CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Avelumab (Bavencio) for metastatic Merkel Cell Carcinoma

March 21, 2018

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1 ECONOMIC GUIDANCE IN BRIEF

The economic analysis submitted to pCODR by EMD-Sereno and Pfizer compared avelumab to chemotherapy and best supportive care in adult patients with previously treated metastatic Merkel cell carcinoma.

Table 1. Submitted Economic Model	
The funding request for avelumab is for the treatment of metastatic Merkel cell carcinoma (mMCC) in previously treated adults	The model was based on part A of the JAVELIN Merkel 200 trial. This was a single arm trial which evaluated patients with metastasic Merkel cell carcinoma (mMCC) who were previously treated with chemotherapy. The model also used data from two observational studies (US2L and EU2L) that evaluated outcomes after chemotherapy used in previously treated mMCC patients.
Type of Analysis	Cost Utility Analysis
Type of Model	3 health state partitioned survival model
Comparator	1) Chemotherapy 2) Best Supportive Care
Year of costs	*2017*
Time Horizon	*15 years*
Annual Discount Rate	*1.5%*
Perspective	*Government Payer*
Cost of avelumab	Avelumab costs $1,325.00 per 200mg vial. At the recommended dose of 10mg/kg day 1 every 2 weeks, the cost of avelumab is $401.85 per day and $11,251.90 per 28-day course. *As per submitted model, assumes 4.246 vials per treatment which was derived using patient weight data from European patients from Merkel JAVELN 200 trial (average 78.5 kg). Drug wastage was assumed.
Cost of chemotherapy *Accessed IMS Brogan on December 5, 2017 and using BSA of 1.7m^2	Based on expert opinion, model assumes 90% CAV and 10% topotecan utilization. **CAV** Cyclophosphamide costs $0.05 per mg. At the recommended dose of 1000mg/m^2 IV on day 1 every three weeks, the cost of cyclophosphamide is $4.21 per day and $118.00 per 28-day course. Doxorubicin costs $5.60 per mg. At the recommended dose of 50mg/m^2 IV on day 1 every three weeks, the cost of doxorubicin is $22.68 per day and $635.10 per 28-day course. Vincristine costs $31.00 per mg. At the recommended dose of 1.2mg/m^2 IV on day 1 every three weeks, the cost of vincristine is $3.01 per day and $84.32 per 28-day course. The total cost for CAV is $29.91 per day and $837.42 per 28-day course. **TOPOTECAN** Topotecan costs $35.44 per mg. At the recommended dose of 1.5 mg/m^2 IV on days 1 to 5 every three weeks, the cost of topotecan is $21.52 per day and $602.44 per 28-day course. **CISPLATIN/CARBOPLATIN + ETOPOSIDE** Cisplatin costs $2.70 mg. At the recommended dose of 25 mg/m^2 IV on days 1 to 3 every three weeks, the cost of cisplatin is $16.39 per day and $459.00 per 28-day course. Carboplatin costs $1.73 per mg.

Table 1. Submitted Economic Model	
	At the recommended dose of AUC 5 IV days 1 every 21 days x 4 to 6 cycles, the cost of carboplatin is $10.65 per day and $298.08 per 28-day course. Etoposide costs $0.75 mg. At the recommended dose of 100 mg/m^2 IV on days 1 to 3, every 21 days x 4 to 6 cycles, the cost of etoposide is $18.21 per day and $510.00 per 28-day course. The total cost for cisplatin-etoposide is $29.91 per day and $837.42 per 28-day course. The total cost for carboplatin-etoposide is $28.86 per day and $808.08 per 28-day course.
Cost of best supportive care	Zero treatment costs for best supportive care
Model Structure	The model was comprised of 3 health states: 1) Progression free; 2) Progressed disease; 3) Dead The following determine the proportion of patient that are in each of the health states every cycle: • Overall Survival • Progression Free Survival
Key Data Sources	<u>JAVELIN Merkel 200 trial:</u> a single arm trial which evaluated avelumab in previously treated adult patients with metastasic Merkel cell carcinoma: • Overall survival for avelumab • Progression free survival for avelumab • Time on treatment for avelumab • Pre progression and post progression utility values • Adverse event rates for avelumab • Mean vials per administration for avelumab <u>US2L and EU2L:</u> single arm observational studies that evaluated chemotherapy treatment in adult patients with metastatic Merkel Cell carcinoma previously treated with chemotherapy • Overall survival for chemotherapy and best supportive care* • Progression free survival for chemotherapy and best supportive care* <u>Various published literature and expert opinion:</u> • Adverse event rates for chemotherapy • Costs of adverse events • Utility decrements for adverse events • Time on treatment for chemotherapy *Due to lack of evidence it was assumed that overall survival and progression free survival for best supportive care were equal to overall survival and progression free survival for chemotherapy

1.1 Submitted and EGP Reanalysis Estimates

1.2 Clinical considerations

According to the pCODR Clinical Guidance Panel (CGP), avelumab demonstrated a net overall clinical benefit in the treatment of patients with incurable metastatic Merkel cell carcinoma of the skin who have previously received first-line chemotherapy. Relevant issues identified included:

- A durable objective tumor response rate clearly superior to second-line chemotherapy was demonstrated in one high-quality uncontrolled trial.
- The CGP concluded that the assessment of overall survival was limited by absence of a control therapy group but appeared improved with avelumab compared to the literature.

Summary of patient input relevant to the economic analysis

- Patients indicated that the side effects of avelumab were manageable and patients were able to have a high quality of life. This is addressed in the economic evaluation as the quality of life impact of adverse events were incorporated in the analysis.
- Patients indicated that mMCC had a negative impact on their ability to work. The economic model does not address this as the analysis was undertaken from the perspective of a publicly funded health care system.

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 aveluamb, which are relevant to the economic analysis:

- PAG noted that the every two week administration schedule may be a barrier to implementation. *The economic evaluation does not address this.*
- PAG noted that treatment with avelumab can be continued as long as clinical benefit is observed or until unacceptable toxicity. The unknown or indefinite treatment duration could be a barrier to implementation and PAG is seeking clarity on treatment discontinuation. *The economic model takes the impact of duration of treatment into account in the calculation of avelumab drug acquisition costs. The time on treatment is based on statistical modelling of what was observed in the JAVELIN Merkel 200 trial for 2 years and expert opinion beyond 2 years.*
- PAG has concerns for incremental costs due to drug wastage, since vial sharing would likely not be possible with the very small number of patients. Dose is based on weight and only one vial size of 200mg will be available. For a 70kg patient, the 10mg/kg dose would be 700mg which requires four vials to be used and any unused portion would be discarded, if vial sharing cannot occur. *The economic evaluation does assume drug wastage in the calculation of drug acquisition costs. The average number of vials used per patient used in the model was based on the average number of vials of avelumab that would be used per administration for European JAVELIN Merkel 200 patients based on their weight.*
- PAG noted that there may be a minimal increase in pharmacy preparation time to prepare the dose due to the number of vials, although this is comparable to preparing cisplatin with etoposide. *This is not addressed in the economic evaluation.*
- PAG noted that additional chemotherapy chair time would be required to administer the pre-medications and to monitor for infusion related reactions. *This is not addressed in the economic evaluation.*
- PAG noted that avelumab is administered every two weeks compared to platinum

based chemotherapy at every three weeks. *This is partially addressed in the economic evaluation. Administration costs are included in the economic model. Administration costs of $162 are applied every two weeks for avelumab. Administration costs of $61.50 are applied every week for chemotherapy. The submitter stated that administration costs are applied every week for chemotherapy due to variation in chemo regimens.*

- Avelumab, being an intravenous drug, would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of toxicities. Intravenous chemotherapy drugs would be fully funded (i.e. no co-payments for patients) in all jurisdictions for eligible patients, which is an enabler for patients. *This issue is not addressed in the economic evaluation.*
- As avelumab is a high cost drug and requires monitoring of immune-mediated reactions post-infusion, PAG noted that smaller outpatient cancer centres may not have the expertise and resources to administer avelumab or treat serious adverse events. This is a barrier for those patients who will need to travel to larger cancer centres that have the resources and expertise to administer avelumab. *This issue is not addressed in the economic evaluation.*

1.3 Submitted and EGP Reanalysis results

The main cost drivers of the Submitter's model were drug acquisition costs and time to when treatment was discontinued (time to off treatment). Other contributors to costs were supportive care costs and adverse event costs.

The main drivers of the clinical outcomes of the model (QALYs, Life Years) were overall survival estimates, the time horizon of the model, progression free survival estimates and utility values. Overall the approach taken in the economic evaluation was reasonable and appropriate.

Table 2: Avelumab vs. Chemotherapy submitted and EGP re-analysis

Estimates (range/point)	Submitted	EGP Reanalysis	
		Lower estimate of cost-effectiveness	Upper estimate of cost-effectiveness
ΔE (LY)	2.55	1.45	1.33
Progression-free	1.81	0.97	0.92
Post-progression	0.74	0.48	0.41
ΔE (QALY)	1.95	1.16	1.13
Progression-free	1.43	0.81	0.78
Post-progression	0.52	0.35	0.30
ΔC ($)	$111,214	$97,282	$126,533
ICER estimate ($/QALY)	$57,051	$84,155	$97,962

Table 3: Avelumab vs. Best Supportive Care submitted and EGP re-analysis

Estimates (range/point)	Submitted	EGP Reanalysis	
		Lower Estimate of cost-effectiveness	Upper Estimate of cost-effectiveness
ΔE (LY)	2.55	1.45	1.33
Progression-free	1.81	0.97	0.92
Post-progression	0.74	0.48	0.41
ΔE (QALY)	1.91	1.13	1.04
Progression-free	1.39	0.78	0.74
Post-progression	0.52	0.35	0.30
ΔC ($)	$123,174	$119,845	$126,533
ICER estimate ($/QALY)	$64,520	$105,838	$121,971

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

- Overall survival and progression free survival: Direct comparative evidence was not used to estimate and project overall survival or progression free between avelumab and its comparators (chemotherapy, best supportive care). Instead, indirect evidence from various sources was used to project OS and PFS. Overall survival and progression free survival projections are a big driver when estimating relative QALYs and cost-effectiveness between comparative treatments.

- Time Horizon: The submitted model uses a 15 year time horizon. Overall and progression free survival estimates are limited to approximately 1 years' worth of data for avelumab and for chemotherapy. Of note, during the review, 24 months of follow-up clinical data from JAVELIN Merkel 200 were available. The Submitter stated that they did not include the 24-month data in their economic model because "1) the updated 24-month clinical data is consistent with extrapolated 12-month data input from the submitted PE model, and with the 18-month results that we described as part of the Clinical Summary included in the Alliance's Avelumab mMCC submission; 2) it was cross-functionally confirmed that the variance between data sets would not significantly change the economic outcomes of the PE model. We offered to present this lengthier follow-up data set in case it would benefit the pCODR review, but in reality this data only further confirms already robust clinical outcomes; 3) the timing involved in updating the PE model with the 24-month data cannot be confirmed, therefore risking undefined delays that could hinder mMCC patients from accessing their treatment, while there is no other effective treatment option reimbursed for those patients in Canada; and 4) there are already 16 SAP patients on avelumab, attesting to the concrete unmet need for an effective treatment accessible to all mMCC patients, which is also why pCODR granted the EMD Serono-Pfizer Alliance priority review. The treatment is approved, and both physicians and patients are anxious to access it as a reimbursed treatment option."[1] Using such a long time horizon can lead to erroneous predictions of long term overall survival and progression free survival based on extrapolation of trial data with limited follow-up. While the updated CADTH guideline recommends that "the time horizon of the analysis should be conceptually driven, based on the natural history of the condition or anticipated impact of the intervention (Page 31)", the guidelines also state that, in cases where that extrapolation is required to estimate long-term effect, external data sources, biology or clinical expert judgement

may be used to justify the plausibility of extrapolation (Page 43).[2] The CGP suggested using a 5 year time horizon because it was more clinically plausible in this patient population.

- Chemotherapy regimens evaluated: The submitter assumed that 90% of patients receiving second-line chemotherapy would receive the CAV regimen while the remaining 10% would receive topotecan. However, the CGP did not think that these regimens are commonly used for 2nd line chemotherapy in this population in Canada. The CGP suggested it would be more appropriate to assume that chemotherapy would be comprised of 50% cisplatin-etoposide and 50% carboplatin-etoposide.

- Statistical model used to extrapolate overall survival for avelumab: For avelumab overall survival, only spline models were considered because the parametric models failed to fully realise the long term survival estimates produced for PFS. This does not seem to be a valid reason to not use parametric models as candidates given that OS generally has a bigger impact on cost-effectiveness than PFS. The specific model chosen to project overall survival can have a big impact on incremental QALYS and incremental cost per QALY.

- Avelumab dosing: The model used individual weight data from European JAVELIN 200 patients to estimate the average number of vials of avelumab used per treatment. However OS, PFS, and time on treatment data were based on all JAVELIN patients, not just European patients. Though some justification is given by the submitter, including only European patient data for this calculation is somewhat selective. The average number of vials of avelumab per treatment would be higher if weight data from all JAVELIN patients were used in the estimate.

1.4 Detailed Highlights of the EGP Reanalysis

- Time Horizon: In the EGP reanalysis, a time horizon of 5 years was used.
- Statistical model used to extrapolate overall survival for avelumab: The log-normal model had the best statistical fit amongst the parametric statistical models used to estimate overall survival for avelumab, In the EGP re-analysis, the model was run with the log-normal statistical model.
- Chemotherapy regimens evaluated: In the EGP reanalysis, it assumed that chemotherapy is comprised of 50% cisplatin-etoposide and 50% carboplatin-etoposide.
- Avelumab dosing: In the EGP re-analysis the number of avelumab vials used per treatment was based on all JAVELIN patients instead of only European JAVELIN patients.

Table 4: Avelumab vs. Chemotherapy detailed EGP re-analysis

Description of Reanalysis	Incremental Costs	Incremental QALYs	Incremental $/QALY	Change in $/QALY from base case
1. Submitter's Base case	$111,214	1.95	$57,051	--
2. Change time horizon from 15 years to 5 years	$108,103	1.17	$92,238	$35,188
3. Change chemotherapy regimens to 50% cisplatin-etoposide and 50% carboplatin-etoposide	$100,156	1.92	$52,179	($4,872)

Description of Reanalysis	Incremental Costs	Incremental QALYs	Incremental $/QALY	Change in $/QALY from base case
4. Use parametric log-normal model for avelumab overall survival	$111,054	1.50	$74,068	$17,017
5. Base average avelumab vials per treatment on all JAVELIN Merkel Trial patients instead of only European patients	$117,142	1.96	$59,806	$2,756
Lower estimate of cost effectiveness (includes changes in 2 and 3)	$97,282	1.16	$84,155	$27,104
Upper estimate of cost effectiveness (includes changes in 2,3,4, and 5)	$103,956	1.06	$97,962	$40,911

Table 5: Avelumab vs. Best Supportive Care detailed EGP re-analysis

Description of Reanalysis	Incremental Costs	Incremental QALYs	Incremental $/QALY	Change in $/QALY from base case
1. Submitter's Base case	$123,173	1.91	$64,520	--
2. Change time horizon from 15 years to 5 years	$120,036	1.13	$106,128	$41,608
3. Change chemotherapy regimens to 50% cisplatin-etoposide and 50% carboplatin-etoposide	$123,174	1.91	$64,520	$0
4. Use parametric log-normal model for avelumab overall survival	$123,005	1.46	$84,314	$19,794
5. Base average avelumab vials per treatment on all JAVELIN Merkel Trial patients instead of only European patients	$129,086	1.92	$67,313	$2,794
Lower estimate of cost effectiveness (includes changes in 2 and 3)	**$119,845**	**1.13**	**$105,838**	**$41,318**
Upper estimate of cost effectiveness (includes changes in 2,3,4, and 5)	**$126,533**	**1.04**	**$121,971**	**$57,450**

1.5 Evaluation of Submitted Budget Impact Analysis

The overall approach of the BIA appears to be reasonable and appropriate. The BIA includes the budget impact on both first and second line treatment even though the funding request is only for patients that have failed on previous treatment. It is unusual to include the increased costs of previous lines of treatment in BIA estimates. The EGP ran several sensitivity analyses on the BIA. The CGP felt that the incidence rates of stage IV mMCC used in the model appeared high, the EGP ran sensitivity analyses reducing the incidence rate which reduced the budget impact. The EGP ran a sensitivity analysis in which only the cost of 2nd line treatment was included. This also reduced the budget impact. In the submitted BIA, it was assumed 4 vials of avelumab would be given per infusion while the cost-utility analysis estimated an average of 4.26 vials using patient weight data from European patients from the JAVELIN trial and 4.46 when using all patients in the JAVELIN trial. Using an increased number of vials of avelumab increased the budget impact.

1.6 Conclusions

The EGP's best estimate of incremental cost per QALY, ΔC and ΔE for avelumab when compared to chemotherapy is:

- The cost per QALY is between $84,155/QALY and $97,962/QALY
- The extra cost of avelumab is between $97,282 and $103,956. Incremental costs were most impacted by drug acquisition costs.
- The extra clinical effect of avelumab is between 1.06 to 1.16 QALYs. Incremental QALYs were most impacted by overall survival estimates and time horizon.

The EGP's best estimate of incremental cost per QALY, ΔC and ΔE for avelumab when compared to best supportive care is:

- The cost per QALY is between $105,838/QALY and $121,971/QALY
- The extra cost of avelumab is between $119,845 and $126,533. Incremental costs were most impacted by drug acquisition costs.
- The extra clinical effect of avelumab is between 1.04 to 1.13 QALYs. Incremental QALYs were most impacted by overall survival estimates and time horizon.

Overall conclusions of the submitted model:
The overall structure of the economic model appears to be appropriate. A key limitation of the economic evaluation is the lack of comparative evidence for key model inputs such as overall survival and progression free survival. The CGP noted the lack of a control group as a limitation in the assessment of the overall survival benefit of avelumab. Though they did note that overall survival did appear to be better for avelumab compared to chemotherapy based on other literature. Other limitations in the evaluation included the statistical model chosen to project avelumab overall survival, the dosing assumptions for avelumab, and the use of a 15 year time horizon.

2 DETAILED TECHNICAL REPORT

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.

3 ABOUT THIS DOCUMENT

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.

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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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