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pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Cemiplimab (Libtayo) for Cutaneous Squamous Cell Carcinoma

January 22, 2020

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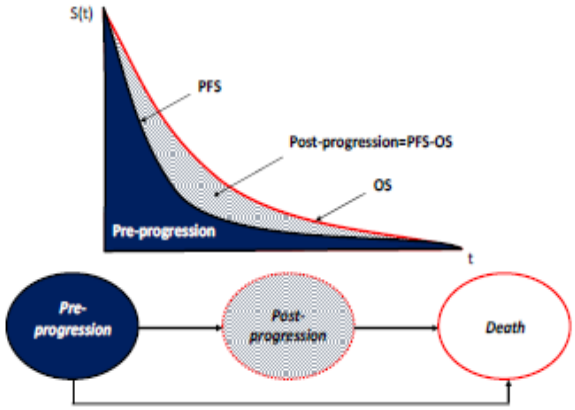
1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Sanofi Genzyme (referred to herein as the sponsor), a division of Sanofi-Aventis Canada Inc., compared cemiplimab to chemotherapy (cisplatin plus 5-fluorouracil; cisplatin+5FU) for the treatment of patients with metastatic or locally-advanced cutaneous squamous cell carcinoma (CSCC) who are not candidates for curative surgery or curative radiation therapy. This is consistent with the reimbursement request and Health Canada indication.

Table 1: Submitted Economic Model

Funding Request/Patient Population Modelled	Metastatic or locally-advanced cutaneous squamous cell carcinoma (CSCC) not candidates for curative surgery or curative radiation therapy/same as funding request
Type of Analysis	CEA, CUA
Type of Model	Partitioned-survival 
Comparator	Chemotherapy (cisplatin+5FU); Best supportive care (BSC) in a scenario analysis
Year of costs	2019
Time Horizon	30 years
Perspective	Public health care payer
Cost of Cemiplimab	• 350 mg/7ml single-vial use: $8,200.00 • 250 mg/5 ml single-vial use: $5,857.14 • Per 21-day cycle: $8,200 (i.e., 350 mg on Day 1) • Per 28-day course: $10,933.33 Treatment to be continued until symptomatic disease progression or unacceptable toxicity

Cost of cisplatin+5FU*
 	
** Price Source: IQVIA Delta PA 2019*
	• Per 21-day course
	  ○ Cisplatin (100 mg/m2 once): $540.00
	  ○ 5-FU (1000 mg/m2 on day 1 to 4): $324.80
	  ○ Total: $1,252.59
	• Per 6-cycle course:
	  ○ Total: $5,188.80

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Model Structure	Partition survival with 3 states: pre-progression, post-progression, death. Main analysis on the pooled patient population, i.e., metastatic CSCC and locally advanced CSCC. Scenario analysis on sub-populations.
Key Data Sources	The EMPOWER-CSCC-1 trial (Study 1540; September 20, 2018 data cut for groups 1 and 3 – metastatic CSCC weight-based and fixed dose; October 10, 2018 data cut for group 2 – locally advanced CSCC weight-base dose) provided cemiplimab efficacy and safety. Cemiplimab efficacy was adjusted via simulated treatment comparison (STC). Cisplatin+5FU efficacy and overall survival (OS) with BSC were sources from the medical literature.[1,2] Cisplatin+5FU safety was also taken from the medical literature.[3] As BSC did not include active treatment, no adverse events were considered. Pre- and post-progression utilities were obtained from Study 1540 while adverse event disutilities were obtained from the medical literature.[4-6] Cemiplimab costs were provided by the sponsor. All other costs were obtained from publicly available sources.

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), patients developing locally advanced, inoperable disease, or distant metastatic disease have a poor prognosis. Treatment of these patients has been largely palliative. Chemotherapy has never been shown to improve either OS or quality of life and is considered off-label in this population. For the purpose of the economic evaluation, chemotherapy and BSC were considered appropriate comparators. The sponsor provided the comparison against chemotherapy as the base case and against BSC as a scenario analysis.

Relevant issues identified included:

- Direct evidence on comparative effectiveness would be difficult to obtain due to the paucity of patients with this disease, non-existing evidence that chemotherapy offers a benefit, pre-existing comorbidities in many patients and the advanced age of the patient population.
- Response rates, the duration of response and the safety profile of cemiplimab seem superior to what could be expected from chemotherapy.
- PFS and OS data are immature and require longer term data to confirm the clinical benefit observed on overall response rate (ORR).
- It was felt that the fixed dose schedule with a treatment duration of 96 weeks was reasonable, but that longer follow-up data are necessary to confirm the interchangeability of the dose schedules.

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.

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Summary of registered clinician input relevant to the economic analysis
Registered clinicians noted that the most common treatments for CSCC are cisplatin+5FU or cetuximab, but that these may not be suitable to elderly patients in whom this disease frequently occurs. Palliative care is the only other option in these situations. Registered clinicians mentioned that cemiplimab would likely be given as first-line therapy, but they would like the product to be available for any line of therapy. The submitted model includes cisplatin+5FU as the main comparator and BSC as a scenario, however it does not include cetuximab. The EGP mentioned that there are patient access issues with cetuximab in the public health care system.

Summary of patient input relevant to the economic analysis
Patients value less pain, scarring and disfigurement, debilitating surgery and effects from radiation. Patients also mentioned that they would like to have access to any therapy that improves their chance of surviving with reasonable quality-of-life. Patients and caregivers were willing to accept some side effects for the trade-off of survival and/or disease control. The model includes utility values obtained from the sponsor's clinical trials. These should have captured any positive impact on pain, scarring and disfigurement that cemiplimab might have provided. Furthermore, the model includes disutilities from adverse events. The impact on surgery and radiation therapy are captured on the cost side. OS and progression-free survival (PFS) are the main inputs of treatment effectiveness.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors (enablers or barriers) relevant to the economic analysis and important to consider if implementing a funding recommendation for cemiplimab: absence of standard of care in this setting, the use of cemiplimab fixed versus weight-based dose (and related wastage) and the additional health care resources needed. PAG is also seeking guidance on treatment duration and the need for increased monitoring and treatment of immune-mediated adverse effects. The model includes the possibility to compare cemiplimab to the most commonly used CSCC treatments in Canada (i.e., cisplatin+5FU, BSC). The model also allows testing of the two dosing regimens and includes drug wastage. On-treatment oncology and general practitioner visits are included in the model but are the same for cemiplimab and the comparator. Increased monitoring and the need for treatment of immune-mediated adverse effects are not included in the model. However, as per CGP input, cemiplimab administration schedule and safety profile are unlikely to warrant additional clinical monitoring.

1.3 Submitted and EGP Reanalysis Estimates

According to the sponsor's base case, the use of cemiplimab rather than cisplatin+5FU would provide an additional 4.75 life-years (LYs; discounted) and 3.34 additional quality-adjusted life-years (QALYs; Table 2). Incremental costs were estimated at $252,155 for an ICUR of $75,426 per QALY with 87% of the 5,000 iterations falling below $100,000 per QALY. Scenario analyses showed that the choice of the parametric function to extrapolate cisplatin+5FU PFS and OS beyond the observed data, the use of the naïve indirect treatment comparison results (rather than the simulated treatment comparison; STC), cemiplimab treatment duration until progression and, subgroup analysis (metastatic only) had the largest impact on the ICUR. Most of the QALY gain (86%) was accrued in the post-progression state and in the extrapolated part of the model (77%) where the uncertainty is the greatest.

The EGP reanalysis of the sponsor's base case showed that the use of cemiplimab rather than cisplatin+5FU was associated with a 1.06 QALY gain and $176,966 incremental costs for an ICUR of $166,221 per QALY (Table 2). The probability of the cemiplimab ICUR being below $100,000 per QALY was only 4% (0% below $50,000 per QALY).

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Table 2: Submitted and EGP Estimates

Estimates (range/point)	Submitted	EGP Reanalysis
ΔE (LY) - undiscounted	5.37	1.61
Progression-free	0.75	0.30
Post-progression	4.63	1.31
ΔE (QALY) - discounted	3.34	1.06
Progression-free	0.54	0.22
Post-progression	2.80	0.84
ΔC ($) - discounted	$252,155	$176,966
ICUR estimate ($/QALY)	$75,426	$166,221

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

- High uncertainty on long-term effect of cemiplimab on OS and PFS: The main source of efficacy and safety inputs for cemiplimab was Study 1540 (EMPOWER-CSCC-1). This study is an ongoing single-group phase 2 study conducted in patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation. Limitations, including the uncontrolled nature of the study and the immaturity of the results (median OS was not reached; a small number of patients [none from the fixed dose group] at risk beyond 18 months), have been described in the Clinical Guidance Report. This 24-month study (with a median follow-up of 9.4 months) was used to extrapolate cemiplimab efficacy on OS and PFS over a 30-year time horizon. The parametric models selected by the sponsor to extrapolate OS and PFS resulted in an unusual large difference between the OS and the PFS curves suggesting an important effect of cemiplimab on post-progression survival. Unfortunately, no information on the post-progression survival was available from Study 1540 to confirm this model result. Furthermore, the OS extrapolation resulted in cemiplimab OS rates being above the OS of the Canadian general population at 9 years and beyond while 42% of the cohort was still alive, and therefore had to be capped at that of the general population for more than two thirds of the time horizon. A situation that was felt to be unlikely by the CGP in this advanced disease population. The EGP addressed this uncertainty on long-term effect by taking a conservative approach (refer to Section 1.4) for the extrapolation of cemiplimab OS and PFS.
- High uncertainty on cemiplimab comparative effectiveness. The efficacy for the cisplatin+5FU comparative group comes from a STC with a 25-patient study (20-patient study for the BSC comparison). The limitations of the STC (i.e., small sample size, missing prognostic factors, insufficient data to assess comparability of study populations, etc.) have been described in the Clinical Guidance Report. The use of the STC resulted in a further shift up of the cemiplimab OS curve. The evidence on the safety of the comparative group comes from the medical literature. The EGP was not able to address the limitation on data quality other than by taking a conservative approach in the estimation of the comparative effectiveness.
- Missing comparator. The sponsor's main analysis compared cemiplimab to chemotherapy (cisplatin+5FU). According to the CGP, BSC is often an option in these patients as this disease mostly affects elderly patients. No sequential analysis was provided by the sponsor, but the model included BSC as a possible comparator and allowed the EGP to conduct a deterministic sequential analysis using the naïve indirect treatment comparison.
- Uncertainty on utility values. The model state utilities were populated from mapping a quality-of-life questionnaire (EORTC-QLQ-C30) to the EQ-5D-3L. CADTH does not recommend the use of mapping algorithms due to the dramatic variation in the predictive

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value between algorithms. The impact on the estimated QALY gain is unknown. The EGP was not able to find more appropriate values in the medical literature.

- Underestimation and overestimation of some costs. Some cemiplimab serious adverse events were missing from the model due to the use of an arbitrary rule to select adverse events of interest (i.e., prevalence of 5% or greater). This had a limited impact on the ICUR. Some costs were overestimated (e.g., adverse events, end-of-life, dressings) and the EGP was able to adjust these costs in reanalyses. Some programming errors were found (i.e., separate sampling for costs used in both treatment groups) and the sponsor was able to correct the model.

1.4 Detailed Highlights of the EGP Reanalysis

To address these limitations, the EGP ran several scenario analyses on the sponsor's base case varying the assumptions on treatment effect beyond observed data, the costs and incidence of adverse events and the costs of pre- and post-progression management.

These analyses confirmed that the assumptions on cemiplimab efficacy and chemotherapy OS (also used in the cemiplimab group) are the most important drivers of cemiplimab benefit. When using the naïve treatment comparison (i.e., not using the STC), the discounted LY gain was reduced by 28% (from 4.73 in the sponsor's base case to 3.39). Similarly, using the Weibull distribution for the chemotherapy OS reduced the LY gain by 32% (from 4.73 to 3.22). Lastly, limiting the treatment effect to 18 months (rather than extrapolating to 36 months as per the sponsor's base case) decreased the LY gain by 44% (4.73 to 2.63). On the cost side, treatment costs were the largest cost drivers. When treatment duration was increased to 24 months as per coverage for other similar products, the ICUR increased by about $2,500 per QALY, while treatment until progression (as per product monograph) increased the ICUR by more than $35,000 per QALY. Using the weight-based dosage increased the ICUR by close to $3,500 per QALY. Other changes had much smaller impacts on the ICUR.

In view of these, the EGP made the following changes to the submitted economic model (EGP best estimate):

- Use of the naïve indirect treatment comparison
- Reduced extrapolation of treatment effect to 18 months (rather than 36 months in the sponsor's base case) after which, the same rates as chemotherapy are used for the rest of the time horizon
- Weibull distribution for chemotherapy OS (including a change in the shape parameter from -2.47 to -2.1 to obtain a 5-year survival between 5% and 10% for the chemotherapy group)
- Correction to cost of wound dressings
- Correction to end-of-life costs

In addition, the EGP ran a few scenarios on the EGP best estimate to identify the upper bound of the EGP reanalyses. These included:

- Increasing treatment duration to 24 months (as for similar product, rather than 22 months as per the study)
- Using the weight-based dosage as this is an alternative dosage in the product monograph for low weight individuals

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- Assuming treatment until progression as indicated in the product monograph

Furthermore, the EGP conducted a sequential analysis including BSC and cisplatin+5FU as comparators as well as price reduction scenarios.

In the EGP best case, the incremental benefit gain was 1.48 LYs and 1.06 QALYs (Table 3). The incremental costs were $176,966 with a resulting ICUR of $166,221 per QALY. An upper bound of $223,828 per QALY was achieved with cemiplimab being administered until treatment progression (no capping at 22 or 24 months). The deterministic sequential analysis showed that for a willingness-to-pay below $52,539 per QALY, BSC would be the preferred option. For a willingness-to-pay between $52,539 and $161,278 per QALY, chemotherapy would be the preferred option, and that cemiplimab would be the preferred option for a willingness-to-pay above $161,278 per QALY. The price reduction scenarios showed that a 40% price reduction would be needed to bring the ICUR around $100,000 per QALY while an 80% price reduction would be required to bring the ICUR around $50,000 per QALY.

Table 3: Detailed Description of EGP Reanalysis (probabilistic results unless otherwise specified)

	ΔC	ΔE QALYs	ΔE LYs	ICUR (QALY)	Δ from baseline submitted ICER
Baseline (Sponsor's best case – original model)	$252,155	3.34	4.75	$75,426	--
Baseline (Sponsor's best case – corrected model)	$251,165	3.33	4.73	$75,438	---
LOWER BOUND					
Naïve comparison (Chemo OS: Gompertz)	$220,132	2.39	3.39	$92,050	16,612
Chemo OS: Weibull	$219,926	2.31	3.22	$95,076	19,638
Treatment effect extrapolated to 18 months	$202,565	1.36	2.63	$108,808	33,382
Cost of dressings reduced to $724.20 per month ($2006 inflated to $2019) rather than $1,186.00	$249,448	3.35	4.77	$74,391	-624
Terminal care costs: reduced from $106,264 *to $26,495 (inflated to 2019)*	$256,674	3.32	4.71	$77,388	1,950
Best case estimate (all of the above parameters)	$176,966	1.06	1.48	$166,221	$90,783
UPPER BOUND					
EGP best estimate + scenario I (treatment until progression)	$239,831	1.07	1.49	$223,828	$148,390
SEQUENTIAL ANALYSIS (deterministic)					
BSC	---	---		---	
Chemotherapy	$22,413*	0.43*		$52,539*	
Cemiplimab	$179,293*	1.11*		$161,278*	
PRICE REDUCTION SCENARIOS					
20% price reduction				$139,937	
40% price reduction				$110,600	
50% price reduction				$94,529	
80% price reduction				$51,522	

*in relation to previous treatment option

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1.5 Evaluation of Submitted Budget Impact Analysis

According to the sponsor's analysis, the factors that most influenced the budget impact analysis (BIA) included the proportion of patients not amenable to curative surgery or curative radiation (43% increase in 3-year budget impact when this proportion goes from 10% to 20%) and optimistic market shares (25% increase in 3-year budget impact). In comparison, the pessimistic market share scenario generated a 25% decrease in budget impact. All other scenarios tested had a 15% or less impact on the 3-year budget.

Key limitations of the BIA model included the assumption on market share of the various chemotherapy regimens (according to the CGP, cisplatin+5FU is the most commonly used chemotherapy regimen in this patient population) and the average cemiplimab treatment duration of 13.5 months (likely too short, if cemiplimab is to be administered until progression). The EGP could modify these parameters. While a change in chemotherapy regimens market share had a limited impact (1% increase), increasing treatment duration to 23 months increased the budget impact by 46%.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for cemiplimab when compared to chemotherapy (i.e., cisplatin+5FU) is:

- $166,221 per QALY gained
- The sequential analysis (deterministic results only) shows that BSC would be the preferred option at a willingness-to-pay below $52,539 per QALY and cemiplimab would be the preferred option at a willingness-to-pay above $161,278 per QALY. In between, chemotherapy would be the preferred option.
- The discounted extra costs related to cemiplimab usage are estimated at $176,966 over the lifetime horizon of the model. The cost of treatment is the main cost driver.
- The discounted QALY gained is estimated at 1.6 QALY over the model time horizon. Most of this QALY gain (70%) is accrued in the post-progression period and in the extrapolated phase of the model.

Overall conclusions of the submitted model:

- The model is extremely sensitive to assumptions made on the long-term effectiveness of cemiplimab (and cisplatin+5FU as the cemiplimab group uses cisplatin-5FU OS and PFS after 3 years) and those made on the duration of treatment.
- Price reduction between 40% and 80% would be required to reduce the ICUR in the $50,000 to $100,000 per QALY range.
- The EGP was not able to address the limitations related to the quality of the data (i.e., small sample size and uncontrolled nature of the cemiplimab clinical study; lack of direct treatment comparison; quality of the STC used to provide comparative effectiveness). Therefore, caution should be exercised when interpreting the results of the economic analysis.
- The availability of cemiplimab to the Canadian public health care system could result in a 3-year budget impact of around $55 million.

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2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

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3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Cutaneous Squamous Cell Carcinoma (CSCC) Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of cemiplimab for metastatic or unresectable locally advanced CSCC. A full assessment of the clinical evidence of [drug name and indication] is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR 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 Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

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

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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