CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Ribociclib (Kisqali) for Metastatic Breast Cancer

April 18, 2018

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by **Novartis Pharmaceuticals Canada Inc.** compared ribociclib in combination with letrozole to letrozole monotherapy for the treatment of postmenopausal women with hormone receptive (HR)-positive, human epidermal growth factor receptor (HER) 2-negative advanced or metastatic breast cancer (ABC) who received no prior therapy. In order to assess the comparative effectiveness of ribociclib-letrozole to other comparators, the submitter provided other comparisons: an indirect treatment comparison (ITC) and matched-adjusted indirect treatment comparison (MAIC) of ribociclib-letrozole to palbociclib-letrozole as well as a network meta-analysis (NMA) comparing endocrine-based therapies and chemotherapy for first-line treatment in post-menopausal women with HR-positive and HER2-negative ABC.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	This aligns with the funding request.
Type of Analysis	*CUA & CEA*
Type of Model	*Partitioned-survival*
Comparator	*Letrozole monotherapy* Indirect treatment comparison *with:* • *Palbociclib plus letrozole* • *Chemotherapy (paclitaxel or capecitabine)* • *Tamoxifen*
Year of costs	*2017*
Time Horizon	*15 years*
Perspective	*Government*
Cost of Ribociclib*	*Ribociclib costs $99.20 per 200mg tablet* • *At the recommended dose of 600mg daily for 21 days, 7 days off, ribociclib costs:* o *$223.21 per day* o *$6,249.99 per 28-day cycle*
Cost of Letrozole*	*Letrozole costs $1.37 per 2.5mg tablet* o *At the recommended dose of 2.5 mg daily throughout the 28-day cycle, letrozole costs:* o *$1.37 per day* o *$38.58 per 28-day cycle*
Cost of Palbociclib*	*Palbociclib costs $297.62 per 125mg tablet* • *At the recommended dose of 125mg daily, palbociclib costs:* o *$223.22 per day* o *$6,250.02 per 28-day cycle*
Cost of Tamoxifen*	*Tamoxifen costs $0.35 per 20mg tablet* • *At the recommended dose of 20mg daily throughout the 28-day cycle, tamoxifen*

	costs: o *$0.35 per day* o *$9.80 per 28-day cycle*
Cost of anastrozole*	*Anastrozole costs $1.27 per 1mg tablet* o *At the recommended dose of 1mg daily throughout the 28-day cycle, letrozole costs:* o *$1.27 per day* o *$35.64 per 28-day cycle*
Cost of Fulvestrant*	*Fulvestrant costs $582.89 per 205mg syringe* • *At the recommended dose of 500mg on days 0, 14, 28 in cycle 1; then every 28 days thereafter, fulvestrant costs:* o *$41.64 per day* o *$1,165.79 per 28-day cycle* o *(calculated based on 1 dose every 28 days)*
Model Structure	*A cohort-based partitioned survival model with 3 health states was developed in Excel: progression-free (PF), post-progression and death. The progression-free state is partitioned further into two sub-states: PF with response (complete or partial response) and PF with stable disease. Patients enter the model in the PF with stable disease state.*
Key Data Sources	*MONALEESA-2 phase III trial*[1]
** Drug costs for all comparators in this table are based on costing information under license from IMS Health Canada Inc. concerning the following information service(s): DeltaPA. and may be different from those used by the submitter in the economic model. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc. Quintile IMS DeltaPA– accessed on August 15, 2017. All calculations are based on 70kg and BSA = 1.7m^2*	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison with letrozole is appropriate. The submitter also provided evidence for other comparators, notably that of palbociclib+letrozole. To address this comparison in addition to tamoxifen and chemotherapy, in the absence of direct comparative evidence, the submitter provided indirect comparisons (an ITC, a MAIC and a NMA). The pCODR Methods Team identified several limitations in the data and the methods used to derive the estimates in the indirect treatment comparisons. The EGP concluded that the results would result in a high level of uncertainty and could not be used to inform credible ICER estimates. Therefore, all other comparisons other than letrozole were excluded from the technical report, with the exception of palbociclib-letrozole, which was included as a scenario-analysis due to its relevance as comparator. Please refer to section 2 in the EGR and section 7 in the CGR for more details on the ITCs provide by the submitter.

- Relevant issues identified included:
    - There is a net overall clinical benefit to the combination of ribociclib- letrozole compared with letrozole alone.
    - There is statistically significant improvement in progression free survival (PFS) by investigator assessment in the ribociclib-letrozole group. PFS is an established and well agreed-upon primary endpoint in the breast cancer literature.
    - Although ribociclib has more toxicity than letrozole, ribociclib is considered to be overall well tolerated.
    - The trial data on overall survival (OS) remains immature and may be confounded by post-trial treatments.
    - There is an urgent need for more effective and durable first-line therapies in the metastatic setting.
    - The CGP acknowledges recent evidence showing similar benefits and side-effect profiles between ribociclib-letrozole and palbociclib-letrozole therapy (PALOMA-1[5] and PALOMA-2[6]). However, there is insufficient evidence to demonstrate superiority of either ribociclib or palbociclib in this patient population, and the CGP cannot recommend one therapy over the other.
    - Given the limitations identified in the ITCs and lack of long term outcomes such as OS and QoL, the comparative effectiveness and safety of ribociclib-letrozole versus comparators, other than letrozole monotherapy, is highly uncertain. Hence, treatment availability, patient values and preferences, and clinical factors should guide treatment selection. (Refer to section 7 in the CGR for the complete critical appraisal of the ITC, MAIC and NMA).

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered that ribociclib-letrozole compared with letrozole alone had improved PFS, delaying the time until patients require chemotherapy. Although ribociclib-letrozole was more toxic (increased risk of neutropenia and diarrhea) than letrozole alone, ribociclib-letrozole was considered to be overall well tolerated. Clinician input reported the benefits and harms of ribociclib-letrozole were likely the same as with palbociclib-letrozole. Ribociclib-letrozole would be sequenced the same as palbociclib-letrozole which is currently not available in the majority of provinces under publicly funded drug plans.

Summary of patient input relevant to the economic analysis
Patients valued disease control, reduction in disease symptoms, improvement of quality of life and diverse treatment options. Patients who have experience with ribociclib reported that the treatment helped to stabilize and control their disease (delaying progression of their disease). The majority of patients with exposure to ribociclib reported that side effects were minimal and that their quality of life (QoL), including productivity and ability to regain mobility and perform daily functioning, had improved on ribociclib. PFS, QoL and adverse events were incorporated into the economic model.

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 ribociclib (in combination with letrozole) which are relevant to the economic analysis:

<u>Barriers</u>

- Monitoring for neutropenia, which is not a requirement for letrozole monotherapy. Increased resource use in the PFS state (on therapy) was considered in the economic model.
- Drug cost. The potential impact of adding on ribociclib was examined in the budget impact.

Enablers

- Ribociclib is administered orally.
- One tablet strength is available and dose adjustments are made by adjusting the number of tablets, resulting in no drug wastage. There is, however, the possibility of pill burden and confusion for some patients as dosing differs from letrozole.

Other issues

- Comparison with palbociclib. This comparator was included through an indirect treatment comparison. Given the data available, there remains a high level of uncertainty in the comparative effectiveness between ribociclib and palbociclib.
- Data for post-progression therapies was taken from the MONALEESA-2 trial. Though the distribution of subsequent treatments differ slightly between the two treatment arms, the average weighted cost of treatment is similar.
- The submitted base case applied a dose distribution (various doses as reflected in the MONALEESA-2 trial). Other dose intensities were explored in scenario analyses.

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Estimates

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
ΔE (LY)	2.14	2.14	0.98
Progression-free	0.98	0.98	0.98
Progression	1.16	1.16	0.00
ΔE (QALY)	1.70	1.32	0.84
Progression-free	0.80	0.80	0.84
Progression	0.90	0.51	0.00
Adverse events	0.00	0.00	0.00
ΔC ($)	$231,283	$231,283	$164,261
ICER estimate ($/QALY)	$136,140	$175,827	$204,805

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

- In addition to the submitted base case, the submitter provided indirect treatment comparisons for tamoxifen, chemotherapy and palbociclib plus letrozole. The indirect treatment comparison to tamoxifen was deemed to be of too low quality to consider in the economic analysis. The submitter also provided an indirect comparison to chemotherapy (paclitaxel or capecitabine). Given the questionable relevance as a comparator and the weak credibility of the NMA, the comparison to chemotherapy was also not considered in the present economic analysis. The CGP indicated that the most relevant comparator for ribociclib plus letrozole is the combination of palbociclib plus letrozole, though the latter is currently only available through private insurance in the majority of provinces across Canada. For further details on the complete critical appraisal of theses comparisons, please refer to section 7 of the Clinical Guidance Report.

- At the latest data cut-off used in the economic analysis (January 2017), median OS was not reached in trial and the hazard ratio presented for OS was not significant. In the submitted base case, the gains observed in the post-progression state were approximately equal to that of the pre-progression state. The submitter rationalized that this benefit of treatment in the post-progression state is due to the transfer of benefit from the pre-progression

state. However, given the lack of significance present in the hazard ratio for OS, and no biological plausibility of benefit beyond progression with ribociclib, the EGP felt that this post-progression incremental benefit was unwarranted.

- The utility values used in the economic model were adjusted for response rates. The CGP stated that there would be no rationale to apply different utility values to those in the progression-free survival state who achieved response versus those who had stable disease. The CGP also felt that the utility values collected in the MONALEESA-2 trial were relatively high for patients with advanced or metastatic breast cancer.

1.4 Detailed Highlights of the EGP Reanalysis

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

- Utility values: The CGP expressed that they felt the utilities collected in the MONALEESA-2 trial were high, notably in the post-progression period. This may be due to the fact that utilities in the trial were collected in patients who were early in their cancer journey and a relatively short follow-up for these patients that doesn't capture the worsening over time. In order to explore the possibility that utilities would be lower in the post-progression period, the EGP elected to use the utilities as collected by Lloyd et al.[17] in the upper bound of the re-analysis.
- Treatment effect after progression: In the submitted economic model, there is an assumption that patients will continue to derive benefit beyond progression. The CGP confirmed there is no clinical plausibility to this. This may be due to the extrapolation of benefit from the limited trial follow-up over the time horizon of 15 years. In the re-analysis, the EGP limited the duration of treatment effect until the end of trial follow-up. By doing this, there was no incremental benefit observed in the post-progression period. This was used in the upper bound only.

Table 3. Detailed Description of EGP Reanalysis

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)	$231,283	1.699	2.141	$136,140	--
LOWER BOUND					
Utilities post-progression as per Lloyd et al. [17]	$231,283	1.315	2.141	$175,827	$39,687
Best case estimate of above one parameter	$231,283	1.315	2.141	$175,827	$39,687
UPPER BOUND					
Utilities post-progression as per Lloyd et al. [17]	$231,283	1.315	2.141	$175,827	$39,687
Duration of treatment effect set to HR=1.0 following progression	$164,261	0.802	0.982	$204,805	$68,665
Best case estimate of above two parameters	$164,261	0.802	0.982	$204,805	$68,665

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis (BIA) include:

1. Assuming that palbociclib would not be reimbursed, as at the time of this review this drug is not funded in a number of provinces across Canada, increases the 3 year budget impact by approximately 24%.

2. Dosing ribociclib as per the indication increases the 3-year budget impact by approximately 5%.

3. Increasing the total population eligible for public payer drug coverage from 73.7% to 100% decreases the 3-year budget impact by approximately 5%.

Key limitations of the BIA model include assuming that the majority of the market share for ribociclib plus letrozole will come from palbociclib plus letrozole. Palbociclib is currently not funded in a number of provinces across Canada. Removing palbociclib from the BIA substantially increases the 3-year budget impact.

Further, a key limitation is the inclusion of only women considered menopausal (aged 51 and over). Pre-menopausal can be rendered post-menopausal. Excluding women under the age of 50 significantly underestimates the budget impact of ribociclib for this patient population.

Finally, estimates on population for breast cancer were taken from US sources which may or may not be relevant to the Canadian setting.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for ribociclib+letrozole when compared to letrozole monotherapy is:

- *Between $175,827/QALY and $204,805/QALY*
- *The extra cost of ribociclib+letrozole is between $164,261 and $231,283. The factors that most influence ΔC include the choice of comparator (letrozole monotherapy vs palbociclib+letrozole), the parametric function for overall survival, and the dose intensity of ribociclib.*
- *The extra clinical effect of ribociclib+letrozole is between 0.802 and 1.315 (ΔE). The factors that most influence ΔE include the choice of comparator, the parametric function for overall survival, and the duration of treatment effect.*

Overall conclusions of the submitted model:

- *The majority of the inputs and assumptions selected for the comparison with letrozole monotherapy were reasonable. The EGP was able to modify those that the CGP disagreed with.*
- *If you believe that there is similar efficacy between ribociclib+letrozole and palbociclib+letrozole, then the ICER is likely close to zero as the agents are similarly priced (if wastage is assumed to be equal between the two treatments). It is difficult to confirm the ICER of this comparison given the limited data.*

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

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.

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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