pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Cemiplimab (Libtayo) **Submitted Reimbursement Request:** Cemiplimab is indicated for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC) who are not candidates for curative surgery or curative radiation.	
Submitted By: Sanofi Genzyme	**Manufactured By:** Sanofi Genzyme
NOC/c Date: April 10, 2019	**Submission Date:** July 9, 2019
Initial Recommendation: January 3, 2019	**Final Recommendation:** January 22, 2020

Approximate per Patient Drug Costs, per Month (28 Days)	Cemiplimab costs $8,200.00 per 350 mg single dose vial or $5,857.14 per 250 mg single dose vial. At the recommended fixed dose of 350 mg every three weeks, administered as an intravenous infusion, cemiplimab costs $8,200.00 per cycle and $10,933.33 per 28-day course.

pERC RECOMMENDATION

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions***

☐ **Do not reimburse**

* If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends reimbursement of cemiplimab (Libtayo) in patients with metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC) who are not candidates for curative surgery or curative radiation, only if the following condition is met:

- Cost-effectiveness is improved to an acceptable level.

If the above condition cannot be met, pERC does not recommend reimbursement of cemiplimab. Treatment should be for previously treated (prior radiation and/or surgery) or treatment naive patients who are not amenable to curative surgery or curative radiation with good performance status. Treatment with cemiplimab should continue up to 24 months (96 weeks) or until symptomatic disease progression or unacceptable toxicity, whichever occurs first.

pERC made this decision because it considered there may be a net clinical benefit of cemiplimab based on the clinically meaningful objective response rate (ORR) and the durability of response observed in patients in Study 1540 (EMPOWER-CSCC-1). pERC also considered the significant unmet need for an approved treatment option in this small patient population who are often elderly and cannot tolerate chemotherapy, and experience considerable pain and disfigurement as a result of their disease; as well as the favourable side effect profile of cemiplimab with no apparent

	detriment on quality of life. However, pERC acknowledged that, because of the non-randomized, non-comparative design of the available study, there was considerable uncertainty about the magnitude of the clinical benefit of cemiplimab relative to currently used systemic treatments or best supportive care. Further, there was also a lack of mature survival data from Study 1540 to validate the observed clinical benefit on response outcomes. pERC agreed that cemiplimab aligns with patient values as there is a significant burden of illness in this population and need for more effective treatment options with tolerable side effects that are associated with less pain, scarring, and disfigurement. pERC concluded that at the submitted price, cemiplimab could not be considered cost-effective compared with cisplatin-based chemotherapy and best supportive care and would require a price reduction to improve cost-effectiveness to an acceptable level. pERC noted that there was considerable uncertainty in the cost-effectiveness estimates due to a lack of robust direct and indirect comparative effectiveness data in the submitted economic evaluation.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given pERC was satisfied that cemiplimab may have a net clinical benefit in patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation, jurisdictions may want to consider pricing arrangements that would improve the cost-effectiveness of cemiplimab to an acceptable level. pERC noted the cost of cemiplimab was high and that drug price was the key driver of the incremental cost-effectiveness estimates. Therefore, to offset the considerable uncertainty in the clinical effect estimates, pERC concluded that a reduction in drug price would be required in order to improve cost-effectiveness. **Collecting Prospective Evidence to Reduce Uncertainty in the Magnitude of Benefit and Cost-Effectiveness** pERC noted that cemiplimab was issued a Notice of Compliance with conditions by Health Canada pending the results of trials to confirm clinical benefit. Given the considerable uncertainty in the magnitude of clinical benefit of cemiplimab in patients with metastatic or locally advanced CSCC, pERC concluded that additional prospective evidence should be collected to confirm the clinical benefit and better inform the true cost-effectiveness of cemiplimab. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

pERC noted that there is currently no standard of care treatment for patients with metastatic and locally advanced cutaneous squamous cell carcinoma (CSCC) who are not candidates for curative surgery or curative radiation. Although chemotherapy with drugs such as cisplatin and 5-fluorouracil (FU) (+/- cetuximab) are used, there is limited evidence that these treatments improve patient outcomes. Many patients receive best supportive care (BSC) when surgery and radiotherapy are not options. Certain patient populations, such as the elderly, immune-compromised patients, and patients with a history of solid organ transplant are at particular risk of developing local or distant recurrences. The majority of CSCC cases occur in the head and neck regions with the potential of causing significant physical impairment that affects a patient's physical, social, and emotional sense of well-being. pERC discussed the burden of metastatic and locally advanced CSCC and considered that the morbidity associated with the disease (pain, scarring, and disfigurement) is a substantial concern. pERC acknowledged there is a significant unmet need for treatment options in this patient population. Cemiplimab is the first systemic treatment to be approved by Health Canada for inoperable locally advanced and metastatic CSCC.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

Two non-randomized, single-group, open-label studies were included in the pCODR systematic review, Study 1423 (phase I; n = 26) and Study 1540 (phase II; n = 193), which both evaluated cemiplimab in patients who were not candidates for curative surgery or curative radiation. pERC deliberations focused on Study 1540 since it included more patients, and results were based on formal hypothesis testing.

pERC noted that in Study 1540 a substantial proportion of patients experienced a response as assessed by an independent central review (ICR). In each treatment group of the study the ORR by ICR met the pre-specified threshold for clinically meaningful treatment effect since the lower 95% confidence interval (CI) limit of the ORR exceeded the pre-specified response rates of 15% (metastatic CSCC) and 25% (locally advanced CSCC), which were based on historical response rates of various systemic therapies. Response rates were also durable in a substantial proportion of patients. pERC considered the response outcomes in each treatment group of Study 1540 to be meaningful for a condition where there are no standard treatment options; however, pERC noted the short duration of follow-up in the study (median of 9.4 months) and the lack of mature data on survival outcomes.

pERC discussed the limitations of relying on non-comparative evidence and concluded that there is considerable uncertainty surrounding the exact magnitude of the clinical benefit of cemiplimab. While pERC agreed a randomized controlled trial would be challenging to do in this patient population due to several factors (the relatively rarity of the diagnosis, an elderly population who may not be able to tolerate chemotherapy, no standard of care and lack of clinical equipoise, and possible issues with obtaining informed consent), they noted that in the absence of robust direct and indirect comparative evidence, longer-term survival data from the current study are needed to confirm the observed clinical benefit on response outcomes. pERC reviewed the critical appraisal of the submitted indirect treatment comparison (ITC) of cemiplimab with platinum-based chemotherapy and BSC that was provided by the sponsor, and agreed with the pCODR Methods Team that the validity of its results are highly uncertain given the breadth of limitations that were identified, which included the small sample sizes and insufficient information on patient populations of the comparator trials, and exclusion of some prognostic factors and treatment effect modifiers from the core analysis. Notwithstanding the noted limitations of all the submitted evidence, pERC concluded that given the burden of illness, the significant unmet need for treatment options, compelling response outcomes, and the favourable side effect profile of cemiplimab, there may be a clinical benefit to cemiplimab in patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation. pERC agreed that treatment with cemiplimab would result in avoiding the toxicities of systemic chemotherapy, help with the psychological impact of the disease, and may potentially offer some patients the opportunity for their disease to become resectable after treatment.

pERC discussed the safety profile of cemiplimab and noted that the most common grade ≥ 3 adverse events were fatigue, nausea, pruritis, cough, headache, rash, and constipation. While they noted that these adverse events can have an impact on a patient's functioning, pERC agreed with the Clinical Guidance Panel (CGP) that the safety profile of cemiplimab is similar to that of other PD-1/PD-L1 immunotherapies and can be effectively managed with dose delays and treatment discontinuation. Additionally, health-related quality of life (HRQoL) data were also captured in Study 1540, assessed as an exploratory outcome using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core Module (QLQ-C30). pERC noted that of all the scales assessed, pain was the only symptom to demonstrate a clinically meaningful change (improvement) from baseline. pERC acknowledged there were limitations of the HRQoL analysis that was performed (identified by the pCODR Methods Team in the Clinical Guidance Report), which included the unpublished nature of the data, missing baseline assessments for a sizable proportion of patients, loss of patients to follow-up, and uncertainty regarding the sensitivity of the HRQoL instrument to capture the QoL experience of CSCC patients); however, the available data suggest that overall QoL, functioning and symptoms that included pain, emotional functioning, insomnia, appetite loss, and constipation, were not affected in a negative way by cemiplimab treatment.

pERC reviewed the patient advocacy group input and noted that patients value a treatment option that offers therapeutic effectiveness with less pain, scarring and disfigurement, and has tolerable side effects. pERC acknowledged that patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation experience severe pain, deformity and social isolation, all of which have a debilitating impact on their QoL, both physically and psychologically. In addition to the data on HRQoL, pERC considered that the response rates from Study 1540 were measures of tumour regression and that patients who experienced such a response would have less disfigurement and, therefore, it would likely improve multiple aspects of their QoL. Patients indicated they are prepared to accept the risks and side effects of new treatments if the treatment is effective. pERC highlighted that cemiplimab is not a replacement therapy for surgery or radiation, but it may lessen the need for invasive treatments and present an opportunity for some patients' tumours to become resectable after treatment. pERC agreed that this therapy addresses the significant burden of illness in this population and the need for more effective treatment options with tolerable side effects that are associated with less pain, scarring, and disfigurement.

pERC deliberated on the cost-effectiveness of cemiplimab compared with cisplatin-based chemotherapy and BSC. As previously noted, due to the limitations of relying on non-randomized, non-comparative evidence from Study 1540 and the limitations of the submitted ITC, as well as the immaturity of survival data from Study 1540 (median follow-up time of 9.4 months; a small number of patients [none from the fixed dose group] at risk beyond 18 months; and median OS was not reached), there was substantial uncertainty in the magnitude of clinical benefit associated with cemiplimab. This made it challenging to estimate the incremental treatment effect with cemiplimab; and consequently, the resulting wide range of incremental cost-effectiveness estimates for cemiplimab reflect this uncertainty. Therefore, pERC concluded that cemiplimab was not cost-effective at the submitted price. pERC considered that since drug price was the key driver of the incremental cost-effectiveness estimates, a reduction in drug price would be required to improve cost-effectiveness to an acceptable level. pERC noted that more mature data on clinical efficacy from Study 1540 would help to decrease the uncertainty in the incremental treatment effect and inform on the true cost-effectiveness of cemiplimab.

pERC discussed the factors that could impact the feasibility of implementing a positive conditional reimbursement recommendation for cemiplimab for the treatment of metastatic and locally advanced CSCC. pERC noted that although the number of patients who are unsuitable for curative surgery and curative radiation is currently small, the number of patients who may seek treatment once cemiplimab is accessible has the potential to increase. It was also noted that cemiplimab will be an additional treatment that will not replace a current treatment in this setting. As such, additional health care resources will be required, particularly for patients receiving BSC who do not receive any systemic treatment; additional costs include those related to pharmacy, nursing, and physician and clinic visits. pERC also discussed the appropriate dosing schedule (fixed versus weight-based) of cemiplimab and whether the two dosing schedules (3 mg/kg every two weeks versus 350 mg every three weeks) used in Study 1540 are considered interchangeable. pERC noted that Health Canada approved the fixed dose of cemiplimab administered every three weeks until symptomatic progression or unacceptable toxicity despite there being shorter median follow-up of patients in the fixed-dose treatment group of Study 1540 (due to later enrolment of this group), with weight-based dosing reserved for patients with low body

weight. pERC considered multiple factors regarding dosing, including that the ORR by ICR met the threshold for clinically meaningful benefit in all treatment groups, the frequency of the dose schedules, and pharmacokinetic analyses from Study 1540 and other immunotherapies that have demonstrated similar treatment exposure and between-patient variability of the dose schedules. pERC noted that the fixed dose offers an advantage due to its less frequent schedule, which is an important consideration in an elderly patient population. pERC agreed with the CGP's assessment that treatment duration should follow Study 1540 and therefore a maximum treatment duration of 96 weeks was reasonable given the relatively short follow-up of the study. Lastly, pERC deliberated on input from PAG on the factors related to the eligible patient population, implementation factors, and sequencing of treatment. Refer to the summary table in Appendix 1 for more details.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the sponsor's economic model and budget impact analysis (BIA)
- Guidance from the pCODR clinical and economic review panels
- Input from two patient advocacy groups (Melanoma Network of Canada [MNC] and Save Your Skin Foundation [SYSF])
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- Two patient advocacy groups, MNC and SYSF
- One registered clinician group, Cancer Care Ontario (CCO) Skin Drug Advisory Committee (DAC)
- The PAG, and
- The sponsor, Sanofi Genzyme

The pERC Initial Recommendation was to conditionally recommend reimbursement of cemiplimab in patients with metastatic or locally advanced cutaneous CSCC who are not candidates for curative surgery or curative radiation only if cost-effectiveness could be improved to an acceptable level.

Feedback on the pERC Initial Recommendation indicated that the sponsor, patient advocacy groups, and the registered clinician group all agreed with the Initial Recommendation.

The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of cemiplimab (Libtayo) for the treatment of adult patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation.

Studies included: One non-randomized, global, multi-centred phase II study was the focus of deliberation

The pCODR systematic review included two clinical studies: Study 1423 and Study 1540 (EMPOWER-CSCC 1). The pCODR review focused on Study 1540 since Study 1423 is a small (n = 26) dose escalation phase I study that lacked formal hypothesis testing and reported results based on descriptive analyses. Therefore, the systematic review, critical appraisal and pERC deliberations focused on the larger phase II study, Study 1540.

Study 1540 is an ongoing, global, multi-centre, non-randomized, single-group, open-label phase II study of cemiplimab monotherapy in patients with invasive CSCC. The study was conducted at 39 sites in the US, Australia, and Germany. A total of 193 patients were enrolled into three groups defined by disease stage (metastatic CSCC and locally advanced CSCC) and treatment dosing schedule:

- Group 1: 59 patients with metastatic CSCC who received a weight-based dose of cemiplimab (3 mg/kg intravenously [IV] every two weeks)
- Group 2: 78 patients with locally advanced CSCC who received a weight-based dose of cemiplimab (3 mg /kg IV every two weeks)

- Group 3: 56 patients with metastatic CSCC who received a fixed dose of cemiplimab (350 mg IV every three weeks)

The pCODR review also included a summary and critical appraisal of the sponsor-submitted ITC. In the absence of randomized controlled trials comparing cemiplimab with currently used treatments, the sponsor conducted the ITC to assess the comparative efficacy and safety of cemiplimab to platinum-based chemotherapy and BSC among patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation.

Patient populations: Previously treated and treatment naive patients with metastatic or locally advanced CSCC who are not candidates for curative treatment

Key eligibility criteria of Study 1540 included age ≥ 18 years, histologically confirmed unresectable metastatic (nodal or distant) or locally advanced CSCC, at least one measurable lesion according to RECIST (version 1.1), an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate organ function, and an anticipated life expectancy of ≥ 12 weeks. Patients were excluded if they had ongoing or recent significant autoimmune disease that required systemic immunosuppressive therapy, untreated/active brain metastases, and previous treatment with agents that block the PD-1 or PD-L1 pathway or other immune modulating drugs that were administered within four weeks of the first cemiplimab dose. Additionally, patients with a history of solid organ transplant or a concurrent cancer, or CSCC of the dry lip or anogenital area were also excluded.
The median age of the 193 patients enrolled in Study 1540 was 72 years (range 38 to 96 years). The majority of patients in the study were male (83.4%) and had an ECOG performance status of 1 (55.4%). Most patients had received prior surgery (90.2%) and prior radiation (67.9%) and approximately one-third of patients had received some form of systemic therapy (33.7%).

Patients in Group 1 and 2 received cemiplimab at a dose of 3 mg/kg administered IV over 30 minutes every two weeks for up to 96 weeks, or until disease progression or unacceptable toxicity. Patients in Group 3 received cemiplimab at a 350 mg fixed dose administered IV over 30 minutes every three weeks for up to 54 weeks, until disease progression or unacceptable toxicity, whichever occurred first. The sponsor confirmed that treatment duration was shorter in Group 3 due to the late addition of this group to the study and having the same close out date as the other two treatment groups. Treatment beyond week 54 was permitted in Group 3 for up to six treatment cycles in patients who had not experienced progressive disease. The sponsor confirmed data on the Group 3 patients who continued treatment beyond the planned treatment duration have not yet been formally analyzed.

Retreatment with cemiplimab was permitted in all three treatment groups for patients who completed the planned maximum number of cycles of cemiplimab in each group without disease progression and subsequently experienced disease progression without any intervening systemic anticancer therapy; resumption of treatment with cemiplimab was permitted in the first six months of post-treatment follow-up. The sponsor confirmed that the number of patients to enter retreatment was low and data from these patients have not yet been formally analyzed.

At the updated data cut-off dates, the median duration of cemiplimab treatment for all patients was 39.1 weeks (range, 2.6 to 60.4). The median duration of cemiplimab treatment in Group 1 was 65.0 weeks (range, 2.0 to 96.1), in Group 2 was 34.6 weeks (range, 2.0 to 96.1), and in Group 3 was 34.3 weeks (range, 2.6 to 60.4). There was a total of 63 patients (32.6%) who remained on treatment, 22 (11.4%) had completed treatment, and 108 patients (56%) had discontinued treatment. The most common reason for treatment discontinuation was disease progression among 51 patients (26.4%).

Key efficacy results: Clinically meaningful response outcomes; immature survival data

Efficacy analyses performed based on the data cut-off dates of September 20, 2018 (Group 1 and Group 3) and October 10, 2018 (Group 2) represent updated analyses that were the first to include the total patient population of 193 patients in Study 1540. Efficacy analyses for all three groups were possible since enrolment was complete, and all patients had at last three response assessments; thus, pERC deliberations focused on these updated analyses.

The key efficacy outcomes deliberated on by pERC were ORR based on ICR, which was the primary outcome of Study 1540; as well as duration (durability) of response (DOR), which was the key secondary outcome of the study. The analyses of efficacy were based on the binomial exact CI approach, which was used to determine whether the lower limit of the 95% CI of the ORR estimate excludes a historical control

response rate that is not deemed clinically meaningful. Therefore, if the lower limit of the 95% CI of the observed ORR excluded 15% for Groups 1 and 3 (metastatic CSCC) and excluded 25% for Group 2 (locally advanced CSCC), the study treatment was deemed effective/clinically meaningful for that group, respectively. All statistical analyses of efficacy outcomes were conducted independently for each group and were analyzed according to the intent-to-treat principle.

At the updated analysis the median duration of follow-up was 9.4 months for all patients, and was 16.5 months, 9.3 months and 8.1 months in Groups 1, 2, and 3, respectively. The observed ORR by ICR was 44.0% (95% CI, 36.9 to 51.3) in all patients, and consisted of complete responses in 11 patients (11.4%) and partial responses in 63 patients (32.6%). The ORR by ICR in each treatment group was 49.2% (95% CI, 35.9 to 62.5) in Group 1, 43.6% (95% CI, 32.4 to 55.3) in Group 2, and 39.3% (95% CI, 26.5 to 53.2) in Group 3. The results in each group met the pre-specified threshold for clinically meaningful treatment effect since the lower 95% CI limit exceeded 15% in Groups 1 (35.9%) and 3 (26.5%), and 25% in Group 2 (32.5%). The median DOR had not been reached in any group as the data were considered immature based on a large percentage of censored patients. The median time-to-response was 2.0 months (range, 1.7 to 9.1) for all patients; and the proportion of responders with an observed DOR exceeding six and 12 months was 75.3% (n = 64 out of 85) and 40.0% (n = 34 out of 85), respectively. Data on progression-free survival (PFS) and overall survival (OS) were also considered immature since a large percentage of patients were censored from these analyses at 58% and 82.4%, respectively. The median PFS was 18.4 months in Group 1, but not reached in Group 2, and 10. 4 months in Group 3; and the median OS was not reached in any group, which was based on a total of 34 (17.6%) deaths in the three treatment groups.

Patient-reported outcomes: Unpublished data suggest no detriment of cemiplimab on quality of life

HRQoL was assessed in Study 1540 using the EORTC-QLQ-C30 questionnaire. Data on this exploratory outcome have not been published and were provided by the sponsor. The percentage of patients who completed a baseline assessment was 74.6%, 87.2% and 67.9% in Group 1, Group 2, and Group 3, respectively. Baseline scores for the global health status/QoL scale and the functional and symptom scales assessed (pain, emotional functioning, insomnia, appetite loss, constipation) indicated patients had moderate-to-high levels of functioning and QoL as well as low symptom scores. A clinically meaningful change on any EORTC-QLQ-C30 scale or domain was defined as a ≥ 10-point change from baseline up to cycle 5.

Considering all CSCC patients, the change from baseline in global health status/QoL improved over time but did not reach the clinically meaningful threshold at any cycle; these results suggest global health status/QoL was not negatively affected by treatment with cemiplimab. Of the functional and symptom scales assessed, pain was the only scale to demonstrate a clinically meaningful change (improvement) from baseline according to the definition of clinically meaningful change. These results suggest treatment with cemiplimab resulted in a clinically meaningful reduction in pain and appeared to stabilize and have no detriment on global health status/QoL, emotional functioning, insomnia, appetite loss, and constipation.

Safety: Favourable safety profile

Treatment emergent adverse events (TEAEs) occurred in almost all patients (99.0%) treated with cemiplimab in Study 1540. The most frequently occurring TEAEs (metastatic CSCC/ locally advanced CSCC) were fatigue (25.4%/42.3%), nausea (23.7%/21.8%), pruritis (16.9%/26.9%), cough (15.3%/19.2%), headache (18.6%/not reported), rash (16.9%/12.8%), and constipation (16.9%/ 10.3%). Grade 3 or higher TEAEs occurred in 44.6% of all patients and serious TEAEs occurred in 35.8% of patients. TEAEs led to a dose reduction, dose interruption/delay, and treatment discontinuation in 1.6%, 35.2%, and 7.8% of all study patients, respectively. There were five patients (2.6%) who experienced a TEAE that resulted in death, of which one was attributed to study treatment.

Limitations: No direct comparative data to currently used treatments

In the absence of direct randomized comparisons of cemiplimab with currently used treatments for metastatic and locally advanced CSCC, the sponsor performed an ITC to assess the comparative efficacy and safety of cemiplimab compared with platinum-based chemotherapy and BSC. The two cemiplimab studies, Study 1423 and Study 1540, as well as two observational studies that evaluated chemotherapy (Jarkowski 2016) and BSC (Sun 2019) met the criteria for inclusion. The sponsor used individual patient data from the two cemiplimab studies to conduct the ITC using different approaches: an unadjusted naive

comparison, a simulated treatment comparison (STC), and a matching-adjusted indirect comparison (MAIC). PFS and OS were the primary outcomes of interest and ORR was assessed as a secondary outcome. Relevant prognostic factors that could influence outcomes were identified through a targeted search of the literature. Prognostic factors included in the core model for the analysis of the Jarkowski 2016 study included disease stage and tumour location; and prognostic factors included in the extended model included the factors in the core model with the addition of gender and prior systemic therapy. Prognostic factors included in the core model for the analysis of the Sun 2019 study included age, disease stage, tumour location, and tumour stage; and prognostic factors included in the extended model included the factors in the core model with the addition of gender, ECOG performance status, and prior radiation therapy. The results of the ITC suggest cemiplimab improved OS (statistically significant) and PFS (not statistically significant) when compared with platinum-based chemotherapy, and improved OS (statistically significant) when compared to BSC, regardless of the analysis model used (i.e., naïve, STC, and MAIC). The pCODR Methods Team appraisal of the ITC concluded that the results of the ITC should be interpreted with caution due to small sample sizes and insufficient information on the patient populations of the observational studies to adequately assess how representative these populations are of the intended treatment population (for cemiplimab). In addition, the STC core model did not consider treatment effect modifiers and excluded all prognostic factors found to be non-statistically significant in each study. In order to obtain an unbiased estimate of differences in the treatment effects, all prognostic factors, and treatment effect modifiers for a given outcome must be adjusted for in the model. It was noted that the MAIC analysis would be subject to similar limitations to those previously outlined for the STC analysis, particularly in relation to the inclusion of key prognostic factors and effect modifiers.

Need and burden of illness: No standard of care; unmet need; treatment options

Locally advanced and metastatic CSCC is an uncommon but devastating malignancy for which, until recently, there were no Health Canada–approved treatments. For patients who develop locally advanced, inoperable disease or distant metastatic disease, the prognosis is poor, and treatment has largely been palliative with chemotherapy or BSC. Results with chemotherapy have relatively low response rates, short duration of response, and poor survival. Certain patient populations such as the elderly, immune-compromised, and transplant patients are at particular risk of developing local or distant recurrences. However, many of these patients are not suitable candidates for chemotherapy due to their advanced age and comorbidities or immunosuppression. As tumours most commonly present on the head and neck regions, significant disfigurement occurs leading to significant declines in physical and psychological well-being. Thus, there is a strong unmet need for novel treatments that could offer improvements in QoL, survival, and acceptable toxicity in this population.

Registered clinician input: High unmet need for a treatment option

pERC deliberated on input from one joint submission on behalf of Cancer Care Ontario's (CCO's) Skin Drug Advisory Committee. The clinicians providing input noted that presently the most common treatments for patients with unresectable metastatic and locally advanced CSCC are cisplatin plus 5-FU or cetuximab; however, they noted these treatments may not be suitable for elderly patients. The clinicians highlighted a large unmet need for CSCC patients who are elderly, as well as patients who have a history of organ transplant; although they noted some clinicians may choose not to use cemiplimab in this latter group of patients. If approved for reimbursement, the clinicians stated cemiplimab would likely be administered as first-line therapy and they anticipated it will be the preferred treatment moving forward in patients who have received other therapies. The safety of cemiplimab was noted to be similar to other PD-1 treatments. Upon progression on cemiplimab, other therapeutic options that would be considered by the clinicians include chemotherapy, cetuximab, palliative care, or clinical trials of other investigational drugs. In terms of the dosing of cemiplimab, the clinicians referenced published data that demonstrate similar pharmacokinetics between the fixed- and weight-based dosing schedules used in Study 1540. The clinicians noted the value of collecting real-world evidence to assess dosing of cemiplimab in this patient population of CSCC patients.

PATIENT-BASED VALUES

Patient values on treatment: Less invasive treatment options with tolerable side effects

pERC deliberated on input received from two patient advocacy groups, Melanoma Network of Canada (MNC) and Save Your Skin Foundation (SYSF). Patients who provided input reported undergoing multiple treatments for CSCC that included chemotherapy, radiation, and Mohs surgery, noting multiple surgeries are typically required. Patients mentioned there is no standard chemotherapy protocol for CSCC. Although

cisplatin-based chemotherapy sometimes shows efficacy, patients indicated these combinations are too toxic for most elderly patients who are more often affected by the disease. Four patient respondents noted they had experience with cetuximab, but reported they had disease progression with the drug. Patients indicated current treatments impose physical side effects that include pain, disfigurement, facial paralysis, itchiness, lymphedema, scarring, nausea, muscle weakness, hematoma, and bleeding; and psychological side effects that include stress and depression. Patients also described the time commitment and financial burden of current treatments; many had to see multiple specialists and some patients had to quit their jobs as a result of their disease and treatment. Caregivers commented on the physical, emotional, and financial burden that is associated with caring for a patient with CSCC, mentioning frequent wound and dressing changes, frequent travel and associated costs to attend medical appointments, and the need for psychosocial support to manage their own depression and anxiety. Patients reported they value a new treatment that is effective at stopping progression, and less invasive with tolerable side effects including less pain. They also indicated a desire for treatments that lessen or eliminate the need for surgery and radiation. Of the MNC patients who had experience with cemiplimab (n = 11), 10 indicated they achieved a complete response and one indicated they achieved stable disease. The most common side effects of cemiplimab reported by these patients were fatigue, skin rash, muscle or joint pain, and fever or flu-like symptoms; and permanent thyroid issues occurred in two patients that was attributed to treatment. SYSF noted that half of the patients with experience with cemiplimab in their sample (n = 3 out of 6) had no side effects, while half experienced fatigue and gastrointestinal issues. Patients expressed that any side effects were worth the results of the treatment.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analyses

The submitted economic model assessed the cost-effectiveness (clinical effects measured as life-years [LYs] gained) and cost-utility (clinical effects measured by quality-adjusted life-years [QALYs] gained) of cemiplimab compared with chemotherapy (cisplatin plus 5-FU) in patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation, which is consistent with the reimbursement request and Health Canada indication. A comparison with BSC (palliative care) was included as a scenario analysis.

Basis of the economic model: Clinical and economic inputs

The sponsor submitted a partitioned survival model comprised of three health states: pre-progression, post-progression, and death. The economic evaluation was based on clinical efficacy (PFS, OS) and safety data from Study 1540 using data from the updated efficacy analysis cut-off dates for all patients (metastatic and locally advanced patients combined). Efficacy data from the study were adjusted through an STC (ITC approach) to enable comparisons with chemotherapy and BSC, where efficacy data were sourced from the medical literature. Utility data (pre- and post-progression) were sourced from Study 1540 and the medical literature (adverse event disutilities).

The costs considered in the economic evaluation included those for drugs and drug administration, medical resource use pre- and post-progression, and adverse events. There were no costs associated with BSC.

Drug costs: High drug cost

Cemiplimab costs $8,200.00 per 350 mg single dose vial or $5,857.14 per 250 mg single dose vial. At the recommended fixed dose of 350 mg every three weeks administered as an intravenous infusion, cemiplimab costs $8,200.00 per cycle and $10,933.33 per 28-day course.

Cost-effectiveness estimates: High uncertainty in cost-effectiveness of cemiplimab

According to the sponsor's base case (probabilistic analysis), the use of cemiplimab would result in incremental costs of $252,155, and incremental benefits of 4.75 additional LYs and 3.34 additional QALYs over a 30-year life-time horizon, for an estimated incremental cost-utility ratio (ICUR) of $75,426 per QALY. Scenario analyses carried out by the sponsor demonstrated that the choice of the parametric function to model chemotherapy PFS and OS, the use of the naive ITC results (versus STC results), cemiplimab treatment being given until disease progression, and the subgroup analysis of only metastatic patients had the largest impact on the ICUR estimate (up to a $30,000 per QALY increase). Most of the QALY gain (86%) was accrued in the post-progression health state. The sponsor did not report the QALY gain accrued in the extrapolated phase of the model (i.e., beyond observed data) where the uncertainty

is the greatest. The largest cost driver of incremental costs (61%) was the cost of cemiplimab, followed by monitoring costs post-progression (34%).

The Economic Guidance Panel (EGP) identified a number of limitations with the submitted economic evaluation, the most significant of which was the overall quality of the data informing the economic model. The main source of efficacy and safety inputs was Study 1540, which was a non-comparative, single-group open-label phase II study that has immature data for survival end points (median follow-up time of 9.4 months; a small number of patients [none from the fixed dose group] at risk beyond 18 months; and median OS was not reached) integral to the economic evaluation. The efficacy inputs used for comparative effectiveness were derived from a STC that was appraised by the pCODR Methods Team and was deemed to have significant limitations that raised concerns about the validity of the estimates obtained (small sample sizes of comparator studies, and missing information on prognostic factors and treatment effect modifiers). Other limitations of the submitted economic evaluation included the omission of an important comparator in the base case analysis, uncertainty on utility values resulting from the use of mapping algorithms, and under- and over-estimation of some costs (related to adverse events, wound dressings, and terminal care).

To address the high uncertainty on the long-term effect of cemiplimab and comparative effectiveness, the EGP made the following changes to the economic model in reanalyses:

- use of the naive ITC results, which provide the most conservative estimates of comparative effectiveness
- reduced extrapolation of treatment effect to 18 months (rather than 36 months in the sponsor's base case) after which, the same rates as chemotherapy were used for the rest of the time horizon
- Weibull distribution for chemotherapy OS (including a change in the shape parameter to obtain a five-year survival between 5% and 10% for the chemotherapy group)
- corrections to the cost of wound dressings and terminal care.

The EGP also conducted a deterministic sequential analysis including BSC and chemotherapy as comparators, price reduction scenarios, and scenario analyses to identify the upper bound of EGP reanalyses, which included the following:

- increasing treatment duration to 24 months, which is similar to other immunotherapies, rather than 22 months as per Study 1540
- using the weight-based dosage as this is an alternative dosage in the Health Canada product monograph for low weight patients
- assuming treatment until progression as indicated in the Health Canada product monograph.

In the EGP's best-case estimate, the incremental cost of cemiplimab was $176,966 and the incremental benefit gain was 1.48 LYs and 1.06 QALYs over a 30-year life-time horizon, for an estimated ICUR of $166,221 per QALY. An upper bound of $223,828 per QALY was achieved with cemiplimab being administered until treatment progression (no capping at 22 or 24 months). The cost of cemiplimab was the main cost driver; and most of the QALY gained (70%) was accrued in the post-progression period and in the extrapolated phase of the model. The deterministic sequential analysis showed that for a willingness-to-pay below $52,539 per QALY, BSC would be the preferred treatment option. For a willingness-to-pay between $52,539 and $161,278 per QALY, chemotherapy would be the preferred option, and that cemiplimab would be the preferred option for a willingness-to-pay above $161,278 per QALY. The price reduction scenarios showed that a 40% price reduction would be needed to bring the ICUR around $100,000 per QALY while an 80% price reduction would be required to bring the ICUR around $50,000 per QALY.

The EGP concluded that the submitted model was extremely sensitive to assumptions made on the long-term clinical effectiveness of cemiplimab and those made on the duration of treatment. The EGP was not able to address the limitations related to the quality of the data informing the model; therefore, caution should be exercised when interpreting the results of the economic analysis.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Additional resources required; budget impact most affected by treatment duration

PAG identified the following factors that could impact the implementation of cemiplimab: potential for drug wastage with a weight-based dosing schedule; additional health care resources, particularly for patients on BSC who do not currently receive any systemic treatment, which include additional resources for pharmacy, nursing, and physician and clinic visits; and increases in monitoring (for infusion reactions and immune-mediated adverse events post-infusion) and supportive care drugs (corticosteroids and immunosuppressants). PAG also requested clarity on implementation-related issues on the eligible patient population, appropriate dosing and schedule, treatment duration and discontinuation criteria, optimal sequencing with currently used treatments after progression on cemiplimab, and retreatment. Refer to Appendix 1 for pERC's recommendations pertaining to these issues.

The sponsor provided an Ontario specific BIA to assess the feasibility of implementing a reimbursement recommendation for cemiplimab for patients with unresectable metastatic and locally advanced CSCC. The sponsor did not provide an analysis for Canada; however, the Canadian population could be chosen as the model population. Based on the sponsor's BIA, the factors that most influenced the BIA included the proportion of patients not amenable to curative surgery or curative radiation and optimistic market shares. The EGP identified several limitations of the submitted BIA; these included underestimation of cisplatin and 5-FU chemotherapy market share, which according to the CGP is the most frequently used chemotherapy combination in Canada and would likely be the most affected treatment following reimbursement of cemiplimab; underestimation of cemiplimab treatment duration, omission of administration costs, and use of an underestimate for body surface area for dosing of comparators. The EGP performed exploratory analyses to assess the impact of a variety of parameters on the budget impact. Including corrections for cisplatin and 5-FU market share and the assumption that only this chemotherapy would be affected by the introduction of cemiplimab led to a small increase (1%) in the three-year budget impact; while increasing treatment duration to 22.9 from 13.5 months led to a larger increase to the budget (46%).

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Michael Crump, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

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

- Dr. Avram Denburg and Dr. Anil Abraham Joy who were not present for the meeting
- Mr. Daryl Bell who did not vote due to his role as a patient member alternate

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of cemiplimab for cutaneous squamous cell carcinoma (CSCC), through their declarations, no members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*.

Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
• Guidance on whether patients with an ECOG performance status of ≥2 should be eligible for cemiplimab. • Clarity on whether patients who are currently receiving other systemic therapies/chemotherapies would need to be addressed on a time-limited basis.	• pERC agreed with the CGP that treatment of patients with an ECOG performance status of ≥2 should be considered on a case by case basis, as some patients have increased comorbidities which may contribute to a poorer performance status. • At the time of implementing a reimbursement recommendation for cemiplimab, jurisdictions may consider addressing the time-limited need of cemiplimab for patients currently on systemic chemotherapy.
• Clarity on the appropriate dosing schedule (fixed dose of 350 mg every three weeks versus weight-based dose of 3 mg/kg every two weeks) and whether dosing schedules are considered interchangeable. PAG noted the Health Canada product monograph indicates the fixed dose is recommended, with the weight-based dose indicated for low body weight. PAG is also seeking clarity on what is considered low body weight; and guidance on consideration of weight-based dosing up to a total dose amount of 350 mg (3 mg/kg up to a dose capped at 350 mg every 3 weeks). • Guidance on treatment duration and discontinuation criteria as the Health Canada product monograph indicates treatment until symptomatic disease progression or unacceptable toxicity.	• pERC noted the fixed dose treatment group was added to Study 1540 later through an amendment to demonstrate comparable efficacy and safety of the dose schedules; therefore, follow-up and treatment duration (54 weeks) were arbitrarily shorter compared with the weight-based dosing treatment groups (96 weeks) in the study in order to have a similar close out date for all groups. Patients in the fixed dose group were permitted to continue treatment with cemiplimab outside of the study period during continued follow-up. pERC agreed with the CGP that the fixed dose schedule with a treatment duration of up to 96 weeks was reasonable considering this schedule is used for immunotherapies in other indications but acknowledged longer follow-up data are needed to confirm interchangeability of the dose schedules. The weight-based dosing schedule of 3 mg/kg every two weeks was approved by Health Canada for patients with low body weight; the CGP defined low body weight as patients with a BMI of < 18.5.
• Guidance on optimal sequencing of cemiplimab with currently available treatments; as well as what treatment options would be available to patients upon progression on cemiplimab. • Guidance on whether there is evidence for cemiplimab in relapsed/recurrent or re-treatment settings; if yes, please clarify the clinical criteria for re-treatment.	• pERC agreed with the CGP and registered clinician input who indicated cemiplimab will be offered as first-line treatment in patients with metastatic or locally advanced CSCC who are not candidates for curative treatment with surgery or radiation. Upon progression on cemiplimab, patients should be offered chemotherapy, palliative care, or enrolment to a clinical trial. • pERC noted that approximately one-third of patients (33.7%) in Study 1540 had received prior systemic therapy; therefore, they agreed there is evidence for the use of cemiplimab in patients with relapsed/recurrent CSCC. Retreatment with cemiplimab was allowed on Study 1540 for patients who experienced disease progression in the first six months of post-treatment follow up; however, data from these patients are not yet available. pERC agreed with the CGP that in patients who have previously achieved a response with cemiplimab and subsequently progressed six months or more after treatment, it would be reasonable to offer retreatment with cemiplimab.

BMI = body mass index; CSCC – Cutaneous Squamous Cell Carcinoma; CGP = Clinical Guidance Panel; ECOG = Eastern Cooperative Oncology Group; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee.