

5.03 CEMIPILIMAB, Solution for IV infusion 350 mg in 7 mL, LIBTAYO®, Sanofi-Aventis Australia Pty Ltd.

1 Purpose of Submission

- 1.1 The submission requested a Section 100 listing (Efficient Funding of Chemotherapy) for cemiplimab for the treatment of patients with metastatic or locally advanced cutaneous squamous cell carcinoma (mCSCC or laCSCC) who are not candidates for curative surgery or curative radiation.
- 1.2 The key components of the clinical issues addressed by the submission are presented below.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation
Intervention	Cemiplimab (LIBTAYO®) 350 mg injection given as an IV infusion over 30 minutes Q3W
Comparator	BSC ± CT
Outcomes	ORR, DOR, PFS, OS and CRR
Clinical claim	In patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation: <ul style="list-style-type: none">• Cemiplimab is superior in terms of effectiveness (improved OS and PFS) compared with BSC ± CT• Cemiplimab is non-inferior in terms of safety compared with BSC ± CT

Source: Table 1.1.1, p3 of the submission

BSC= best supportive care; CRR = complete response rate; CT=chemotherapy; DOR = duration of response; IV= intravenous; laCSCC = locally advanced cutaneous squamous cell carcinoma; mCSCC = metastatic cutaneous squamous cell carcinoma; ORR = objective response rate; OS = overall survival; PFS = progression free survival; Q3W = every three weeks

2 Background

Registration status

2.1 Cemiplimab received provisional approval by the TGA on 2nd of July 2020 for the following indication:

- Treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma (mCSCC or laCSCC) who are not candidates for curative surgery or curative radiation. This indication was approved based on objective response rate (ORR) and duration of response from single arm clinical studies.
- The PBAC noted that the sponsor is required to submit further clinical data to confirm the clinical benefit of the medicine. This includes interim data from a single-arm study in the same population [study 1540 group 6], which will investigate whether programmed death ligand-1 (PD-L1) expression is predictive of efficacy. These results are due by 31 Mar 2023. In addition, the final study report for Groups 1-3 in the study 1540 is due by 31 Oct 2022 (TGA delegate's overview).

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	PBS item code	Maximum Amount	№.of Rpts	Dispensed price for maximum amount	Manufacturer
CEMIPLIMAB cemiplimab 350 mg/7 mL, 10 mL vial	NEW (Public) NEW (Private)	350 mg	4 2	Published price \$ [redacted] public hospital \$ [redacted] private hospital Effective price \$ [redacted] public hospital \$ [redacted] private hospital	Sanofi-Aventis Australia Pty Ltd
Available brands					
Libtayo cemiplimab 350 mg/7 mL, 10 mL vial					

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required): <input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required –[new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Medicare; retrospective audit of patient records possible) <input type="checkbox"/> Authority Required – immediate/real time assessment by Medicare (telephone/online/emergency) <input type="checkbox"/> Authority Required – non-immediate/delayed assessment by Medicare (In-writing only via mail/postal service or electronic upload to Hobart)
Administrative Advice: No increase in the maximum number of repeats may be authorised.

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<p>Administrative Advice: Special Pricing Arrangements apply.</p>
<p>Administrative Advice: Patient should be treated with the recommended dose of cemiplimab according to the TGA approved Product Information.</p>
<p>Severity: Metastatic or locally advanced</p>
<p>Condition: Cutaneous Squamous cell carcinoma</p>
<p>Indication: Metastatic or locally advanced cutaneous Squamous cell carcinoma</p>
<p>Treatment Phase: Initial</p>
<p>Clinical criteria: If locally advanced, the patient must not be a candidate for curative surgery. <i>The condition must be histologically confirmed as cutaneous squamous cell carcinoma.</i> AND <i>The condition must be metastatic.</i> OR <i>The condition must be locally advanced and not be amendable to curative treatment with surgery or radiation.</i></p>
<p>AND</p>
<p>Clinical criteria: If locally advanced, the patient must not be a candidate for curative radiation.</p>
<p>AND</p>
<p>Clinical criteria: <i>Patient must have a WHO performance status of 0 or 1.</i></p>
<p>AND</p>
<p>Clinical criteria: Patient must not receive more than 15-9 weeks of treatment under this restriction.</p>
<p>AND</p>
<p>Clinical criteria: The treatment must be the sole PBS-subsidised therapy for this condition.</p>
<p>AND</p>
<p>Prescribing Instructions: A histological confirmation of CSCC cutaneous squamous cell carcinoma and whether the condition is metastatic or locally advanced must be kept on file.</p>
<p>Definitions: Not a candidate for curative surgery is defined as: <ul style="list-style-type: none"> i. Curative resection is unlikely, such as where CSCC has recurred in the same location after two or more surgical procedures; OR ii. Anticipated substantial morbidity or deformity from surgery or requiring complicated reconstructive surgery (e.g. removal of all or part of a facial structure, such as nose, ear, eyelid, eye; or requirement for limb amputation or free tissue transfer); OR iii. Medical contraindication to surgery. Not a candidate for curative radiation is defined as: <ul style="list-style-type: none"> i. Limitations due to location of tumour; OR ii. Limitations due to cumulative prior radiotherapy dose; OR </p>
<p>Progressive disease despite prior irradiation of locally advanced CSCC.</p>
<p>NOTE: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.</p>

Public Summary Document – November 2020 PBAC Meeting

Name, Restriction, Manner of administration and form	PBS item code	Maximum Amount	No. of Rpts	Dispensed price for maximum amount	Manufacturer
CEMIPLIMAB cemiplimab 350 mg/7 mL, 10 mL vial	NEW (Public) NEW (Private)	350 mg	7	Published price \$ [redacted] public hospital \$ [redacted] private hospital Effective price \$ [redacted] public hospital \$ [redacted] private hospital	Sanofi-Aventis Australia Pty Ltd
Available brands					
Libtayo cemiplimab 350 mg/7 mL, 10 mL vial					

Category / Program:
Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals

Prescriber type: Dental Medical Practitioners Nurse practitioners Optometrists Midwives

Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required):
Unrestricted benefit
Restricted benefit
Authority Required – Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Medicare; retrospective audit of patient records possible)
Authority Required – immediate/real time assessment by Medicare (telephone/online/emergency)
Authority Required – non-immediate/delayed assessment by Medicare (In-writing only via mail/postal service or electronic upload to Hobart)

Administrative Advice:
No increase in the maximum number of repeats may be authorised.

Administrative Advice:
Special Pricing Arrangements apply.

Administrative Advice:
~~Patient should be treated with the recommended dose of cemiplimab according to the TGA-approved Product Information.~~

Severity: ~~Metastatic or locally advanced~~

Condition: ~~Cutaneous Squamous cell carcinoma~~

Indication: ~~Metastatic or locally advanced cutaneous Squamous cell carcinoma~~

Treatment Phase: Continuing

Clinical criteria:
The condition must be histologically confirmed as cutaneous squamous cell carcinoma.
AND
The condition must be metastatic.
OR
The condition must be locally advanced and not be amendable to curative treatment with surgery or radiation.

AND

Clinical criteria:
The treatment must be the sole PBS-subsidised therapy for this condition.

AND

Clinical criteria:
Patient must have previously received PBS-subsidised therapy with this drug for this condition.

AND

Clinical criteria:
Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition.

Clinical criteria:
Patient must not receive more than 24 months of treatment under this restriction.
The treatment must not exceed a lifetime maximum of 96 weeks of therapy.

NOTE:
In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.

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Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required): <input type="checkbox"/> Unrestricted benefit <input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Medicare; retrospective audit of patient records possible) <input type="checkbox"/> Authority Required – immediate/real time assessment by Medicare (telephone/online/emergency) <input type="checkbox"/> Authority Required – non-immediate/delayed assessment by Medicare (In-writing only via mail/postal service or electronic upload to Hobart)
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: Patient should be treated with the recommended dose of cemiplimab according to the TGA-approved Product Information.
Severity: Metastatic or locally advanced
Condition: Cutaneous squamous cell carcinoma
Indication: Metastatic or locally advanced cutaneous Squamous cell carcinoma
Treatment Phase: Grandfathered
Clinical criteria: Patient must have received non-PBS subsidised therapy with this drug for this condition prior to [insert date of listing]
AND
Clinical criteria: Patient must be receiving treatment with this drug for this condition at the time of application.
AND
Clinical criteria: Prior to commencement of non-PBS subsidised treatment with this drug, the patient must have had, if locally advanced, confirmation that the patient is not a candidate for curative surgery or curative radiation.
Clinical criteria: The condition must be histologically confirmed as cutaneous squamous cell carcinoma. AND The condition must metastatic. OR The condition must be locally advanced and is not be amendable to curative treatment with surgery or radiation.
AND
Clinical criteria: Patient must have had a WHO performance status of 0 or 1 prior to initiation of non-PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria: Patient must have demonstrated an adequate response if the patient has received at least 15 weeks of treatment of non-PBS subsidised cemiplimab for this condition.
AND
Clinical criteria: Patient must not receive more than 24 months of treatment under per continuing treatment under this restriction.
AND
Clinical criteria: Patient must not receive more than 24 weeks of treatment under this restriction.
AND

Public Summary Document – November 2020 PBAC Meeting

Clinical criteria:
<i>The treatment must be the sole PBS-subsidised therapy for this condition.</i>
AND
Administrative advice:
<i>Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria. This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.</i>

3.2 The submission requested a special pricing arrangement (SPA). The proposed effective and published ex-manufacturer price per vial of cemiplimab is \$ [REDACTED] and \$ [REDACTED], respectively. The pre-PBAC response offered a 5% reduction on the proposed effective price.

3.3 Overall, the proposed restrictions were consistent with the TGA indication, but were broader than the inclusion criteria in the key studies (1423 and 1540) in terms of:

- No restriction to patients with a performance status (PS) ≤ 1 (which was one of the inclusion criteria of the cemiplimab key studies)
- No restriction to immunocompetent patients (immunosuppressed patients were excluded from the cemiplimab key studies).

The efficacy and safety of cemiplimab among patients with a poorer PS and among immunosuppressed patients was not examined and is, therefore, unknown. The Pre-Sub-Committee Response (PSCR) stated that eligibility criteria with respect to PS and immune status in the cemiplimab trials is common in clinical trials of other PD-1 medicines. However, the PSCR argued that the PBS restrictions for other PD-1 medicines do not exclude immunosuppressed patients or consistently exclude patients based on PS across all indications. The ESC considered that the metastatic CSCC patient population in particular are more likely to be immunocompromised and have a poor PS due to age and/or comorbidities. In addition, the ESC noted that immunosuppression is a risk factor for more aggressive CSCC and is associated with poorer treatment outcomes. As such, the ESC considered the importance of inclusion of PS and immune-status in the cemiplimab restriction may be greater than for other indications. The ESC considered that PBS subsidisation of cemiplimab for immunocompromised patients may be more appropriate once evidence from current trials recruiting such patients are available.*

3.4 Of note, the restriction criteria for the initial treatment did not clearly indicate that patients with mCSCC should not be eligible for curative radiation or curative surgery. In clinical practice, patients with metastatic disease to lymph nodes (without distant

* Cemiplimab-rwlc for Unresectable Locally Recurrent and/or Metastatic CSCCv. Available from: <https://clinicaltrials.gov/ct2/show/NCT04242173>

metastasis) could be eligible for curative surgery or curative radiation[†]. Cemiplimab was not proposed to replace curative therapies in this subpopulation.

- 3.5 The ESC considered that the restriction should clarify if the decision regarding whether a patient is a candidate for curative radiation or surgery could be made based on the clinical opinion of an individual physician or required the consensus of a multidisciplinary team. The ESC considered that the risk of use outside the intended PBS population was high with decision making around the curative radiation or surgery criteria likely to see the use of cemiplimab earlier than intended in the treatment algorithm.
- 3.6 The efficacy and safety data from the 1423 and the 1540 studies were derived mainly from the weight-based dose regimen (3mg/kg intravenous every 2 weeks (Q2W)) groups (study 1423, group 1 and group 2 of study 1540; 74% of the studies' populations), while the recommended dose (350mg intravenous every 3 weeks) was derived from group 3 in study 1540 (26% of the whole cemiplimab studies population) who received a fixed-dose regimen (350mg intravenous every 3 weeks (Q3W)).
- 3.7 The ESC noted that the TGA, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have accepted the fixed-dose (350mg intravenous Q3W) to be as efficacious and safe as the weight-based alternative. This was based on pharmacokinetic analysis which showed that the concentration time profiles of the two dosing regimens were similar.
- 3.8 Consistent with Study 1540, the submission proposed that treatment should be restricted to no more than 24 months. However, the Product Information does not restrict use to 24 months and instead states that treatment may be continued until disease progression or unacceptable toxicity.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Cutaneous malignancies (skin cancer) account for the largest proportion of all human cancers and encompass melanoma and non-melanoma skin cancer. Cutaneous squamous cell carcinoma (CSCC) accounts for approximately 20-30% of non-melanoma skin cancer. CSCC is commonly found in sun-exposed parts of the body and on sites that were previously scarred or sites of chronic ulcerations. Another important risk factor for CSCC is having prolonged immunosuppression. Immunosuppressed CSCC patients have a worse outcome with a higher risk of

[†] Cancer Council Australia (CCA). Clinical practice guidelines for keratinocyte cancer. 2019; Available from: https://wiki.cancer.org.au/australia/Guidelines:Keratinocyte_carcinoma.

developing loco-regional recurrence, and a higher risk of death compared to immunocompetent patients.

- 4.2 In less than 5% of patients with CSCC, the condition can progress to an advanced stage, either by not being eligible for curative surgery or radiation treatment (laCSCC) or by having metastatic disease (mCSCC). Advanced stage CSCC is associated with reduced overall survival and with large and wide spread lesions that can interfere with essential functions and may have a disfiguring effect, which cumulatively reduces the patients' quality of life (QoL).
- 4.3 Non-melanoma skin cancer, including CSCC, is the most common cancer in Australia. The incidence of CSCC in Australia is the highest worldwide, being around 100 fold more compared to northern European countries.
- 4.4 The population proposed for treatment with cemiplimab is patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation. The ESC considered there to be a high unmet clinical need in this population. The ESC noted that the National Cancer Comprehensive Network (NCCN) guidelines[†] include reference to cemiplimab for this indication.
- 4.5 Cemiplimab is a fully recombinant human immunoglobulin G4 monoclonal antibody that targets the programmed death 1 (PD-1) receptor and is part of the pharmacologic class of PD-1 blocking antibodies. Cemiplimab blocks the interaction of PD-1 with its ligands PD-L1 and PD-L2 which potentiates T-cell responses, including anti-tumour responses.
- 4.6 The recommended dose of cemiplimab is 350mg administered as an intravenous infusion over 30 minutes Q3W until symptomatic disease progression or unacceptable toxicity.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated best supportive care (BSC), with or without chemotherapy (CT), as the main comparator.
- 5.2 The main arguments provided in support of the nomination of the comparator were:

[†] National Comprehensive Cancer Network (NCCN) - Version 2. Squamous Cell Skin Cancer 2020 [20 July 2020]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf.

- There are no available treatment options registered by the TGA or listed on the PBS for patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation;
 - BSC consists of palliative surgery or palliative radiotherapy and/or symptomatic management;
 - The chemotherapeutic options in Australia include platinum and non-platinum-based chemotherapy regimens, with no standard regimen listed;
 - Based on an advisory board advice (as per the submission), around 80% of patients with advanced CSCC in Australia are treated with BSC, while only 20% are treated with chemotherapy. The ESC noted that no Australian data were presented in the submission to support the advice of the advisory board.
- 5.3 The ESC considered the nominated comparator was reasonable due to the lack of a standard of care in this setting.
- 5.4 The submission nominated pembrolizumab (another antibody that targets PD-1 receptor) as a potential near market comparator based on recent FDA approval for the use of pembrolizumab in patients with recurrent or mCSCC. Data on pembrolizumab were derived from three ongoing phase II clinical studies. A naïve indirect comparison between cemiplimab and pembrolizumab suggested that ORR with cemiplimab and pembrolizumab were similar. Formal comparison of OS and PFS was not possible as the Kaplan-Meier curves were not reported for the pembrolizumab studies.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician presented clinical case studies, discussed the natural history of the disease and how the drug would be used in practice. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this disease.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (7), health care professionals (19) and organisations (4) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with cemiplimab including addressing an unmet need in these patients with a poor prognosis and improving their quality of life by reducing the disfiguring complications of this disease. The comments also described a reduction in side effects with cemiplimab when compared with chemotherapy.

- 6.3 The PBAC noted the advice received from the Australian College of Dermatologists clarifying the likely use of cemiplimab in clinical practice and suggesting that use may reduce the need for hospitalisations and other less expensive therapies if disease recurrence was reduced.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the cemiplimab submission, categorising it as one of the therapies of “highest priority for PBS listing” on the basis of Study 1540. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for cemiplimab, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement).⁵

Clinical Studies

- 6.5 The submission was based on a naïve indirect comparison between the key studies that represent the use of cemiplimab in laCSCC and/or mCSCC (study 1423 and study 1540) and a total of seven retrospective cohort studies that represent current clinical management of laCSCC and mCSCC:
- Sun et al and Amaral et al representing BSC;
 - Jarkowski et al, Chapalain et al, and Ogata et al representing chemotherapy;
 - Two studies included for sensitivity analysis (Zhu and Chang) and descriptive analysis (Hillen et al).
- 6.6 Cemiplimab: Study 1423 (phase I) and 1540 (phase II single arm) included adult patients with a confirmed diagnosis of laCSCC or mCSCC. Patients included in these studies were not candidates for curative surgery (in study 1423 and study 1540) or curative radiation therapy (only in 1540 study; no relevant criteria mentioned in study 1423).
- All patients included in these studies were immunocompetent (IC), with PS of 0-1 on the Eastern Cooperative Oncology Group (ECOG) scale.
 - All patients enrolled in study 1423 (expansion cohort 7 and 8) and patients in group 1 (mCSCC) and group 2 (laCSCC) in study 1540 received cemiplimab in dose of 3mg/kg intravenous Q2W, while patients in group 3 (mCSCC) in study 1540 received cemiplimab in fixed-dose (350mg intravenous Q3W).
 - Median duration of treatment was 8.27 months and 11.76 months in study 1423 and study 1540 respectively.
- 6.7 All the included BSC and chemotherapy studies were conducted outside Australia and included a variety of treatment regimens (including cetuximab which is not listed in Australia for treating the proposed target patient population). As will be discussed

⁵ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

Public Summary Document – November 2020 PBAC Meeting

in paragraph 6.11, there was significant heterogeneity in patients' characteristics, disease characteristics, duration of treatment and follow up which raised important transitivity concerns.

- 6.8 Publication details of the studies presented in the submission are provided in the table below.

Public Summary Document – November 2020 PBAC Meeting

Table 2: Studies and associated reports presented in the submission

Study ID	Protocol title/ Publication title	Publication citation
Cemiplimab		
Study 1423	A First-in-Human Study of Repeat Dosing with REGN2810, a Monoclonal, Fully Human Antibody to Programmed Death – 1 (PD-1), as Single Therapy and in Combination with Other Anti-Cancer Therapies, in Patients with Advanced Malignancies. Data cut-off for CSCC 2 October 2017	April 2019
	Migden MR, Rischin D, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma.	New England Journal of Medicine 37(4): 341-351.
Study 1540	A Phase 2 Study of REGN2810, a fully human monoclonal antibody to Programmed Death-1 (PD-1), in patients with advanced cutaneous squamous cell carcinoma. Data cut-off for Groups 1 and 3 was 20 September 2018 and for Group 2 was 10 October 2018.	October 2019
	Migden, Rischin D, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous cell carcinoma.	New England Journal of Medicine 37(4): 341-351
	Migden MR, Khushalani NI, et al. Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single-arm study.	Lancet Oncology 2020 Feb;21(2):294-305
Best supportive care studies		
Sun et al (2019)	Sun L, Chin RI, et al. Association of disease recurrence with survival outcomes in patients with cutaneous squamous cell carcinoma of the head and neck treated with multimodality therapy.	JAMA Dermatology 2019; 155(4):442-447.
Amaral et al (2019)	Amaral T, Osewold M, et al. Advanced cutaneous squamous cell carcinoma: real world data of patient profiles and treatment patterns.	Journal of the European Academy of Dermatology and Venereology 2019; 33(S8):44-51.
Zhu and Chang (2015)	Zhu GA and Chang ALS. Overall and progression-free survival of stage 4 cutaneous squamous cell carcinoma at a single large referral centre	Journal of the American Academy of Dermatology 2015; 73(1):165-166.
Hillen et al (2018)	Hillen U, Leiter U, et al. Advanced cutaneous squamous cell carcinoma: A retrospective analysis of patient profiles and treatment patterns—Results of a non-interventional study of the DeCOG	European Journal of Cancer 2018; 96:34-43.
Chemotherapy studies		
Jarkowski et al (2016)	Jarkowski A, Hare R, et al. Systemic Therapy in Advanced Cutaneous Squamous Cell Carcinoma (CSCC): The Roswell Park Experience and a Review of the Literature.	American Journal of Clinical Oncology: Cancer Clinical Studies 2016; 39(6):545-548.
Chapalain et al (2019)	Chapalain M, Baroudjian B, et al. Stage IV cutaneous squamous cell carcinoma: treatment outcomes in a series of 42 patients.	Journal of the European Academy of Dermatology and Venereology 2019 Oct 6.
Ogata et al (2020)	Ogata D, Namikawa K, et al. Systemic treatment of patients with advanced cutaneous squamous cell carcinoma: response rates and outcomes of the regimes used.	European Journal of Cancer 2020; 127:108-117.
Hillen et al (2018)	Hillen U, Leiter U, et al. Advanced cutaneous squamous cell carcinoma: A retrospective analysis of patient profiles and treatment patterns—Results of a non-interventional study of the DeCOG	European Journal of Cancer 2018; 96:34-43.

Source: Table 2.2.1, p40, Table 2.2.4, p45 and Table 2.2.7, p50 of the submission

6.9 The key features of the included evidence are summarised in the table below.

Table 3: Key features of the included evidence – Naïve indirect comparison

Studies	N	Design/ duration	Risk of bias*	Patient population	Outcomes	Use in modelled evaluation
Cemiplimab studies						
Study 1423	26	Phase I single arm, 31.7 months	High	laCSCC/ mCSCC, not candidate for curative surgery or radiation therapy	Safety, tolerability, ORR, DOR, OS, PFS	Used
Study 1540	193	Phase II single arm, 15.7 months	High	laCSCC/ mCSCC, not candidate for curative surgery or radiation therapy	ORR, DOR, OS, PFS and safety	Used
BSC studies						
Sun et al	72	Retrospective study, NR	High	CSCC with loco-regional or distant recurrence after surgery and postoperative RT	OS	Used
Amaral et al	195	Retrospective study, 21 months	High	Stage III or IV CSCC, not candidate for curative surgery	OS	Used
Zhu and Chang	36	Retrospective study, 22 months	High	Stage IV CSCC	PFS, OS	Not used
Hillen et al	190	Retrospective study, NR	High	laCSCC/ mCSCC, not candidate for curative surgery or radiation therapy	OS	Not used
Chemotherapy studies						
Jarkowski et al	25	Retrospective study, 42.8 months	High	laCSCC, not candidate for curative surgery; and mCSCC	ORR, PFS, OS	Used
Chapalain et al	42	Retrospective study, 18.6 months	High	Stage IV CSCC	ORR, PFS, OS and safety	Used
Ogata et al	130	Retrospective study, NR	High	Advanced CSCC, not candidate for surgery or radiotherapy	ORR, PFS, OS and safety	Used

Source: Section 2.3 and 2.4 of the submission

CSCC= cutaneous squamous cell carcinoma; DOR= duration of response; laCSCC = locally advanced cutaneous squamous cell carcinoma; mCSCC = metastatic cutaneous squamous cell carcinoma, NR= not reported; ORR= objective response rate; OS= overall survival; PFS= progression free survival; RT= radiation therapy

*Risk of bias for the naïve indirect comparison using ROBINS-I tool

6.10 The evidence of cemiplimab effectiveness and safety was based on a naïve indirect comparison with no formal statistical analyses conducted. No meta-analysis was presented in the submission. The lack of a common reference arm or an adjustment for prognostic differences between the study arms means that there were important transitivity concerns with the studies being indirectly compared which will have affected the estimated incremental differences between the two treatment modalities.

6.11 The most important transitivity concerns can be summarised as follows:

- PS was not reported in any of the BSC studies nor in Jarkowski et al. However, Chapalain et al, Ogata et al and Hillen et al included patients with a PS of 2 or more (7%, 19% and 11% respectively). All patients in the cemiplimab studies had a PS \leq 1.
- None of the cemiplimab studies included immunosuppressed patients, however, 55.6% of Sun et al, 23.6% of Amaral et al, 25% of Zhu and Chang, 31% of Chapalain et al and 1.5% of Ogata et al were immunosuppressed. Of note, Hillen et al and Jarkowski et al did not report the patients' immune-status. Only Sun et al reported the results by the immune-status.
- The percentage of patients with mCSCC disease in Sun et al, Amaral et al and Zhu and Chang was not reported. From the available information, there were more patients with mCSCC in the chemotherapy studies compared to the cemiplimab studies (pooled data: 88.8% in chemotherapy studies (175/197) versus 59.8% in cemiplimab studies (131/219)).
- There were differences in the duration of follow-up between studies, in addition to not having the duration of follow-up reported in Sun et al and Ogata et al.
- The definition of the OS duration was not consistent across the included studies; while the cemiplimab studies, Jarkowski et al, Chapalain et al and Ogata et al defined the survival duration from the start of treatment, Sun et al, Amaral et al defined the survival duration from the time of diagnosis of stage IV or advanced stage. This means that a pooled estimate of median OS will be unreliable if there is an appreciable delay between diagnosis and the commencement of treatment.

6.12 Most of the heterogeneity in the baseline patient characteristics favours cemiplimab. Overall, the interpretation of the indirect comparison results is very difficult and liable to bias, and thus the magnitude of the difference in effectiveness cannot be estimated. The PSCR acknowledged the transitivity and heterogeneity issues identified and argued that the submission had presented the totality of the clinical evidence for BSC \pm CT and included sensitivity analyses. The ESC noted the transitivity concerns outlined in paragraph 6.11 and considered that the evidence used to inform the comparator group were prone to significant bias noting that it was heterogeneous in its construction and not necessarily generalisable to the Australian population. The ESC agreed with the evaluation that the heterogeneity in the baseline patient characteristics favoured cemiplimab and limited the validity of the indirect comparison as described. The pre-PBAC response argued that patients enrolled in the cemiplimab studies had extensive prior treatment with surgery, radiation and/or systemic therapy. In contrast, the pre-PBAC response argued that all patients in the BSC studies included patients at the point of the CSCC becoming unresectable and the chemotherapy studies included patients without any prior

chemotherapy at baseline. As such the pre-PBAC response argued that the naïve indirect comparisons favoured BSC ± CT.

Comparative effectiveness

- 6.13 Three naïve indirect comparisons were presented in the submission; cemiplimab versus BSC studies only, cemiplimab versus chemotherapy studies only and, cemiplimab versus pooled data from BSC ± CT studies.
- 6.14 To inform the naïve indirect comparison, individual patient data (IPD) were provided from the Phase I (April 20th, 2019 data cut off) and Phase II (Oct 11th, 2019 data cut off) cemiplimab trials. The IPD were included in the analysis. The BSC and chemotherapy studies only had aggregate study-level information available. The pooled OS and PFS were reported for the BSC and chemotherapy studies. The Kaplan-Meier (KM) curves for each treatment arm from each study was digitized using Digitizeit (<http://www.digitizeit.de/>). Then the algorithm proposed by Guyot et** al. 2011^{††} was applied to reconstruct IPD.
- 6.15 The estimated effectiveness of cemiplimab was based mainly on the naïve indirect comparison between pooled data from the cemiplimab studies and pooled data from retrospective studies that represented current clinical management (BSC ± CT) of the target population. Information on the outcomes presented for each treatment arm are given in the following table.

Table 4: Naïve indirect comparison - Analysis of OS, PFS and ORR

	OS	PFS	ORR
Cemiplimab studies			
Study 1423	✓	✓	✓
Study 1540	✓	✓	✓
BSC studies			
Sun et al (2019), unresectable subgroup – IC	✓	NR	NR
Amaral et al (2019), unresectable subgroup	✓	NR	NR
Zhu and Chang (2015)	×	×	×
Chemotherapy studies			
Jarkowski et al (2016), pooled platinum-based and non-platinum-based chemotherapy	✓	✓	✓
Chapalain et al (2019), full cohort from first line treatment	✓	✓	✓
Ogata et al (2020), pooled platinum-based and non-platinum-based chemotherapy	✓	✓	✓
Hillen et al (2018), chemotherapy group	NR	NR	✓

Source: Table 1, p179 of the submission

IC= immunocompetent; NR = not reported in study; ORR= objective response rate; OS = overall survival; PFS = progression-free survival
 ✓ = included in analysis; × = excluded from analysis

- 6.16 The below table summarises the main results of the cemiplimab studies.

** Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol.* 2012;12:9.

Public Summary Document – November 2020 PBAC Meeting

Table 5: Results of the cemiplimab studies

Proportion of patients, n (%)	Study 1423 N= 26	Study 1540 N= 193	Pooled data N= 219
Best overall tumour response			
CR ^a	0	31 (16.1)	31 (14.2)
PR ^a	13 (50.0)	58 (30.1)	71 (32.4)
Response			
ORR (CR + PR)	13 (50.0)	89 (46.1)	102 (46.6)
95% CI ^b	29.9, 70.1	(38.9, 53.4)	-
DCR (CR + PR + SD + Non CR/non PD)	20 (76.9)	31 (16.1)	51 (23.3)
95% CI ^b	(56.4, 91.0)	(11.2, 22.0)	-
Durable DCR ^c	17 (65.4)	117 (60.6)	134 (61.2)
95% CI ^b	(44.3, 82.8)	(53.3, 67.6)	-
Duration of response			
N	13	89	102
Number of events, n (%) ^d	2 (15.4)	22 (24.7)	24 (23.5)
Median (95% CI), months	20.3 (NE, NE)	NR (28.8, NE)	-
Observed DOR, n (%) ^e			
≥6 months	11 (84.6)	81 (91.0)	92 (90.2)
≥12 months	9 (69.2)	65 (73.0)	74 (72.5)
≥24 months	0	22 (24.7)	22 (21.6)
PFS			
Number of events, n (%)	12 (46.2)	97 (50.3)	109 (49.8)
Months, median (95% CI)	22.0 (5.4, 31.4)	18.4 (10.3, 24.3)	18.40 (13.00, 26.00)
Estimated event free probability, % (95% CI)			
6 months	71.8 (49.7, 85.5)	66.4 (58.9, 72.8)	-
12 months	67.3 (45.0, 82.2)	55.3 (47.6, 62.4)	56.8 (50.3, 64.2)
24 months	25.2 (1.8, 62.4)	44.2 (36.1, 52.1)	44.1 (37.0, 52.6)
OS			
Number of events, n (%)	9 (34.6)	52 (26.9)	61 (27.9)
Months, median (95% CI)	NR (16.2, NE)	NR (NE, NE)	NE
Estimated probability of survival, % (95% CI)			
6 months	88.0 (67.1, 96.0)	88.9 (83.5, 92.6)	-
12 months	83.3 (61.3, 93.4)	82.8 (76.6, 87.6)	82.9 (77.9, 88.2)
24 months	60.2 (37.2, 77.0)	73.3 (66.1, 79.2)	71.6 (65.6, 78.2)
48 months	NE (NE, NE)	-	-

Source: Constructed during the evaluation using data from Table 2.5.1, p85, Table 2.5.8, p93, Table 2.5.3, p87, Table 2.5.11, p96, Table 2.5.5, p89, Table 2.5.13, p97, Table 2.5.6, p911 and Table 2.5.14, p98 of the submission.

CI = confidence interval; CR = complete response; DCR = disease control rate, DOR = duration of response; NE = not evaluable; ORR = objective response rate; OS = overall survival; PD = progressive disease; PR = partial response; PFS= progression free survival
a CR/PR must be confirmed by repeated assessments no less than 4 weeks apart.

b Clopper-Pearson exact confidence interval.

c Durable DCR: proportion of patients with CR, PR, or SD for at least 105 days without PD

d Events include progressive disease or deaths. Percentages are based on number of patients with confirmed CR or PR.

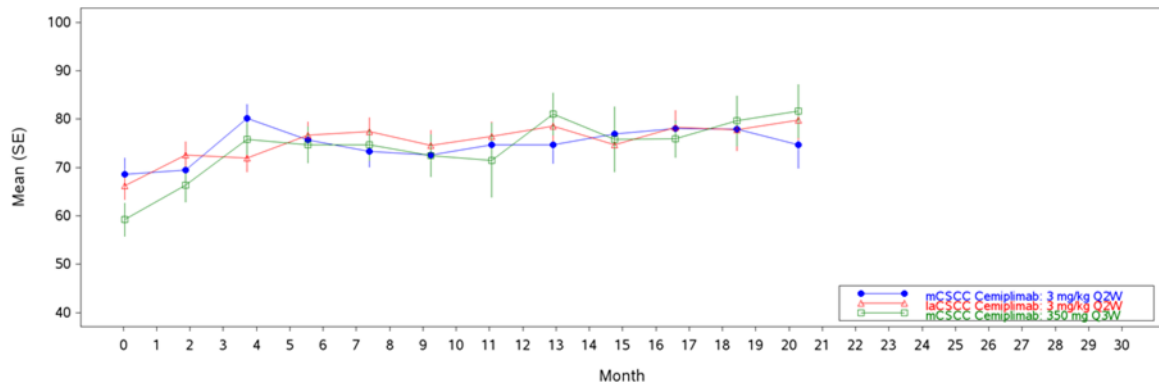
e Percentages are based on number of patients with confirmed CR or PR. The numerator includes the number of patients whose observed duration of response reached at least the specified time. Patients who did not have the opportunity to reach the specified time point were

6.17 Overall, pooled data from the cemiplimab studies showed an ORR of 46.6% with a 14.2% CR rate. The median PFS was 18.4 months, with 57% and 44% of the patients being event free at 12 and 24 months respectively. The median OS was not reached for the cemiplimab studies. Pooled data reported 82.9% and 71.6% of the patients were alive at one and two years respectively. The ESC considered the OS data for cemiplimab to be immature thus limiting interpretation. The pre-PBAC response

stated that more mature data will not be available until late 2022. The PBAC noted that a Phase II study expected to recruit 433 participants is currently being conducted, although completion is not expected until 2025.**

6.18 Study 1540 provided patient reported outcomes which were evaluated using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C30). Overall, mean scores for the five functional status scales and the global health status scale indicated that patients reported moderate to high levels of functioning and health-related quality of life at baseline. Similarly, patients reported low symptom scores across the symptom scales/items, indicating a minimal symptomatic burden at baseline. Over time, the mean change from baseline in global health status/ health-related quality of life (HRQoL) scores indicate a trend towards improvement, with changes ranging from 4.17 (SD: 19.95) and 15.25 (SD: 22.65) in the overall population (Figure 1). There was a statistically and clinically meaningful improvement (change of ≥ 10 points) in pain score by the 3rd treatment cycle. These results should be interpreted in the context that the majority of the patients had a low symptom burden at baseline. Thus the effect of cemiplimab treatment on the QoL in patients with a high symptom burden is unknown.

Figure 1: Longitudinal plots of global health status/quality of life in the EORTC QLQ-C30



Number of Subjects	0	2	4	6	8	10	12	14	16	18	20
mCSCC Cemiplimab: 3 mg/kg Q2W 44	42	37	36	36	31	32	29	26	27	25	24
laCSCC Cemiplimab: 3 mg/kg Q2W 68	60	55	39	41	44	40	33	29	23	18	14
mCSCC Cemiplimab: 350 mg Q3W 38	34	30	29	27	26	12	11	10	9	9	5

Source: Figure 2.5.11, p108 of the submission

CSCC = cutaneous squamous cell carcinoma; laCSCC = locally advanced cutaneous squamous cell carcinoma; mCSCC = metastatic cutaneous squamous cell carcinoma; Q2W = every 2 weeks; Q3W = every 3 weeks; SE = standard error

6.19 The PBAC noted that tumour response by PD-L1 expression status was an exploratory outcome for study 1540. Pre-treatment tumour samples were available for PD-L1 immunohistochemistry testing in 48 of 78 (61.5%) patients in Group 2. Of these patients, 17 were PD-L1 negative (i.e. <1%) and 31 were PD-L1 positive (i.e.

** Study of REGN2810 in Patients With Advanced Cutaneous Squamous Cell Carcinoma <https://clinicaltrials.gov/ct2/show/NCT02760498>

≥1%). The PBAC noted that overall, the ORR and CR rates were numerically higher among patients with PD-L1 ≥1% compared to patients with PD-L1<1% (58% and 13% in PD-L1≥1% and 35% and 6% in PD-L1<1% respectively). However, the CIs were overlapping. As the analysis was not pre-planned and because of the small sample size, the PBAC considered that a larger dataset is required to confirm that PD-L1 expression is not predictive of efficacy. The PBAC noted that further data exploring this issue is due in March 2023 (see paragraph 2.1).

- 6.20 The table below summarises the indirect comparison of the cemiplimab studies with each of the BSC studies and with the chemotherapy studies, respectively, in terms of OS.

Table 6: Summary of OS results of the cemiplimab studies compared to each of the BSC studies and the chemotherapy studies

	Pooled cemiplimab trials	Base case analysis	
		Pooled BSC studies*	Pooled chemotherapy studies**
Patients, n	219	70	197
Cemiplimab versus comparator			
Hazard ratio (95% CI)#	-	0.30 (0.20, 0.45)	0.34 (0.25, 0.46)
OS rate			
12 months, % (95% CI)	82.9 (77.9, 88.2)	55.0 (43.9, 68.8)	62.4 (55.9, 69.6)
24 months, % (95% CI)	71.6 (65.6, 78.2)	38.3 (27.3, 53.7)	33.1 (27.0, 40.6)
Median OS			
Months (95% CI)	NE	13.08 (7.33, 24.08)	15.2 (13.6, 18.3)

Source: Table 2.6.6, p124 and Table 2(a).6.2, p218 of the submission

CI = confidence interval; NE = not estimable; OS = overall survival

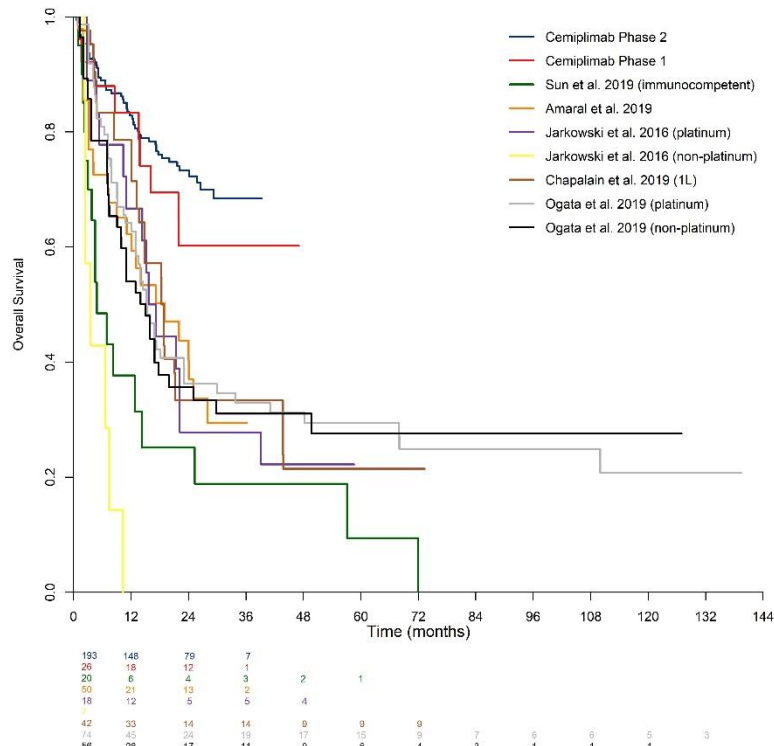
#the time point at which the hazard ratio (HR) was estimated could not be located in the submission

*BSC studies included in the base case analysis: Sun et al (unresectable immunocompetent group) and Amaral et al (unresectable group)

**Chemotherapy studies included in the base case analysis: Jarkowski et al (pooled platinum and non-platinum based), Chapalain et al (full cohort from first line treatment) and Ogata et al (pooled platinum and non-platinum based)

- 6.21 The PSCR stated that OS for patients who were treated with chemotherapy was similar to that of those who were treated predominantly with BSC (Figure 2).

Figure 2. Kaplan-Meier curves for OS for the individual cemiplimab trials, BSC studies, and chemotherapy studies included in the base case



Source: Figure 1, p 5 PSCR

Abbreviations: BSC = best supportive care; OS = overall survival

6.22 Regarding the indirect comparison between the pooled data from the cemiplimab studies versus the pooled data from BSC ± CT studies (Table 7):

- The median OS from the pooled cemiplimab studies was not reached, with 83% and 72% survival reported at one and two years, respectively.
- Based on the naïve indirect comparison, cemiplimab led to a 67% reduction in the risk of death compared to the pooled BSC ± CT studies, although the time point at which the hazard ratio was estimated could not be located in the submission.

Table 7: Naïve indirect comparison (cemiplimab vs pooled BSC and chemotherapy studies) – OS results

Event	Cemiplimab*	Base case pooled BSC + CT**	Absolute Difference	HR (95% CI)#
Median OS (95% CI) months	NE	14.8 (13.1, 17.3)	NE	0.33 (0.25, 0.44)
% Alive at 12 months (95% CI)	82.9 (77.9, 88.2)	60.4 (54.7, 66.7)	22.3%	-----
% Alive at 24 months (95% CI)	71.6 (65.6, 78.2)	33.9 (28.4, 40.4)	37.7%	-----

Source: Table 2.6.9, p134 of the submission

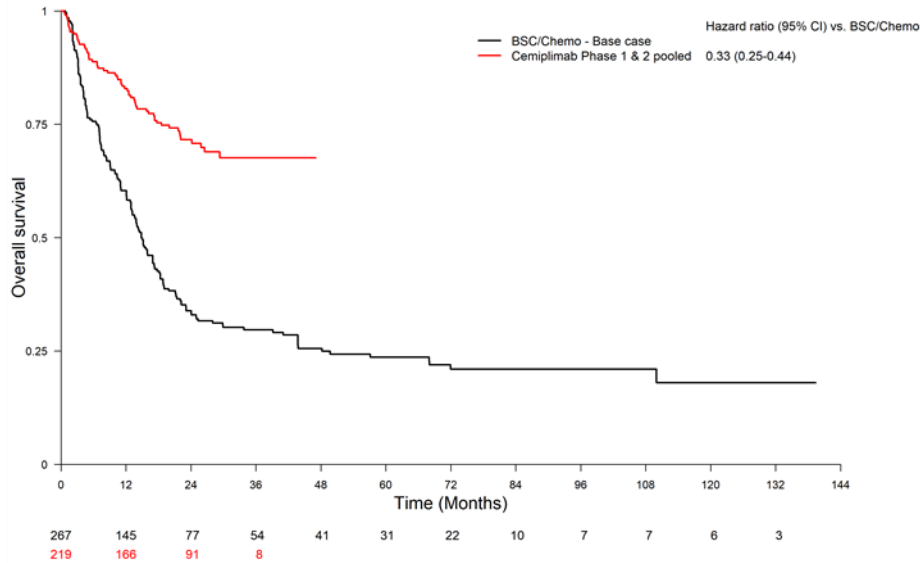
BSC = best supportive care; CI = confidence interval; CT= chemotherapy; NE = not estimable; NR= not reported; OS = overall survival

*Cemiplimab pooled data included study 1423 and study 1540

**Base case analysis included: the unresectable immunocompetent group of Sun et al, Amaral et al unresectable group and the three chemotherapy studies (Jarkowski et al, Chapalain et al and Ogata et al)

#the time point at which the hazard ratio (HR) was estimated could not be located in the submission

Figure 3: Cemiplimab versus pooled BSC + CT – overall survival estimates from naïve indirect comparison



Source: Figure 2.6.16, p137 of the submission

BSC = best supportive care; CI = confidence interval; OS = overall survival

BSC/Chemo included Study 1423 (cemiplimab Phase I); Study 1540 (cemiplimab) Phase II; unresectable, immunocompetent subgroup of Sun et al; unresectable subgroup of Amaral et al; Jarkowski et al (platinum-based and non-platinum-based chemotherapy), Ogata et al (platinum-based and non-platinum-based chemotherapy), and Chapalain et al (measured from start of first-line treatment).

6.23 The PSCR argued that although median OS has not been reached for cemiplimab, there was clear separation between the cemiplimab and comparator Kaplan-Meier (KM) curves of OS within the first few months of treatment in the base case analysis of OS which pooled all the KM curves for the individual BSC studies and chemotherapy studies. Furthermore, the PSCR stated that despite the immature data, the clinical evidence from Study 1423 and Study 1540 clearly demonstrate that cemiplimab offers a significant improvement in OS even when accounting for the uncertainties arising from the naïve comparison. The ESC reiterated that the heterogeneity in the baseline patient characteristics across the studies included in the base case compromised the validity of the indirect comparison and that this was further complicated by the immaturity of the cemiplimab OS data.

6.24 The median PFS of the pooled cemiplimab studies was 18.4 months, with PFS rates of 57% and 44% at one and two years respectively. The median PFS in the base case analysis of the pooled chemotherapy studies (as none of the BSC studies reported PFS) was 4.9 months. Based on this it was estimated that cemiplimab led to 47% reduction in risk of progression compared to chemotherapy.

Table 8: Naïve indirect comparison (cemiplimab vs CT) – PFS analysis

Event	Cemiplimab*	Base case pooled CT**	Absolute Difference	HR (95% CI)#
Median PFS (95% CI) months	18.4 (13.0, 26.0)	4.92 (4.22, 6.37)	13.5 months	0.53 (0.41, 0.68)
PFS rate at 12 months (95% CI)	56.8 (50.3, 64.2)	30.4 (24.5, 37.7)	26.4%	-----
PFS rate at 24 months (95% CI)	44.1 (37.0, 52.6)	19.5 (14.5, 26.2)	24.6%	-----

Source: Table 2.6.12, p144 of the submission

CI = confidence interval; CT= chemotherapy; NE= not estimated; NR= not reported; PFS = progression-free survival

*Cemiplimab pooled data included study 1423 and study 1540

**Base case analysis included: the three chemotherapy studies (Jarkowski et al, Chapalain et al and Ogata et al)

#the time point at which the hazard ratio (HR) was estimated could not be located in the submission

- 6.25 The ESC noted that CSCC is a disfiguring disease and considered the lack of an observed difference in the ORR between the cemiplimab and chemotherapy studies to be of clinical relevance.
- 6.26 Despite the lack of difference in ORR, the submission claimed that the observed PFS benefit was due to a longer duration of response with cemiplimab. Not all the chemotherapy studies reported the duration of response and thus there are uncertainties when interpreting this claim. ORR rates are not applicable in observational BSC studies.

Table 9: Naïve indirect comparison (cemiplimab vs chemotherapy) - Tumour response

Proportion of patients, n (%)	Pooled cemiplimab* N = 219	Pooled chemotherapy** N = 211	Cemiplimab vs chemotherapy		
			RR (95% CI)	RD (95% CI)	OR (95% CI)
ORR (CR + PR)	102 (46.6)	103 (45.3)	1.02 (0.84, 1.25)	0.01 (-0.08, 0.10)	1.05 (0.72, 1.52)
CR	31 (14.2)	34 (14.9)	0.94 (0.60, 1.48)	-0.01(-0.07, 0.06)	0.93 (0.55, 1.58)
PR	71 (32.4)	70 (30.8)	1.06 (0.81, 1.40)	0.02 (-0.07, 0.11)	1.09 (0.73, 1.63)

Source: Table 2(a).6.7, p224 of the submission

CI = confidence interval; CR = complete response; OR = odds ratio; ORR = objective response rate; PR = partial response; RD = risk difference; RR = relative risk

*Cemiplimab pooled data included study 1423 and study 1540

**Base case analysis included: the three chemotherapy studies (Jarkowski et al, Chapalain et al and Ogata et al)

- 6.27 Only study 1540 reported QoL (paragraph 6.14). No other studies presented in the submission reported on QoL; thus, an indirect comparison of cemiplimab versus BSC ± CT cannot be performed for this outcome.
- 6.28 The PSCR argued that to address transitivity concerns population-adjusted comparisons were also presented using both a simulated treatment comparison (STC) and matching adjusted indirect comparison (MAIC) approach. For both these analyses, two different models were constructed with different sets of prognostic factors as covariates:

- Core model: immune status (note 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: same as the core model but also included gender, performance score, prior systemic therapy, and prior radiotherapy.

The PSCR argued that although these analyses were limited by the information on patient characteristics reported in the comparator publications, the results confirm that cemiplimab is associated with superior OS compared to BSC ± CT (Table 10). The ESC noted the hazard ratios for cemiplimab versus BSC studies were more favourable than those for chemotherapy and varied widely for the chemotherapy comparisons depending on whether a STC or MAIC approach was used (e.g. OS HR was 0.45 for STC and 0.80 for MAIC). However, the ESC agreed that the population-adjusted comparisons were limited by the published information available and noted that missing information included duration of treatment and duration of follow-up. In addition, the ESC noted that there were differences in how the OS duration was defined among different studies. The ESC considered that the impact of these factors on the observed treatment effect of cemiplimab compared with BSC ± CT cannot be estimated and, thus, the extent of clinical benefit of cemiplimab for treatment of advanced CSCC is difficult to determine from these population-adjusted comparisons. Hence, the ESC considered that the transitivity concerns with the indirect comparison remain.

Table 10 Overall survival results of the STC and MAIC using the core model and extended model

	Core model	Extended model
	Base case	Base case
Cemiplimab versus BSC studies		
STC HR (95% CI)	0.15 (0.08, 0.26)	0.23 (0.13, 0.41)
MAIC HR (95% CI)	0.15 (0.08, 0.26)	0.21 (0.12, 0.37)
Cemiplimab vs chemotherapy studies		
STC HR (95% CI)	0.45 (0.34, 0.59)	0.33 (0.25, 0.44)
MAIC HR (95% CI)	0.80 (0.62, 1.03)	0.70 (0.54, 0.92)
Cemiplimab vs pooled BSC and chemotherapy studies		
STC HR (95% CI)	0.41 (0.31, 0.53)	0.36 (0.28, 0.48)
MAIC HR (95% CI)	0.69 (0.54, 0.89)	0.41 (0.31, 0.54)

Source: Table 2 p2, Table 3 p3 Appendix 12 of the submission. Abbreviations: BSC = best supportive care; CI = confidence interval; HR = hazard ratio; MAIC = matching adjusted indirect comparison; OS = overall survival; STC = simulated treatment comparison

Comparative harms

- 6.29 Within the cemiplimab studies (study 1423 and 1540), comparable rates were observed in terms of any grade treatment emergent adverse event (TEAE), grade ≥ 3 TEAE and adverse events of special interest. There were numerically higher treatment related adverse events, serious TEAE, and treatment emergent immune related adverse events in study 1540 compared to study 1423. More patients in

study 1540 (38.9%) had TEAE leading to treatment interruption compared to study 1423 (19.2%).

- 6.30 None of the BSC studies reported adverse events. The comparison in safety was only presented between cemiplimab studies and the chemotherapy studies. There were more grade ≥ 3 adverse events with cemiplimab compared to chemotherapy. However, the risk of developing diarrhoea, leukopenia and neutropenia was less.

Table 11: Comparison of adverse events for cemiplimab versus chemotherapy

	Pooled cemiplimab N = 219	Pooled chemotherapy N = 172	RR (95% CI)	RD (95% CI)	OR (95% CI)
Any AE	218 (99.5)	139 (80.8)	1.23 (1.15, 1.33)	0.19 (0.13, 0.25)	104 (6.32, 1711)
Grade 3-5/3-4 AE	106 (48.4)	44 (25.6)	1.89 (1.42, 2.53)	0.23 (0.14, 0.32)	2.73 (1.77, 4.21)
Treatment related	164 (74.9)	NR	NE	NE	NE
Serious TEAE	80 (36.5)	NR	NE	NE	NE
TEAE leading to discontinuation	21 (9.6)	NR	NE	NE	NE
Diarrhoea	2 (0.9)	n = 42 [#] 3 (7.1)	0.13 (0.02, 0.74)	-0.06 (-0.14, -0.02)	0.12 (0.01, 1.10)
Pneumonitis	n = 193* 5 (2.6)	2 (1.2)	2.23 (0.44, 11.34)	0.01 (-0.01, 0.04)	2.26 (0.43, 11.81)
Neutrophil count decreased	1 (0.5)	n = 130^ 14 (10.8)	0.04 (0.01, 0.32)	-0.10 (-0.16, -0.05)	0.04 (0, 0.29)
White blood cell count decreased	1 (0.5)	n = 130^ 12 (9.2)	0.05 (0.01, 0.38)	-0.09 (-0.14, -0.04)	0.05 (0.001, 0.31)

Source: Table 2.6.15, p155 of the submission

AE = adverse event; CI = confidence interval; NR= not reported; NE= not estimated OR = odds ratio; RD = risk difference; RR = relative risk; TEAE = treatment-emergent adverse event

*AE only reported in Study 1540

[#]AE only reported in Chapalain et al

[^]AE only reported in Ogata et al

- 6.31 Overall, 48% of the patients treated with cemiplimab (pooled results) developed grade ≥ 3 treatment emergent adverse events (TEAE), and 36.5% developed serious TEAE. Treatment discontinuation due to TEAE occurred in 9.6% of the patients. The most common TEAEs experienced by at least 15% of patients were fatigue (26.9%), nausea, diarrhoea, constipation (19.2% each), dry mouth, decreased appetite, hypercalcaemia, hypophosphataemia, and urinary tract infection (15.4% each).
- 6.32 The ESC agreed with the evaluation that the net difference in the safety profile and the impact of cemiplimab on QoL compared to the currently used chemotherapy regimens cannot be estimated. The comparison of the safety profile between cemiplimab and chemotherapy should be interpreted in the context of:

- Low number of events, different (and/or missing) information about treatment duration between cemiplimab and chemotherapy;
- The comparison is with chemotherapy and this will have a higher rate of adverse events than if the comparison was with BSC, leading to an under-estimate of the incremental difference in harms associated with cemiplimab vs BSC ± CT;
- The fact that the BSC ± CT pooled safety data were derived mainly from two studies (Chapalain et al and Ogata et al), therefore, it is very difficult to interpret the efficacy and the safety data presented from this comparison together, as different populations were included in each analysis;
- Different range of adverse events and the fact that the chemotherapy studies did not report the effect of treatment on QoL.
- The immaturity of the presented cemiplimab data, such that the risk of late-onset immune adverse events could not be reliably estimated.

In addition, the ESC recalled that the requested fixed-dosing regimen (350 mg intravenously Q3W) was only tested in a minority of patients. The ESC considered that the fixed-dosing regimen would result in a higher cemiplimab dose than weight based dosing for some patients and as such may increase the risk of adverse events in those patients. Hence, the ESC considered that the adverse event data reported in the submission may not be truly reflective of the risk of events in clinical practice.

Benefits/harms

- 6.33 Because of the naïve indirect nature of comparison, and the different (and unreported) duration of treatment in the chemotherapy studies, an assessment of the comparative benefits/harms would be misleading. Overall, the naïve indirect comparison presented in the submission did not allow for a quantitative comparison of the benefits and harms of cemiplimab and BSC ± CT. Accordingly, a benefits/harms table has not been presented.

Clinical claim

- 6.34 The submission described cemiplimab as superior in terms of effectiveness compared to BSC and chemotherapy and non-inferior in terms of safety compared to platinum-based and non-platinum-based chemotherapy.
- 6.35 The evidence presented was based on a naïve indirect comparison between the cemiplimab studies and seven studies for current clinical practice (BSC with or without chemotherapy). All the identified BSC and chemotherapy studies were retrospective studies and they included different treatment regimens (platinum, non-platinum, cetuximab based, and concurrent chemo-radiotherapy).
- 6.36 There were substantial uncertainties regarding the presented claim of superiority in efficacy and non-inferiority in safety. This was mainly because of:

- The high risk of bias associated with the findings derived from the naïve indirect comparison due to the unbalanced distribution of known and unknown prognostic factors between treatment arms.
- The difference in the baseline demographics, including PS and immune-status, percentage of patients with mCSCC, follow-up duration, treatment regimens, heterogeneity in the assessment of overall survival duration, and overall non-comparability of the evidence base.
- The safety data presented were extracted from only two of the retrospective studies (to represent current clinical practice) and would have under-estimated the difference in adverse events between treatment arms. Thus, the efficacy and safety data were not obtained from similar patient populations. The ESC also considered the evidence incomplete as none of the BSC studies reported adverse events.

In addition, the ESC also noted the immaturity of the OS data further contributed to the substantial uncertainty of the claim of superior effectiveness. The ESC considered that additional OS data may address the immaturity issue. However, the ESC considered that the magnitude of difference in effectiveness from using cemiplimab in patients with advanced CSCC who are not candidates for curative surgery or radiation therapy compared to current clinical practice (BSC ± CT) could not be determined from the data presented as it does not allow a valid indirect comparison to be undertaken. The ESC also considered that the magnitude of difference in safety for cemiplimab could not be determined from the data presented.

- 6.37 The PBAC considered that the claim of superior comparative effectiveness was not adequately supported by the data.
- 6.38 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data.

Economic analysis

- 6.39 The submission presented a modelled economic evaluation based on the naïve indirect comparison of the cemiplimab studies (Study 1540 and Study 1423) with the pooled analysis of relevant (sub)groups from the BSC ± CT studies (Sun et al 2019 (unresectable immunocompetent), Amaral et al 2019 (unresectable), Jarkowski et al 2016, Chapalain et al 2019 and Ogata et al 2020). The type of economic evaluation was a cost-utility analysis. The key components of the economic evaluation are summarised below.

Table 12: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Cemiplimab vs. BSC ± CT
Time horizon	10 years in the model base case vs. 15.7-31.7 months in cemiplimab studies and 18.6-42.8 months in BSC and chemotherapy studies (median follow-up) ^a The ESC considered a 10 year time horizon may be appropriate although extrapolation of the outcomes beyond the trial period amplified the uncertainty associated with the estimated gains in LYs and QALYs.
Outcomes	LYs and QALYs
Methods used to generate results	Partitioned survival model.
Health states	Three health states: PFS, progressive disease and death. The proportion of patients in each health state was determined on the basis of the PFS and OS curves.
Cycle length	1 month
Allocation to health states	The Kaplan-Meier estimates for PFS and OS were derived directly from Study 1540 and Study 1423 for cemiplimab, while for BSC ± CT they were from a pooled analysis of the relevant (sub)groups from studies Sun et al 2019 and Amaral et al 2019, Jarkowski et al 2016, Chapalain et al 2019 and Ogata et al 2020, until the extrapolation time point ^b .
Extrapolation method	Parametric distributions fitted to the observed Kaplan-Meier survival estimates were used to extrapolate PFS and OS to the end of the time horizon of the model. In the base case, independent lognormal extrapolation was chosen for cemiplimab PFS, independent exponential extrapolation for cemiplimab OS, and independent log-logistic extrapolation for BSC ± CT PFS and OS. The selection was based on goodness of fit and clinical plausibility. The treatment effect for cemiplimab was extrapolated up to the last observed data point for PFS (36 months) and OS (47 months), after which time point the hazard was set to be the same as that of BSC ± CT. 69.1% of the incremental QALYs (and 12.7% of incremental costs) were generated beyond 30 months (i.e. the extrapolation time point for cemiplimab OS).
Health-related quality of life	EORTC QLQ-C30 data from Study 1540, mapped to EQ-5D values, using the Longworth 2014 mapping algorithm. PFS health state utility: 0.768 Progressive disease health state utility: 0.707 Adverse event-related and age-related utility decrements were also involved in the economic model.

Source: Adapted from Table 3.1.1, p241 of the submission.

BSC ± CT = best supportive care with or without chemotherapy; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 items; EQ-5D = EuroQol - 5 dimensions; LYs = life years; OS = overall survival; PFS = progression-free survival; QALYs = quality-adjusted life years

^a The median follow-up in Study Sun et al 2019 and in Study Ogata et al 2020 was not reported.

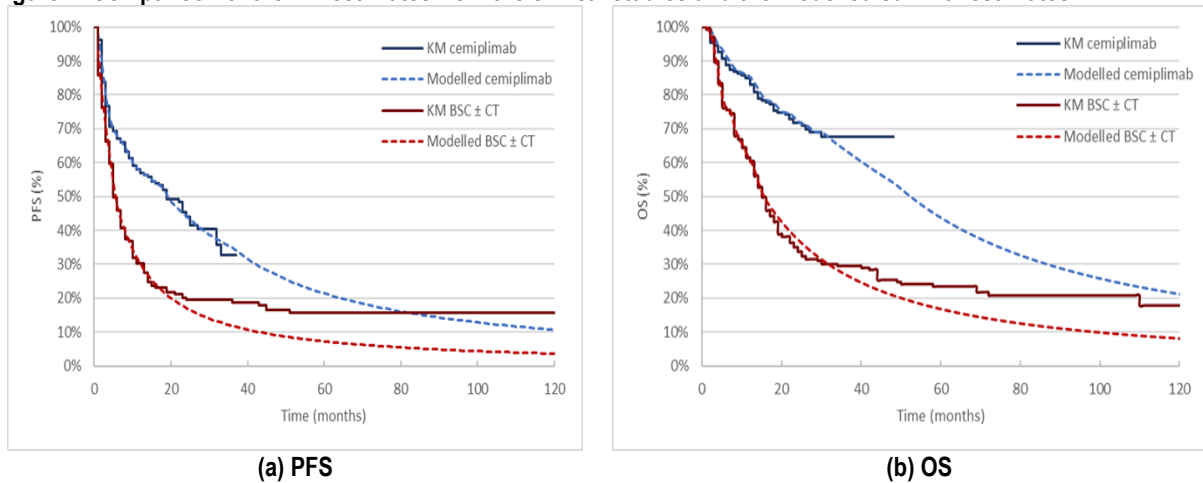
^b 19 months for cemiplimab PFS, 5 months for BSC ± CT PFS, 30 months for cemiplimab OS, and 15 months for BSC ± CT OS.

6.40 The ESC agreed with the evaluation that the modelled survival estimates based on the naïve indirect comparison of cemiplimab with BSC ± CT, with extrapolation up to 10 years, were not an adequate reflection of the clinical benefit of cemiplimab in clinical practice, given that:

- The underpinning transitivity assumption of the indirect comparison is not tenable. Compared with the cemiplimab studies, the BSC and the chemotherapy studies enrolled patients with a poorer performance status and more advanced disease. This favoured cemiplimab. In addition, the comparative treatment effect of cemiplimab versus BSC ± CT was very uncertain, given the lack of a randomised control group and the high risk of bias/confounding in the studies included in the indirect comparison;
- The clinical study data did not provide a reliable basis for extrapolation of cemiplimab OS, as only 27.9% (61/219) of patients in the cemiplimab studies died during the study observation period; and
- The cemiplimab therapy in the clinical studies either had a different dosage regimen (3mg/kg Q2W vs. 350mg Q3W) or a shorter treatment duration (48-54 weeks vs. 104 weeks), compared with the expected use of cemiplimab in the Australian setting. Furthermore, the proportion of patients receiving chemotherapy in the pooled analysis of BSC ± CT studies was higher than that assumed in the economic model (79% vs. 30%). The differences in use of cemiplimab and therapies which form BSC ± CT between the study setting and Australian clinical practice could affect the relative treatment effect of cemiplimab versus BSC ± CT.

6.41 Although the hazard for cemiplimab was assumed to be the same as that for BSC ± CT after the last observed data point for cemiplimab, the modelled OS estimates were greater in the cemiplimab arm than in the BSC ± CT arm up until Year 29, i.e. 27 years after discontinuation of cemiplimab at the maximum treatment duration. The time horizon does however only use data up to 10 years; nevertheless the shape of the extrapolations imply a significant incremental benefit persevering at 10 years, and only reaching zero at 29 years post-treatment initiation. The clinical plausibility of this assumption has not been justified, particularly considering the short follow-up in the cemiplimab studies (15.7-31.7 months). The PBAC guidelines (Version 5.0) state that “if the treatment effect is maintained or increasing, and this is not clinically plausible, apply a hazard ratio such that the intervention and comparator curves converge at a plausible time point” (p75). The PSCR argued that the approach taken, including the fitted parametric functions, was appropriate with the better OS estimates for cemiplimab compared with BSC ± CT relying almost entirely on the observed difference in OS in the early part of the KM curves. The ESC considered that the parametric distributions fitted to the observed KM survival estimate curves were likely appropriate. However, the ESC considered that convergence of the cemiplimab and BSC ± CT curves at 10 years was appropriate given the significant uncertainty associated with the clinical data (see paragraph 6.40). The ESC noted that a sensitivity analysis performed during the evaluation showed that the model was sensitive to the assumption of convergence of the survival curves.

Figure 4: Comparison of the KM estimates from the clinical studies and the modelled survival estimates



Source: Figures from the “Libtayo (cemiplimab) Economic Evaluation” workbook

BSC ± CT = best supportive care with or without chemotherapy; KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival

6.42 The submission derived health state utilities from the EORTC QLQ-C30 data collected in Study 1540, mapped to EQ-5D using a mapping algorithm by Longworth et al (2014). The representativeness of the responders who provided the HRQoL data throughout Study 1540 was uncertain. An insufficient follow-up period in Study 1540 (15.7 months) implied that the disutilities associated with deteriorating progressive disease could not be fully captured during the study observation period. The study-based health state utilities used in the economic model, particularly the progressive disease state utility (0.707), may have been overestimated. The PSCR accepted that the utility value may not fully capture the entire period of gradual deterioration in health and functional status between disease progression following treatment with cemiplimab or BSC ± CT and death. The PSCR argued that revising the utility for the progressive disease health state from 0.707 to the lowest published utility of 0.520 has a marginal impact on the incremental cost-effectiveness ratio (ICER), increasing from \$55,000 to <\$75,000 to \$55,000 to <\$75,000/QALY. The ESC considered that the use of a relatively high utility value for progressive disease favoured cemiplimab because of the substantial increase in time spent in this state for cemiplimab versus BSC ± CT. The ESC noted that the ICER of \$55,000 to \$75,000 reported by the PSCR was derived with the use of health state utilities from cetuximab for squamous cell cancer of head and neck (NICE TA473) for the progressive disease state only with the ICER increasing to \$55,000 to <\$75,000/QALY with the use of health state utilities from this published source for both PFS and progressive disease (see Table 13).

6.43 The planned treatment duration for cemiplimab (48 weeks in Study 1423, 54 weeks in Group 3 of Study 1540, and 96 weeks in Groups 1 & 2 of Study 1540) was shorter than the maximum treatment duration specified in the proposed PBS listing (24 months). To address this issue, patients who stopped treatment at the 11-month stopping rule (as in Study 1423) or at the 12.5-month stopping rule (as in Group 3 of Study 1540) were censored in the pooled analysis of treatment duration for cemiplimab. As the planned treatment duration in the remaining study patients (96

weeks in Groups 1 & 2 of Study 1540) was about 2 months shorter than the maximum proposed treatment duration (24 months), the use of the modelled time-on-treatment curve has still resulted in an underestimation of the treatment cost for cemiplimab. The modelled survival curve showed that around 45% of patients in the cemiplimab arm remained disease-free at the 22-month stopping rule. Despite this, results from a sensitivity analysis conducted during the evaluation suggested that the model was not sensitive to the revision of this input.

Table 13: Key drivers of the model

Description	Method/Value	Impact (Base case ICER: \$██████ ¹ /QALY)
Comparative treatment effect	The economic model was based on a naïve indirect comparison of cemiplimab with BSC ± CT, which contained major transitivity issues.	High, favours cemiplimab The use of a simulated treatment comparison in the model increased the ICER to \$██████ ² /QALY
Extrapolation	The OS estimate in patients receiving cemiplimab was better than that in BSC ± CT patients for up until 29 years.	High, favours cemiplimab Assuming the survival curves of the two treatment arms converge at Year 10, the ICER increased to \$██████ ² /QALY
Utilities	The study-based health state utilities used in the economic model, particularly the progressive disease state utility (0.707), could have been overestimated, due to the short follow-up period in Study 1540 (15.7 months) and the uncertainty regarding the representativeness of the responders who provided the HRQoL data in Study 1540.	Moderate, favours cemiplimab When the lower health state utility values derived from the NICE TA473 submission for patients with recurrent or metastatic SCCHN were applied to the economic model, the ICER increased to \$██████ ¹ /QALY.

Source: Table compiled during the evaluation based on Section 3.9 of the submission and the sensitivity analyses performed during the evaluation.

BSC ± CT = best supportive care with or without chemotherapy; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; OS = overall survival; QALY = quality-adjusted life year; SCCHN = squamous cell cancer of head and neck

The redacted values correspond to the following ranges:

¹\$55,000 to <\$75,000/QALY gained

²\$75,000 to <\$90,000/QALY gained

6.44 The results of the economic evaluation are summarised below.

Public Summary Document – November 2020 PBAC Meeting

Table 14: Results of the stepped economic evaluation

Step and component	Cemiplimab	BSC ± CT	Increment
Step 1: study-based costs and outcomes (time horizon 36 months)			
Costs	\$ [redacted]	\$1,151	\$ [redacted]
LYs	2.23	1.50	0.73
Incremental cost/extra LY gained			\$ [redacted] ³
Step 2: study evidence extrapolated to 10 years			
Costs	\$ [redacted]	\$1,151	\$ [redacted]
LYs	4.17	2.27	1.90
Incremental cost/extra LY gained			\$ [redacted] ¹
Step 3: study evidence extrapolated to 10 years including all resource use			
Costs	\$ [redacted]	\$28,309	\$ [redacted]
LYs	4.17	2.27	1.90
Incremental cost/extra LY gained			\$ [redacted] ¹
Step 4: study evidence extrapolated to 10 years including all resource use and LYs transformed to QALYs			
Costs	\$ [redacted]	\$28,309	\$ [redacted]
QALYs	3.07	1.66	1.41
Incremental cost/extra QALY gained			\$ [redacted] ²

Source: Table 3.8.1, pp305-306 of the submission.

BSC ± CT = best supportive care with or without chemotherapy; LYs = life years; QALYs = quality-adjusted life years

The redacted values correspond to the following ranges:

¹\$35,000 to <\$45,000/QALY gained

²\$55,000 to <\$75,000/QALY gained

³\$95,000 to <\$115,000/QALY gained

6.45 An examination of the relationship between incremental costs and incremental quality-adjusted life years (QALYs) over the time horizon of the model revealed that the difference in cumulative costs between the two treatment arms increased rapidly until around Month 24, corresponding to the maximum treatment duration for cemiplimab, then stabilised; whilst the incremental QALYs increased steadily over the time horizon. Around 70% of the total incremental LYs and QALYs (vs. 13% of incremental costs) were gained during the extrapolation period where the uncertainty was the greatest.

6.46 The results of the key sensitivity analyses are summarised below.

Table 15: Sensitivity analyses

	Incremental costs	Incremental QALYs	ICER (\$/QALY)
Base case	\$ [redacted]	1.41	\$ [redacted] ¹
Economic evaluation based on simulated treatment comparison ^{a*}	\$ [redacted]	1.08	\$ [redacted] ²
Independent exponential function to extrapolate OS for BSC±CT ^{a*}	\$ [redacted]	1.24	\$ [redacted] ¹
Assuming the survival curves of the two treatment arms converge at Year 10 ^{a, b*}	\$ [redacted]	1.05	\$ [redacted] ²
Assuming all patients in the cemiplimab arm receive one additional cycle of cemiplimab ^{a, c*}	\$ [redacted]	1.41	\$ [redacted] ¹
Use of health state utilities from cetuximab for SCCNH (NICE TA473) for both PFS and progressive disease health states	\$ [redacted]	1.17	\$ [redacted] ¹
Time horizon of 7.5 years	\$ [redacted]	1.23	\$ [redacted] ¹

Source: Table 3.9.1, p309 of the submission. *Analyses performed during the evaluation, using the "Libtayo (cemiplimab) Economic Evaluation" workbook

BSC ± CT = best supportive care with or without chemotherapy; ICER = incremental cost-effectiveness ratio; SCCNH = squamous cell cancer of the head and neck; NICE = National Institute for Health and Care; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year

^a Sensitivity analyses performed during the evaluation.

^b Applying a hazard ratio of 1.92 for PFS and a hazard ratio of 1.99 for OS after the last observed data point

^c Adding a cost of \$ [redacted] (drug cost + administration cost) to the cemiplimab arm

The redacted values correspond to the following ranges:

¹\$55,000 to <\$75,000/QALY gained

²\$75,000 to <\$95,000/QALY gained

6.47 Results from the sensitivity analyses indicated that the model was sensitive to the assumed survival benefits of cemiplimab relative to BSC ± CT – and this is the area of greatest uncertainty in the submission. When the ‘predicted’ cemiplimab data from STC were used in the economic model, the ICER increased from \$55,000 to <\$75,000/QALY to \$75,000 to <\$95,000/QALY. However, as the STC was characterised by uncertainty, with major issues relating to the limited data available on relevant prognostic factors from the comparator studies, these results are indicative only of the uncertainty associated with the modelled estimates presented in the submission. The ESC considered the sensitivity analysis using the STC was highly uncertain for the reasons outlined in paragraph 6.28. The ESC noted that the economic model did not allow the option of using MAIC but based on the hazard ratio for OS the Committee considered it likely the ICER would exceed \$95,000 to <\$115,000/QALY gained using this approach. The ESC concluded that the ICER was uncertain and likely underestimated due to the incremental benefit being overestimated in the base case analysis. The pre-PBAC response stated that the economic model was updated to incorporate the MAIC approach using the extended model for OS and the core model for PFS resulting in an ICER of \$75,000 to <\$95,000/QALY. The pre-PBAC response argued that given the limitations of the STC and MAIC, the approach to the base case economic evaluation was reasonable. The PBAC noted that the results using the MAIC based model provided with the pre-PBAC response were not verified and a rationale for using the extended model for OS but the core model for PFS was not provided.

- 6.48 If trial-based survival estimates plus parametric extrapolation until the last observed data point as in the submission's base case analysis was used, followed by convergence of the survival curves for cemiplimab and BSC ± CT at the end of model time horizon of the 10 years, the ICER would increase to \$75,000 to <\$95,000/ QALY (change by 32%). The pre-PBAC response disagreed with the approach taken by the evaluation in this sensitivity analysis and presented an alternative approach involving linear convergence of the OS and PFS curves after the observed data. The PBAC noted the revised ICERs had not been verified.
- 6.49 The change in the health state utility values, the parametric function to extrapolate the OS estimate, and the time horizon would moderately affect the ICER.
- 6.50 The submission presented two scenario analyses which assessed the cost-effectiveness of cemiplimab versus BSC and versus chemotherapy, respectively. Relevant model inputs, e.g. survival curves and proportion of patients receiving chemotherapy, palliative radiation and palliative surgery, were changed according to the scenario. It was noted that the incremental costs and incremental QALYs in Scenario analysis 1 (vs. BSC) were consistently greater than the corresponding base case estimates; whereas Scenario analysis 2 (vs. chemotherapy) results were in the opposite direction. The ICER from Scenario 1 analysis was around \$5,000 to <\$15,000/QALY less than the base case ICER (\$45,000 to <\$55,000/QALY), and the ICER from Scenario 2 was only slightly higher than the base case (\$55,000 to <\$75,000/QALY). Scenario analysis 1 assumed that, throughout the time horizon, all patients in the comparator arm that survived were in the post-progression health state, as neither of BSC studies (Sun et al 2019 and Amaral et al 2019) reported PFS data. This assumption was unrealistic and, consequently, the result was not informative.

Drug cost/patient/course

- 6.51 The per patient drug costs for cemiplimab and chemotherapy are presented in the table below. The drug cost for cemiplimab was estimated to be \$ [REDACTED], using the modelled treatment duration of 13.1 months in the economic evaluation. As discussed above, this cost is a likely underestimate, due to the shorter planned treatment duration in Groups 1 and 2 of Study 1540. The drug cost for chemotherapy would be \$ [REDACTED], based on the PFS curve for BSC ± CT with a maximum of six treatment cycles for both cisplatin+5-FU and paclitaxel. This drug cost for chemotherapy would apply to 30% of patients in the comparator BSC ± CT arm. Costs associated with other interventions which form BSC ± CT, i.e. palliative radiation and palliative surgery, are not included in the table below.

Table 16: Drug cost per patient for cemiplimab and chemotherapy

	Cemiplimab			Chemotherapy ^a		
	Study dose and duration	Model	Financial estimates	Study dose and duration	Model	Financial estimates
Mean dose	Study 1423 and Groups 1 & 2 of Study 1540: 3mg/kg Q2W Group 3 of Study 1540: 350mg Q3W	350mg Q3W	350mg Q3W	NR	Cis: 146mg Q3W 5-FU: 7,797mg Q3W Pac: 156mg every week for 3 weeks in a 4-week treatment cycle	Cis: 146mg Q3W 5-FU: 7,797mg Q3W Pac: 156mg every week for 3 weeks in a 4-week treatment cycle
Mean duration	3mg/kg Q2W: 7.8-13.1 months ^b 350mg Q3W: 10.5 months ^b	13.1 months ^c	13.4 months ^c	NR	Cis+5-FU: 3.4 months ^d Pac: 4.1 months ^d	Cis+5-FU: 4.2 months ^e Pac: 5.5 months ^e
Cost/patient/month	3mg/kg Q2W: \$ [redacted] ^f 350mg Q3W: \$ [redacted]	\$ [redacted] ^g	\$ [redacted] ^g	–	Cis+5-FU: \$ [redacted] ^g Pac: \$ [redacted] ^g	Cis+5-FU: \$ [redacted] ^g Pac: \$ [redacted] ^g
Cost/patient/course*	3mg/kg Q2W: \$ [redacted]-\$ [redacted] 350mg Q3W: \$ [redacted]	\$ [redacted]	\$ [redacted]	–	\$ [redacted] ^h	\$ [redacted] ^h

Source: Table compiled during the evaluation, based on Table 2.4-7, p75, information provided in Section 3.6.1, pp271-290 of the submission, the “Libtayo (cemiplimab) Economic Evaluation” workbook, the “Libtayo (cemiplimab) Predicted Use” workbook. *Values calculated during the evaluation.

5-FU = 5-fluorouracil; BSC ± CT = best supportive care with or without chemotherapy; Cis = cisplatin; NR = not reported; Pac = paclitaxel; Q2W = every 2 weeks; Q3W = every 3 weeks

^a Cisplatin + 5-FU as a proxy for platinum-based chemotherapy and paclitaxel as a proxy for non-platinum-based chemotherapy.

^b The planned treatment duration was 48 weeks in Study 1423, 96 weeks in Groups 1 and 2 of Study 1540, and 54 weeks in Group 3 of Study 1540.

^c The cemiplimab treatment durations used in the economic model and in the financial analysis were both derived from a pooled analysis of time-on-treatment in Study 1423 and Study 1540, with a small difference due to the differential time interval in which the drug cost is accrued (1 month vs. 3 week).

^d In the economic evaluation, the estimated treatment duration was based on the progression-free survival curve with a maximum of six treatment cycles for both cisplatin+5-FU and paclitaxel.

^e In the financial analysis, it was assumed that all patients would receive six treatment cycles of cisplatin+5-FU (3-week cycle) or paclitaxel (4-week cycle).

^f Cemiplimab is only available at a 350mg vial strength. It was assumed that a 3mg/kg Q2W dose regimen would require one vial per administration, resulting in dose wastage for patients weighted <117kg.

^g In the economic evaluation, it was assumed that 47% of the cemiplimab/chemotherapy scripts would be dispensed in a public hospital setting and 53% dispensed in a private hospital setting (based on National Hospitals Cost Data Collection data on chemotherapy services). In the financial analysis a public/private split of 29%/71% was used (based on Services Australia data on services processed for nivolumab and pembrolizumab for Stage III/IV unresectable melanoma)

^h Weighted average, assuming 56.9% of the patients receive cisplatin+5-FU and 43.1% receive paclitaxel

Estimated PBS usage & financial implications

6.52 This submission was considered by DUSC. The financial analysis took an epidemiological approach to estimate the financial impact of the proposed listing of cemiplimab. The key inputs in the financial analysis are summarised in the table below.

Public Summary Document – November 2020 PBAC Meeting

Table 17: Key inputs for financial estimates

Parameter	Value	Source and comment
Australian population	26,301,274 in Year 1 to 28,372,315 in Year 6	DoH utilisation and cost model template which aligns with the ABS Population projections, Series B. Appropriate
Incidence rate and prevalence rate of CSCC in Australia	Prevalence: 0.70% in Year 1 ^a Incidence: 0.69% in Year 2 to 0.70% in Year 6 ^a	2002 NCCI national survey; Staples 2006. Reasonable
Proportion of patients with laCSCC or mCSCC	1.4% in incident patients ^a 1.67% in prevalent patients ^a	Venables 2019. Only mCSCC was considered in this study. This resulted in an underestimation.
Proportion of patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation	45%	Ronconi 2020, IQVIA Research. Appears reasonable
Cemiplimab uptake rates	60% in Year 1, 75% in Year 2 and 90% in Years 3-6	Submission's assumption No justification provided
Grandfathered patients	340 in Year 1	Submission's assumption No justification provided
Mean treatment duration for cemiplimab	58.03 weeks	Modelled time-on-treatment on the basis of the data from Study 1423 and Study 1540. Consistent with the economic evaluation. The planned treatment duration in cemiplimab studies was shorter than that recommended in the submission (e.g. 96 weeks in Groups 1 & 2 of Study 1540 vs. 104 weeks)
Proportion of patients receiving various therapies in current clinical practice	Platinum-based: 17.2% Non-platinum-based: 13% Palliative radiation: 45% Palliative surgery: 20%	Sun 2019, Amaral 2019 and Ogata 2020. Appears reasonable
Treatment duration for chemotherapy	Cisplatin+5-FU: six 3-week cycles Paclitaxel: six 4-week treatment cycles (3 infusions per cycle)	eviQ guidelines 2019. The treatment duration for chemotherapy used in the financial analysis was longer than that in the economic model, as it was assumed that all patients would receive six treatment cycles of chemotherapy, without considering the possibility of disease progression during this treatment period.
IV administration cost: - No more than 1-hour duration - Ambulatory drug delivery device	\$67.10 (MBS item 13915) \$67.30 (MBS item 13942)	MBS. Reasonable data source
Cost for palliative surgery	\$249.90 ^b	
Cost for palliative radiotherapy	\$182.95 ^c	
Cost for radiotherapy planning & verification	\$286.29 ^d	

Source: Table 4.1.1, p311-312, and information provided in Section 4.1, pp311-337 of the submission

5-FU = 5-fluorouracil; ABS = Australian Bureau of Statistics; CSCC = cutaneous squamous cell carcinoma; DoH = Department of Health; IV = intravenous; laCSCC = locally advanced cutaneous squamous cell carcinoma; MBS = Medicare Benefits Schedule; mCSCC = metastatic cutaneous squamous cell carcinoma; NCCI = National Cancer Control Initiative; PBS = Pharmaceutical Benefits Scheme

^a The number of patients likely to receive cemiplimab was estimated on the basis of prevalent patients in Year 1 of listing and on the basis of incident patients from Year 2 to Year 6

^b Weighted average MBS cost based on MBS items 31356, 31358, 31359, 31361-31369, 31423, 31426, 31429, 31432, 31435, 31438, 45200, 45203, 45206, 45201, and 45202

^c Weighted average MBS cost, based on MBS items 15000, 15003, 15224, 15227, 15239, 15242, 15275, and 15100, 15103

^d Weighted average MBS cost, based on MBS items 15550, 15553, 15562, 15556, 15559, 15565, 15555, and 15715

Public Summary Document – November 2020 PBAC Meeting

6.53 The predicted use of cemiplimab and financial implications associated with the proposed listing are summarised in the table below.

Table 18: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed ^a	█ ²	█ ²	█ ²	█ ³	█ ³	█ ³
Estimated financial implications of cemiplimab						
Cost to PBS/RPBS less co-payments	\$█ ⁴	\$█ ⁵	\$█ ⁵	\$█ ⁶	\$█ ⁶	\$█ ⁶
Estimated financial implications for platinum-based chemotherapy (cisplatin+5-FU) and non-platinum-based chemotherapy (paclitaxel)						
Cost to PBS/RPBS less co-payments	-\$█ ⁷	-\$█ ⁷	-\$█ ⁷	-\$█ ⁷	-\$█ ⁷	-\$█ ⁷
Revised ^b	-\$█ ⁷					
Net financial implications						
Net cost to PBS/RPBS	\$█ ⁸	\$█ ⁵	\$█ ⁵	\$█ ⁶	\$█ ⁶	\$█ ⁶
Revised ^b	\$█ ⁸					
Net cost to MBS	\$█ ⁷	\$█ ⁷	\$█ ⁷	\$█ ⁷	\$█ ⁷	\$█ ⁷
Revised ^b	\$█ ⁷					
Net cost to PBS/RPBS/MBS	\$█ ⁸	\$█ ⁵	\$█ ⁵	\$█ ⁶	\$█ ⁶	\$█ ⁶
Revised ^b	\$█ ⁸					

Source: Table 4.2.2, p339, Table 4.2.3, p340, Table 4.4.1, p351, Table 4.5.3, p352 of the submission

5-FU = 5-fluorouracil; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Assuming 19.34 scripts per patient, of which 12.72 scripts are dispensed in the first year of treatment and 6.62 scripts are in the second year of treatment.

^b Revised by removing grandfathered patients in calculating the change in the PBS/RPBS cost of chemotherapy and the MBS costs associated with chemotherapy administration, palliative surgery and palliative radiation

The redacted values correspond to the following ranges:

¹500 to <5,000

²10,000 to <20,000

³20,000 to <30,000

⁴\$60 million to <\$70 million

⁵\$70 million to <\$80 million

⁶\$80 million to <\$90 million

⁷\$0 to <\$10 million

⁸\$50 million to <\$60 million

6.54 The submission assumed that the total cost to the PBS/RPBS of listing cemiplimab would be \$80 to <\$90 million in Year 6, and a total of \$400 to <\$500 million in the first 6 years of listing.

6.55 The submission did not provide the estimated MBS implications relating to disease monitoring and management of adverse events.

6.56 DUSC considered the estimates presented in the submission to be underestimated. The main issues were:

- The estimated proportion of patients with locally advanced cutaneous squamous cell carcinoma (laCSCC) or metastatic cutaneous squamous cell carcinoma (mCSCC) was based on a study which reported epidemiological data on mCSCC, not including locally advanced disease. In addition, patients diagnosed with earlier stages of CSCC who subsequently progress to later stages were not fully considered in the submission.
- Using a prevalence approach in all six years of estimates rather than a mixed prevalence and incidence approach would simplify the estimates and include patients progressing from earlier stages of disease.
- The inclusion of grandfathered patients as an addition to prevalent patients in calculating the number of patients likely to receive cemiplimab in the first year of listing was not justified.
- Sources from the UK and Italy may not be applicable to the Australian population and could over or underestimate utilisation, but appear to represent the best available evidence.
- The treatment duration of cemiplimab is likely overestimated as the PBS population is likely to be older and frailer than the patients in the clinical study.
- The uptake of cemiplimab was not justified by the submission but may be underestimated.

6.57 DUSC requested the three sensitivity analyses below to show the impact on the estimates of:

- Using a prevalence approach rather than a mixed prevalence and incidence approach and removing grandfathered patients
- Removing substitution of chemotherapy as the Committee considered that palliative chemotherapy is likely to be displaced rather than replaced.
- Changing the proportion of patients with metastatic disease from 1.67% to 3.7%.

Public Summary Document – November 2020 PBAC Meeting

Table 19: Sensitivity 1, using prevalence rather than a mixed prevalence and incidence approach and removing grandfathered patients

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed	█ ²	█ ²	█ ³	█ ³	█ ³	█ ³
Estimated financial implications of cemiplimab						
Cost to PBS/RPBS less co-payments	\$█ ⁶	\$█ ⁷	\$█ ⁸	\$█ ⁹	\$█ ⁹	\$█ ⁹
Net financial implications						
Net cost to PBS/RPBS	\$█ ⁶	\$█ ⁷	\$█ ⁸	\$█ ⁹	\$█ ⁹	\$█ ⁹

Source: Table 2 p 7, Cemiplimab DUSC Advice, November 2020 PBAC Meeting (corrected 23/10/2020)

Table 20: Sensitivity 2, Sensitivity 1 plus removing substitution of chemotherapy

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed	█ ²	█ ²	█ ³	█	█ ³	█ ³
Estimated financial implications of cemiplimab						
Cost to PBS/RPBS less co-payments	\$█ ⁶	\$█ ⁷	\$█ ⁸	\$█ ⁹	\$█ ⁹	\$█ ⁹
Net financial implications						
Net cost to PBS/RPBS	\$█ ⁶	\$█ ⁷	\$█ ⁸	\$█ ⁹	\$█ ⁹	\$█ ⁹

Source: Table 3 p 7, Cemiplimab DUSC Advice, November 2020 PBAC Meeting (corrected 23/10/2020)

Table 21: Sensitivity 3, Sensitivity 2 plus change the percentage of prevalent metastatic CSCC patients from 1.67% to 3.7%

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed	█ ³	█ ⁴	█ ⁵	█ ⁵	█ ⁵	█ ⁵
Estimated financial implications of cemiplimab						
Cost to PBS/RPBS less co-payments	\$█ ⁸	\$█ ⁹	\$█ ¹⁰	\$█ ⁰	\$█ ¹⁰	\$█ ¹⁰

Public Summary Document – November 2020 PBAC Meeting

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Net financial implications						
Net cost to PBS/RPBS	\$ [redacted] ⁸	\$ [redacted] ⁹	\$ [redacted] ¹⁰	\$ [redacted] ¹⁰	\$ [redacted] ¹⁰	\$ [redacted] ¹⁰

Source: Table 4 p 8, Cemiplimab DUSC Advice, November 2020 PBAC Meeting (corrected 23/10/2020)

The redacted values correspond to the following ranges:

¹500 to <5,000

²10,000 to <20,000

³20,000 to <30,000

⁴40,000 to <50,000

⁵50,000 to <60,000

⁶\$40 million to <\$50 million

⁷\$70 million to <\$80 million

⁸\$90 million to <\$100 million

⁹\$100 million to <\$200 million

¹⁰\$200 million to <\$300 million

6.58 The pre-PBAC response argued that the prevalence and incidence approach proposed in the submission was appropriate to account for patients who survive for longer than 1 year. The PBAC considered that the prevalence approach provided a mechanism to include patients progressing from earlier stages of disease in the financial estimates.

Quality Use of Medicines

6.59 The submission outlined a number of activities to promote the safe and effective use of cemiplimab in clinical practice, including the development of clinician and patient support materials, and the implementation of a comprehensive pharmacovigilance system.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend cemiplimab for the treatment of patients with metastatic or locally advanced cutaneous squamous cell carcinoma (mCSCC or laCSCC) who are not candidates for curative surgery or curative radiation. The PBAC considered that the data presented were insufficient to adequately determine the magnitude of improvement in effectiveness and safety of cemiplimab compared to best supportive care ± chemotherapy (BSC ± CT) with the comparison of single arm studies highly uncertain. The PBAC considered the incremental cost-effectiveness ratio (ICER) was highly uncertain given the limitations with the clinical data, and substantially underestimated. The PBAC considered the financial impact as estimated in the submission was uncertain and potentially very high.

7.2 The PBAC welcomed the input from individuals, health care professionals and organisations which highlighted an unmet need for therapeutic options for this condition which has a poor prognosis. The PBAC noted that the Medical Oncology Group of Australia (MOGA) had expressed its strong support for the submission (see

paragraph 6.4). The PBAC acknowledged there is a high unmet need in this patient population.

- 7.3 The PBAC considered the nominated comparator of BSC ± CT was reasonable due to the lack of a standard of care in this setting.
- 7.4 The PBAC noted that data for cemiplimab were based on Study 1423 (N=26), a phase I study, and Study 1540 (N=193), a phase II single arm study. The PBAC noted that pooled data from the cemiplimab studies showed an overall response rate of 46.6%, a 14.2% complete response rate, a durable disease control rate of 61.2% and a median progression free survival of 18.4 months. However, the PBAC considered that interpretation of these results were limited by the single arm design of Study 1423 and Study 1540 and small sample sizes. The PBAC also agreed with the ESC that the overall survival (OS) data for cemiplimab were immature thus further limiting interpretation. In addition, the PBAC considered that a larger dataset would be required to confirm that PD-L1 expression is not predictive of efficacy (see paragraph 6.19).
- 7.5 The PBAC noted that the evidence of cemiplimab comparative effectiveness and safety was based on a naïve indirect comparison with BSC ± CT. The PBAC noted the transitivity concerns outlined in paragraph 6.11 and agreed with the ESC that the evidence used to inform the comparator group was prone to significant bias noting that it was heterogeneous in its construction and not necessarily generalisable to the Australian population. The PBAC agreed with the ESC that the magnitude of the improvement in effectiveness from using cemiplimab compared to BSC ± CT could not be reliably determined from the data presented as it does not allow a valid indirect comparison to be undertaken.
- 7.6 The PBAC considered that the safety of cemiplimab compared to BSC ± CT was unclear as none of the BSC trials reported adverse events and limited data were available for a comparison with chemotherapy (see paragraph 6.32).
- 7.7 The PBAC advised that based on the estimated number of patients to be treated with cemiplimab in the submission, the proposed subgroup of CSCC patients eligible for PBS subsidised therapy was not small. The PBAC considered that in this context more certainty regarding the incremental benefit of cemiplimab, ideally from a Phase III trial, would be required. The PBAC acknowledged that Phase III trial data for cemiplimab for this indication is unlikely to be forthcoming given a lack of standard of care and the granting of regulatory approval. However, the PBAC considered the cemiplimab trial data provided in the submission was insufficient in the context of a condition for which it was estimated 500 to <5,000 patients would receive treatment in Year 1.
- 7.8 The PBAC acknowledged that cemiplimab represented a novel therapeutic approach in this disease which has limited therapeutic options. However, the PBAC considered that a larger data set would be required to evaluate the clinical parameters of comparative effectiveness and safety. As such, the PBAC considered the data

presented were insufficient to adequately support the claims of superior clinical effectiveness compared to BSC ± CT and non-inferior safety compared to platinum-based and non-platinum-based chemotherapy.

- 7.9 The PBAC considered that the economic model was unreliable due to the uncertainties in the underpinning clinical data from Study 1423 and Study 1540 and concerns regarding the validity of the indirect comparison with BSC ± CT. The PBAC noted the economic model was sensitive to the hazard ratio for OS and considered that the hazard ratio was uncertain given the evidence on which it was based. The PBAC noted that the shape of the extrapolations imply a significant incremental health gain at 10 years (i.e. the curves remain divergent at that point). The PBAC considered the time horizon optimistic and the incremental health gain at 10 years to be highly uncertain. The PBAC agreed with the ESC that convergence of the cemiplimab and BSC ± CT curves at 10 years would be required given the significant uncertainty associated with the clinical data. Overall, the PBAC considered the ICER as presented in the submission to be uncertain and substantially underestimated. The PBAC noted the 5% price reduction on the proposed effective price offered in the pre-PBAC response but considered it did not address the uncertainties in the clinical data or the concerns with the economic model.
- 7.10 As outlined above, the PBAC considered that the subgroup of CSCC patients eligible for PBS subsidised therapy was not small based on the estimated number of patients treated with cemiplimab proposed in the submission. The PBAC considered the patient estimates to be highly uncertain, and noted the paucity of available Australian data on prevalence of locally advanced and metastatic CSCC. The PBAC noted the DUSC comments that the number of patients treated was likely underestimated as the data source used to determine the proportion of patients with advanced CSCC did not include laCSCC, patients progressing from earlier stages of disease were not fully considered in the estimates, and uptake rates would likely be higher (see paragraph 6.56). The PBAC also considered that, for the likely high proportion of patients with a performance status of 2 or more, BSC rather than cemiplimab was the appropriate approach to management. The PBAC noted that these patients were not excluded from the financial estimates and considered that this added further to the uncertainty of the estimates. The PBAC considered that the base case total cost to the PBS/RPBS of \$400 to <\$500 million over the first 6 years of listing was high and uncertain. In addition, the PBAC was concerned that the total cost to the PBS/RPBS substantially increased to between \$500 to <\$600 million and >\$1 billion over the first 6 years of listing in the sensitivity analyses requested by DUSC (see Table 19 to Table 21).
- 7.11 The PBAC proposed that any future submission should be a major submission. The PBAC advised that, at a minimum, additional data from larger Phase II cemiplimab trials would be required to inform comparative effectiveness and safety considerations. The PBAC considered that the economic model should incorporate more conservative efficacy estimates and extrapolation methods, including

convergence of the survival curves at 10 years. Furthermore, the PBAC recommended that additional sources of mCSCC and laCSCC Australian epidemiological data should be investigated (e.g. ongoing cemiplimab trials with Australian sites such as those identified in paragraph 6.17) and the issues raised by DUSC in paragraph 6.56 addressed to reduce the uncertainty in the financial estimates.

7.12 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

Sanofi is disappointed with the outcome. We are committed to supporting timely access in Australia for a cohort of patients with a life limiting and disfiguring condition associated with significant disease burden, and for whom there are no effective alternative treatment options.