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:
Avelumab (Bavencio)

Submitted Funding Request:
For the treatment of mMCC in previously treated adults

Submitted by:
EMD Serono - Pfizer Alliance

Manufactured by:
EMD Serono - Pfizer Alliance

NOC Date:
December 18, 2017

Submission Date:
October 10, 2017

Initial Recommendation Issued:
March 2, 2018

Approximate Per-Patient Drug Costs, per Month (28 Days)	Avelumab Regimen Costs:
Submitted list price of $1,325.00 per 200 mg vial Note: Costs are calculated based on an average weight of 70 kg and body surface area of 1.7 m^2	$9,275.00 per 28-day course

pERC RECOMMENDATION

pERC conditionally recommends the reimbursement of avelumab (Bavencio) for the treatment of metastatic Merkel cell carcinoma (mMCC) in previously treated adults who have had prior cytotoxic chemotherapy, only if the following condition is met:

- cost-effectiveness being improved to an acceptable level.

If the aforementioned condition cannot be met, pERC does not recommend the drug's reimbursement. Funding should be for patients with a good performance status. Treatment should continue until confirmed disease progression or unacceptable toxicity. For patients who achieve a complete response (CR), treatment should continue for a maximum of 12 months after confirmation of CR.

pERC made this recommendation because it was satisfied that there is a net clinical benefit of avelumab based on an unmet need for effective treatment for this uncommon cancer, clinically meaningful and durable objective response rates, a manageable toxicity profile, and no deterioration in quality of life (QoL). pERC also concluded that avelumab aligns with patient values as it is a treatment option that provides disease control with fewer side effects than currently available therapies.

	However, pERC could not conclude that avelumab is cost-effective because of a lack of robust direct or indirect comparative effectiveness data in the submitted economic evaluation.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Collecting Evidence to Reduce Uncertainty in the Magnitude of Clinical Benefit and the Cost-Effectiveness of Avelumab** Given the uncertainty in the magnitude of clinical benefit of avelumab for the treatment of mMCC in previously treated adults, pERC concluded that additional prospective evidence should be collected to decrease the uncertainty in the incremental effect and provide a greater understanding of the true cost-effectiveness of avelumab. Specific information on long-term efficacy, safety, and QoL would be of particular value. **Pricing Arrangements to Improve Cost-Effectiveness** Given that avelumab has a net overall clinical benefit compared with chemotherapy, jurisdictions may want to consider alternate pricing arrangements and/or cost structures to improve the cost-effectiveness and affordability of avelumab to an acceptable level. **Factors Affecting Budget Impact and Adoption Feasibility** pERC noted that the budget impact of avelumab increased when the average number of vials of avelumab was increased to align with the cost-utility analysis and a large market share expected for the avelumab indication. pERC noted the potential for drug wastage since the dose is based on weight and only one vial size of 200 mg is available. Vial sharing would likely not be possible given the very small number of patients. **Unknown Treatment Duration** Treatment with avelumab is indicated until disease progression or unacceptable toxicity, or for a maximum of 12 months after confirmation of CR. Treatment beyond 12 months in patients with a confirmed CR was allowed on the basis of investigator assessment of potential benefit. Confirmation of progressive disease by radiological assessment was required, preferably six weeks (but no later) after a diagnosis of progression per standard Response Evaluation Criteria in Solid Tumours (RECIST). If progression was based on the occurrence of a new lesion in an area not scanned at baseline, a further on-trial scan was done six weeks later. pERC felt that the criteria for treatment with avelumab in JAVELIN Merkel 200 Part A were reasonable. In JAVELIN Merkel 200 Part A, patients who had a confirmed CR and relapsed after stopping treatment were allowed one re-initiation of treatment. Patients were eligible for retreatment if they did not experience any toxicity that led to treatment discontinuation of the initial avelumab therapy and retreatment was until progression. pERC noted that some patients received avelumab after disease progression with the duration of post-progression treatment ranging from 0.03 to greater than 14.3 months. pERC noted that the actual treatment duration with avelumab is unknown, and jurisdictions will need to consider this during implementation of avelumab reimbursement. **Patients with Contraindications to Cytotoxic Chemotherapy** pERC acknowledged that there may be a number of patients who may be ineligible for treatment with cytotoxic chemotherapy (i.e., have contraindications for cytotoxic chemotherapy) and who would not be able to receive first-line chemotherapy, pERC felt that these patients should be eligible for avelumab.

Note: The Provincial Advisory Group (PAG) implementation questions have been addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

Metastatic Merkel cell carcinoma (mMCC) is an aggressive, uncommon skin cancer that is increasing in incidence. Advanced age and immunosuppression are the main risk factors for mMCC, which can complicate the effective delivery of cytotoxic chemotherapy. pERC noted that patients are currently treated with chemotherapy such as cisplatin plus etoposide, carboplatin plus etoposide, etoposide monotherapy, topotecan monotherapy, cyclophosphamide / doxorubicin / vincristine combination, or paclitaxel monotherapy. Although chemotherapy represents the current therapy option, there is no standard of care for the treatment of mMCC in previously treated adults. Furthermore, chemotherapy is associated with significant toxicities, low response rates, and limited survival. pERC noted that the goals of treatment for patients with mMCC are primarily palliative, that is, to prolong life while maintaining or improving QoL. Given the toxicity and limited efficacy associated with available palliative chemotherapy options, pERC concluded that there is a substantial unmet need for alternative options with fewer and more manageable adverse effects than chemotherapy, to reduce disease burden, and prolong survival.

pERC deliberated upon one non-comparative, multi-centre, open-label, phase II trial (JAVELIN Merkel 200 Part A), which evaluated the use of avelumab in patients with stage IV Merkel cell carcinoma who had progressed after cytotoxic chemotherapy. pERC noted that a substantial proportion of patients (33%) experienced an objective response, which is an important and clinically meaningful outcome in mMCC. pERC noted that the observed response rates were higher than historical responses observed with chemotherapy treatments used to treat mMCC. In addition, it was noted that the median duration of response was not reached, which pERC considered indicative of a durable response. However, pERC noted the robustness of the preliminary overall survival (OS) and progression-free survival (PFS) results are limited due to the short follow-up of the study population and the lack of robust comparative data.

pERC also discussed the QoL data reported in the trial. There were no meaningful changes during treatment and pERC considered that there was no deterioration in QoL with avelumab treatment. pERC also reviewed safety evidence for avelumab from JAVELIN Merkel 200 Part A and considered it to be challenging to assess the safety of avelumab compared with relevant therapies due to the absence of comparative data. The most common treatment-related adverse events were fatigue and rash. pERC noted that 19 patients (21.6%) in the trial had an infusion-related reaction, which were all grade 1 or 2 and occurred at the first or second infusion. pERC agreed with the pCODR Clinical Guidance Panel (CGP) that these infusion-related reactions seemed tolerable and manageable. Given that these patients do not have other effective therapeutic options, pERC concluded that avelumab's toxicity profile appeared reasonable and manageable in this setting.

pERC discussed the limitations of non-comparative studies and considered that, although the JAVELIN Merkel 200 Part A trial was appropriately conducted, the conclusions that can be drawn from non-comparative data are not as robust as those that can be drawn from well-conducted randomized controlled trials (RCTs) with direct comparisons to relevant therapies. pERC agreed with the CGP that despite the significant unmet need in this patient population, conducting a RCT in this setting with avelumab compared with palliative chemotherapy would not be feasible given the rarity of MCC. pERC acknowledged that, because of the non-randomized, non-comparative phase II study design, there was considerable uncertainty around the magnitude of benefit with avelumab. Nonetheless, pERC concluded there was a net clinical benefit with avelumab based on the clinically meaningful and durable response rates, a favourable toxicity profile, no deterioration in QoL, and a substantial need for treatment options in this small population of patients who had been previously treated with mMCC.

pERC agreed with registered clinicians that MCC is a very rare cancer and therefore does not have a high incidence or prevalence. pERC acknowledged and agreed with clinician input that indicated that, in this patient population, avelumab had a good response rate; and most patients were still continuing treatment at ten months; and, avelumab had a low risk of immune-related events but was otherwise well tolerated.

Clinician input indicated that avelumab in second-line treatment would be used following chemotherapy and should be strongly considered as first-line. However, pERC noted that avelumab in the first-line setting for patients with mMCC who were not previously treated was outside the scope of the current review. For patients ineligible for chemotherapy (i.e. have contraindications for cytotoxic chemotherapy) and who would not receive first-line chemotherapy, pERC felt that in these instances, they should be eligible for avelumab.

pERC deliberated on the alignment of avelumab with patient values. The Committee reviewed input from two patient groups, Save Your Skin Foundation (SYSF) and Canadian Cancer Survivor Network (CCSN), which highlighted patient and caregiver experiences. pERC appreciated that the patient groups were able to identify patients with experience with avelumab, despite the rarity of the disease. pERC noted that the patient input was very informative in their deliberations for avelumab. Patient input indicated that there are a number of symptoms associated with mMCC that affect QoL including fear of being diagnosed with a rare deadly cancer, scarring and disfigurement, fatigue, depression, anxiety, and weight loss. Patients noted that given MCC is a rare skin cancer with very low survivorship, patients were willing to tolerate all potential adverse side effects from treatment even for short-term benefit. The following side effects were reported with avelumab: fatigue/lack of energy, diarrhea, nausea, rash, and decreased appetite. All patient respondents reported that side effects were manageable and that they were able to have good QoL. Overall, pERC concluded that avelumab aligns with patient values as there is a substantial unmet need for an effective treatment option that provides disease control, maintains QoL, and has an acceptable toxicity profile.

pERC deliberated upon the cost-effectiveness of avelumab and could not conclude that, at the submitted price, it was cost-effective compared with chemotherapy because of the high level of uncertainty in the clinical inputs used in the economic evaluation. In the absence of direct or indirect comparative data, pERC noted that several data sources from the literature — including retrospective observational studies of chemotherapy — and multiple assumptions were used to populate the clinical inputs within the cost-utility analysis. pERC considered estimates provided by the submitter and reanalysis performed by the pCODR Economic Guidance Panel (EGP). The factor that most influenced the incremental cost was the cost of avelumab. The factors that most influenced the incremental effectiveness were survival estimates and time horizon. The EGP noted that although the economic model was appropriate, the key limitation was the lack of comparative evidence for key survival inputs of OS and PFS. pERC considered that due to the limitations of non-randomized evidence from the JAVELIN Merkel 200 Part A study, there was substantial uncertainty in the magnitude of the clinical benefit associated with avelumab. This made it challenging to estimate the incremental effect of treatment with avelumab and, therefore, the resulting incremental cost-effectiveness ratio (ICER). This considerable uncertainty in the magnitude of clinical benefit of avelumab would likely lead to an even wider range of ICER estimates beyond those computed in the submitted model and using the available, but limited, evidence. pERC also considered that the collection of additional prospective data on the clinical benefit of avelumab would reduce the uncertainty around the magnitude of the benefit and the cost-effectiveness estimates. Therefore, due to limitations in the available non-randomized clinical evidence for avelumab and the absence of long-term data on the potential survival benefit gained in this setting, pERC noted that it was challenging to determine the true ICER. pERC concluded that the true ICER is likely higher than estimated in the EGP's reanalysis estimates, and therefore avelumab could not be considered cost-effective compared with available therapies.

pERC considered the feasibility of implementing a funding recommendation for avelumab. The Committee noted that mMCC is an uncommon cancer; therefore, the burden of illness is likely small in terms of the incident population. pERC noted that the budget impact of avelumab increased when the average number of vials of avelumab was increased to align with the cost-utility analysis and a large market share expected for the avelumab indication. pERC acknowledged input from the pCODR Provincial Advisory Group (PAG) of the potential for drug wastage since the dose is based on weight and only one vial size of 200 mg is available and given that vial sharing would likely not be possible with the very small number of patients. pERC also noted that during implementation of avelumab reimbursement, jurisdictions will need to consider resources for monitoring immune-mediated reactions post-infusion.

PAG noted that the trial was for chemotherapy refractory patients and PAG, therefore, was seeking information on whether results of the trial were generalizable to patients who are not chemotherapy refractory or in other lines of therapy. The Committee agreed with the CGP that there was clinical benefit for all patients who had previously received first-line chemotherapy and that results were generalizable to patients if they had received multiple lines of chemotherapy (i.e. at least one line of prior chemotherapy). pERC noted that avelumab in the first-line setting for patients with mMCC that was

not previously treated was outside of the scope of the current review. However, for patients who are ineligible to receive first-line chemotherapy due to contraindications, pERC felt that in these instances patients should be eligible for avelumab. PAG also requested guidance on whether avelumab would be used before platinum-based chemotherapy or whether avelumab would be used after platinum-based chemotherapy. pERC agreed with the CGP that avelumab would be used after platinum-based chemotherapy as platinum-based chemotherapy is used in the first-line setting.

With respect to treatment duration, treatment with avelumab is indicated until disease progression or unacceptable toxicity or for a maximum of 12 months after confirmation of complete response (CR). Treatment beyond 12 months in patients with a confirmed CR was allowed on the basis of investigator assessment of potential benefit. Confirmation of progressive disease by radiological assessment was required, preferably 6 weeks (but no later) after a diagnosis of progression per standard Response Evaluation Criteria in Solid Tumours (RECIST). If progression was based on the occurrence of a new lesion in an area not scanned at baseline, a further on-trial scan six weeks later was done. pERC felt that the criteria for treatment with avelumab in JAVELIN Merkel 200 Part A was reasonable. In JAVELIN Merkel 200 Part A, patients who had a confirmed CR and relapsed after stopping treatment were allowed one re-initiation of treatment. Patients were eligible for retreatment if they did not experience any toxicity that led to treatment discontinuation of the initial avelumab therapy and retreatment was until progression. pERC noted that some patients received avelumab after disease progression with the duration of post-progression treatment ranging from 0.03 to greater than 14.3 months. pERC noted that the actual treatment duration with avelumab is unknown, and jurisdictions will need to consider this during implementation of avelumab reimbursement.

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 groups (Save Your Skin Foundation and Canadian Cancer Survivor Network)
- input from registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of avelumab compared with an appropriate comparator for the treatment of mMCC in previously treated adults.

Studies included: non-randomized, single-arm, open-label, phase II study

The pCODR systematic review included one non-randomized, non-comparative, open-label, phase II trial (JAVELIN Merkel 200 Part A), which evaluated the use of avelumab in patients with stage IV Merkel cell carcinoma that had progressed after cytotoxic chemotherapy (N = 88). Although the study was multi-centre, no Canadian sites were included. Key inclusion criteria required patients to have had received at least one line of chemotherapy for the treatment of mMCC, at least one unidimensional measurable lesion by Response Evaluation Criteria in Solid Tumors version (RECIST) v1.1, progression after the most recent line of chemotherapy, and Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-1. Patients with active or a history of any autoimmune disease or immune-deficiencies that required treatment with a systemic immunosuppressant were excluded. Avelumab was administered at a dose of 10 mg/kg by one-hour intravenous infusion once every two weeks, until confirmed disease progression or unacceptable toxicity. For patients who achieve a complete response (CR), treatment continued for a maximum of 12 months after confirmation of CR. There were four data cut-off dates: six-month minimum follow-up (March 2016); 12-month minimum follow-up (September 2016); 18-month minimum follow-up (March 2017); and 24-month minimum follow-up (data cut-off not reported).

Patient populations: metastatic mMCC, previous platinum-containing chemotherapy

A total of 88 patients were enrolled in JAVELIN Merkel 200 Part A. The majority of patients were male (74%) and had distant metastatic disease at enrolment with a median time since diagnosis of metastatic disease of 10.4 months. All patients had at least one line of systemic anti-cancer treatment with 41% of patients having received two or more previous lines of therapy. Most patients (68%) had received a platinum-containing regimen in their last treatment. Overall, 56% of patients had an ECOG PS of 0 and 44% of patients had an ECOG PS of one. Tumour PD-L1 expression was assessable for 74 patients, of which 58 (79%) were positive at the 1% cut-off and 21.6% were PD-L1 positive at the 5% cut-off. Merkel cell polyomavirus status was assessed by immunohistochemistry and 60% of the 77 patients assessed were MCV-positive. During a median duration of 17 weeks of treatment (interquartile range [IQR] 7-37), patients received a median of seven doses (IQR 3-18) of avelumab. The mean duration of therapy with avelumab was 23 weeks (range: 2.0 to 76.0). While the study protocol specified dose reductions were not permitted, at least one dose reduction within an administration occurred in eight (9%) of 88 patients. At the primary analysis data cut-off, 30 of 49 patients with investigator-determined progressive disease per RECIST 1.One patient had at least one administration of avelumab after their progression date. The duration of post-progression treatment ranged from 0.03 to greater than 14.3 months.

Key efficacy results: Clinically meaningful improvement in overall response rate (ORR), 18-month OS and PFS rates

The key efficacy outcomes deliberated on by pERC included ORR, the primary end point of JAVELIN Merkel 200 Part A. A planned sample size was calculated at 84 subjects, assuming an ORR of 35% for avelumab

with an overall alpha = 0.025 (one-sided) for the test of the null hypothesis of an ORR ≤ 20%. Response was observed in 29 patients with an ORR of 33.0% (95% CI, 23.3 to 43.8) at the March 2017 data cut-off with 18-month minimum follow-up. Among these, 11.4% were CR, 21.6% were partial response, and 10.2% were stable disease. Overall, 32 (36.4%) of patients had progressive disease.

Secondary outcomes deliberated by pERC included progression-free survival (PFS) and overall survival (OS). At the 18-month minimum follow-up (March 2017), the median PFS was 2.7 months and median OS was 12.6 months. The Kaplan-Meier estimates at 18 months reported a PFS rate of 29% and OS rate of 40%.

Patient-reported outcomes: No deterioration in overall quality of life

Patient-reported outcomes were evaluated in JAVELIN Merkel 200 Part A using Functional Assessment of Cancer Therapy — Melanoma (FACT-M) and Trial Outcome Index. As there are no MCC-specific health-related quality of life (HRQoL) instruments, the FACT-M questionnaire was used. Despite some differences between Merkel cell carcinoma and melanoma, including worse prognosis for Merkel cell carcinoma, the content of the FACT-M seems appropriate to assess HRQoL in subjects with Merkel cell carcinoma. A linear mixed model analysis fitted for change from baseline for each scale was conducted and minimal important differences (MID) were used to interpret meaningful changes. A total of 70 patients were analyzed and no meaningful changes were observed from each scale during treatment. Correlations between reduction in tumour size and improvement in FACT-M were moderate and suggested that HRQoL improved as the tumour shrinks. Mean differences in change from baseline scores between non-progressive disease and progressive disease were also in the range of published MIDs for the scales assessed.

Safety: Manageable toxicity, risk of infusion-related reaction

pERC discussed the safety profile of avelumab and noted it to be manageable. Any treatment-related adverse event (AE) was reported in 75% of patients at the March 2017 18-month minimum follow-up data cut-off point. The most common treatment-related AEs were fatigue (25.0%) and rash (15.9%). A total of 19 patients (21.6%) had an infusion-related reaction, which were all grade 1 or 2 and occurred at the first or second infusion. There were a total of eight (9.1%) grade 3 treatment-related AEs and there were no treatment-related deaths. Immune-related adverse events (irAEs) of any grade were reported in 19.3% of patients, the most common were hypothyroidism (5.7%), rash (5.7%), diarrhea (2.3%) and erythema (2.3%). The incidence of irAEs of grade ≥ 3 was 4.5% and there were no grade ≥ 4 irAEs reported.

Comparator information: Cisplatin plus etoposide or carboplatin plus etoposide

According to the pCODR Clinical Guidance Panel (CGP), patients with previously treated mMCC are treated with cisplatin plus etoposide or carboplatin plus etoposide. pERC noted that the pCODR's PAG indicated that topotecan monotherapy or cyclophosphamide/doxorubicin/vincristine combination are treatments available. Registered clinician input indicated treatments for mMCC also include etoposide monotherapy, paclitaxel monotherapy, or phase I clinical trial if they are eligible.

Contextual information: Non-comparative studies with chemotherapy treatment

The pCODR review also provided contextual information on four studies of treatment with chemotherapy in previously treated mMCC. Two studies were conducted by Merck/Pfizer for which individual-level data were available from patients receiving second-line or later chemotherapy from the European Union (EU) and the US. The US study identified immunocompetent patients in community oncology settings to reflect real-world care in that country (N = 14). The EU study identified immunocompetent patients who were primarily treated in academic centres in Europe (N = 29). Iyer et al. identified 30 patients receiving second-line chemotherapy through chart review. Samlowski et al. reported on a single-arm, open-label, phase II trial of imatinib mesylate in patients with metastatic or unresectable mMCC (N = 23). Descriptively, JAVELIN Merkel 200 Part A suggested that avelumab had a favourable efficacy profile in the second-line or later setting compared with results observed for chemotherapy in the identified studies. However, this evidence has not been confirmed by results from comparative clinical trials. pERC acknowledged that retrospective analyses are prone to reporting bias and these results, though promising, must be interpreted with caution.

Need and burden of illness: More effective treatment options for mMCC

Approximately 100 to 110 cases of mMCC are expected to occur in Canada each year with 30 to 40 deaths. Merkel cell carcinoma is an aggressive, uncommon skin cancer that is increasing in incidence. Advanced age and immunosuppression are the main risk factors for MCC which can complicate the effective delivery

of cytotoxic chemotherapy. Although a minority of patients remain sensitive to platinum-based chemotherapy following the first-line setting, few patients experience durable objective responses from second-line chemotherapy.

Currently available therapies for patients with previously treated mMCC include chemotherapy such as cisplatin plus etoposide, carboplatin plus etoposide, etoposide monotherapy, topotecan monotherapy, cyclophosphamide/doxorubicin/vincristine combination, paclitaxel monotherapy, or phase I clinical trial if eligible. Chemotherapy is associated with significant toxicities, low response rates, and limited survival. pERC noted that the goals of treatment for patients with mMCC are primarily palliative, that is, to prolong life while maintaining or improving QoL. Given the toxicity and limited efficacy associated with available palliative chemotherapy options, pERC concluded that there is a substantial unmet need for alternative options with fewer and more manageable adverse effects than chemotherapy that reduce disease burden, and prolong survival.

Registered clinician input: Unmet need for therapies with durable responses

pERC deliberated on one joint input from four oncologists from the Skin Drug Advisory Committee at Cancer Care Ontario. According to their input, current standard treatment for previously treated patients with mMCC is cisplatin plus etoposide, carboplatin plus etoposide, etoposide monotherapy, paclitaxel monotherapy, or phase I clinical trial if they are eligible. pERC agreed with registered clinicians that MCC is a very rare cancer and therefore does not have a high incidence or prevalence. pERC acknowledged and agreed with clinician input that indicated that, in this patient population, avelumab had a good response rate; and most patients were still continuing treatment at 10 months; and, avelumab had a low risk of immune-related events but was otherwise well tolerated. Clinician input indicated that avelumab in second-line treatment would be used following chemotherapy and should be strongly considered as first-line. However, pERC noted that avelumab in the first-line setting for patients with mMCC that was not previously treated was outside of the scope of the current review.

PATIENT-BASED VALUES

Values of patients with metastatic Merkel Cell Carcinoma: Disease control and survival

Two patient groups, Save Your Skin Foundation (SYSF) and Canadian Cancer Survivor Network (CCSN), provided input on avelumab for the treatment of mMCC in previously treated adults. Patient input indicated that there are a number of symptoms associated with mMCC that affect QoL including fear of being diagnosed with a rare deadly cancer, scarring and disfigurement, fatigue, depression, anxiety, and weight loss. Patient input also indicated that mMCC had a negative impact on patients' ability to work. With previous treatments (including radiation, surgery, and chemotherapy) the toxicities and negative impacts were: nausea, vomiting, diarrhea, loss of appetite, fatigue, constipation and abdominal pain, cough, dry mouth, sores in mouth, disfigurement, hair loss, depression, mobility issues, and loss of work.

Patient values on treatment: Effective but tolerable treatment options

Patients noted that given MCC is a rare skin cancer with very low survivorship, patients were willing to tolerate all potential adverse side effects from treatment even for short-term benefit. pERC noted that SYSF reported that 23.6% of 57 patient respondents had direct experience with avelumab, including four Canadian patients and CCSN reported one patient respondent had experience with avelumab. The following side effects were reported with avelumab: fatigue/lack of energy, diarrhea, nausea, rash, and decreased appetite. All patients reported that they did not experience hair loss during treatment. All patient respondents reported that side effects were manageable and that they were able to have good QoL. One patient respondent noted that they experienced fewer side effects with avelumab compared with previous treatments, especially in terms of fever, nausea, and vomiting. Overall, pERC concluded that avelumab aligns with patient values, as there is a substantial unmet need for an effective treatment option that provides disease control, maintains QoL, and has an acceptable toxicity profile.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis, partitioned-survival analysis

The pCODR Economic Guidance Panel (EGP) assessed a cost-utility analysis comparing avelumab to chemotherapy and best supportive care for adult patients with previously treated mMCC. The comparisons were based on JAVELIN Merkel 200 Part A and data from two observational studies (EU and US) that evaluated outcomes after chemotherapy use in patients previously treated mMCC.

Basis of the economic model: Non-comparative data used in cost-utility analyses

Costs included in the models were drug, drug administration, costs to manage adverse events, cost of disease monitoring, and the cost of end of life.

Key clinical effects considered in the analysis included PFS, OS, and utilities. Given the absence of robust direct evidence, the clinical effect considered in the analysis was based on data for the comparator arm from published retrospective observational studies (EU and US studies). pERC acknowledged considerable limitations in the results of this analysis and agreed that caution should be used in interpreting the results.

Drug costs: Treatment until progression or maximum 12 months

Avelumab costs $1,325.00 per 200 mg vial. At the recommended dose of 10 mg/kg day 1 every two weeks, the cost of avelumab is $331.25 per day and $9,275.00 per 28-day course.

Cisplatin costs $2.70 mg. At the recommended dose of 25 mg/m2 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. 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/m2 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 cost for cisplatin-etoposide is $29.91 per day and $837.42 per 28-day course.
The cost for carboplatin-etoposide is $28.86 per day and $808.08 per 28-day course.

Cost-effectiveness estimates: Substantial uncertainty due to non-comparative data

pERC discussed the submitter's and the EGP's best estimates of the ICER of avelumab compared with chemotherapy and best supportive care for patients with previously treated mMCC. In the absence of direct or indirect comparative data, pERC noted that several data sources from the literature — including retrospective observational studies of chemotherapy—and multiple assumptions were used to populate the clinical inputs within the cost-utility analysis. pERC, however, noted that due to the limitations of non-randomized evidence from the JAVELIN Merkel 200 Part A study, there was substantial uncertainty in the magnitude of the clinical benefit associated with avelumab. This made it challenging to estimate the incremental effect of treatment with avelumab and, therefore, the resulting ICER. This considerable uncertainty in the magnitude of clinical benefit of avelumab would likely lead to an even wider range of ICER estimates beyond those computed in the submitted model and using the available, but limited, evidence. pERC also considered that the collection of additional prospective data on the clinical benefit of avelumab would reduce the uncertainty around the magnitude of the benefit and the cost-effectiveness estimates.

Therefore, due to limitations in the available non-randomized clinical evidence for avelumab and the absence of long-term data on the potential survival benefit gained in this setting, pERC noted that it was challenging to determine the true ICER. pERC concluded that the true ICER is likely higher than estimated in the EGP's reanalysis estimates, and therefore avelumab could not be considered cost-effective compared with available therapies.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: High drug cost, wastage

pERC considered the feasibility of implementing a funding recommendation for avelumab. pERC noted that when the average number of vials of avelumab was increased to align with the cost-utility analysis, the budget impact increased. However, the budget impact analysis took into consideration first-line and second-line treatment of avelumab, only considering first-line reduced the budget impact of avelumab.

As noted in PAG input, there is no standard of care for patients with chemotherapy refractory mMCC. Current treatment options for patients with previously treated mMCC include cisplatin or carboplatin with etoposide, topotecan monotherapy, or cyclophosphamide/doxorubicin/vincristine. PAG noted that the trial was for chemotherapy refractory patients and was seeking information on whether results of the trial were generalizable to patients who were not chemotherapy refractory or who were in other lines of therapy. pERC agreed with the CGP that there was clinical benefit for all patients who had previously received first-line chemotherapy and that results were generalizable to patients if they had received multiple lines of chemotherapy (i.e., at least one line of prior chemotherapy). pERC noted that avelumab

in the first-line setting for patients with mMCC that was not previously treated was outside of the scope of the current review. In response to PAG request for guidance, the CGP noted that avelumab would be used after platinum-based chemotherapy as platinum-based chemotherapy is used in the first-line setting.

With respect to treatment duration, treatment with avelumab is indicated until disease progression or unacceptable toxicity or for a maximum of 12 months after confirmation of CR. Treatment beyond 12 months in patients with a confirmed CR was allowed on the basis of investigator assessment of potential benefit. Confirmation of progressive disease by radiological assessment was required, preferably six weeks (but no later) after a diagnosis of progression per standard Response Evaluation Criteria in Solid Tumours (RECIST). If progression was based on the occurrence of a new lesion in an area not scanned at baseline, a further on-trial scan six weeks later was done. pERC felt that the criteria for treatment with avelumab in JAVELIN Merkel 200 Part A was reasonable. In JAVELIN Merkel 200 Part A, patients who had a confirmed CR and relapsed after stopping treatment were allowed one re-initiation of treatment. Patients were eligible for retreatment if they did not experience any toxicity that led to treatment discontinuation of the initial avelumab therapy and retreatment was until progression. pERC noted that some patients received avelumab after disease progression with the duration of post-progression treatment ranging from 0.03 to greater than 14.3 months. pERC noted that the actual treatment duration with avelumab is unknown, and jurisdictions will need to consider this during implementation of avelumab reimbursement.

DRUG AND CONDITION INFORMATION

Drug Information	• Monoclonal antibody • 200 mg vial • 10 mg/kg of body weight administered intravenously over 60 minutes every 2 weeks until disease progression or unacceptable toxicity or for a maximum of 12 months after confirmation of complete response
Cancer Treated	• Metastatic Merkel cell carcinoma (mMCC) in previously treated adults • Second-line setting and beyond
Burden of Illness	• Rare, aggressive skin cancer • Main risk factors are advanced age and immunosuppression
Current Standard Treatment	• Cisplatin plus etoposide • Carboplatin plus etoposide • Topotecan monotherapy • Cyclophosphamide/doxorubicin/vincristine
Limitations of Current Therapy	• Majority of patients are chemotherapy refractory • Minority of patients remain platinum-sensitive after first-line treatment with platinum-based chemotherapy with etoposide • There remains a need for more effective cancer therapies

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)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Craig Earle, Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

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

- Drs. Craig Earle, Matthew Cheung, and Anil Abraham Joy, who were not present for the meeting
- Cameron Lane, who 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 avelumab (Bavencio) for metastatic Merkel cell carcinoma (mMCC), through their declarations, no

members had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, none 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*. EMD Serono — Pfizer Alliance, as the primary data owner, did not agree to the disclosure of clinical information, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

Use of This Recommendation

This pERC recommendation 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.

Disclaimer

pCODR does not assume any legal liability or responsibility for the accuracy, completeness, or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report. This document is composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR document).

APPENDIX 1: pERC RESPONSES TO PAG IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
• PAG is seeking information on the generalizability of the trial data to use in patients who are not chemotherapy refractory and in other lines of therapy (i.e., first line).	• The Committee agreed with the CGP that there was clinical benefit for all patients who had previously received first-line chemotherapy and that results were generalizable to patients if they had received multiple lines of chemotherapy (i.e., at least one line of prior chemotherapy). • pERC noted that avelumab in the first-line setting for patients with mMCC that was not previously treated was outside of the scope of the current review.
• PAG is seeking guidance on whether avelumab would be used before platinum-based chemotherapy or whether avelumab would be used after platinum-based chemotherapy.	• In response to PAG request for guidance, the CGP noted that avelumab would be used after platinum-based chemotherapy as platinum-based chemotherapy is used in the first-line setting.
• As treatment with avelumab can be continued as long as clinical benefit is observed or until unacceptable toxicity, PAG is seeking information on the range in duration of treatment and clarity on treatment discontinuation.	• Treatment with avelumab is indicated until disease progression or unacceptable toxicity or for a maximum of 12 months after confirmation of complete response (CR). • Treatment beyond 12 months in patients with a confirmed CR was allowed on the basis of investigator assessment of potential benefit. Confirmation of progressive disease by radiological assessment was required, preferably six weeks (but no later) after a diagnosis of progression per standard Response Evaluation Criteria in Solid Tumours (RECIST). If progression was based on the occurrence of a new lesion in an area not scanned at baseline, a further on-trial scan 6 weeks later was done. • In JAVELIN Merkel 200 Part A, patients who had a confirmed CR and relapsed after stopping treatment were allowed one re-initiation of treatment. Patients were eligible for retreatment if they did not experience any toxicity that led to treatment discontinuation of the initial avelumab therapy and retreatment was until progression. • In JAVELIN Merkel 200 Part A, the median duration of therapy with avelumab was 17 weeks (interquartile range: 7 to 37) with a median of seven doses (interquartile range: 3 to 18). The mean duration of therapy with avelumab was 23 weeks (range: 2 to 76.0). • pERC noted that some patients received avelumab after disease progression with the duration of post-progression treatment ranging from 0.03 to greater than 14.3 months. pERC noted that the actual treatment duration with avelumab is unknown, and jurisdictions will need to consider this during implementation of avelumab reimbursement. • The duration of treatment of avelumab in the pharmacoeconomic model is based on statistical modelling of the time-on-treatment data observed in the JAVELIN Merkel 200 Part A trial and expert opinion.