CADTH

CADTH REIMBURSEMENT REVIEW

Clinician Input

DURVALUMAB (Imfinzi)

(AstraZeneca Canada Inc.)

Indication: First-line treatment of adult patients with ES-SCLC in combination with etoposide and either carboplatin or cisplatin.

December 24, 2020

CADTH

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**PC0234-000**
Generic Drug Name (Brand Name)	**Durvalumab** **(Imfinzi)**
Indication	**IMFINZI in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).**
Name of the Clinician Group	**Lung Cancer Canada**
Author of the Submission	[redacted]
Contact information	[redacted]

1. About Your Clinician Group

Lung Cancer Canada is a national charitable organization that serves as Canada's leading resource for lung cancer education, patient support, research and advocacy. Based in Toronto, Ontario, Lung Cancer Canada has a wide reach that includes both regional and pan-Canadian initiatives. Lung Cancer Canada is a member of the Global Lung Cancer Coalition and is the only organization in Canada focused exclusively on lung cancer.

Website Link: www.lungcancercanada.ca

2. Information Gathering

Information gathered for this submission was based on relevant published clinical data and expert evidence-based review amongst lung cancer medical oncologists across Canada.

Key References:

1. Goldman et al; Durvalumab, with or without tremelimumab, plus platinum–etoposide versus platinum–etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol* 2020 Dec; S1470-2045(20)30539-8

2. Paz-Ares et al; Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet* 2019 Nov; 394(10212):1929-1939.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

RESPONSE:

Small cell lung cancer (SCLC) accounts for approximately 15% of all lung cancers. It is seen mainly in the elderly population and the median age at diagnosis is approximately 70 years. Patients present at late stage, and less than 5% of SCLC is diagnosed at a stage that would be amenable to surgical resection. In two thirds of patients the cancer has spread outside the lung and regional lymph nodes (Extensive Stage).

Treatment for extensive stage SCLC is standard around the globe, and *has not changed in 30 years*. First-line treatment consists of four to six cycles of systemic chemotherapy with intravenous etoposide and a platinum compound, either cisplatin or carboplatin. Other agents that have been compared to etoposide/platinum in recent years include amrubicin and topotecan, but neither of these agents was associated with superior PFS or OS in Western patient populations, and neither is used in Canada. With etoposide/platinum, approximately 50-70% of patients respond to treatment, most achieving partial response, with less than 10% achieving complete remission. Relapse occurs early, and reported median survival usually is less than one year in virtually all studies, even in the highly selected populations eligible for the trials. Historically, 2-year survival for extensive SCLC is <5%, and 5-year survival is <2%.

Patients with extensive SCLC have a high tumour burden and are highly symptomatic at presentation. In responding patients, chemotherapy is very effective in reducing symptoms and improving Quality of Life (QOL). Furthermore, these improvements occur promptly, usually after only one chemotherapy cycle. Importantly, chemotherapy is *not* associated with negative effects on QOL.

After chemotherapy, thoracic irradiation and prophylactic cranial irradiation (PCI) may be considered, but is not always administered. Studies of both thoracic irradiation and PCI have demonstrated modest survival benefits after chemotherapy in responding patients with SCLC, although the potential toxicity of both treatments, *particularly PCI*, make patients and physicians alike reluctant to administer radiation on a routine basis.

Small cell lung cancer is characterized, almost universally, by inactivation of the tumour suppressor genes TP53 and RB1. However, attempts to target these genes have been unsuccessful. Similarly, investigational agents targeting other molecular pathways including WEE-1, NOTCH and Aurora Kinase and PARP inhibitors to date, have not improved outcomes, nor have recent studies of antibody-drug conjugates. In brief, there are no molecularly targeted agents approved for SCLC in Canada or elsewhere around the globe.

SCLC occurs mainly in patients with a smoking history. As such, this cancer carries a high rate of somatic mutations in addition to TP53 and RB1 discussed above. Thus, SCLC potentially should benefit from immunotherapy, and in particular agents targeting PD-1 and PDL-1. To date, no immunotherapy agent has been approved for SCLC in Canada.

In summary, chemotherapy is standard of care across Canada for extensive SCLC. There are no molecularly targeted agents or immunotherapeutic agents approved, nor are there special access programmes open for this aggressive and highly lethal form of lung cancer.

New treatments are needed urgently.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

RESPONSE:

Prolongation of *Overall Survival* is always the *primary* goal of treatment for Extensive SCLC. Untreated patients have a median survival of only 6 weeks.

Secondary objectives include response rate, improvement in symptoms, and QOL.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

RESPONSE:

Only two-thirds of patients achieve response with current first-line treatments, and new and better treatments are required for the remaining one third.

Patients who are primarily refractory to current treatment options are highly unlikely to respond to second-line treatment options.

Even in responding patients, recurrence occurs early, and second-line treatments are associated with low response rates and median survivals of 6 months or less.

Thus the focus of treatment must be on finding newer and better *first-line treatments* that provide superior overall survival.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

RESPONSE:

With no progress in over 30 years and median survival less than a year, all patients with extensive small cell lung cancer should be considered “an unmet need”.

Durvalumab in combination with etoposide and carboplatin or cisplatin addresses this unmet need by significantly improving overall survival (HR 0.75) with sustained separation of OS curves with 22.2 vs 14.4% of patients alive at 24 months (median follow-up of 25.1 months). This is particularly noteworthy given the historical difficulty of showing long-term survival benefit for this aggressive disease. Meaningful benefit was also observed across all pre-specified subgroups and key secondary efficacy outcomes of the CASPIAN trial.

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

RESPONSE:

Is there a mechanism of action that would complement other available treatments, and would it be

added to other treatments?

Targeting the immune system is a new treatment paradigm for cancer in general and lung cancer in particular. The addition of immunotherapy to chemotherapy has been shown to result in statistically significant and clinically meaningful benefits in terms of response rates, PFS and OS in many stages of Non-SCLC. Durvalumab has been shown to increase the cure rate in patients with stage III Non-SCLC when administered after chemotherapy and thoracic radiation. Now the CASPIAN trial has shown that durvalumab added to chemotherapy for patients with extensive SCLC improves overall survival in a statistically significant *and clinically meaningful* way.

Importantly, chemotherapy and durvalumab have *non-overlapping* toxicity profiles and so both components can be administered in full dose without unacceptable toxicity.

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

To date, there is no immunotherapy agent approved for SCLC in Canada.

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

It is critical to deliver the best possible therapy *as first-line treatment* in extensive SCLC. Patients who fail to respond or who relapse following first line treatment are critically ill, and frequently suffer a marked decline in performance status. Because of this, at least half of all SCLC patients are not fit enough or eligible for second-line therapy. Life-prolonging treatment should never be delayed until other treatments fail.

Is the drug under review expected to cause a shift in the current treatment paradigm?

First-line treatment for extensive SCLC would move from doublet chemotherapy with etoposide/platinum to triplet therapy with etoposide/platinum/durvalumab

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

RESPONSE:

It would ***not*** be appropriate to recommend that patients try other treatments before initiating treatment with durvalumab in combination with chemotherapy. Only half or even fewer patients are fit enough for second-line treatments if they fail to respond or recur after first-line therapy. The very best treatment *must* be given up-front when patients are fit enough to tolerate treatment, have the greatest chance to benefit, and are most likely to derive durable benefit. There are no studies that show that immunotherapy, including durvalumab is effective either as a single agent or in combination with other treatments in the second-line setting in SCLC. In fact, most second-line treatments are ineffective.

6.3. How would this drug affect the sequencing of therapies for the target condition?

RESPONSE:

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Treatment after failure of first-line therapy for extensive SCLC must be individualized. Only patients of

good performance status would be offered second-line chemotherapy, and selection of drugs would depend on the extent of the drug-free interval. Radiation might be given to localized symptomatic lesions for palliation of symptoms, but with no expectation of prolongation of survival. Many patients receive no second-line treatment and receive only palliative care. It is for this reason that *first-line therapy must be optimized.*

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

There are no data at this time to support durvalumab use in the second-line setting for extensive SCLC.

6.4. Which patients would be best suited for treatment with the drug under review?

RESPONSE:

Which patients are most likely to respond to treatment with the drug under review?

In the CASPIAN trial, the patient population under study was characteristic of patients seen in a general oncology practice. Of note, patients over 80 years of age were included (range 36-88), as were those with brain metastases. Subgroup analyses demonstrated similar benefits from the addition of durvalumab across age groups, ethnic subgroups, presence of brain and liver metastases and geographic region. In fact, there was no patient subgroup that did not benefit from the addition of durvalumab.

Which patients are most in need of an intervention*?*

ALL patients with extensive SCLC are in need of better treatment options. There has been no progress for this disease for over 30 years.

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

All patients of adequate performance status deserve the best first-line treatment for extensive stage SCLC.

6.5. How would patients best suited for treatment with the drug under review be identified?

RESPONSE:

Is the condition challenging to diagnose in routine clinical practice?

All pathologists and pathology departments have the capability to diagnose SCLC.

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion).

All hospitals in Canada have the ability to undertake the pathologic, hematologic, biochemical and radiologic tests necessary to diagnose and treat SCLC. Advanced molecular profiling is ***not*** necessary.

Selection of SCLC patients for immunotherapy, including durvalumab does not require any special testing.

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Misdiagnosis is unlikely. In the case of uncertainly, most local pathology departments would request external review, usually at an academic centre.

Under-diagnosis is not an issue with extensive SCLC

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Virtually all patients with SCLC are symptomatic. They present at an advanced stage and early treatment is essential

6.6. Which patients would be least suitable for treatment with the drug under review?

RESPONSE:

Patients with severe or symptomatic auto-immune disorders should not be treated with durvalumab immunotherapy.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

RESPONSE:

Numerous tumour markers have been evaluated in an attempt to select patients for immunotherapy including PD-1 and PDL-1 inhibitors. Results have been variable, and have been inconsistent across tumour types, and even within individual cancers. The most extensively studied markers in lung cancer are PDL-1 status assessed in tumour samples by immunohistochemistry, and Tumour Mutation Burden (TMB) assessed either in tumour samples or in peripheral blood cell-free DNA.

TMB is not a validated test, and would not be appropriate for patient selection for durvalumab in extensive SCLC.

PDL-1 score was tested in a subset of patients with available tissue samples in the CASPIAN trial, and benefit from the addition of durvalumab was identical in patients who were negative for PDL-1 staining compared to those who were positive. Also, the subset of patients who had tissue available for pDL-1 testing was comparable to that of the study population as a whole, making comparison of that subset clinically valid.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

RESPONSE:

In clinical practice, patients are evaluated for response (and toxicity) before each cycle of therapy by history, physical examination, bloodwork and/or chest radiographs. CT scans and/or MRIs are performed every 2-3 cycles and always at the completion of chemotherapy.

These assessments to determine clinical outcomes aligned with those investigated in the CASPIAN trial.

6.9. What would be considered a clinically meaningful response to treatment?

RESPONSE:

ASCO Guidelines have evaluated “Clinically Meaningful” response for non-small cell lung cancer. For SCLC, this has been less clearly defined owing to the lack of success of studied agents. A two month overall survival benefit for this aggressive disease would be considered meaningful. The CASPIAN trial

not only shows a significant median overall survival with the addition of durvalumab, but also demonstrated a sustained survival benefit. **Whereas long-term survival in extensive SCLC was not expected until recently, now any improvement in survival beyond 18 months is considered very meaningful. CASPIAN showed at 18 months, 32% of patients were alive and at 24 months, 22% were alive with the addition of durvalumab. This added durable survival has become more apparent with the longer follow-up in CASPIAN and is absolutely meaningful in extensive SCLC.**

6.10. How often should treatment response be assessed?

RESPONSE:

See above 6.8.

6.11. What factors should be considered when deciding to discontinue treatment?

RESPONSE:

Platinum-etoposide chemotherapy is never given for more than six cycles, and usually just four cycles.

Immunotherapy, in this setting of extensive SCLC, will continues until:

- Disease progression/recurrence
- Toxicity
- Patient or physician decide to stop for other reasons

6.12. What settings are appropriate for treatment with the drug under review?

RESPONSE:

Chemotherapy and durvalumab can be administered as an out-patient. Treatment most often would be given in a specialized cancer hospital with chemotherapy and immunotherapy expertise. This is standard in most regions of Canada.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

RESPONSE:

Not applicable. Durvalumab is an oncology drug intended for treatment of patients with cancer.

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

RESPONSE:

The results of the CASPIAN trial are notable and approval and funding of durvalumab for extensive SCLC are indicated for several reasons:

- The patient population in the study is reflective of extensive SCLC seen in the general population
- The control arm reflects standard of care treatment in Canada
- The control arm did not underperform (i.e., the benefit from durvalumab is *not* due to unexpectedly poor results with standard chemotherapy)

- ALL patient subsets benefited from the addition of durvalumab
- Benefit was seen and of similar magnitude in patients with and without tissue PDL-1 expression
- The benefit was seen in *overall survival*, the most important outcome in cancer treatment
- More than one fifth of patients remain alive past two years, a truly remarkable milestone in SCLC, that seldom was achieved in any previous trials
- Because the effector cells (the immune cells), circulate freely, and have bull access to the CNS via the blood stream, the concept of a "blood brain barrier" does not apply. PCI was prohibited in the immunotherapy arm of the trial, and yet there was *no increase* in brain metastases seen in this arm. This means that durvalumab treatment may be given without PCI, a treatment that is not widely accepted by patients because of its potential toxicity. Furthermore, patients with brain metastases at study entry derived the same benefit from durvalumab as those without.
- Toxicity was not increased in the durvalumab arm and so the risk/benefit definitely favours the addition of durvalumab

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information	
Name	*Dr. Randeep Sangha*
Position	*Medical Oncologist, Cross Cancer Institute* *Associate Professor, University of Alberta*
Date	*15-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Frances A. Shepherd, OC, OOnt, MD, FRCPC, LLD (honoris causa)*
Position	*Scott Taylor Chair in Lung Cancer Research, Princess Margaret Cancer Centre, University Professor, University of Toronto.*
Date	*15-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
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Astra Zeneca	☐	☒	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	Dr. Ronald Burkes
Position	*Professor of Medicine University of Toronto* *Medical oncologist at Mount Sinai Hospital/Princess Margaret Cancer Centre/University Health Network*

Date	*15-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	Dr. Rosalyn Juergens
Position	*Medical Oncologist and Head of the Department of Clinical Trials at the Juravinski Cancer Centre.*
Date	*15-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
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Bristol Myers Squibb	☒	☐	☐	☐
Astra Zeneca	☐	☒	☐	☐
Merck Sharp and Dohme	☒	☐	☐	☐
Roche	☒	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	Dr. Paul Wheatley-Price
Position	*Associate Professor of Medicine, University of Ottawa* *Division of Medical Oncology, The Ottawa Hospital* *President of Lung Cancer Canada*
Date	*15-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Astra Zeneca	☐	☒	☐	☐
Bayer	☒	☐	☐	☐
Boehringer Ingelheim	☒	☐	☐	☐
Bristol Myers Squibb	☒	☐	☐	☐
Merck	☐	☒	☐	☐
Norvatis	☒	☐	☐	☐

Declaration for Clinician 6

Clinician Information	
Name	Dr. Quincy Chu
Position	*Medical Oncologist, Cross Cancer Institute, Alberta*
Date	*15-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Abbvie	☒	☐	☐	☐
Amgen	☒	☐	☐	☐
Astra Zeneca	☐	☐	☐	☒
Boehringer Ingelheim	☐	☒	☐	☐
Bristol Myers Squibb	☐	☒	☐	☐
Eisai	☒	☐	☐	☐
Merck	☐	☐	☒	☐
Norvatis	☐	☒	☐	☐
Pfizer	☐	☒	☐	☐
Roche	☐	☒	☐	☐

Declaration for Clinician 7

Clinician Information	
Name	Dr. Kevin Jao
Position	*Medical Oncologist, Hôpital du Sacré-Cœur-de-Montréal*
Date	*15-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Bristol-Myers Squibb	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 8

Clinician Information	
Name	Dr. Donna Maziak
Position	*Professor, University of Ottawa* *Thoracic Surgeon, The Ottawa Hospital*
Date	*15-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 9

Clinician Information	
Name	Dr. Jeffrey Rothenstein
Position	*Medical Oncologist, Lakeridge Health, Oshawa*
Date	*15-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Roche	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 10

Clinician Information	
Name	Dr Catherine Labbé
Position	*Pulmonologist, Laval University Institute of Cardiology and Pneumology of Quebec, QC*
Date	*15-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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BMS	☐	☒	☐	☐
Astra Zeneca	☐	☒	☐	☐
Merck	☒	☐	☐	☐
Pfizer	☒	☐	☐	☐

Declaration for Clinician 11

Clinician Information	
Name	Dr. Geoffrey Liu
Position	*Professor of Medicine, University of Toronto* *Medical Oncologist, University Health Network*
Date	*15-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Takeda	☐	☐	☐	☒
Hoffman La Roche	☐	☐	☒	☐
Pfizer	☐	☐	☒	☐
Astra Zeneca	☐	☐	☐	☒
Bristol Myers Squibb	☒	☐	☐	☐
Boehringer Ingelheim	☐	☐	☒	☐
Abbvie	☐	☒	☐	☐
Merck	☐	☒	☐	☐
EMD Serono	☒	☐	☐	☐
Norvatis	☐	☐	☒	☐
Glaxo Smith Kline	☒	☐	☐	☐

Declaration for Clinician 12

Clinician Information	
Name	Dr. Stephen Lam
Position	*Professor of Medicine, University of British Columbia.* *Respirologist, BC Cancer Agency*
Date	*15-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 13

Clinician Information	
Name	Dr. Callista Phillips
Position	*Medical Oncologist and Clinical Lead* *Oncology Clinic* *Joseph Brant Hospital*
Date	*15-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Astra Zeneca	☒	☐	☐	☐
Bayer	☒	☐	☐	☐
Roche	☒	☐	☐	☐

Declaration for Clinician 14

Clinician Information	
Name	Dr. Cheryl Ho
Position	*Medical Oncologist, BC Cancer Agency*
Date	*15-12-2020*

☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Bayer	☒	☐	☐	☐
Roche	☐	☐	☐	☒
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 15

Clinician Information	
Name	Dr. Nicole Bouchard
Position	*Pulmonologist, Sherbrooke University Hospital*
Date	*15-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Astra Zeneca	☒	☐	☐	☐
Bristol-Myers-Squibb	☒	☐	☐	☐
Merck	☒	☐	☐	☐
Bayer	☒	☐	☐	☐
Pfizer	☒	☐	☐	☐
Roche	☒	☐	☐	☐

Declaration for Clinician 16

Clinician Information	
Name	Dr. David Dawe
Position	*Medical Oncologist, CancerCare Manitoba*
Date	*15-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range

	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Astra Zeneca	☐	☐	☒	☐
Merck	☒	☐	☐	☐
Boehringer-Ingelheim	☒	☐	☐	☐

Note, the research grant from AstraZeneca funded research that has been reported to the company and is used in their pCODR submission. That data is not yet published.

Declaration for Clinician 17

Clinician Information	
Name	Dr. Sunil Yadav
Position	*Professor and Medical Oncologist, Saskatoon Cancer Centre*
Date	*16-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Bristol-Myers-Squibb	☒	☐	☐	☐
Astra Zeneca	☒	☐	☐	☐
Merck	☐	☐	☒	☐
Roche	☐	☒	☐	☐
Takeda	☒	☐	☐	☐

Declaration for Clinician 18

Clinician Information	
Name	Dr. Normand Blais
Position	*Medical Oncologist* *Hôpital Notre Dame du CHUM*
Date	*18-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**

Norvatis	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**PC0234-000**
Generic Drug Name (Brand Name)	**durvalumab (Imfinzi)** **AstraZeneca Canada Inc.**
Indication	**Indications:** IMFINZI in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC). **Manufacturer Requested Reimbursement Criteria1**: As per Health Canada indication: in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC).
Name of the Clinician Group	**Ontario Health (Cancer Care Ontario) Lung and Thoracic Cancer Drug Advisory Committee (DAC)**
Author of the Submission	[redacted]
Contact information	Name: [redacted] Title: [redacted] Email: [redacted] Phone:

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

OH-CCO's Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

Please describe how you gathered the information included in the submission.

The comments contained in this input were collected via emails.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

Current treatment would be a platinum agent plus etoposide for 4 to 6 cycles. There may be some patients accessing atezolizumab in combination with this through private insurers. There is a high response rate to platinum and etoposide of 60-70%. However, median PFS is only about 4 months with median OS around 10 months. Only 15% of patients survive beyond two years. Supportive management alone has a median OS of approximately 6-8 weeks.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

The most important goal would be more effective therapy. The primary goal would be improved overall survival. Other important goals would be higher response rates and longer control of the cancer (PFS). Improvement is symptoms and QoL is also important but this is generally linked to effective therapy. More effective therapy is generally associated with better QoL. Lastly it is important that these therapies have tolerable profile of side effects.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*

- *Treatments are needed that are better tolerated*
- *Treatment are needed to improve compliance*
- *Formulations are needed to improve convenience*

Response:

Despite high response rates to initial therapy, many patients progress in a short period of time. Less than half the patients live beyond one year with few surviving beyond two years. Therefore there is a high unmet need for more effective therapies that result in longer disease control and better OS.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

All patients with ES SCLC have high unmet need. The only factors that predict worse outcome are factors associated with a higher tumor burden, so it is not possible to identify sub groups of greater need. The CASPIAN trial did not identify subgroups with greater benefit and so it is not possible to identify a niche population for this drug.

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

Durvalumab would be used as initial systemic therapy in patients with ES SCLC in combination with 4 cycles of platinum and etoposide, followed by maintenance durvalumab until disease progression. The goals of adding durvalumab to platinum and etoposide would be to improve PFS and OS. In particular the hope is that the addition of durvalumab will increase the proportion of patients living beyond 18-24 months.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

The current standard of care is platinum and etoposide. This has been the case for the last three decades. No other agents apart from immune checkpoint inhibitors have demonstrated improved OS as initial therapy for ES SCLC. It would not be appropriate to recommend the addition of other therapy apart from an immune checkpoint inhibitor such as durvalumab.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

Durvalumab is not currently approved in the treatment of ES SCLC. There are no trials demonstrating benefit from an immune checkpoint inhibitor as subsequent therapy. Therefore the addition of durvalumab to platinum and etoposide will not have any downstream impact on other treatment options. Second line therapy would remain either retreatment with platinum and etoposide, or CAV. Topotecan is another option although not funded in all jurisdictions.

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

All patients with ES SCLC are in need of improved therapies. It is not possible to identify subgroups that are more likely to benefit from the addition of durvalumab. Therefore this treatment would be considered for any patient with ES SCLC and ECOG PS of 2 or greater.

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

ES SCLC is a common condition that medical oncologists see and treat on a regular basis. These patients would be identified at the time of initial consultation with a medical oncologist. There are no specific issues for consideration.

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

All patients with ES SCLC and ECOG PS of two or better would be candidates for therapy with platinum etoposide and durvalumab, unless they have specific contraindications to an immune checkpoint inhibitor. Patients with symptomatic brain metastases should have treatment for their brain metastases prior to commencing their systemic therapy.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

As discussed above there are no predictive biomarkers of benefit for the addition of durvalumab to chemotherapy.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

Tumor shrinkage on imaging studies would typically be used to determine if a patient is responding to therapy. Improvement in patients symptoms would also be looked for as a measure of treatment benefit.

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:
A meaningful response to treatment would be tumour shrinkage.

6.10. How often should treatment response be assessed?

Response:

Typically after every three cycles of chemotherapy. For patients receiving platinum etoposide and durvalumab, treatment would continue until disease progression. After six months or so, the frequency of imaging may be extended to every four cycles of therapy.

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

In the CASPIAN trial treatment continued until disease progression. In clinical practice, the reasons to discontinue treatment would be unequivocal disease progression, the development of grade 3 immune related AEs, or patient choice.

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

Treatment would be administered under the supervision of a medical oncologist in any facility accredited to administer anti cancer systemic therapy.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant?

Response:

NA

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

Response:

There have been no significant treatment advances in ES SCLC in more than three decades. The addition of durvalumab represents a modest but real improvement in survival for a group of patients with high unmet need.

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   OH-CCO provided secretariat support to the Lung DAC in completing this input submission.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information	
Name	*Dr. Gail Darling*
Position	*Ontario Cancer Lead; Thoracic Surgeon*
Date	*03 December 2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Dr. Peter Ellis*
Position	*Division Head of Medical Oncology Juravinski Cancer Centre, Member of Lung DAC*
Date	*26 November 2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AstraZeneca	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Dr. Andrew Robinson*
Position	*Medical Oncologist, Member of Lung DAC*
Date	*26 November 2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AstraZeneca – coinvestigator on other AZ trials but no direct financial payment disclosed	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Dr. Natasha Leighl*
Position	*Medical Oncologist, Member of Lung DAC*
Date	*21 December 2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
AstraZeneca	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐