CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Atezolizumab (Tecentriq) for Non-Small Cell Lung Cancer

June 20, 2018

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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TABLE OF CONTENTS

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Roche** compared atezolizumab to docetaxel for patients with advanced or metastatic non-small cell lung cancer (NSCLC) after prior systemic chemotherapy.

Table 1. Submitted Economic Model

Funding Request	Atezolizumab for the treatment of patients with locally advanced or metastatic non-small cell lung cancer who have progressed on or after systemic chemotherapy until loss of clinical benefit.
Type of Analysis	*CUA / CEA*
Type of Model	*partitioned-survival*
Comparator	*Docetaxel* *Nivolumab* *Pembrolizumab*
Year of costs	*2017*
Discounting	*1.5% for both costs and health consequences*
Time Horizon	*10 years*
Cycle length	*1 week with half-cycle correction*
Perspective	*Government*
Cost of atezolizumab	Atezolizumab costs $6,776.00 per 1200mg vial. At the recommended dose of 1200mg IV every 3 weeks, atezolizumab costs: • $322.67 per day • $9,034.67 per 28-day course
Cost of nivolumab*	Nivolumab costs $1955.56 per 100mg vial. At the recommended dose of 3mg/kg IV every 2 weeks, nivolumab costs: • $337.33 per day • $9,445.32 per 28-day course
Cost of pembrolizumab*	Pembrolizumab costs $2200.00 per 50mg vial. At the recommended dose of 2mg/kg IV every 3 weeks, pembrolizumab costs: • $293.33 per day • $8,321.33 per 28-day cycle
Cost of docetaxel*,[&]	Docetaxel costs $11.56 per mg. At the recommended dose of 75mg/m^2 IV ever 3 weeks, docetaxel costs: • $70.20 per day • $1965.64 per 28-day cycle
Model Structure	*Partitioned-survival model with three mutually exclusive health states: progression-free survival (on treatment), progression-free survival (off treatment) and death.*
Key Data Sources	*Phase III OAK trial (January 2017 data cut)*
Main results	*Probabilistic*

** Drug costs for all comparators in this table are based on costing information under license from IMS Health Canada Inc. concerning the following information service(s): DeltaPA. and may be different from those used by the submitter in the economic model. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc. Quintile IMS DeltaPA- accessed on November 30, 2017*

[&]The cost of docetaxel used in the model is substantially cheaper than what is provided here.

All calculations are based on = 70kg and BSA = 1.7m^2

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparisons included in this economic model are appropriate. The Submitter provided a network meta-analysis in order to include the comparison with nivolumab and pembrolizumab (along with docetaxel). These comparisons are included in the submitted base case as a sequential analysis.

- Relevant issues identified included:
  - *Demonstrated superior efficacy of atezolizumab to docetaxel in a randomized controlled trial. This was based on significantly improved overall survival as demonstrated in the two randomised controlled trials, OAK and POPLAR.*
  - *There are no direct comparisons between atezolizumab and other PD-1/PD-L1 inhibitors. However, indirect comparisons suggest that the efficacy of atezolizumab is similar to that of nivolumab, or pembrolizumab.*
  - *Though there are currently treatment alternatives to chemotherapy (docetaxel) for NSCLC patients, atezolizumab offers some advantages given the frequency of administration and fewer clinic visits.*
  - Treatment with atezolizumab should be until disease progression with patients being allowed to continue treatment beyond progression if there is evidence of benefit.

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered the following factors:

- Clinicians feel that immunotherapy is superior to chemotherapy in terms of efficacy, and patient quality of life.
- Currently nivolumab (PDL-1 inhibitor) is the standard of care for NSCLC patients who are not 1) PD-L1 positive, 2) EGFR or ALK-positive and 3) have progressed on first line treatment. Patients who are PD-L-1 positive would be given pembrolizumab (either first or second line).
- Like pembrolizumab, atezolizumab is infused every three weeks. Nivolumab is infused every two weeks. Physicians felt that these advantages could be significant on patient time and hospital resource utilization as about 25% of their immunotherapy patients could be on treatment for more than a year.
- Physicians would not use atezolizumab in patients who have been treated with pembrolizumab first line.
- Adding atezolizumab to funded products does not increase the number of patients that will be given access to immunotherapy. Funding atezolizumab means patients and physicians will have a choice of nivolumab, atezolizumab or pembrolizumab in the second line setting.
- If atezolizumab is priced similarly to nivolumab, usage will result in a cost savings to the system due to its three week dosing schedule as opposed to nivolumab's two week schedule.
- Unlike pembrolizumab, diagnostic testing is not necessary for atezolizumab as it seems to have efficacy regardless of what PD-L1 status.

Summary of patient input relevant to the economic analysis
Two patient advisory groups provided input.

- Patients with NSCLC considered quality of life as important, given their difficult to manage symptoms, especially fatigue and exhaustion. Further, inconvenient treatment scheduling and distant locations can burden a patient. Quality of life and the treatment administration of atezolizumab were considered in this economic analysis.
- Chemotherapy is regarded with fear and immunotherapies are considered much more positively by patients who express a need for more effective and tolerable treatment

options. The economic model includes analysis that incorporate all available immunotherapies (nivolumab and pembrolizumab) as well as chemotherapy.
- Inconvenient treatment scheduling and distant locations of treatment centres can take up valuable time and may result in large financial expenses due to travel.
- Patients and caregivers felt the following need to be addressed by a new treatment: slowing or complete halt of disease progression, reduction of pain, fatigue, cough and shortness of breath, nausea, inability to fight infection, and burning of skin and impact on mood, improvement of appetite and energy, and reduced or eliminated cost burden associated with new treatments. The economic model considered OS, PFS and impacts on quality of life and adverse events.

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 atezolizumab which are relevant to the economic analysis:

- No drug wastage, as atezolizumab is administered as a fixed dose (1200 mg) supplied in 1200 mg vials.
- Testing to determine PD-L1 not necessary as atezolizumab was demonstrated to be effective regardless of PD-L1 expression.
- Nivolumab and pembrolizumab would be the appropriate comparators. Treatments now available in the second line treatment of NSCLC include immunotherapy (nivolumab, pembrolizumab), pemetrexed, docetaxel and oral targeted therapies.
- Additional resources may be required to monitor infusion related reactions and immune related adverse events. However, this would be similar to other immunotherapies.

1.3 Submitted and EGP Reanalysis Estimates

Given that the addition of a new treatment (atezolizumab) to this treatment population would not occur in a setting where only docetaxel is funded, the submitter adopted best practice guidelines to perform a sequential analysis. As outlined in the CADTH Guidelines a "sequential analysis involves calculating the ICER between a less costly comparator and the next most costly comparator, excluding all comparators that are either dominated or subject to extended dominance." This method of analysis compares ICERs relative to a common comparator. All interventions are evaluated first versus the common comparator, and are then evaluated relative to the most cost-effective comparison. In this example, the common comparator is docetaxel, with the interventional therapies comparison pembrolizumab, atezolizumab and nivolumab. The most cost-effective therapy compared to docetaxel subsequently becomes the reference ICER for the sequential analysis. The sequential ICER is then calculated as the incremental costs vs most cost effective therapy.

Table 2. Submitted Estimates Using Sequential Analysis

Interventional therapies	Costs	QALYs	LYs	Incremental cost per QALY	
				vs docetaxel	sequential ICER
Docetaxel	$45,490	0.71	1.17		
Pembrolizumab	$122,859	1.29	1.96	$133,672	$133,672
Atezolizumab	$130,563	1.31	1.99	$142,074	$385,238
Dominated therapies*					
Nivolumab	$134,839	1.28	1.94	$158,875	Dominated*

*nivolumab costs more and is less effective than both pembrolizumab and atezolizumab

Based on the submitted estimates and using a sequential analysis, pembrolizumab is the most cost effective therapy using docetaxel as the common comparator (Table 2) with an ICER of $133,672/QALY. Using pembrolizumab as the most common comparator for subsequent analysis, the ICER for atezolizumab vs. pembrolizumab is $385,238/QALY and nivolumab is dominated.

Table 3. EGP Reanalysis Estimates, atezolizumab sequential analysis

Description	Costs	QALYs	LYs	Incremental cost per QALY**	
				vs docetaxel	sequential ICER
Docetaxel	$45,194	0.66	1.09		
Pembrolizumab	$121,718	1.03	1.57	$206,822	$206,822
Atezolizumab	$126,418	1.04	1.58	$215,028	$644,071
Dominated therapies					
Nivolumab	$130,624	1.02	1.56	$237,306	Dominated***

***NOTE: see Table 21 for baseline submitted results**
****Due to the rounding of values, the numbers may not necessarily add up**
*****nivolumab costs more and is less effective than both pembrolizumab and atezolizumab**

Based on the EGP's re-analysis estimates and using a sequential analysis, pembrolizumab is the most cost effective therapy using docetaxel as the common comparator (Table 3) with an ICER of $206,822/QALY. Using pembrolizumab as the most common comparator for subsequent analysis, the ICER for atezolizumab vs. pembrolizumab is $644,071/QALY and nivolumab is dominated by both pembrolizumab and atezolizumab. In all instances, nivolumab costs more and is less effective. It is notable to point out that the incremental cost and QALY's of each immunotherapy is similar with the largest difference in cost being approximately $9,000 and a maximum difference in QALYs of 0.02. Based on this, any small change in the incremental cost or QALY of any one of the three agents could displace pembrolizumab as the most cost effective agent in the sequential analysis (See Table 5). Notably, the results of the indirect treatment comparison and input from the CGP indicate likely similarity in efficacy between the three agents. Therefore, the cost effectiveness is very sensitive to minor differences in cost between the three agents.

Table 4. Submitted and EGP Estimates for Atezolizumab vs. Relevant Comparisons

Estimates (range/point)	Submitted Atezo vs Doc	EGP Reanalysis Atezo vs Doc	EGP Reanalysis Atezo vs Pembro	EGP Reanalysis Atezo vs Nivolumab
ΔE (LY)	0.82	0.49	0.01	0.02
On treatment	0.45	0.43	0.00	0.00
Off treatment	0.37	0.06	0.01	0.02
ΔE (QALY)	0.60	0.38	0.01	0.02
On treatment	0.32	0.31	0.00	0.00
Off treatment	0.27	0.07	0.01	0.02
ΔC ($)	$85,073	$81,224	$4,700	-$4,206
ICER estimate ($/QALY)	$142,074	$215,028	$644,701	Dominates

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

- Indirect treatment comparison: There were two notable limitations with the indirect treatment comparison provided that informed the health economic model. The submitter was unable to adjust for histology in both nivolumab trials included in the ITS (squamous versus non-squamous). Another limitation, is that the KEYNOTE trial (used to inform

pembrolizumab) restricted by PD-L1 expression (including only patients with ≥1% PD-L1). The OAK trial did not restrict by PD-L1 expression. The submitter concluded that both of these limitations may have produced more conservative estimates. Further, an indirect comparison is unable to account for certain variables that a randomized controlled trial would balance by randomizing patients to groups. Although the economic analysis reports minor differences in QALY's (0.01-0.03 QALY) between the three agents, these incremental differences (at most an addition of 0.3 months or 10 days) are not likely significantly different.

- Cure rate: The submitter assumed that 1% of the patients would be cured by incorporating a cure rate into the parametric modeling of the overall survival curve, as they felt that a proportion of the patients would not die from NSCLC. The CGP stated that there is no long-term data to inform a cure rate in this population (advanced NSCLC). Based on input from the CGP, though a cure rate has been demonstrated with this class of drugs for melanoma, there is no data to inform cure rates in advanced NSCLC. Assuming a cure rate of 1% for atezolizumab, pembrolizumab, and nivolumab lowers the ICER. Due to the lack of data, and clinical plausibility of including this assumption, the EGP explored the removal of the cure rate in the best estimate.
- Treatment duration: The treatment duration for nivolumab and pembrolizumab was assumed to follow that of atezolizumab, as treatment duration data was not available to incorporate into the economic model. Though this assumption may be reasonable, treatment duration may vary between drugs in clinical practice. For example, patients may stay on pembrolizumab for up to three years. The EGP was unable to modify treatment duration directly in the model. It should be noted that treatment duration is a cost-driver in this economic model.
- Subsequent therapies: It was necessary to use adjusted cross-over data in order to minimize the risk of bias in the ITC (there was minimal cross-over in trials with nivolumab and pembrolizumab vs docetaxel), thus the same mix of subsequent therapies was applied to all treatments in the models, resulting in similar subsequent therapy costs. However, costs of subsequent therapies was not a cost-drive in the model, therefore, this had minimal impact on the ICER.

1.4 Detailed Highlights of the EGP Reanalysis

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

- Time horizon: The EGP reduced the time horizon from 10 years to 5 years based on input from the CGP and previous reviews. The CGP felt that 5 years was more clinically reasonable, given the clinical course of the patient population. Further, previous CADTH-pCODR reviews for this population used a time horizon of 5 years.
- OS parametric extrapolation: In the submitted base case, the submitter chose to model overall survival using a cure log-logistic parametric extrapolation. This method assumes that a proportion of the patients long term (base case: 1%) would be cured and have a probability of death similar to the general population (ie not be susceptible to death from NSCLC). In discussion with the CGP, though this class of drugs have indicated that a "cure" is possible in other cancer types, this has yet to be demonstrated in NSCLC; there is no long term data to support this assumption. The EGP elected to use the log-logistic curve, with no cure assumption, in their re-analysis.

Table 5. Detailed Description of EGP Reanalysis

	Atezo vs docetaxel			Atezo vs pembrolizumab			Atezo vs nivolumab		
	ΔCosts	ΔQALYs	ICER	ΔCosts	ΔQALYs	ICER	ΔCosts	ΔQALYs	ICER
Base case	$85,073	0.60	$142,074	$7,704	0.02	$385,238	-$4,275	0.04	Dominates
5-year time horizon	$80,809	0.40	$203,186	$4,659	0.01	$596,624	-$4,233	0.02	Dominates
OS parametric extrapolation - use log-logistic	$85,410	0.54	$159,387	$7,748	0.01	$546,562	-$4,239	0.03	Dominates
Best case estimate of above two parameters	$81,224	0.38	$215,028	$4,700	0.01	$644,071	-$4,206	0.02	Dominates

1.5 Evaluation of Submitted Budget Impact Analysis

In the reference scenario, the 3 year budget impact results in cost saving. The factors that most influence the budget impact analysis include:

- Patient weight: decreasing the patient weight to 64.25 kg from 71.39 kg increases the total 3-year budget impact. Increasing the patient weight to 78.53 kg decreases the total 3-year budget impact further making it more cost saving.
- Wastage: decreasing total wastage increases the total 3-year budget impact.

The key limitation of the 3-year budget impact model is that it is limited to the population of Ontario. Although the EGP was unable to consider the BIA for the Canadian population as a whole, the model allowed separate scenarios for each province.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for atezolizumab when compared to docetaxel is:

- $215,028/QALY
- The extra cost of atezolizumab is $81,224.
- The extra clinical effect of atezolizumab is 0.38 (ΔE).

The results of the indirect treatment comparison in addition to the input from the CGP indicate likely similarity in efficacy between the atezolizumab, pembrolizumab and nivolumab. Further, the extrapolated results from the economic model predict very minor differences in QALY's between the three agents (0.01-0.02 QALYs) over a 5-year time horizon. Due to the relatively small changes in magnitude for incremental costs and QALYs, the changes in the ICER become substantial. Therefore, the cost effectiveness between the three immunotherapies' is very sensitive to minor differences in cost and QALY's. Plausible changes to inputs in the economic model can dramatically change the cost effectiveness of one agent relative to another.

The EGP's best estimate of ΔC and ΔE for atezolizumab when compared to pembrolizumab is:

- $644,701$/QALY
- The extra cost of atezolizumab is $4,700.
- The extra clinical effect of atezolizumab is 0.01 (ΔE).

In all circumstances, atezolizumab dominates nivolumab (nivolumab is more costly and less effective). This is however very sensitive to small changes in cost or QALY's.

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 atezolizumab (Tecentriq) for NSCLC. A full assessment of the clinical evidence of atezolizumab (Tecentriq) 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 non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

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.

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