

CADTH DRUG REIMBURSEMENT REVIEW

# Pharmacoeconomic Report

ENTRECTINIB (ROZLYTREK)

(Hoffmann-La Roche Ltd.)

**Indication:** For the first-line treatment of patients with ROS1 positive locally advanced or metastatic non-small cell lung cancer.

Version: Initial

Publication Date: January 8, 2021

Report Length: 17 Pages

**Disclaimer:** The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the Canadian *Copyright Act* and other national and international laws and agreements. Users are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

**About CADTH:** CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

## Table of Contents

List of Tables.....	4
Abbreviations .....	5
Executive Summary .....	6
Conclusions .....	8
Stakeholder Input Relevant to the Economic Review.....	9
Economic Review .....	10
Appendix 1: Cost Comparison Table.....	11
Appendix 2: Submission Quality .....	12
Appendix 3: Additional Information on the Submitted Economic Evaluation .....	13
Appendix 5: Submitted BIA and CADTH Appraisal .....	15

## List of Tables

Table 1: Submitted for Review.....	6
Table 2: Summary of Economic Evaluation.....	7

## Abbreviations

<b>AE</b>	adverse event
<b>ALK</b>	anaplastic lymphoma kinase
<b>CUA</b>	cost-utility analysis
<b>FISH</b>	fluorescence in situ hybridization
<b>HR</b>	hazard ratio
<b>ICER</b>	incremental cost-effectiveness ratio
<b>IHC</b>	immunohistochemistry
<b>KM</b>	Kaplan-Meier
<b>LY</b>	life-year
<b>MAIC</b>	matching-adjusted indirect comparison
<b>NSCLC</b>	non-small cell lung cancer
<b>OS</b>	overall survival
<b>pCODR</b>	Pan-Canadian Oncology Drug Review
<b>PSM</b>	partitioned survival model
<b>PFS</b>	progression-free survival
<b>QALY</b>	quality-adjusted life-year
<b>ROS1</b>	c-ros oncogene 1
<b>SE</b>	standard error
<b>TKI</b>	tyrosine kinase inhibitor
<b>WTP</b>	willingness-to-pay

## Executive Summary

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

**Table 1: Submitted for Review**

Item	Description
Drug product	entrectinib (Rozlytrek), 100 mg and 200 mg capsules
Submitted price	entrectinib, 200 mg, capsule: \$95.33 per capsule entrectinib, 100 mg, capsule: \$47.66 per capsule
Indication	Treatment of patients with ROS1 positive locally advanced or metastatic NSCLC not previously treated with crizotinib
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	May 05, 2020
Reimbursement request	As monotherapy for the first-line treatment of patients with ROS1-positive locally advanced or metastatic non-small cell lung cancer
Sponsor	Hoffmann-La Roche Limited
Submission history	Previously reviewed: No

NOC = Notice of Compliance; NSCLC = non-small cell lung cancer; ROS1 = c-ros oncogene 1 receptor tyrosine kinase gene.

**Table 2: Summary of Economic Evaluation**

Component	Description
<b>Type of economic evaluation</b>	Cost-utility analysis Partitioned survival model
<b>Target population</b>	Treatment-naïve patients with ROS1-positive locally advanced or metastatic NSCLC. The target population aligns with the sponsor's reimbursement request but does not align with the Health Canada approved indication.
<b>Treatment</b>	Entrectinib
<b>Comparators</b>	(1) Crizotinib (2) Chemotherapy with pemetrexed + cisplatin or carboplatin followed by pemetrexed maintenance (chemotherapy)
<b>Perspective</b>	Canadian publicly funded health care payer
<b>Outcomes</b>	Quality adjusted life years (QALYs), life years (LYs)
<b>Time horizon</b>	10 years
<b>Key data source</b>	<ul style="list-style-type: none"> <li>• Progression-free survival (PFS) and overall survival (OS) data for entrectinib: integrated data from 3 single-arm trials (N=94): ALKA-372-001, STARTRK-1 and STARTRK-2; forming the Overall ROS1 NSCLC Efficacy Evaluable Analysis Set</li> <li>• Hazard ratios (HRs) for PFS and OS for entrectinib versus crizotinib: propensity-score analysis based on Overall ROS1 NSCLC Efficacy Evaluable Analysis Set and the Flatiron database</li> <li>• HR for PFS and OS for crizotinib versus chemotherapy: PROFILE 1014</li> </ul>
<b>Submitted results for base case</b>	Results from a sequential analysis showed that the ICER of entrectinib was \$78,019 per QALY gained compared with chemotherapy. Crizotinib was ruled out by extended dominance by chemotherapy and entrectinib.
<b>Key limitations</b>	<ul style="list-style-type: none"> <li>• The clinical efficacy of entrectinib is uncertain. The individual studies were all open-label, single-arm unblinded trials. Furthermore, considerable heterogeneity was noted between the individual studies and, by pooling, no adjustments were conducted to account for the heterogeneity.</li> <li>• Comparative clinical efficacy for entrectinib compared with crizotinib or chemotherapy was based on multiple different data sources including a propensity score analysis from the Flatiron database and naïve comparison to the PROFILE 1014 trial. The CADTH clinical review highlighted several concerns with the internal validity of the approach given the substantial heterogeneity across the study designs and the populations, and the omission of important prognostic variables in the propensity scoring method. This introduced significant uncertainty into the indirect comparisons that could not be sufficiently explored and integrated into the economic analysis. It was therefore considered inappropriate to perform and interpret the results sequentially.</li> <li>• The predicted OS curve for entrectinib in the sponsor's model lacked face validity and was not aligned with the observed survival expected for this patient population. Overall survival was overestimated according to the clinical experts consulted on this review.</li> <li>• The sponsor's assumptions regarding the distribution of patients receiving subsequent treatments were not reflective of current Canadian practice. As the proportion of patients receiving a tyrosine kinase inhibitor after entrectinib or crizotinib was overestimated, this would consequently increase subsequent treatment costs.</li> <li>• The sponsor did not include the cost of ROS1 testing. As ROS1 testing is not routinely available, the introduction of entrectinib is expected to be associated with an increase in testing costs.</li> </ul>
<b>CADTH reanalysis results</b>	<ul style="list-style-type: none"> <li>• Given the inconclusiveness of the comparative clinical evidence, the cost-effectiveness of entrectinib is unknown. CADTH undertook exploratory reanalyses to correct the sponsor's model using best available evidence, but the validity and interpretability of the results are limited by the comparative evidence.</li> <li>• In light of the lack of direct comparative clinical efficacy information for entrectinib compared to chemotherapy or crizotinib, CADTH's exploratory re-analyses incorporated the relative efficacy</li> </ul>

Component	Description
	<p>(PFS and OS) for entrectinib compared to crizotinib based on a matched adjusted indirect comparison to the PROFILE 1001 trial and included the cost of ROS1 testing. Compared to chemotherapy, the ICER of entrectinib was \$91,447 per QALY. Entrectinib was associated with an ICER of \$119,460 per QALY compared to crizotinib. However, these analyses should be viewed only as exploratory given the absence of any direct comparative clinical data for entrectinib.</p> <ul style="list-style-type: none"> <li>• Sensitivity analyses were conducted which demonstrated that the submitted economic model was sensitive to changes in the assumed OS benefit for entrectinib relative to crizotinib; the survival models used to extrapolate the long-term OS for entrectinib; and, the assumptions regarding treatment waning.</li> </ul>

ICER = incremental cost-effectiveness ratio; HR = hazard ratio; LY = life-year; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression free survival; QALY= quality-adjusted life-year; ROS1 = c-ros oncogene 1 receptor tyrosine kinase gene.

## Conclusions

Several major limitations could not be sufficiently addressed by CADTH, including the lack of direct comparative clinical data and concerns about the quality of the submitted real-world data and the propensity score analysis. Given the inconclusiveness of the comparative evidence, a CADTH base case could not be derived to estimate the cost-effectiveness of entrectinib compared with crizotinib or chemotherapy.

In an exploratory analysis, assuming confidence in the comparative clinical evidence that were estimated from a matching-adjusted indirect comparison to the PROFILE 1001 trial and in which incorporated the costs of ROS1 testing, entrectinib is associated with an ICER of \$119,460 per QALY compared with crizotinib, and an ICER of \$91,447 per QALY compared to chemotherapy. If no difference in OS and PFS is assumed between entrectinib compared with crizotinib, entrectinib would be dominated by crizotinib (i.e., entrectinib is more costly and equally effective). Since the comparative clinical evidence is limited to pairwise comparisons, all comparators could not be considered together within this exploratory analysis to identify the cost-effective therapy(ies) among these three treatments.

Results from CADTH re-analyses were highly sensitive to the relative OS benefit for entrectinib compared to crizotinib; the survival model used to extrapolate long-term OS for entrectinib; and, the assumptions regarding treatment waning. Furthermore, limited data on long-term PFS and OS leads to uncertainty in the cost-effectiveness of entrectinib given that 46% of the incremental QALYs were accrued beyond the trial in comparison to chemotherapy and crizotinib respectively. Together, combined with the concerns in the comparative clinical effects of entrectinib, the cost effectiveness estimates should be viewed as exploratory.

Based on the sponsor's submitted budget impact analysis, the total budget impact was estimated to be \$1,022,214 over the first three years. CADTH re-analysis of the sponsor's submitted BIA suggests that the estimated budget impact of introducing entrectinib would be \$2,635,483 over the first three years.

The Health Canada indication for entrectinib is for the treatment of patients with ROS1 positive locally advanced or metastatic non-small cell lung cancer (NSCLC) not previously treated with crizotinib. The modelled population within the economic analysis focused on treatment-naïve ROS1-positive locally advanced or metastatic NSCLC patients. Uncertainty remains to the cost-effectiveness and budget impact of entrectinib in the full Health Canada indication.



## 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 BIA 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. Pharmacoeconomic evaluation. In: pan-Canadian Oncology Drug Review sponsor submission: Rozlytrek (entrectinib) for ROS1-positive NSCLC, 100 mg and 200 mg capsules. Hoffmann-La Roche Limited. Mississauga (ON): Hoffmann-La Roche Limited; 2020 Jan 8.
2. Sigal D, Tartar M, Xavier M, et al. Activity of entrectinib in a patient with the first reported NTRK fusion in neuroendocrine cancer. *J Natl Compr Canc Netw*. 2017;15(11):1317-1322.
3. Braud FGD, Niger M, Damian S, et al. Alka-372-001: first-in-human, phase I study of entrectinib – an oral pan-trk, ROS1, and ALK inhibitor – in patients with advanced solid tumors with relevant molecular alterations. *J Clin Oncol*. 2015;33(Suppl 15):2517-2517.
4. Patel MR, Bauer TM, Liu SV, et al. STARTRK-1: phase 1/2a study of entrectinib, an oral Pan-Trk, ROS1, and ALK inhibitor, in patients with advanced solid tumors with relevant molecular alterations. *J Clin Oncol*. 2015;33(Suppl 15):2596-2596.
5. Dylon A, Li G, Dogan S, et al. What hides behind the MASC: clinical response and acquired resistance to entrectinib after ETV6-NTRK3 identification in a mammary analogue secretory carcinoma (MASC). *Ann Oncol*. 2016;27(5):920-926.
6. Farago AF, Le LP, Zheng Z, et al. Durable clinical response to entrectinib in NTRK1-rearranged non-small cell lung cancer. *J Thorac Oncol*. 2015;10(12):1670-1674.
7. Clinical Study Report: WO40977. Comparative analysis of ROS1 positive locally advanced or metastatic non-small cell lung cancer between patients treated in entrectinib trials and crizotinib treated patients from real world data [internal sponsor's report]. pan-Canadian Oncology Drug Review sponsor submission: Rozlytrek (entrectinib) for ROS1-positive NSCLC, 100 mg and 200 mg capsules. Hoffmann-La Roche Limited. Mississauga (ON): Hoffmann-La Roche Limited; 2020 Jan 8.
8. Mok T. Overall survival (OS) for first-line crizotinib versus chemotherapy in ALK+ lung cancer: updated results from PROFILE 1014 [abstract]. *Ann Oncol*. 2017;28(Suppl 5):v605-v649.
9. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014;371(23):2167-2177.
10. Labbe C, Leung Y, Silva Lemes JG, et al. Real-world EQ5D health utility scores for patients with metastatic lung cancer by molecular alteration and response to therapy. *Clin Lung Cancer*. 2017;18(4):388-395 e384.
11. Rozlytrek (entrectinib): 100 mg and 200 mg, oral capsules [product monograph]. Mississauga (ON): Hoffmann-La Roche Limited; 2019 May 28.
12. pan-Canadian Oncology Drug Review sponsor submission: Rozlytrek (entrectinib) for ROS1-positive NSCLC, 100 mg and 200 mg capsules. Hoffmann-La Roche Limited. Mississauga (ON): Hoffmann-La Roche Limited; 2020 Jan 8.
13. Crizotinib (Xalkori) for ROS1-positive non-small cell lung cancer. (*pan-Canadian Oncology Drug Review final economic guidance report*) Ottawa (ON): CADTH; 2019: [https://cadth.ca/sites/default/files/pcodr/Reviews2019/10151CrizotinibNSCLC\\_fnEGR\\_EC\\_NOREDACT-ABBREV\\_Post\\_23May2019\\_final.pdf](https://cadth.ca/sites/default/files/pcodr/Reviews2019/10151CrizotinibNSCLC_fnEGR_EC_NOREDACT-ABBREV_Post_23May2019_final.pdf). Accessed 2020 Nov 23.
14. DeltaPA. Ottawa (ON): IQVIA; 2020: <https://www.iqvia.com/>. Accessed 2020 Nov 13.
15. De Oliveira C, Pataky R, Bremner KE, et al. Estimating the cost of cancer care in British Columbia and Ontario: a Canadian inter-provincial comparison. *Healthc Policy*. 2017;12(3):95-108.
16. Ontario Case Costing Initiative (OCCI). Toronto (ON): Ontario Health and Long-Term Care; 2018: <https://data.ontario.ca/dataset/ontario-case-costing-initiative-occi>. Accessed 2020 Dec.
17. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med*. 2014;371(21):1963-1971.
18. Shaw AT, Riely GJ, Bang YJ, et al. Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001. *Ann Oncol*. 2019;30(7):1121-1126.
19. Mescam-Mancini L, Lantuejoul S, Moro-Sibilot D, et al. On the relevance of a testing algorithm for the detection of ROS1-rearranged lung adenocarcinomas. *Lung Cancer*. 2014;83(2):168-173.
20. Rimkunas VM, Crosby KE, Li D, et al. Analysis of receptor tyrosine kinase ROS1-positive tumors in non-small cell lung cancer: identification of a FIG-ROS1 fusion. *Clin Cancer Res*. 2012;18(16):4449-4457.



21. Exceptional Access Program (EAP). Toronto (ON): Ontario Ministry of Health; Ontario Ministry of Long-Term Care; 2020: [http://www.health.gov.on.ca/en/pro/programs/drugs/odbf/odbf\\_except\\_access.aspx](http://www.health.gov.on.ca/en/pro/programs/drugs/odbf/odbf_except_access.aspx). Accessed 2020 Nov 13.
22. Sacco JJ, Botten J, Macbeth F, Bagust A, Clark P. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. *PLoS One*. 2010;5(1):e8933-e8933.
23. Launay-Vacher V, Oudard S, Janus N, et al. Prevalence of renal insufficiency in cancer patients and implications for anticancer drug management: the renal insufficiency and anticancer medications (IRMA) study. *Cancer*. 2007;110(6):1376-1384.
24. Liu D, Offin M, Harnicar S, Li BT, Drilon A. Entrectinib: an orally available, selective tyrosine kinase inhibitor for the treatment of NTRK, ROS1, and ALK fusion-positive solid tumors. *Ther Clin Risk Manag*. 2018;14:1247-1252.
25. Song Z, Su H, Zhang Y. Patients with ROS1 rearrangement-positive non-small-cell lung cancer benefit from pemetrexed-based chemotherapy. *Cancer Med*. 2016;5(10):2688-2693.
26. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian cancer statistics 2017. Toronto (ON): Canadian Cancer Society; 2017: <https://www.cancer.ca/-/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2017-EN.pdf>. Accessed 2020 Mar 25.
27. Pembrolizumab (Keytruda) for non-small cell lung cancer. (*pan-Canadian Oncology Drug Review final clinical guidance report*). Ottawa (ON): CADTH; 2017: [https://www.cadth.ca/sites/default/files/pcodr/pcodr\\_pembrolizumab\\_keytruda\\_nsclc\\_1stln\\_fn\\_cgr.pdf](https://www.cadth.ca/sites/default/files/pcodr/pcodr_pembrolizumab_keytruda_nsclc_1stln_fn_cgr.pdf). Accessed 2020 Mar 25.
28. Canadian Cancer Statistics Advisory Committee. Canadian cancer statistics 2018. Toronto (ON): Canadian Cancer Society; 2018: <https://www.cancer.ca/-/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2018-EN.pdf?la=en>. Accessed 2020 Mar 25.
29. Brule SY, Al-Baimani K, Jonker H, et al. Palliative systemic therapy for advanced non-small cell lung cancer: investigating disparities between patients who are treated versus those who are not. *Lung Cancer*. 2016;97:15-21.
30. Takeuchi K, Soda M, Togashi Y, et al. RET, ROS1 and ALK fusions in lung cancer. *Nat Med*. 2012;18(3):378-381.
31. Bergethon K, Shaw AT, Ou S-HI, et al. ROS1 rearrangements define a unique molecular class of lung cancers. *J Clin Oncol*. 2012;30(8):863-870.
32. Davies KD, Le AT, Theodoro MF, et al. Identifying and targeting ROS1 gene fusions in non-small cell lung cancer. *Clin Cancer Res*. 2012;18(17):4570-4579.
33. Stransky N, Cerami E, Schalm S, Kim JL, Lengauer C. The landscape of kinase fusions in cancer. *Nat Commun*. 2014;5:4846-4846.
34. Scheffler M, Schultheis A, Teixeira C, et al. ROS1 rearrangements in lung adenocarcinoma: prognostic impact, therapeutic options and genetic variability. *Oncotarget*. 2015;6(12):10577-10585.
35. Clavé S, Gimeno J, Muñoz-Mármol AM, et al. ROS1 copy number alterations are frequent in non-small cell lung cancer. *Oncotarget*. 2016;7(7):8019-8028.
36. Canadian Cancer Statistics Advisory Committee. Canadian cancer statistics 2019. Toronto (ON): Canadian Cancer Society; 2019: <https://www.cancer.ca/-/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2019-EN.pdf?la=en>. Accessed 2020 Dec 8.