CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Durvalumab (Imfinzi) for Non-Small Cell Lung Cancer

May 3, 2019

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by AstraZeneca Inc.** compared durvalumab to watch and wait for patients with stage III unresectable non-small cell lung cancer (NSCLC) whose disease has not progressed following platinum-based chemoradiation for up to a maximum of 12 months.

Table 1. **Submitted Economic Model**

Patient Population Modelled	Based on the ITT population of the PACIFIC phase III trial. Patients with unresectable stage III NSCLC who have received chemoradiation.
Comparator	Standard observation
Year of costs	2018
Time Horizon	15 years; cycle length of 2 weeks
Discounting	1.5% for both cost and health consequences
Cost of durvalumab*	• $7.82 / mg or $3,911.11 / 500 mg or $938.67 / 120 mg • At a dose of 10 mg/kg, the bi-weekly cost of durvalumab was $5,890 assuming no vial sharing
Cost of standard observation	• No cost
Type of Model	Partitioned-survival
Model Structure	The model was comprised of 3 health states: progression-free, progressed disease and death. Progression-free health state captured the treatment time for those on durvalumab and remain progression-free; for those in the 'wait and watch' arm, they are monitored until progression. Progressed disease health state captures the time patients are considered to have progressed from stage III, unresectable disease.
Submitted Main Analysis	Probabilistic, 10,000 iterations
Key Efficacy Data Sources	PACIFIC trial[1,2]
Key Utility Data Sources	PACIFIC or other literature values in scenario analyses
Key Resource Data Sources	Canadian data (Ontario-ICES)
**All calculations are based assuming a body weight of 71 kg (PACIFIC trial)*	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. Relevant issues identified included:

- The CGP concluded that there is a clear, significant, net clinical benefit of durvalumab therapy for consolidation of locally advanced unresectable NSCLC following curative intent platinum-based chemoradiation therapy, for a maximum of 12 months.
- The PACIFIC study[1] revealed a significant, clinically meaningful, benefit in OS. The toxicity of durvalumab was manageable with interventions such as high dose steroid medicines, however, could impact negatively on quality of life.
- There is currently no other treatment options available for these patients other than standard observation.
- There is currently no evidence to inform optimal sequencing of therapies after treatment with durvalumab. Treatment will depend on tumour characteristics, patient characteristics and disease course characteristics.

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered that there is currently no active treatment for stage 3 NSCLC patients who have completed concurrent chemoradiation. Clinicians expect this drug to decrease recurrence rates, which will translate to OS benefit. Three of the four clinicians providing input suggested that consideration of PD-1 inhibitors following durvalumab was appropriate in certain cases; the fourth clinician did not support the use of PD-1 inhibitors following durvalumab. The economic analysis does consider the use of PD-1 inhibitors following treatment with durvalumab, however, the proportion was much lower than that of the standard observation group.

Summary of patient input relevant to the economic analysis
Input was received from two patient advocacy groups. Patients felt stress and frustration as the only treatment option currently available is observation. Patients reported that there were few side effects related to durvalumab, though there are a great many side effects related to lung cancer in general and chemoradiation. Patients reported feeling a general sense of well-being that allowed them to take on more activities, including experiencing less fatigue and more functionality. Both quality of life and adverse events were incorporated into the economic model.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for durvalumab which are relevant to the economic analysis:

1. Resource use: Incremental resources required to prepare, administer and monitor durvalumab infusions. Durvalumab is administered intravenously over 60 minutes, once every two weeks, requiring chemotherapy chair time. In the submitted base case, administration costs were not considered. The EGP was able to modify this in scenario analyses.
2. Drug wastage: There is potential for drug wastage due to small number of patients, although there are two vial sizes to minimize drug wastage.
3. Treatment duration: Duration of treatment in the economic model was included as per protocol in the PACIFIC trial, where all patients were discontinued from treatment at or before 12 months. The economic model did not consider re-treatment, as re-treatment with durvalumab is not currently indicated by Health Canada.
4. Sequencing of treatment: Currently funded treatments for metastatic disease include other PD-1 inhibitors, chemotherapy and targeted oral therapies. It is unclear how treatment sequencing would occur after durvalumab. There is limited data from the PACIFIC trial on patients that received subsequent PD-1 inhibitors (nivolumab, pembrolizumab) following progression on durvalumab, and it is unclear whether this data is generalizable to the Canadian clinical setting.

1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP Estimates

Estimates	Submitted	EGP reanalysis best estimate
ΔE - LY	1.24	0.82
Progression-free	1.38	1.37
Post-progression	-0.14	-0.55
ΔE - QALY (95% CI)	1.07 (1.07, 1.08)	0.74 (0.73, 0.74)
Progression-free	1.18	1.17
Post-progression	-0.10	-0.43
ΔC - $ (95% CI)	$122,613 ($122,359, $122,865)	$120,135 ($119,817, $120,452)
ICER estimate ($/LY)	**$98,748**	**$146,269**
ICER estimate ($/QALY)	**$114,065**	**$162,670**

The main assumptions and limitations with the submitted economic evaluation were:

Limitation in submitted model	Practical Implications
Overall survival data immature	The submitted base case data used inputs from the PACIFIC trial. Though this trial provided direct clinical effectiveness estimates, median overall survival was not reached in the durvalumab arm. Further, less than 50% of the data was mature in both arms of the clinical trial. The model relies on the extrapolation of the overall survival data from a median duration of follow-up of 25.2 months to 15 years. Extrapolating immature overall survival data introduces uncertainty into long-term projects of the benefit of durvalumab. Though the CGP supported the choice of the base case time horizon, the uncertainty in this long term projection should be acknowledged as a limitation.
Duration of benefit of durvalumab unknown	The submitter acknowledged that the duration of treatment benefit may not continue indefinitely. In the submitted base case, the economic model incorporated treatment waning commencing at 10 years, that is, after 10 years it was assumed that here is no difference between durvalumab and standard observation and the hazard ratio was set to 1. The EGP and CGP support the inclusion of treatment waning, however, the CGP stated that allowing treatment benefit to accrue until 10 years may be too optimistic, especially in light of immature overall survival data. Given the uncertainty of the data, the EGP selected treatment waning to begin at trial end date, which corresponds to approximately 3 years, as part of their re-analysis.
Calculation of utilities	Utilities were incorporated into the model as a time-to-death approach (in both the progression-free and progressed disease state). To inform this, they used data from patients that died in the progression-free state. This amounted to a total of 47 patients, a relatively small sample size on which to base utilities.

Limitation in submitted model	Practical Implications
Post-progression utility data	The utilities collected in the PACIFIC trial were collected only until 30 days after progression, representing a limited number of observations during which a patient's HRQOL deteriorates substantially. Further, this relatively short period of time does not reflect the full time spent in the progressed health state; patients lived much longer in the post-progression state than 30 days. Therefore, alternative sources from the literature were explored for utilities in the progressed health state. These utility sources were for metastatic patients and therefore are expected to be lower than stage III NSCLC patients. The impact of lower utilities in the post-progression health state on the ICER is minimal.
Administration costs of durvalumab	In the submitted base case, administration costs for durvalumab were excluded as it was assumed that these costs would be included in cancer clinic visits. The definition of "cancer clinic" visit was unavailable, however. The CGP stated that it is reasonable to assume additional administration costs given that this treatment is an addition to current standard of care. The EGP used a Canadian reference which identified a cost (reported in 2018 dollars) of $196.30 for IV drugs.[3] Though the inclusion of administration costs has a relatively minor impact on the ICER, the intensity of this resource should be considered and it is likely that the $196.30 underestimates the true costs of administering durvalumab.
Subsequent treatments	Subsequent treatment usage for this patient population remains relatively unknown. The economic model uses data from the PACIFIC trial, though it is unlikely that this would reflect real world practice (for instance, 17% of patients who received durvalumab went onto receive immunotherapy at disease relapse. This may not be accurate in the Canadian context). Further, some therapies (e.g. crizotinib) are extremely expensive, though used in a very small group of patients. Despite this small number of patients, changing the proportion of patients who receive this therapy would impact the ICER (see deterministic tornado diagram provided by submitter). The CGP confirmed that this patient population does not know their ALK or EGFR status at this stage of the disease, and therefore targeted therapy is difficult to estimate. The EGP explored a scenario analysis where those in the durvalumab arm would not receive any subsequent immunotherapies, but given the lack of data in a real world clinical setting, this scenario was not incorporated into the best case analysis.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the submitted economic model:

1. **Treatment waning OS state:** There is uncertainty in the long-term benefit of durvalumab, given the relatively short-term follow-up of durvalumab. To avoid making assumptions on continued benefit in the progressed disease state, the submitted base case assumed that there would be no further benefit associated with durvalumab after 10 years; that is, after 10 years, the hazard ratio between durvalumab and standard observation was set to 1 for the overall survival curve. The EGP and CGP agreed with this approach, however, it was felt that doing so at trial end date (~36 months was a more conservative approach, given the uncertainty in the long-term benefit and survival associated with durvalumab.
2. **Administration costs for durvalumab**: 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[3] cost of $196.30 for administration of one hour of infusion, which was assumed to account for the following factors: preparation of the regimen, chemotherapy chair time, hourly wage for the pharmacist, hourly wage for the chemotherapy nurse and overhead costs.

The submitter provided feedback on the pERC Initial Recommendation disagreeing with the 3-year treatment waning assumption in the EGP re-analysis. The submitter stated that the 3-year treatment waning assumption underestimated the benefits of durvalumab. The EGP, however, maintains their reanalysis estimates for the following reasons:

- There were no data submitted during the review that demonstrated the benefit of durvalumab beyond the trial period of 3 years. The data provided demonstrates lower risk of progression with durvalumab despite treatment discontinuation occurring at 1 year, however, evidence has not been provided that demonstrates that a longer progression-free period translates to improvement in overall survival. Further, the data demonstrates that the likelihood of death at 2 years for those who progress on durvalumab is higher than those who progress on placebo (~85% versus 75%). This supports the EGP conclusion that there is likely no incremental benefit for patients in the durvalumab treatment arm beyond 3 years.
- In the EGP's re-analysis, it is assumed no further incremental treatment effect of durvalumab beyond 3 years. By implementing treatment waning (at any time period) the treatment effect from durvalumab is not negated. Given the uncertainty around the OS data from the PACIFIC trial (short term follow-up), and to align with previous CADTH reviews in addressing uncertainty in long term incremental treatment effect, the EGP reiterates that a treatment waning effect implemented at 3 years to correspond with trial end date is a reasonable assumption.

In addition, the submitter also provided feedback on the cost of administration, noting that the definition of "cancer clinic" is not standard and that the cost of administration in the analysis including, chair time, infusion, supply costs were captured under the cost of "cancer clinic".

The EGP recognizes that the definition of cancer clinic was not standard, however, given that durvalumab is an additional treatment the EGP included a standard cost of administering the drug, in addition to the other increased care that would be provided to a patient while on treatment (compared to the standard observation group that would be receiving no treatment). This inclusion of administration costs resulted in an increase in the ICER of $2,875, reflecting that increased administration costs are not a cost driver in the model.

Table 3. **EGP Reanalysis Estimates**

Description of Reanalysis	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Baseline (Submitter's best case)	$122,613	1.07	1.24	$114,065	--
Treatment waning - HR set to 1 after 3 years	$116,645	0.74	0.82	$157,970	$43,905
Administration costs included at $196.30 / admin	$126,038	1.08	1.24	$116,940	$2,875
Best case estimate of above 2 parameters (95% CI)	$120,135 ($119,817, $120,452)	0.74 (0.73, 0.74)	0.82	$162,670	$48,605

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include:

- Market share uptake.
- Proportion of patients receiving chemoradiation therapy.
- Treatment until discontinuation.
- Inclusion of subsequent therapies.

Key limitations of the BIA model include the fact that this is a narrow view of treatment stage III NSCLC. Though the 3-year budgetary impact looks large (and is likely an underestimate given the market share estimates), durvalumab is potentially curative. Budget impact of durvalumab may defer therapy costs from downstream. Despite the large upfront costs, the cost savings from this therapy in subsequent lines of therapy are not reflected.

Another limitation of the BIA model is the underestimation in the submitted base case for market share uptake. Assuming a market share of 12% in the first year was considered low, given the alternative of no active treatment.

Finally, the sequencing of treatments post-progression on durvalumab remains uncertain. It is unknown whether jurisdictions will provide funding for subsequent immunotherapy for patients who receive durvalumab.

1.6 Conclusions

The incremental cost-effective ratio of the EGP reanalysis for durvalumab when compared to standard observation:

1. Would likely be: $162,670/QALY.

2. The difference in cost of durvalumab is $120,135 (95%CI: $119,817 - $120,452) (ΔC). The main factors that influence ΔC include treatment waning and time horizon.
2. The difference in clinical effect of durvalumab is 0.74 (95%CI: 0.72 -0.74) (ΔE). The main factors that influence ΔE include treatment waning and time horizon.
3. Given the uncertainty in the long-term benefits of durvalumab due to the relatively short follow-up in the clinical trial, the EGP elected to assume there would be no further benefit associated with durvalumab after 3 years. In doing so, there was a negative incremental benefit in QALYs in the post-progression state, most likely due to the fitting of the curves. This is not ideal, though may be possible, as patients in the standard observation arm would receive immunotherapies which is likely to increase their survival in that state compared to post-progression treatment options in the durvalumab arm.
4. The impact of administration costs was relatively minor, however, this does not negate the importance of accurately costing and including administration costs in economic analyses.

Overall conclusions of the submitted model:

Though the economic model was well conceived, there remains uncertainty in the estimates. The EGP tried to address the uncertainty in overall survival, notably by reducing the incremental benefit of durvalumab after 3 years in the overall survival state. However, other unknowns such as treatment sequencing post-progression exist. In the absence of data in the clinical setting in Canada, it is difficult to estimate how this could impact the economic model with any certainty. If there is incremental benefit in overall survival extending beyond 3 years, then the incremental QALYs would likely increase to those observed in the submitted base case.

Finally, it was acknowledged that despite a comparison with standard observation (i.e. No active treatment), an incremental gain of 1.07 QALYs felt small in magnitude. The CGP, however, concluded that there is net clinical benefit.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Lung Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of durvalumab (Imfinzi) for NSCLC. A full assessment of the clinical evidence of durvalumab for NSCLC is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no information redacted from this publicly available Guidance Report.

This Final Economic Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Economic Guidance Report will supersede this Initial Economic Guidance Report.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

REFERENCES

1. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med.* 2018;379(24):2342-2350.
2. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med.* 2017;377(20):1919-1929.
3. Tam VC, Ko YJ, Mittmann N, et al. Cost-effectiveness of systemic therapies for metastatic pancreatic cancer. Curr Oncol. 2013;20(2):e90-e106
4. Kasymjanova G, A.J., Cohen V. , Survival in patients with stage III, unresectableNSCLC treated with concurrent chemoradiation, in Unpublished. 2018.
5. Hansen R, R.S., Long term survival among stage III unresected NSCLC patients who received chemotherapy and radiation. Report attached in PE folder. 2018.
6. National Institute for Health and Care Excellence (NICE). TA428: Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy. 2017 11 January 2017 28 March 2017]; Available from: https://www.nice.org.uk/guidance/ta428.
7. Seung SJ, H.M., Walton R, Evans WK, Patient characteristics, treatment patterns and survival for unresectable stage III NSCLC in Ontario, Canada, in World Lung Cancer Conference. 2018, Canada: Toronto.
8. Institute for Clinical Evaluative Sciences (ICES), Ontario - Stage III NSCLC final results. 2018.