CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Cemiplimab (Libtayo) for Cutaneous Squamous Cell Carcinoma

January 22, 2020

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List of Abbreviations

BMI	Body mass index
BOR	Best overall response
CCO DAC	Cancer Care Ontario's Skin Drug Advisory Committee
CI	Confidence interval
CGP	Clinical Guidance Panel
CR	Complete response
CSCC	Cutaneous squamous cell carcinoma
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module
HR	Hazard ratio
HRQoL	Health-related quality of life
ICR	Independent central review
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intent-to-treat
IV	Intravenous(ly)
MAIC	Matching adjusted indirect treatment comparison
MNC	Melanoma Network of Canada
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PAG	Provincial Advisory Group
pCODR	pan-Canadian Oncology Drug Review
PD-1/PD-L1 or 2	Programmed cell death protein 1/ Programmed cell death ligand 1 or 2
PFS	Progression-free survival
PR	Partial response
RECIST	Response Evaluation Criteria In Solid Tumors
STC	Simulated treatment comparison
SYSF	Save Your Skin Foundation
TEAE(s)	Treatment-emergent adverse event(s)
WHO	World Health Organization

1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding cemiplimab for locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC). 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 cemiplimab for CSCC conducted by the CSCC Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group (PAG); 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. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on cemiplimab for CSCC, a summary of submitted PAG Input on cemiplimab in CSCC, and a summary of submitted Registered Clinician Input on cemiplimab for CSCC are provided in Sections 2, 3, 4, and 5, respectively.

1.1 Introduction

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

On April 10, 2019, a Notice of Compliance with Conditions (NOC/c) was issued by Health Canada for the following indication: cemiplimab (Libtayo) is indicated for treatment of adult patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation. The marketing authorization with conditions is based on tumour response rate and durability of response, as improvement in overall survival (OS) and progression-free survival (PFS) has not been established in the pivotal single arm Study 1540.[1] The funding reimbursement request and patient population under review by pCODR are the same as the Health Canada indication.

According to the Health Canada product monograph,[2] cemiplimab is a recombinant human immunoglobulin G4 (IgG4) monoclonal antibody that binds to programmed cell death 1 (PD-1) and blocks its interaction with PD-L1 and PD-L2, countering PD-1 mediated inhibition of the immune response, including the anti-tumour immune response.

The recommended dose of cemiplimab is a 350 mg fixed dose administered every three weeks as an intravenous (IV) infusion over 30 minutes until symptomatic disease progression or unacceptable toxicity. Alternatively, a dose of 3 mg/kg administered every two weeks as an IV infusion over 30 minutes may be considered in patients with a low body weight at the discretion of the treating healthcare professional. A planned duration of treatment is not specified; treatment may be continued through initial measurable disease progression until symptomatic disease progression or unacceptable toxicity. Dose reductions are not recommended; and dosing delay or discontinuation may be required based on individual safety or tolerability.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two clinical studies, Study 1423 and Study 1540,[1] which are ongoing phase 1 and 2 studies, respectively. Both studies are funded by the drug sponsors, Regeneron Pharmaceuticals and Sanofi Genzyme.

Study 1423

Study 1423 is a global, multicentre, non-randomized, single-group, open-label, phase 1 ascending dose escalation study of cemiplimab, monotherapy or in combination with other anti-cancer therapies, in patients with advanced solid tumours. Eligible patients included adult patients (≥ 18 years and older) who had CSCC who were not considered candidates for surgery as a result of disease recurrence after two or more surgical procedures, or for whom it was expected that curative resection would be unlikely or result in substantial morbidity or deformity. Patients were required to have at least one measurable lesion according to Response Evaluation Criteria In Solid Tumors (RECIST; (version 1.1), an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ function. The study excluded patients who had any ongoing or recent (last five years) evidence of significant autoimmune disease requiring systemic immunosuppression, primary tumours of the lip or eyelid, a history of solid organ transplant, those with untreated/active brain metastases and prior treatment with other agents that block the PD-1/PD-L1 pathway or immune modulating agents within fewer than four weeks prior to the first dose of cemiplimab.

A total of 26 patients were enrolled in two CSCC expansion cohorts; 16 patients with metastatic CSCC and 10 patients with locally advanced CSCC. Patients received cemiplimab at a dose of 3 mg/kg administered IV over 30 minutes every two weeks. Patients were treated up to six cycles (56-day treatment cycle) for up to 48 weeks or until a patient experienced unacceptable toxicity or had confirmed disease progression. The majority of patients in the study were male (80.8%), had metastatic CSCC (61.5%), an ECOG performance status of 1 (61.5%), and had received prior radiation (80.8%) and systemic therapy (57.7%). The median duration of exposure to cemiplimab was 36 weeks (range, 4.0-71.0) for all patients.

The primary outcome of Study 1423 was safety, which included evaluation of tolerability, side effect profile, and dose-limiting toxicities. Efficacy outcomes were assessed as secondary endpoints and included objective response rate (ORR) by independent central review (ICR) according to RECIST (version 1.1), duration of response (DOR), PFS, and OS. A summary of the results for key outcomes of Study 1423 is available in Table 1.1.

At the primary analysis data cut-off date of October 2, 2017 after a median duration of follow-up of 11.1 months (range: 1.1 to 17) for all CSCC patients (n=26), an ORR of 50.0% (95% confidence interval [CI], 29.9- 70.1) was observed in Study 1423. The median DOR had not been reached at this time; however, it was reported that the DOR exceeded six months in 61.5% of responders. The updated efficacy results for ORR by ICR from June 30, 2018 (duration of median-follow-up not reported) showed no change in the ORR; and median DOR had been reached in metastatic CSCC patients and was 20.3 months (95% CI, 4.6-20.3). In this group, median PFS and OS was 16.2 months (95% CI, 1.8-22.0) and 22 months (95% CI, 13.6-not estimable), respectively.[3]

In terms of safety, there were 26 patients (100%) who experienced any treatment-emergent adverse event (TEAE) and 12 patients (46.2%) who experienced TEAEs grade 3 or higher.[4] The most frequent TEAEs of any grade (that occurred in at least four patients) included fatigue in seven patients (26.9%), while constipation, decreased appetite, diarrhea, hypercalcemia, hypophosphatemia, nausea, and urinary tract infection all occurred in four patients (15.4%). Serious TEAEs were observed in 7 patients (26.9%).[4] A TEAE resulted in death in one patient.

Table 1.1: Key Outcomes of Study 1423 (phase 1).[1,3,4]

Outcomes	Study 1423		
	Metastatic CSCC (n=16)	Locally advanced CSCC (n=10)	Total (n=26)
Median follow up months (range)†	10.0 (range, 1.6-17)	11.1 (range, 1.1-16.7)	11.1 (range, 1.1-17)
Primary Outcome - Safety			
Any TEAE	16 (100)	10 (100)	26 (100)
Grade ≥ 3 TEAE	7 (43.8)	5 (50)	12 (46.2)
Serious TEAE	3 (18.8)	4 (40.0)	7 (26.9)
TEAE leading to drug interruption or delay	2 (12.5)	3 (30.0)	5 (19.2)
TEAE leading to treatment discontinuation	2 (12.5)	0	2 (2.7)
Secondary Efficacy Outcomes			
ORR-ICR % (95% CI)†	43.8% (19-8-70.1)	60.0% (26.2-87.8)	50.0% (29.9-70.1)
CR (n, %)	0	0	0
PR (n, %)	7 (43.8)	6 (60.0)	13 (50.0)
ORR-ICR % (95% CI), updated‡	43.8% (19.8- 70.1)	60.0% (26.2- 87.8)	50.0% (29.9-70.1)
Median DOR in months (95% CI)†	Not reached	Not reached	Not reached
Median DOR in months (95% CI), updated ‡	20.3 (4.6-20.3)	Not reached	20.3 (NE-NE)
Median PFS in months (95% CI)†	Not reached	Not reached	Not reached
Median PFS in months (95% CI), updated‡	16.2 (1.8-22.0)	Not reached	22.0 (5.4-NE)
OS in months (95% CI)†	Not reached	Not reached	Not reached
OS in months (95% CI), updated‡	22.0 (13.6-NE)	Not reached	Not reached

Abbreviations: CSCC – cutaneous squamous cell carcinoma; CI -confidence interval; CR – complete response; DOR - duration of response; ICR - independent central review; ORR - objective response rate; NE – not estimable; OS- overall survival; PFS – progression-free survival; PR – partial response; TEAE – treatment-emergent adverse event.

Notes:
† Data cut-off date: October 2, 2017.[1,4]
‡ Data cut-off date: June 30, 2018 (duration of median follow-up not reported).[3]

Study 1540

Study 1540 is a global, multicentre, non-randomized, single-group, open-label phase 2 trial of cemiplimab monotherapy in patients with invasive CSCC.[1] The targeted enrollment was 175 patients separated into the following three groups defined by disease stage and treatment dosing schedule:

- Group 1: 50 patients with metastatic CSCC who received a weight-based dose of cemiplimab (3 mg/kg IV every two weeks)
- Group 2: 72 patients with locally advanced CSCC who received a weight-based dose of cemiplimab (3 mg /kg IV every two weeks)
- Group 3: 53 patients with metastatic CSCC who received a fixed dose of cemiplimab (350 mg IV every three weeks).

Eligible patients were adults (≥18 years or older) with histologically confirmed unresectable locally advanced or metastatic (nodal or distant) CSCC who had at least one measurable lesion by study criteria. Patients with unresectable locally advanced CSCC were considered either inoperable, had medical contraindications to surgery or radiation, or had not achieved disease control with these forms of treatment. Patients were required to have at least one measurable lesion according to RECIST (version 1.1), an ECOG performance status of 0 or 1, adequate organ function, and an anticipated life expectancy of ≥ 12 weeks. Patients were excluded from the study if they had ongoing or recent significant autoimmune disease that required systemic immunosuppressive therapy, untreated/active brain metastases, previous treatment with agents that block the PD-1 or PD-L1 pathway or other immune modulating agents that either were administered within four weeks of the first dose of cemiplimab or were associated with immune mediated adverse events that were ≥ grade 1 within 90 days prior to the first dose of cemiplimab or were associated with toxicity that resulted in discontinuation of the immune-modulating agent. Patients who had a history of solid organ transplant or a concurrent cancer, or CSCC of the dry lip or anogenital area were also excluded.

Study 1540 enrolled a total of 193 patients; 59 patients in Group 1, 78 patients in Group 2, and 56 patients in Group 3. The majority of patients in the study were male (83.4%), had metastatic disease (59.6%), an ECOG performance status of 1 (55.4%) and had received prior radiation (67.9%). Approximately one third of patients had received some form of systemic therapy (33.7%).

The primary outcome in Study 1540 was ORR based on ICR using the RECIST version 1.1. 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 excluded a historical control ORR that was not deemed clinically meaningful. Therefore, in Study 1540, if the lower limit of the 95% CI of the observed ORRs excluded 15% for Group 1 and Group 3, and excluded 25% for Group 2, the study treatment was deemed effective/clinically meaningful for that group, respectively. The sample sizes in each group were based on the number of patients needed in order to provide sufficient power to reject the null hypotheses of an ORR of 15% in Groups 1 and 3, and 25% in Group 2. All statistical analyses of efficacy outcomes were conducted independently for each group. Patients were analyzed according to the intent-to-treat (ITT) principle.

The key secondary outcome of Study 1540 was DOR; and other secondary outcomes included PFS, OS, and health-related quality of life (HRQoL), which was considered an exploratory endpoint.

The first efficacy analysis, which occurred on October 27, 2017, was planned for six months after the first dose of cemiplimab had been administered in the last patient enrolled in Group 1.[3] On this date, patient enrollment was still ongoing for Group 2 and Group 3.[3] An updated efficacy analysis was performed based on the data cut-off dates of September 20, 2018 (Group 1 and Group 3) and October 10, 2018 (Group 2) and included the total patient population of 193 patients.[3,5] Efficacy analyses for all three groups were possible since all patients had at last three response assessments. The median duration of cemiplimab treatment for all patients was 39.10 weeks (range, 2.6-60.4).[6] A summary of the results for key outcomes of Study 1540 based on the updated data cut-off dates is available in Table 1.2.

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.[3] The observed ORR by ICR was 44.0% (95% CI, 36.9-51.3) in all patients, 49.2% (95% CI, 35.9-62.5) in Group 1, 43.6% (95% CI, 32.4-55.3) in Group 2, and 39.3% (95% CI, 26.5-53.2) in Group 3.[3] The results in each group met the prespecified 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 PFS and OS data were also

immature based on low event rates and a large percentage of patients were censored from these analyses.[3,5] The median PFS was 18.4 months in Group 1, not reached in Group 2, and 10. 4 months in Group 3; and the median OS was not reached in any group.[3]

HRQoL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core Module (QLQ-C30). Baseline scores indicated that patients reported moderate-to-high levels of QoL and functioning as well as low symptom scores.[5] 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.[5] Pain was the only scale to demonstrate a clinically meaningful change (improvement) from baseline based on the aforementioned 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 and the other scales assessed, including emotional functioning, insomnia, appetite loss, and constipation.

In terms of safety, there were 191 patients (99.0%) who experienced any TEAE and 86 patients (44.6%) who experienced TEAEs that were grade 3 or higher.[5] The most frequently occurring TEAEs (Group 1/Group 2) 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).[7,8] Serious TEAEs occurred in 35.8% of all patients; 40.7% in Group 1, 29.5% in Group 2, and 39.3% in Group 3.[5] A TEAE resulted in death in 5 patients (2.6%); two patients in Group 1, two patients in Group 2 and 1 patient Group 3.[7,8]

Table 1.2: Key Outcomes of Study 1540 (phase 2).[3,7,8]

Outcomes†	Study 1540			
	Group 1 Metastatic CSCC (n=59)	Group 2 Locally advanced CSCC (n=78)	Group 3 Metastatic CSCC (n=56)	Total (n=193)
Median follow up months (range)	16.5 (NR)	9.3 (NR)	8.1 (NR)	9.4 (NR)
Primary Outcome – ORR by ICR				
ORR by ICR % (95% CI)†	49.2% (35.9-62.5)	43.6% (32.4-55.3)	39.3% (26.5-53.2)	44.0% (36.9-51.3)
CR (n, %)	10 (19.9)	10 (12.8)	2 (3.6)	22 (11.4)
PR (n, %)	19 (32.2)	24 (30.8)	20 (35.7)	63 (32.6)
Secondary Outcomes				
Median DOR in months (95% CI)	Not reached	Not reached	Not reached	Not reached
Observed DOR ≥ 6 months, n (%)	27 (93.1)	23 (67.6)	14 (63.6)	64 (75.3)
Observed DOR ≥ 12 months, n (%)	22 (75.9)	12 (35.3)	0	34 (40.0)
Median PFS in months (95% CI)‡	18.4 (7.3-NE)	Not reached	10.4 (3.6-NE)	18.4 (9.1-NE)
Estimated PFS probability at 12 months % (95% CI)	53.1 (39.1-65.2)	58.1 (43.7-70.0)	44.6 (26.5-61.3)	53.4 (45.1-60.9)
Median OS in months (95% CI)	Not reached	Not reached	Not reached	Not reached
Estimated OS probability at 12 months % (95% CI)	81.3 (68.7-89.2)	93.2 (84.4-97.1)	76.1 (56.9-87.6)	85.7 (79.6-90.1)
Safety				
Any TEAE	59 (100)	78 (100)	54 (96.4)	191 (99.0)
Grade ≥ 3 TEAE	30 (50.8)	34 (43.6)	22 (39.3)	86 (44.6)
Serious TEAE	24 (40.7)	23 (29.5)	22 (39.3)	69 (35.8)
TEAE leading to drug interruption or delay	22 (3.7)	30 (38.5)	16 (28.6)	68 (35.2)
TEAE leading to treatment discontinuation	6 (10.2)	6 (7.7)	3 (5.4)	15 (7.8)

Outcomes†	Study 1540			
	Group 1 Metastatic CSCC (n=59)	Group 2 Locally advanced CSCC (n=78)	Group 3 Metastatic CSCC (n=56)	Total (n=193)
Abbreviations: CI -confidence interval; CR – complete response; CSCC – cutaneous squamous cell carcinoma; DOR - duration of response; ICR - independent central review; ORR - objective response rate; NE – not estimable; OS- overall survival; NR – not reported; PFS – progression-free survival; PR – partial response; TEAE – treatment-emergent adverse event.				
Notes: †Data cut-off date: September 20, 2018 for Group 1 and Group 3, and October 10, 2018 for Group 2.[3,7,8] ‡Based on Kaplan-Meier estimation for median survival.				

1.2.2 Additional Evidence

See Sections 3, 4, and 5 for a complete summary of patient advocacy group input, PAG Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

Two patient advocacy groups, the Melanoma Network of Canada (MNC) and the Save Your Skin Foundation (SYSF), provided input on cemiplimab for CSCC. For a summary of this input, refer to Section 3.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified clinical and economic factors that could impact the implementation of cemiplimab for CSCC. For a summary of this input, refer to Section 4.

Registered Clinician Input

One joint clinician input was submitted on behalf of four oncologists and one oncology pharmacist from Cancer Care Ontario's (CCO) Skin Drug Advisory Committee (DAC). For a summary of this input, please refer to Section 5.

Summary of Supplemental Questions

- Summary and critical appraisal of the sponsor-submitted indirect treatment comparison (ITC) to estimate the comparative efficacy and safety of cemiplimab versus chemotherapy with platinum and best supportive care (BSC) among patients with metastatic and locally advanced CSCC.[9]

The sponsor provided a systematic literature review (SLR) and ITC to assess the comparative efficacy and safety of cemiplimab compared to chemotherapy with platinum or BSC among patients with metastatic or locally advanced CSCC who were not candidates for curative surgery or curative radiation. A SLR was conducted to identify studies reporting on the efficacy and safety of other treatment options used to treat patients with advanced and metastatic CSCC. The SLR identified Study 1423 and Study 1540 and two observational studies (Jarkowski 2016 and Sun 2019)[10,11] that met the inclusion criteria and evaluated chemotherapy and BSC as the study treatment. The sponsor used individual patient data (IPD) from the two cemiplimab studies.

It was stated in the submitted ITC report that performing a traditional network meta-analysis would not be feasible due to the absence of a comparator group in the cemiplimab studies. Thus, the Sponsor conducted an ITC using three different approaches:

1) an unadjusted naïve comparison;

2) a simulated treatment comparison (STC); and
3) a matching-adjusted indirect comparison (MAIC).

The naïve comparisons involved comparing outcomes from the cemiplimab and comparator studies without accounting for differences in their patient populations. The results from the naïve comparisons were used to inform the pCODR Economic Guidance Panel (EGP)'s base case in reanalyses of the sponsor's economic model as this was the most conservative estimate.

The sponsor also performed a population-adjusted ITC using STC (as the base case analysis) and MAIC (as a sensitivity analysis). The STC approach involved applying regression models (core and extended models) to the IPD from the cemiplimab trials (index population) in order to estimate the effect of different combinations of prognostic factors on the outcomes of interest. The MAIC approach estimated weights for the IPD from the cemiplimab studies so that the weighted mean baseline characteristics matched those observed for the target population. The following outcomes were included in the analyses: PFS and OS as the primary outcomes, and ORR as a secondary outcome. Relevant prognostic factors that could influence the outcomes of interest were identified through a targeted search. 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.

Results of the ITC suggest that cemiplimab improved OS (statistically significant) and PFS (not statistically significant) when compared to platinum-based chemotherapy, and improved OS (statistically significant) when compared to BSC, regardless of the analysis model used (i.e., Naïve, STC, and MAIC). More details are outlined in section 7.1.

Overall, the results of the ITC should be interpreted with caution due to small sample sizes and insufficient information on the patient populations in the included 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 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 effect modifiers for a given outcome must be adjusted for in the model. 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.

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

Table 1.3: Assessment of the generalizability of evidence for cemiplimab in CSCC.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence from Studies 1423 and 1540[1,3]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="3">Population</td><td>ECOG performance status</td><td>Study 1423:
<table><tr><th>ECOG PS, n(%)</th><th>Group 1</th><th>Group 2</th></tr><tr><td>0</td><td>6 (37.5)</td><td>4 (40.0)</td></tr><tr><td>1</td><td>10 (65.0)</td><td>6 (60.0)</td></tr></table>Study 1540:
<table><tr><th>ECOG PS, n(%)</th><th>Group 1</th><th>Group 2</th><th>Group 3</th></tr><tr><td>0</td><td>23 (39.0)</td><td>38 (48.7)</td><td>25 (44.6)</td></tr><tr><td>1</td><td>36 (61.0)</td><td>40 (51.3)</td><td>31 (55.4)</td></tr></table></td><td>Are the trial results generalizable to patients with an ECOG performance status of >2?</td><td>No. There is no evidence to support the use of cemiplimab in patients with a poor performance status. Treatment of patients with an ECOG 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.</td></tr>
<tr><td>Autoimmune disorders</td><td>Patients with ongoing or recent significant autoimmune disease that required systemic immunosuppressive therapy were excluded from both studies.</td><td>Does the exclusion of patients with autoimmune disorders limit the interpretation of the trial results with respect to the target population?</td><td>No. Although these patients were excluded from the studies of cemiplimab, real world evidence and access programs have shown that these treatments can be administered to patients with autoimmune disorders, albeit at a higher incidence of adverse events.</td></tr>
<tr><td>Transplant patients</td><td>Patients who had a history of solid organ transplant were excluded from both studies.</td><td>Does the exclusion of patients with history of solid organ transplant limit the interpretation of the trial results with respect to the target population?</td><td>The transplant population is a small patient group that may benefit from treatment with cemiplimab. In these patients the risk of organ rejection must be weighed against potential clinical benefit. Therefore, these patients should be considered for treatment with cemiplimab on a case by case basis.</td></tr>
<tr><td>Intervention</td><td>Dose and schedule</td><td>In Study 1423 patients received a weight-based dose of cemiplimab (3 mg/kg IV every two weeks); and in Study 1540 patients received a weight-based dose (3 mg/kg IV every two weeks) or a fixed dose of cemiplimab (350 mg IV every three weeks).</td><td>Are the results of the weight-based dose schedule generalizable to, or interchangeable with the fixed dose schedule?</td><td>Longer follow-up data are necessary to determine the interchangeability of the two dosing schedules; however, based on the available evidence there does</td></tr>
</table>

Domain	Factor	Evidence from Studies 1423 and 1540[1,3]	Generalizability Question	CGP Assessment of Generalizability
		The Health Canada product monograph recommends a fixed dose of cemiplimab of 350 mg every three weeks. For patients with a low body weight, the monograph indicates a weight-based dose of 3 mg/kg every two weeks can be considered at the discretion of the treating healthcare professional.		not appear to be any significant differences in outcomes between fixed and weight-based dose schedules.
Outcomes	Appropriateness of primary and secondary outcomes	Study 1423: • Primary outcome - safety, tolerability and DLTs • Secondary outcomes - ORR by ICR, DOR, PFS, OS Study 1540: • Primary outcome - ORR by ICR • Secondary outcomes -DOR, PFS, OS, HRQoL, safety	Are the outcomes being assessed the most important to clinicians; and is the primary outcome appropriately chosen?	Yes. The CGP noted the choice of primary and secondary outcomes were appropriate based on the intent of phase 1 and 2 study design, and in terms of being important measures of efficacy and safety in patients with CSCC.

Abbreviations: CGP – Clinical Guidance Panel; CSCC – cutaneous squamous cell carcinoma; DLTs – dose limiting toxicities; ECOG – Eastern Cooperative Oncology Group; ICR – independent central review; DOR - duration of response; HRQoL – health-related quality of life; ICR - independent central review; IV – intravenous; ORR - objective response rate; OS- overall survival; PFS – progression-free survival; PS – performance status; PR – partial response.

1.2.4 Interpretation

Burden of Illness and Unmet Need

Locally advanced or metastatic CSCC is an uncommon but devastating malignancy for which until recently there were no Health Canada approved treatments. The majority of patients with CSCC present with localized disease and are treated by local therapy such as surgical excision, with a 5-year survival rate of about 95%. Unfortunately, for those patients who develop either locally advanced inoperable disease or distant metastatic disease, prognosis is poor and treatment has largely been palliative. In addition, as the tumours most commonly present on the head and neck region, significant disfigurement occurs leading to significant declines in physical and emotional well being. Chemotherapy has never been shown to improve either OS or QoL, and chemotherapy in this population is considered off-label. In fact, National Comprehensive Cancer Network (NCCN) guidelines recommended that eligible patients be treated in clinical trials. Certain patient populations such as the elderly, immune-compromised and patients with a history of solid organ transplant are at particular risk of developing local or distant recurrences. Thus, there is a strong unmet need for novel treatments that could offer improvements in QoL, survival and acceptable toxicity in this population. Health Canada has approved cemiplimab at a dose of 350 mg IV every three weeks until symptomatic disease progression or unacceptable toxicity for patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation.

Clinical Efficacy and Safety

Two prospective, non-randomized, single-group clinical studies have been performed (and are ongoing) that provide evidence for efficacy in patients with metastatic and inoperable locally advanced CSCC. The first, Study 1423, is a phase 1 dose escalation study that evaluated cemiplimab as monotherapy or in combination with other anti-cancer therapies in patients with advanced solid malignancies.[1] In this study cemiplimab was evaluated at a dose of 3 mg/kg IV every two weeks for up to 48 weeks. The primary outcome was safety, which

included evaluation of tolerability, side effect profile, and dose limiting toxicities. Efficacy outcomes were also assessed as secondary endpoints and included ORR by ICR, DOR, PFS, and OS. Two expansion cohorts of CSCC patients provided preliminary evidence of clinical benefit with cemiplimab monotherapy, with durable responses observed. In the CSCC expansion cohorts, a partial response (PR) to therapy was seen in 13 of 26 patients for an ORR by ICR of 50% (95% CI, 29.9–70.1). Among all patients in the study, 15 (57.7%) had received prior systemic therapy and 20 (77.0%) had received prior radiation.

The second study, Study 1540 (EMPOWER-CSCC 1), is the pivotal phase 2 study where patients with metastatic and inoperable locally advanced CSCC were treated with cemiplimab either at a dose of 3 mg/kg given every two weeks or a fixed dose of 350 mg given every three weeks. The primary outcome was ORR by ICR. The key secondary outcome was DOR, and PFS, OS, and HRQoL were also assessed. Patients in Group 1 received cemiplimab at 3 mg/kg IV over 30 minutes every two weeks for up to 96 weeks; patients in Group 2 received cemiplimab 3 mg/kg IV over 30 minutes every two weeks for up to 96 weeks; and lastly, patients in Group 3 received cemiplimab at the 350 mg fixed dose IV over 30 minutes every three weeks for up to 54 weeks. All groups received cemiplimab for the planned treatment duration or until disease progression or unacceptable toxicity. The first efficacy analysis was planned for six months after the first dose of cemiplimab had been administered in the last patient enrolled in Group 1 (n=59). On this date, patient enrollment was still ongoing for Groups 2 and 3. Group 3 was added later to the study in order to evaluate the efficacy of the fixed dose schedule. Therefore, the first efficacy analysis also included some patients from Group 2 (n=23) but none from Group 3. The median follow-up at the time of the first analysis was 8.56 months (range, 0.8 to 15.9). The overall ORR by IRC was 46.3% (95% CI, 35.3-57.7). A complete response (CR) was observed in 4 patients (68.0%), and a PR was observed in 34 patients (40.7%). The median DOR had not been reached at the time of this analysis; however, DOR exceeded 6 months in 23 of the 34 patients (60.5%). Neither the median PFS nor median OS had been reached. The estimated probability of PFS at 12 months was 53% (95% CI, 37-66).

A recent updated analysis of Study 1540,[3,5] which included a total of 193 patients and was based on a longer median follow-up of 9.4 months, gave further clarity to the efficacy of cemiplimab in patients with CSCC. The updated analysis includes data on all three treatment groups with follow-up durations of 16.53 months in Group 1, 9.3 months in Group 2, and 8.05 months in Group 3. With respect to previous treatment, 65 patients (33.7%) had received prior systemic therapy and 131 patients (67.9%) had received prior radiotherapy. At the time of data cut-off treatment was ongoing in approximately one third of patients (22.0%, 30.8%, and 46.4% for Groups 1, 2 and 3, respectively). The overall ORR by ICR was 44.0% (95% CI, 36.9-51.3) in all patients; 22 patients (11.4%) had a CR and 63 patients (32.6%) had a PR. The ORRs in Groups 1, 2 and 3 were 49.2% (95% CI, 35.9-62.5), 43.6% (95% CI, 32.4-55.3), and 39.3% (95% CI, 26.5-53.2), respectively. The results in each group met the prespecified 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 of the treatment groups; however, 40.0% of patients had maintained a response (CR or PR) for ≥ 12 months and 24.7% maintained a response for ≥ 16 months. Although the PFS data were still immature at the updated analysis, median PFS was 18.4 months in Group 1, not reached in Group 2, and 10.4 months in Group 3, corresponding with an overall median PFS of 18.4 months in all patients. The probability of PFS was 53.4% (95% CI,45.1; 60.9) at 12 months. The median OS had also not been reached; the estimated OS was 85.7% (95% CI, 79.6-90.1) at 12 months and 77.8% (95% CI, 69.8-83.9) at 16 months.

Although limitations of the HRQoL analysis are acknowledged (refer to section 6.3.2.1), the available evidence on QoL as measured by the EORTC QLQ-C30 instrument suggests 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, appetite loss, constipation and insomnia.

Overall, in terms of safety, cemiplimab was well tolerated with an acceptable safety profile; only 7.8% of patients discontinued treatment due to adverse events. The most common adverse events (Group 1/Group 2) 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%), where the majority of events were grade 1 or 2. The incidence of diarrhea (1.7%/0%), fatigue (1.7%/1.3%), nausea (0%/0%), constipation (1.7%/0%) and rash (0%/0%) of grade 3 or greater (Group 1/Group 2) was low in the study. No new safety signals were observed as compared to other PD-1 inhibitors.

In reviewing the evidence from Study 1540, the CGP noted that ORR is an appropriate and meaningful endpoint in phase 2 studies given their intent and generally smaller sample sizes. A randomized trial evaluating cemiplimab would be difficult to conduct both logistically and ethically due to the paucity of patients with CSCC, non-existing evidence that chemotherapy offers a benefit, pre-existing comorbidities in many patients, as well as the advanced age of the patient population. Although there are no randomized trials directly comparing chemotherapy to cemiplimab, response rates, durability of response and safety and tolerability appear superior to chemotherapy. As data on PFS and OS are currently immature, longer term data on these outcomes are needed to confirm the clinical benefit observed on overall response rate.

Other Considerations

The PAG raised several points to be considered if cemiplimab were to be recommended for reimbursement, specifically with respect to dosing, treatment duration, treatment options after progression, retreatment, and generalizability of evidence. The CGP has addressed these points below:

- The appropriate dosing schedule of cemiplimab is still to be determined. Study 1423 and Groups 1 and 2 of Study 1520 used a weight-based dose of 3 mg/kg every two weeks for a maximum duration of 96 weeks. Health Canada approved cemiplimab at a fixed dose of 350 mg IV every three weeks until symptomatic disease progression or unacceptable toxicity. Group 3 was added as an amendment to Study 1540 to demonstrate comparability of doses and schedule with regards to effectiveness and safety. Because this group was added to the study later, the treatment duration was arbitrarily shorter (54 weeks) to have a similar close out date for all groups in the study. Patients were permitted to continue the treatment outside of the study period during continued follow-up. Data are not yet available on those patients who continued treatment beyond the planned treatment duration. Pharmacokinetic analyses of other PD-1 inhibitors support the fixed dose regimen; nivolumab has pharmacokinetic data to support a fixed dose every four weeks and pembrolizumab a higher dose every six weeks. Therefore, the CGP felt the fixed dose schedule with a treatment duration of 96 weeks was reasonable, with the proviso that longer follow up are necessary to confirm the interchangeability of the dose schedules. For patients with low body weight (i.e., BMI <18.5) weight-based dosing of 3 mg/kg has been approved.
- The question of retreatment in patients who have completed their maximum duration of treatment and subsequently relapse is not known. The CGP felt in those patients who had previously responded and subsequently progressed six months or more after treatment, it would be reasonable to offer retreatment. Retreatment was allowed on Study 1540 for patients who experienced disease progression in the first six months of post-treatment follow up; however, the number of patients to enter retreatment is small, and data from these patients are not yet available.

- In terms of optimal sequencing, patients with metastatic and unresectable locally advanced CSCC would be offered cemiplimab as first-line treatment. Upon progression on cemiplimab, patients would be offered enrolment to a clinical trial given the lack of other approved treatments.
- The CGP agreed there is no evidence to support the treatment of patients with an ECOG performance status of 2 as these patients were not enrolled in either cemiplimab study; however, they felt it would be appropriate to offer treatment to these patients on a case by case basis.

1.3 Conclusions

The CGP concluded that there is an overall net clinical benefit to treatment with cemiplimab for patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation. Two prospective studies, Study 1423 and Study 1540, confirmed the high response rate of cemiplimab given as an IV therapy in patients with metastatic or unresectable locally advanced CSCC. More importantly, durability of responses was observed. No new safety signals were seen, and as in other trials of PD-1 inhibitors, tolerability was good with a low percentage of patients who discontinued treatment due to adverse events. Many locally advanced and metastatic patients are not candidates for chemotherapy, or if locally advanced would require extensive disfiguring surgery. Thus, this treatment fulfills an unmet need for new therapies in this patient population. Cemiplimab should be available as a treatment option in treated (prior radiation and/or systemic therapy) or treatment naïve patients.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR CSCC CGP. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Non-melanoma skin cancer (NMSC) is the most common cancer affecting Canadians. There are two main subtypes including CSCC which accounts for approximately 20% of NMSC and basal cell carcinoma (BCC) which accounts for the remaining 80%.[12] The incidence of NMSC is increasing as the population ages and as better screening is identifying an increased number of patients. The lifetime incidence of developing CSCC is estimated at about 5%. Fortunately, the majority of patients present with early stage disease and the five-year survival rate is estimated to be about 95%.[12] Unfortunately for those patients who develop locally advanced inoperable disease, or distant metastatic disease the prognosis is poor and treatment has been largely palliative with 3-year survivals ranging from 22% to 40% for locally advanced disease.[10] Certain patient populations such as the elderly, immune-compromised and transplant patients are at particular risk of developing local or distant recurrences. The majority of CSCC cases occur in the head and neck region with the potential of causing significant physical impairment which will affect a patient's physical, social and emotional sense of well-being.

2.2 Accepted Clinical Practice

There are no Health Canada approved chemotherapy or targeted treatments for metastatic or advanced CSCC, therefore, the use of chemotherapy in this population is considered off-label. Treatment has largely consisted of cisplatin, 5-FU and/or cetuximab with most responses rates ranging between 20% to 80% albeit the patient numbers are small, highly selected and many series are lacking information about patient characteristics such as performance status and tumour characteristics. Based on clinical experience, the true response rate of chemotherapy is low; and more importantly, the duration of response is short. Due to the lack of evidence and the potential toxicity of treatments caution must be exercised in using chemotherapy with or without cetuximab. In addition, many patients are not suitable candidates for chemotherapy due to their advanced age or immunosuppression. In patients who developed distant metastases or unresectable locally advanced disease treatment options are limited. Although there are no randomized trials comparing chemotherapy to BSC several case series involving small numbers of patients have been reported showing variable response rates, short durations of response and poor survival rates.[10] Thus, there is a significant unmet need for new treatments in patients with unresectable locally advanced and metastatic CSCC.

CSCC typically occurs in areas of the skin that are chronically exposed to UV radiation, and as such are associated with a high mutational load. Tumours with high mutational loads are more likely to respond to immune checkpoint therapy. Cemiplimab is a high affinity human monoclonal antibody directed against PD-1. Cemiplimab is the first treatment to be approved by Health Canada in the treatment of metastatic and inoperable locally advanced CSCC.

2.3 Evidence-Based Considerations for a Funding Population

Although the incidence of NMSC is high and in Canada was estimated at approximately 75,000 cases in 2004,[13] most patients present with localized disease and are cured by surgery. Using Ontario as a model, it is estimated that roughly 199 patients in the country would be candidates for cemiplimab treatment. Thus, the economic impact to provincial drug budgets would be small.

2.4 Other Patient Populations in Whom the Drug May Be Used

Patients with locally advanced cancers that are potentially resectable or candidates for radiation may be offered cemiplimab to try and downstage a tumour to minimize the surgery and thus give a better cosmetic outcome. As many of these patients are elderly and may have significant comorbidities that may impact their performance status, treatment of ECOG 2 patients could be considered on a case by case basis. Patients with autoimmune diseases are also potential candidates for treatment based on clinical benefit versus potential exacerbation of their autoimmune disease. This has been well documented in the melanoma population. The transplant population is also a small group that may benefit, yet they were excluded from the studies of cemiplimab. In these patients the risk of organ rejection must be weighed against potential clinical benefit.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy groups provided input on cemiplimab for CSCC and their input is summarized below: Save Your Skin Foundation (SYSF) and Melanoma Network of Canada (MNC).

MNC collected information through an online survey. MNC noted the challenge of obtaining data from Canadian patients that received cemiplimab as very few have been prescribed this treatment. To recruit participants, MNC mailed information about the survey to healthcare providers and promoted it on social media. Due to the limited number of patients receiving cemiplimab in Canada, MNC also reached out to U.S. sites that participated in clinical trials of cemiplimab to connect with patients who had used cemiplimab. The survey was available from June 21-July 20, 2019. There were 67 patient responses and 44 caregiver responses. Of the patient respondents, 39 (58%) were female and 28 (42%) were male. Most patient respondents were early stage or did not know their staging. Among the patient respondents, eight (12%) were from the U.S., one was (1%) from Australia and 58 (87%) were from Canada. Namely, 57% of respondents were from Ontario, 11% from Quebec, 8% from Alberta, 6% from Nova Scotia, 6% from British Columbia, and 12% were from other provinces (Table 3.1). Eleven patients indicated they had been treated with cemiplimab for metastatic disease; ages of all patient respondents are summarized in Table 3.2.

Table 3.1: Country and Canadian Provincial Breakdown of Patient Respondents, MNC.

Country or Canadian Province of Patient Respondent	Patients, n (%)
Among Total Patient Respondents:	
United States	8 (12%)
Australia	1 (1%)
Canada	58 (87%)
Among Canadian Patient Respondents:	
Ontario	NR (57%)
Quebec	NR (11%)
Alberta	NR (8%)
British Columbia	NR (6%)
Nova Scotia	NR (6%)
Other provinces	NR (12%)

NR = not reported

Table 3.2: Age of Patient Respondents, MNC.

Age	Patients, n (%)
18 – 30 years	1 (1%)
31 – 40 years	1 (1%)
41 – 50 years	2 (3%)
51 – 60 years	10 (15%)
61 – 70 years	20 (30%)
> 70 years	33 (49%)
Total responses	67

SYSF collected patient information through surveys and one-on-one conversations. Of the six respondents, five (83%) patients took the survey and one (17%) patient was interviewed via telephone. Two of the respondents were from Canada. All respondents were men older than 50, four (67%) were employed and two (33%) were retired. All respondents had experience with cemiplimab as part of a clinical trial.

Overall, patients with CSCC value the option to choose effective treatments associated with tolerable side effects. Namely, patients value more effective therapies that do not require them to undergo radiation or surgery, as these treatments are often invasive and associated with more side effects and

pain. Thus, patients value less pain, less scarring and disfigurement, and less debilitating side effects. Accordingly, patients highlighted cemiplimab to be an advantageous therapy as it provides an additional option and offers therapeutic effectiveness. Fatigue was reported to be the most common side effect; however, the majority stated that the benefits of the treatment outweigh the side effects.

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

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Cutaneous Squamous Cell Carcinoma

Patients experienced many challenges following a CSCC diagnosis. One SYSF patient described the experience as "horrific," another as a "complete lifestyle change." MNC added that CSCC is distressing due to the visible disfigurement of the head and neck caused by the disease. The advanced age of many patients adds to the distress because older patients may also experience challenges with travel, home support and care, and other health issues. In addition, the side effects associated with surgery and radiation can be debilitating and traumatizing to the patient and their family. Survey responses on disease impact from MCN are summarized in Table 3.3.

Table 3.3. Impact of CSCC on Patients, MNC.

Disease Impact	Patients, n (%)
Scarring or disfigurement	33 (66%)
Fear or anxiety	29 (58%)
Fatigue	21 (42%)
Disrupted sleep	18 (36%)
Negative impact to self-image, family or social life	16 (32%)
Depression	15 (30%)
Pain	15 (30%)
Peripheral neuropathy (nerve pain or damage)	13 (26%)
Edema or fluid retention	10 (20%)
Financial loss or job loss	6 (12%)
Impact on sexuality	3 (6%)
None – there has been no impact	7 (14%)
Total responses	50

According to MCN, the scarring, disfigurement, pain, social isolation and depression due to advanced or metastatic cancer and associated treatment are difficult to fully describe. Nonetheless, accounts in the patients' own words follow:

- "It is so frightening. People stopped coming to see me as my face was so bad. I fell into depression and didn't want to see anyone. I really lost hope and thought I would be better off dead. It is not only painful but is like an acid eating your face and neck. You cannot live like this."
- "Extreme pain. Tumor erupted on the side of my face. There was major paralysis on the left side of my face."
- "Too much pain daily, anger, fear, can't get out of bed some days, depression. Don't do any activities anymore because of pain. Fear of dying. Not on any treatment and cancer spreading more because no treatment available."

"Pain. Fear. All of the concerns associated with terminal illness, including anxiety over whether MAID[i] in the case of incurable disease and intractable pain is moral. Lack of quality of life, and deciding whether, if unable to be independent, moving to a care facility, specifically a hospice, should be a step taken in the near future."

3.1.2 Patients' Experiences with Current Therapy for Cutaneous Squamous Cell Carcinoma

Most locally advanced or metastatic CSCC is treated with surgery and/or radiation. Patients indicated significant issues with surgical procedures and radiation side effects having a negative impact on quality of life. It can be challenging to treat disease on the head and neck, where CSCC most often occurs. There is no standard chemotherapy protocol for CSCC. Although cisplatin-based combinations sometimes show efficacy, these are too toxic for most elderly patients. Cetuximab is also prescribed for head and neck cancers; accordingly, four MNC patients were treated with cetuximab and all had reported progression. Most SYSF patients underwent multiple treatments and surgeries, including chemotherapy, Mohs surgery (surgical removal layer by layer), and radiation. Treatments received by MNC patients are summarized in Table 3.4.

Table 3.4. Treatments Received for CSCC, MNC.

Treatments	Patients, n (%)
Surgical excision	37 (84%)
Topical creams or gels	18 (41%)
Radiation therapy	15 (34%)
Lymph node dissection	13 (30%)
Cryosurgery	10 (23%)
Mohs surgery	10 (23%)
Reconstructive surgery	8 (18%)
Chemotherapy	6 (14%)
Curettage and electrodesiccation	5 (11%)
Photodynamic therapy (PDT)	2 (5%)
Total responses	44

As noted by MNC, current therapies leave patients in horrible pain, often with debilitating side effects and significant physical and emotional scarring. Patients mentioned the following physical side effects: pain, disfigurement, facial paralysis, itchiness, lymphedema, scarring, nausea, muscle weakness, hematoma, and bleeding. Psychological side effects included stress and depression. One patient mentioned post-traumatic stress disorder from "having that cancer surgery sitting in a chair wide awake. It was very stressful just the noise it made scrapping of the bone!" These treatments often had a negative impact on quality of life as they led to other health issues for many patients, including affects on the ability to eat, breathe, swallow, speak, move, and mobility. Patients also described the time commitment and financial burden of these treatments; many had to see multiple specialists and some patients had to quit their jobs.

[i] MAID = medical assistance in dying

In the words of patients,

- "Due to the collateral damage of radiation my left arm is very weak due to muscle damage. Blood vessels in my neck are weak and occasionally burst due to the surgery. Fatigue due to the chemo."
- "Right cheek - cutaneous SCC spread along facial nerve and beyond. 13 hr surgery in 2015 resulted in a full flap to cover the facial defect followed by radiation/ chemo. There is also facial paralysis, articulation difficulties, deafness on the affected side. Still the cancer spread."
- "Surgery and radiation are painful. Creams burned and were not effective to stop it spreading. Every day was worse. So much time spent going back and forth to doctors and hospitals. It is too much for your family."
- "Radiation caused oral and throat burns, resulting in the inability to eat and during and a horrible painful cough, exhaustion, inability to sleep, eat or drink. Symptoms were so severe that end of life steps were taken. MAID was in place and the date was set. Depression was a major problem during this time and I was mainly confined to my bed. Side effects with infusions are more tolerable but whole body aches and flu like symptoms are experienced for a week after each infusion."
- "Radiation on my left side of my neck effected the shoulder muscles so the that my left arm is weak with a limited range of movement. Chemo (six treatments) was extremely debilitating with nausea and physical decline so that any activity was difficult without help. With 65 radiation treatments over about twelve months (45 and then 15 and 5) it was an impost on my family one had to attend with me as I had to take sedation to avoid the claustrophobia due to the mask. I had a small home based business that I had to give up. The initial surgery on my neck has weakened the blood vessels and I have suffered from hematoma and bleeding."

3.1.3 Impact of Cutaneous Squamous Cell Carcinoma and Current Therapy on Caregivers

MNC received input from 44 caregivers. Family members are often tasked with supporting the patient, as this cancer is largely found in patients aged 60 years and older and their spouses often have their own health issues or are deceased. Often, caregivers are drained emotionally and financially with the amount of time and resources required to care for patients with CSCC. Caregivers reported frequent travel expenses and time commitment, as treatment often required three or more hours of travel each way and often several times a week. One family spent nearly $20,000 in one month on travel and hotel to allow for treatment near the cancer centre.

Many caregivers described a need for psychosocial support to manage depression and anxiety. One caregiver described the burden of the disease on their relationships, feeling "…not as close as so much fear and anger regarding cancer. Instead of staying supportive of family a cancer patient can push people away because they are going through so much." Physical care needs are challenging as well, including frequent wound and dressing changes. One caregiver shared, "I did change bandages and wound care daily for years - something I never consider having to do at all!"

In the words of caregivers,

- "The time commitment to attend these multiple medical appointments involved a lot of missed time from work so I retired earlier than anticipated. I feel fortunate that my spouse and I are resilient and tend to take each day as it comes. During my

spouse's radiation/chemo treatments he was too fatigued to accomplish any household/ outside chores. I did it or hired helpers."

- "I moved into their home to help with dad's care, which after radiation was 24 hours a day. I took turns with siblings. I found it exhausting and emotionally debilitating to watch him suffer. I had no social life and breaks away were only for resting and getting my own affairs in order. I live an hour away from my parents. I did housekeeping for them, prepared meals and did shopping. I was suffering from caregiver burnout. It was up to me to arrange for MAID and make arrangements with the crematorium. The emotional pain to do this was incredible. It was the most emotionally consuming I have ever experienced."

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for Cemiplimab

MNC patients valued three characteristics in a treatment: effectiveness at stopping progression, less invasive procedures, and tolerable side effects. As discussed in section 3.1.2, current treatments can have negative side effects which are difficult for most people and often exacerbated in the elderly. Similarly, SYSF respondents indicated that they value treatments with less side effects and pain than surgery and radiation. Patients want to lessen or eliminate the need for radiation or surgery. One patient that responded to MCN's survey indicated that they would find the treatment process less of a mental strain if they knew a medication was available, "Before entering the drug trial, I was told that I could not be in a trial until all existing therapies had been tried. I would like to see future patients skip chemo and surgery and go directly to Libtayo."

3.2.2 Patient Experiences To Date with Cemiplimab

Of the 11 MNC respondents who were treated with cemiplimab, 10 patients (91%) indicated they achieved a complete response and one (9%) indicated stable disease. Patients who received cemiplimab in the U.S. and Australia had access to cemiplimab through clinical trials, while those in Canada had initial access through the special access program and subsequent access through the manufacturer's compassionate access program. According to patients, the advantage of cemiplimab was that the therapy was effective unlike other therapies. As well, it provided an additional option when previously there were none.

All MNC patients expressed that any side effects experienced were worth the results of the treatment. Notably, two patients experienced permanent thyroid issues as a result of cemiplimab, which were resolved with another drug therapy. The side effects of cemiplimab reported by MNC patient respondents are summarized in Table 3.5. In terms of access to treatment, most patients commented on the issues of frequent travel and the cost of parking.

Table 3.5: Side Effects Reported on Cemiplimab, MNC.

Side Effects	Patients, n (%)
Fatigue	6 (55%)
Skin rash	3 (27%)
Muscle or joint pain	3 (27%)
Fever or flu like symptoms	3 (27%)
Shortness of breath, cough or chest pain (pneumonitis)	2 (18%)
Diarrhea or colitis	2 (18%)
Muscle weakness	2 (18%)
Hormone or thyroid problems	2 (18%)

Side Effects	Patients, n (%)
Weight loss or loss of appetite	2 (18%)
Headaches	1 (9%)
Stomach pain	1 (9%)
Sexual impairment	1 (9%)
None	5 (45%)
Total responses	11
Zero patients reported pneumonia, liver problems, kidney problems, autoimmune myocarditis, weight gain, cognitive impairment	

All SYSF respondents (n=6) received cemiplimab through a clinical trial. Four patients completed the full course of treatment; however, two patients missed one dose throughout the entire treatment cycle due to other health issues that arose and not due to side effects from cemiplimab. Half of the patients (n=3) had no side effects, while half (n=3) experienced fatigue and gastrointestinal issues. Of the patients who experienced side effects, two rated them as manageable and one rated them as somewhat manageable. Five (83%) of the six patients said that the benefits of the treatment outweighed the side effects.

Additionally, MNC identified a need among patients to have treatments available at an earlier stage so patients do not have to suffer through extensive surgery and radiation. It was recommended that surgeons and radiologists as well as dermatologists are made aware of the efficacy and availability of cemiplimab treatment. It was stated that it should not be reserved as only a final option for metastatic disease treatment. A SYSF respondent echoed this perspective: "…At my acceptance on the trial you had to have been declared terminal. If I could have had the treatment earlier the co lateral damage would have been minimal. After a visit to Regeneron in New York I now believe due to the information gleaned from my trial cohort it is now available before becoming terminal. This was a great step forward."

Patients described their experience with cemiplimab:

MNC:

- "It seemed to work within a very short time. What could not be done by surgery was now better in very short order. I had a bit of flu like symptoms after each infusion, but saw remarkable change in the lesions and started feeling better within weeks. It also improves your mind - you feel like there is hope and maybe a chance to live again."
- "After being declared terminal in late November 2016 my oncologist actually arranged for me to see if I was a candidate for the clinical trial. Fortunately I was and had my first treatment was the last week of December 2016. I am now cancer free."

SYSF:

- "This was my only option. It was very important to me and my family. I am so blessed to have been included in this Libtayo trial."
- "It was imperative that I use Libtayo. Other than maybe other trials, there were no more treatment options. Hopefully all new treatments should be as effective and painless as Libtayo."
- "It was important in the fact that I was declared terminal and as it was the only alternate treatment offered it saved me. Having been involved with the trial for two years and following publications regarding cemiplimab I see this drug as being a game changer for cSCC sufferers."
- "I know I'm not supposed to say this, but I believe it saved my life. After being told to get my affairs in order, to you are cancer free, was amazing."

- "In the beginning, years of treatment for reoccurring AKs, the 15 - 20 Mohs surgeries, then CSCC in 2015. Then my scalp was removed and replaced with a skin graft. Then a failed attempt with chemo. Began the cemiplimab (Libtayo) in 2016, with all tumors gone in late 2016."
- "The cancer merry go round. Surgery, radiation, with no good news. Then the cemiplimab clinical trial which gave extraordinary results in two months."

3.2.3 Caregiver Experiences To Date with Cemiplimab

Caregivers also provided perspective on cemiplimab treatment. Caregivers were relieved to have access to cemiplimab through a clinical trial and as a result did not have to worry about the expense. Besides frequent appointments, many indicated that the drug did not cause any issues for them or the family.

Comments included:

- "Watching my Dad in pain and suffering was too much to bare. A week away from ending his life with MAID, we were told of the new therapy, and got on it under compassionate access. Within two weeks, the cancer had nearly completely gone. He is still coping with the after effects of the surgery, but the cancer is gone. Truly a miracle."
- "Side effects with infusions are more tolerable but whole body aches and flu like symptoms are experienced for a week after each infusion."
- "Once the drug showed positive results the whole shadow hanging over the family lifted. The result was accepted with reserved positivity due to the fear of side affects. Fortunately for me the side effects were very minor and currently life is back to normal with scans only every four months."

3.3 Companion Diagnostic Test

Not applicable.

3.4 Additional Information

None to report.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The PAG 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 nine** provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- No standard of care in this setting

Economic factors:

- Guidance on dosing schedule (i.e., fixed dose versus weight-based)
- Additional health care resources would be required such as pharmacy, nursing, physician, and clinic visits

Please see below for more details.

4.1 Currently Funded Treatments

PAG noted that there is no standard of care for the treatment of adult patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation. Patients may receive platinum-based chemotherapy (with or without cetuximab), systemic therapies, or observation.

4.2 Eligible Patient Population

The pivotal trial of cemiplimab for CSCC excluded patients with an ECOG PS of ≥2, PAG is seeking guidance on whether these patients should be eligible for cemiplimab.

Patients and clinicians may want to use cemiplimab to downstage disease not amenable to curative surgery or curative radiation; and if there is adequate response, patients may be candidates for local treatment (i.e., surgery or radiation).

If recommended for reimbursement, PAG noted that patients with CSCC, who are currently receiving other systemic therapies/chemotherapies, would need to be addressed on a time-limited basis.

There is a potential for indication creep to: patients who are candidates for curative surgery or curative radiation; superficial squamous cell carcinoma (non-invasive CSCC); and patients with prior treatment with an agent that blocks the PD-1/PD-L1 pathway.

4.3 Implementation Factors

In the pivotal Study 1540, cemiplimab was dosed at 3 mg/kg every 2 weeks (Groups 1 and 2) and at the 350 mg fixed dose every 3 weeks (Group 3). The Health Canada Product Monograph indicates a recommended dose of cemiplimab of 350 mg every 3 weeks or a dose of 3 mg/kg every 2 weeks for patients with a low body weight at the discretion of the treating healthcare professional. PAG is seeking clarity on the appropriate dosing schedule (i.e., fixed dose versus

weight-based), whether dosing schedules are considered interchangeable, and what is considered low body weight.

PAG is also seeking 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), similar to other immunotherapies such as nivolumab and pembrolizumab in other indications.

There is a potential for drug wastage depending on the recommended dose schedule (i.e., fixed dose versus weight-based). If the flat dose is used, wastage would not be anticipated as the vials come in 350 mg vials; however, if a flat dose is not used, wastage will be likely due to the small number of patients.

PAG is seeking guidance on treatment duration and discontinuation criteria as treatment is "until symptomatic disease progression or unacceptable toxicity".

PAG noted that additional health care resources would be required such as pharmacy, nursing, physician, and clinic visits, particularly for patients who do not receive any systemic treatment. Treatment with cemiplimab would require increased: monitoring of infusion reactions and immune-mediated adverse effects post-infusion as well as supportive care drugs (e.g., corticosteroids, immunosuppressants such as mycophenolate mofetil, or infliximab).

4.4 Sequencing and Priority of Treatments

PAG is seeking 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 in this setting.

PAG is also seeking 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.

4.5 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One joint clinician input was submitted on behalf of four oncologists and one oncology pharmacist from Cancer Care Ontario's (CCO) Skin Drug Advisory Committee (DAC). The most common treatments for cutaneous squamous cell carcinoma (CSCC) are cisplatin 5FU or cetuximab; however, these treatments may not be suitable for elderly patients. The clinicians highlighted an unmet need for older patients as well as those who have transplant issues or concerns. The primary advantage of cemiplimab is that it provides a new treatment option for this population. Moreover, cemiplimab does not require companion diagnostic testing. Safety of cemiplimab is similar to what is observed for other programmed cell death ligand (PD-1) treatments. The clinicians found the inclusion and exclusion criteria of the trial to be applicable to clinical practice and stated that cemiplimab would likely be administered as first-line therapy. In patients who have received other treatments, the clinicians expect cemiplimab to be the preferred treatment going forward. It was noted that some clinicians may not use cemiplimab for transplant patients. Furthermore, upon progression on cemiplimab in this setting, clinicians would choose chemotherapy, cetuximab, palliative care or clinical trials of other investigational agents as other therapeutic options. When asked whether there is evidence to support cemiplimab administration at a weight-based dosing schedule up to a cap (i.e., 3 mg/kg up to 350 mg every 3 weeks), the clinicians alluded to expanded cohort data that is expected to be released shortly that demonstrates the efficacy of using a flat dose in patients. They stated that there is also published data exhibiting similar pharmacokinetics between flat dosing and the weight-based dosing schedule used in the trial. Ultimately, the clinicians noted the value of collecting real world evidence for this indication with regards to dosing.

Please see below for details from the clinician input.

5.1 Current Treatment(s) for Cutaneous Small Cell Carcinoma (CSCC)

Clinicians stated that most patients receive cisplatin 5FU or cetuximab as therapy for CSCC. They noted that many patients diagnosed with CSCC are elderly and not always suited to these treatments.

5.2 Eligible Patient Population

The clinicians found the inclusion and exclusion criteria from the trial to be reasonable. They added that cemiplimab should be open to any line of therapy.

5.3 Relevance to Clinical Practice

All individuals submitting input on behalf of CCO Skin DAC had experience administering cemiplimab. They identified a large unmet need in this population and stated that cemiplimab provides an opportunity for clinicians to treat patients who are older or who have transplant issues or concerns. The safety of this treatment is similar to what is observed for other programmed cell death ligand (PD-1) treatments.

5.4 Sequencing and Priority of Treatments with Cemiplimab

• Implementation Question: Please consider the optimal treatment sequencing of cemiplimab in CSCC:

a) Sequencing of cemiplimab with currently available treatments (e.g., platinum-based chemotherapy (with or without cetuximab), systemic therapies, or observation).

Cemiplimab would likely be given as first-line therapy. If patients have already received other treatments, the clinicians would expect cemiplimab to be the preferred treatment

going forward. They added that some clinicians may not use cemiplimab for transplant patients.

b) What treatment options would be available to patients upon progression on cemiplimab in this setting?

Other options would include chemotherapy, cetuximab, palliative care or clinical trials of other investigational agents upon progression on cemiplimab in this setting.

c) Is there evidence for cemiplimab in relapsed/recurrent or re-treatment settings; if yes, please clarify the clinical criteria for re-treatment?

For other PD-1 therapies, there is evidence supporting retreatment. The clinicians expressed that they would like the ability to retreat, especially for patients who need to stop due to toxicity.

5.5 Companion Diagnostic Testing

No companion diagnostic testing required.

5.6 Implementation Questions

5.6.1 In the pivotal trial, cemiplimab was dosed at 3 mg/kg every 2 weeks. However, the Health Canada Product Monograph indicates a recommended dose of cemiplimab of 350 mg every 3 weeks or a dose of 3 mg/kg every 2 weeks for patients with a low body weight at the discretion of the treating healthcare professional.

a) Is there evidence to support administering cemiplimab at a weight-based dosing schedule up to a cap (i.e., 3 mg/kg up to 350 mg every 3 weeks)?

The CCO clinicians did not directly answer this question; however, their response commenting primarily on the availability of published data evaluating the use of flat or weight-based dosing follows. The clinicians stated that there is expanded cohort data, expected to be released shortly, that demonstrates efficacy of the flat dose in patients. There is also published data that demonstrates similar pharmacokinetics between the flat dose and the weight-based dosing schedule used in the trial. In addition to the pending clinical data supporting the flat dose, it may be of interest to collect real world evidence for this indication in terms of dosing.

5.7 Additional Information

None to report.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of cemiplimab 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.

Supplemental questions 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.

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 Table 6.1. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 6.1: Selection Criteria of Systematic Review.

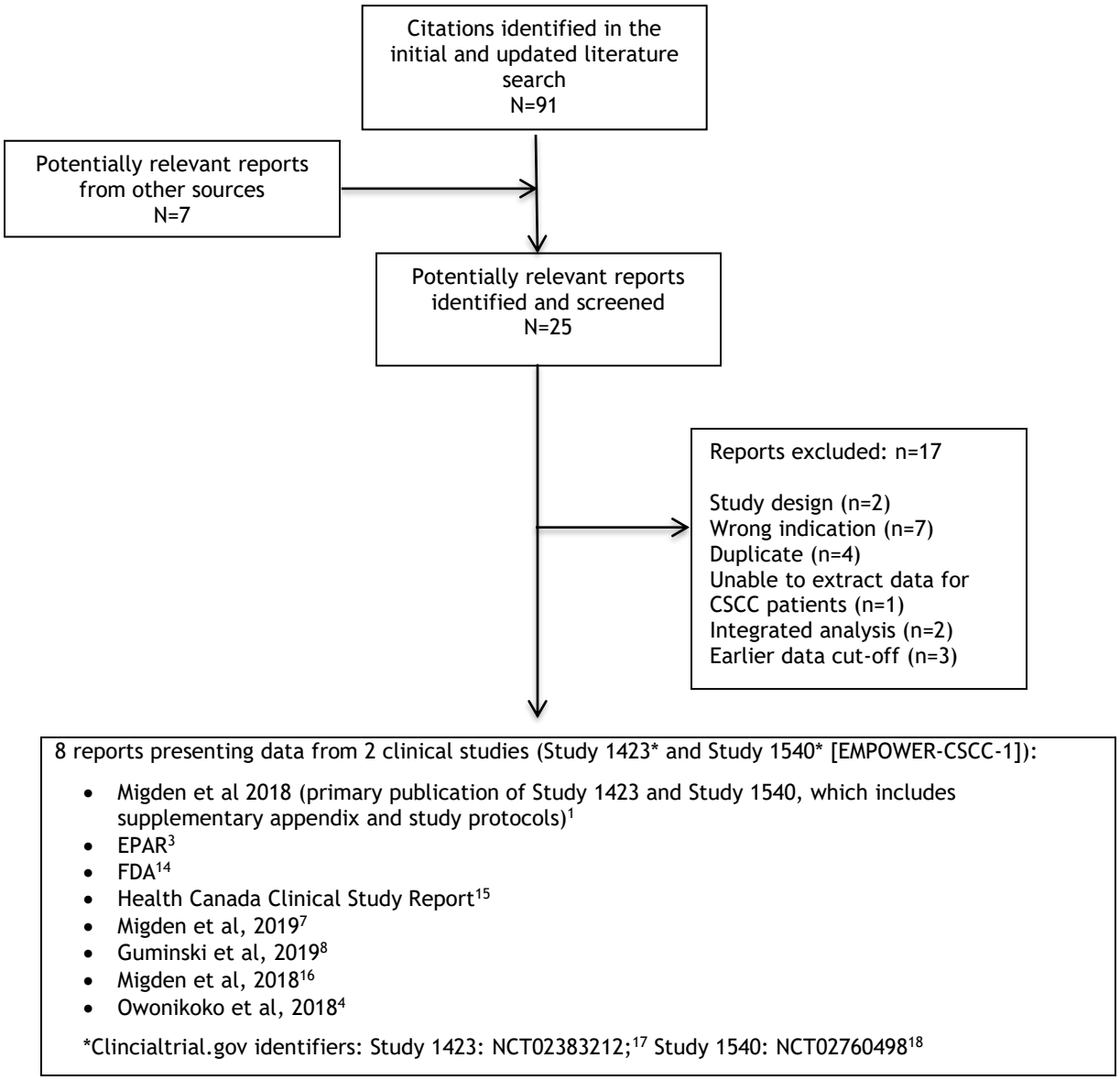
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Randomized and non-randomized controlled trials; single group trials in the absence of comparative evidence	Adult patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation	Cemiplimab	• Chemotherapy • BSC	• OS • PFS • ORR • DOR • Safety • HRQoL • TTP
Abbreviations: BSC – best supportive care; CSCC - cutaneous squamous cell carcinoma; DOR – duration of response; HRQoL – health-related quality of life; ORR – objective response rate; OS – overall survival, PFS – progression-free survival; TTP – time-to-progression. Notes: *Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).				

6.3 Results

6.3.1 Literature Search Results

Among the 25 potentially relevant reports identified by the search, one report[1] that described two clinical studies (one phase 1 and one phase 2), and seven additional reports that reported data on these two clinical studies were included in the pCODR systematic review; the remaining 17 reports were excluded.

Figure 6.1. PRISMA Flow Diagram for Inclusion and Exclusion of Studies



Note: Additional data related to Studies 1423 and 1540 (Clinical Summary,[5] Checkpoint Responses,[19] Clinical Study Reports[6,20]) were obtained through requests to the sponsor by pCODR

6.3.2 Summary of Included Studies

Two clinical studies, referred to herein as Study 1423 and Study 1540 (EMPOWER-CSCC-1),[1] met the selection criteria and were included in the systematic review. The key characteristics of each study are summarized in Table 6.2 and key quality characteristics of each study are summarized in Table 6.3. For the reporting of these studies, emphasis was placed on the pivotal phase 2 study, Study 1540.

6.3.2.1 Detailed Study Characteristics

Table 6.2: Key Characteristics of Included Studies of Cemiplimab in CSCC.[5]

	Study 1423	Study 1540
Study design	Phase I, first-in-human, OL, non-randomized, multicentre, repeat-dose study	Phase II, multicentre, OL, non-randomized, pivotal study
Location	47 sites in the US, Australia, and Spain	39 sites in the US, Australia, and Germany
N	26 (Expansion Cohorts 7 and 8 only)	137 (1st analysis) 193 (2nd updated analysis)
Patient population	Adult (≥ 18 years) patients with advanced solid tumour malignancies	Adult (≥ 18 years) with mCSCC or laCSCC
Intervention	Cemiplimab 3 mg/kg IV over 30 minutes Q2W up to 48 weeks	Cemiplimab 3 mg/kg IV over 30 minutes Q2W (Groups 1 and 2) or 350 mg Q3W IV over 30 minutes (Group 3). Planned treatment duration was: • Groups 1 and 2: 96 weeks treatment duration (twelve 56-day [8-week] treatment cycles) • Group 3: 54 weeks (six 63-day [9-week] treatment cycles
Primary endpoint	Safety, tolerability, and DLTs of cemiplimab	ORR by ICR using RECIST 1.1.
Secondary and other endpoints	Efficacy: ORR by ICR using RECIST 1.1, DCR, DDCR, depth of response, TTR, DOR, DDCR, PFS, OS Safety: DLTs, TEAEs, abnormal laboratory findings Other: PK, ADA	Efficacy: ORR by IA, DOR by ICR and IA, PFS by ICR and IA, OS, CR rate by ICR, HRQoL by EORTC QLQ-C30, TTR by ICR and IA, DCR, DDCR Safety: AEs Other: PK, ADA
Data cut-offs	October 2, 2017*	October 27, 2017 (1st analysis for safety and Group 1 and 2 efficacy data)* September 20, 2018 (2nd updated analysis for Group 1 and Group 3 efficacy and safety data) October 10, 2018 (2nd updated analysis for Group 2 efficacy and safety data)
Median follow-up	11.1 months	8.6 months (1st analysis) 16.53 months (Group 1), 9.30 months (Group 2), and 8.05 months (Group 3) (2nd updated analysis)
Status	On-going	On-going
Notes	Of the n=26 CSCC patients, n=16 mCSCC and n=10 laCSCC	Group 2 and 3 were partially enrolled at time of the 1st analysis

ADA = anti-drug antibodies; AE = adverse event; CR = complete response; CSCC = cutaneous squamous cell carcinoma; DCR = disease control rate; DDCR = durable disease control rate; DLT = dose limiting toxicity; DOR = duration of response; EORTC-QLQ-C30 = European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire; FAS = full analysis set; HRQoL = health-related quality of life; IA = investigator assessment; ICR = independent central review; IV = intravenous; laCSCC = locally advanced cutaneous squamous cell carcinoma; mCSCC = metastatic cutaneous squamous cell carcinoma; PFS = progression-free survival; PK = pharmacokinetics; OL = open-label; ORR = overall response rate; OS = overall survival; Q2W = every two (2) weeks; RECIST = Response Evaluation Criteria in Solid Tumours; TEAEs = treatment-emergent adverse events; TTR = time to treatment response

*Cut-off for data presented in the Clinical Summary unless otherwise specified

Note: ORR = complete response (CR) + partial response (PR); DCR = CR + PR + stable disease (SD) + Non-CR/Non-Progressive Disease (PD); DDCR = CR + PR + SD + Non-PR/Non-PD for at least 105 days without PD

Table 6.3: Select Quality Characteristics of Study 1423 and Study 1540.[1]

Study	Study 1423	Study 1540
Treatment	Cemiplimab	Cemiplimab
Primary outcomes	Safety, including tolerability, side effect profile, and DLT	ORR by ICR
Sample size	Expansion Cohort 7: 10 patients were planned for enrollment to evaluate safety in the metastatic CSCC population. Expansion Cohort 8: 20 patients were planned for enrollment to evaluate safety in the locally advanced CSCC population that is unresectable. The study design did not include formal hypothesis testing for the two expansion cohorts; secondary efficacy outcomes were summarized descriptively (2-sided 95% CI).	Single-stage exact binomial design. Group 1: 50 patients with metastatic CSCC were required to provide at least 85% power to reject a null hypothesis of an ORR of 15% using a 2-sided significance level <5% if the true ORR was 34%. Group 2: 72 patients with locally advanced CSCC were required to provide at least 90% power to reject a null hypothesis of an ORR of 25% using a 2-sided significance level <5% if the true ORR was 44%. The group sample sizes were selected such that the lower limit of the 2-sided 95% CI of the estimated ORR would be clinically meaningful. A Group 3 was introduced later on in the study following an amendment that included an additional 53 patients with metastatic CSCC.[3] The same assumptions for sample size in Group 1 were used for Group 3.
Randomization	Single arm study; randomization not applicable	Single arm study; randomization not applicable.
Masking	Blinding not applicable. ICR was performed for the efficacy endpoint of ORR.	Blinding not applicable. ICR was performed for the primary efficacy endpoint of ORR.
Final analysis	Estimated study completion date is December 19, 2019.[17]	Estimated study completion date is August 11, 2021.[18]
Ethics approval	Yes. Protocols and all amendments were approved by the institutional review board at each participating study site.	Yes. Protocols and all amendments were approved by the institutional review board at each participating study site.
Abbreviations: CSCC - cutaneous small cell carcinoma; ORR – objective response rate; CI – confidence interval; DLT – dose limiting toxicity; ICR – independent central review.		

a) Trials

Study 1423 and Study 1540 are phase 1 and 2 trials, respectively,[1] and are both funded by the drug sponsors Regeneron Pharmaceuticals and Sanofi Genzyme. The sponsor, in collaboration with study investigators, had an active role in the design and conduct of both studies, including data analysis and interpretation, and manuscript writing (performed by sponsor employees).

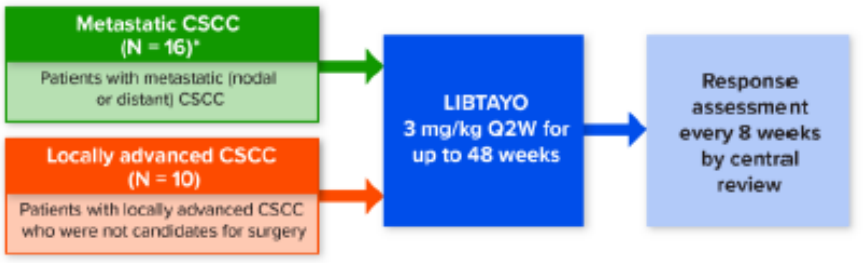
Study 1423

Study 1423 is an ongoing, global, multi-centre, non-randomized, single-group, open-label, phase 1 ascending dose escalation trial of cemiplimab, monotherapy or in combination with other anti-cancer therapies, in patients with advanced solid tumours. A traditional 3+3 dose escalation design was used. The dose established in the dose escalation phase of the study was evaluated in 26 expansion cohorts. Two expansion cohorts evaluated cemiplimab monotherapy in patients with metastatic or locally advanced CSCC. A total of 30 patients were planned for enrollment in the expansion cohorts to evaluate the efficacy and safety of cemiplimab monotherapy; 10 patients with metastatic CSCC and 20 patients with unresectable locally advanced CSCC. The study was conducted in 47 sites in the US, Australia, and Spain.[5]

Eligible patients included adult patients (≥ 18 years and older) who had histologically or cytologically confirmed CSCC who were not considered candidates for surgery as a result of disease recurrence after two or more surgical procedures, or for whom it was expected by the treating clinician that curative resection would be unlikely or result in substantial morbidity or deformity. Patients were required to have at least one measurable lesion according to RECIST (version 1.1), an ECOG performance status of 0 or 1, and adequate organ function. The study excluded individuals who had any ongoing or recent (last five years) evidence of significant autoimmune disease requiring systemic immunosuppression, primary tumours of the lip or eyelid, a history of solid organ transplant, those with untreated/active brain metastases or any invasive malignancy within the last five years, and prior treatment with either agents that block the PD-1/PD-L1 pathway or other immune modulating agents within fewer than four weeks prior to the first dose of cemiplimab.

A total of 26 patients were enrolled in the two CSCC expansion cohorts of Study 1423; 16 patients with metastatic CSCC and 10 patients with locally advanced CSCC. The design of Study 1423 is depicted in Figure 6.2.

Figure 6.2: Design of Study 1423.[5]



CSCC = cutaneous squamous cell carcinoma; Q2W = every two weeks; Data cut-off: October 2, 2017

Study 1540

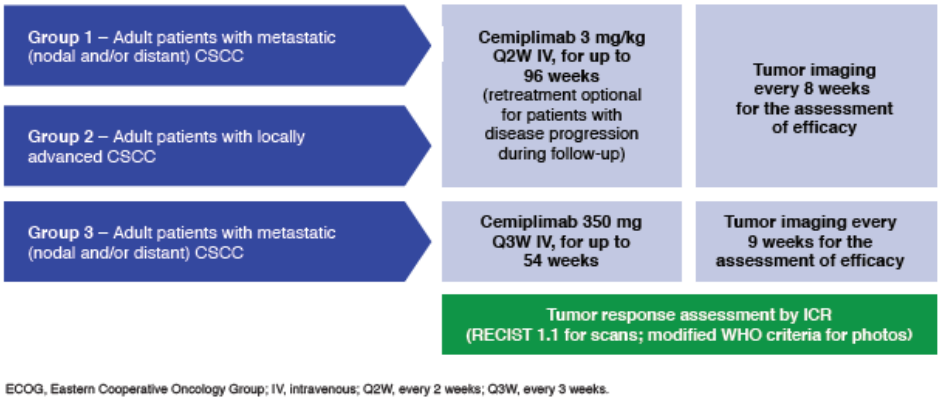
Study 1540 is an ongoing, global, multi-centre, non-randomized, single-group, open-label phase 2 trial of cemiplimab monotherapy in patients with invasive CSCC. The study was conducted at 39 sites in the US, Australia and Germany.[5] The targeted enrollment was 175 patients separated into three groups defined by disease stage and treatment dosing schedule:

- Group 1: 50 patients with metastatic CSCC who received a weight-based dose of cemiplimab (3 mg/kg IV every two weeks)
- Group 2: 72 patients with locally advanced CSCC who received a weight-based dose of cemiplimab (3 mg /kg IV every two weeks)
- Group 3: 53 patients with metastatic CSCC who received a fixed dose of cemiplimab (350 mg IV every three weeks)

Eligible patients were adults (≥18 years or older) with histologically confirmed metastatic (nodal or distant) or unresectable locally advanced CSCC who had at least one measurable lesion by study criteria. Patients with unresectable locally advanced CSCC were considered inoperable or had medical contraindications to surgery or radiation or had not achieved disease control with these forms of treatment. Patients were required to have at least one measurable lesion according to RECIST (version 1.1), an ECOG performance status of 0 or 1, adequate organ function, and an anticipated life expectancy of ≥ 12 weeks. Individuals were excluded from the study if they had ongoing or recent significant autoimmune disease that required systemic immunosuppressive therapy, untreated/active brain metastases, previous treatment with agents that block the PD-1 or PD-L1 pathway or other immune modulating agents that either were administered within four weeks of the first dose of cemiplimab or were associated with immune mediated adverse events that were ≥ grade 1 within 90 days prior to the first dose of cemiplimab or were associated with toxicity that resulted in discontinuation of the immune-modulating agent. Patients who had a history of solid organ transplant or a concurrent cancer, or CSCC of the dry lip or anogenital area were also excluded.

Study 1540 enrolled a total of 193 patients; 59 patients in Group 1, 78 patients in Group 2, and 56 patients in Group 3. The design of Study 1540 is depicted in Figure 6.3.

Figure 6.3: Design of Study 1540.[8]



ECOG, Eastern Cooperative Oncology Group; IV, intravenous; Q2W, every 2 weeks; Q3W, every 3 weeks.

In Study 1540 there were a total of five protocol amendments of which two are noteworthy.[3] In protocol amendment 3, Group 3, which evaluated a fixed dose of cemiplimab in metastatic CSCC patients, was added to the study after the completion of patient enrollment to Group 1. As a consequence of later enrollment, the median treatment exposure and follow-up for outcomes in this group are shorter relative to Groups 1 and 2. The reason for the addition of Group 3 to the study was to obtain data on a fixed and less frequent dose schedule (350 mg every three weeks); the sponsor cited advantages of the fixed schedule over the weight-based schedule (every two weeks) that includes lower administrative burden and preventing drug wastage.[5] The second notable protocol amendment is discussed in the proceeding section.

Outcomes, Statistical Analyses, and Data Analysis Dates

The outcomes assessed in Study 1423 and Study 1540 and the data cut-off dates for data analyses are summarized in Table 6.2.

Study 1423

Primary Outcome

As Study 1423 was a dose-finding study, the primary objective was to evaluate the safety of cemiplimab; therefore, the primary outcome was safety, which included evaluation of tolerability, side effect profile, and dose-limiting toxicities. Adverse events were graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE; version 4.03) and were analyzed in all patients who received at least one dose of study medication. Safety evaluations were performed throughout the treatment phase (baseline and repeated on day 1 of each treatment cycle throughout the study).

Secondary Outcomes

Assessment of anti-tumour activity was a secondary objective of the study, so efficacy outcomes were assessed as secondary endpoints of interest and included ORR according to RECIST (version 1.1), DOR, PFS, and OS. Refer to Table 6.2 for a complete list of efficacy outcomes evaluated in the study. There were provisions in the study protocol (in the form of amendments to the SAP) to assess efficacy endpoints (ORR, DOR) by ICR in the event clinical meaningful benefit was observed by investigator assessment. Tumour assessments were completed at the end of each treatment cycle.

Data Analysis and Data Cut-off Date

The data cut-off date for the first analysis (safety and efficacy) of Study 1423 was October 2, 2017, at which point the median duration of follow-up was 11.1 months in all patients.[5] Formal hypothesis testing for the expansion cohorts was not part of the study design; as such, efficacy outcomes were reported using descriptive statistics. Patients were assessed according to the ITT principle.

An updated efficacy analysis was performed for Study 1423 based on a data cut-off date of June 30, 2018.[3] The median duration of follow-up was not reported.

Study 1540

Primary Outcome

The primary outcome in Study 1540 was ORR based on ICR using the RECIST version 1.1.

The determination of ORR for Groups 1 and 3 (metastatic CSCC) was performed separately from Group 2 (locally advanced CSCC) owing to differences in the use of composite response criteria.[3] The ORR was based on centrally reviewed evaluation of whole-body imaging using RECIST (version 1.1) and/or composite response criteria based on digital medical photographs of the skin. Patients were assessed for a response to cemiplimab every eight weeks with confirmatory imaging performed no less than four weeks after the initial documentation of a response. The best overall response (BOR) of either CR, PR or stable disease (SD) was determined once all data for a patient was known and was recorded during the study as of the data cut-off date. The ORR was defined as the proportion of patients with a BOR of CR or PR in the full analysis (ITT) population by group. Patients with a BOR that was not estimable were considered as not reaching an objective response.

Based on previous clinical studies, a clinically meaningful ORR for an investigational agent in CSCC was determined to be >25% in patients with locally advanced CSCC and >15% in patients with metastatic CSCC; the required sample sizes, which are detailed in Table 6.3, were determined based on these assumptions. The primary analyses of efficacy were based on the binomial exact CI approach, which was used to determine whether the lower limit of the 95% CI excluded a historical control ORR that was not deemed clinically meaningful. Therefore, in Study 1540, if the lower limit of the 95% CI of the observed ORRs excluded 15% for Group 1 and Group 3, and excluded 25% for Group 2, the study treatment was deemed effective/clinically meaningful for that group, respectively. The two-sided 95% CIs of the ORR estimate were derived using the Clopper-Pearson method.

Secondary Outcomes

The key secondary outcome of Study 1540 was DOR by ICR, which was determined for all patients who achieved a BOR of CR or PR. DOR was measured from the time response criteria were met for CR/PR (whichever was recorded first) until the first date of radiographic recurrent or progressive disease or death due to any cause. Patients who did not progress while being followed were censored in the analysis at the last valid tumour measurement. ORR by investigator assessment was also assessed.

The other secondary outcomes evaluated in the study included PFS (measured from the start of treatment until first date of radiographic recurrent or progressive disease or death due to any cause) and OS (measured from the start of treatment until death due to any cause). Patients who did not have a survival event were censored at the last date that patient was known to be alive. Since patients could receive subsequent therapy after disease progression, a variant of OS was also measured as a sensitivity analysis and defined as censoring patients who did not have a survival event on the first date of subsequent therapy. For all time-to-event outcomes (i.e., DOR, PFS, OS), median time-to-event estimates (95% CIs) and survival at fixed time-points were estimated using the Kaplan-Meier method.

Exploratory Outcomes

Subgroup analyses of the primary outcome were performed as exploratory analyses to estimate the treatment effect of cemiplimab in prespecified subgroups of patients; these analyses were performed for hypothesis-generating purposes.

Patient-reported HRQoL was an exploratory endpoint that was assessed using the EORTC QLQ-C30, which encompasses five functional scales (physical, role, cognitive, emotional and social), and three symptom scales (fatigue, pain, nausea and vomiting) and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhea).[3] Patients completed the EORTC QLQ-C30 on day 1 of each treatment cycle and a summary of the change in scores was reported at each follow-up assessment. Compliance was assessed over the course of 12 cycles. A clinically meaningful improvement in any scale was defined as ≥ 10-point change from baseline.[5] No statistical testing was conducted on HRQoL outcomes; therefore, reported results are descriptive in nature.

Data Analyses and Data Cut-off Dates

The first efficacy analysis, which occurred on October 27, 2017, was planned for six months after the first dose of cemiplimab had been administered in the last patient enrolled in Group 1. On this date, patient enrollment was still ongoing for Group 2 and Group 3. Results from Group 1 were published (with the results from Study 1423)[1] but have not been summarized here.

The second notable amendment, Amendment 5, was the addition of an interim analysis of efficacy for patients in Group 2 at the time of the first efficacy analysis of Group 1.[3] The interim analysis was added to the protocol on September 22, 2017 just prior to when the interim analysis was conducted on October 27, 2017. Patients in Group 2 were included in the interim analysis provided they had received approximately 9 months of cemiplimab treatment at the time of the interim analysis date.[3]

All statistical analyses of efficacy outcomes were conducted independently for each group. As such, it was cited that no adjustments to the significance level were required for the purpose of controlling for multiple testing. For the interim analysis in Group 2, a two-sided alpha of 0.0001 was allocated for the interim analysis and a two-sided alpha of 0.0499 was preserved for the final analysis.

At the October 27, 2017 data cut-off date, the median duration of follow-up was 8.56 months. Patient enrollment continued after the first analysis of efficacy, with Group 2 and Group 3 completing enrollment on April 25, 2018 and March 15, 2018, respectively.[5]

An updated efficacy analysis was performed based on the data cut-off dates of September 20, 2018 (Group 1 and Group 3) and October 10, 2018 (Group 2) and include the total patient population of 193 patients.[3,5] Efficacy analyses for all three groups were possible since all patients had at last three response assessments. The median duration of follow-up was 9.4 months for all patients.[3] Patients were analyzed according to the ITT principle, therefore the full analysis set includes all patients who were successfully screened and eligible for the study.

Safety

Treatment-emergent adverse events (TEAEs) were assessed and included in the primary analysis of safety; TEAES were defined as adverse events not present at baseline or represent the exacerbation during the on-treatment period of a condition present at baseline. TEAEs were graded by severity using the NCI-CTCAE (version 4.03). The safety analysis set included all enrolled patients who received any dose of cemiplimab in each group.

Integrated (pooled) Analyses of Efficacy

The sponsor confirmed to pCODR that there is no overlap in patients between Study 1423 and Study 1540.[19] However, an integrated (pooled) analysis of efficacy data from the two studies was conducted for the purpose of marketing authorization.[5] The results of the integrated analyses have not been summarized in this report since they do not synthesize results based on the most recent efficacy data cut-off dates (they include 108 patients from Studies 1423 and 1540).

a) *Populations*

The demographics and baseline disease characteristics of enrolled patients in the cemiplimab studies are presented in Table 6.4 (Study 1423) and Table 6.5 (Study 1540).

Study 1423

In Study 1423, the median age of patients was 72.5 years (range 52-88 years) among the 26 enrolled patients. The majority of patients in the study was male (80.8%), with metastatic CSCC (61.5%) and an ECOG performance status of 1 (61.5%). Most patients had received prior radiation (80.8%) and systemic therapy (57.7%). Refer to Table 6.4 for a breakdown of baseline characteristics by disease stage.

Table 6.4: Patient Demographics and Baseline Disease Characteristics in Study 1423.[5]

	mCSCC (n=16)	laCSCC (n=10)	Total (N=26)
Age, years			
Median (range)	74 (52 to 85)	71 (55 to 88)	72.5 (52 to 88)
< 65 years, n (%)	4 (25.0)	2 (20.0)	6 (23.1)
≥ 65 years, n (%)	12 (75.0)	8 (80.0)	20 (76.9)
Sex, n (%)			
Male	12 (75.0)	9 (90.0)	21 (80.8)
Female	4 (25.0)	1 (10.0)	5 (19.2)
ECOG PS, n (%)			
0	6 (37.5)	4 (40.0)	10 (38.5)
1	10 (62.5)	6 (60.0)	16 (61.5)
Prior systemic therapy, n (%)	11 (68.8)	4 (40.0)	15 (57.7)
Prior radiotherapy, n (%)	11 (68.8)	10 (100)	21 (80.8)

ECOG PS = Eastern Cooperative Oncology Group Performance Status; FAS = full analysis set; laCSCC = locally advanced cutaneous squamous ce
carcinoma; mCSCC = metastatic cutaneous squamous cell carcinoma
Source: CTD Summary of Clinical Efficacy 2.7.3; Data cut-off: October 2, 2017

Study 1540

In Study 1540, the median age of the 193 enrolled patients was 72 years (range 38-96 years). The majority of patients in the study was male (83.4%), with metastatic disease (59.6%) and an ECOG performance status of 1 (55.4%). Most patients in Study 1540 had received prior radiation (67.9%) and approximately one third of patients had received some form of systemic therapy (33.7%). Refer to Table 6.5 for a breakdown of baseline characteristics by group.

Table 6.5: Patient Demographics and Baseline Disease Characteristics in Study 1540.[5]

	Group 1 (mCSCC) (n=59)	Group 2 (laCSCC) (n=78)	Group 3 (mCSCC) (n=56)	Total (N=193)
Age, years				
Median (range)	71.0 (38 to 93)	74.0 (45 to 96)	71.0 (38 to 90)	72.0 (38 to 96)
< 65 years, n (%)	16 (27.1)	19 (24.4)	14 (25.0)	49 (25.4)
≥ 65 years, n (%)	43 (72.9)	59 (75.6)	42 (75.0)	144 (74.6)
Sex, n (%)				
Male	54 (91.5)	59 (75.6)	48 (85.7)	161 (83.4)
Female	5 (8.5)	19 (24.4)	8 (14.3)	32 (16.6)
Race, n (%)				
White	58 (98.3)	75 (96.2)	54 (96.4)	187 (96.9)
Black or AA	1 (1.7)	0	0	1 (0.5)
Asian	0	2 (2.6)	2 (3.6)	4 (2.1)
NR	0	1 (1.3)	0	1 (0.5)
BW, kg				
Mean (SD)	85.04 (15.68)	77.08 (18.02)	82.71 (22.67)	81.15 (19.07)
BMI, kg/m^2				
Mean (SD)	28.31 (4.77)	26.07 (4.85)	27.35 (7.28)	27.13 (5.70)
ECOG PS, n (%)				
0	23 (39.0)	38 (48.7)	25 (44.6)	86 (44.6)
1	36 (61.0)	40 (51.3)	31 (55.4)	107 (55.4)
Prior systemic therapy, n (%)	33 (55.9)	12 (15.4)	20 (35.7)	65 (33.7)
Prior surgery, n (%)	58 (98.3)	66 (84.6)	50 (89.3)	174 (90.2)
Prior radiotherapy, n (%)	50 (84.7)	43 (55.1)	38 (67.9)	131 (67.9)

AA = African American; BMI = body mass index; BW = body weight; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FAS = full analysis set; laCSCC = locally advanced cutaneous squamous cell carcinoma; mCSCC = metastatic cutaneous squamous cell carcinoma; NR = not reported; SD = standard deviation

Source: Sanofi-Genzyme data on file; Data cut-off: September 20, 2018 (Groups 1 and 3) and October 10, 2018 (Group 2)

c) Interventions

Study 1423

In the expansion cohorts of Study 1423, patients received cemiplimab at a dose of 3 mg/kg administered intravenously over 30 minutes every two weeks in an outpatient setting. Following a screening period of 28 days, patients were treated up to six cycles (56-day treatment cycle) for up to 48 weeks, or until a patient experienced unacceptable toxicity or had confirmed disease progression.[1,4]

After a minimum of 24 weeks of treatment, a patient with confirmed CR or tumour assessments of PR or SD maintained for three successive tumour evaluations could opt to discontinue treatment and proceed with follow-up assessments according to schedule. Patients who experienced protocol-defined dose limiting toxicities or grade ≥3 treatment-related toxicity not otherwise specified in the study protocol were required to temporarily discontinue treatment with cemiplimab. The study exercised protocol specified guidelines for dose interruptions, modifications and treatment discontinuations.

Treatment Exposure

At the data cut off October 2, 2017, the median duration of exposure to cemiplimab was 36 weeks (range, 4.0-71.0) for all patients. The median duration of treatment for metastatic and locally advanced patients was 32.80 weeks (range, 4.1-48.9) and 12.65 weeks (range 2.0-49.3), respectively.[20]

Study 1540

In Study 1540, patients in Group 1 and Group 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, or until disease progression or unacceptable toxicity. The sponsor confirmed that the treatment duration was shorter in Group 3 simply to achieve a similar close out date for all groups in the study.[19]

Like Study 1423, in Study 1540 patients who experienced grade ≥3 treatment-related toxicity not otherwise specified in the protocol were required to temporarily discontinue treatment with cemiplimab. Patients could resume treatment once the toxicity resolved to grade 1 or baseline, or when the toxicity was considered stable and manageable through the use of supportive medications. The protocol specified (by treatment group) guidelines for dose interruption, modification and treatment discontinuation. Dose reduction of cemiplimab was permitted in uncommon situations and only after consultation between the investigator and sponsor.

According to the study protocol, treatment beyond week 54 was permitted in Group 3 as it was recognized that some patients experiencing clinical benefit may be reluctant to stop treatment at 54 weeks. While patients were encouraged to stick to the planned duration of treatment, patients who had not experienced progressive disease and were unwilling to stop study treatment could continue treatment if the investigator deemed that there were not unacceptable safety risks with continued treatment. After week 54, patients could continue the same dose and schedule of cemiplimab for up to six treatment cycles. The sponsor confirmed data on the Group 3 patients who continued treatment beyond the planned treatment duration have not yet been formally analyzed.[19]

Concomitant and Prohibited Treatments and Subsequent Therapies

Patients could not receive any standard or investigational agent other than cemiplimab. Under the supervision of the investigator, any other medication that was considered necessary for the patient's welfare, which was not expected to interfere with the evaluation of the study drug, could be given. Immunosuppressive doses of systemic corticosteroids other than for corticosteroid replacement (>10 mg per day of prednisone or equivalent) were prohibited. No information was reported on the actual concomitant medications received by patients during the study, nor was information provided on the subsequent therapies received by patients after progression on cemiplimab.

Patients with locally advanced target lesions that were considered unresectable at baseline but subsequently deemed resectable during the course of the study due to tumour response to cemiplimab had the option of curative intent surgery.

Radiation was not part of the planned study treatment. During the course of the study, if a patient developed a symptomatic lesion for which palliative radiation therapy was deemed appropriate by the investigator, this was in most cases identified as progressive disease and resulted in the patient being removed from the study. Palliative radiation was allowed in circumstances where patients had completed 24 weeks of study treatment. In this situation, resumption of cemiplimab after the radiation was discussed in consultation with the investigator to determine if further treatment with cemiplimab was in the best interest of the patient.

Treatment Exposure

At the updated data cut-off dates of September 20, 2018 for Groups 1 and Group 3 and October 10, 2018 for Group 2, the median duration of cemiplimab treatment for all patients was 39.1 weeks (range, 2.6-60.4).[6] The median duration of cemiplimab treatment in Group 1 was 65.0 weeks (range, 2.0-96.1), in Group 2 was 34.6 weeks (range, 2.0-96.1), and in Group 3 was 34.3 weeks (range, 2.6-60.4).[5] The median number of doses administered in all patients was 15.0 (range,1 to 48) and the median dose intensity was 1.46 mg/kg/week (range, 0.6-1.8).[6]

Retreatment

According to the study protocol, retreatment with cemiplimab was allowed in all three treatment groups. More specifically, 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 has not yet been formally analyzed.[19]

b) *Patient Disposition*

A summary of patient disposition for Study 1423 and Study 1540 are provided in Tables 6.6 and 6.7, respectively.

Study 1423

In Study 1423, at the data cut-off date of October 2, 2017, one patient (3.8%) remained on treatment, 11 patients (42.3%) had completed treatment and 14 patients (53.8%) had discontinued treatment.[5] The most common reason for treatment discontinuation was disease progression (26.9%).[5]

Table 6.6: Patient Disposition in Study 1423.[5]

	mCSCC (n=16)	laCSCC (n=10)	Total (N=26)
On treatment, n (%)	0	1 (10.0)	1 (3.8)
Off treatment, n (%)	16 (100)	9 (90.0)	25 (96.2)
Treatment completed	6 (37.5)	5 (50.0)	11 (42.3)
Treatment discontinued	10 (62.5)	4 (40.0)	14 (53.8)
Primary reason for treatment discontinuation, n (%)			
Disease progression	6 (37.5)	1 (10.0)	7 (26.9)
AE	2 (12.5)	0	2 (7.7)
Death	1 (6.3)	1 (10.0)	2 (7.7)
Patient decision	1 (6.3)	0	1 (3,8)
Physician decision	0	1 (10.0)	1 (3.8)
Withdrew consent	0	1 (10.0)	1 (3.8)

E = adverse event; laCSCC = locally advanced cutaneous squamous cell carcinoma; mCSCC = metastatic cutaneous squamous cell carcinoma
ource: CTD Summary of Clinical Efficacy 2.7.3; Data cut-off: October 2, 2017

Study 1540

In Study 1540, at the updated data cut-off dates for each group there was a total of 63 patients (32.6%) who remained on treatment, 22 (11.4%) who had completed treatment, and 108 patients (56%) who had discontinued treatment.[5] The most common reason for treatment discontinuation was disease progression among 51 patients (26.4%).[5] This pattern of disposition was similar by group (Table 6.7).

Table 6.7: Patient Disposition in Study 1540. [5]

n (%)	Group 1 (mCSCC) (n=59)	Group 2 (laCSCC) (n=78)	Group 3 (mCSCC) (n=56)	Total (N=193)
Treatment on-going	13 (22.0)	24 (30.8)	26 (46.4)	63 (32.6)
Off treatment	46 (78.0)	54 (69.2)	30 (53.6)	130 (67.4)
Treatment completed	13 (22.0)	5 (6.4)	4 (7.1)	22 (11.4)
Treatment discontinued	33 (55.9)	49 (62.8)	26 (46.4)	108 (56.0)
Primary reason for treatment discontinuation:				
AE	6 (10.2)	6 (7.7)	3 (5.4)	15 (7.8)
Pregnancy	0	0	0	0
Death	2 (3.4)	2 (2.6)	3 (5.4)	7 (3.6)
Lost to follow-up	0	0	0	0
Non-compliance	0	2 (2.6)	0	2 (1.0)
Patient decision	2 (3.4)	6 (7.7)	1 (1.8)	9 (4.7)
Sponsor decision	0	0	0	0
Physician decision	1 (1.7)	6 (7.7)	3 (5.4)	10 (5.2)
Disease progression	19 (32.2)	17 (21.8)	15 (26.8)	51 (26.4)
Withdrew consent	0	1 (1.3)	1 (1.8)	2 (1.0)
Other	3 (5.1)	9 (11.5)	0	12 (6.2)
Entered follow-up	20 (33.9)	22 (28.2)	6 (10.7)	48 (24.9)
Study on-going	29 (49.2)	38 (48.7)	33 (58.9)	100 (51.8)

AE = adverse event; FAS = full analysis set; laCSCC = locally advanced cutaneous squamous cell carcinoma; mCSCC = metastatic cutaneous squamous cell carcinoma

Source: Sanofi-Genzyme data on file; Data cut-off: September 20, 2018 (Groups 1 and 3) and October 10, 2018 (Group 2)

Protocol Deviations

A total of 17 major protocol deviations were reported in Study 1540 among 12 patients (8.8%). Most of the deviations were unspecified as "other" (3.6%) or related to inclusion criteria not being met (2.2%).[3]

d) Limitations/Sources of Bias

The clinical studies supporting this submission, Study 1423 and Study 1540, were open-label phase 1 and 2 studies, respectively. As such, investigators and patients were not blinded to the treatment patients received. Open label trials are at risk for biases that can affect internal validity, including patient selection bias and performance bias, because of knowledge of assigned treatment which can lead to exaggerated treatment effects. Both studies implemented ICR of efficacy outcomes to mitigate the risk of biased assessment. Both studies were also single-group. Although it is acknowledged there is no standard of care for patients with metastatic or unresectable locally advanced CSCC, the comparative effectiveness of cemiplimab to currently used treatments (chemotherapy and BSC) was not assessed in these studies. The sponsor provided the results of an ITC that estimated the comparative efficacy and safety of cemiplimab to chemotherapy and BSC. Refer to Section 7 for a summary and critical appraisal of the ITC. Both studies were funded by the sponsor who had an active role in all aspects of study conduct, including data analysis and interpretation, and reporting. Further, not all the data contained in the submission have been published and peer-reviewed; therefore, the extent to which the sponsor may have influenced and/or selectively reported results is unknown. Additional limitations and considerations specific to the individual studies in summarized below:

Study 1423

- Study 1423 was a small (n=26) dose escalation trial that appropriately evaluated safety as the primary outcome. Efficacy outcomes were assessed but there was no

formal hypothesis testing of these outcomes. The small sample size and descriptive nature of the analyses limits the interpretation of the study results.

Study 1540

- Data on important time-to-event outcomes, including PFS and OS, are immature due to short follow-up and a small number of events. Therefore, longer follow-up data are needed to establish whether the clinically meaningful ORRs that were observed in this study translate into clinically meaningful survival benefits. It should be noted that the mature OS and PFS data will still be limited given the non-comparative study design and the fact results may be confounded by the subsequent treatments received by patients.
- The sample sizes of the three groups were powered to detect differences in treatment effect for the primary endpoint only (ORR by ICR); no formal hypothesis testing/statistical analyses were performed for the secondary endpoints (DOR, PFS and OS). The results for these outcomes should therefore be considered as exploratory.
- The Health Canada recommended dose of cemiplimab is a 350 mg fixed dose administered every three weeks. Group 3 from Study 1540 evaluated this dose but because of later enrollment, the median treatment exposure and follow-up for outcomes in this group are shorter relative to Groups 1 and 2 that used weight-based dosing. The sponsor confirmed that the reason for the addition of Group 3 to the study was to demonstrate comparability of the fixed and weight-based dose schedules with regards to efficacy and safety,[5] as they anticipated the fixed dose would become the licenced dose based on the advantage of a less frequent every three week schedule. Pharmacokinetic analyses using safety and efficacy data from the weight-based dose schedule in Groups 1 and 2 (3 kg/mg every two weeks) and the available data from the fixed dose and schedule in Group 3 were performed and demonstrated that the fixed dose achieves exposure and between patient variability similar to the weight-based schedule, which suggests the interchangeability of these two dose schedules.[3]
- Overall, the HRQoL data from the study are difficult to interpret due to the non-comparative study design. Limitations of the HRQoL analysis include the following:
    - A sizable proportion of patients did not complete baseline questionnaires (22%) and the completion rate continued to decline at subsequent assessment time points. Attrition can bias findings since there likely are systematic differences in the characteristics of patients who complete and do not complete questionnaires. Therefore, as currently presented, the HRQoL data may not fully capture the quality of life experience of all patients in the study.
    - There is no validated HRQoL instrument specific to patients with CSCC; therefore, the questionnaire used may not fully capture the anxiety and depression experienced by patients with unresectable locally advanced or metastatic CSCC who typically endure stigma related to the visual disfigurement that accompanies the disease.[22]

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Study 1423

Refer to Table 6.8 for results for BOR and ORR by ICR, as well as other response outcomes based on the primary efficacy analysis.

At the primary analysis data cut-off date of October 2, 2017, after a median duration of follow-up of 11.1 months (range: 1.1 to 17) for all CSCC patients (n=26), an ORR of 50.0% (95% CI: 29.9- 70.1) was observed in Study 1423. The ORR was based on a BOR of PR in 13 patients.[5] The median time-to-response was 2.3 months (range, 1.7-7.3).

The median DOR (95% CI) had not been reached;[5] however, it was reported the DOR exceeded six months in 61.5% of responders (n=8/13). The median PFS and OS also had not been reached.

Table 6.8: Study 1423 Best Overall Tumour Response (BOR) and Objective Response Rate (ORR) by Independent Central Review (ICR).[5]

	mCSCC (n=16)	laCSCC (n=10)	Total (N=26)
Best Overall Tumour Response, n (%)			
CR	0	0	0
PR	7 (43.8)	6 (60.0)	13 (50.0)
SD	4 (25.0)	2 (20.0)	6 (23.1)
Non-CR/Non-PD	1 (6.3)	0	1 (3.8)
PD	3 (18.8)	0	3 (11.5)
NE	1 (6.3)	2 (20.0)	3 (11.5)
Response, n (%)			
ORR [95% CI]	7 (43.8) [19.8; 70.1]	6 (60.0) [26.2; 87.8]	13 (50.0) [29.9; 70.1]
DCR [95% CI]	12 (75.0) [47.6; 92.7]	8 (80.0) [44.4; 97.5]	20 (76.9) [56.4; 91.0]
Durable DCR	10 (62.5) [35.4; 84.8]	7 (70.0) [34.8; 93.3]	17 (65.4) [44.3; 82.8]

CI = confidence interval; CR = complete response; DCR = disease control rate; FAS = full analysis set; laCSCC = locally advanced cutaneous squamous cell carcinoma; mCSCC = metastatic cutaneous squamous cell carcinoma; NE = not estimable; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease
Note: ORR = CR + PR; DCR = CR + PR + SD + Non-CR/Non-PD
Source: CTD Summary of Clinical Efficacy 2.7.3; Data cut-off: October 2, 2017

Updated efficacy results based on the analysis performed on June 30, 2018 (median follow-up not reported) showed no change in the ORR in all patients (50%; 95% CI, 29.9-70.1).[3] However, median DOR had been reached in the seven metastatic CSCC patients with PR responses (ORR=43.8%) and was 20.3 months (95% CI, 4.6-20.3). The median PFS and OS in this group of patients was 16.2 months (95% CI, 1.8-22.0) and 22 months (95% CI, 13.6-not estimable), respectively.[3]

Study 1540

Refer to Table 6.9 for results for BOR and ORR by ICR, as well as other response outcomes based on the first and updated efficacy analyses.

At the first efficacy analysis data cut-off date of October 27, 2017, the median duration of follow-up was 8.56 months (range, 0.8 to 15.9). The patients included in this analysis (n=82) were comprised of fully enrolled Group 1 (n=59) and partially enrolled Group 2 (n=23).[3]

The observed ORR by ICR was 46.3% (95% CI, 35.3-57.7) in all patients, 47.5% (95% CI, 34.3-60.9) in Group 1 and 43.5% (95% CI, 23.2- 65.5) in Group 2.[3] The results in Group 1 met the

prespecified threshold for clinically meaningful treatment effect since the lower 95% CI limit (23.2%) exceeded 15%.

In terms of BOR, a CR was achieved in 4 patients (6.8%), all in Group 1, and PRs were achieved in 24 patients (40.7%) in Group 1 and 10 patients (43.5%) in Group 2.[3]

At this analysis, the median DOR by ICR had not been reached. The proportion of responders with a DOR that had exceeded six months was 60.5% (n=23/38). The median PFS and OS had not been reached.

Updated Efficacy Results

At the updated data cut-off dates, September 20, 2018 for Group 1 and Group 3, and October 10, 2018 for Group 2, 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.[3]

The observed ORR by ICR was 44.0% (95% CI, 36.9-51.3) in all patients, and 49.2% (95% CI, 35.9-62.5) in Group 1, 43.6% (95% CI, 32.4-55.3) in Group 2, and 39.3% (95% CI, 26.5-53.2) in Group 3. The results in each group met the prespecified 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 (32.4%).

In terms of BOR, a CR was achieved in 11 patients (11.4%), 10 patients (16.9%) in Group 1, 10 patients (12.8) in Group 2, and 2 patients (3.6%) in Group 3; and PRs were achieved in 63 patients (32.6%), 19 patients (32.2%) in Group 1, 24 patients (30.8%) in Group 2, and 20 patients (35.7%) in Group 3.[3]

The results of exploratory analyses of ORR by ICR in prespecified subgroups, which were performed by gender, age, race, ECOG performance status, geographical region, prior systemic therapy, prior radiotherapy and metastatic status, showed a treatment effect that was consistent across all groups analyzed.[3]

Table 6.9: Best Overall Tumour Response (BOR) and Objective Response Rate (ORR) by Independent Central Review (ICR) in Study 1540.[3]

	mCSCC Cemiplimab: 3 mg/kg Q2W		laCSCC Cemiplimab: 3 mg/kg Q2W		mCSCC Cemiplimab: 350 mg Q3W		Total	
	MAA (N = 59)	Day 180 (N = 59)	MAA (N = 23)	Day 180 (N=78)	MAA (N = 0)	Day 180 (N=56)	MAA (N = 82)	Day 180 (N=193)
Best Overall Tumor Response, n (%)								
Complete Response (CR) [a]	4 (6.8%)	10 (16.9%)	0	10 (12.8%)	NR	2 (3.6%)	4 (4.9%)	22 (11.4%)
Partial Response (PR) [a]	24 (40.7%)	19 (32.2%)	10 (43.5%)	24 (30.8%)	NR	20 (35.7%)	34 (41.5%)	63 (32.6%)
Stable Disease (SD) [b]	9 (15.3%)	9 (15.3%)	9 (39.1%)	28 (35.9%)	NR	8 (14.3%)	18 (22.0%)	45 (23.3%)
Non-CR/Non-PD [c]	4 (6.8%)	4 (6.8%)	0	0	NR	5 (8.9%)	4 (4.9%)	9 (4.7%)
Progressive Disease (PD)	11 (18.6%)	10 (16.9%)	2 (8.7%)	9 (11.5%)	NR	15 (26.8%)	13 (15.9%)	34 (17.6%)
Not Evaluable (NE) [d]	7 (11.9%)	7 (11.9%)	2 (8.7%)	7 (9.0%)	NR	6 (10.7%)	9 (11.0%)	20 (10.4%)
Response								
Objective Response Rate (ORR: CR+PR)	28 (47.5%)	29 (49.2%)	10 (43.5%)	34 (43.6%)	NR	22 (39.3%)	38 (46.3%)	85 (44.0%)
95% CI for ORR [e]	(34.3%, 60.9%)	(35.9%, 62.5%)	(23.2%, 65.5%)	(32.4%, 55.3%)	NR	(26.5%, 53.2%)	(35.3%, 57.7%)	(36.9%, 51.3%)
Complete Response Rate (CR) [a]	4 (6.8%)	10 (16.9%)	0	10 (12.8%)	NR	2 (3.6%)	4 (4.9%)	22 (11.4%)
95% CI for CR Rate [e]	(1.9%, 16.5%)	(8.4%, 29.0%)	(0.0%, 14.8%)	(6.3%, 22.3%)	NR	(0.4%, 12.3%)	(1.3%, 12.0%)	(7.3%, 16.7%)
Durable DCR [f]	36 (61.0%)	37 (62.7%)	16 (69.6%)	49 (62.8%)	NR	31 (55.4%)	52 (63.4%)	117 (60.6%)
95% CI for Durable DCR [e]	(47.4%, 73.5%)	(49.1%, 75.0%)	(47.1%, 86.8%)	(51.1%, 73.5%)	NR	(41.5%, 68.7%)	(52.0%, 73.8%)	(53.3%, 67.6%)

Data cut-off was 27 Oct 2017 for original MAA submission; Sep 20, 2018 for Groups 1 and 3 patients for Day 180, and Oct 10, 2018 for Group 2 patients for Day 180.
Note: Group 3 efficacy data were not reported (NR) in the original MAA submission because the data were not sufficiently mature for analysis.
[a] CR/PR must be confirmed by repeated assessments no less than 4 weeks apart.
[b] SD criteria must be met at least once after a minimum duration of 39 days after first dose date.
[c] Non-CR/Non-PD is for patients with non-measurable disease only.
[d] Not evaluable response includes the missing and unknown tumor response.
[e] Clopper-Person exact confidence interval.
[f] Durable DCR: proportion of patients with CR, PR, SD or non-CR/Non-PD for at least 105 days without PD.

At the updated analysis, the median DOR had not been reached in any group; the data were considered immature based on a large percentage of censored patients (89.4%; Table 6.10 and Figure 6.4).[3] The median time-to-response was 2.0 months (range, 1.7-9.1) i all patients; and the proportion of responders with an observed DOR exceeding six and 12 months was 75.3% (n=64/85) and 40.0% (n=34/85), respectively.[3]

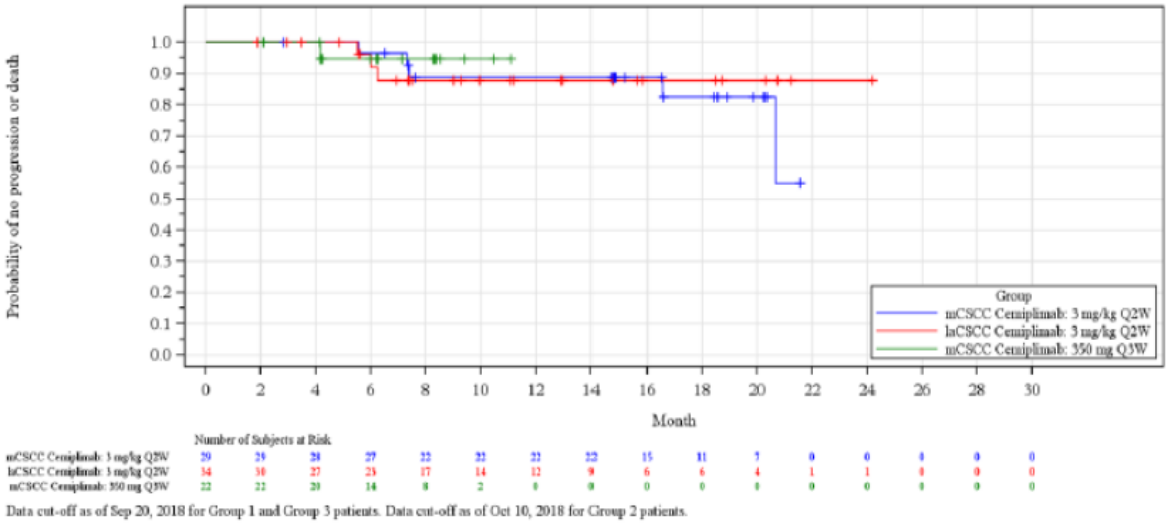
Table 6.10. Duration of Response (DOR) in Study 1540.[3]

	mCSCC Cemiplimab: 3 mg/kg Q2W		laCSCC Cemiplimab: 3 mg/kg Q2W		mCSCC Cemiplimab: 350 mg Q3W		Total	
	MAA (N = 59)	Day 180 (N = 59)	MAA (N = 23)	Day 180 (N=78)	MAA (N = 0)	Day 180 (N=56)	MAA (N = 82)	Day 180 (N=193)
Observed Duration of Response (CR or PR) (months)								
n	28	29	10	34	NR	22	38	85
Min : Max	2.8 : 12.8 +	2.8 : 21.6	1.9 : 12.9+	1.9 : 24.2	NR	2.1 : 11.1	1.9 : 12.9+	1.9 : 24.2
Observed Duration of Response (CR or PR), n (%) [a]								
Total number of responders	28	29	10	34	NR	22	38	85
>=4 months	22 (78.6%)	28 (96.6%)	8 (80.0%)	27 (79.4%)	NR	20 (90.9%)	30 (78.9%)	75 (88.2%)
>=6 months	16 (57.1%)	27 (93.1%)	7 (70.0%)	23 (67.6%)	NR	14 (63.6%)	23 (60.5%)	64 (75.3%)
>=8 months	9 (32.1%)	22 (75.9%)	4 (40.0%)	17 (50.0%)	NR	8 (36.4%)	13 (34.2%)	47 (55.3%)
>=12 months	1 (3.6%)	22 (75.9%)	1 (10.0%)	12 (35.3%)	NR	0	2 (5.3%)	34 (40.0%)
>= 16 months	0	15 (51.7%)	0	6 (17.6%)	NR	0	0	21 (24.7%)
KM Estimation of Duration of Response (CR or PR)								
n	28	29	10	34	NR	22	38	85
Number of events, n (%) [a]	3 (10.7%)	5 (17.2%)	0	3 (8.8%)	NR	1 (4.5%)	3 (7.9%)	9 (10.6%)
Number of censored patients, n (%) [a]	25 (89.3%)	24 (82.8%)	10 (100%)	31 (91.2%)	NR	21 (95.5%)	35 (92.1%)	76 (89.4%)
Median (95% CI), (months)	NR (NE, NE)	NR (20.7, NE)	NR (NE, NE)	NR (NE, NE)	NR	NR (NE, NE)	NR (NE, NE)	NR (20.7, NE)

+ denotes ongoing response

Data cut-off was 27 Oct 2017 for original MAA submission; Sep 20, 2018 for Groups 1 and 3 patients for Day 180, and Oct 10, 2018 for Group 2 patients for Day 180.
Note: Group 3 efficacy data were not reported (NR) in the original MAA submission because the data were not sufficiently mature for analysis.
[a] Percentages are based on number of patients with confirmed CR or PR. The numerator includes the number of patients whose observed duration of response reached at least the specified time. Patients who did not have the opportunity to reach the specified timepoint were included in the denominator only. Because responses for some patients are ongoing, the percentages at the specified timepoints may increase as data mature.
[b] Events include progressive disease or deaths. Percentages are based on number of patients with confirmed CR or PR.

Figure 6.4. Updated Kaplan-Meier Curve for Duration of Response (DOR) in Study 1540.[3]



Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients. Data cut-off as of Oct 10, 2018 for Group 2 patients.

At the updated analysis, the median PFS was 18.4 months (95% CI, 9.1-not estimable) in all patients, which was based on 81 (42%) PFS events.[3] The PFS data were considered immature since over half of patients were censored from the analysis (58.0%). The median PFS was 18.4 months in Group 1, not reached in Group 2, and 10. 4 months in Group 3. Considering all patients, the estimated probability of being progression-free at 12 months was 53.4% (95% CI, 45.1-60.9).[3]

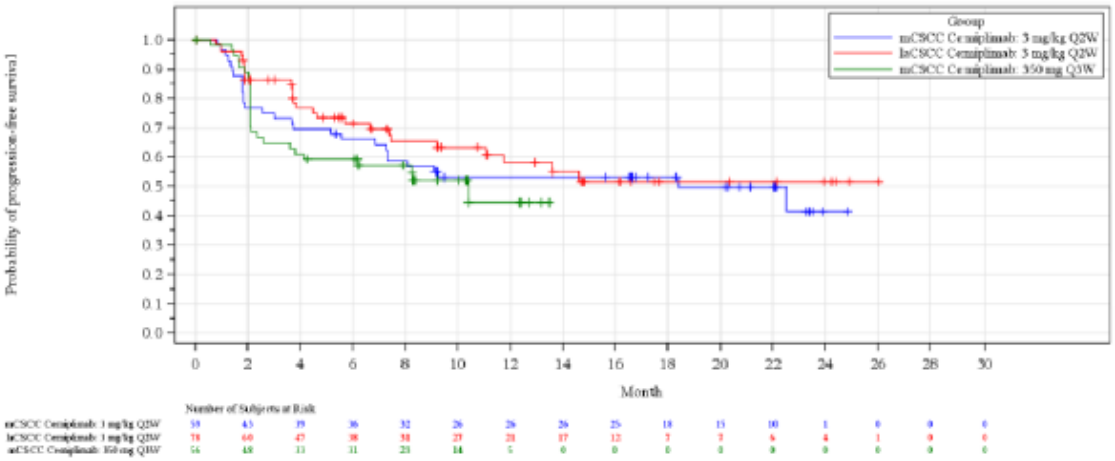
Table 6.11. Updated Kaplan-Meier Curve of Progression-free Survival (PFS) by Independent Central Review (ICR) in Study 1540.[3]

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=78)	mCSCC Cemiplimab: 350 mg Q3W (N=56)	Total (N=193)
KM estimation of Progression Free Survival				
Number of events, n (%)	28 (47.5%)	27 (34.6%)	26 (46.4%)	81 (42.0%)
Progressive Disease, n (%)	22 (37.3%)	24 (30.8%)	21 (37.5%)	67 (34.7%)
Death, n (%)	6 (10.2%)	3 (3.8%)	5 (8.9%)	14 (7.3%)
Number of censored patients, n (%)	31 (52.5%)	51 (65.4%)	30 (53.6%)	112 (58.0%)
Median (95% CI), (months)	18.4 (7.3, NE)	NR (9.2, NE)	10.4 (3.6, NE)	18.4 (9.1, NE)
Estimated Event-Free Probability, % (95% CI)				
4 months	69.6 (55.8, 79.9)	76.7 (64.7, 85.1)	61.1 (46.8, 72.6)	69.9 (62.6, 76.0)
6 months	66.0 (52.0, 76.8)	71.5 (58.9, 80.9)	59.3 (45.0, 71.0)	66.3 (58.8, 72.7)
8 months	58.7 (44.6, 70.3)	65.4 (51.9, 75.9)	57.1 (42.8, 69.1)	60.8 (53.0, 67.7)
12 months	53.1 (39.1, 65.2)	58.1 (43.7, 70.0)	44.6 (26.5, 61.3)	53.4 (45.1, 60.9)
16 months	53.1 (39.1, 65.2)	51.8 (36.6, 65.0)	NE (NE, NE)	51.0 (42.5, 58.9)

Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients. Data cut-off as of Oct 10, 2018 for Group 2 patients.

At the updated analysis, the median OS had not been reached which was based on a total of 34 (17.6%) deaths in the three groups (Figure 6.5).[5] The OS data are considered immature since a large percentage of patients were censored from the analysis (82.4%).[5] Considering all CSCC patients, the estimated probability of being event-free at 12 months was 85.7% (95% CI, 79.6-90.1)[3] and was 77.8% (95% CI, 69.8-83.9) at 16 months.[5]

Figure 6.5: Updated Kaplan-Meier Curve for Overall Survival in Study 1540.[5]



Source: Sanofi-Genzyme data on file. ; Data cut-off: September 20, 2018 (Groups 1 and 3) and October 10, 2018 (Group 2)

Health-related Quality of Life

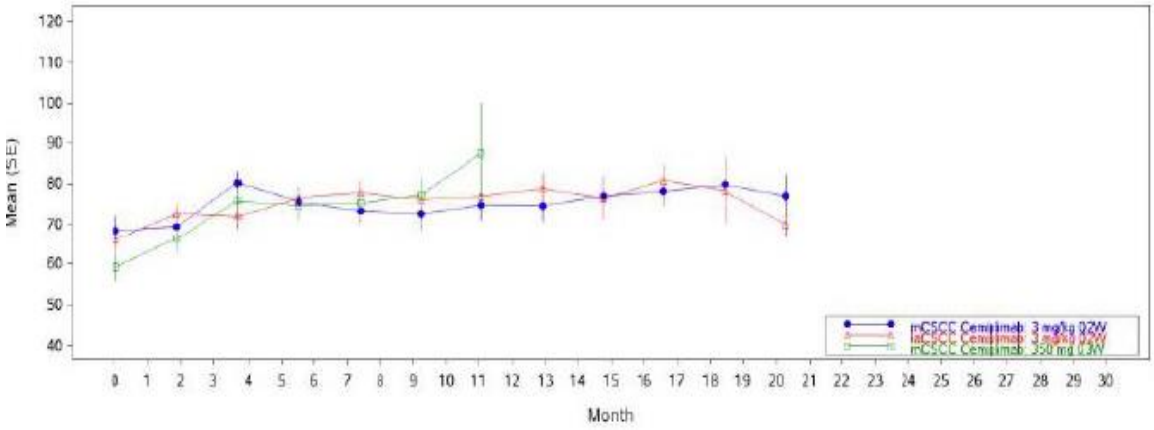
Study 1540

HRQoL was assessed using the EORTC QLQ-C30. Data on this exploratory outcome have not been published and were provided by the sponsor.[5]

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. According to the sponsor, the primary reason for why some patients did not complete a baseline assessment can be attributed to the preparedness of some of the sites to conduct assessments at the time when the initial baseline assessment was conducted.[19] Baseline scores indicated that patients reported moderate-to-high levels of QoL and functioning 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.[5] For reference, treatment cycles were eight weeks in Groups 1 and 2, and nine weeks in Group 3; therefore, the data that have been provided are based on approximately 40-45 weeks (10-11 months) on treatment across the groups.

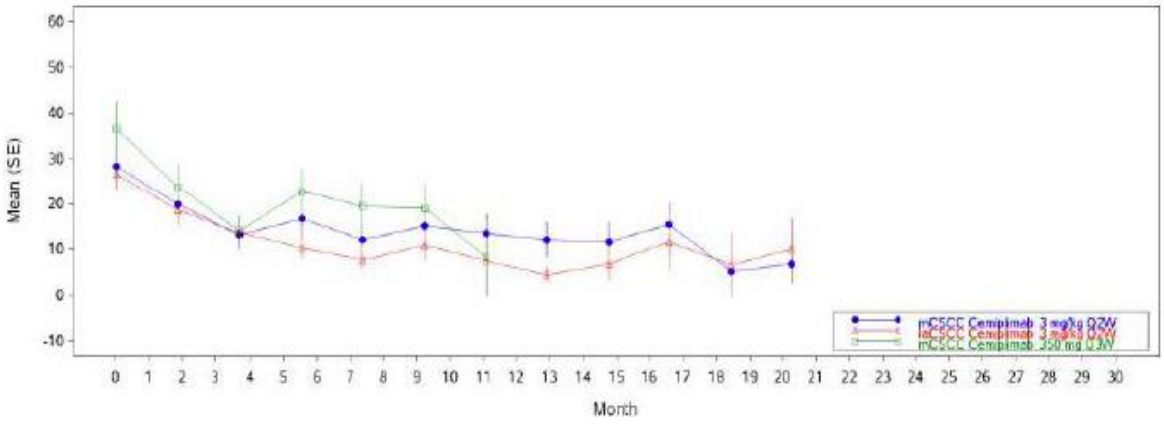
The sponsor reported no consistent changes in the mean global health status/QoL scores across all three groups. Considering all CSCC patients, the change from baseline in global health status/QoL improved over time but did not reach the clinically meaningful threshold at any cycle. These results suggest treatment with cemiplimab appeared to stabilize and had no detriment on global health status/QoL (Figure 6.6).

Figure 6.6: Change in Global Health Status/QoL Over Time in Study 1540.[3]



Of the scales for which data were provided (pain, emotional functioning, insomnia, appetite loss, constipation), the only scale to demonstrate a clinically meaningful change (improvement) from baseline was pain (Figure 6.7). Pain improvement was observed within eight weeks of initiating treatment with cemiplimab (cycle 2). The mean (standard deviation) baseline pain scale score was 29.8 (30.4); and by cycle 3, mean change from baseline was -13.6 (29.96), which continued to decrease over time with changes ranging from -8.76 (29.6) to -24.31 (24.6). These results suggest treatment with cemiplimab resulted in a clinically meaningful reduction in pain and had no detriment on emotional functioning, insomnia, appetite loss, and constipation.

Figure 6.7: Change in Pain Symptom Subscale Over Time in Study 1540.[3]



Safety Outcomes

Study 1423

A summary of the TEAEs in Study 1423 are presented in Table 6.12 based on the data cut-off of October 2, 2017.[5] In total, there were 26 patients (100%) who experienced any TEAE and 12 patients (46.2%) who experienced TEAEs grade 3 or higher. Considering all patients, the most frequent TEAE of any grade (that occurred in at least four patients) included fatigue in seven patients (26.9%), while constipation, decreased appetite, diarrhea, hypercalcemia, hypophosphatemia, nausea, and urinary tract infection all occurred in four patients (15.4%). TEAEs grade 3 or higher occurred in three patients (11.5%); these included hypercalcemia (n=2) and urinary tract infection (n=1). TEAEs were considered related to study treatment in 15 patients (57.5%); and these were grade 3 or higher in five patients (19.2%). Serious TEAEs were observed in 7 patients (26.9%). A TEAE resulted in death in one patient.[14]

Table 6.12. Treatment-emergent Adverse Events (TEAEs) in Study 1423.[5]

	mCSCC (n=16)	laCSCC (n=10)	Total (N=26)
No. of patients with any TEAEs, n (%)	16 (100)	10 (100)	26 (100)
No. of patients with grade ≥ 3 TEAE, n (%)	7 (43.8)	5 (50)	12 (46.2)
No. of patients with serious TEAEs, n (%)	3 (18.8)	4 (40.0)	7 (26.9)
No. of patients who discontinued study treatment due to TEAE, n (%)	2 (12.5)	0	2 (7.7)
No. of patients with any TEAE leading to a drug interruption or delay, n (%)	2 (12.5)	3 (30.0)	5 (19.2)
No. of patients with any TEAE leading to a dose reduction, n (%)	0	0	0
No. of patients with a TEAE resulting in death, n (%)	0	1 (10)	1 (3.8)

aCSCC = locally advanced cutaneous squamous cell carcinoma; mCSCC = metastatic cutaneous squamous cell carcinoma; TEAE = treatment-emergent adverse event

Source: Sanofi-Genzyme data on file; Data cut-off: October 2, 2017

Study 1540

A summary of the TEAEs in Study 1540, based on the updated data cut-off dates are presented in Tables 6.13 and 6.14. Overall, almost all patients treated with cemiplimab experienced a TEAE; 191 patients (99.0%) experienced any TEAE and 86 patients (44.6%) experienced TEAEs that were grade 3 or higher.[5]

Table 6.14 summarizes the TEAEs (any grade) that occurred in at least 10% of patients in Group 1 and Group 2 of Study 1540 (TEAEs by preferred term were not available for Group 3).[7,8] The most frequently occurring TEAEs (Group 1/Group 2) 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).

In Group 1, the most frequent TEAEs grade 3 or higher included cellulitis (6.8%), pneumonitis (5.1%), and anemia, dyspnea, pneumonia, hypercalcemia, and pleural infusion (3.4% each). In Group 2, the most frequently occurring grade 3 or higher TEAEs were hypertension (7.7%), pneumonia (5.1%), and cellulitis and hyperglycemia (3.8% each). The percentage of TEAEs, any grade/grade ≥3, that were considered related to treatment with cemiplimab was 78.0%/15.3% in Group 1 and 79.5%/12.8% in Group 2. Grade 3 or higher immune-related TEAEs occurred in 13.6% of patients in Group 1 and 10.3% of patients in Group 2. Refer to Table 6.14 for a more complete summary of TEAEs occurring in Study 1540.

Serious TEAEs occurred in 35.8% of all patients; 40.7% in Group 1, 29.5% in Group 2 and 39.3% in Group 3.[5] 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; one of these deaths was attributed to study treatment.[5]

Table 6.13: Updated Analysis of Treatment Emergent Adverse Events (TEAEs) in Study 1540.[5]

	Group 1 (mCSCC) (n=59)	Group 2 (laCSCC) (n=78)	Group 3 (mCSCC) (n=56)	Total (N=193)
No. of patients with any TEAEs, n (%)	59 (100)	78 (100)	54 (96.4)	191 (99.0)
No. of patients with any grade 3/4/5 TEAE, n (%)	30 (50.8)	34 (43.6)	22 (39.3)	86 (44.6)
No. of patients with serious TEAEs, n (%)	24 (40.7)	23 (29.5)	22 (39.3)	69 (35.8)
No. of patients who discontinued study treatment due to TEAE, n (%)	6 (10.2)	6 (7.7)	3 (5.4)	15 (7.8)
No. of patients with any TEAE leading to a drug interruption or delay, n (%)	22 (3.7)	30 (38.5)	16 (28.6)	68 (35.2)
No. of patients with any TEAE leading to a dose reduction, n (%)	1 (1.70	1 (1.3)	1 (1.8)	3 (1.6)
No. of patients with any TEAE leading to both a drug interruption/delay and dose reduction, n (%)	0	1 (1.3)	1 (1.8)	2 (1.0)
No. of patients with a TEAE resulting in death, n (%)	2 (3.4)	2 (2.6)	1 (1.8)	5 (2.6)

laCSCC = locally advanced cutaneous squamous cell carcinoma; mCSCC = metastatic cutaneous squamous cell carcinoma; TEAE = treatment-emergent adverse event

Source: Sanofi-Genzyme data on file; Data cut-off: September 20, 2018 (Groups 1 and 3) and October 10, 2018 (Group 2).

Note: The number of patients with a TEAE resulting in death in Group 1 was corrected from n=3 in the previous analysis (data cut-off October 27, 2017) to n=2 in the updated analysis (data cut-off September 20, 2018) after receiving additional updated information.

Table 6.14. Treatment-emergent Adverse Events (TEAEs) in Study 1540.[7,8]

TEAEs[†]	Group 1 – Metastatic CSCC[b] (n=59)		Group 2 – Locally Advanced CSCC[c] (n=78)	
	Any Grade[a]	Grade ≥ 3	Any Grade[a]	Grade ≥ 3
	n (%)	n (%)	n (%)	n (%)
Any	59 (100)	30 (50.8)	78 (100)	34 (43.6)
Diarrhea	17 (28.8)	1 (1.7)	21 (26.9)	0
Fatigue	15 (25.4)	1 (1.7)	33 (42.3)	1 (1.3)
Nausea	14 (23.7)	0	17 (21.8)	0
Headache	11 (18.6)	0	NR	NR
Constipation	10 (16.9)	1 (1.7)	8 (10.3)	0
Pruritus	10 (16.9)	0	21 (26.9)	0
Rash	10 (16.9)	0	10 (12.8)	0
Arthralgia	9 (15.3)	0	8 (10.3)	1 (1.3)
Cough	9 (15.3)	0	15 (19.2)	0
Decreased appetite	8 (13.6)	0	NR	NR
Maculopapular rash	8 (13.6)	0	8 (10.3)	0
Anemia	7 (11.9)	2 (3.4)	8 (10.3)	NR
Dizziness	7 (11.9)	0	NR	NR
Dry skin	6 (10.2)	0	8 (10.3)	0
Dyspnea	6 (10.2)	2 (3.4)	NR	NR
Hypothyroidism	6 (10.2)	0	8 (10.3)	0
Oropharnygeal pain	6 (10.2)	0	NR	NR
Pneumonitis	6 (10.2)	3 (5.1)	NR	2 (2.6)
Upper respiratory tract infection	6 (10.2)	0	NR	NR
Vomiting	6 (10.2)	0	9 (11.5)	1 (1.3)
Abdominal pain	NR	NR	11 (14.1)	0
Actinic keratosis	NR	NR	8 (10.3)	0
Back pain	NR	NR	8 (10.3)	0
Basal cell carcinoma	NR	NR	8 (10.3)	1 (1.3)
Hypertension	NR	NR	NR	6 (7.7)
Pneumonia	NR	2 (3.4)	NR	4 (5.1)
Hyperglycemia	NR	NR	NR	3 (3.8)
Cellulitis	NR	4 (6.8)	NR	3 (3.8)
Hypercalcemia	NR	2 (3.4)	NR	NR
Pleural effusion	NR	2 (3.4)	NR	NR
Breast cancer	NR	NR	NR	2 (2.6)
Hyponatremia	NR	NR	NR	2 (2.6)
Lymphopenia	NR	NR	NR	2 (2.6)
Muscular weakness	NR	NR	NR	2 (2.6)
Sepsis	NR	NR	NR	2 (2.6)
Urinary tract infection	NR	NR	NR	2 (2.6)
Aseptic meningitis	NR	1 (1.7)[b]	NR	NR
Confusional state	NR	1 (1.7)[b]	NR	NR
Neck pain	NR	1 (1.7)[b]	NR	NR
Any treatment-related AE	46 (78.0)	9 (15.3)	62(79.5)	10 (12.8)

Abbreviations: CSCC –cutaneous squamous cell carcinoma; NR – not reported; TEAE – treatment-emergent adverse events.

Notes:
[†] - Extracted data are based on reporting in conference posters and therefore the sum of individual TEAEs may not add up to the reported totals.
[a] -TEAE are listed as indicated on the case report form. Although rash and maculopapular rash may reflect the same condition, they were listed as two distinct events in the safety report. Included in this table are TEAEs of any grade that occurred in at least 10% of the patient population. Events are listed in decreasing order of frequency by any grade.
[b] –TEAEs all occurred in one patient.

6.4 Ongoing Trials

No additional ongoing clinical trials of cemiplimab in patients with metastatic or unresectable locally advanced CSCC were identified.

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of cemiplimab for the treatment of adult patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation:

- Summary and critical appraisal of the sponsor-submitted ITC to estimate the comparative efficacy and safety of cemiplimab versus chemotherapy with platinum and BSC among patients with metastatic or locally advanced CSCC.

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

7.1 Summary and critical appraisal of the sponsor-submitted indirect treatment comparison (ITC) to estimate the comparative efficacy and safety of cemiplimab versus chemotherapy with platinum and best supportive care (BSC) among patients with metastatic and locally advanced CSCC

7.1.1. Background and Objective

The literature search conducted by CADTH did not identify any randomized controlled trials that included a direct, head-to-head comparison between cemiplimab and other potential treatment options in patients with metastatic or locally advanced CSCC. The best available evidence on the efficacy of cemiplimab comes from a single-group phase 2 study (Study 1540). In the absence of direct comparative evidence, the sponsor provided a SLR and ITC of cemiplimab compared with relevant comparators.[9] The objective of the ITC was to assess the comparative efficacy and safety of cemiplimab to chemotherapy with platinum or BSC among patients with locally advanced CSCC who are not candidates for surgery or patients who have regional or distant metastatic CSCC.

7.1.2. Review of Submitted Indirect Treatment Comparison

7.1.2.1 Overview of Methods

Study Selection

The sponsor used IPD from two cemiplimab studies: a phase 1, multicentre, open-label ascending-dose study of cemiplimab monotherapy in patients with advanced CSCC (Study 1423), and a phase 2, open-label, single-group non-randomized study of cemiplimab in the same population (Study 1540). More details on these studies can be found in Section 6.

A SLR was conducted in May 2019 in order to identify studies reporting on the efficacy and safety of other treatment options used to treat patients with advanced CSCC. The time period of the literature search was unclear. The SLR was conducted in Embase, MEDLINE and CENTRAL. A hand search was conducted to identify additional records through other sources including conference abstracts and clinical study reports. The target population was developed based on the inclusion/exclusion criteria used in Study 1540 (Table 7.1). Curative surgical interventions were excluded as these treatments were deemed not representative of the majority of patients in Study 1540.

The Newcastle-Ottawa Scale was used to assess the quality of non-randomized studies. The following criteria were assessed: study group and selection, comparability of the groups within studies, ascertainment of either the exposure or outcomes of interest.

Table 7.1: Inclusion and Exclusion Criteria of the Systematic Review.

Criteria	Inclusion Criteria	Exclusion Criteria
Study design	• Interventional studies (randomized or non-randomized) • Observational studies (prospective or retrospective, with ≥ 10 patients) • Cross-sectional studies	• Case series with < 10 patients • Case reports
Population	Adult patients with CSCC who have: • Locally advanced disease and who are not candidates for surgery • Regional metastasis to the lymph nodes • Distant metastasis	• Adult patients with other skin cancers (e.g. BCC, melanoma) or non-cutaneous SCC (e.g. head and neck) or those with local or locally advanced CSCC who are candidates for treatment with surgery and/or radiation
Intervention	• Cemiplimab • Platinum base chemotherapy • Best supportive care	• Surgical interventions
Comparators	• Any systemic intervention	• Surgical interventions
Outcomes	• Overall survival (in form of Kaplan-Meier curve) • Progression-free survival (in form of Kaplan-Meier curve) • Objective response	
Language restrictions	• Studies published in English	• Studies not published in English

Source: Submitted ITC report (data from Table 1)[9]

The SLR included Study 1423 and Study 1540 and two observational studies meeting the inclusion criteria that evaluated chemotherapy[10] and BSC[11] as the study treatment. Treatment characteristics of the included studies are summarized in Table 7.2.

Results of the study quality assessment using the Newcastle-Ottawa questionnaire demonstrated that the included studies were free from any serious biases in the evaluated domains.

Table 7.2: Treatment Characteristics of Included Studies.

Study	Treatment	Regimen Evaluation
Phase 2 cemiplimab trial (R2810-ONC-1540)	Cemiplimab	Cemiplimab, IV (3 mg/kg or 350 mg; D1; Cycle length: 2 weeks)
Phase 1 cemiplimab trial (R2810-ONC-1423)	Cemiplimab	Cemiplimab, IV (3 mg/kg; D1; Cycle length: 2 weeks; Maximum treatment duration: 48 weeks)
Jarkowski 2016	Chemotherapy	Systemic therapy that included any one of the following: platinums, taxanes, cetuximab, or capecitabine (or a combination thereof)
Sun 2019	Best supportive care	Mostly palliative RT or hospice care without further therapy (a few patients received chemotherapy or cetuximab)

Source: Submitted ITC report (Table 4)[9]

Indirect Treatment Comparisons

In the submitted ITC report, the sponsor rationalized that performing a traditional network meta-analysis would not be feasible due to the absence of a comparator group in the cemiplimab trials. Thus, the sponsor conducted an ITC using three different approaches:

1) Unadjusted naïve comparison: A naïve comparison was performed that involved comparing outcomes from the cemiplimab and comparator studies without accounting for differences in their populations. The results from the naïve comparisons were used to inform the pCODR EGP's base case in reanalyses of the sponsor's economic model as this was the most conservative estimate.

2) Simulated treatment comparison (STC): The STC approach involved creating regression models (core and extended models) and applying them to the IPD from the cemiplimab trials (index population) in order to estimate the effect of different combinations of prognostic factors on the outcomes of interest. The best fitting models based on the Deviance information criterion (DIC) were used to predict outcomes for cemiplimab in each of the populations observed in the comparator studies (target population).

3) A matching-adjusted indirect comparison (MAIC): The MAIC approach estimates weights for the IPD from the cemiplimab trials so that the weighted mean baseline characteristics matched those observed for the target population. Patients that would not have been eligible for inclusion in the comparator study were removed from the IPD sample. A propensity score logistic regression model was then used to estimate weights for the IPD and match the main characteristics of eligible patients from the cemiplimab trials (index population) with those in each of the comparator studies (target population). These weights were incorporated into the estimation of treatment effects. The sponsor noted that no statistic similar to DIC may be used to compare the fit of different MAIC models, thus model selection was based solely on the STC.

It was stated in the ITC report that a naïve comparison of outcomes from studies without taking differences in their populations into consideration may introduce substantial risk of bias to the analysis. Therefore, the sponsor used STC and MAIC to estimate outcomes from the cemiplimab studies for which IPD were available (index population) for a population observed in the identified observational studies for which aggregated data were available (the target population). A limitation of the population-adjusted indirect comparisons (i.e., STC and MAIC) is that these only allow for pairwise comparisons.

In the submitted ITC, the STC was used as the base case analysis, while the MAIC was performed as a sensitivity analysis. The following outcomes were included in the analyses: PFS and OS as the primary outcomes, and ORR as a secondary outcome. Grade 3 and 4 adverse events were originally planned to be included in the ITC but insufficient data were available to allow for the analysis of adverse events. Relative treatment effects were estimated as hazard ratios (HRs) for OS and PFS by means of Cox regression, and odds ratios (ORs) for response rate using either contingency tables (naïve comparisons and MAIC) or logistic regression (STC).

Covariate selection

The sponsor conducted a targeted search in PubMed to identify relevant prognostic factors that may influence the outcomes of interest. Clinicians treating patients with advanced CSCC were consulted to validate the prognostic factors identified by the search. Two different models were constructed based on the search results:

- Core model: Prognostic factors included in the core model for the analysis were those reported as statistically significant in at least one study identified in the review: immune status (immunocompromised patients were excluded from the cemiplimab trials so this could not be adjusted for), age, disease stage, tumour grade, perineural invasion, tumour size, tumour depth, and tumour location.
- Extended model: Additional prognostic factors were included in an extended model were those that were not found to be significant or those that had not been studied in CSCC but had been found to be relevant in other tumour types. These included gender, ECOG performance status, prior systemic therapy and prior radiation therapy.

The covariates included in the core model and in the extended model varied across the comparisons depending on the availability of data on prognostic factors reported in the comparator studies (Table 7.3). The fit of the two alternative models along with other permutations were compared using the DIC for each pairwise comparison, with results presented for the model with the lowest DIC.

Table 7.3: Baseline Characteristics Included as Prognostic Factors in the Core and Extended Models from Each Trial Included in the Analysis.

Prognostic factor		Phase 2 cemiplimab trial (n=193)	Pooled Phase 1 and Phase 2 cemiplimab trials (n=219)	Jarkowski 2016[a] (n=25)	Sun 2019[b] (n=32)
Core model					
Disease stage, n (%)	laCSCC	78 (40.4)	88 (40.2)	13 (72)[a]	16 (50)
	mCSCC	115 (59.6)	131 (59.8)	5 (28)[a]	16 (50)
Age, median (range)		72 (38-96)	72 (38-96)	72 (38-96)	73 (43-89)
Tumor grade	Well differentiated	41 (21.2)	43 (19.6)	--	--
	Moderate/poorly differentiated	128 (66.3)	145 (66.2)	--	--
Tumor location	Head and neck	128 (66.3)	147 (67.1)	11 (44)[c]	32 (100)
	Trunk	25 (13)	27 (12.3)	7 (28)[c]	0 (0)
	Extremities	40 (20.7)	45 (20.5)	3 (12)[c]	0 (0)
Additional covariates in extended model					
Male, n (%)		161 (83.4)	182 (83.1)	18 (72)	26 (81.3)
ECOG PS	0	86 (44.6)	96 (43.8)	--	0(0)
	1	107 (55.4)	123 (56.2)		32 (100)
	2 or above	0 (0)	0 (0)		
Prior systemic therapies		65 (33.7)	80 (36.5)	≤ 8 (32)	--
Prior radiation therapies		131 (67.9)	152 (69.4)[d]	--	32 (100)

Notes: ***a)*** *Proportions among the chemotherapy with platinum subgroup (n=18);* ***b)*** *Patient characteristics were reported for the 32 immunocompetent patients in Sun 2019; characteristics were not reported separately for the target population in that study (i.e. 20 immunocompetent patients with lesions that were not amenable to surgery);* ***c)*** *Two patients had lesions on the genital area, and two patients had unknown tumor locations.* ***d)*** *Data on prior radiation therapy was not available for individual patients from the Phase 1 cemiplimab trial.* ***Abbreviations:*** *CSCC, cutaneous squamous cell carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance score; laCSCC, locally advanced CSCC; mCSCC, metastatic CSCC.*

Source: Submitted ITC report (Table 9)[9]

7.1.2.2 Results of the Indirect Treatment Comparisons

While OS was reported in all of the included studies, PFS was reported in all studies except for Sun 2019. OS was defined as the time from the start of treatment until death due to any cause in the phase 1 and phase 2 cemiplimab studies as well as in Jarkowski 2016.[10] However, for Sun 2019,[11] OS was defined as the time from the date of local, regional, or distant recurrence, whichever occurred first until death. The definition of PFS was consistent across all included studies. Response rates were not reported in Sun 2019.[11] The cemiplimab studies used RECIST(version 1.1), while Jarkowski 2016[10] used the World Health Organization (WHO) response criteria to evaluate ORR. DOR was only reported in the cemiplimab studies. Disease-specific OS was not reported in any of the included studies. The median duration of patient follow-up was not reported for Sun 2019.

Progression-free Survival (PFS)

ITC based on data from Study 1540 showed no statistically significant difference in PFS between cemiplimab and platinum chemotherapy (Naïve HR=0.66 [95% CI, 0.38-1.16]; STC HR=0.64 [95% CI, 0.38-1.11]; MAIC HR=0.67 [95% CI, 0.38-1.16]). However, the direction and magnitude of the HR indicated an improvement in PFS in favour of cemiplimab compared to platinum chemotherapy. Similar results were obtained for the ITC based on the pooled analysis of data from Studies 1423 and 1540 versus platinum chemotherapy. For PFS, there was no comparison of cemiplimab to BSC. Results for PFS are summarized in Table 7.4.

Table 7.4. Hazard Ratios of PFS for Indirect Comparison of Cemiplimab versus Platinum Chemotherapy.

Comparison of cemiplimab to:	Naive HR (95% CI)	STC HR (95% CI)	MAIC HR (95% CI)
Platinum Chemotherapy			
Study 1540 data only	0.66 (0.38-1.16)	0.64 (0.38-1.11)	0.67 (0.38-1.16)
Pooled Study 1423 and Study 1540	0.64 (0.37-1.11)	0.63 (0.37-1.08)	0.64 (0.37-1.12)

Source: Submitted ITC report (data from Figures 8 and 10)[9]

Overall Survival (OS)

ITC based on data from Study 1540 showed a statistically significant difference in OS between cemiplimab and platinum chemotherapy in favour of cemiplimab (Naïve HR=0.30 [95% CI, 0.16-0.58]; STC HR=0.17 [95% CI, 0.09-0.33]; MAIC HR=0.19 [95% CI, 0.10-0.39]). Similarly, the difference in OS between cemiplimab and BSC was statistically significant in favour of cemiplimab (Naïve HR=0.18 [95% CI, 0.09-0.33]; STC HR=0.12 [95% CI, 0.06-0.22]; MAIC HR=0.16 [95% CI, 0.08-0.30]). The magnitude of the HR demonstrated an improvement in OS in favour of cemiplimab compared to platinum chemotherapy and BSC. Similar results were obtained for the ITC based on the pooled analysis of data from Study 1423 and Study 1540 versus platinum chemotherapy (Naïve HR=0.31 [0.16-0.58]; STC HR=0.19 [95% CI, 0.10-0.35]; MAIC HR=0.20 [95% CI, 0.10-0.40]); and versus BSC (Naïve HR=0.18 [95 % CI, 0.10-0.33]; STC HR=0.21 [95% CI, 0.12-0.37]; MAIC HR=0.21 [95% CI, 0.12-0.38]). Results for OS are summarized in Table 7.5.

Table 7.5: Hazard Ratios of OS for Indirect Comparison of Cemiplimab versus Comparators.

Comparison of cemiplimab to:	Naive HR (95% CI)	STC HR (95% CI)	MAIC HR (95% CI)
Platinum chemotherapy			
Study 1540 data only	0.30 (0.16-0.58)	0.17 (0.09-0.33)	0.19 (0.10-0.39)
Pooled Study 1423 and Study 1540	0.31(0.16-0.58)	0.19 (0.10-0.35)	0.20 (0.10-0.40)
Best Supportive Care			
Study 1540 data only	0.18 (0.09-0.33)	0.12 (0.06-0.22)	0.16 (0.08-0.30)
Pooled Study 1423 and Study 1540	0.18 (0.10-0.33)	0.21 (0.12-0.37)	0.21 (0.12-0.38)

Source: Submitted ITC report (data from Figures 8 and 10)[9]

Objective Response Rate (ORR)

ITC based on data from Study 1540 showed that the difference in ORR between cemiplimab and platinum chemotherapy was not statistically significant (Naïve odds ratio [OR]=1.00 [95% CI, 0.40-2.57]; STC OR=0.81 [95% CI, 0.33-1.97); MAIC OR=0.87 [95% CI, 0.33-2.38]). The magnitude of the HR demonstrated an improvement in ORR in favour of cemiplimab compared to platinum chemotherapy. Similar results were obtained for the ITC based on the pooled analysis of the phase 1 and 2 cemiplimab studies versus platinum chemotherapy (Naïve OR=1.03 (95% CI, 0.41-2.63); STC OR=0.80 [95% CI, 0.33-1.92]; MAIC OR=0.87 [95% CI, 0.33-2.36]). For ORR, there was no comparison of cemiplimab to BSC. Results for ORR are summarized in Table 7.6.

Table 7.6. Odds Ratios of ORR for Indirect Comparison of Cemiplimab versus Comparators.

Comparison of cemiplimab to:	Naive OR (95% CI)	STC OR (95% CI)	MAIC OR (95% CI)
Platinum chemotherapy			
Study 1540 data only	1.00 (0.40-2.57)	0.81 (0.33-1.97)	0.87 (0.33-2.38)
Pooled Study 1423 and Study 1540	1.03 (0.41-2.63)	0.80 (0.33-1.92)	0.87 (0.33-2.36)

Source: Submitted ITC report (data from Figures 9 and 11)[9]

7.1.3 Critical Appraisal of the Submitted Indirect Treatment Comparison

The sponsor-submitted ITC was appraised by the pCODR Methods Team by comparing the reported methods against best practice principles for performing STC and MAIC.[23,24]

The reported results are based on a STC as the main analysis without a common comparator between the interventions. Overall, the validity of the STC results is unclear as the treatment effect for the extended model was not reported in the submitted ITC report. The pCODR Methods Team was unable to assess the sensitivity of the conclusions to the model selection process which is concerning since the extended model is the one that includes the most extensive list of prognostic factors.

The main limitations of the STC and MAIC that were identified by the pCODR Methods Team are summarized below.

7.1.3.1. Critical Appraisal of the Simulated Treatment Comparison (STC)

- No common comparator

  The reported results are based on an STC analysis without a common comparator between the interventions. In the absence of a common comparator, unanchored comparison methods are required. Unanchored comparisons make stronger assumptions than anchored comparisons, where treatments are connected through a common comparator. In an unanchored population adjusted ITC, the absolute treatment effects are assumed to be constant at any given level of the effect modifiers and prognostic variables. Unanchored methods also assume that all effect modifiers and prognostic variables are known.[23] These assumptions are generally difficult to meet, and it is unclear if they were satisfied in the submitted ITC.

- Differences in outcome and comparator definitions

  The definition of OS was not consistent for all the studies included in the ITC. In addition, PFS was not reported in Sun 2019, which used BSC as the study treatment. In this study, only OS analyses were reported for BSC. Furthermore, BSC was not clearly defined in this study, nor was it consistent among the 20 included patients and ranged from palliative radiation therapy to hospice care.

- Influence of prognostic factors and effect modifiers

  While a targeted literature search was performed for prognostic factors, no effect modifiers were considered in the analysis. In the Core model, the sponsor only included prognostic factors that were reported as statistically significant in at least one of the studies identified in the SLR. Prognostic factors found to be non-statistically significant were included in the extended model. In order to obtain an unbiased estimate of differences in the treatment effects, all prognostic factors and effect modifiers for a given outcome must be adjusted for in the model.

  Among the 11 clinicians who were consulted on the validation of the identified prognostic factors, key prognostic variables such as DOR, toxicity of the drug and comorbidities were noted as missing. Thus, the prognostic factors missing from the models may have had an influence on the outcomes of interest and the reported estimates therefore may be biased.

- Insufficient data

  Jarkowski 2016 did not have data reported in the publication on ECOG performance status, AJCC T stage, perineural invasion, tumour diameter/size, depth and grade, immunosuppression and prior radiation therapy. Similarly, Sun 2019 did not have data reported on perineural invasion, tumour diameter/size, depth and grade. Due to the observational nature of both studies, there is insufficient information on the patient populations to adequately assess how representative they are of the target treatment population for cemiplimab. Since these observational studies have been used in the ITC to define the target population, the pCODR Methods Team is uncertain whether the results of the ITC will be unbiased estimates of the treatment effects in the index (cemiplimab-treated) population.

  Due to insufficient data available, safety (i.e., grade 3/4 adverse events) was not analyzed.

7.1.3.2 Critical Appraisal of the Matched-Adjusted Indirect Comparison (MAIC)

- Reduced sample sizes

  In the MAIC, the reduction of the sample size after matching was more than 50% (56.2% when using the pooled Study 1423 and Study 1540 data; and 52.2% when using Study 1540 only) for the comparison with platinum chemotherapy and approximately 94% with BSC. Consequently, the MAIC results may be based on small number of individuals as a result of the re-weighting of individuals from the original sample, which poses a potential risk to the validity of the results.

- Prognostic factors

  The MAIC analysis would be subject to similar limitations to those previously outlined for the STC analysis, particularly in relation to the exclusion of key prognostic factors and effect modifiers.

8 COMPARISON WITH OTHER LITERATURE

The pCODR CGP and Methods Team did not identify other relevant literature providing supporting information for this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR CSCC CGP 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 cemiplimab for CSCC. 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.

The Gastrointestional 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 pCODR 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.

The CSCC Clinical Guidance Panel is comprised of three medical 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 June 2019**, Embase** 1974 to 2019 July 17**, Ovid MEDLINE(R) ALL** 1946 to July 17, 2019

#	Searches	Results
1	(Cemiplimab* or Libtayo* or regn2810 or regn 2810 or 6QVL057INT).ti,ab,ot,kf,kw,hw,nm,rn.	157
2	1 use medall	21
3	limit 2 to english language	19
4	1 use cctr	30
5	3 or 4	49
6	*cemiplimab/	26
7	(Cemiplimab* or Libtayo* or regn2810 or regn 2810).ti,ab,kw,dq.	115
8	6 or 7	116
9	8 use oemezd	65
10	limit 9 to english language	62
11	10 not (conference review or conference abstract).pt.	30
12	5 or 11	79
13	remove duplicates from 12	62
14	10 and (conference review or conference abstract).pt.	32
15	limit 14 to yr="2014 -Current"	32
16	13 or 15	94

2. Literature search via PubMed

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

Search	Query	Items Found
#3	Search #1 AND #2	3
#2	Search publisher[sb]	458289
#1	Search cemiplimab [Supplementary Concept] OR Cemiplimab*[tiab] OR Libtayo*[tiab] OR regn2810[tiab] OR regn 2810[tiab] OR 6QVL057INT[rn]	21

3. Cochrane Central Register of Controlled Trials (CENTRAL)

(searched via Ovid)

4. **Grey literature search via:**

Clinical trial registries:

US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

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

Search: Libtayo/ cemiplimab, cutaneous squamous cell carcinoma

Select international agencies including:

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

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

Search: Libtayo/ cemiplimab, cutaneous squamous cell carcinoma

Conference abstracts:

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

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

Search: Libtayo/ cemiplimab, cutaneous squamous cell carcinoma— last five years

Detailed Methodology

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the PRESS (Peer Review of Electronic Search Strategies) checklist (https://www.cadth.ca/resources/finding-evidence/press).[25]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) 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 Libtayo/cemiplimab

No filters were applied to limit the retrieval by study 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 November 14, 2019.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature*

checklist (https://www.cadth.ca/grey-matters).[26] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov and Canadian Partnership Against Cancer Corporation's 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) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. As well, 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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