pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Darolutamide (Nubeqa) for non-Metastatic Castration Resistant Prostate Cancer

April 22, 2020

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Bayer Inc. compared darolutamide plus androgen deprivation therapy (ADT) with the comparator placebo (ADT alone) in patients with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastasis. In addition, an exploratory sensitivity analysis was conducted to compare darolutamide plus ADT versus apalutamide plus ADT as well as enzalutamide plus ADT based on data from an indirect treatment comparison (ITC). The summary of the submitted economic model is presented in Table 1.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	*The patient population in the economic evaluation was consistent with the funding request and the ARAMIS trial patient population of adult patients with high-risk, non-metastatic castration-resistant prostate cancer (nmCRPC).*
Type of Analysis	*Cost-effectiveness (CEA) and cost-utility (CUA) analyses*
Type of Model	*Partitioned-survival*
Comparator	*Main analysis: ADT alone* *Exploratory analyses: apalutamide, enzalutamide (efficacy derived from indirect treatment comparison)*
Year of costs	*2018*
Time Horizon	*10 years*
Perspective	*Public payer*
Cost of darolutamide	• *Cost per 300mg tablet: $28.34* • *Daily dosage of two 300mg tablets twice daily (total of 1200mg per day): $113.38* • *Per 28-day course: $3,174.53*
Cost of ADT ** Price Source: Ontario e-formulary [02/2019]*	*Weighted average of ADT treatments (i.e., degarelix, leuprorelin, goserelin, triptorelin, and buserelin) based on market share assumptions plus steroid treatment prednisone/prednisolone:* *Per pack/dose per pack:* • *Degarelix costs $345.00/120 ml or $255.00/80mg* • *Leuprorelin costs $359.33/3.75mg* • *Goserelin costs $390.50/3.6mg* • *Triptorelin costs $346.31/3.75mg* • *Buserelin costs $84.10/10ml* • *Prednisone costs $13.11/5mg* • *Prednisolone costs $0.17/10mg* *Per 28-day cycle drug costs are:* • *Degarelix costs $255.00 (note that once off dose of 240 mg on Day 1 costs $690.00)* • *Leuprorelin costs $359.33* • *Goserelin costs $390.50*

	• *Triptorelin costs $346.31* • *Buserelin costs $84.10* • *Prednisone costs $13.11* • *Prednisolone costs $0.17*
Cost of apalutamide ** Price Source: pCODR review of apalutamide for nmCRPC*	• *Cost per 60mg tablet: $28.34* • *Daily dosage of four 60 mg tablets once daily (total of 240 mg per day): $113.38* • *Per 28-day course: $3,174.53*
Cost of enzalutamide ** Price Source: pCODR review of enzalutamide for nmCRPC*	• *Cost per 40mg capsule: $29.20* • *Daily dosage of four 40 mg capsules once daily (total per 160mg per day): $116.78* • *Per 28-day course: $3,269.88*
Model Structure	*Partitioned survival model with three health states: pre-progression (nmCRPC), post-progression (mCRPC) and death. The metastatic-free survival (MFS) in the ARAMIS study was used to model pre-progression, overall survival (OS) was used to model death and the difference between MFS and OS was used to model post-progression state.*
Key Data Sources	*Key clinical information such as MFS, OS, health utilities, and side effects came from the ARAMIS trial. Resource utilization information (monitoring costs, end of life care costs, other resource utilization) came from different sources with unit costs reflecting the Canadian setting.*

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparison of darolutamide versus placebo is appropriate, where placebo (ADT alone) is the current standard of care. In addition, the CGP noted that the standard treatment option for high-risk patient nmCRPC is evolving with the recent approval of other androgen-receptor-axis targeted therapies (ARATs), apalutamide and enzalutamide, by Health Canada and positive conditional recommendations by CADTH pCODR in 2018 and 2019, respectively.

Relevant issues identified included:
- The CGP noted that there is a net overall clinical benefit to darolutamide plus ADT compared with ADT alone for high-risk nmCRPC patients based on one high-quality randomized controlled trial . The sponsor conducted an ITC and a network-meta analysis (NMA) to assess the comparative efficacy of darolutamide to apalutamide and enzalutamide in patients with nmCRPC. However, CGP noted that due to high heterogeneity between the three clinical trials, the comparative effectiveness estimates from the ITC and NMA are likely biased with an unknown magnitude and direction of the bias. In addition, there is uncertainty regarding long-term OS given the lack of matured data in all three trials. Overall, CGP concluded that there is insufficient evidence to recommend one ARAT (i.e., darolutamide, apalutamide, or enzalutamide) over another in patients with nmCRPC and, therefore, patient values and preferences, co-morbidities, individual toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection.
  - *The sponsor utilized an ITC as part of an exploratory analysis for cost-effectiveness analyses between the three ARATs. Considering the limitations noted by CGP, the EGP also considered the indirect comparisons between the ARATs as exploratory analyses.*

- o *Regarding uncertainty in long-term OS, the EGP explored the impact of choosing different OS models in reanalysis.*
- Darolutamide was well tolerated and no new toxicities were encountered in the ARAMIS trial when compared to other agents in a similar class.
  - o *The economic evaluation incorporated differences between darolutamide and placebo for Grade 3 or 4 adverse events and symptomatic skeletal events and overall quality of life.*
- The CGP noted that identification of non-metastatic patients in the trial was based principally on PSA and conventional imaging modalities of bone scan and CT while over time advanced imaging techniques may increasingly detect metastases earlier than current imaging techniques.
  - o *The economic evaluation was based on data from the ARAMIS trial that relied on conventional methods to detect metastasis. It is likely that with better detection methods (e.g., PET scans, biomarkers) fewer patients may be eligible to receive nmCRPC treatment; this, however, has yet to be shown.*

Summary of registered clinician input relevant to the economic analysis

Registered clinicians considered comparative treatments, access to treatment, diagnostic and monitoring costs, and market shares as important factors:
- Apalutamide and enzalutamide were identified as relevant comparators with all having similar efficacy but darolutamide potentially having a favorable side effect profile (fewer drug-drug interactions, useful for patients with seizure history and other comorbidities). It was recognized, however, that there is no evidence coming from a head-to-head comparison of these agents. Other factors influencing the use of any of these ARATs include clinician experience and tolerability of the drug by the patient.
  - o *The indirect comparison of the three ARATs was included in this economic evaluation. Both the Sponsor and EGP highlighted the heterogeneity between trials and the uncertainty of the findings.*
- Clinicians stated that there is an unmet need in this population, and that public coverage should be preferred from pharmaceutical/private insurance funded programs or compassionate access programs as they are not secure long-term. It was also stated that only one of the ARATs should be used (and not others sequentially), and if the patient develops a metastatic disease, chemotherapy is the next line of treatment.
  - o *The budget impact analysis (BIA) assumed that the majority of eligible nmCRPC population will receive the drug darolutamide from public insurance, and the assumption was tested in sensitivity analysis.*
- Clinicians agreed that no new diagnostic testing is required, and darolutamide would require minimal clinical monitoring. Usage of tests such as CT, bone scans, and lab work is mandatory in nmCRPC patients to screen for clinical progression; therefore, no additional strain on healthcare system resources is expected.
  - o *Monitoring and diagnostic costs were considered in the economic evaluation, all treatments were assumed to have the same healthcare resource use rates.*
- A clinician mentioned that as the third agent to enter the market after enzalutamide and apalutamide, darolutamide would need to demonstrate significantly improved tolerability and decreased need for physician monitoring to gain market share. Direct medication costs were suggested to likely be similar to competitor agents, but there may be the potential for modest cost saving achieved through fewer physician visits and decreased need for laboratory monitoring.
  - o *The BIA assumed that darolutamide will displace market share from other ARAT therapies. In the base case, only drug acquisition costs are included, with options to include drug administration costs, markups, and dispensing fees. The introduction of darolutamide resulted in cost saving of $327,674.*

Summary of patient input relevant to the economic analysis

- Patients considered the erectile dysfunction as the most significant side effect of prostate cancer treatment affecting quality of life. This side effect however was reported by prostate cancer patients taking drugs other than ARATs. Patients that had direct experience with darolutamide indicated that they continued to maintain their daily activities, did not have any side effects, and maintained good quality of life. However, one patient did indicate feelings of nausea if they took darolutamide without food. One patient experienced issues with their cardiovascular health, however, the patient advocacy group stated that he still thought the benefits of darolutamide outweighed the side effects. Overall, from a patient's perspective, patients value treatments that allow them to maintain their quality of life, have reduced side effects (e.g., erectile dysfunction), and lead to a longer life.
  - *Grade 3 and 4 side effects plus symptomatic skeletal events were considered in the economic evaluation and because of their low rate had minimal effect on cost-effectiveness results. Quality of life and survival were considered in the economic evaluation.*

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

- PAG considered the oral route of administration of darolutamide as an enabler of implementation as it can easily taken in home setting. However, patients taking darolutamide may require more frequent clinic visits for monitoring of side effects compared to ADT alone.
  - *Monitoring and treatment of side effects were considered in the economic evaluation. Same costs for monitoring and treatment of side effects were assumed for all ARATs in the model. Drug administration costs were assessed in sensitivity analyses in the budget impact analysis and were not influential.*
- PAG noted that funding for oral drugs may vary across jurisdictions. Patients may incur deductibles, co-payments or pharmacy dispensing fees in some provinces.
  - *In the economic evaluation and BIA, the sponsor considered that the full cost of the drugs will be covered by third party payers (i.e., state agencies). Partial public funding as well as pharmacy dispensing fees were considered in sensitivity analysis in BIA.*
- The twice daily dosage of darolutamide as opposed to once daily dosage of apalutamide and enzalutamide can potentially reduce patient compliance.
  - *In the economic evaluation and BIA, 100% compliance was considered.*

1.3   Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Estimates

Estimates (point)*	Submitted	EGP Reanalysis
ΔE (LY)	0.93	0.89
ΔE (QALY)	0.82	0.78
ΔC ($)	$116,181	$138,414
ICER estimate ($/QALY)	$141,069	$177,087

*Probabilistic results did not report by health states of MFS and PPS

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

- This was a partitioned survival model with 3 health states reflecting the disease progression in nmCRPC. While accurately reflecting treatment effectiveness and disease progression during the trial, these models can bias the cost-effectiveness results when using immature (i.e., early cut-off) data.
- The OS and MFS estimates reflected trial data for the first 4 years of the time horizon while for the remaining time, data were obtained from extrapolation of survival curves (75% of QALY gain came from extrapolation of MFS and OS). OS data were immature, i.e., the median survival was not reached at the time of data cut-off (Sep 3, 2018) for both groups and the pre-defined level of significance for OS was not met). Therefore, there is high uncertainty in the extrapolation of long-term survival. The spread of survival curves based on different parametric distributions for

OS indicated that the selection of a particular distribution would have a significant impact on cost-effectiveness outcomes (e.g., depending on distribution, the extrapolated median OS varied approximately from 64 months to 168 months for darolutamide and from 49 months to 121 months for ADT). In the submitted base case, at 10 years, the estimated survival was 33% in the darolutamide group and 25% in ADT group.

- New OS curves (November 2019 data cut) became available during the course of the review, but the sponsor did not update the model with these new survival curves. Median OS was still not reached in these new OS curves and the difference between darolutamide and ADT was slightly reduced in particular at month 36 as more patients had reached later timepoints. This suggests that ADT long-term survival might have been underestimated in the sponsor's analysis, thus favouring darolutamide.

- The model's time horizon was 10 years and not reflective of current CADTH guidelines which recommends using a lifetime horizon to fully capture all downstream consequences (i.e., costs and benefit) of the different treatment options.[1]

- The sponsor assumed that the clinical treatment effect continued for six months after the trial end. Considering the immaturity of OS data and the large extent of censored data at the end of the trial, this assumption was further evaluated by EGP.

- Adverse events reflected the rates of grade 3 or 4 adverse events observed in the ARAMIS trial. The rates of these events were low and had minimal effect on cost-effectiveness results and therefore, were not further assessed by the EGP.

- Utility values were based on EQ-5D-3L instrument, assessed at enrollment/screening, baseline, at 16 weeks, and at end of study treatment. UK tariffs were used for base case analysis.

- Drug acquisition cost was the major driver of total costs for both comparators. All patients received background ADT and all patients assumed to continue receiving ADT after progression.

- f comparative effectiveness estimates from the ITC are likely biased, and the magnitude or the direction of the bias cannot be established. Since all ARATs have higher costs and QALYs than ADT, a comparison of cost-effectiveness between the 3 ARATs was indicated. Darolutamide dominated enzalutamide (i.e., less costly and more effective) but was less costly and less effective than apalutamide (cost saver for a small magnitude of QALY loss). These comparisons, however, came with a large uncertainty, the sponsor and EGP considered these exploratory analyses. Probabilistic results illustrated that the point estimates of incremental costs and QALYs (darolutamide vs. apalutamide and darolutamide vs. enzalutamide) were spread in all cost-effectiveness quadrants. In such scenario, using the net monetary benefit (NMB) approach is preferred over incremental cost-effectiveness ratios. Based on NMB evaluation, none of the ARATs were cost-effective under a $200,000/QALY threshold when compared to ADT. Darolutamide had the highest NMB among ARATs up to the willingness-to-pay threshold of $246,000/QALY; however, the probability of its cost-effectiveness never exceeded 35%.

1.4 Detailed Highlights of the EGP Reanalysis
The EGP made the following changes to the submitted economic model:
- **Time point at which equivalent mortality was assumed**: The sponsor assumed that the OS benefits observed during the trial at 46 months (3.83 years) continued for another six months after the end of the trial (using extrapolated data). However, considering the immaturity of OS data, the large drop in the available population at risk starting from approximately 28 months, and the uncertainty in OS extrapolation the EGP decided to take a amore conservative approach and assumed similar risk of mortality between darolutamide and ADT at trial end of 3.8 years. This changed the submitted ICUR to $169, 972/QALY.
- **Extrapolation of OS:** Note that the EGP was unable to conduct analyses with the new OS curves (November 2019 data cut) as the sponsor did not provided an updated model with these new OS curves. All analyses were performed with the Sep 3, 2018 data cut. As per sponsor, based on the visual fit, Weibull, log-logistic and log-normal distributions had the best fit. Therefore, the sponsor selected Weibull distribution (median OS = 86.5 months). The EGP agreed that the Weibull

distribution was appropriate choice for the darolutamide group. For the ADT group, log-normal, log-logistic, Weibull and generalized gamma had close AIC. Considering the uncertainty with long-term extrapolation with immature data, the EGP tested the effect of choosing more optimistic generalized gamma distribution for the ADT group. The median survival on ADT was 62.6 months under generalized gamma and 56.1 under Weibull distribution. Under generalized gamma distribution for ADT, the submitted base case ICUR changed to $174,755/QALY. As there is currently no real-world, long-term data on OS, the EGP applied the generalized gamma parametric distribution for the ADT group to derive the best estimate for ICUR.

- **Extrapolation of ToT distribution:** For the submitted base case the sponsor selected the Gompertz distribution for ToT for darolutamide based on model fit statistics. The EGP decided to choose the Weibull distribution based on model fit statistics (i.e., lowest AIC) in the EGP's best case re-analysis. The EGP tested the effect of choosing Weibull, generalized gamma and log-logistic distributions, which increased the submitted base case ICUR by $15,299/QALY, $14,399/QALY and $45,967/QALY, respectively.
- **Use of Canadian tariffs for utilities:** Upon EGP request, the sponsor provided analysis using Canadian tariffs for EQ-5D (instead of UK tariffs used by the sponsor). The EGP felt that the Canadian tariffs are more appropriate than the UK tariffs as they would better reflect the preference of the Canadian population.
- **Time horizon:** The submitted base case analysis used a 10-year time horizon for the economic evaluation. However, based on the extrapolated data, ~33% of patients in the darolutamide group and ~25% of patients in the ADT group were still alive at the 10-year time horizon. A lifetime time horizon (corresponding to 25-years) was therefore chosen in the EGP's re-analysis to fully capture all downstream consequences (i.e., costs and benefit) of the different treatment options as recommended by CADTH guidelines. CGP noted that the proportions of patients likely to be alive at 10 years seemed reasonable. However, CGP cautioned that survival extrapolations beyond 10 years are speculative, due to insufficient long-term data and lack of knowledge about long term toxicity effects of ARATs and ADT.

Table 3. Detailed Description of EGP Reanalysis

One-way and multi-way sensitivity analyses (Probabilistic)					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR ($/QALY)	Δ from baseline submitted ICUR
1. ADT and Darolutamide equivalent mortality after 3.83 years (46 months)	$114,172	0.68	0.76	168,825	+27,756
2. ADT and Darolutamide equivalent mortality after 2.33 years (28 months)	$113,753	0.33	0.29	346,193	+205,124
3. Generalized gamma distribution for OS for ADT	$114,776	0.68	0.76	168,011	+26,942
4. Weibull distribution for ToT for darolutamide (lowest AIC)	$126,849	0.81	0.93	156,450	+15,381
5. Generalized gamma distribution for ToT for darolutamide (2nd lowest AIC)	$126,381	0.81	0.93	158,036	+16,967
6. Log-logistic distribution for ToT for darolutamide	$151,410	0.82	0.93	185,528	+44,528
7. Canadian tariffs for EQ-5D utilities	$115,486	0.78	0.93	148,486	+7,417
8. Time horizon: 25 years	$125,575	1.10	1.27	114,601	-26,468
EGP's Reanalysis for the Best Case Estimate					
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR ($/QALY)	Δ from baseline submitted ICER
Baseline (Sponsor's best case)	$116,181	0.82	0.93	$141,069	--
EGP's Best case: Combination of 1, 3, 4, 7,	$138,414	0.78	0.89	$177,086	+36018

and 8					
Scenario analyses of EGP's Best estimate					
Scenario analysis: EGP's best case with a 10 – year time horizon (combination of 1, 3, 4, and 7)	$126,324	0.60	0.67	$210,964	+69895
Scenario analysis: EGP's best case with a 15 – year time horizon (combination of 1, 3, 4, and 7)	$135,327	0.74	0.82	$182,380	+41,311
Scenario analysis: EGP's best case with a 25% price reduction of darolutamide:	$105,186	0.79	0.88	133,029	-8,040
Scenario analysis: EGP's best case with a 50% price reduction of darolutamide:	$71,908	0.78	0.89	91,731	-49,338
Scenario analysis: EGP's best case with a 75% price reduction of darolutamide:	$38,596	0.79	0.88	48,615	-92,454

Exploratory analyses whereby darolutamide was compared to apalutamide and enzalutamide. The analysis was conducted using the sponsor's NMA data, and results were presented sequentially through probabilistic analysis. Findings of this exploratory analyses using unadjusted ITC results suggested that darolutamide has roughly the same QALYs at a lower cost when compared to apalutamide and enzalutamide. According to the sponsor, darolutamide is dominant versus enzalutamide and is less costly and has roughly similar QALYs versus apalutamide.

1.5 Evaluation of Submitted Budget Impact Analysis

The factor that influenced the budget impact analysis the most was the market share for ADT (more patients on ADT add darolutamide such as patients with seizures) with potential incremental budget impact rather than cost savings. With all other scenarios, darolutamide continued being a cost saving alternative as there is no anticipated shift in the overall proportion of patients receiving an ARAT, and assuming it takes more market shares from enzalutamide (more costly drug) than from apalutamide (similar costing drug). The CGP felt that market share distributions between the ARATs are difficult to predict at this point given insufficient evidence to choose one ARAT over the other. CGP speculated that it is possible that the choice may trend towards darolutamide as it may be perceived as slightly less toxic than the other ARATs (apalutamide or enzalutamide).

A limitation of the model is the consideration of incident nmCRPC cases only without consideration of prevalent nmCRCP cases at drug launch. The increase of the number of nmCRPC cases, however, will result in higher cost savings.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for darolutamide when compared to ADT is:
- $177,097/QALY; however, there is a large uncertainty in the ICUR estimate (both in sponsor's analysis and EGP's best case) considering the immaturity of overall survival data, the lack of data (e.g., observational data on OS for ADT) to validate the extrapolation and, the fact that more recently available OS data (November 2019 data cut) was not included in the model.
  Given the best estimate, there is a 10% probability that darolutamide is cost-effective at a conventional cost-effectiveness threshold of $100,000/QALY and a 20% probability of cost effectiveness at a threshold of $150,000/QALY.
- The extra cost of darolutamide is $138,414 with drug costs being the key cost driver. A reduction of approximately 50% in the price of darolutamide would likely reduce the ICUR to around $72,000/QALY.

- The extra clinical effect of darolutamide is 0.78 QALY with 78% of the extra gain obtained from the period of extrapolation rather than the clinical trial data. The main factors influencing ∆E include time horizon, time point when equivalent mortality between darolutamide and ADT is assumed, parametric distribution type for OS and time on treatment for darolutamide.

Overall conclusions of the submitted model:
- There is a large uncertainty in OS as indicated by the spread of extrapolated curves under different parametric distributions. If possible, OS analysis should be repeated when longer clinical trial data becomes available.
- The results of indirect comparison of darolutamide with apalutamide and enzalutamide also came with a large uncertainty with incremental cost-effectiveness estimates spread in all four quadrants. Although darolutamide had the highest NMB up to ~$250,000/QALY WTP values, the probability of its cost-effectiveness never exceeded 35%.

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. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Genitourinary 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 darolutamide (Nubeqa) for non-metastatic Castration Resistant Prostate Cancer. A full assessment of the clinical evidence of darolutamide (Nubeqa) for non-metastatic Castration Resistant Prostate 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*.

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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