22 April 2022
EMA/665912/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

LIBTAYO

International non-proprietary name: cemiplimab

Procedure No. EMEA/H/C/004844/R/0029

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure:	24 Jan 2022	24 Jan 2022	☐
☐	CHMP and PRAC Rapporteurs Joint Assessment Report	22 Feb 2022	14 Mar 2022	☐
☐	CHMP and PRAC members comments	28 Feb 2022	28 Feb 2022	☐
☐	Updated CHMP and PRAC Rapporteurs Joint Assessment Report	03 Mar 2022	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	10 Mar 2022	10 Mar 2022	☐
☐	Request for Supplementary Information	24 Mar 2022	24 Mar 2022	☐
☐	MAH responses to (RfSI) received on	30 Mar 2022	30 Mar 2022	☐
☐	Restart date	31 Mar 2022	31 Mar 2022	☐
☐	CHMP and PRAC Rapporteurs' joint assessment report	6 Apr 2022	8 April 2022	☐
☐	PRAC endorsed relevant sections of the assessment report3	07 Apr 2022	07 Apr 2022	☐
☐	CHMP and PRAC members comments	11 Apr 2022	11 Apr 2022	☐
☐	Updated CHMP and PRAC Rapporteurs joint assessment report	13 Apr 2022	n/a	☐
☒	Opinion	22 Apr 2022	22 Apr 2022	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for PRAC plenary discussion: interim results/outcome of the SOB that is a non-interventional PASS study challenging the benefit/risk balance of the product; new imposed non-interventional PASS resulting from the annual renewal (annex II condition); divergent positions between the Committees (CHMP and PRAC Rapp and CHMP and PRAC members) on specific aspects with significant impact on the B/R and any other situation at the discretion of the PRAC rapporteur.

Criteria for CHMP plenary discussion: interim results/outcome of the SOB challenging the benefit/risk balance of the product; fulfilment of all SOBs; non-compliance with SOB(s); new imposed PASS/PAES resulting from the annual renewal (annex II condition or new SOB); divergent positions between the Committees (CHMP and PRAC Rapp and CHMP and PRAC members) on specific aspects with significant impact on the B/R and any other situation at the discretion of the CHMP rapporteur.

[3] Sections related to data on non-interventional PASS imposed as an SOB, Risk Management Plan (safety concerns, Pharmacovigilance plans, Risk minimisation Measures), sections on issues originating from parallel/recent PSUR or signal assessment, additional monitoring, pharmacovigilance inspections and preliminary conclusions on the benefit/risk balance.

Procedure resources	
CHMP Rapporteur:	Aarón Sosa
PRAC Rapporteur:	Menno van der Elst

Declarations

☒The assessor confirms that proprietary information on, or reference to, third parties or products are not included in this assessment, unless there are previous contracts and/or agreements with the third party(ies).

☒ (Non-Clinical/Clinical/Pharmacovigilance) The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report, including in the Product Information, if any.

Whenever the above box is un-ticked please indicate section and page where confidential information is located here:

Table of contents

1. Background information on the annual renewal

The European Commission issued on 28 June 2019, a conditional marketing authorisation (MA) for LIBTAYO This implied that, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 5 of Commission Regulation (EC) No 507/2006, the marketing authorisation holder (MAH) has to complete ongoing studies, or to conduct new studies, as listed in Annex II.E of the MA, the so-called Specific Obligations (SOBs). These data form the basis of the renewal of the conditional MA.

A conditional MA is valid for one year and may be renewed annually upon request by the MAH. Therefore, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 6(2) of Commission Regulation (EC) No 507/2006, the MAH Regeneron Ireland Designated Activity Company (DAC), submitted to the Agency on 6 January 2022 an application for renewal of the conditional MA for LIBTAYO. The expiry date of the MA is 2 July 2022.

While the final CSR is not yet available for Groups 1 to 3, the MAH considers that the additional Group 1 to 3 data further confirm the efficacy and safety of cemiplimab for the treatment of patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation. As such, the MAH proposes that this SOB (ANX/FSR 002) be re-categorised as a post-authorisation efficacy study to be included under commitments in Annex IID of the LIBTAYO EU Product Information, retaining the same due date of 31 Oct 2022, and that the corresponding sections of the EU RMP be updated accordingly. This proposal was agreed upon with the EMA Rapporteurs in May 2021.

The MAH considers that each of the aspects of the 2 SOBs are fulfilled by the data included in the present dossier. The data further confirm the efficacy and safety of cemiplimab for the treatment of patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation. The data further confirm that PD-L1 expression is not predictive of efficacy in advanced CSCC. Furthermore, positive data in additional tumor types (NSCLC and BCC) have further contributed to our understanding of the benefit/risk profile of cemiplimab since the initial CMA was granted. As such, the position of the MAH is that sufficient data are available to grant a standard MA for LIBTAYO within the present annual renewal. The MAH proposes to maintain a commitment to submit the final CSR for Groups 1 to 3 by 31 October 2022.

The application contained a justification in support of the possible granting of a marketing authorisation not subject to specific obligations.

2. Overall conclusions and benefit-risk balance

As part of the CMA two SOBs where adopted. The MAH was asked to provide the final CSR for Groups 1-3 and to add a Group 6 in order to confirm efficacy and safety of cemiplimab in CSCC. As agreed at a meeting in May 2021, the MAH provides updated results from Groups 1-3 and the interim results of Group 6. With the submission of these data, the MAH is proposing is seeking a standard MA for Libtayo within the annual renewal. The MAH commits to submitting the final CSR for Groups 1-3 by 31 October 2022. This can be submitted as a PAM-REC.

The data show overall comparison between Groups 1-3 and Group 6 in terms of baseline characteristics. With regards to efficacy, the updated ORR and DOR from Groups 1-3 continue to show clinically meaningful benefit, and the ORR and DOR observed in Group 6 are in line with Group 1-3. The MAH has excluded two patients from the efficacy evaluation in Group 6. Both patients didn't receive any treatment with cemiplimab. Thus, their exclusion is endorsed.

Approximately half of the 84 patients in scope of the interim analysis in Group 6 had an available baseline tumor sample. The numbers are small, but it can with reasonable likelihood be concluded that

efficacy of cemiplimab is not predicted by PD-L1 expression in CSCC. The results show clinical benefit irrespective of PD-L1 expression. This supports the continued use of cemiplimab in all-comers in this specific clinical setting.

In terms of safety, the observed safety findings in Group 6 are in line with the known safety profile of cemiplimab. Almost all patients experienced an TEAE (98.8%). Approximately 39% experienced a Grade ≥3 AEs, and 40.2% an SAE. The most common AEs continue to be fatigue, pruritus, rash and diarrhoea. There are no new safety findings. A few OCs have been identified and were addressed by the MAH.

Since the last annual renewal in January 2021, the CHMP has given positive opinion for two additional indications in non-small cell lung cancer (NSCLC) and basal cell carcinoma (BCC), resulting in approvals by the European Commission in June 2021. Furthermore, two procedures are ongoing in CHMP at the moment.

Overall, the efficacy of cemiplimab has been confirmed in several different settings, and with the submission of updated data from Groups 1-3 and interim data from Group 6, there are no longer any regulatory nor clinical arguments to keep cemiplimab on CMA.

In conclusion, the Rapporteur is of the opinion that Specific Obligation has been fulfilled, and therefore recommends its deletion from the Annex II.

The B/R balance of Libtayo remains unchanged and positive in the approved indications.

2.1. Specific Obligations (SOBs)

Compliance of SOB data submitted

During the period covered by this annual renewal data on the SOBs have been submitted that overall are compliant in terms of adherence to deadlines and are compliant in terms of acceptability of data submitted.

As part of this annual renewal the CHMP is of the opinion that the following obligations have been fulfilled, and therefore recommends their deletion from the Annex II:

1. In order to confirm the efficacy and safety of cemiplimab for the treatment of patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation, the MAH should provide interim data of a single-arm trial in the same population [study 1540 group 6]. The MAH should investigate biomarkers in order to confirm that PD-L1 expression is not predictive of efficacy. The study should be conducted according to an agreed protocol.
2. In order to confirm the efficacy and safety of cemiplimab for the treatment of patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation, the MAH should submit the final study report for Groups 1-3 in the phase 2 pivotal study 1540.

The last SOB has been fulfilled and the data available concerning this product is considered comprehensive; therefore, there are no remaining Specific Obligations.

2.2. Benefit-risk Balance

During the period covered by this annual renewal, new data have emerged. However, these data do not have an impact on the benefit-risk of LIBTAYO in the approved indications.

The data collected as part of the specific obligations for LIBTAYO during the period covered by this annual renewal supported its positive benefit-risk balance in the approved indications.

3. Recommendations

Based on the review of the available information on the status of the fulfilment of Specific Obligations, the benefit-risk balance for LIBTAYO in its approved indication(s) (please refer to the Summary of Product Characteristics) continues to be favourable and all specific obligations have been fulfilled, and therefore the granting of a marketing authorisation no longer subject to specific obligations is recommended, subject to the conditions and obligations as detailed in this assessment report.

Amendments to the marketing authorisation

In view of new data submitted as part of the renewal application amendments to Annexes I, II and IIIB are recommended.

Updates to the Product Information were made in line with the SmPC guideline and the latest QRD template (version 10.2).

The following obligations has been fulfilled, and therefore it is recommended that it be deleted from the Annex II to the opinion:

1. In order to confirm the efficacy and safety of cemiplimab for the treatment of patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation, the MAH should provide interim data of a single-arm trial in the same population [study 1540 group 6]. The MAH should investigate biomarkers in order to confirm that PD-L1 expression is not predictive of efficacy. The study should be conducted according to an agreed protocol.
2. In order to confirm the efficacy and safety of cemiplimab for the treatment of patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation, the MAH should submit the final study report for Groups 1-3 in the phase 2 pivotal study 1540.

Please refer to the Attachment which includes all agreed changes to the Product Information.

Conditions of the marketing authorisation

The marketing authorisation is subject to the following conditions:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- ***Additional risk minimisation measures***

Prior to launch of LIBTAYO in each Member State, the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where LIBTAYO is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use LIBTAYO have access to/are provided with the following educational package:

- A patient guide

- A patient alert card

- **The patient guide** shall contain the following key messages
    - Description of the main signs or symptoms of the immune-related adverse reactions (pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis and other irARs) and infusion related reactions, and the importance of notifying their treating physician immediately if symptoms occur.
    - The importance of not attempting to self-treat any symptoms without consulting their healthcare professional first.
    - The importance of carrying the Patient Alert Card at all times and to show it at all medical visits to healthcare professionals other than the prescriber (e.g. emergency healthcare professionals).
    - A reminder that all known or suspected adverse drug reactions (ADRs) can also be reported to local regulatory authorities.
- **The patient alert card** shall contain the following key messages:
    - A warning message for health care professionals treating the patient at any time, including in conditions of emergency, that the patient is treated with LIBTAYO.
    - Description of the main signs or symptoms of the immune-related adverse reactions (pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis and other irARs) and infusion related reactions, and the importance of notifying their treating physician immediately if symptoms occur.

The contact details of their LIBTAYO prescriber.

● *Obligation to conduct post-authorisation measures*

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Post authorisation efficacy study (PAES): in order to further characterise the efficacy and safety of cemiplimab in mBCC, the MAH should submit the primary analysis for mBCC and the final study report from clinical study 1620 evaluating objective response rate and duration of response of cemiplimab in patients with mBCC who experienced progression of disease on hedgehog pathway inhibitor therapy or were intolerant of prior hedgehog pathway inhibitor therapy. Submission of final clinical study report	30th June 2024

PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

4. EPAR changes

The table in the "Steps after" module of the EPAR will be updated as follows:

Scope

Renewal of conditional marketing authorisation

Summary

The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated. Furthermore, the CHMP considered that, as all Specific Obligations have been fulfilled, there are no remaining grounds for the marketing authorisations to remain conditional and therefore recommends the granting of the MA no longer subject to Specific Obligations for LIBTAYO.

Annex: Rapporteurs' assessment comments on the renewal

PRAC input:

In this annual renewal,	**Yes**	**No**
- RMP submitted (If yes is ticked, discussion should be included in the Risk management plan section of the Annex)	☒	☐
- Outstanding SOB is a non-interventional PASS study (If yes is ticked, the relevant discussion should be included in the sub-section Outstanding Specific Obligations – status report for period covered of the Annex)	☒	☐
- There are issues originating from a parallel/recent PSUR or signal assessment to be flagged to the CHMP rapporteur (If yes is ticked, the relevant discussion should be included in the Clinical safety section of the Annex)	☐	☐
- PhV inspections have been conducted/are ongoing with an impact on the MA under annual Re-Assessment (If yes is ticked, the relevant discussion should be included in the Pharmacovigilance inspections section of the Annex)	☐	☐

5. Specific Obligations

5.1. Specific Obligations adopted with the initial marketing authorisation

Table 1: Summary of Specific Obligations (SOBs)

Reference Number	Description	Due Date
ANX/FSR 001.1	In order to confirm the efficacy and safety of cemiplimab for the treatment of patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation, the MAH should provide interim data of a single-arm trial in the same population [study 1540 group 6]. The MAH should investigate biomarkers in order to confirm that PD-L1 expression is not predictive of efficacy.	31 March 2023
ANX/PRO 001	The study should be conducted according to an agreed protocol.	Protocol (ANX/PRO 001) was agreed by CHMP on 18 October 2019
ANX/FSR 002	In order to confirm the efficacy and safety of cemiplimab for the treatment of patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation, the MAH should submit the final study report for Groups 1-3 in the phase 2 pivotal study 1540.	31 October 2022

5.2. Outstanding Specific Obligations – status report for period covered

Study 1540

Study 1540 is a phase 2, open-label study of cemiplimab, a recombinant human immunoglobulin (Ig) G4 monoclonal antibody (mAb) directed against programmed death-1 (PD-1)

receptor. Study 1540 is evaluating efficacy, safety, and PK of cemiplimab in patients with either mCSCC or with laCSCC. The patient population for Groups 1, 2, 3, and 6 are as follows:

- Group 1 consists of patients with mCSCC who received cemiplimab 3 mg/kg as an intravenous (IV) infusion over 30 minutes every 2 weeks (Q2W).
- Group 2 consists of patients with laCSCC who were not candidates for surgery or radiation, and received cemiplimab 3 mg/kg as an IV infusion over 30 minutes Q2W.
- Group 3 consists of mCSCC patients who received cemiplimab 350 mg as an IV infusion over 30 minutes Q3W.
- Group 6 consists of both mCSCC and laCSCC patients who are receiving cemiplimab 350 mg as an IV infusion over 30 minutes Q3W.

The primary objective of this study was to estimate the clinical benefit of cemiplimab monotherapy for patients with mCSCC treated with 3 mg/kg Q2W (Group 1), laCSCC treated with 3 mg/kg Q2W (Group 2), or mCSCC treated with 350 mg Q3W (Group 3), as measured by the objective response rate (ORR) according to independent central review (ICR) in each group. For Group 6, the primary objective was to provide additional efficacy and safety data for cemiplimab monotherapy in patients with advanced CSCC (metastatic [nodal or distant] or locally advanced) treated with cemiplimab 350 mg Q3W.

The secondary objectives for all groups included the following:

- To estimate the ORR according to investigator review
- To estimate the duration of response (DOR) and progression-free survival (PFS) by central and investigator review and overall survival (OS)
- To estimate the complete response (CR) rate by ICR
- To assess the safety and tolerability of cemiplimab
- To assess the PK of cemiplimab
- To assess the immunogenicity of cemiplimab

For Groups 1 to 3 only: To assess the impact of cemiplimab on quality of life (QoL) using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

For Group 6 only: To assess relationships between PD-L1 status (by IHC) and efficacy measures (ORR, DOR, PFS).

Methods

Study Participants

Inclusion Criteria

A patient must have met the following criteria to be eligible for inclusion in the study:

1. Histologically confirmed diagnosis of invasive CSCC.

Notes on tumor primary site: Patients whose primary site of squamous cell carcinoma was the dry red lip (vermillion) were not eligible. Patients with tumors arising on the cutaneous hair bearing

(nonglabrous) lip with extension onto dry red lip (vermillion) may have been eligible after communication with and approval from medical monitor.

Patients for whom the primary site of squamous cell carcinoma was the anogenital area (penis, scrotum, and perianal region) were not eligible. Patients for whom the primary site was nose were only eligible if the investigator was able to establish unambiguously that the primary site was the skin, not nasal mucosa with outward extension to skin.

Notes on tumor histology: Patients with mixed histologies (eg, sarcomatoid, adenosquamous) generally were not eligible. Patients with mixed histology in which the predominant histology was invasive CSCC (with only a minimal component of mixed histology) may have been eligible, after communication with and approval from medical monitor.

2. At least 1 lesion that was measurable by study criteria. If a previously radiated lesion was to be followed as a target lesion, progression must have been confirmed by biopsy after radiation therapy. Previously radiated lesions may have been followed as non-target lesions if there was at least 1 other measurable target lesion.

For patients with metastatic (nodal or distant) CSCC: There had to be at least 1 baseline measurable lesion ≥10 mm in maximal diameter (1.5 cm for lymph nodes) according to RECIST 1.1 (Appendix 1 of the study protocol [Appendix 1.1])

Note: In the case of patients with metastatic disease that did not meet target lesion criteria by RECIST 1.1 (eg, bone only lesions, perineural disease; Appendix 1 of the study protocol [Appendix 1.1]) and with externally visible CSCC target lesion(s), Appendix 2 of the study protocol (Appendix 1.1) may have been used, in which bi-dimensional measurements were required (at baseline, perpendicular diameters must both be ≥10 mm). The patient would then have been enrolled with the plan to measure externally visible target lesion(s) by photography with bi-dimensional measurements; the metastatic lesions not measurable by RECIST 1.1 criteria would have been followed as non-target lesions on scans.

For patients with laCSCC: There must have been at least 1 measurable baseline lesion in which the longest diameter and the perpendicular diameter were both ≥10 mm if followed by digital medical photography (Appendix 2 of the study protocol [Appendix 1.1]). Non-measurable disease was defined as either unidimensionally measurable lesions, tumors with margins that were not clearly defined, or lesions with maximum perpendicular diameters less than 10 mm. Patients without measurable disease at baseline were not eligible for the study.

3. ECOG performance status ≤1 (ECOG PS 1 definition: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work; Appendix 7 of the study protocol [Appendix 1.1]). Note: Patients with ECOG PS >1 were ineligible.
4. ≥18 years old.
5. Hepatic function:

   a. Total bilirubin ≤1.5 × upper limit of normal (ULN); if liver metastases ≤3 × ULN). Patients with Gilbert's Disease and total bilirubin up to 3 × ULN may have been eligible after communication with and approval from the medical monitor.

   b. Transaminases ≤3 × ULN (or ≤5.0 × ULN, if liver metastases).

   c. ALP ≤2.5 × ULN (or ≤5.0 × ULN, if liver or bone metastases).

Note for patients with hepatic metastases: If transaminase levels (AST and/or ALT) were >3 × but ≤5 × ULN, total bilirubin was to be ≤1.5 × ULN. If total bilirubin was >1.5 × but ≤3 × ULN, both transaminases (AST and ALT) were to be ≤3 × ULN.

6. Renal function: Serum creatinine ≤1.5 × ULN or estimated creatinine clearance >30 mL/min.
7. Bone marrow function:

   a. Hemoglobin ≥9.0 g/dL.

   b. Absolute neutrophil count (ANC) ≥1.5 × 109/L.

   c. Platelet count ≥75 × 109/L.
8. Ability to provide signed informed consent.
9. Ability and willingness to comply with scheduled visits, treatment plans, laboratory tests, and other study-related procedures.
10. Anticipated life expectancy >12 weeks.
11. Patients with laCSCC: Surgery was deemed contraindicated in the opinion of a Mohs dermatologic surgeon, a head and neck surgeon, or plastic surgeon. A copy of the surgeon's consultation note from a clinical visit within 60 days of enrollment was submitted.

    Acceptable contraindications in the surgeon's note included the following:

    - CSCC that recurred in the same location after 2 or more surgical procedures and
    - curative resection was deemed unlikely.
    - CSCCs with significant local invasion that precluded complete resection.
    - CSCCs in anatomically challenging locations for which surgery may have resulted in severe disfigurement or dysfunction (eg, removal of all or part of a facial structure, such as nose, ear, or eye; or requirement for limb amputation).
    - Other conditions deemed to be contraindicating for surgery were discussed with the medical monitor before enrolling the patient.

12. Patients with laCSCC: Patients were deemed as not appropriate for radiation therapy.

    Specifically, patients met at least 1 of the following criteria:

    a. A patient previously received radiation therapy for CSCC, such that further radiation therapy exceeded the threshold of acceptable cumulative dose, per the radiation oncologist. A copy of the radiation oncologist's consultation note, from a clinical visit within 60 days of enrollment, was to be submitted.

    b. Judgment of radiation oncologist that such tumor was unlikely to respond to therapy. A copy of the radiation oncologist's consultation note, from a clinical visit within 60 days of enrollment, was to be submitted.

    c. A clinic note from the investigator indicating that an individualized benefit:risk assessment was performed by a multidisciplinary team (consisting of, at minimum, a radiation oncologist, and either a medical oncologist with expertise in cutaneous malignancies or a dermato-oncologist, or a head and neck surgeon) within 60 days prior to enrollment in the proposed study, and the radiation therapy was deemed to be contraindicated.

Acceptable contraindications to radiation therapy in the investigator's note for patients

who had not received any prior radiation included the following:

• CSCCs in anatomically challenging locations for which radiation therapy would be associated with unacceptable toxicity risk in the context of the patient's overall medical condition in the opinion of the multidisciplinary team (eg, a neck tumor for which radiation therapy would have resulted in potential need for a percutaneous gastrostomy tube). A copy of the investigator's consultation note documenting the multidisciplinary assessment was to be submitted.

• Other conditions deemed to be contraindicating for radiation therapy were discussed with the medical monitor before enrolling the patient.

13. Groups 1, 2 and 3: All patients in either group consented to provide archived or newly obtained tumor material (either FFPE block or 10 unstained or stained slides) for central pathology review for confirmation of diagnosis of CSCC. This material was received by the sponsor prior to enrollment.
14. Group 2 only (laCSCC patients): Patients consented to undergo biopsies of externally visible CSCC lesions at baseline, cycle 1 day 29 (±3 business days), at time of tumor progression, and at other time points that were clinically indicated in the opinion of the investigator.
15. Patients with laCSCC: An investigator note which stated that the natural history of the patient's advanced CSCC would likely be life-threatening within 3 years with currently available management options outside of a clinical study or cemiplimab.
16. Group 6 only: Patients had to consent to undergo biopsies of CSCC lesions at baseline (and at time of tumor progression, if possible), unless the investigator communicated to the medical monitor that there was unacceptable safety risk associated with tumor biopsy in a particular patient, and at other time points that might be clinically indicated in the opinion of the investigator.

Exclusion Criteria

A patient who met any of the following criteria was excluded from the study:

1. Ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for irAEs. The following were not exclusionary: vitiligo, childhood asthma that had resolved, type 1 diabetes, residual hypothyroidism that required only hormone replacement, or psoriasis that did not require systemic treatment.
2. Prior treatment with an agent that blocks the PD-1/PD-L1 pathway.
3. Prior treatment with other immune modulating agents that was (a) within fewer than

1. 4 weeks (28 days) prior to the first dose of cemiplimab, or (b) associated with immune-related AEs that were grade ≥1 within 90 days prior to the first dose of cemiplimab, or (c) associated with toxicity that resulted in discontinuation of the immune-modulating agent. Examples of immune modulating agents included therapeutic anticancer vaccines, cytokine treatments (other than G-CSF or erythropoietin), or agents that target cytotoxic T-lymphocyte antigen 4, 4-1BB (CD137), PI 3-K-delta, or OX-40.
4. Untreated brain metastasis(es) that were considered active. (Note: patients with brain involvement of CSCC due to direct extension of invading tumor, rather than metastasis, were

allowed to enroll if they did not require greater than 10 mg prednisone daily, after discussion and approval of the medical monitor). Patients with previously treated brain metastases could participate provided that the lesion(s) was (were) stable (without evidence of progression for at least 6 weeks on imaging obtained in the screening period), and there was no evidence of new or enlarging brain metastases, and the patient did not require any immunosuppressive doses of systemic corticosteroids for management of brain metastasis(es) within 4 weeks of first dose of cemiplimab.

5. Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of cemiplimab.

Note: Patients who required brief course of steroids (eg, as prophylaxis for imaging studies due to hypersensitivity to contrast agents) were not excluded.

6. Active infection requiring therapy, including known infection with human immunodeficiency virus (HIV), or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).
7. History of pneumonitis within the last 5 years.
8. Grade ≥3 hypercalcemia at time of enrollment.
9. Any systemic anticancer treatment (chemotherapy, targeted systemic therapy, photodynamic therapy), investigational or standard of care, within 30 days of the initial administration of cemiplimab or planned to occur during the study period (patients receiving bisphosphonates or denosumab were not excluded), radiation therapy within 14 days of initial administration of cemiplimab or planned to occur during the study period.

Note: For patients with multiple CSCCs at baseline that were not designated by the investigator as target lesions, treatment of these non-target CSCCs with surgery could be permitted but must have been discussed with the medical monitor prior to any surgical procedure.

10. History of documented allergic reactions or acute hypersensitivity reaction attributed to antibody treatments.
11. Patients with allergy or hypersensitivity to cemiplimab or to any of the excipients were excluded.
12. Breastfeeding.
13. Positive serum pregnancy test (a false positive pregnancy test, if demonstrated by serial measurements and negative ultrasound, was not exclusionary, upon communication with and approval from the medical monitor).
14. Concurrent malignancy other than CSCC and/or history of malignancy other than CSCC within 3 years of date of first planned dose of cemiplimab, except for tumors with negligible risk of metastasis or death, such as adequately treated BCC of the skin, carcinoma in situ of the cervix, or ductal carcinoma in situ of the breast; low-risk early stage prostate adenocarcinoma (T1-T2aN0M0 and Gleason score ≤6 and prostate specific antigen [PSA] ≤10 ng/mL) for which the management plan was active surveillance; or prostate adenocarcinoma with biochemical-only recurrence with documented PSA doubling time of >12 months for which the management plan was active surveillance (D'Amico, 2005) (Pham, 2016). Patients with hematologic malignancies (eg, chronic lymphocytic leukemia) were excluded.
15. Any acute or chronic psychiatric problems that, in the opinion of the investigator, made the patient ineligible for participation.

16. Continued sexual activity in men** or women of childbearing potential (WOCBP)* who were unwilling to practice highly effective contraception prior to the initial dose/start of the first dose, during the study and until 6 months after the last dose.

    Highly effective contraceptive measures include:

    a. stable use of oral contraceptives such as combined estrogen and progestogen and progestogen only hormonal contraception or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to screening.

    b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS);

    c. bilateral tubal ligation;

    d. vasectomized partner (provided that the male vasectomized partner was the sole sexual partner of the WOCBP study participant and that the vasectomized partner had obtained medical assessment of surgical success for the procedure)

    e. and/or sexual abstinence†, ‡.

* WOCBP was defined as women who were fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods included hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

** A postmenopausal state was defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range could be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement was insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to Clinical Trial Facilitation Group (CTFG) guidance. Pregnancy testing and contraception were not required for women with documented hysterectomy or tubal ligation.

† Sexual abstinence was considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence had to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

‡ Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) were not acceptable methods of contraception. Female condom and male condom could not be used together.

17. Patients with a history of solid organ transplant (patients with prior corneal transplant[s] may have been allowed to enroll after discussion with and approval from the medical monitor).

18. Prior treatment with a BRAF inhibitor.

19. Any medical co-morbidity, physical examination finding, or metabolic dysfunction, or clinical laboratory abnormality that, in the opinion of the investigator, rendered the patient unsuitable for participation in a clinical trial due to high safety risks and/or potential to affect interpretation of results of the study.

Note in clarification: The investigator must have contacted the sponsor's medical monitor regarding any patients that the investigator felt could not provide the required baseline tumor biopsies.

20. Inability to undergo any contrast-enhanced radiologic response assessment.

Notes regarding imaging options: A patient who was unable to undergo computed tomography (CT) with iodinated contrast (eg, due to contrast allergy) was not excluded if his/her disease could be measured by magnetic resonance imaging (MRI) with gadolinium. A patient who was unable to undergo MRI with gadolinium was not excluded if his/her disease could be measured by CT scan with contrast.

Note regarding laCSCC patients only: In selected cases, a patient who was unable to undergo any contrast enhanced radiographic imaging (neither CT with iodinated contrast nor MRI with gadolinium) may have been eligible if the patient's disease could be comprehensively assessed with digital medical photography, after communication with and approval from medical monitor.

Assessment comment

As discussed in the initial approval the inclusion and exclusion criteria seem to represent the patient population afflicted by either locally advanced or metastatic CSCC. The same inclusion/exclusion were applied to Group 6.

Treatments

Cemiplimab was supplied as a liquid in sterile, single-use vials. Each vial of cemiplimab contained a concentration of 50 mg/mL for IV infusion,

Instructions on dose preparation were provided in the pharmacy manual.

Cemiplimab was administered in an outpatient setting as a 30-minute (±10 minutes) IV infusion. Longer infusion durations were acceptable if interruption was required or if a patient had a previous infusion reaction during treatment. Patient doses in Groups 1 and 2 depended on their individual body weight (3 mg/kg). The dose of cemiplimab was adjusted each cycle for changes in body weight of ≥10%. Dose adjustments for changes in body weight of <10% were at the discretion of the investigator. Groups 3 and 6 received a fixed dose of cemiplimab.

Objectives

Primary Efficacy Analyses

Best overall response (BOR: CR/PR/SD/PD/NE) per ICR was summarized by group:

- NE response included the missing and unknown responses.
- CR/PR was confirmed by repeated assessments no less than 4 weeks apart.
- SD criterion was met at least once for a minimum duration of 39 days (7 days/week * 6 weeks–3 days) after the first dose date.

Patients with the BOR of NE were considered as nonresponders in the calculation of ORR. The primary analysis of efficacy was based on the exact binomial CI approach of ORR. The 2-sided 95% exact binomial CIs were derived using the Clopper-Pearson method (Clopper, 1934). If the lower limit of 95% CI of observed ORRs excluded 15% for Group 1 (mCSCC cemiplimab 3 mg/kg Q2W IV) or Group 3 (mCSCC cemiplimab 350 mg Q3W IV) or excluded 25% for Group 2 (laCSCC cemiplimab IV 3 mg/kg Q2W), the study drug was deemed effective for that group.

In addition, ORR along with 2-sided 95% exact binomial CIs for all patients treated with cemiplimab was presented.

Secondary Efficacy Analyses

- ORR was derived from the objective response that was based on investigator review and was analyzed similarly as the primary efficacy variable.
- DOR was summarized by estimated median using the Kaplan-Meier approach. Observed DOR was summarized by range.
- TTR was displayed using swimmer plots and summarized by descriptive statistics.
- PFS was summarized by median (if observed) and PFS rate at milestone time points (4, 6, 8, 12, and 16 months, etc), and displayed by the Kaplan-Meier approach.
- OS was summarized by median (if observed) and OS rate at milestone time points (4, 6, 8, 12, and 16 months, etc) and displayed by the Kaplan-Meier approach. A variant of OS defined by censoring patients at the start date of subsequent therapy was summarized and displayed by Kaplan-Meier approach as a sensitivity analysis.
- Depth of tumor response was displayed using waterfall plots and swimmer plots and summarized by descriptive statistics.
- CR rate with 95% CI was estimated using the Clopper-Pearson method. Absence of residual CSCC in biopsy samples (obtained post-response) from patients with laCSCC achieving a clinical response to cemiplimab, as measured by independent central pathological review, was summarized descriptively.
- Disease control rate (DCR) was determined by the proportion of patients with BOR of CR, PR, or SD.
- Durable disease control rate (dDCR) was defined as the proportion of patients best overall response of CR, PR, or SD without progression for at least 16 weeks (allowing tumor assessment made 1 week earlier than week 16).

Interim Analysis for Group 6

Per the sample size calculation, 167 patients in total were planned for Group 6. A pre-specified interim analysis of the first 84 patients in Group 6 was performed after they had the opportunity to be followed up for a minimum of 28 weeks (27 weeks for 3 tumor assessments + 1-week assessment window). This interim analysis was to include a minimum of 20 locally advanced CSCC patients.

Assessment comment

The objectives of the study are endorsed and considered suitable for an uncontrolled study. In the initial application PD-L1 characterization of the entire population was of particular interest. The MAH was asked to investigate the relationship between PD-L1 expression and efficacy post-approval.

This will be discussed in other sections of this AR.

Outcomes/endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint for this study was overall response based on independent central review evaluation at each time point at which response assessment occurs using the RECIST version 1.1 (Module 5.3.5.2 R2810-ONC-1540 Group 6 Interim CSR Appendix 1.1 [Appendix 1]) or the composite response criteria (Module 5.3.5.2 R2810-ONC-1540 Group 6 Interim CSR Appendix 1.1 [Appendix 2]).

Best overall response (BOR) was determined based on all response assessments until the data cutoff date (11 Oct 2020 for Groups 1 to 3 and 19 Apr 2021 for Group 6). Best overall response of complete response (CR) or PR had to be confirmed by consecutive evaluations of overall response of CR or PR at time points at least 4 weeks apart. Best overall response of stable disease (SD) must have met the response SD criteria at least once ≥39 days (6 weeks*7 days/week -3 days) after start of study treatment. Best overall response of (early) PD did not require confirmation using the RECIST or the composite response criteria. The BOR for patients who did not have any post-baseline tumor assessment was NE.

Objective response rate was determined by the proportion of patients with BOR of CR or PR in the FAS by group. Patients with BOR of NE were considered as not reaching an objective response of CR or PR. Not evaluable response included missing and unknown tumor response. Non-CR/Non-PD is for patients with non-measurable disease only.

Analyses of the primary efficacy endpoint are detailed in the SAP for Study 1540 (Module 5.3.5.2 R2810-ONC-1540 Group 6 Interim CSR Appendix 1.9.1 [Section 5.8.1]).

Secondary Efficacy Endpoints

The secondary endpoints were the following:

- ORR based on investigator-assessed evaluation
- DOR by independent central review and investigator review
- PFS by central review and investigator review
- OS
- CR rate by independent central review
- TTR by independent central review and by investigator assessment
- DCR
- DDCR
- For Group 6 only: assessment of the relationship between PD-L1 status (by IHC) and efficacy measures (ORR, DOR, PFS)
- Change in scores of patient-reported outcomes on EORTC QLQ-C30 (except Group 6)

Analyses of the secondary efficacy endpoints are detailed in the SAP for Study 1540 (Module 5.3.5.2 R2810-ONC-1540 Group 6 Interim CSR Appendix 1.9.1 [Section 5.8.2]).

Assessment comment

The primary endpoint was endorsed in the initial MAA application. Secondary endpoints included ORR assessed by the investigators, DOR, PFS and CR rate. The secondary endpoints were also endorsed but only considered exploratory since no multiplicity corrections were made.

Sample size

For Group 6, 150 patients were required to provide at least 85% power to reject a null hypothesis of an ORR of 28% at a 2-sided significance level of no more than 5% if the true ORR is 40%. The sample size was further increased by 10% to account for patients who withdrew prematurely from the study. Hence, the total planned sample size is approximately 167 patients for Group 6. The ORR of 28% for

Group 6 will be excluded using the lower limit of 95% exact CI if the observed ORR is 35.3% or more, ie, the ORR for Group 6 was significantly different from 28% (Table 10).

Table 10 The 95% Binomial Exact Confidence Intervals for Observed ORR in Group 6 Given a Sample Size of 167 Patients

Number of Responders	Observed ORR	95%CI – lower	95% CI – upper
56	33.5%	26.4%	41.2%
57	34.1%	27.0%	41.9%
58	34.7%	27.5%	42.5%
59	**35.3%**	**28.1%**	**43.1%**
60	35.9%	28.7%	43.7%
61	36.5%	29.2%	44.3%
62	37.1%	29.8%	44.9%

In Group 6, enrollment of metastatic CSCC patients was capped at 133 patients to allow for at least 34 patients with locally advanced CSCC to be enrolled. This mirrors the real-world distribution of metastatic (80%) and locally advanced (20%) patients with CSCC described in retrospective study of advanced CSCC in the US Oncology Network (Cowey, manuscript in preparation). Appendix 10 of the study protocol (Appendix 1.1) presents reference tables for Group 6 subgroup analyses. However, the primary analysis for Group 6 is based on all advanced CSCC patients, both metastatic and locally advanced. These subgroup analyses are descriptive only.

Assessment comment

The sample size for Group 6 was previously endorsed in relation to the assessment of the protocol.

Randomisation

N/A.

Blinding (masking)

N/A

Statistical methods

The efficacy analysis is based on the full analysis set (FAS). The FAS for Groups 1 to 3 included all patients who passed screening and were deemed to be eligible for this study. The FAS for the interim analysis of Group 6 (mCSCC + laCSCC) included all enrolled patients who had passed screening, were eligible for the study, and who had the potential for 3 tumor assessments (28 weeks) on study.

Results

Participant flow

Groups 1 to 3

A total of 270 patients were screened (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Post-text Table 14.1.1.1) in Groups 1 to 3, of whom 193 patients were enrolled and treated (59 patients in Group 1, 78 patients in Group 2, and 56 patients in Group 3) (Table 1).

Table 1 summarizes patient disposition for Groups 1 to 3. As of the 11 Oct 2020 data cutoff, no patients were undergoing treatment. The most common reason for premature treatment discontinuation was disease progression (29.0% [56/193]).

Table 1: Patient Disposition for Groups 1 to 3 (Full Analysis Set)

	Group 1 mCSCC 3 mg/kg Q2W (N=59)	Group 2 laCSCC 3 mg/kg Q2W (N=78)	Group 3 mCSCC 350 mg Q3W (N=56)	Total (N=193)
Treatment Ongoing, n (%)	0	0	0	0
Off Treatment, n (%)	59 (100%)	78 (100%)	56 (100%)	193 (100%)
Treatment Completed	24 (40.7%)	20 (25.6%)	22 (39.3%)	66 (34.2%)
Treatment Discontinued	35 (59.3%)	58 (74.4%)	34 (60.7%)	127 (65.8%)
Primary Reason for Treatment Discontinuation				
ADVERSE EVENT	6 (10.2%)	10 (12.8%)	4 (7.1%)	20 (10.4%)
PREGNANCY	0	0	0	0
DEATH	2 (3.4%)	2 (2.6%)	3 (5.4%)	7 (3.6%)
LOST TO FOLLOW-UP	0	0	0	0
NON-COMPLIANCE WITH STUDY DRUG	0	2 (2.6%)	0	2 (1.0%)
SUBJECT DECISION	2 (3.4%)	7 (9.0%)	2 (3.6%)	11 (5.7%)
SPONSOR DECISION	0	0	0	0
PHYSICIAN DECISION	2 (3.4%)	7 (9.0%)	4 (7.1%)	13 (6.7%)
DISEASE PROGRESSION	20 (33.9%)	18 (23.1%)	18 (32.1%)	56 (29.0%)
WITHDRAWAL OF CONSENT	0	1 (1.3%)	1 (1.8%)	2 (1.0%)
COMPLETE RESPONSE	0	2 (2.6%)	0	2 (1.0%)
OTHER	3 (5.1%)	9 (11.5%)	2 (3.6%)	14 (7.3%)
Number of patients entered follow-up, n (%)	33 (55.9%)	43 (55.1%)	31 (55.4%)	107 (55.4%)

Data cutoff as of 11 Oct 2020.
Source: Study 1540 Group 6 Interim CSR PTT 14.1.1.4f

Group 6 (Interim Analysis)

For patients within scope of the pre-specified Group 6 interim analysis, a total of 104 patients were screened (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Post-text Table 14.1.1.1.g6), of whom 84 were enrolled for treatment in Group 6 (Table 2).

Table 2 summarizes patient disposition for Group 6 (interim analysis) as of 19 Apr 2021. The most common reason for premature treatment discontinuation was disease progression (26.2% [22/84]).

Table 2: Patient Disposition for Group 6 (Full Analysis Set)

	Advanced CSCC Cemiplimab: 350 mg Q3W (Group 6) (N=84)
Patient who received Cemiplimab, n (%)	82 (97.6%)
Treatment Ongoing, (%)	41 (48.8%)
Off Treatment, n (%)	41 (48.8%)
Treatment Completed	0
Treatment Discontinued	41 (48.8%)
Primary Reason for Treatment Discontinuation	
ADVERSE EVENT	9 (10.7%)
PREGNANCY	0
DEATH	7 (8.3%)
LOST TO FOLLOW-UP	1 (1.2%)
NON-COMPLIANCE WITH STUDY DRUG	0
SUBJECT DECISION	1 (1.2%)
SPONSOR DECISION	0
PHYSICIAN DECISION	0
DISEASE PROGRESSION	22 (26.2%)
WITHDRAWAL OF CONSENT	0
COMPLETE RESPONSE	0
OTHER	1 (1.2%)
Number of patients entered follow-up, n (%)	4 (4.8%)

Data cutoff as of 19 Apr 2021
Only patients who started treatment on or prior to Oct 9, 2020 or who enrolled on or prior to Oct 9, 2020 but did not receive treatment are included.
Source: Study 1540 Group 6 Interim CSR PTT 14.1.1.4f.g6

Recruitment

As of the respective data cutoffs for Groups 1, 2, and 3, 35 sites from Australia, Germany, and the United States participated in this study. Groups 1 to 3: Conducted at 35 sites in 3 countries. A total of 270 patients were screened for eligibility, 193 patients were enrolled and treated (59 patients in Group 1, 78 patients in Group 2, and 56 patients in Group 3).

Group 6 (Interim analysis): Conducted at at 26 sites in 4 countries. A total of 104 patients were screened for eligibility, 84 patients were enrolled, and 82 were treated.

Conduct of the study

Table 13 Protocol Amendments

Amendment / Date	Major Changes
Amendment 7 Global / 21 Oct 2019	• Added Group 6 to provide additional efficacy and safety data for cemiplimab monotherapy in patients with advanced CSCC (metastatic or unresectable locally advanced) treated with cemiplimab 350 mg every 3 weeks (Q3W) IV. Group 6 was also designed to provide additional biomarker data. • Collected additional PK samples at follow-up visits 3 and 4 to provide information on non-linearity of PK of cemiplimab. • Removed exclusion of patients with allergy or hypersensitivity to doxycycline or tetracycline as these are not utilized in the current manufacturing process. • Clarified the definitions for efficacy analyses per Regulatory Authority feedback. • Revision of requirements relating to pregnancy and birth control in women of childbearing potential (WOCBP) and their partners in accordance with Clinical Trial Facilitation Group (CTFG) guidance. • Modifications for consistency and clarity, and administrative updates. • Correction of typographical, grammatical, and formatting errors.

Table 14 Changes to the Planned Analyses (SAP amendments)

Version / Date	Major Changes
Version 5.0 / 24 Feb 2021 (see Appendix 1.9.1)	The main change from SAP v4.0 included the addition of sensitivity analysis of ORR using patients who received at least 1 dose of cemiplimab.
Version 4.0 / 20 Sep 2020	This version of the SAP was based on the study protocol R2810-ONC-1540 global amendment 7 dated 21 Oct 2019. The main changes from SAP v3.0 (based on protocol amendment 5) included: 1. Added Groups 4 and 5 per protocol amendment 6 and added Group 6 per protocol amendment 7. 2. Added planned interim analysis for patients in Group 6 per protocol amendment 7. 3. Added exploratory efficacy analysis (ORR based on 18F-FDG-PET using EORTC criteria) for Group 4 per protocol amendment 6.
Version 3.0 / 25 Aug 2017	Added a cohort (Group 3) per protocol amendment 4 (Appendix 1.1) Extended the TEAE observation period to up to 105 days (5 half-lives) after the last dose per protocol amendment 2. Incorporated protocol amendment 2 Planned an interim analysis for patients in Group 2 per protocol amendment 5
Version 2.0 / 10 May 2016	Added some clarifications on the observation period in determining BOR for analysis of primary efficacy endpoint Added some clarifications on the extended observation period in reporting DOR evaluation Renamed the per protocol set as Efficacy Analysis Set (Section 3.2) and removed the requirement of receiving at least 1 dose of cemiplimab to adhere to the intent-to-treat principle Minor edits to clarify sample size justifications Removed the variable definition and analysis plan for duration of disease control, as this was a subset of PFS Removed irRC because it is not part of the protocol Updated background and rationale Added definition of eligible patient Clarified the definitions of the following variables: demographic and baseline characteristics, medical history, secondary efficacy variables, safety variables, anti-drug antibodies, exposure analysis, analysis of efficacy variables and safety variables Reduced the number of PK variables to be assessed Provided data cutoff definition Expanded details on prior/concomitant medication analysis Updated what was to be reported for patient disposition Added section for protocol deviations, PK, ADA, and exploratory biomarker analysis Because the protocol does not contain irRC, it was clarified that a single assessment of PD would be considered PD in the analysis plan Added variant of OS defined by censoring patients at the start date of subsequent therapy Added subgroups and removed others for the subgroup efficacy analysis Specified AEs were to be displayed by SOC and PT and safety analysis population Clarified that there was to be no multiplicity adjustment for the secondary endpoint

ADA=anti-drug antibody; AE=adverse event; BOR=best overall response; EAS=efficacy analysis set; FAS=full analysis set; irRC=immune-related response criteria; laCSCC=locally advanced cutaneous squamous cell carcinoma; mCSCC=metastatic cutaneous squamous cell carcinoma; ORR=objective response rate; OS=overall survival; PD=progressive disease; PFS=progression-free survival; PK=pharmacokinetic; PPS=per-protocol set; PT=preferred term; SAF=safety analysis set; SAP=statistical analysis plan; SOC=system organ class;

Change to Study Conduct Related to the COVID-19 Pandemic

Portions of this study were conducted during the "Coronavirus Disease 2019" (COVID-19) pandemic. The sponsor made a decision that this study would continue based on the assessment that the study

could be conducted without potentially jeopardizing patient safety, data integrity, or compliance with recent Regulatory Guidance.

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight required implementation of temporary or alternative mechanisms.

Formal documentation of deviations to Standard Operating Procedures (SOPs) or other controlled procedural documents can be found in Appendix 1.13.

Other mechanisms employed included:

Phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff.

Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 were granted. All temporary mechanisms utilized, and deviations from planned study procedures were documented as being related to COVID-19 and remained in effect only for the duration of the public health emergency.

Assessment comment

Previous protocol amendments have been assessed in relation to the initial MAA. The latest change to the protocol was made in 2019 and introduced Group 6 as requested by the CHMP. The additional changes are considered minor.

Protocol deviations

Table 17 Important Protocol Deviations Groups 1 to 3 (Full Analysis Set)

	Group 1 mCSCC 3 mg/kg Q2W (N=59)	Group 2 laCSCC 3 mg/kg Q2W (N=78)	Group 3 mCSCC 350 mg Q3W (N=56)	Total (N=193)
Number of Important Protocol Deviations	10	10	14	34
Patients with Any Important Protocol Deviation, n (%)	8 (13.6%)	10 (12.8%)	8 (14.3%)	26 (13.5%)
Type of Important Protocol Deviations, n (%)				
AESI not reported within 24 hours	2 (3.4%)	2 (2.6%)	0	4 (2.1%)
Any active infection requiring therapy including infection with HIV, or active infection with hepatitis B virus or hepatitis C virus	0	0	1 (1.8%)	1 (0.5%)
Any systemic anticancer treatment (chemotherapy, targeted systemic therapy, photodynamic therapy), investigational or standard of care, within 30 days of the initial administration of REGN2810	0	0	1 (1.8%)	1 (0.5%)
Archival sample not submitted before C1D1	2 (3.4%)	2 (2.6%)	1 (1.8%)	5 (2.6%)
Discovered subject enrolled to wrong group after initial dose	0	1 (1.3%)	0	1 (0.5%)
Hemoglobin < 9.0 g/dl	0	0	1 (1.8%)	1 (0.5%)
No central pathology confirmation of diagnosis of CSCC. Biopsy material not sent prior to enrollment	0	1 (1.3%)	1 (1.8%)	2 (1.0%)
Patient received study drug in the setting of onset pneumonitis, grade 2 or higher	1 (1.7%)	0	0	1 (0.5%)
Previously radiated lesion was selected as a target lesion, but no biopsy was done to confirm progression after the radiation	0	1 (1.3%)	0	1 (0.5%)
REGN2810 treatment deviation, flat dose, actual dose (mg) +/- 20% dosing planned dose (group 3, 4, 5 and 6)	0	0	3 (5.4%)	3 (1.6%)
SAE not reported within 24 hours	4 (6.8%)	2 (2.6%)	3 (5.4%)	9 (4.7%)
Screening scans and photos not taken for target lesions, for the locations required by the protocol	0	1 (1.3%)	0	1 (0.5%)

Table 18 Important Protocol Deviations Group 6 Interim Analysis (Full Analysis Set)

	Group 6 Advanced CSCC 350 mg Q3W (N=84)
Number of Important Protocol Deviations	10
Patients with Any Important Protocol Deviation, n (%)	10 (11.9%)
Type of Important Protocol Deviations, n (%)	
Inclusion criteria not met, hemoglobin < 9.0 g/dl	1 (1.2%)
Inclusion criteria not met, previously radiated lesion was selected as a target lesion but no biopsy was done to confirm progression after the radiation	2 (2.4%)
Inclusion criteria not met, other	3 (3.6%)
SAE not reported within 24 hours	3 (3.6%)
Screening assessments were done >28 days prior to the first cemiplimab dose. Dates were flagged for medical review (with the exception of brain MRI dates)	1 (1.2%)

Data cutoff as of 19 Apr 2021.
CSCC=cutaneous squamous cell carcinoma; MRI=magnetic resonance imaging; Q3W=every 3 weeks; SAE=serious adverse event.
Only patients who started treatment on or prior to 9 Oct 2020 or who enrolled on or prior to 9 Oct 2020 but did not receive treatment are included.
Source: PTT 14.1.1.5f.g6

Details of the major protocol deviations are provided by patient in Listing 16.2.2.1.g6.

Assessment comment

In total 10 patients had major protocol deviations. However, no clear pattern is observed. The individual protocol deviations will not impact the overall result, even if these patients were excluded.

Baseline data

Groups 1 to 3

Overall, baseline demographic characteristics were similar among all groups. The majority of patients were white (96.9% [187/193]) and/or male (83.4% [161/193]) (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Table 22). The majority of the patients were 65 years of age or older (74.6% [144/193]), with a mean (standard deviation) age of 71.1 (11.35) years. Patient demographics were consistent with the expected population of patients with advanced CSCC.

In Groups 1 to 3, most patients 67.9% (131/193) had a primary cancer site of head and neck (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Post-text Listing 16.2.4.2 and Post-text Table 14.1.2.2f).

Group 6 (Interim Analysis)

All patients were White and a majority of patients were male (79.8% [67/84]) (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Table 23). The majority of the patients were 75 years of age or older (54.8% [46/84]), with a mean (standard deviation) age of 74.1 (11.07) years. Patient demographics were consistent with the expected population of patients with advanced CSCC.

In Group 6, 64.3% (54/84) of patients had metastatic disease and 35.7% (30/84) of patients had locally advanced disease. In Group 6 most patients 65.5% (55/84) had a primary cancer site of head

and neck (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Post text Listing 16.2.4.2.g6 and Post-text Table 14.1.2.2f.g6).

Previous Anticancer Therapy

A greater percentage of patients in Group 1 (55.9% [33/59]) and Group 3 (35.7% [20/56]) received prior cancer-related systemic therapy than those in Group 2 (15.4% [12/78]) (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Table 26). The most common prior systemic therapies reported in each group were platinum-based antineoplastic agents; (35.6% [21/59] in Group 1, 9.0% [7/78] in Group 2, and 32.1% [18/56] in Group 3) (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Post-text Table 14.1.3.2f). Prior mAb therapy was received by 9.3% (18/193) of all patients ; the mAb was cetuximab in each case (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Post-text Listing 16.2.4.4).

In Group 6, there was 1 patient that received prior cancer related systemic therapy. This patient received the mAb cetuximab (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Post-text Listing 16.2.4.4fg6).

Previous Surgeries and Radiotherapy

Groups 1 to 3

The majority of patients in Group 1, Group 2, and Group 3 had at least 1 prior cancer-related surgery (88.6% [171/193]) (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Post-text Table 14.1.3.3f). The median number of prior cancer-related surgeries was 5 (range: 1 to 28).

The majority of patients had prior cancer-related radiotherapy (67.9% [131/193]) (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Post-text Table 14.1.3.4f). More patients in Groups 1 and 3 had prior cancer-related radiotherapy compared to Group 2, which was expected because patients in these groups had metastatic cancer.

Group 6 (Interim Analysis)

The majority of patients in scope of the interim analysis for Group 6 had at least 1 prior cancer-related surgery (84.5% [71/84]) (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Post-text Table 14.1.3.3f.g6). The median number of prior cancer-related surgeries was 4 (range: 2 to 6).

The majority of patients had prior cancer-related radiotherapy (52.4% [44/84]).

Table 22 Demographics and Baseline Characteristics Groups 1 to 3 (Full Analysis Set)

	Group 1 mCSCC 3 mg/kg Q2W (N=59)	Group 2 laCSCC 3 mg/kg Q2W (N=78)	Group 3 mCSCC 350 mg Q3W (N=56)	Total (N=193)
Age (years)				
n	59	78	56	193
Mean (StDev)	70.4 (10.11)	72.5 (11.15)	69.7 (12.75)	71.1 (11.35)
Median	71.0	74.0	71.0	72.0
Q1 : Q3	64.0 : 77.0	65.0 : 81.0	64.0 : 80.5	64.0 : 80.0
Min : Max	38 : 93	45 : 96	38 : 90	38 : 96
Age Groups (years), n (%)				
<65	16 (27.1%)	19 (24.4%)	14 (25.0%)	49 (25.4%)
≥65	43 (72.9%)	59 (75.6%)	42 (75.0%)	144 (74.6%)
Sex, n (%)				
Male	54 (91.5%)	59 (75.6%)	48 (85.7%)	161 (83.4%)
Female	5 (8.5%)	19 (24.4%)	8 (14.3%)	32 (16.6%)

Race, n (%)				
WHITE	58 (98.3%)	75 (96.2%)	54 (96.4%)	187 (96.9%)
BLACK OR AFRICAN AMERICAN	1 (1.7%)	0	0	1 (0.5%)
ASIAN	0	2 (2.6%)	2 (3.6%)	4 (2.1%)
NOT REPORTED	0	1 (1.3%)	0	1 (0.5%)
Ethnicity, n (%)				
NOT HISPANIC OR LATINO	58 (98.3%)	75 (96.2%)	55 (98.2%)	188 (97.4%)
HISPANIC OR LATINO	1 (1.7%)	2 (2.6%)	1 (1.8%)	4 (2.1%)
NOT REPORTED	0	1 (1.3%)	0	1 (0.5%)
Height (cm)				
n	59	77	56	192
Mean (StDev)	173.19 (6.579)	171.76 (10.304)	174.01 (9.432)	172.86 (9.050)
Median	174.50	173.30	175.00	174.00
Q1 : Q3	169.00 : 177.80	167.00 : 178.00	167.55 : 180.60	167.55 : 178.00
Min : Max	158.5 : 190.5	140.3 : 193.0	145.0 : 190.0	140.3 : 193.0
Body Weight (kg)				
n	59	78	56	193
Mean (StDev)	85.04 (15.682)	77.08 (18.018)	82.71 (22.666)	81.15 (19.072)
Median	84.50	76.90	80.45	80.70
Q1 : Q3	74.90 : 94.40	66.40 : 87.80	67.85 : 89.45	68.70 : 90.50
Min : Max	58.3 : 134.9	31.0 : 138.8	54.0 : 171.6	31.0 : 171.6
BMI (kg/m2)				
n	59	77	56	192
Mean (StDev)	28.313 (4.7718)	26.069 (4.8535)	27.346 (7.2797)	27.131 (5.6963)
Median	28.090	26.020	26.055	26.790
Q1 : Q3	24.700 : 30.340	22.960 : 28.740	22.970 : 28.795	23.285 : 29.760
Min : Max	19.51 : 44.25	13.78 : 37.53	18.16 : 55.46	13.78 : 55.46
ECOG Performance Status, n (%)				
0	23 (39.0%)	38 (48.7%)	25 (44.6%)	86 (44.6%)
1	36 (61.0%)	40 (51.3%)	31 (55.4%)	107 (55.4%)

BMI=body mass index; ECOG=Eastern Cooperative Oncology Group; laCSCC=locally advanced cutaneous squamous cell carcinoma; mCSCC=metastatic cutaneous squamous cell carcinoma; Q=quartile; Q2W=every 2 weeks; Q3W=every 3 weeks; StDev=standard deviation.
Data cutoff as of 11 Oct 2020.
Source: PTT 14.1.2.1f

Table 24 Baseline Tumor Characteristics Groups 1 to 3 (Full Analysis Set)

	Group 1 mCSCC 3 mg/kg Q2W (N=59)	Group 2 laCSCC 3 mg/kg Q2W (N=78)	Group 3 mCSCC 350 mg Q3W (N=56)	Total (N=193)
T Stage at Screening, n (%)				
TX	29 (49.2%)	5 (6.4%)	22 (39.3%)	56 (29.0%)
T0	0	0	6 (10.7%)	6 (3.1%)
T1	4 (6.8%)	8 (10.3%)	4 (7.1%)	16 (8.3%)
T2	13 (22.0%)	27 (34.6%)	13 (23.2%)	53 (27.5%)
T3	3 (5.1%)	14 (17.9%)	3 (5.4%)	20 (10.4%)
T4	10 (16.9%)	24 (30.8%)	8 (14.3%)	42 (21.8%)
N Stage at Screening, n (%)				
NX	9 (15.3%)	5 (6.4%)	8 (14.3%)	22 (11.4%)
N0	10 (16.9%)	71 (91.0%)	12 (21.4%)	93 (48.2%)
N1	15 (25.4%)	0	10 (17.9%)	25 (13.0%)
N2	6 (10.2%)	0	7 (12.5%)	13 (6.7%)
N2A	0	0	2 (3.6%)	2 (1.0%)
N2B	4 (6.8%)	1 (1.3%)	10 (17.9%)	15 (7.8%)
N2C	7 (11.9%)	0	5 (8.9%)	12 (6.2%)
N3	8 (13.6%)	1 (1.3%)	2 (3.6%)	11 (5.7%)
M Stage at Screening, n (%)				
MX	0	0	1 (1.8%)	1 (0.5%)
M0	14 (23.7%)	78 (100%)	12 (21.4%)	104 (53.9%)
M1	45 (76.3%)	0	43 (76.8%)	88 (45.6%)

Data cutoff as of 11 Oct 2020.
laCSCC=locally advanced cutaneous squamous cell carcinoma; mCSCC=metastatic cutaneous squamous cell carcinoma; Q2W=every 2 weeks; Q3W=every 3 weeks.
Source: PTT 14.1.2.2f

Table 25 Baseline Tumor Characteristics Group 6 (Full Analysis Set)

	Group 6 Advanced CSCC 350 mg Q3W (N=84)
T Stage at Screening, n (%)	
TX	17 (20.2%)
T0	11 (13.1%)
T1	7 (8.3%)
T2	13 (15.5%)
T3	17 (20.2%)
T4	19 (22.6%)
N Stage at Screening, n (%)	
NX	8 (9.5%)
N0	44 (52.4%)
N1	6 (7.1%)
N2	5 (6.0%)
N2A	5 (6.0%)
N2B	8 (9.5%)
N2C	3 (3.6%)
N3	5 (6.0%)
M Stage at Screening, n (%)	
MX	1 (1.2%)
M0	39 (46.4%)
M1	44 (52.4%)
Advanced CSCC Type, n (%)	
mCSCC	54 (64.3%)
laCSCC	30 (35.7%)

Data cutoff as of 19 Apr 2021.
CSCC= cutaneous squamous cell carcinoma; Q3W=every 3 weeks.
Source: PTT 14.1.2.2.f.g6

Assessment comment

Overall, the baseline characteristics of Group 6 are similar to those of Group 1-3.

Numbers analysed

Table 20 Analysis Sets Groups 1 to 3 (Full Analysis Set)

Analysis Set, n (%)	Group 1 mCSCC 3 mg/kg Q2W (N=59)	Group 2 laCSCC 3 mg/kg Q2W (N=78)	Group 3 mCSCC 350 mg Q3W (N=56)	Total (N=193)
Full Analysis Set (FAS)	59 (100%)	78 (100%)	56 (100%)	193 (100%)
Safety Analysis Set (SAF)	59 (100%)	78 (100%)	56 (100%)	193 (100%)
Pharmacokinetic Analysis Set (PKA)	59 (100%)	76 (97.4%)	53 (94.6%)	188 (97.4%)
Anti-drug Antibody Analysis Set (ADA)	50 (84.7%)	67 (85.9%)	41 (73.2%)	158 (81.9%)

Data cutoff as of 11 Oct 2020.
laCSCC=locally advanced cutaneous squamous cell carcinoma; mCSCC=metastatic cutaneous squamous cell carcinoma; Q2W=every 2 weeks; Q3W=every 3 weeks.
Source: PTT 14.1.1.3f

Table 21 Analysis Sets Group 6 (Full Analysis Set)

Analysis Set, n (%)	Group 6 Advanced CSCC 350 mg Q3W (N=84)
Full Analysis Set (FAS)	84 (100%)
Safety Analysis Set (SAF)	82 (97.6%)
Pharmacokinetic Analysis Set (PKA)	82 (97.6%)
Anti-drug Antibody Analysis Set (ADA)	63 (75.0%)

Data cutoff as of 19 Apr 2021.
But did not receive any
Only patients who started treatment on or prior to 9 Oct 2020 or who enrolled on or prior to 9 Oct 2020 but did not receive any treatment were included.
ADA= antidrug antibody analysis set; CSCC=cutaneous squamous cell carcinoma; FAS=full analysis set; PKA=pharmacokinetic analysis set; Q3W=every 3 weeks; SAF=safety analysis set.
Source: PTT 14.1.1.3.g6

Patient exposure

Outcomes and estimation

Groups 1 to 3

The ORR by ICR, according to intention-to-treat (ITT) for patients in Group 1 was 50.8% (95% CI: 37.5 to 64.1), Group 2 was 44.9% (95% CI: 33.6 to 56.6), and Group 3 was 46.4% (95% CI: 33.0% to 60.3%) (Table 3). Among 193 patients in the pooled FAS, ORR was 47.2% (95% CI: 39.9 to 54.4).

The prespecified threshold for clinically meaningful ORR was defined as the lower bound of the 95% CIs to be analyzed separately for each group. The prespecified efficacy thresholds were exceeded (ie, the lower bounds of the 95% CIs) exceeded 15% for Groups 1 and 3 and exceeded 25% for Group 2) (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Section 8.3.1).

Clinically meaningful treatment effect (also described by durable DCR) as presented in Table 3 was 61.0% (95% CI: 47.4 to 73.5) for Group 1, 62.8% (95% CI: 51.1 to 73.5) for Group 2, and 57.1% (95% CI: 43.2 to 70.3) for Group 3. The durable DCR for the pooled FAS of Groups 1, 2, and 3 was 60.6% (95% CI: 53.3 to 67.6) (Table 3).

Table 3: Best Overall Tumor Response by Independent Central Review Groups 1 to 3 (Full Analysis Set)

	Group 1 mCSCC 3 mg/kg Q2W (N=59) (Median FU =18.50 Mos)	Group 2 laCSCC 3 mg/kg Q2W (N=78) (Median FU =15.52 Mos)	Group 3 mCSCC 350 mg Q3W (N=56) (Median FU =17.30 Mos)	Total (N=193) (Median FU =15.74 Mos)
Best Overall Tumor Response, n (%)				
Complete Response (CR) [a]	12 (20.3%)	10 (12.8%)	11 (19.6%)	33 (17.1%)
Partial Response (PR) [a]	18 (30.5%)	25 (32.1%)	15 (26.8%)	58 (30.1%)
Stable Disease (SD) [b]	9 (15.3%)	27 (34.6%)	8 (14.3%)	44 (22.8%)
Non-CR/Non-PD [c]	3 (5.1%)	0	2 (3.6%)	5 (2.6%)
Progressive Disease (PD)	10 (16.9%)	10 (12.8%)	14 (25.0%)	34 (17.6%)
Not Evaluable (NE) [d]	7 (11.9%)	6 (7.7%)	6 (10.7%)	19 (9.8%)
Response				
Objective Response Rate (ORR: CR+PR)	30 (50.8%)	35 (44.9%)	26 (46.4%)	91 (47.2%)
95% CI for ORR [e]	(37.5%, 64.1%)	(33.6%, 56.6%)	(33.0%, 60.3%)	(39.9%, 54.4%)
Complete Response Rate (CR) [a]	12 (20.3%)	10 (12.8%)	11 (19.6%)	33 (17.1%)
95% CI for CR Rate [e]	(11.0%, 32.8%)	(6.3%, 22.3%)	(10.2%, 32.4%)	(12.1%, 23.2%)
Disease Control Rate (DCR: CR+PR+SD+Non-CR/Non-PD)	42 (71.2%)	62 (79.5%)	36 (64.3%)	140 (72.5%)
95% CI for DCR [e]	(57.9%, 82.2%)	(68.8%, 87.8%)	(50.4%, 76.6%)	(65.7%, 78.7%)
Durable DCR [f]	36 (61.0%)	49 (62.8%)	32 (57.1%)	117 (60.6%)
95% CI for Durable DCR [e]	(47.4%, 73.5%)	(51.1%, 73.5%)	(43.2%, 70.3%)	(53.3%, 67.6%)

Data cutoff as of 11 Oct 2020.
[a] CR/PR must be confirmed by repeated assessments no less than 4 weeks apart.
[b] SD criteria must be met at least once after a minimum duration of 39 days after first dose date.
[c] Non-CR/Non-PD is for patients with non-measurable disease only.
[d] Not evaluable response includes the missing and unknown tumor response.
[e] Clopper-Person exact confidence interval.
[f] Durable DCR: proportion of patients with CR, PR, SD or non-CR/Non-PD for at least 105 days without PD.
Source: Study 1540 Group 6 Interim CSR PTT 14.2.1.1f and PTT 14.1.1.7f

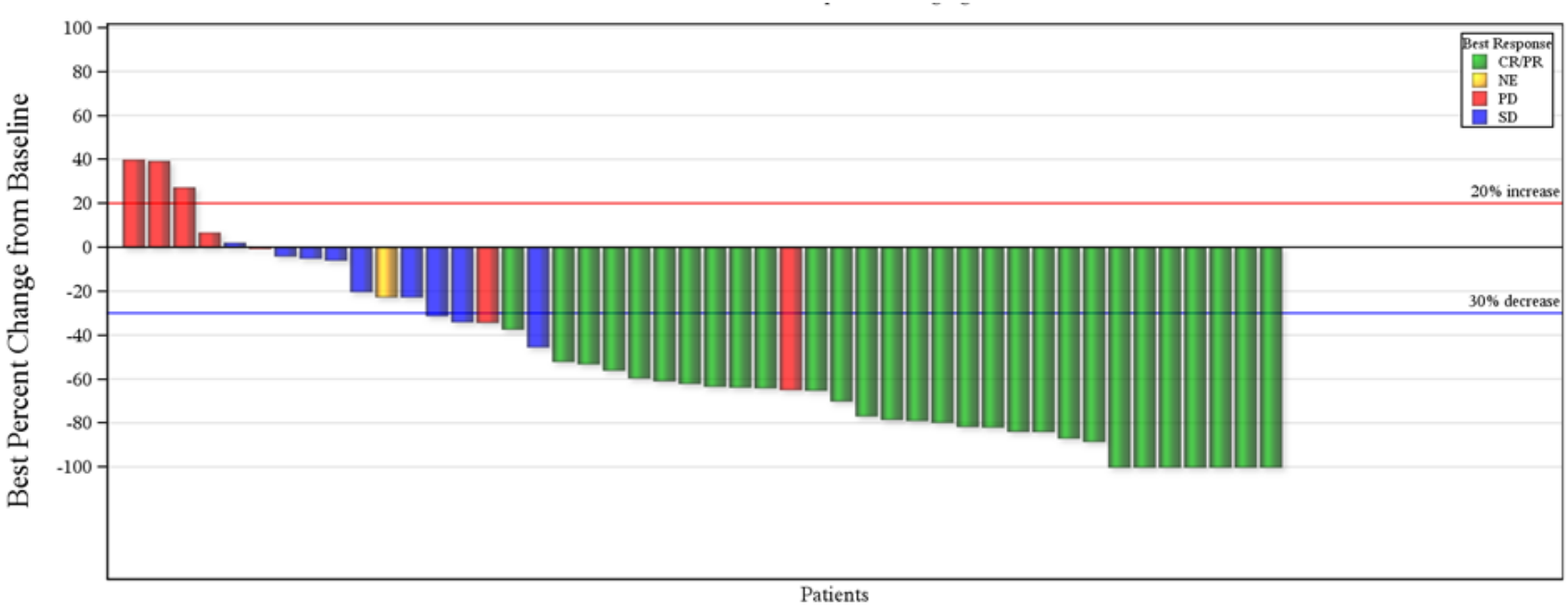
Table 4: Kaplan-Meier Estimation of Duration of Response by Independent Central Review for Groups 1 to 3 (Full Analysis Set - Patients with Confirmed CR or PR)

	Group 1 mCSCC 3 mg/kg Q2W (N=30) (Median FU =18.50 Mos)	Group 2 laCSCC 3 mg/kg Q2W (N=35) (Median FU =15.52 Mos)	Group 3 mCSCC 350 mg Q3W (N=26) (Median FU =17.30 Mos)	Total (N=91) (Median FU =15.74 Mos)
KM Estimation of Duration of Response (CR or PR)				

	Group 1 mCSCC 3 mg/kg Q2W (N=30) (Median FU =18.50 Mos)	Group 2 laCSCC 3 mg/kg Q2W (N=35) (Median FU =15.52 Mos)	Group 3 mCSCC 350 mg Q3W (N=26) (Median FU =17.30 Mos)	Total (N=91) (Median FU =15.74 Mos)
n	30	35	26	91
Number of events, n (%) [a]	10 (33.3%)	10 (28.6%)	4 (15.4%)	24 (26.4%)
Number of censored patients, n (%) [a]	20 (66.7%)	25 (71.4%)	22 (84.6%)	67 (73.6%)
Median (95% CI), (months)	NR (20.7, NE)	NR (18.4, NE)	NR (NE, NE)	NR (31.0, NE)
Estimated Event-Free Probability, % (95% CI)				
4 months	100 (NE, NE)	100 (NE, NE)	100 (NE, NE)	100 (NE, NE)
6 months	96.6 (77.9,99.5)	96.9 (79.8,99.6)	96.2 (75.7,99.4)	96.6 (89.7, 98.9)
8 months	89.5 (70.9,96.5)	90.4 (73.1,96.8)	88.3 (67.9,96.1)	89.5 (80.8, 94.4)
12 months	89.5 (70.9,96.5)	83.2 (64.1,92.7)	88.3 (67.9,96.1)	86.9 (77.6, 92.5)
16 months	89.5 (70.9,96.5)	74.8 (53.9,87.3)	83.9 (62.4,93.6)	82.8 (72.6, 89.5)
20 months	77.8 (57.1,89.4)	70.4 (49.0,84.2)	83.9 (62.4,93.6)	77.2 (66.2, 85.0)
24 months	70.1 (48.8,83.8)	65.7 (43.8,80.8)	83.9 (62.4,93.6)	72.8 (61.2, 81.4)
28 months	70.1 (48.8,83.8)	65.7 (43.8,80.8)	83.9 (62.4,93.6)	72.8 (61.2, 81.4)
32 months	61.3 (39.7,77.1)	58.4 (34.6, 76.2)	NE (NE, NE)	63.8 (49.3, 75.2)
36 months	61.3 (39.7,77.1)	58.4 (34.6, 76.2)	NE (NE, NE)	63.8 (49.3, 75.2)

Data cutoff as of 11 Oct 2020.
[a] Events include progressive disease or deaths. Percentages are based on number of patients with confirmed CR or PR.
Source: Study 1540 Group 6 Interim CSR PTT 14.2.1.3f and PTT 14.1.1.7f

Figure 1: Waterfall Plot of Best Percent Change from Baseline in Target Lesions per RECIST 1.1 by Independent Central Review – Group 1 (mCSCC; Full Analysis Set)



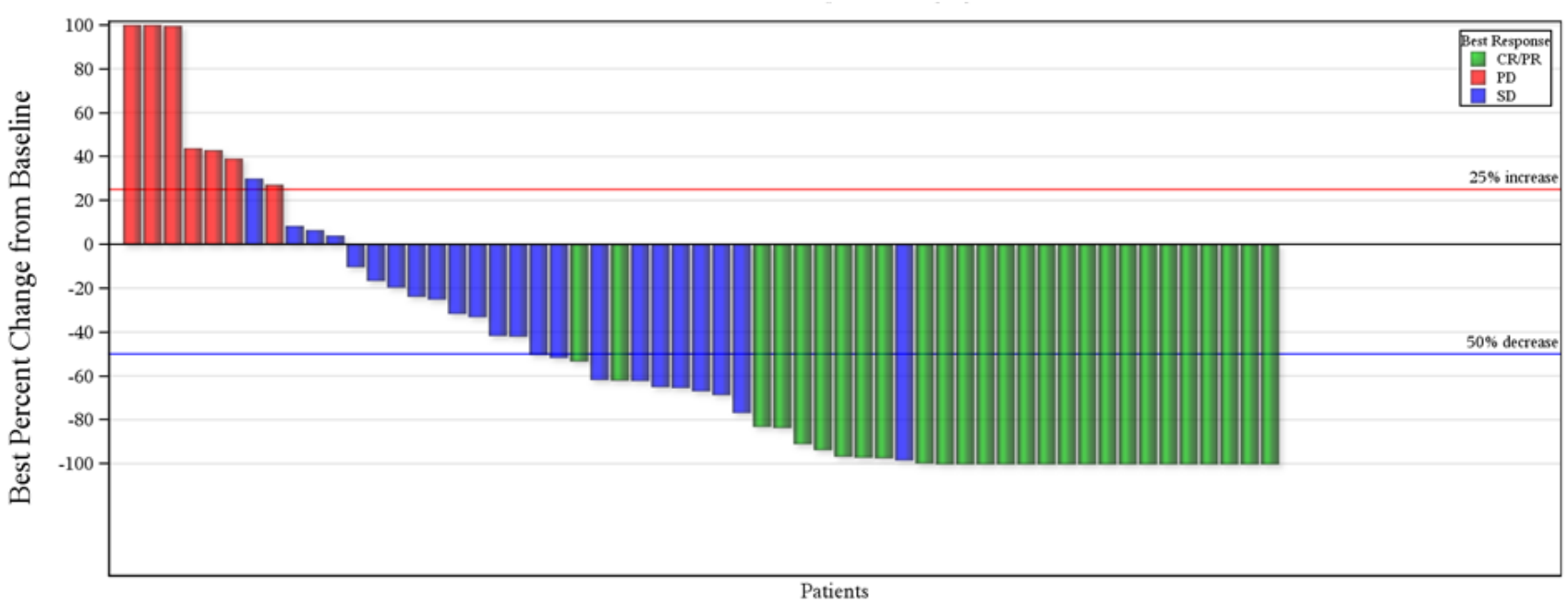
Data cutoff as of 11 Oct 2020.

Waterfall plot displays the best percentage change in the sum of target lesion diameters during study period from baseline, based on radiologic imaging. Lesion measurements after progression are excluded. Patients with new lesions or unequivocal progression of non-target lesions are considered as PD (red bars) regardless of target lesion response. Patients with a single assessment with ≥30% reduction of target lesion(s) are considered SD (blue bars) if there is not confirmatory assessment to establish PR. One patient is NR; this patient had radiologic and photographic data and was, therefore, reviewed by ICRC and assessed as NE (yellow bar). Increase in sum of target lesion diameters greater than 100% is reported as 100%.

CR=complete response; mCSCC=metastatic cutaneous squamous cell carcinoma; NE=not evaluable; NR=not reached; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

Source: Study 1540 Group 6 Interim CSR PTF 14.2.1.3.1

Figure 2: Waterfall Plot of Best Percent Change from Baseline in Target Lesions per WHO Criteria by Independent Central Review – Group 2 (laCSCC; Full Analysis Set)



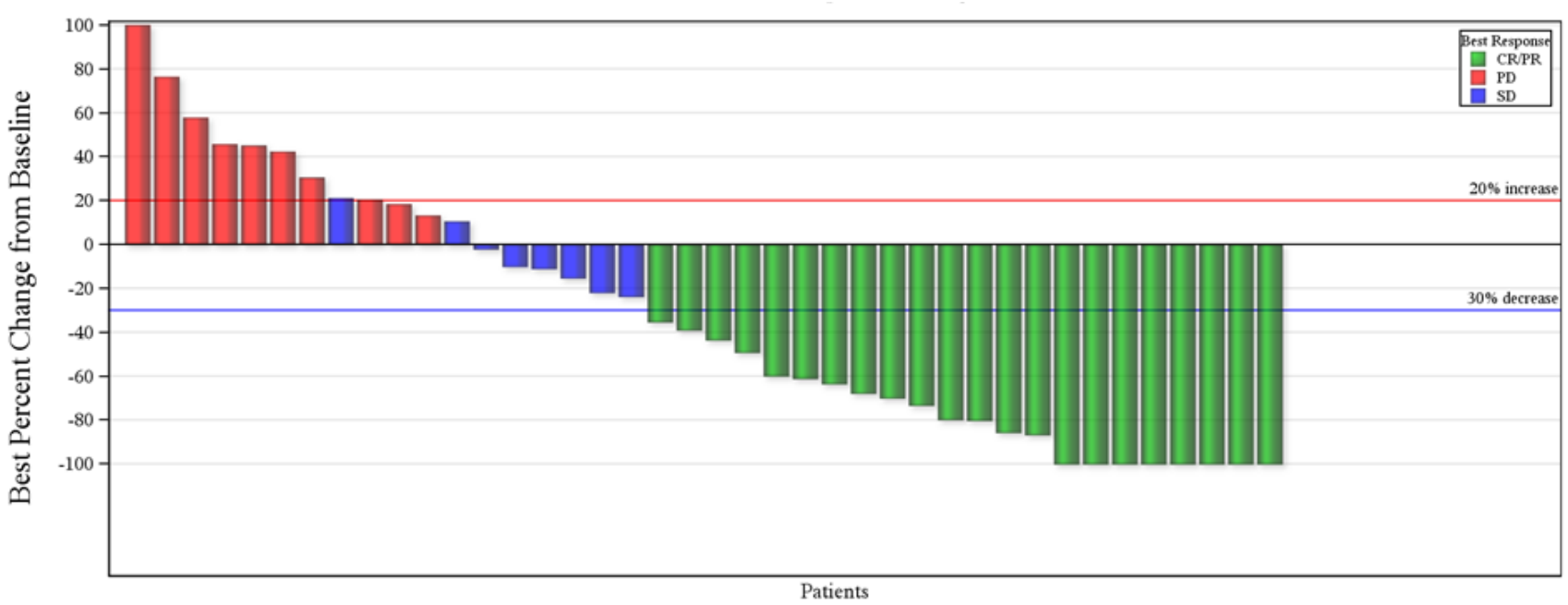
Data cutoff as of 11 Oct 2020.

Waterfall plot displays the best percent change in the sum of product of skin target lesion diameters during study period from baseline, based on digital medical photography. Lesion measurements after progression are excluded. Eight of 35 patients with objective response are not shown in this plot because the response assessments per ICRC included consideration of radiologic results. Patients with a single assessment with ≥50% reduction of target lesion(s) are considered SD (blue bars) if there is not confirmatory assessment to establish PR or if the ICRC adjudicated best overall response status of SD after reviewing radiologic data for the case. Patients with 100% reduction of target lesions but without pathologic confirmation of histologic negativity (CR) were considered to have PR. Increase in sum of product of the skin target lesion diameters greater than 100% is reported as 100%.

CR=complete response; laCSCC=locally advanced cutaneous squamous cell carcinoma; PD=progressive disease; PR=partial response; SD=stable disease, WHO=World Health Organization.

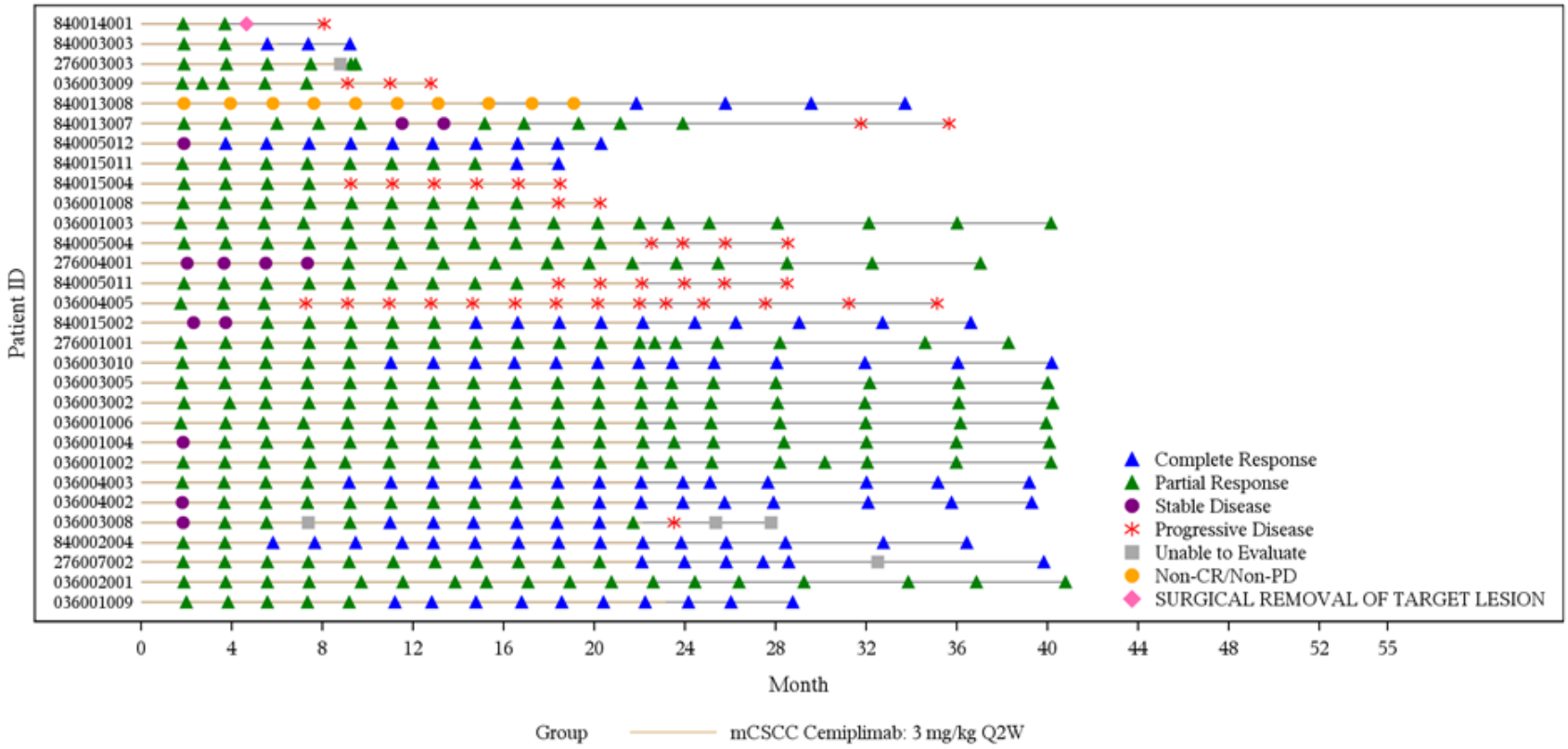
Source: Study 1540 Group 6 Interim CSR PTF 14.2.1.9.2

Figure 3: Waterfall Plot of Best Percent Change from Baseline in Target Lesions per RECIST 1.1 by Independent Central Review – Group 3 (mCSCC treated with 350 mg Q3W; Full Analysis Set)



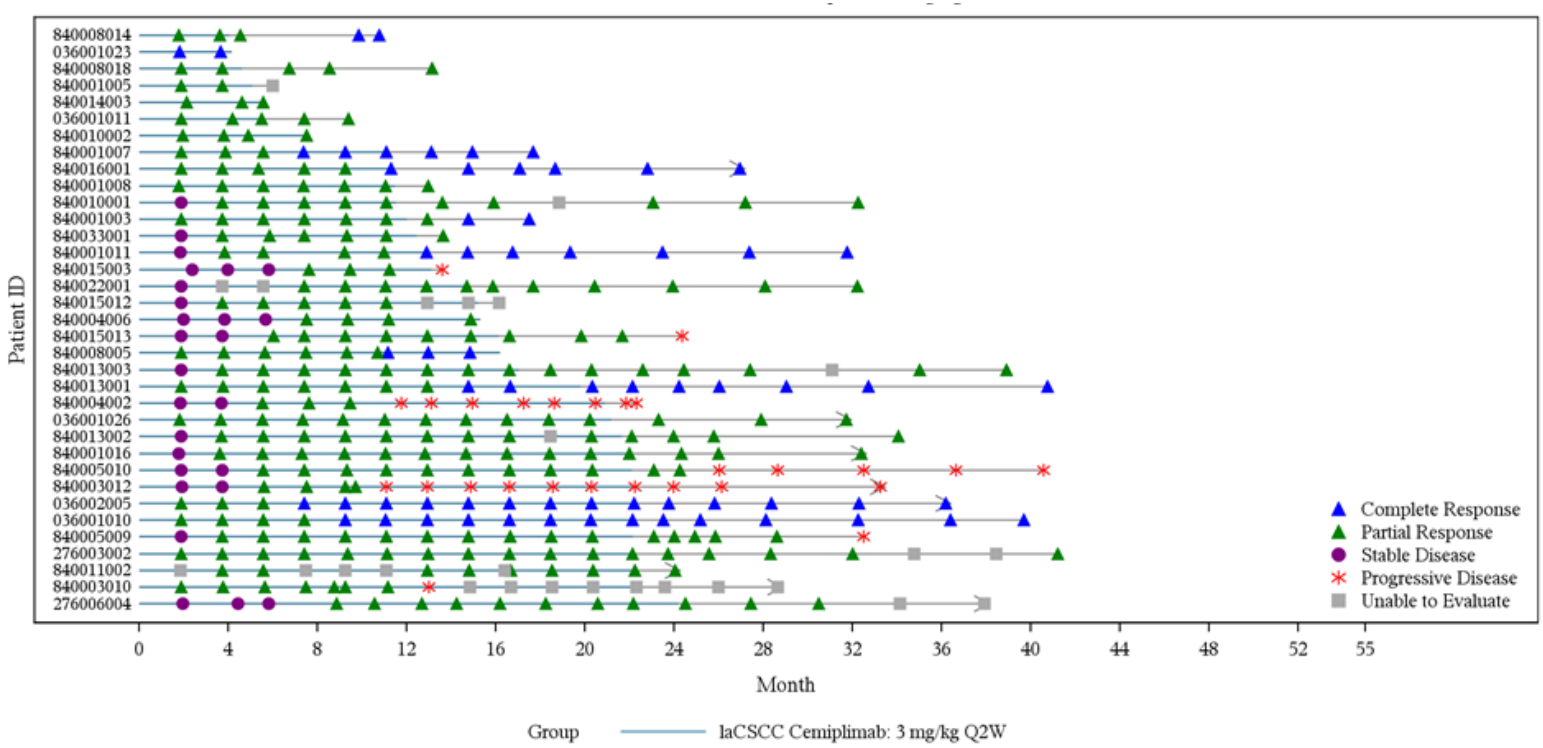
Data cutoff as of 11 Oct 2020.
Waterfall plot displays the best percent change in the sum of target lesion diameters during study period from baseline, based on radiologic imaging. Lesion measurements after progression are excluded. Increase in sum of target lesion diameters greater than 100% is reported as 100%.
CR=complete response; mCSCC=metastatic cutaneous squamous cell carcinoma; NE=not evaluable; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.
Source: Study 1540 Group 6 Interim CSR PTF 14.2.1.3.3.

Figure 4: Swimmer Plot for Patients with Confirmed CR or PR by Independent Central Review – Group 1 (mCSCC; Full Analysis Set-Patients with Confirmed CR or PR)



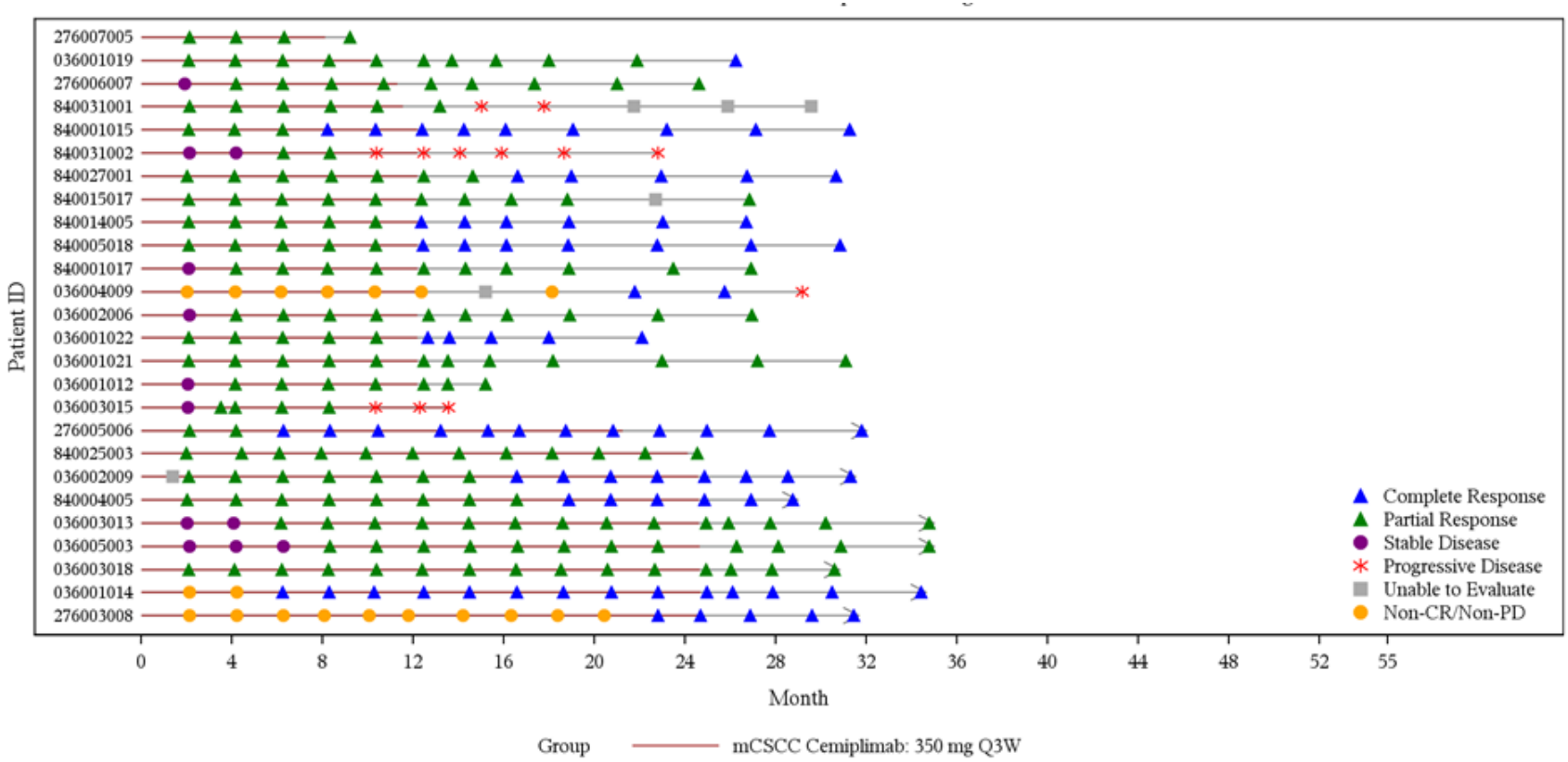
Data cutoff as of 11 Oct 2020.
Arrow in color indicates patient is still on treatment. Arrow in grey indicates patient is still on study.
CR=complete response; laCSCC=locally advanced cutaneous squamous cell carcinoma; mCSCC=metastatic cutaneous squamous cell carcinoma; PD=progressive disease; PR=partial response, Q2W=every 2 weeks.
Source: Study 1540 Group 6 Interim CSR PTF 14.2.1.7.1

Figure 5: Swimmer Plot for Patients with Confirmed CR or PR by Independent Central Review – Group 2 (laCSCC; Full Analysis Set-Patients with Confirmed CR or PR)



Data cutoff as of 11 Oct 2020.
Arrow in color indicates patient is still on treatment. Arrow in grey indicates patient is still on study.
CR=complete response; laCSCC=locally advanced cutaneous squamous cell carcinoma; PR=partial response, Q2W=every 2 weeks.
Source: Study 1540 Group 6 Interim CSR PTF 14.2.1.7.2

Figure 6: Swimmer Plot for Patients with Confirmed CR or PR by Independent Central Review – Group 3 (mCSCC treated with 350 mg Q3W; Full Analysis Set- Patients with Confirmed CR or PR)



Data cutoff as of 11 Oct 2020.
Arrow in color indicates patient is still on treatment. Arrow in grey indicates patient is still on study.
CR=complete response; laCSCC=locally advanced cutaneous squamous cell carcinoma; mCSCC=metastatic cutaneous squamous cell carcinoma; PD=progressive disease; PR=partial response, Q3W=every 3 weeks.
Source: Study 1540 Group 6 Interim CSR PTF 14.2.1.7.3

Group 6 (Interim Analysis)

Two of the 84 patients treated with cemiplimab in Group 6 in scope of the pre-specified Group 6 interim analysis were enrolled but did not receive any cemiplimab dose. Although these patients appeared to meet eligibility at time of enrollment, both patients were unable to receive study treatment because of AEs which, had they occurred prior to study enrollment, would have rendered both patients ineligible for the study: One patient presented tachycardia on day 1 of cycle 1 prior to cemiplimab infusion; the patient progressed rapidly and died; The other patient experienced worsening health status (ECOG PS of 3) after enrollment; the patient presented a SAE of grade 3 hypercalcemia, progressed rapidly and died. These AEs occurred after enrollment but prior to first planned dose of study drug (Module 5.3.5.2 Group 6 Interim CSR Section 8.3.3.2).

Therefore, the efficacy evaluation presented in Table 5 represents data collected for the first 82 patients. For the 82 patients who received at least 1 dose of cemiplimab in Group 6, ORR was 40.2% (95% CI: 29.6 to 51.7).

Table 5: Best Overall Tumor Response Rate by Independent Central Review (Full Analysis Set – Group 6 Patients who Received at Least 1 Dose of Cemiplimab)

	Advanced CSCC Cemiplimab: 350 mg Q3W (Group 6) (N=82)
Best Overall Tumor Response, n (%)	
Complete Response (CR) [a]	5 (6.1%)
Partial Response (PR) [a]	28 (34.1%)
Stable Disease (SD) [b]	20 (24.4%)
Non-CR/Non-PD [c]	1 (1.2%)
Progressive Disease (PD)	16 (19.5%)
Not Evaluable (NE) [d]	12 (14.6%)
Response	
Objective Response Rate (ORR: CR+PR)	33 (40.2%)
95% CI for ORR [e]	(29.6%, 51.7%)
99.69% CI for ORR [e]	(24.9%, 57.1%)
Complete Response Rate (CR) [a]	5 (6.1%)
95% CI for CR Rate [e]	(2.0%, 13.7%)
Disease Control Rate (DCR: CR+PR+SD+Non-CR/Non-PD)	54 (65.9%)
95% CI for DCR [e]	(54.6%, 76.0%)
Durable DCR [f]	46 (56.1%)
95% CI for Durable DCR [e]	(44.7%, 67.0%)

Data cut-off as of Apr 19, 2021. Only patients who started treatment on or prior to 09 Oct 2020 or who enrolled on or prior to 09 Oct 2020 but did not receive treatment are included.
[a] CR/PR must be confirmed by repeated assessments no less than 4 weeks apart.
[b] SD criteria must be met at least once after a minimum duration of 39 days after first dose date.
[c] Non-CR/Non-PD is for patients with non-measurable disease only.
[d] Not evaluable response includes the missing and unknown tumor response.
[e] Clopper-Person exact confidence interval.
[f] Durable DCR: proportion of patients with CR, PR, SD or non-CR/Non-PD for at least 105 days without PD.

Source: Study 1540 Group 6 Interim CSR PTT 14.2.1.1af.g6

Table 6: Best Overall Tumor Response by Independent Central Review in Group 6 (Full Analysis Set)

	Advanced CSCC Cemiplimab: 350 mg Q3W (Group 6) **(N=84)** **(Median FU=6.64 Mos)**
Best Overall Tumor Response, n (%)	
Complete Response (CR) [a]	5 (6.0%)
Partial Response (PR) [a]	28 (33.3%)
Stable Disease (SD) [b]	20 (23.8%)
Non-CR/Non-PD [c]	1 (1.2%)
Progressive Disease (PD)	16 (19.0%)
Not Evaluable (NE) [d]	14 (16.7%)
Response	
Objective Response Rate (ORR: CR+PR)	33 (39.3%)*
95% CI for ORR [e]	(28.8%, 50.5%)
99.69% CI for ORR [e]	(24.2%, 56.9%)
Complete Response Rate (CR) [a]	5 (6.0%)
95% CI for CR Rate [e]	(2.0%, 13.3%)
Disease Control Rate (DCR: CR+PR+SD+Non-CR/Non-PD)	54 (64.3%)
95% CI for DCR [e]	(53.1%, 74.4%)
Durable DCR [f]	46 (54.8%)
95% CI for Durable DCR [e]	(43.5%, 65.7%)

Data cutoff as of 19 Apr 2021

*Note: the ORR of 39.3% does not include a patient who had evidence of deep response on first imaging assessment but had surgical debridement of target lesion prior to confirmatory imaging. Therefore, the response was not confirmed and the patient was classified as NE.

Only patients who started treatment on or prior to 09 Oct 2020 or who enrolled on or prior to 09 Oct 2020 but did not receive treatment are included.

[a] CR/PR must be confirmed by repeated assessments no less than 4 weeks apart.

[b] SD criteria must be met at least once after a minimum duration of 39 days after first dose date.

[c] Non-CR/Non-PD is for patients with non-measurable disease only.

[d] Not evaluable response includes the missing and unknown tumor response.

[e] Clopper-Person exact confidence interval.

[f] Durable DCR: proportion of patients with CR, PR, SD or non-CR/Non-PD for at least 105 days without PD.

Source: Study 1540 Group 6 Interim CSR PTT 14.2.1.1f.g6 and PTT 14.1.1.7f.g6

Table 7: Kaplan-Meier Estimation of Duration of Response by Independent Central Review in Group 6 (Full Analysis Set - Patients with Confirmed CR or PR)

	Advanced CSCC Cemiplimab: 350 mg Q3W (Group 6) (N=33)
KM Estimation of Duration of Response (CR or PR)	
n	33
Number of events, n (%) [a]	2 (6.1%)
Number of censored patients, n (%) [a]	31 (93.9%)
Median (95% CI) (months)	NR (6.6, NE)
Estimated Event-Free Probability, % (95% CI)	
4 months	100 (NE, NE)
6 months	95.0 (69.5, 99.3)
8 months	83.1 (43.0, 96.0)

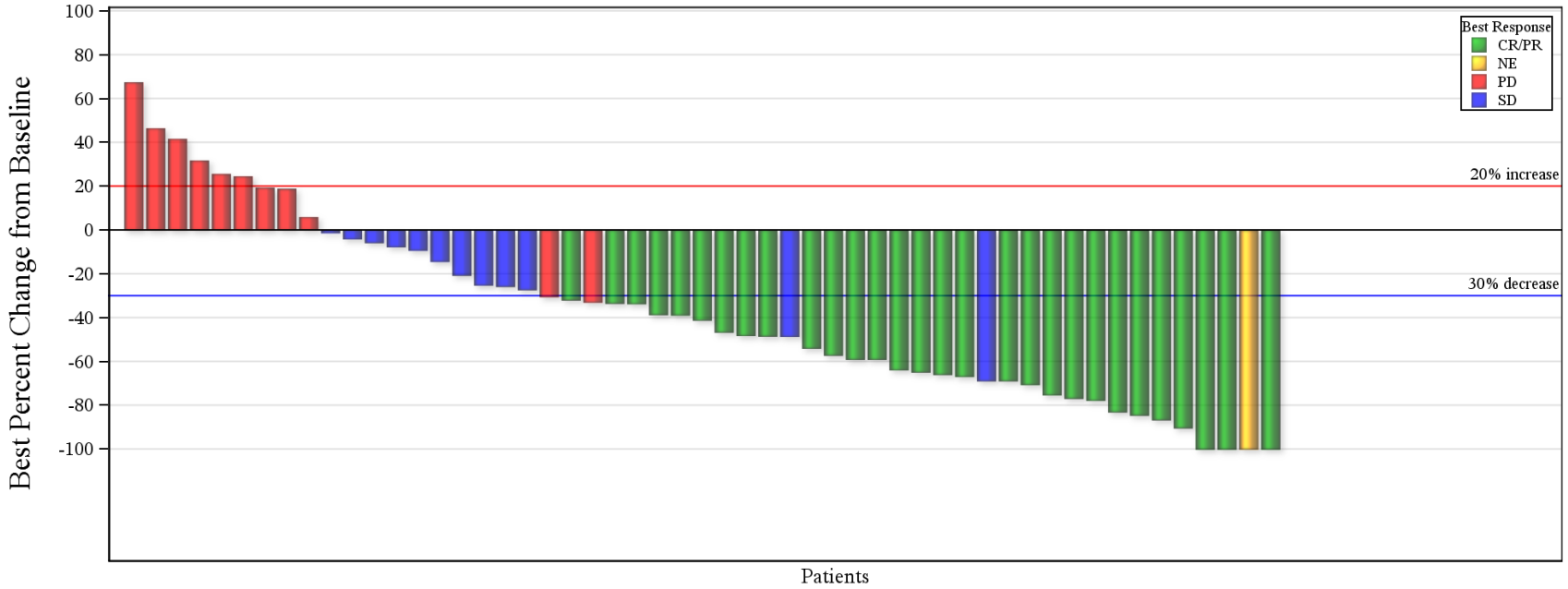
Data cutoff as of 19 Apr 2021

Only patients who started treatment on or prior to 09 Oct 2020 or who enrolled on or prior to 09 Oct 2020 but did not receive treatment are included.

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

Source: Study 1540 Group 6 Interim CSR PTT 14.2.1.3f.g6

Figure 7: Waterfall Plot per RECIST 1.1 by Independent Central Review – Group 6 (mCSCC or laCSCC; Full Analysis Set)



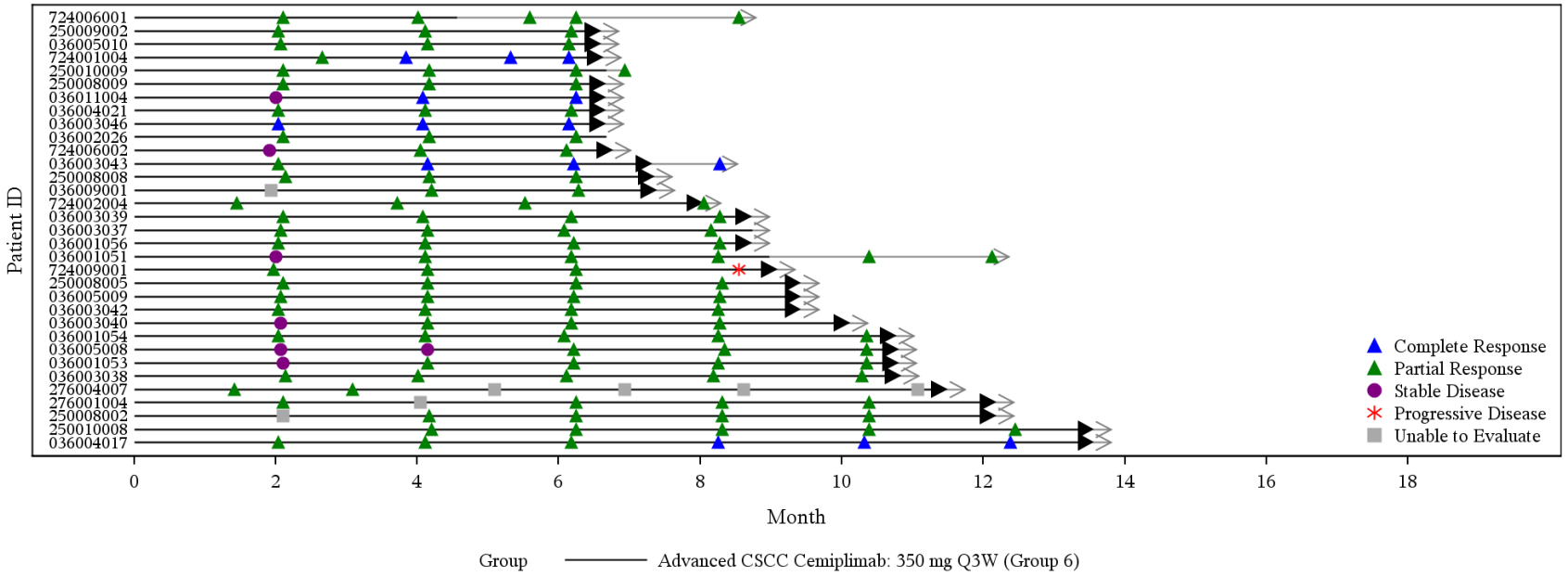
Data cutoff as of 19 Apr 2021

Waterfall plot displays the best percentage change in the sum of target lesion diameters during study period from baseline, based on radiologic imaging. Lesion measurements after progression are excluded. Patients with new lesions or unequivocal progression of non-target lesions were considered as PD (red bars) regardless of target lesion response. Patients with a single assessment with ≥30% reduction of target lesion(s) are considered SD (blue bars) if there is not confirmatory assessment to establish PR. One patient is NE (yellow bar); this patient had both radiologic and photographic data and was assessed by the ICRC as NE, due to surgical debridement of target lesion after initial imaging evidence of response but prior to confirmatory imaging. Increase in sum of target lesion diameters greater than 100% was reported as 100%. Patients with no measurable target lesions or with baseline target lesion measurements but no post-baseline tumor assessments were not included.

CR=complete response; laCSCC=locally advanced cutaneous squamous cell carcinoma; mCSCC=metastatic cutaneous squamous cell carcinoma; NE=not evaluable; NR=not reached; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

Source: Study 1540 Group 6 Interim CSR PTF 14.2.1.3.8.g6

Figure 8: Swimmer Plot for Patients with Confirmed CR or PR by Independent Central Review – Group 6 (mCSCC or laCSCC; Full Analysis Set- Patients with Confirmed CR or PR)



Data cutoff as of 19 Apr 2021
Only patients who started treatment on or prior to 9 Oct 2020 or who enrolled on or prior to 9 Oct 2020 but did not receive treatment, are included
Arrow in color indicates patient is still on treatment. Arrow in grey indicates patient is still on study.
CR=complete response; laCSCC=locally advanced cutaneous squamous cell carcinoma; mCSCC=metastatic cutaneous squamous cell carcinoma; PD=progressive disease; PR=partial response, Q3W=every 3 weeks.
Source: Study 1540 Group 6 Interim CSR PTF 14.2.1.7.8.g6

Assessment comment

The updated ORR and DOR from Groups 1-3 continue to show clinically meaningful benefit, and the ORR and DOR observed in Group 6 are in line with Group 1-3. The MAH has excluded two patients from the efficacy evaluation in Group 6. Both patients didn't receive any treatment with cemiplimab. Thus, their exclusion is endorsed.

Subgroup Analyses

Groups 1 to 3

Exploratory subgroup analyses demonstrated antitumor activity of cemiplimab in all subgroups in Groups 1 to 3. However, there was a numerical difference in ORR related to prior systemic therapy. The ORR in patients within Groups 1 to 3 who had received prior systemic anticancer therapy was 41.5% (27/65; 95% CI: 29.4% to 54.4%) and, in those who had not received prior systemic anticancer therapy, ORR was 50.0% (64/128; 95% CI: 41.0% to 59.0%) (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Post-text Table 14.2.1.1.s6).

Group 6 (Interim Analysis)

Exploratory subgroup analyses demonstrated antitumor activity of cemiplimab in all clinically relevant subgroups in Group 6. These subgroup results should be interpreted with caution due to the small patient numbers in some of the subgroups. The ORR in mCSCC patients in Group 6 (n=54) was 42.6% (23/54; 95% CI: 29.2%, 56.8%) and the ORR in laCSCC patients in Group 6 (n=30) was 33.3% (10/30; 95% CI: 17.3%, 52.8%); (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Post-text Table 14.2.1.1.s11.g6).

Secondary Endpoints

Objective Response Rate and Duration of Response by Investigator Assessment

Groups 1 to 3

Investigator-assessed ORR was prospectively defined as a secondary endpoint. These data are considered supportive to those obtained by ICR and relevant to clinical practice, where treatment decisions are guided by physician assessment and not central review. Point estimates of ORR per investigator assessments in Groups 1, 2, 3, and overall were 50.8% (95% CI: 37.5 to 64.1), 56.4% (95% CI: 44.7 to 67.6), 55.4% (95% CI: 41.5 to 68.7) and 54.4% (95% CI: 47.1 to 61.6), respectively (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Post-text Table 14.2.1.2f).

Group 6 (Interim Analysis)

Point estimates of ORR per investigator assessments for the interim analysis of Group 6 was 52.4% (95% CI: 41.1% to 63.6%) (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Post-text Table 14.2.1.2af.g6) for the 82 patients who had received at least 1 dose of cemiplimab and 51.2% (95% CI: 40.0% to 62.3%) (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Post-text Table 14.2.1.2f.g6) for all 84 patients in Group 6.

Progression-Free Survival

Groups 1 to 3

For all 193 patients in Groups 1, 2, and 3, the median duration of follow-up was approximately 15.74 months (range: 0.6 to 43.2).

The median PFS at the time of data cutoff per ICR, was 18.4 months for Group 1, 18.5 months for Group 2, and 21.7 months for Group 3 (Table 8 and Figure 9). The estimated event-free probability from baseline through 12 months was 53.0% (95% CI: 39.0% to 65.1%) for patients in Group 1, 60.5% (95% CI: 47.5% to 71.3%) for patients in Group 2, and 52.4% (95% CI: 38.4% to 64.6%) for patients in Group 3. For all 3 groups combined, the estimated event-free probability from baseline through 12 months was 55.8% (95% CI: 48.1% to 62.8%).

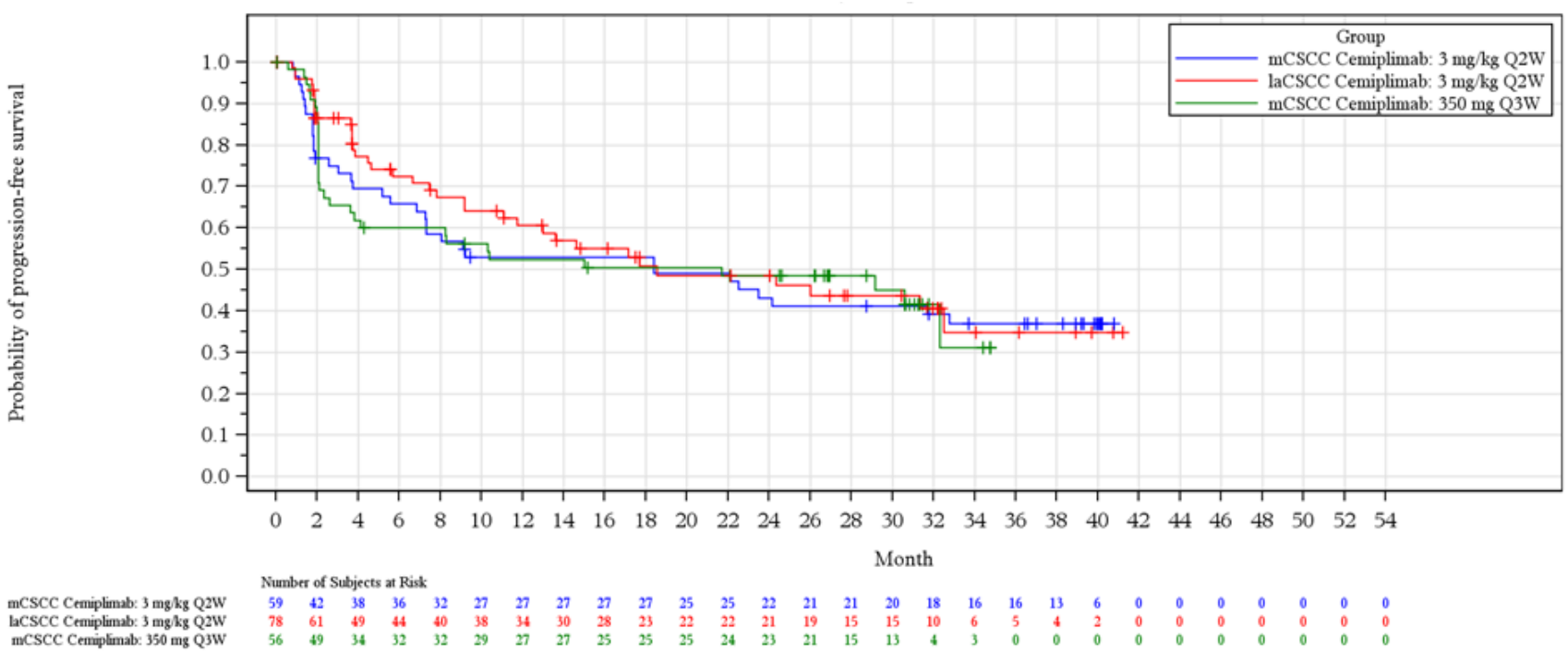
The estimated event-free probability from baseline through 24 months was 43.1% (95% CI: 29.8% to 55.8%) for patients in Group 1, 48.5% (95% CI: 35.1% to 60.7%) for patients in Group 2, and 48.4% (95% CI: 34.6% to 60.9%) for patients in Group 3. For all 3 groups combined, the estimated event-free probability from baseline through 24 months was 46.9% (95% CI: 39.2 to 54.3).

Table 8: Kaplan-Meier Estimation of Progression-Free Survival by Independent Central Review for Groups 1 to 3 (Full Analysis Set)

	Group 1 mCSCC 3 mg/kg Q2W (N=59) (Median FU =18.50 Mos)	Group 2 laCSCC 3 mg/kg Q2W (N=78) (Median FU =15.52 Mos)	Group 3 mCSCC 350 mg Q3W (N=56) (Median FU =17.30 Mos)	Total (N=193) (Median FU =15.74 Mos)
KM estimation of Progression Free Survival				
Number of events, n (%)	34 (57.6%)	36 (46.2%)	31 (55.4%)	101 (52.3%)
Progressive Disease, n (%)	25 (42.4%)	29 (37.2%)	23 (41.1%)	77 (39.9%)
Death, n (%)	9 (15.3%)	7 (9.0%)	8 (14.3%)	24 (12.4%)
Number of censored patients, n (%)	25 (42.4%)	42 (53.8%)	25 (44.6%)	92 (47.7%)
Median (95% CI), (months)	18.4 (6.8, 32.8)	18.5 (11.1, NE)	21.7 (3.6, NE)	18.5 (10.3, 31.3)
Estimated Event-Free Probability, % (95% CI)				
4 months	69.5 (55.6, 79.8)	77.2 (65.4, 85.4)	61.8 (47.7, 73.2)	70.2 (62.9, 76.3)
6 months	65.8 (51.8, 76.7)	72.4 (60.1, 81.5)	60.0 (45.9, 71.5)	66.7 (59.2, 73.1)
8 months	58.5 (44.4, 70.2)	67.4 (54.7, 77.3)	60.0 (45.9, 71.5)	62.5 (54.9, 69.2)
12 months	53.0 (39.0, 65.1)	60.5 (47.5, 71.3)	52.4 (38.4, 64.6)	55.8 (48.1, 62.8)
16 months	53.0 (39.0, 65.1)	55.0 (41.8, 66.4)	50.4 (36.5, 62.8)	53.2 (45.4, 60.3)
20 months	49.0 (35.3, 61.4)	48.5 (35.1, 60.7)	50.4 (36.5, 62.8)	49.7 (42.0, 57.0)
24 months	43.1 (29.8, 55.8)	48.5 (35.1, 60.7)	48.4 (34.6, 60.9)	46.9 (39.2, 54.3)
28 months	41.2 (28.0, 53.9)	43.7 (30.2, 56.3)	48.4 (34.6, 60.9)	44.7 (37.0, 52.2)
32 months	39.1 (26.1, 51.9)	40.6 (26.9, 53.7)	41.5 (27.0, 55.4)	40.7 (32.7, 48.5)
36 months	37.0 (24.2, 49.8)	34.8 (19.7, 50.2)	NE (NE, NE)	36.5 (28.2, 44.9)

Data cutoff as of 11 Oct 2020.
Source: Study 1540 Group 6 Interim CSR PTT 14.2.2.1f and PTT 14.1.1.7f

Figure 9 **Kaplan-Meier Curve for Progression-Free Survival by Independent Central Review - Groups 1 to 3 CSCC Patients**



CSCC=cutaneous squamous cell carcinoma; laCSCC=locally advanced cutaneous squamous cell carcinoma; mCSCC=metastatic cutaneous squamous cell carcinoma, Q2W=every 2 weeks.
Data cutoff as of 11 Oct 2020.
Source: Study 1540 Group 6 Interim CSR PTF 14.2.2.1.4

Group 6 (Interim Analysis)

The median duration of follow-up for the 82 patients who received cemiplimab was approximately 6.64 months (range: 0.3 to 13.1). Per the SAP, PFS can only be calculated for patients treated with cemiplimab, so the 2 patients in Group 6 who were not dosed are not included.

The median PFS at the time of data cutoff per independent central review, was 10.3 months for Group 6 (Table 9). The estimated event-free probability from baseline through 6 months was 63.1% (95% CI: 51.2% to 72.8%) for patients in Group 6.

Only 40.2% of patients had PFS events and therefore the KM estimate of PFS is not stable at the time of this interim analysis (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Post-text Figure 14.2.2.1.8.g6).

Table 9: Kaplan-Meier Estimation of Progression-Free Survival by Independent Central Review for Group 6 (Full Analysis Set)

	Advanced CSCC Cemiplimab: 350 mg Q3W (Group 6) (N=82) (Median FU=6.64 Mos)
KM estimation of Progression Free Survival	
Number of events, n (%)	33 (40.2%)
Progressive Disease, n (%)	23 (28.0%)
Death, n (%)	10 (12.2%)
Number of censored patients, n (%)	49 (59.8%)
Median (95% CI), (months)	10.3 (6.9, NE)
Estimated Event-Free Probability, % (95% CI)	
4 months	67.1 (55.3, 76.4)
6 months	63.1 (51.2, 72.8)
8 months	61.0 (48.7, 71.1)
12 months	34.7 (13.6, 57.1)

Data cutoff as of 19 Apr 2021
Per SAP, PFS was measured from the start of treatment until the first date of recurrent or progressive disease, or death due to any cause; hence, 2 patients who did not receive treatment were excluded.
Only patients who started treatment on or prior to 09 Oct 2020 or who enrolled on or prior to 09 Oct 2020 but did not receive treatment are included.
Source: Study 1540 Group 6 Interim CSR PTT 14.2.2.1f.g6 and PTT 14.1.1.7.g6

Overall Survival

Groups 1 to 3

For all 193 patients in Groups 1, 2, and 3, the median duration of follow-up was approximately 15.74 months (range: 0.6 to 43.2). Median OS was not reached in Group 1, or Group 2, or Group 3 at the time of data cutoff.

The estimated probability of survival from baseline through 12 months for patients in Group 1 was 81.3% (95% CI: 68.7% to, 89.2%), 91.8% (95% CI: 82.6% to 96.2%) for patients in Group 2, and 72.5% (95% CI: 58.6% to 82.5%) for patients in Group 3. For all 193 patients in Groups 1, 2, and 3, the estimated probability of surviving from baseline through 12 months was 82.8% (95% CI: 76.6% to 87.6%) (Table 10 and Figure 10).

The estimated probability of surviving from baseline through 24 months for patients in Group 1 was 68.8% (95% CI: 55.0% to 79.1%), 82.8% (95% CI: 71.6% to 89.9%) for patients in Group 2, and

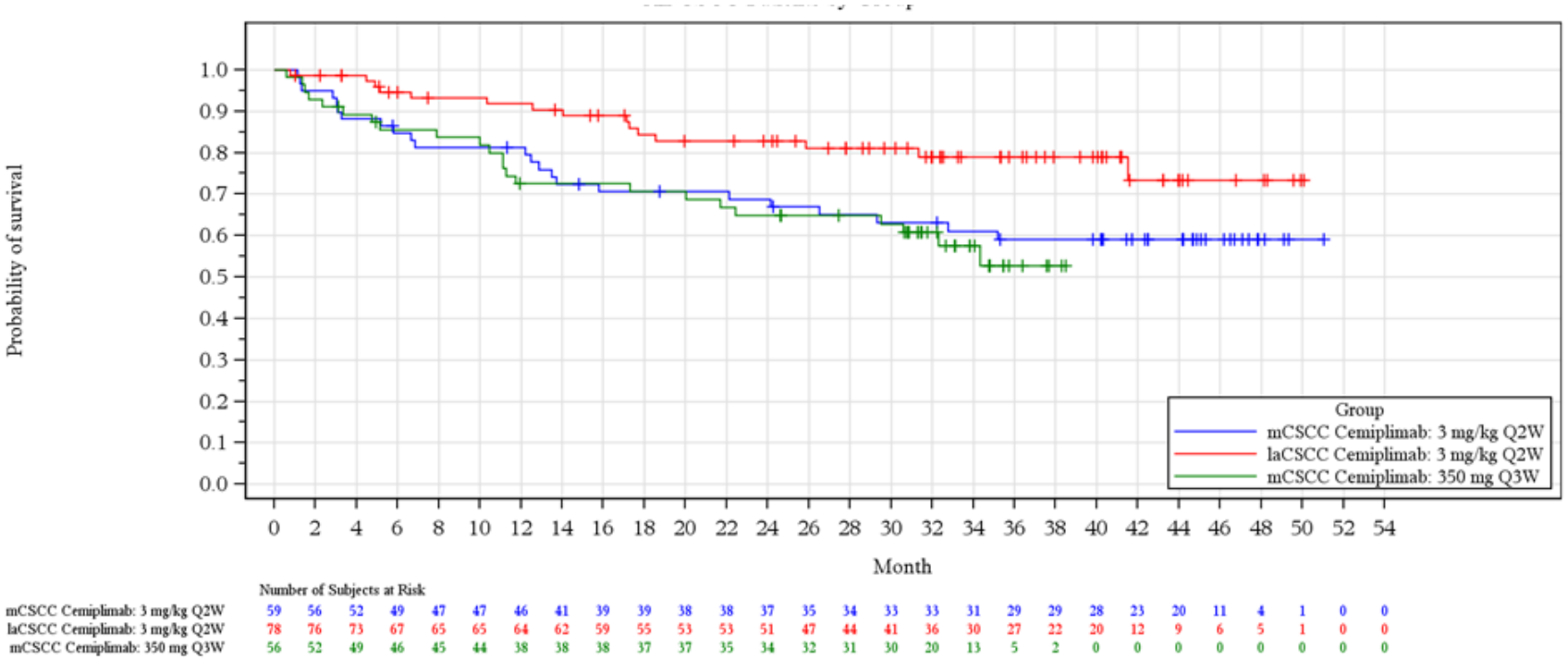
64.9% (95% CI: 50.6% to 76.0%) for patients in Group 3. For all 193 patients in Groups 1, 2, and 3, the estimated probability of surviving from baseline through 24 months was 73.1% (95% CI: 66.0% to 78.9%) (Table 10 and Figure 10).

Table 10: Summary of Overall Survival for Groups 1 to 3 (Full Analysis Set)

	Group 1 mCSCC 3 mg/kg Q2W (N=59) (Median FU =18.50 Mos)	Group 2 laCSCC 3 mg/kg Q2W (N=78) (Median FU =15.52 Mos)	Group 3 mCSCC 350 mg Q3W (N=56) (Median FU =17.30 Mos)	Total (N=193) (Median FU =15.74 Mos)
KM estimation of Overall Survival				
Number of deaths, n (%)	23 (39.0%)	15 (19.2%)	23 (41.1%)	61 (31.6%)
Number of censored patients, n (%)	36 (61.0%)	63 (80.8%)	33 (58.9%)	132 (68.4%)
Median (95% CI), (months)	NR (29.3, NE)	NR (NE, NE)	NR (29.5, NE)	NR (NE, NE)
Estimated Probability of Survival, % (95% CI)				
4 months	88.1 (76.7, 94.2)	98.7 (91.2, 99.8)	89.2 (77.6, 95.0)	92.7 (87.9, 95.6)
6 months	84.7 (72.7, 91.7)	94.6 (86.3, 98.0)	85.6 (73.2, 92.5)	88.9 (83.5, 92.6)
8 months	81.3 (68.7, 89.2)	93.2 (84.5, 97.1)	83.7 (71.0, 91.2)	86.7 (81.0, 90.8)
12 months	81.3 (68.7, 89.2)	91.8 (82.6, 96.2)	72.5 (58.6, 82.5)	82.8 (76.6, 87.6)
16 months	70.6 (57.0, 80.6)	88.9 (79.0, 94.3)	72.5 (58.6, 82.5)	78.3 (71.7, 83.6)
20 months	70.6 (57.0, 80.6)	82.8 (71.6, 89.9)	70.6 (56.6, 80.9)	75.4 (68.5, 81.1)
24 months	68.8 (55.0, 79.1)	82.8 (71.6, 89.9)	64.9 (50.6, 76.0)	73.1 (66.0, 78.9)
28 months	65.0 (51.1, 75.8)	81.0 (69.5, 88.6)	64.9 (50.6, 76.0)	71.2 (64.0, 77.3)
32 months	63.1 (49.1, 74.2)	79.0 (66.9, 87.1)	60.7 (46.3, 72.4)	68.5 (61.0, 74.8)
36 months	59.1 (45.1, 70.7)	79.0 (66.9, 87.1)	52.7 (36.2, 66.8)	65.0 (57.1, 71.8)

Data cutoff as of 11 Oct 2020.
Source: Study 1540 Group 6 Interim CSR PTT 14.2.3.1f and PTT 14.1.1.7f

Figure 10: Kaplan-Meier Curve for Overall Survival – CSCC Patients in Groups 1 to 3



Data cutoff as of 11 Oct 2020.
CSCC=cutaneous squamous cell carcinoma; laCSCC=locally advanced cutaneous squamous cell carcinoma; mCSCC=metastatic cutaneous squamous cell carcinoma, Q2W=every 2 weeks.
Source: Study 1540 Group 6 Interim CSR PTF 14.2.3.1.4

Group 6 (Interim Analysis)

The median duration of follow-up for 82 patients was approximately 6.64 months (range: 0.3 to 13.1). Per the SAP, OS can only be calculated for patients treated with cemiplimab, so the 2 patients in Group 6 who were not dosed are not included. Median OS was not reached in Group 6 at the time of the data cutoff.

The estimated probability of survival from baseline through 6 months for patients in Group 6 who had received at least 1 dose of cemiplimab was 83.8% (95% CI: 73.7 to 90.3) (Table 11). The estimated probability of survival from baseline through 12 months for patients in Group 6 who had received at least 1 dose of cemiplimab was 67.7% (95% CI: 51.5 to 79.5) (Table 11). Only 24.4% of patients had OS events and therefore the KM estimate of OS is not stable at the time of this interim analysis (Module 5.3.5.2 Study 1540 Group 6 Interim Analysis CSR Post-text Figure 14.2.2.1.8.g6).

Table 11: Summary of Overall Survival for Group 6 (Full Analysis Set)

	Advanced CSCC Cemiplimab: 350 mg Q3W (Group 6) (N=82) (Median FU=6.64 Mos)
KM estimation of Overall Survival	
Number of deaths, n (%)	20 (24.4%)
Number of censored patients, n (%)	62 (75.6%)
Median (95% CI), (months)	NR (NE, NE)
Estimated Probability of Survival, % (95% CI)	
4 months	85.1 (75.2, 91.2)
6 months	83.8 (73.7, 90.3)
8 months	75.9 (64.3, 84.2)
12 months	67.7 (51.5, 79.5)

Data cutoff as of 19 Apr 2021
OS is defined in the SAP as from the start of treatment until death due to any cause. Therefore, only patients who had received at least 1 dose of cemiplimab (N=82) were included.
Only patients who started treatment on or prior to 09 Oct 2020 or who enrolled on or prior to 09 Oct 2020 but did not receive treatment are included.
Source: Study 1540 Group 6 Interim CSR PTT 14.2.3.1f.g6 and PTT 14.1.1.7.g6.

Complete Response Rate per Independent Central Review

Groups 1 to 3

For patients in Group 1, the CR rate was 20.3% (12/59; 95% CI: 11.0 to 32.8%) (Table 3). S 1-3

For patients in Group 2, the CR rate was 12.8% (10/78; 95% CI: 6.3% to 22.3%) (Table 3).

Complete response rate for Group 3 was 19.6% (11/56, 95% CI: 10.2% to 32.4%) (Table 3).

For all 193 patients combined from Groups 1, 2, and 3, the CR rate was 17.1% (33/193; 95% CI: 12.1% to 23.2%) (Table 3). As discussed in Section 4, CR rates for Group 1 to 3 patients have increased with longer follow up after the primary analyses for these groups.

Observed median time to CR per ICR was 11.30 months (95% CI: 1.8 to 22.8) for the 3 groups, 11.09 months (95%CI: 3.7 to 22.1) for Group 1, 10.48 months (95% CI: 1.8 to 14.8) for Group 2, and 12.65 months (95%CI: 6.2 to 22.8) for Group 3 (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.2.1.17f).

Group 6 (Interim Analysis)

Complete response rate for the 82 patients who had received at least 1 dose of cemiplimab in Group 6 was 6.1% (5/82, 95% CI: 2.0% to 13.7%) (Table 5). Complete response rate for the first 84 patients in Group 6 was 6.0% (5/84, 95% CI: 2.0% to 13.3%) (Table 6).

Given that median follow up in Group 6 is 6.64 months, and median time to CR was 11.3 months in Groups 1 to 3, the Group 6 CR rate will be re-assessed at future data cut.

Time to Response per Independent Central Review

Groups 1 to 3

Combining the data for all 91 patients with confirmed CR or PR in Groups 1 to 3, the median observed TTR was 2.07 months (range: 1.7 to 22.8 months) (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Table 45), which corresponds to the timing of the first response assessments, approximately 8 weeks (1.8 months) in Groups 1 and 2 , and approximately 9 weeks (2.1 months) in Group 3. The observed TTR supplements evidence of the efficacy of cemiplimab in patients with advanced CSCC. Details are provided in Module 5.3.5.2 Study 1540 Group 6 Interim CSR Section 8.4.5.1.

Group 6 (Interim Analysis)

For patients in Group 6 with confirmed CR or PR, median observed TTR was 2.10 months (range: 1.4 to 6.2 months) (Module 5.3.5.2 Study 1540 Group 6 Interim CSR Table 46). The observed median TTR corresponds to the timing of the first response assessments, approximately 9 weeks (2.1 months) in Group 6. Details are provided in Module 5.3.5.2 Study 1540 Group 6 Interim CSR Section 8.4.5.2.

Assessment comment

The secondary endpoints are not controlled for multiplicity and the time-to-event endpoints should be interpreted with caution. Nonetheless, the results in Groups 1-3 continue to show clinical benefit and support the primary endpoint, and results from Group 6 are in line with Groups 1-3. Given the short follow-up in Group 6 any firm conclusions should be avoided.

Ancillary analyses

Groups 1 to 3

Tumoral PD-L1 expression (TPS) was evaluated on an exploratory basis among advanced CSCC patients in Group 2. PD-L1 expression in tumor cells by immunohistochemistry (IHC) in pretreatment tumor samples was done on an exploratory basis, without formal validation. Pretreatment tumor samples were available for PD-L1 IHC testing in 48 of 78 patients in Group 2.

The samples of the remaining 30 patients were excluded from PD-L1 analysis because the slides were expired (>6 months since slide cut date) or because there were an insufficient number of cells (<100 viable cells) on the slide. Table 12 presents centrally reviewed ORR data and PD-L1 TPS at different cutoffs. Responses are noted at all PD-L1 cutoffs. Among 17 patients in the PD-L1 negative group (TPS <1%), ORR was 35.3% (6/17 patients). Combining data for all PD-L1 positive patients (TPS ≥1%), ORR was 58.06% (18/31 patients). The ORR data demonstrate that PD-L1 is not a useful marker for selection of advanced CSCC patients for cemiplimab therapy. Cemiplimab is active against advanced CSCC in all PD-L1 strata.

In summary, there was no consistent association between baseline PD-L1 status and clinical response, suggesting that baseline PD-L1 testing will have little or no clinical utility in advanced CSCC. Objective

responses per independent central review were observed in PD-L1 negative patients, both metastatic and locally advanced.

Table 12: Best Overall Tumor Response Rate by Independent Central Review (Group 2 Patients Who had Samples Evaluable for PD-L1 Assay)

	PD-L1<1% (N=17)	PD-L1≥1% <5% (N=3)	toPD-L1≥5% <50% (N=21)	toPD-L1>=50% (N=7)
Best Overall Tumor Response, n (%)				
Complete Response (CR) [a]	1 (5.9%)	0	4 (19.0%)	0
Partial Response (PR) [a]	5 (29.4%)	2 (66.7%)	8 (38.1%)	4 (57.1%)
Stable Disease (SD) [b]	8 (47.1%)	1 (33.3%)	4 (19.0%)	1 (14.3%)
Non-CR/Non-PD [c]	0	0	0	0
Progressive Disease (PD)	2 (11.8%)	0	2 (9.5%)	2 (28.6%)
Not Evaluable (NE) [d]	1 (5.9%)	0	3 (14.3%)	0
Response				
Objective Response Rate (ORR: CR+PR)	6 (35.3%)	2 (66.7%)	12 (57.1%)	4 (57.1%)
95% CI for ORR [e]	(14.2%, 61.7%)	(9.4%, 99.2%)	(34.0%, 78.2%)	(18.4%, 90.1%)
Complete Response Rate (CR) [a]	1 (5.9%)	0	4 (19.0%)	0
95% CI for CR Rate [e]	(0.1%, 28.7%)	(0.0%, 70.8%)	(5.4%, 41.9%)	(0.0%, 41.0%)
Disease Control Rate (DCR: CR+PR+SD+Non-CR/Non-PD)	14 (82.4%)	3 (100%)	16 (76.2%)	5 (71.4%)
95% CI for DCR [e]	(56.6%, 96.2%)	(29.2%, 100.0%)	(52.8%, 91.8%)	(29.0%, 96.3%)
Durable DCR [f]	10 (58.8%)	3 (100%)	14 (66.7%)	4 (57.1%)
95% CI for Durable DCR [e]	(32.9%, 81.6%)	(29.2%, 100.0%)	(43.0%, 85.4%)	(18.4%, 90.1%)

Data cutoff as of 11 Oct 2020.

CI=confidence interval; CR=complete response; laCSCC=locally advanced cutaneous squamous cell carcinoma; mCSCC=metastatic cutaneous squamous cell carcinoma; NE=not evaluable; ORR=overall response rate; PD=progressive disease; PD-L1=programmed death ligand; PR=partial response; SD=stable disease.

[a] CR/PR was confirmed by repeated assessments no less than 4 weeks apart.

[b] SD criteria were met at least once after a minimum duration of 39 days after first dose date.

[c] Non-CR/Non-PD is for patients with non-measurable disease only.

[d] Not evaluable response includes the missing and unknown tumor response.

[e] Clopper-Person exact confidence interval.

[f] Durable DCR: proportion of patients with CR, PR, SD or non-CR/Non-PD for at least 105 days without PD.

Source: Study 1540 Group 6 Interim CSR PTT 14.2.1.15f.

Group 6 (Interim Analysis)

Tumoral PD-L1 expression (TPS) was a secondary endpoint in Group 6. Biomarker data are presented for PD-L1 expression by immunohistochemistry (IHC).

Among the 84 patients in scope for the interim analysis in Group 6, a baseline tumor sample for PD-L1 analysis was available for 40 patients. Among 16 patients in the PD-L1 negative group (TPS <1%), ORR was 31.3% (5/16 patients). In PD-L1 positive patients (TPS ≥1%), ORR was 37.5% (9/24 patients) (Table 13). A breakdown of the data for positive patients (TPS ≥1%), showed an ORR of 20.0% (1/5) for patients with TPS ≥1% and <5%, an ORR of 14.3% (1/7) for patients with TPS ≥5% and <50%, and an ORR of 58.3% (7/12) for patients with TPS ≥50% (Table 14). Overall, the ORR data demonstrated that PD-L1 is not a useful marker for selection of advanced CSCC patients for cemiplimab therapy. Cemiplimab is active against advanced CSCC in all PD-L1 strata. Group 6 results were consistent with results from Groups 1 to 3.

Table 13 Best Overall Tumor Response Rate by Independent Central Review Group 6 (mCSCC and laCSCC) (Full Analysis Set Patients Who Had Samples Evaluable for PD-L1 Assay)

	PD-L1<1% (N=16)	PD-L1>=1% (N=24)
Best Overall Tumor Response, n (%)		
Complete Response (CR) [a]	1 (6.3%)	1 (4.2%)
Partial Response (PR) [a]	4 (25.0%)	8 (33.3%)
Stable Disease (SD) [b]	1 (6.3%)	7 (29.2%)
Non-CR/Non-PD [c]	0	0
Progressive Disease (PD)	5 (31.3%)	6 (25.0%)
Not Evaluable (NE) [d]	5 (31.3%)	2 (8.3%)
Response		
Objective Response Rate (ORR: CR+PR)	5 (31.3%)	9 (37.5%)
95% CI for ORR [e]	(11.0%, 58.7%)	(18.8%, 59.4%)
Complete Response Rate (CR) [a]	1 (6.3%)	1 (4.2%)
95% CI for CR Rate [e]	(0.2%, 30.2%)	(0.1%, 21.1%)
Disease Control Rate (DCR: CR+PR+SD+Non-CR/Non-PD)	6 (37.5%)	16 (66.7%)
95% CI for DCR [e]	(15.2%, 64.6%)	(44.7%, 84.4%)
Durable DCR [f]	5 (31.3%)	12 (50.0%)
95% CI for Durable DCR [e]	(11.0%, 58.7%)	(29.1%, 70.9%)

Data cut-off as of 19 Apr 2021.
CI=confidence interval; CR=complete response; CSCC=cutaneous squamous cell carcinoma; NE=not evaluable; ORR=overall response rate; PD=progressive disease; PD-L1=programmed death ligand; PR=partial response; SD=stable disease.
Only patients who started treatment on or prior to 09 Oct 2020 or who enrolled on or prior to 09 Oct 2020 but did not receive treatment are included.
[a] CR/PR must be confirmed by repeated assessments no less than 4 weeks apart
[b] SD criteria must be met at least once after a minimum duration of 39 days after first dose date
[c] Non-CR/Non-PD is for patients with non-measurable disease only
[d] Not evaluable response includes the missing and unknown tumor response
[e] Clopper-Person exact confidence interval
[f] Durable DCR: proportion of patients with CR, PR, SD or non-CR/Non-PD for at least 105 days without PD
Source: Study 1540 Group 6 Interim CSR PTT 14.2.1.16f.g6

Table 14: Best Overall Tumor Response Rate by Independent Central Review Group 6 (Full Analysis Set –Patients Who Had Samples Evaluable for PD-L1 Assay)

	PD-L1<1% (N=16)	PD-L1≥1% <5% (N=5)	toPD-L1≥5% <50% (N=7)	toPD-L1>=50% (N=12)
Best Overall Tumor Response, n (%)				
Complete Response (CR) [a]	1 (6.3%)	0	0	1 (8.3%)
Partial Response (PR) [a]	4 (25.0%)	1 (20.0%)	1 (14.3%)	6 (50.0%)
Stable Disease (SD) [b]	1 (6.3%)	3 (60.0%)	3 (42.9%)	1 (8.3%)
Non-CR/Non-PD [c]	0	0	0	0
Progressive Disease (PD)	5 (31.3%)	1 (20.0%)	3 (42.9%)	2 (16.7%)
Not Evaluable (NE) [d]	5 (31.3%)	0	0	2 (16.7%)
Response				
Objective Response Rate (ORR: CR+PR)	5 (31.3%)	1 (20.0%)	1 (14.3%)	7 (58.3%)
95% CI for ORR [e]	(11.0%, 58.7%)	(0.5%, 71.6%)	(0.4%, 57.9%)	(27.7%, 84.8%)
Complete Response Rate (CR) [a]	1 (6.3%)	0	0	1 (8.3%)
95% CI for CR Rate [e]	(0.2%, 30.2%)	(0.0%, 52.2%)	(0.0%, 41.0%)	(0.2%, 38.5%)
Disease Control Rate (DCR: CR+PR+SD+Non-CR/Non-PD)	6 (37.5%)	4 (80.0%)	4 (57.1%)	8 (66.7%)
95% CI for DCR [e]	(15.2%, 64.6%)	(28.4%, 99.5%)	(18.4%, 90.1%)	(34.9%, 90.1%)
Durable DCR [f]	5 (31.3%)	3 (60.0%)	1 (14.3%)	8 (66.7%)
95% CI for Durable DCR [e]	(11.0%, 58.7%)	(14.7%, 94.7%)	(0.4%, 57.9%)	(34.9%, 90.1%)

Data cutoff as of 19 Apr 2021

CI=confidence interval; CR=complete response; CSCC=cutaneous squamous cell carcinoma; NE=not evaluable; ORR=overall response rate; PD=progressive disease; PD-L1=programmed death ligand; PR=partial response; SD=stable disease.

Only patients who started treatment on or prior to 09 Oct 2020 or who enrolled on or prior to 09 Oct 2020 but did not receive treatment are included.

[a] CR/PR was confirmed by repeated assessments no less than 4 weeks apart.

[b] SD criteria were met at least once after a minimum duration of 39 days after first dose date.

[c] Non-CR/Non-PD is for patients with non-measurable disease at baseline only.

[d] Not evaluable response includes the missing and unknown tumor response.

[e] Clopper-Person exact confidence interval.

[f] Durable DCR: proportion of patients with CR, PR, SD or non-CR/Non-PD for at least 105 days without PD.

Source: Study 1540 Group 6 Interim CSR PTT 14.2.1.15f.g6

Assessment comment

Approximately half of the 84 patients in scope of the interim analysis in Group 6 had an available baseline tumor sample. The numbers are small, but it can be reasonably concluded that efficacy of cemiplimab is not predicted by PD-L1 expression in the CSCC clinical setting. This supports the continued use of cemiplimab in all-comers in CSCC.

Safety

All patients who received at least 1 dose of cemiplimab in Study 1540 Groups 1, 2, 3 and 6 (interim analysis), Study 1423, Study 1676, Study 1620, and Study 1624 (excluding crossover cemiplimab treatment) are included in the analysis. Integrated databases by each pool are presented in Table 2 and described below.

- Safety Pool 1 (CSCC population): All patients who received at least 1 dose of cemiplimab monotherapy in Study 1540 (Groups 1 to 3 and Group 6 [interim analysis]). This pool included 275 patients. This is the primary pool for the analysis of safety of cemiplimab in patients with CSCC.
- Safety Pool 2 (cemiplimab monotherapy population): All patients (N=1198) who received at least 1 dose of cemiplimab as monotherapy in Study 1540 (Groups 1, 2, 3 and 6 [interim analysis], n=275), Study 1676 (n=300), Study 1423 (n=130), Study 1620 (n=138) and Study 1624 (excluding crossover cemiplimab treatment, n=355). This pool is used to evaluate the frequency and characteristics of important risks of cemiplimab (imAEs and IRRs) and allows a broader assessment of the safety profile of cemiplimab monotherapy across solid tumor indications.

The safety data from Study 1540 (Safety Pool 1) is presented side-by-side with integrated safety data from Study 1540 and 4 supportive studies (Safety Pool 2 [cemiplimab monotherapy]).

Exposure

Groups 1 to 3

In Groups 1 to 3, 193 patients were treated with at least 1 dose of cemiplimab, including 137 patients treated with 3 mg/kg Q2W (59 patients in Group 1 and 78 patients in Group 2) and 56 patients with mCSCC treated with 350 mg Q3W (Group 3).

The median duration of exposure was 51.1 weeks (range: 2.0 to 109.3 weeks) and the median number of doses administered was 18.0 (range: 1 to 48 doses) (Table 9). Per group, the median duration of exposure was:

- 65.0 weeks (range: 2.0 to 100.6 weeks) for Group 1
- 49.5 weeks (range: 2.0 to 105.1 weeks) for Group 2
- 48.0 weeks (range: 2.6 to 109.3 weeks) for Group 3

Table 15: Treatment Exposure Groups 1 to 3 (Safety Analysis Set)

	Group 1 mCSCC 3 mg/kg Q2W (N=59) (Patient-Year =63.98)	Group 2 laCSCC 3 mg/kg Q2W (N=78) (Patient-Year =74.25)	Group 3 mCSCC 350 mg Q3W (N=56) (Patient-Year =50.42)	Total (N=193) (Patient-Year =188.64)
Duration of Exposure (weeks)[a]				
n	59	78	56	193
Mean (StDev)	56.58 (39.339)	49.67 (34.439)	46.98 (35.478)	51.00 (36.314)
Median	65.00	49.45	48.00	51.10
Q1 : Q3	10.00 : 96.00	18.00 : 90.90	12.15 : 54.00	16.00 : 95.60
Min : Max	2.0 : 100.6	2.0 : 105.1	2.6 : 109.3	2.0 : 109.3
Duration of Exposure, n (%)				
>=0 weeks	59 (100%)	78 (100%)	56 (100%)	193 (100%)
>=6 weeks	54 (91.5%)	71 (91.0%)	53 (94.6%)	178 (92.2%)
>=12 weeks	42 (71.2%)	65 (83.3%)	43 (76.8%)	150 (77.7%)
>=24 weeks	40 (67.8%)	50 (64.1%)	36 (64.3%)	126 (65.3%)
>=36 weeks	37 (62.7%)	44 (56.4%)	33 (58.9%)	114 (59.1%)
>=48 weeks	34 (57.6%)	44 (56.4%)	28 (50.0%)	106 (54.9%)
>=60 weeks	31 (52.5%)	32 (41.0%)	13 (23.2%)	76 (39.4%)
>=72 weeks	29 (49.2%)	23 (29.5%)	12 (21.4%)	64 (33.2%)
>=84 weeks	25 (42.4%)	21 (26.9%)	11 (19.6%)	57 (29.5%)
>=96 weeks	19 (32.2%)	13 (16.7%)	10 (17.9%)	42 (21.8%)
Number of Doses Administered				
n	59	78	56	193
Mean (StDev)	27.1 (19.01)	23.0 (15.97)	15.0 (11.19)	22.0 (16.43)
Median	32.0	24.0	15.5	18.0
Q1 : Q3	5.0 : 46.0	8.0 : 36.0	3.5 : 18.0	6.0 : 36.0
Min : Max	1 : 48	1 : 48	1 : 36	1 : 48
Number of Doses Administered, n (%)				
>=0	59 (100%)	78 (100%)	56 (100%)	193 (100%)
>=3	56 (94.9%)	71 (91.0%)	51 (91.1%)	178 (92.2%)
>=6	43 (72.9%)	65 (83.3%)	39 (69.6%)	147 (76.2%)
>=12	39 (66.1%)	48 (61.5%)	32 (57.1%)	119 (61.7%)
>=18	36 (61.0%)	44 (56.4%)	24 (42.9%)	104 (53.9%)
>=24	33 (55.9%)	40 (51.3%)	12 (21.4%)	85 (44.0%)
>=30	31 (52.5%)	30 (38.5%)	10 (17.9%)	71 (36.8%)
>=36	27 (45.8%)	21 (26.9%)	1 (1.8%)	49 (25.4%)
>=42	24 (40.7%)	17 (21.8%)	0	41 (21.2%)
>=48	10 (16.9%)	6 (7.7%)	0	16 (8.3%)
Cumulative Dose Administered (mg)				
n	59	78	56	193
Mean (StDev)	6874.5 (4976.58)	5346.2 (4075.13)	5122.4 (3818.98)	5748.5 (4346.15)
Median	7832.0	5033.5	5250.0	5600.0
Q1 : Q3	1344.0 : 11000.0	1805.0 : 7992.0	1225.0 : 6300.0	1552.0 : 9184.8
Min : Max	238 : 14832	186 : 18450	350 : 12600	186 : 18450

	Group 1 mCSCC 3 mg/kg Q2W (N=59) (Patient-Year =63.98)	Group 2 laCSCC 3 mg/kg Q2W (N=78) (Patient-Year =74.25)	Group 3 mCSCC 350 mg Q3W (N=56) (Patient-Year =50.42)	Total (N=193) (Patient-Year =188.64)
Actual Dose Intensity (mg/kg/wk) [b]				
n	59	78	0	137
Mean (StDev)	1.44 (0.119)	1.40 (0.169)		1.42 (0.150)
Median	1.46	1.45		1.46
Q1 : Q3	1.40 : 1.50	1.36 : 1.50		1.38 : 1.50
Min : Max	0.9 : 1.7	0.6 : 1.8		0.6 : 1.8
Actual Dose Intensity (mg/wk) [c]				
n	0	0	56	56
Mean (StDev)			110.80 (17.233)	110.80 (17.233)
Median			116.67	116.67
Q1 : Q3			112.05 : 116.67	112.05 : 116.67
Min : Max			39.1 : 144.1	39.1 : 144.1
Relative Dose Intensity [d]				
n	59	78	56	193
Mean (StDev)	0.96 (0.079)	0.94 (0.112)	0.95 (0.148)	0.95 (0.115)
Median	0.97	0.97	1.00	0.98
Q1 : Q3	0.94 : 1.00	0.91 : 1.00	0.96 : 1.00	0.93 : 1.00
Min : Max	0.6 : 1.1	0.4 : 1.2	0.3 : 1.2	0.3 : 1.2

Data cutoff as of 11 Oct 2020.
laCSCC=locally advanced cutaneous squamous cell carcinoma; mCSCC=metastatic cutaneous squamous cell carcinoma; Q=quartile; Q2W=every 2 weeks; Q3W=every 3 weeks; StDev=standard deviation.
[a] Duration of Exposure (weeks) = Minimum of (last dose date - first dose date +14 days)/7 AND (data cutoff date or death date - first dose date + 1 day)/7 for 3 mg/kg Q2W; Duration of Exposure (weeks) = Minimum of (last dose date - first dose date +21 days)/7 AND (data cutoff date or death date - first dose date + 1 day)/7 for 350 mg Q3W.
[b] Actual Dose Intensity (mg/kg/week) = Total dose received per kg (mg/kg) / Duration of exposure (weeks) for 3mg/kg Q2W.
[c] Actual Dose Intensity (mg/week) = Total dose received (mg) / Duration of exposure (weeks) for 350 mg Q3W.
[d] Relative Dose Intensity = Actual dose intensity / Planned dose intensity. Planned dose intensity (mg/kg/week) = Planned dose (mg/kg) / 2(weeks) for 3mg/kg Q2W. Planned dose intensity (mg/week) = Planned dose (mg) / 3 (weeks) for 350 mg Q3W.
Source: Study 1540 Interim Group 6 CSR PTT 14.1.4.1 and PTT 14.1.4.4.

Group 6 (Interim analysis)

A total of 82 patients of the first 84 included in the planned interim analysis for Group 6 were treated with at least 1 dose of cemiplimab. The median duration of exposure was approximately 29.3 weeks (range: 1.4 to 59.9 weeks) and the median number of doses administered was 10 (range: 4 to 13 doses) (Table 16).

Table 16: Treatment Exposure Group 6 (Interim Analysis; Safety Analysis Set)

	Group 6 Advanced CSCC 350 mg Q3W (N=82) (Patient-Year= 42.32)
Duration of Exposure (weeks)[a]	
n	82
Mean (StDev)	26.93 (15.551)
Median	29.25
Q1 : Q3	12.10: 39.00
Min : Max	1.4: 59.9
Duration of Exposure, n (%)	
≥0 weeks	82 (100%)
≥6 weeks	74 (90.2%)
≥12 weeks	65 (79.3%)
≥24 weeks	49 (59.8%)
≥36 weeks	27 (32.9%)
≥48 weeks	6 (7.3%)
≥60 weeks	0
Number of Doses Administered	
n	82
Mean (StDev)	8.8 (5.09)
Median	10.0
Q1 : Q3	4.0: 13.0
Min : Max	1: 20
Number of Doses Administered, n (%)	
≥	82 (100%)
≥3	71 (86.6%)
≥6	54 (65.9%)
≥12	28 (34.1%)
≥18	3 (3.7%)
≥24	0
Cumulative Dose Administered (mg)	
n	82
Mean (StDev)	3094.5 (1781.66)
Median	3500.0
Q1 : Q3	1400.0: 4550.0
Min : Max	350: 7000
Actual Dose Intensity (mg/wk) [b]	
n	82
Mean (StDev)	117.08 (16.418)
Median	116.67
Q1 : Q3	114.16 : 118.55
Min : Max	92.0 : 245.0

	Group 6 Advanced CSCC 350 mg Q3W (N=82) (Patient-Year= 42.32)
Relative Dose Intensity [c]	
n	82
Mean (StDev)	1.00 (0.141)
Median	1.00
Q1 : Q3	0.98 : 1.02
Min : Max	0.8 : 2.1

Data cutoff as of 19 Apr 2021. Only patients who started treatment on or prior to 09 Oct 2020 are included.
CSCC=cutaneous squamous cell carcinoma; Q=quartile; Q3W=every 3 weeks; StDev=standard deviation.
[a] Duration of Exposure (weeks) = Minimum of (last dose date - first dose date +21 days)/7 AND (data cutoff date or death date - first dose date + 1 day)/7.
[b] Actual Dose Intensity (mg/week) = Total dose received (mg) / Duration of exposure (weeks) for 350 mg Q3W.
[c] Relative Dose Intensity = Actual dose intensity / Planned dose intensity. Planned dose intensity (mg/week) = Planned dose (mg) / 3 (weeks) for 350 mg Q3W.
Source: Study 1540 Interim Group 6 CSR PTT 14.1.4.1.g6 and PTT 14.1.4.4.g6.

Overall Exposure (All Cemiplimab Monotherapy Patients)

In Safety Pool 2, 1198 patients received at least 1 dose of cemiplimab monotherapy for a median duration of 27.0 weeks (range: 0.3 to 144.4 weeks) (Table 17). At least half (640 [53.4%]) of the patients were treated for at least 24 weeks, including 351 (29.3%) patients treated for at least 48 weeks. The duration of exposure was 804.44 patient-years (PY). In Pool 2, 614 patients had treatment exposure of 6 months and 288 patients had a treatment exposure of 12 months (ISS Table 14.1.4.1a).

Table 17: Treatment Exposure for Cemiplimab Pooled Data Sets (Safety Analysis Set)

	Pool 1 All CSCC Patients (N=275)	Pool 2 All Monotherapy Patients (N=1198)
Duration of Exposure (weeks)[a]		
n	275	1198
Mean (StDev)	43.82 (33.425)	35.04 (29.326)
Median	38.00	27.00
Q1 : Q3	12.90 : 66.40	11.60 : 50.00
Min : Max	1.4 : 109.3	0.3 : 144.4
Duration of Exposure, n (%)		
>=0 weeks	275 (100%)	1198 (100%)
>=6 weeks	252 (91.6%)	1084 (90.5%)
>=12 weeks	215 (78.2%)	882 (73.6%)
>=24 weeks	175 (63.6%)	640 (53.4%)
>=36 weeks	141 (51.3%)	488 (40.7%)
>=48 weeks	112 (40.7%)	351 (29.3%)
>=60 weeks	76 (27.6%)	220 (18.4%)
>=72 weeks	64 (23.3%)	173 (14.4%)
>=84 weeks	57 (20.7%)	134 (11.2%)
>=96 weeks	42 (15.3%)	65 (5.4%)
>=108 weeks	8 (2.9%)	14 (1.2%)
>=120 weeks	0	2 (0.2%)

	Pool 1 All CSCC Patients (N=275)	Pool 2 All Monotherapy Patients (N=1198)
>=132 weeks	0	1 (<0.1%)
>=144 weeks	0	1 (<0.1%)
>=156 weeks	0	0

Data cutoff as of 11 Oct 2020 for Study 1540 Groups 1 to3; Data cutoff as of 19 Apr 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to 09 Oct 2020 are included; Data cutoff as of 04 Jan 2021 for Study 1676; Data cutoff as of 30 Jun 2020 for Study 1620; Data cutoff as of 01 Mar 2020 for Study 1624; Data cutoff as of 30 Apr 2019 for Study 1423; [a] Duration of Exposure (weeks) = Minimum of [last dose date - first dose date + (14 or 21 based on Q2W or Q3W dosing schedule)]/7 AND (data cutoff date or death date - first dose date + 1)/7.
StDev=standard deviation

Source: ISS Table 14.1.4.1

Assessment comment

As agreed per protocol this interim analyses of safety in Group 6 includes data from patients that have received at least one dose and had at least a follow-up of 6 months.

Adverse events

Groups 1 to 3

In Groups 1 to 3, 99.5% (192/193) of patients experienced at least 1 TEAE including 95 (49.2%) patients with at least 1 Grade ≥3 TEAE and 75 (38.9%) patients with at least 1 serious adverse event (SAE; Table 14). The proportion of patients who experienced at least 1 TEAE was similar among Groups 1, 2 and 3.

Table 18: Summary of Treatment-Emergent Adverse Events in Groups 1 to 3 (Safety Analysis Set)

	Group 1 mCSCC 3 mg/kg Q2W (N=59) (Patient-Year =63.98)	**Group 2 laCSCC 3 mg/kg Q2W (N=78) (Patient-Year =74.25)**	**Group 3 mCSCC 350 mg Q3W (N=56) (Patient-Year =50.42)**	**Total (N=193) (Patient-Year =188.64)**
Number of TEAEs	702	1055	493	2250
Number of NCI Grade 3/4/5 TEAEs	79	118	51	248
Number of Serious TEAEs	45	65	43	153
Number of Patients with any TEAE, n (%)	59 (100%)	78 (100%)	55 (98.2%)	192 (99.5%)
Number of Patients with any NCI Grade 3/4/5 TEAE, n (%)	30 (50.8%)	41 (52.6%)	24 (42.9%)	95 (49.2%)
Number of Patients with any Serious TEAE, n (%)	24 (40.7%)	28 (35.9%)	23 (41.1%)	75 (38.9%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	6 (10.2%)	10 (12.8%)	4 (7.1%)	20 (10.4%)

	Group 1 mCSCC 3 mg/kg Q2W (N=59) (Patient-Year =63.98)	Group 2 laCSCC 3 mg/kg Q2W (N=78) (Patient-Year =74.25)	Group 3 mCSCC 350 mg Q3W (N=56) (Patient-Year =50.42)	Total (N=193) (Patient-Year =188.64)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	23 (39.0%)	35 (44.9%)	18 (32.1%)	76 (39.4%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	1 (1.7%)	2 (2.6%)	1 (1.8%)	4 (2.1%)
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	0	1 (1.3%)	1 (1.8%)	2 (1.0%)
Number of Patients with any TEAE resulting in death, n (%)	2 (3.4%)	2 (2.6%)	1 (1.8%)	5 (2.6%)

Data cutoff as of 11 Oct 2020.
CTCAE, Common Terminology Criteria for Adverse Events; laCSCC=locally advanced cutaneous squamous cell carcinoma; mCSCC=metastatic cutaneous squamous cell carcinoma; NCI= National Cancer Institute; Q2W=every 2 weeks; Q3W=every 3 weeks; TEAE=treatment-emergent adverse event.
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.
Source: Study 1540 Interim Group 6 CSR PTT 14.3.1.2.1 and PTT 14.1.4.4.

Group 6 (Interim Analysis)

In Group 6, 98.8% (81/82) of patients treated with cemiplimab experienced at least 1 TEAE including 32 (39.0%) patients with at least 1 Grade ≥3 TEAE and 33 (40.2%) patients with at least 1 SAE, which was similar to the incidence in Groups 1 to 3 (Table 19).

Table 19: Summary of Treatment-Emergent Adverse Events Group 6 (Interim Analysis; Safety Analysis Set)

	Group 6 Advanced CSCC 350 mg Q3W (N=82) (Patient-Year =42.32)
Number of TEAEs	625
Number of NCI Grade 3/4/5 TEAEs	66
Number of Serious TEAEs	49
Number of Patients with any TEAE, n (%)	81 (98.8%)
Number of Patients with any NCI Grade 3/4/5 TEAE, n (%)	32 (39.0%)
Number of Patients with any Serious TEAE, n (%)	33 (40.2%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	12 (14.6%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	24 (29.3%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	0

	Group 6 Advanced CSCC 350 mg Q3W (N=82) (Patient-Year =42.32)
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	0
Number of Patients with any TEAE resulting in death, n (%)	9 (11.0%)

Data cutoff as of 19 Apr 2021. Only patients who started treatment on or prior to 09 Oct 2020 are included.
CSCC=cutaneous squamous cell carcinoma; CTCAE=Common Terminology Criteria for Adverse Events; Q2W=every 2 weeks; Q3W=every 3 weeks; TEAE=treatment-emergent adverse event.
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.
Note: 63.4% (52/82) of patients had metastatic disease and 36.6% (30/82) of patients had locally advanced disease
Source: Study 1540 Interim Group 6 CSR PTT 14.3.1.2.1.g6, PTT 14.1.2.2.g6, and PTT 14.1.4.4.g6.

Table 53 Summary of Common Treatment-Emergent Adverse Events by PT Groups 1 to 3 (Occurring in ≥5% of Patients) Presented by System Organ Class, Preferred Term and NCI-CTCAE Grade (Safety Analysis Set)

	Group 1 mCSCC 3 mg/kg Q2W (N=59) (Patient-Year =63.98)		Group 2 laCSCC 3 mg/kg Q2W (N=78) (Patient-Year =74.25)		Group 3 mCSCC 350 mg Q3W (N=56) (Patient-Year =50.42)		Total (N=193) (Patient-Year =188.64)	
System Organ Class, n (%) Preferred Term, n (%)	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Total number of TEAEs	702	79	1055	118	493	51	2250	248
Number of Patients with any TEAE, n (%)	59 (100%)	30 (50.8%)	78 (100%)	41 (52.6%)	55 (98.2%)	24 (42.9%)	192 (99.5%)	95 (49.2%)
Skin and subcutaneous tissue disorders	32 (54.2%)	0	51 (65.4%)	3 (3.8%)	33 (58.9%)	3 (5.4%)	116 (60.1%)	6 (3.1%)
Pruritus	11 (18.6%)	0	23 (29.5%)	0	7 (12.5%)	0	41 (21.2%)	0
Rash	11 (18.6%)	0	11 (14.1%)	1 (1.3%)	10 (17.9%)	0	32 (16.6%)	1 (0.5%)
Actinic keratosis	4 (6.8%)	0	12 (15.4%)	0	7 (12.5%)	0	23 (11.9%)	0
Rash maculo-papular	8 (13.6%)	0	8 (10.3%)	0	7 (12.5%)	1 (1.8%)	23 (11.9%)	1 (0.5%)
Dry skin	6 (10.2%)	0	8 (10.3%)	0	4 (7.1%)	0	18 (9.3%)	0
Erythema	0	0	4 (5.1%)	0	2 (3.6%)	0	6 (3.1%)	0
Gastrointestinal disorders	35 (59.3%)	4 (6.8%)	47 (60.3%)	3 (3.8%)	29 (51.8%)	4 (7.1%)	111 (57.5%)	11 (5.7%)
Diarrhea	17 (28.8%)	1 (1.7%)	23 (29.5%)	1 (1.3%)	13 (23.2%)	0	53 (27.5%)	2 (1.0%)
Nausea	14 (23.7%)	0	20 (25.6%)	0	12 (21.4%)	0	46 (23.8%)	0
Constipation	10 (16.9%)	1 (1.7%)	10 (12.8%)	0	8 (14.3%)	0	28 (14.5%)	1 (0.5%)

	=63.98)		=74.25)		=50.42)			
System Organ Class, n (%) Preferred Term, n (%)	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Vomiting	6 (10.2%)	0	11 (14.1%)	1 (1.3%)	8 (14.3%)	0	25 (13.0%)	1 (0.5%)
Abdominal pain	4 (6.8%)	1 (1.7%)	12 (15.4%)	0	1 (1.8%)	0	17 (8.8%)	1 (0.5%)
Dry mouth	5 (8.5%)	0	2 (2.6%)	0	3 (5.4%)	0	10 (5.2%)	0
Dysphagia	1 (1.7%)	0	4 (5.1%)	0	4 (7.1%)	2 (3.6%)	9 (4.7%)	2 (1.0%)
Gastroesophageal reflux disease	3 (5.1%)	0	3 (3.8%)	0	1 (1.8%)	0	7 (3.6%)	0
Toothache	4 (6.8%)	0	0	0	1 (1.8%)	0	5 (2.6%)	0
Infections and infestations	40 (67.8%)	13 (22.0%)	43 (55.1%)	17 (21.8%)	27 (48.2%)	6 (10.7%)	110 (57.0%)	36 (18.7%)
Upper respiratory tract infection	6 (10.2%)	0	10 (12.8%)	0	5 (8.9%)	0	21 (10.9%)	0
Urinary tract infection	6 (10.2%)	0	6 (7.7%)	2 (2.6%)	3 (5.4%)	1 (1.8%)	15 (7.8%)	3 (1.6%)
Wound infection	4 (6.8%)	1 (1.7%)	8 (10.3%)	1 (1.3%)	3 (5.4%)	0	15 (7.8%)	2 (1.0%)
Cellulitis	5 (8.5%)	4 (6.8%)	4 (5.1%)	3 (3.8%)	4 (7.1%)	1 (1.8%)	13 (6.7%)	8 (4.1%)
Skin infection	5 (8.5%)	1 (1.7%)	5 (6.4%)	1 (1.3%)	2 (3.6%)	1 (1.8%)	12 (6.2%)	3 (1.6%)
Nasopharyngitis	5 (8.5%)	0	2 (2.6%)	0	3 (5.4%)	0	10 (5.2%)	0
Pneumonia	3 (5.1%)	3 (5.1%)	6 (7.7%)	5 (6.4%)	1 (1.8%)	0	10 (5.2%)	8 (4.1%)
Bronchitis	2 (3.4%)	0	4 (5.1%)	0	1 (1.8%)	0	7 (3.6%)	0
Oral candidiasis	5 (8.5%)	0	2 (2.6%)	0	0	0	7 (3.6%)	0
General disorders and administration site conditions	27 (45.8%)	2 (3.4%)	48 (61.5%)	3 (3.8%)	28 (50.0%)	4 (7.1%)	103 (53.4%)	9 (4.7%)
Fatigue	15 (25.4%)	1 (1.7%)	35 (44.9%)	1 (1.3%)	17 (30.4%)	3 (5.4%)	67 (34.7%)	5 (2.6%)
Oedema peripheral	4 (6.8%)	0	4 (5.1%)	0	6 (10.7%)	0	14 (7.3%)	0
Pyrexia	2 (3.4%)	0	7 (9.0%)	0	1 (1.8%)	0	10 (5.2%)	0
Chills	2 (3.4%)	0	6 (7.7%)	0	1 (1.8%)	0	9 (4.7%)	0
Facial pain	1 (1.7%)	0	4 (5.1%)	0	0	0	5 (2.6%)	0
Musculoskeletal and connective tissue disorders	29 (49.2%)	2 (3.4%)	39 (50.0%)	6 (7.7%)	21 (37.5%)	2 (3.6%)	89 (46.1%)	10 (5.2%)
Arthralgia	10 (16.9%)	0	10 (12.8%)	1 (1.3%)	8 (14.3%)	0	28 (14.5%)	1 (0.5%)
Back pain	5 (8.5%)	0	8 (10.3%)	0	6 (10.7%)	0	19 (9.8%)	0
Pain in extremity	4 (6.8%)	0	6 (7.7%)	1 (1.3%)	4 (7.1%)	1 (1.8%)	14 (7.3%)	2 (1.0%)
Myalgia	4 (6.8%)	0	5 (6.4%)	0	2 (3.6%)	0	11 (5.7%)	0
Musculoskeletal pain	3 (5.1%)	0	4 (5.1%)	2 (2.6%)	2 (3.6%)	0	9 (4.7%)	2 (1.0%)
Neck pain	1 (1.7%)	1 (1.7%)	5 (6.4%)	1 (1.3%)	2 (3.6%)	0	8 (4.1%)	2 (1.0%)
Muscular weakness	0	0	4 (5.1%)	2 (2.6%)	1 (1.8%)	0	5 (2.6%)	2 (1.0%)
Respiratory, thoracic and mediastinal disorders	32 (54.2%)	8 (13.6%)	32 (41.0%)	5 (6.4%)	18 (32.1%)	3 (5.4%)	82 (42.5%)	16 (8.3%)
Cough	11 (18.6%)	0	16 (20.5%)	0	5 (8.9%)	0	32 (16.6%)	0
Dyspnea	6 (10.2%)	2 (3.4%)	7 (9.0%)	1 (1.3%)	2 (3.6%)	0	15 (7.8%)	3 (1.6%)

System Organ Class, n (%) Preferred Term, n (%)	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Pneumonitis	6 (10.2%)	3 (5.1%)	6 (7.7%)	3 (3.8%)	2 (3.6%)	0	14 (7.3%)	6 (3.1%)
Oropharyngeal pain	6 (10.2%)	0	4 (5.1%)	0	0	0	10 (5.2%)	0
Nasal congestion	5 (8.5%)	0	2 (2.6%)	0	2 (3.6%)	0	9 (4.7%)	0
Epistaxis	4 (6.8%)	0	3 (3.8%)	0	0	0	7 (3.6%)	0
Dysphonia	0	0	4 (5.1%)	0	0	0	4 (2.1%)	0
Metabolism and nutrition disorders	24 (40.7%)	6 (10.2%)	38 (48.7%)	8 (10.3%)	15 (26.8%)	4 (7.1%)	77 (39.9%)	18 (9.3%)
Decreased appetite	8 (13.6%)	0	7 (9.0%)	0	4 (7.1%)	0	19 (9.8%)	0
Hypokalemia	4 (6.8%)	1 (1.7%)	8 (10.3%)	2 (2.6%)	1 (1.8%)	0	13 (6.7%)	3 (1.6%)
Hyperuricemia	2 (3.4%)	1 (1.7%)	7 (9.0%)	0	1 (1.8%)	0	10 (5.2%)	1 (0.5%)
Hypomagnesemia	3 (5.1%)	0	6 (7.7%)	0	0	0	9 (4.7%)	0
Dehydration	3 (5.1%)	1 (1.7%)	3 (3.8%)	0	2 (3.6%)	2 (3.6%)	8 (4.1%)	3 (1.6%)
Hyperglycemia	1 (1.7%)	1 (1.7%)	7 (9.0%)	3 (3.8%)	0	0	8 (4.1%)	4 (2.1%)
Hyperkalemia	2 (3.4%)	0	6 (7.7%)	0	0	0	8 (4.1%)	0
Hypercalcemia	3 (5.1%)	2 (3.4%)	0	0	3 (5.4%)	1 (1.8%)	6 (3.1%)	3 (1.6%)
Hyponatremia	1 (1.7%)	1 (1.7%)	5 (6.4%)	2 (2.6%)	0	0	6 (3.1%)	3 (1.6%)
Hypoglycemia	3 (5.1%)	1 (1.7%)	1 (1.3%)	0	0	0	4 (2.1%)	1 (0.5%)
Nervous system disorders	26 (44.1%)	1 (1.7%)	28 (35.9%)	3 (3.8%)	16 (28.6%)	2 (3.6%)	70 (36.3%)	6 (3.1%)
Headache	11 (18.6%)	0	7 (9.0%)	0	3 (5.4%)	0	21 (10.9%)	0
Dizziness	8 (13.6%)	0	5 (6.4%)	1 (1.3%)	2 (3.6%)	0	15 (7.8%)	1 (0.5%)
Paresthesia	0	0	3 (3.8%)	0	4 (7.1%)	0	7 (3.6%)	0
Dysgeusia	4 (6.8%)	0	1 (1.3%)	0	1 (1.8%)	0	6 (3.1%)	0
Memory impairment	3 (5.1%)	0	2 (2.6%)	0	0	0	5 (2.6%)	0
Investigations	19 (32.2%)	2 (3.4%)	35 (44.9%)	5 (6.4%)	13 (23.2%)	0	67 (34.7%)	7 (3.6%)
Alanine aminotransferase increased	5 (8.5%)	0	9 (11.5%)	0	2 (3.6%)	0	16 (8.3%)	0
Blood creatinine increased	4 (6.8%)	1 (1.7%)	5 (6.4%)	0	5 (8.9%)	0	14 (7.3%)	1 (0.5%)
Aspartate aminotransferase increased	2 (3.4%)	0	6 (7.7%)	1 (1.3%)	4 (7.1%)	0	12 (6.2%)	1 (0.5%)
Blood alkaline phosphatase increased	4 (6.8%)	0	7 (9.0%)	0	0	0	11 (5.7%)	0
Weight decreased	2 (3.4%)	0	7 (9.0%)	0	1 (1.8%)	0	10 (5.2%)	0
Lymphocyte count decreased	3 (5.1%)	1 (1.7%)	0	0	2 (3.6%)	0	5 (2.6%)	1 (0.5%)
Injury, poisoning and procedural complications	17 (28.8%)	1 (1.7%)	30 (38.5%)	4 (5.1%)	13 (23.2%)	1 (1.8%)	60 (31.1%)	6 (3.1%)
Fall	5 (8.5%)	1 (1.7%)	6 (7.7%)	2 (2.6%)	4 (7.1%)	0	15 (7.8%)	3 (1.6%)

System Organ Class, n (%) Preferred Term, n (%)	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Infusion related reaction	2 (3.4%)	0	4 (5.1%)	0	2 (3.6%)	0	8 (4.1%)	0
Skin laceration	0	0	3 (3.8%)	0	3 (5.4%)	0	6 (3.1%)	0
Contusion	4 (6.8%)	0	1 (1.3%)	0	0	0	5 (2.6%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	14 (23.7%)	5 (8.5%)	26 (33.3%)	7 (9.0%)	9 (16.1%)	0	49 (25.4%)	12 (6.2%)
Basal cell carcinoma	2 (3.4%)	1 (1.7%)	10 (12.8%)	2 (2.6%)	3 (5.4%)	0	15 (7.8%)	3 (1.6%)
Squamous cell carcinoma of skin	3 (5.1%)	2 (3.4%)	4 (5.1%)	1 (1.3%)	3 (5.4%)	0	10 (5.2%)	3 (1.6%)
Squamous cell carcinoma	0	0	4 (5.1%)	2 (2.6%)	2 (3.6%)	0	6 (3.1%)	2 (1.0%)
Tumour pain	3 (5.1%)	1 (1.7%)	1 (1.3%)	0	1 (1.8%)	0	5 (2.6%)	1 (0.5%)
Eye disorders	11 (18.6%)	1 (1.7%)	25 (32.1%)	0	6 (10.7%)	0	42 (21.8%)	1 (0.5%)
Lacrimation increased	2 (3.4%)	0	4 (5.1%)	0	1 (1.8%)	0	7 (3.6%)	0
Eye swelling	1 (1.7%)	0	4 (5.1%)	0	0	0	5 (2.6%)	0
Dry eye	3 (5.1%)	0	1 (1.3%)	0	0	0	4 (2.1%)	0
Blood and lymphatic system disorders	10 (16.9%)	2 (3.4%)	17 (21.8%)	3 (3.8%)	9 (16.1%)	6 (10.7%)	36 (18.7%)	11 (5.7%)
Anemia	7 (11.9%)	2 (3.4%)	8 (10.3%)	1 (1.3%)	7 (12.5%)	5 (8.9%)	22 (11.4%)	8 (4.1%)
Thrombocytopenia	0	0	5 (6.4%)	0	0	0	5 (2.6%)	0
Vascular disorders	12 (20.3%)	3 (5.1%)	13 (16.7%)	8 (10.3%)	11 (19.6%)	3 (5.4%)	36 (18.7%)	14 (7.3%)
Hypertension	5 (8.5%)	1 (1.7%)	8 (10.3%)	7 (9.0%)	1 (1.8%)	1 (1.8%)	14 (7.3%)	9 (4.7%)
Hypotension	2 (3.4%)	0	2 (2.6%)	1 (1.3%)	4 (7.1%)	0	8 (4.1%)	1 (0.5%)
Lymphoedema	3 (5.1%)	0	0	0	2 (3.6%)	0	5 (2.6%)	0
Psychiatric disorders	11 (18.6%)	2 (3.4%)	13 (16.7%)	0	9 (16.1%)	2 (3.6%)	33 (17.1%)	4 (2.1%)
Insomnia	2 (3.4%)	0	8 (10.3%)	0	3 (5.4%)	0	13 (6.7%)	0
Depression	5 (8.5%)	1 (1.7%)	1 (1.3%)	0	2 (3.6%)	1 (1.8%)	8 (4.1%)	2 (1.0%)
Delirium	1 (1.7%)	0	2 (2.6%)	0	3 (5.4%)	1 (1.8%)	6 (3.1%)	1 (0.5%)
Endocrine disorders	8 (13.6%)	1 (1.7%)	12 (15.4%)	0	9 (16.1%)	0	29 (15.0%)	1 (0.5%)
Hypothyroidism	6 (10.2%)	0	9 (11.5%)	0	7 (12.5%)	0	22 (11.4%)	0
Renal and urinary disorders	9 (15.3%)	1 (1.7%)	11 (14.1%)	1 (1.3%)	7 (12.5%)	3 (5.4%)	27 (14.0%)	5 (2.6%)
Hematuria	1 (1.7%)	0	1 (1.3%)	0	3 (5.4%)	2 (3.6%)	5 (2.6%)	2 (1.0%)
Renal failure	3 (5.1%)	0	0	0	0	0	3 (1.6%)	0
Cardiac disorders	5 (8.5%)	3 (5.1%)	11 (14.1%)	3 (3.8%)	6 (10.7%)	2 (3.6%)	22 (11.4%)	8 (4.1%)
Atrial fibrillation	1 (1.7%)	0	3 (3.8%)	0	3 (5.4%)	1 (1.8%)	7 (3.6%)	1 (0.5%)

Group 6

Table 54 Summary of Treatment-Emergent Adverse Events Group 6 (Safety Analysis Set)

	Group 6 Advanced CSCC 350 mg Q3W (N=82)
Number of TEAEs	625
Number of NCI grade 3/4/5 TEAEs	66
Number of Serious TEAEs	49
Number of Patients with any TEAE, n (%)	81 (98.8%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	32 (39.0%)
Number of Patients with any Serious TEAE, n (%)	33 (40.2%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	12 (14.6%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	24 (29.3%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	0
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	0
Number of Patients with any TEAE resulting in death, n (%)	9 (11.0%)

Data cutoff as of 19 Apr 2021.
Only patients who started treatment on or prior to 9 Oct 2020 are included.
CSCC=cutaneous squamous cell carcinoma; Q2W=every 2 weeks; Q3W=every 3 weeks; TEAE=treatment-emergent

Table 55 Summary of Common Treatment-Emergent Adverse Events by PT Group 6 (Occurring in all Grades ≥5% of Patients or Grade 3/4/5 in >2% of Patients) Presented by System Organ Class, Preferred Term and NCI-CTCAE Grade (Safety Analysis Set)

	Group 6 Advanced CSCC 350 mg Q3W (N=82)	
System Organ Class, n (%) Preferred Term, n (%)	All Grades	Grades 3/4/5
Total number of TEAEs	625	66
Number of Patients with any TEAE, n (%)	81 (98.8%)	32 (39.0%)
General disorders and administration site conditions	52 (63.4%)	5 (6.1%)
Fatigue	22 (26.8%)	0
Asthenia	10 (12.2%)	1 (1.2%)
Oedema peripheral	9 (11.0%)	0
Pyrexia	8 (9.8%)	1 (1.2%)
General physical health deterioration	5 (6.1%)	3 (3.7%)
Skin and subcutaneous tissue disorders	48 (58.5%)	1 (1.2%)
Pruritus	23 (28.0%)	1 (1.2%)
Rash maculo-papular	10 (12.2%)	1 (1.2%)
Actinic keratosis	7 (8.5%)	0
Skin lesion	6 (7.3%)	0
Rash	5 (6.1%)	0
Gastrointestinal disorders	40 (48.8%)	5 (6.1%)
Diarrhea	18 (22.0%)	0
Nausea	15 (18.3%)	0
Constipation	10 (12.2%)	0
Vomiting	7 (8.5%)	0
Dysphagia	2 (2.4%)	2 (2.4%)
Infections and infestations	31 (37.8%)	10 (12.2%)
Skin infection	6 (7.3%)	0
Wound infection	3 (3.7%)	2 (2.4%)
Pneumonia	2 (2.4%)	2 (2.4%)
Staphylococcal infection	2 (2.4%)	2 (2.4%)
Investigations	23 (28.0%)	2 (2.4%)
Alanine aminotransferase increased	5 (6.1%)	0
Nervous system disorders	23 (28.0%)	2 (2.4%)
Dizziness	6 (7.3%)	0
Metabolism and nutrition disorders	19 (23.2%)	6 (7.3%)
Decreased appetite	8 (9.8%)	1 (1.2%)
Hypokalemia	5 (6.1%)	1 (1.2%)
Musculoskeletal and connective tissue disorders	18 (22.0%)	0
Arthralgia	7 (8.5%)	0

System Organ Class, n (%) Preferred Term, n (%)	(N=82) All Grades	 Grades 3/4/5
Vascular disorders	18 (22.0%)	4 (4.9%)
Hypertension	8 (9.8%)	4 (4.9%)
Injury, poisoning and procedural complications	15 (18.3%)	5 (6.1%)
Fall	6 (7.3%)	3 (3.7%)
Blood and lymphatic system disorders	10 (12.2%)	3 (3.7%)
Anemia	5 (6.1%)	2 (2.4%)
Cardiac disorders	6 (7.3%)	4 (4.9%)
Cardiac failure	3 (3.7%)	3 (3.7%)

Data cutoff as of Apr 19, 2021. Only patients who started treatment on or prior to 9 Oct 2020 are included.
CSCC=cutaneous squamous cell carcinoma; Q2W=every 2 weeks; Q3W=every 3 weeks; TEAE=treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 23.1. NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a system organ class/preferred term.
For SOCs, the table is sorted by decreasing frequency of all grades. Within each SOC, PTs are sorted by decreasing frequency.
Source: PTT 14.3.1.2.4.g6.

Assessment comment

The observed safety findings in Group 6 are in line with the known safety profile of cemiplimab. Almost all patients experienced an TEAE (98.8%). Approximately 39% experienced a Grade ≥3 AEs, and 40.2% an SAE. The most common AEs continue to be fatigue, pruritus, rash and diarrhea. There are no new safety findings.

Serious adverse event/deaths/other significant events

Deaths

Groups 1 to 3

For Groups 1 to 3, 10.9% (21/193) of all patients died during the on-treatment period (Table 20). The most frequently reported primary cause of death was progression of disease (7.3% [14/193]). Most deaths due to progression of disease occurred in the mCSCC groups (10.2% [6/59] in Group 1 and 12.5% [7/56] in Group 3) versus laCSCC (1.3% [1/78]) in Group 2.

Table 20: Summary of Deaths during On-Treatment Period in Groups 1 to 3 (Safety Analysis Set)

	Group 1 mCSCC 3 mg/kg Q2W (N=59) (Patient-Year =63.98)	Group 2 laCSCC 3 mg/kg Q2W (N=78) (Patient-Year =74.25)	Group 3 mCSCC 350 mg Q3W (N=56) (Patient-Year =50.42)	Total (N=193) (Patient-Year =188.64)
Number of Deaths, n (%)	9 (15.3%)	4 (5.1%)	8 (14.3%)	21 (10.9%)
Primary cause of death				
Adverse event	2 (3.4%)	2 (2.6%)	1 (1.8%)	5 (2.6%)
Progression/Recurrence of disease	6 (10.2%)	1 (1.3%)	7 (12.5%)	14 (7.3%)
Other*	1 (1.7%)	1 (1.3%)	0	2 (1.0%)

Data cutoff as of 11 Oct 2020.
laCSCC=locally advanced cutaneous squamous cell carcinoma; mCSCC=metastatic cutaneous squamous cell carcinoma; Q2W=every 2 weeks; Q3W=every 3 weeks.
*One patient had Grade 3 adverse events of esophagitis, duodenal ulcer, and duodenal hemorrhage that resolved prior to this death. On study day 89, the patient developed Grade 3 Hypercalcemia. The patient died on study day 92. Hypercalcemia (Grade 3) had not resolved at the time of death. The cause of death was reported as "other", further specified as failure-to-thrive. The last cemiplimab dose was on study day 43.
Another patient discontinued treatment due to progression of disease. The patient died on study day 427 due to cardiopulmonary arrest. The last dose of study drug was administered on study day 323. The cause of death was given as "other", further specified as cardiopulmonary arrest.
Source: Study 1540 Interim Group 6 CSR PTL 14.3.2.1.1, PTT 14.3.2.3.3, and PTT 14.1.4.4.

As of the data cutoff in Groups 1 to 3, 2.6% (5/193) of patients in Groups 1 to 3 experienced TEAEs resulting in death (Table 21). Detailed patient narratives are provided in Module 5.3.5.2 Study 1540 Interim Group 6 CSR Section 13.

Table 21: Summary of Treatment-Emergent Adverse Events Resulting in Death Groups 1 to 3 by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class, n (%) Preferred Term, n (%)	Group 1 mCSCC 3 mg/kg Q2W (N=59) (Patient-Year =63.98)	Group 2 laCSCC 3 mg/kg Q2W (N=78) (Patient-Year =74.25)	Group 3 mCSCC 350 mg Q3W (N=56) (Patient-Year =50.42)	Total (N=193) (Patient-Year =188.64)
Total number of TEAEs resulting in death	2	2	1	5
Number of Patients with any TEAE resulting in death, n (%)	2 (3.4%)	2 (2.6%)	1 (1.8%)	5 (2.6%)
General disorders and administration site conditions	1 (1.7%)	1 (1.3%)	0	2 (1.0%)
Death	1 (1.7%)	1 (1.3%)	0	2 (1.0%)
Infections and infestations	0	1 (1.3%)	0	1 (0.5%)
Pneumonia	0	1 (1.3%)	0	1 (0.5%)

Respiratory, thoracic and mediastinal disorders	1 (1.7%)	0	0	1 (0.5%)
Acute respiratory distress syndrome	1 (1.7%)	0	0	1 (0.5%)
Vascular disorders	0	0	1 (1.8%)	1 (0.5%)
Arterial hemorrhage	0	0	1 (1.8%)	1 (0.5%)

Data cutoff as of 11 Oct 2020.
laCSCC=locally advanced cutaneous squamous cell carcinoma; mCSCC=metastatic cutaneous squamous cell carcinoma; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q2W=every 2 weeks; Q3W=every 3 weeks; SOC=system organ class; TEAE=treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 22.1.
A patient is counted only once for multiple occurrences within a system organ class/preferred term.
For SOCs, the table is sorted by decreasing frequency in the total group. Within each SOC, PTs are sorted by decreasing frequency in the total group.
Source: Study 1540 Interim Group 6 CSR PTT 14.3.2.3.1 and PTT 14.1.4.4.

Group 6 (Interim Analysis)

For Group 6, 20.7% (17/82) of all patients included in the SAF died during the on-treatment period (Table 22).

Table 22: Summary of Deaths During On-Treatment Period Group 6 (Interim Analysis; Safety Analysis Set)

	Group 6 Advanced CSCC 350 mg Q3W (N=82) (Patient-Year =42.32)
Number of Deaths, n (%)	17 (20.7%)
Primary cause of death	
Adverse event	7 (8.5%)
Progression/Recurrence of disease	8 (9.8%)
Other*	2 (2.4%)

Data cutoff as of 19 Apr 2021. Only patients who started treatment on or prior to 09 Oct 2020 are included.
CSCC=cutaneous squamous cell carcinoma; Q3W=every 3 weeks; SAE=serious adverse event.
63.4% (52/82) of patients had mCSCC and 36.6% (30/82) of patients had laCSCC
*A Patient died as a result of Grade 5 meningitis on study day 22, however, the cause of death was reported as "other" as the investigator could not say if the death was due to sepsis [infectious] or carcinomatous meningitis [progression], and no lumbar puncture was done. Another Patient experienced sudden death on study day 139. The death certificate states the cause of death as 'elderly subject'. These 2 patients are included in Table 23.
Source: Study 1540 Interim Group 6 CSR PTL 14.3.2.3.1.g6, PTT 14.1.2.2.g6, PTT 14.3.2.3.3.g6, and PTT 14.1.4.4.g6

In Group 6, 11.0% (9/82) of patients experienced TEAEs resulting in death (Table 23). None of the TEAEs resulting in death were considered related to cemiplimab treatment (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.2.3.2.g6). No patients died due to treatment-emergent sponsor identified imAEs (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.2.10.1.g6). Six of the 9 patients were aged ≥79 years old and the remaining 3 patients were >60

years old. Out of the 9 fatal TEAEs, 4 TEAEs (Sepsis, Meningitis, Cardiac failure, and COVID-19 pneumonia; Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Listing 16.2.7.4.g6) occurred on or before study day 25 and the deaths could be attributed to the patient's underlying medical condition, disease progression, or concomitant/intercurrent illnesses.

Advanced age of the patients, concurrent comorbidities intercurrent illnesses, and the disease severity at the time of screening (63.4% [52/82] of patients had mCSCC of which the majority [80.8% (42/52)] had distant metastasis, and 41.5% [34/82] of patients had T3 or T4 stage disease at screening; Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.1.2.2.g6), are some possible contributory factors for the deaths in this group. Full details, including disease stage are included in the patient narratives provided in Module 5.3.5.2 Study 1540 Interim Group 6 CSR Section 13.

Table 23: Summary of Treatment-Emergent Adverse Events Resulting in Death Group 6 by System Organ Class and Preferred Term (Interim Analysis; Safety Analysis Set)

System Organ Class, n (%) **Preferred Term, n (%)**	**Group 6** **Advanced CSCC** **350 mg Q3W** **(N=82)** **(Patient-Year =42.32)**
Total number of TEAEs resulting in death	9
Number of Patients with any TEAE resulting in death, n (%)	9 (11.0%)
Infections and infestations	4 (4.9%)
COVID-19 pneumonia	1 (1.2%)
Meningitis	1 (1.2%)
Pneumonia	1 (1.2%)
Sepsis	1 (1.2%)
Respiratory, thoracic and mediastinal disorders	2 (2.4%)
Pulmonary embolism	1 (1.2%)
Pulmonary edema	1 (1.2%)
Cardiac disorders	1 (1.2%)
Cardiac failure	1 (1.2%)
Gastrointestinal disorders	1 (1.2%)
Duodenal ulcer hemorrhage	1 (1.2%)
General disorders and administration site conditions	1 (1.2%)
Sudden death	1 (1.2%)

Data cutoff as of 19 Apr 2021. Only patients who started treatment on or prior to 09 Oct 2020 are included.
CSCC=cutaneous squamous cell carcinoma; Q3W=every 3 weeks; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event
Only patients who started treatment on or prior to 09 Oct 2020 are included.
All adverse events were coded using MedDRA Version 23.1.
A patient is counted only once for multiple occurrences within a system organ class/preferred term.
For SOCs, the table is sorted by decreasing frequency. Within each SOC, PTs are sorted by decreasing frequency.
Source: Study 1540 Interim Group 6 CSR PTT 14.3.2.3.1.g6 and PTT 14.1.4.4.g6.

Assessment comment

There were slightly more TEAE resulting in death in Group 6. The MAH claim that none of them are treatment related. The MAH is asked to provide brief case narratives and discuss these in more detail. **(OC)**

SAE

Groups 1 to 3

For Groups 1 to 3, 38.9% (75/193) of patients experienced at least 1 serious TEAE (Table 24).

The serious TEAEs by PT occurring in ≥2% of all patients were Cellulitis and Pneumonia (3.6% [7/193] each), and Sepsis (2.1% [4/193]) (Table 24).

Overall, 11.4% (22/193) of patients experienced at least 1 treatment-related serious TEAE (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.2.2.3). Of those, Pneumonitis (3.1% [6/193]) and Autoimmune hepatitis (1.0% [2/193]) were the serious treatment-related TEAEs Grade ≥3 reported in more than 1 patient (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.2.2.4). Both Pneumonitis and Autoimmune hepatitis are listed as adverse reactions in the product information.

Table 24: Summary of Serious Treatment-Emergent Adverse Events in Patients in Groups 1 to 3 by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class, n (%) Preferred Term, n (%)	Group 1 mCSCC 3 mg/kg Q2W (N=59) (Patient-Year =63.98)	Group 2 laCSCC 3 mg/kg Q2W (N=78) (Patient-Year =74.25)	Group 3 mCSCC 350 mg Q3W (N=56) (Patient-Year =50.42)	Total (N=193) (Patient-Year =188.64)
Total number of serious TEAEs	45	65	43	153
Number of Patients with any serious TEAE , n (%)	24 (40.7%)	28 (35.9%)	23 (41.1%)	75 (38.9%)
Infections and infestations	13 (22.0%)	13 (16.7%)	8 (14.3%)	34 (17.6%)
Cellulitis	4 (6.8%)	2 (2.6%)	1 (1.8%)	7 (3.6%)
Pneumonia	2 (3.4%)	5 (6.4%)	0	7 (3.6%)
Sepsis	1 (1.7%)	2 (2.6%)	1 (1.8%)	4 (2.1%)
Skin infection	1 (1.7%)	1 (1.3%)	1 (1.8%)	3 (1.6%)
Urinary tract infection	0	1 (1.3%)	1 (1.8%)	2 (1.0%)
Abscess bacterial	0	0	1 (1.8%)	1 (0.5%)
Arthritis infective	1 (1.7%)	0	0	1 (0.5%)
Catheter site infection	1 (1.7%)	0	0	1 (0.5%)
Cystitis	0	0	1 (1.8%)	1 (0.5%)
Encephalitis	0	1 (1.3%)	0	1 (0.5%)
Erysipelas	0	1 (1.3%)	0	1 (0.5%)
Escherichia urinary tract infection	0	0	1 (1.8%)	1 (0.5%)
Extradural abscess	0	1 (1.3%)	0	1 (0.5%)
Fungal skin infection	0	0	1 (1.8%)	1 (0.5%)
Gastroenteritis	0	1 (1.3%)	0	1 (0.5%)
Groin infection	1 (1.7%)	0	0	1 (0.5%)
Influenza	0	1 (1.3%)	0	1 (0.5%)
Meningitis aseptic	1 (1.7%)	0	0	1 (0.5%)
Pneumonia influenzal	0	1 (1.3%)	0	1 (0.5%)
Psoas abscess	0	1 (1.3%)	0	1 (0.5%)
Pyelonephritis	1 (1.7%)	0	0	1 (0.5%)
Soft tissue infection	0	1 (1.3%)	0	1 (0.5%)
Staphylococcal infection	0	1 (1.3%)	0	1 (0.5%)
Upper respiratory tract infection	0	1 (1.3%)	0	1 (0.5%)
Wound infection	0	1 (1.3%)	0	1 (0.5%)
Respiratory, thoracic and mediastinal disorders	9 (15.3%)	8 (10.3%)	2 (3.6%)	19 (9.8%)
Pneumonitis	4 (6.8%)	4 (5.1%)	1 (1.8%)	9 (4.7%)
Dyspnoea	1 (1.7%)	1 (1.3%)	0	2 (1.0%)
Acute respiratory distress syndrome	1 (1.7%)	0	0	1 (0.5%)
Chronic obstructive pulmonary disease	1 (1.7%)	0	0	1 (0.5%)
Epistaxis	0	1 (1.3%)	0	1 (0.5%)

System Organ Class, n (%) Preferred Term, n (%)	Group 1 mCSCC 3 mg/kg Q2W (N=59) (Patient-Year =63.98)	Group 2 laCSCC 3 mg/kg Q2W (N=78) (Patient-Year =74.25)	Group 3 mCSCC 350 mg Q3W (N=56) (Patient-Year =50.42)	Total (N=193) (Patient-Year =188.64)
Hypoxia	0	1 (1.3%)	0	1 (0.5%)
Pleural effusion	1 (1.7%)	0	0	1 (0.5%)
Pneumonia aspiration	0	1 (1.3%)	0	1 (0.5%)
Pneumothorax	1 (1.7%)	0	0	1 (0.5%)
Pulmonary oedema	1 (1.7%)	0	0	1 (0.5%)
Respiratory failure	0	0	1 (1.8%)	1 (0.5%)
Injury, poisoning and procedural complications	1 (1.7%)	4 (5.1%)	3 (5.4%)	8 (4.1%)
Fall	1 (1.7%)	2 (2.6%)	0	3 (1.6%)
Hip fracture	0	1 (1.3%)	1 (1.8%)	2 (1.0%)
Eye contusion	0	1 (1.3%)	0	1 (0.5%)
Limb injury	0	0	1 (1.8%)	1 (0.5%)
Radius fracture	0	1 (1.3%)	0	1 (0.5%)
Spinal fracture	0	0	1 (1.8%)	1 (0.5%)
Subdural haematoma	0	1 (1.3%)	0	1 (0.5%)
Nervous system disorders	2 (3.4%)	3 (3.8%)	3 (5.4%)	8 (4.1%)
Cerebral infarction	1 (1.7%)	0	0	1 (0.5%)
Cerebral ischaemia	0	1 (1.3%)	0	1 (0.5%)
Cerebrovascular accident	0	1 (1.3%)	0	1 (0.5%)
Focal dyscognitive seizures	1 (1.7%)	0	0	1 (0.5%)
Ischaemic stroke	0	1 (1.3%)	0	1 (0.5%)
Lethargy	0	0	1 (1.8%)	1 (0.5%)
Paraesthesia	0	0	1 (1.8%)	1 (0.5%)
Syncope	0	0	1 (1.8%)	1 (0.5%)
Cardiac disorders	2 (3.4%)	2 (2.6%)	2 (3.6%)	6 (3.1%)
Myocardial infarction	1 (1.7%)	1 (1.3%)	0	2 (1.0%)
Atrial fibrillation	0	0	1 (1.8%)	1 (0.5%)
Atrioventricular block complete	1 (1.7%)	0	0	1 (0.5%)
Myocarditis	0	1 (1.3%)	0	1 (0.5%)
Pericarditis	0	0	1 (1.8%)	1 (0.5%)
Gastrointestinal disorders	2 (3.4%)	1 (1.3%)	3 (5.4%)	6 (3.1%)
Abdominal pain	1 (1.7%)	0	0	1 (0.5%)
Duodenal ulcer	1 (1.7%)	0	0	1 (0.5%)
Duodenal ulcer haemorrhage	0	0	1 (1.8%)	1 (0.5%)
Dysphagia	0	0	1 (1.8%)	1 (0.5%)
Oesophagitis	1 (1.7%)	0	0	1 (0.5%)
Proctitis	0	1 (1.3%)	0	1 (0.5%)
Small intestinal haemorrhage	1 (1.7%)	0	0	1 (0.5%)
Small intestinal obstruction	0	0	1 (1.8%)	1 (0.5%)
General disorders and administration site conditions	1 (1.7%)	3 (3.8%)	2 (3.6%)	6 (3.1%)
Death	1 (1.7%)	1 (1.3%)	0	2 (1.0%)
Pyrexia	0	2 (2.6%)	0	2 (1.0%)
Fatigue	0	1 (1.3%)	0	1 (0.5%)
General physical health deterioration	0	0	1 (1.8%)	1 (0.5%)
Peripheral swelling	0	0	1 (1.8%)	1 (0.5%)
Musculoskeletal and connective tissue disorders	0	4 (5.1%)	2 (3.6%)	6 (3.1%)
Muscular weakness	0	2 (2.6%)	0	2 (1.0%)
Pain in extremity	0	1 (1.3%)	1 (1.8%)	2 (1.0%)
Arthralgia	0	1 (1.3%)	0	1 (0.5%)
Musculoskeletal pain	0	1 (1.3%)	0	1 (0.5%)
Soft tissue necrosis	0	0	1 (1.8%)	1 (0.5%)
Metabolism and nutrition disorders	2 (3.4%)	0	3 (5.4%)	5 (2.6%)
Dehydration	0	0	2 (3.6%)	2 (1.0%)
Hypercalcaemia	1 (1.7%)	0	1 (1.8%)	2 (1.0%)
Hypoglycaemia	1 (1.7%)	0	0	1 (0.5%)

System Organ Class, n (%) Preferred Term, n (%)	Group 1 mCSCC 3 mg/kg Q2W (N=59) (Patient-Year =63.98)	Group 2 laCSCC 3 mg/kg Q2W (N=78) (Patient-Year =74.25)	Group 3 mCSCC 350 mg Q3W (N=56) (Patient-Year =50.42)	Total (N=193) (Patient-Year =188.64)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.7%)	3 (3.8%)	1 (1.8%)	5 (2.6%)
B-cell lymphoma	1 (1.7%)	1 (1.3%)	0	2 (1.0%)
Breast cancer	0	2 (2.6%)	0	2 (1.0%)
Renal cell carcinoma	0	1 (1.3%)	0	1 (0.5%)
Squamous cell carcinoma of skin	0	0	1 (1.8%)	1 (0.5%)
Renal and urinary disorders	1 (1.7%)	0	3 (5.4%)	4 (2.1%)
Haematuria	0	0	2 (3.6%)	2 (1.0%)
Acute kidney injury	1 (1.7%)	0	0	1 (0.5%)
Urinary retention	0	0	1 (1.8%)	1 (0.5%)
Blood and lymphatic system disorders	0	0	3 (5.4%)	3 (1.6%)
Anaemia	0	0	1 (1.8%)	1 (0.5%)
Coagulopathy	0	0	1 (1.8%)	1 (0.5%)
Pancytopenia	0	0	1 (1.8%)	1 (0.5%)
Psychiatric disorders	2 (3.4%)	0	1 (1.8%)	3 (1.6%)
Adjustment disorder	0	0	1 (1.8%)	1 (0.5%)
Delirium	1 (1.7%)	0	0	1 (0.5%)
Suicidal ideation	1 (1.7%)	0	0	1 (0.5%)
Vascular disorders	0	1 (1.3%)	2 (3.6%)	3 (1.6%)
Arterial haemorrhage	0	0	1 (1.8%)	1 (0.5%)
Deep vein thrombosis	0	0	1 (1.8%)	1 (0.5%)
Hypertension	0	1 (1.3%)	0	1 (0.5%)
Hepatobiliary disorders	0	2 (2.6%)	0	2 (1.0%)
Autoimmune hepatitis	0	2 (2.6%)	0	2 (1.0%)
Cholecystitis	0	1 (1.3%)	0	1 (0.5%)
Investigations	0	1 (1.3%)	1 (1.8%)	2 (1.0%)
Influenza A virus test positive	0	1 (1.3%)	0	1 (0.5%)
International normalised ratio increased	0	0	1 (1.8%)	1 (0.5%)
Skin and subcutaneous tissue disorders	0	1 (1.3%)	1 (1.8%)	2 (1.0%)
Dermatitis atopic	0	1 (1.3%)	0	1 (0.5%)
Rash maculo-papular	0	0	1 (1.8%)	1 (0.5%)
Endocrine disorders	1 (1.7%)	0	0	1 (0.5%)
Hypophysitis	1 (1.7%)	0	0	1 (0.5%)
Eye disorders	0	1 (1.3%)	0	1 (0.5%)
Ulcerative keratitis	0	1 (1.3%)	0	1 (0.5%)

Data cutoff as of 11 Oct 2020.
laCSCC=cutaneous squamous cell carcinoma; mCSCC=metastatic cutaneous squamous cell carcinoma; MedDRA= Medical Dictionary for Regulatory Activities; PT=preferred term; Q2W=every 2 weeks; Q3W=every 3 weeks; SOC= system organ class; TEAE=treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 22.1.
A patient is counted only once for multiple occurrences within a system organ class/preferred term.
For SOCs, the table is sorted by decreasing frequency in the total group. Within each SOC, PTs are sorted by decreasing frequency in the total group.
Source: Study 1540 Interim Group 6 CSR PTT 14.3.2.1.3 and PTT 14.1.4.4.

Group 6 (Interim Analysis)

For Group 6, 40.2% (33/82) of patients included in the SAF experienced at least 1 serious TEAE (Table 25).

The most common serious TEAEs by PT (occurring in ≥2% of all patients) were Fall (4.9% [4/82]), Pneumonia, Wound infection, Pyrexia, Cardiac failure, Confusional state (2.4% [2/82] each) (Table 25).

Four patients (4.9%) experienced at least 1 treatment-related serious TEAE namely Febrile neutropenia, Adrenal insufficiency, Hypophysitis, Fatigue and Dermatitis bullous (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.2.2.3.g6).

Overall, the proportion of patients who experienced at least 1 treatment-related serious TEAE and the proportion of patients with treatment-emergent sponsor identified serious imAEs was lower in Group 6 than Groups 1 to 3 (treatment-related serious TEAE: 4.9% [4/82; Section 0] vs 11.4% [22/193; Section 0]; treatment-emergent sponsor identified serious imAEs: 2.4% [2/82; Section 0] vs 7.8% [15/193; Section 0]). No sponsor identified serious imAEs in Group 6 or Groups 1 to 3 had a fatal outcome.

Table 25: Summary of Serious Treatment-Emergent Adverse Events in Patients in Group 6 by System Organ Class and Preferred Term (Interim Analysis; Safety Analysis Set)

System Organ Class, n (%) Preferred Term, n (%)	Group 6 Advanced CSCC 350 mg Q3W (N=82)
Total number of serious TEAEs	49
Number of Patients with any serious TEAE , n (%)	33 (40.2%)
Infections and infestations	10 (12.2%)
Pneumonia	2 (2.4%)
Wound infection	2 (2.4%)
COVID-19 pneumonia	1 (1.2%)
Meningitis	1 (1.2%)
Respiratory tract infection	1 (1.2%)
Sepsis	1 (1.2%)
Soft tissue infection	1 (1.2%)
Staphylococcal infection	1 (1.2%)
Injury, poisoning and procedural complications	6 (7.3%)
Fall	4 (4.9%)
Hip fracture	1 (1.2%)
Skin laceration	1 (1.2%)
Wound complication	1 (1.2%)
General disorders and administration site conditions	4 (4.9%)
Pyrexia	2 (2.4%)
Drug withdrawal syndrome	1 (1.2%)
Fatigue	1 (1.2%)
Sudden death	1 (1.2%)
Cardiac disorders	3 (3.7%)
Cardiac failure	2 (2.4%)
Cardiac arrest	1 (1.2%)
Gastrointestinal disorders	3 (3.7%)
Duodenal ulcer haemorrhage	1 (1.2%)
Dysphagia	1 (1.2%)
Small intestinal obstruction	1 (1.2%)
Blood and lymphatic system disorders	2 (2.4%)
Anaemia	1 (1.2%)
Febrile neutropenia	1 (1.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.4%)
Infected neoplasm	1 (1.2%)
Rectal cancer	1 (1.2%)
Nervous system disorders	2 (2.4%)
Brain oedema	1 (1.2%)
Ischaemic stroke	1 (1.2%)
Psychiatric disorders	2 (2.4%)
Confusional state	2 (2.4%)
Renal and urinary disorders	2 (2.4%)
Nephrolithiasis	1 (1.2%)
Renal failure	1 (1.2%)

System Organ Class, n (%) Preferred Term, n (%)	Group 6 Advanced CSCC 350 mg Q3W (N=82)
Respiratory, thoracic and mediastinal disorders	2 (2.4%)
Pulmonary embolism	1 (1.2%)
Pulmonary oedema	1 (1.2%)
Endocrine disorders	1 (1.2%)
Adrenal insufficiency	1 (1.2%)
Hypophysitis	1 (1.2%)
Hepatobiliary disorders	1 (1.2%)
Cholecystitis	1 (1.2%)
Investigations	1 (1.2%)
General physical condition abnormal	1 (1.2%)
Metabolism and nutrition disorders	1 (1.2%)
Hyponatraemia	1 (1.2%)
Skin and subcutaneous tissue disorders	1 (1.2%)
Dermatitis bullous	1 (1.2%)
Vascular disorders	1 (1.2%)
Hypertension	1 (1.2%)

Data cutoff as of 19 Apr 2021. Only patients who started treatment on or prior to 09 Oct 2020 are included.
CSCC=cutaneous squamous cell carcinoma; MedDRA= Medical Dictionary for Regulatory Activities; PT=preferred term; Q3W=every 3 weeks; SOC=system organ class; TEAE=treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 23.1.
A patient is counted only once for multiple occurrences within a system organ class/preferred term.
For SOCs, the table is sorted by decreasing frequency. Within each SOC, PTs are sorted by decreasing frequency.
Source: Study 1540 Interim Group 6 CSR PTT 14.3.2.1.3.g6.

Assessment comment

In line with the observations made in Groups 1-3, the most frequent SAEs are related to infections. There are no new safety findings.

AESI

Infusion-Related Reactions

Groups 1 to 3

For Groups 1 to 3, 9.8% (19/193) of patients experienced at least 1 IRR, including 1 patient who experienced 2 IRRs (both Grade 2; Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Listing 14.3.2.9.1) (Tongue/Lip Swelling on study day 1. Treatment was interrupted for 148 minutes; the patient was treated with steroids, and cemiplimab treatment was completed. Dyspnea/Flushing on study day 71, treatment was interrupted for 112 minutes, patient was treated with steroids, and cemiplimab treatment was completed). All subsequent infusions were given at a slower rate, and no premedication regimens were recorded. At time of data cutoff, the patient had received another 10+ months of cemiplimab without further IRRs.

Three patients experienced Grade 3 IRRs. No patient experienced a Grade 4 or 5 IRR. No patients required permanent discontinuation due to an IRR (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Listing 14.3.2.9.1).

Group 6 (Interim Analysis)

For Group 6, 8.5% (7/82) of patients experienced at least 1 IRR.

One patient experienced a Grade 3 IRR. No patient experienced a Grade 4 or 5 IRR. No patients required permanent treatment discontinuation due to an IRR (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Listing 14.3.2.9.1.g6).

Treatment-Emergent Sponsor Identified Immune-Mediated Adverse Events

The Sponsor used the following approach to identify imAEs:

- The sponsor created a customized list of MedDRA PTs for the identification of imAEs called "Sponsor List of Potential imAE PTs".
- Any treatment-related PT that was included in the sponsor list of potential imAE PTs was assessed as a "potential imAE" (Module 5.3.5.2 Study 1540 Interim Group 6 Analysis CSR Section 5.2.1.6.2.1).
- Any potential imAE that required treatment with systemic corticosteroid and/or other immunosuppressants or was an immune-mediated endocrinopathy was assessed as an "identified imAE" (Module 5.3.5.2 Study 1540 Interim Group 6 Analysis CSR Section 5.2.1.6.2.2).

Groups 1 to 3

In Groups 1 to 3, 21.8% (42/193) of patients experienced at least 1 treatment-emergent sponsor identified imAE; 5.2% (10/193) of patients discontinued study treatment due to imAEs.

Overall, 9.8% (19/193) had treatment-emergent sponsor identified imAE of Grade ≥3 and 7.8% (15/193) of patients had serious treatment-emergent sponsor identified imAEs .There were 2 patients in Group 2 with a Grade 4 treatment-emergent sponsor identified imAE of Pneumonitis. No patient had a Grade 5 imAE.

The most common (≥5% of patients) sponsor identified imAEs of any grade was Pneumonitis (6.7% [13/193) of patients).

Group 6 (Interim Analysis)

A total of 17.1% (14/82) of patients experienced a treatment-emergent sponsor identified imAE

A total of 2.4% (2/82) of patients had a serious Grade 3 treatment-emergent sponsor identified imAEs and no patient had a Grade 4 or Grade 5 treatment-emergent sponsor identified imAE.

The treatment-emergent sponsor identified imAEs of any grade reported in more than 1 patient were hypothyroidism (3.7% [3/82]) and arthralgia (2.4% [2/82]).

Assessment comment

Overall, there are no new findings in Group 6 with regards to immune-mediated AEs.

Laboratory findings

Hematology

Groups 1 to 3

In Study 1540, there were no clinically meaningful trends in mean or median changes from baseline in any hematology parameters in any treatment group by study visit The majority of hematology abnormalities were lower than Grade 3.

Overall, 73.7% (140/190) of patients with at least 1 postbaseline value experienced at least 1 laboratory abnormality in hematology parameters.

The incidence of Grade 3/4 new or worsened hematology laboratory abnormalities was 12.6% (24/190) of patients. Grade 3/4 Lymphocyte count decreased (parameter lymphocytes) was reported by 10.0% patients (19/190) and Grade 3/4 Anemia (parameter hemoglobin) was reported by 5.3% (10/190) patients. Grade 3/4 Neutrophil count decreased and Platelet count decreased were reported by 1/189 patients (0.5%) and 1/190 patients (0.5%), respectively.

There were few incidences of TEAEs associated with hematology abnormalities. Anemia was considered a TEAE in 22 patients (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.1.2.6), and 4 patients were reported to have treatment-related Anemia (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.1.3.4). Lymphopenia was reported as a treatment-related TEAE in 2 patients (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.1.3.4).

Group 6 (Interim Analysis)

There were no clinically meaningful trends in mean or median changes from baseline in any hematology parameters in any treatment group by study visit (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.1.4g6). The majority of hematology abnormalities were lower than Grade 3 (Post-text Table 14.3.3.1.1g6).

Overall, 57.3% (43/75) of patients with at least 1 postbaseline value experienced at least 1 laboratory abnormality in hematology parameters (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.1.1g6).

The incidence of Grade 3/4 new or worsened hematology laboratory abnormalities was 5.3% (4/75) of patients. Grade 3/4 Anemia was reported by 2.7% patients (2/75) and Grade 3/4 Lymphocyte count decreased and Neutrophil count decreased were reported by 1/75 (1.3%) of patients each (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.1.1g6).

There were few incidences of TEAEs associated with hematology abnormalities. Anemia was considered a TEAE in 5 patients (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.1.2.6g6), and none were treatment-related (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.1.3.4g6). Neutropenia was considered a TEAE in 2 patients (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.1.2.6g6), one of which was reported as treatment-related (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.1.3.4g6), Lymphopenia and Thrombocytopenia were considered a TEAE in 1 patient each (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.1.2.6g6), both were reported as treatment-related (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.1.3.4g6).

Chemistry

Groups 1 to 3

There were no clinically meaningful trends in mean or median changes from baseline in any treatment group by study visit in the following:

- Electrolytes (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.2.4)
- Chemistry (other) (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.4.4)

The majority of electrolyte and chemistry (other) abnormalities were lower than Grade 3 (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.2.1 and Post-text Table 14.3.3.4.1, respectively).

Overall, 73.7% (140/190) of patients experienced at least 1 laboratory abnormality in electrolytes (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.2.1) and 80.0% (152/190) of patients experienced at least 1 abnormality in chemistry (other) (creatinine or glucose) (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.4.1).

The incidence of Grade 3/4 electrolyte laboratory abnormalities (new or worsened) was 16.9% (10/59) of patients in Group 1, and 11.7% (9/77) of patients in Group 2, and 13.0% (7/54) of patients in Group 3 (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.2.1). Grade 3/4 laboratory abnormalities reported by ≥ 2 patients during the study were for the following parameters calcium (Hypercalcemia [uncorrected calcium]), phosphate (Hypophosphatemia) and sodium (Hyponatremia). All other Grade 3/4 laboratory abnormalities in electrolyte and other chemistry parameters were reported by no more than 1 patient in any treatment group. One patient reported a Grade 3/4 abnormality in creatinine (creatinine increased) and no abnormalities were reported in glucose (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.4.1).

Group 6 (Interim Analysis)

There were no clinically meaningful trends in mean or median changes from baseline in any treatment group by study visit in the following:

- Electrolytes (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.2.4g6)
- Chemistry (other) (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.4.4g6)

The majority of electrolyte and chemistry (other) abnormalities were lower than Grade 3 (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.2.1g6 and Post-text Table 14.3.3.4.1g6, respectively).

Overall, 68.0% (51/75) of patients experienced at least 1 laboratory abnormality in electrolytes (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.2.1g6) and 73.3% (55/75) of patients experienced at least 1 abnormality in chemistry (other) (creatinine or glucose) (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.4.1g6).

The incidence of Grade 3/4 electrolyte laboratory abnormalities (new or worsened) was 10.7% (8/75) of patients (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.2.1g6). The incidence of Grade 3/4 chemistry (other) laboratory abnormalities (new or worsened) was 73.3% (55/75) of patients (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.4.1g6). Grade 3/4 laboratory abnormalities reported by ≥ 2 patients during the study were for the parameters of calcium (Hypocalcemia) (2 patients), phosphate (Hypophosphatemia) (2 patients)

and sodium (Hyponatremia) (3 patients). No Grade 3/4 chemistry (other) laboratory abnormalities were reported (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.2.1g6 and Post-text Table 14.3.3.4.1g6).

Urinalysis

Groups 1 to 3

There were no clinically meaningful trends in mean or median changes from baseline in urinalysis parameters in any treatment group (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.5.4).

Grade 1 Proteinuria was reported as a treatment-related TEAE in 1 patient (Patient 840005007) in Group 2 (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.1.3.6). The event of Proteinuria was associated with Nephritis, considered an irAE and the event of Nephritis resulted in a dose interruption/delay (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Listing 14.3.2.4.1). The patient received steroids for the nephritis, and the event resolved. Proteinuria was reported as ongoing at the time of study completion. The patient had discontinued cemiplimab treatment due to disease progression prior to the onset of proteinuria.

Group 6 (Interim Analysis)

There were no clinically meaningful trends in mean or median changes from baseline in urinalysis parameters (Specific gravity and pH) in any treatment group (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.5.4g6).

The event of Blood creatinine increased was associated with Grade 2 immune-mediated nephritis in 1 out of 82 (1.2%) patients, considered an irAE and the event of Nephritis resulted in a dose interruption/delay (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Listing 14.3.2.10.1.g6, Post-text Table 14.3.2.10.13g6 and Post-text Table 14.3.2.10.14g6).

Liver Function

Groups 1 to 3

There were no clinically meaningful trends in mean or median changes from baseline in any treatment group by study visit in liver function (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.3.4). The majority of liver function abnormalities were lower than Grade 3 (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.3.1).

Group 6 (Interim Analysis)

There were no clinically meaningful trends in mean or median changes from baseline in any treatment group by study visit in liver function (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.3.4g6). The majority of liver function abnormalities were lower than Grade 3 (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.3.1g6).

Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital Signs

Groups 1 to 3

Small variations in mean and median weight, and heart rate and blood pressure were seen over time, but none indicated a trend towards an overall increase or decrease (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post text Table 14.3.1.2.4 and Post-text Table 14.3.4.1).

Group 6 (Interim Analysis)

Decreased weight was reported in 3 of 82 patients, however, no trend was observed (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.1.2.4g6). Small variations in mean and median blood pressure and heart rate occurred during the study, but none indicated a trend (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.4.1g6).

Electrocardiogram

Groups 1 to 3

Small variations in ECGs occurred during the study, but none indicated a trend (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.4.4).

Clinically significant ECG abnormalities were seen in a patient in Group 1 on study day 114 within the context of an IRR. The abnormalities included the following values: ECG ventricular rate (52 beats/minute), PR duration (224 msec), QRS duration (106 msec), QT duration (466 msec; baseline value was 464 msec), and RR duration (1153 msec). The repeat ECG, which was taken 1 minute after the clinically significant ECG abnormalities were observed, did not have clinically significant abnormalities (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Listing 16.2.9.3). An IRR of Atrioventricular Block First Degree was reported for this patient (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Listing 14.3.2.9.1). At the time of data cutoff, the patient had received another 10+ months of cemiplimab without other IRRs or cardiac events and continued study treatment (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Listing 16.2.5.1 and Post-text Listing 16.2.7.3).

Group 6 (Interim Analysis)

ECG was only collected at screening (per protocol) and therefore no summary tables were generated.

Physical Examination

Groups 1 to 3

There were no clinically meaningful trends in physical findings from baseline in any physical examination parameters in any treatment group (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.4.2). Following the data cut for this report, an error was discovered in the electronic data capture (EDC) pages for limited physical exams that occur during mid-cycle (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Section 9.5.1.4.1). These pages lacked the log line for the heart, although heart findings were captured on EDC pages for complete physical exams that occur at screening, at start of each cycle, and at the end of study. All clinically significant physical exam abnormalities were reported as AEs. Therefore, this deviation did not impact data integrity or patient safety.

Group 6 (Interim Analysis)

There were no clinically meaningful trends in physical findings from baseline in any physical examination parameters in any treatment group (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.4.2g6).

Immunogenicity

Groups 1 to 3

One hundred and fifty-eight patients (Group 1, N=50, Group 2, N=67, Group 3, N=41) were included in the anti-drug antibody (ADA) population. None of these patients (0%) experienced ADA or neutralizing antibody (Nabs) to cemiplimab. Overall, the results indicate that the immunogenicity associated with the current dosing regimen of cemiplimab is very low in adult patients with advanced CSCC. Additional details may be found in the CP report R2810-ONC-1540 02V2 available as an appendix of the Primary analysis CSR (approval date: 09 Jul 2019).

Group 6 (Interim Analysis)

Overall, immunogenicity in patients with advanced CSCC in Group 6 was low. Treatment emergent ADA with indeterminate response was observed in 3 patients at low titer (titer 30), with no presence of NAbs. No association between immunogenicity and cemiplimab concentrations in serum was observed, when evaluable. The presence of ADA was not associated with significant AEs or imAEs.

Additional details including a summary table of immunogenicity results across Groups 1 to 3 and Group 6, may be found in Module 5.3.5.2 Study 1540 Interim Group 6 CSR Appendix 5.

Summary for Vital Signs, Physical Findings, and Other Observations Related to Safety

Cemiplimab treatment generally did not result in clinically significant changes in vital signs or ECG findings.

Assessment comment

Overall, there seems to be no clinically meaningful differences between Groups 1-3 and Group 6. However, the MAH is asked to provide a tabulated overview of laboratory values for Group 1-3 and Group 6 side by side, and discuss any relevant difference **(OC)**.

Safety in special populations

Intrinsic Factors

Age

Safety analyses according to age are applicable to Pool 2. There was a trend towards an increasing frequency of serious TEAEs and discontinuations due to TEAEs with increasing age, which is expected given the increase in comorbidities with increasing age in the general population. In addition, the sample size (n=44, 3.7%) in the age group ≥85 years is small and this limits the ability to draw conclusions in this age group (Table 29). There was no pattern in the reported events which would suggest a different risk profile in the elderly population, and the events were generally consistent with concomitant diseases in an elderly population. Overall, there was no clinically meaningful difference in the safety profile across the age groups beyond what would be expected for elderly patients with advanced solid malignancies.

Table 26: Distribution of AEs, SAEs, and Discontinuations According to Age Group (Safety Analysis Set) – Pool 2 (All Monotherapy Patients)

	Age: <65 years (N=654)	Age: 65 to 74 years (N=312)	Age: 75 to 84 years (N=188)	Age: ≥85 years (N=44)	Total (N=1198)
Number of TEAEs	4773	2486	1665	467	9391
Number of patients with any TEAE, n (%)	589 (90.1%)	294 (94.2%)	185 (98.4%)	44 (100%)	1112 (92.8%)
Number of serious TEAEs	293	163	140	55	651
Number of patients with any serious TEAE, n (%)	178 (27.2%)	96 (30.8%)	75 (39.9%)	25 (56.8%)	374 (31.2%)
Fatal	30 (4.6%)	20 (6.4%)	7 (3.7%)	6 (13.6%)	63 (5.3%)
Life-threatening	14 (2.1%)	10 (3.2%)	8 (4.3%)	5 (11.4%)	37 (3.1%)
Hospitalization/prolonged existing hospitalization	165 (25.2%)	84 (26.9%)	71 (37.8%)	23 (52.3%)	343 (28.6%)
Disability/incapacity	9 (1.4%)	0	3 (1.6%)	1 (2.3%)	13 (1.1%)
Congenital abnormality or birth defect	0	0	0	0	0
Other (medically significant)	5 (0.8%)	6 (1.9%)	6 (3.2%)	3 (6.8%)	20 (1.7%)
Number of patients who discontinued study treatment due to TEAE, n (%)	48 (7.3%)	24 (7.7%)	26 (13.8%)	11 (25.0%)	109 (9.1%)

AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
Data cutoffs: 11 Oct 2020 for Study 1540 Groups 1 to 3; Data cutoff as of 19 Apr 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to 09 Oct 2020 are included; Data cutoff as of 04 Jan 2021 for Study 1676; Data cutoff as of 30 Jun 2020 for Study 1620; Data cutoff as of 01 Mar 2020 for Study 1624; Data cutoff as of 30 Apr 2019 for Study 1423.
A patient is only counted once for multiple occurrences within a category.
Source: ISS Table 14.3.2.8.1.p2

Sex

Safety analyses according to sex are applicable to Pool 2. There were more male patients (n=721) than female patients (n=477) in Pool 2 (ISS Table 14.1.2.1.s2).

There was no apparent difference in the AE profile with regard to sex (ISS Table 14.3.1.2.1.s2). In Pool 2, the number of patients with any TEAE was 94.2% (42.7% of which were Grade ≥3) in males and 90.8% (43.0% of which were Grade ≥3) in females (ISS Table 14.3.1.2.4.s2). Similar proportions (<65%) of males and females in Pool 2 experienced treatment-related TEAEs of any grade (ISS Table 14.3.1.3.4.s2), approximately 30% in each sex had serious TEAEs and <10% discontinued study treatment due to a TEAE (<10%) (ISS Table 14.3.1.2.1.s2).

Race

The demographic and baseline characteristics by race are displayed in ISS Table 14.1.2.1.s4. Most patients were White (269 patients in Pool 1; 982 patients in Pool 2); the remaining patients reported

"Other" (5 patients in Pool 1; 168 patients in Pool 2) or unknown/not reported (1 patients in Pool 1; 48 patients in Pool 2) race. Patient disposition and treatment exposure by race are presented for Pool 2 in ISS Table 14.1.1.1.s4 and ISS Table 14.1.4.1s4, respectively.

Pool 2 TEAEs are summarized by SOC, PT, and NCI grade by race in ISS Table 14.3.1.2.4.s4. Treatment-related TEAEs, serious TEAEs, and treatment-related serious TEAEs are summarized by race in ISS Table 14.3.1.3.4.s4, ISS Table 14.3.2.1.2.s4, and ISS Table 14.3.2.2.2.s4, respectively.

In Pool 2, there was no apparent difference in the AE profile with regard to race (ISS Table 14.3.1.2.1.s4). The number of patients with any TEAE was 93.1% (41.5% of which were Grade ≥3) in white patients, 89.9% (47.6% of which were Grade ≥3) in patients of other race, and 97.9% (52.1% of which were Grade ≥3) in patients whose race was reported as missing. Treatment-related TEAEs were comparable between patients who were White (623 [63.4%] patients) and those of other race (104 [61.9%] patients); for those with missing race data treatment-related TEAEs were reported in 40 (83.3%) patients (ISS Table 14.3.1.3.4.s4). There were no apparent differences in the incidence of serious TEAEs regardless of race (299 [30.4%] in white patients and 59 [35.1%] patients in those of other race) in Pool 2; for those with missing race data serious TEAEs were reported in 16 (33.3%) patients (ISS Table 14.3.2.1.2.s4). The proportion of patients who discontinued study treatment due to a TEAE was <9% regardless of race (White and Other); 16.7% of patients with missing race had TEAEs leading to discontinuation of study treatment (ISS Table 14.3.1.2.1.s4).

Assessment comment

As expected TEAEs are observed more frequently with higher age due to comorbidities. According to the MAH there continues to be no clinically relevant differences in terms of race and sex. Nonetheless, the MAH is asked to provide a tabulated overview with regards to sex and race, and discuss the differences. Also, the MAH is asked to provide updated safety with regards to patients with hepatic and renal impairment **(OC)**.

Extrinsic Factors

Region

The demographic and baseline characteristics by region are displayed in ISS Table 14.1.2.1.s5a. Most patients in Pool 1 were from North America (111 patients), Europe (74 patients) followed by rest of the world (ROW; 90 patients). In Pool 2, most patients were from Europe (600 patients), North America (298 patients) and then ROW (300 patients).

Pool 2 TEAEs are summarized by SOC, PT, and NCI grade by region in Table 14.3.1.2.4.s5a. Treatment-related TEAEs, serious TEAEs, and treatment-related serious TEAEs are summarized by region in ISS Table 14.3.1.3.4.s5a, ISS Table 14.3.2.1.2.s5a, and ISS Table 14.3.2.2.2.s5a, respectively.

In Pool 2, there was no apparent difference in the AE profile with regard to region (ISS Table 14.3.1.2.1.s5a). The number of patients with any TEAE was 97.0% (44.3% of which were Grade ≥3) in those from North America, 90.0% (41.2% of which were Grade ≥3) in those from Europe, and 94.3% (44.7% of which were Grade ≥3) in those from ROW. Treatment-related TEAEs of any grade were reported in fewer patients from Europe (57.3%) than in ROW (67.3%) or North America (74.2%) (ISS Table 14.3.1.3.4.s5a). A lower proportion of patients in North America (26.5%) had serious TEAEs compared with Europe (32.0%) and ROW (34.3%), (ISS Table 14.3.2.1.2.s5a). A similar proportion of patients from the 3 regions discontinued study treatment due to a TEAE (ISS Table 14.3.1.2.1.s5a).

Assessment comment

The MAH is asked to provide a tabulated overview of updated safety as function of region, prior systemic therapy and prior radiotherapy **(OC)**.

Safety related to drug-drug interactions and other interactions

No pharmacokinetic drug-drug interaction studies have been conducted with cemiplimab.

Discontinuation due to adverse events

Groups 1 to 3

For Groups 1 to 3, 10.4% (20/193) of patients experienced at least 1 TEAE resulting in discontinuation of study treatment (10.2% [6/59] of patients in Group 1 [mCSCC], 12.8% [10/78] of patients in Group 2 [laCSCC], and 7.1% [4/56] patients in Group 3 [mCSCC] [Module 5.3.5.2 Study 1540 Interim Group 6 CSR Table 61]).

Most (16/20, 80%) TEAEs leading to discontinuation were considered by the investigator to be treatment-related (Study 1540 Interim Group 6 CSR Post text Table 14.3.2.3.6).

The most common TEAE leading to discontinuation was Pneumonitis (3.1%), reported by 6 patients (6.8% [4/59] in Group 1, 2.6% [2/78] in Group 2, 0% [0/56] in Group 3) (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Table 61). All other TEAEs that resulted in discontinuation were reported by 1 patient each.

Group 6 (Interim Analysis)

For Group 6, 14.6% (12/82) of patients experienced at least 1 TEAE resulting in discontinuation of study treatment (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Table 62).

Seven of the 12 (58%) TEAEs leading to discontinuation were considered by the investigator to be treatment-related (Cortisol decreased, Dermatitis bullous, Febrile neutropenia, Immune-mediated gastritis, Neuropathy peripheral, Pneumonitis, and Pruritus). TEAEs leading to treatment discontinuation that were not considered treatment related were General physical health deterioration (2 patients), Duodenal ulcer hemorrhage, Cardiac failure, and Fall.

In Group 6 [interim], fewer TEAEs leading to treatment discontinuation were considered treatment related (58% [7/12]) compared with Groups 1 to 3 (80% [16/20]; Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.2.3.6.g6).

Treatment-Emergent Adverse Events Leading to Dose Reductions

In Groups 1 to 3, there were 4 (2.1%) patients with TEAEs that resulted in dose reductions (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Table 49 and Post-text Table 14.3.1.2.1).

In Group 6, there were no patients with TEAEs that resulted in dose reductions (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Table 51 and Post-text Table 14.3.1.2.1.g6). Of note, dose reductions were not part of the AE management plan for Group 6.

Treatment Emergent Adverse Events Leading to Dose Delays or Interruptions

Groups 1 to 3

Overall, 39.4% (76/193) of patients experienced at least 1 TEAE resulting in dose interruption or delay (39.0% [23/59] in Group 1, 44.9% [35/78] in Group 2, and 32.1% [18/56] in Group 3 (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Table 63).

The 3 most frequently reported TEAEs (PT) resulting in dose interruption or delay were Diarrhea (5.7% [11/193]), Pneumonitis (3.6% [7/193]), and Infusion-related Reaction (3.6% [7/193]). Post-IRR, infusion was restarted in all 7 patients (at a slower rate for 4 patients) and completed on the day of administration. These events are listed as ADRs in the product information.

Group 6 (Interim Analysis)

There were 29.3% (24/82) of patients experienced at least 1 TEAE resulting in dose interruption or delay (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Table 64). The TEAEs (PTs) resulting in dose interruption or delay that occurred in more than 1 patient were Diarrhea and Infusion related reaction (2.4% each [2/82] each). These events are listed as ADRs in the product information. Twenty-one (21) of the 24 TEAEs leading to dose interruption/delay were considered treatment-related, which occurred in 14.6% (12/82) of patients (Module 5.3.5.2 Study 1540 Interim Group 6 CSR Post-text Table 14.3.2.3.13.g6).

Assessment comment

Overall, there are no clinically meaningful differences between Groups 1-3 and Group 6.

Discussion

As part of the CMA two SOBs where adopted. The MAH was asked to provide the final CSR for Groups 1-3 and to add a Group 6 in order to confirm efficacy and safety of cemiplimab in CSCC. As agreed at a meeting in May 2021, the MAH provides updated results from Groups 1-3 and the interim results of Group 6. With the submission of these data, the MAH is proposing is seeking a standard MA for Libtayo within the annual renewal. The MAH commits to submitting the final CSR for Groups 1-3 by 31 October 2022.

The data show overall comparison between Groups 1-3 and Group 6 in terms of baseline characteristics. With regards to efficacy, the updated ORR and DOR from Groups 1-3 continue to show clinically meaningful benefit, and the ORR and DOR observed in Group 6 are in line with Group 1-3. The MAH has excluded two patients from the efficacy evaluation in Group 6. Both patients didn't receive any treatment with cemiplimab. Thus, their exclusion is endorsed.

Approximately half of the 84 patients in scope of the interim analysis in Group 6 had an available baseline tumor sample. The numbers are small, but it can with reasonable likelihood be concluded that efficacy of cemiplimab is not predicted by PD-L1 expression in CSCC. The results show clinical benefit irrespective of PD-L1 expression. This supports the continued use of cemiplimab in all-comers in this specific clinical setting.

In terms of safety, the observed safety findings in Group 6 are in line with the known safety profile of cemiplimab. Almost all patients experienced an TEAE (98.8%). Approximately 39% experienced a Grade ≥3 AEs, and 40.2% an SAE. The most common AEs continue to be fatigue, pruritus, rash and diarrhoea. There are no new safety findings.

Since the last annual renewal in January 2021, the CHMP has given positive opinion for two additional indications in non-small cell lung cancer (NSCLC) and basal cell carcinoma (BCC), resulting in approvals by the European Commission in June 2021. Furthermore, two procedures are ongoing in CHMP at the moment.

Overall, the efficacy of cemiplimab has been confirmed in several different settings, and with the submission of updated data from Groups 1-3 and interim data from Group 6, there are no longer any regulatory nor clinical arguments to keep cemiplimab on CMA.

In conclusion, the Rapporteur is of the opinion that Specific Obligation has been fulfilled, and therefore recommends its deletion from the Annex II, if satisfactory responses are given to the few OCs that have been identified.

5.3. Overall conclusion on Specific Obligations

During the period covered by this annual renewal, new data regarding the following SOBs have emerged. The SOBs are considered fulfilled, if satisfactory responses are given to the few OCs that have been identified.

6. Additional scientific data provided relevant for the assessment of the benefit/risk balance

6.1. Quality

Not Applicable

6.2. Non-clinical

Not Applicable

6.3. Clinical pharmacology

Not Applicable

6.4. Clinical efficacy

Since the last annual renewal in January 2021, the CHMP has given positive opinion for two additional indications in non-small cell lung cancer (NSCLC) and basal cell carcinoma (BCC), resulting in approvals by the European Commission in June 2021.

Furthermore, two procedures are ongoing in CHMP at the moment; cemiplimab monotherapy for the treatment of recurrent/metastatic cervical cancer was submitted in November 2021, and cemiplimab in combination with chemotherapy for the treatment of locally advanced/ metastatic NSCLC was submitted in January 2022. Thus, the totality of evidence for cemiplimab in different cancer patient populations continue to show clinically meaningful results.

In conclusion, the efficacy of cemiplimab has been confirmed in several different settings, and with the submission of updated data from Groups 1-3 and interim data from Group 6, there are no longer any regulatory nor clinical arguments to keep cemiplimab on CMA.

6.5. Clinical safety

Post Marketing Data

Since the last annual renewal with DLP 27 September 2020, the fourth PSUR (reporting period from 28 September 2020 to 27 March 2021; EMEA/H/C/PSUSA/00010780/202103) has been assessed and the fifth PSUR (reporting period from 28 March 2021 to 27 September 2021; EMEA/H/C/PSUSA/00010780/202109) is currently under review.

Based on the data submitted in this annual renewal procedure, the cumulative exposure to cemiplimab in clinical studies is estimated to be 122,151 patient-weeks (104595.7 patient-weeks in Regeneron studies and 17555.3 patient-weeks in non-Regeneron studies). The cumulative postmarketing exposure to cemiplimab is estimated to be 9,867 patient-years.

Actions taken for safety reasons in the reporting interval
On 08 July 2021, PRAC recommended submission of a variation with the agreed changes to the product information in relation to signal evaluation procedure (EPITT ref. No. 19610) on noninfective cystitis for the class of checkpoint inhibitors. The variation was subsequently submitted.

On 11 Nov 2021, following PRAC review of PBRER#4 (PSUSA/00010780/202103), the CHMP adopted a positive opinion in relation to the addition of agreed language on diabetic ketoacidosis to the Libtayo PL.

Identification important risks
A detailed review of the safety concerns have been submitted in the PSURs and have been assessed in PSUSA procedures (EMEA/H/C/PSUSA/00010780/202103 and EMEA/H/C/PSUSA/00010780/202109). No new important risk was identified.

Signals
A total of four signals have been discussed in the PSURs covering the review period of this renewal. One signal (immune-mediated cystitis) was assessed in separate procedure (EPITT no: 19610) and led to an SmPC update. The review of two signals (scleroderma and scleroderma-like events and sclerosing cholangitis) did not lead to any new concern. Closure of these signals was accepted. The assessment of the last signal (Tumour Lysis Syndrome) is ongoing. The review of this signal will be provided as part of the next PSUSA.

Monitored events
From the previous PSUSA, the MAH was requested to continue to monitor the risk of rhabdomyolysis and return to the topic in future PSURs should relevant new information arise. No new significant safety concerns have been identified for risk of rhabdomyolysis, and other topics under review from previous PSURs (cholestasis, hemophagocytic lymphohistiocytosis, eosinophilic fasciitis, vitiligo and scleroderma/scleroderma like events).

Conclusion on Safety:

Overall, no new relevant safety information became available from the post-marketing experience during the reporting period of this annual renewal procedure. Of note: The fifth PSUR is currently under assessment (PSUSA/00010780/202109).

7. Risk management plan

The MAH states that an updated RMP (v4.0), among others also related to this renewal procedure, has been submitted as part of an ongoing variation procedure (EMEA/H/C/004844/II/0028) with the purpose of extending the indication to non-small cell lung cancer (NSCLC) in combination with chemotherapy. Note that RMP version 3.0 to add the cervical cancer (CC) indication is currently under review under Procedure Number EMEA/H/C/004844/II/0026.

The summary of safety concerns is not amended in RMP version 3.0 and 4.0.

As part of RMP version 4.0, the MAH states that the conversion of the conditional MA into a standard MA is requested. Furthermore, RMP Part III is updated to reflect completion of additional PV activities:

Study R2810-ONC-1540 (A Phase 2 Study of REGN2810, A Fully Human Monoclonal Antibody to Programmed Cell Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma-Group 6) and study R2810-ONC- 1540 (A Phase 2 Study of REGN2810, a fully human monoclonal antibody to programmed cell death-1 (PD-1), in patients with advanced cutaneous squamous cell carcinoma - Group 1,2 and 3) are removed from list of additional pharmacovigilance activities. The MAH states that all studies from RMP part III have been completed. There are no additional pharmacovigilance activities.

Part IV is updated to reflect completion of a post-authorisation efficacy study. Study R2810-ONC-1540 (A Phase 2 Study of REGN2810, A Fully Human Monoclonal Antibody to Programmed Cell Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Group 6) is removed from table of planned and on-going post-authorisation efficacy studies.

The assessment of the results of the above mentioned studies is currently ongoing.

In addition, Part VII, Annex 4 is updated with new versions of follow-up questionnaires - minor format changes only.

The proposed updates (removal of the SOBs from part III and IV, as well as updates related to Part VII, annex 4) are accepted.

8. Changes to the Product Information

Changes to the Product Information (PI), based on the submitted data within the scope of this procedure, are introduced during the assessment of this renewal (see attached PI with comments).

Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, LIBTAYO (cemiplimab) is included in the additional monitoring list as <include reason(s)>

- It is a biological product that is not covered by the previous category and authorised after 1 January 2011;

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Request for Supplementary Information - RfSI

The MAH should provide the following supplementary information in response to Day 60 RfSI:

9.1. Major objections

None

9.2. Other concerns

Specific obligations

1. There were slightly more TEAE resulting in death in Group 6. The MAH claim that none of them are treatment related. The MAH is asked to provide brief case narratives and discuss these in more detail.
2. Overall, there seems to be no clinically meaningful differences between Groups 1-3 and Group 6. However, the MAH is asked to provide a tabulated overview of laboratory values for Group 1-3 and Group 6 side by side, and discuss any relevant difference.
3. As expected TEAEs are observed more frequently with higher age due to comorbidities. According to the MAH there continues to be no clinically relevant differences in terms of race and sex. Nonetheless, the MAH is asked to provide a tabulated overview with regards to sex and race, and discuss the differences. Also, the MAH is asked to provide updated safety with regards to patients with hepatic and renal impairment.
4. The MAH is asked to provide a tabulated overview of updated safety as function of region, prior systemic therapy and prior radiotherapy.

Quality aspects

None

Non clinical aspects

None

Clinical aspects

None

Risk Management Plan

None

10. Assessment of the MAH responses to the RfSI

10.1. Major objections

None

10.2. Other concerns

Specific Obligation

Question 1

There were slightly more TEAE resulting in death in Group 6. The MAH claim that none of them are treatment related. The MAH is asked to provide brief case narratives and discuss these in more detail.

MAH's response

The Applicant has provided detailed narratives for the 9 cases with TEAEs resulting in death in Group 6 in Appendix 1. These narratives contain a detailed summary and discussion. Based on the review of the cases described in the narratives, the Applicant confirms its position that none of these TEAEs in Group 6 are treatment related per investigator and sponsor assessment.

APPENDIX 1. NARRATIVES

■ SERIOUS ADVERSE EVENT/ ADVERSE EVENT LEADING TO DEATH

AE MedDRA SOC / Preferred Term / Verbatim Term	Start / Stop Day of Event	Related to Study Drug / Study Procedure (Yes/No)	Serious AE (Yes/No)	AE Initial Grade / Most Extreme Grade	Action Taken with Study Drug / Outcome of AE	AE of Special Interest (Yes/No)	AE of Special Interest Criteria
Gastrointestinal disorders / Small intestinal obstruction / SMALL BOWEL OBSTRUCTION	206 / Ongoing	N / N	Yes	3 / 3	Drug interrupted/delayed/ Not recovered/not resolved	No	Not applicable
Respiratory, thoracic and mediastinal disorders / Pulmonary embolism / PULMONARY EMBOLISM	211 / 211	N / N	Yes	4 / 5	Not applicable / Fatal	No	Not applicable

■ NARRATIVE SUMMARY

A 79-year-old White, not Hispanic or Latino, male, was enrolled in the Phase 2 study R2810-ONC-1540 in patients with advanced cutaneous squamous cell carcinoma and experienced serious events of Grade 3 small intestinal obstruction (small bowel obstruction) and Grade 5 pulmonary embolism (pulmonary embolism) [initially Grade 4].

Relevant medical history included actinic keratosis, right ear cutaneous squamous cell carcinoma, atrial fibrillation, cardiomyopathy, hypertension, left facial pain, arachnoiditis, left occipital haematoma, left posterior temporal stroke, right superior hemi-retinal vein occlusion, and type 2 diabetes.

Medications ongoing on study day 1 included the following: carmellose sodium, irbesartan, paracetamol, spironolactone, apixaban, prochlorperazine, and zinc.

Advanced cutaneous squamous cell carcinoma was diagnosed on 02 May 2018. At the time of enrollment, the patient had target lesions in subcutaneous tissue, and zygoma and non-target lesion in the subcutaneous tissue.

Previous cancer treatment included 6000 cGy radiation therapy to the left side of head alone (from study day -575 to study day -534).

Previous procedures included shave biopsy of the left zygoma (study day -757), punch biopsy of the left zygoma (study day -743), excision of the left zygoma (study day -686), and fine needle aspiration of the left zygoma (study day -49).

The patient was enrolled in the Group 6 cohort and was assigned to receive cemiplimab 350 mg IV administered over 30 minutes (±10 minutes) every 21 days for up to 108 weeks. The patient received the first dose of cemiplimab on study day 1 and the final dose on study day 190 for a total of 10 doses.

Other TEAEs complicating the patient's course included cough, dizziness, fall, fatigue, hypothyroidism, and rash maculo-papular.

SERIOUS ADVERSE EVENT: SMALL INTESTINAL OBSTRUCTION

SERIOUS ADVERSE EVENT/ ADVERSE EVENT LEADING TO DEATH: PULMONARY EMBOLISM

In the morning of study day 206, 16 days after the tenth dose of the study drug, the patient experienced umbilical pain, nausea, vomiting, and was admitted to the hospital for investigation. He was diagnosed with Grade 3 small intestinal obstruction (small bowel obstruction). An electrocardiogram (ECG) was done, and venous blood gases were tested (results not reported).

On study day 207, a computerized tomography scan of the abdomen and pelvis showed small bowel obstruction. A nasogastric tube was inserted, and paracetamol (1g PRN) and ondansetron (8 mg PRN) were started as treatment for the small intestinal obstruction. On the same day, a urine analysis was done (results not reported), and an indwelling urinary catheter was placed. On study day 208, additional treatment for the event of small intestinal obstruction included ondansetron (4 mg PRN) and buprenorphine (0.2 mg BID). On the same day, an abdominal Xray was done (results not reported).

On study day 210, a peripherally inserted central catheter was inserted for venous access. On the same day, the patient underwent laparotomy, small bowel resection, and division of peritoneal adhesions, with additional treatment medication ondansetron (4 mg PRN) for the event of small intestinal obstruction. Histopathology results of the bowel resection indicated that the cause of the small bowel obstruction was ischemic necrosis.

On study day 211, 21 days after the tenth dose of the study drug, the patient developed a non-serious event of Grade 1 cough (cough). Later the patient became unresponsive and cyanotic with episodes of apnea. The patient's blood pressure was unreadable. An ECG was done (results not reported). The patient was not for cardiopulmonary resuscitation as per the acute resuscitation plan. The patient became persistently apneic, developed pallor, and had no carotid pulse present. On the same day, at 23:35 hours, the patient was pronounced dead as a result of a serious event of Grade 5 pulmonary embolism (pulmonary embolism) [initially Grade 4]. No treatment was reported for the event of pulmonary embolism. An autopsy was not performed.

At the time of the patient's death, the events of small intestinal obstruction and cough were considered not recovered/not resolved.

Action taken with study drug as a result of the event of small intestinal obstruction was drug interrupted/delayed. Dosing of the study drug was not resumed. Action taken with study drug as a result of the event of pulmonary embolism was not applicable.

The investigator assessed the event of small intestinal obstruction as Grade 3, serious, and not related to study drug. The event was not suspected to be immune-related and was reported to be due to ischemic necrosis.

The investigator assessed the event of pulmonary embolism as Grade 5 (initially Grade 4), serious, and not related to study drug. The event was not suspected to be immune-related and was reported to be due to a blood clot.

The sponsor agrees with the investigator’s causality assessments.

■ SERIOUS ADVERSE EVENT/ ADVERSE EVENT LEADING TO DEATH

AE MedDRA SOC / Preferred Term / Verbatim Term	Start / Stop Day of Event	Related to Study Drug / Study Procedure (Yes/No)	Serious AE (Yes/No)	AE Initial Grade / Most Extreme Grade	Action Taken with Study Drug / Outcome of AE	AE of Special Interest (Yes/No)	AE of Special Interest Criteria
Infections and infestations / Sepsis / SEVERE SEPSIS	4 / 10	N / N	Yes	4 / 5	Dose not changed / Fatal	No	Not applicable

■ NARRATIVE SUMMARY

A 61-year-old White, Hispanic or Latino, male, was enrolled in the Phase 2 study R2810-ONC-1540 in patients with advanced cutaneous squamous cell carcinoma and experienced a serious event of sepsis (sever sepsis) [Grade 5, initially Grade 4].

Relevant medical history included ischemic cardiopathy, arterial hypertension, hepatic cytolysis, hypercholesterolemia, anemia, suspected herpetic infection, hidradenitis suppurativa, malnutrition, and malignant tumoral pain.

Medications ongoing on study day 1 included the following: acetylsalicylic acid, bisoprolol, ramipril, simvastatin, paracetamol, enoxaparin, dietary supplement, macrogol 3350/potassium chloride/sodium bicarbonate/sodium chloride, sodium phosphate dibasic/sodium phosphate dibasic dodecahydrate, potassium bitartrate/sodium bicarbonate, pregabalin, nefopam, liquid paraffin, clonazepam, cyamemazine, pantoprazole, oxycodone hydrochloride, oxycodone, and gabapentin.

Advanced cutaneous squamous cell carcinoma was diagnosed on 14 May 2020. Stage at screening was Stage IV. Metastasis was detected on 12 Aug 2020. At the time of enrollment, the patient had target lesions in the retroperitoneal lymph node, left iliac lymph node, and left and right inguinal lymph nodes and a non-target lesion on the skin of the left buttock.

No previous cancer treatments were reported.

Previous procedure included carcinoma resection of the skin lesion on the left lower back (study day -120).

The patient was enrolled in the Group 6 cohort and was assigned to receive cemiplimab 350 mg IV administered over 30 minutes (±10 minutes) every 21 days for up to 108 weeks. The patient received the first and only dose of cemiplimab on study day 1.

Other TEAEs complicating the patient's course included hepatocellular injury and vitamin K deficiency.

SERIOUS ADVERSE EVENT/ ADVERSE EVENT LEADING TO DEATH: SEPSIS

On study day 1, the patient experienced non-serious events of Grade 1 hepatocellular injury (hepatic cytolysis) and Grade 2 vitamin K deficiency (vitamin K deficiency). Laboratory test results included elevated alkaline phosphatase 240 IU/L (normal range: 40 to 150 IU/L), alanine aminotransferase (ALT) 145 IU/L (normal range: 0 to 55 IU/L), and aspartate aminotransferase (AST) 99 IU/L (normal range: 5 to 34 IU/L) and normal bilirubin 7 µmol/L (normal range: 3 to 21 µmol/L) [vitamin K levels not reported]. Treatment included phytomenadione for the event of vitamin K deficiency, while no treatment was provided for the event of hepatocellular injury. On the same day, the event of vitamin K deficiency was considered recovered/resolved.

On study day 4, 3 days after the first and only dose of the study drug, the patient was hospitalized due to a serious event of Grade 4 sepsis (severe sepsis), which most likely originated from the patient's

necrotizing dermo-hypodermitis on the left thigh coming from an inguinal fistulized tumor adenopathy. On the same day, the event of hepatocellular injury worsened to Grade 3. A computed tomographic scan with contrast showed new lesions in the left adrenal gland and mediastinal and hilar lymph nodes. Upon a multi-disciplinary decision, supportive treatments were given along with antibiotic therapy, including gentamicin (210 mg QD), piperacillin sodium/tazobactam sodium (4 g TID), and vancomycin (875 mg BID). On the same day, study drug was withdrawn due to progressive disease as confirmed by a radiologic/photographic assessment.

On study day 6, the patient experienced a non-serious event of Grade 3 cardiac failure (cardiac decompensation), which was considered recovered/resolved on the same day after treatment with furosemide.

On study day 10, the event of hepatocellular injury was considered recovered/resolved; however, the patient died due to the serious event of Grade 5 sepsis on the same day. An autopsy was not performed.

No records of infectious work-up (chest X-ray or cultures of blood, urine, or wound) were provided.

Action taken with study drug as a result of the event of sepsis was dose not changed.

The investigator assessed the event of sepsis as Grade 5 (initially Grade 4), serious, and not related to study drug. The event was not immune-related and was reported to be due to an infection. The sepsis origin was most probably the patient's necrotizing hypodermitis on the left thigh, which came from an inguinal fistulized tumoral adenopathy. Other suspected cause included the patient's disease under study as the event occurred because of the disease, but it would not necessarily happen as a typical progression of the event. It was rather an unexpected and clinically important event as it resulted to the patient's death.

The sponsor agreed with the investigator's assessment.

■ SERIOUS ADVERSE EVENT/ ADVERSE EVENT LEADING TO DEATH

AE MedDRA SOC / Preferred Term / Verbatim Term	Start / Stop Day of Event	Related to Study Drug / Study Procedure (Yes/No)	Serious AE (Yes/No)	AE Initial Grade / Most Extreme Grade	Action Taken with Study Drug / Outcome of AE	AE of Special Interest (Yes/No)	AE of Special Interest Criteria
Investigations / General physical condition abnormal / ALTERATION OF GENERAL STATE	50 / Ongoing	N / N	Yes	2 / 3	Dose not changed/ Not recovered/not resolved	No	Not applicable
Respiratory, thoracic, and mediastinal disorders / Pulmonary oedema / PULMONARY EDEMA	71 / 71	N / N	Yes	5 / 5	Dose not changed / Fatal	No	Not applicable

■ NARRATIVE SUMMARY

A 64-year-old White, not Hispanic or Latino, female, was enrolled in the Phase 2 study R2810-ONC-1540 in patients with advanced cutaneous squamous cell carcinoma and experienced serious events of general physical condition abnormal (alteration of general state) [Grade 3, initially Grade 2] and Grade 5 pulmonary oedema (pulmonary edema).

Relevant medical history included hypoalbuminemia, anemia, pain of left arm, C-reactive protein increased, gamma-glutamyltransferase increase, and iron deficiency.

At the time of enrollment, pain medications were oxycontin LP 10 mg PO BID and oxynormoro 10 mg PO Q4h.

Advanced cutaneous squamous cell carcinoma was diagnosed on 01 Sep 2020. Stage at screening was Stage III. Metastasis was detected on an unknown date. At the time of enrollment, the patient had a skin target lesion in the left shoulder.

No previous cancer treatments were reported.

Previous procedures included skin biopsy of the left shoulder (study day -24).

The patient was enrolled in the Group 6 cohort and was assigned to receive cemiplimab 350 mg IV administered over 30 minutes (±10 minutes) every 21 days for up to 108 weeks. The patient received the first dose of cemiplimab on study day 1 and the final dose on study day 63 for a total of 4 doses.

Other TEAEs complicating the patient's course included xerosis, hyponatraemia, vulvovaginal mycotic infection, lymphopenia, presyncope, folliculitis, hypokalaemia, tongue coated, anxiety, and lymphoedema.

SERIOUS ADVERSE EVENTS: GENERAL PHYSICAL CONDITION ABNORMAL AND PULMONARY OEDEMA

During the first week on the study, fentanyl 100 mg buccal prn was added. On study day 50, 9 days after the third dose of the study drug, the patient experienced a serious event of Grade 2 general physical condition abnormal (alteration of general state) as well as events of Grade 1 diarrhoea (diarrhea) and Grade 1 vomiting (vomiting).

On study day 55, stool culture was negative.

On study day 60, the serious event of general physical condition abnormal became Grade 3, and the patient was subsequently hospitalized with severe pain localized on the malignancy site (left arm), diarrhea, and vomiting. On the same day, the patient also experienced an event of Grade 2 atrial fibrillation (paroxysmal atrial fibrillation). The patient was treated with diosmectite for the event of diarrhoea, metoclopramide hydrochloride for the event of vomiting, as well as bisoprolol, enoxaparin sodium, and tinzaparin sodium for the event of atrial fibrillation. Morphine IV Patient Controlled Anesthesia was introduced during hospitalization to reduce the pain.

On study day 61, blood cortisol was 206.4 ng/mL (normal range: 62.4 to 180 ng/mL).

On study day 63, blood cortisol was 192.3 ng/mL, blood thyroid-stimulating hormone (TSH) was 2.10 IU/mL (normal range: 0.2 to 4 IU/mL), and thyroxine was 11.1 pg/mL (normal range: 8.5 to 18 pg/mL).

On study day 64 (27 Nov 2020), the serious event general physical condition abnormal became less than Grade 3, pain was controlled, and patient was discharged from the hospital.

On study day 71 (04 Dec 2020), the patient died due to a serious event of Grade 5 pulmonary oedema (pulmonary edema), which was reported to be probably caused by a new episode of atrial fibrillation.

No treatment was reported for the event of pulmonary oedema, but morphine was administered to treat symptom of dyspnea. The high dose of morphine caused the patient to lose alertness. Autopsy was not performed. No further details were reported.

An X-ray or a computed tomography scan of the chest or an echocardiogram were not done.

At the time of the patient's death, the events of general physical condition abnormal, diarrhoea, vomiting, and atrial fibrillation were considered not recovered/not resolved.

Action taken with study drug as a result of the events of general physical condition abnormal and pulmonary oedema was dose not changed.

The investigator assessed the events as follows:

- General physical condition abnormal: Grade 3 (initially Grade 2), serious, and not related to study drug. The event was not immune-related but due to the symptoms of malignancy. Other suspected causes included disease under study and concurrent illness of anemia.
- Pulmonary oedema: Grade 5, serious, and not related to study drug. The event was not immune-related but probably caused by an atrial fibrillation.

The sponsor agreed with the investigator's assessment

■ SERIOUS ADVERSE EVENTS/ADVERSE EVENT LEADING TO DEATH

AE MedDRA SOC / Preferred Term / Verbatim Term	Start / Stop Day of Event	Related to Study Drug / Study Procedure (Yes/No)	Serious AE (Yes/No)	AE Initial Grade / Most Extreme Grade	Action Taken with Study Drug / Outcome of AE	AE of Special Interest (Yes/No)	AE of Special Interest Criteria
Gastrointestinal disorders / Dysphagia / DYSPHAGIA WORSENING	2 / Ongoing	N / N	Yes	3 / 3	Not applicable/ Not recovered/not resolved	No	Not applicable
Infections and infestations / Meningitis / SUSPECTED CARCINOMATOUS MENINGITIS	19 / 22	N / N	Yes	3 / 5	Not applicable/ Fatal	No	Not applicable

■ NARRATIVE SUMMARY

A 67-year-old White, (ethnicity not reported), male, was enrolled in the Phase 2 study R2810-ONC-1540 in patients with advanced cutaneous squamous cell carcinomaand experienced serious events of Grade 3 dysphagia (dysphagia worsening) and meningitis (suspected carcinomatous meningitis) [Grade 5, initially Grade 3].

Relevant medical history included dysphagia (due to mucositis post-radiotherapy), allogeneic bone marrow transplant (transplant 16 years prior to study enrollment for history of multiple myeloma), neck pain (managed with fentanyl and lyrica), colonic polyps, and myocardial infarction.

Medications ongoing on study day 1 included the following: sulfamethoxazole/trimethoprim, pantoprazole, valaciclovir, ramipril, atorvastatin calcium, acetylsalicylic acid/clopidogrel bisulfate, pregabalin, paracetamol, tamsulosin, and fentanyl.

Advanced cutaneous squamous cell carcinoma was diagnosed on 12 Oct 2018. Stage at screening was Stage IV. Metastasis was detected on 21 Apr 2020. At the time of enrollment, the patient had a target lesion in the neck measuring 96 mm and non-target lesions in left necrotic temporal bone lymph node and right cervical lymph node.

Previous cancer treatments included the following: 5400 cGy radiation therapy to the cervical lymph node alone and 6000 cGy radiation therapy to the skin lesion on the back of the neck and vertex alone (from study day -351 to study day -302).

Previous procedures included exeresis of the skin lesion on the back of the neck (study day - 566), back of the neck wide margin exeresis (study day -496 and study day -447), and biopsy ofthe skin lesion on the back of the neck (study day -36).

The patient was enrolled in the Group 6 cohort and was assigned to receive cemiplimab 350 mgIV administered over 30 minutes (±10 minutes) every 21 days for up to 108 weeks. The patient received the first and only dose of cemiplimab on study day 1.

Other TEAE complicating the patient's course included impetigo.

SERIOUS ADVERSE EVENT: DYSPHAGIA

SERIOUS ADVERSE EVENT/ADVERSE EVENT LEADING TO DEATH: MENINGITIS

On study day 2, 1 day after the first and only dose of the study drug, the patient experienced a serious event of Grade 3 dysphagia (dysphagia worsening) and a non-serious event of Grade 2 headache (acute cephalgia).

On study day 12, the patient was hospitalized to identify the origin of the event of worsening dysphagia. On the same day, the patient experienced a non-serious event of Grade 1 impetigo (back of hand impetigo). Physical examination upon admission showed sclerous neck; facial asymmetry, which was probably caused by facial paralysis; and extreme difficulty in eating, drinking, and taking oral treatments. Treatment included nefopam hydrochloride, morphine, and diazepam for the event of headache and amoxicillin/clavulanic acid for the event of impetigo; no treatment medication was provided for the event of dysphagia.

On study day 13, a gastronomy tube insertion was planned but was deemed impossible.

On study day 16, the patient underwent digestive fibroscopy and gastronomy tube installation as treatment for the event of dysphagia.

On study day 19, 18 days after the first and only dose of the study drug, the patient experienced a serious event of Grade 3 meningitis (suspected carcinomatous meningitis) and a non-serious event of Grade 3 malnutrition (phosphore carency due to denutrition). On the same day, a cerebral angiography scan showed no cerebral thrombophlebitis. A lumbar puncture was

indicated, but the patient's family disagreed with the procedure. The patient received antibiotic therapy with meropenem (2 g Q8H) and vancomycin (1 g Q12H) for the event of meningitis.

Additional treatment for the event of malnutrition included glucose 1-phosphate disodium. On study day 20, the event of malnutrition improved to less than Grade 3.

On study day 21, antibiotic therapy was stopped and only palliative care was given as the patient's general state worsened.

On study day 22, the patient died as a result of the serious event of Grade 5 meningitis. Cancer was a contributing factor to the patient's death, and cause of death may be due to sepsis (infectious) or carcinomatous meningitis (disease progression). The cause of death was reported as "other" because

the investigator cannot definitively say whether the death is due to sepsis (infectious) or carcinomatous meningitis (disease progression) and no lumbar puncture, brain imaging or neurology consult was performed. It was unknown whether an autopsy was performed.

At the time of the patient's death, the events of dysphagia, headache, impetigo, and malnutrition were considered not recovered/not resolved.

Action taken with study drug as a result of the events of dysphagia and meningitis was not applicable.

The investigator assessed the events as follows:

- Dysphagia: Grade 3, serious, and not related to study drug. The event was assessed as not immune-related but due to a post-radiotherapy complication. Other suspected cause was the patient's medical history of dysphagia due to mucositis, which occurred post-radiotherapy. The origin of the worsening dysphagia was unknown but could also be due to a local inflammation or tumoral infiltration.
- Meningitis: Grade 5 (initially Grade 3), serious, and not related to study drug. The event was assessed as not immune-related but possibly due to infectious meningitis or carcinomatous meningitis; precise diagnosis was impossible since no lumbar puncture was performed. Other suspected causes were the patient's disease under study and concurrent illness of acute cephalgia.

The sponsor agreed with the investigator's assessment.

■ SERIOUS ADVERSE EVENT/ADVERSE EVENT LEADING TO STUDY DRUG DISCONTINUATION/ADVERSE EVENT LEADING TO DEATH

AE MedDRA SOC / Preferred Term / Verbatim Term	Start / Stop Day of Event	Related to Study Drug / Study Procedure (Yes/No)	Serious AE (Yes/No)	AE Initial Grade / Most Extreme Grade	Action Taken with Study Drug / Outcome of AE	AE of Special Interest (Yes/No)	AE of Special Interest Criteria
Gastrointestinal disorders / Duodenal ulcer haemorrhage / HEMORRAGIC DUODENAL BULBAR ULCER	194 / 199	N / N	Yes	3 / 5	Drug withdrawn permanently / Fatal	No	Not applicable

■ NARRATIVE SUMMARY

An 81-year-old White, (ethnicity not reported), male, was enrolled in the Phase 2 study R2810-ONC-1540 in patients with advanced cutaneous squamous cell carcinoma and experienced a serious event of duodenal ulcer haemorrhage (hemorrhagic duodenal bulbar ulcer) [Grade 5, initially Grade 3].

Relevant medical history included right knee meniscopathy, asthenia, hypercholesterolemia, and type 2 noninsulin dependent diabetes.

Medications ongoing on study day 1 included the following: gliclazide, metformin hydrochloride/vildagliptin, and paracetamol.

Advanced cutaneous squamous cell carcinoma was diagnosed on 19 Jul 2017. Stage at screening was Stage IV. Metastasis was detected on 10 Jul 2020. At the time of enrollment, the patient had target lesions in the right pleura and left axillary lymph node and non-target lesions in the lung, left arm

necrotic lymph node, left supraclavicular lymph node, left pleura, pectoral external (left side) lymph node, subcutaneous thickening on the left arm, and thickening on the left thoracoabdomen.

Previous cancer treatments included radiation therapy to the left elbow (on an unknown date in 2017).

Previous procedures included exeresis in the left elbow (study day -1106), and left arm trans humeral amputation and biopsy of the left axilla, left arm, and left internal face (study day -63).

The patient was enrolled in the Group 6 cohort and was assigned to receive cemiplimab 350 mg IV administered over 30 minutes (±10 minutes) every 21 days for up to 108 weeks. The patient received the first dose of cemiplimab on study day 1 and the final dose on study day 190 for a total of 10 doses.

Other AEs complicating the patient's course included lymphocele, pruritus, and depression.

SERIOUS ADVERSE EVENT/ADVERSE EVENT LEADING TO STUDY DRUG DISCONTINUATION/ADVERSE EVENT LEADING TO DEATH: DUODENAL ULCER HAEMORRHAGE

On study day -6, laboratory test results at screening included hemoglobin 141 g/L (normal range: 130 to 160 g/L) and platelet count 280 g/L (normal range: 150 to 400 g/L).

On study day 64, a computed tomography (CT) scan with contrast revealed new lesions in the pleura and left supraclavicular lymph node.

On study day 105, the patient experienced an event of Grade 1 weight decreased (weight loss).

On study day 127, a CT scan with contrast revealed new lesions in the left osteolytic iliac, osteolytic rachis, osteolytic ribs, and osteolytic sternum.

On study day 169, the patient experienced an event of Grade 2 decreased appetite (anorexia). No treatment was reported for the events of weight decreased and decreased appetite.

On study day 190, the patient experienced an event of Grade 3 general physical health deterioration (general state alteration), for which no treatment was reported.

On study day 194, 4 days after the tenth dose of study drug, the patient experienced a serious event of Grade 3 duodenal ulcer haemorrhage (hemorrhagic duodenal bulbar ulcer) and was hospitalized due to general health deterioration. Laboratory test results included hemoglobin 6 g/dL (normal range not reported), and the patient received a transfusion of red blood cells (RBC) as treatment for the event. On the same day, the study drug was withdrawn due to the adverse event of duodenal ulcer haemorrhage.

On study day 198, the patient received another transfusion of RBC as treatment for the event of duodenal ulcer haemorrhage.

On study day 199, an esophagogastroduodenoscopy confirmed a hemorrhagic ulcer and the patient was diagnosed with Grade 3 oesophagitis (oesophagitis). No treatment was reported for the event of oesophagitis. After a review, it was decided that the patient will receive palliative care; however, the patient's condition rapidly deteriorated, and the patient died on the same day. An autopsy was not performed.

At the time of the patient's death, the events of weight decreased, decreased appetite, general physical health deterioration, and oesophagitis were considered not recovered/not resolved.

The investigator assessed the event of duodenal ulcer haemorrhage as Grade 5 (initially Grade 3), serious, and not related to study drug. The event was due to hemorrhagic ulcer of unknown origin and was not suspected to be immune-related.

The sponsor agreed with the investigator's causality assessment.

■ SERIOUS ADVERSE EVENT/ ADVERSE EVENT LEADING TO STUDY DRUG DISCONTINUATION/ ADVERSE EVENT LEADING TO DEATH

AE MedDRA SOC / Preferred Term / Verbatim Term	Start / Stop Day of Event	Related to Study Drug / Study Procedure (Yes/No)	Serious AE (Yes/No)	AE Initial Grade / Most Extreme Grade	Action Taken with Study Drug / Outcome of AE	AE of Special Interest (Yes/No)	AE of Special Interest Criteria
Cardiac disorders / Cardiac failure / WORSENING HEART INSUFFICIENCY	18 / 18	N / N	Yes	4 / 5	Drug withdrawn permanently / Fatal	No	Not applicable

■ NARRATIVE SUMMARY

A 90-year-old White, not Hispanic or Latino, male, was enrolled in the Phase 2 study R2810-ONC-1540 in patients with advanced cutaneous squamous cell carcinoma and experienced a serious event of cardiac failure (worsening heart insufficiency) [Grade 5, initially Grade 4]

Relevant medical history included anaemia, coronary heart disease, gout, hyperkalaemia, hypercholesterolemia, hypertension, hyperuricemia, and lung embolism.

Medications ongoing on study day 1 included the following: bisoprolol, hydrochlorothiazide, simvastatin, pantoprazole, ramipril, allopurinol, paracetamol, tramadol, pregabalin, and rivaroxaban.

Advanced cutaneous squamous cell carcinoma was diagnosed on 29 Jan 2020. Stage at screening was Stage IV. Metastasis was detected on 03 Jul 2020. At the time of enrollment, the patient had a target lesion in the left parotid; no non-target lesions were reported.

No previous cancer treatments were reported.

Previous procedures included squamous cell carcinoma excision of the skin lesion on the right hand (study day -193), SCC excision of the skin lesion on the left forehead (unknown study day [Feb 2020]), and SCC metastasis biopsy of the skin lesion on the left forehead (study day -18).

The patient was enrolled in the Group 6 cohort and was assigned to receive cemiplimab 350 mg IV administered over 30 minutes (±10 minutes) every 21 days for up to 108 weeks. The patient received the first and only dose of cemiplimab on study day 1.

Other TEAEs complicating the patient's course included rash.

■ SERIOUS ADVERSE EVENT/ ADVERSE EVENT LEADING TO STUDY DRUG DISCONTINUATION/ADVERSE EVENT LEADING TO DEATH: CARDIAC FAILURE

On study day 18, 17 days after the first and only dose of the study drug, the patient fell asleep and died at home due to a serious event of Grade 5 cardiac failure (worsening heart insufficiency) [initially Grade 4]. No treatment was provided for the event, and no further information was available.

Echocardiogram and chest X-ray were not done. Troponin level was not reported.

Action taken with study drug as a result of the event of cardiac failure was drug withdrawn permanently.

The investigator assessed the event of cardiac failure as Grade 5 [initially Grade 4], serious, and not related to study drug. The event was not suspected to be immune-related but was suspected

to be due to the patient's concomitant illness (coronary heart disease), which started on an unknown date in 2009. In response to query, the study site stated: "No further information. Dueto information from home doctor, the patient fell asleep peacefully at home. No autopsy was performed."

The sponsor agreed with the investigator's assessment.

■ SERIOUS ADVERSE EVENT/ADVERSE EVENT LEADING TO DEATH

AE MedDRA SOC / Preferred Term / Verbatim Term	Start / Stop Day of Event	Related to Study Drug / Study Procedure (Yes/No)	Serious AE (Yes/No)	AE Initial Grade / Most Extreme Grade	Action Taken with Study Drug / Outcome of AE	AE of Special Interest (Yes/No)	AE of Special Interest Criteria
Infections and infestations / COVID-19 pneumonia / BILATERAL PNEUMONIA DUE TO COVID-19	20 / 25	N / N	Yes	3 / 5	Dose not changed/ Fatal	No	Not applicable

■ NARRATIVE SUMMARY

An 81-year-old White, not Hispanic or Latino, male, was enrolled in the Phase 2 study R2810-ONC-1540 in patients with advanced cutaneous squamous cell carcinoma and experienced a serious event of COVID-19 pneumonia (bilateral pneumonia due to COVID-19) [Grade 5, initially Grade 3].

Relevant medical history included type 2 diabetes mellitus, dyslipidaemia, hypertension, and obesity.

Medications ongoing on study day 1 included the following: paracetamol, acetylsalicylic acid, ibuprofen, amlodipine, enalapril, allopurinol, insulin aspart/insulin aspart protamine (crystalline), simvastatin, vildagliptin, furosemide, and calcifediol.

Advanced cutaneous squamous cell carcinoma was diagnosed on 29 Mar 2012. Stage at screening was Stage IV. Metastasis was detected on 24 Jan 2020. At the time of enrollment, the patient had target lesions in the left lung, upper lobe of the right lung, and right cervical lymph node and non-target lesions in the central mediastinal lymph node and lung.

No previous cancer treatments were reported.

Previous procedures included scalp biopsy (study day -2896), scalp excision (study day -2834), right forehead excision (study day -2575), left parietal excision (study day -2128 and study day - 1320), enlargement of the surgical margins of the left parietal region (study day -1250), right pre-auricular and right laterocervical excisions (study day -529), biopsy of the right pre-auricular region (study day -145), and right pre-auricular excision (study day -116).

The patient was enrolled in the Group 6 cohort and was assigned to receive cemiplimab 350 mg IV administered over 30 minutes (±10 minutes) every 21 days for up to 108 weeks. The patient received the first and only dose of cemiplimab on study day 1.

Other TEAE complicating the patient's course included thyroid pain.

SERIOUS ADVERSE EVENT/ADVERSE EVENT LEADING TO DEATH: COVID-19 PNEUMONIA

On study day -1, laboratory test results at screening included white blood cell count

11.41 × 10^9/L (normal range: 4.00 to 11.00 × 10^9/L), neutrophil count 5.7 × 10^9/L (normal range:

2.0 to 7.0 × 10^9/L), hemoglobin 12.4 g/dL (normal range: 13.0 to 17.0 g/dL), and lymphocyte count 4.0 × 10^9/L (normal range: 1.2 to 3.5 × 10^9/L).

On study day 17, the patient started to experience fever (body temperature of 37.5°C), cough, and rhinorrhea.

On study day 20, 19 days after the first and only dose of the study drug, the patient presented to the emergency room with fever (body temperature of 38°C), chills, liquid stool without pathological products, and skin dehydration. Oxygen saturation (SpO2) was 92%, which later improved to 97%. The patient was diagnosed with a serious event of Grade 3 COVID-19 pneumonia (bilateral pneumonia due to COVID-19) and was hospitalized. A polymerase chain reaction test was positive for severe acute respiratory syndrome coronavirus 2. The patient's SpO2 ranged from 95% to 96% following administration of oxygen 2 L/minute via nasal cannula. A thoracic X-ray showed pulmonary parenchyma with patchy and poorly defined increases in density, bilateral and peripheral distribution. An abdominal X-ray was also performed (results not reported). A blood culture was positive for an unknown species and was negative for *Staphylococcus plasmocoagulase*. A stool culture was negative for *Clostridium difficile*, salmonella, shigella, yersinia, campylobacter, and aeromonas. A urine ionogram results included urea/creatinine 7.89 mg/mg, sodium/creatinine 1.8 mol/mol, and potassium/creatinine

3.6 mol/mol (normal ranges not reported). Treatment for the event included azithromycin

(500 mg QD), ceftriaxone (1 g QD), hydroxychloroquine (400 mg BID), lopinavir (400 mg QD), and ritonavir (100 mg QD).

On study day 22, the patient's renal function impairment persisted with blood creatinine value of

2.9 mg/dL (normal range not reported).

On study day 25, the patient died due to the adverse event of Grade 5 COVID-19 pneumonia (bilateral pneumonia due to COVID-19). An autopsy was not performed, and discharge summary was not provided.

Action taken with study drug as a result of the event of COVID-19 pneumonia was dose not changed.

The investigator assessed the event of COVID-19 pneumonia as Grade 5 (initially Grade 3), serious, and not related to study drug. The event was not immune-related but due to an infection. There were no other suspected causes.

The sponsor agrees with the investigator's assessment. Risk factors included the history of cancer, advanced age, and obesity.

■ SERIOUS ADVERSE EVENTS/ADVERSE EVENT LEADING TO DEATH

AE MedDRA SOC / Preferred Term / Verbatim Term	Start / Stop Day of Event	Related to Study Drug / Study Procedure (Yes/No)	Serious AE (Yes/No)	AE Initial Grade / Most Extreme Grade	Action Taken with Study Drug / Outcome of AE	AE of Special Interest (Yes/No)	AE of Special Interest Criteria
Infections and infestations / Pneumonia / LEFT BASAL PNEUMONIA	24 / 36	N / N	Yes	3 / 3	Dose not changed/ Recovered/resolved	No	Not applicable
Infections and infestations / Pneumonia / BRONCHOASPIRATORY PNEUMONIA	106 / 108	N / N	Yes	3 / 5	Not applicable/ Fatal	No	Not applicable

■ NARRATIVE SUMMARY

An 83-year-old White, not Hispanic or Latino, male, was enrolled in the Phase 2 study R2810-ONC-1540 in patients with advanced cutaneous squamous cell carcinoma and experienced serious events of Grade 3 pneumonia (left basal pneumonia) and Grade 5 pneumonia (bronchoaspiratory pneumonia) [initially Grade 3].

Relevant medical history included diabetes mellitus type II, corneal ulcer, albumin decrease, choking sensation, gastroesophagic reflux, and magnesium decrease.

Medications ongoing on study day 1 included the following: omeprazole, insulin glargine, dapagliflozin propanediol monohydrate, tapentadol hydrochloride, dexketoprofen trometamol, trazodone hydrochloride, and moxifloxacin hydrochloride.

Advanced cutaneous squamous cell carcinoma was diagnosed on 30 May 2018. Stage at screening was Stage IV. Metastasis was detected on 05 Jul 2020. At the time of enrollment, the patient had a target lesion in the left laterocervical mass and a non-target lesion in the left bone.

Previous cancer treatments included 5510 cGy radiation therapy to the cervical lymph node alone and 6380 cGy radiation therapy to the left retroauricular region alone (from study day -226 to study day -178) and 1200 cGy radiation therapy to the cervical lymph node alone and 3000 cGy radiation therapy to the left retroauricular region alone (from study day -61 to study day -43).

Previous procedures included retroauricular lesion resection (study day -778) and retroauricular relapse resection (study day -301).

The patient was enrolled in the Group 6 cohort and was assigned to receive cemiplimab 350 mg IV administered over 30 minutes (±10 minutes) every 21 days for up to 108 weeks. The patient received the first dose of cemiplimab on study day 1 and the final dose on study day 85 for a total of 5 doses.

Other TEAEs complicating the patient's course included post procedural infection, dyspnoea, mucosal inflammation, and blood phosphorus decreased.

SERIOUS ADVERSE EVENT: PNEUMONIA

On study day 24, 1 day after the second dose of the study drug, the patient went to the emergency room (ER) due to dyspnea and total impossibility of ingestion. The patient was hospitalized due to a serious event of Grade 3 pneumonia (left basal pneumonia), which was confirmed by a chest X-ray. On the same day, the patient underwent a percutaneous endoscopic gastrostomy (PEG) tube placement for the underlying cancer. Treatment for the event of

pneumonia included ceftriaxone (2 g QD), clindamycin (600 mg Q8H), and amoxicillin/clavulanic acid (875/125 mg QD).

On study day 34, the patient developed a non-serious event of Grade 2 post procedural infection (percutaneous endoscopic gastrostomy infection) at the site of the PEG tube. Treatment for the event of post procedural infection included amoxicillin/clavulanic acid.

On study day 35, a port-a-cath was placed for the patient's underlying cancer.

On study day 36, the event of pneumonia was considered recovered/resolved. On the same day, the patient had a good clinical progress and was discharged from the hospital.

On study day 41, the event of post procedural infection was considered recovered/resolved.

Action taken with study drug as a result of the event of pneumonia was dose not changed.

The investigator assessed the event of pneumonia as Grade 3, serious, and not related to study drug. The event was not suspected to be immune-related but due to an infection. Other suspected cause included tumoral obstruction.

The sponsor agreed with the investigator's assessment.

SERIOUS ADVERSE EVENT/ADVERSE EVENT LEADING TO DEATH:PNEUMONIA

On study day -13, laboratory test result at screening included phosphate 3.3 mg/dL (normal range: 2.7 to 4.5 mg/dL).

On study day 62, the patient experienced a non-serious event of Grade 1 dyspnoea (dyspnea). Treatment for the event of dyspnoea included amoxicillin/clavulanic acid.

On study day 63, the event of dyspnoea was considered recovered/resolved.

On study day 106, 21 days after the fifth dose of the study drug, the patient went to a scheduled oncology visit, and a physical examination showed clinically significant abnormality of the lungs. The patient was then referred to the ER and was diagnosed with a serious event of Grade 3pneumonia (bronchoaspiratory pneumonia). On the same day, a non-serious event of Grade 1 blood phosphorus decreased (phosphorus decreased) was noted. The patient had an Eastern Cooperative Oncology Group performance status of 2 to 3, worsening of respiratory problems, and cough. Vital signs included blood pressure 80/52 mmHg, heart rate 104 beats per minute, respiratory rate 16 breaths per minute, and body temperature 36.1°C. A chest X-ray showed no parenchymal infiltrates and no pleural effusion. A polymerase chain reaction test for COVID-19 was negative, which also confirmed the diagnosis of pneumonia. Laboratory test results showed low phosphate 2.2 mg/dL, albumin 2.28 g/dL (normal range: 3.50 to 5.00 g/dL), magnesium

1.36 mg/dL (normal range: 1.40 to 2.40 mg/dL), and lymphocyte count 0.68 × 10^9/L (normal range: 1.00 to 4.50 × 10^9/L) and elevated urea 72 mg/dL (normal range: 15 to 45 mg/dL).

Treatment for the event of pneumonia included piperacillin/tazobactam (4/0.5 g Q6H). No treatment was reported for the event of blood phosphorus decreased. The patient's condition didnot improve with rapid clinical deterioration.

On study day 108, the patient died due to the adverse event of Grade 5 pneumonia bronchoaspiratory pneumonia). An autopsy was not performed.

At the time of the patient's death, the event of blood phosphorus decreased was considered not recovered/not resolved.

Action taken with study drug as a result of the event of pneumonia was not applicable.

The investigator assessed the event of pneumonia as Grade 5 [initially Grade 3], serious, and not related to study drug. The patient's death was due to bronchoaspiratory pneumonia, which was not suspected to be an immune-related event. There were no other suspected causes.

The sponsor assessed the event of fatal aspiration pneumonia on study day 108 as not related to study drug. The patient had prior hospitalization for pneumonia (study day 24) in which PEG tube was placed due to inability to tolerate oral intake. This clinical situation is a well establishedclinical risk factor for subsequent aspiration pneumonia, which caused death on study day 108.

■ SERIOUS ADVERSE EVENT/ ADVERSE EVENT LEADING TO DEATH

AE MedDRA SOC / Preferred Term / Verbatim Term	Start / Stop Day of Event	Related to Study Drug / Study Procedure (Yes/No)	Serious AE (Yes/No)	AE Initial Grade / Most Extreme Grade	Action Taken with Study Drug / Outcome of AE	AE of Special Interest (Yes/No)	AE of Special Interest Criteria
General disorders and administration site conditions / Sudden death / SUDDEN DEATH	139 / 139	N / N	Yes	5 / 5	Not applicable / Fatal	No	Not applicable

■ NARRATIVE SUMMARY

An 88-year-old White, not Hispanic or Latino, male, was enrolled in the Phase 2 study R2810-ONC-1540 in patients with advanced cutaneous squamous cell carcinoma and experienced a serious event of Grade 5 sudden death (sudden death).

Relevant medical history included arterial hypertension, diuresis, hypocalcemia, hypothyroidism, insomnia, and ulcer malignant tumor right ear (confirmed focus of cutaneous squamous cell carcinoma).

Medications ongoing on study day 1 included the following: aliskiren, diazepam, furosemide, lercanidipine, tramadol, venlafaxine, levothyroxine, imiquimod, and ferrous sulfate.

Advanced cutaneous squamous cell carcinoma was diagnosed on 12 Jun 2009. Stage at screening was Stage III. Metastasis was detected on an unknown date. At the time of enrollment, the patient had a left retroauricular target lesion (110 X 80mm) and non-target lesions in regional lymph nodes.

No previous cancer treatments were reported.

Previous procedures included left auricular pavilion lesion exeresis of the head and neck (study day -4060) and Mohs surgery of the head and neck (study day -164).

The patient was enrolled in the Group 6 cohort and was assigned to receive cemiplimab 350 mg IV administered over 30 minutes (±10 minutes) every 21 days for up to 108 weeks. The patient received the first dose of cemiplimab on study day 1 and the final dose on study day 109 for a total of 6 doses.

No other AEs complicating the patient's course were reported during the study.

SERIOUS ADVERSE EVENT/ ADVERSE EVENT LEADING TO DEATH: SUDDEN DEATH

On study day 126, the patient's Response Evaluation Criteria in Solid Tumors showed progressive disease per investigator assessment.

On study day 139, 30 days after the sixth dose of the study drug, the patient experienced a serious event of Grade 5 sudden death (sudden death). No treatment was reported. The patient died at home and was visited by a primary care staff from a different sanitary department. No autopsy was performed, and the death certificate supported cause of death as due to old age. No other possible reasons for the event of sudden death were reported. The patient had not experienced any adverse events related to cemiplimab prior to his death.

Action taken with study drug as a result of the event of sudden death was not applicable.

Per the study site: The death certificate supports the cause of 'elderly subject' for this SAE and no other possible reasons for the sudden death are reported.

The investigator assessed the event of sudden death as Grade 5, serious, and not related to study drug. Other suspected causes included disease under study, concurrent illness, and old age.

The sponsor assessed the event of sudden death as not related to study drug. Limited information on the circumstances surrounding the event was provided, but the event was presented 1 month after the administration of the last dose. The sponsor concurs with the investigator's assessment that there is no evidence that sudden death was related to study drug in this 88 year-old patient with progressive advanced CSCC and no prior cemiplimab toxicity.

Assessment of the MAH's response

The MAH has provided brief case narratives for the 9 patients. These have been carefully reviewed and the MAH's position is endorsed. There seems to be no relationship between these TEAEs leading to death and the use of cemiplimab.

Conclusion

Issue resolved.

Question 2

Overall, there seems to be no clinically meaningful differences between Groups 1-3 and Group 6. However, the MAH is asked to provide a tabulated overview of laboratory values for Group 1-3 and Group 6 side by side, and discuss any relevant difference.

MAH's response

The Applicant has provided the requested tables in Table 1 (hematology), Table 2 (electrolytes), Table 3 (liver function), and Table 4 (chemistry; other). Clinically relevant laboratory abnormalities were captured in the proposed ADR table in the SmPC. While there appear to be heterogeneity within expected variability between the groups, excluding laboratory abnormalities associated with identified immune-mediated adverse events (imAEs), there are no clinically relevant differences in laboratory values for Groups 1 to 3 and Group 6.

Table 1: Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade for Hematology (Groups 1, 2, 3 and 6) – Safety Analysis Set

	mCSCC Cemiplimab: 3 mg/kg Q2W Group 1[1] (N=59)		laCSCC Cemiplimab: 3 mg/kg Q2W Group 2[1] (N=78)		mCSCC Cemiplimab: 350 mg Q3W Group 3[1] (N=56)		Advanced CSCC Cemiplimab: 350 mg Q3W Group 6[2] (N=82)	
Parameter (CTCAE Term)	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Number of patients with at least one lab abnormality, n (%)	47/59 (79.7%)	8/59 (13.6%)	58/77 (75.3%)	6/77 (7.8%)	35/54 (64.8%)	10/54 (18.5%)	43/75 (57.3%)	4/75 (5.3%)
Hemoglobin (Anemia)	30/59 (50.8%)	3/59 (5.1%)	35/77 (45.5%)	3/77 (3.9%)	17/54 (31.5%)	4/54 (7.4%)	24/75 (32.0%)	2/75 (2.7%)
Hemoglobin (Hemoglobin increased)	2/59 (3.4%)	0/59	5/77 (6.5%)	0/77	0/54	0/54	1/75 (1.3%)	0/75
Leukocytes (White blood cell decreased)	9/59 (15.3%)	0/59	10/77 (13.0%)	1/77 (1.3%)	8/54 (14.8%)	0/54	7/75 (9.3%)	0/75
Lymphocytes (Lymphocyte count decreased)	32/59 (54.2%)	7/59 (11.9%)	31/77 (40.3%)	4/77 (5.2%)	19/54 (35.2%)	8/54 (14.8%)	20/75 (26.7%)	1/75 (1.3%)
Lymphocytes (Lymphocyte count increased)	0/59	0/59	2/77 (2.6%)	0/77	1/54 (1.9%)	0/54	2/75 (2.7%)	0/75
Neutrophils (Neutrophil count decreased)	4/59 (6.8%)	0/59	7/77 (9.1%)	1/77 (1.3%)	2/53 (3.8%)	0/53	3/75 (4.0%)	1/75 (1.3%)
Platelets (Platelet count decreased)	6/59 (10.2%)	0/59	12/77 (15.6%)	1/77 (1.3%)	12/54 (22.2%)	0/54	5/75 (6.7%)	0/75

[1]For Groups 1 to 3: Data cutoff as of 11 Oct 2020.
[2]For Group 6: Data cutoff as of 19 Apr 2021. Only patients who started treatment on or prior to 09 Oct 2020 are included.
CSCC, Cutaneous squamous cell carcinoma; CTCAE, Common Terminology Criteria for Adverse Events; laCSCC, Locally advanced cutaneous squamous cell carcinoma; mCSCC, Metastatic cutaneous squamous cell carcinoma; NCI CTCAE, National Cancer Institute - Common Terminology Criteria for Adverse Events; Q2W, Every 2 weeks; Q4W, Every 4 weeks.
NCI grades were coded using CTCAE Version 4.03.
Percentages are based on the number of patients with at least one post-baseline value available for that parameter.
Post-baseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.
Source: Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.1.1 and Table 14.3.3.1.1.g6

Table 2: Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade for Electrolytes (Groups 1, 2, 3 and 6) – Safety Analysis Set

	mCSCC Cemiplimab:3 mg/kg Q2W; Group 1[1] (N=59)		laCSCC Cemiplimab:3 mg/kg Q2W; Group 2[1] (N=78)		mCSCC Cemiplimab:350 mg Q3W; Group 3[1] (N=56)		Advanced CSCC Cemiplimab:350 mg Q3W; Group 6[2] (N=82)	
Parameter (CTCAE Term)	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Number of patients with at least one lab abnormality, n (%)	43/59 (72.9%)	10/59 (16.9%)	64/77 (83.1%)	9/77 (11.7%)	33/54 (61.1%)	7/54 (13.0%)	51/75 (68.0%)	8/75 (10.7%)
Calcium (Hypercalcemia (Uncorrected Calcium))	9/59 (15.3%)	2/59 (3.4%)	7/77 (9.1%)	0/77	7/54 (13.0%)	2/54 (3.7%)	6/75 (8.0%)	1/75 (1.3%)
Calcium (Hypocalcemia (Uncorrected Calcium))	14/59 (23.7%)	0/59	19/77 (24.7%)	0/77	9/54 (16.7%)	0/54	20/75 (26.7%)	2/75 (2.7%)
Magnesium (Hypermagnesemia)	3/59 (5.1%)	0/59	5/77 (6.5%)	0/77	2/54 (3.7%)	0/54	4/75 (5.3%)	0/75
Magnesium (Hypomagnesemia)	8/59 (13.6%)	0/59	13/77 (16.9%)	0/77	3/54 (5.6%)	0/54	15/75 (20.0%)	1/75 (1.3%)
Phosphate (Hypophosphatemia)	21/58 (36.2%)	6/58 (10.3%)	22/77 (28.6%)	3/77 (3.9%)	7/54 (13.0%)	1/54 (1.9%)	15/75 (20.0%)	2/75 (2.7%)
Potassium (Hyperkalemia)	12/59 (20.3%)	0/59	24/77 (31.2%)	0/77	3/54 (5.6%)	1/54 (1.9%)	12/75 (16.0%)	0/75
Potassium (Hypokalemia)	10/59 (16.9%)	1/59 (1.7%)	18/77 (23.4%)	2/77 (2.6%)	5/54 (9.3%)	1/54 (1.9%)	4/75 (5.3%)	1/75 (1.3%)
Sodium (Hypernatremia)	2/59 (3.4%)	0/59	3/77 (3.9%)	0/77	2/54 (3.7%)	0/54	2/75 (2.7%)	0/75
Sodium (Hyponatremia)	14/59 (23.7%)	3/59 (5.1%)	24/77 (31.2%)	5/77 (6.5%)	12/54 (22.2%)	2/54 (3.7%)	17/75 (22.7%)	3/75 (4.0%)

[1]For Groups 1 to 3: Data cutoff as of 11 Oct 2020.
[2]For Group 6: Data cutoff as of 19 Apr 2021. Only patients who started treatment on or prior to 09 Oct 2020 are included.
CSCC, Cutaneous squamous cell carcinoma; CTCAE, Common Terminology Criteria for Adverse Events; laCSCC, Locally advanced cutaneous squamous cell carcinoma; mCSCC, Metastatic cutaneous squamous cell carcinoma; NCI CTCAE, National Cancer Institute - Common Terminology Criteria for Adverse Events; Q2W, Every 2 weeks; Q3W, Every 3 weeks.
NCI grades were coded using CTCAE Version 4.03.
Percentages are based on the number of patients with at least one post-baseline value available for that parameter.
Post-baseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.
Source: Study 1540 Group 6 Interim CSR Post-text Table 14.3.3.2.1 and 14.3.3.2.1.g6

Table 3: Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade for Liver Function (Groups 1, 2, 3 and 6) – Safety Analysis Set

	mCSCC Cemiplimab:3 mg/kg Q2W ; Group 1[1] (N=59);		laCSCC Cemiplimab:3 mg/kg Q2W, Group 2[1] (N=78);		mCSCC Cemiplimab:350 mg Q3W, Group 3[1] (N=56);		Advanced CSCC Cemiplimab:350 mg Q3W, Group 6[2] (N=82)	
Parameter (CTCAE Term)	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Number of patients with at least one lab abnormality, n (%)	40/59 (67.8%)	1/59 (1.7%)	46/77 (59.7%)	3/77 (3.9%)	33/54 (61.1%)	1/54 (1.9%)	51/75 (68.0%)	1/75 (1.3%)
Alanine Aminotransferase (Alanine aminotransferase increased)	11/59 (18.6%)	0/59	19/77 (24.7%)	1/77 (1.3%)	10/54 (18.5%)	0/54	16/75 (21.3%)	0/75
Albumin (Hypoalbuminemia)	24/59 (40.7%)	1/59 (1.7%)	21/77 (27.3%)	0/77	19/54 (35.2%)	0/54	27/75 (36.0%)	1/75 (1.3%)
Alkaline Phosphatase (Alkaline phosphatase increased)	14/59 (23.7%)	0/59	16/77 (20.8%)	1/77 (1.3%)	8/54 (14.8%)	0/54	19/75 (25.3%)	0/75
Aspartate Aminotransferase (Aspartate aminotransferase increased)	11/58 (19.0%)	0/58	20/77 (26.0%)	3/77 (3.9%)	15/54 (27.8%)	1/54 (1.9%)	12/75 (16.0%)	0/75
Bilirubin (Blood bilirubin increased)	6/59 (10.2%)	0/59	12/77 (15.6%)	0/77	5/54 (9.3%)	0/54	10/74 (13.5%)	0/74

[1]For Groups 1 to 3: Data cutoff as of 11 Oct 2020.
[2]For Group 6: Data cutoff as of 19 Apr 2021. Only patients who started treatment on or prior to 09 Oct 2020 are included.
CSCC, Cutaneous squamous cell carcinoma; CTCAE, Common Terminology Criteria for Adverse Events; laCSCC, Locally advanced cutaneous squamous cell carcinoma; mCSCC, Metastatic cutaneous squamous cell carcinoma; NCI CTCAE, National Cancer Institute - Common Terminology Criteria for Adverse Events; Q2W, Every 2 weeks; Q3W, Every 3 weeks.
NCI grades were coded using CTCAE Version 4.03.
Percentages are based on the number of patients with at least one post-baseline value available for that parameter.
Post-baseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.
Source: Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.3.1 and 14.3.3.3.1.g6

Table 4: Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade for Chemistry (Other) Groups 1, 2, 3, and 6 (Safety Analysis Set)

	mCSCC Cemiplimab:3 mg/kg Q2W; Group 1[1] (N=59)		laCSCC Cemiplimab:3 mg/kg Q2W; Group 2[1] (N=78)		mCSCC Cemiplimab:350 mg Q3W; Group 3[1] (N=56)		Advanced CSCC Cemiplimab:350 mg Q3W; Group 6[2] (N=82)	
Parameter (CTCAE Term)	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Number of patients with at least one lab abnormality, n (%)	44/59 (74.6%)	1/59 (1.7%)	64/77 (83.1%)	0/77	44/54 (81.5%)	0/54	55/75 (73.3%)	0/75
Creatinine (Creatinine increased)	44/59 (74.6%)	1/59 (1.7%)	63/77 (81.8%)	0/77	43/54 (79.6%)	0/54	53/75 (70.7%)	0/75
Glucose (Hypoglycemia)	7/58 (12.1%)	0/58	6/77 (7.8%)	0/77	8/54 (14.8%)	0/54	4/75 (5.3%)	0/75

[1]For Groups 1 to 3: Data cutoff as of 11 Oct 2020.
[2]For Group 6: Data cutoff as of 19 Apr 2021. Only patients who started treatment on or prior to 09 Oct 2020 are included.
CSCC, Cutaneous squamous cell carcinoma; CTCAE, Common Terminology Criteria for Adverse Events; laCSCC, Locally advanced cutaneous squamous cell carcinoma; mCSCC, Metastatic cutaneous squamous cell carcinoma; NCI CTCAE, National Cancer Institute - Common Terminology Criteria for Adverse Events; Q2W, Every 2 weeks; Q3W, Every 3 weeks.
NCI grades were coded using CTCAE Version 4.03.
Percentages are based on the number of patients with at least one post-baseline value available for that parameter.
Post-baseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.
Source: Study 1540 Interim Group 6 CSR Post-text Table 14.3.3.4.1 and 14.3.3.4.1.g6

Assessment of the MAH's response

The MAH has provided the requested tables. Despite small differences, none are considered clinically meaningful. It seems to be confirmed that no clinically meaningful differences between Groups 1-3 and Group 6 exist.

Conclusion

Issue resolved.

Question 3

As expected TEAEs are observed more frequently with higher age due to comorbidities. According to the MAH there continues to be no clinically relevant differences in terms of race and sex. Nonetheless, the MAH is asked to provide a tabulated overview with regards to sex and race, and discuss the differences. Also, the MAH is asked to provide updated safety with regards to patients with hepatic and renal impairment.

MAH's response

The Applicant has provided tabulated overviews for Pool 1 (all CSCC patients) and Pool 2 (all cemiplimab monotherapy patients) based on:

Group	Reference Table
Sex	Table 1 (male), Table 2 (female)
Race	Table 3 (white), Table 4 (other), and Table 5 (missing)
Renal Impairment	Table 6 (normal), Table 7 (mild), Table 8 (moderate), Table 9 (severe), Table 10 (under dialysis), and Table 11 (missing)
Hepatic Impairment	Table 12 (normal), Table 13 (mild), Table 14 (moderate), and Table 15 (missing)

Sex

There were minor numerical differences between gender groups (males compared to females) for both the CSCC population and Pool 2, which were not clinically relevant. For the CSCC patients the comparisons are summarised below.

- Number of patients with any TEAE (99.6% vs. 98.0%)
- Number of patients with any TEAE ≥ grade 3 (46.9% vs. 42.9%)
- Number of patients with any serious TEAE (38.5% vs. 42.9%)
- Number of patients who discontinued treatment due to TEAE (11.1% vs. 14.3%)
- Number of patients with any TEAE leading to drug interruption/delay (35.0% vs. 42.9%)
- Number of patients with any TEAE leading to death (5.3% vs. 4.1%)

Table 1: Summary of Treatment-Emergent Adverse Events by Sex (Safety Analysis Set)

Sex: Male

	Pool 1 All CSCC Patients (N=226)	Pool 2 All Monotherapy Patients (N=721)
Number of TEAEs	2331	5724
Number of NCI grade 3/4/5 TEAEs	250	653
Number of serious TEAEs	152	395
Number of Patients with any TEAE, n (%)	225 (99.6%)	679 (94.2%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	106 (46.9%)	308 (42.7%)
Number of Patients with any serious TEAE, n (%)	87 (38.5%)	234 (32.5%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	25 (11.1%)	64 (8.9%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	79 (35.0%)	224 (31.1%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	3 (1.3%)	6 (0.8%)
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	1 (0.4%)	4 (0.6%)
Number of Patients with any TEAE resulting in death, n (%)	12 (5.3%)	51 (7.1%)

Source: Table 14.3.1.2.1.s2

Data cut-off as of Oct 11, 2020 for Study 1540 Groups 1-3; Data cut-off as of Apr 19, 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to Oct 9, 2020 are included; Data cut-off as of Jan 4, 2021 for Study 1676; Data cut-off as of Jun 30, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624; Data cut-off as of Apr 30, 2019 for Study 1423;
TEAE: Treatment-emergent adverse event.
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.

Table 2: Summary of Treatment-Emergent Adverse Events by Sex (Safety Analysis Set)

Sex: Female

	Pool 1 All CSCC Patients (N=49)	Pool 2 All Monotherapy Patients (N=477)
Number of TEAEs	544	3667
Number of NCI grade 3/4/5 TEAEs	64	475
Number of serious TEAEs	50	256
Number of Patients with any TEAE, n (%)	48 (98.0%)	433 (90.8%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	21 (42.9%)	205 (43.0%)
Number of Patients with any serious TEAE, n (%)	21 (42.9%)	140 (29.4%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	7 (14.3%)	45 (9.4%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	21 (42.9%)	139 (29.1%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	1 (2.0%)	1 (0.2%)
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	1 (2.0%)	1 (0.2%)
Number of Patients with any TEAE resulting in death, n (%)	2 (4.1%)	12 (2.5%)

Source: Table 14.3.1.2.1.s2

Data cut-off as of Oct 11, 2020 for Study 1540 Groups 1-3; Data cut-off as of Apr 19, 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to Oct 9, 2020 are included; Data cut-off as of Jan 4, 2021 for Study 1676; Data cut-off as of Jun 30, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624; Data cut-off as of Apr 30, 2019 for Study 1423;
TEAE: Treatment-emergent adverse event.
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.

Race

Due to the nature of the underlying disease, CSCC, the vast majority (267/269) of patients in Pool 1 were white, with only 5 patients with "Other" race, and one patient with "Missing" race. The small number of patients with "Other" or "Missing" race limits the ability to make comparisons between groups. Most patients in Pool 2 were also white (n=982), with fewer patients in "Other" (n=168) and "Missing" (n=48) race. Overall, there were no relevant differences in the safety profile based on race.

Table 3: Summary of Treatment Emergent Adverse Events by Race (Safety Analysis Set)

Race: White

	Pool 1 All CSCC Patients (N=269)	Pool 2 All Monotherapy Patients (N=982)
Number of TEAEs	2811	7626
Number of NCI grade 3/4/5 TEAEs	302	853
Number of serious TEAEs	197	515
Number of Patients with any TEAE, n (%)	267 (99.3%)	914 (93.1%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	123 (45.7%)	408 (41.5%)
Number of Patients with any serious TEAE, n (%)	105 (39.0%)	299 (30.4%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	31 (11.5%)	87 (8.9%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	98 (36.4%)	299 (30.4%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	3 (1.1%)	6 (0.6%)
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	2 (0.7%)	5 (0.5%)
Number of Patients with any TEAE resulting in death, n (%)	14 (5.2%)	54 (5.5%)

Source: Table 14.3.1.2.1.s4

Data cut-off as of Oct 11, 2020 for Study 1540 Groups 1-3; Data cut-off as of Apr 19, 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to Oct 9, 2020 are included; Data cut-off as of Jan 4, 2021 for Study 1676; Data cut-off as of Jun 30, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624; Data cut-off as of Apr 30, 2019 for Study 1423;
TEAE: Treatment-emergent adverse event.
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.

Table 4: Summary of Treatment-Emergent Adverse Events by Race (Safety Analysis Set)

Race: Other

	Pool 1 All CSCC Patients (N=5)	Pool 2 All Monotherapy Patients (N=168)
Number of TEAEs	60	1199
Number of NCI grade 3/4/5 TEAEs	11	209
Number of serious TEAEs	4	104
Number of Patients with any TEAE, n (%)	5 (100%)	151 (89.9%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	3 (60.0%)	80 (47.6%)
Number of Patients with any serious TEAE, n (%)	2 (40.0%)	59 (35.1%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	1 (20.0%)	14 (8.3%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	2 (40.0%)	45 (26.8%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	1 (20.0%)	1 (0.6%)
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	0	0
Number of Patients with any TEAE resulting in death, n (%)	0	5 (3.0%)

Source: Table 14.3.1.2.1.s4

Data cut-off as of Oct 11, 2020 for Study 1540 Groups 1-3; Data cut-off as of Apr 19, 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to Oct 9, 2020 are included; Data cut-off as of Jan 4, 2021 for Study 1676; Data cut-off as of Jun 30, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624; Data cut-off as of Apr 30, 2019 for Study 1423;
TEAE: Treatment-emergent adverse event.
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.

Table 5: Summary of Treatment-Emergent Adverse Events by Race (Safety Analysis Set)

Race: Missing

	Pool 1 All CSCC Patients (N=1)	Pool 2 All Monotherapy Patients (N=48)
Number of TEAEs	4	566
Number of NCI grade 3/4/5 TEAEs	1	66
Number of serious TEAEs	1	32
Number of Patients with any TEAE, n (%)	1 (100%)	47 (97.9%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	1 (100%)	25 (52.1%)
Number of Patients with any serious TEAE, n (%)	1 (100%)	16 (33.3%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	0	8 (16.7%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	0	19 (39.6%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	0	0
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	0	0
Number of Patients with any TEAE resulting in death, n (%)	0	4 (8.3%)

Source: Table 14.3.1.2.1.s4

Data cut-off as of Oct 11, 2020 for Study 1540 Groups 1-3; Data cut-off as of Apr 19, 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to Oct 9, 2020 are included; Data cut-off as of Jan 4, 2021 for Study 1676; Data cut-off as of Jun 30, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624; Data cut-off as of Apr 30, 2019 for Study 1423;
TEAE: Treatment-emergent adverse event.
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.

Renal and Hepatic Impairment

In general, there was a slight trend towards a higher proportion of patients with any TEAE across all categories of organ function, including normal organ function, in Pool 1 compared with Pool 2, which likely reflects the higher median age and associated burden of comorbidities of patients in Pool 1 (all CSCC patients) compared with Pool 2 (all cemiplimab monotherapy patients). The trend is not considered to be clinically relevant. There was no relevant difference in the type of TEAEs observed based on severity of organ impairment.

Table 6: Summary of Treatment-Emergent Adverse Events by Renal Impairment (Safety Analysis Set)

Renal Impairment: Normal

	Pool 1 All CSCC Patients (N=92)	Pool 2 All Monotherapy Patients (N=467)
Number of TEAEs	987	3779
Number of NCI grade 3/4/5 TEAEs	101	418
Number of serious TEAEs	56	238
Number of Patients with any TEAE, n (%)	91 (98.9%)	436 (93.4%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	39 (42.4%)	192 (41.1%)
Number of Patients with any serious TEAE, n (%)	31 (33.7%)	138 (29.6%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	12 (13.0%)	40 (8.6%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	34 (37.0%)	132 (28.3%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	1 (1.1%)	3 (0.6%)
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	1 (1.1%)	3 (0.6%)
Number of Patients with any TEAE resulting in death, n (%)	5 (5.4%)	28 (6.0%)

Source: Table 14.3.1.2.1.s11

Data cut-off as of Oct 11, 2020 for Study 1540 Groups 1-3; Data cut-off as of Apr 19, 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to Oct 9, 2020 are included; Data cut-off as of Jan 4, 2021 for Study 1676; Data cut-off as of Jun 30, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624; Data cut-off as of Apr 30, 2019 for Study 1423;
TEAE: Treatment-emergent adverse event.
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.

Table 7: Summary of Treatment-Emergent Adverse Events by Renal Impairment (Safety Analysis Set)

Renal Impairment: Mild

	Pool 1 All CSCC Patients (N=108)	Pool 2 All Monotherapy Patients (N=462)
Number of TEAEs	1150	3503
Number of NCI grade 3/4/5 TEAEs	117	404
Number of serious TEAEs	59	227
Number of Patients with any TEAE, n (%)	107 (99.1%)	424 (91.8%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	50 (46.3%)	189 (40.9%)
Number of Patients with any serious TEAE, n (%)	36 (33.3%)	131 (28.4%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	11 (10.2%)	40 (8.7%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	35 (32.4%)	135 (29.2%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	2 (1.9%)	2 (0.4%)
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	1 (0.9%)	1 (0.2%)
Number of Patients with any TEAE resulting in death, n (%)	3 (2.8%)	20 (4.3%)

Source: Table 14.3.1.2.1.s11

Data cut-off as of Oct 11, 2020 for Study 1540 Groups 1-3; Data cut-off as of Apr 19, 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to Oct 9, 2020 are included; Data cut-off as of Jan 4, 2021 for Study 1676; Data cut-off as of Jun 30, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624; Data cut-off as of Apr 30, 2019 for Study 1423;
TEAE: Treatment-emergent adverse event.
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.

Table 8: Summary of Treatment-Emergent Adverse Events by Renal Impairment (Safety Analysis Set)

Renal Impairment: Moderate

	Pool 1 All CSCC Patients (N=65)	Pool 2 All Monotherapy Patients (N=246)
Number of TEAEs	634	1921
Number of NCI grade 3/4/5 TEAEs	73	268
Number of serious TEAEs	67	164
Number of Patients with any TEAE, n (%)	65 (100%)	229 (93.1%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	32 (49.2%)	119 (48.4%)
Number of Patients with any serious TEAE, n (%)	36 (55.4%)	98 (39.8%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	8 (12.3%)	27 (11.0%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	26 (40.0%)	88 (35.8%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	1 (1.5%)	2 (0.8%)
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	0	1 (0.4%)
Number of Patients with any TEAE resulting in death, n (%)	6 (9.2%)	15 (6.1%)

Source: Table 14.3.1.2.1.s11

Data cut-off as of Oct 11, 2020 for Study 1540 Groups 1-3; Data cut-off as of Apr 19, 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to Oct 9, 2020 are included; Data cut-off as of Jan 4, 2021 for Study 1676; Data cut-off as of Jun 30, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624; Data cut-off as of Apr 30, 2019 for Study 1423;
TEAE: Treatment-emergent adverse event.
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.

Table 9: Summary of Treatment-Emergent Adverse Events by Renal Impairment (Safety Analysis Set)

Renal Impairment: Severe

	Pool 1 All CSCC Patients (N=5)	Pool 2 All Monotherapy Patients (N=8)
Number of TEAEs	52	60
Number of NCI grade 3/4/5 TEAEs	14	15
Number of serious TEAEs	15	15
Number of Patients with any TEAE, n (%)	5 (100%)	8 (100%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	3 (60.0%)	4 (50.0%)
Number of Patients with any serious TEAE, n (%)	3 (60.0%)	3 (37.5%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	1 (20.0%)	1 (12.5%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	3 (60.0%)	4 (50.0%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	0	0
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	0	0
Number of Patients with any TEAE resulting in death, n (%)	0	0

Source: Table 14.3.1.2.1.s11

Data cut-off as of Oct 11, 2020 for Study 1540 Groups 1-3; Data cut-off as of Apr 19, 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to Oct 9, 2020 are included; Data cut-off as of Jan 4, 2021 for Study 1676; Data cut-off as of Jun 30, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624; Data cut-off as of Apr 30, 2019 for Study 1423;
TEAE: Treatment-emergent adverse event.
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.

Table 10: Summary of Treatment-Emergent Adverse Events by Renal Impairment (Safety Analysis Set)

Renal Impairment: Under Dialysis

	Pool 1 All CSCC Patients (N=1)	Pool 2 All Monotherapy Patients (N=1)
Number of TEAEs	7	7
Number of NCI grade 3/4/5 TEAEs	1	1
Number of serious TEAEs	0	0
Number of Patients with any TEAE, n (%)	1 (100%)	1 (100%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	1 (100%)	1 (100%)
Number of Patients with any serious TEAE, n (%)	0	0
Number of Patients who discontinued study treatment due to TEAE, n (%)	0	0
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	0	0
Number of Patients with any TEAE leading to a dose reduction, n (%)	0	0
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	0	0
Number of Patients with any TEAE resulting in death, n (%)	0	0

Data Source: Table 14.3.1.2.1.s11

Data cut-off as of Oct 11, 2020 for Study 1540 Groups 1-3; Data cut-off as of Apr 19, 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to Oct 9, 2020 are included; Data cut-off as of Jan 4, 2021 for Study 1676; Data cut-off as of Jun 30, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624; Data cut-off as of Apr 30, 2019 for Study 1423;
TEAE: Treatment-emergent adverse event.
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.

Table 11: Summary of Treatment-Emergent Adverse Events by Renal Impairment (Safety Analysis Set)

Renal Impairment: Missing

	Pool 1 All CSCC Patients (N=4)	Pool 2 All Monotherapy Patients (N=14)
Number of TEAEs	45	121
Number of NCI grade 3/4/5 TEAEs	8	22
Number of serious TEAEs	5	7
Number of Patients with any TEAE, n (%)	4 (100%)	14 (100%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	2 (50.0%)	8 (57.1%)
Number of Patients with any serious TEAE, n (%)	2 (50.0%)	4 (28.6%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	0	1 (7.1%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	2 (50.0%)	4 (28.6%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	0	0
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	0	0
Number of Patients with any TEAE resulting in death, n (%)	0	0

Data Source: Table 14.3.1.2.1.s11

Data cut-off as of Oct 11, 2020 for Study 1540 Groups 1-3; Data cut-off as of Apr 19, 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to Oct 9, 2020 are included; Data cut-off as of Jan 4, 2021 for Study 1676; Data cut-off as of Jun 30, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624; Data cut-off as of Apr 30, 2019 for Study 1423;
TEAE: Treatment-emergent adverse event.
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.

Table 12: Summary of Treatment-Emergent Adverse Events by Hepatic Impairment (Safety Analysis Set)

Hepatic Impairment: Normal

	Pool 1 All CSCC Patients (N=268)	Pool 2 All Monotherapy Patients (N=1156)
Number of TEAEs	2818	9114
Number of NCI grade 3/4/5 TEAEs	305	1087
Number of serious TEAEs	197	633
Number of Patients with any TEAE, n (%)	266 (99.3%)	1074 (92.9%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	124 (46.3%)	495 (42.8%)
Number of Patients with any serious TEAE, n (%)	106 (39.6%)	364 (31.5%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	32 (11.9%)	105 (9.1%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	98 (36.6%)	348 (30.1%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	4 (1.5%)	7 (0.6%)
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	2 (0.7%)	5 (0.4%)
Number of Patients with any TEAE resulting in death, n (%)	14 (5.2%)	61 (5.3%)

Source: Table 14.3.1.2.1.s12

Data cut-off as of Oct 11, 2020 for Study 1540 Groups 1-3; Data cut-off as of Apr 19, 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to Oct 9, 2020 are included; Data cut-off as of Jan 4, 2021 for Study 1676; Data cut-off as of Jun 30, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624; Data cut-off as of Apr 30, 2019 for Study 1423;
TEAE: Treatment-emergent adverse event.
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.

Table 13: Summary of Treatment-Emergent Adverse Events by Hepatic Impairment (Safety Analysis Set)

Hepatic Impairment: Mild

	Pool 1 All CSCC Patients (N=2)	Pool 2 All Monotherapy Patients (N=25)
Number of TEAEs	5	144
Number of NCI grade 3/4/5 TEAEs	0	17
Number of serious TEAEs	0	10
Number of Patients with any TEAE, n (%)	2 (100%)	21 (84.0%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	0	8 (32.0%)
Number of Patients with any serious TEAE, n (%)	0	5 (20.0%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	0	1 (4.0%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	0	7 (28.0%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	0	0
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	0	0
Number of Patients with any TEAE resulting in death, n (%)	0	0

Source: Table 14.3.1.2.1.s12

Data cut-off as of Oct 11, 2020 for Study 1540 Groups 1-3; Data cut-off as of Apr 19, 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to Oct 9, 2020 are included; Data cut-off as of Jan 4, 2021 for Study 1676; Data cut-off as of Jun 30, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624; Data cut-off as of Apr 30, 2019 for Study 1423;
TEAE: Treatment-emergent adverse event.
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.

Table 14: Summary of Treatment-Emergent Adverse Events by Hepatic Impairment (Safety Analysis Set)

Hepatic Impairment: Moderate

	Pool 1 All CSCC Patients (N=1)	Pool 2 All Monotherapy Patients (N=5)
Number of TEAEs	7	38
Number of NCI grade 3/4/5 TEAEs	1	10
Number of serious TEAEs	0	2
Number of Patients with any TEAE, n (%)	1 (100%)	5 (100%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	1 (100%)	4 (80.0%)
Number of Patients with any serious TEAE, n (%)	0	2 (40.0%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	0	1 (20.0%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	0	4 (80.0%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	0	0
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	0	0
Number of Patients with any TEAE resulting in death, n (%)	0	2 (40.0%)

Source: Table 14.3.1.2.1.s12

Data cut-off as of Oct 11, 2020 for Study 1540 Groups 1-3; Data cut-off as of Apr 19, 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to Oct 9, 2020 are included; Data cut-off as of Jan 4, 2021 for Study 1676; Data cut-off as of Jun 30, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624; Data cut-off as of Apr 30, 2019 for Study 1423;
TEAE: Treatment-emergent adverse event.
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.

Table 15: Summary of Treatment-Emergent Adverse Events by Hepatic Impairment (Safety Analysis Set)

Hepatic Impairment: Missing

	Pool 1 All CSCC Patients (N=4)	Pool 2 All Monotherapy Patients (N=12)
Number of TEAEs	45	95
Number of NCI grade 3/4/5 TEAEs	8	14
Number of serious TEAEs	5	6
Number of Patients with any TEAE, n (%)	4 (100%)	12 (100%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	2 (50.0%)	6 (50.0%)
Number of Patients with any serious TEAE, n (%)	2 (50.0%)	3 (25.0%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	0	2 (16.7%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	2 (50.0%)	4 (33.3%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	0	0
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	0	0
Number of Patients with any TEAE resulting in death, n (%)	0	0

Source: Table 14.3.1.2.1.s12

Data cut-off as of Oct 11, 2020 for Study 1540 Groups 1-3; Data cut-off as of Apr 19, 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to Oct 9, 2020 are included; Data cut-off as of Jan 4, 2021 for Study 1676; Data cut-off as of Jun 30, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624; Data cut-off as of Apr 30, 2019 for Study 1423;
TEAE: Treatment-emergent adverse event.
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.

Assessment of the MAH's response

The MAH has provided the requested tables and a short discussion. There are no clinically meaningful difference between men and women. With regards to race, most patients are white, so no firm conclusions can the drawn. Concerning, renal and hepatic impairment, no new signal are observed.

Conclusion

Issue resolved.

Question 4

The MAH is asked to provide a tabulated overview of updated safety as function of region, prior systemic therapy and prior radiotherapy.

MAH's response

The Applicant has provided a tabulated overview in Table 5 (region), Table 6 (Prior systemic therapy), and Table 7 (Prior radiotherapy), respectively.

Table 5: Summary of Treatment-Emergent Adverse Events by Region (Safety Analysis Set)

	North America		Europe		ROW	
	Pool 1 All CSCC Patients (N=111)	Pool 2 All Monotherapy Patients (N=298)	Pool 1 All CSCC Patients (N=74)	Pool 2 All Monotherapy Patients (N=600)	Pool 1 All CSCC Patients (N=90)	Pool 2 All Monotherapy Patients (N=300)
Number of TEAEs	1349	3170	577	3755	949	2466
Number of NCI grade 3/4/5 TEAEs	165	321	70	477	79	330
Number of serious TEAEs	87	147	62	319	53	185
Number of Patients with any TEAE, n (%)	111 (100%)	289 (97.0%)	73 (98.6%)	540 (90.0%)	89 (98.9%)	283 (94.3%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	55 (49.5%)	132 (44.3%)	36 (48.6%)	247 (41.2%)	36 (40.0%)	134 (44.7%)
Number of Patients with any serious TEAE, n (%)	37 (33.3%)	79 (26.5%)	40 (54.1%)	192 (32.0%)	31 (34.4%)	103 (34.3%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	13 (11.7%)	30 (10.1%)	12 (16.2%)	53 (8.8%)	7 (7.8%)	26 (8.7%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	40 (36.0%)	95 (31.9%)	25 (33.8%)	182 (30.3%)	35 (38.9%)	86 (28.7%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	2 (1.8%)	4 (1.3%)	0	1 (0.2%)	2 (2.2%)	2 (0.7%)
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	1 (0.9%)	3 (1.0%)	0	1 (0.2%)	1 (1.1%)	1 (0.3%)

	North America		Europe		ROW	
	Pool 1 All CSCC Patients (N=111)	Pool 2 All Monotherapy Patients (N=298)	Pool 1 All CSCC Patients (N=74)	Pool 2 All Monotherapy Patients (N=600)	Pool 1 All CSCC Patients (N=90)	Pool 2 All Monotherapy Patients (N=300)
Number of Patients with any TEAE resulting in death, n (%)	5 (4.5%)	9 (3.0%)	8 (10.8%)	45 (7.5%)	1 (1.1%)	9 (3.0%)

Data cutoff as of 11 Oct 2020 for Study 1540 Groups 1 to 3; Data cutoff as of 19 Apr 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to 09 Oct 9, 2020 are included; Data cutoff as of 04 Jan 2021 for Study 1676; Data cutoff as of 30 Jun 2020 for Study 1620; Data cutoff as of 01 Mar 2020 for Study 1624; Data cutoff as of 30 Apr 2019 for Study 1423.

TEAE: Treatment-emergent adverse event.

NCI grades were coded using CTCAE Version 4.03.

A patient is counted only once for multiple occurrences within a category.

Source: ISS Table PTT 14.3.1.2.1.s5a

Table 6: Summary of Treatment-Emergent Adverse Events by Prior Systemic Therapy (Safety Analysis Set)

	Prior Systemic Therapy: Y		Prior Systemic Therapy: N	
	Pool 1 All CSCC Patients (N=66)	Pool 2 All Monotherapy Patients (N=634)	Pool 1 All CSCC Patients (N=209)	Pool 2 All Monotherapy Patients (N=564)
Number of TEAEs	655	5161	2220	4230
Number of NCI grade 3/4/5 TEAEs	54	610	260	518
Number of serious TEAEs	32	322	170	329
Number of Patients with any TEAE, n (%)	66 (100%)	592 (93.4%)	207 (99.0%)	520 (92.2%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	29 (43.9%)	280 (44.2%)	98 (46.9%)	233 (41.3%)
Number of Patients with any serious TEAE, n (%)	22 (33.3%)	188 (29.7%)	86 (41.1%)	186 (33.0%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	6 (9.1%)	60 (9.5%)	26 (12.4%)	49 (8.7%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	21 (31.8%)	184 (29.0%)	79 (37.8%)	179 (31.7%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	1 (1.5%)	4 (0.6%)	3 (1.4%)	3 (0.5%)
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	1 (1.5%)	4 (0.6%)	1 (0.5%)	1 (0.2%)

	Prior Systemic Therapy: Y		Prior Systemic Therapy: N	
	Pool 1 All CSCC Patients (N=66)	Pool 2 All Monotherapy Patients (N=634)	Pool 1 All CSCC Patients (N=209)	Pool 2 All Monotherapy Patients (N=564)
Number of Patients with any TEAE resulting in death, n (%)	2 (3.0%)	17 (2.7%)	12 (5.7%)	46 (8.2%)

Data cutoff as of 11 Oct 2020 for Study 1540 Groups 1 to 3; Data cutoff as of 19 Apr 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to 09 Oct 2020 are included; Data cutoff as of 04 Jan 2021 for Study 1676; Data cutoff as of 30 Jun 2020 for Study 1620; Data cutoff as of 01 Mar 2020 for Study 1624; Data cutoff as of 30 Apr 2019 for Study 1423.

TEAE: Treatment-emergent adverse event.

NCI grades were coded using CTCAE Version 4.03.

A patient is counted only once for multiple occurrences within a category.

Table 7: Summary of Treatment Emergent Adverse Events by Prior Radiotherapy (Safety Analysis Set)

	Prior Radiotherapy: Y		Prior Radiotherapy: N	
	Pool 1 All CSCC Patients (N=173)	Pool 2 All Monotherapy Patients (N=647)	Pool 1 All CSCC Patients (N=102)	Pool 2 All Monotherapy Patients (N=551)
Number of TEAEs	1727	5294	1148	4097
Number of NCI grade 3/4/5 TEAEs	191	647	123	481
Number of serious TEAEs	116	350	86	301
Number of Patients with any TEAE, n (%)	171 (98.8%)	606 (93.7%)	102 (100%)	506 (91.8%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	79 (45.7%)	289 (44.7%)	48 (47.1%)	224 (40.7%)
Number of Patients with any serious TEAE, n (%)	65 (37.6%)	202 (31.2%)	43 (42.2%)	172 (31.2%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	19 (11.0%)	71 (11.0%)	13 (12.7%)	38 (6.9%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	58 (33.5%)	194 (30.0%)	42 (41.2%)	169 (30.7%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	2 (1.2%)	3 (0.5%)	2 (2.0%)	4 (0.7%)
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	1 (0.6%)	2 (0.3%)	1 (1.0%)	3 (0.5%)

	Prior Radiotherapy: Y		Prior Radiotherapy: N	
	Pool 1 All CSCC Patients (N=173)	Pool 2 All Monotherapy Patients (N=647)	Pool 1 All CSCC Patients (N=102)	Pool 2 All Monotherapy Patients (N=551)
Number of Patients with any TEAE resulting in death, n (%)	8 (4.6%)	19 (2.9%)	6 (5.9%)	44 (8.0%)

Data cutoff as of 11 Oct 2020 for Study 1540 Groups 1 to 3; Data cutoff as of 19 Apr 2021 for Study 1540 Group 6. Only patients who started treatment on or prior to 09 Oct 2020 are included; Data cutoff as of 04 Jan 2021 for Study 1676; Data cutoff as of 30 Jun 2020 for Study 1620; Data cutoff as of 01 Mar 2020 for Study 1624; Data cutoff as of 30 Apr 2019 for Study 1423.

TEAE: Treatment-emergent adverse event.

NCI grades were coded using CTCAE Version 4.03.

A patient is counted only once for multiple occurrences within a category.

Assessment of the MAH's response

The MAH has provided the requested tables. No clinically meaningful differences are seen between the different regions, prior systemic therapy (Y/N) or prior radiotherapy (Y/N). This is reassuring.

Conclusion

Issue resolved.

Quality aspects

None

Non-clinical aspects

None

Clinical aspects

None

Risk Management Plan

None