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CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

ENZALUTAMIDE (XTANDI)

(Astellas Pharma Canada, Inc.)

Indication: In combination with androgen-deprivation therapy for the treatment of patients with metastatic castration sensitive prostate cancer.

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AAP + ADT	abiraterone acetate plus prednisone in combination with androgen deprivation therapy
ADT	androgen deprivation therapy
AE	adverse event
APA + ADT	apalutamide in combination with androgen deprivation therapy
BIA	budget impact analysis
BSC	best supportive care
CAD	Canadian Dollars
CGP	clinical guidance panel
DOC + ADT	docetaxel in combination with androgen deprivation therapy
ENZ + ADT	enzalutamide in combination with androgen deprivation therapy
ICER	incremental cost-effectiveness ratio
IV	intravenous
LHRH	luteinizing hormone-releasing hormone
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
NMA	network meta-analysis
OS	overall survival
QALY	quality-adjusted life year
QoL	quality of life
rPFS	radiographic progression-free survival
TTD	time to treatment discontinuation
UK	United Kingdom
WTP	willingness-to-pay

Executive Summary

The executive summary is comprised of two tables (Table 1: Background and Table 2: Economic) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug Product	Enzalutamide (Xtandi), 40 mg capsule
Submitted Price	Enzalutamide, 40 mg capsule: $29.20
Indication	For the treatment of patients with metastatic castration-sensitive prostate cancer
Health Canada Approval Status	Under review (pre-NOC)
Health Canada review pathway	Standard review
NOC Date	Jun 2, 2020
Reimbursement Request	As per indication
Sponsor	Astellas Canada
Submission History	Previously Reviewed: Yes 1. Indication: For the treatment of metastatic castration-resistant prostate cancer. Recommendation date: Jul 23, 2013 Recommendation: Recommended.[1] 2. Indication: For the first line treatment of metastatic castration-resistant prostate cancer. Recommendation date: Jun 22, 2015 Recommendation: Recommended on the condition of cost-effectiveness being improved to an acceptable level.[2] 3. Indication: For the treatment of non-metastatic castration-resistant prostate cancer. Recommendation date: Mar 26, 2019 Recommendation: Recommended on the condition of cost-effectiveness being improved to an acceptable level and feasibility of the budget impact being addressed.[3]

NOC = Health Canada Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of Economic Evaluation	Cost-utility analysis Markov Model
Target Population	Adult male patients with metastatic castration-sensitive prostate cancer (aligned with reimbursement request)
Treatment	Enzalutamide in combination with androgen deprivation therapy (ENZ + ADT)
Comparators	Androgen deprivation therapy (ADT) alone Docetaxel in combination with ADT (DOC + ADT) Apalutamide in combination with ADT (APA + ADT) Abiraterone acetate plus prednisone in combination with ADT (AAP + ADT)
Perspective	Canadian publicly-funded health care payer
Outcomes	QALYs, LYs
Time Horizon	15 years
Key Data Source	ARCHES and ENZAMET trials and sponsor submitted network meta-analysis (NMA) reporting overall survival (OS) and radiographic progression-free survival (rPFS)
Submitted Results for Base Case	• The sequential ICER for ENZ + ADT is: ○ ENZ + ADT vs. DOC + ADT: $132,000 per QALY (1.35 inc. QALYs; $178,694 inc. costs)
Key Limitations	• Based on the limited duration of the clinical trials and immaturity of the survival data, there was substantial uncertainty regarding the duration of treatment effect and the long-term extrapolation of OS for ENZ + ADT. • The rPFS extrapolations selected by the sponsor were not considered to be clinically feasible as rPFS was greater than overall survival at specified time points. • The sponsor used direct trial data rather than the NMA results to inform ENZ + ADT efficacy, which biased cost-effectiveness results in favour of ENZ + ADT. Indirect evidence captured as part of the NMA is therefore precluded from the analyses. Given that comparator treatments (i.e., APA + ADT, AAP + ADT, DOC + ADT) were informed using NMA results, there is further uncertainty when incorporating separate data sources. • The sponsor utilized a 15-year time horizon, however with interventions that have differential effects on mortality, a lifetime time horizon of 20-years, was considered more appropriate as per CADTH Guidelines. • Drug dose intensity was assumed to be equal for all treatments (100% compliance), however this assumption was considered overtly optimistic for DOC + ADT given the expected toxicity and lower compliance compared to oral treatments. • Non-cancer mortality was not included and the sponsor assumed general population mortality is representative of mCSPC patients. However, patients with mCSPC have an elevated risk of mortality due to comorbidities compared with the general population.
CADTH Reanalysis Results	• CADTH reanalyses included: a revised dose intensity for DOC + ADT; extending the time horizon; using ENZ + ADT NMA results; including non-cancer mortality; modifying rPFS extrapolations; and, applying a treatment waning effect. • The sequential ICER for ENZ + ADT is: ○ ENZ + ADT vs. DOC + ADT: $294,805 per QALY (0.24 inc. QALYs; $72,381 inc. costs) • The probability of ENZ + ADT being considered cost-effective at a WTP threshold of $50,000 per QALY was 0%. • At a WTP threshold of $50,000 per QALY, a price reduction of approximately 75% would be required for ENZ+ADT.

AAP + ADT = abiraterone acetate plus prednisone in combination with androgen deprivation therapy; ADT = androgen deprivation therapy; APA + ADT = apalutamide in combination with androgen deprivation therapy; DOC + ADT = docetaxel in combination with androgen deprivation therapy; ENZ + ADT = enzalutamide in combination with androgen deprivation therapy; inc. = incremental; ICER = incremental cost-effectiveness ratio; LY = life year; NMA = network meta-analysis; OS = overall survival; QALY= quality-adjusted life-year; rPFS = radiographic progression-free survival; WTP = willingness-to-pay.

Note: Extendedly dominated refers to a treatment having a higher ICER when compared to both the previous and next most effective treatment. Dominated treatments are more costly and less effective versus the comparator.

Conclusions

CADTH undertook reanalyses to address limitations that included a revised dose intensity, extending the time horizon, using ENZ + ADT NMA results, including non-cancer mortality, modifying rPFS extrapolations, and applying a treatment waning effect.

CADTH's findings were aligned with the sponsor's results where APA + ADT remained extendedly dominated and AAP + ADT remained dominated. However, OS and rPFS estimates for ENZ + ADT were not statistically different when compared to APA + ADT and the sponsor's NMA was associated with multiple limitations. Therefore, it cannot be concluded that ENZ + ADT efficacy would be substantially different from APA + ADT, which utilizes a similar mechanism of action. Based on CADTH base case reanalyses, ENZ + ADT is not a cost-effective treatment option at $100,000 and $50,000 per QALY WTP thresholds with an ICER of $294,805 per QALY versus DOC + ADT. Based on current list prices, at WTP thresholds of $100,000 and $50,000 per QALY, respective price reductions of at least 60% and 75% are required.

Based on the sponsor's submitted budget impact analysis, [redacted]. (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this economic information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).* CADTH reanalyses suggest that the budget impact of introducing enzalutamide to the market was underestimated [redacted]. CADTH's revised results estimated an increase to budgets of $3,139,045 over the first 3 years. (*Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this economic information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Stakeholder Input Relevant to the Economic Review

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. 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.

Economic Review

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. 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.

Appendix 1: Cost Comparison Table

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. 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.

Appendix 2: Submission Quality

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. 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.

Appendix 3: Additional Information on the Submitted Economic Evaluation

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. 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.

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. 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.

Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. 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.

References

1. pCODR Expert Review Committee final recommendation: Xtandi for metastatic castration resistant prostate cancer. Toronto (ON): CADTH; 2013: https://www.cadth.ca/sites/default/files/pcodr/pcodr-xtandi-fn-rec.pdf. Accessed 2020 Mar 30.

2. pCODR Expert Review Committee final recommendation: Xtandi first line metastatic castration-resistant prostate cancer. Toronto (ON): CADTH; 2015: https://www.cadth.ca/sites/default/files/pcodr/pcodr_enzalutamide_xtandi_1stln_mcrpc_fn_rec.pdf. Accessed 2020 Mar 30.

3. pCODR Expert Review Committee final recommendation: Xtandi for non-metastatic castration-resistant prostate cancer. Toronto (ON): CADTH; 2019: https://www.cadth.ca/sites/default/files/pcodr/Reviews2019/10149Enzalutamidenm-CRPC_FnRec_EarlyConv_2019-03-26-v4_Post_26Mar2019_final.pdf. Accessed 2020 Mar 30.

4. Pharmacoeconomic evaluation. In: pan-Canadian Oncology Drug Review sponsor submission: Xtandi (enzalutamide) 40 mg capsules. Markham (ON): Astellas Pharma Canada; 2020.

5. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. *J Clin Oncol.* 2019;37(32):2974-2986.

6. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *NEJM.* 2019;381(2):121-131.

7. [PR]Zoladex® LA (goserelin acetate): 10.8 mg inj [product monograph]. Mississauga (ON): AstraZeneca; 2017: https://pdf.hres.ca/dpd_pm/00042729.PDF. Accessed 2020 Mar 30.

8. [PR]Firmagon® (degarelix for injection): 80 mg and 120 mg vial [product monograph]. North York (ON): Ferring Pharmaceuticals 2016: https://pdf.hres.ca/dpd_pm/00034229.PDF. Accessed 2020 Mar 30.

9. [PR]Lupron® (leuprolide acetate injection): 5 mg/mL / [PR]Lupron Depot® (leuprolide acetate for suspension); 7.5 mg/syringe, 22.5 mg/syringe, 30.0 mg/syringe [product monograph]. St-Laurent (QC): AbbVie; 2019: https://pdf.hres.ca/dpd_pm/00051910.PDF. Accessed 2020 Mar 30.

10. [PR]Docetaxel injection (docetaxel injection USP): 20 mg/mL, 80 mg/4 mL, 160 mg/8 mL one-vial formulation, for intravenous infusion [product monograph]. St. Catharines (ON): Biolyse Pharma; 2016: https://pdf.hres.ca/dpd_pm/00036571.PDF. Accessed 2020 Mar 30.

11. Erleada® (apalutamide): 60 mg tablets, oral [product monograph]. Toronto (ON): Janssen; 2019 Jun 12.

12. [PR]Zytiga® (abirateron acetate): 250 mg uncoated tablets, 500 mg film-coated tablets, for oral use [product monograph]. Toronto (ON): Janssen; 2019: https://www.janssen.com/canada/sites/www_janssen_com_canada/files/prod_files/live/zytiga_cpm.pdf. Accessed 2020 Mar 30.

13. Malone S, Shayegan B, Basappa NS, et al. Management algorithms for metastatic prostate cancer. *CUAJ.* 2019;14(2):50-60.

14. Saad F, Aprikian A, Finelli A, et al. 2019 Canadian Urological Association (CUA)-Canadian Uro Oncology Group (CUOG) guideline: Management of castration-resistant prostate cancer (CRPC). *CUAJ.* 2019;13(10):307-314.

15. Saad F, Canil C, Finelli A, et al. Controversial issues in the management of patients with advanced prostate cancer: results from a Canadian consensus forum. *CUAJ.* 2019;14(4):E137-149.

16. Pfizer. NCT01212991: A safety and efficacy study of oral MDV3100 in chemotherapy-naive patients with progressive metastatic prostate cancer (PREVAIL). *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2020: https://clinicaltrials.gov/ct2/show/results/NCT01212991. Accessed 2020 Mar 30.

17. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *NEJM.* 2019;381(1):13-24.

18. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *NEJM.* 2017;377(4):352-360.

19. Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2013;14(2):149-158.

20. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *NEJM.* 2015;373(8):737-746.

21. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health.* 2012;15(5):708-715.

22. Pfizer. NCT00974311: Safety and efficacy study of MDV3100 in patients with castration-resistant prostate cancer who have been previously treated with docetaxel-based chemotherapy (AFFIRM). *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2018: https://clinicaltrials.gov/ct2/show/results/NCT00974311. Accessed 2020 Mar 30.

23. Exceptional Access Program (EAP). Toronto (ON): Ontario Ministry of Health and Long-Term Care; 2019: http://www.health.gov.on.ca/en/pro/programs/drugs/odbf/odbf_except_access.aspx. Accessed 2020 Mar 30.

24. Ontario Ministry of Health and Long-Term Care. Drug Benefit Formulary/Comparative Drug Index. 2019; https://www.formulary.health.gov.on.ca/formulary/. Accessed 2020 Mar 30.

25. pan-Canadian Oncology Drug Review final economic guidance report: enzalutamide (Xtandi) for non-metastatic castration-resistant prostate cancer. Ottawa (ON): CADTH; 2019: https://www.cadth.ca/sites/default/files/pcodr/Reviews2019/10149Enzalutamidenm-CRPC_fnEGR_EC_NOREDACT-ABBREV_Post_26Mar2019_final.pdf. Accessed 2020 Mar 30.

26. DeltaPA [Database on Internet]. Ottawa (ON): IQVIA; 2020: https://www.iqvia.com/. Accessed 2020 May 29.

27. Hollander MJ. Costs of end-of-life care: findings from the province of Saskatchewan. *Healthc Q.* 2009;12(3):50-58.

28. Krahn MD, Bremner KE, Zagorski B, et al. Health care costs for state transition models in prostate cancer. *Med Decis Making.* 2014;34(3):366-378.

29. Schedule of benefits for physician services under the Health Insurance Act: effective October 1, 2019. Toronto (ON): Ontario Ministry of Health and Long-Term Care; 2016: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/. Accessed 2020 Mar 30.

30. Krahn MD, Zagorski B, Laporte A, et al. Healthcare costs associated with prostate cancer: estimates from a population-based study. *BJU Int.* 2010;105(3):338-346.

31. Schedule of benefits for laboratory services under the Health Insurance Act: effective January 1, 2020. Toronto (ON): The Ministry of Health and Long-Term Care; 2020: http://www.health.gov.on.ca/en/pro/programs/ohip/sob/lab/lab_mn2020.pdf. Accessed 2020 Mar 30.

32. Clarke NW, Ali A, Ingleby FC, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. *Ann Oncol.* 2019;30(12):1992-2003.

33. Gravis G, Boher JM, Joly F, et al. Androgen deprivation therapy (ADT) plus docetaxel versus ADT alone in metastatic non castrate prostate cancer: impact of metastatic burden and long-term survival analysis of the randomized phase 3 GETUG-AFU15 trial. *Eur Urol.* 2016;70(2):256-262.

34. James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet (London, England).* 2016;387(10024):1163-1177.

35. Kamba T, Kamoto T, Maruo S, et al. A phase III multicenter, randomized, controlled study of combined androgen blockade with versus without zoledronic acid in prostate cancer patients with metastatic bone disease: results of the ZAPCA trial. *Int J Clin Oncol.* 2017;22(1):166-173.

36. Kyriakopoulos CE, Chen YH, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. *J Clin Oncol.* 2018;36(11):1080-1087.

37. Marchioni M, Di Nicola M, Primiceri G, et al. New antiandrogen compounds compared to docetaxel for metastatic hormone sensitive prostate cancer: results from a network meta-analysis. *J Urol.* 2020;203(4):751-759.

38. Sathianathen NJ, Koschel S, Thangasamy IA, et al. Indirect comparisons of efficacy between combination approaches in metastatic hormone-sensitive prostate cancer: a systematic review and network meta-analysis. *Eur Urol.* 2020;77(3):365-372.

39. Guidelines for the economic evaluation of health technologies: Canada 4th edition. Ottawa (ON): CADTH; 2017: https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf. Accessed 2020 Mar30.

40. Methods for mapping between the EQ-5D-5L and the 3L for technology appraisal. Sheffield (UK): Decision Support Unit, ScHARR, University of Sheffield; 2017: http://nicedsu.org.uk/wp-content/uploads/2017/05/Mapping-5L-to-3L-DSU-report.pdf. Accessed 2020 May 19.

41. Position statement on use of the EQ-5D-5L value set for England (updated October 2019). 2019; https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l. Accessed 2020 May 19.

42. Hatswell AJ, Porter J, Lee D, Hertel N, Latimer NR. The cost of costing treatments incorrectly: errors in the application of drug prices in economic evaluation due to failing to account for the distribution of patient weight. *Value Health.* 2016;19(8):1055-1058.

43. Baade PD, Fritschi L, Eakin EG. Non-cancer mortality among people diagnosed with cancer (Australia). *Cancer Causes Control.* 2006;17(3):287-297.

44. Government of Canada. Generic submissions under review. 2020; https://www.canada.ca/en/health-canada/services/drug-health-product-review-approval/generic-submissions-under-review.html. Accessed 2020 Mar 30.

45. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *NEJM.* 2004;351(15):1502-1512.

46. Bahl A, Oudard S, Tombal B, et al. Impact of cabazitaxel on 2-year survival and palliation of tumour-related pain in men with metastatic castration-resistant prostate cancer treated in the TROPIC trial. *Ann Oncol.* 2013;24(9):2402-2408.

47. Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases. *Technology appraisal guidance TA412*. London (UK): National Institute for Clinical Excellence; 2016: https://www.nice.org.uk/guidance/ta412/resources/radium223-dichloride-for-treating-hormonerelapsed-prostate-cancer-with-bone-metastases-pdf-82604599866565. Accessed 2020 Mar 30.

48. Radium-223 dichloride 1000kBq/mL solution for injection (Xofigo®). Glasgow (UK): Scottish Medicines Consortium; 2015: https://www.scottishmedicines.org.uk/media/2205/radium_223__xofigo__final_sept_2015_160915_for_website.pdf. Accessed 2020 Mar 30.

49. Purchasing power parities (PPP). Paris (FR): OECD; 2018: https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm. Accessed 2020 Mar 30.

50. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *NEJM.* 2012;367(13):1187-1197.

51. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol.* 2012;13(10):983-992.

52. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet (London, England).* 2010;376(9747):1147-1154.

53. Canadian Cancer Society Advisory Committee. Canadian cancer statistics. a 2018 special report on cancer incidence by stage. Toronto (ON): Canadian Cancer Society; 2018: http://www.cancer.ca/Canadian-Cancer-Statistics-2018-EN. Accessed 2020 Mar 31.

54. Cancer Care Ontario. Ontario Cancer Statistics 2018. Cancer Care Ontario,; 2018: https://www.cancercareontario.ca/sites/ccocancercare/files/assets/ANI_32628719_OCS2018_AODA_Mar2019_V02.pdf. Accessed 2020 Mar 31.

55. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2019. Toronto (ON): Canadian Cancer Society; 2019: https://www.cancer.ca/~/media/cancer.ca/CW/publications/Canadian%20Cancer%20Statistics/Canadian-Cancer-Statistics-2019-EN.pdf. Accessed 2020 May 29.

56. Pharmacoeconomic report: apalutamide (Erleada). *CADTH Drug reimbursement review*. Ottawa (ON): CADTH; 2020: https://cadth.ca/sites/default/files/pcodr/Reviews2020/10200ApalutamidemCSPC_fnEGR_REDACT-ABBREV_EC_22Apr2020_final.pdf. Accessed 22 May 2020.

57. Annual demographic estimates: Canada, provinces and territories. Ottawa (ON): Statistics Canada; 2019: https://www150.statcan.gc.ca/n1/en/pub/91-215-x/91-215-x2019001-eng.pdf?st=TFS9x2Wd. Accessed 2020 May 27.