PFS or OS events.*
- *Expanding the treatment indications to include the rare male patient with mBC, and those who have HER2 double-equivocal tumors would be reasonable.*
- *The CGP recommends that palbociclib + fulvestrant use should be restricted to patients who have only received 1 prior line of chemotherapy for mBC, as permitted in the PALOMA-3 trial.*

- *Many Canadian clinicians will already have experience in the use of palbociclib, with letrozole, in the first-line treatment of mBC, and most cancer centres will have processes in place for the appropriate safety monitoring of palbociclib treatment. Administration of fulvestrant requires loading doses and monthly IM injections, which can be uncomfortable for patients and will be associated with extra costs. There are similar issues related to the delivery of LHRH agonist injections for pre/perimenopausal women.*

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered the following:

- There are limited treatment options for patients with metastatic hormone receptor positive, HER2-negative breast cancer who have progressed on previous endocrine therapy, outside of chemotherapy. Patients in this category are common and continued treatment with alternate endocrine and other non-chemotherapeutic approaches is generally preferred by clinicians.
- Clinicians consider palbociclib plus fulvestrant to be a safe and effective next line therapy for patients who have developed resistance to endocrine therapy including aromatase inhibitors. This combination would naturally replace second line aromatase inhibition. Clinicians value the potential choice of using palbociclib in either the first or second line setting.
- Oncologists believe that palbociclib and fulvestrant constitute an advantageous treatment strategy to overcome primary endocrine resistance. Clinicians reasoned that since fulvestrant plus palbociclib is more effect than fulvestrant alone, the combination is also likely more effective than next line single-agent hormonal therapy and hence would be preferred.
- Palbociclib would improve PFS in all subsets. According to clinicians, PFS improvement is clinically meaningful and substantially delays symptomatic deterioration and the need for chemotherapy.
- PFS data does not allow comparison with exemestane plus everolimus or chemotherapy, but the side-effect profile of palbociclib plus fulvestrant is more favourable. Exemestane plus everolimus is often poorly tolerated due to mucositis, nausea, diarrhea and rash, and may particularly affect patients with significant lung disease not related to cancer.

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

- There is an ongoing need for new therapies that can control mBC and maintain quality of life.
- Patients rated the change to their quality of life on palbociclib compared to other therapies they had received. Overall, respondents felt that the palbociclib-based treatment led to a modest improvement in quality of life and a substantial improvement in disease control. The patients expressed a preference for prioritizing disease control and the vast majority believed that palbociclib had such an effect.
- Treatment with palbociclib and fulvestrant led to successful disease control in seven of the eight CBCN patients. These patients reported positive impact on their quality of life.
- RBC recorded patient experiences (n=17) regarding side effects associated with palbociclib. More than half gave their side effects a score of less than 5 on a scale of 1 (completely tolerable) to 10 (completely intolerable), with an average score of 4.47. Fatigue (82%) and neutropenia (65%) were the most commonly cited side effects associated with palbociclib.
- Similarly, CBCN compiled patient feedback on side effects caused by palbociclib/fulvestrant. Seven of the eight patients reported side effects which included fatigue, hair thinning, diarrhea, sore mouth and neutropenia. Some patients were taking additional medication to manage the side effects, but most were able to manage them with rest, laxatives and a controlled diet. All patients interviewed indicated that the side effects they experienced were acceptable.

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 palbociclib plus fulvestrant which are relevant to the economic analysis:

- Various treatments are available for patients with metastatic breast cancer previously treated with endocrine therapy. These include exemestane plus everolimus, tamoxifen, and chemotherapy. PAG noted that the comparator in the PALOMA-3 trial was fulvestrant and fulvestrant is not publically funded in any provinces for metastatic breast cancer. Exemestane plus everolimus is not funded after palbociclib plus letrozole in the first-line setting.
- The PAG input focused on concerns that fulvestrant is not publically funded in any provinces for use in mBC, leading to extra costs for drugs and administration, and also on the other extra costs related to increased level of monitoring for patients on palbociclib, and possible drug wastage.
- PAG noted that this is a large patient population.
- As an oral drug, palbociclib can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is an enabler to implementation.
- Fulvestrant is available as 250mg pre-filled syringes. Pharmacy preparation is not required and there is no wastage concern as the dose is 500mg given as two separate injections. This is an enabler to implementation. PAG noted that fulvestrant must be refrigerated and as fulvestrant comes in a large box, fridge space can become a concern. Fulvestrant requires nursing resources to administer the intramuscular injection. The volume and viscosity of fulvestrant can be a challenge for health care professionals. Patients would need monthly treatment visits, which requires incremental resources over patients who receive oral endocrine therapy.

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Estimates (Deterministic)

	Base Case		EGP Reanalysis: lower and upper bounds	
Estimates	**Fulvestrant**	**Everolimus + Exemestane**	**Fulvestrant**	**Everolimus + Exemestane**
ICER estimate ($/QALY), range/point	$191,613	$122,172	$224,756 to $294,552	$633,600 to $698,289
ΔE (QALY), range/point	0.47	0.163	0.273 to 0.467	0.026-0.142
ΔE (LY), range/point	0.54	0.214	0.153 to 0.54	0
ΔC ($), range/point	$89,472	$19,856	$75,039 to $98,244	$7,454 to $29,302

The main assumptions and limitations with the submitted economic evaluation were:
In summary, the key assumptions that have the most impact on the results of the economic evaluation are: the difference in OS between palbociclib + fulvestrant and comparator groups, the extrapolation methods of the clinical benefits after the trial period, the dose intensity of palbociclib and the utility values. Changes to the time horizon have only a small impact in this economic evaluation.

- ***Network Meta-Analysis**: the main analysis on the submitted economic evaluation presented palbociclib + fulvestrant compared to fulvestrant alone. A network meta-analysis (NMA) was performed to compare palbociclib + fulvestrant to other endocrine therapies used within the indicated patient population for which no head-to-head clinical trial data were available. Results of the fixed effect NMA for both PFS and OS showed that palbociclib + fulvestrant was associated with an increased clinical benefits (PFS/TTP) compared with each of the comparators except everolimus + exemestane for which no difference was found. The submitter performed sensitivity analyses on palbociclib + fulvestrant and each of the comparators anastrozole, exemestane, everolimus + exemestane and letrozole, using HRs estimates of the NMA. As the HR's were significant and HRs of OS showed a certain trend to significance, this was a good approach for anastrozole, exemestane and*

letrozole. This was however not appropriate for everolimus + exemestane as both HRs for PFS and OS showed similar clinical benefits when compared to palbociclib + fulvestrant. In this case, a HR equal to 1 should have been used in the economic model. The EGP and CGP consider everolimus and exemestane as an important comparator. The model allowed the EGP to perform several re-analyses, which had a high impact on ICER.

- *Notably, tamoxifen is also a relevant comparator in this setting however the submitter noted that the lack of clinical trial data evaluating tamoxifen in patients who progressed on an endocrine therapy prevented its inclusion in the NMA and the economic evaluation.*

- ***Method of Extrapolation**: to extrapolate the PFS and OS outcomes beyond the trial follow-up period, the following parametric models were fitted independently to both treatment arms: Weibull, exponential, lognormal, log logistic, and Gompertz. The submitted base-case was based on exponential and Weibull models for PFS and OS, respectively. An alternative extrapolation method using HRs observed in PALOMA-3 trial (for fulvestrant group) and the NMA (all the other comparators) was provided. The final choice of parametric models was based on graphical inspection, which resulted in the rejection of the models with the lowest AIC or BIC value. The EGP performed several re-analyses choosing the Weibull and Gompertz parametric models for PFS, and Gompertz for OS. These models showed similar AIC or BIC values as the models chosen by the submitter in the base case scenario, with plausible shapes as shown by the graphical illustration. The EGP noted a low to moderate impact on the ICER.*
  - *In addition, three assumptions were available to estimate clinical benefit after the trial period: extrapolated benefit, retained benefit and stop and drop benefit. The EGP consider the options of retained benefits and stop and drop, more plausible than the extrapolated benefits option used in base case. The graphical representation of the KM curve of the OS doesn't support the extrapolation benefits option, as the curves merge at the end of the study period (at 48 months). The model allowed the EGP to perform several re-analyses, which had a high impact on the ICER.*

- Following the posting of the pERC initial recommendation comments were received from the manufacturer regarding the setting of the EGP's use of a HR equal to 1 for both PFS and OS for the comparison between everolimus plus exemestane and palbociclib plus fulvestrant. The EGP disagrees with the submitter's assertion that the approach to set the HR equal to 1 is not methodologically sound and goes against general health economic evaluation principle. The EGP decision to set the HR for this comparison was based on the following points. In addition, the probabilistic results have been now integrated into the EGP report, in accordance with CADTH guidelines for the economic evaluation.
  - The EGP re-analyses align with the CGP interpretation on the results of the NMA, which indicated that there is no difference between the two agents. Furthermore, the NMA results should be interpreted with caution, given the limitation identified in the analysis. This is further elaborated upon on page 7 of the final clinical guidance report where it is mentioned: *''Results of the submitted NMA showed that palbociclib + fulvestrant was associated with a superior PFS/TTP compared with endocrine monotherapies, and no difference compared with everolimus + exemestane for the treatment of patients with HR+/HER2- locally advanced or metastatic breast cancer who progressed after prior endocrine therapy. A trend towards improvement in OS was observed when the palbociclib + fulvestrant combination was indirectly compared with other endocrine therapies. However, OS differences were not statistically significant based on the overlapping 95% credible intervals (CrIs). Although alignment of these findings with direct evidence lends credibility to the analysis, these results should be interpreted with attention to the limitations that arise from the lack of closed loops in the network, large number of single-study connections in the network, and lack of indirect comparisons for safety data, other efficacy outcomes (objective response rate, etc.), and patient-reported outcomes.''*
  - The EGP agrees with the methods proposed by Karl Claxton (1999) when the results are derived from clinical trials. Yet, the EGP doesn't agree with the usage of this method in the current

situation, when the results are derived from analyses which have a high level of uncertainty, as is the case with the submitted NMA, and for the points specified above. Furthermore, this article was published in 1999, sometime before NMAs were widely used in the HTA community. A more recent publication by Tianjing Li et al., BMC Medicine, 2011, indicates that *'Network meta-analysis (are) highly attractive but more methodological research is needed*' while assessing the merits of a NMA.

- Finally, The NMA takes into account only data obtained over the studies' follow-up durations, and no assumption regarding the clinical benefits beyond the studies terminations was made. While the EGP explored some assumptions regarding the clinical benefit for the main comparison, the model did not allow the alteration of clinical benefits estimated in the NMA. On page 5 of the EGP report it was mentioned: *''The EGP consider the options of retained benefits and stop and drop, more plausible than the extrapolated benefits option used in base case. The graphical representation of the KM curve of the OS doesn't support the extrapolation benefits option, as the curves merge at the end of the study period (at 48 months). The model allowed the EGP to perform several re-analyses, which had a high impact on the ICER.''*

- ***Dose intensity**: a dose intensity of 86.9% was used for palbociclib, as observed in PALOMA-3 trial. Yet, for all the other comparators a dose intensity of 100% was used, except fulvestrant for which the dose intensity observed in the PALOMA-3 trial was used. This was an assumption made by the submitter and no source was mentioned. As all these therapies are oral, a similar dose intensity is expected. The EGP conducted several re-analyses which has an important impact on the incremental cost of palbociclib, and the ICER, respectively.*

- ***Utilities**: another key assumption that has the most impact on the results of the economic evaluation are the utility values. While utilities were captured within the PALOMA-3 trial for the palbociclib + fulvestrant and fulvestrant alone groups, for all the other comparators and for the post-progression state (active treatment and BSC/chemotherapy) utilities were estimated using the Lloyd formula (2006). This study reports health state utility values from the UK general public for health states related to stable, responding and progressive metastatic breast cancer, and six toxicities related to chemotherapy treatment. Health state descriptions were developed from interviews and focus groups with experts in breast cancer, reviewed by clinical and psychometric experts and piloted on members of the general public. The method was used in previous submission on advances breast cancer. The model allowed the EGP to perform several re-analyses, which had a moderate impact on ICER.*
  - Following the posting of the pERC initial recommendation comments were received from the manufacturer regarding the source of utility values used in the model. Although the manufacturer noted that all sources for utilities for the comparison between palbociclib plus fulvestrant to fulvestrant were derived from the PALOMA-3 trial, the EGP re-iterated that the post-progression utilities for both active treatment and BSC/chemotherapy were derived from the Lloyd formula. This is apparent in the utilities tab of the model.

- ***Time horizon**: a time horizon of 15 years was considered in the base-case scenario. This was longer then the time horizon of 10 years considered in the economic evaluation of palbociclib in combination with letrozole (pCODR 10093). Given that the previous pCODR economic evaluation, conducted in an earlier line of treatment, used a shorter time horizon, the EGP and CGP agreed that it is reasonable to shorten the time horizon and conduct a re-analysis using a 10-year time horizon. The EGP noted that reducing the time horizon resulted in only a small increase in the ICER, likely because the clinical benefit was accrued in the earlier years.*

1.4 Detailed Highlights of the EGP Reanalysis

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

Two main comparator groups were considered important in this economic evaluation, and in consultation with the CGP, were further explored in the EGP re-analyses. These are: 1) fulvestrant alone; and 2) everolimus + exemestane. All the rest of comparators (anastrozole, exemestane and letrozole) were very similar with fulvestrant alone in terms of clinical benefits, difference of costs and ICERs compared to palbociclib + fulvestrant. The CGP agreed with this assumption made by the EGP.

The following re-analyses have been performed by varying components of the model that were significant drivers of either the incremental effect or the incremental cost, such as clinical benefit (between palbociclib + fulvestrant and everolimus + exemestane), the extrapolation methods of the clinical benefits after the trial period, the dose intensity of palbociclib and the utility values.

- *The EGP noted that in the submitted model the clinical benefit of everolimus + exemestane compared to palbociclib + fulvestrant was calculated using HRs which were non statistically significant. A correction was made by using a HR equal to 1 for both PFS and OS.*
- *Several re-analyses were performed to assess impact of the OS and PFS extrapolation methods, as well as of the uncertainty related with the maintenance of the clinical benefit after the trial period (extrapolated benefit, retained benefit and stop and drop benefit).*
- *The EGP noted a discrepancy between the estimates of dose intensity among treatment groups. While the dose intensity for palbociclib was the actual dose observed in the PALOMA-3 trial, an assumption of 100% dose intensity was used for everolimus. The EGP performed two re-analyses using the same dose intensity for both palbociclib and everolimus (either 86.9% as observed in PALOMA-3 or 100% as assumed for everolimus).*
- *The EGP conducted re-analyses investigating utility values. The submitted model integrates two assumptions on utility values: 1) the utility values for palbociclib + fulvestrant and fulvestrant alone derived from the PALOMA-3 trial, and for all other comparators, calculated using Lloyd formula (2006), and 2) all the utility values calculated using Lloyd formula (2006). As the first assumption on utility values was used in base case scenario, the second assumption was used in re-analyses by the EGP, to reduce differences due to different methods of calculation.*
- *Finally, a time-horizon of 10-year was considered by the EGP.*

Table 3. Detailed Description of EGP Reanalysis

Detailed Description of EGP Reanalysis for the Comparison to Fulvestrant - Deterministic				
	ΔC ($)	ΔE (QALY)	ICER ($/QALY)	Δ from baseline submitted ICER
Baseline (Submitter's best case)	$89,472	0.47	$191,613	--
LOWER BOUND				
PFS parametric models Weibull	$84,865	0.42	$202,087	$10,474
Retained clinical benefits after the trial period	$78,441	0.37	$211,755	$20,142
Time horizon 10y	$88,433	0.458	$193,105	$1,492
Best case estimate of above 3 parameters	$75,039	0.285	$224,756	$33,143
UPPER BOUND				
Stop and drop benefits after the trial period	$78,441	0.312	$231,237	$39,624
Utility values estimated by Lloyd formula	$89,472	0.426	$209,981	$18,368
Dose intensity of palbociclib = 100%	$98,244	0.467	$210,397	$18,784
Time horizon 10y	$88,433	0.458	$193,105	$1,492
Best case estimate of above 4 parameters	$80,325	0.273	$294,552	$102,939
Detailed Description of EGP Reanalysis for the Comparison to Fulvestrant - Probabilistic				

Detailed Description of EGP Reanalysis for the Comparison to Fulvestrant - Deterministic				
	ΔC ($)	ΔE (QALY)	ICER ($/QALY)	Δ from baseline submitted ICER
	ΔC ($)	ΔE (QALY)	ICER ($/QALY)	Δ from baseline submitted ICER
Baseline (Submitter's best case)	$89,326	0.47	$191,348	--
LOWER BOUND				
Best case estimate of the 3 parameters:	$74,809	0.3315	$225,648	$64,035
UPPER BOUND				
Best case estimate of the 4 parameters	$80,706	0.2715	$297,254	$105,641

Detailed Description of EGP Reanalysis for the Comparison to Everolimus plus Exemestane - Deterministic				
	ΔC ($)	ΔE (QALY)	ICER ($/QALY)	Δ from baseline submitted ICER
Baseline (Submitter's best case)	$19,856	0.163	$122,172	--
LOWER BOUND				
HRs for OS and PFS =1	$7,454	0.046	$162,216	$40,044
Utility values estimated by Lloyd formula	$19,856	0.142	$139,653	$17,481
Dose intensity for palbociclib =100%	$28,627	0.163	$176,141	$53,969
Best case estimate of above 3 parameters	$16,226	0.026	$633,600	$511,428
UPPER BOUND				
HRs for OS and PFS =1	$7,454	0.046	$162,216	$40,044
utility values estimated by Lloyd formula	$19,856	0.142	$139,653	$17,481
dose intensity for everolimus =86.9%	$29,302	0.163	$180,291	$58,119
Best case estimate of above 3 parameters	$17,882	0.026	$698,289	$576,117
Detailed Description of EGP Reanalysis for the Comparison to Everolimus plus Exemestane - Probabilistic				
	ΔC ($)	ΔE (QALY)	ICER ($/QALY)	Δ from baseline submitted ICER
Baseline (Submitter's best case)	$14,545	0.09	$157,051	--
LOWER BOUND				
Best case estimate (*HRs for OS and PFS =1; Dose intensity for palbociclib =100%)*[*]	$10,925	-0.0254	Dominated	-
UPPER BOUND				
Best case estimate (*HRs for OS and PFS =1; Dose intensity for everolimus =86.9%)*[*]	$12,336	-0.0254	Dominated	-

* The probabilistic analyses consider Lloyd formula in all groups, ** Palbociclib plus fulvestrant s dominated

In response to the feedback received from the submitter on the initial EGP report, the EGP presented the probabilistic reanalyses for the upper and lower bounds of both comparisons (fulvestrant and everolimus plus exemestane). In addition, a sequential re-analysis was performed.

Table 4 Submitted Estimates Using Sequential Analysis

Treatment	Total Costs	Total QALYs	Incremental Costs (vs. ref)	Incremental QALYs (vs. ref)	ICER (vs. ref)	Incremental Analysis
Cost-effectiveness plane						
ANA	$ 89,292	1.12	-	-	-	reference
EXE	$ 102,632	1.26	$ 13,341	0.14	$ 94,290	$ 94,290 vs. ANA
PAL + FUL	$ 192,494	1.66	$ 103,202	0.54	$ 191,355	$ 225,875 vs. EXE
Subject to extended dominance						
LET	$ 97,087	1.16	$ 7,795	0.04	$ 189,724	ANA, EXE
FUL	$ 107,484	1.27	$ 18,192	0.16	$ 116,768	EXE, PAL + FUL
EVE + EXE	$ 177,949	1.56	$ 88,657	0.45	$ 198,467	EXE, PAL + FUL

Abbreviations: ANA = anastrozole; EVE = everolimus; EXE = exemestane; FUL = fulvestrant; ICER = incremental cost-effectiveness ratio; LET = letrozole; LY = life-year; PAL = palbociclib; QALY = quality-adjusted life-year.

Table 5 EGP Reanalysis Estimates Using Sequential Analysis

Treatment	Costs	QALYs	Incremental Costs (vs Ref)	Incremental QALYs (vs Referent)	ICER (vs Referent)	Incremental Costs (Sequential)	Incremental QALYs (Sequential)	ICER (Sequential)	Dominated (Sequential)
Anastrozole	$89,075	1.1143	$0	0.0000					
Letrozole	$95,751	1.1464	$6,676	0.0320	$208,335	$6,676	0.0320	$208,335	
Exemestane	$100,592	1.2392	$11,517	0.1249	$92,242	$4,841	0.0928	$52,159	
Fulvestrant	$106,798	1.2675	$17,723	0.1532	$115,706	$6,206	0.0283	$219,163	
Everolimus + Exemestane	$187,073	1.6549	$97,998	0.5406	$181,291	$80,275	0.3874	$207,224	
Palbociclib + Fulvestrant	$200,220	1.6493	$111,145	0.5349	$207,777	$13,147	-0.0056	-$2,333,964	Dominated*

* Dominated by Everolimus + Exemestane

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include the percentage of patients eligible for provincial coverage and market share distribution.

- First, increasing the percentage of provincial coverage increases the number of patients receiving second-line palbociclib plus fulvestrant. Increasing the proportion of patients eligible for provincial coverage by about 9% and 20% (based on the base case and sensitivity analysis in the previous palbociclib plus letrozole submission), increased the 3-year budgetary impact by similar proportions. The budget impact analysis model allowed the modification of this parameter.
- Secondly, the submitted BIA considered that the majority of patients currently on everolimus plus exemestane will receive palbociclib plus fulvestrant, and so the market share for everolimus plus exemestane be most impacted by the introduction of palbociclib plus fulvestrant. The EGP noted that these combinations, everolimus plus exemestane and palbociclib plus fulvestrant, have approximately the same total drug costs, and the BIA is likely to be underestimated in the situation where more patients will switch from less costly therapy, such as single agents, to palbociclib plus fulvestrant. In this case, the market share of everolimus plus exemestane will be less affected, and, the BIA will be much higher than the one estimated by the submitter. As there is an uncertainty regarding what scenario will be more likely to happen (ie. whether palbociclib plus fulvestrant will replace single agent s or everolimus plus exemestane), the EGP conducted re-analyses to explore this. Based on this, when palbociclib plus fulvestrant replaces single agents only, the submitted BIA increased by about 40%.
- Third, the EGP and CGP noted that fulvestrant is not publicly funded in Canada, resulting in an underestimation of the BIA. In the submitter BIA, fulvestrant single agent was given a market share only in the reference scenario and not in the treatment funded scenario. The EGP therefore redistributed the market share given to single agent fulvestrant proportionally among the other single agents. This resulted in approximately a 7% increase in the incremental 3-year impact of the submitted BIA. In addition, a generic fulvestrant is expected to become available in the near future; the EGP conducted re-analyses considering a price reduction of fulvestrant of 25%, 50% and 75%. The EGP also included the redistribution of the market share of fulvestrant in this analysis. Based on this, a price reduction on fulvestrant only impacted the cost of palbociclib plus fulvestrant combination treatment. When the price reductions were applied, the corresponding incremental 3 year budgetary impact was decreased by approximately 9%, 17% and 26%, respectively.
- When the redistribution of the market share of single agent fulvestrant was applied to the EGP's modifications as described above (in bullet 2 where the majority of the market share for

palbociclib plus fulvestrant is coming from single agents), the EGP's 3 year incremental BIA increased by approximately 4%.
- Finally, the EGP and CGP considered appropriate the percentage of market share for palbociclib plus fulvestrant assumed by the submitter, as the patients that might receive palbociclib plus letrozole in 1st line settings, will be ineligible to receive 2nd line treatment with palbociclib plus fulvestrant.

Key limitations of the BIA model include the actual percentage of patients eligible for provincial coverage and market share distribution in both a world with and without palbociclib. These parameters were able to be modified and explored by the EGP, and described above.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for Palbociclib + Fulvestrant when compared to Fulvestrant alone is:

- Between $224,756/QALY and $294,552/QALY. The EGP further notes that this range is due to the uncertainty in the magnitude of long term benefit and palbociclib dose intensity.
- Within this range, the best estimate would likely be: $294,552/QALY. *This corresponds to the scenario with stop and drop benefits after the trial period, utility values estimated with the same method (Lloyd formula), a dose intensity of palbociclib = 100% and over a 10-year time horizon.*
- The extra cost of palbociclib + fulvestrant is between $75,039 and $98,244. *The factor that most influences the costs is the dose intensity of palbociclib.*
- The extra clinical effect of palbociclib + fulvestrant is between 0.273 and 0.467 QALY (ΔE). *The factors that most influence the incremental clinical benefit are the maintenance or not of the clinical benefits after trial duration, the time horizon and the survival extrapolation methods used.*

The EGP's best estimate of ΔC and ΔE for Palbociclib + Fulvestrant when compared to Everolimus plus Exemestane is:

- Between $633,600/QALY and $698,289/QALY. The EGP further notes that this range is due to the uncertainty in the magnitude of the improvement of the quality of life, and respectively utility values, as well as of dose intensity of palbociclib and everolimus.
- Within this range, the best estimate would likely be $698,289/QALY (upper bound), *corresponding to the scenario HRs for OS and PFS =1, utility values estimated by Lloyd formula and a dose intensity for everolimus of 86.9% over a 15-year time horizon.*
- The extra cost of palbociclib + fulvestrant is between $7,454 and $29,302. *The factor that most influences the costs is the dose intensity of palbociclib and everolimus.*
- The extra clinical effect of palbociclib + fulvestrant is between 0.026 and 0.142 QALY. *The factors that most influence the incremental clinical benefit are the utility values.*
- *The EGP noted that no clinical benefit was observed in term of LYs between these therapies, and palbociclib + fulvestrant was dominated by everolimus + exemestane. In addition, the estimated clinical benefit in term of QALY is also very small, and because of the limitation of the utility values calculation methods mentioned above, the actual QALY difference is unknown, and cannot be reasonable estimated. However, the CGP noted that a certain advantage of palbociclib + fulvestrant might be expected in term of more favorable profile of toxicity when compared to everolimus plus exemestane.*

Overall conclusions of the submitted model:

- *Despite the fact that the submitted model included many appropriate assumptions and an extensive set of sensitivity analysis on fulvestrant, it included only a limited number of scenarios that could be applicable to everolimus + exemestane. As such the EGP was limited in term of the re-analyses that could be performed.*

- *As all the potential single agent comparators (anastrozole, exemestane and letrozole) were very similar with fulvestrant alone in term of clinical benefits, costs, and ICERs of palbociclib + fulvestrant, the EGP focused on two comparators, fulvestrant and everolimus + exemestane while conducting re-analyses.*
- *An important driver in this economic evaluation was the choice of comparator. Mainly, the clinical benefits after the trial period, the utility values and the dose intensity of palbociclib. These factors had the largest impact on the ICER for fulvestrant, but only at a moderate level. Yet, the utility values and the dose intensity of palbociclib and everolimus were important factors with a high impact on the results of this economic evaluation when the comparator group was everolimus + exemestane. The submitted model allowed the EGP to evaluate the impact of these factors (time horizon, projected clinical benefits and extrapolation parametric curves and utility values) contributing to long term benefit. Other important factors related with the cost of palbociclib were the duration of palbociclib treatment and drug intensity. The submitted model allowed the EGP to explore their impact on the ICER. Despite the fact that the duration of palbociclib couldn't be evaluated directly, as the patients were treated until disease progression, this was performed indirectly by different parametric models explored and by different scenarios on the clinical benefit.*

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 Palbociclib (Ibrance) plus Fulvestrant (Faslodex) for metastatic breast cancer. A full assessment of the clinical evidence of Palbociclib (Ibrance) plus Fulvestrant (Faslodex) 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.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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