pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial ministries of health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug: Durvalumab (Imfinzi)

Submitted Reimbursement Request: For the treatment of patients with locally advanced, unresectable non-small cell lung cancer (NSCLC) following curative intent platinum-based chemoradiation therapy, for up to a maximum of 12 months

Submitted by: AstraZeneca Canada

Manufactured by: AstraZeneca Canada

NOC Date: May 4, 2018

Submission Date: September 21, 2018

Initial Recommendation Issued: March 7, 2019

Approximate per Patient Drug Costs	• $3,911.11 per 500 mg vial or $938.67 per 120 mg vial • At a dose of 10 mg/kg, the biweekly cost of durvalumab is $5,890.00[a] [a] Assuming a body weight of 71 kg as per the PACIFIC trial

pERC RECOMMENDATION

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions***

☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends the reimbursement of durvalumab (Imfinzi) for the treatment of patients with locally advanced, unresectable stage III non-small cell lung cancer (NSCLC) following curative intent platinum-based concurrent chemoradiation therapy, if the following conditions are met:

- cost-effectiveness being improved to an acceptable level
- feasibility of adoption (budget impact) being addressed

Eligible patients include those with good performance status who are deemed fit following curative intent platinum-based concurrent chemoradiation therapy. Treatment should continue until unacceptable toxicity or disease progression to a maximum of 12 months.

The Committee made this recommendation because it was satisfied that there is a net clinical benefit of durvalumab in this patient population compared with standard of care (observation) based on a statistically significant and clinically meaningful improvement in progression-free survival (PFS) and overall survival (OS). Furthermore, durvalumab is associated with manageable toxicities and there is no detriment in quality of life (QoL) with durvalumab compared with standard of care (observation).

Additionally, pERC considered that there is an unmet need for patients with stage III NSCLC as there are no curative intent treatment options after concurrent chemoradiation therapy which is associated with a poor prognosis.

	pERC agreed that durvalumab aligns with patient values of having more effective treatment options that prolong survival, offer disease control, with manageable toxicities. The Committee concluded that, based on the submitted price, durvalumab is not cost-effective in this patient population when compared with standard of care (observation) and would require a substantial price reduction to improve the cost-effectiveness to an acceptable level. In addition, pERC concluded that the market uptake will be higher than estimated; therefore the submitted budget impact is underestimated and the actual budget impact will be substantially greater. pERC had concerns about the affordability of durvalumab and the capacity for jurisdictions to implement reimbursement of durvalumab.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness and Budget Impact** Given that pERC was satisfied that there is a net clinical benefit of durvalumab, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness to an acceptable level and improve affordability (budget impact). pERC noted that, due to the short trial follow-up, there is some uncertainty in the magnitude of the long-term benefit of durvalumab in this patient population. In order to offset this uncertainty, a substantial reduction in price would be required. **Insufficient Evidence to Support the Use of Durvalumab After Radiation and Chemotherapy Given Sequentially or for Patients With Stage III Disease Who Do Not Receive Concurrent Chemoradiation Therapy** pERC noted that there is currently insufficient evidence to support the use of durvalumab in settings other than after curative intent concurrent chemoradiation therapy. However, pERC noted there are ongoing studies evaluating durvalumab in other settings. pERC noted that a new submission to pCODR would be required to consider reimbursement for durvalumab in other settings. **No Evidence for Optimal Sequencing in the Metastatic Setting** pERC noted that there is currently no clinical trial evidence to inform the optimal sequencing of durvalumab and subsequent therapies if disease progression occurs, and therefore the optimal sequencing of treatments is unknown. pERC acknowledged that, in the metastatic setting, there are currently funded treatments including PD-1 inhibitors, chemotherapy, and targeted oral therapies. The Committee acknowledged that there is neither direct comparative evidence investigating the efficacy and safety nor the appropriate sequence of subsequent therapies. Upon the implementation of reimbursement of durvalumab, pERC recognized that collaboration among provinces to develop a national, uniform approach to optimal sequencing and shared collection of outcomes would be of value. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

There are approximately 28,000 new cases of lung cancer and 21,000 deaths from lung cancer each year in Canada, of which 85% are non-small cell lung cancer (NSCLC). Stage III NSCLC represents approximately 20% of NSCLC cases with up to 50% of patients with stage III NSCLC being eligible for treatment. The current standard of care for more than 20 years for patients with unresectable stage III cancer with a good performance status is cytotoxic chemotherapy concurrent with radiotherapy. However, most patients experience disease progression with a median progression-free survival (PFS) of approximately eight months with only 15% of patients are alive at five years. There have been no major advances in treatment for these patients. No active treatments are available following curative intent platinum-based concurrent chemoradiation therapy and observation is the current standard of care. Therefore, pERC concluded that there is a significant need for an effective treatment that will delay progression and prolong survival in this patient population.

pERC's Deliberative Framework for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of one phase III, multi-centre, international randomized controlled trial, PACIFIC. The trial assessed the efficacy and safety of durvalumab compared with placebo in patients with stage III NSCLC who received curative intent platinum-based chemotherapy concurrent with radiotherapy. pERC noted that there was a statistically significant and clinically meaningful improvement in PFS and OS for patients treated with durvalumab compared with placebo. pERC noted that the median OS was not reached in the durvalumab group, and discussed that the long-term benefit of durvalumab is uncertain due to the short period of trial-follow-up. Furthermore, pERC also discussed the fact that patients with disease progression in the trial went on to receive subsequent anti-cancer therapies. pERC acknowledged that even with sufficient follow-up OS could be evaluated but may be confounded by subsequent post-trial treatments. Additionally, pERC noted that patients were not stratified by biomarker status and this may have had an impact on the difference in treatment effect. Nevertheless, pERC considered that overall, there was a difference in favour of durvalumab in PFS and OS among all subgroups evaluated.

The Committee also discussed the Clinical Guidance Panel (CGP)'s conclusions regarding the generalizability of treatment with durvalumab to particular subgroups of patients who were not included in the PACIFIC trial. pERC agreed that patients with ECOG 2 performance status due to unresolved toxicities after concurrent curative intent chemoradiation therapy should be eligible to receive durvalumab. pERC agreed with the CGP that patients treated with therapy other than concurrent curative intent chemoradiation would not be eligible for durvalumab. However, pERC noted there are ongoing studies evaluating durvalumab in other settings and these may form the basis for future submissions to pCODR.

pERC deliberated on the safety of durvalumab. The most common grade 3 to 4 adverse events (AEs) reported among patients receiving durvalumab were pneumonia, pneumonitis, radiation pneumonitis, and anemia. Overall, pERC noted that the safety profile between durvalumab and placebo was similar. The Committee acknowledged that AEs may have been associated with previous treatment with concurrent chemoradiation therapy as patients were enrolled into the PACIFC trial within six weeks of ending concurrent chemoradiation therapy. The Committee noted that, overall the side effects of durvalumab are manageable through appropriate monitoring. Additionally, pERC discussed the quality of life (QoL) data collected in the PACIFIC trial. pERC noted the results across all subscales did not demonstrate any meaningful difference in symptom deterioration, function, and the overall QoL between the durvalumab and placebo groups. pERC concluded that there is a net clinical benefit of durvalumab compared with standard of care (observation) for patients with stage III NSCLC who received curative intent platinum-based concurrent chemoradiation therapy for up to a maximum of 12 months, based on a statistically significant and clinically meaningful improvement in PFS and OS, the manageable toxicity profile and the lack of detriment to QoL.

pERC deliberated on patient input from two patient advocacy groups. Patient input indicated that patients value an effective treatment that will slow progression, improve survival, and improve QoL. Additionally, pERC noted that patients want an option to receive treatment at home rather than having to travel to a treatment centre. However, pERC noted that patients would have to travel to a treatment centre to receive durvalumab by infusion. pERC considered that there are no curative intent treatment options following concurrent chemoradiation therapy and that there is a significant need for treatment that will delay progression and prolong survival for patients with stage III NSCLC. The Committee discussed that toxicities associated with current treatments are difficult for patients to tolerate. Furthermore, pERC considered that caregivers' work, finances, relationships, and daily activities were all impacted by their family member's condition along with a heavy emotional toll. Overall, pERC agreed that durvalumab aligns with patient values in that it is an effective treatment option that delays disease progression and prolongs survival and has manageable toxicities with no observed detriment to QoL.

pERC deliberated on the cost-effectiveness of durvalumab compared with standard of care (observation) based on the submitted economic evaluation and the reanalysis provided by the pCODR Economic Guidance Panel (EGP). The Committee noted that the factor that most influenced the incremental effect was the duration of treatment benefit of durvalumab. pERC discussed the fact that the duration of treatment benefit of durvalumab is unknown because of the short trial follow-up. The Committee noted that OS data was immature with approximately three years of trial data and that the submitted economic model assumed 10 years of treatment benefit, as the Submitter acknowledged that the duration of treatment benefit may not continue indefinitely. The Committee considered that the CGP stated that assuming the treatment benefit of durvalumab to accrue until 10 years may be too optimistic. pERC agreed with the EGP's approach of setting the relative treatment effect for OS for durvalumab and observation to be the same at three years that corresponds to the trial end date. The Committee concluded that the magnitude of long-term benefit of durvalumab is unknown and that the assumption of 10 years of treatment benefit may overestimate the long-term benefit anticipated with the use of durvalumab. Furthermore, pERC noted that administration costs for durvalumab were not considered in the submitted economic analysis. The Committee discussed that there would be additional administration costs for durvalumab given that this treatment would be provided in place of standard of care where no treatment is currently given. Overall, pERC agreed with the EGP's best estimate of the incremental cost-effectiveness ratio (ICER) and concluded that compared with standard of care and at the submitted price, durvalumab is not cost-effective.

pERC discussed the feasibility of implementing a reimbursement recommendation for durvalumab. Overall, pERC noted that the submitted budget impact estimate was very low at 12% of the market share in the first year. pERC discussed that the market share was underestimated and that it would be substantially higher based on the CGP's expert opinion of estimates of eligible patients pERC expressed concern about the affordability of durvalumab and the capacity for jurisdictions to implement reimbursement of durvalumab. pERC discussed that increasing the market share uptake and the number of patients who receive concurrent chemoradiation will increase the budget impact. However, pERC recognized that given that treatment with durvalumab is potentially curative, the high budget impact may defer therapy costs downstream.

pERC noted the Provincial Advisory Group (PAG)'s request for advice on appropriate treatment if disease progression occurs after treatment with durvalumab. The Committee discussed that for metastatic disease, currently funded treatments include PD-1 inhibitors (nivolumab, pembrolizumab), chemotherapy, and targeted oral therapies. pERC considered the CGP's expert opinion and agreed that treatment after durvalumab will depend on the tumour characteristics (PD-L1, biomarker status), patient characteristics (performance status, tolerance for chemotherapy, and tolerance for other therapies), and disease course characteristics (time and burden of recurrence). Furthermore, pERC discussed that there is currently insufficient evidence to support re-treatment with durvalumab upon disease progression. Overall, pERC noted that there is currently no clinical trial evidence to inform the optimal sequencing of durvalumab and subsequent therapies if disease progression occurs, and therefore sequencing is unknown.

Additionally, pERC noted PAG's request for clarity regarding the time frame for initiating durvalumab after completion of concurrent chemoradiation therapy. pERC discussed that treatment with durvalumab should start up to six weeks following completion of concurrent chemoradiation as per the PACIFIC trial. However, pERC recognized that patients may have unresolved toxicities after concurrent chemoradiation that may preclude a patient from starting durvalumab within six weeks of completing therapy. pERC noted that initiating durvalumab after more than six weeks of completion of concurrent chemoradiation

therapy may be done on a case-by-case basis, recognizing that beginning treatment at a later time period may have an unknown impact on efficacy.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from the pCODR clinical and economic review panels
- Input from two patient advocacy group(s) (Lung Cancer Canada [LCC] and Ontario Lung Association [OLA])
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of this review is to evaluate the safety and efficacy of durvalumab (Imfinzi) for the treatment of patients with locally advanced, unresectable stage III NSCLC following curative intent platinum-based chemotherapy concurrent with radiation, for up to a maximum of 12 months.

Studies included: One randomized phase III trial

The pCODR systematic review included one randomized, double blind, placebo controlled, international phase III trial that evaluated the safety and efficacy of treatment with durvalumab at a dose of 10 mg per kg of body weight intravenously (n = 476) compared with placebo (n = 237) in patients with stage III NSCLC who did not have disease progression after two or more cycles of platinum-based chemotherapy concurrent with radiotherapy. Patients were randomly assigned in a 2:1 ratio to receive durvalumab intravenously or matching placebo every two weeks up for up to 12 months. Randomization was stratified according to age (< 65 vs. ≥ 65 years), sex, and smoking history (current or former smoker versus never smoked). The study drug was administered one to 42 days after patients had received concurrent chemoradiotherapy. Treatment continued until disease progression or unacceptable toxicity for up to a maximum of 12 months. Re-treatment with study drug was permitted if disease control had been achieved at the end of the 12 months of therapy but disease progression occurred during follow-up. The study is ongoing with an estimated completion date of July 9, 2019.

Patient populations: Locally advanced, unresectable Stage III NSCLC who did not have disease progression after two or more cycles of curative intent platinum-based chemotherapy

Key eligibility criteria included patients with locally advanced, unresectable (stage III) NSCLC who received at least two cycles of platinum-based chemotherapy concurrent with radiation therapy, which must be completed within one to 42 days before randomization in the study. Patients must have not progressed following definitive, platinum-based, concurrent chemoradiation therapy. Additionally, patients must have had a World Health Organization (WHO) performance status of 0 or 1 and adequate organ and marrow function.

The median age of patients in the trial was 64 years (range 23 to 90 years). The majority of patients were male (70%) with a WHO PS of 0 to 1 (99.6%), white (69.3%) and previous smokers (74.6%). The majority of patients were epidermal growth factor receptor (EGFR) mutation status negative (67.6%), and 26.4% of patients had an unknown EGFR mutation status. Additionally, 41% of patients had a PD-L1 expression level < 25% and 36.7% of patients had an unknown PD-L1 expression level.

A small proportion (3.8%) of patients was re-treated with durvalumab upon disease progression after completing 12 months of treatment in the follow-up phase.

Overall, 50.6% of patients discontinued treatment with durvalumab and 64.6% discontinued treatment with placebo. Of those, 41% of patients in the durvalumab group and 54% of patients in the placebo group initiated a post-discontinuation therapy. The most common post-discontinuation anti-cancer therapies included: chemotherapy (26.9% in the durvalumab group versus 30% in the placebo group); radiotherapy (17.2% in the durvalumab group versus 23.6% in the placebo group); immunotherapy (8% in the durvalumab group versus 22.4% in the placebo group); targeted therapy (9.9% in the durvalumab group versus 13.1% in the placebo group); and other therapies (0.2% in the durvalumab group versus 0.4% in the placebo group)

Key efficacy results: Statistically significant improvement in PFS and OS

The key efficacy outcomes deliberated on by pERC include the two primary co-end points of PFS and OS. The median follow-up time at the February 13, 2017 data cut-off date was 14.5 months (range 0.2 to 29.9 months). At the updated analysis at the March 22, 2018 data cut-off date, the median follow-up time was 25.2 months (range 0.2 to 43.1 months).

At the interim analysis (data cut-off date February 13, 2017) the median PFS was 16.8 months (95% CI, 13.0 to 18.1) in durvalumab group and 5.6 months (95% CI, 4.6 to 7.8) in placebo group. The stratified hazard ratio for disease progression or death was 0.52; (95% CI, 0.42 to 0.65, $P < 0.001$). This analysis was considered the final analysis for PFS since PFS achieved statistical significance. At a later data cut-off on the results for PFS were consistent with the earlier analysis. The updated median PFS was 17.2 months (95% CI, 13.1 to 23.9) in the durvalumab group, and 5.6 months (95% CI, 4.6 to 7.7) in the placebo group respectively. The stratified hazard ratio (HR) was 0.51 (95% CI, 0.41 to 0.63), *P* not reported. Subgroup analyses demonstrated similar treatment effect in favour of durvalumab compared with placebo.

At the first interim analysis for OS, at the March 22, 2018 data cut-off date, durvalumab demonstrated a statistically significant benefit in OS compared with placebo, with a 32% reduction in the risk of death. The stratified HR was 0.68; 99.73% CI, 0.47 to 0.997; $P = 0.0025$. The median OS in the durvalumab group was not reached and was 28.7 months (95% CI, 22.9 to not reached) in the placebo group. This analysis was considered the final analysis for OS since the OS achieved statistical significance. The 24 month OS rates were 66.3% (95% CI, 61.7 to 70.4) in durvalumab group versus 55.6% (95% CI, 48.9 to 61.8) in the placebo group, $P = 0.005$. Subgroup analyses demonstrated similar treatment effect in favour of durvalumab compared with placebo. While this analysis was considered the final analysis, patients will continue to be followed for long-term survival.

Secondary outcomes including objective response rate, duration of response, time from randomization to second progression or death (PFS2), time to death or metastases, and time to first and second subsequent therapy or death favoured the treatment with durvalumab compared with placebo.

Patient-reported outcomes: No meaningful differences in quality of life between durvalumab and placebo groups

QoL was a secondary outcome and was measured with the European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire C30 (QLQ-C30) including time to symptom deterioration (e.g., fatigue, pain), time to QoL/function deterioration (e.g., physical function, role function, emotional function, global health status/QoL); and EORTC Lung Cancer Module (LC13) including time to symptom deterioration (e.g., dyspnea, cough, hemoptysis, chest pain). Health-related QoL showed a high level of compliance (> 80%) for both groups for up to 48 weeks. Results across all subscales did not indicate any meaningful difference in symptom deterioration, function, and the overall QoL between the durvalumab and placebo groups, despite a longer duration of study therapy for the durvalumab group.

Safety: Manageable toxicity profile; higher frequency of pneumonitis in the durvalumab treatment group

At the March 22, 2018 data cut-off, 183 (38.4%) patients with durvalumab and 116 (48.9%) patients with placebo had died. The majority of deaths were related to NSCLC only (147/183 [80.3%] and 86/116 [74.1%], respectively). A total of 21 (4.4%) patients with durvalumab and 17 (7.2%) patients with placebo died due to an AE or due to both the NSCLC and an AE. Based on the earlier February 13, 2017 date cut-off, the most frequently reported serious AEs were pneumonia (5.7% in durvalumab group versus 5.1% in placebo groups), pneumonitis (3.4% in durvalumab group vs 3.0% in placebo group), and radiation pneumonitis (3.6% in durvalumab group versus 1.3% in placebo group).

The majority of patients in the trial experienced an AE (96.8% of patients in the durvalumab group vs. 94.9% patients in the placebo group). Grade 3 or 4 AEs of any cause occurred in 30.5% of the patients in the durvalumab group and in 26.1% of those in the placebo group respectively. Additionally, 66.7% of the patients in the durvalumab group and 49.1% of the patients in the placebo group reported at least one AE of special interest which was defined as immune related AEs. A total of 60 (12.6%) patients in the durvalumab group and 18 (7.7%) patients in the placebo group experienced pneumonitis.

Need and burden of illness: Unmet need for patients with stage III NSCLC who are likely to recur following concurrent chemoradiation therapy

There are approximately 28,000 new cases of lung cancer and 21,000 deaths from lung cancer each year in Canada, of which 85% are NSCLC cases. Stage III NSCLC represents approximately 20% of NSCLC with up to 50% of patients with stage III NSCLC being eligible for treatment. The current standard of care for over 20 years for patients with a good performance status and unresectable stage III cancer is cytotoxic chemotherapy concurrent with radiotherapy. However, most patients experience disease progression with a median PFS of approximately eight months with only 15% of patients alive at five years. There have been no major advances in treatment for these patients. No active treatments are available following curative intent platinum-based concurrent chemoradiation therapy and observation is the current standard of care. Therefore, there is a significant need for effective treatment that will delay progression and prolong survival in this patient population.

Registered clinician input: Significant unmet need; observation is the current standard of care

Input from clinicians noted that there is a significant unmet need, as the current standard of care for patients following curative intent concurrent chemoradiation is observation. Durvalumab would serve as a new treatment for patients with locally advanced, unresectable stage III NSCLC following curative intent platinum-based chemoradiation therapy for up to 12 months. Clinicians also commented on the favourable toxicity profile of durvalumab. The clinicians agreed that the patient eligibility criteria in the PACIFIC trial would be applicable to clinical practice.

PATIENT-BASED VALUES

Experience of patients with stage III NSCLC: High burden of illness

Patient input was received from two patient groups: LCC and OLA. Patient input noted that patients with stage III NSCLC experience a number of symptoms including fatigue, pain, shortness of breath, coughing up blood, weakness, anxiety, and depression. Patient input indicated that stage III NSCLC affects a patient's ability to work, travel, socialize, and participate in leisure and physical activities that are part of daily life. In addition, patient input noted the desire for fewer medical appointments and for a lower cost burden. Patient input also noted the impact stage III NSCLC has on caregivers. Patient input expressed that caregiver's work, finances, relationships, and daily activities are negatively affected by their family member's condition.

Patient values on treatment: Improve symptoms, slow progression, prolong survival, and improve quality of life

Patient input noted that there are currently no available curative intent therapies for patients following concurrent chemoradiation therapy. Patient expectations of durvalumab are to improve symptoms, provide disease control, prolong survival, and improve quality of life. Some patients providing input had direct experience with durvalumab. Patients with direct experience with durvalumab reported that side effects associated with durvalumab were manageable. Patients with direct experience with durvalumab reported they had a better sense of well-being, better functionality, and increased independence. Additionally, patient input stated that patients want an option to receive treatment at home rather than having to travel to a treatment centre. Currently, patients would have to travel to a treatment centre to receive durvalumab by infusion.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis

The pCODR Economic Guidance Panel (EGP) assessed the cost-effectiveness and cost-utility analyses comparing durvalumab and placebo (observation).

Basis of the economic model: Clinical and cost inputs

Costs considered included drug acquisition costs, subsequent therapies. Drug administration costs were not considered in the submitted model. Key clinical effect estimates considered in the analysis include OS, PFS, utilities, and disutilities.

Drug costs: High drug cost

The cost of durvalumab is $7.82/mg or $3,911.11/500 mg or $938.67/120 mg. At a dose of 10 mg/kg, assuming a body weight of 71 kg as per the PACIFIC trial, the biweekly cost of durvalumab is $5,890.00 assuming no vial sharing.

There is no cost for standard observation.

Clinical effect estimates: Uncertainty in the long-term benefit of durvalumab

Direct clinical effectiveness estimates were derived from the PACIFIC trial. Median OS was not reached in the durvalumab arm. Thus, the model relied on the extrapolation of overall survival data from a median duration of follow-up in the PACIFIC trial of 25.2 months to the 15 years modelled in the economic evaluation. The EGP noted that extrapolating immature OS data introduces uncertainty in the long-term benefit of durvalumab. The duration of treatment benefit of durvalumab is unknown. In the submitted base case, the economic model incorporated treatment waning beginning at 10 years assuming no difference in treatment effect between durvalumab and standard observation. The EGP and Clinical Guidance Panel (CGP) noted that assuming 10 years of treatment benefit of durvalumab is too optimistic. Given the short follow-up period for the OS data, and subsequent uncertainty in the long-term benefit of durvalumab, the EGP selected treatment waning to begin at the trial end date, which corresponds to three years in the reanalysis. The hazard ratio was set to 1 for the overall survival curve. This set the relative treatment effect for OS and durvalumab and observation to be the same at three years.

Additionally, the submitted base case assumed that any necessary administration costs for durvalumab would be included in cancer clinic visits; however, an exact definition of cancer clinic costs was unavailable. The EGP and CGP noted that this is not an adequate reflection of actual resource use. The EGP and CGP identified that it is reasonable to assume additional administration costs for durvalumab, given that this treatment would be provided in addition to standard care (where no treatment is currently given), and not in lieu of any current treatment. The EGP used a Canadian reference cost of $196.30 for administration of one hour of infusion, which was assumed to account for preparation of the regimen, chemotherapy chair time, hourly wage for the pharmacist, hourly wage for the chemotherapy nurse, and overhead costs.

Cost-effectiveness estimates: Not cost-effective at the submitted price

The EGP's ICER estimate ($162,670 per quality-adjusted life-year) was higher than the submitter's estimate ($114,065 per quality-adjusted life-year). The EGP's best estimate ICER was based on treatment waning to begin at the trial end date, which corresponds to three years and the addition of administration cost for infusion of durvalumab. The magnitude of long-term benefit of durvalumab is unknown given the lack of long-term survival data from the PACIFIC trial. Additionally, treatment sequencing post-progression is not certain and the true impact on the ICER is unknown.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Use of subsequent therapies after durvalumab in the metastatic setting is uncertain; Submitted budget impact is substantially underestimated

The Provincial Advisory Group (PAG) identified the following factors that could impact the implementation of durvalumab: drug wastage, additional resources and chemotherapy chair time to prepare and administer durvalumab, and additional resources required to monitor and manage infusion related reactions and AEs.

PAG requested clarity on treatments after progression on durvalumab, the duration of treatment of durvalumab, and the eligibility criteria for patients who would or would not be eligible for durvalumab

including patients who received radiation and chemotherapy sequentially or for patients who did not receive chemoradiation therapy. Additionally, PAG requested advice on treatment if disease progression occurs after treatment with durvalumab. There are currently funded treatments for metastatic disease including PD-1 inhibitors (nivolumab, pembrolizumab), chemotherapy, and targeted oral therapies. The CGP noted that the choice of treatment after durvalumab will depend on the tumour characteristics (PD-L1, EGFR status), patient characteristics (performance status, tolerance for chemotherapy, and tolerance for other therapies), and disease course characteristics (time and burden of recurrence).

The submitted budget impact is underestimated and the actual budget impact will be substantial. The factors that increase the budget impact include market share and the proportion of patients with stage III NSCLC who receive chemoradiation. The factors that decrease the budget impact include decreasing the treatment duration from 12 months to discontinuation if a patient progresses before completing therapy and subsequent therapies. There is the potential for increased cost savings downstream given that treatment with durvalumab is potentially curative.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Anil Abraham Joy was excluded from voting due to a conflict of interest.
- Daryl Bell did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of durvalumab (Imfinzi) for NSCLC, through their declarations, one member had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, one of these members was excluded from voting.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the

quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
• PAG is seeking clarity on the patients who would eligible and those who would not be eligible for treatment with durvalumab such as: o disease stage o Patients with stage III disease who do not receive chemoradiation therapy. o Patients with resectable disease who receive. neoadjuvant or adjuvant chemoradiation therapy. o Patients that either receive thoracic radiotherapy alone, or followed by sequential chemotherapy (i.e., not concurrent). o Whether durvalumab is after concurrent chemoradiation therapy only or after radiation and chemotherapy given sequentially.	• pERC noted the CGP's conclusions regarding the generalizability of treatment with durvalumab to particular subgroups of patients who were not included in the PACIFIC trial. pERC agreed that patients with a good performance status with unresolved toxicities after concurrent chemoradiation therapy may be eligible to receive durvalumab. However, pERC noted there is currently insufficient evidence to support the use of durvalumab in settings other than stage III NSCLC after curative concurrent chemoradiation therapy and such patients would not be eligible for durvalumab. However, pERC noted there are ongoing studies evaluating durvalumab in other settings and that these may form the basis for a future submission to pCODR.
• PAG is seeking clarity on the duration of treatment, whether treatment should be stopped at 12 months or if options to continue beyond 12 months or re-starting at time of disease progression if stopped at 12 months should be recommended, as these are options described in the trial.	• pERC noted that a small number of patients who completed 12 months of therapy and had stable disease, partial response or complete response at completion, and subsequently had disease progression, were offered re-treatment with durvalumab. pERC felt that there is currently insufficient evidence to support re-treatment with durvalumab upon disease progression and noted that the Health Canada indication does not include re-treatment with durvalumab. • pERC noted that treatment with durvalumab should continue until unacceptable toxicity or disease progression to a maximum of 12 months.
• PAG is seeking clarity that treatment should start up to 6 weeks (1 to 42 days) following completion of concurrent chemoradiation as per the PACIFIC study.	• pERC noted that treatment with durvalumab should start up to 6 weeks following completion of concurrent chemoradiation as per the PACIFIC trial. However, pERC recognized that patients may have unresolved toxicities after concurrent chemoradiation which may preclude a patient from starting durvalumab within 6 weeks of completing therapy. pERC noted that initiating durvalumab after more than 6 weeks of completion of concurrent chemoradiation therapy may be done on a case-by-case basis, recognizing that beginning treatment at a later time period may have an unknown impact on efficacy.
• PAG is seeking advice on treatments after durvalumab, when patients progress and have metastatic disease. For metastatic disease, currently funded treatments include PD-1 inhibitors (nivolumab, pembrolizumab), chemotherapy, and targeted oral therapies. PAG is seeking data on the use of other PD-1 inhibitors and PD-L1 inhibitors in the treatment of metastatic	• pERC considered the CGP's expert opinion that treatment after durvalumab will depend on the tumour characteristics (PD-L1, EGFR status), patient characteristics (performance status, tolerance for chemotherapy, and tolerance for other therapies), and disease course characteristics (time and burden of recurrence). pERC noted that for patients who recur after having completed 12 months of durvalumab therapy and an appropriate interval, treatment will likely be given for first-line NSCLC in the metastatic setting. For patients who recur while on durvalumab therapy, treatment will be dependent on what previous systemic therapy was received, but will likely not include immunotherapy

disease after progression on durvalumab.	at this time. For patients who experience a recurrence a short interval after receiving durvalumab therapy, optimal treatment and treatment patterns are unknown.
• PD-L1 testing was conducted in the trial but the trial concluded that benefit with durvalumab was observed irrespective of PD-L1 expression.	• PD-L1 testing is not required to initiate treatment with durvalumab.

PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.