CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Apalutamide (Erleada) for Castration-Resistant Prostate Cancer

November 1, 2018

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Janssen Inc.** compared apalutamide in combination with androgen deprivation therapy (ADT) with ADT monotherapy for patients with non-metastatic castrate-resistant prostate cancer (nm-CRPC).

The economic model only accounts for nm-CRPC patients who are at high risk for the development of metastases, which is defined as a prostate-specific antigen (PSA) doubling time of 10 months or less during continuous ADT according to the SPARTAN[1] trial eligibility criteria, while the pCODR requested reimbursement indication is for broader population.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	**Funding request:** Patients with nm-CRPC. **Patient Population Modelled:** Consistent with SPARTAN[1] study population: Adult men who have confirmed adenocarcinoma of the prostrate that is castration-resistant (no detectable distant metastases by either CT scan, MRI or technetium-99m bone scan) and are at high risk for the development of metastases; high risk defined as a PSA doubling time of 10 months or less during continuous ADT.
Type of Analysis	*CUA & CEA*
Type of Model	*Partitioned-survival*
Comparator	*Androgen deprivation therapy*
Year of costs	*2018*
Time Horizon	*15 years*
Perspective	*Government*
Cost of apalutamide*	*Apalutamide costs:* • *$28.34 per 60 mg tablet* *At the recommended dose of 240 mg (four 60 mg tablets) administered orally once daily, apalutamide costs:* • *$113.38 per day* • *$3,174.53 per 28-day cycle*
Cost of leuprolide*	*Leuprolide costs:* • *$39.60 per mg* *At the recommended dose of a 22.5 mg subcutaneous depot injection once every 3 months, leuprolide costs:* • *$10.60 per day* • *$297.00 per 28-day cycle*
Cost of bicalutamide*	*Bicalutamide costs:* • *$1.27 per 50 mg tablet* *At the recommended dose of 50 mg once daily, bicalutamide costs:* • *$1.27 per day*

	• *$35.56 per 28-day cycle*
Cost of goserelin*	*Goserelin costs:* • *$111.55 per mg* *At the recommended dose of one depo injection 10.8 mg administered once every 13 weeks, goserelin costs:* • *$13.29 per day* • *$370.69 per 28-day cycle*
Cost of degarelix*	*Degarelix costs:* • *$3.19 per mg* *At the recommended dose of one depo injection 80 mg per months, degarelix costs:* • *$9.12 per day* • *$255.00 per 28-day cycle*
Model Structure	The model was comprised of 3 health states: metastasis-free survival, metastatic castrate resistant prostate cancer and death. These events were assumed to be progressive, mutually exclusive and irreversible. Patients enter the model in metastasis-free survival state and upon detection of metastases, transition to the metastatic state.
Key Data Sources	*SPARTAN[1] phase III RCT*
** 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 April, 2018. All calculations are based on 70kg and BSA = 1.7m^2*	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate as there is no defined and generally accepted or approved standard therapy for patients with high risk nm-CRPC.

- Relevant issues identified included:
  - There is a net overall clinical benefit to apalutamide in combination with ADT compared to ADT alone for this patient population.
  - The SPARTAN trial demonstrated statistically significant and clinically meaningful benefit in metastasis-free survival (primary end point) for apalutamide plus ADT. Overall survival is currently immature.
  - Apalutamide is well tolerated, with few clinically relevant grade 3 and grade 4 side effects.
  - There are currently no treatment options for patients with non-metastatic castration resistant prostate cancer.
- Generalizability issues include:
  - The trial limited inclusion to patients with ECOG performance status of 0 and 1.
  - The trial included only high risk patients.

Summary of registered clinician input relevant to the economic analysis
Clinicians providing input all expressed that there is currently no funded standard of care for patients with nm-CRPC and that apalutamide does fill an unmet need. It was noted that adding apalutamide to the available drug options may affect which treatment a patient receives if they become metastatic. There is no diagnostic testing required for this drug.

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

- access to additional funded treatments
- quality of life
- overall survival
- delayed disease progression.

Overall, patients valued improvement of quality of life, reduction in side effects, delayed disease progression and diverse treatment options other than surgery. Patients who have experience with apalutamide reported that their treatment had minimal or no side effects and that the benefits of apalutamide outweigh the risk of the side effects. Relative to the experienced side effects, participants had an overall positive attitude toward apalutamide. Metastatic free survival, overall survival, quality of life, adverse events and access to additional funded treatments 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 apalutamide which are relevant to the economic analysis:
Barriers:

- Drug cost. The potential impact of adding apalutamide to existing ADT treatment was examined in the budget impact analysis.
- There may be more frequent clinic visits for monitoring of blood work and side effects compared to ADT alone. It was not possible to examine increased resource use for the apalutamide arm only in the provided economic model.

Enablers:

- Apalutamide is an oral treatment that can be administered in the patient's home and chemotherapy chair time is not required.
- Apalutamide is available in one tablet strength and the dose is four tablets daily. Dose adjustments are made by adjusting the number of tablets and there would be minimal drug wastage.

Other issues:

- Treatments following apalutamide in the metastatic setting, sequencing issues are not clear.

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Reanalysis Estimates

Estimates (range/point)	Submitted	EGP Reanalysis
ΔE (LY)	0.67	0.61
Metastatic free survival	2.17	1.98
Metastatic	-1.50	1.38

Estimates (range/point)	Submitted	EGP Reanalysis
ΔE (QALY)	0.63	0.57
Metastatic free survival	1.86	1.70
Metastatic	-1.23	-1.13
ΔC ($)	$95,098	$113,035
ICER estimate ($/QALY)	$151,811	$198,826

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

- Structural uncertainty of economic model: There was variance of up to 3% when running the probabilistic sensitivity analysis with 5,000 iterations. This indicates structural uncertainty in the economic model.
- Modeling of survival: Median overall survival was not reached in the clinical trial. The follow-up in the trial was less than two years, but the chosen time horizon for the model was 15 years. Extrapolating immature survival data (less than 2 years) to a long time horizon (15 years) requires substantial extrapolation, and introduces uncertainty. Further, given the method chosen to model time to treatment discontinuation, the parametric curves chosen were not the best fitting (i.e. same curve for both treatment arms, therefore not the best fitting curve).
- Subsequent treatments: The model only accounted for one line of subsequent treatment in the metastatic health state; the CGP indicated that this is not a reasonable assumption as patients in the metastatic health state may go on to up to 5 lines of subsequent treatments.
- Treatment compliance: In the submitted base case, the submitter used the treatment compliance from the SPARTAN trial for the non-metastatic setting. In the metastatic health state, however, the submitter assumed that the treatment compliance would be similar to that of the first-line setting and vary depending on which treatment was received in first line. The CGP confirmed that treatment compliance from first-line setting should have no impact on treatment compliance in the second line setting (i.e. the treatment compliance of those on apalutamide in the non-metastatic setting would not impact the treatment compliance on subsequent therapies in the metastatic setting).

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the economic model:

- Time horizon: The EGP changed the time horizon from 15 years to 10 years based on feedback from the CGP regarding the survival of patients with castrate-resistant prostate cancer.
- Treatment compliance: The CGP could not find a clinically plausible reason for why there would be a difference in treatment compliance in a real-world setting for patients in both the first-line (non-metastatic setting) and the metastatic setting. In order to reflect this, the EGP set the treatment compliance for all drugs in the economic model at 94.83%.
  In their feedback on the initial recommendation the submitter disagreed with the EGP's assumption of equal treatment compliance between apalutamide (an oral therapy self-administered in the patient's home) and ADT (predominantly injection therapies administered by healthcare professionals) in the non-metastatic setting. The submitter provided 3 published articles regarding: (i) adherence to ADT therapy in the prostate cancer setting, (ii) adherence to abiraterone in the metastatic prostate cancer setting,

and (iii) adherence to therapies in the metastatic renal cell carcinoma setting. The submitter noted that the published literature provided, suggests that: (i) the compliance results for apalutamide plus ADT observed in the controlled setting of the SPARTAN trial are higher than adherence to oral anticancer medications observed in real-world settings, and (ii) adherence to ADT is higher than the adherence to oral anticancer agents for treatment of prostate and other cancers. Consequently, the submitter did not agree with the EGP's assumption of equal treatment compliance between apalutamide plus ADT and ADT treatment arms, but proposed to keep the submitter's original input in the model, which assumed the compliance rates from the SPARTAN trial for the non-metastatic setting.
The EGP maintains its choice of setting treatment compliance equally for both treatment arms (apalutamide plus ADT and ADT) in the economic model at 94.83% for the following reason:
    - The CGP felt that:
        - apalutamide is well tolerated and there is no clinical reason for low compliance.
        - from a clinician point of view, clinicians always strive for the highest dose intensity possible and educate their patients accordingly. Therefore, it is reasonable to assume a conservative scenario in which patients actually take their medications (apalutamide and ADT) as prescribed.
        - one could argue that the compliance rate for intravenous drugs could be lower, too, as in clinical practice cycles are commonly being delayed or skipped.
- Parametric curve time to treatment discontinuation: The submitter wished to fit the same parametric curve for both the treatments for treatment discontinuation. As there was no curve that ideally fit both treatments, in the submitted base case they selected the Weibull curve, the 3rd best for apalutamide plus ADT and 4th best for placebo plus ADT. The EGP examined the gamma curve, which was tied for 3rd best fit with the Weibull curve for apalutamide plus ADT and was the second best fit for placebo plus ADT.

Table 3. EGP Reanalysis Estimates, 10,000 iterations

Baseline (Submitter's best case)	$95,098 ($73,140, $113,735)	0.63 (-0.21, 1.40)	0.67 (=0.04, 1.38)	$151,811	--
Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
BEST ESTIMATE					
Time horizon - 10 years	$94,895	0.56	0.62	$163,988	$12,177
Treatment compliance - 94.83%	$99,142	0.64	0.69	$154,095	$2,284
Time to treatment discontinuation parametric curve -gamma	$111,722	0.65	0.68	$172,816	$21,005
Best case estimate of above 3 parameters	$113,035 ($85,874, $132,664)	0.57 (-0.23, 1.38)	0.61 (-0.03, 1.28)	$198,826	$47,015

1.5 Evaluation of Submitted Budget Impact Analysis

Key limitations of the BIA model include the assumption that patients that progress to the metastatic state at some point during the year have been excluded from the BIA upfront. That is, after identifying a population of non-metastatic castrate-resistant prostate cancer patients for the first year, the submitter excludes a certain proportion of patients receiving apalutamide plus ADT and ADT monotherapy from the BIA based on the assumption that these patients would be expected to progress to metastatic disease and would therefore be ineligible for treatment in the non-metastatic setting. In reality patients would be eligible to receive apalutamide plus ADT or ADT monotherapy for some time before they progress to metastatic disease and become ineligible for further treatment. This assumption is therefore extremely conservative. Including all patients in the BIA (that is all non-metastatic patients with the assumption that none progress during the year and all are eligible for treatment in the non-metastatic setting) would over-estimate the budget impact. The true budget impact lies somewhere between these two extremes.

The submitter in the base case BIA assumed the same differential treatment compliance as that observed in the economic model (91.12% for apalutamide plus ADT and 94.83% for ADT monotherapy). Setting treatment compliance at 94.83% for all treatments increases the 3-year budget impact by ~5%.

The BIA also includes only estimates of non-metastatic prostate cancer patients in Ontario, which represent 38.5% of all prostate cancers in Canada. The budget impact would therefore be higher if estimating for all of Canada.

Finally, the EGP did not receive an adequate answer to explain the discrepancy in the population of nm-CRPC patients between the current scenario and the new market scenario. The EGP could not identify why the introduction of apalutamide plus ADT on the market would affect the reference population.

It should be noted that the number of patients confirmed as "true" non-metastatic may decrease in the future with newer diagnostic imaging tests. This would have an impact on the budget impact as it would reduce the number of patients eligible for apalutamide. However, at the current time, the sensitivity

and specificity of such a diagnostic test is not quantified and the impact on the number of patients is unknown.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for apalutamide in combination with ADT when compared to ADT monotherapy is:

- $198,826/QALY
- The extra cost of apalutamide plus ADT is $113,035 (ΔC). *The main factors that influence ΔC are the time to treatment discontinuation curve and the duration of treatment effect.*
- The extra clinical effect of apalutamide plus ADT is 0.57 (ΔE). *The main factors that influence ΔE are the duration of treatment effect, the time horizon and the source of utilities.*

Overall conclusions of the submitted model:

- *There is uncertainty in the model structure as evidenced by the variability in the ICER, despite running 10,000 simulations.*
- *There is a large variability in the incremental QALYs.*
- *The EGP was unable to address all the limitations noted above through scenario analyses.*

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 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 apalutamide (Erleada) for non-metastatic castration-resistant prostate cancer. A full assessment of the clinical evidence of [drug name and indication] 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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