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High response rate with extended dosing of cemiplimab in advanced cutaneous squamous cell carcinoma

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ABSTRACT

Background Cemiplimab (Libtayo®), a human monoclonal immunoglobulin G4 antibody to the programmed cell death-1 receptor, is approved for the treatment of patients with advanced cutaneous squamous cell carcinoma (CSCC), who are not candidates for curative surgery or curative radiation, using an every-3-weeks (Q3W) dosing interval. Pharmacokinetic modeling indicated that C_{trough} of extended intravenous dosing of 600 mg every 4 weeks (Q4W) would be comparable to the approved intravenous dosage of 350 mg Q3W. We examined the efficacy, pharmacokinetics, and safety of cemiplimab dosed Q4W.

Methods In this open-label, phase II trial (ClinicalTrials.gov identifier NCT02760498), the cohort of patients ≥18 years old with advanced CSCC received cemiplimab 600 mg intravenously Q4W for up to 48 weeks. Tumor measurements were recorded every 8 weeks. The primary endpoint was objective response rate by independent central review.

Results Sixty-three patients with advanced CSCC were treated with cemiplimab. The median duration of follow-up was 22.4 months (range: 1.0–39.8). An objective response was observed in 39 patients (62%; 95% CI: 48.8% to 73.9%), with 22% of patients (n=14) achieving complete response and 40% (n=25) achieving partial response. The most common treatment-emergent adverse events were diarrhea, pruritus, and fatigue.

Conclusions Extended dosing of cemiplimab 600 mg intravenously Q4W exhibited substantial antitumor activity, rapid and durable responses, and an acceptable safety profile in patients with advanced CSCC. These results confirm that cemiplimab is a highly active therapy for advanced CSCC. Additional data would help ascertain the benefit–risk profile for the 600 mg intravenous dosing regimen compared with the approved regimen.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The approved intravenous dose and schedule for cemiplimab for the treatment of advanced cutaneous squamous cell carcinoma (CSCC) is 350 mg every 3 weeks (Q3W). Pharmacokinetic modeling indicated that C_{trough} of extended intravenous dosing of 600 mg every 4 weeks (Q4W) would be comparable to the approved intravenous dosage.

WHAT THIS STUDY ADDS

⇒ Cemiplimab dosed Q4W showed significant efficacy and an acceptable safety profile in patients with advanced CSCC. Maintenance of C_{trough} levels was comparable to the approved cemiplimab Q3W dose.

HOW THIS STUDY MIGHT AFFECT RESEARCH PRACTICE OR POLICY

⇒ Cemiplimab administered Q4W may provide a less burdensome dosing regimen than the approved Q3W regimen, and offers the potential for a higher objective response rate.

BACKGROUND

Advanced cutaneous squamous cell carcinoma (CSCC), which includes metastatic CSCC and locally advanced CSCC that is not suitable for curative surgery or curative radiotherapy, had a very poor prognosis prior to the availability of antiprogrammed cell death-1 (PD-1) therapy.[1 2] The median overall survival time with chemotherapy or epidermal growth factor inhibitors has been reported to be ~15 months or shorter.[3 4] Until recently, no systemic therapy was approved for patients with advanced CSCC.[1]

Cemiplimab (Libtayo®) is a high-affinity, highly potent, hinge-stabilized, human immunoglobulin G4 monoclonal antibody to the PD-1 receptor.[5] It is approved by the US Food and Drug Administration (under the name cemiplimab-rwlc) and other national health authorities for the treatment of patients with

Table 1 Patient demographics and baseline characteristics

Characteristics	Advanced CSCC (group 4, n=63)
Age, median (range), years	74 (23–94)
Male sex, n (%)	53 (84)
ECOG performance status, n (%)	
0	25 (40)
1	38 (60)
Extent of disease, n (%)	
Metastatic	39 (62)
Locally advanced	24 (38)
Prior cancer-related radiotherapy, n (%)	38 (60)
Number of cancer-related systemic therapy regimens at baseline, n (%)	
0	54 (86)
1	7 (11)
2	2 (3)

Data cut-off date: 20 April 2022.
CSCC, cutaneous squamous cell carcinoma; ECOG, Eastern Cooperative Oncology Group.

metastatic CSCC or locally advanced CSCC who are not candidates for curative surgery or curative radiation.[6 7] The approved dose and schedule is 350 mg administered intravenously every 3 weeks (Q3W).[6 7] In an integrated analysis of the registration-enabling cohorts of the pivotal study (ClinicalTrials.gov identifier NCT02760498), the overall objective response rate (ORR) per independent central review (ICR) was 46.1% (95% CI: 38.9% to 53.4%),[1 8–10] and the median time to complete response was 11.2 months.[8] Of the patients with partial response or complete response, 87.8% (95% CI: 78.5% to 93.3%) had ongoing responses at 12 months from the first objective response.[8] A total of 192 (99.5%) patients experienced ≥1 treatment-emergent adverse event (TEAE) and 19 (9.8%) patients discontinued treatment due to a TEAE.[8] Fatigue (n=67, 34.7%), diarrhea (n=53, 27.5%), and nausea/vomiting (n=46, 23.8%) were the most common TEAEs.[8]

Pharmacokinetic (PK) modeling indicated that, while an extended dosing regimen of cemiplimab 500 mg intravenously every 4 weeks (Q4W) would provide similar cemiplimab exposure (AUC_{12W}) to that of a 3 mg/kg every 2 weeks (Q2W) dose, a slightly higher dose would achieve cemiplimab trough concentrations (C_{trough}) during the Q4W dosing that remain between those observed at 3 mg/kg Q2W and 350 mg Q3W. Therefore, a dosing regimen of 600 mg Q4W was selected, which would result in a steady-state C_{trough} value of 59 mg/L, while maximum concentration (C_{max}) and AUC_{12W} would be slightly higher, by around 51% for C_{max} and about 29% for AUC_{12W}, than observed at a 350 mg intravenous Q3W dose. Previous PK data have demonstrated that the safety profile is flat between 3 mg/kg Q2W and 10 mg/kg Q2W.[11] Herein, we report the final analysis of the efficacy and safety data with the extended dosing regimen of intravenous cemiplimab 600 mg Q4W (group 4) in patients with advanced CSCC.

METHODS

Study design and participants

Adult patients with advanced CSCC were enrolled in group 4 of the phase II open-label study of efficacy and safety of cemiplimab. Advanced CSCC is a term that encompasses patients with metastatic (nodal or distant) CSCC and patients with locally advanced CSCC who are not candidates for curative surgery or curative radiation. The methods and inclusion/exclusion criteria for this study were previously described in reports of data from patients in groups 1–3.[1 9 12]

Study procedures and assessments

Briefly, at screening (≤28 days prior to study initiation) participants received standard digital medical photography of externally visible lesions, or radiologic imaging of all target lesions, to meet baseline imaging requirements. Patients were excluded if they had received radiation therapy within 14 days of the planned cemiplimab start date.

Eligible patients in group 4 received cemiplimab 600 mg intravenously as a 30 min infusion Q4W for up to 48 weeks or until disease progression, unacceptable toxicity or withdrawal of consent. The protocol also contained a provision that, if patients completed 48 weeks of treatment without disease progression, it was permissible to repeat up to another 48 weeks (plus visit windows) of cemiplimab treatment if the investigator felt this to be in the best interest of the patient.

Assessments of tumor response were performed every 8 weeks by ICR per Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1[13] for radiologic imaging (CT or MRI) and modified WHO criteria for digital medical photography. Conventional imaging was performed as previously described.[9] Confirmatory imaging assessments were performed ≥4 weeks after initial documentation of all responses. Unconfirmed responses were considered stable disease for the best overall response assessment. For externally visible target lesions in patients with locally advanced CSCC, a complete response determined by digital medical photography was required to be confirmed by biopsies. In the statistical analysis, any patient who received radiation therapy after starting cemiplimab was considered to have disease progression.

In addition to conventional imaging, exploratory assessments for tumor response were quantified using optional ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) by ICR per European Organisation for Research and Treatment of Cancer (EORTC) PET criteria.[14] Optional PET scans were performed at screening, in addition to 6-month intervals (at the end of cycles 3 and 6) and at the end of the study (excluding

Table 2 Tumor response per independent central review and investigator assessment

Endpoint	Conventional imaging (primary endpoint, n=63)*		Endpoint	FDG-PET imaging (exploratory endpoint, n=55)†	
	Independent central review	Investigator assessment		Independent central review	Investigator assessment
ORR, n (%)	39 (61.9)	40 (63.5)	ORR, n (%)	35 (63.6)	38 (69.1)
95% CI‡	48.8–73.9	50.4–75.3	95% CI‡	49.6–76.2	55.2–80.9
Complete response, n (%)	14 (22.2)	12 (19.0)	Complete metabolic response, n (%)	17 (30.9)	20 (36.4)
Partial response, n (%)	25 (39.7)	28 (44.4)	Partial metabolic response, n (%)	18 (32.7)	18 (32.7)
Stable disease, n (%)	7 (11.1)	6 (9.5)	Stable metabolic disease, n (%)	5 (9.1)	2 (3.6)
Non-complete response/non-progressive disease, n (%)	3 (4.8)				
Progressive disease, n (%)	9 (14.3)	11 (17.5)	Progressive metabolic disease, n (%)	3 (5.5)	2 (3.6)
Not evaluable,§ n (%)	5 (7.9)	6 (9.5)	Not evaluable,§ n (%)	12 (21.8)	13 (23.6)
Disease control rate, n (%)	49 (77.8)	46 (73.0)			
95% CI‡	65.5–87.3	60.3–83.4			
Durable disease control rate, n (%)	48 (76.2)	45 (71.4)			
95% CI‡	63.8–86.0	58.7–82.1			
Number of doses, median (range)	11 (1–24)				
Duration of exposure, median (range), weeks	47.4 (4.0–97.0)				
Follow-up, median (range), months	22.4 (1.0–39.8)				

Data cut-off date: 20 April 2022.
*Conventional imaging data were reviewed first to establish the primary endpoint, and FDG-PET data were subsequently reviewed for the exploratory endpoint.
†Excludes patients from Germany as PET scans were not required for patients enrolled in Germany.
‡Clopper-Pearson exact CI.
§Includes missing and unknown tumor response.
FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography; NA, not applicable; ORR, objective response rate; PET, positron emission tomography.

patients who completed cycle 6). Of the PET scans included, none were performed in Germany.

For PK analyses, blood samples to measure serum concentrations of cemiplimab were collected before the initiation of cemiplimab infusion and immediately (within 10 min) post infusion for treatment cycle 1 (days 1 and 29±3) and cycles 2–6 (day 1), as well as at the end of the study. Population PK analysis was performed using non-linear mixed-effects modeling with NONMEM (V.7.4, ICON Development Solutions, Ellicott City, Maryland, USA), as described previously.[15] Procedures for assessment of programmed cell death-ligand 1 (PD-L1) expression and tumor mutational burden were previously reported.[9]

Outcomes

The primary endpoint was ORR, defined as the proportion of patients with best overall response of complete or partial response as assessed by ICR. Patients deemed not evaluable by RECIST V.1.1 were considered as not reaching partial or complete responses. Secondary outcomes included assessment of ORR using investigator response assessments, progression-free survival, overall survival, adverse events (AEs) and PK. Exploratory outcomes included FDG-PET (by ICR according to EORTC criteria) associations between clinical activity of cemiplimab and biomarkers of PD-L1 immunohistochemistry or tumor mutational burden.

Statistical analysis

All enrolled patients were analyzed as an intention-to-treat population. The primary efficacy analysis was based on an exact binomial CI approach, with a null hypothesis that the ORR would be 20%. A sample size of 60 patients with advanced CSCC was estimated to provide 92% power to reject the null hypothesis of 20% at a

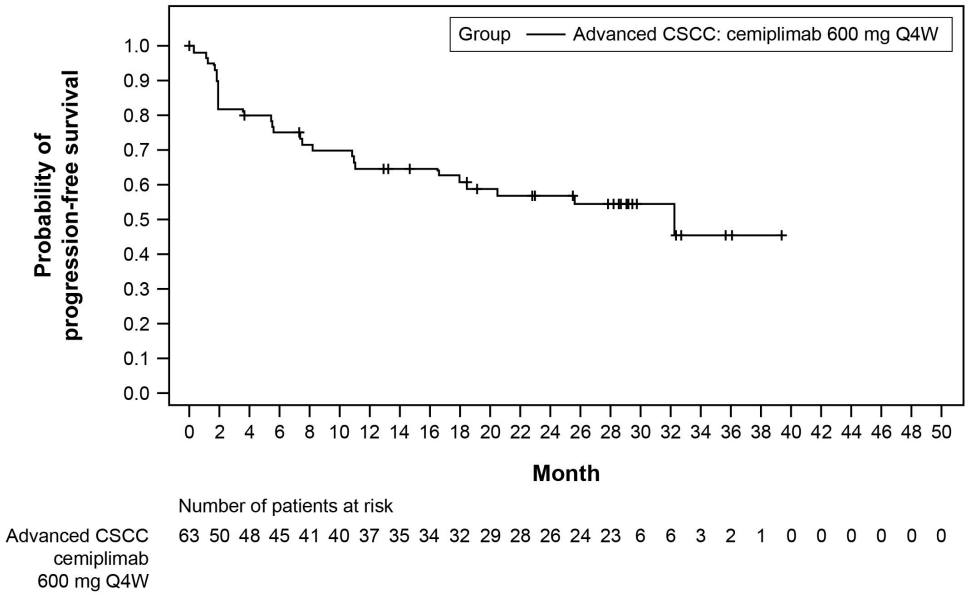

Figure 1 Progression-free survival in advanced CSCC, group 4. Data cut-off date: 20 April 2022. CSCC, cutaneous squamous cell carcinoma; Q4W, every 4 weeks.

two-sided significance level of 5%, if the true ORR was 40%. Accounting for premature patient withdrawal from the study, the sample size was increased by 5% to a total of 63 patients.

All efficacy endpoints were analyzed using the full analysis set, which included all eligible patients. Durable response was defined as the absence of progressive disease for ≥105 days. All enrolled patients who received at least one dose of cemiplimab were analyzed as part of the safety analysis set. Demographics, safety, and biomarker results were summarized using descriptive statistics. The PK analysis set included all patients who received any cemiplimab (safety analysis set) and had at least one non-missing cemiplimab measurement following the first dose of cemiplimab.

Statistical analyses were performed using SAS V.9.4 (SAS, Cary, North Carolina, USA). The prespecified timing for primary analysis was the date when the final enrolled patient had the opportunity for three tumor assessments as part of per-protocol study follow-up visits, corresponding to 24 weeks on study. The date for the final database lock for group 4 was 25 July 2022. The data cut-off date for the primary analysis was 20 April 2020.

The Strengthening the Reporting of Observational Studies in Epidemiology cohort reporting guidelines was used to develop the manuscript (available at: https://www.equator-network.org/reporting-guidelines/strobe/).

RESULTS

Patient disposition and characteristics

Between 28 November 2018 and 22 October 2019, 63 patients with metastatic CSCC (n=39) and locally advanced CSCC (n=24) were enrolled in group 4. Of these 63 patients, 43% (n=27) completed the planned 48 weeks of treatment and 57% (n=36) discontinued treatment. The reasons for discontinuation included disease progression (22%, n=14), AEs (16%, n=10, of which seven were considered possibly treatment-related), death (10%, n=6, of which one was considered treatment-related), physician decision (2%, n=1), patient decision (3%, n=2), withdrawal of consent (2%, n=1), and other reasons (8%, n=5). Baseline clinical characteristics are summarized in table 1. The median number of cemiplimab doses was 11 (range: 1–24) and the median duration of exposure was 47.4 weeks (range: 4.0–97.0). At the time of data cut-off, the median duration of follow-up was 22.4 months (range: 1.0–39.8).

Clinical efficacy

Per ICR, the ORR was 62% (n=39; 95% CI: 49% to 74%), with 22% (n=14) of patients achieving a complete response and 40% (n=25) of patients achieving a partial response (table 2). The median Kaplan-Meier estimation of duration of response was not reached (online supplemental figure S1); however, Kaplan-Meier estimation of the ongoing response at 12 months was 84% (95% CI: 68% to 93%). The disease control rate was 78% (n=49; 95% CI: 66% to 87%), and the durable disease control rate was 76% (95% CI: 64% to 86%) (table 2). The median progression-free survival per ICR and median overall survival had not been reached. Kaplan-Meier estimations of progression-free survival (figure 1) and probability of overall survival (online supplemental figure S2) at 12 months were 65% (95% CI: 51% to 76%) and 73% (95% CI: 60% to 83%), respectively.

Among the 55 patients who had optional baseline PET, ORR and complete metabolic response rates from ICR were 64% (95% CI: 50% to 76%) and 31%, respectively (table 2). Per ICR, the ORR and complete metabolic response of the primary analysis (online supplemental table S1) were comparable to the final analysis (table 2).

Table 3 Treatment-emergent AEs

Patients, n (%)	Advanced CSCC (group 4, n=63)	
	Any grade*	Grade ≥3
Any TEAE	63 (100)	34 (54)
Any serious TEAE	34 (54)	27 (43)
TEAEs leading to treatment discontinuation	11 (18)	8 (13)
TEAEs leading to death	6 (10)	6 (10)
Most common TEAEs (>10% of patients)†		
Diarrhea	17 (27)	1 (2)
Pruritus	16 (25)	0 (0)
Fatigue	14 (22)	0 (0)
Constipation	14 (22)	0 (0)
Rash	12 (19)	0 (0)
Arthralgia	12 (19)	0 (0)
Anemia	9 (14)	3 (5)
Maculopapular rash	8 (13)	1 (2)
Actinic keratosis	8 (13)	0 (0)
Upper respiratory tract infection	8 (13)	0 (0)
Dermatitis	7 (11)	0 (0)
Dyspnea	7 (11)	2 (3)
Acute kidney injury	7 (11)	1 (2)
Decreased appetite	7 (11)	1 (2)
Back pain	7 (11)	1 (2)
Headache	7 (11)	0 (0)
Skin infection	7 (11)	0 (0)
Cough	7 (11)	0 (0)
Peripheral edema	7 (11)	0 (0)

Data cut-off date: 20 April 2022.
*The severity of TEAEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
†TEAEs reported in≥10% of patients ordered by frequency of any-grade events.
AE, adverse event; CSCC, cutaneous squamous cell carcinoma; TEAE, treatment-emergent adverse event.

Safety

All patients experienced at least one TEAE, including 34 (54%) patients who experienced at least one grade ≥3 TEAE. The most common TEAEs of any grade reported by ≥20% of patients were diarrhea, pruritus, fatigue and constipation (table 3). Eleven (18%) patients discontinued treatment due to TEAEs, of which none occurred in more than one patient. Fifty-two (83%) patients experienced at least one treatment-related AE, including 10 (16%) with at least one grade ≥3 treatment-related AE (online supplemental table S2). The most common treatment-related AEs of any grade were pruritus, fatigue and rash (online supplemental table S2). Immune-related AEs by investigator assessment were reported in 48 (76%) patients, 10 (16%) of whom experienced grade ≥3 AEs. The most common immune-related AEs by investigator assessment and occurring in at least 15% of patients were pruritus and rash (online supplemental table S3).

TEAEs led to death in six (10%) patients; these were one event each of pneumonia, sepsis, cerebrovascular accident, myocardial infarction, unspecified lung disorder, and encephalopathy. Only the encephalopathy occurrence was considered by investigators as treatment related.

A comparison of TEAEs and treatment-related AEs between group 4 and groups 1–3 is shown in online supplemental table S4.

Pharmacokinetics

The extended dosing regimen of intravenous cemiplimab 600 mg Q4W resulted in a higher observed mean C_{max} compared with 350 mg Q3W (group 3) or 3 mg/kg Q2W (groups 1 and 2), as predicted using the population pharmacokinetic model (table 4). The observed mean C_{trough} values were similar for all dose groups. The predicted cemiplimab concentrations using the population PK model closely aligned with the observed cemiplimab concentrations at steady state.

Exploratory biomarker assessments

Among the 63 patients enrolled, 41 (65%) had samples available for assessment of tumor PD-L1 status at baseline. An objective response was observed in 4 of 10 patients (40%; 95% CI: 12% to 74%) with PD-L1 membrane staining of <1%, and in 22 of 31 patients (71%; 95% CI: 52% to 86) with detectable PD-L1 membrane staining of ≥1%. ORRs were observed in patients irrespective of baseline PD-L1 membrane staining (online supplemental table S5).

Among 47 (75%) patients with pretreatment tumor mutational burden assessments, the median (IQR) tumor mutational burden was 87.85 (39.19 to 121.44) mutations per megabase for 29 responders (per ICR) and 20.92 (7.83 to 53.43) mutations per megabase for 18 non-responders (per ICR). Overall, broad ranges in tumor mutational burden were observed for both patients who did and did not respond to cemiplimab treatment (online supplemental figure S3).

DISCUSSION

Since US Food and Drug Administration approval in 2018, intravenous cemiplimab 350 mg Q3W has become a standard of care indicated for patients with advanced CSCC.[6 16] The primary analysis in this cohort of patients established that the extended dosing regimen of intravenous cemiplimab 600 mg Q4W was a highly active therapy and had a safety profile generally consistent with that of the approved dose. Per ICR, cemiplimab 600 mg dosed intravenously Q4W resulted in an ORR of 62%, including a 22% complete response rate.

Table 4 Pharmacokinetics in patients with CSCC following intravenous administration of cemiplimab

Group, dose	Observed cemiplimab concentrations at steady state (weeks 17–19)					
	C_{trough}, mg/L			C_{max}, mg/L		
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)
Groups 1 and 2, 3 mg/kg Q2W	96	68.4 (26.1)	72.0 (49.9–80.8)	96	150 (79.0)	141 (113–162)
Group 3, 350 mg Q3W	34	62.7 (28.3)	65.3 (44.3–77.3)	33	151 (46.2)	165 (129–181)
Group 4, 600 mg Q4W	44	62.5 (24.1)	65.4 (50.7–80.4)	41	281 (235)	239 (205–268)

Cemiplimab dose	Predicted cemiplimab concentrations at steady state using population PK model (n=1062)					
	C_{trough}, mg/L		C_{max}, mg/L		C_{av}, mg/mL	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
350 mg Q3W	60.8 (27.4)	56.6 (42.4–74.1)	173 (47.3)	168 (139–198)	92.9 (33.0)	88.4 (70.1–111)
600 mg Q4W	68.4 (33.2)	63.2 (45.9–84.4)	260 (69.1)	254 (211–297)	119 (42.5)	114 (90.1–143)

Data cut-off date: 20 April 2020.
C_{av}, average concentration; C_{max}, maximum concentration; CSCC, cutaneous squamous cell carcinoma; C_{trough}, trough concentration; PK, pharmacokinetics; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks.

The observed C_{trough} and C_{max} values at steady state with the cemiplimab 600 mg Q4W intravenous dosing regimen agreed with the population PK modeling predictions that this extended dosing regimen would have the same C_{trough} as the approved dosing regimen for cemiplimab. Consistent with the population PK model, the extended dosing regimen of cemiplimab resulted in observed mean C_{trough} values that were similar across all the dosing regimens and in observed mean C_{max} values that were higher with the extended dosing regimen compared with the other dosing regimens. Overall, this extended dosing regimen provided comparable cemiplimab exposure and a convenient alternative.

The observed ORR and complete response rates with intravenous cemiplimab 600 mg Q4W were numerically higher compared with the response rates in the trials of Q2W and Q3W schedules of cemiplimab (43%–51%)[12] and in the reported pembrolizumab trials (200 mg Q3W; 34%–50%).[17–19] The 12-month estimates of progression-free survival and overall survival, however, appeared similar to earlier studies. A numerical increase in treatment discontinuations and deaths due to TEAEs was observed with the extended dosing regimen compared with the trials investigating Q2W and Q3W schedules of cemiplimab,[12] although the sample size is small for this group 4 cohort and the number of treatment-related AEs leading to death is comparable.

Comparisons between non-randomized phase II cohorts have major limitations. Baseline characteristics may have resulted in enrichment within one group of patients who had more favorable clinical characteristics. For example, more patients in group 4 (86%) received cemiplimab as first-line therapy compared with groups 1–3 (66%) (table 1).[10] In the analysis of groups 1–3, the response rates without and with systemic therapy were 48% and 42%, respectively.[8] Imbalances in baseline characteristics between non-randomized cohorts may have contributed to differences in clinical outcomes. Studies with different anti-PD-1 agents suggest the exposure–response curve is flat in other tumor types.[20] Extended-interval dose administration with other anti-PD-1 agents has been adopted based on modeling rather than head-to-head comparisons.[20 21]

In this prospective study, exploratory results suggested that FDG-PET had comparable sensitivity to conventional imaging to detect objective responses (62% vs 59% by ICR) yet detected a greater percentage of complete responses versus conventional imaging (31% vs 22%; online supplemental table S4). This preliminary finding may suggest that FDG-PET scans have a higher sensitivity than conventional imaging to detect complete responses in patients with advanced CSCC. Further study and longer follow-up are needed to determine whether FDG-PET can be used in the clinic to identify both patients likely to have durable responses and those in whom cemiplimab therapy can be stopped earlier after documentation of complete metabolic response.[22]

The results of exploratory biomarker assessments of PD-L1 expression and tumor mutational burden for group 4 were similar to previously published results for groups 1–3. Although the response rates in the PD-L1 negative group and in the low tumor mutational burden groups were lower, there was considerable overlap, with many responses still occurring in both these groups. Hence, when using these cut-points these biomarkers do not have any utility in predicting clinical benefit.

These data demonstrate substantial antitumor activity, rapid and durable responses, and an acceptable safety

profile with an extended dosing regimen of cemiplimab 600 mg Q4W intravenously in patients with advanced CSCC who were not candidates for curative surgery or curative radiation. However, the non-randomized nature of the data has inevitably led to imbalances in baseline characteristics and potentially other unknown confounders. The approved dose and schedule for cemiplimab in the treatment of advanced CSCC remain intravenous 350 mg Q3W.

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Correction notice This article has been corrected since it was first published online. The author Axel Hauschild was incorrectly listed as Axel Hausschild.

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Contributors Conceptualization: MGF, IL, FS. Drafting of study protocol and analysis plan: MGF. Data acquisition: DR, BGMH, NB-S, DS, SB, STM, FM, TE, VCE, BS, MB-B, SD, BD, MRM, AH, CDS, AML, AG. Formal analysis: AJP and AP, J-HN (PK analysis), MGF, EO. Writing – review and editing: DR, BGMH, NB-S, DS, SB, STM, FM, TE, VCE, BS, MB-B, SD, BD, MRM, AH, CDS, AML, S-YY, AJP, AP, J-HN, EO, FS, JB, IL, MGF, AG. Guarantor: DR.

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Patient consent for publication Not applicable.

Ethics approval The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines, and was overseen by a steering committee. All patients provided written informed consent prior to enrollment. The following Institutional Review Boards approved the study: Peter MacCallum Cancer Centre Ethics Governance (ID: EC00235); Northern Sydney Local Health District HREC (ID: EC00112); Sir Charles Gairdner Osborne Park Health Care Group RG Office (ID: RGS0000001838); Tenille Baker (ID: ICON/2022/05/03). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing once the product and indication has been approved by major health authorities (eg, FDA, EMA, PMDA, etc.), if there is legal authority to share the data and there is not a reasonable likelihood of participant reidentification. Submit requests to https://vivli.org/.

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