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pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Nivolumab (Opdivo) for classical Hodgkin Lymphoma

May 3, 2018

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by Bristol-Myers Squibb Canada** compared nivolumab to (1) brentuximab vedotin (BV) for patients who failed to achieve a response or progressed after autologous stem cell transplant (ASCT) or (2) active treatment (mix of chemotherapies) for patients who failed to achieve a response or progressed after ASCT and BV in patients with relapsed/refractory classical Hodgkin lymphoma (cHL).

These comparisons were assessed through two economic models:

- Decision problem 1: this economic model compared nivolumab to BV in the submitted base case. The population is based on patients in cohort A from the Checkmate 205 trial,[1,2,3] who failed to achieve a response or progressed after ASCT and are BV naïve.
- Decision problem 2: this economic model compared nivolumab to active treatment in the submitted base case. The population is based on patients in cohort B from the Checkmate 205 trial,[1,2,3] who failed to achieve a response or progressed after ASCT and subsequent BV.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	*The two target populations as defined above are based on the inclusion/exclusion criteria of Cohort A (Decision problem 1) and Cohort B (Decision problem 2) within the Checkmate 205 study.*
Type of Analysis	*CUA & CEA*
Type of Model	*A three health-state (pre-progression, post-progression, and death) partitioned-survival model*
Comparator	*Decision problem 1: brentuximab vedotin (BV)* *Decision problem 2: active treatment (mix of chemotherapies* based on estimated frequency of usage). *Currently there is no standard of care in this setting.*
Year of costs	*2017*
Time Horizon	*15 years*
Perspective	*Government (public payer perspective)*
Cost of Nivolumab*	*Nivolumab costs $782.22 for 40 mg vial and $1,955.56 for 100 mg vial, or $19.556 per mg* *At the recommended dose of 3 mg/kg every two weeks, nivolumab costs:* • *$293.34 per day* • *$8,213.35 per 28-day cycle* *Calculations assume no wastage*
Cost of brentuximab vedotin (BV)*	*BV costs $4,840 per 50mg vial*

	At the recommended dose of 1.8 mg/kg intravenously, every 3 weeks, brentuximab vedotin costs: • *$691.43 per day* • *$19,360 per 28-day cycle* *Total of 126 mg used (3 vials) once per 21-day cycle for average body weight of 70 kg*
Cost of active treatment Active treatment was a weighted average of approximately 30 chemotherapy regimens and agents based on frequency of usage.	*As per submitter the combination of chemotherapies produced an average weighted cost of $3,095.00 per 28-day model cycle.* *The three single chemotherapy agents out of the submitted combination of chemotherapies with the highest frequency of usage were selected to provide cost estimates (everolimus with frequency of 11%, gemcitabine with frequency of 12%; and lenalidomide with frequency of 9%).* • *Everolimus* costs $201.25 per tablet (10 mg).* *At the dose of 10mg per day, everolimus costs:* *o $201.25 per day* *o $ 5,635 per 28-day cycle* • *Gemcitabine* costs $270.00 per 1000 mg vial* *At the dose of 1000mg/m2; two times (days 1 and 8) in a 21 day cycle, gemcitabine costs:* *o $43.71 per day* *o $1,223.88 per 28-day course* *Calculations based on BSA of 1.7m2 or weight of 70kg* • *Lenalidomide* costs $424.00 per capsule (25 mg)* *At the dose of 25 mg daily of 21 days of repeated 28-day cycles lenalidomide costs:* *o $318.00 per day* *o $ 8,904.00 per 28-day course*
Model Structure	*A partitioned survival model with three discrete health states was developed to evaluate the cost-utility of nivolumab in patients with cHL. The 3 health state were: pre-progression, post-progression, and death. State occupancies were estimated using parametric survival models. Given the parameter uncertainty surrounding long-term survival, the submitted base case used a probabilistic analysis approach with the probabilistic mean presented as the main results.*

Key Data Sources	*Checkmate-205[1,2,3]: an ongoing multicentre, non-comparative, multicohort, single-arm phase 2 study*
** 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 August 15, 2017. All calculations are based on 70kg and BSA = 1.7m^2*	

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), these comparisons are appropriate.

Relevant issues identified included:

Decision problem 1: Patients who have relapsed or progressed after ASCT and are BV-naïve; Cohort A

- There is not a net clinical benefit to nivolumab compared with BV.
- Magnitude of effect of nivolumab compared with BV cannot be determined, given lack of comparative data and long-term outcomes.
- Indirect treatment comparisons are inherently subject to bias, especially due to lack of comparative evidence in this setting and insufficient follow-up data for nivolumab.
- Patients in this setting have currently the option to receive BV.
- However, the CGP agreed that the results of cohort A strongly suggest that Nivolumab is a very reasonable treatment option for those patients who have relapsed after ASCT and are not appropriate candidates to receive BV due to severe peripheral neuropathy.

Decision problem 2: Patients who have relapsed or progressed after ASCT followed by BV; Cohort B

- There is a net clinical benefit to Nivolumab compared with chemotherapy.
- Notwithstanding the absence of randomized phase III data, results suggest greater clinical benefit than what would be expected from standard chemotherapy regimens in this setting.
- Nivolumab has a favourable toxicity profile compared to chemotherapy.
- Clinically meaningful overall response rate and encouraging early PFS.
- High unmet need for more effective treatment options.
- The data supporting this conclusion are from non-randomized studies. Indirect treatment comparison are inherently subject to bias and make these comparisons difficult to interpret. Hence there is no reliable estimate of the comparative efficacy or effectiveness of nivolumab to chemotherapy. However, since equipoise between nivolumab and a palliative chemotherapy agent does not exist it is unlikely that a randomized controlled trial would be conducted in the setting.

Decision problem 2, Scenario analysis: Patients who had BV before ASCT, after ASCT or before and after ASCT; Cohort C

- There may be a net clinical benefit to nivolumab compared with chemotherapy.
- Insufficient evidence to support assumption that treatment effect of nivolumab is the same in all three subgroups of cohort C.
- Treatment options may vary across different patient subgroups within cohort C. Patients who responded to BV + salvage chemotherapy and then an ASCT may be retreated with BV; however, patients who failed on both ASCT and subsequent BV will be treated with palliative chemotherapy.

- Proportion of patients in cohort C who received BV before (33%), after (58%) and both before and after ASCT (9%) are not representative of patients in Canadian practice. The CGP estimates that in Canada approximately 95% of patients will receive BV after ASCT.

Summary of registered clinician input relevant to the economic analysis
Registered clinicians indicated that nivolumab fills a gap in treatment for patients who have relapsed disease following stem cell transplant and BV. They noted that nivolumab offers patients hope of long term cure, given the high response rates and remissions. The magnitude of benefits allows patients, who are typically 20 to 30 years old, to return to work and enjoy an excellent quality of life. The side effects are manageable. Both progression-free survival and adverse events were incorporated into the model.

Summary of patient input relevant to the economic analysis
Patients value a treatment option that offers disease control and remission and has manageable side effects. Patients with experience with nivolumab noted that it positively impacted their quality of life and reported few side effects. Both quality of life and adverse events were incorporated into the 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 nivolumab which are relevant to the economic analysis:

Enablers

- New treatment option that fills unmet need for relapsed or refractory classical Hodgkin Lymphoma who have failed ASCT
- Administered in an outpatient chemotherapy centre

Barriers

- As nivolumab is an intravenous therapy, additional resources would be required to prepare and administer nivolumab. Nivolumab is administered every two weeks whereas both pembrolizumab and BV are administered every three weeks.
- High cost drug
- Nivolumab requires monitoring of immune-mediated reactions post-infusion. Hence, smaller outpatient cancer centres may not have the expertise and resources to administer nivolumab.
- There is potential for drug wastage with the weight based dose. However, this would be minimized with the two different vial sizes and with vial sharing, given that nivolumab is currently used for many other indications. A dose cap of 240 mg would avoid drug waste for all patients 80 kg and over.

Other

- PAG is also seeking information on the appropriateness of using cost saving dosing strategies of 3mg/kg up to a dose cap of 240mg every two weeks and 6mg/kg up to a dose cap of 480mg every four weeks. Nivolumab 240mg and 480 mg flat doses are not yet approved on the market in Canada. The CGP noted that the CGP confirmed that while flat dosing is widely used in solid tumours, there is currently insufficient evidence available to recommend using cost saving dosing strategies of 3mg/kg up to a dose cap of 240mg every two weeks and 6mg/kg up to a dose cap of 480mg every four weeks. Scenario analyses with flat doses of 240 mg and 480 mg are included.
- Nivolumab treatment duration is until disease progression. PAG is seeking information on the mean and the range of treatment duration.

1.3 Submitted and EGP Reanalysis Estimates

A. Decision problem 1: post-ASCT, BV naive

Table 2. Submitted and EGP Reanalysis Estimates: nivolumab versus BV, patients who failed on ASCT and are BV naïve (probabilistic model)

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
ΔE (LY)	3.61	2.36	N/A
Pre-progression	-0.98	-0.50	
Post-progression	4.60	2.86	
ΔE (QALY)	3.01	0.51	N/A
Pre-progression	-0.88	-0.37	
Post-progression	3.86	0.85	
Adverse events	-0.01	-0.02	
ΔC ($)	$144,480	$155,140	
ICER estimate ($/QALY)	$48,075	**$304,200**	**N/A**

B. Decision problem 2: post-ASCT followed by BV

Table 3. Submitted and EGP Reanalysis Estimates: nivolumab versus active treatment (mix of chemotherapies)

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
ΔE (LY)	7.61	5.96	N/A
Pre-progression	1.77	1.65	
Post-progression	5.84	4.32	
ΔE (QALY)	6.00	2.42	N/A
Pre-progression	1.49	1.10	
Post-progression	4.50	1.29	
Adverse events	0.01	0.02	
ΔC ($)	$273,020	$256,640	N/A
ICER estimate ($/QALY)	**$45,540**	**$106,230**	

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

- Lack of direct comparative effectiveness estimates: There are no head-to-head clinical trials comparing nivolumab to the comparators included in this review. Due to this lack of comparative effectiveness data, the economic model was informed by naïve indirect treatment comparisons, where differences in populations between included trials were not accounted for. This limits the generalizability of the results and makes it difficult to determine the incremental effectiveness of nivolumab.

- Extrapolation of overall survival using short term data: The median follow-up in the Checkmate 205 trial was relatively short (median follow-up of 19.12 months in cohort A and 22.70 months in cohort B), with insufficient long term follow up (overall survival data are immature).

- Utilities: The CGP identified that the utilities included in the economic model were relatively high. Though the utilities were collected alongside the Checkmate 205 study, they may not be

reflective of all cHL patients, notably the relatively high utilities in the post-progression period. In order to align with previous cHL reviews and other reviews of nivolumab in the cHL population (notably that of the Scottish Medicines Consortium[16]), the EGP elected to use utilities values sourced from the literature[4] (as shown in Table 13).

- Treatment duration of BV: The submitted economic model used a treatment duration of 12 months for BV. The CGP noted that few patients who receive BV complete all cycles of treatment in a 12-month period and that a treatment duration of 9 months seems more appropriate for BV.

1.4 Detailed Highlights of the EGP Reanalysis

A. Decision Problem 1: post-ASCT, BV naive

The EGP made the following changes to the economic model:

- *Time horizon*: 10 years (instead of 15 years in submitted base case). The time horizon was shortened to address the uncertainly in survival estimates based on extrapolation of short-term trial data (median OS was not reached in CHECKMATE-205 with median follow-up of 19.12 months in cohort A and 22.70 months in cohort B) and the lack of incorporation of subsequent treatments. Given the lack of data to inform overall survival in patients with multiple relapsed cHL, the CGP and EGP felt it was appropriate to align the time horizon with previous reviews for patients with multiple relapsed cHL.
- *Utilities:* The CGP identified that the utilities included in the economic model were relatively high. Though the utilities were collected alongside the Checkmate 205 study, they may not be reflective of all cHL patients, notably the relatively high utilities in the post progression period. In order to align with previous cHL reviews and other reviews of nivolumab in the cHL population (notably that of the Scottish Medicines Consortium[16]), the EGP elected to use utilities values sourced from the literature [4] (as shown in Table 13).
- *Treatment duration of BV:* The CGP expressed that the median number of BV treatment cycles was not as high as the 12 months included in the economic model, as few patients completed all cycles of treatment in a 12 month period. The CGP expressed that the median treatment duration was more likely between 6 – 7 months (8 – 9 treatment cycles). The EGP and CGP agreed to use 9 months as a treatment duration for BV as a conservative estimate.
- *Comparative effectiveness:* There was no comparative effectiveness data available for nivolumab versus BV. The data to inform this economic model was taken from a naïve indirect comparison where adjustments for key baseline factors were not made. As such, the EGP elected to not present an upper bound for their re-analysis to encompass the uncertainty around the magnitude of benefit of nivolumab.
- In the feedback to the initial recommendation, the submitter asked that the recommendation specifically addresses cHL patients who have relapsed or progressed after 3 or more lines of systemic therapy (including ASCT) and who are BV ineligible. The submitter also reiterated that their scenario analysis for this group of patients (i.e., the submitter's scenario analysis of nivolumab vs. chemotherapy for BV ineligible patients) results in a probabilistic ICER of between $60,000 and $65,000/QALY (see section 8.8.6 and 8.8.7 of the PE report). The EGP acknowledges the submitter's feedback, and since the submitter's feedback does not include any comments specific to the EGP's included one-way scenario analysis nor proposes any changes to the original submitted scenario analysis, the EGP confirms no changes are required. The EGP stands by the deterministic one-way scenario analysis of the nivolumab versus chemotherapy comparison, as presented in Table 21 of the EGR.

Table 4. EGP Reanalysis Estimates for Decision Problem 1 (post-ASCT, BV naive; probabilistic model)

Description of Reanalysis	ΔC	ΔE QALYs	ICUR (QALY)	Δ from baseline submitted ICER
Submitted base case	**$144,480**	**3.01**	**$48,080**	**----**
EGP's Reanalysis for the Best Case Estimate				
LOWER BOUND				
Time horizon - 10 years	$117,600	1.97	$59,600	
Utilities source - Swinburn et al.[4]	$144,000	0.70	$205,800	
Treatment duration BV - 9 months	$181,800	2.99	$60,830	
Best case estimate - lower bound	*$155,140*	*0.51*	*$304,200*	
UPPER BOUND				
Not applicable				
Best case estimate - upper bound	*No upper bound given uncertainty of data*			

B. Decision Problem 2: post-ASCT followed by BV

The EGP made the following changes to the economic model:

- *Time horizon*: 10 years (instead of 15 years in submitted base case). The time horizon was shortened to address the uncertainly in survival estimates based on extrapolation of short-term trial data (median OS was not reached in CHECKMATE-205 with median follow-up of 19.12 months in cohort A and 22.70 months in cohort B) and the lack of incorporation of subsequent treatments. Given the lack of data to inform overall survival in patients with multiple relapsed cHL, the CGP and EGP felt it was appropriate to align the time horizon with previous reviews for patients with multiple relapsed cHL.
- *Utilities:* The CGP identified that the utilities included in the economic model were relatively high. Though the utilities were collected alongside the Checkmate 205 study, they may not be reflective of all cHL patients, notably the relatively high utilities in the post-progression period. In order to align with previous cHL reviews and other reviews of nivolumab in the cHL population (notably that of the Scottish Medicines Consortium[16]), the EGP elected to use utility values sourced from the literature [4] (as shown in Table 13).
- *Comparative effectiveness:* There was no comparative effectiveness data available for nivolumab versus active therapy (best standard of care). The data to inform this economic model was taken from a naïve indirect comparison where adjustments for key baseline factors were not made. As such, the EGP elected to not present an upper bound for their re-analysis to encompass the uncertainty around the magnitude of benefit of nivolumab.

Table 5. EGP Reanalysis Estimates for Decision Problem 2 (pts failed on ASCT followed by BV; probabilistic model)

Description of Reanalysis	ΔC	ΔE QALYs	ICUR (QALY)	Δ from baseline submitted ICER
Submitted base case	**$273,020**	**6.00**	**$45,540**	

EGP's Reanalysis for the Best Case Estimate				
LOWER BOUND				
Time horizon 10 years	$256,710	4.72	$54,440	
Utilities source – Swinburn et al.[4]	$271,590	2.02	$134,780	
Best case estimate of above two parameters	*$256,640*	*2.42*	*$106,230*	
UPPER BOUND				
Not applicable				
Best case estimate of above four parameters	*No upper bound given uncertainty of data*			

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis (BIA) for decision problem 1 (post-ASCT, BV naïve) include:

- Market share.
- The change in the number of nivolumab eligible patients.
- Inclusion of administration costs.
- Allowing vial wastage (no vial sharing).
- Inclusion of the costs of treatment post-progression.

The factors that most influence the BIA for decision problem 2 (post-ASCT followed by BV) include:

- The change in the number of nivolumab eligible patients.
- Inclusion of administration costs.
- Inclusion of the costs of treatment post-progression.
- Allowing vial wastage (no vial sharing).

Key limitations of the BIA model include incorrect assumption on market share of nivolumab in the treatment-funded scenario for decision problem 1. The CGP noted that clinicians are not likely to use nivolumab in place of BV. This parameter was explored by the EGP.

1.6 Conclusions

Decision problem 1 (post-ASCT, BV naïve)

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

- Between $304,200/QALY and unknown
- The extra cost of nivolumab is between $155,140 and unknown. *The main factors that influence ΔC are the assessment of PFS outcomes for nivolumab (independent versus investigator assessment), the population under consideration (naïve indirect comparison versus matched adjusted indirect comparison) and the comparator (BV vs other active therapy).*

- The extra clinical effect of nivolumab is between 0.51 QALYs and unknown. *The main factors that influence ΔE include the time horizon (15 years versus shorter), the parametric curve used to extrapolate overall survival and the source of utilities (Checkmate 205[1,2,3] versus Swinburn et la.[4]).*

Decision problem 2 (patients failed on ASCT and BV)

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

- Between $106,320/QALY unknown
- The extra cost of nivolumab is between $256,640 and unknown. *The main factors that influence ΔC are the time horizon (15 years versus shorter), the assessment of PFS outcomes for nivolumab (independent versus investigator assessment) and vial sharing.*
- The extra clinical effect of nivolumab is between 2.42 QALYs and unkown. *The main factors that influence ΔE include the time horizon (15 years versus shorter), the source of survival data for the comparator for PFS (BCCA[6] versus Cheah[7]) and the source of utilities (Checkmate 205[1,2,3] versus Swinburn et al.[4]).*

Overall conclusions of the submitted model:

- *Given the lack of comparative effectiveness estimates and the poor quality of the indirect treatment comparison, it is not possible to place an upper bound on the ICER; it is difficult to have an idea of where the ICER would lie.*
- *Though there is consensus from the CGP that there is net clinical benefit to nivolumab compared with chemotherapy in patients who have relapsed or progressed after ASCT followed by BV it is not possible to determine the upper bound of the magnitude of this benefit given the available data*

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 Lymphoma 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 nivolumab for classical Hodgkin lymphoma. A full assessment of the clinical evidence of nivolumab for classical Hodgkin lymphoma 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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