26 April 2019
EMA/CHMP/368468/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

LIBTAYO

International non-proprietary name: cemiplimab

Procedure No. EMEA/H/C/004844/0000

Note

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

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List of abbreviations

ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BA	Bioavailability
BOR	Best objective response
C_{max}	Peak concentration
CI	Confidence interval
CLcr	Creatinine clearance
CNS	Central Nervous System
CR	Complete response
CRF	Case report form
CSCC	Cutaneous squamous cell carcinoma
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough concentration at the end of the dosing interval
CYP	Cytochrome P450
CV	Coefficient of variation
DCR	Disease control rate
DOR	Duration of response
DP	Drug product
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EudraCT	European Clinical Trials Database
FAS	Full analysis set
FDA	Food and Drug Administration
FIH	First in Human

GM-CSF	Granulocyte-macrophage colony-stimulating factor
HCC	Hepatocellular carcinoma
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
irAE	Immune-related adverse event
IRR	Infusion-related reaction
iSAP	Integrated Statistical Analysis Plan
ISE	Integrated Summary of Efficacy
ITT	Intention-to-treat
IV	Intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
n	Total number of patients in the group
N	Total number of patients
NAb	Neutralizing antibody
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1, PD-L2	Programmed death-ligand 1, programmed death-ligand 2
PF	Platinum + 5-fluorouracil
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
PT	Preferred term
Q2W	Every 2 weeks
Q3W	Every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAF	Safety analysis set
SD	Stable disease

SJS	Stevens-Johnsons syndrome
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TEN	Toxic epidermal necrolysis
TMB	Tumor mutation burden
TTR	Time to response
ULN	Upper limit of normal
UV	Ultraviolet
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Regeneron Ireland U.C. submitted on 6 March 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for LIBTAYO, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication: LIBTAYO as monotherapy is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma or patients with locally advanced cutaneous squamous cell carcinoma who are not candidates for surgery.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included EMA Decision P/0385/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0385/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14(9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance cemiplimab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific Advice on the development relevant for the approved indication from the CHMP on 25 February 2015. The Scientific Advice pertained to the following quality, non-clinical and clinical aspects of the dossier:

- the overall nonclinical toxicology program to support the clinical development and marketing authorisation of Libtayo.
- the study design for R2810-ONC-1540, including the patient population (i.e. separation of the metastatic/locally advanced cohorts, absence of requirement for prior systemic therapy, criteria for prior radiation therapy for locally advanced CSCC and definition of resectability of the patients with locally advanced CSCC), the acceptability of ORR as primary endpoint and whether the study as designed, would be sufficient to support full or conditional marketing authorisation.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Tuomo Lapveteläinen

The application was received by the EMA on	6 March 2018
The procedure started on	29 March 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 June 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	18 June 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	29 June 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 July 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	30 November 2018
– The GCP inspection at two clinical investigator sites in Australia and Spain and the CRO site in United States was performed from 24 July to 19 October 2018. – The outcome of the inspection carried out was issued on	17 December 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	8 January 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	17 January 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	31 January 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 February 2019

The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	13 March 2019
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	26 March 2019
The CHMP agreed on a second list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	28 March 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	3 April 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	10 April 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional marketing authorisation to LIBTAYO on	26 April 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Cutaneous squamous cell carcinoma (CSCC) is a disease arising from the malignant transformation and proliferation of epidermal keratinocytes with invasion of the dermis and is distinguished from non-invasive precursor lesions such as actinic keratoses[1]. For most patients with CSCC, surgery is the recommended line of treatment which can lead to curative intent. However, for a small percentage of patients who develop metastatic CSCC or locally advanced CSCC, collectively referred to as advanced CSCC, the disease can be devastating and life threatening.

2.1.2. Epidemiology

Worldwide incidence of CSCC varies widely, with the highest incidence in Australia and the lowest incidence in parts of Africa[2]. In Nordic countries including Norway, Finland, and Denmark, the age-standardized incidence rate of CSCC was less than 10/100,000 person-years before the 1990s. However, the age-standardized incidence rate in these countries reached approximately 15/100,000 person-years in the last decade. In Switzerland, Sweden, South Wales, Germany, and the Netherlands, the age-standardized incidence rate was reported to be around 20/100,000 person-years or higher. In Europe, Ireland had the highest age-standardized incidence rate as reported in the literature, which was 37.6/100,000 person-years from 1994 to 2003. The exact incidence of CSCC is unknown, but it has been reported to be from 8.9 to 37.6/100,000 person-years in different European countries[3,4,5,6,7]. These differences suggest that comprehensiveness of case recording may account more for incidence variability rather than phenotypic variability[8]. The incidence of CSCC seems to have increased over the past 30 years by 50 and up to 200%, with stabilization trends or slower rates of increase in certain countries[2]. When only invasive forms are taken into account, it is the second most common form of non-melanoma skin cancer and accounts for 20% of all cutaneous malignancies[9].

Risk factors for CSCC include ultraviolet (UV) exposure, advanced age, male sex, and immunosuppression[10, 11].

2.1.3. Biologic features

UV light damages DNA, initiating a series of changes that can result in malignant transformation. Other risk factors that interact with UV light exposure include having skin that burns easily and does not tan or tans poorly, light-coloured hair, northern European ancestry, older age, exposure to PUVA phototherapy,

[1] Fernandez Figueras MT. From actinic keratosis to squamous cell carcinoma: pathophysiology revisited. J Eur Acad Dermatol Venereol. 2017 Mar;31 Suppl 2:5-7.
[2] Lomas A, Leonardi-Bee J, Bath-Haxtall F. A systemic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol 2012;166(5):1069-80.
[3] Osterlind A, Hou-Jensen K. Incidence of cutaneous malignant melanoma in Denmark1978-1982. Anatomic site distribution, histologic types, and comparison with nonmelanoma skin cancer. Br J Cancer 1988;58(3):385.
[4] Hannuksela-Svahn A, Pukkala E, Karvonen J. Basal cell skin carcinoma and other nonmelanoma skin cancers in Finland from 1956 through 1995. Arch Dermatol 1999;135(7):781-6.
[5] Iversen T, Tretli S. Trends for invasive squamous cell neoplasia of the skin in Norway. Br J Cancer 1999;81(3):528-31.
[6] Robsahm TE, Helsing P, Veierød MB. Cutaneous squamous cell carcinoma in Norway 1963-2011: increasing incidence and stable mortality. Cancer Med 2015;4(3):472-80.
[7] Carsin A, Sharp L, Comber H. Geographical, urban/rural and socioeconomic variations in nonmelanoma skin cancer incidence: a population-based study in Ireland. Br J Dermatol
[8] Xiang F, Lucas R, Hales S, Neale R. Incidence of nonmelanoma skin cancer in relation to ambient UV radiation in white populations, 1978-2012: empirical relationships. JAMA Dermatol. 2014 Oct;150(10):1063-71.
[9] Rogers H, Weinstock M, Harris A, Hinckley MR, Feldman SR, Fleischer AB, et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. Arch Dermatol 2010 Mar;146(3):283-7.
[10] Alam M, Ratner D. Cutaneous squamous cell carcinoma. N Engl J Med 2001;344:975-83.
[11] Madan V, Lear J, Szeimies R. Non-melanoma skin cancer. Lancet 2010;375(9715):673-85.

immunosuppressive treatment, exposure to radiation and other industrial carcinogens, and smoking. Chronic inflammation and rare inherited disorders also are associated with an increased risk of cutaneous SCC[10, 11, 12].

2.1.4. Clinical presentation, diagnosis and stage/prognosis

CSCCs are common lesions that are cured with local therapy (surgical excision, cryotherapy, electrosurgery, and radiation therapy) in over 90 percent of cases. A recent analysis on surgical interventions for CSCC showed that the local recurrence rates were 3.0% following Mohs surgery and 5.4% after standard surgical excision[13] . Most local recurrences can be removed surgically, and less than 5% of patients with CSCC develop disease that cannot be cured surgically[14, 15].

CSCC can metastasize initially to regional lymph nodes and subsequently to distant sites, rate of metastasis being from 2% to 5% as a cautious estimation. Despite its low distant metastatic potential, the presence of distant metastasis is associated with a dismal prognosis and a median survival of less than 2 years[16]. Delayed diagnosis or inadequate treatment can result in increased morbidity or death. The risk of local regional recurrence and regional or distant metastasis is the most important factor in determining the approach to the treatment of CSCC.

2.1.5. Management

The major treatment options for CSCC with features that suggest a low-risk for recurrence and metastasis are surgical excision, cryotherapy, electrosurgery, and radiation therapy. The specific choice of treatment modality depends upon the experience of the clinician, the expected cure rate, cosmetic factors, and patient preference. Topical chemotherapy with 5-fluorouracil (5-FU) or imiquimod and photodynamic therapy are additional treatment options for patients with Bowen's disease (CSCC in situ). Radiation therapy is an additional option for the management of primary CSCCs in older patients and those who are not surgical candidates. Careful follow-up is required to evaluate for evidence of local recurrence, regional or distant metastasis, and treatment-related complications.

Although the probability of surgical cure for most patients with CSCC is high, the disease course is devastating for the small percentage of patients who develop metastatic CSCC or locally advanced CSCC, collectively referred to as advanced CSCC. There is no approved systemic treatment for advanced CSCC and there are no guidelines available for locally advanced and metastatic CSCC. As a summary, management guidelines on invasive CSCC by European Dermatology Forum (EDF) – European Association of Dermato-Oncology (EADO) – European Organization for Research and Treatment of Cancer (EORTC) expert panel[16] are the following:

- Mono- or poly-chemotherapy can be used in metastatic cSCC; however, there is no established standard regimen and responses are usually short-lived
- Targeted therapies, such as Epidermal growth factor receptor (EGFR) inhibitors, either in combination with chemotherapy or in the neo-adjuvant setting, have shown encouraging results in locally advanced or metastatic CSCC and their use is encouraged in the setting of clinical trials

[12] Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma. J Am Acad Dermatol 2018;78(2):237-47.
[13] Lansbury, L, Bath-Hextall F, Perkins W, Stanton W, Leonardi-Bee J.. Interventions for non-metastatic squamous cell carcinoma of the skin: systematic review and pooled analysis of observational studies. BMJ 2013;347:f6153.
[14] Rowe DE, Carroll RJ, Day CL Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip: implications for treatment modality selection. J Am Acad Dermatol 1992 (6):976-90.
[15] Kauvar AN, Arpey CJ, Hruza G, Olbricht SM, Bennett R, Mahmoud BH. Consensus for nonmelanoma skin cancer treatment, part II: squamous cell carcinoma, including a cost analysis of treatment methods. Dermatol Surg 2015;41(11):1214-40.
[16] Stratigos A, Garbe C, Lebbe C, Malvehy J, del Marmol V, Pehamberger H, et al. On behalf of the European Dermatology Forum, the European Association of Dermato-Oncology, and the European Organization for Research and Treatment of Cancer. Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. Eur J Cancer 2015;51(14):1989-2007.

Table 1: Synopsis of prospective studies of systemic therapies in advanced or metastatic cutaneous squamous cell carcinoma (adapted from Breuninger et al., 2012[17]).[16]

Reference	Trial design	Patients	Chemotherapy	RR	Comments
Chemotherapy					
Cartei *et al*. (2000)	Prospective Observational	14	Oral 5-FU 175 mg/m^2 for 3 weeks every 5 weeks	2 PR (14.3%) 7 SD (50%)	Aggressive, multiple, recurrent SCCs in aged patients
Sadek *et al*. (1990)	Prospective observational	14/13 evaluable	Cisplatin bolus injection 5-FU and Bleomycin continuous 5-day infusion	4 CR (30%) 7 PR (54%) 2 SD (16%)	Advanced SCC of the skin or lip
Guthrie *et al*. (1990)	Prospective Observational	12	Cisplatin and doxorubicin (n = 7) Neoadjuvant to surgery or radiation (n = 5)	4 CR (33%) 3 PR (25%)	
Khansur *et al*. (1991)	Prospective observational	7	Cisplatin and 5-FU every 21 days	3 CR (43%) 3 PR (43%) 1 SD (14%)	
No authors listed, 1976	Phase III randomised control trial	70 advanced SCC – 6 CSCC	Bleomycin twice weekly versus other cytotoxic drugs	39% RR	Only three patients with CSCC in the treatment arm
Targeted therapies/EGFR Inhibitors					
Maubec et al. (2011)	Phase II uncontrolled trial	36	Cetuximab administered weekly	2 CR 8 PR 25 DCR (disease control rate)	Unresectable or metastatic CSCC. Chemotherapy-naive patients
Glisson *et al*. (2006)	Phase II uncontrolled trial	18/17 evaluable	Gefitinib orally for 4 weeks	4 SD	
Lewis (2012)	Prospective phase II clinical trial	23/22 evaluable	Gefitinib for two cycles prior to surgery and/or radiotherapy (plus maintenance gefitinib for 12 months)	4 CR 6 PR 5 SD 7 PD	Aggressive CSCC of the head and neck
Heath *et al*. (2013)	Non-randomised single-arm phase I clinical trial	15	Erlotinib combined with postoperative adjuvant therapy	2 year OS 65% 2 year DFS 60%	
Kalapurakal *et al*. (2012)	Retrospective study	4	Cetuximab administered weekly	3 CR 1 PR	Recurrent CSCC with a history of multiple recurrences in the past
Read (2007)	Case report	3	Erlotinib for 1–3 months	1 CR 1 PD 1 PR	

EGFR inhibitors and cytotoxic chemotherapy have been used, and the limited data highlight the need for new therapies. The largest prospective studies in the last 15 years for patients with advanced CSCC are studies evaluating EGFR-targeting agents, illustrating the dire prognosis of this disease. The response rate with gefitinib (N = 40) was 16%, and median overall survival (OS) was 12.9 months[18]. The response

[17] Breuninger H, Brantsch K, Eigentler T, Häfner HM. Comparison and evaluation of the current staging of cutaneous carcinomas. J Dtsch Dermatol Ges. 2012 Aug;10(8):579-86.
[18] William WN, Feng L, Ferraraotto R, Ginsberg L, Kies M, Lippman S, et al. Gefitinib for patients with incurable cutaneous squamous cell carcinoma: a single-arm phase II clinical trial. J Am Acad Dermatol 2017;77(6):1110-3.e2.

rate with cetuximab (N = 36) was 28%, and median OS was 8.1 months[19]. The response rate with panitumumab (N = 16) was 31%, and median OS was 11 months[20]. Cytotoxic chemotherapies, mostly platinum-based, were evaluated in older studies that did not utilize independent central review of tumour responses. Two studies of platinum + 5-fluorouracil (PF)-based chemotherapy enrolled 14 and 7 advanced CSCC patients and were unable to provide conclusive evidence of therapeutic advantage[21, 22]. The triplet regimen of cisplatin + interferon alpha + 13-*cis*-retinoic acid (N = 39 patients enrolled, 35 evaluable for response) showed a response rate of 34% and a median OS of 14.6 months[23]. This regimen did not provide compelling evidence of therapeutic benefit and was not further developed. Overall, use of commercially available treatments is limited by inconclusive efficacy data and substantial safety risks due to the advanced age of the CSCC population. Therefore, there is an unmet medical need for an effective treatment option with an acceptable safety profile in patients with advanced CSCC.

About the product

Cemiplimab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with its ligands PD-L1 and PD-L2. Engagement of PD-1 with its ligands PD-L1 and PD-L2, which are expressed by antigen presenting cells and may be expressed by tumour cells and/or other cells in the tumour microenvironment, results in inhibition of T cell function such as proliferation, cytokine secretion, and cytotoxic activity. Cemiplimab potentiates T cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands.

Type of Application and aspects on development

This application concerns a centralised procedure and was submitted as a complete and independent application in accordance with article 8(3) of Directive 2001/83/EC and Regulation (EC) No 726/2004.

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the limitations of the clinical data provided to support the request for accelerated assessment, since only limited data (with no PFS and OS data) from small uncontrolled trials and no long-term outcomes were available at that time.

The applicant applied for the following indication:

- LIBTAYO as monotherapy is indicated for the treatment of patients with metastatic cutaneous squamous cell carcinoma or patients with locally advanced cutaneous squamous cell carcinoma who are not candidates for surgery.

The final agreed indication is as follows:

- LIBTAYO as monotherapy is indicated for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation.

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

[19] Maubec E, Petrow P, Scheer-Senyarich I, Duvillard P, Lacroix L, Gelly J, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. J Clin Oncol 2011;29(25):3419-26.
[20] Foote MC, McGrath M, Guminski A, Hughes BGM, Meakin J, Thomson D, et al. Phase II study of single-agent panitumumab in patients with incurable cutaneous squamous cell carcinoma. Ann Oncol 2014;25(10):2047-52.
[21] Sadek H, Azli N, Wendling JL, Cvitkovic E, Rahal M, Mamelle G, et al. Treatment of advanced squamous cell carcinoma of the skin with cisplatin, 5-fluorouracil, and bleomycin. Cancer 1990;66(8):1692-6.
[22] Khansur T, Kennedy A. Cisplatin and 5-fluorouracil for advanced locoregional and metastatic squamous cell carcinoma of the skin. Cancer 1991;67(8):2030-2.
[23] Shin DM, Glisson BS, Khuri FR, Lippman SM, Ginsberg L, Diaz E Jr, et al. Phase II study of induction chemotherapy with paclitaxel, ifosfamide, and carboplatin (TIC) for patients with locally advanced squamous cell carcinoma of the head and neck. Cancer 2002;95(2):322-30.

Posology

Recommended dose

The recommended dose of LIBTAYO is 350 mg, every 3 weeks, administered as an intravenous infusion over 30 minutes.

Treatment may be continued until disease progression or unacceptable toxicity. No dose reductions are recommended.

Recommended treatment modifications to manage adverse reactions are provided in Table 1 in the SmPC.

One ml of concentrate contains 50 mg of cemiplimab.

Each vial contains 350 mg of cemiplimab in 7 ml of solution.

Cemiplimab is produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture.

For the full list of excipients, see SmPC section 6.1.

Method of administration

LIBTAYO is for intravenous use. It must be administered by intravenous infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low-protein binding, in-line or add-on filter (0.2 micron to 5 micron pore size).

Other medicinal products should not be co-administered through the same infusion line.

For instructions on dilution of the medicinal product before administration, see SmPC section 6.6.

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies. ATC code: not yet assigned

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

Pharmaceutical form

Concentrate for solution for infusion (sterile concentrate).

Clear to slightly opalescent, colourless to pale yellow solution with a pH of 6.0 and osmolality between 300 and 360 mmol/kg. The solution may contain trace amounts of translucent to white particles in a single-use vial.

2.2. Quality aspects

2.2.1. Introduction

The finished product (FP) Libtayo is presented as a concentrate for solution for infusion containing 50 mg/ml of cemiplimab as active substance (AS) in the concentrate.

Other ingredients are: L-histidine, L-histidine monohydrochloride monohydrate, Sucrose, L-proline, Polysorbate 80 and Water for injections.

The product is available in a 10 ml glass vial made of clear Type 1 glass, equipped with a grey chlorobutyl stopper with FluroTec coating and seal cap with a flip-off button. Each carton contains 1 vial and each vial contains 350 mg of cemiplimab in 7 ml of solution.

2.2.2. Active Substance

General information

Cemiplimab is a fully human monoclonal antibody (IgG4 isotype), a covalent heterotetramer consisting of two disulfide-linked human heavy chains, each covalently linked through a disulfide bond to a human kappa light chain. The antibody, based on the primary sequence (in the absence of N-linked glycosylation), has a molecular weight of 143,567.1 Da (chemical formula $C_{6380}H_{9808}N_{1688}O_{2000}S_{44}$), taking into account the formation of 16 disulfide bonds and removal of Lys444 from each heavy chain terminus. The complementarity determining regions (CDRs) within the heavy and light chain variable domains combine to form the binding sites of cemiplimab to its target, PD-1 (human programmed cell death-1). General information is provided on the nomenclature, sequence and schematic structure with location of the disulfide bonds and Fc N-linked glycosylation site.

Manufacture, characterisation and process controls

Manufacturer

The manufacture of cemiplimab takes place at Regeneron Pharmaceuticals, 81 Columbia Turnpike, Rensselaer, 12144, NY, USA until formulated active substance (FAS). Testing is performed by sites in the US and Ireland. The manufacturing and testing facilities are listed with company name and addresses as appropriate. Valid GMP certificates are provided. The virus tests are also performed by Regeneron and an approved contract lab.

Description of the manufacturing process and process controls

Cemiplimab is produced by a cell culture process using recombinant Chinese hamster ovary (CHO) cells. The process begins with thawing a frozen vial of the working cell bank (WCB) and expanding through a series of seed train bioreactors.

The recombinant protein product is harvested. Cemiplimab protein is then purified using a series of chromatographic and membrane filtration techniques. To prepare cemiplimab FAS, the AS is compounded to the desired concentration and formulation with the addition of a concentrated excipient buffer.

The upstream manufacturing process for cemiplimab is comparable in process steps and scale for seed train and bioreactor to what is common for monoclonal antibodies. The process flow is presented in table format where the process step, stage and function is described in conjunction with the process conditions (in target values).

The virus inactivation steps are low pH and virus-retentive filtration were validated based on applicable industry standards.

The resin and filter lifetimes and the duration of each manufacturing step and the hold times are validated.

The manufacture and formulation, and the holding times are supported by the stability studies. The stability of the AS during freeze-thaw cycles is also supported by the stability studies.

The cleaning process for the material is appropriate.

A short concise description of the function, elements and in-process control sampling points of each manufacturing step is given, including the validated allowed duration of the individual step.

For the entire process, the in-process controls are adequately discussed in the manufacturing process development section.

Container closure

The container closure systems for cemiplimab AS and FAS are polycarbonate (PC) bottles with a silicone-lined polypropylene screw cap, respectively.

The suitability of the container closure system is demonstrated including a leachables study confirming no leachables at or above the analytical evaluation threshold (AET) for the duration of the shelf life.

The suitability and safety of the primary AS container closure system is considered to be demonstrated.

Control of materials

Sufficient information on raw materials used in the manufacturing process has been submitted. Compendial raw materials are tested according with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are present.

All raw materials are enrolled in a material qualification program, in which an evaluation of virological and TSE safety as well as chemical and microbiological testing and assessment of leachables/extractables is performed as applicable.

Animal derived raw materials were used during early cell line development only. There was no direct use of animal derived materials in the preparation of the cemiplimab MCB or WCBs nor in the manufacturing process of cemiplimab other than the CHO production cells. Based on the virological and TSE safety assessment performed, the applicant concludes that the risk of contamination by adventitious agents is remote. This conclusion is supported by the documentation provided.

A thorough risk assessment of extractables and leachables from all components used in the cemiplimab manufacturing process has been performed, taking into account the level of exposure to the process stream and product. Based on the risk assessment performed, it is concluded that the risk for the presence of leachables in cemiplimab finished product at levels, which exceed the recommended exposure limits is low, and that no further mitigation nor monitoring of leachables is required.

Source, history and generation of cell substrate

The anti-PD1 antibody REGN2810 was generated by establishment of hybridomas through standard methods. Hybridomas were selected based on binding specificity and inhibition of PD-1 activity. The variable regions of the heavy and light chains of REGN2810 were polymerase chain reaction (PCR) amplified and cloned into two individual expression plasmids, designated pRGN7541 and pRGN7571, respectively. The pRGN7541 and pRGB7571 plasmids were transfected into a CHO host cell line.

Master and working cell banks

The cemiplimab MCB was established through expansion of cells from the development cell bank. No animal derived raw materials were used in the preparation or storage of the MCB.

The MCB testing was performed in accordance with ICH guidelines (i.e. ICH Q5D and ICH Q5A). The results of the testing complied with the acceptance criteria and documented the integrity and correct sequence of the REGN2810 genes and mRNA transcripts.

Cemiplimab WCBs have been generated from MCB. No animal derived raw materials were used for preparation nor storage of the WCBs. The testing was performed mostly in accordance with ICH Q5D and

ICH Q5A. The results complies with the acceptance criteria. Stability of the WCBs is tested once a year with the same acceptance criteria as set for the cemiplimab MCB.

Further testing for the absence of virological contaminants was performed at the end of production cells (EPC), cultured to the limit of *in vitro* age (LIVCA). No evidence of infectious viral or non-viral contamination was observed at this level. Genetic characterisation of the EPC was performed.

The results of genetic characterisation of the MCB, the WCBs and EPCs demonstrated genetic stability of the production cell line, as the correct coding sequence of cemiplimab was maintained in the MCB, WCBs and throughout the production run. Specifications for MCB, WCB, and EPCs are aligned with the characterisation tests.

Control of critical steps and intermediates

The control of critical steps and intermediates of cemiplimab is performed under an In-Process control program which consist of the process monitoring activities performed to confirm that operational and performance parameters (process inputs) and attributes (process outputs) are maintained within justified and/or validated limits or ranges.

The in-process control (IPC) program is based on the Quality by Design (QbD) approach. The selection of operational and performance parameters (process inputs) and attributes (process outputs) as In-Process Controls are described and adequately justified for the commercial GMP manufacturing process.

Process performance qualification (PPQ) lots were used to establish the IPC program covering the seed expansion through the sucrose adjusted AS. A process performance monitoring plan (PPM) is made which defines the appropriate monitoring tools for each IPC including statistical process controls. The PPM is continuously monitoring the IPC program during the life cycle management of cemiplimab.

The applied process controls have been divided into operational and performance parameters (process inputs) and performance attributes (process outputs) which are maintained within justified and/or validated limits or ranges, and trending of performance over time via statistical process control (SPC), where appropriate. The QbD approach used by the applicant was not considered to be fully in line with the definition given in ICH Q8 (R2): "*A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality*". The applicant was reminded that a process parameter that has an impact on a CQA per definition remains critical independently of detectability, controllability and occurrence. The applicant has confirmed that for every proposed change to process parameters and quality attribute, the appropriate variation procedure will be determined in accordance with EU regulation, which is accepted.

Process validation

The commercial manufacturing process for cemiplimab AS has been validated. In general, the PPQ batches have been manufactured within the defined ranges for critical and general process parameters. Process validation has been performed against predefined limits from historical batches.

The applicant has provided a clear summary of Proven Acceptable Range (PAR) studies including the studied parameter ranges as well as the data justifying the final operational ranges.

The impurity clearances of process and product related impurities have been adequately demonstrated.

For viral clearance, model viruses representing a wide range of physicochemical characteristics, were used to test the ability of purification steps. Virus clearance studies were performed for each individual step, using spiked process material. The mechanism of virus removal/inactivation differs between the steps tested, for which reason they are considered as orthogonal. In conclusion, the design of the virus clearance studies were considered to be in accordance with ICH Q5A and the results obtained acceptable.

Manufacturing process development

A QbD approach has been used in the optimisation process for the changes made between the initial manufacturing process, used for the non-clinical and clinical phases, and the intended commercial process. The comparability between the clinical and commercial manufacturing processes has been studied and is considered adequately documented.

Pilot scale activities prior to the technology transfer which cover AS manufacture until formulation have been described.

Preliminary Critical Quality Attributes (pCQA) were defined for the pilot scale by the QbD approach with the cross-functional risk assessment. When these pCQA were met by the commercial process, the optimisation of the manufacturing process was continued with high level risk assessment defining pCQA and preliminary General Quality Attributes (pGCA) for measure of process consistency. The low level risk analysis defines, through multivariate process models, the factors and responses that influences the pCQA. The impacting factors are defined as preliminary Critical Process Parameters (pCPP) when the impact on the CQA is beyond the acceptable range. The design and scale robustness was verified through scale up and process confirmation batch runs.

The pCQA definition and ranges were established leveraging (i) product quality from historical manufacturing capability for the clinical process, (ii) preclinical data with clinical material, (iii) extensive product characterisation of clinical material, (iv) preclinical and clinical experience with similar Regeneron monoclonal antibodies leveraging same proprietary cell line technologies and (v) peer reviewed literature data.

The pCQAs related to product and process were identified. The terminology used by the applicant for process parameters (PPs) and quality attributes (QAs) are not fully in line with the terminology used in ICH Q8. The applicant has confirmed that for every proposed change to process parameters and quality attribute, the appropriate variation procedure will be determined in accordance with EU regulation, which is accepted.

Clinical manufacturing process development and comparability with commercial process

The early clinical trials were supplied by the clinical process material. Comparability with the commercial process has been demonstrated by orthogonal techniques evaluating lots of each process.

Characterisation

The characterisation of the structural, physiochemical and biological properties of cemiplimab has been performed with state-of-the-art analytical methods.

Cell-based, functional, PD-1 bioassays were also set up to study the biological activity of cemiplimab.

Multiple lots manufactured in 2016 by the commercial manufacturing process and one lot manufactured using the clinical manufacturing process were characterized as part of the comparability exercise between the manufacturing processes. The description of the physicochemical properties of the protein making up cemiplimab is presented with an appropriate level of detail, an appropriate method description and references to literature on corresponding IgG4 characterisation. The samples analysed are highly similar throughout all analysis including charge variants and glycosylation profiles known to be affected by many manufacturing process parameters. The characterisation results of the samples give the impression of a well-controlled manufacturing process throughout the development program and process validation.

Functional cell-based bioassays documented that all cemiplimab lots tested were comparable.

As part of product-related impurities high molecular weight species (HMW), low molecular weight species (LMW), charge variants, and oxidised species were examined. In general, all relevant product related impurity variants were considered.

Process related impurities has been addressed in sufficient detail.

Specification

The release and end of shelf-life specifications for formulated AS includes appropriate physicochemical tests and tests for identity, potency, and purity.

Analytical procedures and reference standards

The analytical methods are considered to be state of the art and acceptable.

It is noted that for the characterisation of AS purity orthogonal methods are used and the more sensitive method is chosen for the release test of the HMW- and LMW- variants.

The presentation of the validation of the analytical methods used for the IPC of cemiplimab AS and release test of cemiplimab FDS is sufficiently detailed and found appropriate.

Reference standard

A primary-and working-standard is established. Description of generation, characterisation and testing of the primary- and working standard is provided and do not call for additional comments. Initial certification and possible extension is supported by ongoing stability annual monitoring.

Batch analysis

Batch release data are provided for FAS and AS manufactured by the commercial process. All test results are within specifications.

It is noted from the complete batch data including the results of the tests that are later omitted for release testing, that the more sensitive methods for the detection of the HMW and LMW variants are used when comparing the results.

Stability

A shelf life is proposed for the AS and FAS.

Data from primary stability studies and supporting stability studies are available. Stability test results meet the commercial acceptance criteria at the long-term storage condition for all primary and supporting stability lots. Overall the data obtained to date, indicate that cemiplimab AS and FAS are stable when stored at the proposed long-term storage temperatures. The stability studies have been performed according to ICH Q5C.

Release testing and extended characterisation testing has demonstrated that cemiplimab AS manufactured from the commercial manufacturing process is comparable to the quality of cemiplimab AS produced using the clinical manufacturing process. The applicant has provided updated stability study results from their on-going stability studies which supports the proposed shelf-life. Furthermore, appropriate justification for the proposed testing intervals in the post-approval stability protocol, with appropriate explanation for why they are not according to stability guideline, are provided.

The stability studies of the primary and supporting cemiplimab AS and FAS batches at the long-term storage will be completed according to the stability protocol. A commitment is provided to place a minimum of one batch of cemiplimab AS and FAS on long-term stability at the recommended storage

condition every year of manufacturing. The batches will be tested according to the analysis plan and the results must meet the end-of-shelf-life specifications.

Accelerated and stressed conditions stability studies have been performed according to ICH Q5C. The results obtained from these studies support the relevance of the selected stability indicating parameters.

Photostability studies, forced degradation studies and freeze-thaw studies have been performed according to relevant guidelines.

In conclusion, the stability results indicate that the AS and FAS are sufficiently stable and justify the proposed shelf life in the proposed container.

Comparability exercise for Active Substance

See under Manufacturing process development.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Description of the product and Pharmaceutical Development

Cemiplimab solution for infusion (50 mg/mL) is a clear to slightly opalescent, colorless to pale yellow, aqueous buffered, sterile solution that may contain trace amounts of translucent to white particles.

The FP is formulated as a 350 mg vial of cemiplimab and is manufactured by filling 50 mg/mL cemiplimab into a single-use 10 mL glass vial. An overfill is added to the vials. The cemiplimab FP contains well-known compendial excipients and their quality is compliant with Ph.Eur. standards. There are no novel excipients used in the FP formulation. The composition is adequately described and depicted in Table 3.

Table 2. Composition of Libtayo finished product

Component	Function	Reference to Quality Standard
Cemiplimab	Active pharmaceutical ingredient	Manufacturer's specification
L-Histidine	Buffer	USP, Ph. Eur., JP
L-Histidine Monohydrochloride Monohydrate$_{(a)}$	Buffer	Ph. Eur., JP
Sucrose	Stabilizer	NF, Ph. Eur., JP
L-Proline	Stabilizer	USP, Ph. Eur., JP
Polysorbate 80	Stabilizer	NF, Ph. Eur., JP
Water for Injection	Solvent	USP, Ph. Eur.

(a) Named L-histidine hydrochloride hydrate in JP.

JP, Japanese Pharmacopeia; NF, National Formulary; Ph. Eur., European Pharmacopeia; QS, quantity sufficient; USP, United States Pharmacopeia

Libtayo finished product is packed in 10 ml clear Type 1 glass vial with a grey chlorobutyl stopper with FluroTec coating and seal cap with a flip-off button. Each carton contains 1 vial. Not all pack sizes may be marketed. The choice of the container closure system has been validated by stability data and is adequately described for the intended use of the product.

Pharmaceutical development

Formulation development has been appropriately described and the rationale for the selection of the formulation adequately addressed and justified. Different cemiplimab FP formulations were tested during clinical development. Cemiplimab at a concentration of 50 mg/ml was selected for the final FP formulation for IV infusion.

Manufacturing process development has been described in detail. All of the FP manufacturing processes during development utilized similar processing steps including thawing, pooling, and mixing of the formulated active substance (FAS), sterilising filtration, and aseptic filling and stoppering of the final container. The acceptable batch size was updated, based on the validated batch size determined during PPQ. Minor process changes were also made to mixing times and process hold times based on process validation activities.

The results of the FP comparability studies are presented in the dossier. All results met the comparability acceptance criteria's demonstrating comparability between batches of 250 mg FP and 350 mg FP. As the major equipment, formulation, and materials of construction remain the same, no comparability studies were performed between the 5.5 ml fill volume (250 mg FP) late-stage clinical and commercial manufacturing processes. Of note, only the 350 mg FP presentation has been applied for.

A compatibility study with the infusion system demonstrated that the FP diluted into 0.9% Sodium Chloride Injection or 5% Dextrose injection were compatible with the infusion system and the diluents. Compatibility has been adequately described.

In conclusion the pharmaceutical development of cemiplimab FP is described in sufficient detail.

Manufacture of the product and process controls

Manufacture

The sites involved in manufacturing, in-process testing, testing, labelling and packaging, final batch release and importation are listed in the dossier.

A batch size range, expressed as the amount of cemiplimab FAS used to manufacture a batch of 50 mg/ml cemiplimab finished product vials, is indicated. The applicant initially applied for 2 strengths, however on the basis of the approval of the 350 mg strength and as agreed with EMA, the 250 mg strength is no longer pursued. There is only one FP form applied for: 350 mg vial of cemiplimab FP.

The Libtayo manufacturing process consists of the following steps: thawing of cemiplimab FAS, pooling and mixing of cemiplimab FAS, filtration, aseptic filling of vials, stoppering, capping, and tray loading of filled vials and 100% inspection of cemiplimab FP. The manufacturing process is well described and considered acceptable. Flow charts of the manufacturing process steps, including identification of critical process parameters critical in-process parameters have been provided and a narrative description of each step, including labelling and packaging, has been included.

Cemiplimab can be stored at 2 – 8 °C for limited times at specific stages during the manufacturing process. The validated hold times are set at the shortest of the hold times achieved for the three PPQ lots.

Time out of refrigeration (TOR) was recorded any time the cemiplimab FAS temperature was maintained above 5 ± 3 °C during PPQ. The shortest of the hold times achieved for the three PPQ lots is considered the validated hold time for each step. The maximum TOR from end of thaw until the end of 100% visual inspection is defined as the shortest TOR achieved during PPQ.

The holding times are adequately described and validated. No reprocessing steps have been described.

Cemiplimab solution may contain trace amounts of translucent to white particles in a single-use vial. The identity of the particles was confirmed mainly as cemiplimab protein. The applicant has committed to further demonstrate during post-authorisation that particles can be correctly identified (during release testing) in relation to their source.

The cemiplimab FP is presented in single-use vials without preservative. The measurements to control microbiological quality and sterility of the FP are considered acceptable. The container-closure system and the assessment of the suitability of the components are described. Results of extractable and leachable studies revealed no unexpected components.

The excipients in the cemiplimab FP formulation comply with compendial monographs. No excipients of human or animal origin are used and no novel excipients are used in the FP formulation.

Process controls

The controls and parameters evaluated were derived from development data, process risk assessments, parameters selected for monitoring during PPQ, historical process performance data (process experience), and laboratory scale process characterisation data. The IPCs and process parameters associated with each manufacturing process step were determined and in-process controls and process parameters were classified as critical, key, or non-key. Action limits, acceptance criteria, and ranges were established with consideration of historical manufacturing experience, process capability (non-statistical) as determined during manufacture of late-stage clinical material, validation experience and risk.

Based on the provided in-process testing and release testing product quality data it is demonstrated that the manufacturing process for Libtayo FP is capable of consistent and homogenous performance.

Process- and product-related impurities have been adequately discussed. Other than visible particles, there are no FP-related impurities apart from those described for AS and FAS. The FP manufacturing process is designed to limit the exposure to factors that can cause particle formation. The level of visible particulates is controlled by 100% visual inspection. In conclusion, the measures taken by the applicant to control visible particles in the FP are considered acceptable.

Process validation

The manufacturing process was validated using PPQ batches of the 250 mg vial presentation and the 350 mg vial presentation. Of note only the 350 mg vial presentation has been applied for. The batch size range corresponds to the commercial scale. On the basis of the data submitted it is considered that the manufacturing process for the 350 mg vial presentations is considered validated.

Aseptic process validation has been performed by microbial challenge tests. Shipping validation has been performed.

Based on the provided validation data on in-process and release testing it has been demonstrated that the manufacturing process for Libtayo finished product is capable of consistent and homogenous performance.

Product specification

Specifications

The release and end-of-shelf-life specifications of the finished product have been provided.

The cemiplimab FP release and shelf-life specifications are considered adequate to ensure the quality of Libtayo FP.

An elemental impurities risk assessment has been performed according to ICH Q3D to evaluate cemiplimab FP for the presence of elemental impurities. It concluded that the risk for the presence of elemental impurities in cemiplimab FP at levels which exceeded 30% of the permitted daily exposure (PDE) was low, and no additional controls were required.

Analytical methods

Specification tests were selected based on ICH Q6B. The methods have been described and validation studies performed. The validation studies and transfer qualification information presented are considered acceptable.

Suitability tests have been provided for the following tests: Endotoxin (LAL), sterility and container closure integrity.

Reference standard

The reference standard is the same as for AS and FAS.

Batch analysis

Batch information is provided in the dossier, including the status, manufacturing date, batch size, reference standard used for release testing, AS manufacturing process, description, manufacturing site, disposition in clinic, PPQ, and stability studies. Batch analysis results of batches of 50 mg/ml cemiplimab FP are presented in the dossier. Batch analysis data of historical cemiplimab FP batches have also been provided. The batch data presented complies with the FP specification and demonstrates manufacturing consistency.

Container closure

The primary packaging for Libtayo FP is a 10 ml clear Type 1 glass vial, with a grey chlorobutyl stopper with FluroTec coating and seal cap with a flip-off button. All packaging materials in contact with the finished product comply with relevant pharmacopeial requirements.

The container-closure system used for cemiplimab FP is adequately described. Compatibility of the container-closure system with cemiplimab FP has been demonstrated and stability information included. The sterilization of the primary packaging has been sufficiently addressed.

Stability of the product

The proposed shelf life for Libtayo is 18 months at 5 ±3°C. The product should not be frozen and it should be stored in the original carton to protect it from light.

Stability test results presented meet the set acceptance criteria at the long-term storage condition for all primary and supporting stability lots. The results obtained from these studies support the relevance of the selected stability indicating parameters. Over all the data obtained to date indicate that Libtayo FP is stable when stored at the proposed long-term storage temperatures.

The primary and supportive stability studies have been performed according to ICH Q5C. The data presented for the 250 mg FP is considered sufficient to support the proposed shelf-life for the FP according to ICH Q5C. Of note, only the 350 mg presentation has been applied for.

The SmPC indicates in section 6.3 that the diluted solution, after opening and preparation of the infusion, should be administered immediately. If the diluted solution is not administered immediately, it may be stored temporarily either at room temperature of up to 25°C for no more than 8 hours from the time of preparation or under refrigeration at 2°C to 8°C for no more than 24 hours from the time of infusion preparation. Stability data to demonstrate the diluted product can be stored temporarily, at 25°C for not more than 8 hours and under refrigeration at 2 -8°C for not more than 24 hours has been provided in the dossier.

The stability studies of the primary and supporting cemiplimab FP batches at the long-term storage condition of 5 ± 3°C, will be completed according to the stability protocol. As per GMP requirements the applicant will place a minimum of one batch of cemiplimab FP on long-term stability at the recommended storage condition every year of manufacturing. The batches will be tested according to the analysis plan and the results must meet the end-of-shelf-life specifications.

Adventitious agents

Complementary approaches have been implemented in order to control potential adventitious agents (i.e. bacteria, fungi, virus, TSE/BSE agents) in cemiplimab AS and FAS: controlled sourcing and safety of the raw materials used during cell line development and in the manufacturing process, testing of cell banks and testing at appropriate stages of the production process and evaluation of the effectiveness and robustness of the viral inactivation and removal during the product purification process.

Safety of raw materials

The direct use of animal derived raw materials was confined to early stages of cell line development. An in-house virological and TSE safety assessment has been performed on raw materials of direct or indirect animal origin, used throughout cell line development, establishment of cell banks and the current cemiplimab manufacturing process. The safety assessments performed demonstrate a minimal risk for transmission of TSE, as well as potential viral contamination.

Testing of host cell line, cell banks, and EPCs

The MCB, WCBs, and EPCs have been extensively tested according to ICH Q5A. The *in vitro* assay for adventitious viruses (IVA) was designed according to current guidelines. The MCB and WCB were tested for viruses. No non-viral contaminants were detected in any of the tests performed at any cell level. The MCB and EPCs were (slightly) positive for reverse transcriptase (RT) activity. However, no identifiable virus-like particles other than budding A- and C-type retrovirus-like particles (RVLP), which are generally known to be present in CHO cells. The MCB and EPC were negative for retroviruses in the additional retrovirus specific tests performed. Apart from the observed RVLPs, no other virus was detected in cells at any level. Thus, the overall test results demonstrate that the cell banks used for the manufacture of cemiplimab are virologically safe.

Unprocessed bulk (UPB) in-process testing

Each batch of UPB is tested using a number of different assays in accordance with current guidelines. Results from PPQ lots are provided. No detection of adventitious agents was reported except in the bioburden test of the AS lot, where 1 CFU/ml was observed. An investigation performed concluded that the bioburden recovery was likely to have been introduced during testing.

Virus clearance evaluation

The manufacturing process, which includes several purification steps, has been adequately demonstrated to be capable of viral clearance using model viruses representing different physicochemical characteristics.

The information provided is considered adequate and in support of cemiplimab as being safe with regards to endogenous retroviruses and adventitious agents.

GMO

Not applicable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The applicant has submitted a dossier of acceptable quality and follows the CTD format. The cemiplimab AS manufacturing process has been sufficiently described and documented. It has been demonstrated by appropriate validation that the manufacturing process produces an AS of consistent quality. Appropriate controls are in place for the release of cemiplimab AS. FP manufacture, control and release have been well documented and are considered to be acceptable. Minor issues have been identified during the assessment of the dossier and these were resolved in a satisfactory manner by the applicant. One recommendation related to an identification method for particles was agreed.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Libtayo active substance and finished product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral and TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- to further demonstrate that (during routine release testing) particles can be correctly identified in relation to their source.

2.3. Non-clinical aspects

2.3.1. Introduction

Cemiplimab is a fully human IgG4 isotype monoclonal antibody (mAb) that binds specifically to human and cynomolgus monkey programmed cell death-1 (PD-1) receptors. Cemiplimab was evaluated in nonclinical studies to determine its ability to block PD-L1-induced inhibitory signalling. Since cemiplimab does not bind to mouse or rat PD-1, its ability to induce anti-tumour immunity was evaluated in PD-1$^{hum/hum}$ genetically humanized mice expressing the human PD-1 extracellular domain, fused with the transmembrane and intracellular portions of mouse PD-1 instead of the equivalent mouse gene products.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro

Binding Affinity (REGN2810-MX-14078)

SPR-Biacore technology was used to determine the kinetic binding parameters for the interaction of cemiplimab with recombinant PD-1 proteins from multiple species at 25°C and pH 7.4.

Table 3: Summary of Kinetic Binding Parameters for the Interaction of cemiplimab with Recombinant PD-1 Proteins at 25°C

Protein	Antibody	Kinetic Binding Parameters			
		k_a ($M^{-1}s^{-1}$)(1)	k_d (s^{-1})(2)	K_D (M)(3)	$t_{1/2}$ (min) (4)
Human hPD-1.mmH	REGN2810	$1.37x10^5$	$7.68x10^{-4}$	$5.61x10^{-9}$	15.0
Human hPD-1.mFc	REGN2810	$2.37x10^5$	$1.37x10^{-4}$	$5.77x10^{-10}$	84.4
Cynomolgus monkey MfPD-1.mmH	REGN2810	$1.09x10^5$	$8.28x10^{-4}$	$7.61x10^{-9}$	14.0
Cynomolgus monkey MfPD-1.mFc	REGN2810	$2.64x10^5$	$1.32x10^{-4}$	$4.99x10^{-10}$	87.8
Rat rPD-1.mmH	REGN2810	NB(5)			
Mouse mPD-1.mmH	REGN2810	NB			

1) Association rate constant

2) Dissociation rate constant

3) Equilibrium dissociation constant

4) Dissociative half-life ($t_{1/2}$); amount of time required for 50% of bound PD-1 to dissociate from antibody

5) No detectable binding under assay conditions used

Abbreviations: hPD-1.mmH=human PD-1with a C-terminal myc-myc-hexahistidine tag (monomer); hPD-1.mFc=human PD-1fused with mouse Fc domain (dimer); MfPD-1=cynomolgus monkey PD-1; rPD-1=rat PD-1; mPD-1= mouse PD-1

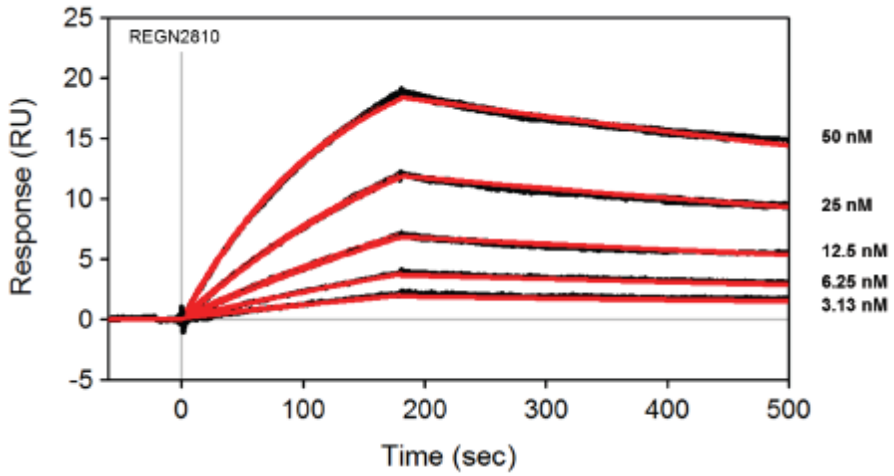


Figure 1: Biacore Sensorgrams for Anti-hFc Captured REGN2810 Interacting with hPD-1.mmH

Ability of cemiplimab to antagonize PD-L1 mediated PD-1 signaling (REGN2810-MX-14079)

Cemiplimab and both comparator PD-1 antibodies (REGN1672 and REGN2626) were evaluated for their ability to increase T cell activation by blocking PD-1/PD-L1-mediated T cell inhibitory signaling (Figure 3). Jurkat/PD-1-CD 300a/AP-1-Luc cells and Raji/PD-L1 cells were activated with the T cell activating bispecific (CD3xCD20) antibody. Cemiplimab restored T cell activation to approximately 75% of the maximum value, with a corresponding EC_{50} value of 1.37 nM.

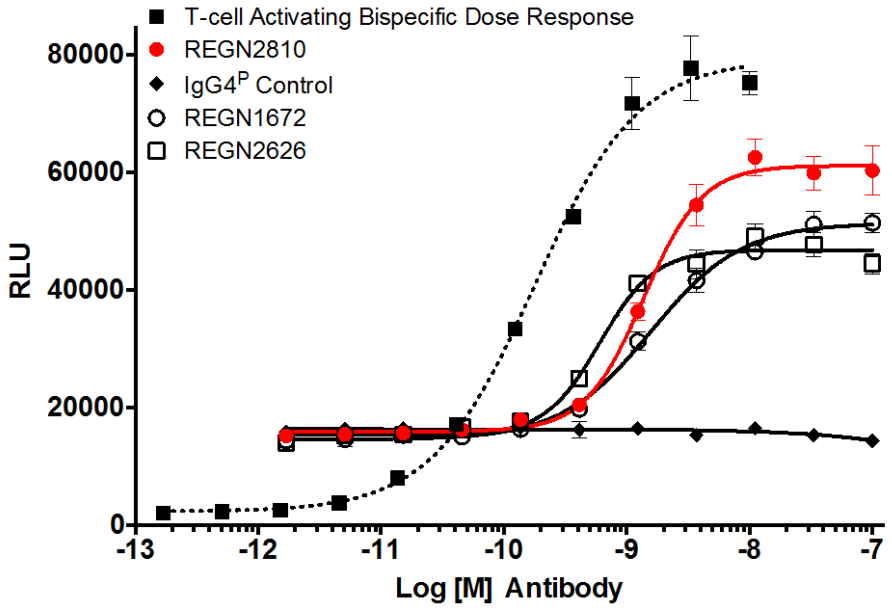


Figure 2: Cemiplimab and Comparator Antibodies Rescue T Cell Activation in a First-Generation PD-1 Bioassay in the Presence of PD-L1 Expressing Cells

Cemiplimab was further evaluated for its effects on T cell activation in the second generation PD-1 bioassay. Jurkat/PD-1/AP-1-Luc cells were activated by addition of HEK293/mIgE/PD-L1 cells.

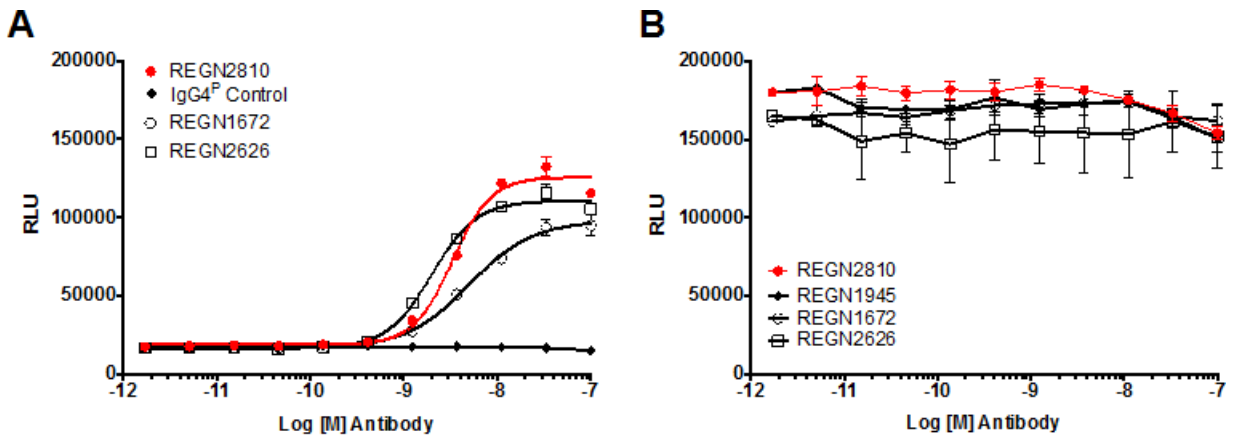


Figure 3: Cemiplimab Displays Antagonist but not Agonist Activity in a Second-Generation PD-1 Bioassay

The antagonist (**Panel A**) and agonist (**Panel B**) activity of cemiplimab (**closed red circles**), REGN1672 (**open black circles**), REGN2626 (**open black squares**), or hIgG4^{p} isotype control (REGN1945) (**closed black diamonds**) were evaluated in the second-generation PD-1 bioassay. **Panel A**) To evaluate antagonist activity, serial dilutions of antibodies (1.7pM-100nM) were incubated with Jurkat/PD-1/AP-1-Luc and HEK293/mIgE/PD-L1 cells. TCR activity was monitored by the AP1-luciferase reporter gene and is expressed as RLU (Relative Luminescence Units). **Panel B**) To evaluate agonist activity, serial dilutions of antibody (1.7pM-100nM) were incubated with Jurkat/PD-1/AP-1-Luc and HEK293/mIgE cells.

In Vitro Functional Assays-ADCC

Using hPBMC as effector cells, cemiplimab did not induce ADCC in Jurkat, CD3/CD28 stimulated Jurkat, HEK293/PD-1 or HEK293 target cells.

In Vitro Functional Assays-CDC

Cemiplimab did not mediate CDC in Jurkat, CD3/CD28 stimulated Jurkat, HEK293/PD-1 or HEK293 cells.

In Vitro Functional Assay-CIC C1q

C1q binding was not observed with either cemiplimab and PD-1.mmH or the hIgG4^{p} isotype control antibody and PD-1.mmH solutions, whereas the heat-aggregated human gamma globulin controls fell within the range of expected values.

Human CD4^{+} Primary T Cell Anti-CD3/Anti-PD-1 Immuno-bead Assay

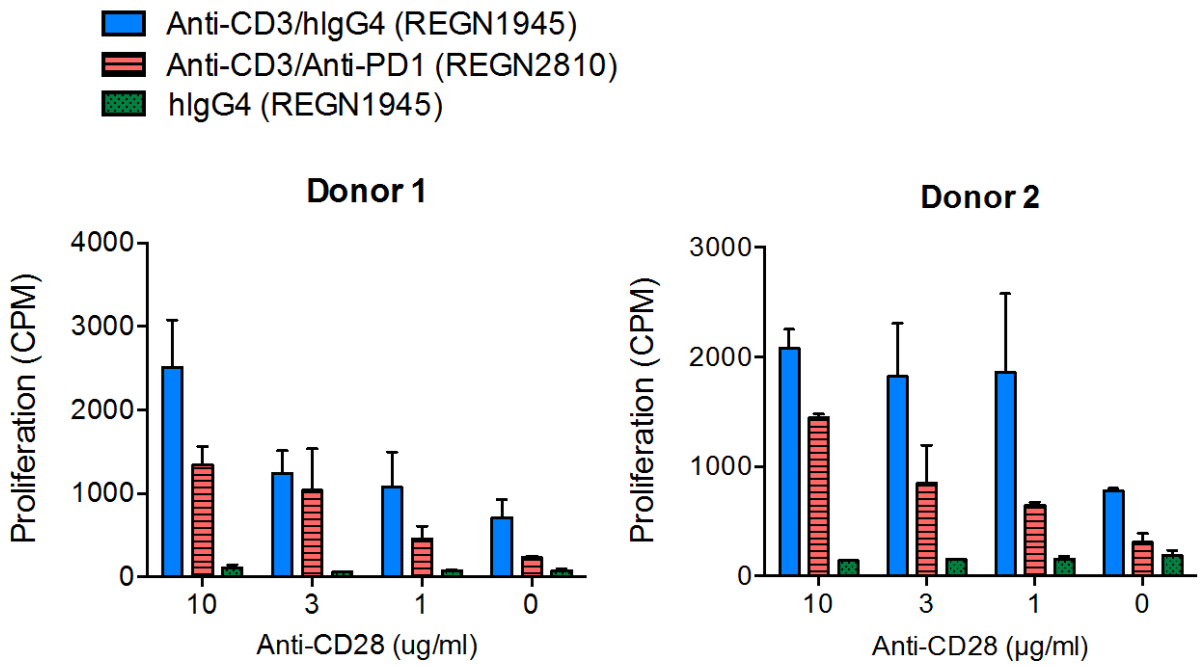


Figure 4: T Cell Activation in a Human CD4+ Primary T Cell/Immuno-bead Bioassay

Immuno-beads (Dynabeads M-450 Tosyl activated, Invitrogen) were coated with anti-CD3 (R&D clone UCHTI) and hIgG4^{P} isotype control antibody, REGN1945 **(blue bars**), anti-CD3 (R&D clone UCHTI) and anti-PD-1 cemiplimab (**red striped bars**) or hIgG4^{P} isotype REGN1945 alone (negative control, **green bars**). Beads were washed with PBS and then incubated together with CD4^{+} primary T cells from 2 different healthy donors. Beads and T cells were mixed together at 1:1 ratio in the presence of increasing concentration of soluble anti-CD28 mAb (BD clone 28.2) in media, as indicated on the graph. Proliferation was measured at 37°C by tritiated thymidine incorporation during the last 6-12 hours of a 72 hour incubation. Soluble anti-CD28 antibody increased T cell activation in a dose dependent manner.

In vivo

Anti-tumor Activity of cemiplimab in PD-1 Humanized Mice at Doses of 5 mg/kg and 10 mg/kg

The effect of cemiplimab on the growth of syngeneic colorectal carcinoma tumours (MC38.Ova) was examined in PD-1 humanized mice genetically engineered to express a human/mouse PD-1 chimeric receptor from the mouse *Pd1* locus. This human/mouse PD-1 chimeric receptor consists of the human PD-1 extracellular domain fused to the transmembrane and cytoplasmic domains of mouse PD-1. Using huPD-1 mice, cemiplimab and the comparator anti-PD-1 antibodies, REGN1672 and REGN2626, were tested for their effect on MC38.Ova tumour allograft growth and mouse survival in two independent experiments at 5 mg/kg and 10 mg/kg (Cemiplimab and REGN1672) and at 2.5 mg/kg and 5 mg/kg (Cemiplimab , REGN1672, and REGN2626).

The two *in vivo* pharmacology models both showed significant reductions in tumour volumes at all doses tested for cemiplimab, REGN1672 and REGN2626. At 10 mg/kg of cemiplimab and REGN1672 complete tumour regression was seen in all animals at day 21. At both 5 mg/kg and 2.5 mg/kg for cemiplimab, REGN1672 and REGN2626 complete regression of the tumour was seen in all animals except one animal in each group at day 21. All animals that did not show complete regression at day 21 actually showed tumour growth over the time course of the study.

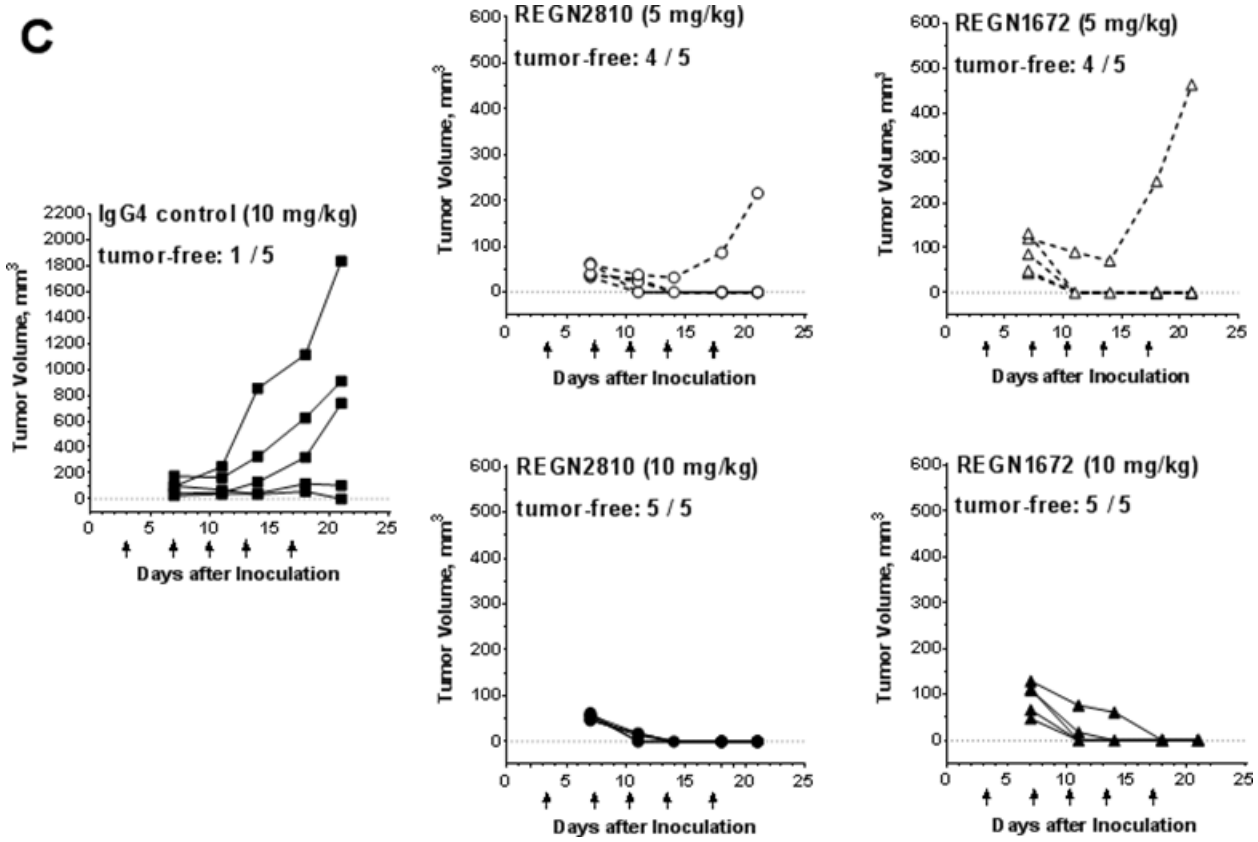


Figure 5: Cemiplimab at 5 mg/kg and 10 mg/kg Inhibits MC38.Ova Tumor Growth in PD-1 Humanized Mice

The individual tumor volume for each mouse within each group over the 21 days of treatment is shown. The number of tumor-free mice (n/N) at day 21 in each group is noted. Cemiplimab: 5 mg/kg (**open circle**) and 10 mg/kg (**closed circle**), REGN1672: 5 mg/kg (**open triangle**) and 10 mg/kg (**closed triangle**), and 10 mg/kg isotype control antibody, REGN1945 (**closed square**).

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies have been conducted with cemiplimab (see non-clinical discussion).

Safety pharmacology programme

No dedicated safety pharmacology studies have been conducted with cemiplimab. The safety pharmacology endpoints were integrated into the repeat dose toxicology studies in cynomolgus monkeys for cemiplimab administered at IV doses of 2, 10, or 50 mg/kg/week for 5- or 26-weeks with an 8-week or 12-week recovery phase, respectively. These included an evaluation of cardiac conduction (ECG's) by Jacketed External Telemetry (JET) as well as hemodynamics (heart rate and blood pressure), respiratory rates (breaths/minute), and CNS evaluation by neurological exams. During the toxicology studies, there were no drug-related effects observed in food consumption, body weights, CNS, body temperature effects, heart rate, blood pressure, ECG parameters or respiratory effects.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been conducted (see non-clinical discussion).

2.3.3. Pharmacokinetics

The pharmacokinetics (PK) of cemiplimab were characterized following single-dose intravenous (IV) PK and repeat-dose IV toxicology studies (toxicokinetic analysis). Additionally, a single-dose subcutaneous (SC) PK study was conducted to support the potential use of SC administration in clinical trials.

Table 4: Summary of mean PK parameters of cemiplimab in monkey serum following single IV or SC dose in cynomolgus monkey

Study No. Compliance	**Route**	**Dose** mg/kg	**t_{max}** day	**C_{max}** µg/mL	**terminal $t_{½}$**[a] day	**beta $t_{½}$** day	**AUC**[b] day• µg/mL	**V_{ss}** mL/kg	**CL** mL/day /kg	**F**[c] %
REGN2810-PK-14065 (non-GLP)	IV infusion	1	0,13	33,3	1,19	9,84	168	37,3	5,99	NA
		5	0,0471	121	2,02	10,9	1100	63,4	4,56	
		15	0,0979	355	9,85	12,4	3950	65,6	3,68	
REGN2810-PK-14152 (GLP)	SC	1	3	12,1	NA	9,72	77	NA	NA	86,5
		5	3	67,7		11,9	428			
		15	4	188		16,2	1250			

[a] In the 15 mg/kg group, terminal $t_{1/2}$ may not represent the true terminal half-life due to the limited study duration.

[b] AUC_{last} (AUC computed from time zero to the time of the last measurable concentration) is reported for REGN2810-PK-14065 and $AUC_{0\text{-}8days}$ (AUC computed from time zero to the last time point before an anti-drug antibody response was observed in any animal) is reported for REGN2810-PK-14152.

[c] Bioavailability was estimated together with data from a pharmacokinetic and a toxicology study following IV dosing of cemiplimab in the monkey (REGN2810-PK-14065 and REGN2810-TX-14059) by a population PK approach (REGN2810-PK-14152).
NA = Not applicable

Following a single SC dose of 1 to 15 mg/kg cemiplimab to monkeys, C_{max} increased dose-proportionally.

In the repeat-dose toxicity studies, toxicokinetics were determined to be linear for doses ≤ 10 mg/kg/week during the dosing phase. Accumulation of cemiplimab was determined after weekly IV infusion of cemiplimab and stabilised at approximately 3 after 8 doses at the time steady state is reached.

In monkeys, a single IV or SC dose of cemiplimab triggered a prominent antidrug –antibody response; ADAs were detected in all treated animals and in all dose levels (1, 5 and 15 mg/kg) at day 28 and day 56 post dose (after SC; ADAs were determined only at day 56 post dose). Measured ADA values (counts) correlated with lower cemiplimab serum concentration levels. Throughout the PK and TK studies, the concentrations of 'outliers or likely impacted by ADA' were excluded from PK and TK analysis. ADA response was graded as 'weak' (i.e. mean peak counts that were ~3 fold greater than pre-dose), 'strong' (*i.e.*, mean peak counts 200-500 fold greater than pre-dose) or 'very strong' (i.e. 1000-fold the pre-dose values). Only 2 out of 15 monkeys were graded as 'weak' in ADA response scale, and 4/15 strong and 9/15 very strong in ADA response scale.

2.3.4. Toxicology

The toxicity testing program of cemiplimab consisted of:

- **Study REGN2810-TX-14059:** 4-week IV toxicology study in monkey.
- **Study REGN2810-TX-14153:** 26-week IV toxicity and TK study with a 12-week recovery period.
- **Study REGN2810-TX-15151:** 13-week IV fertility assessment and TK study with a 12-week recovery period.

Single dose toxicity

Single dose toxicity studies were not submitted (see non-clinical discussion).

Repeat dose toxicity

Table 5: Summary of repeat-dose toxicity studies

Study ID	Species/Sex/ Number/Group	Dose/ Route	Duration	NOAEL (mg/kg/ week)	Major findings
REGN2810-TX-14059	Cynomolgus monkey/5/M+F	2, 10, 50 mg/kg/week IV inf	4 weeks	50	ADA associated findings primarily microscopic including vascular changes in adrenal, spleen, liver and lymph nodes
REGN2810-TX-14153	Cynomolgus monkey/6/M+F	2, 10, 50 mg/kg/week IV inf	26 weeks	50	Clinical signs (severe hypersensitivity reactions) associated with antidrug antibody formation leading to early euthanasia of one monkey
REGN2810 15151	Cynomolgus monkey/6/M+F	2, 10, 50 mg/kg/week IV inf	13 weeks	50	No noteworthy findings of clinical signs or fertility parameters including microscopic evaluation of reproductive tissue

REGN2810-TX-14059

There were no unscheduled deaths during the study and no test article-related clinical signs evident. There were no test article-related effects on body weights, food consumption, ophthalmic or cardiovascular endpoints, blood pressure, heart rate, body temperature, respiration rate and pulse oximetry, neurological examination parameters, clinical pathology parameters (hematology, coagulation parameters, clinical chemistry, and urinalysis) and PBMC stimulation analysis. There were no test article-related macroscopic findings.

It has been evaluated the cemiplimab-related effects on the counts of proliferating T-lymphocytes, a pharmacologically relevant measure for prediction of effect in humans. The effects were limited to dose-independent increases in the frequency and absolute counts of proliferating T-lymphocytes, T-helper lymphocytes, and T-cytotoxic lymphocytes (as determined by Ki67 labeling) that were present at Day 9 and to a lesser extent on Day 23, and generally returned to predose levels by Day 50.

Cemiplimab was highly immunogenic in monkeys illustrated by the widespread immune complex depositions in connection to adverse vascular findings in adrenal gland, spleen, liver and lymph nodes in animals. Immune complex depositions were confirmed by positive staining for C3, IgG and IgM providing a plausible explanation for the vascular dilation, local hemorrhage, arterial hypertrophy/hyperplasia and vascular necrosis in several organs. In the recovery animals the immune complex related findings were decreased in incidence and severity, suggesting only a trend towards reversibility. It should be noted here, that cemiplimab exposure was still evident at end of recovery for doses 10 and 50 mg/kg/week at 15-23% of exposure at end of treatment. NOAEL can be set to the highest dose 50 mg/kg/week.

REGN2810-TX-14153

There were no cemiplimab-related alterations to T-lymphocyte, T-cytotoxic lymphocyte, T-helper lymphocyte, monocyte, B-lymphocyte, and natural-killer (NK) cell populations. Minor alterations in these

populations observed in the control and dosed animals did not demonstrate a dose-dependent pattern and were sporadic; therefore, these changes were attributed to normal variability in these populations.

Continuous exposure to cemiplimab was maintained throughout the 26-week treatment period in 3 of 12 (25%), 7 of 12 (58%), and 8 of 12 (67%) animals in the 2, 10, and 50 mg/kg/week groups, respectively. Throughout the 12-week recovery period, concentrations of cemiplimab were detected in 2 of 3 (67%) animals in the 10 mg/kg/week group and all animals in the 50 mg/kg/week groups and were not detected in any animals in the 2 mg/kg/week dose group due to ADA impact.

The adverse vascular findings so prominent in the 4-week study were not found in this study, except in one animal in dose group 10 mg/kg. Instead severe clinical signs of hyperactivity against cemiplimab was observed in several animals.

The NOAEL was considered to be 50 mg/kg/week in all repeat-dose toxicity studies in monkeys, the highest dose administered. However, while setting this dose as the NOAEL any adverse reactions as a consequence of high immunogenicity was excluded. Given that in 26-week toxicity study in monkeys two animals died (one in 10 and 50 mg/kg dose groups in each) due to immune complex deposition and associated tissue damage.

Cemiplimab was strongly immunogenic in monkeys. Immunogenicity was moderate to high across all studies, with the incidence of anti-cemiplimab antibodies (anti-drug antibodies, ADA) and the intensity of the response being inversely correlated with the cemiplimab dose level. A positive ADA response almost always correlated with lower serum cemiplimab concentrations, compared to ADA-negative animals in the same dose group. A positive ADA response almost always correlated with lower serum cemiplimab concentrations, compared to ADA-negative animals in the same dose group.

Table 6: Calculation of safety margins to exposure at dose recommended in SmPC

Study ID	**Weekly Dose (mg/kg)**	**Animal AUC_{1week}** Mean of male and female **(µg/mL*day)[a]**	**Human exposure at steady state for 350 mg dose AUC_{3weeks} (µg/mL*day)[b]**	**Animal:Human Exposure Multiple**
26-week study REGN2810-TX-14153	50	12200	3800	9.6
13 week fertility studyREGN2810-TX15151	50	15600	3800	12.3

[b:] AUC_{tau} of 50 mg/kg/week at 26 and 13 weeks from Toxicology Summary page 14 and 24, respectively, [a]: AUC_{0-6w} for 350 mg Q3W of 3800 µg/mL (from table 18 in report R2810-MX18022-SR01V1, page 77)

Genotoxicity

No genotoxicity studies have been submitted (see non-clinical discussion).

Carcinogenicity

No carcinogenicity studies have been submitted (see non-clinical discussion).

Reproduction Toxicity

The applicant provided a summary of literature studies showing that blocking the PD-1/PD-L1 axis induce increased risk for abortion and premature delivery in mice. Fertility were evaluated in a 13-week toxicity study.

13-Week Intravenous Toxicology Fertility Assessment Study in Sexually Mature Cynomolgus Monkeys With a 12-Week Recovery Period (REGN2810-TX-15151)

The primary objective of this study was to look into potential effects of cemiplimab on fertility by evaluating a range of parameters prerequisites of adequate fertility. After the dosing phase of 13 weeks, very few findings were evident from histopathological evaluation. In males minimal infiltration of mononuclear cells in epididymis was found in 1/4 animals in the low dose group and in 2/4 animals in the high dose group with none in the control group. After the recovery phase, the incidence was 1 out of 2 in all three groups. In the recovery group, tubular hypoplasia was found in testis in 1 out of 2 animals in the low dose group (marked) and in both animals in the high dose group (minimal). Thymus, spleen, liver, adrenal etc. was also undergoing histopathological evaluation, but no findings were observed.

No cemiplimab-related microscopic findings were observed in male or female reproductive tissues. NOAEL for fertility is considered to be 50 mg/kg/week in both males and females, the highest dosage administered.

No studies were submitted to study cemiplimab effects on prenatal and postnatal development or maternal function (see non-clinical discussion).

No studies in juvenile animals were submitted (see non-clinical discussion).

Toxicokinetic data

Table 7: Summary of toxicokinetic parameters at steady state (end of dosing phase) for all three repeat–dose toxicity studies (pool of male and female)

Study ID	Dose mg/kg/ week	Duration (weeks)	C_{max} (µg/mL)	C_{trough} (µg/mL)	AUC_{tau} (µg/mL*day)	ADA	Age of animals
REGN2810-TX-14059	2	4[a]	98.0	33.5	355	10/10	3-6 years
	10	4[a]	378	136	1480	7/10	3-6 years
	50	4[a]	2010	790	8030	6/10	3-6 years
REGN2810-TX-14153	2	26	112	NA[b]	NA[b]	11/12	2-5 years
	10	26	608	317	2930	4/12	2-5 years
	50	26	2820	1410	12200	4/12	2-5 years
REGN2810-TX-15151	10	13	619	398	3250	6/12	5-7 years
	50	13	3180	1850	15600	2/12	5-7 years

[a]: Steady state not yet reached

[b]: In the 2 mg/kg group, the 3 animals with continuous exposure were last samples at 72 hours post dose 26 and the recovery animals had concentrations which were BLQ at 168 hours post dose 26, which prevented calculation of C_{trough} and AUC_{tau} for this dose interval

Local Tolerance

Local tolerability of the IV administration of cemiplimab was evaluated as part of the GLP repeat-dose 4-week and 26-week toxicology studies in monkeys. There were no adverse clinical, macroscopic, or

microscopic changes evident at sites of administration, up to the highest cemiplimab dose of 50 mg/kg/week (12.5 and 25 mg/mL in the 4- and 26-week studies, respectively). In both studies, only microscopic findings (minimal to mild subcutaneous hemorrhage and fibroplasia, minimal thrombosis, and/or minimal to mild mononuclear, neutrophilic, and/or mixed cell infiltrates) were observed.

Other toxicity studies

Antigenicity

Table 8: Overview of incidence of immune complex adverse effects by study and dose

Study ID	Dose mg/kg/ week	Duration (weeks)	Microscopic signs of immune-ge nicity	Clinical signs of immuno-ge nicity	Death/eutha-nasia	ADA	Age of animals
REGN2810-TX-14059	2	4	>3/10	1/10 (hives)	None	10/10	3-6 years
	10	4	>3/10		None	7/10	3-6 years
	50	4	>3/10		None	6/10	3-6 years
REGN2810-TX-14153	2	26	Only in animals showing clinical signs of hyper-sensiti vity	1/12	-	11/12	2-5 years
	10	26		2/12	1 animal Day 36	4/12	2-5 years
	50	26		3/12	1 animal Day 94	4/12	2-5 years
REGN2810-TX-15151	10	13	None	None	None	6/12	5-7 years
	50	13	None	None	None	2/12	5-7 years

2.3.5. Ecotoxicity/environmental risk assessment

The applicant did not submit an ERA but submitted a justification for an exclusion from preparation of environmental risk assessment studies according to Section 2 of the 2006 CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use Guideline because cemiplimab is a monoclonal antibody consisting of linked naturally occurring amino acids. Per the ERA Guideline, proteins are exempted because they are unlikely to result in significant risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacology

The non-clinical pharmacology of cemiplimab was well characterised *in vitro* and the effects were considered to be pharmacologically relevant.

Cemiplimab was tested *in vitro* for cytokine release activity, antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. The results showed binding of cemiplimab to PD-1 and activation of target T cells compared to isotype control. Cemiplimab was also evaluated in two *in vivo* pharmacology models in PD-1 humanized mice. In these models cemiplimab showed significant reductions in tumour volumes at all doses tested for cemiplimab. At 10 mg/kg of cemiplimab complete tumour regression was seen in all animals at day 21. At both 5 mg/kg and 2.5 mg/kg for cemiplimab complete regression of the tumour was seen in all animals except one animal in each group at day 21. All animals that did not show complete regression at day 21 actually showed initial reduced tumour growth and then progressed over the time course of the study. At the highest concentration, all animals showed tumour regression. The

reason is unknown and could be the result from differences of physiological, metabolic or immunological origin between individual animals.

Pharmacokinetics

Pharmacokinetics of cemiplimab was as expected for an antibody in monkeys with indications of target mediated clearance at lower doses and plasma concentrations. Several monkeys showed precipitation like increase in clearance just after 14 days treatment probably due to antidrug antibodies. This finding is not considered to have a significant impact on the overall conclusion on the TK and PK samples selection. The immunogenicity findings in monkey studies are generally not predictive for human antigenicity and therefore are not considered of clinical relevance.

Toxicology

The toxicity of cemiplimab was evaluated in the repeat dose toxicity studies of 4, 13 and 26-weeks duration in monkeys. The 13-week study was dedicated to evaluation of fertility endpoints. The 4-weeks study included endpoints to evaluate cemiplimab impact on immune cells. Cemiplimab induced only a transient increase in T cell proliferation. No single dose toxicity study was performed, which is acceptable considering the clinical schedule of administration.

In the 4-week study, vascular findings of depositions of immune complexes were associated with antidrug antibodies. In the 26-weeks study findings of immune complexes were low or absent, however, incidents of clinical signs similar to hypersensitivity reactions occurred, which led to early euthanasia of 1 animal on day 36 and death of one animal on day 94. In the 13-week study, no such concerns were identified. The differences in immunogenicity observed between the individual studies are most probably due to the differences in study design and/or the age and source of the animals used in the studies. The lower incidence of antigenicity in the 13-week study could be due to the use of older animals, source of animals, time point for examination for ADAs, or other differences in study design.

It is agreed that the immune complex response is considered to be of no translational significance to humans and NOAEL can be set to the highest dose 50 mg/kg/week.

No studies have been performed for secondary pharmacodynamics drug interactions and secondary PD studies which is acceptable as no PD effects other than those already described are expected for this class of agents. Since other checkpoint inhibitors have shown to induce abortion and premature delivery in monkeys, the risk is already identified,hence it is acceptable that no studies have been performed to test the potential of cemiplimab for carcinogenicity, genotoxicity, pre and postnatal development and juvenile studies. Animal reproduction studies have not been conducted with cemiplimab (see SmPC section 4.6). As reported in the literature, PD-1 / PD-L1 signalling pathway plays a role in sustaining pregnancy by maintaining immunological tolerance and studies have shown that PD-1 receptor blockade results in early termination of pregnancy. The increase of spontaneous abortion and/or resorption in animals with restricted PD-L1 expression (knock-out or anti-PD1 / PD-L1 monoclonal antibodies) has been shown in both mice and monkeys. These animal species have similar maternal-foetal interface to that in humans.

No clinical data are available on the possible effects of cemiplimab on fertility. No effects on fertility assessment parameters or in the male and female reproductive organs were observed in a 3-month repeat dose fertility assessment study with sexually mature cynomolgus monkeys.

Animal reproduction studies have not been conducted with cemiplimab. There are no available data on the use of cemiplimab in pregnant women. Animal studies have demonstrated that inhibition of the PD 1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing foetus resulting in foetal death (see SmPC section 5.3). Women of childbearing potential should use effective contraception during treatment with cemiplimab and for at least 4 months after the last dose of cemiplimab.

No concerns regarding local tolerance of cemiplimab arose during or after the repeat-dose toxicity studies.

Cemiplimab is a protein composed of natural amino acids. Proteins are biodegradable in the environment and thus do not pose any environmental risk. Therefore, according to the "Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2), it is acceptable that no ERA studies were submitted for cemiplimab.

2.3.7. Conclusion on the non-clinical aspects

In conclusion, the non-clinical studies (pharmacology, pharmacokinetics and toxicology), submitted for the marketing authorisation application for cemiplimab, were considered adequate and acceptable for the assessment of non-clinical aspects. As also discussed during scientific advice, the lack of carcinogenicity, genotoxicity, fertility and pre/post-natal and juvenile development were agreed and are considered acceptable and well justified. Based on cynomolgus monkey studies, there is a potential risk for foetal loss in humans. This risk is adequately addressed in the SmPC.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 9: Clinical studies in patients with mCSCC or laCSCC where PK data were collected

Study Identifier	Location of Synopsis and Study Report	Design	Primary and Secondary Variables	Dose Regimen/Duration/Follow-up	N	Study Status; Type of Report
5.3.5.2 Study Reports of Uncontrolled Clinical Studies						
R2810-ONC-1423	Module 5.3.5.2	Phase 1 First-in-human, open-label, repeat dose study with cemiplimab as monotherapy and combination therapy Adult patients (≥18 years old, males/females) with advanced solid malignancies	The efficacy variables used to assess the activity of cemiplimab are: • ORR as assessed based on the RECIST 1.1 • DCR • DDCR • depth of response • TTR • DOR • duration of disease control • PFS • OS Primary safety variables are: • Incidence of DLTs • Incidence and severity of treatment-emergent adverse events (TEAEs) through 48 weeks of treatment • Abnormal laboratory findings through 48 weeks of treatment Other outcome measures are: • Serum concentration and PK of cemiplimab • Anti-cemiplimab antibodies	• 10 mg/kg cemiplimab administered IV over 30 minutes Q2W for 48 weeks • Cemiplimab 200 mg dose IV infusion over 30 minutes Q2W for 48 weeks • Cemiplimab at 1 or 3 mg/kg administered IV over 30 minutes Q2W days for 48 weeks, alone or in combination with: – Radiotherapy (30 Gy administered as 5 doses of 6 Gy over 1 week) given 1 week after the first dose of cemiplimab OR – Radiotherapy (27 Gy administered as 3 doses of 9 Gy over 1 week) given 1 week after the first dose of cemiplimab OR – Low-dose cyclophosphamide (200 mg/m2 IV) approximately once Q2W for 4 doses, starting day –1, and given 1 day prior to each of the first 4 cemiplimab doses, OR – Radiotherapy (30 Gy) plus low-dose cyclophosphamide each administered as described above – Radiotherapy (27 Gy) plus low-dose cyclophosphamide each administered as described above Post-treatment follow-up: approximately 5.5 months	397 patients	**Ongoing Interim CSR**

Study Identifier	Location of Synopsis and Study Report	Design	Primary and Secondary Variables	Dose Regimen/Duration/Follow-up	N	Study Status; Type of Report
R2810 ONC-1540	Module 5.3.5.2	Phase 2 Non-randomized, multicenter, pivotal study with cemiplimab 3 mg/kg or 350 mg as monotherapy Adult patients (≥ 18 years old, males/females) with mCSCC (nodal and/or distant; Group 1) and laCSCC (Group 2)	The primary efficacy variable is ORR according to independent central review during the 12 treatment cycles. The secondary efficacy variables are: • ORR by investigator review • DOR • PFS • OS • CR rate by independent central review • patient-reported quality of life as measured by the EORTC QLQ-C30 • TTR • DCR • DDCR Other secondary outcome measures: • Adverse events (AEs) • Cemiplimab concentrations in serum (at select sites) • Anti-cemiplimab antibodies	Treatment duration (Groups 1 and 2): 96 weeks (twelve 56-day [8-week] treatment cycles); tumor assessment at the end of each 8-week cycle Treatment duration (Group 3): 54 weeks (six 63-day [9-week] treatment cycles); tumor assessment at the end of each 9-week cycle. Post-treatment follow-up: approximately 6.4 months	137 patients	**Ongoing Interim CSR**

2.4.2. Pharmacokinetics

All studies presented have been performed in adult patients with various types of advanced solid tumors; there are no studies in healthy subjects.

PK characteristics of cemiplimab are based on data from Study 1423 and Study 1540, the clinical studies supporting the marketing application in patients with CSCC. Primarily, the 3 mg/kg Q2W dosing regimen and the proposed monotherapy dose regimen of 350 mg Q3W were evaluated. At the time of filing the MAA submission, study 1540 was ongoing for group 2 and 3 (350 mg Q3W) where the applicant subsequently provided additional data from remaining patients with CSCC in both Studies 1423 and 1540. These data include 53 patients in Study 1540 who received cemiplimab 350 mg Q3W (from Group 3), of which 31 patients had reached 80% of steady state at cycle 2 day 1.

In study 1423 cemiplimab PK was characterized in a Phase 1, repeated-dose, study as mono-therapy and combination therapy. Dense sampling was applied after the first dose followed by sparse sampling at pre-infusion (Ctrough) and end-of-infusion (Ceoi) throughout the 48-week administration period, ie, up to 6 treatment cycles of 56-days (8 weeks).

In study 1540, Cemiplimab PK was characterized in a Phase 2 study as monotherapy. Sparse sampling was performed.

Analytical methods

Cemiplimab in human serum was measured using an ELISA method, and the anti-drug-antibodies in patient sera were detected using a three-tiered strategy with screening, confirmatory and titer assays based on an electrochemiluminescent bridging immunoassay, and the neutralizing antibodies were detected by an electrochemiluminescence-based CLB method. The bioanalytical assay for measurement of cemiplimab levels fulfilled the predefined acceptance criteria, with an ULOQ in undiluted human serum, which is 20x fold lower than the C_{max} concentrations at end of infusion.

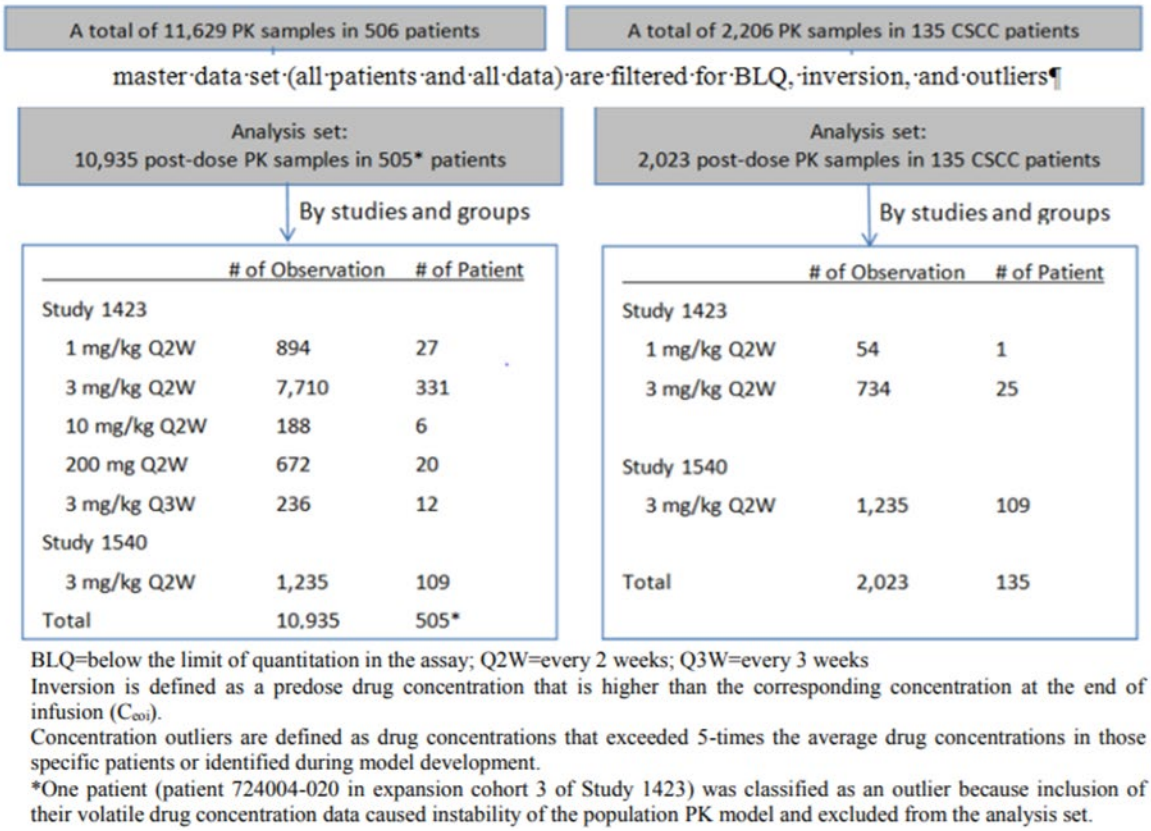
Pharmacokinetic data analysis

PK parameters after the first dose of cemiplimab were determined by use of conventional non-compartmental analysis.

The pharmacokinetics of cemiplimab were also assessed in an integrated analysis with population PK methods. The PK characteristics of cemiplimab in patients with solid tumors were first analysed as a function of the dose in the dose escalation cohorts (1 mg/kg, 3 mg/kg, and 10 mg/kg Q2W), for monotherapy and for combination therapy (Study 1423). The concentrations of cemiplimab were then further investigated in the expansion cohorts in the broader population of patients with different solid tumor types receiving monotherapy or combination therapy.

Evaluation and Qualification of Models

Patients included in the pop PK model are presented in Figure 7.



	# of Observation	# of Patient
Study 1423		
1 mg/kg Q2W	894	27
3 mg/kg Q2W	7,710	331
10 mg/kg Q2W	188	6
200 mg Q2W	672	20
3 mg/kg Q3W	236	12
Study 1540		
3 mg/kg Q2W	1,235	109
Total	10,935	505*

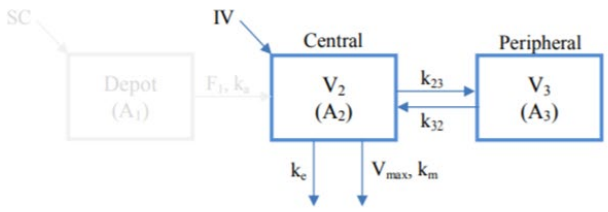
	# of Observation	# of Patient
Study 1423		
1 mg/kg Q2W	54	1
3 mg/kg Q2W	734	25
Study 1540		
3 mg/kg Q2W	1,235	109
Total	2,023	135

BLQ=below the limit of quantitation in the assay; Q2W=every 2 weeks; Q3W=every 3 weeks
Inversion is defined as a predose drug concentration that is higher than the corresponding concentration at the end of infusion (C_{eoi}).
Concentration outliers are defined as drug concentrations that exceeded 5-times the average drug concentrations in those specific patients or identified during model development.
*One patient (patient 724004-020 in expansion cohort 3 of Study 1423) was classified as an outlier because inclusion of their volatile drug concentration data caused instability of the population PK model and excluded from the analysis set.

Figure 6: Population pharmacokinetic model: Summary of patients included in the model by study and dose group

In response to the question regarding limited data on the fixed dose 350 mg Q3W, the parameters of the PopPK model were re-estimated based on a dataset that was updated to include 43 patients with CSCC who received 350 mg Q3W (from Group 3 of Study 1540), of which 23 patients had reached 80% of steady state exposure following administration of 350 mg Q3W.

A two-compartment model with parallel linear and nonlinear (Michaelis-Menten) elimination was selected as a starting model structure. Figure 8 provides a schematic for the initial two-compartment structural PK model with parallel linear and nonlinear (Michaelis-Menten) elimination.



Note: the grayed diagram of SC administration is not applicable to cemiplimab clinical development at this time or indication. However, actual model codes were structured flexibly to accommodate possible route changes in future. SC = subcutaneous; IV = intravenous; F1 = F = bioavailability; k_a = absorption rate constant; V_2 = Vc = volume of distribution (central compartment); V_3 = Vp = volume of distribution (peripheral compartment); Q = inter-compartmental clearance between the central and peripheral compartments; k_{23}, k_{32} – inter-compartmental rate constants; k_e – elimination rate constant; Vm – maximum target-mediated rate of elimination; k_m – Michaelis-Menten constant. CL is plasma clearance, derived from k_e*V_2. A_1 is the amount of cemiplimab dosed via SC route and patient to bioavailability F, A_2 is the amount of cemiplimab in the central compartment with a volume V_2, A_3 is the amount of cemiplimab in the peripheral compartment with a volume V_3.

Figure 7: A general structural representation of a two-compartment model with parallel linear and Michaelis-Menten elimination for both IV and SC administration

The inclusion of a time-varying change on clearance (models LN011 to LN014) significantly improved the model fit and resulted in a reduction of the minimum objective function value (MOFV) greater than 300 points, as shown in Table 12.

Table 10: Comparison of model parameter estimate between the linear elimination base models and the corresponding time dependent clearance models, relative to the primary base model (LN001)

Parameters	LN001	LN002	LN003	LN004	LN011	LN012	LN013	LN014
ofv	-21986	-21605	-21927	-21719	-22374	-22434	-22532	-22624
diff_ofv	0	381.20	58.830	266.51	-388.33	-448.28	-546.56	-638.40
minimization_successful	1	1	1	1	1	1	1	1
covariance_step_successful	1	1	1	1	1	1	0	1
condition_number	12.9178	12.371	11.7503	15.0594	25.5709	28.1924	---	32.8076
TVCL	0.212	0.210	0.211	0.216	0.283	0.270	0.380	0.302
TVV2	3.38	3.40	3.39	3.37	3.35	3.35	3.35	3.35
TVQ	0.590	0.523	0.593	0.620	0.635	0.672	0.529	0.643
TVV3	2.91	2.86	2.93	2.82	1.94	1.89	1.73	1.68
RUVCV	0.186	0.187	0.186	0.198	0.183	0.183	0.181	0.179
RUVSD	2.31	2.78	2.3	---	1.54	1.51	1.6	1.39
EMAX	---	---	---	---	-0.393	-0.278	-0.730	-0.424
T50	---	---	---	---	45.0	42.2	12.1	29.6
HILL	---	---	---	---	---	2.35	---	2.84
WGT_ON_CLQ	0.361	0.365	0.380	0.460	0.410	0.429	0.415	0.437
WGT_ON_VSS	0.528	0.543	0.546	0.545	0.528	0.528	0.533	0.525
IIV_CLQ	0.1624	0.1579	0.1651	0.1604	0.1518	0.1421	0.1005	0.1187
IIV_VSS	0.0493	0.0554	0.0507	0.0500	0.0454	0.0460	0.0446	0.0459
IIV_EMAX	---	---	---	---	5.82e-01	6.03e-01	1.09e-01	2.23e-01
IIV_T50	---	---	---	---	---	---	3.682	0.808
OMEGA.2.1.	0.0349	0.0484	---	0.0359	0.0469	0.0451	0.0493	0.0480

Note: models of LN001, LN002, LN003 and LN004 are linear elimination models without time-varying clearance; models of LN011, LN012, LN013, and LN014 are linear elimination models with time-varying clearance. The differences between these models are described in details in Table 4. The description of the model parameters were given in Table 8. ofv: objective function value, diff_ofv: difference in ofv relative to the primary base model LN001.

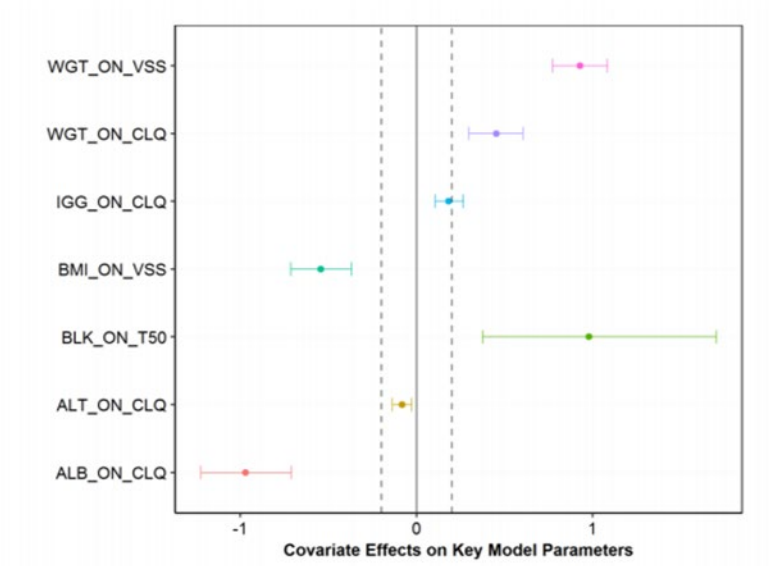
As such, the POP PK analysis suggested a 2-compartment model with zero-order IV infusion and first-order elimination (LN014). A time-varying CL with sigmoid-E_{max} functional form was implemented in the model.

The final model was fitted to 1,000 bootstrap replicate datasets to evaluate its stability and performance. Nonparametric bootstrap was performed and resulted in 95% CIs for population PK parameter estimates, which are presented in Table 13.

The covariate effects are presented in a forest plot, in Figure 9.

Table 11: Summary of parameter values after modelling with original NONMEM input data file or 1,000 bootstrap datasets for the Final model (LN900)

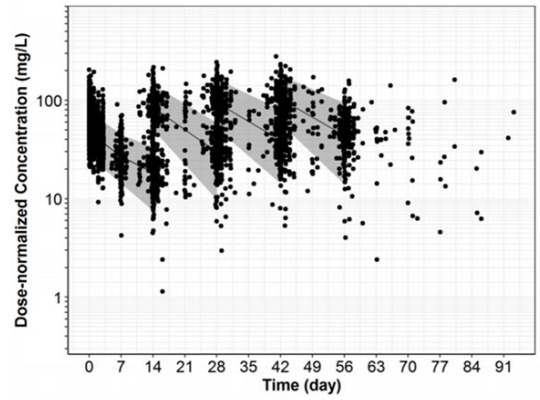
Parameter	Estimate from (Analysis Set)	Estimate from 1,000 Bootstrap	
	Point Estimate	Mean(CV)	Median[CI95]
TVCL	0.287	0.290(3.12%)	0.290[0.274-0.309]
TVV2	3.34	3.34(0.930%)	3.34[3.28-3.40]
TVQ	0.647	0.647(5.69%)	0.647[0.579-0.722]
TVV3	1.69	1.68(4.65%)	1.68[1.53-1.85]
RUVCV	0.180	0.180(2.06%)	0.180[0.173-0.187]
RUVSD	1.34	1.22(41.7%)	1.33[0.0245-1.95]
EMAX	-0.382	-0.392(9.44%)	-0.390[-0.476--0.324]
T50	32.1	31.1(11.9%)	31.0[24.0-38.6]
HILL	3.17	3.15(14.3%)	3.11[2.33-4.13]
WGT_ON_CLQ	0.454	0.456(17.2%)	0.456[0.300-0.609]
WGT_ON_VSS	0.935	0.932(8.18%)	0.936[0.779-1.08]
ALT_ON_CLQ	-0.0818	-0.0817(34.9%)	-0.0823[-0.137--0.0240]
ALB_ON_CLQ	-1.00	-0.976(13.4%)	-0.973[-1.23--0.722]
IGG_ON_CLQ	0.182	0.185(22.0%)	0.183[0.110-0.270]
BMI_ON_VSS	-0.553	-0.545(15.8%)	-0.547[-0.707--0.378]
BLK_ON_T50	0.946	0.998(32.2%)	0.972[0.417-1.70]
IIV_CLQ	0.0893	0.0883(15.5%)	0.0876[0.0655-0.120]
IIV_VSS	0.0412	0.0410(8.47%)	0.0408[0.0345-0.0484]
IIV_EMAX	0.260	0.253(20.4%)	0.250[0.159-0.357]



Note: * the interpretation of exponent α in the covariate model was described in Section 3.6.5.1. See discussions of covariate effects on exposure metrics such as C_{trough} and $AUC_{6wk,ss}$ in Section 4.6.2. WGT: weight (kg), IgG: immunoglobulin G (g/L), BMI: body mass index, BLK: black, ALT: alanine aminotransferase (IU/L), ALB: albumin (g/L).

Figure 8: Forest plot of covariate effects (exponent α*) on Model parameters, estimated by the final model LN900, relative to the parameter values of a reference patient

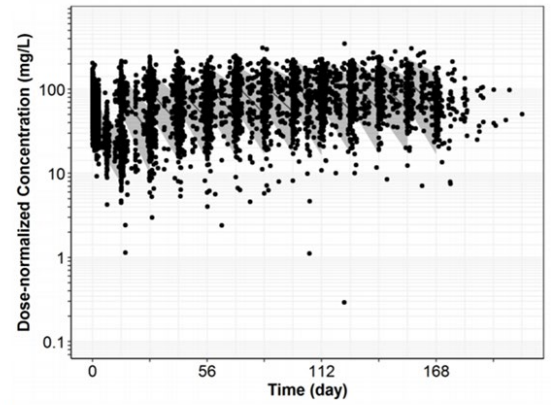
The covariates identified as sources of intrinsic PK variability were body weight, albumin, race (Black) and IgG levels. Internal and external model validation suggested good predictive performance of the pop PK final model.



Note:

1. Dots are observed data and the solid lines represent the median of the simulated data, and the shaded areas represent the simulation-based 95% confidence intervals for the 2.5th and 97.5th percentiles of the predicted data. Patient at 3 mg/kg Q3W were not included in this plot.
2. In the dose group of 10 mg/kg Q2W in study 1423, one patient (R2810-ONC-1423-840004-006) who received the wrong dose (1 mg/kg) on Day 1 was excluded in this plot.

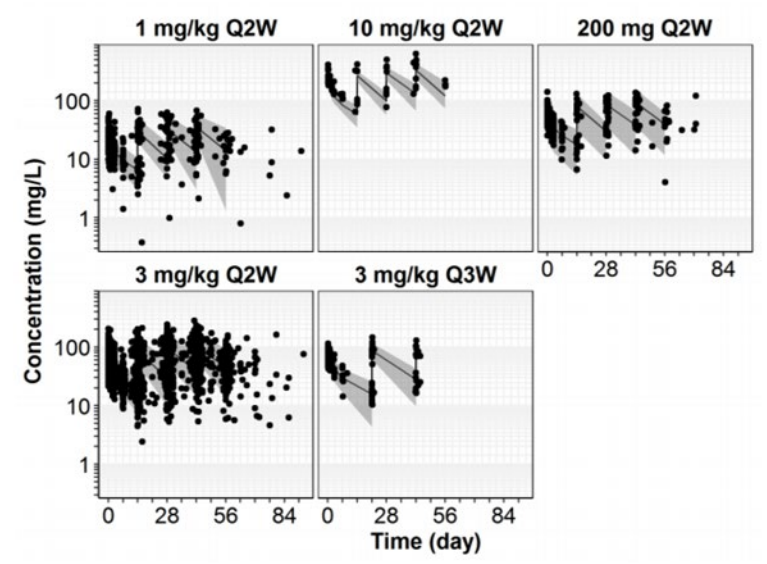
Figure 9: Visual predictive check from final pop PK model: Dose-normalised cemiplimab concentration (Log scale) versus time in the first treatment cycle (up to 56 nominal days) with median and predicted 95% confidence intervals, in the dose groups of 1, 3, 10 mg/kg Q2W and 200 mg Q2W



Note:

1. Dots are observed data and the solid lines represent the median of the simulated data, and the shaded areas represent the simulation-based 95% confidence intervals for the 2.5th and 97.5th percentiles of the predicted data. Patients with 3 mg/kg Q3W were not included in this plot.
2. In the dose group of 10 mg/kg Q2W in study 1423, one patient (R2810-ONC-1423-840004-006) who received the wrong dose (1 mg/kg) on Day 1 was excluded in the plot.

Figure 10: Visual predictive check from final pop PK model: dose-normalised cemiplimab concentrations (Log scale) versus time after dose in the first three treatment cycle (up to 168 nominal days) with median and predicted 95% confidence intervals in dose groups of 1, 3, 10 mg/kg Q2W and 200 mg Q2W.



Note:

1. Dots are observed data and the solid lines represent the median of the simulated data, and the shaded areas represent the simulation-based 95% confidence intervals for the 2.5th and 97.5th percentiles of the predicted data. Patients with 3 mg/kg Q3W were not included in this plot.
2. In the dose group of 10 mg/kg Q2W in study 1423, one patient (R2810-ONC-1423-840004-006) who received the wrong dose (1 mg/kg) on Day 1 was excluded in the plot.

Figure 11: Visual predictive check from final pop model: Cemiplimab concentrations (Log scale) versus time in the first treatment cycle (up to 56 nominal days) stratified by dosage regimens, with median and predicted 95% confidence intervals from the simulation based on the final population model

Patients included in the E/R analyses are presented in Figure 13.

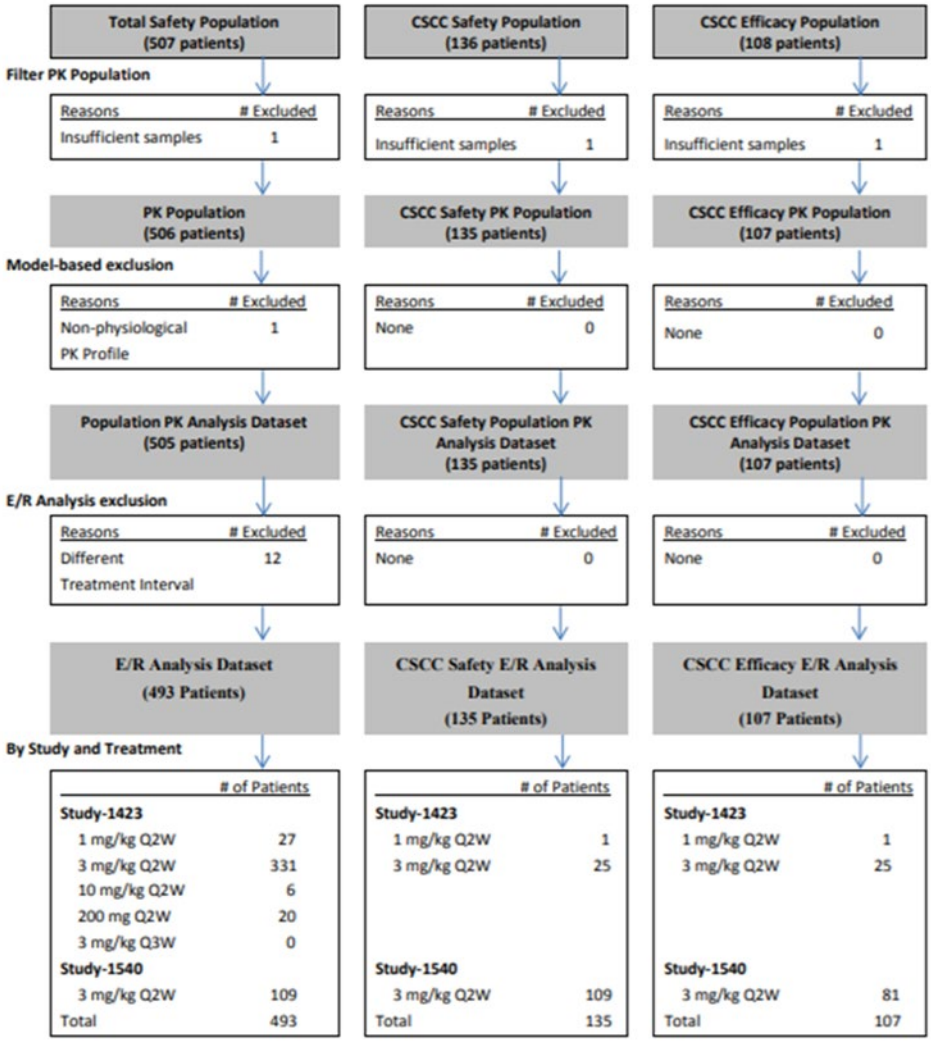


Figure 12: Derivation of analysis E/T datasets - accounting of patients included in safety and efficacy analyses

Absorption

Bioavailability

Cemiplimab was administered IV as a 30-minute infusion and hence bioavailability is complete. Peak concentrations are typically reached at the end-of-infusion, ie, at 0.5 hours. Based on population PK analysis, the mean C_{max} after the first dose was 69.5 mg/L for 3 mg/kg Q2W regimen Table 14.

Table 12: Descriptive statistics of post-hoc analysis for cemiplimab PK parameters in patients with solid tumours estimated at 3 mg/kg Q2W and 350 mg Q3W regimen using the final PK population model

3 mg/kg Q2W				350 mg Q3W			
Parameter	**Units**	**Mean(CV)**	**SD**	**Parameter**	**Units**	**Mean(CV)**	**SD**
$C_{max,2wk}$	mg/L	69.5 (23.2%)	16.1	$C_{max,3wk}$	mg/L	107(24.6%)	26.3
$C_{max,ss}$	mg/L	135 (28.4%)	38.4	$C_{max,ss}$	mg/L	166(27.8%)	46.1
$C_{trough,2wk}$	mg/L	18.9 (30.3%)	5.73	$C_{trough,3wk}$	mg/L	20.4(37.4%)	7.61
$C_{trough,ss}$	mg/L	65.7(42.8%)	28.1	$C_{trough,ss}$	mg/L	58.7(47.7%)	28.0
AUC_{0-6wk}	mg*day/L	1880(27.6%)	520	AUC_{0-6wk}	mg*day/L	2050(29.6%)	606
$AUC_{6wk,ss}$	mg*day*/L	3710(35.9%)	1330	$AUC_{6wk,ss}$	mg*day*/L	3800(37.2%)	1410
N=505 patients							

Bioequivalence

The cemiplimab IV formulation used in the clinical trials (1423 and 1540) providing the PK/PD data evaluated are in concordance with the intended-to-be-marketed formulation, which mean that there is no need for bioequivalence studies.

Dose rationale for 350 mg Q3W

The proposed recommended dose is 350 mg Q3W administered as an intravenous infusion over 30 minutes until the observation of symptomatic disease progression or unacceptable toxicity.

The fixed 350 mg Q3W dose was selected to achieve similar exposure compared to the 3 mg/kg Q2W dose. The population PK model was used to compare cemiplimab exposure at 350 mg Q3W and 3 mg/kg Q2W in a simulated patient population with a body-weight range similar to that observed in population PK dataset. In addition, the simulated concentration time profiles for 350 mg Q3W were compared to the available observed cemiplimab concentration data from 350 mg Q3W. Cemiplimab exposure metrics at steady state ($C_{trough,ss}$, $C_{max,ss}$ and $AUC_{6wk,ss}$), shown as median with 95% CI and as mean (CV%), were compared for the 2 dosing regimens Table 15.

Table 13: Cemiplimab exposure parameters (C trough, Cmax and AUC6wk) at steady state for 3mg/kg Q2W and 350 mg Q3W

Metrics	Dose	N	Mean(CV)	SE	SD	Median(CI 95)	GEOmean
$C_{trough,ss}$ (mg/L)	3 mg/kg Q2W	505	65.7(42.8%)	1.25	28.1	62.0(21.5-134)	59.8(38.1-93.8)
	350 mg Q3W	505	58.7(47.7%)	1.24	28.0	54.9(16.5-131)	52.4(32.1-85.7)
$C_{avg,6wk,ss}$ (mg/L)	3 mg/kg Q2W	505	88.4(35.9%)	1.41	31.7	84.5(35.4-164)	82.8(57.2-120)
	350 mg Q3W	505	90.6(37.2%)	1.50	33.7	85.3(39.1-178)	84.8(58.7-122)
$C_{max,ss}$ (mg/L)	3 mg/kg Q2W	505	135(28.4%)	1.71	38.4	132(71.3-229)	130(97.5-173)
	350 mg Q3W	505	166(27.8%)	2.05	46.1	160(92.5-281)	160(122-209)
$AUC_{6wk,ss}$ (day*mg/L)	3 mg/kg Q2W	505	3710(35.9%)	59.3	1330	3550(1490-6900)	3480(2400-5030)
	350 mg Q3W	505	3800(37.2%)	62.9	1410	3580(1640-7460)	3560(2470-5140)

Table 14: Descriptive statistics of cemiplimab concentrations by nominal time in patients with mCSCC treated at 350 mg Q3W - Study 1540 (Group 3)

Week	Dose #	Visit Cycle Day	Dose Time	N	Cemiplimab Concentrations (mg/L)								
					Mean	SD	CV%	SE	Min	Q1	Median	Q3	Max
0	0	C1 D1	PRE	35	0.0	0.00		0.00	0.0	0.0	0.0	0.0	0.0
0	1	C1 D1	EOI	35	146.1	246.45	168.70	41.66	0.0	78.3	106.0	128.0	1540.0
3	1	C1 D22	PRE	22	31.5	20.17	64.05	4.30	9.1	21.5	28.9	33.7	108.0
3	2	C1 D22	EOI	22	156.8	103.81	66.23	22.13	17.5	102.0	144.5	187.0	559.0
6	2	C1 D43	PRE	19	43.5	17.82	40.92	4.09	2.3	32.8	43.7	51.1	75.6
6	3	C1 D43	EOI	18	179.8	69.27	38.53	16.33	92.1	134.0	169.0	220.0	342.0
9	3	C2 D1	PRE	16	53.3	20.69	38.79	5.17	0.2	45.3	58.2	59.8	86.9
9	4	C2 D1	EOI	15	164.5	45.10	27.41	11.64	66.7	141.0	165.0	194.0	240.0
18	6	C3 D1	PRE	5	49.0	28.38	57.91	12.69	13.3	25.9	59.2	65.3	81.3
18	7	C3 D1	EOI	4	141.4	57.44	40.61	28.72	55.7	110.4	166.0	172.5	178.0
-	-	EOS	-	3	34.8	11.84	34.05	6.84	21.1	21.1	41.3	41.9	41.9

N = Number of patients; C = Cycle; D = Day; EOS = End of study; PRE = Pre-infusion; EOI = End-of-infusion; SD = Standard deviation; SE = Standard error; Q = Quartile; - = Not applicable
Note: Week 0 corresponds to Study Week 1
PRE at C2D1 or C3D1 = Pre-infusion sample at C2D1 or C3D1, ie, C_{trough} after the 3rd and 6th dose, respectively
For descriptive statistics; concentrations below the LLOQ were set to zero.

The POP PK simulations were used to predict steady state exposure for the 350 mg Q3W dose. The applicant has provided additional data from patients with CSCC in both Studies 1423 and 1540. These

data include 53 patients in Study 1540 who received cemiplimab 350 mg Q3W (from Group 3), of which 31 patients had reached 80% of steady state at cycle 2 day 1.

Table 15: Number of patients in the updates analysis sets - Study 1540

Study 1540	Patient Type	Dose	N for PK	N for ADA	N for Full and Safety Analysis
Group 1	mCSCC	3 mg/kg Q2W	59	41	59
Group 2	laCSCC	3 mg/kg Q2W	76	59	78
Group 3	mCSCC	350 mg Q3W	53	35	56
Total	CSCC	3 mg/kg Q2W 350 mg Q3W	188	135	193

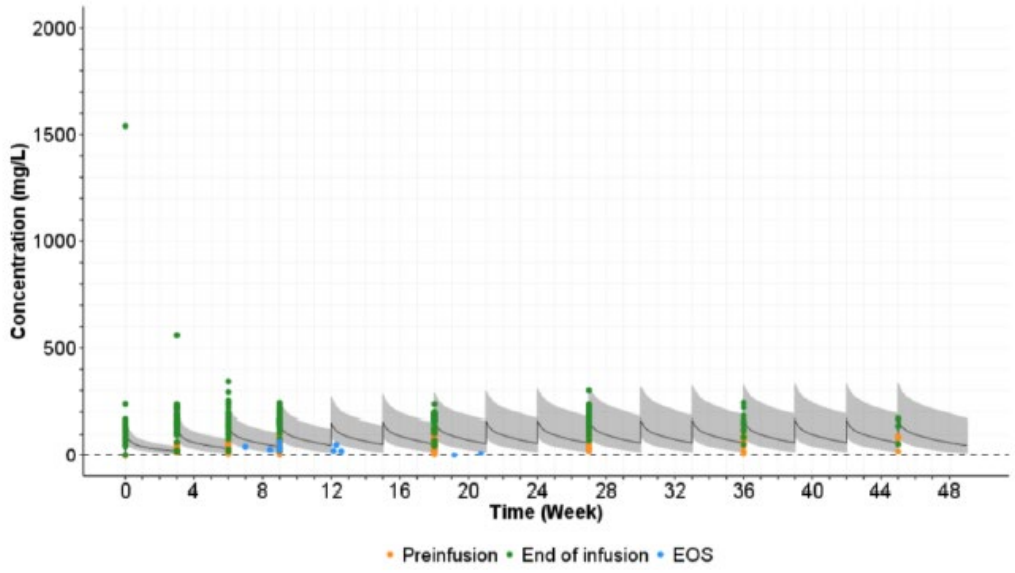
Source: Data cut-off June 30, 2018; 80% of steady stated was reached by C2D1 (Module 2.7.2 Tables 8 and 11, CP Report R2810-ONC-1540-02V1)
N = number of patients; N for ADA analysis set is smaller than that for the PK analysis set, because the first post-dose sample that justifies patient inclusion in the ADA analysis set is at Cycle 3 Day 1. None of the patients with CSCC showed a positive response (see Clinical Efficacy Question 113, Table 6).

Cemiplimab exposure parameters (Ctrough and Ceoi) based on the updated observed data at 3 mg/kg Q2W (Groups 1 and 2) and at 350 mg Q3W (Group 3) are presented after the first dose and at cycle 3 day 1 in Table 18.

Table 16: Observed cemiplimab concentrations in patients with CSCC in groups 1 and 2 at 3mg/kg Q2W and in group 3 at 350 mg Q3W - Study 1540 (Updated)

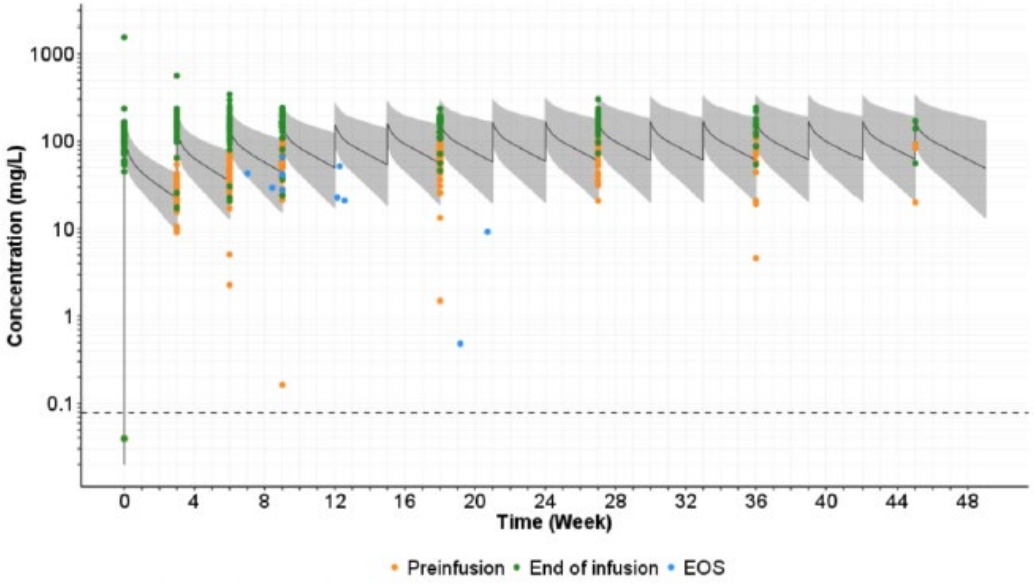
Dose (Group; Patient Type)		Cycle 1 Day 1					Cycle 3 Day 1			
		C_{trough} (mg/L)		C_{eoi} (mg/L)			C_{trough} (mg/L)		C_{eoi} (mg/L)	
	N	Mean (CV%)	Median [95Th Perc.]	Mean (CV%)	Median [95Th Perc.]	N	Mean (CV%)	Median [95Th Perc.]	Mean (CV%)	Median [95Th Perc.]
3 mg/kg Q2W (Group 1; mCSCC)	53;58	21.5 (33%)	21.5 [19.5-23.4]	108 (136%)	79.4 [69.2-146]	38;38	69.9 (28%)	73.4 [63.5-76.2]	151 (55%)	159 [124-179]
3 mg/kg Q2W (Group 2, laCSCC)	71;74	26.3 (54%)	23.7 [22.9-29.7]	85.3 (123%)	70.4 [60.9-110]	56;56	68.2 (43%)	66.3 [60.3-76.2]	149 (52%)	165 [129-170]
350 mg Q3W (Group 3; mCSCC)	47;52	34.2 (94%)	29.5 [24.8-43.6]	132 (154%)	115 [75.7-189]	28;31	63.9 (45%)	65.3 [53.3-74.5]	154 (29%)	167 [136-171]

Source: Data Cut-off June 30, 2018; N = Number of patients for C_{trough};C_{eoi}, respectively. CV% = coefficient of variation (%). Cycle 3 Day 1 = Week 16 for Q2W and Week 18 for Q3W - for the Q2W dose regimen, 1 cycle equals 8 weeks (56 days). For the Q3W dosing regimen, one cycle equals 9 weeks (63 days).



Source: Data Cut-off June 30, 2018; EOS = End of Study.

Figure 13: Simulated cemiplimab concentration-time profile (linear scale) using the model LN900A (with 95%CI) overlaid with observed exposure at 350 mg Q3W in 53 patients with CSCC - Study 1540



Source: Data Cut-off June 30, 2018; EOS = End of Study.

Figure 14: Simulated cemiplimab concentration-time profile (Log scale) using the Model LN900A (with 95%CI) overlaid with observed exposure at 350 mg Q3W in patients with CSCC - Study 1540

Distribution

Cemiplimab is primarily distributed in the vascular system. Based on population PK analysis, the total volume of distribution at steady-state is 5.20 L (Table 19).

Table 17: Descriptive statistics for post-hoc cemiplimab PK parameters in patients with solid tumours estimated using the final PK population model

Parameter	Mean (CV)	SD
$t_{1/2,beta,2wk}$ (day)	12.5 (22.4%)	2.79
$t_{1/2,beta,ss}$ (day)	19.2 (29.5%)	5.68
Baseline Clearance (L/day)	0.325 (40.0%)	0.130
Clearance at ss (L/day)	0.211 (39.5%)	0.0832
Reduction in CL (%)	34.6 (28.5%)	9.87
Volume of distribution at ss (L)	5.20 (24.3%)	1.26

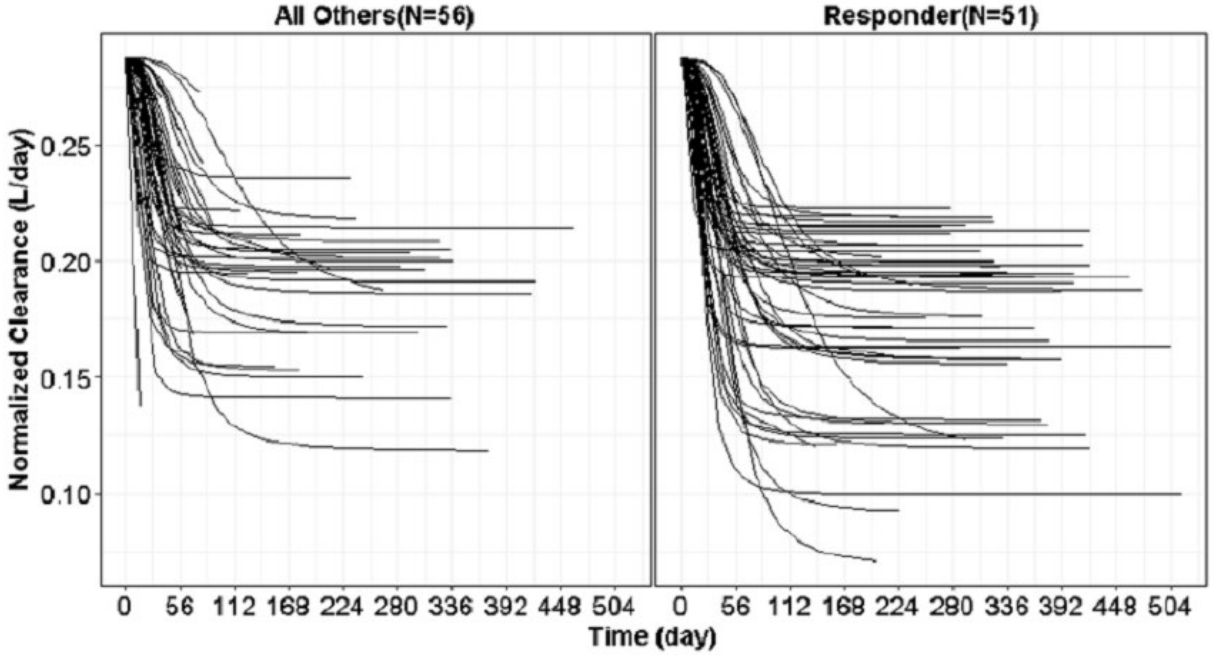
ss=steady-state; $t_{1/2,beta,2wk}$ = the half-life at the first dose; $t_{1/2,beta,ss}$ = the half-life at steady-state.

Metabolism

No clinical studies have been performed to characterise cemiplimab excretion (see pharmacology discussion).

Elimination

The primary elimination pathways of cemiplimab are protein catabolism via RES or target-mediated disposition. Following a single dose, the clearance of cemiplimab was observed to be independent of dose for the regimens studied (1 mg/kg to 10 mg/kg Q2W), but the population PK analysis did identify a time-dependent component to the clearance of cemiplimab on multiple dosing. The mean cemiplimab $T_{1/2}$ after the first dose was 12.5 days (based on NCA) and mean $T_{1/2}$ at steady state was 19.2 days (POP PK estimate). In the overall patient population, the total clearance of cemiplimab appeared to decrease over time by about 34.6% over the first 2 months of treatment, ie. from a baseline value of 0.325 L/day down to 0.211 L/day (Table 19, above). The change in clearance was larger in patients with CSCC who were considered responders to cemiplimab; the mean was 39.5% in those patients considered responders vs. 33.5% in "all others".

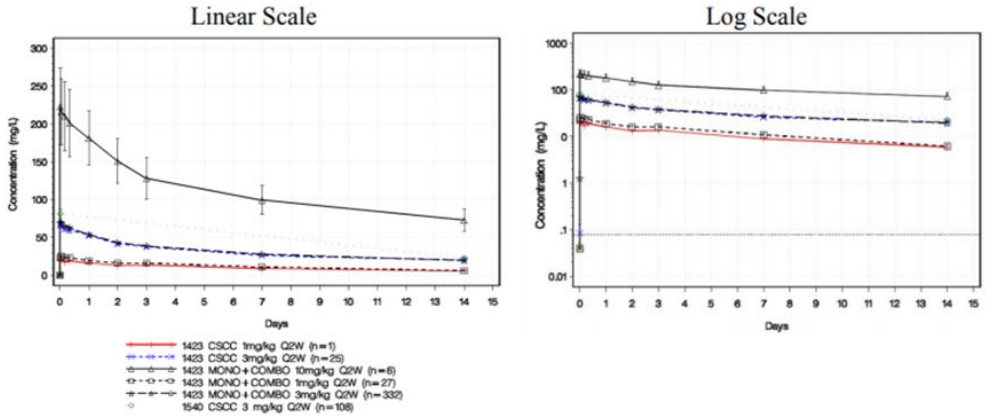


Note: A total of 107 patients in efficacy population (51 patients considered to be responders, 56 "all others") were included.
Except for 1 patient considered a responder (R2810-ONC-1423, 840004003) who received cemiplimab at 1 mg/kg Q2W, the other patients with CSCC received cemiplimab 3 mg/kg Q2W.

Figure 15: Post-hoc individual estimates of the clearance of cemiplimab over time by treatment response in patients with CSCC

Dose proportionality and time dependencies

Generally, the PK of cemiplimab are linear and dose-proportional over the 1 mg/kg to 10 mg/kg Q2W dose range.



Note: Concentrations below the LLOQ were set to 0 for linear scale or set to LLOQ/2 for log scale.
MONO + COMBO represents the overall patient population.
Study 1423 evaluated patients with various solid tumors, including CSCC who received cemiplimab at 1 mg/kg Q2W, 3 mg/kg Q2W, and 10 mg/kg Q2W as monotherapy or in combination with anti-cancer treatments.
Study 1540 evaluated only patients with CSCC who received cemiplimab 3 mg/kg Q2W as monotherapy. Only C_{trough} over time was collected in Study 1540.

Figure 16: Observed concentrations (Mean[SE]) of cemiplimab after the first dose in patients with solid tumours, including CSCC - Linear and LoG Scale - Study 1423 and Study 1540

For the overall patient population, observed C_{trough} at the 1 mg/kg dose level (after the first dose) shows a trend towards nonlinearity, especially when compared to observed C_{trough} at 10 mg/kg.

In Study 1540, concentrations of cemiplimab observed in patients with CSCC after the end of the infusion of the first dose and C_{trough} on day 14 before the second dose of a 3 mg/kg Q2W dosing regimen were consistent with concentration-time profiles at 3 mg/kg Q2W observed in patients with CSCC in Study 1423.

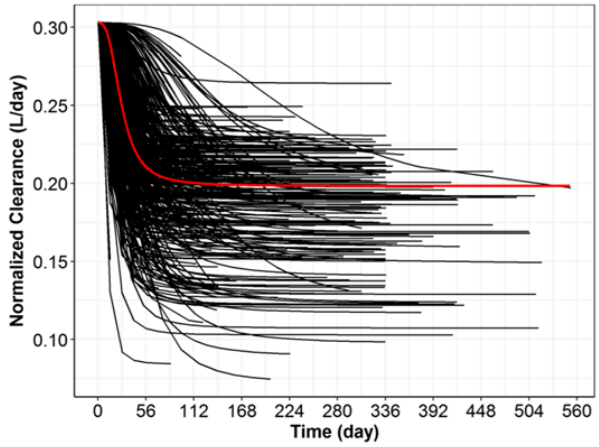
Time dependency

As determined by the population PK, patients achieve >90% of steady-state after 16 weeks dosing for the 3 mg/kg dose Q2W regimen (observed and simulated) and for the 350 mg Q3W regimen (simulated). The simulated mean accumulation index in $AUC_{6wk,ss}$ was 1.96 for the 3 mg/kg Q2W - and 1.84 for the 350 mg Q3 dosing regimen.

Table 18: Descriptive statistics for cemiplimab PK parameters in patients with solid tumours using the final PK population model, estimated at 3 mg/kg Q2W and 350 mg Q3W regimen
Q2W

3 mg/kg Q2W			350 mg Q3W		
Parameter	**Mean (CV)**	**SD**	**Parameter**	**Mean (CV)**	**SD**
Accumulation Index in $AUC_{6wk,ss}$	1.95 (20.0%)	0.391	Accumulation Index in $AUC_{6wk,ss}$	1.84 (19.7%)	0.364
Percentage of $AUC_{tau,ss}$ during (56,70] days	81.2% (11.9%)	9.71	Percentage of $AUC_{tau,ss}$ during (63,84] days	85.2% (10.7%)	9.13
Percentage of $AUC_{tau,ss}$ during (98,112] days	92.4% (7.59%)	7.02	Percentage of $AUC_{tau,ss}$ during (105,126] days	94.0% (6.64%)	6.24

On average clearance decreases by more than 30% over time compared to the baseline clearance, i.e. from ~0.30 L/day to ~0.20 L/day within 16 weeks of treatment. The half-life (T50) of time-varying clearance was estimated to be ~30 days in a typical patient.



Note: Each black line represents normalized clearance-time profiles relative to population mean clearance (0.302 L/day); the red line represents the overall time-course of population mean clearance.

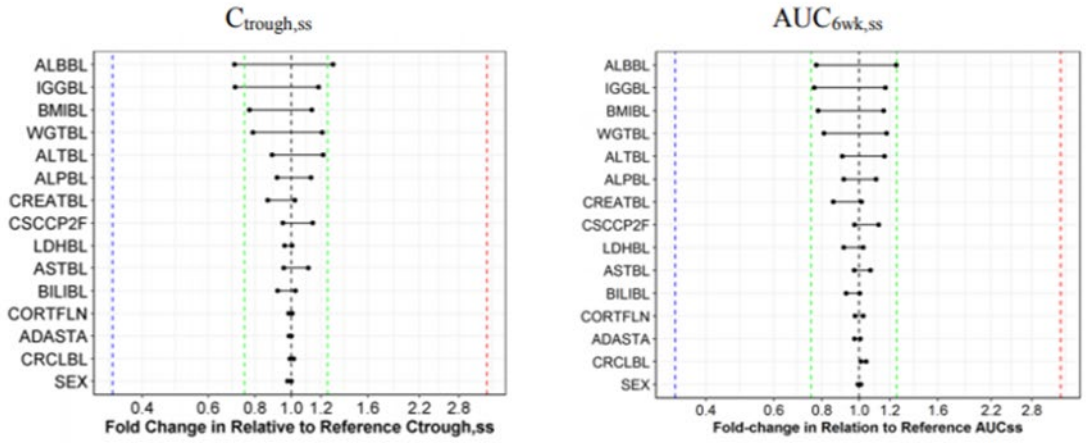
Figure 17: Post-hoc individual clearance decreases over the course of treatment duration using the final base model (LN014)

Special populations

No dedicated special population studies have been submitted. However, different demographic and pathophysiological covariates were evaluated to assess their impact of inter-individual variability of cemiplimab.

Table 19: Summary (mean+/- SD) of individual post-hoc estimates of exposure of cemiplimab at steady state (AUC6wk,ss and Ctrough,ss) for the 3 mg/kg Q2W and 350 mg Q3W regimens, by covariate or other intrinsic factor - Population PK model

Covariate	Value	N	3 mg/kg Q2W		350 mg Q3W	
			$AUC_{6wk,ss}$ (day*mg/L)	$C_{trough,ss}$ (mg/L)	$AUC_{6wk,ss}$ (day*mg/L)	$C_{trough,ss}$ (mg/L)
Reference Exposure for typical patient[a]		505	3550	62.0	3580	54.9
Study[b]	1423	396	3590 (±1300)	63.0 (±27.0)	3730 (±1400)	56.9 (±27.2)
	1540	109	4170 (±1350)	75.3 (±29.9)	4080 (±1430)	65.0 (±29.9)
Weight Quantile (kg)	[30.9,65.3]	127	3110 (±1180)	54.4 (±24.7)	4280 (±1610)	65.0 (±32.0)
	(65.3,76.1]	126	3730 (±1340)	66.4 (±28.6)	4070 (±1450)	63.6 (±29.4)
	(76.1,88.9]	126	3880 (±1220)	69.1 (±26.4)	3690 (±1190)	57.6 (±24.5)
	(88.9,156]	126	4140 (±1370)	72.8 (±29.3)	3160 (±1090)	48.4 (±22.0)
Albumin (g/L)	<30	34	2790 (±1120)	45.3 (±23.9)	2740 (±857)	36.3 (±17.5)
	(30,35]	132	3240 (±1220)	56.0 (±24.9)	3340 (±1210)	49.5 (±23.1)
	>35	339	3990 (±1300)	71.5 (±27.7)	4090 (±1430)	64.5 (±28.5)
IgG (g/L)	[1.29,7.95]	127	4070 (±1370)	73.8 (±28.7)	4240(±1530)	68.0(±30.4)
	(7.95,9.63]	127	3830 (±1270)	67.9 (±26.4)	3960(±1350)	61.4(±26.8)
	(9.63,11.9]	126	3670 (±1350)	64.7 (±29.0)	3670(±1400)	56.3(±27.4)
	(11.9,27.9]	125	3270 (±1220)	56.0 (±25.4)	3340(±1210)	48.8(±23.5)
Sex	F	209	3660 (±1380)	64.3 (±28.4)	4150(±1510)	63.3(±30.0)
	M	296	3750 (±1300)	66.6 (±27.8)	3560(±1280)	55.4(±26.0)
Race	Asia	8	3820 (±1650)	67.5 (±34.6)	4490(±2120)	69.3(±41.1)
	Black	20	3850 (±1040)	67.2 (±19.1)	3810(±867)	57.4(±14.8)
	Others	21	3330 (±1030)	57.7 (±20.4)	3370(±898)	50.3(±17.0)
	White	456	3720(±1350)	65.9(±28.6)	3810(±1440)	58.9(±28.5)
Ethnicity	Hispanic or Latino	38	3520 (±1480)	61.3(±30.5)	3670(±1430)	55.3(±28.2)
	Missing	16	3220(±1070)	56.5 (±20.5)	3400 (±769)	51.6 (±14.6)
	Not Hispanic or Latino	451	3750 (±1330)	66.4 (±28.1)	3830 (±1430)	59.2 (±28.3)
Age group (year)	<65	250	3750 (±1350)	66.3 (±28.3)	3850 (±1490)	59.5 (±29.4)
	≥65 to <75	162	3590 (±1250)	63.2 (±26.5)	3660 (±1270)	55.9 (±24.8)
	≥75	93	3820 (±1420)	68.2 (±30.1)	3930 (±1420)	61.2 (±29.0)
ADA status Treatment emergent	NA	1	2110	32.6	2890	36.0
	Negative	499	3720 (±1330)	65.9 (±28.1)	3810 (±1410)	58.9 (±28.0)
	Positive	5	2980 (±1150)	49.7 (±21.4)	3050 (±1400)	42.4 (±22.3)
Neutralized AB status	NA	495	3730 (±1340)	66.0 (±28.2)	3820 (±1420)	59.0 (±28.1)
	Negative	10	2900 (±913)	48.8 (±16.5)	2990 (±959)	42.5 (±15.4)
Tumor type 1	CSCC[b]	135	4090 (±1330)	73.9 (±29.5)	4040 (±1390)	64.2 (±29.0)
	NSCLC	71	3440 (±1250)	59.5 (±26.5)	3590 (±1320)	53.5 (±26.5)
	Others	299	3600 (±1320)	63.4 (±27.1)	3750 (±1440)	57.4 (±27.5)
Tumor type 2	laCSCC	60	4130 (±1200)	74.9 (±25.6)	4260 (±1420)	68.4 (±28.9)
	mCSCC	75	4070 (±1430)	73.1 (±32.4)	3850 (±1350)	60.9 (±28.8)
	NSCLC	71	3440 (±1250)	59.5 (±26.5)	3590 (±1320)	53.5 (±26.5)
	Others	299	3600 (±1320)	63.4 (±27.1)	3750 (±1440)	57.4 (±27.5)
Baseline ECOG	NA	2	3780 (±1590)	66.1 (±31.3)	2790 (±1050)	42.3 (±19.2)
	0	196	3950 (±1220)	71.1 (±26.2)	4040 (±1490)	64.0 (±29.6)



Note: The black dashed reference line represents steady-state exposure (C_{trough}=62.0 mg/L, $AUC_{6wk,ss}$ =3550 day*mg/L) at 3 mg/kg Q2W for a typical patient. Each solid black line represents a relevant covariate, continuous variables or categorical variables; the black dots represent the relative exposure in certain sub-population (either the top 90% percentile or bottom 10% of the relevant covariates), if continuous variables, and in the sub-population indicated by categorical variables such as (male vs. female, negative vs. positive in ADA status, etc) The length of bar from the dashed reference line represents the fold-change of $C_{trough,ss}$ and $AUC_{6wk,ss}$ in relative to the reference exposure at 3 mg/kg Q2W. The blue line and red line represent the median C_{trough} of 20.7 mg/L and 207 mg/L at 1 mg/kg Q2W and 10 mg/kg in the left panel, and median exposures of 1180 day*mg/L and 11800 day*mg/L at 1 mg/kg Q2W and 10 mg/kg Q2W on the right panel. The green lines represent the 75% or 125% of the reference exposure.

Reference patient: A typical patient in this studied patient population was a 60-year-old white male weighing 75 kg with a baseline BMI of 26.5 kg/m^2, albumin level (ALB) of 38 g/L, lactate dehydrogenase (LDH) of 250 IU/L, alkaline phosphatase (ALP) of 90 IU/L, alanine aminotransferase (ALT) of 21 IU/L, creatinine (CREAT) of 75 µmol/L, immunoglobulin G (IgG) of 9.7 g/L, body surface area (BSA) of 1.88 m^2, ADASTA: ADA status, CORTFLN: Corticosteroid (yes or no), CSCCP2F: CSCC flag based on 1540 criteria.

Figure 18: Effect of relevant intrinsic factors on post-hoc steady state cemiplimab exposure - Ctrough,ss and AUC6wk,ss

Impaired renal function

No formal PK study has been submitted in patients with renal impairment.

Based on the POP PK analysis Report 18022, the exposure of cemiplimab was evaluated in patients with mild (CLcr 60 to 89 mL/min;n=177), moderate (CL_{cr} 30 to <60 mL/min; n=83), or severe (CL_{cr} <30 mL/min; n=4) renal impairment (Table 10, below). Cemiplimab AUC did not appear to be affected by mild to moderate impaired renal function. In patients with severe renal impairment, AUC was reduced by 30 %. However, only 4 patients with severe renal impairment were included in the analysis.

Table 20: Summary statistics (Mean, SD) of post-hoc AUC6wk,ss categorised by creatinine clearance and relevant covariates at 3 mg/kg Q2W

Demographic Values							
CRCL (mL/min)	**N**	**AUC (day*mg/L)**	**WGT (kg)**	**ALB (g/L)**	**IgG (g/L)**	**CRCL (mL/min)**	**ALP (IU/L)**
≤30	4	2460(617)	52.6(7.77)	32.8(2.22)	14.4(2.63)	27.0(2.13)	140(94.7)
>30 ≤60	83	3590(1280)	65.2(13.3)	37.6(4.23)	9.96(3.29)	49.2(7.37)	98.8(53.1)
>60 ≤89	177	3740(1310)	76.0(14.8)	37.1(4.81)	10.3(3.70)	74.5(8.41)	111(81.4)
>89	241	3750(1370)	84.4(19.4)	37.5(4.56)	10.3(4.04)	123(34.6)	115(81.4)

CRCL=Creatine clearance; AUC=Area-under-the –concentration-time-curve; WGT=Weight; ALB=Albumin; IgG=Immunoglobulin; ALP=Alkaline phosphatase

Impaired hepatic function

No formal PK study has been submitted in patients with hepatic impairment.

The exposure of cemiplimab was evaluated by population PK analysis in 5 patients with mild hepatic impairment (total bilirubin [TB] greater than 1.0 to 1.5 times the upper limit of normal [ULN] and any

AST) and 1 patient with moderate (>1.5 ULN of total bilirubin) hepatic impairment (see Table below). No data were available in patients with severe hepatic impairment. 488 patients had normal hepatic function.

Table 21: Summary (mean ±SD) of estimates of exposure at steady state (AUC6wk,ss and Ctrough) of cemiplimab for the 3 mg/kg Q2W and 350 mg Q3W regimens by covariate

Covariate	Value	N	3 mg/kg Q2W		350 mg Q3W	
			$AUC_{6wk,ss}$ (day*mg/L)	$C_{trough,ss}$ (mg/L)	$AUC_{6wk,ss}$ (day*mg/L)	$C_{trough,ss}$ (mg/L)
	1	307	3560 (±1380)	62.2 (±28.8)	3660 (±1350)	55.4 (±26.4)
Creatinine Clearance (mL/min)	<30	4	2460 (±617)	39.6 (±10.5)	3780 (±1470)	50.3 (±21.3)
	(30,60]	83	3590 (±1280)	64.0 (±27.1)	4390 (±1660)	68.3 (±32.7)
	(60,89]	177	3740 (±1310)	66.4 (±27.2)	3880 (±1340)	60.2 (±26.8)
	>89	241	3750 (±1370)	66.1 (±29.1)	3540 (±1310)	54.4 (±26.3)
Total Bilirubin (µmol/L)	<3	11	4150 (±1480)	75.1 (±33.2)	4500 (±1730)	71.4 (±35.5)
	(3,25]	488	3700 (±1330)	65.4 (±28.0)	3790 (±1410)	58.5 (±27.9)
	(25,38]	5	3870 (±1260)	69.4 (±26.9)	3230 (±1030)	50.8 (±20.6)
	>38	1	3870	69.4	3510	55.2
AST (IU/L)	<10	11	3760 (±1330)	66.8 (±27.3)	3920 (±1760)	60.8 (±29.9)
	(10,40]	418	3690 (±1340)	65.1 (±28.2)	3770 (±1380)	57.9 (±27.3)
	(40,60]	35	3710 (±1360)	66.6 (±28.5)	3770 (±1440)	59.6 (±29.0)
	>60	41	3890 (±1270)	69.9 (±26.9)	4090 (±1650)	65.1 (±33.2)
ALT (IU/L)	<7	13	3020 (±1050)	51.0 (±21.4)	3590 (±1500)	51.6 (±26.1)
	(7,56]	457	3700 (±1340)	65.5 (±28.3)	3770 (±1400)	58.0 (±27.6)
	(56,84]	18	4060 (±1170)	73.1 (±23.1)	4310 (±1230)	68.5 (±22.3)
	>84	17	4070 (±1260)	74.1 (±28.6)	4350 (±1870)	71.0 (±40.0)

Source: Module 5.3.3.5 Population PK Report 18022 Table 21

[a] Median exposure is presented. A typical patient in this studied patient population was a 60-year-old white male weighing 75 kg with a baseline BMI of 26.5 kg/m2, albumin level (ALB) of 38 g/L, lactate dehydrogenase (LDH) of 250 IU/L, alkaline phosphatase (ALP) of 90 IU/L, alanine aminotransferase (ALT) of 21 IU/L, creatinine (CREAT) of 75 µmol/L, immunoglobulin G (IgG) of 9.7 g/L, body surface area (BSA) of 1.88 m2, ADASTA: ADA status, CORTFLN: Corticosteroid (yes or no), CSCCP2F: CSCC flag based on 1540 criteria.

[b] Patients with CSCC combined from Study 1423 and Study 1540.

Baseline albumin

The covariate analysis showed that baseline albumin had a significant effect on CL with a magnitude of the effect size of 1, indicating a linear relationship. Cemiplimab exposures (steady-state AUC6wk) in patients with lower than normal albumin were lower than in patients with normal albumin levels.

Table 22: Summary statistics (Mean,SD) of post-hoc AUC6wk,ss categorised by albumin (g/L) relevant covariates at 3 mg/kg Q2W

Albumin (g/L)	N	$AUC_{6wk,ss}$ (day*mg/L)	WGT (kg)	ALB (g/L)	IgG (g/L)	CRCL (mg/min)	ALP (IU/L)
<30	34	2790(1120)	80.1(21.5)	27.9(2.48)	11.8(5.05)	99.2(52.2)	150(120)
(30,35]	132	3240(1220)	77.4(21.0)	33.3(1.33)	10.1(4.31)	93.3(43.8)	122(81.9)
>35	339	3990(1300)	78.1(16.9)	39.9(2.87)	10.2(3.43)	92.1(34.8)	103(68.6)

Gender

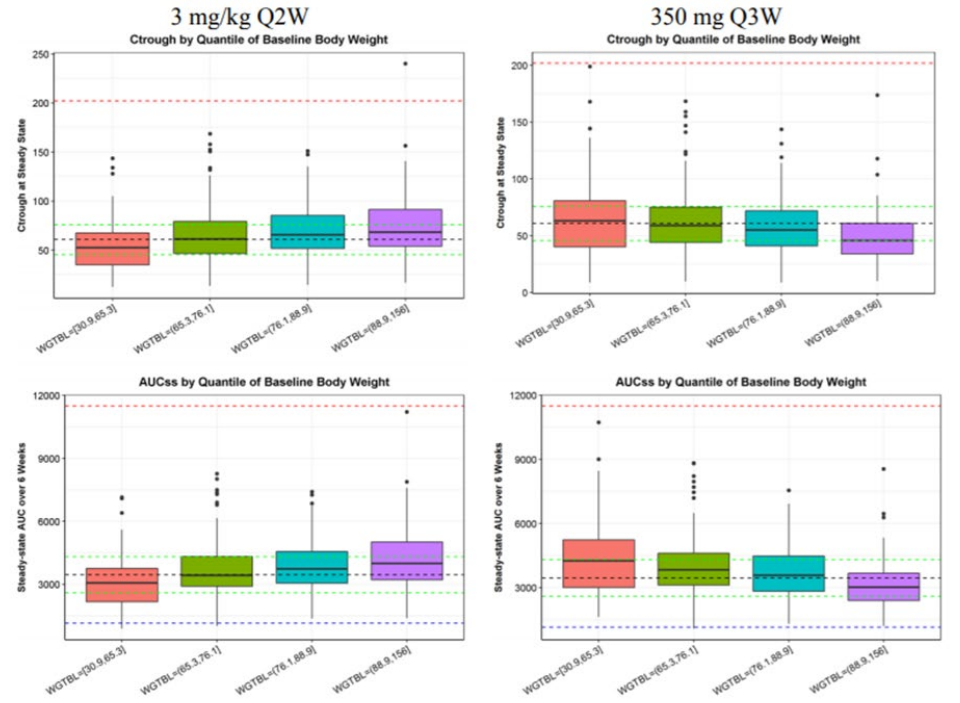
Based on the POP PK analysis, gender does not appear to have an impact on the steady state PK of cemiplimab.

Race

Maximum reduction in time-dependents Cl was achieved more slowly in black vs. white patients (75 vs. 30 days). Based on the POP PK analysis, race was not found to have an impact on the steady state PK ($C_{trough,ss}$ and AUC_{ss}) of cemiplimab.

Weight

When cemiplimab is administered with body weight-based doses (eg, 3 mg/kg Q2W) patients with higher body weight shows a trend of higher exposure, while for the 350 mg Q3W the trend is reversed. The C_{trough} for patients with BMI > 39.4 kg/m^2 were not much lower compared to patients with BMI < 18 kg/m^2. In addition, no major differences in AUC at steady state is predicted.



Note: The box plots represent median (bold line), 25th, and 75th percentiles of the $C_{trough,ss}$ and $AUC_{6wk,ss}$ distribution. The whiskers represent 5th and 95th percentiles of the distribution. The black reference line represents the median $C_{trough,ss}$ (62.0 mg/L) or $AUC_{6wk,ss}$ (3550 day*mg/L) at 3 mg/kg Q2W. The green lines represent the 75% or 125% of the reference exposure. The blue line and red line represent the median exposures of $AUC_{6wk,ss}$ (1180 day*mg/L and 11800 day*mg/L) or $C_{trough,ss}$ (20.7 mg/L and 207 mg/L) at 1 mg/kg Q2W and 10 mg/kg Q2W, respectively.

Figure 19: Population PK model: Individual post-hoc cemiplimab Ctrough,ss or AUC6wk,ss at 3 mg/kg Q2W and 350 Q3W by quantiles of baseline body weight

Individual Post-hoc estimates of cemiplimab exposure at steady state for weight and BMI extremes at steady state for 350 mg fixed Q3W fixed dosing regimen and 3 mg/kg Q2W have been illustrated. The 3 mg/kg Q2W weight adjusted regimen leads to the smallest differences in exposure between the different weight groups. It is noted that C_{trough} for patients with BMI > 39.4 kg/m^2 not are much lower compared to patients with BMI < 18 kg/m^2. No major differences in AUC at steady state is predicted. The applicant states that the variability observed is not relevant to safety or efficacy with either the BW-adjusted or the flat dose and this is agreed.

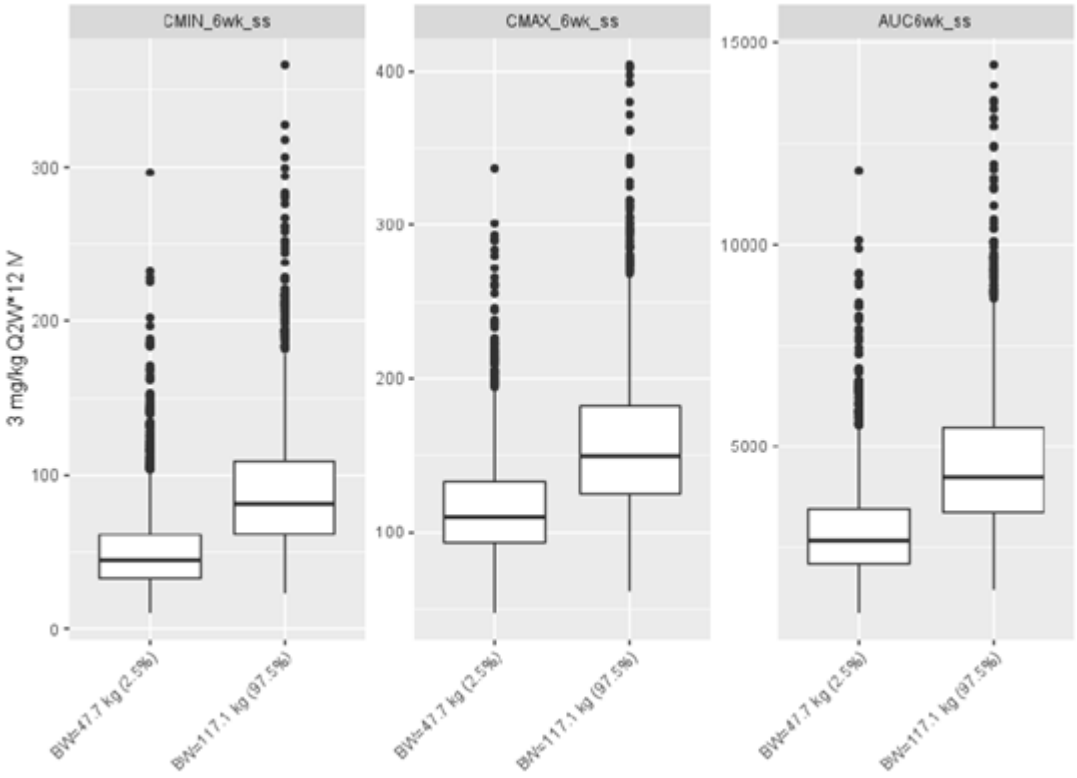


Figure 20: Boxplot of individual post-hc estimates of cemiplimab exposure for BW extremes at steady state for 3 mg/kg Q2W BW-adjusted dosing regimen

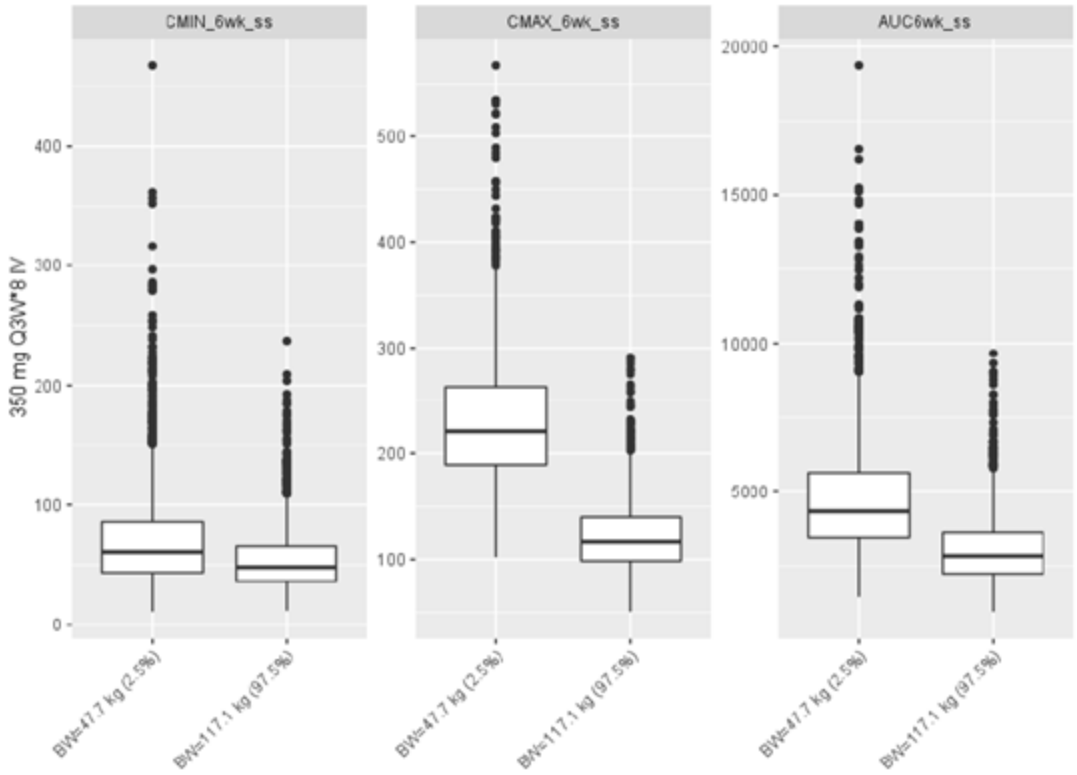


Figure 21: Boxplot of individual post-hoc estimates of cemiplimab exposure for BW extremes at steady state for 350 mg Q3W fixed dosing regimen

Elderly

Based on the population PK analysis, age did not affect the PK of cemiplimab. The patients' ages in Study 1423 and Study 1540 ranged from 27 years to 96 years.

Table 23: Summary of individual post-hoc estimates of cemiplimab exposure at steady state for the 3 mg/kg Q2W and 350mg Q3W regimens by age brackets

Dosing regimen	*Age Bracket (year)*	*Number of Patients*	$C_{min,ss}$ *(mg/L)*	$C_{max,ss}$ *(mg/L)*	$AUC_{6wk,ss}$ *(day*mg/L)*
3 mg/kg Q2W	<65	250	64.5 (±26.9)	134 (±38.1)	3620 (±1270)
	65-74	162	61.1 (±23.7)	129 (±33.3)	3460 (±1110)
	75-84	77	66.2 (±27.9)	133 (±36.1)	3660 (±1270)
	85+	16	67.2 (±25.7)	144 (±40.6)	3840 (±1280)
350 mg Q3W	<65	250	57.7 (±27.8)	165 (±46.9)	3730 (±1400)
	65-74	162	53.8 (±22.9)	158 (±42.5)	3530 (±1190)
	75-84	77	59.2 (±27.3)	163 (±41.3)	3750 (±1310)
	85+	16	60.3 (±21.1)	181 (±33.4)	4010 (±1040)

Note: Mean (±SD)

Children

No dedicated studies of cemiplimab have been conducted in pediatric patients. PK data was only collected from adults.

Other covariates

The population PK covariate analysis showed that baseline IgG is a statistically significant covariate on CL with a magnitude of the effect size of 0.18. Cemiplimab exposure was slightly lower in patients with higher IgG levels.

The population PK covariate analysis showed a small effect for baseline lactate dehydrogenase (LDH) on cemiplimab CL, whereas tumour type did not have significant impact on the PK of cemiplimab.

Pharmacokinetic interaction studies

No formal pharmacokinetic drug interaction studies have been conducted with cemiplimab. Since cemiplimab is a human monoclonal antibody and hence cleared from the circulation through catabolism, and not subject to protein transportes, no metabolic drug-drug interactions are expected. It is therefore endorsed that interactions studies have not been provided. However, other forms of interaction need to be discussed. The effect of systemic immunosuppression through use of corticosteroids and other immunosuppressants concomitantly with cemiplimab have been addressed in the SmPC section 4.5

Pharmacokinetics using human biomaterials

No pharmacokinetics using human biomaterials studies have been submitted with cemiplimab (see clinical pharmacology discussion).

2.4.3. Pharmacodynamics

Mechanism of action

No studies on the mechanism of action have been submitted with cemiplimab (see clinical pharmacology discussion).

Primary and Secondary pharmacology

QTc and ECG changes

The applicant did not submit QT and ECG studies (see clinical pharmacology discussion).

Immunogenicity

The incidence of treatment-emergent ADA in all patients with solid tumors was low (1.26% [5/398]). The incidence of treatment-emergent ADA in the subset of patients who received cemiplimab 3 mg/kg Q2W was similarly low (1.17% [4/341]). Only 1 patient who received cemiplimab 3 mg/kg Q2W in combination therapy had a persistent ADA response. No patients were positive for NAbs.

Table 24: Summary of ADA category in patients with CSCC by dose - Study 1423 and Study 1540

ADA Category	1 mg/kg Q2W[a]	**3 mg/kg Q2W[b,c,d]**	Overall
Total ADA N (%)	1 (100%)	**92 (100%)**	93 (100%)
Negative & Pre-Existing	1 (100%)	**92 (100%)**	93 (100%)
Treatment Boosted Response	0 (0%)	0 (0%)	0 (0%)
Treatment Emergent Response	0 (0%)	0 (0%)	0 (0%)
Persistent[c]	0 (0%)	0 (0%)	0 (0%)
Transient	0 (0%)	0 (0%)	0 (0%)
Indeterminate	0 (0%)	0 (0%)	0 (0%)

ADA=anti-drug antibody; CSCC=cutaneous squamous cell carcinoma; N = Number of patients; Q2W=every 2 weeks.

Source: Study 1423 and Study 1540 datasets

[a] 1 patient from Study 1423

[b] 21 patients from Study 1423 and 71 patients from Study 1540

[c] There were 14 patients with mCSCC and 8 patients with laCSCC from Study 1423.

[d] There were 41 patients with mCSCC and 30 patients with laCSCC in Study 1540.

As of the cutoff date of 30 Jun 2018, of a total of 135 patients with CSCC in Study 1540, none showed positive ADA-response (41 patients in group 1 and 59 patients in group 2 treated at 3 mg/kg every 2 weeks [Q2W]; 35 patients in group 3 treated at 350 mg every 3 weeks [Q3W]).

Exposure response relationship - Efficacy

Exposure-response analyses were conducted to evaluate the relationship between cemiplimab exposure metrics ($C_{trough1}$, C_{max1} and AUC_1) and efficacy endpoints (BOR, ORR, and DOR) in patients with CSCC. The vast majority of patients included in the analysis received cemiplimab (monotherapy) at 3 mg/kg Q2W. Steady-state exposure was not used in the exposure-response analysis of efficacy as a large portion of patients in the efficacy population did not receive a dose 2 weeks before the 6-months efficacy endpoint assessment due to drop-out or other reasons. Patients dropped-out early from the study when not responding to cemiplimab resulted in 47% and 43% of the patients with CSCC remaining in the efficacy data set on week 8 and week 16, respectively, and in 85% and 57% of the patients remaining in the safety data set on week 8 and week 16, respectively. E-R relationships for efficacy and safety were mainly impacted by the number of drop-outs. Therefore, interpretation of these E-R relationships is hampered by the limited number of patients in the analysis and the narrow exposure range considered.

Exposure-Response relationship - Safety

Table 25: Patients exposed to cemiplimab by study and included in the population pharmacokinetic model

Total Safety Population (507 patients)		CSCC Safety Population (136 patients)		CSCC Efficacy Population (108 patients)	
total dataset is filtered by population PK analysis set and exposure-response analysis exclusion[a]					
Total Exposure-Response Analysis Dataset (493 patients)		CSCC Safety Exposure-Response Analysis Dataset (135 patients)		CSCC Efficacy Exposure-Response Analysis Dataset (107 patients)	
		By Study and Treatment			
Study 1423		**Study 1423**		**Study 1423**	
1 mg/kg Q2W	27	1 mg/kg Q2W	1	1 mg/kg Q2W	1
3 mg/kg Q2W	331	3 mg/kg Q2W	25	3 mg/kg Q2W	25
10 mg/kg Q2W	6				
200 mg Q2W	20				
3 mg/kg Q3W[b]	0				
Study 1540		**Study 1540**		**Study 1540**	
3 mg/kg Q2W	109	3 mg/kg Q2W	109	3 mg/kg Q2W	81
Total	**493**	**Total CSCC**	**135**	**Total CSCC**	**107**

Source: Module 5.3.3.5 Exposure-Response Report 18023 Figure 1

[a] Two patients were excluded from population PK analysis and, therefore, the E/R analysis. One patient with CSCC (patient 840008003 of Study 1540) had insufficient number of observations to be included in the PK population. The second patient, (patient 724004020 in expansion cohort 3 of Study 1423) was classified as an outlier due because inclusion of their volatile drug concentration data caused instability of the population PK model (Section 2.3.1).

[b] The 3 mg/kg Q3W regimen was excluded from the exposure-response analysis (12 patients; none were patients with CSCC). The rationale for the exclusion is the 3-week treatment interval, which is different from the treatment interval in all other treatment groups.

The simulated cemiplimab exposure metrics at steady state are shown below.

Table 26: Post-hoc estimates of cemiplimab exposure parameters at steady-state over a 6-weeks dosing period in patients with solid tumours

Metrics	Dose	N	Mean(CV)	SE	SD	Median(CI 95)	GEOmean
$C_{trough,ss}$	3 mg/kg Q2W	505	65.7(42.8%)	1.25	28.1	62.0(21.5-134)	59.8(38.1-93.8)
(mg/L)	350 mg Q3W	505	58.7(47.7%)	1.24	28.0	54.9(16.5-131)	52.4(32.1-85.7)
$C_{avg,6wk,ss}$	3 mg/kg Q2W	505	88.4(35.9%)	1.41	31.7	84.5(35.4-164)	82.8(57.2-120)
(mg/L)	350 mg Q3W	505	90.6(37.2%)	1.50	33.7	85.3(39.1-178)	84.8(58.7-122)
$C_{max,ss}$	3 mg/kg Q2W	505	135(28.4%)	1.71	38.4	132(71.3-229)	130(97.5-173)
(mg/L)	350 mg Q3W	505	166(27.8%)	2.05	46.1	160(92.5-281)	160(122-209)
$AUC_{6wk,ss}$	3 mg/kg Q2W	505	3710(35.9%)	59.3	1330	3550(1490-6900)	3480(2400-5030)
(day*mg/L)	350 mg Q3W	505	3800(37.2%)	62.9	1410	3580(1640-7460)	3560(2470-5140)

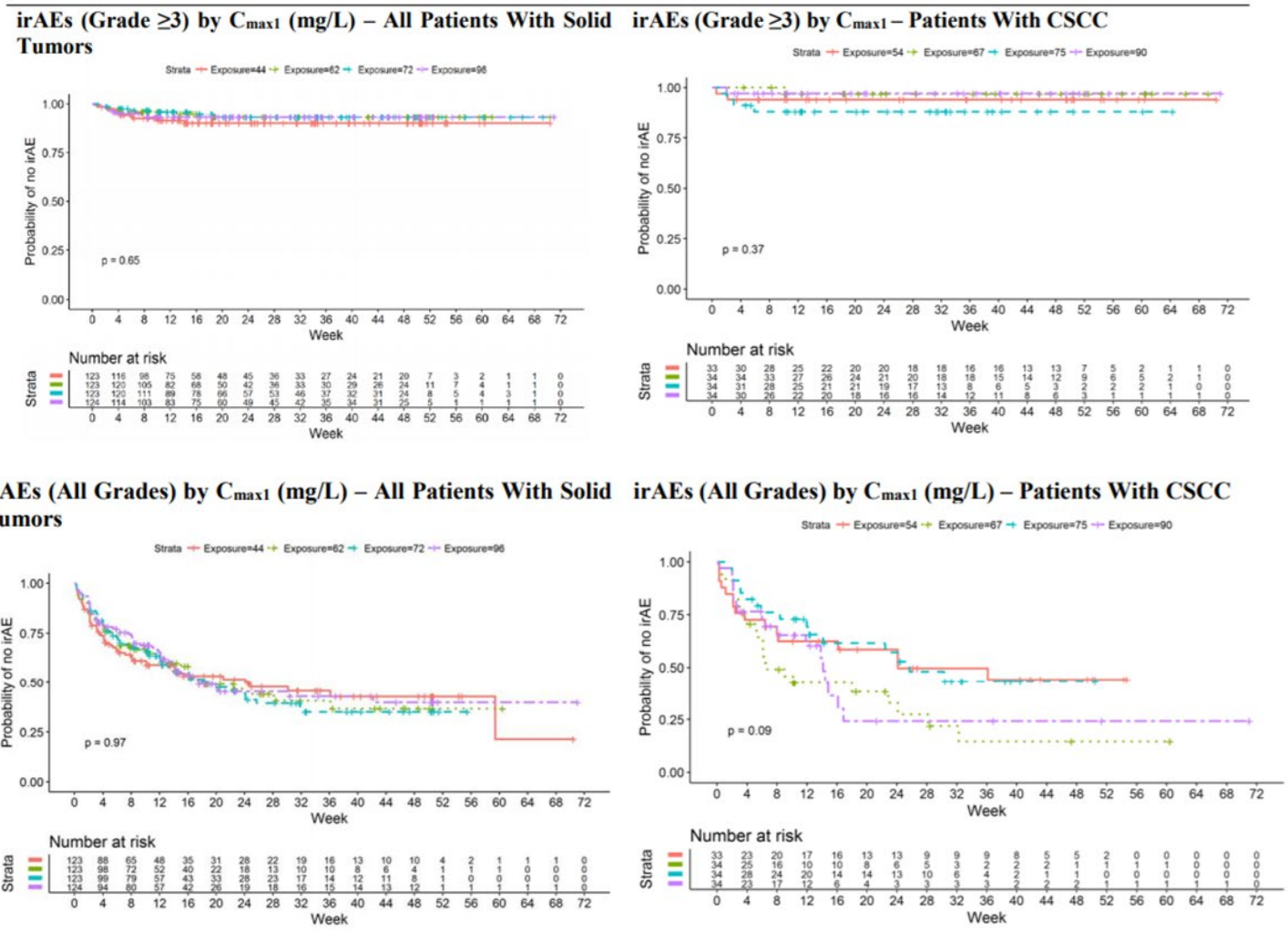
After IV administration, cemiplimab in serum reached C_{max} by end of infusion. The estimated mean $C_{max,2w}$ was 69.5 ± 16.1 µg/ml and 107 ± 26.3 µg/ml after 3 mg/kg Q2W and 350 mg Q3W, respectively, after single dose infusion. The C_{max} at steady state was estimated to be 135.0 ± 38.4 µg/ml and 166 ± 46.1 µg/ml after 3 mg/kg Q2W and 350 mg Q3W, respectively.

$C_{max,ss}$ appears to be higher for the fixed dosing regimen as compared to the weight based dosing regimen (166 vs. 135 mg/L).

Kaplan-Meier plots of grade ≥3 irAEs and irAEs regardless of grade are provided by quartiles of exposure for patients with solid tumors, patients with CSCC, and the subgroups for patients with laCSCC and patients with mCSCC. Log-rank test was conducted and p-values were provided for the Kaplan-Meier analyses. For all these E-R analyses, the number of patients decreases over time in each quartile ranges. The Kaplan-Meier plots of all irAEs by exposure metrics C_{max1}, AUC_1, or $C_{trough1}$, for all patients with solid tumors and for patients with CSCC, did not show a statistically significant exposure-response relationship.

This is shown for C_{max1} for ≥3 irAEs and irAEs regardless of grade. In patients with mCSCC, a statistically significant relationship between grade ≥3 irAEs and C_{max1} was observed. However, the order of the Kaplan-Meier plots was inconsistent.

Kaplan-Meier plots of grade ≥3 irAEs and irAEs regardless of grade are provided by quartiles of exposure for patients with solid tumors, patients with CSCC (Figure 23), and the subgroups for patients with laCSCC and patients with mCSCC.



Note: Strata represent the mean interquartile values of the C_{max1} exposure metric. Kaplan-Meier plots are provided for each strata. Pluses in each plot represent censoring time. Numbers at risk represent number of patients in each strata and for each time point.
Descriptive statistics of exposure including quartiles, as well as descriptive statistics of interquartile values of exposure, are provided in the Exposure-Response Report 18032 Appendix 8.2. The duration of response in patients not categorized as responders ("all others") was imputed as zero

Figure 22: Exposure-Response KM plot of immune-related adverse events by quartiles of Cmax1 (mg/L)

2.4.4. Discussion on clinical pharmacology

Overall, the analytical methods used were acceptable. The bioanalytical method for quantitative determination of cemiplimab appears to be adequately validated and suitable for its purpose. Assay performance, in terms of inter-assay precision and inter-assay relative error was considered acceptable.

The PK characteristics of cemiplimab in patients with solid tumours were first analysed as a function of the dose in the dose escalation cohorts (1 mg/kg, 3 mg/kg, and 10 mg/kg Q2W), for monotherapy and for combination therapy (Study 1423). The concentrations of cemiplimab were then further investigated in the expansion cohorts in the broader population of patients with different solid tumour types receiving monotherapy or combination therapy. The design of the two clinical studies providing PK data are overall adequate. Concentration data were collected in 548 patients with various solid tumours, including 178 patients with CSCC, who received cemiplimab. At dosing regimens of 1 mg/kg to 10 mg/kg every 2 weeks and 350 mg every 3 weeks, kinetics of cemiplimab were observed to be linear and dose proportional, suggesting saturation of the target-mediated pathway over the dosing interval. Similar exposures to cemiplimab are achieved with the doses of 350 mg every 3 weeks and 3 mg/kg every 2 weeks. With 350 mg every 3 weeks, the mean steady-state concentration of cemiplimab ranged between C_{max} of 168 mg/l and a C_{trough} of 61 mg/l. Steady-state exposure is achieved after approximately 4 months of treatment. A Linear elimination model was best to describe the PK of cemiplimab, although a parallel elimination comprising both a linear and a non-linear elimination pathway was expected for cemiplimab in line with other monoclonal antibodies and cemiplimab non-human data. In case cemiplimab was cleared primarily by target mediated drug disposition, dose-dependent nonlinear elimination would occur. However, incorporating a Michaelis-Menten elimination term did not improve the goodness of fit compared to the corresponding linear models. This may be due to lack of sufficient data or due to limited availability of the target receptors resulting in limited or no relevant contributions of target mediated drug disposition. The applicant should provide further information about the non-linear phase of cemiplimab disposition in the further analysis of studies 1423 and 1540.

Cemiplimab is administered via the intravenous route and hence is completely bioavailable. Cemiplimab is primarily distributed in the vascular system. The POP PK model based mean clearance and volume of distribution in steady state were 0.211 L/day and 5.2 L, respectively, which is in line with the expected principal PK parameters for a monoclonal antibody administered IV. This corresponds to a half-life of approximately 19.2 (POP PK estimated value). Inter-individual variability (% CV) for CL (40 %) and Volume of Distribution at SS (24.3%) was moderate. While the available single dose cemiplimab concentration data was best described by a 2-compartment linear model, the population PK analysis did identify a time-dependent component to the clearance of cemiplimab on multiple dosing.

Clearance of cemiplimab is linear at doses of 1 mg/kg to 10 mg/kg every two weeks. Cemiplimab clearance after the first dose is approximately 0.33 L/day. The total clearance appears to decrease by approximately 35% over time, resulting in a steady state clearance (CLss) of 0.21 L/day; the decrease in CL is not considered clinically relevant. The within dosing interval half-life at steady state is 19.4 days. In the overall patient population after repeated dosing, the total clearance of cemiplimab decreased over time by about 34.6% over the first 2 months of treatment, ie, from a baseline value of 0.325 L/day down to 0.211 L/day. It is hypothesized that the change in antibody clearance may serve as an early marker for drug efficacy. Based on the data provided, it is acceptable that dose adjustment is not necessary in that the cemiplimab exposure is not expected to affect efficacy or safety.

The POP PK analysis comprised predominantly data from the dosing regimen 3 mg/kg Q2W (totally n=440). 53 patients from Group 3 (350 mg Q3W) were included in the updated PK analysis set. Comparison of the observed data and the updated model predictions indicates that the performance of the PopPK model was consistent with the original analysis. A population PK analysis suggests that the following factors have no clinically significant effect on the exposure of cemiplimab: age, gender, body weight, race, cancer type, albumin level, mild hepatic impairment and renal impairment.

The applicant has not conducted a QT study. Considering that no clinically relevant effect on cardiac repolarization was noted for any of the checkpoint inhibitors, the lack of QT study is acceptable.

No pharmacokinetic interactions through metabolic enzymes or transporters are expected for an IgG antibody. Specific metabolism studies were not conducted because cemiplimab is a protein. Cemiplimab is expected to degrade to small peptides and individual amino acids. No pharmacokinetic drug-drug interaction studies have been conducted with cemiplimab. The use of systemic corticosteroids or immunosuppressants before starting cemiplimab, except for physiological doses of systemic corticosteroid (≤10 mg/day prednisone or equivalent), should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of cemiplimab. However, systemic corticosteroids or other immunosuppressants can be used after starting cemiplimab to treat immune-related adverse reactions (see SmPC section 4.2).

The 350 mg Q3W group was comparable to the population predicted exposure based on a dataset that was updated to include 43 patients with CSCC who received 350 mg Q3W (from Group 3 of Study 1540), of which 23 patients had reached 80% of steady state exposure following administration of 350 mg Q3W. Therefore, it can be agreed that the observed exposure for the 350 mg Q3W dosing regimen appear to be comparable to that observed for the 3 mg/kg Q2W dosing regimen. The PopPK modelling with PK data from the 350 mg Q3W dose has confirmed comparable exposure parameters between the two dosing regimens. The applicant has also presented additional clinical efficacy and safety data for patients treated with the fixed 350 mg Q3W dose, and the conclusion following assessment of these data is that the 350 mg Q3W dose is overall as efficacious and safe as the 3 mg/kg Q2W dose (see clinical efficacy section). Based on the cemiplimab exposure data at steady state, the preliminary antitumor activity observed at 3 mg/kg Q2W dose in Study 1423 and the similar exposures achieved with the doses of 350 mg every 3 weeks and 3 mg/kg every 2 weeks, the fixed 350 mg Q3W dose is acceptable.

Cemiplimab showed a low immunogenicity potential (1.26%) in all patients receiving cemiplimab 3 mg/kg Q2W (n=398). The validation range for the functional cemiplimab bioanalytical assay is in undiluted human serum. The ADA screening assay sensitivity was determined to be 15 ng/mL in presence of 150 µg/mL cemiplimab. The performance of the ADA assay should be more stringently controlled. The presently set acceptance criteria do not set the analyses to any certain level, but rather allow drifting of the measured values without any limits. Although the outcome of an analysis of a sample is either ADA positive or ADA negative, the technical read-out obtained from the analysis is numerical and the results obtained from the control samples must level from one analysis to another. This is a prerequisite for controlling the consistency and reliability of the assay at levels close to the assay cut point. Therefore, it is recommended that the applicant should develop such assay acceptance criteria that anchor the level of the assay to a certain read-out range for further use. No dose adjustment is recommended for elderly patients. Cemiplimab exposure is similar across all age groups (see SmPC sections 5.1 and 5.2).

The effect of renal impairment on the exposure of cemiplimab was evaluated by a population PK analysis in patients with mild (CLcr 60 to <89 ml/min; n= 197), moderate (CLcr 30 to <60 ml/min; n= 90), or severe (CLcr <30 ml/min; n= 4) renal impairment. No clinically important differences in the exposure of cemiplimab were found between patients with renal impairment and patients with normal renal function. Cemiplimab has not been studied in patients with CLcr <25 ml/min.

No dose adjustment of LIBTAYO is recommended for patients with renal impairment. There are limited data for LIBTAYO in patients with severe renal impairment CLcr <30ml/min (see sections 4.2 and 5.2 of the SmPC).

The effect of hepatic impairment on the exposure of cemiplimab was evaluated by population PK analysis. In patients with mild hepatic impairment (n= 5) (total bilirubin [TB] greater than 1.0 to 1.5 times the upper limit of normal [ULN] and any aspartate aminotransferase [AST]); no clinically important differences in the exposure of cemiplimab were found compared to patients with normal hepatic function. Cemiplimab has not been studied in patients with moderate or severe hepatic impairment. There are insufficient data in patients with moderate or severe hepatic impairment for dosing recommendations.

No dose adjustment is recommended for patients with mild hepatic impairment. LIBTAYO has not been studied in patients with moderate or severe hepatic impairment. There are insufficient data in patients with moderate or severe hepatic impairment for dosing recommendations (see sections 4.2 and 5.2 of the SmPC 4.2).

The applicant originally applied for two strengths of 250 mg and 350 mg of cemiplimab. During the assessment, the applicant withdrew the 250 mg strength due to the anticipated approval of the 350mg Q3W dosing regimen.

2.4.5. Conclusions on clinical pharmacology

In conclusion, pharmacokinetics of cemiplimab has been mainly characterized by PK results from studies 1423 and 1540 as well as a PopPK model which is considered acceptable. The 350 mg Q3W dose is considered comparable between the two dosing regimens and has been appropriately investigated. The CHMP is of the opinion that the performance of ADA assay should be more stringently controlled.

The CHMP recommends the following measures to address the issues related to pharmacology:

- The performance of the ADA assay should be more stringently controlled. The presently set acceptance criteria do not set the analyses to any certain level, but rather allow drifting of the measured values without any limits. Although the outcome of an analysis of a sample is either ADA positive or ADA negative, the technical read-out obtained from the analysis is numerical and the results obtained from the control samples must level from one analysis to another. This is a prerequisite for controlling the consistency and reliability of the assay at levels close to the assay cut point. Therefore, it is recommended that the applicant should develop such assay acceptance criteria that anchor the level of the assay to a certain read-out range for further use.
- To provide more information about the non-linear phase of cemiplimab disposition in the further analysis of Studies 1423 and 1540 currently planned.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

In the Dose Escalation (DE) phase of Study 1423, 3 dose levels of cemiplimab were administered (1, 3, or 10 mg/kg) intravenously (IV) every 2 weeks (Q2W). A 3 + 3 model was used and the safety of cemiplimab was evaluated as monotherapy and in combination with potentially immune-enhancing treatments (cyclophosphamide [CTX], hypofractionated radiotherapy [hfRT], and the combination of combined hfRT plus CTX) in DE:

Cohort	Dose Escalation Cohort Regimen
DE -1	0.3 mg/kg cemiplimab monotherapy ***(contingency cohort, only to be enrolled if maximum-tolerated dose [MTD] exceeded in DE cohort 1)***
DE 1	1 mg/kg cemiplimab monotherapy*
DE 2	3 mg/kg cemiplimab monotherapy
DE 3	10 mg/kg cemiplimab monotherapy
DE 4	1 mg/kg cemiplimab + RT (6 Gy × 5)
DE 5	1 mg/kg cemiplimab + RT (9 Gy × 3)
DE 6	3 mg/kg (or MTD) cemiplimab + CTX
DE 7	3 mg/kg (or MTD) cemiplimab + RT (6 Gy × 5)
DE 8	3 mg/kg (or MTD) cemiplimab + RT (9 Gy × 3)
DE 9	3 mg/kg (or MTD) cemiplimab + RT (6 Gy × 5) + CTX
DE 10	3 mg/kg (or MTD) cemiplimab + RT (9 Gy × 3) + CTX

After recommended dose of cemiplimab, alone and in combination with hfRT and/or CTX, was established in the DE portion of the study, multiple Expansion Cohorts were opened:

Expansion Cohort*	Indication	Treatment
1	NSCLC	200 mg cemiplimab
2	NSCLC	3 mg/kg cemiplimab + RT (9 Gy × 3)
3	HNSCC	3 mg/kg cemiplimab + RT (9 Gy × 3) + CTX + GM-CSF
4	BC	3 mg/kg cemiplimab + RT (9 Gy × 3) + CTX
5	Advanced solid tumors –Previous treatment with an anti PD-1/PD-L1 antibody	3 mg/kg cemiplimab+ RT (9 Gy × 3) + CTX + GM-CSF
6	Advanced solid tumors (excluding NSCLC, HNSCC, and BC)	3 mg/kg cemiplimab+ RT (9 Gy × 3) + CTX + GM-CSF
7	Metastatic (M1) CSCC	3 mg/kg cemiplimab
8	Locally and/or regionally advanced CSCC (M0) that is unresectable	3 mg/kg cemiplimab
9	Metastatic colorectal cancer with MSI	3 mg/kg cemiplimab
10	Metastatic endometrial cancer with MSI	3 mg/kg cemiplimab: closed due to insufficient accrual
11	Castrate recurrent prostate cancer with MSI	3 mg/kg cemiplimab : closed due to insufficient accrual
12	Any other advanced solid tumor with MSI	3 mg/kg cemiplimab

The Expansion Cohorts involved cemiplimab as monotherapy and as combination therapy in various combinations with chemotherapy or radiotherapy (RT) in selected indications. In both DE and Expansion Cohort portions of the study, the initial planned treatment with cemiplimab was Q2W for up to 48 weeks, with approximately 24 weeks of follow-up observation. Patients who had disease progression during the follow-up period had the option to resume treatment with cemiplimab if eligibility criteria were still met.

The rationale for the use of 3 mg/kg cemiplimab IV Q2W dose in Group 1 (mCSCC) and Group 2 (laCSCC) from Study 1540 was based on data from the ongoing Study 1423. The rationale for the use of cemiplimab 350 mg IV Q3W dose in Group 3 (mCSCC) from Study 1540 and for all subsequent studies was based on population PK modelling (see clinical pharmacology section).

2.5.2. Main study(ies)

R2810-ONC-1540: A phase 2 study of REG2810, a fully human monoclonal antibody to programmed death – 1 (PD-1), in patients with advanced cutaneous squamous cell carcinoma.

Methods

Study Participants

The study included eligible patients with mCSCC (nodal and/or distant) (Groups 1 and 3) and laCSCC (Group 2). Group 3 (mCSCC) was opened for enrollment only after enrollment to Group 1 (mCSCC) was completed.

Inclusion Criteria

1. Histologically confirmed diagnosis of invasive CSCC.
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.

   Group 1 (mCSCC) and Group 3 (mCSCC): 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(Eisenhauer, 2009).

   Group 2 (laCSCC): There must have been at least 1 measureable baseline lesion in which the longest diameter and the perpendicular diameter were both ≥10 mm if followed by digital medical photography. Nonmeasurable disease for Group 2 (laCSCC) 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.
3. ECOG performance status ≤1
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)
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. Group 2 (laCSCC) only: Surgery was deemed contraindicated in the opinion of a Mohs dermatologic surgeon, a head and neck surgeon, or plastic surgeon
12. Group 2 (laCSCC) only: 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 therapyld go ov 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 tumour was unlikely to respond to therapy.
    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.
13. 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 applicant prior to enrollment.
14. Group 2 (laCSCC) only: 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. Group 2 (laCSCC) only: 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.

Exclusion Criteria

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 has resolved, type 1 diabetes, residual hypothyroidism that required only hormone replacement, or psoriasis that does 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 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
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 are not excluded), radiation therapy within 14 days of initial administration of cemiplimab or planned to occur during the study period
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. Specifically, because of the presence of trace components in cemiplimab, patients with allergy or hypersensitivity to doxycycline or tetracycline 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 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. 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 who were unwilling to practice highly effective contraception during the study and until 6 months after the last dose of study drug (highly effective contraceptive measures include 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; intrauterine device; intrauterine hormone-releasing system; bilateral tubal ligation; vasectomy, and sexual abstinence).

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.
20. Inability to undergo any contrast-enhanced radiologic response assessment.
21. Prior treatment with idelalisib

Treatments

Patients with CSCC received either:

- 3 mg/kg cemiplimab intravenous (IV) every 2 weeks (Q2W) in Group 1 (mCSCC) and group 2 (laCSCC)
- 350 mg cemiplimab IV every 3 weeks (Q3W) in Group 3 (mCSCC)

Duration of treatment: Group 3 (mCSCC) patients received 350 mg cemiplimab IV Q3W for up to 54 weeks (whereas patients in Group 1 [mCSCC] and Group 2 [laCSCC] received 3 mg/kg cemiplimab IV Q2W for up to 96 weeks).

Dose modification or interruption: Toxicity management guidelines in the protocol indicated scenarios in which interruption or discontinuation of study treatment was required. Dose reduction of cemiplimab was allowed only in uncommon situations and only after discussion and agreement between the investigator and sponsor.

Objectives

Primary Objective

The primary objective of this study was to estimate the clinical benefit of cemiplimab monotherapy for patients with mCSCC treated Q2W (Group1), laCSCC treated Q2W (Group 2), or mCSCC treated Q3W (Group 3), as measured by the ORR according to independent central review in each group.

Secondary Objectives

- 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 OS
- To estimate the CR rate by independent central review
- To assess the safety and tolerability of cemiplimab
- To assess the PK of cemiplimab (at select sites only)
- To assess the immunogenicity of cemiplimab
- To assess the impact of cemiplimab on quality of life using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

Exploratory Objectives (Group 2 [laCSCC] only)

The exploratory objectives include evaluation of the pharmacodynamics of cemiplimab in tumor biopsies obtained at baseline, during treatment, and at progression in CSCC patients treated with cemiplimab and assessed predictive potential and correlation to clinical response for biomarkers of interest including but not limited to the following:

- Tumour RNA expression
- Number and distribution of tumour-infiltrating lymphocytes (cluster of differentiation [CD]8+ T cells, CD4+ T cells, T regulatory cells, and tissue permitting, other subtypes such as B cells, myeloid-derived cells, natural killer cells, etc.)
- Expression levels (messenger RNA and/or protein) of PD-L1, glucocorticoid-induced tumor necrosis factor receptor family related gene, lymphocyte activation gene-3, and possibly other checkpoint modulators
- Mutations in known oncogenes and potential tumour neoantigens
- Tumour mutation burden

Outcomes/endpoints

The primary efficacy variable for this study was ORR according to independent central review. The following independent central review committees determined ORR separately for Group 1 (mCSCC) and Group 2 (laCSCC):

- For Group 1 and Group 3 (mCSCC), Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was used to determine ORR. For patients in whom all response assessments were performed on radiologic scans according to RECIST 1.1, the determination of the Independent Radiologic Review Committee (IRRC) served as the central response assessment. Clinical or composite response criteria was used for patients with externally visible target lesions, if all metastatic lesions were not measureable by RECIST (such as may occur in patients with bone-only metastases).
- For Group 2 (laCSCC), composite response criteria were used for the centrally reviewed ORR. Composite response was based on photographic assessment of externally visible lesions according to modified WHO-criteria by the Independent Photographic Review Committee (IPRC) AND assessment of radiologic data according to RECIST 1.1 by the IRRC. The central response assessments for Group 2 (laCSCC) patients were determined by the ICRC, which integrated all of the information provided by the IPRC and the IRRC for each patient.

<u>Primary Efficacy Variable: Objective response rate (ORR)</u>

Objective response rate was based on a centrally reviewed evaluation at each time point at which a response assessment occurred using RECIST 1.1 or the composite response criteria.

Best overall response (BOR) was determined once all the data for the patient were known. The BOR was the best response recorded during the study as of the data cutoff date. A BOR of CR or partial response (PR) must have been confirmed by evaluations of overall response of CR or PR at time points at least 4 weeks apart. A BOR 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 drug. Best overall response of (early) progressive disease (PD) did not require confirmation using the RECIST 1.1 or the composite response criteria. For patients who did not have any post-baseline tumor assessment, BOR was not evaluable (NE). Patients with BOR of NE were considered as not reaching an objective response of CR or PR.

Objective response rate was determined by the proportion of patients with BORs of CR or PR in the full analysis set (FAS) by group. Patients with BOR of NE were considered as not reaching an objective response of CR or PR.

Key secondary endpoint: Duration of response by central-reviewed evaluation (DOR)

It is determined for patients with best overall response of CR or PR. DOR is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date of recurrent or progressive disease (radiographic), or death due to any cause. Patients who never progress while being followed will be censored at the last valid tumour measurement.

Other Secondary Efficacy Variables

- ORR based on investigator-assessed evaluation using the RECIST version 1.1 or the composite response
- Progression-free survival (PFS) is measured from the start of treatment until the first date of recurrent or progressive disease (radiographic), or death due to any cause. Patients who never progress while being followed will be censored at the last valid tumour measurement. If a patient has no post-baseline evaluation, the patient will be censored at first treatment date.
- Overall survival (OS) is measured from the start of treatment until death due to any cause. Patients who do not have a survival event will be censored at the last date that patient is documented to be alive. As many patients may receive subsequent therapy after disease progression, a variant of OS will also be defined as censoring patients who do not have a survival event at the first date of a subsequent therapy is taken.
- CR rate is determined by the proportion of patients with best overall response of CR after tumour biopsy confirmation. Patients with best overall response of NE will be considered as not reaching an objective response of CR.
- Time to response (TTR) was determined by independent central review and by investigator assessment.
- Patient-reported quality of life is measured by the EORTC QLQ-C30: The global health status/QoL, five functional scales (physical, role, cognitive, emotional and social), and three symptom scales (fatigue, pain, nausea and vomiting) and a number of single items assessing additional symptom commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease will be computed using the QLQ-C30 scoring procedures. Change scores are defined as change of summary score of EORTC QLQ-C30 from day 1 of first treatment cycle.

For all of the above time-to-event variables, the time-to-event (day) was the date of event/censor minus the date of first study drug + 1.

Sample size

Based on previous studies, a clinically meaningful ORR for an investigational agent was expected to be >15% for patients with metastatic disease or >25% for patients with laCSCC.

For Group 1 (mCSCC), 50 patients were required to provide at least 85% power to reject a null hypothesis of an ORR of 15% at a 2-sided significance level of no more than 5% if the true ORR was 34%. For Group 2 (laCSCC), 72 patients were required to provide at least 90% power to reject a null hypothesis of an ORR of 25% at a 2-sided significance level of no more than 5% if the true ORR was 44%.

The sample sizes for each group were selected such that the lower limit of the 2-sided 95% confidence interval (CI) of the estimated ORR would be clinically meaningful. The non-clinically meaningful ORR of 15% for Group 1 (mCSCC) was excluded using the lower limit of 95% CI if the observed ORR was around 28.0% or more (i.e., the ORR for Group 1 [mCSCC] was significantly different from 15%). The non-clinically meaningful ORR of 25% for Group 2 (laCSCC) was excluded using the lower limit of 95% CI if the observed ORR was around 36.1% or more; i.e., the ORR for Group 2 (laCSCC) was significantly different from 25%.

At later stage during the conduction of the study (Amendment 3), a third cohort including 53 additional patients with metastatic CSCC was enrolled in a new group, Group 3. The same assumptions for the sample size made for Group 1 were used for Group 3.

An exact binomial test was applied for the calculations.

Randomisation

Study 1540 was a single arm study, therefore randomization was not applicable.

Blinding (masking)

Study 1540 was a single arm study, therefore blinding was not applicable.

Statistical methods

Interim Analysis for Study 1540

At the time of the planned primary efficacy analysis for Group 1 (mCSCC) (6 months after last patient, first dose), an interim analysis of efficacy for patients in Group 2 (laCSCC) was performed. These changes were introduced at a late stage in the protocol as Amendment 5 (22 Sept 2017).

The efficacy analysis for patients in Group 2 (laCSCC) was restricted to those with potential for "adequate" follow-up, defined as patients who had the opportunity to receive approximately 9 months of study drug at the time of the interim analysis.

For the primary variable of ORR, the following null and alternative hypotheses were tested for

Group 1 (mCSCC) and Group 2 (laCSCC), respectively:

- Group 1 (mCSCC): H0: ORR = 15% vs. H1: ORR ≠ 15%
- Group 2 (laCSCC): H0: ORR = 25% vs. H1: ORR ≠ 25%
- Group 3 (mCSCC): H0: ORR = 15% vs. H1: ORR ≠ 15%

Different approaches were taken regarding the alpha level:

- No correction to the alpha level for the interim analysis: the overall response rate and associated 95% confidence interval were applied. As the primary objective of the interim analysis is point estimation on ORR and characterizing the precision of point estimation, there is no hypothesis testing associated with this interim analysis. Also, no decisions will be made regarding study conduct associated with the interim analysis. Therefore, Type I error adjustment is not applicable for this planned interim analysis.
- The alpha level was corrected for the interim analysis: for Group 2 a two sided alpha of 0.0001 was allocated for interim analysis and two-sided alpha of 0.0499 will be preserved for the final analysis. Correspondingly, for the interim analysis of primary endpoint of ORR in group 2

patients, the precision of ORR will be estimated by adjusted and two-sided 99.99% exact confidence interval. The un-adjusted and two-sided 95% exact confidence interval will also be reported at the time of interim analysis. At the time of the final analysis for group 2 patients, both adjusted 95.01% and un-adjusted 95% exact confidence interval will be reported.

The data cut-off for the planned primary analysis of metastatic CSCC Group 1 in pivotal Study 1540 was 6 months after enrolment of the last patient into Group 1, at a time when the locally advanced CSCC Group 2 was still enrolling. The data cut-off for the interim analysis of the local advanced CSCC Group 2 in pivotal study was decided to be the same time as the cut-off for Group 1.

The data for the interim analysis of Group 2 was limited to patients with at least 9 months of follow-up.

Study populations

- Full Analysis Set (FAS): all patients who has passed screening and are eligible for the study. This is population used for the efficacy variables.
- Safety Analysis Set (SAF): all enrolled patients who have received at least one dose of cemiplimab. Treatment compliance/administration and all clinical safety variables will be analysed or summarised using the SAF.
- PK Analysis Set (PKA): all patients who have received any cemiplimab and who have at least one non-missing drug concentration after the first dose of study drug.
- Anti-drug Antibody Set (ADA): all patients who have received cemiplimab and who have at least one post-dose ADA result.
- Biomarker Analysis Set (BAS): all patients who have received cemiplimab and who have at least one sample assayed (only relevant for Study 1540).

Analysis variables

For continuous variables, descriptive statistics include the following: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum. In addition, 25th percentile and 75th percentile was provided.

For categorical or ordinal data, frequencies and percentages was displayed for each category.

For time-to-event variables, median time-to-event (and the survival rate at a fixed time point) and its 95% confidence intervals was summarised by the Kaplan-Meier method. The confidence interval for the proportion of patients with BORs of CR or PR was calculated using the Clopper-Person method.

Statistical analysis for efficacy was conducted independently for each group.

Results

Participant flow

As of the data cutoff of the interim analysis, a total of 194 patients had been screened, and a total of 137 patients had been enrolled and treated (59 patients in Group 1 [mCSCC], 55 patients in Group 2 [laCSCC], and 23 patients in Group 3 [mCSCC]) at 31 sites in 3 countries.

The reasons for the 57 screen failures are detailed as follows:

	Total (N=57)
Reason for screen failure, n (%)	
Adverse Event	0
Serious Adverse Event	1 (1.8%)
Does not meet Inclusion/Exclusion Criteria	41 (71.9%)
Withdrawal of Consent	8 (14.0%)
Lost to follow-up	1 (1.8%)
Death	1 (1.8%)
Other	5 (8.8%)

Detailed patient disposition for the safety analysis set (N=137):

Table 14.1.1.4 Patient Disposition
(Safety Analysis Set)

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=55)	mCSCC Cemiplimab: 350 mg Q3W (N=23)	Total (N=137)
Treatment Ongoing, n (%)	35 (59.3%)	40 (72.7%)	21 (91.3%)	96 (70.1%)
Off Treatment, n (%)	24 (40.7%)	15 (27.3%)	2 (8.7%)	41 (29.9%)
Treatment Completed	0	0	0	0
Treatment Discontinued	24 (40.7%)	15 (27.3%)	2 (8.7%)	41 (29.9%)
Primary Reason for Treatment Discontinuation				
ADVERSE EVENT	4 (6.8%)	1 (1.8%)	0	5 (3.6%)
PREGNANCY	0	0	0	0
DEATH	2 (3.4%)	2 (3.6%)	1 (4.3%)	5 (3.6%)
LOST TO FOLLOW-UP	0	0	0	0
NON-COMPLIANCE WITH STUDY DRUG	0	1 (1.8%)	0	1 (0.7%)
SUBJECT DECISION	2 (3.4%)	1 (1.8%)	0	3 (2.2%)
SPONSOR DECISION	0	0	0	0
PHYSICIAN DECISION	1 (1.7%)	1 (1.8%)	0	2 (1.5%)
DISEASE PROGRESSION	14 (23.7%)	7 (12.7%)	0	21 (15.3%)
WITHDRAWAL OF CONSENT	0	0	1 (4.3%)	1 (0.7%)
OTHER	1 (1.7%)	2 (3.6%)	0	3 (2.2%)
Number of patients entered follow-up, n (%)	13 (22.0%)	6 (10.9%)	0	19 (13.9%)

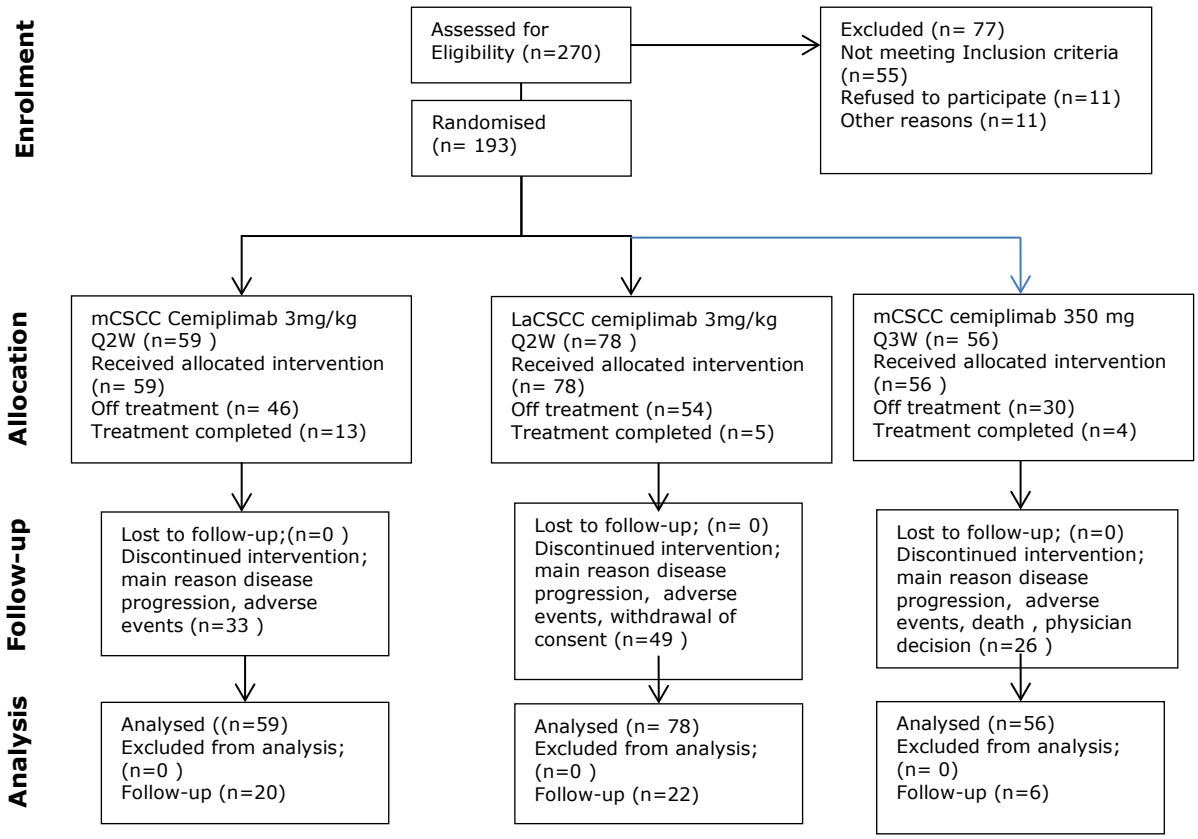
Data cut-off as of October 27, 2017

Detailed patient disposition for the full efficacy analysis set (N=82):

Table 14.1.1.4f Patient Disposition
(Full Analysis Set)

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=23)	Total (N=82)
Treatment Ongoing, n (%)	35 (59.3%)	13 (56.5%)	48 (58.5%)
Off Treatment, n (%)	24 (40.7%)	10 (43.5%)	34 (41.5%)
Treatment Completed	0	0	0
Treatment Discontinued	24 (40.7%)	10 (43.5%)	34 (41.5%)
Primary Reason for Treatment Discontinuation			
ADVERSE EVENT	4 (6.8%)	1 (4.3%)	5 (6.1%)
PREGNANCY	0	0	0
DEATH	2 (3.4%)	2 (8.7%)	4 (4.9%)
LOST TO FOLLOW-UP	0	0	0
NON-COMPLIANCE WITH STUDY DRUG	0	1 (4.3%)	1 (1.2%)
SUBJECT DECISION	2 (3.4%)	1 (4.3%)	3 (3.7%)
SPONSOR DECISION	0	0	0
PHYSICIAN DECISION	1 (1.7%)	1 (4.3%)	2 (2.4%)
DISEASE PROGRESSION	14 (23.7%)	3 (13.0%)	17 (20.7%)
WITHDRAWAL OF CONSENT	0	0	0
OTHER	1 (1.7%)	1 (4.3%)	2 (2.4%)
Number of patients entered follow-up, n (%)	13 (22.0%)	4 (17.4%)	17 (20.7%)

In the updated analysis, data cut-off was September 20, 2018 for Group 1 and Group 3 patients and October 10, 2018 for Group 2 patients. The patient disposition was as follows:



Recruitment

According to sample size calculations, up to 182 adult patients (53 patients in Group 1 [mCSCC], 76 patients in Group 2 [laCSCC], and 53 patients in Group 3 [mCSCC]) were expected to be enrolled. However, 193 patients were finally enrolled.

The following table clarifies the numbers on the current results from study 1540:

Study 1540	**Group 1 mCSCC** cemiplimab 3 mg/kg Q2W	**Group 2 laCSCC** cemiplimab 3 mg/kg Q2W	**Group 3 mCSCC** cemiplimab 350 mg Q3W
Expected enrollment (from sample size calculation)	53	76	53
Submitted efficacy data (after at least 3 response assessments)§	59*	78*	56*

§ Data cutoff is 20 Sep 2018 for Groups 1 and 3, and 10 Oct 2018 for G2.
*Fully enrolled

The updated centrally reviewed efficacy results for Groups 1, 2 and 3 have been provided by the applicant. Data cutoff is 20 September 2018 for Groups 1 and 3, and 10 October 2018 for Group 2. Primary analysis was finally possible for the entire population of the study since all 193 patients (in the 3 groups) have had the opportunity for at least 3 response assessments.

Median follow-up times in Groups 1, 2, and 3 were 16.5, 9.3, and 8.1 months, respectively. For the entire study population (N=193 patients), median follow-up time is 9.4 months.

At the time of the primary analysis for Group 1 (27 Oct 2017), enrollment was still ongoing for Group 2 (locally advanced CSCC [laCSCC], 3 mg/kg every 2 weeks [Q2W) and Group 3 (mCSCC, 350 mg Q3W). Group 2 completed enrollment on 25 Apr 2018 and Group 3 completed enrollment on 15 Mar 2018. In the SAF, 41 (29.9%) patients had discontinued study drug prematurely. The most common primary reason for premature treatment discontinuation was disease progression (15.3% [21/137]).

Conduct of the study

Protocol amendments: There were several minor changes performed to the SAP. The change in the SAP that may affect the presented results is related to the time-point for the interim analysis of Group 2. Amendment 5 of the protocol was finalised in 22 Sept 2017 and the data cut-off date was 27th Oct 2017.

In protocol amendment 3, Group 3 (mCSCC) was added:

Group 3 (mCSCC) - Patients with mCSCC: This group opened after the completion of enrollment to Group 1 (mCSCC) and included patients with mCSCC. As with Group 1 (mCSCC) patients, Group 3 (mCSCC) patients were required to have metastatic disease. As in Group 1 (mCSCC), Group 3 (mCSCC) included patients with both nodal metastatic and distant metastatic disease.

Patients with mCSCC receive either 3 mg/kg cemiplimab intravenous (IV) every 2 weeks (Q2W) in Group 1 (mCSCC) or cemiplimab 350 mg IV every 3 weeks (Q3W) in Group 3 (mCSCC). Patients with laCSCC receive 3 mg/kg cemiplimab IV Q2W in Group 2.

The updated centrally reviewed efficacy results for Groups 1, 2 and 3 have been provided by the applicant. Data cutoff is 20 Sep 2018 for Groups 1 and 3, and 10 Oct 2018 for Group 2. Primary analysis

was finally possible for the entire population of the study since all 193 patients (in the 3 groups) have had the opportunity for at least 3 response assessments.

Median follow-up times in Groups 1, 2, and 3 are now 16.5, 9.3, and 8.1 months, respectively. For the entire study population (N=193 patients), median follow-up time is 9.4 months.

At the time of the primary analysis for Group 1 (27 Oct 2017), enrollment was still ongoing for Group 2 (locally advanced CSCC [laCSCC], 3 mg/kg every 2 weeks [Q2W) and Group 3 (mCSCC, 350 mg Q3W). Group 2 completed enrollment on 25 Apr 2018 and Group 3 completed enrollment on 15 Mar 2018.

The PK/ADA data cutoff date (Groups 1 and 2) was 06 Oct 2017. The last PK collection date for Group 3 was 21 Dec 2017.

Major protocol deviations: Seventeen major protocol deviations were reported in 12 patients in the SAF. Major protocol deviations by individual patient in the SAF are described in Table 29. A total of 12 subjects (8.8%) were reported with 1 or more major protocol deviations. The applicant implemented 100% source data verification.

Table 27: Summary of major protocol deviations – Study 1540 (Safety analysis set)

	Group 1 mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	Group 2 laCSCC Cemiplimab: 3 mg/kg Q2W (N=55)	Group 3 mCSCC Cemiplimab: 350 mg Q3W (N=23)	Total (N=137)
Number of Major Protocol Deviations	6	5	6	17
Patients with Any Major Protocol Deviation, n (%)	4 (6.8%)	5 (9.1%)	3 (13.0%)	12 (8.8%)
Type of Major Protocol Deviations, n (%)				
ENROLLMENT ERROR-PATIENT ENROLLED TO WRONG TREATMENT	0	1 (1.8%)	0	1 (0.7%)
EXCLUSION CRITERIA MET BUT PATIENT ENROLLED	0	0	2 (8.7%)	2 (1.5%)
INCLUSION CRITERIA NOT MET BUT PATIENT ENROLLED	0	1 (1.8%)	2 (8.7%)	3 (2.2%)
OTHER [a]	2 (3.4%)	2 (3.6%)	1 (4.3%)	5 (3.6%)
PROCEDURE NOT PERFORMED	0	1 (1.8%)	0	1 (0.7%)
SAEs/AESIs NOT REPORTED WITHIN 24 HOURS TO PVRM	2 (3.4%)	0	0	2 (1.5%)
TREATMENT DEVIATION	1 (1.7%)	0	0	1 (0.7%)

Baseline data

Table 28: Demographics and baseline characteristics - Study 1540 (Safety analysis set)

	Group 1 mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	Group 2 laCSCC Cemiplimab: 3 mg/kg Q2W (N=55)	Group 3 mCSCC Cemiplimab: 350 mg Q3W (N=23)	Total (N=137)
Age (years)				
n	59	55	23	137
Mean (SD)	70.4 (10.15)	71.6 (12.05)	67.1 (12.34)	70.3 (11.34)
Median	71.0	73.0	69.0	71.0
Q1 : Q3	64.0 : 77.0	63.0 : 81.0	61.0 : 75.0	63.0 : 78.0
Min : Max	38 : 93	45 : 96	38 : 87	38 : 96
Age Groups (years), n (%)				
<65	16 (27.1%)	16 (29.1%)	7 (30.4%)	39 (28.5%)
≥65	43 (72.9%)	39 (70.9%)	16 (69.6%)	98 (71.5%)
Sex, n (%)				
Male	54 (91.5%)	42 (76.4%)	21 (91.3%)	117 (85.4%)
Female	5 (8.5%)	13 (23.6%)	2 (8.7%)	20 (14.6%)
Race, n (%)				
WHITE	58 (98.3%)	53 (96.4%)	22 (95.7%)	133 (97.1%)
BLACK OR AFRICAN AMERICAN	1 (1.7%)	0	0	1 (0.7%)
ASIAN	0	1 (1.8%)	1 (4.3%)	2 (1.5%)
NOT REPORTED	0	1 (1.8%)	0	1 (0.7%)
Ethnicity, n (%)				
NOT HISPANIC OR LATINO	58 (98.3%)	52 (94.5%)	23 (100%)	133 (97.1%)
HISPANIC OR LATINO	1 (1.7%)	2 (3.6%)	0	3 (2.2%)
NOT REPORTED	0	1 (1.8%)	0	1 (0.7%)
Height (cm)				
n	59	54	23	136
Mean (SD)	173.19 (6.579)	171.86 (9.877)	174.10 (9.592)	172.82 (8.520)
Median	174.50	174.00	175.00	174.00
Q1 : Q3	169.00 : 177.80	167.20 : 178.00	167.60 : 181.00	167.80 : 178.00
Min : Max	158.5 : 190.5	140.3 : 188.0	152.4 : 190.0	140.3 : 190.5
Body Weight (kg)				
n	59	55	23	137
Mean (SD)	85.04 (15.682)	77.02 (17.291)	82.23 (20.460)	81.35 (17.462)
Median	84.50	77.10	81.10	81.10
Q1 : Q3	74.90 : 94.40	66.50 : 89.00	66.70 : 92.10	69.80 : 92.00
Min : Max	58.3 : 134.9	31.0 : 111.8	59.5 : 145.0	31.0 : 145.0
BMI (kg/m^2)				
n	59	54	23	136
Mean (SD)	28.313 (4.7718)	26.008 (4.3827)	27.157 (6.1918)	27.203 (4.9681)
Median	28.090	26.350	26.480	27.060
Q1 : Q3	24.700 : 30.340	23.220 : 28.630	22.210 : 30.120	24.005 : 29.760
Min : Max	19.51 : 44.25	13.78 : 33.86	18.16 : 41.47	13.78 : 44.25
ECOG Performance Status, n (%)				
0	23 (39.0%)	31 (56.4%)	8 (34.8%)	62 (45.3%)
1	36 (61.0%)	24 (43.6%)	15 (65.2%)	75 (54.7%)

Data cutoff as of 27 Oct 2017

Table 29: Baseline tumour characteristics - Study 1540 (Safety analysis set)

	Group 1 mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	Group 2 laCSCC Cemiplimab: 3 mg/kg Q2W (N=55)	Group 3 mCSCC Cemiplimab: 350 mg Q3W (N=23)	Total (N=137)
T Stage at Screening, n (%)				
TX	29 (49.2%)	4 (7.3%)	12 (52.2%)	45 (32.8%)
T0	0	0	2 (8.7%)	2 (1.5%)
T1	4 (6.8%)	4 (7.3%)	0	8 (5.8%)
T2	13 (22.0%)	21 (38.2%)	4 (17.4%)	38 (27.7%)
T3	3 (5.1%)	8 (14.5%)	1 (4.3%)	12 (8.8%)
T4	10 (16.9%)	18 (32.7%)	4 (17.4%)	32 (23.4%)
N Stage at Screening, n (%)				
NX	9 (15.3%)	3 (5.5%)	4 (17.4%)	16 (11.7%)
N0	10 (16.9%)	51 (92.7%)	5 (21.7%)	66 (48.2%)
N1	15 (25.4%)	0	5 (21.7%)	20 (14.6%)
N2	6 (10.2%)	0	2 (8.7%)	8 (5.8%)
N2A	0	0	1 (4.3%)	1 (0.7%)
N2B	4 (6.8%)	1 (1.8%)	3 (13.0%)	8 (5.8%)
N2C	7 (11.9%)	0	3 (13.0%)	10 (7.3%)
N3	8 (13.6%)	0	0	8 (5.8%)
M Stage at Screening, n (%)				
M0	14 (23.7%)	55 (100%)	5 (21.7%)	74 (54.0%)
M1	45 (76.3%)	0	18 (78.3%)	63 (46.0%)

Table 30: Summary of prior cancer-related systemic therapy by setting - Study 1540 (Safety analysis set)

	Group 1 mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	Group 2 laCSCC Cemiplimab: 3 mg/kg Q2W (N=55)	Group 3 mCSCC Cemiplimab: 350 mg Q3W (N=23)	Total (N=137)
Number of Patients with any prior cancer-related systemic therapy, n (%)	33 (55.9%)	12 (21.8%)	10 (43.5%)	55 (40.1%)
Number of Regimens at baseline, n (%)				
0	26 (44.1%)	43 (78.2%)	13 (56.5%)	82 (59.9%)
1	22 (37.3%)	10 (18.2%)	6 (26.1%)	38 (27.7%)
2	7 (11.9%)	2 (3.6%)	2 (8.7%)	11 (8.0%)
3	3 (5.1%)	0	1 (4.3%)	4 (2.9%)
4	1 (1.7%)	0	1 (4.3%)	2 (1.5%)
Number of Regimens at baseline				
N	33	12	10	55
Mean (SD)	1.5 (0.80)	1.2 (0.39)	1.7 (1.06)	1.5 (0.79)
Median	1.0	1.0	1.0	1.0
Q1 : Q3	1.0 : 2.0	1.0 : 1.0	1.0 : 2.0	1.0 : 2.0
Min : Max	1 : 4	1 : 2	1 : 4	1 : 4

Table 31: Prior cancer-related surgery - Study 1540 (Safety analysis set)

	Group 1 mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	Group 2 laCSCC Cemiplimab: 3 mg/kg Q2W (N=55)	Group 3 mCSCC Cemiplimab: 350 mg Q3W (N=23)	Total (N=137)
Number of Patients with any Prior Cancer-related Surgery, n (%)	58 (98.3%)	49 (89.1%)	19 (82.6%)	126 (92.0%)
Number of Prior Cancer-related Surgeries, n (%)				
0	1 (1.7%)	6 (10.9%)	4 (17.4%)	11 (8.0%)
1	2 (3.4%)	1 (1.8%)	0	3 (2.2%)
2	10 (16.9%)	4 (7.3%)	4 (17.4%)	18 (13.1%)
3	10 (16.9%)	12 (21.8%)	4 (17.4%)	26 (19.0%)
>3	36 (61.0%)	32 (58.2%)	11 (47.8%)	79 (57.7%)
Number of Prior Cancer-related Surgeries				
n	58	49	19	126
Mean (SD)	5.0 (2.90)	6.3 (5.00)	4.9 (3.05)	5.5 (3.90)
Median	4.0	5.0	4.0	4.0
Q1 : Q3	3.0 : 7.0	3.0 : 8.0	3.0 : 6.0	3.0 : 7.0
Min : Max	1 : 15	1 : 28	2 : 11	1 : 28

Table 32: Prior cancer-related radiotherapy - Study 1540 (Safety analysis set)

	Group 1 mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	Group 2 laCSCC Cemiplimab: 3 mg/kg Q2W (N=55)	Group 3 mCSCC Cemiplimab: 350 mg Q3W (N=23)	Total (N=137)
Number of patients with any prior cancer-related radiotherapy, n (%)	50 (84.7%)	33 (60.0%)	15 (65.2%)	98 (71.5%)
Number of Prior Cancer-Related Radiotherapies, n (%)				
0	9 (15.3%)	22 (40.0%)	8 (34.8%)	39 (28.5%)
1	30 (50.8%)	25 (45.5%)	10 (43.5%)	65 (47.4%)
2	7 (11.9%)	5 (9.1%)	3 (13.0%)	15 (10.9%)
3	6 (10.2%)	3 (5.5%)	2 (8.7%)	11 (8.0%)
>3	7 (11.9%)	0	0	7 (5.1%)

Numbers analysed

In accordance with ICH E9 Statistical Principles for Clinical Trials (1998), the following analysis populations were used for the statistical analysis as specified:

Full Analysis Set: The FAS included all enrolled patients in Group 1 (mCSCC) and patients enrolled on or before 27 Jan 2017 in Group 2 (laCSCC). The FAS by group was the primary analysis population for the efficacy variables.

Safety Analysis Set: The safety analysis set (SAF) included all enrolled patients who received at least 1 dose of cemiplimab. Treatment compliance/administration and all clinical safety variables was analyzed or summarized using the SAF.

Pharmacokinetic Analysis Set: The PK analysis set included all treated patients who received any amount of study drug and had at least 1 non-missing functional cemiplimab measurement following the first dose of study drug. The PK/ADA cutoff date for Groups 1 and 2 is 06 Oct 2017, and the last PK collection for Group 3 is 21 Dec 2017.

Anti-Drug Antibody Analysis Set: The ADA analysis set included all treated patients who received any amount of study drug at the PK/ADA cutoff date of 06 Oct 2017 and had at least 1 non-missing anti-cemiplimab antibody result following the first dose of study drug.

Biomarker Analysis Set: The biomarker analysis set included all patients who received any dose of cemiplimab and who had at least 1 sample assayed.

Table 33: Patient numbers in the analysis sets - Study 1540

PK / ADA Cutoff Date	Group	Population	Cemiplimab Dosing Regimen	N for Safety (SAF)	N for Efficacy (FAS)	N for PK	N for ADA	Planned N[a]
06 Oct 2017	1	mCSCC	3 mg/kg Q2W	59	59	59	41	53
06 Oct 2017	2[b]	laCSCC	3 mg/kg Q2W	55	23	50	30	76
21 Dec 2017	3[c]	mCSCC	350 mg Q3W	23	0	35	0	53

Note: The N for PK and ADA analysis sets are smaller compared to the SAF and FAS due to the data cutoff for inclusion in the PK and ADA datasets occurring 1 month earlier. The N for ADA analysis set is smaller than that for PK analysis set because the first post-dose sample that justifies patient inclusion in the ADA analysis set is at cycle 3 day 1; this Visit extended beyond the planned cutoff date for some patients.

Module 5.3.5.2 Study 1540 Section 4.2.1, Table 12, and CP Report 1540 CP-02V1 Table 1

[a] The total number of patients planned to be enrolled for the group.

[b] The study is ongoing for Group 2.

[c] The study is ongoing for Group 3 (350 mg Q3W). The PK results for this group are not presented in the interim CSR. The PK results are presented in the CP Report 1540 CP-02V1. There were no ADA results at the time of this dossier preparation. The N for the PK Analysis set is larger than that for the Safety Set because the data cutoff for inclusion in the PK Analysis Set is later than that for the Safety Set.

Table 34: Analysis sets (SAF)

Analysis Set, n (%)	Group 1 mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	Group 2 laCSCC Cemiplimab: 3 mg/kg Q2W (N=55)	Group 3 mCSCC Cemiplimab: 350 mg Q3W (N=23)	Total (N=137)
Full Analysis Set (FAS)	59 (100%)	23 (41.8%)	0	82 (59.9%)
Safety Analysis Set (SAF)	59 (100%)	55 (100%)	23 (100%)	137 (100%)
Pharmacokinetic Analysis Set (PKA)	59 (100%)	50 (90.9%)	0	109 (79.6%)
Anti-drug Antibody Analysis Set (ADA)	41 (69.5%)	30 (54.5%)	0	71 (51.8%)

Data cutoff as of 27 Oct 2017

The ADA analysis set was updated and now it includes 135 patients (41 from Group 1, 59 from Group 2 and 35 from Group 3).

Outcomes and estimation

Primary endpoint – ORR by ICR

Table 35: Best overall tumour response rate by independent central review – Study 1540 Original MAA submission and updated datasets

	mCSCC Cemiplimab: 3 mg/kg Q2W		laCSCC Cemiplimab: 3 mg/kg Q2W		mCSCC Cemiplimab: 350 mg Q3W		Total	
	MAA (N = 59)	Day 180 (N = 59)	MAA (N = 23)	Day 180 (N=78)	MAA (N = 0)	Day 180 (N=56)	MAA (N = 82)	Day 180 (N=193)
Best Overall Tumor Response, n (%)								
Complete Response (CR) [a]	4 (6.8%)	10 (16.9%)	0	10 (12.8%)	NR	2 (3.6%)	4 (4.9%)	22 (11.4%)
Partial Response (PR) [a]	24 (40.7%)	19 (32.2%)	10 (43.5%)	24 (30.8%)	NR	20 (35.7%)	34 (41.5%)	63 (32.6%)
Stable Disease (SD) [b]	9 (15.3%)	9 (15.3%)	9 (39.1%)	28 (35.9%)	NR	8 (14.3%)	18 (22.0%)	45 (23.3%)
Non-CR/Non-PD [c]	4 (6.8%)	4 (6.8%)	0	0	NR	5 (8.9%)	4 (4.9%)	9 (4.7%)
Progressive Disease (PD)	11 (18.6%)	10 (16.9%)	2 (8.7%)	9 (11.5%)	NR	15 (26.8%)	13 (15.9%)	34 (17.6%)
Not Evaluable (NE) [d]	7 (11.9%)	7 (11.9%)	2 (8.7%)	7 (9.0%)	NR	6 (10.7%)	9 (11.0%)	20 (10.4%)
Response								
Objective Response Rate (ORR: CR+PR)	28 (47.5%)	29 (49.2%)	10 (43.5%)	34 (43.6%)	NR	22 (39.3%)	38 (46.3%)	85 (44.0%)
95% CI for ORR [e]	(34.3%, 60.9%)	(35.9%, 62.5%)	(23.2%, 65.5%)	(32.4%, 55.3%)	NR	(26.5%, 53.2%)	(35.3%, 57.7%)	(36.9%, 51.3%)
Complete Response Rate (CR) [a]	4 (6.8%)	10 (16.9%)	0	10 (12.8%)	NR	2 (3.6%)	4 (4.9%)	22 (11.4%)
95% CI for CR Rate [e]	(1.9%, 16.5%)	(8.4%, 29.0%)	(0.0%, 14.8%)	(6.3%, 22.3%)	NR	(0.4%, 12.3%)	(1.3%, 12.0%)	(7.3%, 16.7%)
Durable DCR [f]	36 (61.0%)	37 (62.7%)	16 (69.6%)	49 (62.8%)	NR	31 (55.4%)	52 (63.4%)	117 (60.6%)
95% CI for Durable DCR [e]	(47.4%, 73.5%)	(49.1%, 75.0%)	(47.1%, 86.8%)	(51.1%, 73.5%)	NR	(41.5%, 68.7%)	(52.0%, 73.8%)	(53.3%, 67.6%)

Data cut-off was 27 Oct 2017 for original MAA submission; Sep 20, 2018 for Groups 1 and 3 patients for Day 180, and Oct 10, 2018 for Group 2 patients for Day 180.
Note: Group 3 efficacy data were not reported (NR) in the original MAA submission because the data were not sufficiently mature for analysis.
[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 Interim CSR, Table 20; Table 14.2.1.1f

Following the SAP, primary analysis was finally possible for the entire population of the study since all 193 patients (in the 3 groups) have had the opportunity for at least 3 response assessments, acknowledging that median follow-up time for the ITT population is still limited (9.4 months since start of treatment).

Data cutoff is 20 September 2018 for Groups 1 and 3, and 10 October 2018 for Group 2. As from the last data cutoff (30 June 2018), current IRC-assessed ORR results are consistent for each group: 49.2% in Group 1, 43.6% in Group 2 and 39.3% in Group 3. Of note, the lower bound of the 95% CI is beyond the range of clinically insignificant effect (≤15% ORR in Group 1 and Group 3, ≤25% in Group 2) in all 3 groups.

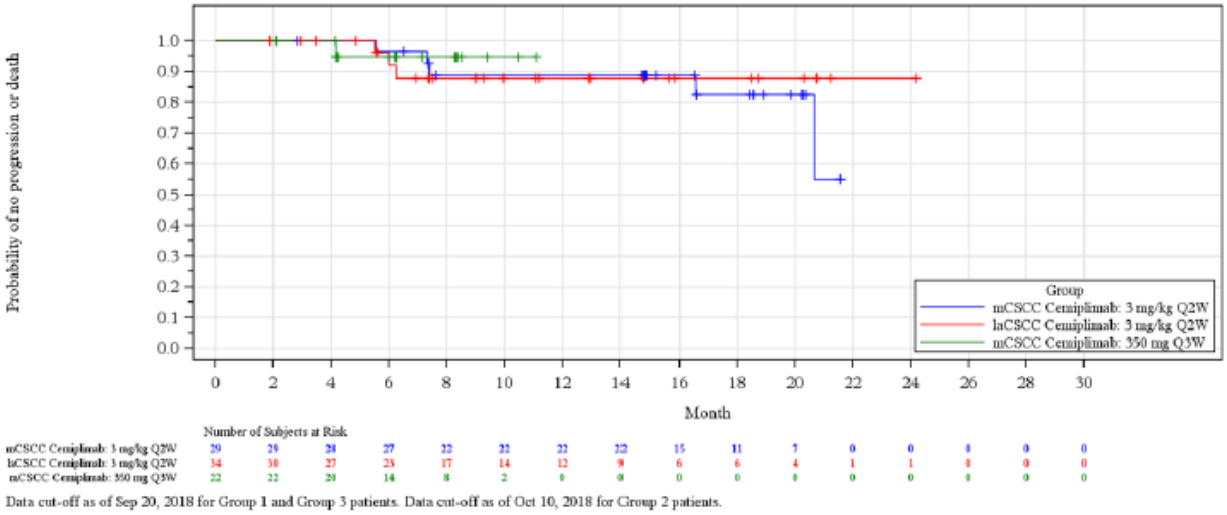
Secondary endpoint – DoR by ICR

Table 36: Duration of response by independent central review - Study 1540 Original MAA submission and updated datasets

	mCSCC Cemiplimab: 3 mg/kg Q2W		laCSCC Cemiplimab: 3 mg/kg Q2W		mCSCC Cemiplimab: 350 mg Q3W		Total	
	MAA (N = 59)	Day 180 (N = 59)	MAA (N = 23)	Day 180 (N=78)	MAA (N = 0)	Day 180 (N=56)	MAA (N = 82)	Day 180 (N=193)
Observed Duration of Response (CR or PR) (months)								
n	28	29	10	34	NR	22	38	85
Min : Max	2.8 : 12.8 +	2.8 : 21.6	1.9 : 12.9+	1.9 : 24.2	NR	2.1 : 11.1	1.9 : 12.9+	1.9 : 24.2
Observed Duration of Response (CR or PR), n (%) [a]								
Total number of responders	28	29	10	34	NR	22	38	85
>=4 months	22 (78.6%)	28 (96.6%)	8 (80.0%)	27 (79.4%)	NR	20 (90.9%)	30 (78.9%)	75 (88.2%)
>=6 months	16 (57.1%)	27 (93.1%)	7 (70.0%)	23 (67.6%)	NR	14 (63.6%)	23 (60.5%)	64 (75.3%)
>=8 months	9 (32.1%)	22 (75.9%)	4 (40.0%)	17 (50.0%)	NR	8 (36.4%)	13 (34.2%)	47 (55.3%)
>=12 months	1 (3.6%)	22 (75.9%)	1 (10.0%)	12 (35.3%)	NR	0	2 (5.3%)	34 (40.0%)
>= 16 months	0	15 (51.7%)	0	6 (17.6%)	NR	0	0	21 (24.7%)
KM Estimation of Duration of Response (CR or PR)								
n	28	29	10	34	NR	22	38	85
Number of events, n (%) [a]	3 (10.7%)	5 (17.2%)	0	3 (8.8%)	NR	1 (4.5%)	3 (7.9%)	9 (10.6%)
Number of censored patients, n (%) [a]	25 (89.3%)	24 (82.8%)	10 (100%)	31 (91.2%)	NR	21 (95.5%)	35 (92.1%)	76 (89.4%)
Median (95% CI), (months)	NR (NE, NE)	NR (20.7, NE)	NR (NE, NE)	NR (NE, NE)	NR	NR (NE, NE)	NR (NE, NE)	NR (20.7, NE)

+ denotes ongoing response

Data cut-off was 27 Oct 2017 for original MAA submission; Sep 20, 2018 for Groups 1 and 3 patients for Day 180, and Oct 10, 2018 for Group 2 patients for Day 180.
Note: Group 3 efficacy data were not reported (NR) in the original MAA submission because the data were not sufficiently mature for analysis.
[a] Percentages are based on number of patients with confirmed CR or PR. The numerator includes the number of patients whose observed duration of response reached at least the specified time. Patients who did not have the opportunity to reach the specified timepoint were included in the denominator only. Because responses for some patients are ongoing, the percentages at the specified timepoints may increase as data mature.
[b] Events include progressive disease or deaths. Percentages are based on number of patients with confirmed CR or PR.
Source: Study 1540 Interim CSR, Tables 19, 20, and 21; Table 14.2.1.3f; Table 14.2.1.5f



Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients. Data cut-off as of Oct 10, 2018 for Group 2 patients.

Source: Figure 14.2.1.1.4

Figure 23: Kaplan-Meier curve of duration of response by independent central review (full analysis set - patients with confirmed CR or PR) - All CSCC patients by group

The efficacy data showed that although most of the responders in Group 1 (22 out of 29) achieved PR or CR at the first assessment (week 8), 4 patients achieved it at the second assessment (week 16), 2 at the third (week 24) and there was also one very late responder at the fifth assessment (week 40).

Considering the longer follow-up for Group 1, 27 out of 29 patients (93%) had a response that has lasted for 6 months or longer.

DoR is ≥6 months for 68% of patients from G2 (23 out 34) and 64% of patients from G3 (14 out of 22).

Immaturity of the current DoR data is reflected in the degree of censoring (9 events in 85 responders: 89.4% of censoring), which in turn hinders interpretation of the K-M graph for DoR (median DoR not reached in any of the groups).

Secondary endpoint – ORR based on investigator-assessed RECIST v1.1

Table 37: Best overall tumour response rate by investigator assessment (FAS)

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=78)	mCSCC Cemiplimab: 350 mg Q3W (N=56)	Total (N=193)
Best Overall Tumor Response, n (%)				
Complete Response (CR) [a]	4 (6.8%)	13 (16.7%)	3 (5.4%)	20 (10.4%)
Partial Response (PR) [a]	25 (42.4%)	28 (35.9%)	26 (46.4%)	79 (40.9%)
Stable Disease (SD) [b]	14 (23.7%)	22 (28.2%)	11 (19.6%)	47 (24.4%)
Progressive Disease (PD)	11 (18.6%)	9 (11.5%)	12 (21.4%)	32 (16.6%)
Not Evaluable (NE) [c]	5 (8.5%)	6 (7.7%)	4 (7.1%)	15 (7.8%)
Response				
Objective Response Rate (ORR:CR+PR)	29 (49.2%)	41 (52.6%)	29 (51.8%)	99 (51.3%)
95% CI for ORR [d]	(35.9%, 62.5%)	(40.9%, 64.0%)	(38.0%, 65.3%)	(44.0%, 58.5%)
Complete Response Rate (CR) [a]	4 (6.8%)	13 (16.7%)	3 (5.4%)	20 (10.4%)
95% CI for CR Rate [d]	(1.9%, 16.5%)	(9.2%, 26.8%)	(1.1%, 14.9%)	(6.4%, 15.6%)
Disease Control Rate (DCR: CR+PR+SD)	43 (72.9%)	63 (80.8%)	40 (71.4%)	146 (75.6%)
95% CI for DCR [d]	(59.7%, 83.6%)	(70.3%, 88.8%)	(57.8%, 82.7%)	(69.0%, 81.5%)
Durable DCR [e]	38 (64.4%)	55 (70.5%)	34 (60.7%)	127 (65.8%)
95% CI for Durable DCR [d]	(50.9%, 76.4%)	(59.1%, 80.3%)	(46.8%, 73.5%)	(58.6%, 72.5%)

Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients. Data cut-off as of Oct 10, 2018 for Group 2 patients.
[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 (6 weeks*7 days/week - 3 days) after first dose date.
[c] Not evaluable response includes the missing and unknown tumor response.
[d] Clopper-Person exact confidence interval.
[e] Durable DCR: proportion of patients with CR, PR or SD for at least 105 days without PD.

Secondary endpoint – Time to response by independent central review (FAS – patients with confirmed CR or PR)

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=29)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=34)	mCSCC Cemiplimab: 350 mg Q3W (N=22)	Total (N=85)
Observed Time to Response (CR or PR) (months)				
n	29	34	22	85
Mean (SD)	2.61 (1.697)	3.29 (1.983)	3.10 (1.787)	3.01 (1.841)
Median	1.87	1.91	2.07	2.00
Q1 : Q3	1.81 : 1.97	1.87 : 3.71	2.07 : 4.17	1.87 : 3.71
Min : Max	1.7 : 9.1	1.8 : 8.8	2.0 : 8.3	1.7 : 9.1
Observed Time to Response (CR or PR), n (%) [a]				
<2 months	22 (75.9%)	18 (52.9%)	1 (4.5%)	41 (48.2%)
2 to 4- months	4 (13.8%)	9 (26.5%)	14 (63.6%)	27 (31.8%)
4 to 6- months	2 (6.9%)	3 (8.8%)	4 (18.2%)	9 (10.6%)
>=6 months	1 (3.4%)	4 (11.8%)	3 (13.6%)	8 (9.4%)

Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients. Data cut-off as of Oct 10, 2018 for Group 2 patients.
[a] Percentages are based on number of patients with confirmed CR or PR.

Secondary endpoint – Time to response by investigator assessment (FAS – patients with confirmed CR or PR)

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=29)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=41)	mCSCC Cemiplimab: 350 mg Q3W (N=29)	Total (N=99)
Observed Time to Response (CR or PR) (months)				
n	29	41	29	99
Mean (SD)	2.81 (1.739)	4.06 (3.801)	3.64 (2.385)	3.57 (2.942)
Median	1.87	2.04	2.10	2.07
Q1 : Q3	1.84 : 3.65	1.87 : 4.17	2.07 : 4.21	1.87 : 4.17
Min : Max	1.7 : 9.2	1.7 : 20.5	1.4 : 10.3	1.4 : 20.5
Observed Time to Response (CR or PR), n (%) [a]				
<2 months	19 (65.5%)	20 (48.8%)	3 (10.3%)	42 (42.4%)
2 to 4- months	6 (20.7%)	10 (24.4%)	14 (48.3%)	30 (30.3%)
4 to 6- months	3 (10.3%)	5 (12.2%)	6 (20.7%)	14 (14.1%)
>=6 months	1 (3.4%)	6 (14.6%)	6 (20.7%)	13 (13.1%)

Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients. Data cut-off as of Oct 10, 2018 for Group 2 patients.
[a] Percentages are based on number of patients with confirmed CR or PR.

Secondary endpoint - Progression Free Survival by ICR

Table 38: Kaplan-Meier estimation of PFS by independent central review (Full analysis set)

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=78)	mCSCC Cemiplimab: 350 mg Q3W (N=56)	Total (N=193)
KM estimation of Progression Free Survival				
Number of events, n (%)	28 (47.5%)	27 (34.6%)	26 (46.4%)	81 (42.0%)
Progressive Disease, n (%)	22 (37.3%)	24 (30.8%)	21 (37.5%)	67 (34.7%)
Death, n (%)	6 (10.2%)	3 (3.8%)	5 (8.9%)	14 (7.3%)
Number of censored patients, n (%)	31 (52.5%)	51 (65.4%)	30 (53.6%)	112 (58.0%)
Median (95% CI), (months)	18.4 (7.3, NE)	NR (9.2, NE)	10.4 (3.6, NE)	18.4 (9.1, NE)
Estimated Event-Free Probability, % (95% CI)				
4 months	69.6 (55.8, 79.9)	76.7 (64.7, 85.1)	61.1 (46.8, 72.6)	69.9 (62.6, 76.0)
6 months	66.0 (52.0, 76.8)	71.5 (58.9, 80.9)	59.3 (45.0, 71.0)	66.3 (58.8, 72.7)
8 months	58.7 (44.6, 70.3)	65.4 (51.9, 75.9)	57.1 (42.8, 69.1)	60.8 (53.0, 67.7)
12 months	53.1 (39.1, 65.2)	58.1 (43.7, 70.0)	44.6 (26.5, 61.3)	53.4 (45.1, 60.9)
16 months	53.1 (39.1, 65.2)	51.8 (36.6, 65.0)	NE (NE, NE)	51.0 (42.5, 58.9)

Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients. Data cut-off as of Oct 10, 2018 for Group 2 patients.

In relationship to the previous 30-June-2018 data cutoff, updated IRC-PFS results are nearly identical for Group 1 (28 events in 59 patients, mPFS 18.4 months, 6-month-PFS 66.0%) and minimally improved for Group 3 (26 events in 56 patients, mPFS 10.4 months, 6-month-PFS 59.3%).

Secondary endpoint – Overall Survival

Table 39: Overall survival at 12 months for metastatic CSCC, locally advanced CSCC and combined - Study 1540

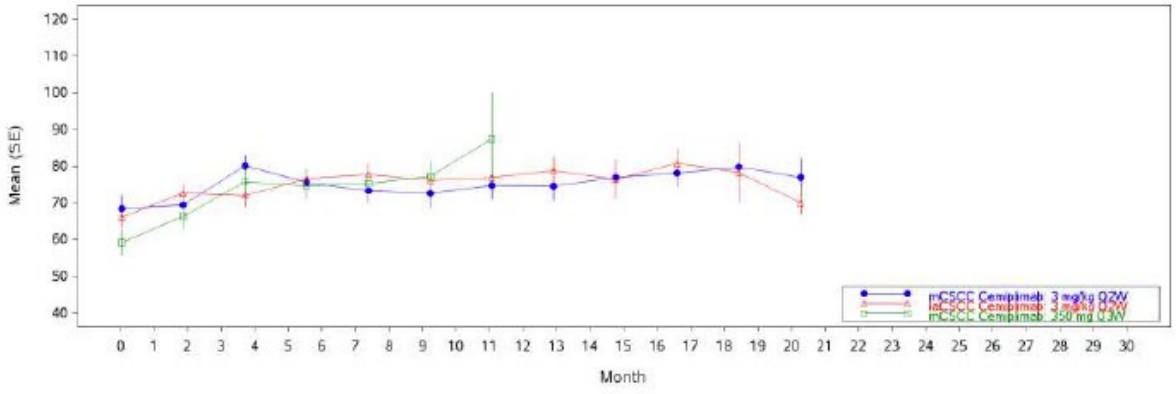
	mCSCC Cemiplimab: 3 mg/kg Q2W (Group 1) (N = 59)	laCSCC Cemiplimab: 3 mg/kg Q2W (Group 2) (N = 78)	mCSCC Cemiplimab: 350 mg Q3W (Group 3) (N=56)	Total (N=193)
Overall Survival[a, c, d]				
12 months	81.3 (68.7, 89.2)	93.2 (84.4, 97.1)	76.1 (56.9, 87.6)	85.7 (79.6, 90.1)

Data cut-off was Sep 20, 2018 for Groups 1 and 3 patients, and Oct 10, 2018 for Group 2 patients.

Secondary endpoint - Quality of life

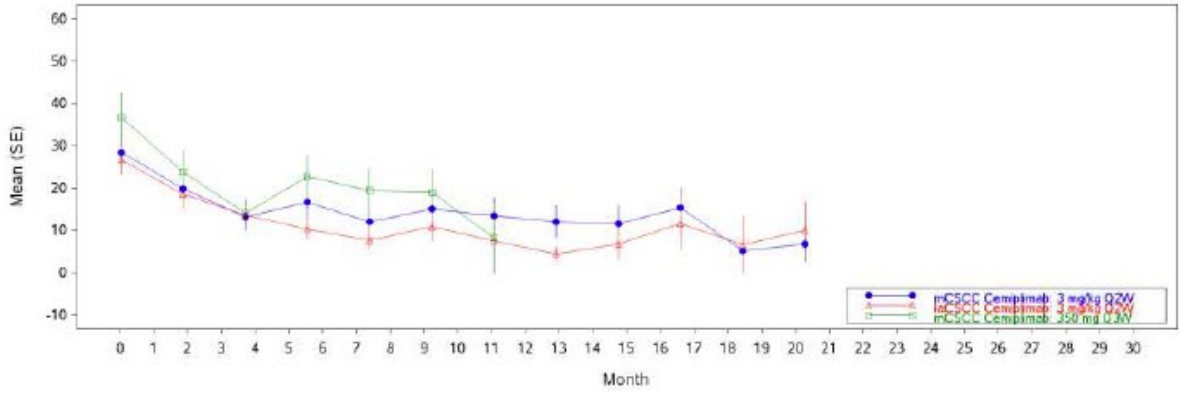
Quality of life was assessed using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). Changes in mean EORTC QLQ-C30 scores generally did not indicate consistent changes in quality of life with the exception of the pain symptom subscale.

Table 40: Global health status /QoL - All CSCC patients by group



Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients. Data cut-off as of Oct 10, 2018 for Group 2 patients.

Table 41: Symptom subscale Pain - all CSCC patients by group



Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients. Data cut-off as of Oct 10, 2018 for Group 2 patients.

Ancillary analyses

Sensitivity analyses

Two sensitivity analyses that assign either an OS or PFS event to patients who had ended the study due to other reasons and were not undergoing active follow-up have been provided by the applicant.

In the overall survival (OS) analysis presented in the original MAA (27 Oct 2017), 13 patients died and 69 were censored. Among these 69 patients, 51 patients were still ongoing in the study and 18 patients had end of study (EOS). Per protocol, study patients who had EOS due to reasons other than death have quarterly survival follow-up (ie, a phone call) after EOS. To provide an analysis for this question regarding OS, the algorithm for patients who were censored for OS and had EOS is presented below:

- If a patient is still in active survival follow-up (ie, last survival follow-up was within 4 months before the data cutoff), the patient is censored at last known alive date (N=10).
- For other patients, the imputed death date will be = last known alive date+1 (N=8).

Table 42: Summary of Overall Survival - Sensitivity analysis (FAS)

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=23)	Total (N=82)
KM estimation of Overall Survival			
Number of deaths, n (%)	17 (28.8%)	4 (17.4%)	21 (25.6%)
Number of censored patients, n (%)	42 (71.2%)	19 (82.6%)	61 (74.4%)
Median (95% CI), (months)	NR (NE, NE)	NR (NE, NE)	NR (NE, NE)
Estimated Probability of Survival, % (95% CI)			
4 months	86.4 (74.7, 93.0)	91.3 (69.5, 97.8)	87.8 (78.5, 93.2)
6 months	81.3 (68.8, 89.2)	87.0 (64.8, 95.6)	82.9 (72.9, 89.5)
8 months	73.7 (60.1, 83.3)	82.6 (60.1, 93.1)	76.4 (65.5, 84.3)
12 months	67.6 (52.3, 78.9)	82.6 (60.1, 93.1)	72.5 (60.7, 81.3)
16 months	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Data cutoff as of October 27, 2017. Only patients who started treatment at least 9 months prior to the data cutoff date are included in Group 2 (laCSCC).
KM = Kaplan-Meier; CI = confidence interval; NE = Not evaluable; NR = Not reported.

Table 43: Kaplan-Meier estimation by independent central review - Sensitivity analysis (FAS)

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=23)	Total (N=82)
KM estimation of Progression Free Survival			
Number of events, n (%)	29 (49.2%)	12 (52.2%)	41 (50.0%)
Number of censored patients, n (%)	30 (50.8%)	11 (47.8%)	41 (50.0%)
Median (95% CI), (months)	9.2 (5.6, NE)	9.3 (3.7, NE)	9.2 (6.0, NE)
Estimated Event-Free Probability, % (95% CI)			
4 months	66.1 (52.5, 76.6)	69.6 (46.6, 84.2)	67.1 (55.8, 76.1)
6 months	62.5 (48.8, 73.5)	56.5 (34.3, 73.8)	60.6 (49.1, 70.3)
8 months	56.3 (42.4, 68.1)	56.5 (34.3, 73.8)	56.4 (44.8, 66.5)
12 months	44.0 (29.0, 58.0)	46.2 (24.9, 65.2)	44.7 (32.3, 56.2)
16 months	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Data cutoff as of October 27, 2017. Only patients who started treatment at least 9 months prior to the data cutoff date are included in Group 2 (laCSCC).
KM = Kaplan-Meier.

In this worst-case scenario, the established OS and PFS outcome of patients with advanced CSCC treated with cemiplimab is maintained.

Subgroup analyses

PD-L1 status

In Study 1540, tumour biopsies during the screening period were required for laCSCC patients (Group 2), but not for mCSCC patients (Groups 1 and 3). Among 78 patients in Group 2, 48 had samples that were appropriate for PD-L1 IHC testing. For 30 patients, there was no sample available for PD-L1 IHC testing, either because the sample was not obtained or because slides were expired (>6 months since slide cut date) or because of an insufficient number of cells (<100 viable tumour cells) on the slide. For Groups 1 and 3 patients (mCSCC patients) in Study 1540, archived tumour samples for PD-L1 testing were available for 13 patients (5 patients in Group 1, 8 patients in Group 3). For all other patients in Groups 1 and 3, PD-L1 testing was not possible because tumour material was depleted by H&E staining for clinical pathology review, or slides were expired (>6 months since slide cut date), or there was insufficient number of cells (<100 viable cells) on the slide. For Group 2 patients who had the opportunity for 3 response assessments, the tables below provide ORR, PFS, and OS stratified by PD-L1 positivity at different cutoffs (eg, <1%, ≥1% to <5%, ≥5% to <50%, and ≥50%). This was not a planned subgroup analysis.

Table 44: Best overall tumour response rate by independent central review for group 2 patients who had opportunity for at least 3 response assessments stratified by PD-L1 expression level – Study 1540

	PD-L1<1% (N=12)	PD-L1>=1% to <5% (N=3)	PD-L1>=5% to <50% (N=18)	PD-L1>=50% (N=6)
Best Overall Tumor Response, n (%)				
Complete Response (CR) [a]	1 (8.3%)	0	2 (11.1%)	0
Partial Response (PR) [a]	2 (16.7%)	2 (66.7%)	9 (50.0%)	2 (33.3%)
Stable Disease (SD) [b]	6 (50.0%)	1 (33.3%)	4 (22.2%)	2 (33.3%)
Non-CR/Non-PD [c]	0	0	0	0
Progressive Disease (PD)	1 (8.3%)	0	1 (5.6%)	2 (33.3%)
Not Evaluable (NE) [d]	2 (16.7%)	0	2 (11.1%)	0
Response				
Objective Response Rate (ORR: CR+PR)	3 (25.0%)	2 (66.7%)	11 (61.1%)	2 (33.3%)
95% CI for ORR [e]	(5.5%, 57.2%)	(9.4%, 99.2%)	(35.7%, 82.7%)	(4.3%, 77.7%)

Data cut-off as of June 30, 2018
PD-L1 = Programmed death-ligand 1; CI = confidence interval.
[a] CR/PR were confirmed by repeated assessments no less than 4 weeks apart.
[b] SD criteria was 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.

Table 45: Best overall tumour response rate by independent central review for group 2 patients who had samples evaluable for PD-L1 assay - Study 1540 (FAS)

	PD-L1<1% (N=17)	PD-L1>=1% to <5% (N=3)	PD-L1>=5% to <50% (N=21)	PD-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%)	3 (42.9%)
Stable Disease (SD) [b]	8 (47.1%)	1 (33.3%)	4 (19.0%)	2 (28.6%)
Non-CR/Non-PD [c]	0	0	0	0
Progressive Disease (PD)	2 (11.8%)	0	1 (4.8%)	2 (28.6%)
Not Evaluable (NE) [d]	1 (5.9%)	0	4 (19.0%)	0
Response				
Objective Response Rate (ORR: CR+PR)	6 (35.3%)	2 (66.7%)	12 (57.1%)	3 (42.9%)
95% CI for ORR [e]	(14.2%, 61.7%)	(9.4%, 99.2%)	(34.0%, 78.2%)	(9.9%, 81.6%)
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 cut-off as of Oct 10,2018 for Group 2 patients.
[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.

Table 46: Kaplan-Meier estimate of PFS by independent central review in Group 2 patients who had opportunity for at least 3 response assessments stratified by PD-L1 expression levels - Study 1540

Table 12 Study 1540: Kaplan-Meier Estimate of PFS by Independent Central Review in Group 2 Patients who had Opportunity for at Least 3 Response Assessments Stratified by PD-L1 Expression Level

	PD-L1<1% (N=12)	PD-L1>=1% to <5% (N=3)	PD-L1>=5% to <50% (N=18)	PD-L1>=50% (N=6)
KM estimation of Progression Free Survival				
Number of events, n (%)	6 (50.0%)	1 (33.3%)	6 (33.3%)	3 (50.0%)
Progressive Disease, n (%)	4 (33.3%)	1 (33.3%)	6 (33.3%)	3 (50.0%)
Death, n (%)	2 (16.7%)	0	0	0
Number of censored patients, n (%)	6 (50.0%)	2 (66.7%)	12 (66.7%)	3 (50.0%)
Median (95% CI), (months)	7.4 (1.9, NE)	NR (5.7, NE)	NR (7.5, NE)	3.7 (1.0, NE)
Estimated Event-Free Probability, % (95% CI)				
4 months	68.2 (28.6, 88.9)	100 (NE, NE)	81.3 (52.5, 93.5)	44.4 (6.6, 78.5)
6 months	51.1 (13.8, 79.7)	50.0 (0.6, 91.0)	81.3 (52.5, 93.5)	44.4 (6.6, 78.5)
8 months	34.1 (5.3, 67.4)	50.0 (0.6, 91.0)	74.5 (45.4, 89.6)	NE (NE, NE)
12 months	17.0 (0.8, 51.9)	NE (NE, NE)	74.5 (45.4, 89.6)	NE (NE, NE)
16 months	17.0 (0.8, 51.9)	NE (NE, NE)	53.2 (22.0, 76.8)	NE (NE, NE)
20 months	17.0 (0.8, 51.9)	NE (NE, NE)	53.2 (22.0, 76.8)	NE (NE, NE)
24 months	17.0 (0.8, 51.9)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Data cut-off as of June 30, 2018
PD-L1 = Programmed death-ligand 1; KM = Kaplan- Meier; CR = complete response; PR = partial response; CI = confidence interval; NE = not evaluable; NR = not reported.

Table 47: Kaplan-Meier estimate of OS in Group 2 patients who had opportunity for at least 3 response assessments stratified by PD-L1 expression levels - Study 1540

	PD-L1<1% (N=12)	PD-L1>=1% to <5% (N=3)	PD-L1>=5% to <50% (N=18)	PD-L1>=50% (N=6)
KM estimation of Overall Survival				
Number of deaths, n (%)	3 (25.0%)	0	0	0
Number of censored patients, n (%)	9 (75.0%)	3 (100%)	18 (100%)	6 (100%)
Median (95% CI), (months)	NR (4.5, NE)	NR (NE, NE)	NR (NE, NE)	NR (NE, NE)
Estimated Probability of Survival, % (95% CI)				
4 months	91.7 (53.9, 98.8)	100 (NE, NE)	100 (NE, NE)	100 (NE, NE)
6 months	82.5 (46.1, 95.3)	100 (NE, NE)	100 (NE, NE)	100 (NE, NE)
8 months	82.5 (46.1, 95.3)	100 (NE, NE)	100 (NE, NE)	100 (NE, NE)
12 months	82.5 (46.1, 95.3)	NE (NE, NE)	100 (NE, NE)	100 (NE, NE)
16 months	70.7 (32.9, 89.8)	NE (NE, NE)	100 (NE, NE)	NE (NE, NE)
20 months	70.7 (32.9, 89.8)	NE (NE, NE)	100 (NE, NE)	NE (NE, NE)
24 months	70.7 (32.9, 89.8)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Data cut-off as of June 30, 2018
KM = Kaplan- Meier; CR = complete response; PR = partial response; CI = confidence interval; NE = Not evaluable; NR = Not reported.

Prior cancer-related radiotherapy

In the interim clinical study report (CSR) for Study 1540 in the original MAA, cemiplimab demonstrated efficacy both in patients who had received any prior radiation therapy (RT; objective response rate [ORR] 43.8% [28/64]) per independent central review) as well as in those who had not received any prior RT (ORR 55.6% [10/18] per independent central review).

In the updated submission, the applicant has evaluated whether prior RT could have provided added benefit to cemiplimab therapy for advanced CSCC.

Table 48: Tumour response by independent review for patients who had radiotherapy within 90 days prior to first dose of cemiplimab - FAS

Group	Patient ID	Interval between last date of RT and first dose of Cemiplimab, days	BOR	DOR (months), if applicable
mCSCC Cemiplimab: 3 mg/kg Q2W	036001006	34	PR	9.23
	036001008	47	PR	3.71
	036003002	35	PR	9.20
	840005003	33	SD	.
	840008006	33	NE	.
	840015008	90	PD	.
	840018003	38	NE	.
laCSCC Cemiplimab: 3 mg/kg Q2W	840003001	53	NE	.
	840005010	76	PR	7.39
	840013003	61	PR	9.23

Table 49: Tumour response by independent review for patients who had high cumulative dose of prior radiotherapy (≥150 Gy) - Study 1540 (FAS)

Group	Patient ID	Cumulative dose of prior radiotherapy (>= 150 Gy)	BOR	DOR (months), if applicable
mCSCC Cemiplimab: 3 mg/kg Q2W	036001006	176	PR	9.23
	036001008	456	PR	3.71
	036002003	432	SD	.
	036003008	182.88	PR	5.55
	276001001	166.5	PR	7.52
laCSCC Cemiplimab: 3 mg/kg Q2W	840003002	188	SD	.

There is a tendency for response that is observed in patients that have had high cumulative dose of prior radiotherapy, with 4 PRs and 2 SDs in the 6 patients who had received a high dose of radiotherapy.

Prior systemic chemotherapy

Table 52 summarizes prior anti-cancer systemic therapy for all patients (total) included in this analysis, and for patients in Groups 1, 2, and 3 individually. In the total efficacy population (right column), 63.5% (106/167) of patients had not received any prior anti-cancer systemic therapy. There were 36.5% (61/167) of patients who received any prior systemic therapy and 11.4% 19/167) of patients who had received more than 1 prior regimen.

Table 53 and Table 54 present ORR data for the entire efficacy population, subgrouped according to previously treated and previously untreated patients. ORR was 41.0% (95% CI: 28.6, 54.3) in previously treated patients and 47.2% (95% CI: 37.4, 57.1) in previously untreated patients.

Table 50: Prior anti-cancer systemic therapy for patients who had opportunity for at least 3 response assessments - Study 1540

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=59)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=64)	mCSCC Cemiplimab: 350 mg Q3W (N=44)	Total (N=167)
Number of Patients with any prior cancer-related systemic therapy, n (%)	33 (55.9%)	12 (18.8%)	16 (36.4%)	61 (36.5%)
Number of Regimens at baseline, n (%)				
0	26 (44.1%)	52 (81.3%)	28 (63.6%)	106 (63.5%)
1	22 (37.3%)	10 (15.6%)	10 (22.7%)	42 (25.1%)
2	7 (11.9%)	2 (3.1%)	4 (9.1%)	13 (7.8%)
3	3 (5.1%)	0	1 (2.3%)	4 (2.4%)
4	1 (1.7%)	0	1 (2.3%)	2 (1.2%)
Number of Regimens at baseline				
n	33	12	16	61
Mean (SD)	1.5 (0.80)	1.2 (0.39)	1.6 (0.89)	1.4 (0.76)
Median	1.0	1.0	1.0	1.0
Q1 : Q3	1.0 : 2.0	1.0 : 1.0	1.0 : 2.0	1.0 : 2.0
Min : Max	1 : 4	1 : 2	1 : 4	1 : 4

Data cut-off as of June 30, 2018

Table 51: Best overall response by independent central review - with prior anti-cancer systemic therapy- in patients with opportunity for at least 3 response assessments - Study 1540

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=33)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=12)	mCSCC Cemiplimab: 350 mg Q3W (N=16)	Total (N=61)
Prior systemic anticancer therapy: Yes				
Best Overall Tumor Response, n (%)				
Complete Response (CR) [a]	5 (15.2%)	0	0	5 (8.2%)
Partial Response (PR) [a]	9 (27.3%)	3 (25.0%)	8 (50.0%)	20 (32.8%)
Stable Disease (SD) [b]	5 (15.2%)	5 (41.7%)	3 (18.8%)	13 (21.3%)
Non-CR/Non-PD [c]	3 (9.1%)	0	0	3 (4.9%)
Progressive Disease (PD)	7 (21.2%)	2 (16.7%)	3 (18.8%)	12 (19.7%)
Not Evaluable (NE) [d]	4 (12.1%)	2 (16.7%)	2 (12.5%)	8 (13.1%)
Response				
Objective Response Rate (ORR: CR+PR)	14 (42.4%)	3 (25.0%)	8 (50.0%)	25 (41.0%)
95% CI for ORR [e]	(25.5%, 60.8%)	(5.5%, 57.2%)	(24.7%, 75.3%)	(28.6%, 54.3%)
99.99% CI for ORR [e]		(0.6%, 80.5%)	(9.7%, 90.3%)	
Complete Response Rate (CR) [a]	5 (15.2%)	0	0	5 (8.2%)
95% CI for CR Rate [e]	(5.1%, 31.9%)	(0.0%, 26.5%)	(0.0%, 20.6%)	(2.7%, 18.1%)

Data cut-off as of June 30, 2018
[a] CR/PR confirmed by repeated assessments no less than 4 weeks apart.
[b] SD criteria 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.

Table 52: Best overall response by independent central review - without prior anti-cancer systemic therapy- in patients with opportunity for at least 3 response assessments - Study 1540

	mCSCC Cemiplimab: 3 mg/kg Q2W (N=26)	laCSCC Cemiplimab: 3 mg/kg Q2W (N=52)	mCSCC Cemiplimab: 350 mg Q3W (N=28)	Total (N=106)
Prior systemic anticancer therapy: No				
Best Overall Tumor Response, n (%)				
Complete Response (CR) [a]	4 (15.4%)	7 (13.5%)	0	11 (10.4%)
Partial Response (PR) [a]	11 (42.3%)	19 (36.5%)	9 (32.1%)	39 (36.8%)
Stable Disease (SD) [b]	4 (15.4%)	16 (30.8%)	6 (21.4%)	26 (24.5%)
Non-CR/Non-PD [c]	0	0	2 (7.1%)	2 (1.9%)
Progressive Disease (PD)	4 (15.4%)	5 (9.6%)	8 (28.6%)	17 (16.0%)
Not Evaluable (NE) [d]	3 (11.5%)	5 (9.6%)	3 (10.7%)	11 (10.4%)
Response				
Objective Response Rate (ORR: CR+PR)	15 (57.7%)	26 (50.0%)	9 (32.1%)	50 (47.2%)
95% CI for ORR [e]	(36.9%, 76.6%)	(35.8%, 64.2%)	(15.9%, 52.4%)	(37.4%, 57.1%)
99.99% CI for ORR [e]		(24.2%, 75.8%)	(6.6%, 69.6%)	
Complete Response Rate (CR) [a]	4 (15.4%)	7 (13.5%)	0	11 (10.4%)
95% CI for CR Rate [e]	(4.4%, 34.9%)	(5.6%, 25.8%)	(0.0%, 12.3%)	(5.3%, 17.8%)

Data cut-off as of June 30, 2018
[a] CR/PR confirmed by repeated assessments no less than 4 weeks apart.
[b] SD criteria 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.

Relationship between ADA development and efficacy

In the Interim CSR for pivotal Study1540, all 41 patients with mCSCC (Group 1) and all 30 patients with laCSCC (Group 2) were negative in the anti-drug antibody (ADA) assay. As such, subgroup analysis was not performed.

Updated data on ADA based on data locks of 20 Sep 2018 for Groups 1 and Group 3 and 10 Oct 2018 for Group 2 were reviewed. 140 patients were included in the ADA population from Study 1540 including 41 patients from Group 1 (3mg/kg cemiplimab in metastatic CSCC), 60 patients from Group 2 (3mg/kg cemiplimab in locally advanced CSCC) and 39 patients from Group 3 (350 mg cemiplimab in metastatic CSCC patients). None of these patients (0%) experienced ADA or neutralizing antibodies to cemiplimab.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table: Summary of efficacy for Study 1540

Title: A phase 2 study of REGN2810, a fully human monoclonal antibody to programmed death – 1 (PD-1), in patients with advanced cutaneous squamous cell carcinoma		
Study identifier	R2810-ONC-1540, NCT02760498, EudraCT No. 2016-000105-36	
Design	Ongoing phase 2, single-arm, 3-group, multicenter	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	A96 weeks (54 weeks for Group 3) Up to 28 days (screening) N/A
Hypothesis	Exploratory: Improved ORR	
Treatments groups	Group 1 (mCSCC)	Cemiplimab 3 mg/kg Q2W for 96 weeks. 59 patients included, results available for 59 patients

	Group 2 (laCSCC)		Cemiplimab 3 mg/kg Q2W for 96 weeks. 78 patients included, results available for 64 patients
	Group 3 (mCSCC)		Cemiplimab 350 mg Q3W for 54 weeks. 56 patients included, results available for 44 patients
Endpoints and definitions	Primary endpoint	IRC-assessed ORR	Objective response rate based on a centrally reviewed evaluation. ORR was defined as the proportion of patients with complete or partial response by group.
	Secondary endpoints	INV-assessed ORR	Objective response rate based on investigator review
		DoR	Duration of response (in responding patients)
		TTR	Time to treatment response (in responding patients)
		mPFS	Median progression-free survival
		mOS	Median overall survival
		QoL	Patient-reported quality of life, measured by the EORTC QLQ-C30 on day 1 of every cycle
Database lock	20-Sep-2018 for Groups 1 and 3, 10-Oct-2018 for Group 2		
Results and Analysis			
Analysis description	Primary Analysis for mCSCC and laCSCC patients		
Analysis population and time point description	Primary analysis for 59/59 patients of Group 1 Primary analysis for 78/78 patients of Group 2 Primary analysis for 56/56 patients of Group 3		

Treatment group	Group 1	Group 2	Group 3
Number of subjects	59	78	56
IRC-assessed ORR, %	49.2	43.6	39.3
95% CI, %	35.9, 62.5	32.4, 55.3	26.5, 53.2
IRC-assessed median DoR, months	Not reached	Not reached	Not reached
95% CI, months	20.7, NE*	NE, NE	NE, NE
IRC-assessed median PFS, months	18.4	Not reached	10.4
95% CI, months	7.3, NE	9.2, NE	3.6, NE

Notes	mDoR and mOS have not been reached for any group *NE = not evaluable

Analysis performed across trials (pooled analyses and meta-analysis)

Table 53: Best overall tumour response rate by independent central review for PD-L1 <1% patients - Combined PD-L1 IHC results in studies 1423 and 1540 (FAS)

	mCSCC (N=5)	laCSCC (N=17)	Total (N=22)
Best Overall Tumor Response, n (%)			
Complete Response (CR) [a]	0	1 (5.9%)	1 (4.5%)
Partial Response (PR) [a]	3 (60.0%)	5 (29.4%)	8 (36.4%)
Stable Disease (SD) [b]	1 (20.0%)	8 (47.1%)	9 (40.9%)
Non-CR/Non-PD [c]	0	0	0
Progressive Disease (PD)	0	2 (11.8%)	2 (9.1%)
Not Evaluable (NE) [d]	1 (20.0%)	1 (5.9%)	2 (9.1%)
Response			
Objective Response Rate (ORR: CR+PR)	3 (60.0%)	6 (35.3%)	9 (40.9%)
95% CI for ORR [e]	(14.7%, 94.7%)	(14.2%, 61.7%)	(20.7%, 63.6%)
Durable DCR [f]	4 (80.0%)	10 (58.8%)	14 (63.6%)
95% CI for Durable DCR [e]	(28.4%, 99.5%)	(32.9%, 81.6%)	(40.7%, 82.8%)

Study1423: Data cut-off as of June 30, 2018. Study1540: Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients; Data cut-off as of Oct 10, 2018 for Group 2 patients.
[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 at baseline only.
[d] Not evaluable response includes the missing and unknown tumor response.
[e] Clopper-Pearson exact confidence interval.
[f] Durable DCR: proportion of patients with CR, PR, SD or Non-PR/Non-PD for at least 105 days without PD.

Table 54: Best overall tumour response rate by independent central review for PD-L1≥1% patients - Combined PD-L1 IHC results in studies 1423 and 1540 (FAS)

	mCSCC (N=16)	laCSCC (N=37)	Total (N=53)
Best Overall Tumor Response, n (%)			
Complete Response (CR) [a]	2 (12.5%)	4 (10.8%)	6 (11.3%)
Partial Response (PR) [a]	7 (43.8%)	16 (43.2%)	23 (43.4%)
Stable Disease (SD) [b]	1 (6.3%)	8 (21.6%)	9 (17.0%)
Non-CR/Non-PD [c]	2 (12.5%)	0	2 (3.8%)
Progressive Disease (PD)	2 (12.5%)	3 (8.1%)	5 (9.4%)
Not Evaluable (NE) [d]	2 (12.5%)	6 (16.2%)	8 (15.1%)
Response			
Objective Response Rate (ORR: CR+PR)	9 (56.3%)	20 (54.1%)	29 (54.7%)
95% CI for ORR [e]	(29.9%, 80.2%)	(36.9%, 70.5%)	(40.4%, 68.4%)
Durable DCR [f]	12 (75.0%)	24 (64.9%)	36 (67.9%)
95% CI for Durable DCR [e]	(47.6%, 92.7%)	(47.5%, 79.8%)	(53.7%, 80.1%)

Study1423: Data cut-off as of June 30, 2018. Study1540: Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients; Data cut-off as of Oct 10, 2018 for Group 2 patients.
[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 at baseline only.
[d] Not evaluable response includes the missing and unknown tumor response.
[e] Clopper-Pearson exact confidence interval.
[f] Durable DCR: proportion of patients with CR, PR, SD or Non-PR/Non-PD for at least 105 days without PD.

PD-L1 status is now available for 34% (75 out of 219) of patients from studies 1540 and 1423. ORR is 41% in patients with PD-L1 <1% and 55% in patients with PD-L1 ≥1%. Only 13 of out these 75 patients with valid PD-L1 status had mCSCC, the rest had laCSCC.

Clinical studies in special populations

Age subgroups

Table 55: Subgroup analysis - Number of patients in each age subgroup

	Age < 65 (Subjects/ total number) [a]	Age 65-74 (Older subjects number /total number)[a]	Age 75-84 (Older subjects number /total number) [a]	Age 85+ (Older subjects number /total number) [a]	Total
Controlled Trials	0/0	0/0	0/0	0/0	0/0
Non Controlled Trials – Study 1540					
mCSCC (Group 1)	16/59	23/59	14/59	6/59	59
laCSCC (Group 2)	16/64	19/64	21/64	8/64	64
mCSCC (Group 3)	10/44	18/44	12/44	4/44	44
Total	**42**	**60**	**47**	**18**	**167**

a. Total number refers to the total number of patients in each group who had sufficient follow-up for primary analysis (ie, at least 3 tumor response assessments). Response rates for each group who had are presented in

Table 56: Best overall tumour response rate by independent central review according to Age (FAS- Group 1 patients)

	Age <65 (N=16)	Age >=65 - 74 (N=23)	Age >=75 - 84 (N=14)	Age >=85 (N=6)	Total (N=59)
Best Overall Tumor Response, n (%)					
Complete Response (CR) [a]	3 (18.8%)	6 (26.1%)	0	0	9 (15.3%)
Partial Response (PR) [a]	5 (31.3%)	7 (30.4%)	7 (50.0%)	1 (16.7%)	20 (33.9%)
Stable Disease (SD) [b]	3 (18.8%)	3 (13.0%)	1 (7.1%)	2 (33.3%)	9 (15.3%)
Non-CR/Non-PD [c]	0	2 (8.7%)	0	1 (16.7%)	3 (5.1%)
Progressive Disease (PD)	5 (31.3%)	2 (8.7%)	3 (21.4%)	1 (16.7%)	11 (18.6%)
Not Evaluable (NE) [d]	0	3 (13.0%)	3 (21.4%)	1 (16.7%)	7 (11.9%)
Response					
Objective Response Rate (ORR: CR+PR)	8 (50.0%)	13 (56.5%)	7 (50.0%)	1 (16.7%)	29 (49.2%)
95% CI for ORR [e]	(24.7%, 75.3%)	(34.5%, 76.8%)	(23.0%, 77.0%)	(0.4%, 64.1%)	(35.9%, 62.5%)

Data cut-off as of June 30, 2018
[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.

Table 57: Best overall tumour response rate independent central review according to age (FAS - Group 2 patients who had opportunity for at least 3 tumour scans)

	Age <65 (N=16)	Age >=65 - 74 (N=19)	Age >=75 - 84 (N=21)	Age >=85 (N=8)	Total (N=64)
Best Overall Tumor Response, n (%)					
Complete Response (CR) [a]	2 (12.5%)	2 (10.5%)	3 (14.3%)	0	7 (10.9%)
Partial Response (PR) [a]	4 (25.0%)	7 (36.8%)	7 (33.3%)	4 (50.0%)	22 (34.4%)
Stable Disease (SD) [b]	10 (62.5%)	5 (26.3%)	5 (23.8%)	1 (12.5%)	21 (32.8%)
Non-CR/Non-PD [c]	0	0	0	0	0
Progressive Disease (PD)	0	3 (15.8%)	4 (19.0%)	0	7 (10.9%)
Not Evaluable (NE) [d]	0	2 (10.5%)	2 (9.5%)	3 (37.5%)	7 (10.9%)
Response					
Objective Response Rate (ORR: CR+PR)	6 (37.5%)	9 (47.4%)	10 (47.6%)	4 (50.0%)	29 (45.3%)
95% CI for ORR [e]	(15.2%, 64.6%)	(24.4%, 71.1%)	(25.7%, 70.2%)	(15.7%, 84.3%)	(32.8%, 58.3%)

Data cut-off as of June 30, 2018
[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.

Table 58: Best overall tumour response rate by independent central review according to age (FAS - Group 3 patients who had opportunity for at least 3 tumour scans)

	Age <65 (N=10)	Age >=65 - 74 (N=18)	Age >=75 - 84 (N=12)	Age >=85 (N=4)	Total (N=44)
Best Overall Tumor Response, n (%)					
Complete Response (CR) [a]	0	0	0	0	0
Partial Response (PR) [a]	4 (40.0%)	7 (38.9%)	3 (25.0%)	3 (75.0%)	17 (38.6%)
Stable Disease (SD) [b]	1 (10.0%)	6 (33.3%)	1 (8.3%)	1 (25.0%)	9 (20.5%)
Non-CR/Non-PD [c]	0	0	2 (16.7%)	0	2 (4.5%)
Progressive Disease (PD)	3 (30.0%)	4 (22.2%)	4 (33.3%)	0	11 (25.0%)
Not Evaluable (NE) [d]	2 (20.0%)	1 (5.6%)	2 (16.7%)	0	5 (11.4%)
Response					
Objective Response Rate (ORR: CR+PR)	4 (40.0%)	7 (38.9%)	3 (25.0%)	3 (75.0%)	17 (38.6%)
95% CI for ORR [e]	(12.2%, 73.8%)	(17.3%, 64.3%)	(5.5%, 57.2%)	(19.4%, 99.4%)	(24.4%, 54.5%)

Data cut-off as of June 30, 2018
[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.

Table 59: Best overall tumour response rate by independent central review according to age (FAS - Patients who had opportunity for at least 3 tumour scans)

Table 12 Best Overall Tumor Response Rate by Independent Central Review According to Age (Full Analysis Set - Patients who had Opportunity for at Least 3 Tumor Scans)

	Age <65 (N=42)	Age >=65 - 74 (N=60)	Age >=75 - 84 (N=47)	Age >=85 (N=18)	Total (N=167)
Best Overall Tumor Response, n (%)					
Complete Response (CR) [a]	5 (11.9%)	8 (13.3%)	3 (6.4%)	0	16 (9.6%)
Partial Response (PR) [a]	13 (31.0%)	21 (35.0%)	17 (36.2%)	8 (44.4%)	59 (35.3%)
Stable Disease (SD) [b]	14 (33.3%)	14 (23.3%)	7 (14.9%)	4 (22.2%)	39 (23.4%)
Non-CR/Non-PD [c]	0	2 (3.3%)	2 (4.3%)	1 (5.6%)	5 (3.0%)
Progressive Disease (PD)	8 (19.0%)	9 (15.0%)	11 (23.4%)	1 (5.6%)	29 (17.4%)
Not Evaluable (NE) [d]	2 (4.8%)	6 (10.0%)	7 (14.9%)	4 (22.2%)	19 (11.4%)
Response					
Objective Response Rate (ORR: CR+PR)	18 (42.9%)	29 (48.3%)	20 (42.6%)	8 (44.4%)	75 (44.9%)
95% CI for ORR [e]	(27.7%, 59.0%)	(35.2%, 61.6%)	(28.3%, 57.8%)	(21.5%, 69.2%)	(37.2%, 52.8%)

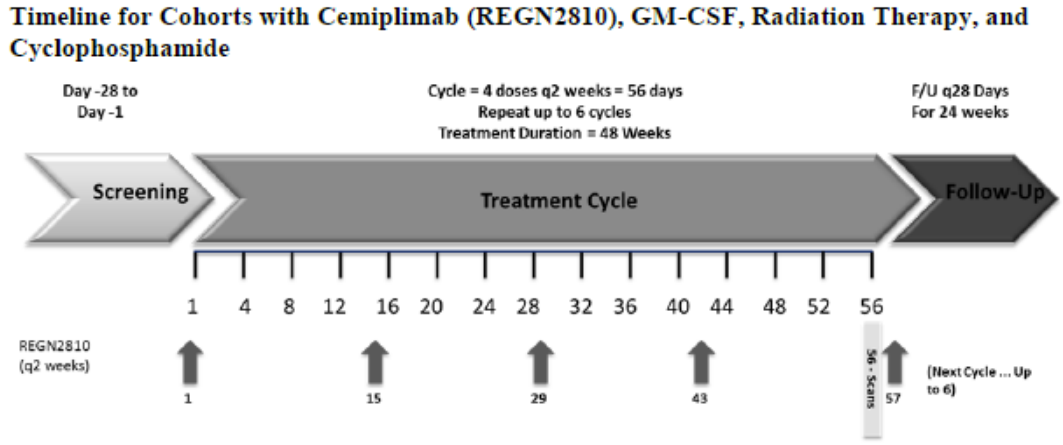
Data cut-off as of June 30, 2018
[a] CR/PR must be confirmed by repeated assessments no less than 4 weeks apart.
[b] SD criteria must be met at least once after a minimum duration of 39 days after first dose date.
[c] Non-CR/Non-PD is for patients with non-measurable disease only.
[d] Not evaluable response includes the missing and unknown tumor response.
[e] Clopper-Person exact confidence interval.

Supportive study(ies)

R2810-ONC-1423: A First-in-Human Study of Repeat Dosing with REGN2810, a Monoclonal, Fully Human Antibody to Programmed Death – 1 (PD-1), as Single Therapy and in Combination with Other Anti-Cancer Therapies, in Patients with Advanced Malignancies

Study 1423 is a phase 1, first-in-human, open-label, repeat dose study with cemiplimab as monotherapy and combination therapy. 397 adult patients (≥18 years old, males/females) with advanced solid malignancies in multiple cohorts have been enrolled, among them 26 with CSCC: Expansion Cohort 7 evaluated cemiplimab 3 mg/kg Q2W monotherapy in 16 CSCC patients with distant metastatic disease (M1), and Expansion Cohort 8 evaluated cemiplimab 3 mg/kg Q2W monotherapy in 10 patients with locally and/or regionally advanced CSCC.

Table 60: Overall patient treatment and follow-up timeline



CPA=cyclophosphamide (CTX); F/U=follow-up; XRT

The last patient enrolled in Expansion Cohort 7 received the first treatment with cemiplimab on 25 Oct 2016, and the last patient enrolled in Expansion Cohort 8 received the first treatment with cemiplimab on 24 Jan 2017. The data cutoff date for this efficacy analysis is 02 Oct 2017.

The report submitted by the applicant presents the results of an unplanned interim analysis, specifically performed to support the marketing applications of cemiplimab for the treatment of mCSCC and laCSCC.

Patient disposition: Among 26 CSCC patients, 11 (42.3%) patients completed the planned 48-week treatment regimen. The most common reason for treatment discontinuation was progression of disease (26.9% [7/26] of patients). Death was the primary reason for discontinuation of 2 patients and AEs in 2 additional patients.

Numbers analysed: All 26 CSCC patients who were in the FAS were also included in the SAF and in the PKAS.

Baseline data: The CSCC population consisted predominantly of older white males. Median age was 72.5 years, 80.8% of patients were male, and 92.3% of patients were white. Notably, the median age of the CSCC patient population (72.5 years) was greater than that of the overall study population (62.0 years). No patients with ECOG PS 2 were allowed to participate, 16 patients had ECOG PS 1 and the other 10 had ECOG PS 0. Approximately 58% of CSCC patients had been treated with a cancer-related systemic therapy at baseline. The most common agents were monoclonal antibodies (7 out of 26 patients, 27%) and platinum compounds (7 out of 26 patients, 27%). Taxanes had been received by 3 patients. Most patients had had prior cancer-related surgery (median 3.0 procedures [range 1 to 17]). Most mCSCC patients (68.8% [11/16]) and all laCSCC patients (100% [10/10]) had received prior cancer-related RT.

Efficacy: Updated efficacy results for the CSCC patients using the 30 Jun 2018 data cutoff date are presented.

Table 61: Best overall tumour response by independent central review in CSCC patients (Full analysis set) - Study 1423

	mCSCC (N=16)	laCSCC (N=10)	Total (N=26)
Best Overall Tumor Response, n (%)			
Complete Response (CR) [a]	0	0	0
Partial Response (PR) [a]	7 (43.8%)	6 (60.0%)	13 (50.0%)
Stable Disease (SD) [b]	4 (25.0%)	2 (20.0%)	6 (23.1%)
Non-CR/Non-PD [c]	1 (6.3%)	0	1 (3.8%)
Progressive Disease (PD)	3 (18.8%)	0	3 (11.5%)
Not Evaluable (NE) [d]	1 (6.3%)	2 (20.0%)	3 (11.5%)
Response			
Objective Response Rate (ORR: CR+PR)	7 (43.8%)	6 (60.0%)	13 (50.0%)
95% CI for ORR [e]	(19.8%, 70.1%)	(26.2%, 87.8%)	(29.9%, 70.1%)

Data cut-off as of June 30, 2018.
[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 at baseline only.
[d] Not evaluable response includes the missing and unknown tumor response.
[e] Clopper-Pearson exact confidence interval.

Table 62: Summary of duration of response by independent central review for CSCC patients - Study 1423 (Full analysis set)

	mCSCC (N=7)	laCSCC (N=6)	Total (N=13)
KM Estimation of Duration of Response (CR or PR)			
n	7	6	13
Number of events, n(%) [a]	2 (28.6%)	0	2 (15.4%)
Number of Censored Patients, n(%) [a]	5 (71.4%)	6 (100%)	11 (84.6%)
Median (95% CI), (months)	20.3 (4.6, 20.3)	NR (NE, NE)	20.3 (NE, NE)
Observed Duration of Response (CR or PR) (months)			
n	7	6	13
Min : Max	4.6 : 20.3	1.0 : 15.5	1.0 : 20.3
Observed Duration of Response (CR or PR), n (%) [b]			
>=4 months	7 (100%)	5 (83.3%)	12 (92.3%)
>=6 months	6 (85.7%)	5 (83.3%)	11 (84.6%)
>=8 months	6 (85.7%)	5 (83.3%)	11 (84.6%)
>=12 months	5 (71.4%)	4 (66.7%)	9 (69.2%)
>=16 months	2 (28.6%)	0	2 (15.4%)

Data cut-off as of June 30, 2018.
KM = Kaplan-Meier; CR = complete response; PR = partial response; CI = confidence interval.
[a] Events include progressive disease or deaths. Percentages are based on number of patients with confirmed CR or PR.
[b] Percentages are based on number of patients with confirmed CR or PR. The numerator includes the number of patients whose observed duration of response reached at least the specified time. Patients who did not have the opportunity to reach the specified timepoint were included in the denominator only.

Table 63: Kaplan-Meier estimation of Progression-Free Survival by independent central review in CSCC patients - Study 1423 (Full analysis set)

	mCSCC (N=16)	laCSCC (N=10)	Total (N=26)
KM estimation of Progression Free Survival			
Number of events, n (%)	10 (62.5%)	1 (10.0%)	11 (42.3%)
Progressive Disease, n (%)	7 (43.8%)	0	7 (26.9%)
Death, n (%)	3 (18.8%)	1 (10.0%)	4 (15.4%)
Number of censored patients, n (%)	6 (37.5%)	9 (90.0%)	15 (57.7%)
Median (95% CI), (months)	16.2 (1.8, 22.0)	NR (1.1, NE)	22.0 (5.4, NE)
Estimated Event-Free Probability, % (95% CI)			
4 months	68.8 (40.5, 85.6)	88.9 (43.3, 98.4)	76.0 (54.2, 88.5)
6 months	62.5 (34.9, 81.1)	88.9 (43.3, 98.4)	71.8 (49.7, 85.5)
8 months	62.5 (34.9, 81.1)	88.9 (43.3, 98.4)	71.8 (49.7, 85.5)
12 months	55.6 (28.6, 75.9)	88.9 (43.3, 98.4)	67.3 (45.0, 82.2)
16 months	55.6 (28.6, 75.9)	88.9 (43.3, 98.4)	67.3 (45.0, 82.2)

Data cut-off as of June 30, 2018.
KM = Kaplan-Meier.

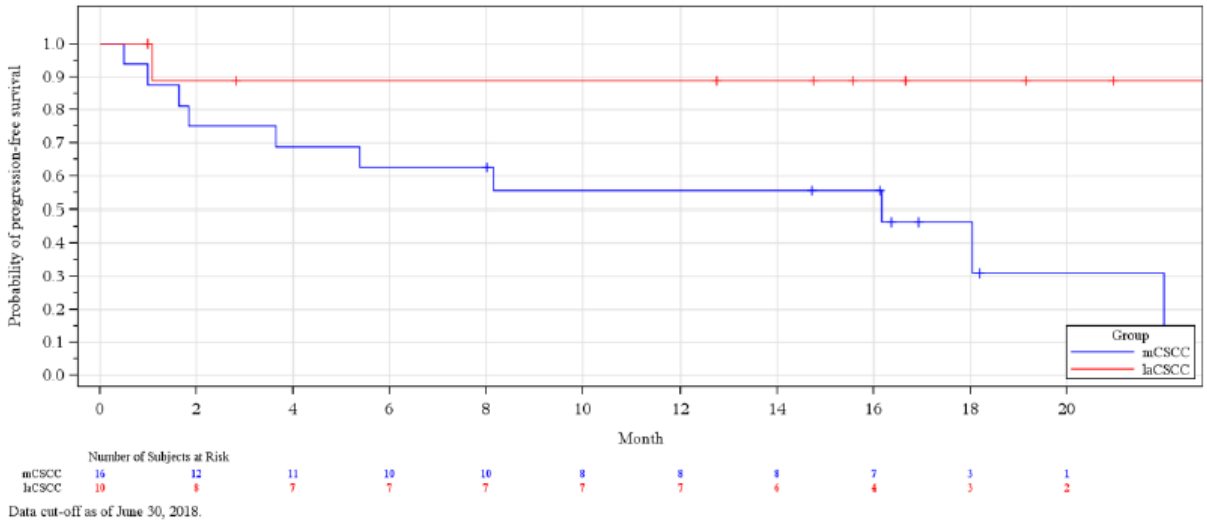


Figure 24: Kaplan-Meier curve for Progression-Free Survival by independent central review for CSCC patients - Study 1423 (Full analysis set)

Table 64: Kaplan-Meier estimation of Overall survival for CSCC patients - Study 1423 (Full analysis set)

	mCSCC (N=16)	laCSCC (N=10)	Total (N=26)
KM estimation of Overall Survival			
Number of deaths, n (%)	7 (43.8%)	1 (10.0%)	8 (30.8%)
Number of censored patients, n (%)	9 (56.3%)	9 (90.0%)	18 (69.2%)
Median (95% CI), (months)	22.0 (13.6, NE)	NR (1.1, NE)	NR (16.2, NE)
Estimated Probability of Survival, % (95% CI)			
4 months	93.8 (63.2, 99.1)	90.0 (47.3, 98.5)	92.1 (72.1, 98.0)
6 months	87.5 (58.6, 96.7)	90.0 (47.3, 98.5)	88.0 (67.1, 96.0)
8 months	87.5 (58.6, 96.7)	90.0 (47.3, 98.5)	88.0 (67.1, 96.0)
12 months	80.2 (50.1, 93.2)	90.0 (47.3, 98.5)	83.3 (61.3, 93.4)
16 months	65.6 (35.8, 84.1)	90.0 (47.3, 98.5)	74.1 (50.9, 87.5)

Data cut-off as of June 30, 2018.
KM = Kaplan-Meier.

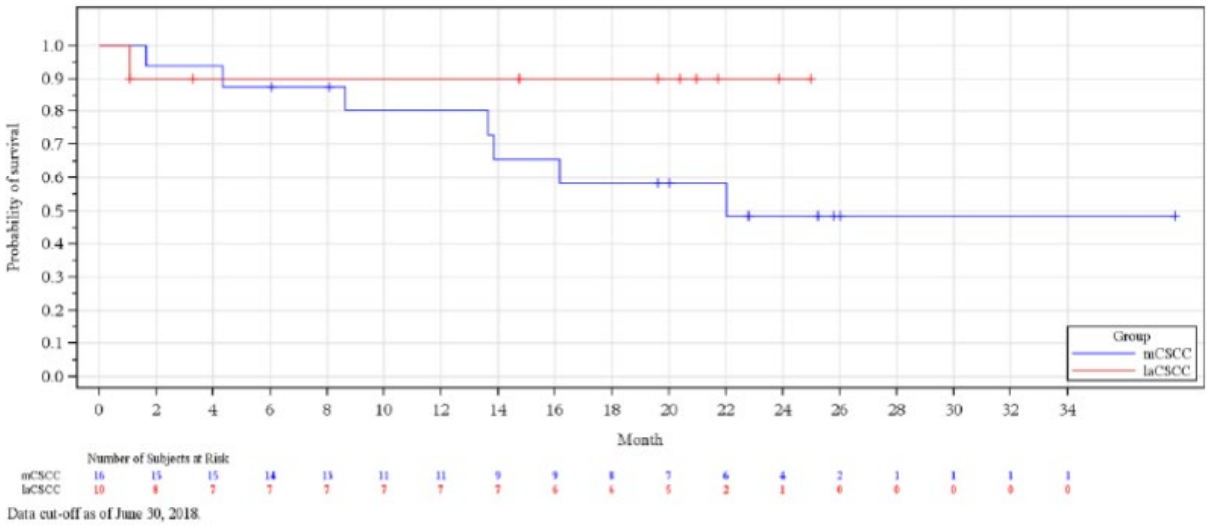


Figure 25: Kaplan-Meier curve for overall survival for CSCC patients - Study 1423 (Full analysis set)

ORR has not changed from the previous submission: 43.8% (95% CI 19.8, 70.1) in mCSCC and 60% (95% CI 26.2, 87.8) in laCSCC. Updated survival curves show that median PFS (16.2 months, 95% CI

1.8, 22.0) and median OS (22 months, 95% CI 13.6, NE) have been reached for the mCSCC group, suggesting durable responses.

The Dermatologic Cooperative Oncology Group (DeCOG) analysis of CSCC patients

A larger "real world" experience regarding advanced CSCC patients in the European Union (EU) was reported recently (Hillen, 2018). The Dermatologic Cooperative Oncology Group (DeCOG) retrospectively analysed 190 patients with advanced CSCC (114 metastatic, 76 locally advanced) from 20 German and Austrian clinical sites between 2010 to 2011. Advanced CSCC comprised laCSCC or mCSCC. Locally advanced CSCC was defined as a tumour that could not be cured or was unlikely to be curable by either surgery, radiotherapy, or both (based on decision by an interdisciplinary tumour board). Metastatic CSCC included patients with local nodal metastases, distant metastases, or both local nodal and distant metastases. Table 67 summarizes the baseline characteristics in the DeCOG study population (N =190 patients) and baseline characteristics from fully enrolled Groups 1, 2, and 3 in Study 1540 (N=193 patients).

Table 65: Characteristics of advanced CSCC patients in DeCOG Study and in Study 1540

Characteristic	DeCOG Study (N = 190 patients)	Study 1540, Groups 1 to 3 (N = 193 patients)
Median Age, years (range)	78 (32 – 98)	72 (38 – 96)
ECOG performance status of 0 or 1, n (%)	99 (83)[1]	193 (100)
Sex, n (%)		
Male	127 (67)	161 (83.4)
Female	63 (33)	32 (16.6)
Primary Tumor Site,[2] n (%)		
Head and Neck[3]	143 (75.3)	130 (67.3)
Extremity[4]	28 (14.7)	41 (21.2)
Trunk	18 (9.5)	22 (11.4)
Not Specified	1 (0.1)	0
Number of patients with any prior cancer-related surgery, n (%)[5]	175 (92%)	174 (90.2%)
Number of patients with any prior cancer-related radiotherapy, n (%)[6]	22 (12%)	131 (67.9%)
Patients with Metastatic Disease, nodal and/or distant, n patients (%)	114 (60.0)	115 (59.6%)

Table 68 summarizes ORR and BOR results from the DeCOG manuscript and from Study 1540 patients in Groups 1, 2, and 3 who had the potential for at least 6 months on study as of the 30 Jun 2018 data cutoff date.

Table 66: ORR and BOR for advanced CSCC patients in DeCOG study and in Study 1540

	DeCOG	Study 1540, Groups 1 - 3
Number of treatment regimens	39[1]	167[2]
Best Overall Response, n (%)		
Complete Response	2 (5.1)	16 (9.6)
Partial Response	8 (20.6)	59 (35.3)
Stable Disease	16 (41.0)	39 (23.4)
Non-CR/non-PD	0	5 (3.0)
Progressive Disease	13 (33.3)	29 (17.4)
Not evaluable	0	19 (11.4)
Objective Response Rate, n PR + CR, (%)	10 (25.6)	75 (44.9)

1. DeCOG ORR and BOR data are derived from 39 treatment regimens among 30 evaluable patients. PFS was not reported in the DeCOG study.
2. Study 1540 efficacy data are derived from 167 patients who had the opportunity for at least 3 on-treatment response assessments, as described in response to Agency Question 71. Each patient is counted as 1 cemiplimab regimen, according to intention-to-treat.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy and safety of cemiplimab in patients with metastatic (nodal or distant) CSCC (mCSCC) or locally advanced CSCC (laCSCC) who were not candidates for curative surgery or curative radiation were studied in clinical trial R2810-ONC-1540 (Study 1540). Study 1540 was a phase 2, open-label, multi-centre study that had enrolled 193 patients with mCSCC or laCSCC with a combined median follow-up time of 9.4 months. Median follow-up was 16.5 months for the mCSCC 3 mg/kg every 2 weeks group (Group 2), 9.3 months for the laCSCC 3 mg/kg every 2 weeks group (group 1) and 8.1 months for the mCSCC 350 mg every 3 weeks group (group 3).

Patients with any of the following were excluded: autoimmune disease that required systemic therapy with immunosuppressant agents within 5 years; history of solid organ transplant; history of pneumonitis within the last 5 years; prior treatment with anti-PD-1/PD-L1 or other immune checkpoint inhibitor therapy; active infection requiring therapy, including known infection with human immunodeficiency virus, or active infection with hepatitis B or hepatitis C virus; chronic lymphocytic leukaemia (CLL); brain metastases or Eastern Cooperative Oncology Group (ECOG) performance score $\geqslant$ 2. Regarding

recruitment, 4 out of 193 patients had not been confirmed by independent central pathology review to have the diagnosis of invasive CSCC, which could have affected the results. However, several sensitivity analyses for efficacy endpoints provide reassurance for the primary efficacy analysis. Previous treatment with BRAF-inhibitors was an exclusion criterion because BRAF-induced CSCCs are biologically and clinically different from UV-induced CSCCs. However, no patients were excluded from participation in the trial due to this criterion.

The study design is open-label and uncontrolled, thus being difficult to interpret in the pivotal setting. The sought indication has only been tested in 59 patients in group 1, 78 patients in group 2 and 56 patients in Group 3. In Study 1540, patients received cemiplimab until progression of disease, unacceptable toxicity or completion of planned treatment [3 mg/kg every 2 weeks for 96 weeks or 350 mg every 3 weeks for 54 weeks]. If patients with locally advanced disease showed sufficient response to treatment, surgery with curative intent was permitted. Tumour response assessments were performed every 8 or 9 weeks (for patients receiving 3 mg/kg every 2 weeks or 350 mg every 3 weeks, respectively). In general, the study design is considered acceptable. Although such design was considered an acceptable way forward at the time of scientific advice, the CHMP highlighted that demonstrating longer survival benefit, in a randomised controlled study would have been a preferable option.

Overall, ORR can be accepted as the primary endpoint of the phase II study, but robustness of the response assessment and compelling results for ORR would be considered highly important for single arm uncontrolled studies. At present, it is not known whether ORR or PFS are surrogates for OS or clinical benefit in patients with CSCC that receive immunotherapy. Important secondary efficacy endpoints such as DoR, PFS and OS, were not corrected for multiplicity, hence are only considered exploratory.

The planned interim analysis for Group 2 was finalised on 22 September 2017. at a very late stage when the study was ongoing (amendment 5) and the first data cut-off date was 27th October 2017. This initially prompted a major objection as it cannot be excluded that the decision to conduct an interim analysis on Group 2 was not data driven. However, the updated efficacy results from data cutoff of 20 September 2018 for Groups 1 and 3, and 10 October 2018 for Group 2.showed that there were a majority of patients that had duration of response longer than 6 months, which is considered clinically meaningful, providing some reassurance on the robustness of the data. However, median follow-up time since start of treatment is still limited (16.5, 9.3, and 8.1 months in Groups 1, 2 and 3 respectively; 9.4 months for the ITT population).

Study 1423, a phase 1 study of cemiplimab with 2 expansion cohorts designed to obtain preliminary clinical experience with cemiplimab in patients with advanced CSCC was considered as supportive study.

Efficacy data and additional analyses

Results are presented from 193 patients in Study 1540. Of these 193 patients, 115 had mCSCC and 78 had laCSCC. The median age was 72 years (range: 38 to 96): seventy-eight (40.4%) patients were 75 years or older, 66 patients (34.2%) were 65 to less than 75 years, and 49 patients (25.4%) were less than 65 years. A total of 161 (83.4 %) patients were male, and 187 (96.9%) patients were White; the ECOG performance score was 0 (44.6%) or 1 (55.4%). Almost all recruited patients were white (98.3% in mCSCC and 100% in laCSCC group) and male (enrolment rate was 57% for females and 74% for males) which is in line with epidemiological data on CSCC.

Thirty-three and 7/10 per cent (33.7%) of patients had received at least 1 prior anti-cancer systemic therapy, 90.2% of patients had received prior cancer related surgery, and 67.9% of patients had received prior radiotherapy. Among patients with mCSCC, 76.5% had distant metastases, and 22.6% had only nodal metastases.

A primary analysis was possible for the entire population of the study since all 193 patients (in the 3 groups) had the opportunity for at least 3 response assessments. The current IRC-assessed ORR results are consistent for each group: 49.2% in Group 1, 43.6% in Group 2 and 39.3% in Group 3 (the commercially intended dose). Of note, the lower bound of the 95% CI is beyond the range of clinically insignificant effect (≤15% ORR in Group 1 and Group 3, ≤25% in Group 2) in all 3 groups. INV-assessed response –a secondary endpoint– produced similar data and is considered supportive. An ORR of 44.0% (95% CI: 36.9, 51.3) in advanced CSCC patients may represent clinical benefit for this population, particularly when considering known ORRs for other available treatments (34-86% for chemotherapy,[21], [22], [23],[3] 16% for gefitinib,[18] 28% for cetuximab[19] and 31% for panitumumab[20]). The DeCOG analysis provides some "real world" experience in advanced CSCC in the EU, although the number of patients included in the analysis as well as information on the treatments received by patients is very limited. The ORR achieved in the analysis was 25.6%.

DoR is a secondary endpoint which is critical in order to establish a clinical benefit. Taking into consideration the mechanism of action of cemiplimab, it is assumed that the establishment of partial or complete response could occur in the first or in a second or ulterior assessment (delayed response from immunotherapy). Hence, DoR may not be considered as a valid endpoint until all the data are sufficiently mature. In addition, DoR analysis is affected by the low number of events, i.e., relapses. Overall, only 10.6% of the responding patients have relapsed, 17.2%, 8.8% and 4.5% in Groups 1 to 3, respectively. At this point, only data from Group 1 (median follow-up 16.5 months) have enough maturity for an accurate assessment. Considering the longer follow-up for Group 1, 27 out of 29 patients (93%) have a response that has lasted for 6 months or longer. DoR is ≥6 months for 68% of patients from Group 2 (23 out 34) and 64% of patients from Group 3 (14 out of 22), although it is expected that these rates might increase with further follow-up.

Two sensitivity analyses that assign either an OS or PFS event to patients who had ended the study due to other reasons and were not undergoing active follow-up were requested from the applicant. In this worst-case scenario, there is no detrimental effect on OS and PFS outcome of patients with advanced CSCC treated with cemiplimab. Compared to the initial analyses before 30-June-2018 data cut-off, updated IRC-PFS results are nearly identical for Group 1 (28 events in 59 patients, mPFS 18.4 months, 6-month-PFS 66.0%) and minimally improved for Group 3 (26 events in 56 patients, mPFS 10.4 months, 6-month-PFS 59.3%).

PFS is increased for patients treated with cemiplimab at a dose of 3 mg/kg Q2W in mCSCC patients compared with the fixed dose of 350 mg Q3W: 18.4 vs. 10.4 months. The data is based on median PFS estimates where roughly half of the events have occurred in both groups (47.5% in Group1, 46.4% in Group 3). There is no clear explanation for this discrepancy, however, the data is based on few patients and it is expected that with longer follow-up, the PFS for Group 3 will improve with further follow up.

With 9.4 months of median follow-up time and 18% of events (34 in 193 patients), OS results are too immature to draw any clear conclusion.

Of the 219 patients with mCSCC and laCSCC treated with cemiplimab, 25.1% (55/219) were less than 65 years, 34.2% (75/219) were 65 to less than 75 years, and 40.6% (89/219) were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

In the 193 patients in the efficacy analysis, the objective response rate by ICR (95% CI) was 40.8% (27.0%, 55.8%) in patients less than 65 years, 48.5% (36.0%, 61.1%) in patients 65 to less than 75 years, and 42.3% (31.2%, 54.0%) in patients 75 years or older.

The relationship between PD-L1 status and efficacy was analysed post-hoc in patients with available tissue samples and not from a systematic biopsy sampling of the patients' tumours. Based on the limited

number of patients with tumour samples, clinical activity seems to be observed regardless of tumour PD-L1 expression status (see section 5.1 of SmPC). An updated analysis was provided where the PD-L1 status from 75 out of 219 patients with advanced CSCC treated with cemiplimab (61 from Study 1540 and 14 from 1423) was presented. ORR for mCSCC patients and laCSCC designated PD-L1 <1% was 60% and 35.3%, respectively (total was 41%) whereas in patients designated PD-L1 ≥1%, ORR was 56.3% and 54.1%, respectively (Total was 55%). Only 21 of out these 75 patients with valid PD-L1 status had mCSCC, the rest had laCSCC. This suggests that for patients with laCSCC that had low PD-L1 expression, ORR was also lower compared with mCSCC and hence, PD-L1 might not be predictive for efficacy for this patient population with cemiplimab. Nonetheless, while the data is not conclusive, based on the mechanism of action of cemiplimab, the results for mCSCC are considered clinically meaningful. There is not enough data to be able to restrict the indication based on PD-L1 expression, and hence, further investigation of efficacy by PD-L1 would be warranted. Therefore, the MAH should investigate biomarkers in order to confirm that PD-L1 expression is not predictive of efficacy.

As study 1540 was a single arm trial, no firm conclusion can be drawn from the QoL data, although no detrimental effect was observed in any of the EORTC QLQ-30 subscales.

None of the patients experienced ADA or neutralizing antibody to cemiplimab. The titers that were observed were low and there was no indication of clinical impact or exposure. The fact that none of the 140 patients included in the immunogenicity population developed ADAs or neutralizing antibodies to cemiplimab does not preclude from the risk of ADA. Data are too scarce and there is also a concern about the ADA test's sensitivity. Although additional experiments suggest that the methods for immunogenicity testing are considered adequate with regard to drug tolerance, the current immunogenicity database is too limited to conclude on the risk. For these reasons, the phrase "lack of effect due to anti-drug antibodies" has been included at the RMP.

The European Medicines Agency has deferred the obligation to submit the results of studies with cemiplimab in all subsets of the paediatric population in the treatment of all conditions included in the category of malignant neoplasms, except haematopoietic and lymphoid tissue (see section 4.2 for information on paediatric use).

Additional efficacy data needed in the context of a conditional MA

The data from study 1540 shows a compelling ORR rate of 44% in patients with laCSCC and mCSCC treated with cemiplimab. DoR, the key secondary efficacy endpoint, is beyond 6 months for at least 93% of patients from Group 1 (limited follow-up challenges interpretation of DoR for Groups 2 and 3). ORR is a clinically relevant endpoint in this cutaneous malignancy. However, the study did not have a comparator and there were few patients recruited and treated with the recommended posology of 350 mg Q3W for mCSCC, especially in the patient population for laCSCC. These uncertainties cannot be answered by the current single arm trial 1540 alone and hence further confirmatory data is needed on 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. Therefore, the CHMP has requested that the applicant conducts a prospective single-arm study in the same population with a defined sample size to confirm the clinical efficacy and safety of cemiplimab in the intended indication and posology of 350 mg Q3W. The study should incorporate an investigative plan to provide biomarker data to confirm the predictive value of PD-L1. Furthermore, it is recommended that the study characterises other possible biomarkers which may predict efficacy responses in patients treated with cemiplimab. The study protocol should be discussed within 3 months of the approval and before initiation of the study/cohort. Since there is no long term efficacy data, it is still unknown whether responses to cemiplimab are durable and that may lead to a prolongation of duration of response and/or an effect on PFS and ultimately an improved OS

in the long term. The final clinical study report for Study 1540 (Groups 1-3) should be submitted in order to provide comprehensive data on DoR, PFS and OS.

2.5.4. Conclusions on the clinical efficacy

The study 1540 has shown a compelling ORR rate of 44% in patients with laCSCC and mCSCC treated with cemiplimab. DoR, the key secondary efficacy endpoint, is beyond 6 months for at least 93% of patients from Group 1 (limited follow-up challenges interpretation of DoR for Groups 2 and 3) which provides further support to the efficacy observed. The available data on the expression of PD-L1 suggest that this biomarker may lack predictive value to determine tumour responses in the intended indication. Although the magnitude of the effect is not completely defined, the efficacy in terms of ORR is considered clinically relevant and suggests that a proportion of patients may benefit from a prolongation in the duration of response which could ultimately result in a positive effect on PFS or OS.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- 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. Due date 31st March 2023
- 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. Due date 31st October 2022.

The CHMP recommends the following measures to address the issues related to efficacy:

- To investigate and characterise in all ongoing and planned studies, a biomarker or set of biomarkers that can predict efficacy responses in patients treated with cemiplimab.

2.6. Clinical safety

Safety data from Study R2810-ONC-1423 and Study R2810 ONC 1540 were combined in the integrated safety analysis.

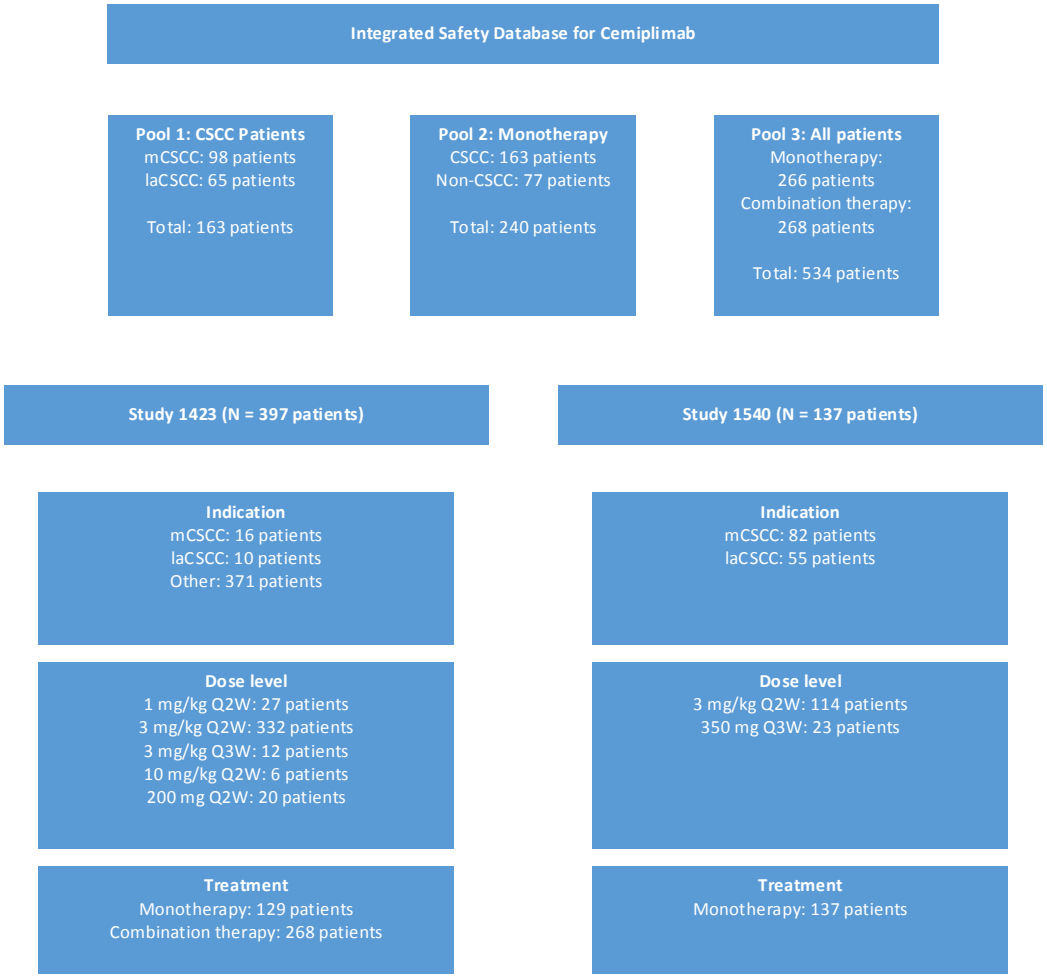


Figure 26: Studies of Cemiplimab in the CSCC Program

[a] As of safety data cutoff dates
Abbreviations: CSCC, cutaneous squamous cell carcinoma; laCSCC, locally advanced cutaneous squamous cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; N, total number of patients; Q2W, every 2 weeks; Q3W, every 3 weeks. Patients with CSCC from Study 1423 were recategorized according to the Study 1540 definitions of mCSCC and laCSCC.

Safety data are presented mainly from two studies and data have been pooled into three pools. As the sought indication for cemiplimab is monotherapy, the safety pool that is considered most relevant is the monotherapy patients, because patients in safety pool 3 had cemiplimab in combination with chemotherapy or radiotherapy. The patients in safety pool 2 or the Monotherapy Pool encompassed CSCC patients from pool 1 (n=163 patients) plus all non-CSCC patients receiving monotherapy, except HCC (n=77 patients), but with updated safety data the numbers increased to 297 monotherapy patients in total. The number of patients who received the proposed dosing regimen of 350 mg cemiplimab Q3W has increased from 23 to 56 patients.

Patient exposure

Table 67: Treatment exposure for cemiplimab (Safety analysis set)

	Pool 1 - All CSCC Patients (N=163)	Pool 2 - All Monotherapy Patients (Excluding HCC) (N=240)	Pool 3 - All Patients (N=534)
Duration of exposure (weeks)[a]			
n	163	240	534
Mean (SD)	25.79 (19.910)	25.80 (19.579)	22.51 (17.244)
Median	20.00	19.65	16.00
Q1 : Q3	7.90 : 45.40	8.00 : 47.30	8.00 : 35.40
Min : Max	0.4 : 71.0	0.4 : 71.0	0.4 : 71.0
Duration of exposure, n (%)			
≥0 weeks	163 (100%)	240 (100%)	534 (100%)
≥6 weeks	136 (83.4%)	205 (85.4%)	467 (87.5%)
≥12 weeks	103 (63.2%)	154 (64.2%)	343 (64.2%)
≥24 weeks	76 (46.6%)	111 (46.3%)	203 (38.0%)
≥36 weeks	53 (32.5%)	80 (33.3%)	130 (24.3%)
≥48 weeks	33 (20.2%)	56 (23.3%)	86 (16.1%)
Number of doses administered, n (%)			
≥0	163 (100%)	240 (100%)	534 (100%)
≥3	137 (84.0%)	206 (85.8%)	469 (87.8%)
≥6	98 (60.1%)	148 (61.7%)	332 (62.2%)
≥12	73 (44.8%)	107 (44.6%)	184 (34.5%)
≥18	54 (33.1%)	81 (33.8%)	130 (24.3%)
≥24	31 (19.0%)	49 (20.4%)	76 (14.2%)
Number of doses administered			
n	163	240	534
Mean (SD)	12.5 (9.86)	12.5 (9.62)	10.7 (8.43)
Median	10.0	10.0	8.0
Q1 : Q3	3.0 : 21.0	4.0 : 22.0	4.0 : 17.0
Min : Max	1 : 36	1 : 36	1 : 36
Cumulative dose administered (mg)			
n	163	240	534
Mean (SD)	3026.1 (2455.94)	3078.9 (2800.52)	2525.4 (2398.29)
Median	2104.0	2080.8	1627.9
Q1 : Q3	1010.0 : 4788.0	868.8 : 4800.0	820.0 : 3754.0
Min : Max	160 : 12062	160 : 19008	144 : 19008
Actual dose intensity (mg/kg/wk)[b]			
n	140	197	491
Mean (SD)	1.52 (0.500)	1.59 (0.743)	1.45 (0.536)
Median	1.50	1.50	1.49
Q1 : Q3	1.44 : 1.53	1.43 : 1.53	1.41 : 1.51
Min : Max	0.5 : 7.0	0.4 : 7.0	0.3 : 7.0
Actual dose intensity (mg/wk)[c]			
n	23	43	43
Mean (SD)	140.22 (30.622)	118.84 (32.974)	118.84 (32.974)
Median	136.11	116.67	116.67
Q1 : Q3	120.49 : 159.78	98.82 : 136.11	98.82 : 136.11
Min : Max	69.0 : 222.7	60.0 : 222.7	60.0 : 222.7
Relative dose intensity[d]			
n	163	240	534
Mean (SD)	1.04 (0.325)	1.02 (0.275)	0.99 (0.201)
Median	1.00	1.00	1.00
Q1 : Q3	0.96 : 1.04	0.96 : 1.02	0.96 : 1.01
Min : Max	0.6 : 4.7	0.6 : 4.7	0.3 : 4.7

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.
b Actual Dose Intensity (mg/kg/week) = Total dose received per kg (mg/kg) / Duration of exposure (weeks).
c Actual Dose Intensity (mg/week) = Total dose received (mg) / Duration of exposure (weeks) for the 200 mg Q2W and 350 mg Q3W dosing schedules.
d Relative Dose Intensity = Actual dose intensity / Planned dose intensity. Planned dose intensity (mg/kg/week) = Planned dose (mg/kg) / (2 or 3 weeks based on Q2W or Q3W dosing schedule). Planned dose intensity (mg /week) = Planned dose (mg) / (2 or 3 weeks based on Q2W or Q3W dosing schedule).
Abbreviations: CSCC, cutaneous squamous cell carcinoma; HCC, hepatocellular carcinoma; Max, maximum; Min, minimum; N, number of patients; Q1, Quarter 1; Q2W, every 2 weeks; Q3, Quarter 3; Q3W, every 3 weeks; SD, standard deviation; wk, week
Data cutoff as of 02 Oct 2017 for CSCC patients with cemiplimab monotherapy in Study 1423; data cutoff as of 01 Sep 2017 for all other patients in Study 1423; data cutoff as of 27 Oct 2017 for all patients in Study 1540.

Table 68: Duration of exposure to cemiplimab by dose level (Safety analysis set)

	CSCC Patients Cemiplimab: 350 mg Q3W		All CSCC Patients		Monotherapy Patients (excluding HCC)	
Dose Level	n	Patient-year	n	Patient-year	n	Patient-year
1 mg/kg Q2W			1	0.9	6	3.4
3 mg/kg Q2W			162	125.2	209	150.1
10 mg/kg Q2W					6	3.0
200 mg Q2W					20	11.2
350 mg Q3W	56	27.3	56	27.3	56	27.3
Total	56	27.3	219	153.5	297	195.0

Data cut-off as of June 30, 2018.

Table 69: Treatment exposure for cemiplimab (Safety analysis set)

	CSCC Patients Cemiplimab: 350 mg Q3W (N=56)	All CSCC Patients (N=219)	Monotherapy Patients (excluding HCC) (N=297)
Duration of Exposure (weeks)[a]			
n	56	219	297
Mean (SD)	25.46 (13.741)	36.56 (27.337)	34.26 (26.020)
Median	26.65	30.60	28.70
Q1: Q3	12.15 : 37.70	12.00 : 53.90	10.10 : 48.70
Min : Max	2.6 : 49.9	2.0 : 109.7	1.4 : 109.7
Duration of Exposure, n (%)			
>=0 weeks	56 (100%)	219 (100%)	297 (100%)
>=6 weeks	53 (94.6%)	200 (91.3%)	270 (90.9%)
>=12 weeks	43 (76.8%)	167 (76.3%)	220 (74.1%)
>=24 weeks	30 (53.6%)	127 (58.0%)	165 (55.6%)
>=36 weeks	15 (26.8%)	96 (43.8%)	127 (42.8%)
>=48 weeks	3 (5.4%)	75 (34.2%)	100 (33.7%)
>=60 weeks	0	47 (21.5%)	49 (16.5%)
>=72 weeks	0	30 (13.7%)	32 (10.8%)
>=84 weeks	0	18 (8.2%)	19 (6.4%)
>=96 weeks	0	3 (1.4%)	3 (1.0%)

Data cut-off as of June 30, 2018.
[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 cut-off date or death date - first dose date + 1)/7.

The applicant present updated safety data from data cut 30 June 2018 with approximately 8 additional months of follow up.

Table 70: Patient exposure as of 30 June 2018

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range (350 mg Q3W)	Patients with long term* safety data
Placebo-controlled	0	0	0	0
Active -controlled	0	0	0	0
Open studies (Studies 1423 and 1540)	591	591	56	≥24 weeks: 264/591 (44.7%) ≥48 weeks: 140/591 (23.7%)
Post marketing	0	0	0	0
Compassionate use	0	0	0	0

* This refers to ≥24 weeks and ≥48 weeks of continuous exposure data.

In total, median FU for the monotherapy patients is now ~28 weeks (~27 weeks for the 56 patients, who received the proposed dosing (from now on also referred to as CSCC 350mg patients). The total duration of exposure to cemiplimab monotherapy was 195 patient-years, including more than 152 patient-years of exposure at either 350 mg Q3W (27.3 patient-years) or at 3 mg/kg Q2W (125.2 patient-years).

Table 71: Duration of Exposure - Overall population (SAP)

Duration of exposure (weeks)	Number of Patients exposed (n)	Duration of Exposure (Patient-years)
< 12 weeks	179	22.35
>=12 weeks	412	307.44
>=24 weeks	278	265.38
>=36 weeks	204	223.71
>=48 weeks	157	185.24
Total number of patient exposed	591	329.79

Study1423: Data cut-off as of June 30, 2018. Study1540: Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients; Data cut-off as of Oct 10, 2018 for Group 2 patients.
[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 cut-off date or death date - first dose date + 1)/7.
[b] Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients * 7/365.25.

Table 72: Exposure by dose level and frequency - Overall population (SAP)

Dose level and frequency	Number of Patients exposed (n)	Duration of Exposure (Patient-years)
1 mg/kg Q2W	27	15.10
3 mg/kg Q2W	470	258.10
3 mg/kg Q3W	12	8.47
10 mg/kg Q2W	6	2.97
200 mg Q2W	20	11.20
350 mg Q3W	56	33.95
Total	591	329.79

Study1423: Data cut-off as of June 30, 2018. Study1540: Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients; Data cut-off as of Oct 10, 2018 for Group 2 patients.
[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 cut-off date or death date - first dose date + 1)/7.
[b] Duration of Exposure (patient-years) = Sum of Duration of Exposure (weeks) for all patients * 7/365.25.

Adverse events

Table 73: Summary of treatment-emergent adverse events (Safety analysis set)

	CSCC Patients Cemiplimab: 350 mg Q3W (N=56)	All CSCC Patients (N=219)	Monotherapy Patients (excluding HCC) (N=297)
Number of TEAEs	358	1961	2565
Number of NCI grade 3/4/5 TEAEs	42	210	274
Number of serious TEAEs	34	135	160
Number of Patients with any TEAE, n (%)	53 (94.6%)	216 (98.6%)	291 (98.0%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	21 (37.5%)	96 (43.8%)	127 (42.8%)
Number of Patients with any serious TEAE, n (%)	21 (37.5%)	74 (33.8%)	92 (31.0%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	3 (5.4%)	16 (7.3%)	19 (6.4%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	14 (25.0%)	68 (31.1%)	92 (31.0%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	1 (1.8%)	3 (1.4%)	4 (1.3%)
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	1 (1.8%)	2 (0.9%)	3 (1.0%)
Number of Patients with any TEAE resulting in death, n (%)	1 (1.8%)	6 (2.7%)	7 (2.4%)

Data cut-off as of June 30, 2018.
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 74: Updated Summary of treatment-emergent adverse events (Safety analysis set)

	Pool 1 All CSCC Patients (N=219)	Pool 2 All Monotherapy Patients (excluding HCC) (N=297)	Pool 3 All Patients (N=591)
Number of TEAEs	2149	2753	5487
Number of NCI grade 3/4/5 TEAEs	237	301	653
Number of serious TEAEs	147	172	318
Number of Patients with any TEAE, n (%)	217 (99.1%)	292 (98.3%)	584 (98.8%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	98 (44.7%)	129 (43.4%)	281 (47.5%)
Number of Patients with any serious TEAE, n (%)	76 (34.7%)	94 (31.6%)	181 (30.6%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	17 (7.8%)	20 (6.7%)	41 (6.9%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	72 (32.9%)	96 (32.3%)	193 (32.7%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	3 (1.4%)	4 (1.3%)	8 (1.4%)
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	2 (0.9%)	3 (1.0%)	7 (1.2%)
Number of Patients with any TEAE resulting in death, n (%)	6 (2.7%)	7 (2.4%)	12 (2.0%)

Study1423: Data cut-off as of June 30, 2018. Study1540: Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients; Data cut-off as of Oct 10, 2018 for Group 2 patients.
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 75: Updated Summary of treatment-emergent adverse events by system organ class (Safety analysis set)

System Organ Class, n (%)	Pool 1 All CSCC Patients (N=219)	Pool 2 All Monotherapy Patients (excluding HCC) (N=297)	Pool 3 All Patients (N=591)
Total number of TEAEs	2149	2753	5487
Number of Patients with any TEAE, n (%)	217 (99.1%)	292 (98.3%)	584 (98.8%)
Gastrointestinal disorders	118 (53.9%)	159 (53.5%)	358 (60.6%)
General disorders and administration site conditions	113 (51.6%)	152 (51.2%)	335 (56.7%)
Musculoskeletal and connective tissue disorders	94 (42.9%)	126 (42.4%)	261 (44.2%)
Skin and subcutaneous tissue disorders	120 (54.8%)	144 (48.5%)	255 (43.1%)
Metabolism and nutrition disorders	86 (39.3%)	117 (39.4%)	250 (42.3%)
Infections and infestations	118 (53.9%)	147 (49.5%)	247 (41.8%)
Respiratory, thoracic and mediastinal disorders	79 (36.1%)	113 (38.0%)	233 (39.4%)
Nervous system disorders	69 (31.5%)	93 (31.3%)	204 (34.5%)
Investigations	71 (32.4%)	84 (28.3%)	168 (28.4%)
Blood and lymphatic system disorders	39 (17.8%)	56 (18.9%)	129 (21.8%)
Injury, poisoning and procedural complications	62 (28.3%)	77 (25.9%)	127 (21.5%)
Psychiatric disorders	32 (14.6%)	45 (15.2%)	110 (18.6%)
Vascular disorders	40 (18.3%)	50 (16.8%)	86 (14.6%)
Eye disorders	48 (21.9%)	55 (18.5%)	82 (13.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	45 (20.5%)	51 (17.2%)	70 (11.8%)
Renal and urinary disorders	29 (13.2%)	36 (12.1%)	68 (11.5%)

Endocrine disorders	29 (13.2%)	37 (12.5%)	62 (10.5%)
Cardiac disorders	19 (8.7%)	19 (6.4%)	38 (6.4%)
Ear and labyrinth disorders	21 (9.6%)	26 (8.8%)	36 (6.1%)
Reproductive system and breast disorders	9 (4.1%)	13 (4.4%)	32 (5.4%)
Hepatobiliary disorders	6 (2.7%)	7 (2.4%)	22 (3.7%)
Immune system disorders	3 (1.4%)	5 (1.7%)	6 (1.0%)
Product issues	0	0	1 (0.2%)
Social circumstances	0	0	1 (0.2%)

Study1423: Data cut-off as of June 30, 2018. Study1540: Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients; Data cut-off as of Oct 10, 2018 for Group 2 patients.
TEAE: Treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 20.0.
A patient is counted only once for multiple occurrences within a system organ class.
The table is sorted by decreasing frequency in the total group.

Table 76: Summary of most common (≥10% in any group) treatment-emergent adverse events by system organ class and preferred term (Safety analysis set)

System Organ Class, n (%) Preferred Term, n (%)	CSCC Patients Cemiplimab: 350 mg Q3W (N=56)	All CSCC Patients (N=219)	Monotherapy Patients (excluding HCC) (N=297)
Total number of TEAEs	358	1961	2565
Number of Patients with any TEAE , n (%)	53 (94.6%)	216 (98.6%)	291 (98.0%)
Gastrointestinal disorders			
Diarrhoea	8 (14.3%)	50 (22.8%)	64 (21.5%)
Nausea	9 (16.1%)	44 (20.1%)	54 (18.2%)
Constipation	6 (10.7%)	27 (12.3%)	40 (13.5%)
Vomiting	5 (8.9%)	20 (9.1%)	30 (10.1%)
General disorders and administration site conditions			
Fatigue	15 (26.8%)	69 (31.5%)	93 (31.3%)
Skin and subcutaneous tissue disorders			
Pruritus	6 (10.7%)	40 (18.3%)	47 (15.8%)
Rash	9 (16.1%)	31 (14.2%)	31 (10.4%)
Rash maculo-papular	5 (8.9%)	22 (10.0%)	28 (9.4%)
Musculoskeletal and connective tissue disorders			
Arthralgia	5 (8.9%)	25 (11.4%)	37 (12.5%)
Metabolism and nutrition disorders			
Decreased appetite	4 (7.1%)	21 (9.6%)	35 (11.8%)
Respiratory, thoracic and mediastinal disorders			
Cough	4 (7.1%)	31 (14.2%)	43 (14.5%)
Blood and lymphatic system disorders			
Anaemia	6 (10.7%)	24 (11.0%)	34 (11.4%)
Endocrine disorders			
Hypothyroidism	6 (10.7%)	22 (10.0%)	30 (10.1%)

Data cut-off as of June 30, 2018.
TEAE: Treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 20.0.
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 monotherapy patients (excluding HCC) group. Within each SOC, PTs are sorted by decreasing frequency in the monotherapy patients (excluding HCC) group.

Table 77: Summary of most common (≥2% in any group) grade 3 or greater treatment-emergent adverse events by system organ class and preferred term (Safety analysis set)

System Organ Class, n (%) Preferred Term, n (%)	CSCC Patients Cemiplimab: 350 mg Q3W (N=56)	All CSCC Patients (N=219)	Monotherapy Patients (excluding HCC) (N=297)
Total number of Grade 3 or greater TEAEs	42	210	274
Number of Patients with any Grade 3 or greater TEAE , n (%)	21 (37.5%)	96 (43.8%)	127 (42.8%)
Infections and infestations			
Pneumonia	0	6 (2.7%)	9 (3.0%)
Cellulitis	1 (1.8%)	7 (3.2%)	7 (2.4%)
Sepsis	1 (1.8%)	5 (2.3%)	5 (1.7%)
Skin infection	1 (1.8%)	5 (2.3%)	5 (1.7%)
Metabolism and nutrition disorders			
Hypercalcaemia	1 (1.8%)	5 (2.3%)	5 (1.7%)
Dehydration	2 (3.6%)	3 (1.4%)	4 (1.3%)
Blood and lymphatic system disorders			
Anaemia	3 (5.4%)	6 (2.7%)	11 (3.7%)
Lymphopenia	1 (1.8%)	3 (1.4%)	6 (2.0%)
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism	2 (3.6%)	2 (0.9%)	3 (1.0%)
General disorders and administration site conditions			
Fatigue	3 (5.4%)	5 (2.3%)	6 (2.0%)
Gastrointestinal disorders			
Dysphagia	2 (3.6%)	2 (0.9%)	2 (0.7%)
Vascular disorders			
Hypertension	0	6 (2.7%)	6 (2.0%)
Nervous system disorders			
Syncope	2 (3.6%)	3 (1.4%)	4 (1.3%)
Renal and urinary disorders			
Haematuria	2 (3.6%)	2 (0.9%)	3 (1.0%)

Data cut-off as of June 30, 2018.
TEAE: Treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 20.0.
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 monotherapy patients (excluding HCC) group. Within each SOC, PTs are sorted by decreasing frequency in the monotherapy patients (excluding HCC) group.

Table 78: Summary of treatment-related treatment-emergent adverse events by system organ class (Safety analysis set) - All monotherapy patients (excluding HCC)

System Organ Class, n (%)	CSCC Patients (N=163)	Non-CSCC Patients (N=77)	Total (N=240)
Total number of treatment-related TEAEs	377	146	523
Number of Patients with any treatment-related TEAE, n (%)	109 (66.9%)	54 (70.1%)	163 (67.9%)
General disorders and administration site conditions	40 (24.5%)	24 (31.2%)	64 (26.7%)
Skin and subcutaneous tissue disorders	49 (30.1%)	15 (19.5%)	64 (26.7%)
Gastrointestinal disorders	41 (25.2%)	16 (20.8%)	57 (23.8%)
Musculoskeletal and connective tissue disorders	20 (12.3%)	14 (18.2%)	34 (14.2%)
Investigations	19 (11.7%)	6 (7.8%)	25 (10.4%)
Respiratory, thoracic and mediastinal disorders	15 (9.2%)	7 (9.1%)	22 (9.2%)
Endocrine disorders	16 (9.8%)	5 (6.5%)	21 (8.8%)
Metabolism and nutrition disorders	13 (8.0%)	6 (7.8%)	19 (7.9%)
Nervous system disorders	15 (9.2%)	4 (5.2%)	19 (7.9%)
Blood and lymphatic system disorders	7 (4.3%)	4 (5.2%)	11 (4.6%)
Injury, poisoning and procedural complications	8 (4.9%)	1 (1.3%)	9 (3.8%)
Infections and infestations	6 (3.7%)	2 (2.6%)	8 (3.3%)
Eye disorders	2 (1.2%)	3 (3.9%)	5 (2.1%)
Vascular disorders	5 (3.1%)	0	5 (2.1%)
Psychiatric disorders	2 (1.2%)	2 (2.6%)	4 (1.7%)
Renal and urinary disorders	3 (1.8%)	1 (1.3%)	4 (1.7%)

Hepatobiliary disorders	3 (1.8%)	0	3 (1.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.2%)	0	2 (0.8%)
Cardiac disorders	1 (0.6%)	0	1 (0.4%)
Ear and labyrinth disorders	0	1 (1.3%)	1 (0.4%)
Immune system disorders	0	1 (1.3%)	1 (0.4%)
Reproductive system and breast disorders	0	1 (1.3%)	1 (0.4%)

Data cut-off as of Oct 2, 2017 for CSCC patients with Cemiplimab monotherapy in Study 1423; Data cut-off as of Sep 1, 2017 for all other patients in Study 1423; Data cut-off as of Oct 27, 2017 for all patients in Study 1540.
TEAE: Treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 20.0.
A patient is counted only once for multiple occurrences within a system organ class.
The table is sorted by decreasing frequency in the total group.

Adverse drug reactions

The safety of cemiplimab has been evaluated in 591 patients with advanced solid malignancies including 219 advanced CSCC patients who received cemiplimab monotherapy in 2 clinical studies (R2810 ONC 1423 and R2810 ONC 1540). Immune related adverse reactions occurred in 20.1% of patients treated with cemiplimab in clinical trials including Grade 5 (0.7%), Grade 4 (1.2%) and Grade 3 (6.1%). Immune-related adverse reactions led to permanent discontinuation of cemiplimab in 4.4% of patients. The most common immune-related adverse reactions were hypothyroidism (7.1%), pneumonitis (3.7%), immune-related skin adverse reactions (2.0%), hyperthyroidism (1.9%) and hepatitis (1.9%) (see "Description of selected adverse reactions" below, Special warnings and precautions for use in section 4.4 and Recommended treatment modifications in section 4.2). Adverse reactions were serious in 8.6% patients and led to permanent discontinuation of cemiplimab in 5.8% of patients.

Listed below are adverse reactions by system organ class and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 79: Tabulated list of adverse reactions in patients treated with cemiplimab

System Organ Class **Preferred Term**	**Grade I–V** **(Frequency Category)**	**Grade I–V** **(%)**	**Grade III-V (%)**
Immune system disorders			
Infusion related reaction	Common	4.1	0
Sjogren's syndrome	Uncommon	0.5	0
Immune thrombocytopenic purpura	Uncommon	0.2	0
Vasculitis	Uncommon	0.2	0
Endocrine disorders			
Hypothyroidism	Common	9.6	0
Hyperthyroidism	Common	2.7	0
Type 1 diabetes mellitus[a]	Uncommon	0.7	0.7
Adrenal insufficiency	Uncommon	0.5	0.5
Hypophysitis	Uncommon	0.5	0.5
Thyroiditis	Uncommon	0.2	0

System Organ Class Preferred Term	Grade I–V (Frequency Category)	Grade I–V (%)	Grade III-V (%)
Nervous system disorders			
Paraneoplastic encephalomyelitis	Uncommon	0.2	0.2
Chronic inflammatory demyelinating polyradiculoneuropathy	Uncommon	0.5	0
Encephalitis	Uncommon	0.5	0.5
Meningitis[b]	Uncommon	0.5	0.5
Guillain-Barre syndrome	Uncommon	0.2	0.2
Central nervous system inflammation	Uncommon	0.2	0
Neuropathy peripheral[c]	Uncommon	0.5	0
Myasthenia gravis	Uncommon	0.2	0
Cardiac disorders			
Myocarditis[d]	Uncommon	0.5	0.5
Pericarditis	Uncommon	0.5	0.5
Respiratory, thoracic and mediastinal disorders			
Pneumonitis	Common	5.9	2.3
Gastrointestinal disorders			
Diarrhoea[e]	Very common	13.2	0.5
Stomatitis	Common	2.4	0
Hepatobiliary disorders			
Hepatitis[f]	Common	1.4	1.4
Skin and subcutaneous skin disorders			
Rash[g]	Very common	23.3	1.4
Pruritus[h]	Very common	12.3	0
Musculoskeletal and connective tissue disorders			
Arthralgia	Common	5.0	0
Musculoskeletal pain[i]	Common	4.1	0.5
Arthritis[j]	Common	1.4	0.5
Muscular weakness	Uncommon	0.9	0
Eye Disorders			
Keratitis	Uncommon	0.5	0

System Organ Class Preferred Term	Grade I–V (Frequency Category)	Grade I–V (%)	Grade III-V (%)
Renal and urinary disorders			
Nephritis	Uncommon	0.5	0
General disorders and administration site conditions			
Fatigue[k]	Very common	21.5	0.9
Investigations			
Alanine aminotransferase increased	Common	5.5	0.5
Aspartate aminotransferase increased	Common	5.0	0.9
Blood alkaline phosphatase increased	Common	2.7	0
Blood creatinine increased	Common	1.8	0

Version v.4.03 of NCI CTCAE was used to grade toxicity.

a. Type 1 diabetes mellitus is a composite term that includes diabetes mellitus, diabetic ketoacidosis and Type 1 diabetes mellitus.
b. Meningitis is a composite term that includes meningitis and meningitis aseptic.
c. Neuropathy peripheral is a composite term that includes neuropathy peripheral and neuritis.
d. Myocarditis is a composite term that includes autoimmune myocarditis and myocarditis.
e. Diarrhoea is a composite term that includes diarrhoea and colitis.
f. Hepatitis is a composite term that includes hepatitis and autoimmune hepatitis.
g. Rash is a composite term that includes rash maculo-papular, rash, dermatitis, rash generalised, dermatitis bullous, drug eruption, erythema, pemphigoid, psoriasis, rash erythematous, rash macular, rash pruritic and skin reaction.
h. Pruritus is a composite term that includes pruritus and pruritus allergic.
i. Musculoskeletal pain is a composite term that includes back pain, musculoskeletal pain, myalgia, neck pain and pain in extremity.
j. Arthritis is a composite term that includes arthritis and polyarthritis.
k. Fatigue is a composite term that includes fatigue and asthenia.

Immune-related events

Table 80: Summary of treatment-emergent potential immune-related adverse events by composite/Preferred term and NCI Grade (Safety analysis set)

Table 20: Summary of Treatment-Emergent Potential Immune-Related Adverse Events by Composite/Preferred Term and NCI Grade (Based on Sponsor-Provided List; Safety Analysis Set)

	Pool 1 - All CSCC Patients (N=163)		Pool 2 - All Monotherapy Patients (excluding HCC) (N=240)		Pool 3 - All Patients (N=534)	
Composite*/Preferred Term, n (%)	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Total number of treatment-emergent potential irAEs	169	18	226	23	471	57
Number of patients with any treatment-emergent potential irAE, n (%)	84 (51.5%)	15 (9.2%)	119 (49.6%)	20 (8.3%)	254 (47.6%)	48 (9.0%)
Immune-related skin adverse reaction*	33 (20.2%)	2 (1.2%)	41 (17.1%)	2 (0.8%)	89 (16.7%)	9 (1.7%)
Immune-related colitis*	20 (12.3%)	1 (0.6%)	27 (11.3%)	1 (0.4%)	53 (9.9%)	3 (0.6%)
Arthralgia	8 (4.9%)	0	18 (7.5%)	0	38 (7.1%)	0
Pruritus*	17 (10.4%)	0	22 (9.2%)	0	36 (6.7%)	1 (0.2%)
Hypothyroidism*	12 (7.4%)	0	17 (7.1%)	0	32 (6.0%)	1 (0.2%)
Immune-related hepatitis*	11 (6.7%)	4 (2.5%)	13 (5.4%)	4 (1.7%)	28 (5.2%)	14 (2.6%)
Myalgia*	4 (2.5%)	1 (0.6%)	7 (2.9%)	2 (0.8%)	24 (4.5%)	2 (0.4%)
Immune-related Pneumonitis*	6 (3.7%)	2 (1.2%)	10 (4.2%)	3 (1.3%)	14 (2.6%)	5 (0.9%)
Stomatitis	0	0	0	0	14 (2.6%)	0
Immune-related nephritis*	5 (3.1%)	0	7 (2.9%)	1 (0.4%)	9 (1.7%)	2 (0.4%)
Hyperthyroidism*	3 (1.8%)	0	3 (1.3%)	0	8 (1.5%)	1 (0.2%)
Neuropathy peripheral*	1 (0.6%)	0	2 (0.8%)	0	7 (1.3%)	0
Blood alkaline phosphatase increased	3 (1.8%)	0	3 (1.3%)	0	5 (0.9%)	0
Arthritis*	2 (1.2%)	1 (0.6%)	3 (1.3%)	1 (0.4%)	4 (0.7%)	1 (0.2%)
Type 1 diabetes mellitus*	0	0	1 (0.4%)	1 (0.4%)	4 (0.7%)	4 (0.7%)
Muscular weakness	2 (1.2%)	0	2 (0.8%)	0	3 (0.6%)	0
Adrenal insufficiency*	1 (0.6%)	1 (0.6%)	1 (0.4%)	1 (0.4%)	2 (0.4%)	1 (0.2%)
Blood creatine phosphokinase increased	1 (0.6%)	0	2 (0.8%)	0	2 (0.4%)	0
Blood thyroid stimulating hormone increased	0	0	0	0	2 (0.4%)	0
Meningitis*	1 (0.6%)	1 (0.6%)	1 (0.4%)	1 (0.4%)	2 (0.4%)	2 (0.4%)
Autoimmune myocarditis*	1 (0.6%)	1 (0.6%)	1 (0.4%)	1 (0.4%)	1 (0.2%)	1 (0.2%)
Central nervous system inflammation	0	0	0	0	1 (0.2%)	0
Chronic inflammatory demyelinating polyradiculoneuropathy	1 (0.6%)	0	1 (0.4%)	0	1 (0.2%)	0
Encephalitis*	0	0	0	0	1 (0.2%)	1 (0.2%)
Guillain-Barre syndrome	0	0	0	0	1 (0.2%)	1 (0.2%)
Hypophysitis	1 (0.6%)	1 (0.6%)	1 (0.4%)	1 (0.4%)	1 (0.2%)	1 (0.2%)
Immune thrombocytopenic purpura	0	0	1 (0.4%)	0	1 (0.2%)	0
Myasthenia gravis*	0	0	0	0	1 (0.2%)	0
Paraneoplastic encephalomyelitis	0	0	1 (0.4%)	1 (0.4%)	1 (0.2%)	1 (0.2%)
Sjogren's syndrome	1 (0.6%)	0	1 (0.4%)	0	1 (0.2%)	0
Vasculitis	0	0	0	0	1 (0.2%)	0

Abbreviations: AE, adverse event; CSCC, cutaneous squamous cell carcinoma; CTCAE, Common Terminology Criteria for Adverse Events; HCC, hepatocellular carcinoma; irAE, immune-related adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; NCI, National Cancer Institute; PT, preferred term

Data cutoff as of 02 Oct 2017 for CSCC patients with cemiplimab monotherapy in Study 1423; data cutoff as of 01 Sep 2017 for all other patients in Study 1423; data cutoff as of 27 Oct 2017 for all patients in Study 1540.

All AEs were coded using MedDRA Version 20.0. NCI grades were coded using CTCAE Version 4.03.

* Each composite term includes multiple MedDRA PTs based on Regeneron defined list. Refer to Table 14.3.2.4.11p0.

A patient is counted only once for multiple occurrences within a composite term/PT.

The table is sorted by decreasing frequency of all grades in the total group.

Table 81: Summary of treatment-emergent potential immune-related adverse events based on Sponsor-provided list by composite/preferred term and NCI grade (Safety analysis set)

	CSCC Patients Cemiplimab: 350 mg Q3W (N=56)		All CSCC Patients (N=219)		Monotherapy Patients (excluding HCC) (N=297)	
Composite*/Preferred Term, n (%)	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Total number of treatment-emergent potential irAEs	45	3	267	21	328	26
Number of Patients with any treatment-emergent potential irAE, n (%)	28 (50.0%)	3 (5.4%)	128 (58.4%)	18 (8.2%)	164 (55.2%)	23 (7.7%)
Immune related skin adverse reaction*	11 (19.6%)	2 (3.6%)	48 (21.9%)	3 (1.4%)	58 (19.5%)	3 (1.0%)
Immune related colitis*	3 (5.4%)	0	27 (12.3%)	1 (0.5%)	34 (11.4%)	1 (0.3%)
Pruritus*	2 (3.6%)	0	27 (12.3%)	0	32 (10.8%)	0
Hypothyroidism*	6 (10.7%)	0	21 (9.6%)	0	26 (8.8%)	0
Arthralgia	1 (1.8%)	0	11 (5.0%)	0	21 (7.1%)	0
Immune related hepatitis*	5 (8.9%)	1 (1.8%)	19 (8.7%)	4 (1.8%)	20 (6.7%)	4 (1.3%)
Immune related Pneumonitis*	1 (1.8%)	0	11 (5.0%)	4 (1.8%)	16 (5.4%)	5 (1.7%)
Immune related nephritis*	2 (3.6%)	0	6 (2.7%)	0	9 (3.0%)	1 (0.3%)
Myalgia*	0	0	5 (2.3%)	0	8 (2.7%)	1 (0.3%)
Blood alkaline phosphatase increased	0	0	7 (3.2%)	0	7 (2.4%)	0
Hyperthyroidism*	2 (3.6%)	0	6 (2.7%)	0	6 (2.0%)	0
Arthritis*	1 (1.8%)	0	3 (1.4%)	1 (0.5%)	4 (1.3%)	1 (0.3%)
Blood creatine phosphokinase increased	0	0	1 (0.5%)	0	2 (0.7%)	0
Muscular weakness	0	0	2 (0.9%)	0	2 (0.7%)	0
Neuropathy peripheral*	0	0	1 (0.5%)	0	2 (0.7%)	0
Adrenal insufficiency*	0	0	1 (0.5%)	1 (0.5%)	1 (0.3%)	1 (0.3%)
Autoimmune myocarditis*	0	0	1 (0.5%)	1 (0.5%)	1 (0.3%)	1 (0.3%)
Blood thyroid stimulating hormone increased	0	0	1 (0.5%)	0	1 (0.3%)	0
Chronic inflammatory demyelinating polyradiculoneuropathy	0	0	1 (0.5%)	0	1 (0.3%)	0
Encephalitis*	0	0	1 (0.5%)	1 (0.5%)	1 (0.3%)	1 (0.3%)
Hypophysitis	0	0	1 (0.5%)	1 (0.5%)	1 (0.3%)	1 (0.3%)
Immune thrombocytopenic purpura	0	0	0	0	1 (0.3%)	0
Meningitis*	0	0	1 (0.5%)	1 (0.5%)	1 (0.3%)	1 (0.3%)
Paraneoplastic encephalomyelitis	0	0	0	0	1 (0.3%)	1 (0.3%)
Sjogren's syndrome	0	0	1 (0.5%)	0	1 (0.3%)	0
Stomatitis	0	0	1 (0.5%)	0	1 (0.3%)	0
Thyroiditis*	0	0	0	0	1 (0.3%)	0
Type 1 diabetes mellitus*	0	0	0	0	1 (0.3%)	1 (0.3%)

Data cut-off as of June 30, 2018.
irAE: Immune-related adverse event.
All adverse events were coded using MedDRA Version 20.0. NCI grades were coded using CTCAE Version 4.03.
* Each composite term includes multiple MedDRA preferred terms based on Regeneron defined list. Refer to Table 14.3.2.4.11p0.
A patient is counted only once for multiple occurrences within a composite term/preferred term.
The table is sorted by decreasing frequency of all grades in the monotherapy patients (excluding HCC) group.

Table 82: Summary of treatment-emergent identified immune-related adverse events by composite/preferred term and NCI grade (irAEs requiring systemic corticosteroids and endocrine-related irAEs based on sponsor-provided list (Safety analysis set)

	Pool 1 - All CSCC Patients (N=163)		Pool 2 - All Monotherapy Patients (Excluding HCC) (N=240)		Pool 3 - All Patients (N=534)	
Composite*/Preferred Term, n (%)	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Total number of treatment-emergent identified irAEs	49	16	66	21	126	49
Number of patients with any treatment-emergent sponsor-identified irAE, n (%)	35 (21.5%)	13 (8.0%)	49 (20.4%)	18 (7.5%)	92 (17.2%)	42 (7.9%)
Hypothyroidism*	12 (7.4%)	0	17 (7.1%)	0	32 (6.0%)	1 (0.2%)
Immune-related Pneumonitis*	5 (3.1%)	2 (1.2%)	9 (3.8%)	3 (1.3%)	13 (2.4%)	5 (0.9%)
Immune-related hepatitis*	3 (1.8%)	3 (1.8%)	3 (1.3%)	3 (1.3%)	11 (2.1%)	11 (2.1%)
Immune-related skin adverse reaction*	1 (0.6%)	1 (0.6%)	1 (0.4%)	1 (0.4%)	9 (1.7%)	6 (1.1%)
Hyperthyroidism*	3 (1.8%)	0	3 (1.3%)	0	8 (1.5%)	1 (0.2%)
Arthralgia	2 (1.2%)	0	4 (1.7%)	0	6 (1.1%)	0
Immune-related colitis*	4 (2.5%)	1 (0.6%)	4 (1.7%)	1 (0.4%)	5 (0.9%)	2 (0.4%)
Type 1 diabetes mellitus*	0	0	1 (0.4%)	1 (0.4%)	4 (0.7%)	4 (0.7%)
Immune-related nephritis*	1 (0.6%)	0	2 (0.8%)	1 (0.4%)	3 (0.6%)	2 (0.4%)
Adrenal insufficiency*	1 (0.6%)	1 (0.6%)	1 (0.4%)	1 (0.4%)	2 (0.4%)	1 (0.2%)
Meningitis*	1 (0.6%)	1 (0.6%)	1 (0.4%)	1 (0.4%)	2 (0.4%)	2 (0.4%)
Myalgia*	1 (0.6%)	1 (0.6%)	2 (0.8%)	2 (0.8%)	2 (0.4%)	2 (0.4%)
Stomatitis	0	0	0	0	2 (0.4%)	0
Arthritis*	1 (0.6%)	1 (0.6%)	1 (0.4%)	1 (0.4%)	1 (0.2%)	1 (0.2%)
Autoimmune myocarditis*	1 (0.6%)	1 (0.6%)	1 (0.4%)	1 (0.4%)	1 (0.2%)	1 (0.2%)
Chronic inflammatory demyelinating polyradiculoneuropathy	1 (0.6%)	0	1 (0.4%)	0	1 (0.2%)	0
Encephalitis*	0	0	0	0	1 (0.2%)	1 (0.2%)
Hypophysitis	1 (0.6%)	1 (0.6%)	1 (0.4%)	1 (0.4%)	1 (0.2%)	1 (0.2%)
Immune thrombocytopenic purpura	0	0	1 (0.4%)	0	1 (0.2%)	0
Muscular weakness	1 (0.6%)	0	1 (0.4%)	0	1 (0.2%)	0
Neuropathy peripheral*	1 (0.6%)	0	1 (0.4%)	0	1 (0.2%)	0
Paraneoplastic encephalomyelitis	0	0	1 (0.4%)	1 (0.4%)	1 (0.2%)	1 (0.2%)
Pruritus*	0	0	0	0	1 (0.2%)	1 (0.2%)
Sjogren's syndrome	1 (0.6%)	0	1 (0.4%)	0	1 (0.2%)	0
Vasculitis	0	0	0	0	1 (0.2%)	0

Abbreviations: AE, adverse event; CSCC, cutaneous squamous cell carcinoma; CTCAE, Common Terminology Criteria for Adverse Events; HCC, hepatocellular carcinoma; irAE, immune-related adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; NCI, National Cancer Institute; PT, preferred term

Data cutoff as of 02 Oct 2017 for CSCC patients with cemiplimab monotherapy in Study 1423; data cutoff as of 01 Sep 2017 for all other patients in Study 1423; data cutoff as of 27 Oct 2017 for all patients in Study 1540.

All AEs were coded using MedDRA Version 20.0. NCI grades were coded using CTCAE Version 4.03.

* Each composite term includes multiple MedDRA PTs based on Regeneron defined list. Refer to Table 14.3.2.4.11ap0.

A patient is counted only once for multiple occurrences within a composite term/PT.

The table is sorted by decreasing frequency of all grades in the total group.

Table 83: Summary of treatment-emergent immune-related adverse events (irAEs requiring systemic corticosteroids and endocrine-related irAEs based on Sponsor-provided list) by composite/preferred term and NCI grade (Safety analysis set)

	CSCC Patients Cemiplimab: 350 mg Q3W (N=56)		All CSCC Patients (N=219)		Monotherapy Patients (excluding HCC) (N=297)	
Composite*/Preferred Term, n (%)	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Total number of treatment-emergent sponsor identified irAEs	12	1	75	18	93	23
Number of Patients with any treatment-emergent sponsor identified irAE, n (%)	9 (16.1%)	1 (1.8%)	56 (25.6%)	15 (6.8%)	70 (23.6%)	20 (6.7%)
Hypothyroidism*	6 (10.7%)	0	21 (9.6%)	0	26 (8.8%)	0
Immune related Pneumonitis*	1 (1.8%)	0	10 (4.6%)	4 (1.8%)	14 (4.7%)	5 (1.7%)
Arthralgia	0	0	4 (1.8%)	0	6 (2.0%)	0
Hyperthyroidism*	2 (3.6%)	0	6 (2.7%)	0	6 (2.0%)	0
Immune related colitis*	1 (1.8%)	0	6 (2.7%)	1 (0.5%)	6 (2.0%)	1 (0.3%)
Immune related skin adverse reaction*	0	0	3 (1.4%)	1 (0.5%)	4 (1.3%)	1 (0.3%)
Immune related hepatitis*	1 (1.8%)	1 (1.8%)	3 (1.4%)	3 (1.4%)	3 (1.0%)	3 (1.0%)
Arthritis*	0	0	2 (0.9%)	1 (0.5%)	2 (0.7%)	1 (0.3%)
Immune related nephritis*	0	0	1 (0.5%)	0	2 (0.7%)	1 (0.3%)
Adrenal insufficiency*	0	0	1 (0.5%)	1 (0.5%)	1 (0.3%)	1 (0.3%)
Autoimmune myocarditis*	0	0	1 (0.5%)	1 (0.5%)	1 (0.3%)	1 (0.3%)
Chronic inflammatory demyelinating polyradiculoneuropathy	0	0	1 (0.5%)	0	1 (0.3%)	0
Encephalitis*	0	0	1 (0.5%)	1 (0.5%)	1 (0.3%)	1 (0.3%)
Hypophysitis	0	0	1 (0.5%)	1 (0.5%)	1 (0.3%)	1 (0.3%)
Immune thrombocytopenic purpura	0	0	0	0	1 (0.3%)	0
Meningitis*	0	0	1 (0.5%)	1 (0.5%)	1 (0.3%)	1 (0.3%)
Muscular weakness	0	0	1 (0.5%)	0	1 (0.3%)	0
Myalgia*	0	0	0	0	1 (0.3%)	1 (0.3%)
Neuropathy peripheral*	0	0	1 (0.5%)	0	1 (0.3%)	0
Paraneoplastic encephalomyelitis	0	0	0	0	1 (0.3%)	1 (0.3%)
Pruritus*	0	0	1 (0.5%)	0	1 (0.3%)	0
Sjogren's syndrome	0	0	1 (0.5%)	0	1 (0.3%)	0
Type 1 diabetes mellitus*	0	0	0	0	1 (0.3%)	1 (0.3%)

Data cut-off as of June 30, 2018.
irAE: Immune-related adverse event.
All adverse events were coded using MedDRA Version 20.0. NCI grades were coded using CTCAE Version 4.03.
* Each composite term includes multiple MedDRA preferred terms based on Regeneron defined list. Refer to Table 14.3.2.4.11ap0.
A patient is counted only once for multiple occurrences within a composite term/preferred term.
The table is sorted by decreasing frequency of all grades in the monotherapy patients (excluding HCC) group.
Source: Table 75.35

Immune-related AEs (irAEs) were reported as potential and identified events (required steroids or were endocrinopathies), and overall all grade potential irAEs occurred frequently in approximately half of the patients but ≥grade 3 events rarely occurred (7.7% for monotherapy patients). Identified irAEs were observed of all grade in approximately a quarter of the patients and ≥grade 3 events were observed in 6.7% of the monotherapy patients vs only 1.8% in the CSCC 350mg patients. Common identified irAEs were hypothyroidism (8.8%), pneumonitis (4.7%), and arthralgia (2.0%). Considering the sample size of the CSCC 350mg patients (n=56), it may be concluded that the AEs, SAEs, and irAEs were observed of similar incidence between the groups and no major safety concerns are raised at this point.

The selected adverse reactions described below are based on the safety of cemiplimab in monotherapy patients and in the total 591 patients in uncontrolled clinical studies.

Pneumonitis

Potential Immune-Related Pneumonitis: Updated safety data show that 16 (5.4%) of the monotherapy patients had an event of all grade and 1.7% had a grade 3-5 event.

Identified Immune-Related Pneumonitis: Updated safety data show that 14 (4.7%) of the monotherapy patients had an event of all grade and 1.7% had a grade 3-5 event. Pneumonitis is an uncommon event, rarely of high-grade and seldom treated with high-dose corticosteroids. However, the event led to permanent discontinuation and is potentially fatal. In conclusion, the event was rare and seem clinically manageable.

Immune-related pneumonitis occurred in 22 (3.7%) of 591 patients receiving cemiplimab, including 2 (0.3%) patients with Grade 5, 2 (0.3%) patients with Grade 4, and 6 (1.0%) patients with Grade 3 pneumonitis. Immune-related pneumonitis led to permanent discontinuation of cemiplimab in 11 (1.9%) of 591 patients. Among the 22 patients with immune-related pneumonitis, the median time to onset was 3.8 months (range: 7 days to 18 months) and the median duration of pneumonitis was 21.5 days (range: 5 days to 6.5 months). Eighteen patients (3.0%) received high-dose corticosteroids for a median of 8.5 days (range: 1 day to 5.9 months). Resolution of pneumonitis had occurred in 14 (63.6%) of the 22 patients at the time of data cut-off.

Colitis

Potential Immune-Related Colitis: Updated safety data show that 34 (11.4%) of the monotherapy patients had an event of all grade and 0.3% had a grade 3-5 event.

Identified Immune-Related Colitis: Updated safety data show that 6 (2.0%) of the monotherapy patients had an event of all grade and 0.3% had a grade 3-5 event.

Potential events of colitis were rather frequent (11.4%), but the identified events were actually very rare (2.0%) and there were only 1 grade 4-5 event, which is reassuring. These numbers may reflect that diarrhea was common with cemiplimab but not immune-related.

Immune-related diarrhoea or colitis occurred in 7 (1.2%) of 591 patients receiving cemiplimab including 2 (0.3%) with Grade 3 immune-related diarrhoea or colitis. Immune-related diarrhoea or colitis led to permanent discontinuation of cemiplimab in 1 (0.2%) of 591 patients. Among the 7 patients with immune-related diarrhoea or colitis, the median time to onset was 3.8 months (range: 15 days to 6.0 months) and the median duration of immune-related diarrhoea or colitis was 30 days (range: 4 days to 8.6 months). Four patients (0. 7%) with immune-related diarrhoea or colitis received high-dose corticosteroids for a median of 29 days (range: 19 days to 2.0 months). Resolution of immune-related diarrhoea or colitis had occurred in 4 (57.1%) of the 7 patients at the time of data cut-off.

Hepatitis

Potential Immune-Related Hepatitis: Updated safety data show that 20 (6.7%) of the monotherapy patients had an event of all grade and 1.3% had a grade 3-5 event.

Identified Immune-Related Hepatitis: Updated safety data show that 3 (1.0%) of the monotherapy patients had an event of all grade and 1.0% had a grade 3-5 event.

Potential immune-related hepatitis was observed in approximately 7% of patients; however, few of these had identified events. These events were rarely grade 3 or more, and the patients were treated with high-dose corticosteroids with good results so immune-related hepatitis is not considered a major clinical concern with cemiplimab.

Immune-related hepatitis occurred in 11 (1.9%) of 591 patients receiving cemiplimab including 1 (0.2%) patient with Grade 5, 1 (0.2%) patient with Grade 4, and 9 (1.5%) patients with Grade 3 immune-related hepatitis. Immune-related hepatitis led to permanent discontinuation of cemiplimab in 5 (0.8%) of 591 patients. Among the 11 patients with immune-related hepatitis, the median time to onset was 1.0 month (range: 7 days to 4.2 months) and the median duration of hepatitis was 15 days (range: 8 days to 2.7 months). Ten (1.7%) patients with immune-related hepatitis received high-dose corticosteroids for a median of 10.5 days (range: 2 days to 1.9 months). Resolution of hepatitis had occurred in 8 (72.7%) of the 11 patients at the time of data cut-off.

Hyperthyroidism

Identified Immune-Related Hyperthyroidism: Updated safety data show that six (2.0%) of the monotherapy patients had an event of all grade and none had a grade 3-5 event.

Hyperthyroidism occurred in 11 (1.9%) of 591 patients receiving cemiplimab including 1 (0.2%) patient with Grade 3 hyperthyroidism. No patient discontinued cemiplimab due to hyperthyroidism. Among the 11 patients with hyperthyroidism, the median time to onset was 1.9 months (range: 28 days to 14.8 months).

Hypothyroidism

Identified Immune-Related Hypothyroidism: Updated safety data show that 26 (8.8%) of the monotherapy patients had an event of all grade and none had a grade 3-5 event.

Hypothyroidism occurred in 42 (7.1%) of 591 patients receiving cemiplimab including 1 (0.2%) patient with Grade 3 hypothyroidism. No patient discontinued cemiplimab due to hypothyroidism. Among the 42 patients with hypothyroidism, the median time to onset was 4.2 months (range: 15 days to 18.9 months).

Hypophysitis

Identified Immune-Related Hypophysitis: Updated safety data show that one (0.3%) of the monotherapy patients had a grade 3-5 event.

Immune-related hypophysitis occurred in 1 (0.2%) of 591 of patients receiving cemiplimab. The event was Grade 3 hypophysitis.

Adrenal insufficiency

Identified Immune-Related Adrenal Insufficiency: Updated safety data show that 1 (0.3%) of the monotherapy patients had a grade 3-5 event.

Adrenal insufficiency occurred in 3 (0.5%) of 591 patients receiving cemiplimab including 1 (0.2%) patient with Grade 3 adrenal insufficiency. No patient discontinued cemiplimab due to adrenal insufficiency. Among the 3 patients with adrenal insufficiency, the median time to onset was 11.5 months (range: 10.4 months to 12.3 months). One of the 3 patients was treated with systemic corticosteroids.

Diabetes

Identified Immune-Related Type 1 Diabetes Mellitus: Updated safety data show that 1 (0.3%) of the monotherapy patients had a grade 3-5 event.

Type 1 diabetes mellitus without an alternative aetiology occurred in 4 (0.7%) of 591 patients including 3 (0.5%) patients with Grade 4 and 1 (0.2%) patient with Grade 3 type 1 diabetes mellitus. Type 1 diabetes mellitus led to permanent discontinuation of cemiplimab in 1(0.2%) of 591 patients. Among the 4 patients with Type 1 diabetes mellitus, the median time to onset was 2.3 months (range: 28 days to 6.2 months).

Skin reactions

Potential Immune-Related Skin Adverse Reactions: Updated safety data show that 58 (19.5%) of the monotherapy patients had an event of all grade and 1.0% had a grade 3-5 event.

Identified Immune-Related Skin Adverse Reactions: Updated safety data show that four (1.3%) of the monotherapy patients had an event of all grade and 0.3% had a grade 3-5 event.

Many of the potential immune-related skin events were not confirmed, so the frequency of identified events is low. The event required high-dose steroids in the vast majority of patients, but it is considered a manageable event. The underlying disease may also mimic skin reactions and therefore it is acceptable that so many events were considered potential immune-related skin events.

Immune-related skin adverse reactions occurred in 12 (2.0%) of 591 patients receiving cemiplimab including 6 (1.0%) patients with Grade 3 immune-related skin adverse reactions. Immune-related skin adverse reactions led to permanent discontinuation of cemiplimab in 2 (0.3%) of 591 patients. Among the 12 patients with immune-related skin adverse reactions, the median time to onset was 1.5 months (range: 2 days to 10.9 months) and the median duration was 4.4 months (range: 14 days to 9.6 months). Nine patients (1.5%) with immune-related skin adverse reactions received high-dose corticosteroids for a median of 16 days (range: 7 days to 2.6 months). Resolution had occurred in 6 (50%) of 12 patients at the time of data cut-off.

Nephritis

Potential Immune-Related Nephritis: Updated safety data show that nine (3.0%) of the monotherapy patients had an event of all grade and 0.3% had a grade 3-5 event.

Identified Immune-Related Nephritis: Updated safety data show that two (0.7%) of the monotherapy patients had an event of all grade and 0.3% had a grade 3-5 event.

Possible immune-related nephritis was observed in 9 patients but less than a third of these had identified events. Two patients had high-dose steroids and all of the events were resolved at data cut-off, which is considered encouraging. In conclusion, immune-related nephritis is considered acceptable and clinically manageable.

Immune-related nephritis occurred in 3 (0.5%) of 591 patients receiving cemiplimab including 2 (0.3%) patients with Grade 3 immune-related nephritis. Immune-related nephritis led to permanent discontinuation of cemiplimab in 1 (0.2%) of 591 patients. Among the 3 patients with immune-related nephritis, the median time to onset was 1.8 months (range: 29 days to 4.1 months) and the median duration of nephritis was 18 days (range: 9 days to 29 days). Two (0.3%) patients with immune-related nephritis received high-dose corticosteroids for a median of 1.5 months (range: 16 days to 2.6 months). Resolution of nephritis had occurred in all patients at the time of data cut-off.

Other immune-related adverse reactions

The following clinically significant identified immune-related AEs occurred in the monotherapy patients: Meningitis (1 patient;), Myalgia (1 patient),, Arthritis (2 patients), Autoimmune Myocarditis (1 patient), Chronic Inflammatory Demyelinating Polyradiculoneuropathy (1 patient), Encephalitis (1 patient), Immune Thrombocytopenic Purpura (1 patient), Paraneoplastic Encephalomyelitis (1 patient), Sjogren's Syndrome (1 patient), and Vasculitis (1 patient; Grade 2).

Other immune-related events were rarely observed, however, they included serious events such as meningitis, autoimmune myocarditis, and a cluster of events in the CNS. These autoimmune events are expected and acceptable at this level with a PD-1 inhibitor, and updated safety data with longer exposure has not increased the incidences, so the low observed risk seems reliable.

The following clinically significant, immune-related adverse reactions occurred at an incidence of less than 1% of 591 patients treated with cemiplimab. The events were grade 3 or less unless stated otherwise:

Nervous system disorders: Meningitis[a] (Grade 4), Paraneoplastic encephalomyelitis (Grade 5), Guillain-Barre syndrome, central nervous system inflammation, Chronic inflammatory demyelinating polyradiculoneuropathy, Encephalitis[b], Myasthenia gravis, Neuropathy peripheral.

Cardiac Disorders: Myocarditis[c], Pericarditis

Immune system disorders: Immune thrombocytopenic purpura

Vascular disorders: Vasculitis

Musculoskeletal and connective tissue disorders: Myalgia, Arthritis[d], Sjogren's syndrome

Eye disorders: Keratitis

Gastrointestinal disorders: Stomatitis

[a]meningitis and meningitis aseptic

[b] encephalitis and noninfective encephalitis

[c] autoimmune myocarditis and myocarditis

[d]arthritis and polyarthritis

Immune-Related Adverse Reactions in Patients Previously Treated With Idelalisib

Two patients in Study R1979-ONC-1504, a study of cemiplimab as monotherapy or in combination with REGN1979 (CD20xCD3 bispecific antibody) in patients with B-cell malignancies, experienced fatal mucocutaneous toxicity after a single dose of cemiplimab monotherapy, and a third patient developed life-threatening Myositis and Myasthenia Gravis following 2 doses of cemiplimab. A common element in their prior treatment history was therapy with idelalisib.

A total of 8 patients in Study R1979-ONC-1504 received idelalisib, including 1 patient who received idelalisib after discontinuing cemiplimab. Of the other 5 patients, 3 patients did not develop severe toxicity at any time during therapy, and 2 patients experienced SAEs or TEAEs of special interest:

Infusion-related reactions

Table 84: Summary of infusion reactions by system organ class, preferred term and NCI grade (safety analysis set)

	CSCC Patients Cemiplimab: 350 mg Q3W (N=56)		All CSCC Patients (N=219)		Monotherapy Patients (excluding HCC) (N=297)	
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
Total number of infusion reactions (based on sponsor definition)	7	0	28	0	32	0
Number of Patients with any infusion reaction (based on sponsor definition), n (%)	4 (7.1%)	0	19 (8.7%)	0	23 (7.7%)	0
Injury, poisoning and procedural complications	2 (3.6%)	0	8 (3.7%)	0	10 (3.4%)	0
Infusion related reaction	2 (3.6%)	0	8 (3.7%)	0	10 (3.4%)	0
Gastrointestinal disorders	1 (1.8%)	0	7 (3.2%)	0	8 (2.7%)	0
Nausea	1 (1.8%)	0	5 (2.3%)	0	5 (1.7%)	0
Abdominal pain	0	0	2 (0.9%)	0	3 (1.0%)	0
Vomiting	1 (1.8%)	0	1 (0.5%)	0	1 (0.3%)	0
General disorders and administration site conditions	0	0	2 (0.9%)	0	3 (1.0%)	0
Pyrexia	0	0	1 (0.5%)	0	2 (0.7%)	0
Chills	0	0	1 (0.5%)	0	1 (0.3%)	0
Respiratory, thoracic and mediastinal disorders	1 (1.8%)	0	2 (0.9%)	0	2 (0.7%)	0
Dyspnoea	0	0	1 (0.5%)	0	1 (0.3%)	0
Wheezing	1 (1.8%)	0	1 (0.5%)	0	1 (0.3%)	0
Immune system disorders	0	0	1 (0.5%)	0	1 (0.3%)	0
Hypersensitivity	0	0	1 (0.5%)	0	1 (0.3%)	0
Skin and subcutaneous tissue disorders	1 (1.8%)	0	1 (0.5%)	0	1 (0.3%)	0
Rash	1 (1.8%)	0	1 (0.5%)	0	1 (0.3%)	0
Vascular disorders	0	0	1 (0.5%)	0	1 (0.3%)	0
Flushing	0	0	1 (0.5%)	0	1 (0.3%)	0

Data cut-off as of June 30, 2018.
All adverse events were coded using MedDRA Version 20.0. 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 in the monotherapy patients (excluding HCC) group. Within each SOC, PTs are sorted by decreasing frequency in the monotherapy patients (excluding HCC) group.

Infusion-related reactions occurred in 54 (9.1%) of 591 of patients treated with cemiplimab including 1 (0.2%) patient with Grade 3 infusion-related reaction. Infusion-related reaction led to permanent discontinuation of cemiplimab in 2 (0.3%) patients. The most common symptoms of infusion-related

reaction were nausea, pyrexia, vomiting, abdominal pain, chills and flushing. All patients recovered from the infusion-related reaction.

Serious adverse event/deaths/other significant events

Deaths

Table 85: Summary of all deaths (safety analysis set)

	CSCC Patients Cemiplimab: 350 mg Q3W (N=56)	All CSCC Patients (N=219)	Monotherapy Patients (excluding HCC) (N=297)
Number of Deaths, n (%)	8 (14.3%)	36 (16.4%)	67 (22.6%)
Primary cause of death			
PROGRESSION/RECURRENCE OF DISEASE	7 (12.5%)	27 (12.3%)	56 (18.9%)
ADVERSE EVENT	1 (1.8%)	6 (2.7%)	7 (2.4%)
OTHER	0	3 (1.4%)	4 (1.3%)

Data cut-off as of June 30, 2018.

Table 86: Summary of treatment-emergent adverse events resulting in death by system organ class and preferred term (Safety analysis set)

System Organ Class, n (%) Preferred Term, n (%)	CSCC Patients Cemiplimab: 350 mg Q3W (N=56)	All CSCC Patients (N=219)	Monotherapy Patients (excluding HCC) (N=297)
Total number of TEAEs resulting in death	1	6	7
Number of Patients with any TEAE resulting in death, n (%)	1 (1.8%)	6 (2.7%)	7 (2.4%)
General disorders and administration site conditions	0	2 (0.9%)	2 (0.7%)
Death	0	2 (0.9%)	2 (0.7%)
Infections and infestations	0	1 (0.5%)	1 (0.3%)
Pneumonia	0	1 (0.5%)	1 (0.3%)
Nervous system disorders	0	0	1 (0.3%)
Paraneoplastic encephalomyelitis	0	0	1 (0.3%)
Renal and urinary disorders	0	1 (0.5%)	1 (0.3%)
Acute kidney injury	0	1 (0.5%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	0	1 (0.5%)	1 (0.3%)
Acute respiratory distress syndrome	0	1 (0.5%)	1 (0.3%)
Vascular disorders	1 (1.8%)	1 (0.5%)	1 (0.3%)
Arterial haemorrhage	1 (1.8%)	1 (0.5%)	1 (0.3%)

Data cut-off as of June 30, 2018.
TEAE: Treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 20.0.
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 monotherapy patients (excluding HCC) group. Within each SOC, PTs are sorted by decreasing frequency in the monotherapy patients (excluding HCC) group.

Serious adverse events

Table 87: Summary of serious treatment-emergent adverse events (Safety analysis set)

	Pool 1 All CSCC Patients (N=219)	Pool 2 All Monotherapy Patients (excluding HCC) (N=297)	Pool 3 All Patients (N=591)
Number of Serious TEAEs	135	160	306
Number of Treatment-Related Serious TEAEs	25	29	60
Number of Patients with any Serious TEAE, n (%)	74 (33.8%)	92 (31.0%)	179 (30.3%)
Fatal	6 (2.7%)	7 (2.4%)	12 (2.0%)
Life-threatening	9 (4.1%)	10 (3.4%)	18 (3.0%)
Hospitalization/prolong existing hospitalization	71 (32.4%)	89 (30.0%)	173 (29.3%)
Disability/incapacity	1 (0.5%)	3 (1.0%)	4 (0.7%)
Congenital abnormality or birth defect	0	0	0
Other (medically significant)	3 (1.4%)	4 (1.3%)	9 (1.5%)
Number of Patients with any Treatment-Related Serious TEAE, n (%)	18 (8.2%)	22 (7.4%)	50 (8.5%)
Fatal	1 (0.5%)	2 (0.7%)	6 (1.0%)
Life-threatening	1 (0.5%)	1 (0.3%)	4 (0.7%)
Hospitalization/prolong existing hospitalization	17 (7.8%)	21 (7.1%)	46 (7.8%)
Disability/incapacity	0	0	0
Congenital abnormality or birth defect	0	0	0
Other (medically significant)	1 (0.5%)	1 (0.3%)	4 (0.7%)

Data cut-off as of June 30, 2018.
TEAE: Treatment-emergent adverse event.
A patient is counted only once for multiple occurrences within a category.

Table 88: Summary of serious treatment-emergent adverse events by system organ class and preferred term (Safety analysis set)

System Organ Class, n (%) Preferred Term, n (%)	CSCC Patients Cemiplimab: 350 mg Q3W (N=56)	All CSCC Patients (N=219)	Monotherapy Patients (excluding HCC) (N=297)
Total number of serious TEAEs	34	135	160
Number of Patients with any serious TEAE , n (%)	21 (37.5%)	74 (33.8%)	92 (31.0%)
Infections and infestations	7 (12.5%)	33 (15.1%)	41 (13.8%)
Pneumonia	0	5 (2.3%)	8 (2.7%)
Cellulitis	1 (1.8%)	6 (2.7%)	6 (2.0%)
Sepsis	1 (1.8%)	5 (2.3%)	5 (1.7%)
Skin infection	1 (1.8%)	4 (1.8%)	4 (1.3%)
Urinary tract infection	1 (1.8%)	3 (1.4%)	4 (1.3%)
Cystitis	1 (1.8%)	1 (0.5%)	2 (0.7%)
Abscess limb	0	0	1 (0.3%)
Arthritis infective	0	1 (0.5%)	1 (0.3%)
Bacteraemia	0	0	1 (0.3%)
Catheter site infection	0	1 (0.5%)	1 (0.3%)
Encephalitis	0	1 (0.5%)	1 (0.3%)
Escherichia urinary tract infection	1 (1.8%)	1 (0.5%)	1 (0.3%)
Extradural abscess	0	1 (0.5%)	1 (0.3%)
Fungal skin infection	1 (1.8%)	1 (0.5%)	1 (0.3%)

Infections and infestations			
Groin infection	0	1 (0.5%)	1 (0.3%)
Influenza	0	1 (0.5%)	1 (0.3%)
Lung infection	0	1 (0.5%)	1 (0.3%)
Meningitis aseptic	0	1 (0.5%)	1 (0.3%)
Pneumonia influenzal	0	1 (0.5%)	1 (0.3%)
Pneumonia streptococcal	0	0	1 (0.3%)
Psoas abscess	0	1 (0.5%)	1 (0.3%)
Pyelonephritis	0	1 (0.5%)	1 (0.3%)
Soft tissue infection	0	1 (0.5%)	1 (0.3%)
Staphylococcal infection	0	1 (0.5%)	1 (0.3%)
Upper respiratory tract infection	0	1 (0.5%)	1 (0.3%)
Wound infection	0	1 (0.5%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	1 (1.8%)	15 (6.8%)	18 (6.1%)
Pneumonitis	1 (1.8%)	7 (3.2%)	9 (3.0%)
Acute respiratory distress syndrome	0	1 (0.5%)	1 (0.3%)
Chronic obstructive pulmonary disease	0	1 (0.5%)	1 (0.3%)
Dyspnoea	0	1 (0.5%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders			
Epistaxis	0	1 (0.5%)	1 (0.3%)
Haemoptysis	0	0	1 (0.3%)
Hypoxia	0	1 (0.5%)	1 (0.3%)
Pleural effusion	0	1 (0.5%)	1 (0.3%)
Pneumothorax	0	1 (0.5%)	1 (0.3%)
Pulmonary oedema	0	1 (0.5%)	1 (0.3%)
Gastrointestinal disorders	1 (1.8%)	4 (1.8%)	10 (3.4%)
Gastrointestinal haemorrhage	0	0	2 (0.7%)
Intestinal obstruction	0	0	2 (0.7%)
Abdominal pain upper	0	1 (0.5%)	1 (0.3%)
Ascites	0	0	1 (0.3%)
Duodenal ulcer	0	1 (0.5%)	1 (0.3%)
Dysphagia	1 (1.8%)	1 (0.5%)	1 (0.3%)
Gastritis	0	0	1 (0.3%)
Oesophagitis	0	1 (0.5%)	1 (0.3%)
Proctitis	0	1 (0.5%)	1 (0.3%)
Small intestinal haemorrhage	0	1 (0.5%)	1 (0.3%)
Gastrointestinal disorders			
Small intestinal obstruction	0	0	1 (0.3%)
General disorders and administration site conditions	2 (3.6%)	6 (2.7%)	7 (2.4%)
Death	0	2 (0.9%)	2 (0.7%)
Pyrexia	0	2 (0.9%)	2 (0.7%)
Fatigue	0	1 (0.5%)	1 (0.3%)
General physical health deterioration	1 (1.8%)	1 (0.5%)	1 (0.3%)
Non-cardiac chest pain	0	0	1 (0.3%)
Peripheral swelling	1 (1.8%)	1 (0.5%)	1 (0.3%)
Injury, poisoning and procedural complications	2 (3.6%)	7 (3.2%)	7 (2.4%)
Fall	0	2 (0.9%)	2 (0.7%)
Eye contusion	0	1 (0.5%)	1 (0.3%)
Hip fracture	0	1 (0.5%)	1 (0.3%)
Limb injury	1 (1.8%)	1 (0.5%)	1 (0.3%)
Postoperative wound complication	0	1 (0.5%)	1 (0.3%)
Radius fracture	0	1 (0.5%)	1 (0.3%)
Injury, poisoning and procedural complications			
Spinal fracture	1 (1.8%)	1 (0.5%)	1 (0.3%)
Metabolism and nutrition disorders	3 (5.4%)	6 (2.7%)	7 (2.4%)
Hypercalcaemia	1 (1.8%)	3 (1.4%)	3 (1.0%)
Dehydration	2 (3.6%)	2 (0.9%)	2 (0.7%)
Diabetic ketoacidosis	0	0	1 (0.3%)
Hypoglycaemia	0	1 (0.5%)	1 (0.3%)
Hyponatraemia	0	1 (0.5%)	1 (0.3%)
Nervous system disorders	2 (3.6%)	6 (2.7%)	7 (2.4%)
Cerebral infarction	0	1 (0.5%)	1 (0.3%)
Cerebral ischaemia	0	1 (0.5%)	1 (0.3%)
Cerebrovascular accident	0	1 (0.5%)	1 (0.3%)
Focal dyscognitive seizures	0	1 (0.5%)	1 (0.3%)
Lethargy	1 (1.8%)	1 (0.5%)	1 (0.3%)
Paraneoplastic encephalomyelitis	0	0	1 (0.3%)
Syncope	1 (1.8%)	1 (0.5%)	1 (0.3%)

Cardiac disorders	2 (3.6%)	6 (2.7%)	6 (2.0%)
Myocardial infarction	0	2 (0.9%)	2 (0.7%)
Atrial fibrillation	1 (1.8%)	1 (0.5%)	1 (0.3%)
Atrioventricular block complete	0	1 (0.5%)	1 (0.3%)
Myocarditis	0	1 (0.5%)	1 (0.3%)
Pericarditis	1 (1.8%)	1 (0.5%)	1 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.8%)	4 (1.8%)	6 (2.0%)
Breast cancer	0	2 (0.9%)	2 (0.7%)
B-cell lymphoma	0	1 (0.5%)	1 (0.3%)
Keratoacanthoma	0	0	1 (0.3%)
Squamous cell carcinoma of skin	1 (1.8%)	1 (0.5%)	1 (0.3%)
Tumour ulceration	0	0	1 (0.3%)
Musculoskeletal and connective tissue disorders	1 (1.8%)	5 (2.3%)	5 (1.7%)
Muscular weakness	0	2 (0.9%)	2 (0.7%)
Arthralgia	0	1 (0.5%)	1 (0.3%)
Musculoskeletal pain	0	1 (0.5%)	1 (0.3%)
Pain in extremity	0	1 (0.5%)	1 (0.3%)
Musculoskeletal and connective tissue disorders			
Soft tissue necrosis	1 (1.8%)	1 (0.5%)	1 (0.3%)
Renal and urinary disorders	3 (5.4%)	5 (2.3%)	5 (1.7%)
Acute kidney injury	0	2 (0.9%)	2 (0.7%)
Haematuria	2 (3.6%)	2 (0.9%)	2 (0.7%)
Urinary retention	1 (1.8%)	1 (0.5%)	1 (0.3%)
Vascular disorders	2 (3.6%)	4 (1.8%)	5 (1.7%)
Deep vein thrombosis	1 (1.8%)	2 (0.9%)	2 (0.7%)
Arterial haemorrhage	1 (1.8%)	1 (0.5%)	1 (0.3%)
Hypertension	0	1 (0.5%)	1 (0.3%)
Hypotension	0	0	1 (0.3%)
Investigations	1 (1.8%)	3 (1.4%)	4 (1.3%)
Alanine aminotransferase increased	0	1 (0.5%)	1 (0.3%)
Aspartate aminotransferase increased	0	1 (0.5%)	1 (0.3%)
Blood creatinine increased	0	0	1 (0.3%)
Influenza A virus test positive	0	1 (0.5%)	1 (0.3%)
Investigations			
International normalised ratio increased	1 (1.8%)	1 (0.5%)	1 (0.3%)
Psychiatric disorders	1 (1.8%)	3 (1.4%)	3 (1.0%)
Adjustment disorder	1 (1.8%)	1 (0.5%)	1 (0.3%)
Delirium	0	1 (0.5%)	1 (0.3%)
Suicidal ideation	0	1 (0.5%)	1 (0.3%)
Blood and lymphatic system disorders	2 (3.6%)	2 (0.9%)	2 (0.7%)
Anaemia	1 (1.8%)	1 (0.5%)	1 (0.3%)
Coagulopathy	1 (1.8%)	1 (0.5%)	1 (0.3%)
Skin and subcutaneous tissue disorders	1 (1.8%)	2 (0.9%)	2 (0.7%)
Dermatitis atopic	0	1 (0.5%)	1 (0.3%)
Rash maculo-papular	1 (1.8%)	1 (0.5%)	1 (0.3%)
Endocrine disorders	0	1 (0.5%)	1 (0.3%)
Hypophysitis	0	1 (0.5%)	1 (0.3%)

SAEs were common during treatment and most often related to infections.

Table 89: Summary of serious treatment-emergent adverse events by system organ class, preferred term and NCI grade (Safety analysis set)

System Organ Class, n (%) Preferred Term, n (%)	Pool 1 - All CSCC Patients (N=163)		Pool 2 - All Monotherapy Patients (Excluding HCC) (N=240)		Pool 3 - All Patients (N=534)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Blood and lymphatic system disorders	21 (12.9%)	3 (1.8%)	38 (15.8%)	12 (5.0%)	110 (20.6%)	50 (9.4%)
Anaemia	13 (8.0%)	2 (1.2%)	23 (9.6%)	7 (2.9%)	67 (12.5%)	27 (5.1%)
Lymphopenia	4 (2.5%)	1 (0.6%)	7 (2.9%)	4 (1.7%)	20 (3.7%)	12 (2.2%)
Neutropenia	1 (0.6%)	0	1 (0.4%)	0	13 (2.4%)	9 (1.7%)
Psychiatric disorders	20 (12.3%)	4 (2.5%)	32 (13.3%)	4 (1.7%)	95 (17.8%)	9 (1.7%)
Insomnia	7 (4.3%)	0	11 (4.6%)	0	44 (8.2%)	0
Delirium	4 (2.5%)	2 (1.2%)	4 (1.7%)	2 (0.8%)	7 (1.3%)	3 (0.6%)
Injury, poisoning and procedural complications	31 (19.0%)	2 (1.2%)	43 (17.9%)	2 (0.8%)	92 (17.2%)	8 (1.5%)
Fall	9 (5.5%)	0	13 (5.4%)	0	25 (4.7%)	2 (0.4%)
Vascular disorders	25 (15.3%)	8 (4.9%)	35 (14.6%)	9 (3.8%)	68 (12.7%)	14 (2.6%)
Hypertension	10 (6.1%)	5 (3.1%)	11 (4.6%)	5 (2.1%)	15 (2.8%)	6 (1.1%)
Renal and urinary disorders	15 (9.2%)	4 (2.5%)	22 (9.2%)	6 (2.5%)	52 (9.7%)	9 (1.7%)
Acute kidney injury	3 (1.8%)	2 (1.2%)	3 (1.3%)	2 (0.8%)	7 (1.3%)	3 (0.6%)
Endocrine disorders	18 (11.0%)	2 (1.2%)	24 (10.0%)	2 (0.8%)	47 (8.8%)	5 (0.9%)
Hypothyroidism	14 (8.6%)	0	20 (8.3%)	0	37 (6.9%)	1 (0.2%)
Cardiac disorders	10 (6.1%)	7 (4.3%)	10 (4.2%)	7 (2.9%)	29 (5.4%)	12 (2.2%)
Atrial fibrillation	3 (1.8%)	2 (1.2%)	3 (1.3%)	2 (0.8%)	7 (1.3%)	3 (0.6%)
Myocardial infarction	2 (1.2%)	2 (1.2%)	2 (0.8%)	2 (0.8%)	2 (0.4%)	2 (0.4%)
Hepatobiliary disorders	3 (1.8%)	3 (1.8%)	4 (1.7%)	3 (1.3%)	19 (3.6%)	15 (2.8%)
Autoimmune hepatitis	2 (1.2%)	2 (1.2%)	2 (0.8%)	2 (0.8%)	6 (1.1%)	6 (1.1%)

Abbreviations: AE, adverse event; CSCC, cutaneous squamous cell carcinoma; CTCAE, Common Terminology Criteria for Adverse Events; HCC, hepatocellular carcinoma; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; NCI, National Cancer Institute; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event

Data cut-off as of 02 Oct 2017 for CSCC patients with cemiplimab monotherapy in Study 1423; Data cut-off as of 01 Sep 2017 for all other patients in Study 1423; Data cut-off as of 27 Oct 2017 for all patients in Study 1540.

All AEs were coded using MedDRA Version 20.0. NCI grades were coded using CTCAE Version 4.03.

A patient is counted only once for multiple occurrences within a SOC/PT.

For SOCs, the table is sorted by decreasing frequency of all grades in the total group. Within each SOC, PTs are sorted by decreasing frequency in the total group.

Table 90: Summary of treatment-related serious treatment-emergent adverse events by system organ class and preferred term (Safety analysis set)

System Organ Class, n (%) Preferred Term, n (%)	CSCC Patients Cemiplimab: 350 mg Q3W (N=56)	All CSCC Patients (N=219)	Monotherapy Patients (excluding HCC) (N=297)
Total number of treatment-related serious TEAEs	5	25	29
Number of Patients with any treatment-related serious TEAE , n (%)	4 (7.1%)	18 (8.2%)	22 (7.4%)
Respiratory, thoracic and mediastinal disorders	1 (1.8%)	7 (3.2%)	9 (3.0%)
Pneumonitis	1 (1.8%)	7 (3.2%)	9 (3.0%)
Cardiac disorders	1 (1.8%)	2 (0.9%)	2 (0.7%)
Myocarditis	0	1 (0.5%)	1 (0.3%)
Pericarditis	1 (1.8%)	1 (0.5%)	1 (0.3%)
Gastrointestinal disorders	0	2 (0.9%)	2 (0.7%)
Duodenal ulcer	0	1 (0.5%)	1 (0.3%)
Oesophagitis	0	1 (0.5%)	1 (0.3%)
Proctitis	0	1 (0.5%)	1 (0.3%)
Small intestinal haemorrhage	0	1 (0.5%)	1 (0.3%)
General disorders and administration site conditions	0	2 (0.9%)	2 (0.7%)
Death	0	1 (0.5%)	1 (0.3%)

General disorders and administration site conditions			
Pyrexia	0	1 (0.5%)	1 (0.3%)
Infections and infestations	0	2 (0.9%)	2 (0.7%)
Encephalitis	0	1 (0.5%)	1 (0.3%)
Meningitis aseptic	0	1 (0.5%)	1 (0.3%)
Nervous system disorders	1 (1.8%)	1 (0.5%)	2 (0.7%)
Lethargy	1 (1.8%)	1 (0.5%)	1 (0.3%)
Paraneoplastic encephalomyelitis	0	0	1 (0.3%)
Blood and lymphatic system disorders	1 (1.8%)	1 (0.5%)	1 (0.3%)
Anaemia	1 (1.8%)	1 (0.5%)	1 (0.3%)
Endocrine disorders	0	1 (0.5%)	1 (0.3%)
Hypophysitis	0	1 (0.5%)	1 (0.3%)
Hepatobiliary disorders	0	1 (0.5%)	1 (0.3%)
Autoimmune hepatitis	0	1 (0.5%)	1 (0.3%)
Investigations	0	1 (0.5%)	1 (0.3%)
Alanine aminotransferase increased	0	1 (0.5%)	1 (0.3%)
Aspartate aminotransferase increased	0	1 (0.5%)	1 (0.3%)
Metabolism and nutrition disorders	0	0	1 (0.3%)
Diabetic ketoacidosis	0	0	1 (0.3%)
Skin and subcutaneous tissue disorders	1 (1.8%)	1 (0.5%)	1 (0.3%)
Rash maculo-papular	1 (1.8%)	1 (0.5%)	1 (0.3%)

Data cut-off as of June 30, 2018.
TEAE: Treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 20.0.
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 monotherapy patients (excluding HCC) group. Within each SOC, PTs are sorted by decreasing frequency in the monotherapy patients (excluding HCC) group.

In all CSCC patients, most patients (98.6%) had at least one AE and 43.8% had high-grade events (≥ grade 3). Two-thirds (66.%) of these patients had treatment-related AEs, most frequently fatigue (31.5%), diarrhea (22.8%), nausea (20.1%), pruritus (18.3%) and maculo-papular rash (10%).

Overall, the most common TEAEs in the All CSCC patients were fatigue, diarrhea, nausea, and pruritus. It is noted that for the CSCC 350mg patients, rash was more fr equently observed (16.1% vs. 14.2%) while diarrhea was less frequent (14.3% vs 22.8%). More than grade 3 events occurred in 43.8% of all CSCC monotherapy patients and 11% of the patients had at least 1 treatment-related grade ≥ 3 event. The incidence for the CSCC 350mg patients were similar, i.e. 37.5% and 12.5% had ≥grade 3 events and treatment-related ≥grade 3 events, respectively.

Laboratory findings

For the ongoing studies R2810-ONC-1423 and R2810-ONC-1540, the applicant has notified the Rapporteur on the 15th of June that they have identified some errors in units and normal ranges for some laboratory values.

The applicant has prepared and sumitted an erratum, which includes corrections to the original laboratory data due to new or updated laboratory normal ranges (LNRs) and the overview has been updated accordingly. No new safety concerns have been raised.

Haematology

Table 91: Summary of new or worsened laboratory results by NCI-CTCAE grade for haematology (Safety analysis set)

NOTE: All differences between updated and original tables are highlighted in red font

UPDATED

	Pool 1 - All CSCC Patients (N=163)		Pool 2 - All Monotherapy patients (excluding HCC) (N=240)		Pool 3 - All patients (N=534)	
Parameter (CTCAE Term)	**All Grades**	**Grades 3/4**	**All Grades**	**Grades 3/4**	**All Grades**	**Grades 3/4**
Number of pts. with at least one post-baseline lab abnormality, n (%)	111/157 (70.7%)	13/157 (8.3%)	185/234 (79.1%)	37/234 (15.8%)	445/527 (84.4%)	127/527 (24.1%)
Hemoglobin (Anemia)	66/157 (42.0%)	4/157 (2.5%)	113/234 (48.3%)	9/234 (3.8%)	284/527 (53.9%)	31/527 (5.9%)
Hemoglobin (Hemoglobin increased)	4/157 (2.5%)	0/157	4/234 (1.7%)	0/234	8/527 (1.5%)	0/527
Leukocytes (White blood cell decreased)	22/157 (14.0%)	0/157	46/234 (19.7%)	1/234 (0.4%)	136/527 (25.8%)	15/527 (2.8%)
Lymphocytes (Lymphocyte count decreased)	65/157 (41.4%)	11/157 (7.0%)	110/233 (47.2%)	29/233 (12.4%)	295/524 (56.3%)	98/524 (18.7%)
Lymphocytes (Lymphocyte count increased)	2/157 (1.3%)	0/157	5/234 (2.1%)	0/234	7/527 (1.3%)	0/527
Neutrophils (Neutrophil count decreased)	9/157 (5.7%)	0/157	23/233 (9.9%)	0/233	76/523 (14.5%)	14/523 (2.7%)
Platelets (Platelet count decreased)	14/157 (8.9%)	0/157	26/234 (11.1%)	0/234	99/527 (18.8%)	2/527 (0.4%)

Data cut-off as of Oct 2, 2017 for CSCC patients with Cemiplimab monotherapy in Study 1423; Data cut-off as of Sep 1, 2017 for all other patients in Study 1423; Data cut-off as of Oct 27, 2017 for all patients in Study 1540.
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.

Table 92: Summary of new or worsened laboratory results by NCI-CTCAE grade for coagulation (Safety analysis set)

NOTE: All differences between updated and original tables are highlighted in red font

UPDATED

	Pool 1 - All CSCC Patients (N=163)		Pool 2 - All Monotherapy patients (excluding HCC) (N=240)		Pool 3 - All patients (N=534)	
Parameter (CTCAE Term)	**All Grades**	**Grades 3/4**	**All Grades**	**Grades 3/4**	**All Grades**	**Grades 3/4**
Number of pts. with at least one post-baseline lab abnormality, n (%)	24/121 (19.8%)	3/121 (2.5%)	45/181 (24.9%)	6/181 (3.3%)	109/390 (27.9%)	11/390 (2.8%)
Activated Partial Thromboplastin Time (Activated partial thromboplastin time prolonged)	15/116 (12.9%)	0/116	32/173 (18.5%)	2/173 (1.2%)	79/372 (21.2%)	4/372 (1.1%)
Prothrombin Intl. Normalized Ratio (INR increased)	14/106 (13.2%)	3/106 (2.8%)	23/166 (13.9%)	4/166 (2.4%)	53/375 (14.1%)	7/375 (1.9%)

Data cut-off as of Oct 2, 2017 for CSCC patients with Cemiplimab monotherapy in Study 1423; Data cut-off as of Sep 1, 2017 for all other patients in Study 1423; Data cut-off as of Oct 27, 2017 for all patients in Study 1540.
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.

Haematological toxicity and coagulation deficiencies were very rarely observed as high-grade events and the commonly observed low-grade events in this category may not be treatment-related but caused by the underlying disease.

Electrolytes

Table 93: Summary of new or worsened laboratory results by NCI-CTCAE grade for electrolytes (Safety analysis set)

NOTE: All differences between updated and original tables are highlighted in red font

UPDATED

Parameter (CTCAE Term)	Pool 1 - All CSCC Patients (N=163)		Pool 2 - All Monotherapy patients (excluding HCC) (N=240)		Pool 3 - All patients (N=534)	
	All Grades	Grades 3/4	All Grades	Grades 3/4	All Grades	Grades 3/4
Number of pts. with at least one post-baseline lab abnormality, n (%)	101/157 (64.3%)	13/157 (8.3%)	164/233 (70.4%)	22/233 (9.4%)	408/526 (77.6%)	81/526 (15.4%)
Calcium (Hypercalcemia (Uncorrected Calcium))	15/157 (9.6%)	2/157 (1.3%)	18/233 (7.7%)	2/233 (0.9%)	43/526 (8.2%)	6/526 (1.1%)
Calcium (Hypocalcemia (Uncorrected Calcium))	30/157 (19.1%)	0/157	53/233 (22.7%)	0/233	176/526 (33.5%)	2/526 (0.4%)
Magnesium (Hypermagnesemia)	6/157 (3.8%)	0/157	11/233 (4.7%)	2/233 (0.9%)	27/526 (5.1%)	4/526 (0.8%)
Magnesium (Hypomagnesemia)	21/157 (13.4%)	0/157	35/233 (15.0%)	0/233	92/526 (17.5%)	2/526 (0.4%)
Phosphate (Hypophosphatemia)	32/156 (20.5%)	6/156 (3.8%)	44/231 (19.0%)	8/231 (3.5%)	122/523 (23.3%)	30/523 (5.7%)
Potassium (Hyperkalemia)	24/157 (15.3%)	1/157 (0.6%)	30/233 (12.9%)	2/233 (0.9%)	55/526 (10.5%)	3/526 (0.6%)
Potassium (Hypokalemia)	24/157 (15.3%)	1/157 (0.6%)	44/233 (18.9%)	2/233 (0.9%)	108/526 (20.5%)	8/526 (1.5%)
Sodium (Hypernatremia)	5/157 (3.2%)	0/157	13/233 (5.6%)	0/233	32/526 (6.1%)	0/526
Sodium (Hyponatremia)	38/157 (24.2%)	5/157 (3.2%)	61/233 (26.2%)	9/233 (3.9%)	169/526 (32.1%)	39/526 (7.4%)

Data cut-off as of Oct 2, 2017 for CSCC patients with Cemiplimab monotherapy in Study 1423; Data cut-off as of Sep 1, 2017 for all other patients in Study 1423; Data cut-off as of Oct 27, 2017 for all patients in Study 1540.
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.

High-grade events were observed in almost 10% of the patients in the monotherapy patients, most frequently hypophosphatemia and hyponatremia, which can be frequently observed in under-nourished cancer patients and the elderly. The risk of deviating electrolytes during treatment with cemiplimab is not of major concern.

Liver function

Table 94: Summary of new or worsened laboratory results by NCI-CT AE grade for liver function (Safety analysis set)

NOTE: All differences between updated and original tables are highlighted in red font

UPDATED

Parameter (CTCAE Term)	Pool 1 - All CSCC Patients (N=163)		Pool 2 - All Monotherapy patients (excluding HCC) (N=240)		Pool 3 - All patients (N=534)	
	All Grades	Grades 3/4	All Grades	Grades 3/4	All Grades	Grades 3/4
Number of pts. with at least one post-baseline lab abnormality, n (%)	84/157 (53.5%)	7/157 (4.5%)	142/233 (60.9%)	12/233 (5.2%)	372/526 (70.7%)	56/526 (10.6%)
Alanine Aminotransferase (Alanine aminotransferase increased)	20/157 (12.7%)	1/157 (0.6%)	35/233 (15.0%)	1/233 (0.4%)	115/526 (21.9%)	16/526 (3.0%)
Albumin (Hypoalbuminemia)	52/157 (33.1%)	2/157 (1.3%)	88/233 (37.8%)	3/233 (1.3%)	233/526 (44.3%)	8/526 (1.5%)
Alkaline Phosphatase (Alkaline phosphatase increased)	22/157 (14.0%)	1/157 (0.6%)	38/233 (16.3%)	1/233 (0.4%)	137/526 (26.0%)	15/526 (2.9%)
Aspartate Aminotransferase (Aspartate aminotransferase increased)	25/156 (16.0%)	5/156 (3.2%)	42/232 (18.1%)	7/232 (3.0%)	144/525 (27.4%)	26/525 (5.0%)
Bilirubin (Blood bilirubin increased)	8/157 (5.1%)	0/157	17/233 (7.3%)	4/233 (1.7%)	60/526 (11.4%)	15/526 (2.9%)

Data cut-off as of Oct 2, 2017 for CSCC patients with Cemiplimab monotherapy in Study 1423; Data cut-off as of Sep 1, 2017 for all other patients in Study 1423; Data cut-off as of Oct 27, 2017 for all patients in Study 1540.
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.

Even though low-grade events were frequent (60.9%), high-grade events were seldom (5.2%) and present to an acceptable extent, considering the patient population and the prognosis of the underlying disease.

Other chemistry

Table 95: Summary of new or worsened laboratory results by NCI-CTCAE grade for chemistry (other) (Safety analysis set)

Parameter (CTCAE Term)	Pool 1 - All CSCC Patients (N=163)		Pool 2 - All Monotherapy Patients (Excluding HCC) (N=240)		Pool 3 - All patients (N=534)	
	All Grades	Grades 3/4	All Grades	Grades 3/4	All Grades	Grades 3/4
Number of pts. with at least one post-baseline lab abnormality, n (%)	45/157 (28.7%)	1/157 (0.6%)	75/233 (32.2%)	5/233 (2.1%)	152/526 (28.9%)	6/526 (1.1%)
Creatinine (Creatinine increased)	37/157 (23.6%)	1/157 (0.6%)	61/233 (26.2%)	5/233 (2.1%)	117/526 (22.2%)	6/526 (1.1%)
Glucose (Hypoglycemia)	13/156 (8.3%)	0/156	25/232 (10.8%)	0/232	56/525 (10.7%)	0/525

Abbreviations: CSCC, cutaneous squamous cell carcinoma; CTCAE, Common Terminology Criteria for Adverse Events; HCC, hepatocellular carcinoma; N, number of patients; NCI, National Cancer Institute
Data cut-off as of 02 Oct 2017 for CSCC patients with Cemiplimab monotherapy in Study 1423; Data cut-off as of 01 Sep 2017 for all other patients in Study 1423; Data cut-off as of 27 Oct 2017 for all patients in Study 1540.
NCI grades were coded using CTCAE Version 5.0 for Creatinine; NCI grades were coded using CTCAE Version 4.03 for Glucose.
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.

Table 96: Selected treatment-emergent laboratory abnormalities in ≥15% in all grades of pool 1 patients

Laboratory Tests	All Grades (N=163) n/N (%)	Grade 3/4 (N=163) n/N (%)
Chemistry		
Aspartate aminotransferase increased	25/156 (16.0%)	5/156 (3.2%)
Creatinine increased	37/157 (23.6%)	1/157 (0.6%)
Hematology		
Anemia	66/157 (42.0%)	3/157 (1.9%)
Lymphopenia	65/157 (41.4%)	11/157 (7.0%)

Treatment-emergent consists of new onset of laboratory abnormality or worsening of baseline laboratory abnormality.
Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter.

Creatinine was increased in a quarter of the patients but grade 3-4 events were rarely observed. This is considered a reflection of the pre-treated elderly patient population, commonly treated with platinum-containing chemotherapy. Therefore, this event is not considered to be of any major concern.

It is agreed that the high frequency of hypoalbuminaemia even in cemiplimab monotherapy group (37.8%, grade 3 to 4, 1.3%) is related to the poor nutritional status of the study patients and it is not considered a new safety signal.

Vital signs

Vital signs were assessed prior to each cemiplimab infusion Q2W or Q3W and approximately 30 minutes (Study 1423) or 15 minutes (Study 1540) after the completion of each infusion. In addition, since there was no clinical experience with cemiplimab at the inception of Study 1423, on cycle 1 day 1, vital signs were collected every 30 minutes for the first 4 hours post-infusion and at 6 and 8 hours after study drug administration. Small variations in mean and median weight, blood pressure, and heart rate were seen over time, but none indicated a trend towards an overall increase or decrease.

Electrocardiogram

In Pool 3, there were some shifts from normal to abnormal in ECG findings during the studies; a clinically significant shift was reported in 1 (0.2%) patient. This patient was in Study 1540 (Patient 036004001) in Group 1 (mCSCC 3 mg/kg cemiplimab IV Q2W) on study day 114. 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. An AE of Atrioventricular Block First Degree was reported for this patient. 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.

There were no clinically relevant changes from baseline in the QTc interval or ECG abnormalities; observed ECG findings were typical of the patient population (Table 29). Monoclonal antibodies such as cemiplimab, in general, are not expected to prolong QT intervals.

Table 97: Summary of patients with potential treatment-emergent ECG abnormalities (Safety analysis set)

	Pool 1 - All CSCC Patients (N=163)	Pool 2 - All Monotherapy Patients (Excluding HCC) (N=240)	Pool 3 - All patients (N=534)
Number of patients with at least one abnormality, n (%)	72/151 (47.7%)	101/227 (44.5%)	211/519 (40.7%)
QTcB (msec)			
>450	21/151 (13.9%)	25/227 (11.0%)	78/519 (15.0%)
>480	9/151 (6.0%)	15/227 (6.6%)	35/519 (6.7%)
>500	4/151 (2.6%)	8/227 (3.5%)	19/519 (3.7%)
Increase from baseline>30	22/151 (14.6%)	31/227 (13.7%)	69/519 (13.3%)
Increase from baseline>60	6/151 (4.0%)	8/227 (3.5%)	18/519 (3.5%)
QTcF (msec)			
>450	16/151 (10.6%)	22/227 (9.7%)	48/519 (9.2%)
>480	7/151 (4.6%)	9/227 (4.0%)	19/519 (3.7%)
>500	2/151 (1.3%)	4/227 (1.8%)	9/519 (1.7%)
Increase from baseline>30	21/151 (13.9%)	27/227 (11.9%)	58/519 (11.2%)
Increase from baseline>60	5/151 (3.3%)	6/227 (2.6%)	13/519 (2.5%)

Abbreviations: CSCC, cutaneous squamous cell carcinoma; ECG, electrocardiogram; HCC, hepatocellular carcinoma; N, number of patients; QTcB, QTc corrected by Bazett's formula; QTcF, QTc corrected by Fridericia's formula

Data cut-off as of 02 Oct 2017 for CSCC patients with Cemiplimab monotherapy in Study 1423; Data cut-off as of 01 Sep 2017 for all other patients in Study 1423; Data cut-off as of 27 Oct 2017 for all patients in Study 1540.

Treatment-Emergent ECG Abnormalities included those developed or worsened during on-treatment period.

Percentages are based on the number of patients with at least one post-baseline value available for that parameter.

A patient is counted only once for multiple occurrences for the same category.

Events concerning vital signs and ECG changes are not considered of major concern and it may be agreed that the observed events may be due to the elderly patient population and not the study drug.

Immunogenicity

Approximately 1.17% of all patients receiving 3 mg/kg cemiplimab IV Q2W developed treatment-emergent antibodies to cemiplimab. Antibody titers were low to moderate. No patients developed neutralizing antibodies. None of the patients with CSCC developed treatment-emergent antibodies.

Approximately 0.29% of all patients receiving 3 mg/kg cemiplimab IV Q2W had persistent antibody responses defined as having at least 2 consecutive positive post-baseline samples separated by at least 16 weeks.

As with all therapeutic proteins, there is a potential for immunogenicity with cemiplimab. Five out of 398 patients (1.3%) administered cemiplimab developed treatment-emergent antibodies, with 1 out of 398 patients (0.3%) exhibiting persistent antibody responses. No neutralizing antibodies have been observed. There was no evidence of an altered pharmacokinetic or safety profile with anti-cemiplimab antibody development.

In the few patients who developed anti-cemiplimab antibodies, there was no evidence of altered PK profile. The presence of ADA was not associated with significant AEs or irAEs.

ADA was rarely associated to cemiplimab treatment at the present time.

Safety in special populations

Table 98: Distribution of AEs, SAEs and deaths according to age group (Pool 2 - all monotherapy patients excluding HCC)

MedDRA Terms	Age <65 Number = 105 (percentage)	Age 65-74 Number = 90 (percentage)	Age 75-84 Number = 81 (percentage)	Age 85+ Number = 21 (percentage)
Total AEs	101 (96.2%)	88 (97.8%)	81 (100%)	21 (100%)
Serious AEs – Total	22 (21.0%)	23 (25.6%)	34 (42.0%)	13 (61.9%)
- Fatal	1 (1.0%)	2 (2.2%)	2 (2.5%)	2 (9.5%)
- Hospitalization/prolong existing hospitalization	22 (21.0%)	22 (24.4%)	32 (39.5%)	13 (61.9%)
- Life-threatening	1 (1.0%)	1 (1.1%)	5 (6.2%)	3 (14.3%)
- Disability/incapacity	2 (1.9%)	0	0	1 (4.8%)
- Other (medically significant)	0	2 (2.2%)	2 (2.5%)	0
AE leading to drop-out	4 (3.8%)	4 (4.4%)	8 (9.9%)	3 (14.3%)
Psychiatric disorders	17 (16.2%)	14 (15.6%)	12 (14.8%)	2 (9.5%)
Nervous system disorders	38 (36.2%)	23 (25.6%)	23 (28.4%)	7 (33.3%)
Accidents and injuries[a]	26 (24.8%)	26 (28.9%)	15 (18.5%)	5 (23.8%)
Cardiac disorders	1 (1.0%)	2 (2.2%)	9 (11.1%)	4 (19.0%)
Vascular disorders	18 (17.1%)	15 (16.7%)	9 (11.1%)	5 (23.8%)
Cerebrovascular disorders[b]	N/A	N/A	N/A	N/A
Infections and infestations	48 (45.7%)	37 (41.1%)	46 (56.8%)	12 (57.1%)
Anticholinergic syndrome	0	0	0	0
Quality of life decreased[c]	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[d]	18 (17.1%)	11 (12.2%)	8 (9.9%)	5 (23.8%)
<other AE appearing more frequently in older patients>	N/A	N/A	N/A	N/A

Source: Table 140a_p1; 140b_p1; 140c_p1; 140d_p1; 140e_p1

a) Identified using the MedDRA SOC of "Injury, poisoning and procedural complications".
b) Covered under MedDRA SOCs of "Nervous system disorders" and "Vascular disorders".
c) Identified using the following MedDRA PTs (Quality of life decreased, Impaired quality of life, Performance status decreased and Eastern Cooperative Oncology Group performance status worsened)
d) Identified using the following MedDRA PTs (Orthostatic hypotension, Fall, Loss of consciousness, Syncope, Dizziness, Ataxia, Pathological fracture, Hip fracture, Wrist fracture, Sternal fracture, Cervical vertebral fracture, Clavicle fracture, Femur fracture, Lower limb fracture, Lumbar vertebral fracture, Patella fracture, Radius fracture, Rib fracture, Stress fracture and Fracture)

Table 99: Summary of treatment-emergent adverse events by system organ class, preferred term, and NCI grade in patients ≥75 - All monotherapy patients (excluding HCC) Safety analysis set

System Organ Class, n (%) Preferred Term, n (%)	Total (N=102) All Grades	Grades 3/4/5	Related Any Grade	Related Grade 3/4/5
Cardiac disorders	13 (12.7%)	7 (6.9%)	2 (2.0%)	2 (2.0%)
Atrial fibrillation	3 (2.9%)	1 (1.0%)	0	0
Myocardial infarction	2 (2.0%)	2 (2.0%)	0	0
Palpitations	2 (2.0%)	0	0	0
Angina pectoris	1 (1.0%)	1 (1.0%)	0	0
Atrioventricular block complete	1 (1.0%)	1 (1.0%)	0	0
Cardiac failure	1 (1.0%)	0	0	0
Extrasystoles	1 (1.0%)	0	0	0
Myocarditis	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)
Pericarditis	1 (1.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)
Sinus bradycardia	1 (1.0%)	0	0	0

Data cut-off as of June 30, 2018

All adverse events were coded using MedDRA Version 20.0. 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.

Intrinsic factors

Table 100: Summary of most frequent treatment-emergent adverse events (≥5% patients in total group) by system organ class and preferred term and by age group (Safety analysis set) - All monotherapy patients (excluding HCC patients)

System Organ Class Preferred Term, n (%)	Age: <65 years (N=105)	Age: 65 to 74 years (N=90)	Age: 75 to 84 years (N=81)	Age: >= 85 years (N=21)	Total (N=297)
Total number of TEAEs	913	827	635	190	2565
Number of Patients with any TEAE, n (%)	101 (96.2%)	88 (97.8%)	81 (100%)	21 (100%)	291 (98.0%)
Gastrointestinal disorders					
Diarrhoea	19 (18.1%)	23 (25.6%)	16 (19.8%)	6 (28.6%)	64 (21.5%)
Nausea	25 (23.8%)	16 (17.8%)	11 (13.6%)	2 (9.5%)	54 (18.2%)
Constipation	19 (18.1%)	11 (12.2%)	8 (9.9%)	2 (9.5%)	40 (13.5%)
Vomiting	15 (14.3%)	8 (8.9%)	4 (4.9%)	3 (14.3%)	30 (10.1%)
Abdominal pain	10 (9.5%)	5 (5.6%)	8 (9.9%)	2 (9.5%)	25 (8.4%)
Dry mouth	6 (5.7%)	4 (4.4%)	6 (7.4%)	1 (4.8%)	17 (5.7%)
General disorders and administration site conditions					
Fatigue	39 (37.1%)	26 (28.9%)	22 (27.2%)	6 (28.6%)	93 (31.3%)
Oedema peripheral	6 (5.7%)	8 (8.9%)	5 (6.2%)	3 (14.3%)	22 (7.4%)
Pyrexia	5 (4.8%)	4 (4.4%)	4 (4.9%)	2 (9.5%)	15 (5.1%)
Infections and infestations					
Upper respiratory tract infection	12 (11.4%)	4 (4.4%)	5 (6.2%)	0	21 (7.1%)
Infections and infestations					
Urinary tract infection	5 (4.8%)	2 (2.2%)	10 (12.3%)	3 (14.3%)	20 (6.7%)
Skin infection	3 (2.9%)	6 (6.7%)	4 (4.9%)	2 (9.5%)	15 (5.1%)
Skin and subcutaneous tissue disorders					
Pruritus	12 (11.4%)	15 (16.7%)	15 (18.5%)	5 (23.8%)	47 (15.8%)
Rash	7 (6.7%)	13 (14.4%)	11 (13.6%)	0	31 (10.4%)
Rash maculo-papular	11 (10.5%)	9 (10.0%)	6 (7.4%)	2 (9.5%)	28 (9.4%)
Dry skin	6 (5.7%)	6 (6.7%)	7 (8.6%)	0	19 (6.4%)
Musculoskeletal and connective tissue disorders					
Arthralgia	15 (14.3%)	7 (7.8%)	11 (13.6%)	4 (19.0%)	37 (12.5%)
Pain in extremity	12 (11.4%)	7 (7.8%)	0	2 (9.5%)	21 (7.1%)
Back pain	2 (1.9%)	6 (6.7%)	7 (8.6%)	4 (19.0%)	19 (6.4%)
Myalgia	7 (6.7%)	5 (5.6%)	5 (6.2%)	0	17 (5.7%)
Metabolism and nutrition disorders					
Decreased appetite	17 (16.2%)	8 (8.9%)	8 (9.9%)	2 (9.5%)	35 (11.8%)
Metabolism and nutrition disorders					
Hypokalaemia	8 (7.6%)	3 (3.3%)	5 (6.2%)	2 (9.5%)	18 (6.1%)
Respiratory, thoracic and mediastinal disorders					
Cough	14 (13.3%)	13 (14.4%)	12 (14.8%)	4 (19.0%)	43 (14.5%)
Dyspnoea	4 (3.8%)	11 (12.2%)	6 (7.4%)	1 (4.8%)	22 (7.4%)
Pneumonitis	3 (2.9%)	7 (7.8%)	5 (6.2%)	1 (4.8%)	16 (5.4%)
Nervous system disorders					
Headache	12 (11.4%)	5 (5.6%)	7 (8.6%)	2 (9.5%)	26 (8.8%)
Dizziness	8 (7.6%)	4 (4.4%)	4 (4.9%)	2 (9.5%)	18 (6.1%)
Investigations					
Blood creatinine increased	6 (5.7%)	5 (5.6%)	8 (9.9%)	1 (4.8%)	20 (6.7%)
Alanine aminotransferase increased	6 (5.7%)	4 (4.4%)	2 (2.5%)	4 (19.0%)	16 (5.4%)
Aspartate aminotransferase increased	5 (4.8%)	4 (4.4%)	4 (4.9%)	2 (9.5%)	15 (5.1%)

Injury, poisoning and procedural complications					
Fall	7 (6.7%)	7 (7.8%)	4 (4.9%)	3 (14.3%)	21 (7.1%)
Blood and lymphatic system disorders					
Anaemia	13 (12.4%)	15 (16.7%)	4 (4.9%)	2 (9.5%)	34 (11.4%)
Vascular disorders					
Hypertension	6 (5.7%)	5 (5.6%)	2 (2.5%)	3 (14.3%)	16 (5.4%)
Psychiatric disorders					
Insomnia	7 (6.7%)	7 (7.8%)	2 (2.5%)	1 (4.8%)	17 (5.7%)
Endocrine disorders					
Hypothyroidism	11 (10.5%)	9 (10.0%)	7 (8.6%)	3 (14.3%)	30 (10.1%)

Data cut-off as of June 30, 2018.
TEAE: Treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 20.0.
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.

There were more upper respiratory tract infections (10.9%), headache (12.7%), and dizziness (10.9%) in the <65 years group. In the older groups over 65 years, cough (13-16%) and increased creatinine (4-11.6%) were more frequently observed.

Gender

There was a high proportion of male patients in all 3 Pools (75.8% of the monotherapy patients).

Table 101: Summary of most frequent treatment-emergent adverse events (≥5% patients in total group) by system organ class and preferred term and by sex (Safety analysis set) - all monotherapy (excluding HCC patients)

System Organ Class Preferred Term, n (%)	Male (N=225)	Female (N=72)	Total (N=297)
Total number of TEAEs	1935	630	2565
Number of Patients with any TEAE, n (%)	223 (99.1%)	68 (94.4%)	291 (98.0%)
Gastrointestinal disorders			
Diarrhoea	41 (18.2%)	23 (31.9%)	64 (21.5%)
Nausea	38 (16.9%)	16 (22.2%)	54 (18.2%)
Constipation	34 (15.1%)	6 (8.3%)	40 (13.5%)
Vomiting	19 (8.4%)	11 (15.3%)	30 (10.1%)
Abdominal pain	16 (7.1%)	9 (12.5%)	25 (8.4%)
Dry mouth	16 (7.1%)	1 (1.4%)	17 (5.7%)
General disorders and administration site conditions			
Fatigue	66 (29.3%)	27 (37.5%)	93 (31.3%)
Oedema peripheral	16 (7.1%)	6 (8.3%)	22 (7.4%)
Pyrexia	10 (4.4%)	5 (6.9%)	15 (5.1%)
Infections and infestations			
Upper respiratory tract infection	14 (6.2%)	7 (9.7%)	21 (7.1%)
Urinary tract infection	12 (5.3%)	8 (11.1%)	20 (6.7%)
Infections and infestations			
Skin infection	12 (5.3%)	3 (4.2%)	15 (5.1%)
Skin and subcutaneous tissue disorders			
Pruritus	33 (14.7%)	14 (19.4%)	47 (15.8%)
Rash	26 (11.6%)	5 (6.9%)	31 (10.4%)
Rash maculo-papular	22 (9.8%)	6 (8.3%)	28 (9.4%)
Dry skin	15 (6.7%)	4 (5.6%)	19 (6.4%)
Musculoskeletal and connective tissue disorders			
Arthralgia	27 (12.0%)	10 (13.9%)	37 (12.5%)
Pain in extremity	12 (5.3%)	9 (12.5%)	21 (7.1%)
Back pain	12 (5.3%)	7 (9.7%)	19 (6.4%)
Myalgia	12 (5.3%)	5 (6.9%)	17 (5.7%)
Metabolism and nutrition disorders			
Decreased appetite	27 (12.0%)	8 (11.1%)	35 (11.8%)
Hypokalaemia	10 (4.4%)	8 (11.1%)	18 (6.1%)

Respiratory, thoracic and mediastinal disorders			
Cough	28 (12.4%)	15 (20.8%)	43 (14.5%)
Dyspnoea	16 (7.1%)	6 (8.3%)	22 (7.4%)
Pneumonitis	13 (5.8%)	3 (4.2%)	16 (5.4%)
Nervous system disorders			
Headache	19 (8.4%)	7 (9.7%)	26 (8.8%)
Dizziness	14 (6.2%)	4 (5.6%)	18 (6.1%)
Investigations			
Blood creatinine increased	15 (6.7%)	5 (6.9%)	20 (6.7%)
Alanine aminotransferase increased	12 (5.3%)	4 (5.6%)	16 (5.4%)
Aspartate aminotransferase increased	10 (4.4%)	5 (6.9%)	15 (5.1%)
Injury, poisoning and procedural complications			
Fall	16 (7.1%)	5 (6.9%)	21 (7.1%)
Blood and lymphatic system disorders			
Anaemia	25 (11.1%)	9 (12.5%)	34 (11.4%)
Vascular disorders			
Hypertension	13 (5.8%)	3 (4.2%)	16 (5.4%)
Psychiatric disorders			
Insomnia	13 (5.8%)	4 (5.6%)	17 (5.7%)
Endocrine disorders			
Hypothyroidism	22 (9.8%)	8 (11.1%)	30 (10.1%)

Data cut-off as of June 30, 2018.
TEAE: Treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 20.0.
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.

Adverse events according to sex show increased risk of diarrhea (31.9% vs 18.2%), cough (20.8% vs 12.4%), UTIs (11.1% vs. 5.3%), pain in extremity (12.5% vs. 5.3%) in female patients compared to male patients.

Ethnicity

Adverse events according to ethnicity is very difficult to assess as the vast majority of patients were categorized as not hispanic or latino (n=276) and only 17 patients were in the one other category (hispanic or latino). There are no obvious safety concerns but considering the small sample size of the comparator group, no firm conclusions can be made from these data.

Race

For monotherapy patients, no conclusions can be drawn with regard to race as the majority of patients were White (n=280) and the comparable groups contained 5 or 6 patients each. In the larger population of Pool 3, there was no apparent difference in the AE profile with regard to race. However, no obvious safety concerns are raised.

Table 102: Summary of most frequent treatment-emergent adverse events (≥5% patients in total group) by system organ class and preferred term and by race (Safety analysis set) - all monotherapy patients (excluding HCC patients)

Infections and infestations					
Urinary tract infection	20 (7.1%)	0	0	0	20 (6.7%)
Skin infection	15 (5.4%)	0	0	0	15 (5.1%)
Skin and subcutaneous tissue disorders					
Pruritus	44 (15.7%)	1 (20.0%)	2 (33.3%)	0	47 (15.8%)
Rash	31 (11.1%)	0	0	0	31 (10.4%)
Rash maculo-papular	27 (9.6%)	1 (20.0%)	0	0	28 (9.4%)
Dry skin	18 (6.4%)	1 (20.0%)	0	0	19 (6.4%)
Musculoskeletal and connective tissue disorders					
Arthralgia	35 (12.5%)	1 (20.0%)	0	1 (16.7%)	37 (12.5%)
Pain in extremity	21 (7.5%)	0	0	0	21 (7.1%)
Back pain	18 (6.4%)	0	0	1 (16.7%)	19 (6.4%)
Myalgia	17 (6.1%)	0	0	0	17 (5.7%)
Metabolism and nutrition disorders					
Decreased appetite	33 (11.8%)	0	2 (33.3%)	0	35 (11.8%)

System Organ Class Preferred Term, n (%)	White (N=280)	Black or African American (N=5)	Asian (N=6)	Other (N=6)	Total (N=297)
Total number of TEAEs	2480	38	15	32	2565
Number of Patients with any TEAE, n (%)	276 (98.6%)	5 (100%)	5 (83.3%)	5 (83.3%)	291 (98.0%)
Gastrointestinal disorders					
Diarrhoea	61 (21.8%)	1 (20.0%)	1 (16.7%)	1 (16.7%)	64 (21.5%)
Nausea	52 (18.6%)	1 (20.0%)	1 (16.7%)	0	54 (18.2%)
Constipation	38 (13.6%)	0	1 (16.7%)	1 (16.7%)	40 (13.5%)
Vomiting	29 (10.4%)	1 (20.0%)	0	0	30 (10.1%)
Abdominal pain	24 (8.6%)	1 (20.0%)	0	0	25 (8.4%)
Dry mouth	17 (6.1%)	0	0	0	17 (5.7%)
General disorders and administration site conditions					
Fatigue	88 (31.4%)	2 (40.0%)	1 (16.7%)	2 (33.3%)	93 (31.3%)
Oedema peripheral	22 (7.9%)	0	0	0	22 (7.4%)
Pyrexia	15 (5.4%)	0	0	0	15 (5.1%)
Infections and infestations					
Upper respiratory tract infection	20 (7.1%)	1 (20.0%)	0	0	21 (7.1%)
Metabolism and nutrition disorders					
Hypokalaemia	16 (5.7%)	1 (20.0%)	0	1 (16.7%)	18 (6.1%)
Respiratory, thoracic and mediastinal disorders					
Cough	42 (15.0%)	0	0	1 (16.7%)	43 (14.5%)
Dyspnoea	22 (7.9%)	0	0	0	22 (7.4%)
Pneumonitis	15 (5.4%)	1 (20.0%)	0	0	16 (5.4%)
Nervous system disorders					
Headache	25 (8.9%)	0	0	1 (16.7%)	26 (8.8%)
Dizziness	17 (6.1%)	0	0	1 (16.7%)	18 (6.1%)
Investigations					
Blood creatinine increased	19 (6.8%)	0	0	1 (16.7%)	20 (6.7%)
Alanine aminotransferase increased	16 (5.7%)	0	0	0	16 (5.4%)
Aspartate aminotransferase increased	15 (5.4%)	0	0	0	15 (5.1%)

Extrinsic factors

Region

Most patients were from North America (101 patients in Pool 1; 371 patients in Pool 3), followed by Europe (22 patients in Pool 1; 119 patients in Pool 3), and "Others" (40 patients in Pool 1; 44 patients in Pool 3).

Adverse events according to region were presented with 3 categories: North America (n=184), Europe (n=58) and others (n=55). GI disorders, fatigue, cough and hypothyroidism were increased in the North American group. No major safety concern arise considering the differences of sample size (data not shown).

Prior systemic therapy

Updated safety data show that the adverse events did not increase clinically significantly with increasing lines of prior systemic therapy (data not shown).

Prior radiotherapy

It is noted that more than 2/3 of the patients had 0 or 1 prior radiotherapy. There are no apparent correlation between increasing number of radiotherapy and adverse events, however, the limited number of patients who received more than 2 numbers of radiotherapy should be taken into consideration. There are no major safety concerns regarding increasing risk of AEs with increasing prior therapies (data not shown).

Safety related to drug-drug interactions and other interactions

No PK drug-drug interaction studies have been submitted (see assessment of clinical pharmacology).

Discontinuation due to adverse events

Table 103: Summary of treatment-related treatment-emergent adverse events (Safety analysis set)

	Pool 1 All CSCC Patients (N=219)	Pool 2 All Monotherapy Patients (excluding HCC) (N=297)	Pool 3 All Patients (N=591)
Number of treatment-related TEAEs	575	729	1432
Number of NCI grade 3/4/5 treatment-related TEAEs	35	42	97
Number of serious treatment-related TEAEs	25	29	60
Number of Patients with any treatment-related TEAE, n (%)	157 (71.7%)	212 (71.4%)	429 (72.6%)
Number of Patients with any NCI grade 3/4/5 treatment-related TEAE, n (%)	27 (12.3%)	33 (11.1%)	77 (13.0%)
Number of Patients with any serious treatment-related TEAE, n (%)	18 (8.2%)	22 (7.4%)	50 (8.5%)
Number of Patients who discontinued study treatment due to treatment-related TEAE, n (%)	15 (6.8%)	18 (6.1%)	33 (5.6%)
Number of Patients with any treatment-related TEAE leading to a drug interruption/delay, n (%)	36 (16.4%)	49 (16.5%)	93 (15.7%)
Number of Patients with any treatment-related TEAE leading to a dose reduction, n (%)	2 (0.9%)	3 (1.0%)	7 (1.2%)
Number of Patients with any treatment-related TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	2 (0.9%)	3 (1.0%)	7 (1.2%)
Number of Patients with any treatment-related TEAE resulting in death, n (%)	1 (0.5%)	2 (0.7%)	6 (1.0%)

Data cut-off as of June 30, 2018.
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.

AEs leading to withdrawal

Treatment-emergent adverse events leading to discontinuation

Table 104: Summary of treat-emergent adverse events resulting in treatment discontinuation by system organ class and preferred term (Safety analysis set)

System Organ Class, n (%) Preferred Term, n (%)	Pool 1 - All CSCC Patients (N=163)	Pool 2 - All Monotherapy Patients (Excluding HCC) (N=240)	Pool 3 - All Patients (N=534)
Total number of TEAEs resulting in treatment discontinuation	13	16	39
Number of Patients with any TEAE resulting in treatment discontinuation, n (%)	8 (4.9%)	11 (4.6%)	31 (5.8%)
Respiratory, thoracic, and mediastinal disorders	3 (1.8%)	4 (1.7%)	9 (1.7%)
Pneumonitis	2 (1.2%)	3 (1.3%)	7 (1.3%)
Cough	1 (0.6%)	1 (0.4%)	1 (0.2%)
Pleural effusion	0	0	1 (0.2%)
Hepatobiliary disorders	1 (0.6%)	1 (0.4%)	5 (0.9%)
Autoimmune hepatitis	0	0	3 (0.6%)
Hepatic failure	0	0	1 (0.2%)
Hepatitis	1 (0.6%)	1 (0.4%)	1 (0.2%)
Infections and infestations	1 (0.6%)	1 (0.4%)	5 (0.9%)
Liver abscess	0	0	1 (0.2%)
Meningitis	0	0	1 (0.2%)
Meningitis aseptic	1 (0.6%)	1 (0.4%)	1 (0.2%)
Pneumonia	0	0	1 (0.2%)
Infections and infestations			
Pneumonia escherichia	0	0	1 (0.2%)
Injury, poisoning, and procedural complications	0	0	3 (0.6%)
Infusion related reaction	0	0	2 (0.4%)
Femur fracture	0	0	1 (0.2%)
Lower limb fracture	0	0	1 (0.2%)
Investigations	1 (0.6%)	1 (0.4%)	3 (0.6%)
Blood bilirubin increased	0	0	2 (0.4%)
Alanine aminotransferase increased	1 (0.6%)	1 (0.4%)	1 (0.2%)
Aspartate aminotransferase increased	1 (0.6%)	1 (0.4%)	1 (0.2%)
Blood alkaline phosphatase increased	1 (0.6%)	1 (0.4%)	1 (0.2%)
Musculoskeletal and connective tissue disorders	2 (1.2%)	3 (1.3%)	3 (0.6%)
Arthralgia	0	1 (0.4%)	1 (0.2%)
Muscular weakness	1 (0.6%)	1 (0.4%)	1 (0.2%)
Neck pain	1 (0.6%)	1 (0.4%)	1 (0.2%)
Cardiac disorders	1 (0.6%)	1 (0.4%)	2 (0.4%)
Autoimmune myocarditis	1 (0.6%)	1 (0.4%)	1 (0.2%)
Cardiac disorders			
Ventricular arrhythmia	0	0	1 (0.2%)
Nervous system disorders	1 (0.6%)	2 (0.8%)	2 (0.4%)
Complex regional pain syndrome	1 (0.6%)	1 (0.4%)	1 (0.2%)
Paraneoplastic encephalomyelitis	0	1 (0.4%)	1 (0.2%)
Gastrointestinal disorders	0	0	1 (0.2%)
Colitis	0	0	1 (0.2%)
Metabolism and nutrition disorders	0	0	1 (0.2%)
Diabetes mellitus	0	0	1 (0.2%)
Psychiatric disorders	1 (0.6%)	1 (0.4%)	1 (0.2%)
Confusional state	1 (0.6%)	1 (0.4%)	1 (0.2%)

System Organ Class, n (%) Preferred Term, n (%)	Pool 1 - All CSCC Patients (N=163)	Pool 2 - All Monotherapy Patients (Excluding HCC) (N=240)	Pool 3 - All Patients (N=534)
Renal and urinary disorders	0	0	1 (0.2%)
Acute kidney injury	0	0	1 (0.2%)

Abbreviations: AE, adverse event; CSCC, cutaneous squamous cell carcinoma; HCC, hepatocellular carcinoma; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event

Data cut-off as of 02 Oct 2017 for CSCC patients with Cemiplimab monotherapy in Study 1423; Data cut-off as of 01 Sep 2017 for all other patients in Study 1423; Data cut-off as of 27 Oct 2017 for all patients in Study 1540.

All AEs were coded using MedDRA Version 20.0.

A patient is counted only once for multiple occurrences within a SOC/PT.

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.

Serious adverse events leading to discontinuation

Table 105: Summary of treatment-emergent adverse events resulting in treatment discontinuation (Safety analysis set)

	Pool 1 All CSCC Patients (N=219)	Pool 2 All Monotherapy Patients (excluding HCC) (N=297)	Pool 3 All Patients (N=591)
Number of Patients with any TEAE leading to treatment discontinuation, n (%)	16 (7.3%)	19 (6.4%)	40 (6.8%)
Number of Patients with any treatment-related TEAE leading to treatment discontinuation, n (%)	15 (6.8%)	18 (6.1%)	33 (5.6%)
Number of Patients with any NCI grade 3/4/5 TEAE leading to treatment discontinuation, n (%)	11 (5.0%)	13 (4.4%)	30 (5.1%)
Number of Patients with any treatment-related NCI grade 3/4/5 TEAE leading to treatment discontinuation, n (%)	10 (4.6%)	12 (4.0%)	24 (4.1%)
Number of Patients with any serious TEAE leading to treatment discontinuation, n (%)	10 (4.6%)	12 (4.0%)	26 (4.4%)
Number of Patients with any treatment-related serious TEAE leading to treatment discontinuation, n (%)	9 (4.1%)	11 (3.7%)	22 (3.7%)

Data cut-off as of June 30, 2018.

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 106: Summary of treatment-related serious treatment-emergent adverse events resulting in treatment discontinuation by system organ class and preferred term (Safety analysis set)

System Organ Class, n (%) Preferred Term, n (%)	Pool 1 All CSCC Patients (N=163)	Pool 2 All Monotherapy Patients (excluding HCC) (N=240)	Pool 3 All Patients (N=534)
Total number of treatment-related serious TEAEs resulting in treatment discontinuation	4	6	17
Number of Patients with any treatment-related serious TEAE resulting in treatment discontinuation, n (%)	4 (2.5%)	6 (2.5%)	17 (3.2%)
Respiratory, thoracic and mediastinal disorders	2 (1.2%)	3 (1.3%)	6 (1.1%)
Pneumonitis	2 (1.2%)	3 (1.3%)	6 (1.1%)
Hepatobiliary disorders	0	0	3 (0.6%)
Autoimmune hepatitis	0	0	2 (0.4%)
Hepatic failure	0	0	1 (0.2%)
Infections and infestations	1 (0.6%)	1 (0.4%)	2 (0.4%)
Meningitis	0	0	1 (0.2%)
Meningitis aseptic	1 (0.6%)	1 (0.4%)	1 (0.2%)
Cardiac disorders	1 (0.6%)	1 (0.4%)	1 (0.2%)
Autoimmune myocarditis	1 (0.6%)	1 (0.4%)	1 (0.2%)
Gastrointestinal disorders	0	0	1 (0.2%)
Colitis	0	0	1 (0.2%)
Injury, poisoning and procedural complications	0	0	1 (0.2%)
Infusion related reaction	0	0	1 (0.2%)
Metabolism and nutrition disorders	0	0	1 (0.2%)
Diabetes mellitus	0	0	1 (0.2%)
Nervous system disorders	0	1 (0.4%)	1 (0.2%)
Paraneoplastic encephalomyelitis	0	1 (0.4%)	1 (0.2%)
Renal and urinary disorders	0	0	1 (0.2%)
Acute kidney injury	0	0	1 (0.2%)

Data cut-off as of Oct 2, 2017 for CSCC patients with Cemiplimab monotherapy in Study 1423; Data cut-off as of Sep 1, 2017 for all other patients in Study 1423; Data cut-off as of Oct 27, 2017 for all patients in Study 1540.
TEAE: Treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 20.0.
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.

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Table 107: Summary of treatment-emergent adverse events resulting in treatment discontinuation by system organ class and preferred term (Safety analysis set)

System Organ Class, n (%) Preferred Term, n (%)	CSCC Patients Cemiplimab: 350 mg Q3W (N=56)	All CSCC Patients (N=219)	Monotherapy Patients (excluding HCC) (N=297)
Total number of TEAEs resulting in treatment discontinuation	3	22	25
Number of Patients with any TEAE resulting in treatment discontinuation, n (%)	3 (5.4%)	16 (7.3%)	19 (6.4%)
Respiratory, thoracic and mediastinal disorders	0	6 (2.7%)	7 (2.4%)
Pneumonitis	0	5 (2.3%)	6 (2.0%)
Cough	0	1 (0.5%)	1 (0.3%)
Musculoskeletal and connective tissue disorders	1 (1.8%)	4 (1.8%)	5 (1.7%)
Arthralgia	0	1 (0.5%)	2 (0.7%)
Muscular weakness	0	1 (0.5%)	1 (0.3%)
Neck pain	0	1 (0.5%)	1 (0.3%)
Soft tissue necrosis	1 (1.8%)	1 (0.5%)	1 (0.3%)
Nervous system disorders	1 (1.8%)	2 (0.9%)	3 (1.0%)
Complex regional pain syndrome	0	1 (0.5%)	1 (0.3%)
Lethargy	1 (1.8%)	1 (0.5%)	1 (0.3%)
Paraneoplastic encephalomyelitis	0	0	1 (0.3%)
Infections and infestations	0	2 (0.9%)	2 (0.7%)
Encephalitis	0	1 (0.5%)	1 (0.3%)
Meningitis aseptic	0	1 (0.5%)	1 (0.3%)
Skin and subcutaneous tissue disorders	1 (1.8%)	2 (0.9%)	2 (0.7%)
Psoriasis	1 (1.8%)	1 (0.5%)	1 (0.3%)
Rash maculo-papular	0	1 (0.5%)	1 (0.3%)
Gastrointestinal disorders	0	1 (0.5%)	1 (0.3%)
Proctitis	0	1 (0.5%)	1 (0.3%)

System Organ Class, n (%) Preferred Term, n (%)	CSCC Patients Cemiplimab: 350 mg Q3W (N=56)	All CSCC Patients (N=219)	Monotherapy Patients (excluding HCC) (N=297)
Hepatobiliary disorders	0	1 (0.5%)	1 (0.3%)
Hepatitis	0	1 (0.5%)	1 (0.3%)
Investigations	0	1 (0.5%)	1 (0.3%)
Alanine aminotransferase increased	0	1 (0.5%)	1 (0.3%)
Aspartate aminotransferase increased	0	1 (0.5%)	1 (0.3%)
Blood alkaline phosphatase increased	0	1 (0.5%)	1 (0.3%)
Psychiatric disorders	0	1 (0.5%)	1 (0.3%)
Confusional state	0	1 (0.5%)	1 (0.3%)

Data cut-off as of June 30, 2018.
TEAE: Treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 20.0.
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 monotherapy patients (excluding HCC) group. Within each SOC, PTs are sorted by decreasing frequency in the monotherapy patients (excluding HCC) group.

Approximately 6% of patients in the monotherapy pool discontinued treatment. Patients discontinued cemiplimab due to pneumonitis, and a number of rare events comprising the musculoskeletal, cardiac, and CNS areas.

AEs leading to dose reduction or interruption

Table 108: Summary of treatment-emergent adverse events resulting in drug interrupted delayed by system organ class and preferred term (Safety analysis set) - All monotherapy patients (excluding HCC patients)

System Organ Class, n (%) Preferred Term, n (%)	CSCC Patients (N=219)	Non-CSCC Patients (N=78)	Total (N=297)
Total number of TEAEs resulting in drug interrupted/delayed	150	37	187
Number of Patients with any TEAE resulting in drug interrupted/delayed, n (%)	72 (32.9%)	24 (30.8%)	96 (32.3%)
Infections and infestations	24 (11.0%)	5 (6.4%)	29 (9.8%)
Pneumonia	5 (2.3%)	1 (1.3%)	6 (2.0%)
Cellulitis	5 (2.3%)	0	5 (1.7%)
Urinary tract infection	5 (2.3%)	0	5 (1.7%)
Sinusitis	3 (1.4%)	0	3 (1.0%)
Bronchitis	2 (0.9%)	0	2 (0.7%)
Herpes zoster	2 (0.9%)	0	2 (0.7%)
Sepsis	2 (0.9%)	0	2 (0.7%)
Viral upper respiratory tract infection	2 (0.9%)	0	2 (0.7%)
Abscess limb	1 (0.5%)	0	1 (0.3%)
Bacteraemia	0	1 (1.3%)	1 (0.3%)
Diverticulitis	0	1 (1.3%)	1 (0.3%)
Extradural abscess	1 (0.5%)	0	1 (0.3%)
Fungal skin infection	1 (0.5%)	0	1 (0.3%)
Groin infection	1 (0.5%)	0	1 (0.3%)
Infections and infestations			
Pneumonia influenzal	1 (0.5%)	0	1 (0.3%)
Pneumonia streptococcal	0	1 (1.3%)	1 (0.3%)
Psoas abscess	1 (0.5%)	0	1 (0.3%)
Skin infection	1 (0.5%)	0	1 (0.3%)
Soft tissue infection	1 (0.5%)	0	1 (0.3%)
Staphylococcal infection	1 (0.5%)	0	1 (0.3%)
Upper respiratory tract infection	0	1 (1.3%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	14 (6.4%)	6 (7.7%)	20 (6.7%)
Pneumonitis	7 (3.2%)	3 (3.8%)	10 (3.4%)
Cough	1 (0.5%)	2 (2.6%)	3 (1.0%)
Dyspnoea	2 (0.9%)	0	2 (0.7%)
Hypoxia	1 (0.5%)	0	1 (0.3%)
Idiopathic pulmonary fibrosis	1 (0.5%)	0	1 (0.3%)
Lung infiltration	0	1 (1.3%)	1 (0.3%)
Pleural effusion	1 (0.5%)	0	1 (0.3%)
Pulmonary oedema	1 (0.5%)	0	1 (0.3%)
Respiratory failure	1 (0.5%)	0	1 (0.3%)
Gastrointestinal disorders	12 (5.5%)	3 (3.8%)	15 (5.1%)
Diarrhoea	9 (4.1%)	0	9 (3.0%)
Abdominal pain	1 (0.5%)	1 (1.3%)	2 (0.7%)
Abdominal pain upper	1 (0.5%)	0	1 (0.3%)
Ascites	0	1 (1.3%)	1 (0.3%)
Colitis	1 (0.5%)	0	1 (0.3%)
Duodenal ulcer haemorrhage	1 (0.5%)	0	1 (0.3%)
Gastrointestinal haemorrhage	0	1 (1.3%)	1 (0.3%)
Mouth ulceration	1 (0.5%)	0	1 (0.3%)
Nausea	1 (0.5%)	0	1 (0.3%)
Vomiting	1 (0.5%)	0	1 (0.3%)
Injury, poisoning and procedural complications	10 (4.6%)	2 (2.6%)	12 (4.0%)
Infusion related reaction	7 (3.2%)	1 (1.3%)	8 (2.7%)
Fall	1 (0.5%)	1 (1.3%)	2 (0.7%)
Hip fracture	2 (0.9%)	0	2 (0.7%)
Limb injury	1 (0.5%)	0	1 (0.3%)
Radius fracture	1 (0.5%)	0	1 (0.3%)
Investigations	8 (3.7%)	3 (3.8%)	11 (3.7%)
Alanine aminotransferase increased	3 (1.4%)	0	3 (1.0%)
Aspartate aminotransferase increased	2 (0.9%)	1 (1.3%)	3 (1.0%)
Blood creatinine increased	2 (0.9%)	1 (1.3%)	3 (1.0%)
Blood alkaline phosphatase increased	2 (0.9%)	0	2 (0.7%)
Blood bilirubin increased	0	1 (1.3%)	1 (0.3%)
Blood lactate dehydrogenase increased	1 (0.5%)	0	1 (0.3%)
Influenza A virus test positive	1 (0.5%)	0	1 (0.3%)
International normalised ratio increased	1 (0.5%)	0	1 (0.3%)
Lipase increased	1 (0.5%)	0	1 (0.3%)
Weight decreased	0	1 (1.3%)	1 (0.3%)
Musculoskeletal and connective tissue disorders	9 (4.1%)	1 (1.3%)	10 (3.4%)
Arthralgia	5 (2.3%)	1 (1.3%)	6 (2.0%)
Muscle spasms	2 (0.9%)	0	2 (0.7%)
Musculoskeletal pain	1 (0.5%)	0	1 (0.3%)
Pain in extremity	1 (0.5%)	0	1 (0.3%)
Polyarthritis	1 (0.5%)	0	1 (0.3%)

Blood and lymphatic system disorders	6 (2.7%)	2 (2.6%)	8 (2.7%)
Anaemia	3 (1.4%)	1 (1.3%)	4 (1.3%)
Lymphopenia	2 (0.9%)	0	2 (0.7%)
Thrombocytopenia	1 (0.5%)	1 (1.3%)	2 (0.7%)
Immune thrombocytopenic purpura	0	1 (1.3%)	1 (0.3%)
Leukopenia	0	1 (1.3%)	1 (0.3%)
Neutropenia	0	1 (1.3%)	1 (0.3%)
General disorders and administration site conditions	5 (2.3%)	3 (3.8%)	8 (2.7%)
Fatigue	3 (1.4%)	1 (1.3%)	4 (1.3%)
Pyrexia	2 (0.9%)	0	2 (0.7%)
Catheter site pain	0	1 (1.3%)	1 (0.3%)
Influenza like illness	1 (0.5%)	0	1 (0.3%)
Oedema peripheral	0	1 (1.3%)	1 (0.3%)
Nervous system disorders	3 (1.4%)	2 (2.6%)	5 (1.7%)
Brain oedema	1 (0.5%)	0	1 (0.3%)
Cognitive disorder	0	1 (1.3%)	1 (0.3%)
Facial nerve disorder	0	1 (1.3%)	1 (0.3%)
Peripheral motor neuropathy	1 (0.5%)	0	1 (0.3%)
Syncope	1 (0.5%)	0	1 (0.3%)
Skin and subcutaneous tissue disorders	4 (1.8%)	1 (1.3%)	5 (1.7%)
Dermatitis bullous	1 (0.5%)	0	1 (0.3%)
Pemphigoid	1 (0.5%)	0	1 (0.3%)
Rash	1 (0.5%)	0	1 (0.3%)
Rash erythematous	0	1 (1.3%)	1 (0.3%)
Rash maculo-papular	1 (0.5%)	0	1 (0.3%)
Vascular disorders	4 (1.8%)	0	4 (1.3%)
Hypertension	3 (1.4%)	0	3 (1.0%)
Deep vein thrombosis	1 (0.5%)	0	1 (0.3%)
Cardiac disorders	3 (1.4%)	0	3 (1.0%)
Atrioventricular block complete	1 (0.5%)	0	1 (0.3%)
Myocardial infarction	1 (0.5%)	0	1 (0.3%)
Pericarditis	1 (0.5%)	0	1 (0.3%)
Endocrine disorders	1 (0.5%)	2 (2.6%)	3 (1.0%)
Hypothyroidism	0	2 (2.6%)	2 (0.7%)
Hypophysitis	1 (0.5%)	0	1 (0.3%)
Eye disorders	3 (1.4%)	0	3 (1.0%)
Eye pain	1 (0.5%)	0	1 (0.3%)
Lacrimation increased	1 (0.5%)	0	1 (0.3%)
Ocular myasthenia	1 (0.5%)	0	1 (0.3%)
Optic atrophy	1 (0.5%)	0	1 (0.3%)
Vision blurred	1 (0.5%)	0	1 (0.3%)
Metabolism and nutrition disorders	2 (0.9%)	1 (1.3%)	3 (1.0%)
Dehydration	1 (0.5%)	0	1 (0.3%)
Diabetic ketoacidosis	0	1 (1.3%)	1 (0.3%)
Hypophosphataemia	1 (0.5%)	0	1 (0.3%)
Renal and urinary disorders	2 (0.9%)	1 (1.3%)	3 (1.0%)
Nephritis	1 (0.5%)	1 (1.3%)	2 (0.7%)
Acute kidney injury	1 (0.5%)	0	1 (0.3%)
Hepatobiliary disorders	2 (0.9%)	0	2 (0.7%)
Autoimmune hepatitis	2 (0.9%)	0	2 (0.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.9%)	0	2 (0.7%)
Basal cell carcinoma	1 (0.5%)	0	1 (0.3%)
Squamous cell carcinoma of skin	1 (0.5%)	0	1 (0.3%)
Psychiatric disorders	1 (0.5%)	0	1 (0.3%)
Delirium	1 (0.5%)	0	1 (0.3%)
Reproductive system and breast disorders	0	1 (1.3%)	1 (0.3%)
Genital rash	0	1 (1.3%)	1 (0.3%)

Study1423: Data cut-off as of June 30, 2018. Study1540: Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients; Data cut-off as of Oct 10, 2018 for Group 2 patients.
TEAE: Treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 20.0.
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.

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The updated table demonstrates that the proportion of patients with TEAEs that result in cemiplimab interruption or delay in patients with CSCC has slightly increased (from 28% to 33%) regarding the first data cut-off (original MAA). The main cause for such interruptions/delays remains infections/infestations (24 out of 72 patients – one third overall), with respiratory disorders in second place (14 out of 72) and GI disorders in third (12 out of 72). The most common specific symptoms/syndromes leading to interruptions or delays in the administration of cemiplimab were diarrhoea (9 out of 72, 12.5%), pneumonitis (10%) and infusion-related reactions (10%). This accounts for the expected safety profile from an anti-PD-1 antibody.

Post marketing experience

No post-marketing experience was submitted as the product has not yet been approved.

2.6.1. Discussion on clinical safety

The safety of cemiplimab has been evaluated in 591 patients with advanced solid malignancies including 219 advanced CSCC patients who received cemiplimab monotherapy in 2 clinical studies (R2810-ONC-1423 and R2810-ONC-1540). Immune-related adverse reactions occurred in 20.1% of patients treated with cemiplimab in clinical trials including Grade 5 (0.7%), Grade 4 (1.2%) and Grade 3 (6.1%). Immune-related adverse reactions led to permanent discontinuation of cemiplimab in 4.4% of patients. The most common immune-related adverse reactions were hypothyroidism (7.1%), pneumonitis (3.7%), skin adverse reactions (2.0%), hyperthyroidism (1.9%) and hepatitis (1.9%) (see "Description of selected adverse reactions" below, Special warnings and precautions for use in section 4.4 and Recommended treatment modifications in section 4.2). Adverse reactions were serious in 8.6% patients and led to permanent discontinuation of cemiplimab in 5.8% of patients.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with cemiplimab treatment (see section 4.4).

Immune-related adverse reactions can occur with cemiplimab. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of cemiplimab (see "Description of selected adverse reactions" below).

A tabulated list of adverse reactions and description of selected adverse reactions is displayed in the SmPC section 4.8.

Almost every monotherapy patient (98%) had at least one AE and a third of these events were of high grade (≥grade 3). Two-thirds of the patients had treatment-emergent AEs, most frequently fatigue (31.3%), diarrhea (21.5%), and nausea (18.2%). Treatment-related high-grade events were rarer, i.e. 33 (11.1%) patients experienced at least one grade ≥3 treatment-related TEAE. There were no clinically meaningful differences in treatment-related AEs between patients with CSCC and non-CSCC.

Adverse events of special interest include immune-related events and the most commonly identified events were hypothyroidism and pneumonitis, of which only a small fraction of pneumonitis were high-grade events and this is considered reassuring. Overall, endocrinopathies were observed in a number of patients, the events were mostly clinically manageable and the frequency of events was as expected with this class of immunotherapy.

Hyperthyroidism was rare and none of the events required high-dose steroids to resolve. The duration was long and only approximately a third of the events had resolved by data cutoff, reflecting that this is mostly a non-serious but prolonged event that is considered clinically manageable. Hypothyroidism on

the other hand, is much more frequent (8.8%), which is expected with PD-1 inhibitors, and could also be managed without high-dose steroids. Hypophysitis was rare and the one patient observed with this event had to be treated with high-dose steroids. The serious event of adrenal insufficiency was also rare and observed in only 1 patient on monotherapy. Diabetes was seldom observed, but the event lead to discontinuation of cemiplimab in one patient. overall, endocrinopathies were observed in a number of patients, the events were mostly clinically manageable as well as expectable with this class of immunotherapy.

Immune-related endocrinopathies, defined as treatment-emergent endocrinopathies with no clear alternate aetiology, have been observed in patients receiving cemiplimab (see section 4.8).

Thyroid disorders (Hypothyroidism/Hyperthyroidism)

Immune-related thyroid disorders have been observed in patients receiving cemiplimab. Thyroid disorders can occur at any time during the treatment. Patients should be monitored for changes in thyroid function at the start of treatment and periodically during the treatment as indicated based on clinical evaluation (see section 4.8). Patients should be managed with hormone replacement therapy (if indicated) and cemiplimab treatment modifications. Hyperthyroidism should be managed according to standard medical practice (see section 4.2).

Hypophysitis

Immune-related hypophysitis has been observed in patients receiving cemiplimab (see section 4.8). Patients should be monitored for signs and symptoms of hypophysitis and managed with cemiplimab treatment modifications and corticosteroids (see section 4.2).

Adrenal insufficiency

Adrenal insufficiency has been observed in patients receiving cemiplimab (see section 4.8). Patients should be monitored for signs and symptoms of adrenal insufficiency during and after treatment and managed with cemiplimab treatment modifications and corticosteroids (see section 4.2).

Type 1 Diabetes mellitus

Immune-related type 1 diabetes mellitus, including diabetic ketoacidosis, has been observed in patients receiving cemiplimab (see section 4.8). Patients should be monitored for hyperglycaemia and signs and symptoms of diabetes as indicated based on clinical evaluation and managed with oral anti-hyperglycaemics or insulin and cemiplimab treatment modifications (see section 4.2).

Cemiplimab should be withheld and anti-hyperglycaemics or insulin should be administered in patients with severe or life-threatening (Grade ≥ 3) hyperglycaemia. Cemiplimab should be resumed when metabolic control is achieved on insulin replacement or anti-hyperglycaemics (see section 4.2).

Severe and fatal immune-related adverse reactions have been observed with cemiplimab (see section 4.8). These immune-related reactions may involve any organ system. Most immune-related reactions initially manifest during treatment with cemiplimab; however, immune-related adverse reactions can occur after discontinuation of cemiplimab.

Immune-related adverse reactions should be managed with cemiplimab treatment modifications, hormone replacement therapy (if clinically indicated), and corticosteroids. For suspected immune-related adverse reactions, patients should be evaluated to confirm an immune-related adverse reaction and to exclude other possible causes. Depending upon the severity of the adverse reaction, cemiplimab should be withheld or permanently discontinued (see section 4.2).

Overall, 67 monotherapy patients died during the studies, most frequently due to disease progression. There were only few deaths that could be considered treatment-related (7 patients), considering the

stage of disease, the large fraction of heavily pre-treated and elderly patients in the study population, this is considered acceptable.

Treatment-emergent SAEs were common during treatment (30.3% in the monotherapy pool) and most often related to pneumonitis or infections (12.1%). This may be due to the underlying disease as the damaged skin or ulcerations functions as an entry for bacteria, causing both local and systemic infections. The elderly patient population is also more prone to urinary tract infections, which was also relatively commonly observed. However, the level of treatment-emergent SAEs is considered acceptable since there were few treatment-related events recorded, as well as considering the underlying disease, its prognosis, and the patient population.

Immune-related skin adverse reactions, defined as requiring use of systemic corticosteroids with no clear alternate aetiology, including severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (some cases with fatal outcome), and other skin reactions such as rash, erythema multiforme, pemphigoid, have been reported in association with cemiplimab treatment (see section 4.8).

Patients should be monitored for evidence of suspected severe skin reactions and exclude other causes. Patients should be managed with cemiplimab treatment modifications and corticosteroids (see section 4.2).

Cases of SJS, fatal TEN and stomatitis occurred following 1 dose of cemiplimab in patients with prior exposure to idelalisib, who were participating in a clinical trial evaluating cemiplimab in Non-Hodgkins Lymphoma (NHL), and who had recent exposure to sulfa containing antibiotics (see section 4.8). Patients should be managed with cemiplimab treatment modifications and corticosteroids as described above (see section 4.2).

Immune-related pneumonitis, defined as requiring use of corticosteroids with no clear alternate aetiology, including fatal cases, has been observed in patients receiving cemiplimab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis. Patients with suspected pneumonitis should be evaluated with radiographic imaging as indicated based on clinical evaluation and managed with cemiplimab treatment modifications and corticosteroids. (see section 4.2).

Immune-related diarrhoea or colitis, defined as requiring use of corticosteroids with no clear alternate aetiology, has been observed in patients receiving cemiplimab (see section 4.8). Patients should be monitored for signs and symptoms of diarrhoea or colitis and managed with cemiplimab treatment modifications, anti-diarrhoeal agents, and corticosteroids (see section 4.2).

Immune-related hepatitis, defined as requiring use of corticosteroids with no clear alternate aetiology, including fatal cases, has been observed in patients receiving cemiplimab (see section 4.8). Patients should be monitored for abnormal liver tests prior to and periodically during treatment as indicated based on clinical evaluation and managed with cemiplimab treatment modifications and corticosteroids (see section 4.2).

Immune-related nephritis

Immune-related nephritis, defined as requiring use of corticosteroids with no clear alternate aetiology, has been observed in patients receiving cemiplimab (see section 4.8). Patients should be managed with cemiplimab treatment modifications and corticosteroids (see section 4.2).

Other immune-related adverse reactions

Other fatal and life-threatening immune-related adverse reactions have been observed in patients receiving cemiplimab including paraneoplastic encephalomyelitis and meningitis (see section 4.8 for other immune-related adverse reactions).

Patients should be monitored for signs and symptoms of immune-related adverse reactions and managed with cemiplimab treatment modifications and corticosteroids (see section 4.2).

Infusion-related reactions

Cemiplimab can cause severe or life-threatening infusion-related reactions (see section 4.8). Patients should be monitored for signs and symptoms of infusion-related reactions and managed with cemiplimab treatment modifications and corticosteroids. Cemiplimab should be interrupted or the rate of infusion slowed for mild or moderate infusion-related reactions. The infusion should be stopped and cemiplimab should be permanently discontinued for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions (see section 4.2).

Approximately 6% of patients in the monotherapy pool discontinued treatment while 32.3% of the patients had drug interruption or delay. The main cause for such interruptions/delays remains infections/infestations (24 out of 72 patients – one third overall), with respiratory disorders in second place (14 out of 72) and GI disorders in third (12 out of 72). The most common specific symptoms/syndromes leading to interruptions or delays in the administration of cemiplimab were diarrhoea (9 out of 72, 12.5%), pneumonitis (10%) and infusion-related reactions (10%).

Increasing number of patients had serious adverse events with increasing age, and it is noted that the rate doubled when comparing patients <65 years of age (21.0%) to patients aged 75-84 years of age (42.0%). There were also more events with increasing age leading to hospitalisation and that were considered life threatening. The rate of AEs leading to drop out, cardiac disorders and infections and infestations increased markedly with increasing age. As the group of patients over 85 years consisted of 21 patients, no firm conclusions can be drawn from the results from this small subgroup.

ADA was rarely associated to cemiplimab treatment at the present time.

Patients excluded from clinical studies

Patients that had active infections or that were immunocompromised were not included in the main study. For a full list of patients excluded from clinical trials, see section 5.1. In the absence of data, cemiplimab should be used with caution in these populations after careful evaluation of the balance of benefits and risks for the patient.

The safety and efficacy of LIBTAYO in children and adolescents below the age of 18 years have not been established. No data are available.

Human IgG4 is known to cross the placental barrier and cemiplimab is an IgG4; therefore, cemiplimab has the potential to be transmitted from the mother to the developing foetus. Cemiplimab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Lactation

It is unknown whether cemiplimab is secreted in human milk. It is known that antibodies (including IgG4) are secreted in human milk; a risk to the breast-feeding newborns/infants cannot be excluded. If a lactating woman chooses to be treated with cemiplimab, she should be instructed not to breast-feed while being treated with cemiplimab and for at least 4 months after the last dose.

Cemiplimab has no or negligible influence on the ability to drive and use machines. Fatigue has been reported following treatment with cemiplimab (see section 4.8).

In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V. In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Additional safety data needed in the context of a conditional MA

The safety database shows no new safety concern for cemiplimab. The ADRs were mostly manageable and toxicity was tolerable with the recommended treatment modifications as described in the SmPC as well as with the additional risk minimisation activities. It is of note that only a fraction of patients in the safety database have received the proposed dosing regimen of 350 mg Q3W (n=56 patients). Duration of exposure is 171.8 patient-years for the 219 CSCC patients, out of which 33.9 patient-years correspond to the 350 mg Q3W dose. Thus, a comprehensive safety profile and long term safety of comprehensive safety profile of cemiplimab in the proposed dosing cannot be characterized at the present time. However the available safety data are considered adequate in the context of a conditional marketing authorisation; due to the limited exposure and sample size of patients who received the intended dosing regimen, in addition to no randomisation with a control arm of another comparable treatment, the remaining uncertainties should be addressed with the collection of additional safety data in the context of the specific obligation of study 1540 group 6 for the conditional marketing authorisation.

2.6.2. Conclusions on the clinical safety

No new unexpected safety concerns have been raised during the course of the study for cemiplimab, an anti-PD-1 antibody. Considering the disease being treated and the aging patient population from studies 1540 and 1423, the safety profile of cemiplimab corresponds to what can be expected from an anti-PD-1 antibody. The level of observed adverse events and immune-related events are considered acceptable, however due to limited exposure and small sample size of patients who received the dosing regimen intended for commercialisation, safety data will be collected in the context of the specific obligation of study 1540 group 6 for the conditional marketing authorisation.

All prescribers of LIBTAYO should be familiar with the educational materials and inform the patients about the Patient Alert Card explaining what to do should they experience any symptom of immune-related adverse reactions and infusion-related reactions. The physician will provide the Patient Alert Card to each patient. In addition, a patient guide is also distributed as part of the educational material on identifying, notifying and reporting suspected ADRs.

2.7. Risk Management Plan

Safety concerns

Summary of Safety Concerns	
Important identified risks	Immune-related adverse reactions (pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis, and other irARs) Infusion-related reactions
Important potential risks	Lack of effect due to anti-drug antibodies

Summary of Safety Concerns	
Missing information	Long-term safety data

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
R2810-ONC-1540 A Phase 2 Study of REGN 2810, A Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Group 6) Planned	To confirm the clinical efficacy and safety of cemiplimab monotherapy for patients with advanced CSCC (metastatic or unresectable locally advanced) treated with cemiplimab 350 mg Q3W IV.	• irARs (ir pneumonitis, colitis, hepatitis, endocrinopathies, skin adverse reactions, nephritis, and other irARs) • Infusion related reactions • Long-term safety data • Lack of effect due to ADA	Protocol submission	30/09/2019
			FPFV	31/01/2020
			LPLV	28/02/2022
			Interim report	31/03/2023
R2810-ONC-1540 A Phase 2 Study of REGN 2810, A Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Group 1, 2 and 3) Ongoing	To estimate the clinical efficacy and safety of cemiplimab monotherapy for patients with advanced CSCC (metastatic or unresectable locally advanced) treated with cemiplimab 350 mg Q3W IV. The study will provide additional safety data up to approximately 3.5 years of safety data for patients in Groups 1 and 2, and approximately 2.5 years of safety data for patients in Group 3.	Long-term safety Data	Protocol completion	23/11/2015
			FPFV	07/04/2016
			LPLV	31/10/2021
			Final report	31/10/2022

Pharmacovigilance plan

Risk minimisation measures

Table 109: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation activities	Proposed pharmacovigilance activities
Important identified risk: Immune-related adverse reactions Immune-related adverse reactions **(**immune-related pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis, and other irARs)	Routine risk communication messages: SmPC section 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: See SmPC sections 4.2 and 4.4 See PL section 2 and 3 Other routine risk minimisation measures beyond the Product Information: Legal status: Cemiplimab is supplied subject to restricted medical prescription, and treatment must be initiated and supervised by physicians experienced in the treatment of cancer. Additional risk minimisation measures: Patient Guide and Alert Card	Routine pharmacovigilance Use of specific follow-up questionnaire for spontaneous postmarketing reports of immune-related adverse reactions Additional pharmacovigilance activities: Study short name and title: A Phase 2 Study of REGN 2810, A Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Group 6)
Important identified risk: Infusion-related reactions	Routine communication messages: SmPC section 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC sections 4.2, 4.3, and 4.4. PL sections 2 and 3 Other routine risk minimisation measures beyond the Product Information: Legal status: Cemiplimab is supplied subject to restricted medical prescription and treatment must be initiated and supervised by physicians experienced in the treatment of cancer. Additional risk minimisation measures: Patient Guide and Alert Card	Routine pharmacovigilance Use of specific follow-up questionnaire for spontaneous post-authorisation reports of infusion-related reactions Additional pharmacovigilance activities: Study short name and title: A Phase 2 Study of REGN 2810, A Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Group 6)

Safety concern	Risk minimisation activities	Proposed pharmacovigilance activities
Important Potential Risk: Lack of effect due to anti-drug antibodies	Routine communication messages SmPC section 4.8 Other routine risk minimisation measures beyond the Product Information: Legal status: Cemiplimab is subject to restricted medical prescription and treatment must be initiated and supervised by physicians experienced in the treatment of cancer.	Routine pharmacovigilance Additional pharmacovigilance activities: Study short name and title: A Phase 2 Study of REGN 2810, A Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Group 6)
Missing information **Long-Term Safety Data**	Not applicable	Routine pharmacovigilance Additional pharmacovigilance activities: Study short name and title: A Phase 2 Study of REGN 2810, A Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Groups 1, 2, 3 and 6)

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 28.09.2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that cemiplimab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers cemiplimab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

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

- it contains a new active substance authorised in the EU after 1 January 2011;
- it has been given a conditional approval (where the applicant that is going to market the medicine must provide more data about it)

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.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The applicant is seeking the following indication:

LIBTAYO as monotherapy is indicated for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation.

3.1.2. Available therapies and unmet medical need

The major treatment options for CSCC with features that suggest a low-risk for recurrence and metastasis are surgical excision, cryotherapy, electrosurgery, and radiation therapy. Radiation therapy is an additional option for the management of primary CSCCs in older patients and those who are not surgical candidates.

Although the probability of surgical cure for most patients with CSCC is high, the disease course is devastating for the small percentage of patients who develop metastatic CSCC or locally advanced CSCC, collectively referred to as advanced CSCC. There is no approved systemic treatment or guidelines for advanced CSCC. Overall, use of available treatments is limited by inconclusive efficacy data and substantial safety risks due to the advanced age of CSCC population. Therefore, there is an unmet medical need for an effective treatment option with an acceptable safety profile in patients with advanced CSCC.

3.1.3. Main clinical studies

The applicant has submitted results from Studies 1423 and 1540 evaluating cemiplimab in patients with locally advanced and metastatic CSCC.

Study 1540 is an ongoing, phase 2, open-label, single-arm, 3-group, multicentre pivotal study evaluating efficacy, safety, and PK of cemiplimab in patients with metastatic CSCC (mCSCC) (Group 1: 3mg/kg Q2W and Group 3:350 mg Q3W) or locally advanced CSCC (laCSCC) (Group 2: 3mg/kg Q2W) who are not candidates for surgery or radiation. The primary endpoint is ORR, and the key secondary endpoint is DoR. Data cutoff is 20 Sep 2018 for Groups 1 and 3, and 10 Oct 2018 for Group 2. Median follow-up time since start of treatment is still limited (16.5, 9.3, and 8.1 months in Groups 1, 2 and 3 respectively; 9.4 months for the ITT population).

Primary analysis was possible for the entire population of the study since all 193 patients (59 patients in Group 1, 78 in Group 2 and 56 in Group 3) have had the opportunity for at least 3 response assessments.

Study 1423 (considered supportive) is a phase 1, open-label, ascending-dose escalation study of cemiplimab, alone and in combination with various combination therapy treatments in patients with advanced solid tumours. Two expansion cohorts (7 and 8) were designed to obtain additional clinical experience with cemiplimab 3 mg/kg Q2W in patients with metastatic and unresectable locally advanced CSCC, respectively.

3.2. Favourable effects

Study 1540:

The IRC-assessed ORR results are consistent for each group: 49.2% in Group 1, 43.6% in Group 2 and 39.3% in Group. The lower bound of the 95% CI is beyond the range of predefined clinically insignificant effect (≤15% ORR in Group 1 and Group 3, ≤25% in Group 2) in all 3 groups.

DoR is ≥6 months for 68% of patients from Group 2 (23 out 34) and 64% of patients from Group 3 (14 out of 22). It is of note that there is a longer follow-up for Group 1 (median 16.5 months) where 27 out of 29 patients (93%) have a response that has lasted for 6 months or longer.

Updated PFS results are nearly identical for Group 1 (28 events in 59 patients, mPFS 18.4 months, 6-month-PFS 66.0%) and minimally improved for Group 3 (26 events in 56 patients, mPFS 10.4 months, 6-month-PFS 59.3%).

Responses were seen with a similar ORR in most age subgroups across all three groups of treatment. In 75 patients assessable for PD-L1 status, responses occurred across PD-L1 subgroups, even in low-expressing subjects.

3.3. Uncertainties and limitations about favourable effects

Although the ORR data is considered compelling, data are limited to a small number of patients and is not considered comprehensive, especially in Group 3 which was treated with the 350 mg Q3W posology. The applicant has committed to provide updated efficacy data from Study 1540 (from Groups 1-3) and additional efficacy and safety data from a new cohort (Group 6 in study 1540) in post-authorisation to confirm the efficacy data (see SOB).

The limited data available to assess the impact of PD-L1 expression on the efficacy of cemiplimab do not indicate that PD-L1 status has a predictive value for response to treatment. Although cemiplimab use is not restricted to PD-L1 positive patients, it is of importance to evaluate the predictive value of PD-L1 as well as other biomarkers in CSCC. As a consequence, the applicant should provide additional robust data

on PD-L1 in the confirmatory single arm study to confirm the use of cemiplimab in all patients regardless of PD-L1 status.

There is also uncertainty as to whether the efficacy observed in terms of tumour response is maintained for a prolonged period in the long term by cemiplimab treatment leading to an improvement in PFS or OS. With 9.4 months of median follow-up time and 18% of events (34 in 193 patients), OS results are too immature to be assessed.

Because of the uncertainty on long term efficacy with cemiplimab, the applicant should submit the final results of study 1540 for ORR, PFS and OS.

3.4. Unfavourable effects

The safety of cemiplimab has been evaluated in 591 patients with advanced solid malignancies including 219 advanced CSCC patients who received cemiplimab monotherapy in 2 clinical studies (R2810 ONC 1423 and R2810 ONC 1540).

The most common adverse reactions were: diarrhoea, rash, pruritus and fatigue. Immune related adverse reactions occurred in 20.1% of patients treated with cemiplimab in clinical trials including Grade 5 (0.7%), Grade 4 (1.2%) and Grade 3 (6.1%).

Immune-related adverse reactions led to permanent discontinuation of cemiplimab in 4.4% of patients. The most common immune-related adverse reactions were hypothyroidism (7.1%), pneumonitis (3.7%), immune-related skin adverse reactions (2.0%), hyperthyroidism (1.9%) and hepatitis (1.9%) (see section 4.8 SmPC). Adverse reactions were serious in 8.6% patients and led to permanent discontinuation of cemiplimab in 5.8% of patients.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with cemiplimab treatment (see section SmPC 4.4).

There were 12 patients (2%) that had a fatal TEAE.

Infusion-related reactions occurred in 54 (9.1%) of 591 patients treated with cemiplimab including 1 (0.2%) patient with Grade 3 infusion-related reaction.

3.5. Uncertainties and limitations about unfavourable effects

Only a fraction of patients have received the proposed dosing regimen of 350 mg Q3W (n=56 patients). Duration of exposure is 171.8 patient-years for the 219 CSCC patients, out of which 33.9 patient-years correspond to the 350 mg Q3W dose. Therefore, there is uncertainty of the safety of cemiplimab in the long term and for the safety at the dose to be used in clinical practice. As a comprehensive safety dataset of cemiplimab in the proposed dosing is not available at the present time, the applicant has committed to collect safety data in the confirmatory study as part of the conditional marketing authorisation.

The fact that apparently none of the 140 patients –with ADA samples available– across groups tested positive for ADAs has raised doubts on the detection method (ADA screening assay). Therefore, there is uncertainty on the lack of effect due to anti-drug antibodies as no ADA was detected in the ADA detection assays. This has been included in the RMP as an important potential risk.

3.6. Effects Table

Effects Table for LIBTAYO indicated as monotherapy for the treatment of patients with metastatic cutaneous squamous cell carcinoma or patients with locally advanced cutaneous squamous cell carcinoma who are not candidates for surgery (data cut-off June 30 2018).

Effect	Short Description	Unit	Group 1 mCSCC (n=59)	Group 2 laCSCC (n=78)	Group 3 mCSCC (n=56)	References
Favourable Effects						
ORR	Overall response rate	% (95% CI)	49.2 (35.9, 62.5)	43.6 (32.4, 55.3)	39.3 (26.5, 53.2)	
DoR	Duration of Response	% of patients >6 months or longer	93.1%	67.6%	63.6%	
mPFS 6 months PFS		Months (95%CI)	18.4 (7.3, NE) 66.0%	Not reached	10.4 (3.6, NE) 59.3%	
Unfavourable Effects (total population n=591)						
Rash	Grade I-V Grade 3-5	%	23.3 0			
Fatigue	Grade I-V Grade 3-5	%	21.5 0.9			
Diarrhoea	Grade I-V Grade 3-5	%	13.2 0.5			
Pruritus	Grade I-V Grade 3-5	%	12.3 0			
IR-AE* (all grades)		%	20.1			
pneumonitis	Grade ≥3	%	1.6			
colitis	Grade ≥3	%	0.3			
hepatitis	Grade ≥3	%	1.9			
Endocrinopathies	Grade ≥3	%	Hypothyroidism = 0.2 Hyperthyroidism = 0.2 Adrenal insufficiency = 0.2 Hypophysitis =0.2 Type 1 diabetes =0.7			
Skin adverse reactions	Grade ≥3	1.0%				
nephritis	Grade ≥3	0.3%				
Infusion-related reactions	Grade ≥3	0.2%				

* IR-AE = immune-related AE (identified by investigator and requiring supportive therapy).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The applicant has presented PK, clinical efficacy and safety data for patients treated with the fixed 350 mg Q3W dose and 3mg/kg Q2W, and the conclusion following assessment of these data is that the 350 mg Q3W dose is overall as efficacious and safe as the 3 mg/kg Q2W dose. The applicant has shown a compelling total ORR rate of 44% in patients with laCSCC and mCSCC treated with cemiplimab. DoR, the key secondary efficacy endpoint, is beyond 6 months for at least 93% of patients from Group 1 (limited follow-up challenges interpretation of DoR for Groups 2 and 3), which brings some reassurance to the robustness of the clinical efficacy. The limited available clinical data in patients that have undergone biopsies so far seem to suggest that expression of PD-L1 lacks predictive value in CSCC patients in the intended indication.

There were no new safety risks identified with cemiplimab. Considering the disease being treated and the aging patient population from studies 1540 and 1423, the safety profile of cemiplimab corresponds to what can be expected from an anti-PD-1 antibody. The most common adverse reactions were rash, fatigue, diarrhoea and pruritus. The most common immune-related adverse reactions were hypothyroidism, pneumonitis, immune-related skin adverse reactions, hyperthyroidism and hepatitis. Pneumonitis events were low which was considered reassuring and overall, endocrinopathies were observed in a number of patients, the events were mostly clinically manageable as well as expectable with this class of immunotherapy. Therefore, the level of observed adverse events and immune-related events are considered acceptable, however due to limited exposure and small sample size of patients who received the recommended dosing regimen, additional safety data will need be included in the confirmatory study.

3.7.2. Balance of benefits and risks

The high unmet medical need for patients with advanced CSCC has been acknowledged as there are few systemic treatment options that have shown efficacy. The clinical benefit observed for cemiplimab in this population is encouraging and is considered clinically meaningful in terms of ORR. Therefore, the clinical benefit outweighs the toxicity and safety risks which are considered manageable through recommendations in the SmPC as well as additional risk minimisation activities, which include a patient guide and patient alert card. Although the efficacy and safety data are still not considered comprehensive enough for a full marketing authorisation, the benefit risk balance is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

In order to exclude patients who were not appropriate candidates for curative radiation, the wording of the indication has been amended to include patients who are not candidates for curative surgery or curative radiation. The indication also includes the word "adult" in order to clarify the target age group. As the efficacy has been shown in patients exposed or not to previous systemic chemotherapy treatment, the indication was not restricted to a line of therapy.

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was proposed by the CHMP during the assessment, after having consulted the applicant.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating and life-threatening disease as CSCC can metastasize and inadequate treatment can result in increased morbidity and death.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed above. The applicant has presented clinically meaningful ORR and DOR in both laCSCC and mCSCC. The safety is clinically manageable and in line with other anti PD1/PD-L1 agents.
- It is likely that the applicant will be able to provide comprehensive data. The efficacy data in mCSCC is based in only 56 patients that have had more than 3 response assessments at the recommended posology of 350 mg Q3W and for laCSCC efficacy is based in 78 patients in a posology of 3 mg/kg Q2W. Therefore, the applicant has committed to providing confirmatory data from a new cohort of patients (cohort 6 from study 1540) which will enrol both mCSCC and laCSCC and treated with the recommended posology of 350 mg Q3W. The new cohort of patients with the same disease characteristics for advanced CSCC (mCSCC and laCSCC) will be adequate to confirm both efficacy and safety of cemiplimab at the recommended posology 350 mg Q3W. In addition, further follow up efficacy for PFS and OS will be submitted as part of the specific obligation in the final study report for Study 1540 (Groups 1-3), providing further confirmatory data.
- Unmet medical needs will be addressed, as currently there is no standard of care or approved therapy for advanced CSCC and patients have usually been treated with EGFR targeting drugs and/or chemotherapy which have shown to have low rates of ORR and DOR and no compelling effect on other important endpoints such as PFS and OS, which are of very short duration.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. Cemiplimab has shown efficacy in advanced CSCC and a clinical benefit in terms of a compelling effect on ORR with a DoR ≥6 months in 93% of patients in group 1, 68% of patients from Group 2 (23 out 34) and 64% of patients from Group 3 (14 out of 22). Cemiplimab is an anti-PD-1 which is a class of products that have been on the market for some years. This is the first treatment option in this setting for which a beneficial effect has been demonstrated. The submitted PFS data is promising and therefore it is expected that PFS will be improved in the long term. Although few patients were treated with the 350 mg Q3W, it was demonstrated that the 350 mg Q3W dose was overall as efficacious and safe as the 3 mg/kg Q2W dose. No unexpected safety concerns have been identified during the assessment of cemiplimab compared to the known safety profile for this class of products. Treating physicians are becoming more familiar with managing immune-related ADRs associated with anti-PD-1 treatment, in addition, cemiplimab will be marketed with additional risk minimisation activities (patient guide and alert card), which will minimise any of the risks related to the important safety concerns.

3.8. Conclusions

The overall B/R of LIBTAYO is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of LIBTAYO is favourable in the following indication:

LIBTAYO as monotherapy is indicated for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation.

Based on the need to provide comprehensive data to confirm the efficacy and safety of cemiplimab in the intended indication with the recommended posology, a conditional marketing authorisation is proposed by the CHMP, after having consulted the applicant.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Libtayo in each Member State, the Marketing Authorisation Holder (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

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
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.	31 March 2023
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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that cemiplimab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.