Comparative efficacy of cemiplimab versus other systemic treatments for advanced cutaneous squamous cell carcinoma

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Aim: To estimate the comparative efficacy of cemiplimab, a programmed cell death protein 1 inhibitor, versus EGFR inhibitors, pembrolizumab and platinum-based chemotherapy in terms of overall survival (OS) and progression-free survival. **Patients & methods:** We performed an indirect treatment comparison of cemiplimab and other available systemic therapies for patients with advanced cutaneous squamous cell carcinoma. **Results:** Cemiplimab was associated with benefits in OS (hazard ratios range: 0.07–0.52) and progression-free survival (hazard ratios range: 0.30–0.67) versus EGFR inhibitors and pembrolizumab (data from KEYNOTE-629). Cemiplimab was more efficacious versus platinum-based chemotherapy in terms of OS. **Conclusion:** Cemiplimab may offer improvements in survival for advanced cutaneous squamous cell carcinoma patients compared with existing systemic therapies.

Lay abstract: Cutaneous squamous cell carcinoma (CSCC) is a common type of skin cancer that is usually cured by surgery. For some patients, it progresses to a form that cannot be cured by surgery and/or radiotherapy, classified as advanced CSCC. Due to a historical lack of treatment options, other medications have been used in these patients without formal approval. Cemiplimab is a therapy that helps patients fight some types of cancer by boosting the body's natural defenses. Cemiplimab is the first treatment approved for advanced CSCC in the USA and is also approved in Australia, Brazil, Canada, Europe and Israel. Pembrolizumab, another therapy similar to cemiplimab, has also been investigated and was recently approved in the USA. Currently, there are no clinical trials directly comparing how well cemiplimab works versus existing treatments in patients with advanced CSCC. We performed an indirect treatment comparison using data from clinical studies of cemiplimab and these other systemic therapies. The findings suggest that cemiplimab improves survival relative to other systemic therapies in patients with advanced CSCC.

Tweetable abstract: Compared with other systemic treatments, #cemiplimab may increase survival in patients with advanced cutaneous squamous cell carcinoma. #CSCC #cemiplimab #ComparativeEfficacy #advancedCSCC #PDL1 #EGFR #skincancer #cutaneoussquamouscellcarcinoma #nonmelanomaskincancer.

Graphical abstract:

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Keywords: cemiplimab • cutaneous squamous cell carcinoma • immuno-oncology • indirect treatment comparison • nonmelanoma skin cancer

Cutaneous squamous cell carcinoma (CSCC) is now equivalent in incidence to basal cell carcinoma, each with an estimated incidence of around 1.5 million cases per year in the USA making them by far the most common cancers [1]. Worldwide, reports show a rise in CSCC incidence of 3–7% per year in most countries [2]. The most common cause of CSCC is exposure to ultraviolet rays, which makes those with light skin at highest risk of developing the disease as they lack protective melanin [3,4]. Other risk factors include male gender, advanced age and a compromised immune system [5–9]. Lesions generally form on the parts of the body that are regularly exposed to ultraviolet rays, most frequently the head and neck area, followed by the trunk and the extremities [10,11].

The current treatment of choice for localized disease is surgical excision, with Mohs micrographic surgery having the highest reported cure rate, although other treatments such as radiotherapy (RT) or curettage/electrodesiccation may be used in selected cases [12,13]. Prognosis for CSCC patients with localized disease is highly favorable (5-year survival rates are 99% with Mohs micrographic surgery) [12,13]; however, it is estimated that 1% of patients (based on disease-specific mortality rates) go on to develop advanced disease for whom prognosis is often poor [14–16].

Advanced CSCC is generally defined as either locally advanced disease not amenable to curative surgery/RT (from here on referred to as laCSCC) or metastatic disease (mCSCC), particularly distant metastases or large, multiple and extracapsular nodal disease which has a significant recurrence risk despite lymphadenectomy and radiation [17]. Systemic therapy has generally been used to treat advanced CSCC despite only a small number of prospective

uncontrolled studies supporting clinical activity and safety [18,19]. A large retrospective study recently showed that multiple regimens have historically been used in this population with no clear standard and that outcomes are poor with 3-year survival rates being about 30 and 10% for laCSCC and mCSCC patients, respectively [20]. Large clinical trials have not been undertaken among patients with advanced CSCC and a single standard-of-care systemic treatment has not yet been established for this population. This lack of information has hindered the development of definitive treatment guidelines, causing clinicians to rely on evidence of efficacy in other tumor types, such as mucosal squamous cell carcinoma of the head and neck, to guide treatment decisions [19,21]. The limited data that exists for such empiric therapies (e.g., platinum chemotherapy and EGFR inhibitors) have demonstrated limited efficacy in the advanced CSCC population [22–25].

CSCC tumors harbor a high mutation burden, which in other malignancies has been associated with clinical benefit from antibodies directed against PD-1 immune checkpoint receptor, such as cemiplimab [26–28]. In 2018, cemiplimab (as cemiplimab-rwlc) was granted approval by the US FDA for patients with mCSCC or laCSCC, becoming the first licensed treatment for this specific population [29,30]. The FDA approval for cemiplimab-rwlc was based on data from two clinical trials evaluating patients with advanced CSCC: an open-label, Phase I, multicenter study (ClinicalTrials.gov: NCT02383212) and a follow-up multicohort, multicenter, Phase II, open-label, single-arm, interventional trial (NCT02760498), where interim results from the two trials showed a centrally reviewed objective response of 47.2% after a median follow-up duration of 8.9 months [29]. Subsequent research based on approximately 1 year of additional follow-up from the Phase II cemiplimab trial indicated that median overall survival (OS) has not been reached and the estimated OS at 24 months was 73.3% (95% CI: 66.1–79.2) [31]. In 2020, pembrolizumab, another PD-1 inhibitor, was approved by the FDA for advanced CSCC based on data from the KEYNOTE-629 study [32].

No comparative efficacy data currently exists for therapies used to treat advanced CSCC despite being of interest to patients, treating clinicians and reimbursement agencies. The objective of this study was to identify published evidence on the efficacy of systemic treatments used for advanced CSCC to estimate the comparative efficacy of cemiplimab versus other available systemic treatments using three different approaches: an unadjusted (commonly referred to as ‘naïve’) comparison, a regression-based simulated treatment comparison (STC) and a matching-adjusted indirect comparison (MAIC) using propensity score weighting. These comparison methods are further described below. Cemiplimab was chosen as the comparator against which other systemic therapies were measured since cemiplimab-rwlc was the only FDA-approved option for CSCC at the time of the analysis and more outcome data is available for patients treated with cemiplimab than for other systemic treatments studied previously. Therefore, physicians and patients may benefit from knowing how cemiplimab performs as compared with other systemic treatment options.

Patients & methods

Systematic literature review

A systematic literature review (SLR) was conducted in May 2019 to identify available studies reporting outcomes of systemic therapy for advanced CSCC. Study eligibility criteria were defined in terms of the population, interventions, comparisons, outcomes and study design structure as outlined in Table 1. Curative surgery was not an intervention of interest since patients in the cemiplimab trials were generally not eligible for this treatment. Furthermore, since there is a lack of consensus over current standard of care for patients with advanced CSCC, no restrictions were placed on the systemic therapies that were eligible for inclusion in the SLR. Relevant studies were identified by searching Excerpta Medica Database (Embase), Medical Literature Analysis and Retrieval System Online (MEDLINE) and Cochrane Central Register of Controlled Trials (CENTRAL) with predefined search strategies (details in the Supplementary data). The database searches were augmented with hand searches of the bibliographies of reviews and meta-analyses along with searches of specific conference proceedings as well as WHO International Clinical Trials Registry Platform (WHO ICTRP) (<http://www.who.int/ictcp/search/en/>) to identify ongoing and completed clinical trials through May 2019 (Supplementary Table 1). Additional hand searches were conducted in December 2019 to ensure any reports on the identified studies published since the original search were also captured.

Two reviewers (A Mojebi and S Keeping), working independently, reviewed all abstracts and proceedings identified by the search as well as full-texts of those citations deemed eligible for inclusion according to the population, interventions, comparisons, outcomes and study design criteria. Discrepancies in the decisions between the two reviewers were first reconciled and then a third reviewer (S Cope) was involved to reach a consensus for

Table 1. Eligibility criteria for the inclusion of studies.

Criteria	Inclusion criteria	Exclusion criteria
Population	Adult patients with CSCC who: <ul style="list-style-type: none"> • Have locally advanced disease and who are not candidates for surgery, radical RT or • Have regional metastasis to the lymph nodes or • Have distant metastasis. 	Adult patients with other skin cancers (e.g., BCC and melanoma) or noncutaneous SCC (e.g., head and neck) or those with local or locally advanced CSCC who are candidates for treatment with surgery and/or RT
Interventions	Any systemic intervention	Surgical interventions
Comparators	Any systemic intervention	Surgical interventions
Outcomes	Efficacy outcomes: <ul style="list-style-type: none"> • Overall survival • Disease-specific overall survival • Progression-free survival • Objective response rate • Complete response rate • Partial response rate • Duration of response • Duration of disease control Health-related quality of life Prognostic factors	Adverse events <grade 3
Study design	Interventional studies (randomized or nonrandomized) Observational studies (prospective or retrospective, with ≥10 patients) Cross-sectional studies	Case series with <10 patients Case reports
Others	Studies published in English No time limits	Studies not published in English

BCC: Basal cell carcinoma; CSCC: Cutaneous squamous cell carcinoma; PICOS: Population, interventions, comparators, outcomes and study design; RT: Radiotherapy; SCC: Squamous cell carcinoma.

any remaining discrepancies. The process of study identification and selection was summarized with a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram [33]. Studies involving RT in combination with systemic therapy were excluded since patients in the cemiplimab trials were generally not eligible for curative RT. Studies were also excluded if they did not report the primary study end points of OS or progression-free survival (PFS) via Kaplan–Meier (KM) survival curves as KM data was required to be incorporated in the analysis. Lastly, studies with fewer than 10 patients with advanced CSCC were excluded from this SLR. For the final list of included studies, the initial two reviewers extracted data on study characteristics, interventions, patient characteristics and outcomes. The same process was followed for reconciliation. The Newcastle–Ottawa Scale was used to assess the quality of the studies [34].

Statistical methods for population-adjusted comparisons between studies

Since CSCC systemic therapy studies lack untreated control arms, it cannot be determined which component of an observed outcome is attributable to treatment (i.e., the treatment effect) and which part is attributable to prognostic factors or the natural course of disease (i.e., patient study population effect). Therefore, outcome comparisons between studies should be adjusted for differences in their patient populations to enhance accuracy of the comparisons. Population-adjusted comparisons apply statistical methods to individual patient data (IPD) from a given study to estimate how the treatment administered would perform if it had been given to the population from another study. These adjustments are made in order to facilitate a more accurate comparison between the two studies. Thus, in addition to an unadjusted comparison where the observed OS and PFS from each study were compared with those same end points from the cemiplimab trials, two different methods were used for population-adjusted comparisons. These methods (described below) generate estimates of what the OS and PFS would have been if cemiplimab had been included as an arm in the trial/study: regression-based STC and MAIC using propensity score weighting [35].

A targeted review was conducted to identify which patient and disease factors are prognostic for OS and/or PFS and should therefore be adjusted in the population-adjusted comparisons (see details in the [Supplementary Table 2](#)) [7,15,36–60]. Based on the results of the review, two different models were constructed. Prognostic factors included in the core model for the analysis were those reported as statistically significant in at least one study identified in the review: age, disease stage (laCSCC vs mCSCC), tumor grade (well differentiated vs other) and tumor location

(head and neck vs other). Additional factors included in the extended model were those not found to be significant or not studied in CSCC but which had been found to be relevant in other tumor types: gender, Eastern Cooperative Oncology Group performance score ($0 \leq 1$), prior systemic therapy (yes vs no) and prior RT (yes vs no).

The reported KM curves for all treatment arms of included studies were first digitized (DigitizeIt; <http://www.digitizeit.de/>). The algorithm proposed by Guyot *et al.* was then applied to reconstruct IPD, in other words, survival or censoring times for each patient [61].

In the STC, the core and extended regression models were first fitted to the IPD from the cemiplimab trials in order to estimate the outcomes of interest (OS and PFS) as a function of the different combinations of prognostic factors. The best fitting models were then used to predict outcomes for cemiplimab in each of the populations from the comparator studies (i.e., OS and PFS if cemiplimab were to be used in the patient population evaluated in the comparator study) and these predicted cemiplimab ‘arms’ were compared with the reported outcomes from each study separately. The goodness of fit was assessed using akaike information criterion (AIC). Bootstrap samples were used to estimate the standard errors of the predicted survival estimates.

For the MAIC, patients who would not have been eligible for enrolment in the comparator study (based on its inclusion and exclusion criteria) were first removed from the cemiplimab sample. A logistic regression incorporating a propensity score (i.e., the probability of being enrolled in one study vs the other) was then used to estimate weights for the IPD so that, in the MAIC analysis, mean prognostic characteristics of the cemiplimab patients matched those in the populations of comparator studies. These weights were incorporated into the estimation of treatment effects. The distribution of the estimated weights and effective sample sizes are reported in the results section. Note there is no statistic similar to AIC which can be used to compare the fit of different MAIC models, therefore model selection for the MAIC was based on the STC. Relative treatment effects were estimated as hazard ratios (HRs) for OS and PFS by means of Cox regression.

Results

Systematic literature review

Searches were executed on 1 May 2019 and a total of 7682 citations were identified through Embase, MEDLINE and CENTRAL. The PRISMA flow diagram for the study selection process used in the SLR is presented in Figure 1. Searches through other sources resulted in a total of 165 citations categorized as additional records identified through other sources. Overall, 42 citations, corresponding to 27 studies were included [22–25,32,62–97]. The search of the WHO ICTRP found 96 studies, 25 of which were completed ($n = 4$) or ongoing ($n = 21$) clinical trials that met the eligibility criteria and were not already captured in the main search. The majority of these trials investigated the use of targeted therapies such as pembrolizumab, nivolumab and panitumumab, as monotherapy or in combination with other therapies. The ongoing trials generally started in or after 2017. None of these 25 studies had any results reported on the WHO ICTRP, ClinicalTrials.gov, or ClinicalTrialsRegister.eu platforms. However, manual searches in December 2019 identified two conference posters reporting on one of these trials (KEYNOTE-629).

Details of the 27 included studies are presented in Supplementary Table 3. Fourteen of these studies were clinical trials and the remaining 13 were observational studies. None of the clinical trials were randomized or blinded. In terms of stage of disease, the cemiplimab trials recruited both laCSCC and mCSCC patients. Di Monta *et al.* [67] and Huis In 't Veld *et al.* [74] only included patients with laCSCC, while Gold *et al.* [22] and Berliner *et al.* [63] only included patients with mCSCC. Although all subgroups of patients with advanced CSCC were eligible in Foote *et al.* [69], all 16 patients in this study had regional and/or distant mCSCC. The remaining studies recruited a mix of laCSCC and mCSCC populations. The criteria used to assess whether patients with locally advanced disease were eligible for curative surgery/RT were not always reported and where they were, substantial variation was seen across studies. Overall, the studies in patients with advanced CSCC were of good quality with at least four stars earned on the Newcastle–Ottawa risk of bias assessment scale [34]. Detailed information on the quality assessment of all the included studies can be found in Supplementary Table 4.

Study selection for comparisons against cemiplimab

From the 27 studies identified in the SLR, 11 single-arm or retrospective observational studies (representing data from 617 patients) were deemed suitable for inclusion in the comparisons given that they involved systemic drug monotherapy (without RT) and reported OS or PFS via KM survival curves. Analyses were conducted using data from the registrational trial of cemiplimab (i.e., the Phase II study; NCT02760498); therefore, the Phase I trial of

Figure 1. Study flow diagram based on preferred reporting items for systematic reviews and meta-analyses.

[†]Six conference abstracts were excluded by outcome at this stage.

[‡]Includes citations that also included patients with resectable locally advanced disease (n = 11); citations that also included patients with local CSCC (n = 9).

[§]Includes two narrative reviews, one letter, a citation in German and a conference abstract corresponding to an included full-text citation (Nottage *et al.* [98]) with no additional data.

CENTRAL: Cochrane Central Register of Controlled Trials; CSCC: Cutaneous squamous carcinoma; Embase: Excerpta Medica Database; MEDLINE: Medical Literature Analysis and Retrieval System Online; RT: Radiotherapy; SLR: Systematic literature review.

cemiplimab (NCT02383212) was not included in the comparisons. Beyond the Phase II cemiplimab trial (n = 193), seven studies evaluated EGFR inhibitors: Gold *et al.* (n = 39) evaluated erlotinib; Picard *et al.* [24] (n = 31), Maubec *et al.* [23] (n = 36) and Peyrade *et al.* [84] (n = 58) evaluated cetuximab; William *et al.* [25] (n = 40) evaluated gefitinib; Cavalieri *et al.* [64] (n = 42) evaluated dacomitinib and Foote *et al.* (n = 16) evaluated panitumumab. The remaining three studies were Maubec *et al.* 2019 [96] (n = 39) and Grob *et al.* [32] (n = 105) who evaluated pembrolizumab and Jarkowski *et al.* [95] (n = 18) who evaluated chemotherapy with platinum.

Fifteen studies (Supplementary Table 3) were excluded from the analysis because they fell into either of the following categories: studies that did not provide KM curves of OS or PFS (n = 12), on those including RT in addition to systemic therapy (n = 3). The three studies excluded for inclusion of RT evaluated cisplatin plus RT [80], cetuximab alone or in combination with carboplatin and/or RT [66] and cetuximab plus radiochemotherapy [92].

A summary of the 11 included studies is presented in Table 2. Although all included studies enrolled patients with advanced CSCC as defined previously (laCSCC or mCSCC), the distribution of laCSCC and mCSCC patients within those populations showed some variation. For example, while almost the entire population consisted of mCSCC patients in Gold *et al.* [22] (100% mCSCC), Foote *et al.* [69] (100% mCSCC), William *et al.* [25] (90% mCSCC) and Maubec *et al.* [96] (88% mCSCC), other studies had smaller proportions of patients in this category (of note, only patients with distant mCSCC were categorized as ‘metastatic’ in Grob *et al.* [32]). None of the patients in the Phase II cemiplimab trial were immunosuppressed, which was also the case for Maubec *et al.* [23], Maubec

Table 2. Characteristics of patients and interventions evaluated in the cemiplimab trials and the nine comparator studies included in the analyses.

Study (trial no./year)	Treatment	n	Age	Male	ECOG PS 0 or 1	Immunosuppressed	mCSCC	Tumor histological grade			Tumor location			Ref.
								1	2	3	H & N	Trunk	Ext.	
Cemiplimab studies														
Phase I trial (NCT02383212)	Cemiplimab, IV (3 mg/kg every 2 weeks; maximum treatment duration: 48 weeks)	26	72.5 (52–88)	21 (80.8)	26 (100)	0 (0) [†]	16 (61.5)	2 (8)	6 (23)	11 (42)	19 (73)	2 (7.7)	5 (19.2)	
Phase II trial (NCT02760498)	Cemiplimab, IV (3 mg/kg every 2 weeks, or 350 mg every 3 weeks)	193	72 (38–96)	161 (83.4)	193 (100)	0 (0) [†]	115 (59.6)	41 (21.2)	63 (32.6)	65 (33.7)	128 (66.3)	25 (13)	40 (20.7)	
Comparator studies														
Gold <i>et al.</i> (2018)	Erlotinib, PO (150 mg daily; cycle length: 28 days; UDP)	39	68 (45–88)	34 (87)	34 (87)	– [‡]	39 (100)	–	–	–	31 (79)	3 (8)	5 (13)	[22]
Jarkowski <i>et al.</i> (2016)	Platinum-based chemotherapy	25	66.4 (2.8) [‡]	18 (72)	–	–	6 (24)	–	–	–	11 (44)	7 (28)	3 (12)	[95]
Maubec <i>et al.</i> (2011)	Cetuximab, IV (250 mg/m ² weekly; maximum treatment duration: 48 weeks)	36	79 (32–95)	21 (58)	28 (78)	0 (0)	19 (53)	–	–	–	5 (14)	17 (47)	14 (39)	[23]
Picard <i>et al.</i> (2017)	Cetuximab, IV (250 mg/m ² weekly; UDP)	31	86 (48–96)	22 (71)	20 (64)	15 (48)	19 (61)	15 (48)	8 (26)	7 (23)	22 (71)	3 (10)	6 (19)	[24]
William <i>et al.</i> (2017)	Gefitinib, PO (250 mg daily; cycle length: 28 days; UDP)	40	67 (37–95)	30 (75)	36 (90)	–	36 (90)	–	–	–	32 (80)	2 (5)	6 (15)	[25]
Cavalleri <i>et al.</i> (2018), (DA-COMINT14)	Dacomitinib, PO (Initially 30 mg daily followed by 45 mg daily; cycle length: 28 days; UDP)	42	77 (45–91)	33 (79)	41 (97)	9 (21)	30 (71)	–	–	–	28 (67)	3 (7)	11 (26)	[64]
Foote <i>et al.</i> (2014)	Panitumumab, IV (6 mg/kg every 2 weeks; max. treatment duration: 9 cycles)	16	68 (47–86)	14 (88)	14 (88)	–	16 (100)	–	–	–	–	–	–	[69]
Maubec <i>et al.</i> (2019), (CARSKIN)	Pembrolizumab, IV (200 mg every 3 weeks; max. treatment duration: 24 months)	39	80 (43–99)	31 (79.5)	39 (100)	0 (0) [†]	34 (88)	–	–	–	24 (62)	3 (8)	12 (31)	[96]
Grob <i>et al.</i> (2019), (KEYNOTE-629)	Pembrolizumab, IV (200 mg every 3 weeks; max. treatment duration: 24 months, or UDP)	105	72 (29–95)	80 (76.2)	105 (100)	0 (0) [†]	≥58 (55.2) [§]	–	–	–	–	–	–	[32]
Peyrade <i>et al.</i> (2018)	Cetuximab (dose and schedule were not reported)	58	83.2 (47–96)	38 (66)	32 (55)	–	20 (34.5)	–	–	–	–	–	–	[84]
Values for age are reported as median (range). All other values are reported as n (%).														
[†] Per eligibility criteria.														
[‡] Mean (standard deviation) was reported.														
[§] Only patients with distant metastasis were included in the 'metastatic' category in Grob <i>et al.</i> [32] (KEYNOTE-629). Therefore, there may have been some patients with regional mCSCC who were not included in that category.														
[¶] Indicate that the characteristic was not reported in the study.														
CSCC: Cutaneous squamous cell carcinoma; Ext: Extremities; IV: Intravenous; ECOG PS: Eastern Cooperative Oncology Group performance score; H & N: Head and neck; mCSCC: Metastatic CSCC; PO: Per os (oral); UDP: Until disease progression.														

et al. [96] and Grob *et al.* [32]; however, almost half of the patients in Picard *et al.* [24] and over 20% of patients in Cavalieri *et al.* [64] were immunosuppressed, while other studies did not report on this characteristic. Where reported, tumors were predominantly located in the head and neck area in all studies except Maubec *et al.* [23] and Jarkowski *et al.* [95], with 14 and 44% of patients having lesions in those areas, respectively. On the other hand, studies were comparable in terms of patient demographics and performance status: populations were predominantly male across all included studies, with the majority of patients having an Eastern Cooperative Oncology Group performance score of either 0 or 1, where reported. Studies generally had elderly populations with median ages that ranged from 65 years (in Gold *et al.* [22]) to 86 years (in Picard *et al.* [24]). Of note, histologic tumor grades were only reported in the IPD of the Phase II cemiplimab trial and in Picard *et al.* [24], with just over 20% of patients in the former and almost half of the patients in the latter having well-differentiated tumors.

There were also some differences in terms of the prior treatment experience of enrolled patients. Similar to the Phase II cemiplimab trial, Grob *et al.* [32] excluded patients if they had received prior treatment with PD-1 or programmed death-ligand 1 inhibitors, with no restriction for prior chemotherapy or EGFR inhibitors. Patients in Cavalieri *et al.* [64] had not received prior EGFR inhibitors. Gold *et al.* [22] and William *et al.* [25] had the same restriction and also could have only received up to one prior chemotherapy regimen (i.e., patients were receiving their first- or second-line of systemic treatment). The population in Peyrade *et al.* [84] had not received prior EGFR inhibitors or chemotherapy in the advanced stage of the disease. Maubec *et al.* [23] and Maubec *et al.* (2019) [96] had the most restrictive eligibility criteria and only included patients who were receiving their first-line of systemic treatment. In Picard *et al.* [24], only three patients (10%) had received prior chemotherapy, which was in conjunction with surgery and RT; the remaining patients had never received chemotherapy prior to study entry. Furthermore, patients who had prior treatment experience with EGFR inhibitors were excluded according to the eligibility criteria of this study. It was, therefore, concluded that the population in Picard *et al.* [24] were receiving their first-line of systemic treatment in the advanced stage. Jarkowski *et al.* [96] and Foote *et al.* [69] did not have any restrictions for prior treatment experience.

Reported outcomes

Both OS and PFS were reported across all included studies with the exception of Picard *et al.* [24], which did not provide a KM curve for PFS. Figures 2 & 3 present the reported KM curves from included studies for OS and PFS, respectively. Median OS was not reached for cemiplimab in the Phase II clinical trial (after median follow-up duration of 11.9 months). In Jarkowski *et al.* [95], chemotherapy with platinum was associated with a median OS of 15.1 months. For treatment with cetuximab, median OS was reported as 13 months (range 1–36) and 17.5 months (95% CI: 9.4–43.1) in Picard *et al.* [24] and Peyrade *et al.* [84], respectively, and a mean OS of 8.1 months (95% CI: 6.9–9.3) was reported in Maubec *et al.* [23]. Survival with gefitinib and erlotinib were comparable, with a median OS of 12.9 months (95% CI: 8.5–25.0) in William *et al.* [25] for the former and 14.9 months (95% CI: 11.7–25.2) in Gold *et al.* [22] for the latter. Median OS was 11 months with both dacomitinib (Cavalieri *et al.* [64]; 95% CI: 9–13) and panitumumab (Foote *et al.* [69]). Median OS was not reached with pembrolizumab in either Maubec *et al.* 2019 [96] or Grob *et al.* [32].

An estimated median PFS of 18.4 months (95% CI: 9.2–not evaluable) was reported for the Phase II cemiplimab trial. Median PFS was 9.8 months for platinum-based chemotherapy in Jarkowski *et al.* [95]. Treatment with cetuximab resulted in a median PFS of 4.1 months (95% CI: 1.7–5.0) in Maubec *et al.* (2011) [23], 9 months (range 0–36) in Picard *et al.* [24] and 9.7 months (95% CI: 4.8–43.4) in Peyrade *et al.* [84]. PFS estimates for gefitinib and erlotinib were comparable, with medians of 3.8 months (95% CI: 2.2–5.7) in William *et al.* [25] for the former and 4.8 months (95% CI: 3.6–7.1) in Gold *et al.* [22] for the latter. Similar to OS, median PFS was comparable for dacomitinib (Cavalieri *et al.* [64]) and panitumumab (Foote *et al.* [69]) and was reported as 6 months (95% CI: 4–9) and 8 months, respectively. Median PFS with pembrolizumab was 14.2 and 6.9 months in Maubec *et al.* [96] and Grob *et al.* [32], respectively.

Indirect comparisons

For OS, the best fitting model in terms of AIC was the extended model for all comparisons except chemotherapy with platinum, where the core model provided a better fit. For PFS, the core model was the best fit for all comparisons.

Figure 4 shows the naive (unadjusted), STC and MAIC comparisons of cemiplimab versus the EGFR inhibitors. Cemiplimab was superior to EGFR inhibitors in all comparisons and under all methods (except only three HR

Figure 2. Kaplan–Meier curves for overall survival extracted from included studies.
OS: Overall survival.

estimates that were not statistically significant, but still favored cemiplimab), with estimated HRs ranging from 0.30 to 0.67 for PFS and from 0.07 to 0.47 for OS, indicating cemiplimab is protective against disease progression and death, respectively, as compared with EGFR inhibitors.

Figure 5 shows the results of the comparisons with the remaining interventions (chemotherapy with platinum and pembrolizumab). Cemiplimab was again more efficacious than both treatments in terms of OS (HRs ranging from 0.17 to 0.52). It was also more efficacious in terms of PFS when compared with pembrolizumab (HRs ranging from 0.49 to 0.55), using data from Grob *et al.* [32]; however, 95% CIs included one when using data from Maubec *et al.* [96]. Estimated 95% CIs also included one for the PFS comparison versus chemotherapy with platinum.

Discussion

This study represents the first attempt to estimate the comparative efficacy of available systemic monotherapies for CSCC. Published OS and PFS data were compared between cemiplimab and other treatments using three different approaches; an unadjusted/naïve comparison, an STC and an MAIC. The latter two approaches mathematically adjust data for differences in study populations. These available adjusted and unadjusted data indicate cemiplimab is protective against disease progression and death as compared with EGFR inhibitors (HRs ranging from 0.30 to 0.67 and from 0.07 to 0.47 for PFS and OS, respectively). Cemiplimab also showed better OS as compared with platinum chemotherapy (HRs ranging from 0.17 to 0.30) and pembrolizumab (HRs ranging from 0.21 to 0.52) and better PFS when data from the largest ($n = 105$) study of pembrolizumab was used (HRs ranging from 0.49 to 0.55).

Although CSCC has been estimated to cause deaths comparable in number to melanoma in some regions of the USA [99], it is usually easily cured with surgical removal and locally advanced and metastatic forms of the disease comprise only a small subset of all CSCC. Cohort studies indicate that approximately 80% of CSCC patients who die from disease do not have internal metastases and succumb to local and/or nodal disease [14,15]. This has historically led to relatively few referrals for systemic therapy, an under-recognition of advanced CSCC

Figure 3. Kaplan–Meier curves for progression-free survival extracted from included studies.
PFS: Progression-free survival.

as a significant disease entity and a relatively slow evolution of therapeutic standards for advanced disease failing surgery and RT. However, since CSCC is known to be a highly immunologically mediated cancer (given the elevated incidence of aggressive CSCC in patients with organ transplants or chronic lymphocytic leukemia), immunotherapy was considered worthy of investigation in advanced CSCC with trials leading to the approval of cemiplimab and pembrolizumab. Population-adjusted treatment comparisons of cemiplimab versus other systemic monotherapies were used in this analysis since no controlled comparative trial exists for advanced CSCC. The data herein supports cemiplimab therapy over other available systemic options for laCSCC and mCSCC not amenable to cure with surgery and/or RT.

The primary limitation of this study is the low number of comparator studies available and the small numbers of patients enrolled in some studies. The latter was despite the fact that studies with fewer than ten patients were excluded from the current review; of note, many such studies were included in a recent SLR that identified a number of case studies evaluating PD-1 inhibitors in patients with nonmelanoma skin cancers [28]. PFS was not found to be significantly different between cemiplimab and platinum chemotherapy (Jarkowski *et al.* [95], $n = 18$) or when using data from the smaller study of pembrolizumab (Maubec *et al.* [2019] [96], $n = 39$). Given the small number of patients, these data may have been underpowered to detect a difference between therapies. This is supported by the statistically superior PFS seen with cemiplimab when using data from the larger study of pembrolizumab (Grob *et al.* [32], $n = 105$). Since trials directly comparing systemic treatment options do not exist for CSCC, treatment comparisons adjusted for differences in study populations had to be undertaken. The methods used for both the STC and MAIC follow best practice for population-adjusted comparisons and can be considered the best attempt to account for between-study differences given the challenge of evaluating comparative efficacy on the basis of single-arm clinical trials [35]. However, as with any analysis of single-arm trials, it is uncertain whether any unknown or unmeasured prognostic factors missing from the models may have influenced the outcomes of interest. For example, many trials did not report information regarding tumor differentiation despite the established importance of this prognostic factor in both earlier stage and advanced CSCC. Another example is that responses

Figure 4. Forest plot of hazard ratios of overall survival and progression-free survival survival for cemiplimab versus epidermal growth factor receptor inhibitors.

MAIC: Matching-adjusted indirect comparison; OS: Overall survival; PFS: Progression-free survival; STC: Simulated treatment comparison.

Figure 5. Forest plot of hazard ratios of overall survival and progression-free survival survival for cemiplimab versus other interventions.

MAIC: Matching-adjusted indirect comparison; OS: Overall survival; PFS: Progression-free survival; STC: Simulated treatment comparison.

were centrally reviewed or assessed by independent radiologists in some of the studies (e.g., the Phase II cemiplimab trial, Maubec *et al.* [2011] [23], Foot et al. [69]) while this was not the case for others; while not expected to affect OS, this difference in response assessment may impact the time when disease progression is actually diagnosed (i.e., a PFS event) and, therefore, can influence the estimated PFS HRs. Additionally, analyses could not account for population differences between the Phase II cemiplimab trial and the comparator studies in cases where certain

patients were excluded from the former but were present in the latter; for example, nearly half of the population in Picard *et al.* [24] were immunosuppressed, whereas such patients were not eligible in the cemiplimab trials. Another limitation is that efficacy analyses were not based on the intention-to-treat population in Cavalieri *et al.* [64], as there were two patients in this study who withdrew consent after receiving less than 1 month of dacomitinib and were excluded from the analyses. Efficacy estimates would have been lower for this study if these two patients had been included; however, hazards were unlikely to be greatly altered given the 42 remaining patients analyzed. A final limitation is that in the Maubec *et al.* [96] study (ASCO 2019 conference poster), the numbers of patients at risk were identical at all time points for both OS and PFS, suggesting that patients may have been erroneously censored for OS at the time of progression, thus underestimating OS. The OS comparisons of cemiplimab with pembrolizumab using data from Maubec *et al.* [96] should therefore be interpreted with caution.

Conclusion

Cemiplimab demonstrates improvements in OS that are greater than that observed in studies of other systemic treatments. Results regarding PFS were equivocal. Improvement in PFS with cemiplimab was observed in comparisons with EGFR inhibitors and one of the pembrolizumab trials (KEYNOTE-629). However, PFS with cemiplimab was not greater than that observed with platinum-based chemotherapy. Taken together, these analyses indicate that cemiplimab is the systemic therapy with the strongest evidence of clinical benefit to support its use in patients with advanced CSCC.

Future perspective

Until recently, there was no approved systemic therapy for patients with advanced CSCC. Previous studies have demonstrated that cemiplimab provides substantial antitumor activity, durable response and acceptable safety profile in patients with CSCC. As cemiplimab was the first treatment approved for advanced CSCC in the USA and is also approved in Australia, Brazil, Canada, Europe and Israel, we anticipate that cemiplimab will play a central role in the treatment of those patients over the next 5–10 years. Ongoing studies in patients with CSCC will provide additional data on pre-operative cemiplimab; cemiplimab alone and in combination with RP1, an investigational genetically modified herpes simplex type 1 virus; cemiplimab in allogeneic hematopoietic stem cell transplantation/solid organ transplantation recipients; cemiplimab before and after surgery; cemiplimab in combination with other agents such as AST-008, a TLR9 agonist and ASP-1929, an anti-EGFR; and real-world use and benefit of cemiplimab, particularly in comparison with other emerging immunotherapies such as pembrolizumab. As clinical evidence supporting cemiplimab matures and real-world evidence is collected, we anticipate that cemiplimab will continue to be a mainstay treatment for patients with CSCC requiring systemic therapy.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2020-0823

Author contributions

Conception/design was performed by S Keeping, S Cope, A Mojebi, D Ayers, E Popoff, C Chen, A Kuznik, Y Xu, M Sasane, G Konidaris, R Allen and T-M-T Huynh. Provision of study material or patients was provided by C Chen, A Kuznik, Y Xu, M Sasane, G Konidaris, R Allen, T-M-T Huynh, M Freeman, ML Andria, MG Fury, K Singh, E Stockfleth, A Challapalli and CD Schmults. Collection and/or assembly of data was performed by S Keeping, S Cope, A Mojebi, D Ayers, E Popoff and CD Schmults. Data analysis and interpretation were performed by S Keeping, S Cope, A Mojebi, D Ayers, E Popoff, C Chen, A Kuznik, Y Xu, M Sasane, G Konidaris, R Allen, T-M-T Huynh, M Freeman, ML Andria, MG Fury, K Singh, E Stockfleth, A Challapalli and CD Schmults. Manuscript writing was performed by S Keeping. Final approval of manuscript was provided by S Keeping, S Cope, A Mojebi, D Ayers, E Popoff, C Chen, A Kuznik, Y Xu, M Sasane, G Konidaris, R Allen, T-M-T Huynh, M Freeman, ML Andria, MG Fury, K Singh, E Stockfleth, A Challapalli and CD Schmults.

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Summary points

- Cemiplimab is a programmed cell death protein 1 inhibitor approved in the USA (as cemiplimab-rwlc), Australia, Brazil, Canada, Europe and Israel for the treatment of advanced cutaneous squamous cell carcinoma (CSCC).
- We aimed to systematically identify evidence on efficacy of available systemic treatments for patients with advanced CSCC and to estimate the comparative efficacy of cemiplimab versus other systemic inhibitors in terms of overall survival (OS) and progression-free survival (PFS).
- A systematic literature review of Embase, MEDLINE and Cochrane Central Register of Controlled Trials conducted in May 2019 identified studies reporting OS or PFS of systemic therapy for patients with locally advanced and/or metastatic CSCC.
- The effect of treatment on OS or PFS for cemiplimab versus other systemic monotherapies were reported via an unadjusted comparison, a regression-based simulated treatment comparison and a matching-adjusted indirect comparison using propensity score weighting.
- A total of 27 systemic therapy studies were identified. Of these, 11 studies of systemic monotherapy reporting OS or PFS were included in the comparisons, representing data from 617 patients. Cemiplimab data was based a Phase II trial (ClinicalTrials.gov: NCT02760498; n = 193). Comparator treatments included EGFR inhibitors, pembrolizumab and platinum-based chemotherapy.
- Cemiplimab was associated with improved OS (hazard ratios ranging from 0.07 to 0.47) and PFS (hazard ratios ranging from 0.30 to 0.67) versus EGFR inhibitors and pembrolizumab (data from the largest trial, KEYNOTE-629). Cemiplimab was also more efficacious in terms of OS relative to platinum-based chemotherapy (hazard ratios ranging from 0.17 to 0.30).
- These analyses suggest that cemiplimab may offer improvements in survival for advanced CSCC compared with existing systemic therapies.

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