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Guideline Endorsement 7-3 Version 4 REQUIRES UPDATING

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Ontario Health (Cancer Care Ontario)

Recommendations for the Treatment of Patients with Clinical Stage III Non-Small Cell Lung Cancer: Endorsement of the 2019 National Institute for Health and Care Excellence Guidance and the 2018 Society for Immunotherapy of Cancer Guidance

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This document describes the OH (CCO)-Lung Cancer Disease Site Group endorsement of the recommendations for the treatment of patients with clinical stage III N2 non-small cell lung cancer from © NICE [2019] Lung cancer: diagnosis and management. The original publication is available at www.nice.org.uk/guidance/ng122. The recommendations were also endorsed for patients with non-operable stage III non-small cell lung cancer from Brahmer JR, et al. The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC). J Immunother Cancer. 2018;6(1):75.

An assessment conducted in November 2022 indicated that Guideline Endorsement 7-3 Version 4 REQUIRES UPDATING. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

You can access the full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/43311

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For information about the PEBC and the most current version of all reports, please visit the OH (CCO) website at https://www.cancercareontario.ca/en/guidelines-advice or contact the PEBC office at: Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

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Section 1: Guideline Endorsement

ENDORSEMENT

Recommendations 1 and 4 were endorsed by the Lung Cancer Disease Site Group (DSG) of Ontario Health (Cancer Care Ontario) from the 2017 guideline on the treatment of patients with stage III (N2 or N3) non-small cell lung cancer (NSCLC) conducted by the Program in Evidence-Based Care (PEBC). Recommendation 2 was endorsed from the Society for Immunotherapy of Cancer (SITC) consensus statement on immunotherapy for the treatment of NSCLC [1].[1] Recommendation 3 was endorsed from the Lung cancer: diagnosis and management guideline, published by the National Institute for Health and Care Excellence (NICE) [2]. Recommendation 3 is reprinted with the permission of NICE.[2]

The endorsement of these guidelines does not imply whether chemotherapy/radiation/surgery OR chemotherapy/radiation/immunotherapy OR a combination of all four (quad-therapy) are preferred options in patients with N2 disease. It should be noted that the NICE recommendations for surgery after chemoradiation are for patients with potentially resectable stage III N2 NSCLC, while the SITC recommendations are for inoperable patients only. A formal literature search comparing these strategies was not performed and is beyond the scope of these endorsements.

RECOMMENDATIONS

Recommendation 1
Concurrent chemoradiation should be used for curative-intent treatment of patients with unresectable, lymph node-positive (N2 or N3) stage III NSCLC. • There is insufficient evidence to recommend a specific concurrent chemotherapy regimen. Reasonable treatment options include cisplatin combined with one of etoposide, vinorelbine, vinblastine, or pemetrexed and carboplatin combined with paclitaxel. Chemotherapy regimens should be similar to those given in randomized clinical trial protocols. • A standard dose fractionation of 60 to 66 Gy given in fractions of 2 Gy once per day over six weeks is recommended. Dose escalation beyond 66 Gy with conventional fractionation is not recommended.

- Hyperfractionated radiotherapy regimens that do not result in acceleration of the treatment course, even though the total nominal radiotherapy dose may be modestly increased, are not recommended.
- Routine use of induction chemotherapy prior to concurrent chemoradiotherapy is not recommended; however, this treatment paradigm can be considered for the management of bulky tumours to allow for radical planning after chemotherapy response.

Qualifying Statements for Recommendation 1

- Parameters to determine suitability for chemoradiation or other treatment options include but are not limited to performance status, weight loss, and comorbidities.
- Increased toxicity, particularly esophagitis and hematologic events, is associated with the addition of chemotherapy to radiotherapy.
- Although the impact of increasing the predicted biologic equivalent dose via accelerated radiotherapy regimens is unclear, further study of accelerated hypofractionated regimens is of interest to optimize the therapeutic ratio of treatment, particularly in the context of advanced imaging, radiotherapy planning, and treatment delivery.
- Depending on a patient's response to chemoradiation, surgery as salvage or completion of definitive treatment (preferably by lobectomy) may be an option in a subset of patients and should be discussed at a multidisciplinary case conference. Factors to consider include whether the cancer is potentially technically resectable, patient performance status, and patient preferences.

Recommendation 2

Durvalumab should be used in patients with stage III NSCLC who have not progressed post-chemoradiation and have no contraindications to an immune checkpoint inhibitor.

Qualifying Statements for Recommendation 2

- This was based on evidence from patients with stage III NCSLC using the 7th edition staging system. Durvalumab may be considered for patients who have stage migrated to stage III NSCLC using the 8th edition staging system.
- Patients should have received a volume of lung receiving 20 Gy dose (V20) of less than 35% of the total lung volume, and should have all toxicities resolved to grade 1 or less.
- Patients with any pneumonitis history or interstitial lung disease history, or evidence of radiation pneumonitis of grade 2 or above, or with V20s of greater than 35% should be considered at a higher risk of toxicity and generally counseled on the uncertainty and potentially excluded.
- At this time, it is inappropriate to exclude patients from therapy based solely on a biomarker such as epidermal growth factor receptor or programmed death-ligand 1 status.

- Durvalumab can be given at a dose of 10 mg per kilogram of body weight intravenously within one to 42 days after chemoradiotherapy and continued for a duration of 12 months.

Recommendation 3

For patients with operable, single-station, stage IIIA/B-N2 NSCLC who can have surgery and are well enough for multimodality therapy, consider chemoradiotherapy with surgery.

Qualifying Statements for Recommendation 3

- Discuss the benefits and risks with the person before starting chemoradiotherapy with surgery, including that:
  - chemoradiotherapy with surgery improves progression-free survival
  - chemoradiotherapy with surgery may improve overall survival.
- For patients with stage IIIA/B–N2 NSCLC who are having chemoradiotherapy and surgery, ensure that their surgery is scheduled for three to five weeks after the chemoradiotherapy.
- Multidisciplinary teams that provide chemoradiotherapy with surgery should have expertise in the combined therapy and in all of the individual components.

Recommendation 4

For patients with unresectable, stage III (N2 or N3) NSCLC who cannot tolerate concurrent chemoradiation, one of the following options is recommended after a full discussion of the benefits, limitations, and toxicities of therapy:

- Sequential chemotherapy followed by radical radiation
  - Increasing the biologic equivalent dose using accelerated hyperfractionated radiotherapy following induction chemotherapy may be considered.

- Radical radiotherapy alone
  - A minimum dose of 60 Gy is recommended.
  - Options for altered fractionation schedules may include hyperfractionation (lower dose per fraction over the standard treatment duration), accelerated fractionation (conventional fraction size and same total dose, given in a shorter period of time), accelerated hyperfractionation (combination of these two), and hypofractionation (higher dose per fraction and fewer fractions).
  - Options for specific altered fractionation schemes may include 40 to 45 Gy/15 daily fractions (hypofractionation), 69.6 Gy/58 fractions twice daily

(hyperfractionation), 54 Gy/36 fractions three times daily over 12 consecutive days (continuous, hyperfractionated, accelerated radiotherapy, accelerated hyperfractionation), and 60 Gy/40 fractions three times daily over 18 days (continuous hyperfractionated accelerated radiotherapy weekend-less, accelerated hyperfractionation).

- Radiation for symptom palliation
    - Higher dose/fractionation external beam radiotherapy regimens (e.g., 30 Gy/10 fraction equivalent or greater) are associated with modest improvements in survival and total symptom score and can be used primarily in patients with good performance status. As these improvements are also associated with an increase in side effects or adverse effects, such as radiation esophagitis, various shorter fractionation schedules (e.g., 20 Gy in five fractions, 17 Gy in two weekly fractions, 10 Gy in one fraction) have been demonstrated to provide good symptomatic control with fewer side effects, and can be used for patients requesting shorter treatment courses and/or with poor performance status.

Qualifying Statements for Recommendation 4

- Palliative chemotherapy or palliative care for patients with stage III disease is not reviewed in this guideline, but may be appropriate options for patients with stage III NSCLC who are not suitable for radical intent therapy.

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Section 2: Endorsement Methods Overview

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Ontario Health (Cancer Care Ontario). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of OH (CCO) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC is editorially independent from the OMH.

BACKGROUND FOR GUIDELINE

Stage III NSCLC occurs in a heterogeneous group of patients and treatment varies considerably largely because of patient-related issues that impact application of guideline recommended treatment. Survival varies considerably. New evidence suggests that immunotherapy may be important in improving survival in these patients. The goal of this guideline was to update the 2017 OH (CCO) guideline (7-3 version 3) recommendations to include new evidence on immunotherapy. In turn, this has implications for funding of new therapies. A second goal of this project was to update and consolidate information in two OH (CCO) guidelines (7-3 version 3 and 7-4 version 2) into one document on the management of stage III NSCLC. The 7-3 version 3 guideline focused on patients with unresectable stage III NSCLC, whereas the 7-4 version 2 guideline focused on patients with potentially resectable stage III NSCLC. This current 7-3 version 4 guideline combines these two guidelines into one guideline for patients with stage III NSCLC.

GUIDELINE ENDORSEMENT DEVELOPERS

This endorsement project was developed by the Treatment of Stage III NSCLC Guideline Development Group (GDG) (Appendix 1), which was convened at the request of the OH (CCO)'s Lung Cancer DSG and the Thoracic Cancers Advisory Committee. The project was led by a small Working Group of the Treatment of Stage III NSCLC GDG, which was responsible for reviewing the evidence base and recommendations in the National Institute for Health and Care Excellence (NICE) 2019 Lung cancer: diagnosis and management guideline [2] and the Society for Immunotherapy of Cancer (SITC) 2018 consensus statement on immunotherapy for the treatment of NSCLC [1] in detail and making an initial determination as to any necessary changes, drafting the first version of the endorsement document, and responding to comments received during the document review process. The Working Group members had expertise in radiation oncology, medical oncology, and health research methodology and included three patient representatives. Other members of the Treatment of Stage III NSCLC GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

PATIENT CONSULTATION PANEL

Three patient representatives participated as Consultation Panel members for the Treatment of Stage III NSCLC Working Group. They reviewed copies of the project plan and provided feedback on their comprehensibility, appropriateness, and feasibility to the Working Group's Health Research Methodologist. The Health Research Methodologist relayed the feedback to the Working Group for consideration.

ENDORSEMENT METHODS

The PEBC endorses guidelines using the process outlined in OH (CCO)'s Guideline Endorsement Protocol [3]. This process includes selection of a guideline, assessment of the recommendations, drafting the endorsement document by the Working Group members, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC assesses the quality of guidelines using the AGREE II tool [4]. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines.

Implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations may be provided along with the recommendations for information purposes.

Selection of Guidelines

As a first step in developing this document, a search for recent guidelines that addressed the research questions was conducted. Research questions for tri-modality therapy and consolidation immunotherapy were developed to update the 7-3 version 3 and the 7-4 version 2 guidelines. Guidelines older than two years (published before 2017) were excluded. Evidence-based guidelines with systematic reviews that addressed the following research questions were included:

1. Should neoadjuvant chemoradiation plus surgery vs. neoadjuvant chemotherapy plus surgery be used in patients with potentially resectable stage III N2 NSCLC?
2. Should neoadjuvant chemoradiation plus surgery vs. neoadjuvant chemoradiation and no surgery be used in patients with potentially resectable stage III N2 NSCLC?
3. Should patients with unresectable clinical stage III NSCLC who have not progressed following completion of concurrent chemoradiation be considered for consolidation immunotherapy vs. concurrent chemoradiation alone?

The following sources were searched for existing guidelines on April 11, 2019 with the search term lung cancer: National Institute for Health and Care Excellence Evidence Search, Canadian Partnership Against Cancer database, Canadian Medical Association Journal Infobase, ECRI Guidelines Trust, Scottish Intercollegiate Guidelines Network, American Society of Clinical Oncology, National Health and Medical Research Council – Australia Clinical Practice Guidelines Portal, and Cancer Council Australia – Cancer Guidelines Wiki. Also, on May 16, 2019, MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews were searched for existing guidelines using the search strategy found in Appendix 2. Two guidelines met the inclusion criteria [1,2]. The NICE 2019 guideline [2] addressed research questions 1 and 2 and the SITC 2018 guideline [1] addressed research question 3.

Assessment of Guidelines

Guidelines were considered for endorsement if the Working Group answered yes to the following questions:

1. Do you agree with the recommendations and think that no new evidence would change the recommendations?
2. Do you think the recommendations would be acceptable in Ontario?

Both guidelines met the criteria for endorsement [1,2]. The overall quality of both guidelines was assessed using the AGREE II tool [4] (Table 2-1). The pre-planned threshold for a high-quality guideline was a rigour of development score above 70% based on the AGREE II tool. Both guidelines met this criterion (Table 2-1).

Table 2-1. Results of AGREE II Tool quality rating of the evidence-based guidelines

Guidelines	AGREE II Domain Scores					
	Scope and Purpose (%)	Stakeholder Involvement (%)	Rigour of Development (%)	Clarity and Presentation (%)	Applicability (%)	Editorial Independence (%)
NICE 2019 [2]	100	86	91	100	88	75
SITC 2018 [1]	80	72	71	81	40	72

Abbreviations: NICE, National Institute for Health and Care Excellence; SITC, Society for Immunotherapy of Cancer

DESCRIPTION OF ENDORSED GUIDELINES

The NICE 2019 guideline covered a broad topic on the diagnosis and management of lung cancer and included recommendations on the treatment of patients with stage III NSCLC [2]. These recommendations were based on a systematic review that included a network meta-analysis of six randomized controlled trials (RCTs) comparing chemoradiotherapy and surgery versus chemoradiotherapy alone versus chemotherapy and surgery. Therefore, their network meta-analysis addressed research questions 1 and 2 mentioned above. NICE's 2019 guideline was reviewed by stakeholders and their Guideline Executive.

The SITC 2018 document also covered a broad topic on immunotherapy in NSCLC and included recommendations on the treatment of patients with stage III NSCLC [1]. This guidance document was based on a systematic review that addressed research question 3 mentioned above and included a large phase III RCT for durvalumab. The recommendations were reviewed by the SITC membership during an open comment period.

ENDORSEMENT PROCESS

The recently completed 7-3 version 3 PEBC guideline included recommendations for patients with unresectable, stage III (N2 or N3) NSCLC who can or cannot tolerate chemoradiation. The Working Group members decided to endorse these recent recommendations and the justifications for these recommendations is described further below. The Working Group developed new research questions for tri-modality therapy and consolidation immunotherapy to update the 7-3 version 3 and 7-4 version 2 PEBC guidelines. The NICE and SITC guidelines addressed these research questions. The Working Group held two meetings to review the recommendations from NICE and SITC to assess whether they agreed with the interpretation of the evidence with respect to the magnitude of the desirable and undesirable effects of treatment and took into account the certainty of the evidence, the values of key stakeholders (e.g., patients, clinicians, policy makers, etc.), and the potential impact on equity, acceptability and feasibility of implementation according to GRADE's evidence-to-

decision framework [5]. The evidence from NICE and SITC for each comparison was summarized within this GRADE framework to help the Working Group members consider the evidence used by the NICE and SITC groups and to then make a judgement as to whether they agreed with the way NICE and SITC interpreted and used the evidence. The evidence from NICE and SITC and the judgements of the Working Group can be found in Appendices 3 and 4.

Taking into consideration all of these factors within the GRADE framework, the Working Group members decided to endorse the NICE recommendations, but clarified that the recommendations applied to patients with single-station N2 disease and also applied to patients with stage IIIB NSCLC. The Working Group members also endorsed NICE's recommendation to schedule surgery three to five weeks after chemoradiotherapy because this was the schedule used in the studies.

The Working Group members endorsed SITC's recommendation for durvalumab in patients with stage III NSCLC who have not progressed post-chemoradiation. The Working Group decided to clarify that these patients should have no contraindications to an immune checkpoint inhibitor. Also, the Working Group members added four qualifying statements to further clarify the patient population. These clarifications were based on the inclusion and exclusion criteria of the durvalumab trial [6]. Furthermore, the Working Group decided to replace SITC's recommendation about the duration of durvalumab, "Limited data is available concerning durvalumab duration, and this recommendation will be reassessed as more results become available" with a qualifying statement that indicates the dose, schedule, and duration of durvalumab that was used in the trial.

The recommendation for concurrent chemoradiation for curative-intent treatment of patients with unresectable, lymph node-positive (N2 or N3) stage III NSCLC was endorsed from the 2017 7-3 version 3 PEBC guideline. In this prior version, the recommendation was adapted from the PEBC 2005, the American College of Chest Physicians 2013, the American Society of Radiation Oncology (ASTRO) 2015, and the American Society of Clinical Oncology (ASCO) 2015 guidelines [7-11]. Concurrent chemoradiation has been recommended in all of these guidelines. Carboplatin and paclitaxel have been added to the options of chemotherapy regimens since the PEBC 2005 guideline [9]. This is consistent with the ASTRO 2015 and ASCO 2015 guidelines [8,11]. Also, cisplatin and pemetrexed have been added to options of chemotherapy regimens since the PEBC 2005 guideline [9]. This is based on the PROCLAIM trial [12]. Standard dose-fractionation of 60 to 66 Gy was consistent across the guidelines. The dose per fraction has been altered to 2 Gy per fraction to be consistent with current standards recommended by the ASTRO 2015 and ASCO 2015 guidelines [8,11]. The recommendation against the routine use of induction chemotherapy was consistent across these guidelines.

The recommendations for patients with unresectable, stage III (N2 or N3) NSCLC who cannot tolerate concurrent chemoradiation were also endorsed from the 2017 7-3 version 3 PEBC guideline. In this third version, the recommendations for sequential chemotherapy followed by radical radiation or radical therapy alone were endorsed from the ASTRO 2015 guideline [11]. Also, the recommendation for radiation for symptom palliation was endorsed from the ASTRO 2011 guideline [13].

ENDORSEMENT REVIEW AND APPROVAL

Internal Review

For the endorsement document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP) with methodology expertise must unanimously approve the document. The Expert Panel and RAP may specify that

approval is conditional, and that changes to the document are required. Results of this review are reported in Section 3.

External Review

Feedback on the approved draft endorsement document is obtained from content experts through Professional Consultation. Relevant care providers and other potential users of the endorsement document are contacted and asked to provide feedback on the recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners. Results of this review are reported in Section 3.

DISSEMINATION

The endorsement document will be published on the OH (CCO) website. The Professional Consultation of the External Review is intended to facilitate the dissemination of the endorsement document to Ontario practitioners. OH (CCO)-PEBC guidelines are routinely included in several international guideline databases including the Canadian Partnership Against Cancer database, the Canadian Medical Association Infobase, NICE Evidence Search, and the Guidelines International Network Library.

UPDATING THE ENDORSEMENT

The Lung Cancer DSG will review the endorsement on an annual basis to ensure that it remains relevant and appropriate for use in Ontario.

ACKNOWLEDGEMENTS

The Treatment of Stage III NSCLC GDG would like to thank the following individuals for their assistance in developing this report:

- Fulvia Baldassarre and Nadia Coakley for completing the AGREE II assessments
- Xiaomei Yao for reviewing draft versions of this endorsement
- Sara Miller for copyediting

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Section 3: Internal and External Review

INTERNAL REVIEW

The endorsement was evaluated by the GDG Expert Panel and the PEBC RAP (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 24 members of the GDG Expert Panel, 22 members voted, for a total of 92% response in January 2020. Of those who voted, 22 approved the document (100%). The main comment from the Expert Panel and the Working Group's response is summarized in Table 3-1.

Table 3-1. Summary of the Working Group's response to a comment from the Expert Panel.

Comments	Responses
1. I suggest in Recommendation 2 that if we are going to include the current dose of durvalumab, we should also include the current schedule (since it may subsequently change, along with the dose).	The schedule for durvalumab was added to the qualifying statement for Recommendation 2.

RAP Review and Approval

Two RAP members reviewed this document in January and February 2020. The RAP approved the document on February 3, 2020.

EXTERNAL REVIEW

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the endorsement document. Ninety-two health care professionals in Ontario with an interest in lung cancer taken from the PEBC database were contacted by email to inform them of the survey. Eight (9%) responses were received. One oncologist stated that they were unavailable to review this endorsement document at the time. The results of the feedback survey from seven people are summarized in Table 3-2.

Table 3-2. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	0	0	3 (43)	4 (57)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)

2. I would make use of this guideline in my professional decisions.	0	0	0	1 (14)	6 (86)
3. I would recommend this guideline for use in practice.	0	0	0	1 (14)	6 (86)
4. What are the barriers or enablers to the implementation of this guideline report?	Another year of durvalumab after chemoradiation may be difficult for patients unless they are initially primed to the idea of continued treatments.				

CONCLUSION

The final endorsed recommendations contained in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel.

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Appendix 1: Affiliations and Conflict of Interest Declarations

In accordance with the PEBC Conflict of Interest Policy, the Members of the Treatment of Stage III NSCLC GDG Working Group, Expert Panel, Report Approval Panel, and Patient Consultation Panel were asked to disclose potential conflicts of interest.

Name and Affiliation	Declarations of interest
Working Group	
Peter Ellis Medical Oncologist Lung Cancer Disease Site Group	Received $500 or more in a single year to act in a consulting capacity for Takeda and as an advisory board member for AstraZeneca
John Goffin Medical Oncologist Lung Cancer Disease Site Group	• Received honoraria from Amgen (2014), Boehringer Ingelheim (2015), Bristol-Myers Squibb (2015), and Merck (2018) • Received conference travel support from AstraZeneca (2017) • Received a speaking fee from Amgen (2018)
Wael Hanna Surgeon St. Joseph's Hospital, Hamilton ON	• Received $500 or more in a single year to act in a consulting capacity as a member of a Data Safety Monitoring Committee for Roche/Genentech and as a speaker for Minogue Medical • Published an opinion on this topic: Hanna WC. N2 is not N2 is not N2. J Thorac Cardiovasc Surg. 2015 Dec;150(6): 1494-5. Hanna WC. Four Percent Matters. J Thorac Dis. 2017 Aug;9(8):2286-2287
Donna Maziak Surgeon Lung Cancer Disease Site Group	None declared
Andrew Robinson (Lead) Medical Oncologist Lung Cancer Disease Site Group	Received grants from multiple clinical trials with Merck, Astra Zeneca (MYSTIC), Roche, and Pfizer
Anand Swaminath Radiation Oncologist Lung Cancer Disease Site Group	• Received $500 or more in a single year to act in a consulting capacity for Astra Zeneca • Received an educational grant of $500 or more in a single year from Accuray
Yee Ung Radiation Oncologist Lung Cancer Disease Site Group	None declared
Emily Vella Health Research Methodologist Program in Evidence-Based Care	None declared
Lung Cancer Disease Site Group Expert Panel	
Abdollah Behzadi Surgeon Lung Cancer Disease Site Group	None declared
Penelope Bradbury Medical Oncologist Lung Cancer Disease Site Group	• Received $500 or more in a single year to act in a consulting capacity for honoraria from AbbVie, Lilly, and Merck and as an advisory board member from AbbVie, and BI • Been a local principal investigator for the PACIFIC clinical trial
Adrien Chan Medical Oncologist Lung Cancer Disease Site Group	None declared

Susanna Cheng Medical Oncologist Lung Cancer Disease Site Group	• Received $500 or more in a single year to act in a consulting capacity as an advisory board member for MERCK, Astra Zeneca, and Roche • Been a site principal investigator for the PACIFIC clinical trial
Medhat El-Mallah Radiation Oncologist Lung Cancer Disease Site Group	Received $500 or more in a single year to act in a consulting capacity for an honorarium for attending an Astra Zeneca multidisciplinary regional advisory board meeting in 2018
Conrad Falkson Radiation Oncologist Lung Cancer Disease Site Group	None declared
Ronald Feld Medical Oncologist Lung Cancer Disease Site Group	None declared
Richard Gregg Medical Oncologist Lung Cancer Disease Site Group	Was the local principal investigator for BR.31
Donald Jones Surgeon Lung Cancer Disease Site Group	None declared
Jaro Kotalik Bioethicist Lung Cancer Disease Site Group	None declared
Swati Kulkarni Medical Oncologist Lung Cancer Disease Site Group	None declared
Sara Kuruvilla Medical Oncologist Lung Cancer Disease Site Group	None declared
Scott Laurie Medical Oncologist Lung Cancer Disease Site Group	• Received $500 or more in a single year to act in a consulting capacity for Astra Zeneca • Received grants or other research support from Astra Zeneca
Natasha Leighl Medical Oncologist Lung Cancer Disease Site Group	Received $500 or more in a single year to act in a consulting capacity for Excovery
Robert MacRae Radiation Oncologist Lung Cancer Disease Site Group	Received $500 or more in a single year to act in a consulting capacity as an advisory board member for Astra Zeneca
Richard Malthaner Surgeon Lung Cancer Disease Site Group	None declared
Andrew Pearce Radiation Oncologist Lung Cancer Disease Site Group	None declared
Kevin Ramchandar Radiation Oncologist Lung Cancer Disease Site Group	None declared

Alexander Sun Radiation Oncologist Lung Cancer Disease Site Group	Received $500 or more in a single year to act in a consulting capacity for Astra Zeneca, and Merck
Mojgan Taremi Radiation Oncologist Lung Cancer Disease Site Group	None declared
Mark Vincent Medical Oncologist Lung Cancer Disease Site Group	• Received $500 or more in a single year to act in a consulting capacity on advisory boards • Received financial support of $500 or more in a single year as a principal investigator for Astra Zeneca • Had managerial responsibility for an organization or department that has received $5,000 or more in a single year from the Lawson Institute of the London Health Sciences Centre for a clinical trial
Kazuhiro Yasufuku Surgeon Lung Cancer Disease Site Group	None declared
Edward Yu Radiation Oncologist Lung Cancer Disease Site Group	None declared
Robert Zeldin Surgeon Lung Cancer Disease Site Group	None declared
Report Approval Panel	
Sheila McNair Managing Director, Program in Evidence-Based Care, Ontario Health McMaster University, Hamilton	None declared
Jonathan Sussman Scientific Director, Program in Evidence-Based Care Chair, Department of Oncology Juravinski Cancer Centre, Hamilton	None declared
Patient Consultation Panel	
Lise Craig	None declared
Patricia Sevean	None declared
Laurel Warr	None declared

Appendix 2: Literature Search Strategy

Database(s): Embase 1996 to 2019 May 16, OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, EBM Reviews - Cochrane Central Register of Controlled Trials April 2019, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to May 16, 2019
Search Strategy:

#	Searches
1	exp lung neoplasms/ or exp lung cancer/
2	(((lung or thorax or thoracic or pulmonary) adj3 (cancer$ or neoplasm$ or carcinom$ or malignan$ or tumo?r$ or adenocarcinoma$)) or NSCLC).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy, sh, tx, ct]
3	1 or 2
4	exp cisplatin/ or exp carboplatin/ or exp platinum/
5	(chemotherap$ or chemoradio$ or radiochemo$ or platin$ or cisplatin$ or platamin$ or neoplatin$ or cismaplat$ or CDDP or CBDCA or carboplatin$ or paraplatin$).mp.
6	4 or 5
7	3 and 6
8	exp evidence based practice/ or exp practice guideline/ or exp consensus development conference/ or guideline.pt. or practice parameter$.tw. or practice guideline$.mp. or (guideline: or recommend: or consensus or standards).ti. or (guideline: or recommend: or consensus or standards).kw.
9	exp meta analysis/ or exp "meta analysis (topic)"/ or exp meta-analysis as topic/ or exp "systematic review"/ or exp "systematic review (topic)"/ or ((exp "review"/ or exp "review literature as topic"/ or review.pt.) and ((systematic or selection criteria or data extraction or quality assessment or jaded scale or methodologic$ quality or study) adj selection).tw.) or meta-analysis.mp. or (meta-analy: or metaanaly: or meta analy:).tw. or (systematic review or systematic overview).mp. or ((cochrane or medline or embase or cancerlit or hand search$ or hand-search$ or manual search$ or reference list$ or bibliograph$ or relevant journal$ or pooled analys$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview$ or systematic) adj2 (review$ or overview$)).tw. or (medline or med-line or pubmed or pub-med or embase or cochrane or cancerlit).ab.
10	exp phase 3 clinical trial/ or exp "phase 3 clinical trial (topic)"/ or exp clinical trial, phase iii/ or exp clinical trials, phase iii as topic/ or exp phase 4 clinical trial/ or exp "phase 4 clinical trial (topic)"/ or exp clinical trial, phase iv/ or exp clinical trials, phase iv as topic/ or exp randomized controlled trial/ or exp "randomized controlled trial (topic)"/ or exp controlled clinical trial/ or exp randomized controlled trials as topic/ or exp randomization/ or exp random allocation/ or exp double-blind method/ or exp single-blind method/ or exp double blind procedure/ or exp single blind procedure/ or exp triple blind procedure/ or exp placebos/ or exp placebo/ or ((exp phase 2 clinical trial/ or exp "phase 2 clinical trial (topic)"/ or exp clinical trial, phase ii/ or exp clinical trials, phase ii as topic/ or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/) and random$.tw.) or (((phase

	II or phase 2 or clinic$) adj3 trial$) and random$).tw. or ((singl$ or double$ or treple$ or tripl$) adj3 (blind$ or mask$ or dummy)).tw. or placebo?.tw. or (allocat: adj2 random:).tw. or (random$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw. or (random$ adj3 trial$).mp. or "clinicaltrials.gov".mp.
11	7 not ((comment or letter or note or editorial or case reports or historical article).pt. or exp case report/ or exp case study/)
12	8 and 11
13	limit 12 to yr=2012-current
14	remove duplicates from 13
15	9 and 11
16	limit 15 to yr=2012-current
17	remove duplicates from 16
18	10 and 11
19	limit 18 to yr=2012-current
20	from 19 keep 1-6000
21	remove duplicates from 20
22	from 19 keep 6001-12000
23	remove duplicates from 22
24	from 19 keep 12001-15461
25	remove duplicates from 24
26	14 or 17 or 21 or 23 or 25
27	animal/ not (exp human/ or humans/)
28	26 not 27
29	limit 28 to english language [Limit not valid in CDSR; records were retained]

Appendix 3: Questions for recommendation endorsement for neoadjuvant chemoradiation plus surgery vs. neoadjuvant chemotherapy plus surgery vs. chemoradiation alone in patients with potentially resectable stage III N2 NSCLC

Criteria	Questions	JUDGEMENTS ← NOT RECOMMEND				RECOMMEND →		NICE Evidence/Considerations Neoadj chemorad + surgery vs. neoadj chemo + surgery vs. chemoradiation alone in patients with resectable NSCLC	PEBC Working Group discussion
Desirable effects	1a. How substantial are the desirable anticipated effects?	☐ Trivial	☐ Small	☐ Don't know	☐ Varies	☑ Moderate	☐ Large	The fixed effects network meta-analyses found that patients receiving chemoradiotherapy and surgery spent significantly longer progression free than those receiving chemotherapy and surgery or chemoradiotherapy alone, that patients receiving chemoradiotherapy alone spent significantly longer in the post-progression state than those receiving the surgical options and that there was a strong but statistically insignificant trend favouring chemoradiotherapy and surgery over the other two interventions for overall survival time and probability of survival at study endpoint. While model fit statistics did not suggest that it fit the data any better, the random effects network meta-analyses used in sensitivity analysis found no statistically significant difference for any outcome between any of the interventions. The committee noted that only one of the RCTs found a statistically significant difference in PFS but that it was also the case that the direction of effect for this outcome in each of the studies was positive for chemoradiotherapy and surgery. The committee was aware that PFS is a less reliable outcome than overall survival and discussed the potential for radiotherapy scarring to affect reliability. They did not think that there would be systematic overdiagnosis of disease progression in the non-surgical arms of the RCTs and thereby overestimation of the PFS benefit associated with surgery. Indeed, they noted that it is possible that subtle changes in disease status are missed in patients undergoing chemoradiotherapy because of radiotherapy scarring. They therefore felt that if bias towards incorrect recording of progression exists, it could work in either direction.	The Working Group believed there would be moderate desirable effects, especially for PFS, for patients receiving chemoradiotherapy and surgery.

Criteria	Questions	JUDGEMENTS ← NOT RECOMMEND				RECOMMEND →		NICE Evidence/Considerations Neoadj chemorad + surgery vs. neoadj chemo + surgery vs. chemoradiation alone in patients with resectable NSCLC	PEBC Working Group discussion
Undesirable effects	1b. How substantial are the undesirable anticipated effects?	☐ Large	☐ Moderate	☐ Don't know	☑ Varies	☐ Small	☐ Trivial	The adverse event profile of the different interventions is uncertain but pairwise and network meta-analyses estimates conducted for the health economic model favoured chemoradiotherapy and surgery. The committee discussed the evidence from a network meta-analysis conducted for the economic model which showed the odds ratio of death before progression was higher in the surgical interventions. They felt that this outcome was unsurprising in interventions that are more invasive in nature and noted that the other network meta-analyses had already accounted for this. Additionally, death before progression occurred in relatively few patients in any arm of any included study. They felt that discussing the risks and benefits of any surgery with patients is common practice.	The undesirable effects vary in the context of the type of surgery being performed. For example, right-sided pneumonectomy may be associated with increased mortality compared with left-sided pneumonectomy or lobectomy.
Certainty of evidence	1c. What is the overall certainty of this evidence?	☐ Very low	☑ Low	☐ No included studies		☑ Moderate	☐ High	The committee agreed that the six trials most relevant to current practice were Pless 2015 [14], Katakami 2012 [15], Albain 2009 [16], Eberhardt 2015 [17], Girard 2010 [18] and van Meerbeeck 2007 [19]. For the first four of these trials, outcomes were largely graded as moderate-quality evidence. For the final two, outcomes were largely graded as low-quality evidence.	The Working Group believed the certainty of the evidence was low to moderate. They were moderately confident that PFS was improved significantly, but had low confidence that overall survival would be improved.
Values	1d. Is there important uncertainty about or variability in how much the target population value the outcomes?	☐ Important uncertainty or variability		☐ Possibly important uncertainty or variability		☑ Probably no important uncertainty or variability	☐ No important uncertainty or variability	The committee agreed that the outcome that matters the most is mortality. This is because the purpose of chemotherapy, radiotherapy and surgery is to reduce mortality as much as possible. Secondary outcomes were PFS, severe adverse events and quality of life.	Three OH (CCO) patient representatives believed survival and quality of life were the most important outcomes. The Working Group believed there would be some variability in how much patients valued the outcomes, but believed that most patients would value survival and more specifically overall survival.

Criteria	Questions	JUDGEMENTS ← NOT RECOMMEND					RECOMMEND →		NICE Evidence/Considerations Neoadj chemorad + surgery vs. neoadj chemo + surgery vs. chemoradiation alone in patients with resectable NSCLC	PEBC Working Group discussion
Balance of effects	2. What is the balance between the benefits and the harms?	☐ Benefits < Harms	☐ Benefits ≤ Harms	☐ Don't know	☐ Benefits = Harms	☐ Varies	☑ Benefits ≥ Harms	☐ Benefits > Harms	Based on the network meta-analyses, the committee agreed that it is likely that (particularly) PFS and overall survival are better for chemoradiotherapy and surgery than the other two options if patients are well enough for it. The network meta-analysis found that chemoradiotherapy and surgery was associated with a 4 month (0.32 year) improvement in PFS versus chemoradiotherapy. The adverse event profile of the different interventions is uncertain but pairwise and network meta-analyses estimates conducted for the health economic model favoured chemoradiotherapy and surgery. The committee was unsure about the clinical plausibility of this, given that chemoradiotherapy and surgery is the most intensive intervention but agreed that there was no evidence that it was more harmful than the other two interventions. The committee agreed it was likely that there would be some quality of life loss in the months following the interventions as patients recovered. This was expected to be particularly true of the interventions including surgery. They decided that a 'consider' recommendation in favour of chemoradiotherapy and surgery was justified by the evidence. This is because there were a number of key uncertainties in the clinical data. Specifically, that none of the RCTs included in the network meta-analysis found any difference in overall survival, which was the most important outcome. Also, the 3- to 5-week wait for surgery is recommended to give people time to recover from the chemoradiotherapy.	The Working Group believed that the benefits would outweigh the harms, but that the values of the patients would need to be taken into consideration. A discussion about the effects of chemoradiotherapy and surgery on PFS and overall survival with the patient would need to occur.

Criteria	Questions	JUDGEMENTS ← NOT RECOMMEND					RECOMMEND →		NICE Evidence/Considerations Neoadj chemorad + surgery vs. neoadj chemo + surgery vs. chemoradiation alone in patients with resectable NSCLC	PEBC Working Group discussion
Equity	3. What would be the impact on health equity?	☐ Reduced	☑ Probably reduced	☐ Don't know	☐ Probably no impact	☐ Varies	☐ Probably increased	☐ Increased	Not reported	The Working Group believed that recommending surgery may reduce equity because some patients may need to travel longer distances to receive surgery and some patients may have difficulty taking time off from work or may not have the social supports needed for the surgery and recovery.
Acceptability	4. Is the option acceptable to key stakeholders (e.g., patients and providers)?	☐ No	☐ Probably no	☐ Don't know	☐ Varies	☑ Probably yes	☐ Yes		Not reported	The Working Group believed that most patients would find chemoradiotherapy and surgery acceptable; if they believed the benefits outweighed the harms.
Feasibility	5. Is the option feasible to implement?	☐ No	☐ Probably no	☐ Don't know	☐ Varies	☑ Probably yes	☐ Yes		The committee thought that chemoradiotherapy and surgery is likely to be the most cost-effective intervention and that chemoradiotherapy was unlikely to be cost-effective compared to the other two interventions. The committee thought that only a small number of stage IIIA-N2 patients are currently treated with chemoradiotherapy and surgery and that these recommendations therefore represent an increase in resource use, which will depend on the extent of take-up. Chemoradiotherapy with surgery is not often offered in current practice. In addition, there are specific factors to take into account when offering all these treatments together. Therefore, multidisciplinary teams providing it should have expertise both in the combined therapy, and in all the individual components.	The Working Group believed chemoradiation and surgery are probably feasible to implement in Ontario because we have Centres of Excellence in thoracic surgery and regionalized care, which is largely integrated with radiation.

Criteria	Questions	JUDGEMENTS ← NOT RECOMMEND				RECOMMEND →	NICE Evidence/Considerations Neoadj chemorad + surgery vs. neoadj chemo + surgery vs. chemoradiation alone in patients with resectable NSCLC	PEBC Working Group discussion
Generalizable	6. Is this evidence generalizable to the entire target population?	☐ No	☑ Probably no	☐ Don't know	☐ Probably yes	☐ Yes	The committee noted that patient fitness and patient choice were important factors in deciding between interventions and tried to reflect this in their recommendations.	The Working Group believed that chemoradiation and surgery would only be appropriate for people with operable stage IIIA-N2 NSCLC who can have surgery and are well enough for multimodality therapy.

Abbreviations: NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; PEBC, Program in Evidence-Based Care; PFS, progression-free survival; RCT, randomized controlled trial

Appendix 4: Questions for recommendation endorsement for consolidation immunotherapy vs. concurrent chemoradiation alone in patients with unresectable clinical stage III NSCLC who have not progressed following completion of concurrent chemoradiation

Criteria	Questions	JUDGEMENTS ← NOT RECOMMEND					RECOMMEND →	SITC Evidence/Considerations Chemorad + immunotherapy vs. chemorad alone in patients with unresectable NSCLC	PEBC Working Group discussion
Desirable effects	1a. How substantial are the desirable anticipated effects?	☐ Trivial	☐ Small	☐ Don't know	☐ Varies	☐ Moderate	☑ Large	In this randomized, phase III study, 713 patients received durvalumab (n = 476) or placebo (n = 237) as consolidation therapy following chemoradiation [6]. Median PFS was significantly longer in patients who received durvalumab compared with placebo (16.8 vs. 5.6 months; HR 0.52; 95% CI: 0.42–0.65; p < 0.001), with an ongoing PFS rate advantage at 18-months (44.2% vs. 27.0%; p < 0.0001). Results were consistent across pre-specified demographic and clinical subgroups, including never-smokers, irrespective of baseline PD-L1 tumor expression. In addition, durvalumab illustrated superior outcomes for secondary endpoints including overall response rate (26% vs. 14%; p < 0.001) and median duration of response (72.8% vs. 46.8% at 18 months). Overall survival results from this study remain immature. On February 16th, 2018, durvalumab gained approval at a dose of 10 mg/kg IV every 2 weeks, for a maximum of 1 year, for patients with locally advanced, unresectable NSCLC whose disease has not progressed following chemoradiotherapy.	An updated abstract has found that overall survival was significantly longer in patients who received durvalumab compared with placebo, (stratified hazard ratio for death, 0.68; 99.73% CI, 0.47 to 0.997; P=0.0025) [20]. Based on the results of this study, the Working Group believed the survival benefit would be large for patients with unresectable clinical stage III NSCLC who have not progressed following completion of concurrent chemoradiation.
Undesirable effects	1b. How substantial are the undesirable anticipated effects?	☐ Large	☐ Moderate	☐ Don't know	☐ Varies	☑ Small	☐ Trivial	The incidence of grade 3/4 adverse events was similar with durvalumab (29.9%) and placebo (26.1%), although a higher proportion of patients taking durvalumab discontinued treatment as a result (15.4% vs. 9.8%).	The Working Group believed the adverse effects would be small with durvalumab compared with placebo because the incidence of grade 3/4 adverse events was similar between the groups.
Certainty of evidence	1c. What is the overall certainty of this evidence?	☐ Very low	☐ Low	☐ No included studies		☑ Moderate	☐ High	Not reported	The Working Group was moderately certain in the estimate of effects for durvalumb. Even though it was one study, it was quite large.

Criteria	Questions	JUDGEMENTS ← NOT RECOMMEND RECOMMEND →	SITC Evidence/Considerations Chemorad + immunotherapy vs. chemorad alone in patients with unresectable NSCLC	PEBC Working Group discussion
Values	1d. Is there important uncertainty about or variability in how much the target population value the outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ☑ No important uncertainty or variability	Not reported	Three OH (CCO) patient representatives believed survival and quality of life were the most important outcomes. The Working Group also believed that most patients would value overall survival and would consider quality of life important.
Balance of effects	2. What is the balance between the benefits and the harms?	☐ Benefits < Harms ☐ Benefits ≤ Harms ☐ Don't know ☐ Benefits = Harms ☐ Varies ☐ Benefits ≥ Harms ☑ Benefits > Harms	A majority of the task force agreed that durvalumab should be used in stage III patients who have not progressed post-chemoradiation, based on Level A evidence. Limited data is available concerning durvalumab duration, and this recommendation will be reassessed as more results become available.	The Working Group believed that the large increase in overall survival benefits would outweigh any grade 3/4 adverse events associated with durvalumab.
Equity	3. What would be the impact on health equity?	☐ Reduced ☐ Probably reduced ☐ Don't know ☑ Probably no impact ☐ Varies ☐ Probably increased ☐ Increased	Not reported	Since these patients would have received chemoradiotherapy, the Working Group believed there would probably be no impact on equity with the addition of durvalumab.
Acceptability	4. Is the option acceptable to key stakeholders (e.g., patients and providers)?	☐ No ☐ Probably no ☐ Don't know ☐ Varies ☐ Probably yes ☑ Yes	Not reported	The Working Group believed that most patients would find treatment with durvalumab acceptable.
Feasibility	5. Is the option feasible to implement?	☐ No ☐ Probably no ☐ Don't know ☐ Varies ☐ Probably yes ☑ Yes	Not reported	The Working Group believed that consolidation treatment with durvalumab would be feasible to implement in Ontario.

Criteria	Questions	JUDGEMENTS ← NOT RECOMMEND			RECOMMEND →		SITC Evidence/Considerations Chemorad + immunotherapy vs. chemorad alone in patients with unresectable NSCLC	PEBC Working Group discussion
Generalizable	6. Is this evidence generalizable to the entire target population?	☐ No	☐ Probably no	☐ Don't know	☑ Probably yes	☐ Yes	Not reported	The Working Group believed that the evidence applies to most patients with unresectable clinical stage III NSCLC who have not progressed following completion of concurrent chemoradiation. However, clinicians should be aware that there will be some patients who have stage migrated to stage III in the 8th edition staging system that would not have been eligible for the trial, and the extrapolation of results to this group seems warranted. Patients should have received a V20 of less than 35% of the total lung volume, and should have all toxicities resolved to grade 1 or less. Patients with any pneumonitis history or interstitial lung disease history, or evidence of radiation pneumonitis of grade 2 or above, or with V20's of greater than 35% should be considered at a higher risk of toxicity and generally counselled on the uncertainty and potentially excluded.

Abbreviations: IV, intravenous; NSCLC, non-small cell lung cancer; PCI, prophylactic cranial irradiation; PD-L1, programmed death-ligand 1; PEBC, Program in Evidence-Based Care; SITC, Society for Immunotherapy of Cancer