Drugs (2020) 80:813–819
https://doi.org/10.1007/s40265-020-01302-2

ADIS DRUG EVALUATION

Cemiplimab: A Review in Advanced Cutaneous Squamous Cell Carcinoma

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Published online: 18 April 2020

Abstract

Cemiplimab (Libtayo®) is an antibody immunotherapy that stimulates an anti-cancer response via programmed cell death protein-1 (PD-1) blockade. It is the first approved treatment in the USA and EU for patients with locally advanced (laCSCC) or metastatic (mCSCC) cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiotherapy. Approval was based largely on positive results from the phase II EMPOWER-CSCC 1 trial in this patient population. In this pivotal trial, treatment with intravenous cemiplimab 3 mg/kg once every 2 weeks or 350 mg once every 3 weeks resulted in a clinically significant objective response rate across laCSCC and mCSCC patient groups. Furthermore, responses appear to be durable, as the median duration of response has not yet been reached. Similarly, the median overall survival has also not yet been reached as of the latest data cut-off date. The safety and tolerability profile of cemiplimab was acceptable, with most immune-related adverse events being clinically manageable with appropriate therapy or discontinuation of cemiplimab. Overall, cemiplimab has a durable, clinically significant effect and an acceptable tolerability and safety profile. As the first approved treatment for this indication, cemiplimab represents a welcome therapeutic advance for patients with advanced CSCC.

Cemiplimab: clinical considerations in advanced cutaneous squamous cell carcinoma

First approved systemic treatment in patients who are not candidates for curative radiotherapy or surgery
Human IgG monoclonal antibody that binds to PD-1 to potentiate an anti-cancer immune response
Clinically significant objective response rate with durable efficacy
Acceptable safety and tolerability profile

Enhanced material for this Adis Drug Evaluation can be found at https://doi.org/10.6084/m9.figshare.11987502.

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1 Introduction

Cutaneous squamous cell carcinoma (CSCC) is a non-melanoma skin cancer, which in the USA affected ~ 700,000 people [1] and was responsible for ~ 3900–8800 deaths (2012 estimates) [2]. In Europe, the age-standardised incidence of CSCC was 9–96 per 100,000 males and 5–68 per 100,000 females (2002–2007 estimates) [3]. Most simple CSCC cases can be surgically treated with a > 90% cure rate [4]; however, ≤ 5% of patients may present with non-resectable disease [5]. These cases of advanced CSCC include locally advanced (laCSCC) or metastatic (mCSCC) disease [6]. Until recently, treatment options for such patients have been limited to off-label chemotherapy or anti-epidermal growth factor receptor therapies [7–9]. However, the clinical evidence for these options is limited [4, 7, 9] and chemotherapy is associated with a high risk of significant adverse events [10], especially in patients of advanced age [5].

The immune system plays a pivotal role in controlling CSCC, as evidenced by immunosuppression being a significant risk factor for CSCC [3], and the efficacy of immunomodulators in actinic (solar) keratoses, a precursor to CSCC [4]. The immunogenicity of CSCC is attributed to the production of neoantigens by CSCC tumours, which have a high tumour mutational burden (TMB) caused by

chronic UV exposure [11]. Checkpoint inhibitors, which block programmed cell death protein-1 (PD-1) are of interest in CSCC, as the expression of the corresponding PD-L1 ligand by tumours is associated with regional recurrence and nodal metastases [4].

Cemiplimab (Libtayo®) is a fully human IgG4 antibody against PD-1, and is the first approved systemic treatment for advanced CSCC [4]. It is indicated for use in patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiotherapy in the USA [12], and conditionally approved in adults for the same indication in the EU [13]. This article reviews the pharmacology, efficacy and tolerability of cemiplimab for the treatment of advanced CSCC.

2 Pharmacodynamic Properties of Cemiplimab

Cemiplimab may potentiate an anti-tumour immune response by inhibiting PD-1 expressed on activated T cells. In a healthy immune system, PD-1 has an important role in regulating the immune response, such as preventing autoimmune reactions or immune over-activation. Its cognate ligands, PD-L1 and PD-L2, are expressed by antigen-presenting cells and cells from non-haematopoietic lineages (e.g. endothelial cells); however, these ligands may also be expressed by tumour cells to evade the immune system [14]. Thus, PD-1 blockade by cemiplimab has the potential to relieve the immunosuppression associated with PD-L1 or PD-L2 expression [11].

Cemiplimab exhibits a high affinity for human PD-1; the equilibrium disassociation constant of cemiplimab was 6.11 nmol/L and 628 pmol/L for monomeric and dimeric human PD-1, respectively, during in vitro experiments. In addition, cemiplimab potently inhibited PD-1 from binding with PD-L1 and PD-L2 (half maximal inhibitory concentration 0.6 nmol/L and 0.13 nmol/L). Inhibition of PD-1/PD-L1 engagement was also evident with cemiplimab in cell-based bioassays, with the drug attenuating PD-L1-dependent inhibition of both T cell receptor signalling in a T-cell line overexpressing PD-1 and proliferation of primary T cells expressing PD-1. Cemiplimab is unlikely to elicit antibody-dependent cell-mediated cytotoxicity or complement-dependent cytotoxicity, on the basis of in vitro data [15].

In a human PD-1 knock-in syngeneic murine carcinoma model, cemiplimab dose-dependently inhibited tumour growth, regardless of whether it was administered before measurable tumours were predicted to appear or once tumours were established; the drug also prolonged survival in the former setting [15].

Treatment-emergent antibodies to cemiplimab were detected in 1.3% of human patients (5/398 patients) enrolled in uncontrolled clinical studies. Of these patients, one patient (0.3%) had persistent antibody responses, and no neutralizing antibodies were observed [13].

3 Pharmacokinetic Properties of Cemiplimab

Cemiplimab is completely bioavailable due to systemic, intravenous administration, and it exhibits linear and dose-proportional pharmacokinetics [12, 13] that suggest saturation of the target-mediated pathway over the dosing interval [13]. As the pivotal phase II trial for cemiplimab examined two dosage regimens (Sect. 4), exposure to cemiplimab was calculated using a population pharmacokinetic model [16]. The post hoc estimated mean area under the curve over 6 weeks at steady state values for the weight-based dosage of 3 mg/kg once every 2 weeks (3710 day·mg/L) and the fixed dosage of 350 mg once every 3 weeks (3800 day·mg/L) were comparable to each other [16].

After administration, cemiplimab was generally confined to the vascular system (steady-state volume of distribution ~ 5 L [12, 13]) and, as a protein, is expected to be degraded into peptides and amino acids [13]. The clearance of cemiplimab is ~ 0.33 L/day after the first dose and 0.21 L/day at steady state [12, 13] (with the ~ 35% reduction in clearance over time not considered to be clinically relevant [13]). Steady state is reached in ~ 4 months, and the half-life within the dosing interval is ~ 19 days [12, 13].

Age, gender, bodyweight, race, cancer type and albumin levels had no clinically relevant impact on cemiplimab exposure in a population pharmacokinetic analysis [12, 13]. Cemiplimab exposure was also not impacted to any clinically significant extent by renal impairment (no studies in patients with creatinine clearance < 25 ml/min) [12, 13], or mild hepatic impairment (total bilirubin 1.0–1.5 times upper limit of normal plus any aspartate aminotransferase [13]; total bilirubin ≤ 45 µmol/L [12]), with no dosage adjustments recommended for these populations [12, 13]. Cemiplimab has not been evaluated in moderate or severe hepatic impairment [12, 13]; dosing recommendations cannot be made for these settings [13]. There is no evidence to suggest that the pharmacokinetic profile of cemiplimab is altered by anti-drug antibodies (Sect. 2) [13].

4 Therapeutic Efficacy of Cemiplimab

The efficacy of intravenous cemiplimab in patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation was investigated in two expansion cohorts of a phase I multicohort study (Study 1423, $n = 26$) [11, 17], and in a pivotal phase II study (Study 1540

[EMPOWER-CSCC 1], $n = 193$); both trials were of open-label, multicentre design [11, 13]. Across the mCSCC and laCSCC expansion cohorts of the phase I trial, cemiplimab 3 mg/kg once every 2 weeks for up to 48 weeks was associated with an objective response rate (ORR) of 50.0% (13/26 patients), a complete response (CR) rate of 7.7% (2/26 patients) and a partial response (PR) rate of 42.3% (11/26 patients) as of the 20 January 2018 data cut-off [17]. This trial is not discussed further however, as efficacy was evaluated as a secondary endpoint, and data are supplanted by the larger phase II EMPOWER-CSCC 1 study. EMPOWER-CSCC 1 evaluated cemiplimab 3 mg/kg once every 2 weeks [18, 19] or 350 mg once every 3 weeks [20], and data are available for three of the four planned treatment groups at the latest data cut-off (Table 1).

In EMPOWER-CSCC 1, patients aged ≥ 18 years with an Eastern Cooperative Oncology Group performance status score of 0–1 and ≥ 1 measurable tumour according to RECIST version 1.1 were eligible for enrolment [11]. Key exclusion criteria were ongoing or recent (≤ 5 years) autoimmune disease that required systemic immunosuppressive treatment, previous treatment with anti-PD-1 or anti-PD-L1 therapy, prior solid organ transplant, or concurrent life-threatening/non-indolent or haematological cancer [11]. The median age across all EMPOWER CSCC-1 groups was 72 years, and patients were predominantly white (96.9%) and male (83.4%) [13]. Prior systemic treatment for cancer had been received by 33.7% of patients, while 90.2% of patients had previously had surgery for their cancer and 67.9% had received prior radiotherapy [13].

Patients were assigned to three parallel treatment groups (Table 1): those with mCSCC received either cemiplimab 3 mg/kg once every 2 weeks (Group 1) or 350 mg once every 3 weeks (Group 3) and those with laCSCC received 3 mg/kg once every 2 weeks (Group 2). Population pharmacokinetic analyses predicted that the exposure to cemiplimab is similar with each of the two regimens (Sect. 3); the approved dosage is 350 mg once every 3 weeks (Sect. 6) [12, 13]. The primary endpoint of the trial was ORR, which was assessed by independent central review [11]. For mCSCC patients without externally visible target lesions, RECIST 1.1 criteria were used to determine ORR; and for mCSCC and laCSCC patients with externally visible target lesions, ORR was determined using a composite endpoint with RECIST 1.1 criteria and medical photography (WHO criteria) [13]. For patients treated with cemiplimab 3 mg/kg once every 2 weeks, tumours were evaluated every 8 weeks with treatment continued for up to 96 weeks or unacceptable toxicity; patients receiving cemiplimab 350 mg once every 3 weeks were evaluated every 9 weeks and were treated for up to 54 weeks (or unacceptable toxicity) [11, 18, 19].

The efficacy of cemiplimab in the treatment of advanced CSCC was demonstrated in EMPOWER-CSCC 1 [5, 18–20]. Clinical benefit was observed with cemiplimab across the three parallel treatment groups [i.e. 3 mg/kg once every 2 weeks in Groups 1 (mCSCC) and 2 (laCSCC); 350 mg once every 3 weeks in group 3 (mCSCC)], with approximately 40–50% of patients achieving an objective response (primary endpoint; Table 1). All reported ORRs were clinically relevant, as the lower values of the 95% confidence intervals were above predetermined cut-offs for a clinically insignificant effect (≤ 15% for mCSCC groups and ≤ 25% for the laCSCC group) [5]. The median time to response was 1.9 months with cemiplimab 3 mg/kg every 2 weeks [i.e. in Groups 1 (mCSCC) and 2 (laCSCC)] and 2.1 months with cemiplimab 350 mg once every 3 weeks (Group 3; mCSCC) [13].

The efficacy of cemiplimab was supported by other endpoints, including the rate of CR (a key secondary endpoint [11], Table 1), PR (Table 1) and stable disease [15.3% of mCSCC patients treated with cemiplimab 3 mg/kg once every 2 weeks (Group 1), 14.3% of mCSCC patients receiving cemiplimab 350 mg once every 3 weeks (Group 3), and 35.9% of laCSCC patients treated with cemiplimab 3 mg/kg once every 2 weeks (Group 2)]. Progressive disease was reported in 16.9% and 26.8% of mCSCC patients (Groups 1 and 3), and 11.5% of laCSCC patients (Group 2) [13, 18, 19].

The response seen with cemiplimab in patients with advanced CSCC appeared to be durable based on interim analyses of duration of response (DOR) and median survival. As of the latest data cut-off, the median DOR is yet

Table 1 Efficacy of cemiplimab in adults with locally advanced or metastatic cutaneous squamous cell cancer in EMPOWER-CSCC 1

Group (no. of pts)	ORR[a] (95% CI) [% of pts]	Best response [% of pts]	
		CR	PR
Cemipliab 3 mg/kg once every 2 weeks[b]			
Group 1 mCSCC (59) [13, 18]	49.2 (35.9–62.5)	16.9	32.2
Group 2 laCSCC (78) [13, 19]	43.6 (32.4–55.3)	12.8	30.8
Cemiplimab 350 mg once every 3 weeks			
Group 3 mCSCC (56) [20]	41.1 (28.1–55.0)	5.4	35.7

Responses were centrally reviewed unless otherwise stated. Data cut-off dates were 20 Sept 2018 for Groups 1 and 3, and 10 Oct 2018 for Group 2. Median duration of follow-up was 16.5, 8.1 and 9.3 for Groups 1, 3 and 2, respectively

CR complete response, *laCSCC* locally advanced cutaneous squamous cell cancer, *mCSCC* metastatic cutaneous squamous cell cancer, *ORR* objective response rate, *PR* partial response, *pts* patients

[a]Primary endpoint

[b]Not a recommended dosage

to be reached across all treatment groups [19, 20]. The number of patients with a DOR ≥ 12 months was also reported for mCSCC patients receiving cemiplimab 3 mg/kg once every 2 weeks (Group 1) [22 of 29 complete/partial responders] [18] and laCSCC patients receiving cemiplimab 3 mg/kg every 2 weeks (Group 2) [12 of 34 complete/partial responders] [19]. Median overall survival (OS) and progression-free survival (PFS) were yet to be reached by any treatment group as of the latest data cut-off date following a median duration of follow up of 16.5, 8.1 and 9.3 months for Groups 1, 3 and 2, respectively [19, 20].

Treatment with cemiplimab did not appear to have a beneficial or detrimental effect on health-related quality of life (HR-QOL) across the mCSCC and laCSCC treatment groups, where HR-QOL was measured with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) [5]. However, a gradual improvement in the pain subscale score was observed across the mCSCC and laCSCC treatment groups [5].

4.1 Pooled and Subgroup Analyses

A pooled analysis across the mCSCC patient groups (Groups 1 and 3, $n = 59$ and 56) was supportive of the efficacy of cemiplimab seen with the individual dosages; the pooled ORR was 45.2% (95% CI 35.9–54.8%), with a CR rate of 11.3%, PR rate of 33.9%, stable disease rate of 14.8% and progressive disease rate of 20.9% [20].

Cemiplimab was effective regardless of age and tumour PD-L1 expression in subgroup analyses. In terms of patient age, the ORR across the treatment groups of EMPOWER-CSCC 1 ($n = 193$) was 40.8%, 48.5% and 42.3% in patients aged < 65 years, ≥ 65 to < 75 years or ≥ 75 years, respectively [13]. With respect to PD-L1 expression, the ORR was 40.9% (9/22 patients) when PD-L1 expression was < 1% and 54.7% (29/53 patients) when expression was ≥ 1% in a pooled analysis of phase I and phase II data ($n = 75$) [13]. In addition, cemiplimab demonstrated clinical activity in laCSCC patients, irrespective of the reason for their ineligibility for curative surgery [19].

Consistent with the prediction that cemiplimab would be effective in CSCC due to its high TMB (Sect. 1), the median TMB in responders and non-responders in EMPOWER-CSCC 1 was 53.2 and 19.4 per megabase (Mb) in mCSCC patients receiving cemiplimab 3 mg/kg once every 2 weeks (Group 1) [$n = 17$ and 20] [20], 61.4 and 13.7 per Mb in mCSCC patients receiving cemiplimab 350 mg once every 3 weeks (Group 3) [$n = 16$ and 26] [20] and 74.2 and 28.7 per Mb in laCSCC patients receiving cemiplimab 3 mg/kg once every 2 weeks (Group 2) [$n = 21$ and 29] [19].

5 Tolerability of Cemiplimab

In clinical trials, cemiplimab had an acceptable safety/tolerability profile consistent with those of anti-PD-1 or -PD-L1 therapies [5, 11]. In a pooled analysis of 591 patients with advanced solid malignancies, including 219 patients with advanced CSCC from EMPOWER-CSCC 1 and the phase I study discussed in Sect. 4. Very common (incidence ≥ 10%) adverse reactions to cemiplimab were rash (any-grade incidence 23.3%, grade ≥ 3 incidence 1.4%), fatigue (21.5%, 0.9%), diarrhoea (13.2%, 0.5%) and pruritus (12.3%, 0%), and the most common grade ≥ 3 adverse reactions were pneumonitis (2.3%), hepatitis (1.4%) and rash (1.4%) [13]. Serious adverse reactions were reported in 8.6% of patients, and treatment was permanently discontinued in 5.8% of patients due to adverse reactions [13]. Although treatment-emergent antibodies were detected in some patients (Sect. 2), there is no evidence to suggest they altered the safety profile of cemiplimab [13].

Safety and tolerability data specific to advanced CSCC are available from EMPOWER-CSCC 1. Treatment-related adverse events (TRAE) were reported in 78.0% of 59 mCSCC patients treated with cemiplimab 3 mg/kg once every 2 weeks (Group 1) [18], 64.3% of 56 mCSCC patients treated with cemiplimab 350 mg once every 3 weeks (Group 3) [20], and 79.5% of 78 laCSCC patients treated with cemiplimab 3 mg/kg once every 2 weeks (Group 2) [19]. The incidence of grade ≥ 3 TRAEs in the respective treatment groups was 15.3% [18], 12.5% [20] and 12.8% [19]. The most commonly reported grade ≥ 3 treatment-emergent adverse events (TEAEs) in mCSCC patient groups were pneumonitis (3 patients, 5.1%), anaemia and dyspnea (2 patients each, 3.4%) in Group 1; and anaemia (5 patients, 8.9%), fatigue (3 patients, 5.4%) and maculopapular rash (1 patient, 1.8%) in Group 3 [20]. The frequency of grade ≥ 3 TEAEs in the laCSCC patient group (Group 2) did not exceed one patient [19], thus no TEAEs are deemed 'most common'. Overall, the safety profiles of the individual treatment groups were generally similar to pooled analyses of all three groups [5], and the pooled analysis of the two mCSCC patient groups (Groups 1 and 3, $n = 115$) [20]. Adverse events led to death in six patients during EMPOWER-CSCC 1 [18–20], one of which was considered to be study related (in Group 2) [19].

As seen with other immune checkpoint inhibitors [21], cemiplimab has been associated with immune-related (IR) adverse events [12, 13]. In the large pooled analysis, IR adverse reactions were reported in 20.1% of 591 patients treated with cemiplimab, and the incidence of grade ≥ 3 IR adverse reactions was 8.0% (0.7% grade 5) [13]. The most common IR adverse reactions were infusion-related reactions (any-grade incidence 9.1%, grade ≥ 3 incidence 0.2%) hypothyroidism (7.1%, 0.2%), pneumonitis (3.7%, 1.6%) and

skin adverse reactions (2.0%, 1.0%) [13]. Most reactions were resolved with appropriate therapy or withdrawal of cemiplimab, including all 54 patients with infusion-related reactions, pneumonitis (resolved in 14/22 patients), hepatitis (8/11), skin adverse reactions (6/12), diarrhoea/colitis (4/7) and nephritis (3/3) [13]. Cemiplimab was permanently discontinued due to IR adverse reactions in 4.4% of patients; where reported, withdrawals were predominantly due to pneumonitis (11 patients) and hepatitis (5 patients) [13]. Monitoring patients for symptoms of IR adverse events is recommended; such events may be managed by withholding cemiplimab and administering appropriate additional therapies [12, 13].

6 Dosage and Administration of Cemiplimab

Cemiplimab is indicated for use in patients [12] (specifically adults [13]) with laCSCC or mCSCC who are not candidates for curative surgery or curative radiation in the USA [12] and conditionally approved in the EU [13]. The recommended dosage of cemiplimab is 350 mg once every 3 weeks administered by intravenous infusion over 30 min. Treatment may be continued until disease progression or unacceptable toxicity. Dose reduction of cemiplimab is not recommended; however, dosage delay or discontinuation may be required to manage individual adverse reactions. Consult local prescribing information for recommended treatment modifications, contraindications, use in special populations, warnings and precautions.

7 Place of Cemiplimab in the Management of Advanced Cutaneous Squamous Cell Carcinoma

Cemiplimab is the first approved systemic treatment for laCSCC and mCSCC patients who are not candidates for curative surgery or curative radiotherapy, with this reflected in US [22], European [23] and UK [10] guidelines. Cemiplimab is the preferred systemic treatment option by the US National Comprehensive Cancer Network (NCCN) for locally advanced, regionally recurring or metastatic disease when surgery or radiotherapy are not treatment options, or for regional disease where radiotherapy is not amenable. These recommendations are based on lower-quality evidence and uniform NCCN consensus [22]. European guidelines strongly recommend anti-PD-1 antibodies (with cemiplimab currently the only approved option) for first line therapy in patients with laCSCC or mCSCC who are not candidates for curative surgery or radiotherapy based on level 2 evidence (Oxford classification) and unanimous consensus; prior to the availability of cemiplimab, all therapies were considered as palliative treatments (level 2 evidence, 95% consensus) [23]. UK National Institute for Health and Care Excellence (NICE) recommends the use of cemiplimab within the UK Drugs Fund as an option for adults with laCSCC or mCSCC when curative radiotherapy or surgery is inappropriate [10]. However, careful consideration of the risk [22] or alternative therapy may be required [10] for patients with a solid organ transplant [10, 22] or significant autoimmune disease [10]. No specific guidance was offered in European guidelines for the use of cemiplimab in advanced CSCC patients who also require immunosuppressive therapy or have underlying haematological malignancies [23]. Although a maximum duration of treatment is not currently indicated in the manufacturer's prescribing information [12, 13], UK NICE recommends treatment for up to 24 months or until disease progression [10].

Efficacy of cemiplimab for the treatment of advanced CSCC was demonstrated in the pivotal, open-label, phase II EMPOWER-CSCC 1 trial. Cemiplimab provided a clinically significant ORR in the mCSCC and laCSCC patient groups; up to approximately half of cemiplimab-treated patients experienced an objective response (Sect. 4). The fixed-dose and weight-based dosage regimens of cemiplimab demonstrated comparable efficacy (Sect. 4), which was expected, as they each provided similar exposure to the drug in a pharmacokinetic model (Sect. 3). Interim indicators of durability of response with cemiplimab were positive for both mCSCC and laCSCC patients; median DOR, OS and PFS were not yet reached across all treatment groups (Sect. 4). As long-term efficacy and survival data are not yet available, more mature DOR and survival data will be of interest.

Also of interest is the potential predictive value of biomarkers, such as PD-L1 expression or TMB (Sect. 4). Currently, TMB and PD-L1 expression do not have clinical utility in predicting responses to cemiplimab in patients with advanced CSCC [19]; however, there is special interest in investigating the predictive value of PD-L1 expression. Therefore, a proportion of patients may experience a prolongation in DOR, and thus improvements in PFS or OS [5].

Some previously utilized off-label chemotherapies carry a high risk of significant adverse events that result in some patients choosing best supportive care over treatment [10]. The tolerability profile of cemiplimab was acceptable and considered to be consistent with that of other anti-PD-1 or -PD-L1 therapies (Sect. 5). As cemiplimab is an immunotherapy, monitoring for immune-specific adverse reactions is recommended; however, most reactions resolve with appropriate therapy or discontinuation of treatment (Sect. 5). Although the safety/tolerability profile of cemiplimab is acceptable, some uncertainties remain, as the approved dosage (350 mg once every 3 weeks) was administered to only mCSCC patients in EMPOWER-CSCC 1, who represented 29% of all patients in the trial (56/193 patients). Therefore, an additional treatment group for EMPOWER-CSCC 1 is

planned with laCSCC and mCSCC patients receiving the approved dosage. IR adverse reactions, infusion reactions and the effect of anti-drug antibodies or PD-L1 expression will be examined in this group, in addition to long-term safety and efficacy in all groups [5]. These additional data have been requested by the EMA for conditional marking authorization [5], and are awaited with interest.

Cemiplimab was recommended for use within the UK Cancer Drugs Fund following pharmacoeconomic analyses presented to UK NICE using a partitioned survival model [10]. Although cemiplimab was not predicted to be cost-effective for routine use (and is thus not recommended for such), the analyses are considered to be very uncertain; they were conducted with immature efficacy data from single-arm trials (Sect. 4), and the comparator data were not considered to be reliable due to concerns over sample size, study design, and population. More robust analyses are expected, and as data mature, the cost-effectiveness of cemiplimab may change [10].

In summary, current data indicate that cemiplimab has a durable, clinically significant effect and an acceptable safety and tolerability profile in laCSCC and mCSCC patients who are not candidates for surgery or radiotherapy. As the first treatment approved for this indication, cemiplimab represents a welcome therapeutic advance for these patients.

Data Selection Cemiplimab: 126 records identified	
Duplicates removed	23
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	64
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	16
Cited efficacy/tolerability articles	11
Cited articles not efficacy/tolerability	12
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were cemiplimab, Libtayo, cutaneous squamous cell carcinoma, REGN2810, SER439684. Records were limited to those in English language. Searches last updated 12 Mar 2020	

Acknowledgements During the peer review process, the manufacturer of cemiplimab was also offered an opportunity to review this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

Compliance with Ethical Standards

Funding The preparation of this review was not supported by any external funding.

Conflicts of interest Arnold Lee, Sean Duggan and Emma Deeks are salaried employees of Adis International Ltd/Springer Nature, are responsible for the article content and declare no relevant conflicts of interest.

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