pan-Canadian Oncology Drug Review Final Clinical Guidance Report

Avelumab (Bavencio) for metastatic Merkel Cell Carcinoma

March 21, 2018

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INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendation to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding avelumab (Bavencio) for metastatic Merkel Cell Carcinoma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding avelumab (Bavencio) for metastatic Merkel Cell Carcinoma conducted by the Skin & Melanoma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on avelumab (Bavencio) for metastatic Merkel Cell Carcinoma, a summary of submitted Provincial Advisory Group Input on avelumab (Bavencio) for metastatic Merkel Cell Carcinoma, and a summary of submitted Registered Clinician Input on avelumab (Bavencio) for metastatic Merkel Cell Carcinoma, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the efficacy and safety of avelumab for the treatment of metastatic Merkel Cell (mMCC) in previously treated adults.

Health Canada issued a Notice of Compliance with Conditions (NOC/c) for avelumab (Bavencio) for the treatment of metastatic Merkel Cell carcinoma (MCC) in previously treated adults. This marketing authorization with conditions requires the manufacturer to provide the results of further trials to verify its clinical benefit. Marketing authorization with conditions was based on tumour response and durability of response, an improvement in survival or disease-related symptoms has not yet been established. The funding request under review by pCODR aligns with the Health Canada indication.

Avelumab is a fully human immunoglobulin G1 (IgG1) monoclonal antibody directed against the programmed death ligand 1 (PD-L1). The recommended dose of avelumab is 10 mg/kg body weight administered intravenously over 60 minutes every 2 weeks. It is recommended that patients be treated with avelumab until loss of clinical benefit or unmanageable toxicity. Patients with clinically stable disease may remain on treatment until disease progression is confirmed.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One multicentre, international, prospective, single-arm, open-label, phase II study was identified that met the eligibility criteria and is included in the pCODR systematic review.[1] The JAVELIN Merkel 200 Part A study evaluated the efficacy and safety of treatment with avelumab in patients with stage IV Merkel Cell carcinoma that had progressed after cytotoxic chemotherapy.

Key inclusion criteria were as follows: adults aged at least 18 years who had received at least one line of chemotherapy for the treatment of mMCC; estimated life expectancy of more than 12 weeks; at least one unidimensional measurable lesion by Response Evaluation

Criteria in Solid Tumors version (RECIST) v1.1; histologically confirmed Stage IV MCC; progression after the most recent line of chemotherapy; immune-competent, and naïve to therapies targeting T-cell co-regulatory proteins; no activated vaccines within 4 weeks of going on trial or while on the trial; Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-1 and adequate haematological, hepatic, and renal function.[1] Key exclusion criteria included: concurrent treatment with an anticancer treatment or other non-permitted drug; prior therapy with any drug targeting T cell coregulatory proteins; concurrent systemic therapy with corticosteroids or other immunosuppressive agents, or use of any investigational drug within 28 days before starting trial drug; active central nervous metastases, previous malignant disease (other than MCC) within the last 5 years, prior organ transplantation, including allogenic stem-cell transplantation; known history of or positive test for HIV/AIDS, HBV, or HCV and active or history of any autoimmune disease or immune-deficiencies that required treatment with a systemic immunosuppressant.[1]

Efficacy endpoints were analyzed in all subjects who received at least one dose of avelumab (modified intention to treat (ITT) analysis set). The primary endpoint was confirmed best overall response, defined as complete response, partial response, stable disease, or progressive disease, according to RECIST v1.1. Response was assessed by an independent endpoint review committee. Secondary endpoints included duration of response, progression-free survival, overall survival, response status by RECIST at 6 and 12 months, safety, population pharmacokinetic profile, and immunogenicity of avelumab. Exploratory endpoints included tumour assessment by investigator using RECIST v1.1 and modified immune-related response criteria, and tumour shrinkage in target lesions from baseline.[1]

RESULTS:

PRIMARY OUTCOME: Best Overall Response (BOR)

The analysis for BOR, updated to assess long term efficacy after at least 18 months (24 March 2017 cut-off) found the proportion of patients who achieved an objective response according to independent review committee (IRC) assessment by RECIST version 1.1 was 33% (95% CI: 23.3-43.8), of which 11.4% (10/88) were complete responses and 21.6% (19/88) were partial responses.[2-4] Of the 18 patients whose responses were not evaluable, 14 were due to the lack of a post-baseline assessment, 2 were due to insufficient or missing radiologic scans, 1 was due to a new anticancer therapy stated prior to the first post-baseline assessment, and 1 was due to a stable disease of insufficient duration.[5]

SECONDARY ENDPOINTS
Duration of Response
The updated efficacy analysis with a minimum of 18 months follow-up, reported continuing responses with only one additional subject experiencing disease progression. Among subjects with a confirmed response (n=29), a total of 26 subjects (Kaplan-Meier [KM] estimate: 93%; 95% CI: 75, 98) had a duration of response ≥6 months, and 18 subjects (KM estimate: 71%; 95% CI: 51, 85) had a duration of response ≥12 months.[4] The proportion of patients with a duration of response ≥18 months was 66% (KM estimate) (95% CI: 44-81).[4] The median duration of response was not estimable (NE) (95% CI: 18.0 months, NE). The maximum duration of response was ongoing at 24.9 months.[2]

Progression-free Survival
As of the March 24, 2017 data cut-off, median progression-free survival was 2.7 months (95% CI 1.4-6.9), and the KM estimated progression-free survival rates at 12 and 18 months were each 29% (95% CI: 19-39).[2,4] The Kaplan-Meier curve for PFS shows a plateau in

survival being reached, with data still maturing. Such a plateau is not evident in chemotherapy data (See section 7). The plateau for PFS beyond 6 months was driven by subjects with prolonged responses (25 of 29 progression-free subjects at 6 months) with only 3 due to prolonged stable disease and 1 due to non-CR/non-progressive disease.

Overall Survival

As of the March 24, 2017 cut-off date, 54 (61.4%) subjects had died and the median OS was 12.6 months (95% CI: 7.5-19.0).[2,4] The KM estimated survival rate was 51% (95% CI: 40-61) at 12-months, and 40% (95% CI: 29-50) at 18-months.[2,4]

Quality of Life[1,6]

Functional Assessment of Cancer Therapy – Melanoma (FACT-M) and Trial Outcome Index (TOI)

A linear mixed model (LMM) analysis fitted for change from baseline for each scale was conducted and minimal important differences (MID) were used to interpret meaningful changes.[6] A total of 70 patients were analyzed and no meaningful changes were observed from each scale during treatment. Correlations between reduction in tumor size and improvements in FACT-M were moderate at week 7 for Functional Well-being (-0.47), TOI (-0.36), FACT-M total (-0.36), and FACT-G total (-0.34), suggesting that QoL improves as the tumour shrinks.[6] Mean differences in change from baseline scores between non-PD and PD were in the range of published MIDs for melanoma subscale (difference = 2.79, p = 0.005), melanoma surgery scale (difference = 1.48, p = 0.089), TOI (difference = 5.68, p = 0.004), FACT-G total score (difference = 4.37, p = 0.022), FACT-M total score (difference = 7.03, p = 0.006), EQ-5D VAS (difference = 7.04, p = 0.024) and EQ-5D utility score (difference = 0.07, p = 0.003).[6] A decrement in all scales was seen at end of treatment, which was attributed to disease progression for the most part. Sensitivity analyses, conducted to explore the impact of missing data, found consistent results with modest increases in estimated differences.[1]

Harms Outcomes[1,5,7]

As of the March 24, 2017 data cut-off, a total of 66 (75%) patients experienced any treatment-related AEs (all CTCAE grades) (Table 8). The most common treatment-related AE was fatigue, occurring in 25% of patients, followed by rash at 15.9%. A total of 19 patients (21.6%) had an infusion-related reaction (IRR), which were all grade 1 or 2 and occurred at the first or second infusion. Nausea and diarrhea were equally as common, seen in 11.4% of patients (Table 9).[2,4] There was a total of eight (9.1%) grade 3 treatment-related adverse events. There were no treatment-related deaths.[4]

Overall, as of the March 24, 2017 data cut-off, immune-related adverse events (irAEs) of any grade were reported in 19.3% of subjects. Individual types of irAEs were relatively infrequent, with no one type of event occurring in > 6% of subjects. The most common (> 1% of subjects) irAEs included hypothyroidism (5.7%), rash (5.7%), diarrhea (2.3%) and erythema (2.3%). The incidence of Grade ≥ 3 irAEs was 4.5%.[4] There were no Grade ≥4 irAEs reported in this study.

Table 1: Highlights of Key Outcomes

	JAVELIN Merkel 200 Part A (n=88)		
	12 month minimum follow-up (Sept 3, 2016 data cut-off)[7]	18 month minimum follow-up (March 24, 2017 data cut-off)[2,4]	24 month minimum follow-up[8] (data cut-off not reported)
Median follow-up (months)	16.4	23.0	NR
	N (%)	N (%)	N (%)
BOR per RECIST 1.1 by IRC			
Complete Response (CR)	10 (11.4)	10 (11.4)	NR
Partial Response (PR)	19 (21.6)	19 (21.6)	NR
Stable Disease	9 (10.2)	9 (10.2)	NR
Progressive Disease	32 (36.4)	32 (36.4)	NR
Non-CR/Non-PD	0	0	NR
Not evaluable	18 (20.5)	18 (20.5)	NR
Objective Response Rate (ORR)			
Response rate (CR+PR) (95% CI)	29 (33.0) (23.3-43.8)	29 (33.0) (23.3-43.8)	29 (33.0) (23.3-43.8)
Duration of Response* (DOR)			
Median, months (95% CI)	NE (18.0-NE)	NE (18.0-NE)	NE (18.0-NE)
Progression-free Survival (PFS)			
Median, months (95% CI)	2.7 (1.4 - 6.9)	2.7 (1.4 - 6.9)	2.7 (1.4 - 6.9)
PFS by KM, % (95%CI)	30 (19-39)	29 (19-39)	26 (16-36)
Overall Survival (OS)			
Median, months (95%CI)	12.9 (7.5-NE)	12.6 (7.5-19.0)	12.6 (7.5-17.1)
OS rate by KM, % (95% CI)	12 month: 52 (41-62)	18 month: 40 (29-50)	36 (26-46)

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient's perspective, there are a number of symptoms associated with mMCC that impact quality of life, which include fear (of being diagnosed with a rare deadly cancer), scarring and disfigurement, fatigue, depression, anxiety, and weight loss. SYSF patient respondents indicated that mMCC also had a negative impact on their ability to work. Further, SYSF reported that patient respondents experienced the following limitations: lack of information on this type of cancer, lack of knowledge of this type of cancer by some physicians which leads to misdiagnosis, being told surgery, radiation and chemotherapy were the only treatment options, barriers to participating in clinical trials, and psychological barriers. The symptoms reported by the CCSN patient respondents included fast-growing lump and anxiety. One patient respondent identified diarrhea and abdominal pain as the most difficult side effects to manage. SYSF patient respondents reported the following toxicities and impacts associated with their previous treatments (including radiation, surgery, and chemotherapy) 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. Notably, patient respondents realized this was a rare skin cancer with very low survivorship and were willing to tolerate all potential adverse side effects from treatment even for short-term benefit. In terms of patients' expectations about a new drug, patient respondents expressed hope with a new treatment option in face of a rare and deadly cancer. All SYSF patient respondents were willing to

take the risk of participating in a clinical trial for any life gain whether short or long term. One CCSN patient respondent indicated that patients were most concerned about stopping disease progression, especially with a cancer like mMCC; they would like to see a treatment that could control disease symptoms with fewer side effects and improve quality of life. Approximately 24% of SYSF patient respondents, including four Canadian patients, have experience with avelumab and reported the following side effects: fatigue/lack of energy, diarrhea, nausea, rash, and decreased appetite.All patients reported that they had not experienced hair loss while being treated with avelumab, which made them very happy, as hair loss was a particular concern to them. In terms of how avelumab impacts patients' quality of life, all patient respondents reported that side effects were manageable and that they were able to have good quality of life. The one CCSN patient respondent who had been treated with avelumab indicated they experienced less side effects than with previous treatments, especially in terms of fever, nausea and vomiting; he/she also noted that avelumab had stopped disease progression.

Provincial Advisory Group (PAG) Input

Input was obtained from all provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:
- Rare cancer that has limited treatment options

Economic factors:
- Drug wastage
- Cost of treatment compared to platinum chemotherapy
- Additional chemotherapy chair time required for pre-medications and for monitoring of infusion related reactions

Registered Clinician Input

One clinician input was received as a joint submission by four oncologists on behalf of the Skin Drug Advisory Committee at Cancer Care Ontario (CCO). Avelumab is to be used for the treatment of mMCC in previously treated adults.

Summary of Supplemental Questions

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of avelumab for the treatment of patients with metastatic Merkel cell carcinoma who have been previously treated:

- Critical appraisal of the manufacturer-submitted data from observational studies used as historical controls.

Given the rarity of the disease and poor prognosis for patients with stage IV disease, it is unlikely there will ever be randomized head-to-head trials comparing treatment with avelumab to other therapies. Thus, to properly contextualize and interpret the outcomes of the single-arm avelumab clinical trial, observational retrospective analyses become necessary. The objective of this supplemental question is to summarize and critically appraise the methods and findings of the manufacturer-submitted data from observational studies used as historical controls.

For second-line patients, information is available from four sources: the EU and US studies conducted by Merck/Pfizer, for which individual-level data are available;[9,10] the study by Iyer et al.,[11] which reports a Kaplan–Meier for PFS and a median OS for 30 second-line patients; and the study by Samlowski et al.,[12]

which reports the outcomes for 23 second-line patients treated with imatinib (only 14 of whom had received prior chemotherapy).

1.2.1.1 US Second-line Study[10]

No patient achieved a CR to 2L+ chemotherapy, although four patients (all immunocompetent) had a PR. In the primary analysis population (immunocompetent), the ORR was 28.6% (95% CI: 8.4–58.1% [n = 4/14]). Responses to chemotherapy were of limited duration in this population: the median DOR was 1.7 months (95% CI: 0.5–3.0 months; range: 0.5–3.0 months). The median PFS was 2.2 months (95% CI: 1.2–3.5 months) and median OS was 4.3 months (95% CI: 2.1–6.2 months). No patient had a response lasting ≥6 months, and hence the DRR was 0%.

1.2.1.2 EU Second-line Study[9]

Analysis of the immunocompetent population showed an ORR of 10.3% (95% CI: 2.2-27.4) and a median DOR of 1.9 months (95% CI: 1.3-2.1). At 6 months, the DRR was 0%.

Median PFS was 3.0 months (95% CI, 2.5%-3.2%), and the PFS rate at 6 months was 3.4% (95% CI,0.3%-14.9%). Median OS was 5.3 months (95% CI, 4.3%-6.0%), and the OS rate at 6 months was 27.5% (95% CI,13.0%-44.2%). The OS rate at 12 months was 0%.

1.2.1.3 Iyer et al study[11]

The response rate to second-line chemotherapy was 23% (7 of the 30 patients; 1 CR, 6 PR). Of patients, 73% (22 of the 30) had progressive disease and one (3%, 1/30) had stable disease. Median PFS among the 30 patients who received second-line chemotherapy was 61 days (range: 11–354 days). The one patient with a CR remained progression free for 105 days; among the six patients that had a PR, median PFS was 227 days (range: 60–354 days). Of patients treated with second-line chemotherapy, 80% developed progressive disease by 105 days, while 95% did so by 230 days. For patients who had a CR or PR following second-line chemotherapy, the median DOR was 101 days after best response (range: 6–225 days). For the one patient who had a CR, DOR was 21 days and among the six patients that had a PR, median DOR was 107 days (range: 6–225 days). Of the 30 patients who received second-line chemotherapy, 25 died of MCC by the end of the study period, 1 patient died of an unknown cause, and 4 patients were alive (1 had a PR and 3 had PD at end of study). Of note, all seven patients who received topotecan, the most commonly used agent for second-line chemotherapy in this cohort, experienced progressive disease without any evidence of response. The only patient to achieve a complete response received carboplatin plus etoposide, although the duration of this response was only 21 days. For patients who received second-line chemotherapy, the median overall survival time from the start of second-line chemotherapy was 5.7 months (range: 35 days to 2.4 years; data not shown).

1.2.1.4 Samlowski et al study[12]

There were no complete responses (0%) and one confirmed partial response (4%) in the 23 evaluable patients (4% objective response rate, 95% CI 0 – 22%). In addition, stable disease was observed in 3 patients (9, 4 and 3 months). At the time of analysis, all evaluable patients had developed progressive disease. The estimated median progression-free survival was 1 month (95% CI: 1-2 months), with an estimated 6-month PFS of 4% (95% CI: 0% – 13%). The estimated median overall survival was 5 months (95% CI: 2-8 months). The estimated one-year overall survival was

17% (95% CI: 0% – 33%). There were three deaths on study, all were attributed to progressing tumor.

Overall Results[13]

Due to the differences in study design, assessments and study populations, formal statistical comparisons between the JAVELIN study and the observational studies were not planned or performed. Instead, results are presented side-by-side in a descriptive way to put the results of JAVELIN Merkel 200 Part A into context and should be interpreted with caution.[14] Caution is needed due to a very high risk of bias when comparing across studies (i.e., the observed difference in effect might be due to differences in prognostic factors and effect modifiers between the studies rather than solely due to differences in the treatments).

Overall, the JAVELIN Merkel 200 Part A study suggests avelumab has a favourable efficacy profile in the second-line or later setting compared with the results observed for chemotherapy in the observational studies. The ORR was higher in subjects treated with avelumab (33.0%; 95% CI: 23.3-43.8) than for chemotherapy-treated immunocompetent subjects in US cohort (28.6%; 95% CI: 8.4-58.1) EU cohort (10.3%; 95% CI: 2.2-27.4), Iyer et al study (7%; 95% CI: 9.9-42.3), and Samlowski et al study (4%; 95% CI: 0-22). The proportion of subjects with a CR was higher in subjects treated with avelumab than those treated with chemotherapy across observational studies. The 6-month DRR was greater with avelumab treatment (30.6%; 95% CI: 20.9-40.3) than with chemotherapy (US cohort: 0.0% [95% CI: 0.0-23.2]; EU cohort: 0.0% [95% CI: 0.0-11.9]; Iyer et al: 6.7% [95% CI: 0.8-22.1]). Responses were also prolonged with avelumab treatment (6-month durability by K-M: 92% [95% CI: 70-98] vs. 0%, with no subjects having a response longer than 3 months across the US and EU cohorts of the observational study).

Treatment with avelumab also resulted in greater PFS and OS rates at 12 months than did treatment with chemotherapy, as reported in the 4 observational studies. Also of note, the KM curve for PFS shows a plateau in the JAVELIN study, while the Kaplan-Meier curves for the US and EU studies show a continued decline in survival with chemotherapy.

See section 7.1 for more information.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for avelumab in metastatic Merkel cell carcinoma in previously treated adults.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	ECOG PS	Inclusion criteria specified patients were required to have an ECOG PS 0-1. ECOG PS – 0: 49 (56%) ECOG PS – 1: 39 (44%)	Do the results apply to patients with ECOG PS >1?	Yes, safety profile of avelumab supports generalizability of the results to ECOG PS 2 patients. The main factor when considering further treatment is whether the patient can tolerate the treatment and that while ECOG PS is an indicator of whether a patient may tolerate treatment, it is really due to a combination of other factors.
	Biomarkers	Post-hoc subgroup analyses results of PD-L1 tumour expression and MCPyV status showed an odds ratio of 2.3 and 1.6, respectively. Note the analyses may not have been adequately powered to detect a difference in effect <table><tr><td>Tumour PD-L1 expression PD-L1–positive (n=58) PD-L1–negative (n=16) Not evaluable (n=14)</td><td>ORR 20 (34·5 [22·5–48·1]) 3 (18·8 [4·0–45·6]) 5 (35·7 [12·8–64·9])</td><td>OddS Ratio In Response Rate 2·28 (0·53, 13·78 [0·3610])</td></tr><tr><td>Tumour MCPyV status MCPyV-positive (n=46) MCPyV-negative (n=31) Not evaluable (n=11)</td><td>12 (26·1 [14·3–41·1]) 11 (35·5 [19·2–54·6]) 5 (45·5 [16·7-76·6])</td><td>1·56 (0·51, 4·67 [0·4497])</td></tr></table>	Are there expected differences in effect based on biomarker status? Are the results applicable to all subgroups equally?	No predictive biomarkers identified. The results are equally applicable to all subgroups.
	Autoimmune Disorders	Patients with autoimmune disease were excluded.	Do the results apply to patients with existing autoimmune diseases?	Yes with consideration of the clinical situation and after informed discussion between the patient and an experienced clinician — data continues to emerge and there is not clear guidance on this point as yet.
	Previous treatment	The current funding request is for the treatment of mMCC in previously treated adults. The JAVELIN Merkel 200 Part A trial included patients that must have progressed after at least 1 line of prior chemotherapy.	Do the results apply to those patients who have been previously treated with other non-systemic treatments?	No, patients should have had previous chemotherapy, non-systemic treatments would include radiation and surgery.
Intervention	Previous treatment	Inclusion criteria specified patients must have received at least 1 line of chemotherapy for the treatment of mMCC and must have received at least one of the following chemotherapy regimens for treatment of mMCC: cyclophosphamide, topotecan, doxorubicin, epirubicin, vincristine, carboplatin, cisplatin, etoposide in combination with carboplatin or cisplatin.	Given the funding request is for those "previously treated", do the results apply to patients with any previous 2L+ systemic treatment?	Yes, at least one line of chemotherapy.

1.2.4 Interpretation

Merkel cell carcinoma (MCC) is an aggressive type of primary skin cancer that is currently considered rare but is noted to be increasing in incidence.[15] MCC is considered more lethal than malignant melanoma and most patients die within five years of diagnosis. For patients with unresectable, recurrent or metastatic disease, standard treatment consists of radiation therapy for palliation and chemotherapy for disease control. Advanced age and immunosuppression are the main risk factors for MCC and often complicate the effective delivery of cytotoxic chemotherapy. Although a minority of patients may remain platinum-sensitive after first-line treatment with etoposide/platinum chemotherapy and show objective response, few patients experience durable benefits from second-line chemotherapy.[9-11] Two uncontrolled trials have reported benefits of therapeutic monoclonal antibodies targeting PD-1/PD-L1 signalling in patients with incurable MCC. Nghiem et al reported a 56% objective tumor response rate in 26 incurable MCC patients treated with pembrolizumab (anti-PD-1 monoclonal antibody) as first-line therapy.[16]

This current review focuses on another larger prospective trial that reported the results of treatment with avelumab (anti-PD-L1 monoclonal antibody) in 88 incurable MCC patients with progressive disease who had at least one previous line of chemotherapy for metastatic disease.[1,2] In this trial, patients received avelumab 10 mg/kg IV every 2 weeks, and were required to have measurable disease as the primary endpoint of the trial was objective tumor response rate (ORR). A median of 7 doses of avelumab (IQR 3-18 doses) were given. As of March 24, 2017, the confirmed ORR was 33% (95% CI, 23.3-43.8%) which compares favourably to recently reported historical data for second-line chemotherapy (ORR 10.8-28.6%).[1,2,9-11] The probability of OR did not appear to be influenced by tumor PD-L1 expression or Merkel cell polyomavirus status. Secondary endpoints included OR duration, progression-free and overall survival, and ORR at 6 and 12 months. OR duration was not reached (range, 2.8 to 24.9 months), median progression-free survival was 2.7 months (95% CI, 1.4-6.9 months), and median overall survival was 12.6 months (95% CI, 7.5-19.0 months).[2] MCC response to second-line chemotherapy treatment is typically very short and less than 10% of patients remain in remission at 6 months. An important observation in this trial was that 30.6% of avelumab patients had durable tumor responses maintained at 6 months, and most of these still had disease control at 12 months. As tumor progression would usually equate with death due to cancer for these patients, these data make a compelling case for the efficacy of avelumab. An exploration of the association between OR and OS in mMCC patients with avelumab suggested that for avelumab, OR was associated with long-term survival, likely driven by the rapid time to response, substantial tumour reductions including complete responses and durable response not reported in the chemotherapy literature for mMCC.[17]

Anti-PD-1 and anti-PD-L1 monoclonal antibody therapies are typically very well tolerated, with severe but treatable immune toxicities such as rash, diarrhea, and pneumonia reported in less than 15% of patients. The worst toxicities reported with avelumab in this trial were asymptomatic laboratory grade 3 events in only 5% of patients. There were no grade 4 events or treatment-related deaths. An unusual observation unique to avelumab, was low grade acute infusion reactions, which were reported in 17% of patients. These reactions would increase chemotherapy unit chair time for the administration of pre-medications and monitoring of the infusion reaction.

Kaufman et al. provide data that establish efficacy and safety, and suggest that avelumab may be an effective treatment for incurable MCC that has progressed after first-line chemotherapy in a population of patients with median age 72.5 years (range, 64.5 to 77.0 years).[1] The results are consistent with a report by Nghiem et al,[16] which noted even higher ORRs with a similar agent in chemotherapy-naïve MCC patients. A confirmatory randomized trial in MCC patients previously treated with chemotherapy would be useful to confirm the effectiveness of avelumab; however, such a trial is likely not feasible due to the rarity of mMCC. Although second-line chemotherapy in the elderly patient population could be less expensive, it is also ineffective and toxic, so there is

clearly a need for more effective treatment. In view of these specific factors and the strength of the data provided by Kaufman et al, it is reasonable to extrapolate the benefits in overall survival and health-related quality of life with avelumab from the consistent results observed in randomized trials comparing similar drugs to second-line chemotherapy in non-small cell lung, head and neck, and urothelial cancers.[18-21] As first-line chemotherapy has a high ORR in MCC, patients should not be treated with avelumab first-line for incurable MCC in the absence of data from a randomized clinical trial confirming its superiority to chemotherapy. Exceptions for patients considered unsuitable for first-line chemotherapy could be considered (e.g., inadequate bone function, severe liver disease, myelodysplastic syndrome, and myelosuppression).

1.3 Conclusions

The Clinical Guidance Panel concluded that there *is* a net overall clinical benefit to avelumab in the treatment of patients with incurable metastatic Merkel cell carcinoma of the skin who have previously received first-line chemotherapy and suffer progressive disease based on one high-quality uncontrolled trial that demonstrated a durable objective tumor response rate that is clearly superior to second-line chemotherapy results reported in the literature. Assessment of overall survival was limited by the absence of a control therapy group but appears improved with avelumab compared to the literature. Although low grade acute infusion reactions occurred in 17% of patients, the adverse event profile of avelumab was extremely favourable with asymptomatic grade 3 toxicity experienced in only 5% of patients. When symptomatic severe immune toxicities of avelumab occur they can usually be treated effectively with corticosteroids. This supports a favourable quality of life experience for patients treated with avelumab compared to chemotherapy. Response to avelumab was not predicted by tumor PD-L1 expression or Merkel cell polyomavirus positivity. The Clinical Guidance Panel also considered:

- Another uncontrolled trial with a similar drug has shown a high objective tumor response rate in chemotherapy naïve Merkel cell carcinoma patients, supporting the efficacy of this approach.
- The Clinical Guidance Panel considered the limited evidence on the treatment of mMCC in view of its rarity and the need for more effective treatments for patients with this highly aggressive and uniformly fatal disease when formulating its conclusions.
- The Clinical Guidance Panel was uncertain about the net overall clinical benefit in chemotherapy naïve MCC patients but considered, based on expert opinion, avelumab to be a reasonable choice for such patients if cytotoxic chemotherapy is contraindicated. The use of avelumab in previously untreated patients is beyond the scope of this review, therefore the pCODR review did not search for evidence for this population.
- The Clinical Guidance Panel also considered it reasonable to generalize the trial results to include patients if they have received multiple lines of chemotherapy, do not have measureable disease, or are ECOG performance status 2. There is uncertainty about the use of immune checkpoint inhibitors in patients with pre-existing autoimmune or inflammatory conditions, and the use of avelumab in such patients should be considered carefully by informed discussion between an experienced clinician and the patient. Avelumab is contraindicated in patients with solid organ allografts.
- In response to Provincial Advisory Group request for guidance, avelumab would be used after platinum-based chemotherapy as platinum-based chemotherapy is used in the first-line setting.

2   BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Skin & Melanoma Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Merkel cell carcinoma (MCC) is a type of primary skin cancer first described in 1972.[22] Different subtypes have been described but do not seem to influence clinical behaviour. Risk factors include chronic UV radiation exposure, fair skin, increasing age, and immunosuppression. Typical patients are fair skinned, elderly, and have had other types of UV-related skin cancer but MCC may occur in much younger patients who are immunosuppressed for organ transplantation. A specific polyoma virus (Merkel cell polyoma virus) has been isolated in up to 80% of cases, but its role in tumor pathogenesis is unclear.[23]

MCC is considered to be an aggressive cancer with relatively high locoregional recurrence rates and a higher lethality than malignant melanoma. Rates for death within 5 years range from 55% (localized) to 84% (metastatic). Often MCC manifests on the sun exposed areas of the body. The usual initial presentation is with a painless, rapidly growing reddish or purple cutaneous nodule.

MCC is considered a rare cancer with an incidence ranging from 0.13 per 100,000 (Europe) to 1.6 per 100,000 (Australia); however, incidence is increasing. Precise incidence and mortality rates for Canada are not available. The incidence rate in the United States has been estimated at 3 per million annually and the mortality rate has been estimated at 33%.[24,25] Extrapolating from these data, about 100-110 cases of MCC would be expected to occur in Canada each year and about 30-40 deaths.

2.2 Accepted Clinical Practice

MCC is best managed by a multidisciplinary team experienced in skin cancer and/or head and neck cancer treatment. Localized MCC is treated with wide surgical excision to achieve clear surgical margins with or without regional lymph node dissection or sentinel lymph node biopsy. The role of adjuvant radiation therapy is unclear for patients with clear surgical margins.

As MCC is considered an aggressive neuroendocrine cancer, systemic treatment typically consists of cytotoxic chemotherapy drugs used in the treatment of small cell lung cancer (etoposide, cisplatin or carboplatin). The role of adjuvant chemotherapy is uncertain and it is usually only considered in patients with incurable locoregional or metastatic disease. Use of chemotherapy in the MCC population is often difficult due to advanced patient age, comorbidity, and/or immunosuppression.

PD-1 (pembrolizumab) and PD-L1 (avelumab) inhibitors have been studied in MCC in uncontrolled trials and reasonably high durable objective tumor response rates accompanied by low toxicity rates have been reported.[1,16] As current options for disease control/palliation are limited for this disease, such treatments could be quite valuable for patients with disease progression despite standard chemotherapy or who cannot tolerate or have contraindications to standard chemotherapy. However, these treatments would be relatively contraindicated in patients with solid organ transplants.

2.3 Evidence-Based Considerations for a Funding Population

The funding population to which this funding recommendation applies consists of patients with histologically confirmed recurrent or metastatic MCC unsuitable for curative treatment who require systemic therapy for disease control. Patients who have progressive disease despite standard chemotherapy, who have excessive or chronic toxicity from standard chemotherapy, or who could not receive standard chemotherapy would be potential candidates for treatment with a checkpoint inhibitor. Such patients will be easily identified by their treating medical oncologists. Patients receiving immunosuppression for solid organ transplants should not receive this treatment unless they are prepared to accept organ rejection. At this point no useful specific biomarkers to select MCC patients for checkpoint inhibitor therapy have been identified. It is estimated that 40 patients annually in Canada would be potential candidates for this therapy.

2.4 Other Patient Populations in Whom the Drug May Be Used

Checkpoint inhibitors are now widely used in cancer therapy for incurable melanoma, lung cancer, renal cancer, head and neck cancer, and bladder cancer. Some data support their use in any incurable cancer with microsatellite instability "high" tumors or tumors with high mutational burden. There is also data supporting their use in the adjuvant setting for high-risk resected melanoma of the skin. Therefore, there are an additional number of potential off label uses and funding criteria should be quite explicit about their use.

3   SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Two patient advocacy groups, Save Your Skin Foundation (SYSK) and Canadian Cancer Survivor Network (CCSN), provided input on avelumab for the treatment of metastatic Merkel Cell Carcinoma (mMCC) in previously treated adults.

SYSF conducted one online survey and received input from a total of 57 respondents from Canada (6 patient respondents, 6 caregiver respondents), the United States and Europe (45 patient respondents).Please refer to Table 1 for a summary of patient respondents' demographic information.

Table 1: Demographic information of SYSF survey respondents.	
Patient Characteristics	Patient respondents with mMCC (n=57)
Age: 51-65 years old Over 66 years old 51-65 years old when first diagnosed	Over 57% Over 40% Over 57%
Sex: Male Female	Over 70% Under 30%
Patients who have had other non-MCC	Over 36%
Patients who had mass removed by surgery	Over 80%
Patients with comprised lymph gland	Over 60%
Notes: mMCC = metastatic Merkel Cell Carcinoma	

In addition, CCSN conducted a survey in collaboration with SYSF, the Skin Patient Alliance, and the Canadian Organization for Rare Disorders (CORD). Responses were collected from October 11th to October 27th, 2017. CCSN noted that given the rareness of this cancer, information on the survey was also circulated to skin cancer organizations in other English-speaking countries. Overall, CCSN received input from two patient respondents and one caregiver respondent.

Summary:

From a patient's perspective, there are a number of symptoms associated with mMCC that impact quality of life, which include fear (of being diagnosed with a rare deadly cancer), scarring and disfigurement, fatigue, depression, anxiety, and weight loss. SYSF patient respondents indicated that mMCC also had a negative impact on their ability to work. Further, SYSF reported that patient respondents experienced the following limitations: lack of information on this type of cancer, lack of knowledge of this type of cancer by some physicians which leads to misdiagnosis, being told surgery, radiation and chemotherapy were the only treatment options, barriers to participating in clinical trials, and psychological barriers. The symptoms reported by the CCSN patient respondents included fast-growing lump and anxiety. One patient respondent identified diarrhea and abdominal pain as the most difficult side effects to manage. SYSF patient respondents reported the following toxicities and impacts associated with their previous treatments (including radiation, surgery, and chemotherapy) 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. Notably, patient

respondents realized this was a rare skin cancer with very low survivorship and were willing to tolerate all potential adverse side effects from treatment even for short-term benefit. In terms of patients' expectations about a new drug, patient respondents expressed hope with a new treatment option in face of a rare and deadly cancer. All SYSF patient respondents were willing to take the risk of participating in a clinical trial for any life gain whether short or long term. One CCSN patient respondent indicated that patients were most concerned about stopping disease progression, especially with a cancer like mMCC; they would like to see a treatment that could control disease symptoms with fewer side effects and improve quality of life Approximately 24% of SYSF patient respondents, including four Canadian patients, have experience with avelumab and reported the following side effects: fatigue/lack of energy, diarrhea, nausea, rash, and decreased appetite. All patients reported that they had not experienced hair loss while being treated with avelumab, which made them very happy, as hair loss was a particular concern to them. In terms of how avelumab impacts patients' quality of life, all patient respondents reported that side effects were manageable and that they were able to have good quality of life. The one CCSN patient respondent who had been treated with avelumab indicated they experienced less side effects than with previous treatments, especially in terms of fever, nausea and vomiting; he/she also noted that avelumab had stopped disease progression.

Please see below for a summary of specific input received from SYSF and CCSN. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that were reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with mMCC

SYSF Survey:

SYSF indicated that patient respondents with mMCC reported the following symptoms associated with their disease: fear (of being diagnosed with a rare deadly cancer), scarring and disfigurement, fatigue, depression and weight loss. Notably, patient respondents indicated that mMCC had a negative impact on their ability to work. SYSF reported that patient respondents also experienced the following limitations: lack of information on this type of cancer, lack of knowledge of this type of cancer by some physicians which leads to misdiagnosis, being told surgery, radiation and chemotherapy were the only treatment options, barriers to participating in clinical trials, and psychological barriers.

CCNS Survey:

CCSN indicated that the two patient respondents with mMCC reported the following two symptoms associated with their disease: fast-growing lump (n=2/2) and anxiety (n=1/2).

3.1.2 Patients' Experiences with Current Therapy for mMCC

SYSF Survey:

SYSF reported that the previous treatments received by patient respondents were limited to surgery, radiation and chemotherapy. The specific chemotherapy regimens received by patients were not specified. The previous treatments received by SYSF patient respondents are summarized in Table 2.

Table 2: Previous treatments received by SYSF survey respondents.	
Types of previous treatment	**Patient respondents with mMCC (n=57)**
Patients who had surgery to biopsy the mass	70%
Patients who had surgery to remove the mass and surrounding tissue	54%
Patients who had surgery to remove the mass, surrounding tissue and lymph nodes	60%
Patients who had radiation	60%
Patients who had immune therapy	22%
Patients who had chemotherapy	18%
Patients who participated in a clinical trial	16%
Patients who have not had re-occurrence	61%
Notes: mMCC = metastatic Merkel Cell Carcinoma	

Regarding side effects of current treatments, patient respondents reported the following adverse events of radiotherapy: nausea, vomiting, diarrhea, fatigue, dry mouth, and sores in mouth. All patient respondents (100%; n=57/57) reported that side effects were temporary. Patient respondents reported the following adverse events of surgery: loss of work, mobility issues, disfigurement, and depression. SYSF noted that, while reported side effects of chemotherapy varied depending on the dose received by patients, patients reported at least three of the following side effects: hair loss, loss of appetite, nausea and vomiting, and depression.

SYSF reported that 100% (n=57/57) of patient respondents realized this was a rare skin cancer with very low survivorship and were willing to tolerate all potential adverse side effects from treatment even for short-term benefit.

CCSN Survey:

CCSN confirmed that the two patient respondents had previously received treatment for mMCC. One patient had been treated with carboplatin/etoposide and one patient had received a treatment that was not listed in CCSN's survey and was not identified.

In terms of perceived effectiveness of current treatment options, the following treatments were identified as being somewhat effective by either patient respondent: surgery, external radiation and carboplatin/etoposide. Cisplatin/etoposide and carboplatin/etoposide were each considered not effective at all by either patient respondent.

Regarding side effects of current treatment options, CCSN noted that diarrhea and abdominal pain were identified as the most difficult side effects to manage. While fatigue was reported by both patient respondents, the following side effects were experienced in varying degrees: nausea and vomiting, loose bowels or diarrhea, decreased appetite, cough, constipation and abdominal pain.

In terms of patient access to treatments, CCNS reported that one patient respondent experienced difficulty in accessing treatment due to limited availability in his/her community.

3.1.3 Impact of mMCC and Current Therapy on Caregivers

SYSF Survey

SYSF reported on the challenges that caregivers face with this type of cancer; six Canadian caregiver respondents contributed to the survey. SYSF noted that all caregiver respondents were surprised at the lack of knowledge and awareness around this type of cancer. Other challenges identified by caregiver respondents were: inability to go to work, taking on a more active role with house hold duties, living knowing that their loved one might not make it and the resulting anxiety and depression.

CCSN Survey

CCSN reported on the response of one caregiver faced with this type of cancer. The caregiver respondent expressed that dealing with a loved one with mMCC was *"a roller coaster like journey"* and that they were *"trying to keep a positive frame of mind after 3 recurrences and the experimental Avelumab therapy."*

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Avelumab

Based on no experience with avelumab:

SYSF Survey

SYSF enquired about patients' expectations for avelumab. All SYSF patient respondents (100%; n=57/57) expressed hope with a new treatment option in face of a rare and deadly cancer. Patients anticipated they would take a new drug notwithstanding side effects. SYSF noted that 100% of patient respondents expressed the following expectations:

- Patients were glad to be part of a clinical trial and were willing to take the risk for any life gain whether short or long term.
- Patients had heard about the new treatments coming to cancer and were thrilled that something was on the horizon for MMCC and that they had the opportunity to take part.
- Patients understood the survival benefit and the side effects but were willing to go through that for a chance to have more time with their family and loved ones.
- Patients expressed hope with a new treatment option in face of a very bleak diagnosis.
- Patients are living with the anxiety of knowing their mMCC could comeback. They reported being told at their first appointment that this type of cancer was rare and deadly.
- All patients with mMCC understood that not a lot is known about this type of cancer and there is a high risk of developing other skin cancers.

CCSN Survey

Regarding patients' expectations for avelumab both patients respondents were most concerned about stopping disease progression, especially with a cancer like mMCC. They also indicated they would like to see a treatment that could control disease symptoms with fewer side effects and improve quality of life.

3.2.1 What Experiences Have Patients Had To Date with Avelumab

Based on experience using avelumab:

SYSF Survey:

SYSF reported 23.6% of patient respondents have direct experience with avelumab, including four Canadian patients. Regarding side effects experienced with avelumab, patients surveyed reported at least three of the following side effects (highest to lowest): fatigue/lack of energy, diarrhea, nausea, rash, and decreased appetite. Of note, patient respondents stated that they had not experienced hair loss while being treated with avelumab, which made them very happy. All patient respondents agreed that hair loss was of particular concern to them and the hardest side effect experienced. They were able to deal with nausea and fatigue but not with hair loss.

In terms of how avelumab impacts patients' quality of life, all patient respondents reported that side effects were manageable and that they were able to have good quality of life.

SYSF noted that all patient respondents agreed that administration of the treatment was generally uneventful and that they had a clear understanding of what to expect during and after treatment.

CCSN Survey:

Regarding side effects experienced with avelumab, the one patient respondent who had experience with avelumab reported that there was a reduction in side effects (especially fever, nausea and vomiting) compared with previous treatments they had received and that avelumab had stopped disease progression. The side effects reported with avelumab were diarrhea and extreme fatigue.

3.3 Additional Information

SYSF Survey:

SYSF provided the following additional information: "*This submission reminded me of the first submission we did for our Canadian Melanoma patients back in 2011. It was hard to find surviving patients to interview. But we also understood from this survey similar to the Melanoma submission we did in 2011, is that there is a lack of education of this type of cancer, there is little hope, and current treatment options are surgery, radiation and chemotherapy and that anything new and innovative gives these patients HOPE.* "

CCSN Survey:

No additional information provided.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Rare cancer that has limited treatment options

Economic factors:

- Drug wastage

- Cost of treatment compared to platinum chemotherapy

- Additional chemotherapy chair time required for pre-medications and for monitoring of infusion related reactions

Please see below for more details.

4.1 Factors Related to Comparators

The standard of care for patients with Merkel cell carcinoma is cisplatin or carboplatin with etoposide in the first-line setting. For second-line treatment, topotecan or cyclophosphamide/doxorubicin/vincristine combination are treatments available. There is no standard of care for patients who are chemotherapy refractory.

4.2 Factors Related to Patient Population

Merkel cell carcinoma is a rare cancer with a lack of effective treatment options resulting in an unmet need. Avelumab is a novel new agent that provides another treatment option.

PAG noted that the trial is for chemotherapy refractory patients but the funding request under review does not limit avelumab to chemotherapy refractory patients. 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). PAG is seeking guidance on whether avelumab would be used before platinum-based chemotherapy or whether avelumab would be used after platinum-based chemotherapy.

4.3 Factors Related to Dosing

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.

4.4 Factors Related to Implementation Costs

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

PAG noted that incremental resources for pharmacy dose preparation and chemotherapy would not be significantly impacted given the very small number of patients treated.

4.5 Factors Related to Health System

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.

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.

4.6 Factors Related to Manufacturer

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One clinician input was received as a joint submission by four oncologists on behalf of the Skin Drug Advisory Committee at Cancer Care Ontario (CCO). Avelumab is to be used for the treatment of mMCC in previously treated adults.

Please see below for a summary of the specific input provided by the registered clinicians.

5.1 Current Treatment(s) for this Type of Cancer

The clinicians providing input identified that the current standard treatment for previously treated patients with mMCC is Cisplatin/etoposide or carboplatin/etoposide, single agent etoposide, Paclitaxel (second line), or phase I clinical trial if they are eligible.

5.2 Eligible Patient Population

The clinicians providing input indicated that Merkel cell is very rare and therefore does not have a high incidence or prevalence.

5.3 Identify Key Benefits and Harms with New Drug Under Review

One of the key benefits of this drug noted by the clinicians was that it has a good response rate of 31% and that most patients were ongoing at 10 months (82%). It was also noted by the clinicians from CCO that this drug has a low risk of immune related events but is otherwise well tolerated.

5.4 Advantages of New Drug Under Review Over Current Treatments

The clinicians from CCO stated that chemotherapy responses currently are short lived and that mMCC is a rare tumour with an unmet need for therapies with durable responses.

5.5 Sequencing and Priority of Treatments with New Drug Under Review

The clinicians providing input from CCO indicated that avelumab in second line would be used post chemotherapy, as well in both treatment naïve and second line, and state that avelumab should strongly be considered as first line. Additionally, the clinicians from CCO note that those patients who are already receiving chemotherapy should have access to avelumab as well, as clinical data strongly supports the benefit.

5.6 Companion Diagnostic Testing

The physicians providing feedback identified no companion diagnostic testing for the drug under review.

5.7 Additional Information

None identified.

6 SYSTEMATIC REVIEW

6.1 Objectives

The primary objective of this review is to evaluate the efficacy and safety of avelumab (Bavencio) monotherapy for the treatment of metastatic Merkel cell carcinoma (mMCC) in previously treated adults.

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

A Supplemental Question, covered in detail in Section 7, considers the critical appraisal of the manufacturer-submitted data from observational studies used as historical controls.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 3. Selection Criteria

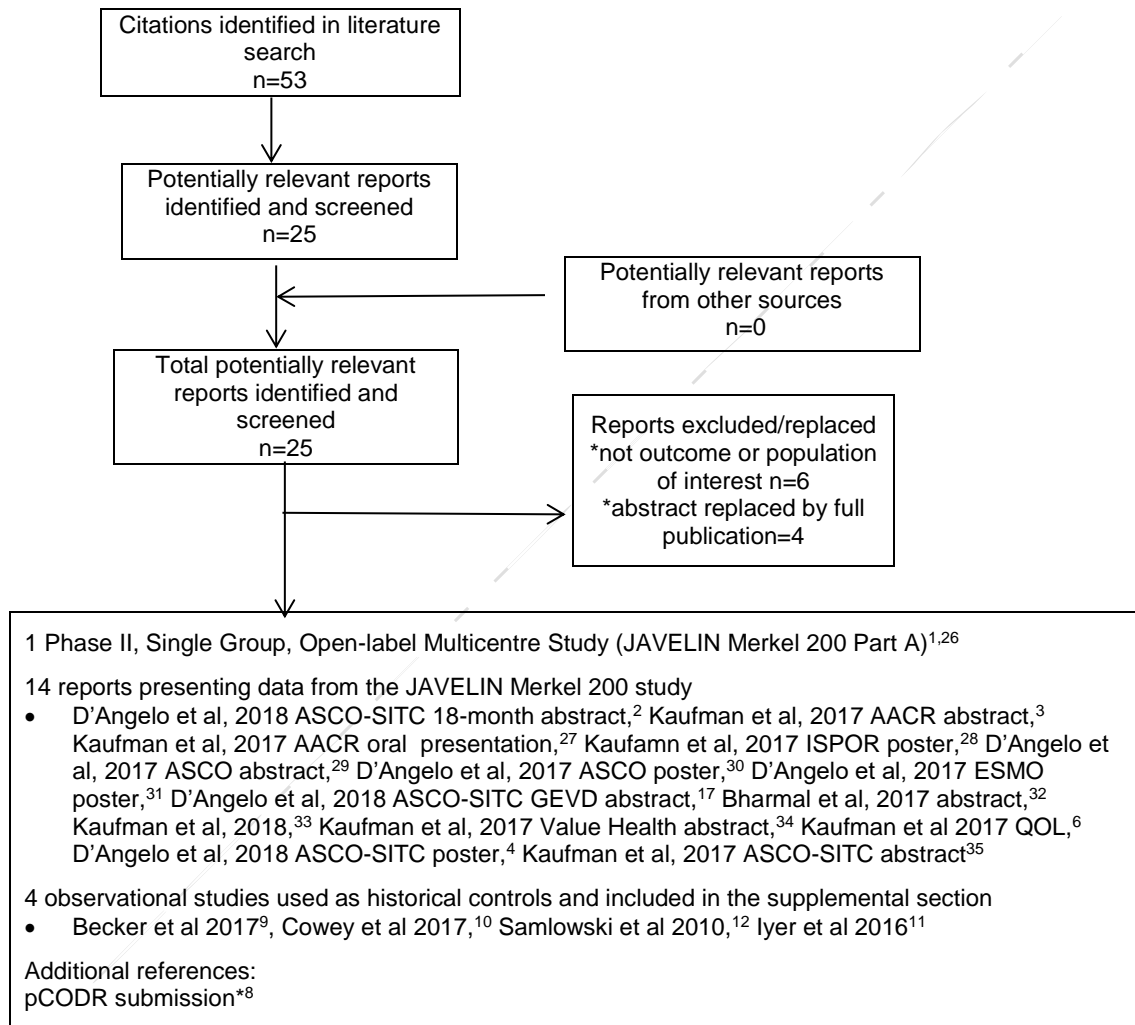| Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs. In the absence of RCTs, fully published non-comparative clinical trials investigating efficacy and safety of avelumab should be included.	Adult patients with metastatic MCC who were previously treated.	Avelumab	All appropriate chemotherapy regimens including but not limited to: • cisplatin ± etoposide • carboplatin ± etoposide • Topotecan • CAV Best supportive care	<u>Primary</u> • BOR, defined as CR, PR, SD or PD <u>Secondary</u> • DoR • **PFS** • OS • **HRQoL** <u>Safety</u> • **AE** • SAE • WDAE • irAE
RCT = randomized controlled trial; MCC = Merkle cell carcinoma; CAV= Cyclophosphamide, Doxorubicin, Vincristine; BOR = best overall response; CR= complete response; PR = partial response; SD= stable disease; PD = progressive disease; DoR = duration of response; PFS = progression-free survival; OS=overall survival; HRQoL = health-related quality of life; AE = adverse events; SAE = serious adverse events; WDAE = withdrawals due to adverse events; irAE= immune-related adverse events				

Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)

6.3 Results

6.3.1 Literature Search Results

Of the 25 potentially relevant reports identified, 1 trial[1,26] with data presented in 14 reports was included in the pCODR systematic review,[2-4,6,17,27-35] 6 studies were excluded and 5 were abstracts that were replaced by subsequent full publications. Studies were excluded because they did not include an outcome or the correct population of interest.

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies

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┌──────────────────────────────┐
│ Citations identified in       │
│ literature search             │
│ n=53                          │
└──────────────┬───────────────┘
               │
               ▼
┌──────────────────────────────┐
│ Potentially relevant reports  │
│ identified and screened       │        ┌──────────────────────────────┐
│ n=25                          │◄───────│ Potentially relevant reports  │
└──────────────┬───────────────┘        │ from other sources            │
               │                        │ n=0                           │
               ▼                        └──────────────────────────────┘
┌──────────────────────────────┐
│ Total potentially relevant    │        ┌──────────────────────────────┐
│ reports identified and        │        │ Reports excluded/replaced     │
│ screened                      │───────►│ *not outcome or population    │
│ n=25                          │        │ of interest n=6               │
└──────────────┬───────────────┘        │ *abstract replaced by full    │
               │                        │ publication=4                 │
               ▼                        └──────────────────────────────┘
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1 Phase II, Single Group, Open-label Multicentre Study (JAVELIN Merkel 200 Part A)[1,26]

14 reports presenting data from the JAVELIN Merkel 200 study
- D'Angelo et al, 2018 ASCO-SITC 18-month abstract,[2] Kaufman et al, 2017 AACR abstract,[3] Kaufman et al, 2017 AACR oral presentation,[27] Kaufamn et al, 2017 ISPOR poster,[28] D'Angelo et al, 2017 ASCO abstract,[29] D'Angelo et al, 2017 ASCO poster,[30] D'Angelo et al, 2017 ESMO poster,[31] D'Angelo et al, 2018 ASCO-SITC GEVD abstract,[17] Bharmal et al, 2017 abstract,[32] Kaufman et al, 2018,[33] Kaufman et al, 2017 Value Health abstract,[34] Kaufman et al 2017 QOL,[6] D'Angelo et al, 2018 ASCO-SITC poster,[4] Kaufman et al, 2017 ASCO-SITC abstract[35]

4 observational studies used as historical controls and included in the supplemental section
- Becker et al 2017[9], Cowey et al 2017,[10] Samlowski et al 2010,[12] Iyer et al 2016[11]

Additional references:
pCODR submission*[8]

Note: Additional data related to JAVELIN Merkel 200 were also obtained through requests to the Submitter by pCODR[8]

6.3.2 Summary of Included Studies

One multicentre, international, prospective, single-arm, open-label, phase 2 study was identified that met the eligibility criteria and is included in this systematic review (Please see Table 4). The JAVELIN Merkel 200 Part A study evaluated the efficacy and safety of treatment with avelumab in patients with stage IV Merkel cell carcinoma that had progressed after cytotoxic chemotherapy. An assessment of study quality is found in Table 5.

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of Trial Characteristics of the Included Studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Study NCT02155647 JAVELIN Merkel 200 Other Study ID numbers EMR100070-003 Title: Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial A Phase II, Single Group, Open-label Multicentre Study Active, recruiting, 35 cancer treatment centres from the USA, Europe including Germany, Italy, France, Spain, Switzerland, and Japan and Australia N enrolled = 88 Patient Enrollment Dates: From July 3, 2014 Data cut-off: March 3, 2016 (primary analysis, 6 month) Sept 3, 2016 (12 month) March 24, 2017 (18 month) Estimated completion date: June 30, 2025	Key Inclusion Criteria: • Age ≥ 18 years • Histologically confirmed diagnosis of MCC including immunohistochemical detection of CK 20 (or other appropriate cytokeratin expression) in the tumour cell • Patients must have had metastatic disease that had progressed after at least 1 line of prior chemotherapy • Treatments much have included one of the following: cyclophosphamide, topotecan, doxorubicin, epirubicin, vincristine, carboplatin, cisplatin, etoposide in combination with carboplatin or cisplatin • Biopsy material was required (archival tissue was acceptable if patient could not provide fresh or recent biopsy) • ECOG performance status score of 0 to 1 at study entry • Estimated life expectancy ≥12 weeks • At least one unidimensional measurable lesion by RECIST v1.1 (including skin lesions) • Adequate haematological, hepatic, and renal function Key Exclusion Criteria: • Concurrent treatment with an anticancer treatment or other nonpermitted drug • Radiotherapy was not allowed if lesions were considered target lesions in the efficacy evaluation • Prior therapy with any drug targeting T cell coregulatory proteins • Major surgery for any reason within 4 weeks • Concurrent systemic therapy with corticosteroids or other immunosuppressive agents • Patients with active central nervous metastases were excluded, and patients with previously treated CNS metastases were not eligible unless they had fully	Avelumab solution at 10 mg/kg by 1 hour intravenous infusion once every 2 weeks, given until disease progression, unacceptable toxicity, or for patients who achieved a confirmed complete response (CR) a maximum of 12 months after confirmation	Primary • BOR per RECIST by IRC, defined as CR, PR, SD or PD Secondary • DoR • PFS • OS • Response status • Safety • Population pharmacokinetic profile • Immunogenicity of avelumab Exploratory • Tumour assessment by investigator • Tumour shrinkage in target lesions from baseline

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
September 27, 2019 (Final data collection date for primary outcome measure) Sponsor: EMD Serono in the USA and Merck KGaA for all other countries	recovered from treatment, demonstrated no progression for at least 2 months, and did not require steroid therapy • Previous malignant disease (other than MCC) within the last 5 years, with the exclusion of basal or squamous cell carcinoma of the skin or cervical carcinoma in situ • Prior organ transplantation, known history/ testing positive for HIV/AIDS, HBV, or HCV • Active or history of any autoimmune disease or immune-deficiencies that required treatment with a systemic immunosuppressant • Persisting toxicity related to prior therapy that was grade >1 according to NCI-CTCAE v4.0; grade ≤2 sensory neuropathy was allowed • Pregnancy or lactation • Known alcohol or drug use • Clinically significant cardiovascular disease or other significant diseases, which in the investigator's opinion may have influenced the patient's tolerance of trial treatment		

MCC = Merkel cell carcinoma; BOR = best overall response; CR= complete response; PR = partial response; SD= stable disease; PD = progressive disease; DoR = duration of response; PFS = progression-free survival; OS=overall survival;

Table 5: Select quality characteristics of the included trial of avelumab in patients with mMCC

Domain	Assessment	Methods Team Comments
Bias due to confounding	Moderate risk	Insufficient adjustment for confounders
Bias in selection of participants into the study	Low risk	No concerns in patient selection
Bias in classification of interventions	Low risk	No concerns with intervention
Bias due to deviations from intended interventions	Moderate risk	Protocol deviations not adequately explained
Bias due to missing data	Low risk	Missing data explained
Bias in measurement of outcomes	High risk	Prone to bias due to lack of blinding
Bias in selection of the reported result	Low risk	Unlikely to be manipulated
Overall*	*Moderate risk*	

a) Trial

JAVELIN Merkel 200 Part A study was conducted in 35 centres in North America, Europe, Australia, and Asia and was sponsored by EMD Serono in the USA and Merck KGaA for all other countries.

Between July 2014 and September 2015 88 eligible adult patients with histologically confirmed stage IV Merkel cell carcinoma refractory to chemotherapy were enrolled.[1] Patients received avelumab 10 mg/kg by 1 hour intravenous infusion once every 2 weeks until confirmed disease progression, unacceptable toxicity, or occurrence of any other criteria for withdrawal.[1] Treatment with avelumab is indicated until disease progression or unacceptable toxicity or for patients who achieved a confirmed complete response a maximum of 12 months after confirmation. Treatment beyond 12 months in these patients 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 6 weeks later was done. Remaining on treatment beyond observation of progressive disease was permitted provided there was no significant clinical deterioration.[1] Patients who had a confirmed complete response 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. Dose-level reductions were not permitted.[1]

Key inclusion criteria were as follows: adults aged 18 years who had received at least one line of chemotherapy for the treatment of mMCC; estimated life expectancy of more than 12 weeks; at least one unidimensional measurable lesion by RECIST v1.1; histologically confirmed Stage IV MCC; progression after the most recent line of chemotherapy; immune-competent, and naïve to therapies targeting T-cell co-regulatory proteins; no activated vaccines within 4 weeks of trial or while on trial; ECOG PS 0-1 and adequate haematological, hepatic, and renal function.[1]

Key exclusion criteria included: concurrent treatment with an anticancer treatment or other non-permitted drug; prior therapy with any drug targeting T cell coregulatory proteins; concurrent systemic therapy with corticosteroids or other immunosuppressive agents, or use of any investigational drug within 28 days before starting trial drug; active central nervous metastases, previous malignant disease (other than MCC) within the last 5 years, prior organ transplantation, including allogenic stem-cell transplantation; known history or testing positive for HIV/AIDS, HBV, or HCV and active or history of any autoimmune disease or immune-deficiencies that required treatment with a systemic immunosuppressant.[1]

Efficacy endpoints were analyzed in all subjects who received at least 1 dose of avelumab (modified ITT analysis set). The primary endpoint was confirmed best overall response, defined as complete response, partial response, stable disease, or progressive disease, according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). It was assessed by an independent endpoint review committee. Secondary endpoints included duration of response, progression-free survival, overall survival, response status by RECIST at 6 and 12 months, safety, population pharmacokinetic profile, and immunogenicity of avelumab. Exploratory endpoints included tumour assessment by investigator using RECIST v1.1 and modified immune-related response criteria, and tumour shrinkage in target lesions from baseline.[1]

The sample size calculation assumed an ORR of 35% for avelumab with an overall alpha = 0.025 (1-sided) for the test of the null hypothesis of an ORR ≤ 20%. A group

sequential testing strategy was employed to assess efficacy in an interim analysis 6 months after start of treatment for the first 56 subjects, as well as in the primary analysis 6 months after the first treatment of the last subject (EPAR report 2017). The planned total sample size was calculated to be 84 subjects.[1]

A total of 13.6% (12/88) subjects had one or more important protocol deviations that included the following:[7]

- 5 patients were enrolled although ineligible (1 subject had prior therapy with antibody targeting T-cell co-regulatory proteins, 1 subject had a previous malignancy within 5 years, 2 subjects had lymphocytes below the required level at screening, 1 subject had brain metastases)
- 5 subjects took prohibited medications (steroids used not to treat irAEs)
- 3 subjects did not receive premedication

Minor deviations also occurred and were mainly related to laboratory assessment (e.g. missing tests), visit schedule (e.g. out of planned range) and study procedure (e.g. ECG not performed).

b) Populations[1,7]

Details for baseline characteristics for JAVELIN Merkel 200 Part A are listed in Table 6. There were a total of 88 eligible patients enrolled in the study. The median age was 72.5 and ranged from 64.5 to 77.0. The majority of patients were males (74%) and all patients had distant metastatic disease at time of enrolment, with a median time since diagnosis of metastatic disease of 10.4 months (range 6.3 to 17.2 months). All patients had at least one previous line of systemic anticancer treatment, including at least one for metastatic disease; 36 patients (41%) had received two or more previous lines of therapy. The median time since last disease progression following prior systemic treatment was 1.3 months (range 0.8 to 2.0 months). The majority of patients (68%) received a platinum-containing regimen in their last previous treatment. Skin was the primary tumour site in most patients (76%) and visceral metastases were present in just over half of all patients. 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 polyoma virus status was assessed by immunohistochemistry and 60% of the 77 patients assessed were MCV-positive.

Subjects had a median follow-up time of 10.4 months (range 6.0 to 19.3 months), defined as the time from first trial treatment to primary analysis cut-off date (3 March 2016).[28]

Table 6. Baseline Characteristics of JAVELIN Merkel 200 Part A Trial[1]

Characteristics	Avelumab (N=88) n (%)
Gender	
Male	65 (74)
Female	23 (26)
Age (range)	72.5 (64.5-77.0)
<65 years	22 (25)
≥65 years	66 (75)
ECOG performance status score	
0	49 (56)
1	39 (44)
Site of primary tumour	

Characteristics	Avelumab (N=88) n (%)
Skin	67 (76)
Lymph node	12 (14)
Other	2 (2)
Missing	7 (8)
Number of prior systemic anticancer treatments	
1	52 (59.1)
2	26 (29.5)
>3	10 (11.4)
Visceral disease at study entry	
Present	47 (53)
Absent	41 (47)
Tumour PD-L1 expression†	
Positive	58 (66)
Negative	16 (18)
Not assessable*	14 (16)
Tumour MCPyV status††	
Positive	46 (52)
Negative	31 (35)
Not assessable*	11 (13)
*†Concentrations of PD-L1 protein and Merkel cell polyomavirus (MCPyV) large T-antigen expression by tumour cells were measured by immunohistochemical analysis of formalin-fixed, paraffin-embedded blocks or slides of the most recent biopsy or surgical specimen. PD-L1 positivity was defined in this study as a threshold level of 1% positive tumour cells of any intensity. *Non-assessable specimens included those that were missing, of poor quality, or otherwise not available to provide results.*	

c) Intervention[1]

Avelumab was administered as a 1-hour IV infusion at 10 mg/kg once every 2-week treatment cycle.(clinical protocol) The dose of avelumab was calculated based on the weight of the subject determined on the day of each drug administration.[36] Subjects also received a pre-treatment H1-antihistamine, such as diphenhydramine, and acetaminophen before avelumab treatment for the first 4 infusions of avelumab in order to mitigate infusion-related reactions.[36] Premedication for subsequent avelumab doses was administered based upon clinical judgment and presence / severity of prior infusion reactions.[36] Steroids as premedication were not permitted.

Over a median duration of 17 weeks (IQR 7-37) of treatment, patients received a median of seven doses (IQR 3-18) of avelumab. The mean duration of therapy with avelumab was 23 weeks (range: 2-76.0). 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 least one dose was delayed in 39 (44%) of 88 patients, with delays of 3 to 6 days in 10 (11%) and 7 or more days in 29 (33%) patients.[1] As of the 3 March 2016 data cut-off, 30 out of 49 patients with investigator-determined progressive disease (PD) (per RECIST 1.1 criteria) had at least one administration of avelumab after their progression date.[8] The duration of the post-progression treatment ranged from 0.03 months to greater than 14.3

months.[8] Two patients were reported to have subsequent radiologic tumor response after their PD, with one having a partial followed by subsequent complete response and the other patient a complete response.[8]

d)   Patient Disposition[2,5]

As of the March 2016 cutoff date, 88 subjects had received at least 1 dose of study treatment. Of the 62 subjects who discontinued treatment (not due to non-compliance or lost to follow-up), 7 (8%) discontinued due to death, 44 (50%) for disease progression, 3 (3%) due to adverse events, 4 (5%) withdrew consent, and 3 (3%) for other reasons.[5] There were 15 (17.0%) subjects who discontinued treatment but were still in follow-up.[5] Updated data for the 18 month follow-up indicate that 73 subjects had discontinued treatment, 10 (11.4%) due to death, 42 (47.7%) due to disease progression, 8 (9%) due to adverse events, 4 (4.5%) withdrew consent, and , and 7(8.0%) for other reasons.[2,4]

Table 7. Summary of JAVELIN Merkel 200 Part A patient disposition[2,4]

	Avelumab (n=88)
	Number (%) of patients
Patients screened	125
Patients who received at least 1 dose of study treatment	88 (100.0)
Treatment ongoing at 18 month data cut-off, 24 March 2017	19 (21.6)
Off treatment	73 (83.0)
Patient who discontinued study treatment	73 (83.0)
• Adverse events	8 (9.1)
• Death	10 (11.4)
• Disease progression	42 (47.7)
• Withdrew consent	4 (4.5)
• Other	7 (8.0)
• Lost to follow-up	1 (1.1)
• Protocol noncompliance	1 (1.1)
Subjects discontinued treatment with continuing responses*	7 (8)*
*5 complete responses + 2 partial responses	

e)   Limitations/Sources of Bias

Overall results are limited by the level of evidence and ability to inform comparative efficacy against relative comparators in the second-line treatment of metastatic Merkel cell carcinoma setting. This is a single-arm, non-randomized, open-label study that lacked blinding of all participants and investigators. As such, it is at risk for biases that can affect internal validity, such as performance bias due to knowledge of the study treatment. The single-arm, non-randomized design also makes interpreting the efficacy and safety/adverse event attributable to avelumab challenging, since all patients received the same treatment.

Furthermore, reported results are from analyses with relatively few data points, which may lead to imprecise estimates.

Other potential sources of bias from the JAVELIN Merkel 200 Part A study include the following:

- Eighteen (20%) patients out of 88 patients were not assessable for confirmed best overall response. The true estimate of effect with avelumab is unknown; patients may have experienced response, stable disease, or progressive disease with avelumab treatment.
- There is no Merkel cell carcinoma-specific quality of life instrument available and as such FACT-Melanoma was used to measure health-related quality of life with avelumab treatment. A psychometric validation study published in abstract form only suggests that the FACT-M may be appropriate to assess the HRQoL of patients with MCC; however, the results should still be interpreted with some caution.[37]
- There were no Canadian sites for JAVELIN Merkel 200 Part A, thus the generalizability of results to Canadian clinical practice is unknown.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

PRIMARY OUTCOME
Best Overall Response (BOR)

Analysis for BOR, initially performed based on the March 3 2016 cut-off, was updated to assess long term efficacy after at least 18 months. At the 24 March 2017 cut-off, the proportion of patients who achieved an objective response according to independent review committee (IRC) by RECIST version 1.1 was 33% (95% CI: 23.3-43.8), 11.4% (10/88) of which had complete responses and 21.6% (19/88) of whom had partial responses.[2,3] (Table 8) Of the 18 patients whose responses were not evaluable, 14 were due to no post-baseline assessment, 2 were due to insufficient or missing radiologic scans, 1 was due to a new anticancer therapy stated prior to first post-baseline assessment, and 1 was due to an SD of insufficient duration.[5] Of note, the concordance between the Investigator and the IERC in their assessments of subjects classified either as having a response or as not having a response reached 91%.[1]

A further post-hoc sensitivity analysis in 64 patients who met key eligibility criteria, had measurable disease at baseline by independent review committee assessment, and had at least one post-baseline assessment was also conducted to evaluate the robustness of the primary analysis results. The proportion of patients who achieved an objective response in this analysis was 40.6% (95% CI 28.5–53.6).[1]

Exploratory post-hoc subgroup analyses of objective response were done on the basis of patient and disease characteristics at baseline. Baseline features, including age, region, functional status, lymph node metastases, or known/unknown primary status did not show differences in response. Notably, response was seen irrespective of the presence of visceral metastases and high tumour burden. The effect of the number of previous systemic treatments on outcomes was also analysed and showed patients with one line of prior systemic therapy (n=52)

responded better to treatment than those patients with at least two prior lines of therapy (n=36) (ORR: 40.4% [95% CI: 27.0-54.9] vs. 19.4% [95% CI, 7.5-37.5].[35]

Among biomarkers, meaningful responses were observed in all subgroups including permutations of combined PD-L1 and MCPyV status. PD-L1 expression, defined by a cut-off of 1% positive tumor cells, was associated with an ORR of 18.8% (95% CI: 4.0, 45.6) for PD-L1 negative subjects, and an ORR of 36.2% (95% CI: 24.0, 49.9) for PD-L1 positive subjects, resulting in an odds ratio (OR) for response of 2.46, (95% CI: 0.57, 14.62).[7] When PD-L1 expression was defined by a 5% cut-off, the ORR was 57.9% (95% CI: 33.5,79.7) for PD-L1 positive subjects and 23.6% (95% 13.2, 37.0) for PD-L1-negative subjects, resulting in an OR of 4.44 (95% CI: 1.26, 15.51).[7] For tumor MCV-positive status by IHC, the ORR was 26.1% for positive status and 35.5% for negative status with OR of 1.56 (95% CI: 0.51, 46.7) indicating no clear trend due to the wide CI.[38] Responses were observed in all combinations of PD-L1 (either 1% or 5%) and MCV.

Secondary Endpoints
Duration of Response
The updated efficacy analysis with a minimum of 18 months follow-up, reported continuing responses with only one additional subject experiencing disease progression. Among subjects with a confirmed response (n=29), a total of 26 subjects (Kaplan-Meier [KM] estimate: 93%; 95% CI: 75, 98) had a duration of response ≥6 months, and 18 subjects (KM estimate: 71%; 95% CI: 51, 85) had a duration of response ≥12 months.[4] The proportion of patients with a duration of response ≥18 months was 66% (KM estimate) (95% CI: 44-81).[4] The median duration of response was not estimable (NE) (95% CI: 18.0 months, NE).[2] The maximum duration of response was ongoing at 24.9 months.[2]

Progression-free Survival
As of the March 24, 2017 data cut-off, the KM estimated progression-free survival rates at 12 and 18 months were each 29% (95% CI: 19-39).[2,4] The Kaplan-Meier curve for PFS shows a plateau in survival being reached, with data still maturing. Such a plateau is not evident in chemotherapy data (See section 7). The plateau for PFS beyond 6 months was driven by subjects with prolonged responses (25 of 29 progression-free subjects at 6 months) with only 3 due to prolonged stable disease and 1 due to non-CR/non-progressive disease.

Overall Survival
As of the March 24, 2017 cut-off date, 54 (61.4%) subjects had died and the median OS was 12.6 months (95% CI: 7.5-19.0). The KM estimated survival rate was 51% (95% CI: 40-61) at 12-months and 40% (95% CI: 29, 50) at 18-months.[2,4]

Conditional landmark analyses were used to compare OS between patients with and without an independently confirmed OR up to day 47.[17] A total of 20 patients had an initial OR reported up to day 47, with 7 further patients having an OR between day 48 and day 89, and 2 patients having an OR after day 89, including 10 complete responses. There were 5 patients who died and 1 withdrew consent before day 47 (all without OR).[17] Survival probabilities 18 months after treatment initiation were 0.900 (95%CI: 0.656-0.974) for patients with OR up to day 47 vs. 0.262 (95% CI 0.157-0.378) for patients without OR but alive up to day 47.[17] Similar results were observed for the 89-day landmark. In an unadjusted Cox model, OR was associated with a 94% risk reduction of death (hazard ratio: 0.064 [95% CI: 0.022; 0.181]). The

hazard ratio in the adjusted model (controlling for age, visceral disease, and number of previous therapies) was 0.052 (95% CI: 0.018-0.152).

Tumour Shrinkage[7]

An exploratory analysis considered the percentage change from baseline in target lesions over time and the pattern of responses to avelumab. Most decreases in target lesions begin within the first 6 weeks of treatment while few subjects had at least a 20% increase from baseline in target lesions followed by a decrease. The majority of responses with at least a 30% decrease from baseline in target lesions (n=29) were persistent and durable (≥12 months).

Table 8: Summary of Key Efficacy Outcomes in JAVELIN Merkel 200 Part A Trial[1,2,4,33,39]

	JAVELIN Merkel 200 Part A (n=88)		
	12 month minimum follow-up (data cut-off 3 Sept 2016)[7]	**18 month minimum follow-up** (data cut-off 24 March 2017)[2,4]	**24 month minimum follow-up** (data cut-off NR)[8]
Median follow-up (months)	16.4	23.0	NR
	N (%)	N (%)	N (%)
BOR per RECIST 1.1 by IRC			
Complete Response (CR)	10 (11.4)	10 (11.4)	NR
Partial Response (PR)	19 (21.6)	19 (21.6)	NR
Stable Disease	9 (10.2)	9 (10.2)	NR
Progressive Disease	32 (36.4)	32 (36.4)	NR
Non-CR/Non-PD	0	0	NR
Not evaluable	18 (20.5)	18 (20.5)	NR
Objective Response Rate (ORR)			
Response rate (CR+PR) (95% CI)	29 (33.0) (23.3-43.8)	29 (33.0) (23.3-43.8)	29 (33.0) (23.3-43.8)
Duration of Response* (DOR)			
Median, months (95% CI)	NE (18.0-NE)	NE (18.0-NE)	NE (18.0-NE)
Durable Response Rate (DRR)			
% (95% CI)	28.4 (NR)	30.6 (21.0-40.3)	NR
Response Status			
Proportion of duration of response, % (95% CI)	At 12 months: 74 (53-87)	≥ 18 months: 66 (44-81)	NR
Progression-free Survival (PFS)			
Median, months (95% CI)	2.7 (1.4 - 6.9)	2.7 (1.4 - 6.9)	2.7 (1.4-6.9)
PFS by KM, % (95%CI)	30 (19-39)	29 (19-39)	26 (16-36)
Time to Response			
Median, weeks	8.6 ± 6.1	NR	NR
Overall Survival (OS)			
Median, months (95%CI)	12.9 (7.5-NE)[33]	12.6 (7.5-19.0)	12.6 (7.5-17.1)
OS rate by KM, % (95% CI)	12 month: 52 (41-62)[33]	18 month: 40 (29-50)	24 month: 36 (26-46)

*Based on number of subjects with confirmed response (CR+PR)

Quality of Life (QOL)[6,34]

Functional Assessment of Cancer Therapy – Melanoma (FACT-M) and Trial Outcome Index (TOI)

As there are no MCC-specific QOL instruments, the FACT-M questionnaire was used. Despite some differences between MCC and melanoma, including worse prognosis for MCC, the content of the FACT-M seems appropriate to assess health-related quality of life (HRQoL) in subjects with MCC[6,37] It is comprised of physical, social/family, emotional and functional well-being subscales, as well as the additional concerns scale consisting of specific melanoma cancer symptoms. All FACT-M scales are scored so that a high score represents better HRQoL.[38] FACT-M was completed by patients at baseline, week 7, every 6 weeks until disease progression and at the end of treatment.[6]

A linear mixed model (LMM) analysis fitted for change from baseline for each scale was conducted and minimal important differences (MID) were used to interpret meaningful changes.[6] A total of 70 patients were analyzed and no meaningful changes were observed from each scale during treatment. Correlations between reduction in tumor size and improvements in FACT-M were moderate at week 7 for Functional Well-being (-0.47), TOI (-0.36), FACT-M total (-0.36), and FACT-G total (-0.34), suggesting that QoL improves as the tumour shrinks. Mean differences in change from baseline scores between non-PD and PD were in the range of published MIDs for melanoma subscale (difference = 2.79, p = 0.005), melanoma surgery scale (difference = 1.48, p = 0.089), TOI (difference = 5.68, p = 0.004), FACT-G total score (difference = 4.37, p = 0.022), FACT-M total score (difference = 7.03, p = 0.006), EQ-5D VAS (difference = 7.04, p = 0.024) and EQ-5D utility score (difference = 0.07, p = 0.003).[6] A decrement in all scales was seen at end of treatment, which was attributed to disease progression for the most part. Sensitivity analyses, conducted to explore the impact of missing data, found consistent results with modest increases in estimated differences.[1]

Follow-up results 12 months after enrollment of the last patient, showed that, overall no meaningful changes from baseline were seen for FACT-M scales during treatment visits up to week 49 in 70 analyzed patients.[32] However, there was a meaningful worsening in HRQoL observed for all scales at the final assessment before end of treatment (EOT) and at EOT this was primarily associated with disease progression(63.6%).[32] LMM showed significant differences between patients who had disease progression and those that did not in the expected directions. Mean changes were in the range of MIDs for physical well-being (1.40), emotional well-being (1.52), melanoma (3.07), TOI (5.68), FACT-G total (4.37) and FACT-M total (7.03).[32] The models showed improvement in emotional well-being (1.70) for patients without disease progression and a worsening in physical well-being (-1.68), TOI (-4.01), FACT-G total (-4.44) and FACT-M total (-5.64) for patients with disease progression.[32] Outcomes did not differ by timing of dropout, as demonstrated by sensitivity analysis.

Associations between changes in tumour size during treatment (sum of target lesion size (SLD)) and changes in HRQoL were also evaluated.[34] Mean HRQoL score changes corresponding to a 30% reduction in tumour size were predicted and interpreted in the context of published MID. The median SLD at baseline was 83mm (range: 16-404mm).[34] A 30% SLD reduction at week 7 was associated with clinically meaningful improvements (mean change) in Functional Well-being (1.89), FACT-M Trial

Outcome Index (4.20), FACT-G total (3.84), FACT-M total (5.52) and EQ-5D-5L utility index (0.06).[34] Gain in EQ5D-5L utility index remained at week 13 (0.03) but no other associations were observed at subsequent time points[34].

Harms Outcomes[2,4,7]

As of the March 24, 2017 data cut-off, a total of 66 (75%) patients experienced any treatment-related AEs (all CTCAE grades). The most common treatment-related AE was fatigue, occurring in 25% of patients, followed by rash at 15.9%. A total of 19 patients (21.6%) had an infusion-related reaction (IRR), which were all grade 1 or 2 and occurred at the first or second infusionNausea and diarrhea were equally as common, seen in 11.4% of patients (Table 9).[2,4] There was a total of eight (9.1%) grade 3 treatment-related adverse events. There were no treatment-related deaths.[4] Table 10 outlines the treatment-emergent adverse events (TEAE) from the March 3, 2016 data cut-off.

Overall, as of the March 24, 2017 data cut-off, immune-related adverse events (irAEs) of any grade were reported in 19.3% of subjects. Individual types of irAEs were relatively infrequent, with no one type of event occurring in > 6% of subjects. The most common (> 1% of subjects) irAEs included hypothyroidism (5.7%), rash (5.7%), diarrhea (2.3%) and erythema (2.3%). The incidence of Grade ≥ 3 irAEs was 4.5%.[4] There were no Grade ≥4 irAEs reported in this study

Table 9. Treatment-related Adverse Events (Any Grade) in >1 patient[2,4]

Patients with any treatment-related adverse event, n (%)	Avelumab (n=88)	
	All Grades (1-3)	**Grade ≥3**
	66 (75.0)	8 (9.1)
Fatigue	22 (25.0)	0
Rash**	14 (15.9)	
Infusion-related reaction*	13 (14.8)	0
Nausea	10 (11.4)	0
Diarrhea	10 (11.4)	0
Blood CPK increased	6 (6·8)	2 (2.3)
Hypothyroidism	6 (6.8)	1 (1.1)
ALT increase	4 (4.5)	1 (1.1)
GGT increase	2 (2.3)	1 (1.1)
Autoimmune disorder	1 (1.1)	1 (1.1)
Blood cholesterol increased	1 (1.1)	1 (1.1)
Ileus	1 (1.1)	1 (1.1)
Transaminases increased	1 (1.1)	1 (1.1)

*An infusion-related reaction in this analysis was based on a composite definition with 5 different MedDRA terms. Signs and symptoms of a potential infusion-related reaction (eg, fever, chills, or rigors) reported on the day of infusion were queried with investigators to ascertain whether an AE of "infusion-related reaction" should be recorded.
**Includes rash, rash maculopapular, and rash pruritic

Table 10. Treatment Emergent Adverse Events (TEAE)[1,7]

	Total number (%) of patients[a]
	Avelumab (N=88)
TEAE category	
Any TEAE	86 (97.7)

Any TEAE of Grade 3 or higher	54 (61.4)
Related TEAE	62 (70.5)
Related TEAE of Grade 3 or higher	4 (4.5)
TEAE leading to permanent treatment discontinuation	2 (2.3)
Related TEAE leading to permanent treatment discontinuation	1 (1.1)
Serious TEAE	36 (40.9)
Related Serious TEAE	5 (5.7)
TEAE leading to death	8 (9.1)
Related TEAE leading to death	0
IrAE	14 (15.9)
IRR*	19 (21.6)
Treatment related IRR	19 (21.6)

[a] As of the March 3, 2016 data cut-off
* IRRs are defined by a pre-specified MedDRA PT query including signs and symptoms of IRRs and time to first onset of the event
Note: irAEs and IRRs according to the updated case definition.
irAE = immune-related adverse event, IRR = infusion-related reaction, MedDRA = Medical Dictionary for Regulatory Activities, and TEAE = treatment-emergent adverse event

6.4 Ongoing Trials

Ongoing trials of avelumab for the treatment of metastatic Merkel cell carcinoma (mMCC) in previously treated adults are listed below.

Table 11: Ongoing trials of avelumab in metastatic Merkel cell carcinoma

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
JAVELIN Merkel 200 Part B NCT02155647 2014-000445-79 (EudraCT Number) Multicentre, international, single-arm, open-label interventional study N: 200 Start date: July 3, 2014 End date: primary completion date (final data collection) is September 27, 2019 and estimated completion date is June 30, 2025. Sponsor: EMD Serono/Merck KGaA	<u>Key Inclusion Criteria:</u> • Confirmed metastatic MCC naïve to systemic treatment • Age ≥ 18 years • ECOG PS 0-1 at study entry • Estimated life expectancy ≥12 weeks • At least one unidimensional measurable lesion by RECIST v1.1 • Adequate haematological, hepatic, and renal function <u>Key Exclusion Criteria:</u> • Concurrent treatment with an anticancer treatment or other nonpermitted drug • Radiotherapy was not allowed • Prior therapy with any drug targeting T cell coregulatory proteins • Major surgery within 4 weeks • Concurrent systemic therapy with corticosteroids or other immunosuppressive agents • Patients with active CNS metastases • Previous malignant disease within the last 5 years, • Prior organ transplantation, known history/ testing positive for HIV/AIDS, HBV, or HCV, clinically significant CV disease • Active or history of any autoimmune disease or immune-deficiencies that required treatment with a systemic immunosuppressant • Persisting toxicity related to prior therapy	Avelumab 10 mg/kg 1 hour IV infusion once every 2 week No comparator	<u>Primary:</u> Durable Response <u>Secondary:</u> BOR DoR PFS OS TEAE

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Localized Radiation Therapy or Recombinant Interferon Beta and Avelumab With or Without Cellular Adoptive Immunotherapy in Treating Patients With Metastatic Merkel Cell Carcinoma NCI-2014-02462 FHCRC 9245 NCT02584829 Non-randomized open-label interventional **N**: 20 Sponsor: Fred Hutchinson Cancer Research Center.; EMD Serono; National Cancer Institute Phase 1/2 Start date: Nov 2015 End date July 2019	Inclusion: • Age ≥18 • Confirmation of MCC • If an accessible lesion is present, a biopsy within 6 weeks of intervention • Evidence of MCPyV TAg tumor expression by IHC • ECOG PS ≤ 2 • At least one bi-dimensionally measurable lesion • For patients designated to be treated on Group 2: cardiac ejection fraction ≥ 35%; • At least 3 weeks since any of the following: systemic corticosteroids, immunotherapy, pentoxifylline, other small molecule or chemotherapy cancer treatment, other investigational agents or other systemic agents that target MCC Exclusion • Known active infections • WBC < 200/mcl, Hb < 8 g/dL, ANC < 1000/mcl, Platelets < 50,000/mcl • CV disease • Clinically significant pulmonary dysfunction • Active autoimmune disease • Symptomatic and untreated CNS metastasis; • Clinically significant and ongoing immune suppression • Patients may not be on any other treatments for their cancer aside from those included in the protocol; • Vaccination with live inactivated viral strains within 4 weeks of the start of the study treatment	Avelumab every 2 weeks for 12 months Group 1: Patients who do not have a HLA type for which T cells can be generated or for whom T cells cannot be generated for technical issues receive avelumab intravenously (IV) over 1 hour every 2 weeks for 12 months. Within 7-10 days after completion of 1-3 doses of avelumab, patients receive MHC class I up-regulation intervention comprising either localized radiation therapy or recombinant interferon beta via intra-tumor injection. Group 2: Patients who have an HLA type for which T cells can be generated receive avelumab IV over 1 hour every 2 weeks for 12 months. Patients also receive MHC class I up-regulation intervention as in Group 1 between 7-10 days after the first infusion of avelumab and 2-5 days before the first infusion of MCPyV TAg-specific polyclonal autologous CD8+ T cells. Patients receive two infusions of MCPyV TAg-specific polyclonal autologous CD8+ T cells IV over 60-120 minutes.	Primary: Evidence of response, based on median time to new metastasis AEs Secondary: Disease response Evidence of epitope spreading MCC-specific survival
BOR = best overall response; DoR = duration of response; PFS = progression-free survival; OS=overall survival; TEAE= treatment-emergent adverse event			

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of avelumab for the treatment of patients with metastatic Merkel cell carcinoma who have been previously treated:

- Critical appraisal of the manufacturer-submitted data from observational studies used as historical controls.

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Critical appraisal of the observational studies used as controls

7.1.1 Objective

Given the rarity of the disease and poor prognosis for patients with stage IV disease, it is unlikely there will be randomized head-to-head trials comparing treatment with avelumab to other therapies. Thus, to properly contextualize and interpret the outcomes of the single-arm avelumab clinical trial, observational retrospective analyses become necessary. The objective of this section is to summarize and critically appraise the methods and findings of the data from observational studies used as historical controls.

7.1.2 Observational studies used as controls

For second-line patients, information is available from four sources: the EU and US studies conducted by Merck/Pfizer, for which individual-level data are available;[9,10] the study by Iyer et al.,[11] which reports a Kaplan–Meier for PFS and a median OS for 30 second-line patients; and the study by Samlowski et al.,[12] which reports the outcomes for 23 second-line patients treated with imatinib (only 14 of whom had received prior chemotherapy).

Through a series of analyses, including Weibull curves fit to pooled EU and US studies, inverse variance meta-analysis of the parameters of the Weibull distribution fitted to each available study, and bivariate normal models for PFS and OS accounting for correlation between shape and scale parameters, the manufacturer-submitted report on comparator efficacy indicated:

> "while no single analysis can conclusively estimate the outcomes that would have been seen had JAVELIN Merkel 200 been randomised, the similarity of data from each of the studies indicates that there is very little difference in outcomes."[13]

As such, they conclude that the estimates from the observational studies are a good representation of the likely estimates of outcomes that would have been seen in a randomized trial with chemotherapy as the control.[13]

7.1.2.1 US Second-line Study[10]

Design
This was a retrospective chart review and registry-based study of patients with distant mMCC who have received 2L and later (2L+) chemotherapy. The focus was on subjects in community oncology settings as a way to reflect real-world care in the US.

Population

Patients in this analysis were adults (≥18 years of age) diagnosed with distant mMCC. The primary analysis population of focus was composed solely of immunocompetent patients treated with two or more lines (for the 2L+ analysis) of systemic chemotherapy. Qualifying chemotherapeutic agents for distant mMCC must have included a platinum-based agent (cisplatin or carboplatin) ± etoposide; cyclophosphamide + doxorubicin + vincristine; topotecan; gemcitabine; irinotecan; paclitaxel; nab–paclitaxel; or docetaxel. Patients with a history of any solid tumor, except basal or squamous cell carcinoma of the skin, bladder carcinoma in situ or cervical carcinoma in situ within 3 years prior to the start of treatment for MCC, were excluded from the study. In addition, patients were excluded if they were previously treated with any antibody or drug targeting T-cell coregulatory proteins.

Out of these 39 patients with evidence of 2L+ chemotherapy for metastatic disease, 20 qualified for analysis of which 14 were immunocompetent. The median age was 75.2 years and 78.6% of patients were male. Nearly all patients in the primary analysis population (92.9% [n = 13]) had an ECOG PS of 1 at the start of 2L+ therapy. Most 2L+ patients were initially diagnosed with stage I–III disease, and the most common primary tumor sites were the lower limb or trunk (50.0%), face (21.4%) and upper limb (14.3%). All patients had discontinued treatment at the time of data collection. The most commonly cited reason for discontinuation of treatment was disease progression (57.1% [n = 8]); for 35.7% of patients (n = 5), toxicity was the reason for discontinuation.

Efficacy Results

No patient achieved a CR to 2L+ chemotherapy, although four patients (all immunocompetent) had a PR. In the primary analysis population (immunocompetent), the ORR was 28.6% (95% CI: 8.4–58.1% [n = 4/14]) (Table 13). Responses to chemotherapy were of limited duration in this population: the median DOR was 1.7 months (95% CI: 0.5–3.0 months; range: 0.5–3.0 months). The median PFS was 2.2 months (95% CI: 1.2–3.5 months) (Table 14) and median OS was 4.3 months (95% CI: 2.1-6.2 months). No patient had a response lasting ≥6 months, and hence the DRR was 0%.

7.1.2.2 EU Second-line Study[9]

Design

This was a retrospective a chart review and registry-based study of patients with distant mMCC who have received 2L and later (2L+) chemotherapy. Included were primarily subjects in academic centers in Europe.

Population

Patients included in this study were ≥18 years, diagnosed with distant metastatic MCC, and must have received ≥2 lines of prior systemic chemotherapy for distant metastatic MCC. Patients were excluded if they had a diagnosis of any other solid tumour within 3 years before the start of treatment for MCC, with the exception of basal or squamous cell carcinoma, bladder carcinoma in situ, or cervical carcinoma in situ, were immunocompromised status due to specific haematologic diseases or immunosuppressive treatments were eligible.

Thirty four patients with distant metastatic MCC and who received 2nd or later line chemotherapy were identified and included. Of these 34, 29 were eligible for the subgroup analyses of immunocompetent patients. Among all patients, 64.7% were male and the mean age of this cohort was 64.4 years. (Table 12)

Efficacy Results

Analysis of the immunocompetent population showed an ORR of 10.3% (95% CI: 2.2-27.4) and a median DOR of 1.9 months (95% CI: 1.3-2.1). At 6 months, the DRR was 0%. (Table 13).

Median PFS was 3.0 months (95% CI, 2.5%-3.2%), and the PFS rate at 6 months was 3.4% (95% CI,0.3%-14.9%). (Table 14) Median OS was 5.3 months (95% CI, 4.3%-6.0%), and the OS rate at 6 months was 27.5% (95% CI,13.0%-44.2%). The OS rate at 12 months was 0%.

7.1.2.3 lyer et al study[11]

Design

Detailed medical records of patients with distant metastatic MCC who received cytotoxic chemotherapy were evaluated for efficacy outcome in this retrospective observational study.

Population

The study cohort included 30 patients with distant metastatic MCC receiving second-line chemotherapy. Cases were only included if there was adequate information available on the details of chemotherapy including agent(s) used, the dates of administration, and tumor responses (including follow-up radiologic evaluation). Patients were excluded if tumors could not be evaluated for the efficacy of chemotherapy alone, for example when distant metastatic tumors had been treated with concurrent radiation and/or surgery.

Median follow-up at the end of the study period among all 30 patients who received second-line chemotherapy was 634 days (range 201–2056 days) and among the four living patients who received second-line chemotherapy was 365.5 days (range 201–1477 days). Median time from initiation of treatment to first imaging study (among 58 of the 62 patients with available radiological data) who received first-line chemotherapy was 58 days (range 10–274 days).

Efficacy Results

The response rate to second-line chemotherapy was 23% (7 of the 30 patients; 1 CR, 6 PR) (Table 12). Of patients, 73% (22 of the 30) had progressive disease and one (3%, 1/30) had stable disease. Median PFS among the 30 patients who received second-line chemotherapy was 61 days (range: 11–354 days). Among the one patient with a CR, PFS was 105 days and among the six patients that had a PR, median PFS was 227 days (range: 60–354 days). Of patients treated with second-line chemotherapy, 80% developed progressive disease by 105 days, while 95% did so by 230 days. For patients who had a CR or PR following second-line chemotherapy, the median DOR was 101 days after best response (range: 6–225 days). For the one patient who had a CR, DOR was 21 days and among the six patients that had a PR, median DOR was 107 days (range: 6–225 days). Of the 30 patients who received second-line chemotherapy, 25 died of MCC by the end of the study period, 1 patient died of an unknown cause, and 4 patients were alive (1 had a PR and 3 had PD at end of study). Of note, all seven patients who received topotecan, the most commonly used agent for second-line chemotherapy in this cohort, experienced progressive disease without any evidence of response. The only patient to achieve complete response received carboplatin plus etoposide, although the duration of this response was only 21 days. For patients who received second-line chemotherapy, the median overall survival time from the start of second-line chemotherapy was 5.7 months (range: 35 days to 2.4 years; data not shown).

7.1.2.4 Samlowski et al study[12]

Design
Single arm, open label phase II trial of Imatinib mesylate (Gleevec®), administered at a dose of 400 mg p.o. daily.

Population
Patients enrolled in this trial were required to have biopsy proven MCC (Cutaneous Neuroendocrine Carcinoma) that was metastatic or unresectable. Tumor expression of c-KIT (by immunohistochemistry) and a history of a previous skin primary were required (to exclude metastatic small cell carcinoma of non-cutaneous origin). Patients with an unknown primary site were, therefore, not eligible. Patients were required to have at least one site of measurable disease. Patients with treated, stable, asymptomatic brain metastases were allowed on study.

All radiotherapy, chemotherapy, biologic therapy or any other investigational drug treatment was required to be completed at least 28 days prior to registration. Patients were not allowed to have had major surgery within 14 days prior to registration. Additional eligibility requirements included: adequate hematologic, renal, and hepatic function and a Zubrod performance status ≤ 2. Patients with a second malignancy, as well as women who were pregnant or nursing were excluded from the study. Patients with Class 3/4 cardiac problems by the New York Heart Association Criteria were not eligible, nor were patients taking therapeutic doses of coumadin (warfarin) or those with severe and/or uncontrolled concurrent medical disease.

Median age was 77.1 (with a range of 56.9 to 91.9 years). Seventeen patients (74%) were men, 6 (26%) were women and all were Caucasian. (Table 12)

Efficacy Results
There were no complete responses (0%) and 1 confirmed partial response (4%) in the 23 evaluable patients (4% objective response rate, CI 0 – 22%). In addition, stable disease was observed in 3 patients (9, 4 and 3 months). At the time of analysis, all evaluable patients had developed progressive disease. The estimated median progression-free survival was 1 month (95% CI: 1–2 months), with an estimated 6-month PFS of 4% (95% CI: 0% – 13%) (Table 14). The estimated median overall survival was 5 months (95% CI: 2–8 months). The estimated one-year overall survival was 17% (95% CI: 0% – 33%).(Table 14) There were three deaths on study, all were attributed to progressing tumor.

7.1.3 Summary

Baseline demographics

In general, the demographic and baseline characteristics of the JAVELIN Merkel 200 Part A study and the observational studies were similar. Median age was slightly higher among patients included in the Samlowski et al study. A greater proportion of patients in the US observational and the Samlowski et al studies had a worse PS than patients in the JAVELIN study. Stage at diagnosis was somewhat variable across studies.

To test for any impact of patient characteristics on outcome, the manufacturer performed a series of analyses. The results suggest that no baseline patient characteristic in isolation is a significant predictor of either PFS or OS in second-line MCC using regression analysis, nor do any characteristics appear to affect the outcomes of patients on the Kaplan–Meier plots.[13]

Table 12: Baseline Characteristics[1,7,9-12,38]

Characteristics	JAVELIN Merkel 200 Part A[1] (N=88)	Study 100070[10]-Obs001 US Cohort Immunocompetent (N=14)	Study 100070[9]-Obs001 EU Cohort Immunocompetent (N=29)	Iyer et al[11] Second-line cohort (N=30)	Samlowski et al[12] Second-line with imatinib (N=23)
Gender men/women (%)	65/23 (73.9/26.1)	11/3 (78.6/21.4)	18/11 (62.1/37.9)	24/6 (80/20)	17/6 (74/26)
Age					
Mean, years (SD) Median, (range)	69.7 (10.7) 72.5 (64.5-77.0)	72.5 (11.7) 75.2 (63.6-81.1)	64.4 (11.6) 67.0 (36-80)	NR 69.7 (49-96)	NR 77.1 (56.9-91.9)
Region					
North America (US)	51 (58.0)	14 (100.0)	0	30 (100)	23 (100)
Europe	29 (33.0)	0	29 (100.0)	0	0
Rest of world	8 (9.1)	0	0	0	0
ECOG, n (%)					Zubrod PS
0	49 (55.7)	0	NA	NR	11 (48)
1	39 (44.3)	13 (92.9)	NA	NR	9 (39%)
2	0	0	NA	NR	3 (13%)
Unknown	0	1 (7.1)	NA	NR	0
Stage at diagnosis, n (%)					
I, IA, or IB	13 (14.8)	1 (7.1)	3 (10.4)	2 (7)	NR
II, IIA, or IIB	11 (12.5)	6 (42.9)	5 (17.2)	6 (20)	NR
III, IIIA, or IIIB	26 (29.5)	4 (28.6)	14 (48.3)	13 (43.3)	NR
IV	16 (18.2)	1 (7.1)	7 (24.1)	9 (30)	NR
Missing, unconfirmed, or unknown	22 (25.0)	2 (14.3)	NA	0	NR

Results

Due to the differences in study design, assessments and study populations, formal statistical comparisons between the JAVELIN study and the observational studies were not planned or performed. Instead, results are presented side-by-side in a descriptive way to put the results of JAVELIN Merkel 200 Part A into context and should be interpreted with caution.[14] Caution is needed due to a very high risk of bias when comparing across studies (i.e., the observed difference in effect might be due to differences in prognostic factors and effect modifiers between the studies rather than solely due to differences in the treatments).

Overall, the JAVELIN Merkel 200 Part A study suggests avelumab has a favourable efficacy profile in the second-line or later setting compared with the results observed for chemotherapy in the observational studies. The ORR was higher in subjects treated with avelumab (33.0%; 95% CI: 23.3-43.8) than for chemotherapy-treated immunocompetent subjects in US cohort (28.6%; 95% CI: 8.4-58.1) EU cohort (10.3%; 95% CI: 2.2-27.4), Iyer et al study (7%; 95% CI: 9.9-42.3), and Samlowski et al study (4%; 95% CI: 0-22).[14] (Table 12). The proportion of subjects with a CR was higher in subjects treated with avelumab than those treated with chemotherapy across observational studies. The 6-month DRR was greater with avelumab treatment (30.6%; 95% CI: 20.9-40.3) than with chemotherapy (US cohort: 0.0% [95% CI: 0.0-23.2]; EU cohort: 0.0% [95%

CI: 0.0-11.9]; Iyer et al: 6.7% [95% CI: 0.8-22.1]) (Table 13). Responses were also prolonged with avelumab treatment (6-month durability by K-M: 92% [95% CI: 70-98] vs. 0%, with no subjects having a response longer than 3 months across the US and EU cohorts of the observational study).

Treatment with avelumab also resulted in greater PFS and OS rates at 12 months than did treatment with chemotherapy, as reported in the 4 observational studies. (Table 13) Also of note, the KM curve for PFS shows a plateau in the JAVELIN study, while the Kaplan-Meier curves for the US and EU studies show a continued decline in survival with chemotherapy.

Table 13. Response rates in second-line or later subjects

Efficacy parameter	JAVELIN Merkel 200 Part A ≥18-month follow up[2,4] (n=88)	Study 100070[10]-Obs001 US Cohort Immunocompetent (n=14)	Study 100070[9]-Obs001 EU Cohort Immunocompetent (n=29)	Iyer 2016[11] Retrospective study (n=30)	Samlowski et al [12] Second-line with imatinib (N=23)
BOR per RECIST 1.1					
CR, n (%)	10 (11.4)	0	0	1 (3.3)	0
PR, n (%)	19 (21.6)	4 (28.6)	3 (10.3)	6 (20.0)	1 (4)
SD, n (%)	9 (10.2)	2 (14.3)	3 (10.3)	1 (3.3)	3 (13)
PD, n (%)	32 (36.4)	5 (35.7)	23 (79.3)	22 (73.3)	23 (100)
Non-CR/Non-PD*, n	0	0	0	0	NR
Not evaluable, n (%)	18 (20.5)	3 (21.4)	0	0	0
ORR					
Response rate (CR+PR) (95% CI)	33.0 (23.3-43.8)	28.6 (8.4-58.1)	10.3 (2.2-27.4)	7 (23.3) (9.9-42.3)	1 (4) (0-22)
DoR[d]					
Median, months (95% CI)	NE (18.0-NE)	1.7 (0.5-3.0)	1.9 (1.3-2.1)	3.3	NR
DRR					
At 6 months, % (95% CI)	30.6 (21.0-40.3)	0.0 (0.0-23.2)	0.0 (0.0-11.9)	6.7 (0.8-22.1)	NR

Table 14. Progression-free survival and overall survival rates in second-line or later

Efficacy parameter	JAVELIN Merkel 200 Part A ≥18-month follow up[2,4] (n=88)	Study 100070[10]-Obs001 US Cohort Immunocompetent[a] (n=14)	Study 100070[9]-Obs001 EU Cohort Immunocompetent[a] (n=29)	Iyer 2016[11] Retrospective study[b] (n=30)	Samlowski et al [12] Second-line with imatinib (N=23)
PFS					
Median, months (95% CI)	2.7 (1.4-6.9)	2.2 (1.2-3.5)	3.0 (2.5-3.2)	2.0 (1.3-2.7)	1.0 (1-2)
12- month PFS rate by KM, % (95% CI)	29 (19-39)	0	0	13	NR
OS					

Efficacy parameter	JAVELIN Merkel 200 Part A ≥18-month follow up[2,4] (n=88)	Study 100070[10]- Obs001 US Cohort Immunocompetent[a] (n=14)	Study 100070[9]- Obs001 EU Cohort Immunocompetent[a] (n=29)	Iyer 2016[11] Retrospective study[b] (n=30)	Samlowski et al [12] Second-line with imatinib (N=23)
12-month OS rate by KM, % (95% CI)	51 (40-61)	0	0	NR	17 (0-33)

[a]No responses occurred in the immunocompromised group in the US Cohort (n=6) and EU Cohort (n=5)
[b]Data from Iyer 2016 was reported after 2L chemotherapy and not-specific for immunocompetent patients (13.3% had systemic immune suppression) CI: Confidence interval; KM: Kaplan-Meier; OS: Overall survival; NR: Not reported; PFS: Progression-free survival

Limitations/Sources of Bias

Three of the studies were carried out retrospectively and the inherent limitations of retrospective designs should be taken into consideration.

All studies, with the exception of the European observational study, assessed treatment response according to RECIST. Yet, there are limitations to capturing traditional RECIST-based responses in the retrospective setting.[10] Outside of a trial, clinicians are not typically required to record treatment responses consistent with RECIST and thus, response assessments in the real-world setting can be more subjective than assessments in a controlled clinical trial.[10] As such, it can be expected that the rate of confirmed responses as required by RECIST for efficacy evaluation in prospective clinical trials would be lower than the rate of best responses observed in the retrospective studies, as many of the initial responses were not durable until a confirmatory scan.[11] Moreover, non-evaluable data are generally excluded in retrospective studies which also can inflate the reported response.[38] Assessment of study outcome by investigator rather than an independent review occurred in the Iyer et al study, which also has the potential to exaggerate outcomes. The extent to which response is inflated in the retrospective studies is unknown, but should be considered as a possibility.

While the prospective single-arm study by Samlowski et al included a heavily pretreated patient population, 9 of 23 patients (39%) were in the first line.[12] As these first-line patients are earlier on in the disease pathway and, thus, have a better prognosis their inclusion could also inflate measures of efficacy and effect the generalizability of the results.

8 COMPARISON WITH OTHER LITERATURE

None identified.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Skin & Melanoma Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on avelumab (Bavencio) for metastatic Merkel Cell carcinoma. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH 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 Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines.

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

The Skin & Melanoma Clinical Guidance Panel is comprised of three oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials September 2017, Embase 1974 to 2017 October 18, Ovid MEDLINE(R) ALL 1946 to October 18, 2017

#	Searches	Results
1	(Bavencio* or avelumab* or MSB-0010718C or MSB0010718C or MSB0010682 or MSB-0010682 or MSB-10682 or MSB10682 or MSB-10718C or MSB10718c or KXG2PJ551I or 1537032-82-8).ti,ab,ot,kf,kw,hw,rn,nm.	613
2	Carcinoma, Merkel Cell/ or (merkel or merkle).ti,ab.	9561
3	1 and 2	67
4	3 use medall	13
5	3 use cctr	11
6	avelumab/ or (Bavencio* or avelumab* or MSB-0010718C or MSB0010718C or MSB0010682 or MSB-0010682 or MSB-10682 or MSB10682 or MSB-10718C or MSB10718c or KXG2PJ551I).ti,ab,kw.	588
7	Merkel cell tumor/ or (merkel or merkle).ti,ab.	9909
8	6 and 7	80
9	8 use oemezd	56
10	9 and conference abstract.pt.	19
11	limit 10 to yr="2012 -Current"	19
12	limit 11 to english language	19
13	9 not 10	37
14	4 or 5 or 13	61
15	limit 14 to english language	61
16	remove duplicates from 15	48
17	11 or 16	67

2. Literature search via PubMed
A limited PubMed search was performed to capture records not found in MEDLINE.

#	Query	Items found
#4	Search #3 AND publisher[sb] Filters: English	3
#3	Search #1 AND #2 Filters: English	14
#2	Search Carcinoma, Merkel cell[mh] OR merkel[tiab] OR merkle[tiab]	3897
#1	Search Bavencio*[tiab] OR avelumab*[tiab] OR MSB-0010718C [tiab] OR MSB0010718C[tiab] OR MSB0010682[tiab] OR MSB-0010682[tiab] OR MSB-10682[tiab] OR MSB10682[tiab] OR MSB-10718C [tiab] OR MSB10718c[tiab] OR KXG2PJ551I [tiab] OR 1537032-82-8[rn]	67

3. **Cochrane Central Register of Controlled Trials (Central)**
    Searched via Ovid

4. **Grey Literature search via:**

    Clinical trial registries:

    U.S. NIH ClinicalTrials.gov
    http://www.clinicaltrials.gov/

    Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
    http://www.canadiancancertrials.ca/

    Search: Bavencio/avelumab, Merkel cell carcinoma

    Select international agencies including:

    Food and Drug Administration (FDA):
    http://www.fda.gov/

    European Medicines Agency (EMA):
    http://www.ema.europa.eu/

    Search: Bavencio/avelumab, Merkel cell carcinoma

    Conference abstracts:

    American Society of Clinical Oncology (ASCO)
    http://www.asco.org/

    Search: Bavencio/avelumab, Merkel cell carcinoma - last 5 years

Detailed Methodology of Literature Review

The literature search was performed by the pCODR Methods Team using the search strategy provided above.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-2017Oct18) with Epub ahead of print, in-process records & daily updates via Ovid; Embase (1974-2017Oct18) via Ovid; The Cochrane Central Register of Controlled Trials (Sept 2017) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Bavencio, avelumab and Merkel cell carcinoma.

No filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of February 1, 2018.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant

conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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