20 May 2021
EMA/319415/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

LIBTAYO

International non-proprietary name: cemiplimab

Procedure No. EMEA/H/C/004844/II/0012

Note

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

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Table of contents

List of abbreviations

Abbreviation	Definition
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BCC	Basal cell carcinoma
BOR	Best objective response
CI	Confidence interval
C_{max}	Peak concentration
CNS	Central Nervous System
CR	Complete response
CSCC	Cutaneous squamous cell carcinoma
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough concentration at the end of the dosing interval
CYP	Cytochrome P450
DCR	Disease control rate
dDCR	Durable disease control rate
DOR	Duration of response
DP	Drug product
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
E-R	Exposure-response
EU	Europe/European Union
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
Hh	Hedgehog
HHI	Hedgehog (pathway) inhibitor
ICR	Independent central review
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
imAE	Immune-mediated adverse event (also referred to as irAE)
irAE	Immune-related adverse event (also referred to as imAE)
IRR	Infusion-related reaction
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intention-to-treat
IV	Intravenous(ly)
K-M	Kaplan-Meier
laBCC	Locally advanced basal cell carcinoma
laCSCC	Locally advanced cutaneous squamous cell carcinoma
mBCC	Metastatic basal cell carcinoma
mCSCC	Metastatic cutaneous squamous cell carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
N	Total number of patients
NAb	Neutralizing antibody
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCT	National Clinical Trial
NE	Not evaluable

NSCLC	Non-small cell lung cancer
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
PFS	Progression-Free survival
PK	Pharmacokinetic(s)
PopPK	Population PK
PR	Partial response
PT	Preferred term
Q2W	Every 2 weeks
Q3W	Every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
QoL	Quality of life
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SD	Stable disease
SJS	Stevens-Johnsons syndrome
SMO	Smoothened
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
US	United States
UV	Ultraviolet
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Regeneron Ireland Designated Activity Company (DAC) submitted to the European Medicines Agency on 25 August 2020 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include LIBTAYO as monotherapy is indicated for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) previously treated with a hedgehog pathway inhibitor. SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 have been revised. The PL has been updated accordingly. A revised RMP has been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0385/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP 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 MAH 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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 10 November 2016 (SA/3225/3/2016). The Scientific Advice pertained to clinical aspects of the dossier.

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: Johanna Lähteenvuo

Timetable	Actual dates
Submission date	25 August 2020
Start of procedure:	12 September 2020
CHMP Rapporteur Assessment Report	6 November 2020
CHMP Co-Rapporteur Assessment Report	6 November 2020
PRAC Rapporteur Assessment Report	13 November 2020
PRAC Outcome	26 November 2020
CHMP members comments	30 November 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	4 December 2020
Request for supplementary information (RSI)	10 December 2020
CHMP Rapporteur Assessment Report	23 February 2021
PRAC Rapporteur Assessment Report	23 February 2021
PRAC members comments	3 March 2021
Updated PRAC Rapporteur Assessment Report	18 March 2021
PRAC Outcome	11 March 2021
CHMP members comments	15 March 2021
Updated CHMP Rapporteur Assessment Report	18 March 2021
Request for supplementary information (RSI)	25 March 2021
CHMP Rapporteur Assessment Report	05 May 2021
CHMP members comments	10 May 2021
Updated CHMP Rapporteur Assessment Report	12 May 2021
Opinion	20 May 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The proposed indication for cemiplimab is as monotherapy for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) previously treated with a hedgehog pathway inhibitor (HHI).

Epidemiology and risk factors

Keratinocyte carcinomas are the most common cancers worldwide, and BCC represents approximately 80% of keratinocyte carcinomas. There is a strong inverse relationship between the incidence of BCC and country geographic latitude combined with pigment status, with the highest rates in Australia followed by the United States and Europe. Precise incidence rates are not known because these carcinomas are generally not included in cancer registries. The total annual incidence of individuals diagnosed with BCC in the US has been estimated to be 2 million, and incidence appears to be increasing. In European countries, incidence rates for BCC are also reported to be increasing.

The most common risk factors for BCC are chronic ultraviolet (UV) radiation exposure, advanced age, male gender, and light skin pigmentation. Consistent with the predominance of UV expose as a risk factor, most BCCs arise in sun-exposed skin of the head and neck. Solid organ transplant recipients also have an approximately 6-to 16-fold increased risk of BCC compared to the general population. The reported median age of onset of BCC at diagnosis is 67 years. The risk is also increased in patients treated with chronic immunosuppression for autoimmune diseases. These findings are consistent with the hypothesis that these cancers are normally controlled by immune mechanisms.

Aetiology and pathogenesis

Basal cell carcinoma is a malignant proliferation of basal cells with invasion of the dermis. Although the term "nonmelanoma skin cancer" has traditionally been used to refer to all skin cancers except melanoma, "keratinocyte carcinoma" is becoming the preferred term for BCC and Cutaneous squamous cell carcinoma (CSCC) because of the shared lineage with epidermal keratinocytes.

At the molecular level, BCC is one of the mostly highly mutated tumors due to UV-mediated mutagenesis. The best characterized oncogenic alterations in BCC are the Hedgehog (Hh) signalling pathway, including loss of function mutations in PTCH1 (encoding the inhibitory receptor patched) in ›70% of sporadic BCCs, and activating mutations in smoothened (SMO) (encoding the signal transducer smoothened downstream of patched) in approximately 20% of sporadic BCCs. A PTCH mutation results in loss of patched-mediated inhibition of the G protein coupled receptor Smoothened (SMO), thereby enhancing downstream signalling that results in uncontrolled cellular proliferation. Gorlin Syndrome, also known as nevoid basal cell carcinoma syndrome, is a rare inherited genetic disorder in which patients carry a germline mutation in PTCH1 or other pathway genes that result in aberrant oncogenic signalling of the Hh pathway. The

reported median age of onset of Gorlin syndrome ranges from 25 to 44 years, depending on genetic variant.

Clinical presentation, diagnosis and stage/prognosis

Common histologic subtypes of BCC are superficial and nodular, and less common subtypes that may be more clinically aggressive include morpheaphorm, basosqamous, mixed, and micronodular. More than 95% of BCCs are cured by surgery. Other local modality treatments, such as topical imiquimod, are highly effective treatment options for low-risk BCCs. Most BCCs are slow growing and have low metastatic potential. A small percentage of BCCs follow a more aggressive course and are not amenable to radiation, surgery, or other local modality treatments. The term "advanced BCC" includes patients with locally advanced BCC who have exhausted options for surgery and radiation therapy and patients with metastatic BCC. The estimated rate of BCC metastasis ranges from 0.0028% to 0.55%, with regional lymph nodes, lung, bones, skin and liver as common metastatic sites. Locally advanced BCCs can cause significant destruction of local tissues due to invasive growth patterns when treatment is delayed or inadequate.

Management

Advanced BCC is a serious condition that includes potentially life-threatening disease for metastatic patients and persistent invasive and disfiguring tumors for patients with locally advanced BCC. Despite the practice-changing efficacy observed with the HHIs vismodegib and sonidegib for first-line therapy for advanced BCC, the limitations of HHIs are that approximately half of patients do not experience objective responses (per central review), most responses are partial, and the side effect profiles of these agents can create difficulties for long-term therapy. Among ›1400 advanced BCC patients (mostly locally advanced BCC patients) treated with vismodegib in the STEVIE and MIKIE studies, approximately 8% (116 patients) achieved a durable CR. In addition to the low CR rate, up to 80% of patients interrupted or discontinued treatment due to grade ≥3 TEAEs. Lack of efficacy/progressive disease was another common reason for discontinuation in advanced BCC patients treated with vismodegib and sonidegib.

Several small pilot studies of experimental agents in the second-line BCC setting after HHI therapy have not provided efficacy signals and/or an acceptable safety profile to warrant further development.

Itraconazole, an antifungal agent, has been identified as a potent inhibitor of the hedgehog signaling pathway. In a proof of concept study, itraconazole was studied in 19 patients, with an average of 4.8 cutaneous basal cell carcinomas per patient. In one cohort, 15 patients were treated with 200 mg twice daily for four weeks prior to surgery; in the other cohort, four patients received 100 mg twice daily for one to four months (mean, 2.3 months). Eight patients had tumor reduction and re-epithelialization. Of note, none of the three patients previously treated with vismodegib responded. Additional clinical studies will be required to determine whether itraconazole has a role in the management of patients with basal cell carcinoma.

Because of the rarity of metastatic basal cell carcinoma, the approach to systemic chemotherapy treatment is based primarily upon isolated case reports, with only a few small case series. A case report of one patient with basal cell carcinoma metastatic to the lungs observed a complete response with a combination of carboplatin and paclitaxel. The authors also reviewed the literature and found 12 other patients with metastatic basal cell carcinoma who were treated with platinum-containing regimens. Among these 12, five had a complete response and four had a partial response.

2.1.2. 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. Cemiplimab has been already licenced and shown to provide benefit in patients with CCSC, which is a very similar disease with BCC, with shared lineage with epidermal keratinocytes.

The initially applied indication was for the treatment of adult patients with locally advanced basal cell carcinoma (laBCC) previously treated with a hedgehog pathway inhibitor.

The finally approved indication is for the treatment of adult patients with locally advanced or metastatic basal cell carcinoma (laBCC or mBCC) who have progressed on or are intolerant to a hedgehog pathway inhibitor

The proposed dose of cemiplimab is 350 mg every 3 weeks (Q3W) administered as an intravenous (IV) infusion over 30 minutes. This cemiplimab dose and regimen is currently approved for the treatment of advanced cutaneous squamous cell carcinoma (CSCC). Treatment may be continued through initial measurable disease progression until symptomatic disease progression or unacceptable toxicity to maximize opportunity for patients to experience clinical benefit.

2.1.3. The development programme/compliance with CHMP guidance/scientific adviceThe MAH received

Scientific advice from the CHMP on 10 November 2016 (SA/3225/3/2016). The Scientific advice pertained to clinical aspects of the dossier.

2.1.4. General comments on compliance with GCP

The MAH claims that this study is conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

A claim of exclusion from preparation of environmental risk assessment studies is made according to Section 2 of the 2006 CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (ERA Guideline) (1) because cemiplimab is a monoclonal antibody consisting of linked naturally occurring amino acids. Per the ERA Guideline, "Vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted because they are unlikely to result in significant risk to the environment."

The justification for not performing any ERA studies is considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

The MAH 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

	Study Population	Study Phase Study Design	Dose and Regimen	Data Included in This Application/Data Cutoff Dates for Efficacy, Safety, and PK	Duration of Follow-up
R2810-ONC-1620 (NCT 02760498; EudraCT 2016-003112-16) Study ongoing	Adult patients with mBCC (Group 1) and laBCC (Group 2)	Phase 2 Open-label, nonrandomized, 2-group, multicenter study	350 mg cemiplimab administered IV over 30 min Q3W Planned treatment duration is up to 93 weeks.	Efficacy data from BCC patients in the FAS (n = 112 patients; 84 laBCC and 28 mBCC) Safety data from all patients in the SAF (n = 132 patients; 84 laBCC and 48 mBCC) PK data from the PKA set (n = 132 patients; 84 laBCC and 48 mBCC) ADA data from the ADA analysis set (n = 125 patients; 81 laBCC and 44 mBCC) Data cutoff for efficacy and safety: 17 Feb 2020 Data cutoff for PK/ADA: 17 Apr 2020	Planned study period was up to ~39 months (~ 21 months [93 weeks of planned treatment + ~1.5 years of posttreatment follow-up). Median duration of follow-up was 13.26 months (range: 0.5 to 27.2) in the FAS and 11.17 months (range: 0.0 to 27.2) in the SAF.

	Study Population	Study Phase Study Design	Dose and Regimen	Data Included in This Application/Data Cutoff Dates for Efficacy, Safety, and PK	Duration of Follow-up
R2810-ONC-1423 (NCT 02383212; EudraCT 2015-002132-41) Study complete	Adult patients (N = 398) with advanced solid tumor malignancies Six patients with BCC enrolled (2 patients in dose escalation; 4 patients in Expansion Cohort 25)	Phase 1 (FIH) Open-label, repeat-dose, multicenter study with cemiplimab as monotherapy (n = 130 patients) and combination therapy (n = 268 patients). Combinations included radiotherapy, GM-CSF, and cytotoxic chemotherapies.	Cemiplimab administered IV over 30 minutes Q2W at: - 3 mg/kg (n = 333 patients) - 1 mg/kg (n = 27 patients) - 10 mg/kg (n = 6 patients) - 200 mg (n = 20 patients) Cemiplimab 3 mg/kg Q3W administered IV over 30 minutes (n = 12 patients) For all patients, planned treatment duration was up to 48 weeks, and posttreatment follow-up of approximately 5.5 months.	Efficacy data for CSCC patients[a] (n = 26 patients; 16 mCSCC and 10 laCSCC). Safety data from all patients in the SAF (n = 398 patients) PK data from the PK analysis set (n = 398 patients [including 4 with BCC in Expansion Cohort 25]) ADA data from the ADA analysis set (n = 337 patients [including 4 with BCC in Expansion Cohort 25]) Data cutoff for efficacy, safety, and PK/ADA: 30 Apr 2019	Planned study period was 16.5 months (approximately 11 months [48 weeks] of planned treatment + 5.5 months of post-treatment follow-up) Median duration of follow-up was 13.3 months (range: 1.1 to 21.0) for all 26 advanced CSCC patients in the FAS.
R2810-ONC-1540 (NCT 02760498; EudraCT 2016-000105-36) Study ongoing	Adult patients (N = 193) with advanced CSCC (mCSCC [Groups 1 and 3] or laCSCC [Group 2])	Phase 2 Open-label, nonrandomized, multicenter study	Cemiplimab administered IV over 30 minutes at: - 3 mg/kg Q2W (Groups 1 and 2) - 350 mg Q3W (Group 3) Planned treatment duration was up to 96 weeks for Groups 1 and 2 and up to 54 weeks in Group 3	Efficacy data from CSCC patients (n = 193 patients; 115 metastatic CSCC [59 in Group 1 and 56 in Group 3] and 78 locally advanced CSCC) Safety data from all patients in the SAF (n = 193 patients) PK data from the PK analysis set (n = 188 patients) ADA data from the ADA analysis set (n = 140 patients) Data cutoffs for efficacy, safety and PK/ADA: 20 Sep 2018 (Groups 1 and 3) and 10 Oct 2018 (Group 2)	Planned study period was up to ~ 39 months (~ 21 months [96 weeks Groups 1 and 2; 54 weeks Group 3] of planned treatment + ~1.5 years of posttreatment follow-up). Median duration of follow-up was 9.4 months (range: 0.6 to 27.9) for all 193 advanced CSCC patients in the FAS.

	Study Population	Study Phase Study Design	Dose and Regimen	Data Included in This Application/Data Cutoff Dates for Efficacy, Safety, and PK	Duration of Follow-up
R2810-ONC-1624 (NCT 03088540; EudraCT 2016-004407-31) Study ongoing	Adult patients (N = 710) with advanced or metastatic NSCLC whose tumors express PD-L1 in ≥50% of tumor cells	Phase 3 Open-label, randomized, 2-group, multicenter study	350 mg cemiplimab administered IV over 30 min Q3W OR chemo Planned treatment duration was up to 108 weeks.	Efficacy data from NSCLC patients in the ITT (n = 710 patients; 356 cemiplimab, 354 chemo), mITT-1 (n = 563 patients; 283 cemiplimab, 280 chemo), mITT-2 (n=475; 238 cemiplimab, 237 chemo) Safety data from all patients in the SAF (n = 697 patients; 355 cemiplimab, 342 PBC) PK data from the PK analysis set (n = 345 patients; all cemiplimab) ADA data from the ADA analysis set (n = 221 patients; all cemiplimab) Data cutoff: 01 Mar 2020	Planned study period was up to ~48 months (~ 2 years [2 years of planned treatment + ~7 months of posttreatment follow-up). Median duration of follow-up was 13.08 months (range: 0.1 to 32.4 months) for all patients in the ITT.

[a] Excludes anogenital SCC (1 patient). Abbreviations: ADA, anti-drug antibody; BCC, basal cell carcinoma; chemo, chemotherapy; CSCC, cutaneous squamous cell carcinoma; EudraCT, European Clinical Trials Database; FAS, full analysis set; GM-CSF, granulocyte-macrophage colony stimulating factor; IV, intravenous(ly); laBCC, locally advanced basal cell carcinoma; laCSCC, locally advanced mCSCC, mBCC, metastatic basal cell carcinoma; metastatic CSCC; n, number of patients in the group; mITT, modified intent-to-treat; N, total number of patients; NCT, National Clinical Trial; NSCLC, Non-small cell lung cancer; PD-L1, programmed death-ligand 1; PK, pharmacokinetics; PKA, PK analysis set; Q2W, every 2 weeks; Q3W, every 3 weeks; SAF, safety analysis set Source: Module 2.7.2 Table 1; R2810-ONC-1620 Interim CSR; R2810-ONC-1423 Final CSR; R2810-ONC-1540 Primary Analysis for Groups 2 and 3 CSR; R2810-ONC-1624 Primary Analysis CSR

2.3.2. Pharmacokinetics

The PK and immunogenicity of cemiplimab were assessed in 4 clinical studies: Study 1620 (advanced BCC), Study 1423 (FIH), Study 1540 (advanced CSCC), and Study 1624 (advanced NSCLC).

Table 1 List of clinical trials in patients with solid tumours, including advance BCC, where PK, PD, ADA data were collected

Study Number **Phase** **Data Cutoff/Status**	**Study Title** **(N = Number Enrolled)**	**Patients Evaluated for PK and ADA**	**Patients at 350 mg Q3W Evaluated for PK, PD, and ADA**	**Patients with Advanced BCC** **Evaluated for PK, PD, and ADA**
R2810-ONC-1423 Phase 1 30 Apr 2019/complete	A First-In-Human Study of Repeat Dosing with REGN2810, A Monoclonal, Human Antibody to Programmed Death-1 (PD-1), As Single Therapy and In Combination with Other Anti-Cancer Therapies, In Patients with Advanced Malignancies (N = 398)	PK: 398 (including 4 with advanced BCC in EXP25) ADA: 337 (including 4 with advanced BCC in EXP25)	NA	PK: 4 ADA: 4
R2810-ONC-1540 Phase 2 20 Sep 2018 (Groups 1 + 3); 10 Oct 2018 (Group 2)/ongoing	A Phase 2 Study of REGN2810, A Human Monoclonal Antibody to Programmed Death-1 (PD-1), In Patients with Advanced Cutaneous Squamous Cell Carcinoma (N = 193)	PK: 188 ADA: 140	PK: 53 ADA: 39	NA
R2810-ONC-1620 Phase 2 17 Feb 2020/ongoing	A Phase 2 Study of REGN2810, A Human Monoclonal Antibody to Programmed Death-1, In Patients with Advanced Basal Cell Carcinoma Who Experienced Progression of Disease on Hedgehog Pathway Inhibitor Therapy, Or Were Intolerant of Prior Hedgehog Pathway Inhibitor Therapy (N = 132)	PK: 132 ADA: 125	PK: 132 PD: 81 (17 mBCC; 64 laBCC) ADA: 125	PK: 132 (48 mBCC; 84 laBCC) PD: 81 (17 mBCC; 64 laBCC) ADA: 125 (44 mBCC; 81 laBCC)
R2810-ONC-1624 Phase 3 01 Mar 2020/ongoing	A Global, Randomized, Phase 3, Open-Label Study of REGN2810 (Anti-PD-1 Antibody) Versus Platinum-Based Chemotherapy in First-Line Treatment of Patients with Advanced or Metastatic PD-L1 + Non-Small Cell Lung Cancer (N = 710 [356 randomized to cemiplimab])	PK: 345 ADA: 221	PK: 345 ADA: 221	NA
TOTAL		**PK: 1063** **ADA: 823**		**PK: 136** **PD: 81** **ADA: 129**

ADA = anti-drug antibody; BCC = basal cell carcinoma; EXP25 = expansion cohort 25; laBCC = locally advanced BCC; mBCC = metastatic BCC; NA = not applicable; PK = pharmacokinetics; REGN2810 = cemiplimab.

Analytical methods

For all 4 studies, serum samples for quantitation of functional cemiplimab were analysed using a validated enzymelinked immunosorbent assay with a lower limit of quantitation of 78 ng/mL cemiplimab in neat serum. The validated method for detecting ADA is a non-quantitative, titer-based, electrochemiluminescent bridging immunoassay for screening, confirmation and titer determination. The method determined a drug tolerance of 415 µg/mL cemiplimab at a 100 ng/mL ADA sensitivity level. The NAb method is an electrochemiluminescence-based competitive ligand binding assay. The bioanalytical methods used to determine the concentration of functional cemiplimab and to assess immunogenicity in human serum samples are the same assays assessed in the original cemiplimab marketing application for CSCC.

Population PK analyses

The population PK of cemiplimab has been characterized by nonlinear mixed-effects modelling using FOCE with interaction in NONMEM; Uppsala University R version 3.6.1 and R packages of "margsolve" (0.8.12) were used for figures and for simulations.

The initial PopPK model for cemiplimab was a two-compartment model with zero-order IV infusion, linear elimination, residual error modelled as additive and proportional residual error and time-varying clearance described by a sigmoid-E_{max} function including a Hill exponent. The initial Pop PK model was based on data (N=505) from studies 1423 and 1540 at an earlier data cut-off and later updated with more data (N=48) from Study 1540. In the current submission, the Pop PK model was updated with new data from patients with different solid tumor types (BCC, CSCC, NSCLC and others) who received cemiplimab 350 mg Q3W from Studies 1423, 1540, 1620 and 1624. The Pop PK population included a total of 17193 post dose concentration data from 1062 patients of which 81 concentrations were BLQ.

Table 2 Summary of population by tumour type in the analysis dataset

Tumor Type	Study ID	Number of Patients	Total
BCC	Study 1423	4	136
	Study 1620	132	
CSCC	Study 1423	26	214
	Study 1540	188	
NSCLC	Study 1423	71	416
	Study 1624	345	
OTHERS	Study 1423	296	296
Total			1062

CSCC = Cutaneous squamous-cell carcinoma; BCC = Basal cell carcinoma; NSCLC = Non-small cell lung cancer
Note: Others includes non-specified in dose escalation (DE) cohorts, ie, HN = Head and neck; BC = Breast cancer; ST = Solid tumors; CRC = Colorectal cancer; HCC = Hepatocellular carcinoma; GBM = Glioblastoma multiforme; rGBM = Recurrent glioblastoma; HIV = Human immunodeficiency virus; CC = Cervical cancer in study 1423.

The final base model (BASE006) for cemiplimab in patients with solid tumors was a 2-compartment model with zero-order IV infusion, linear elimination with a time-dependent clearance (sigmoid E_{max} function) and time-varying albumin and baseline body weight as covariates.

Elimination of cemiplimab by a concentration-dependent clearance was evaluated in the initial Pop PK report (not available) and tested again. Base models incorporating a concentration-dependent clearance

(Michaelis–Menten elimination) did not provide a better fit. Inclusion of both concentration-dependent clearance and time-dependent clearance did not perform better than using time-dependent CL only. Albumin was inversely correlated with the clearance of cemiplimab, ie, the higher albumin level, the lower clearance. The testing also indicated time-dependent CL could be induced by other unknown factors, aside of time-varying albumin.

Covariate screening was conducted graphically using plots of empirical Bayes estimates of random effects. Potential covariates that are predictive of PK variability of cemiplimab were tested using a stepwise covariate search that includes a forward selection process followed by a backward elimination procedure with statistical significance testing. The final covariate model included four covariates, weight, albumin, IgG (only applicable to studies 1423 and 1540), and disease type (NSCLC relative to CSCC) on the elimination clearance CL. Baseline body weight was incorporated into the base structural model with the exponent fixed to 0.75 and 1.0 for CL/Q and V1/V2, respectively. Patients with NSCLC tended to have higher CL and thus lower exposure than patients with CSCC and BCC, but the resulting exposure across tumor types were comparable (<25%).

Nonparametric bootstrap was performed on 500 replicate datasets and resulted in 95% CIs for population PK parameter estimates. Of the 500 runs, 238 (~47.6%) runs converged. Table 25 show the final parameter estimates with bootstrap results. The η-shrinkage ranged from 18.5 to 30.4%. The highest η-shrinkage was observed for EMAX. The conditional number was <10.

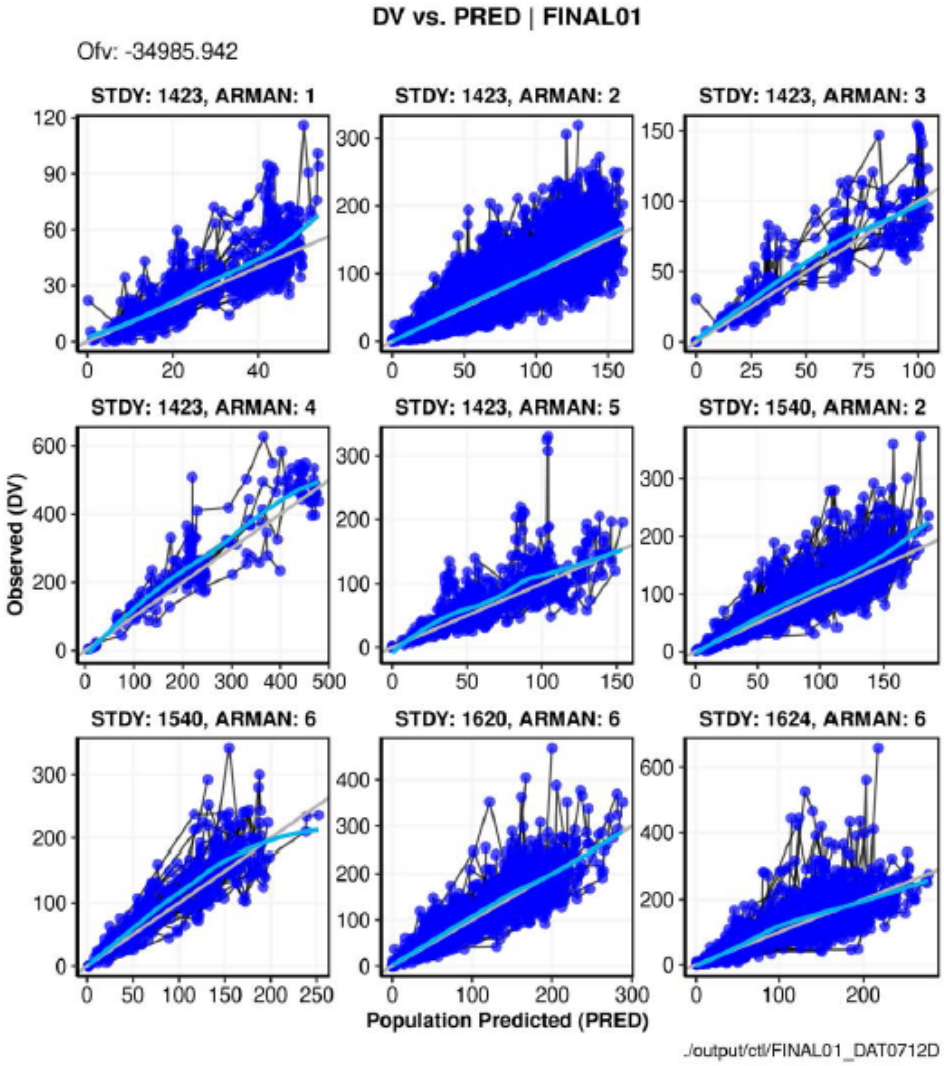
Table 25: Summary of Parameter Values after Modelling with Analysis Dataset or Bootstrap Datasets for the Final Model

Parameter	Unit	Analysis Dataset	Bootstrap Datasets (N=238/500)		
		Estimate (RSE%)	Mean	Median	CI95
TVCL	L/day	0.262(1.43%)	0.260	0.261	[0.245-0.271]
TVQ	L/day	0.617(3.38%)	0.620	0.619	[0.544-0.696]
TVV1	L	3.29(0.837%)	3.296	3.295	[3.24-3.36]
TVV2	L	1.92(2.03%)	1.929	1.930	[1.79-2.08]
TVEMAX		-0.359(3.53%)	-0.354	-0.357	[-0.397--0.301]
TVT50	day	30.6(5.09%)	32.697	32.467	[26.1-39.5]
CL_ALB	unitless	-1.01(2.14%)	-1.009	-1.012	[-1.12--0.872]
CL_IGGBL	unitless	0.214(11%)	0.220	0.221	[0.160-0.279]
CL_NSCLC	unitless	0.184(10.4%)	0.182	0.182	[0.141-0.221]
IIV_CLQ		0.259(2.45%)	0.256	0.256	[0.236-0.280]
IIV_VSS		0.24(2.1%)	0.241	0.240	[0.228-0.254]
IIV_EMAX		0.405(6.19%)	0.411	0.406	[0.346-0.497]
IIV_T50		0.951(5.25%)	0.954	0.951	[0.845-1.08]

*HILL was fixed at 2.50.

The final model was evaluated by diagnostic plots. Figures below show population predicted vs observed concentrations, residual plots of CWRES vs time and predicted concentration. Visual predictive checks were constructed to evaluate the model predictability.

Figure 1 Population predicted (PRED) vs Observed (DVOR) concentrations by dose groups obtained from the final model



STDY = Study ID; ARMAN = Dose arm number; group 1 = 1 mg/kg Q2W; group 2 = 3 mg/kg Q2W; group 3 = 3 mg/kg Q3W; group 4 = 10 mg/kg Q2W; group 5 = 200 mg Q2W; group 6 = 350 mg Q3W
Note: The solid gray line is the unity line, the solid blue line is the loess smoothing line.

Figure 4.3.4.2 Left: Conditional Weighted Residuals (CWRES) vs Time and Right: Conditional Weighted Residuals (CWRES) vs Population Predicted Concentration (PRED), from the Final Model. Reference: Report R2810-PK-20039-SR-01V1, Figure 41 and Figure 42

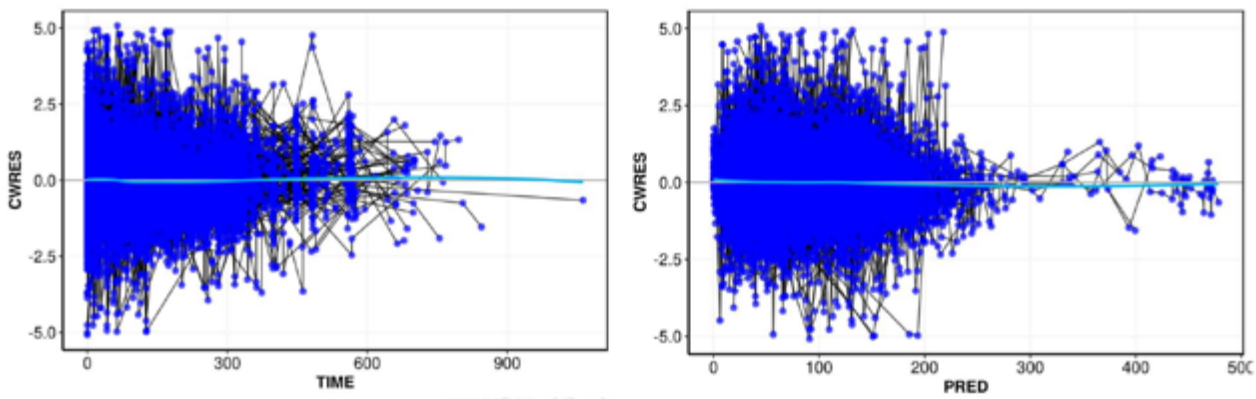
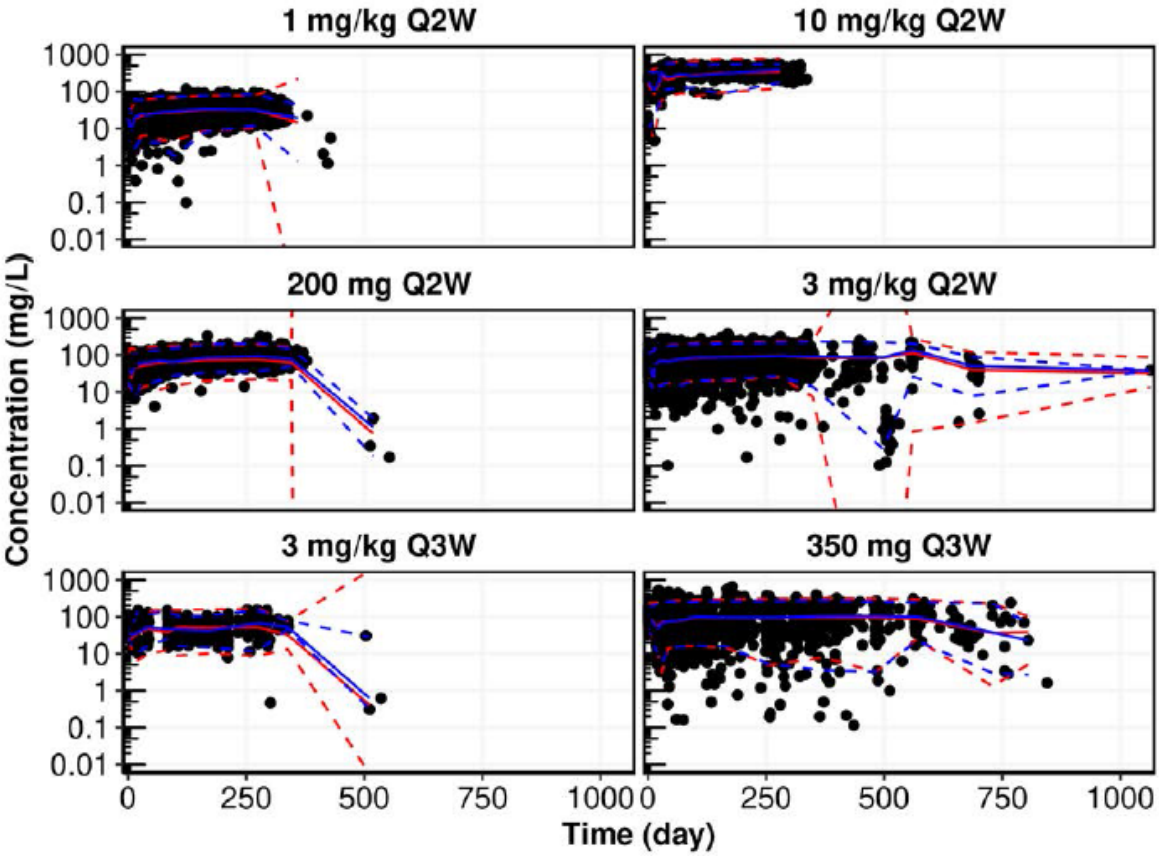


Figure 2 Visual predictive check for the final covariate model by dose groups



Note: Black solid circles correspond to individually observed concentrations, black solid lines, red and blue dashed lines correspond to geometric mean observed concentrations, geometric mean individually predicted concentrations (IPRED) and geometric mean typical predicted concentrations (PRED), respectively.

Updated Population PK Model

The interindividual variability (IIV) estimates on Emax and T50 were removed from the model since the data may not contain sufficient subject-level information to support the estimation of IIV for these parameters. The error structure was simplified by removing the estimation of proportional error and estimating log-additive error only. The off-diagonal covariance between inter-individual random effects on CLQ and VSS was also removed. The fixed effects structure was added a covariate effect of NSCLC on T50, which introduces a delay to the maximum time-varying clearance for NSCLC patients compared to the reference population but does not lead to a difference in steady-state clearance values. Goodness-of-fit and pcVPC plots are provided below.

Table 3 Population PK parameter estimates for the updated model

Table 3: Population Pharmacokinetic Parameter Estimates for the Updated Model (Run 6_6)

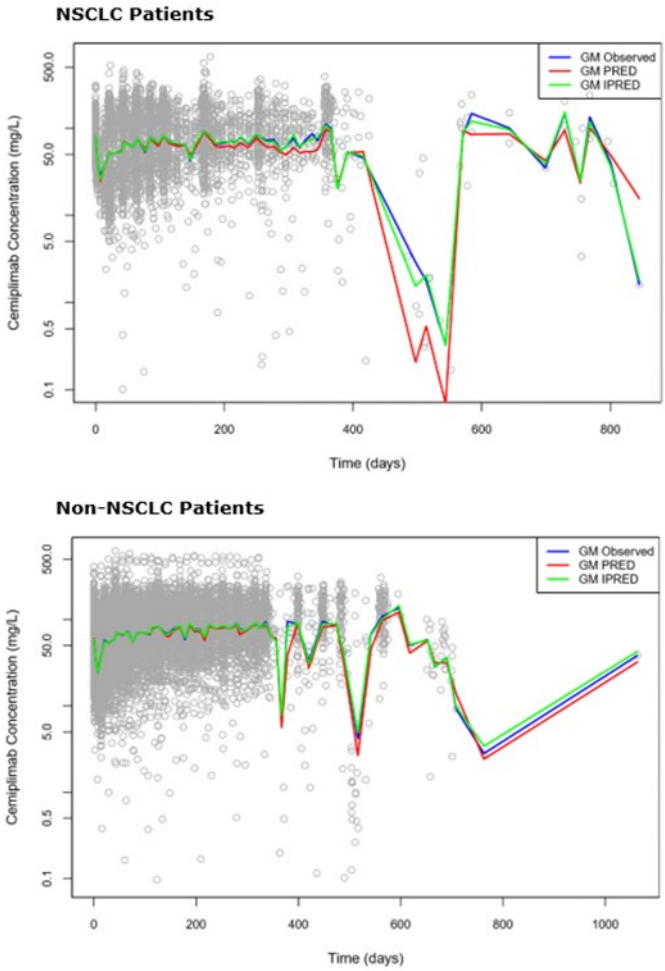
Parameter (Units)	Label	Estimate	%RSE	95% CI	Original Model Estimate	% Change in Estimate
TVCL0 (L/day)	Typical value of clearance at baseline	0.221	1.44	(0.215, 0.227)	0.262	-15.5
TVQ (L/day)	Typical value of inter-compartmental clearance	0.623	2.94	(0.588, 0.659)	0.617	1.1
TVV1 (L)	Typical value of central volume of distribution	3.30	0.97	(3.24, 3.36)	3.29	0.25
TVV2 (L)	Typical value of peripheral volume of distribution	2.48	1.21	(2.42, 2.54)	1.92	29.2
TVEMAX	Typical maximum effect in sigmoid model	-0.169	3.95	(-0.182, -0.156)	-0.359	53.0
TVT50 (day)	Typical half-life to achieve half of the maximum effect	34.8	6.21	(30.5, 39.0)	30.6	13.8
HILL	Hill exponent in sigmoid E_{max} model	2.50 FIX	-	-	2.50 FIX	-
CL_{ALB}	Covariate impact of time-varying albumin on CL	-1.12	1.63	(-1.15, -1.08)	-1.01	10.7
CL_{IGGBL}	Covariate impact of baseline IgG on CL	0.257	9.35	(0.210, 0.304)	0.214	19.9
CL_{NSCLC}	Covariate impact of NSCLC on CL	0.194	12.0	(0.148, 0.240)	0.184	5.2
$T50_{NSCLC}$	Covariate impact of NSCLC on T50	0.831	19.5	(0.514, 1.15)	-	-
CL_{WGTBL}	Covariate impact of weight on CL	0.75 FIX	-	-	0.75 FIX	-
Q_{WGTBL}	Covariate impact of weight on Q	0.75 FIX	-	-	0.75 FIX	-
$V1_{WGTBL}$	Covariate impact of weight on V1	1 FIX	-	-	1 FIX	-
$V2_{WGTBL}$	Covariate impact of weight on V2	1 FIX	-	-	1 FIX	-
IIV_CLQ	IIV on CL and Q	0.088 (29.7%)[a]	4.22	(0.0809, 0.0954)	0.067 (25.9%)[a]	31.7
IIV_CLQ_VSS	Correlation coefficient between IIV_CLQ and IIV_VSS	-	-	-	0.040	-
IIV_VSS	IIV on VSS	0.060 (24.6%)[a]	4.49	(0.0551, 0.0657)	0.058 (24.0%)[a]	4.6
IIV_EMAX	IIV on Emax	-	-	-	0.164 (40.5%)[a]	-
IIV_T50	IIV on ET50	-	-	-	0.904 (95.1%)[a]	-
RUVCV	proportional error (log-scale)	-	-	-	-1.73	-
RUVSD	additive error (log-scale)	0.196 [b]	0.24	(-0.197, -0.195)	0.163	-

%RSE = percent relative standard error; CI = confidence interval, calculated as +/- 1.96*standard error; WGT = body weight; ALB = albumin; IIV = inter-individual variability; CV = approximate coefficient of variation; $TVCL_{ss} = TVCL0 \cdot exp\left(\frac{Emax \cdot T^{\gamma}}{T50^{\gamma} + T^{\gamma}}\right)$

[a] Value represents percent coefficient of variation (CV%)
[b] Residual error is represented as a positive value by calculating the square root of (estimate)^2

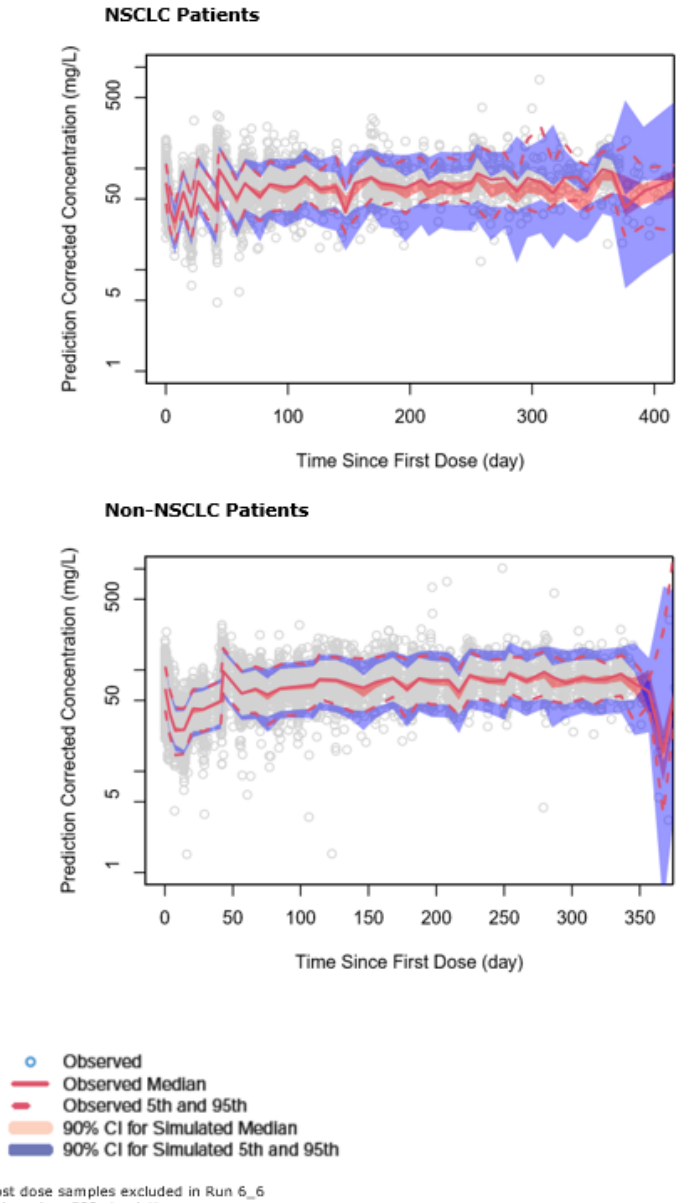
Note: 465 post dose samples were excluded in Run 6_6
Note: Eta shrinkage was 5.9% for CL and Q and 7.1% for VSS in Run 6_6

Figure 4: **Goodness-of-Fit for Updated Model (Run 6_6)**



IIV = inter-individual variability; GM = geometric mean
Note: 465 post dose samples excluded in Run 6_6

Figure 5: **Prediction-Corrected Visual Predictive Check for Updated Model (Run 6_6)**



Note: 465 post dose samples excluded in Run 6_6
Note: pcVPC based on 500 simulations

Simulation of exposure metrics

The final population PK model was used to generate the post-hoc estimates of individual PK parameters and exposure metrics for each subject in the analysis population. The post-hoc analysis indicated that cemiplimab clearance (mean, percent coefficient of variation [CV%]) at baseline is 0.293 L/day (33.1%) and that clearance decreased by 29.4% (35.3% in responders) to 0.203 L/day (40.2%) at steady-state. The elimination half-life of cemiplimab at steady state was 20.3 days (29.2%) in the overall population and slightly longer, 22.2 days (25.9%), in responders.

Table 4 Descriptive statistics (mean, CV) of post -hoc estimates of Exposure metrics

(C_{min}, C_{max}, AUC_{6wks}) of Cemiplimab at First Dose and Steady-State in PopPK Patient Population (N=1062) with Solid Tumors Using the Final PK Population Model

Dose	First Dose			Steady-State		
	AUC_{6wks} (day*mg/L)	C_{max} (mg/L)	C_{min} (mg/L)	AUC_{6wks} (day*mg/L)	C_{max} (mg/L)	C_{min} (mg/L)
1 mg/kg Q2W	442(24.0%)	23.3(23.0%)	6.41(28.5%)	1230(34.5%)	45.1(27.4%)	22.0(40.9%)
3 mg/kg Q2W	1330(24.0%)	70.0(23.0%)	19.2(28.6%)	3670(34.5%)	135(27.4%)	65.9(40.9%)
10 mg/kg Q2W	4430(24.0%)	233(23.0%)	64.0(28.6%)	12200(34.5%)	449(27.4%)	220(40.9%)
350 mg Q3W	1770(26.6%)	112(25.9%)	22.1(34.0%)	3880(35.5%)	171(27.5%)	60.9(44.9%)

CV% = percent coefficient of variation; Q2W = Once every 2 weeks; Q3W = Once every 3 weeks
Note: N=1062 for each dosing regimen.

Table 5 Descriptive statistics (mean, CV) of post -hoc estimates of Exposure metrics of

Cemiplimab at First Dose and Steady-State at 350 mg Q3W in PopPK Patient Population (N=1062) with Solid Tumors Using the Final PK Population Model

Tumor Type	N	First Dose			Steady-State		
		AUC_{3wks} (day*mg/L)	C_{max} (mg/L)	C_{min} (mg/L)	AUC_{3wks} (day*mg/L)	C_{max} (mg/L)	C_{min} (mg/L)
All Tumor Types	1062	885(26.6%)	112(25.9%)	22.1(34.0%)	1940(35.5%)	171(27.5%)	60.9(44.9%)
BCC	136	943(25.5%)	110(25.5%)	25.9(29.6%)	2220(37.0%)	182(29.5%)	73.9(45.0%)
CSCC	214	915(26.4%)	110(27.2%)	24.1(30.3%)	2110(30.9%)	177(26.3%)	68.6(37.3%)
NSCLC	416	871(25.1%)	117(24.2%)	20.1(32.9%)	1800(33.5%)	168(25.4%)	53.3(43.8%)
OTHERS	296	855(28.5%)	106(26.6%)	21.6(36.0%)	1900(37.0%)	165(29.4%)	60.1(45.5%)

CV% = Percent coefficient of variation; CSCC = Cutaneous squamous-cell carcinoma; BCC = Basal cell carcinoma; NSCLC = Non-small cell lung cancer
Note: Others includes non-specified in dose escalation (DE) cohorts, ie, HN = Head and neck; BC = Breast cancer; ST = Solid tumors; CRC = Colorectal cancer; HCC = Hepatocellular carcinoma; GBM = Glioblastoma multiforme; rGBM = Recurrent glioblastoma; HIV = Human immunodeficiency virus; CC = Cervical cancer in study 1423.

Table 30: Descriptive Statistics (Mean, CV%) of Individual Predicted Estimates of Exposure of Cemiplimab at First Dose and Steady-State for the 350 mg Q3W Regimen by Tumor Type and by Response Category

Tumor Type	Responder/ All others	N	First Dose			Steady-State		
			AUC_{3wks} (day*mg/L)	C_{max} (mg/L)	C_{min} (mg/L)	AUC_{3wks} (day*mg/L)	C_{max} (mg/L)	C_{min} (mg/L)
BCC	0	106	975(26.9%)	113(27.4%)	27.0(29.8%)	2310(35.6%)	188(29.8%)	77.0(41.7%)
	1	30	917(18.6%)	106(16.1%)	25.2(28.1%)	2240(42.1%)	180(28.1%)	75.7(55.3%)
CSCC	0	118	917(26.8%)	111(27.1%)	24.1(31.8%)	2100(31.4%)	177(26.3%)	68.3(38.0%)
	1	96	886(20.4%)	105(21.1%)	23.5(23.8%)	2140(27.1%)	175(21.4%)	71.5(33.9%)
NSCLC	0	279	838(25.7%)	112(25.2%)	19.3(33.5%)	1690(33.9%)	160(26.0%)	49.7(44.7%)
	1	137	939(23.0%)	120(23.0%)	22.7(29.0%)	2100(29.1%)	184(23.1%)	65.8(36.8%)
OTHERS	0	295	861(29.0%)	106(26.9%)	22.0(36.5%)	1940(36.8%)	166(29.6%)	61.8(44.7%)
	1	1	888(0%)	105(0%)	23.9(0%)	1830(0%)	161(0%)	57.2(0%)

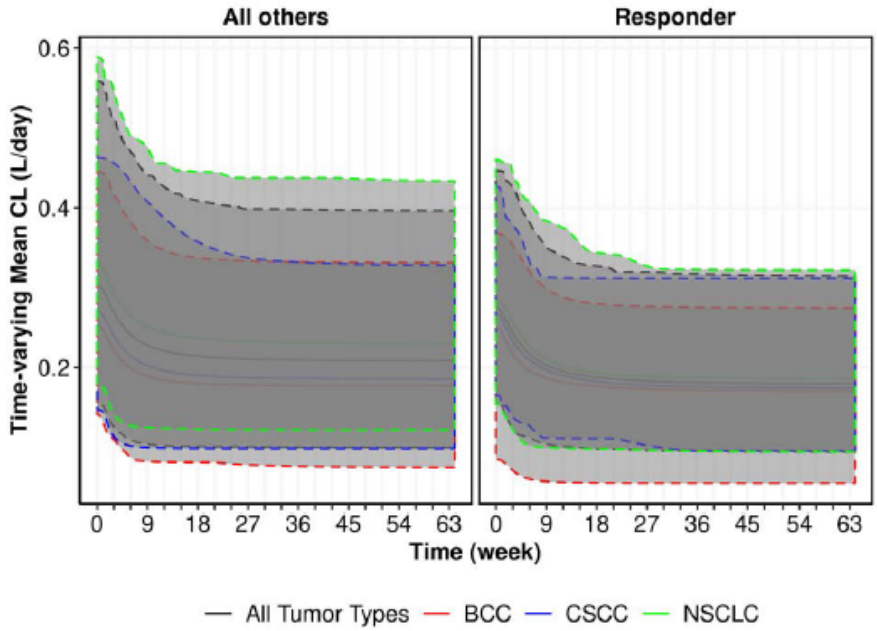
CV% = Percent coefficient of variation; N = Number of patients; CSCC = Cutaneous squamous-cell carcinoma; BCC = Basal cell carcinoma; NSCLC = Non-small cell lung cancer
Note: Others includes non-specified in dose escalation (DE) cohorts, ie, HN = Head and neck; BC = Breast cancer; ST = Solid

Table 35: Descriptive Statistics (Mean, CV%) for Individual Cemiplimab PK Parameters (CL and Half-Life) for the 350mg Q3W Regimen after the First Dose and at Steady-State by Tumor Type and by Response Category in PopPK Patient Population (N=1062) with Solid Tumors Estimated Using the Final PK Population Model

Tumor Type	Responder/All others	N	First Dose		Steady-State	
			CL (L/day)	Half-life (day)	CL (L/day)	Half-life (day)
BCC	0	106	0.248(30.9%)	16.2(17.6%)	0.188(38.9%)	22.1(25.0%)
	1	30	0.252(20.9%)	15.7(15.7%)	0.167(27.9%)	23.8(21.0%)
CSCC	0	118	0.268(30.4%)	15.0(20.7%)	0.197(39.6%)	21.0(28.8%)
	1	96	0.266(25.6%)	15.3(17.4%)	0.171(28.7%)	23.8(25.1%)
NSCLC	0	279	0.328(30.8%)	12.0(22.2%)	0.244(39.4%)	16.7(30.4%)
	1	137	0.280(29.7%)	13.3(21.5%)	0.177(30.5%)	20.7(26.0%)
OTHERS	0	295	0.307(35.5%)	14.0(20.4%)	0.212(40.9%)	20.3(27.2%)
	1	1	0.258(NA)	15.0(NA)	0.180(NA)	21.1(NA)

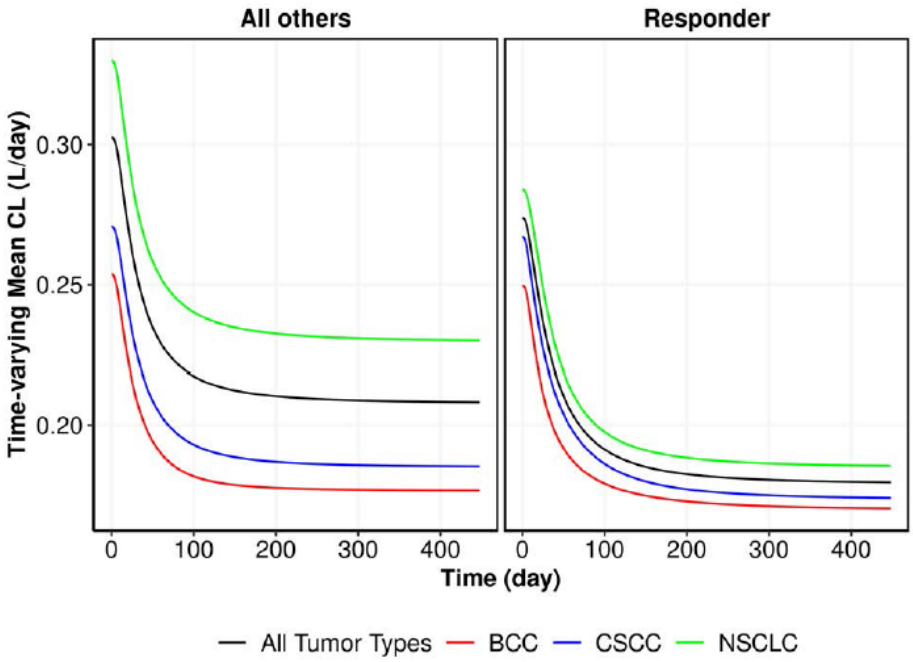
N = Number of patients; CV% = Percent coefficient of variation; CSCC = Cutaneous squamous-cell carcinoma; BCC = Basal cell carcinoma; NSCLC = Non-small cell lung cancer
Note: Responder: 1, All others: 0. Others includes non-specified in dose escalation (DE) cohorts, ie, HN = Head and neck; BC = Breast cancer; ST = Solid tumors; CRC = Colorectal cancer; HCC = Hepatocellular carcinoma; GBM = Glioblastoma multiforme; rGBM = Recurrent glioblastoma; HIV = Human immunodeficiency virus; CC = Cervical cancer in study 1423.

Figure 9: **Clearance Over Time (with 95%CI) in Responders vs All Others in Patients with BCC, CSCC, or NSCLC Compared to the Overall Patients**



CSCC = Cutaneous squamous-cell carcinoma; BCC = Basal cell carcinoma; NSCLC = Non-small cell lung cancer
Note: All Tumor types = In the overall PopPK patient population (n=1062), including advanced BCC: All Others (n=106), Responders (n=30); CSCC = All Others (n=118), Responders (n=96); NSCLC = All Others (n=279), Responders (n=137). Solid colored lines are for median CL for the corresponding tumor types, the dashed lines and shaded gray area represent 95% CI.

Figure 52: **Clearance Over Time in Responders vs All Others in Patients with BCC, CSCC, or NSCLC Compared to the Overall Patients**



CSCC = Cutaneous squamous-cell carcinoma; BCC = Basal cell carcinoma; NSCLC = Non-small cell lung cancer
Note: All Tumor types = In the overall PopPK patient population (n=1062), including advanced BCC: All Others (n=106), Responders (n=30); CSCC = All Others (n=118), Responders (n=96); NSCLC = All Others (n=279), Responders (n=137).

Covariate effects on exposure: The main identified sources of PK variability were body weight, albumin, baseline IgG (only applicable to studies 1423 and 1540), and tumor type (NSCLC relative to CSCC). Body weight increased slightly during the treatment period, however time-varying body weight was not identified as significant covariate. Cemiplimab clearance was greater in patients with lower

albumin levels, relative to a typical patient in the overall population. It was also observed that the albumin level was elevated in patients during the treatment period. Baseline PD-L1 levels did not affect cemiplimab exposure. The effect of these covariates on the post-hoc estimations of exposure (C_{max}, C_{trough}, and AUC) was relatively small (<25%), and within the typical PK variability observed (approximately 30%).

Figure 47: Boxplot of Individual Post-Hoc Estimates of $AUC_{6wks,ss}$ by Quartiles of Baseline Body Weight for 350 mg Q3W

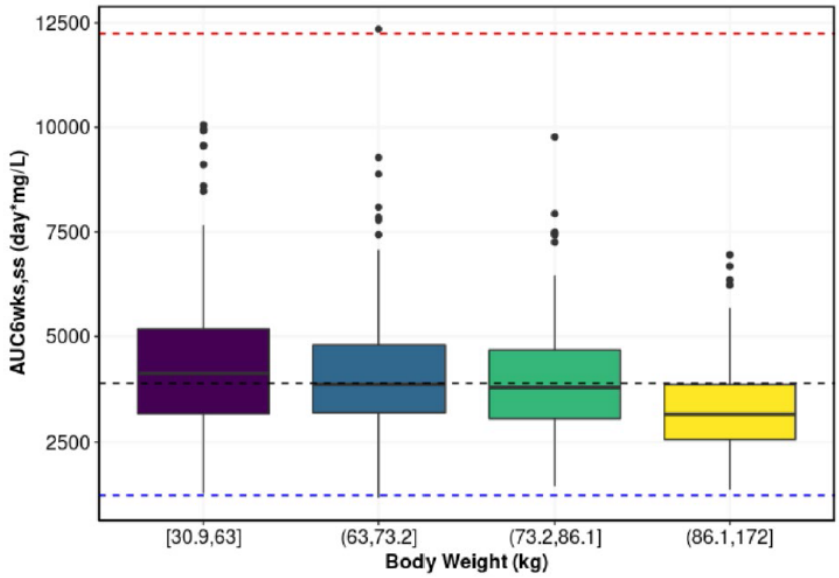


Figure 49: Boxplot of Individual Post-Hoc Estimates of $AUC_{6wks,ss}$ by Quartiles of Baseline Albumin for 350 mg Q3W

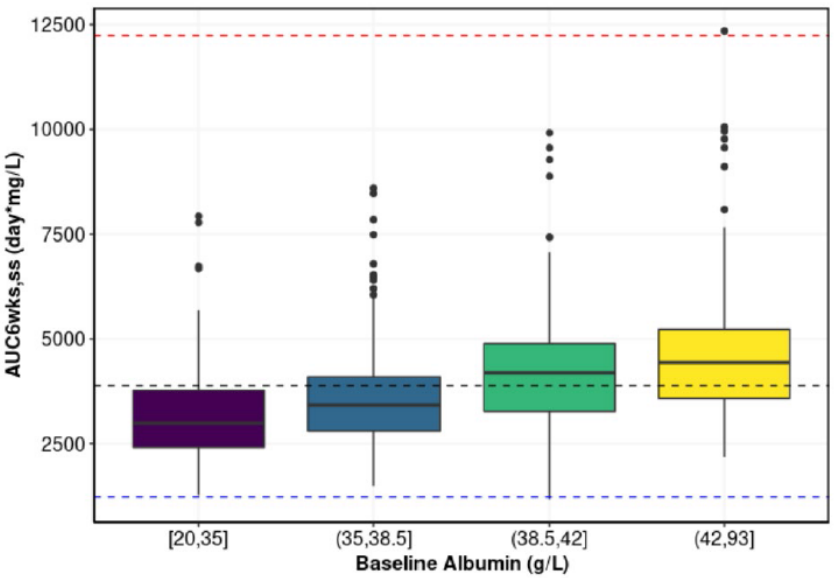


Figure 51: **Boxplot of Individual Post-Hoc Estimates of $AUC_{6wks,ss}$ by Quartiles of Baseline IgG for 350 mg Q3W**

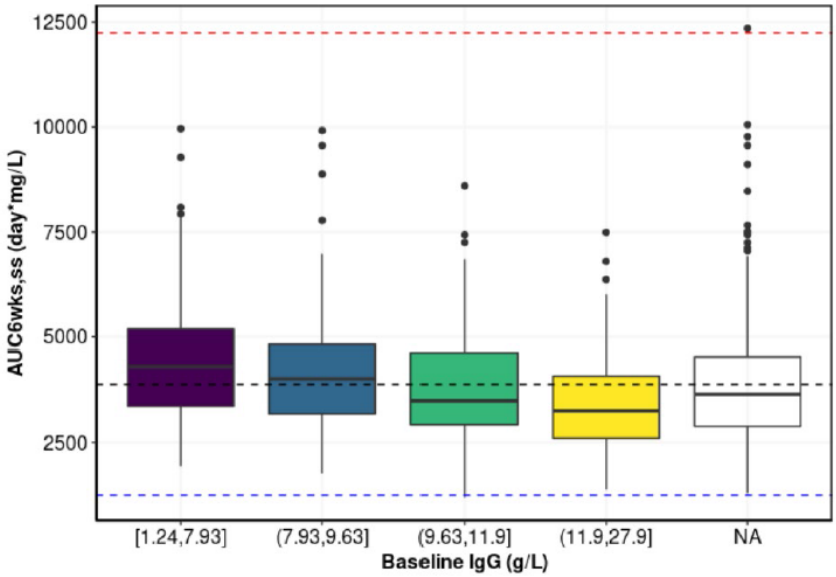
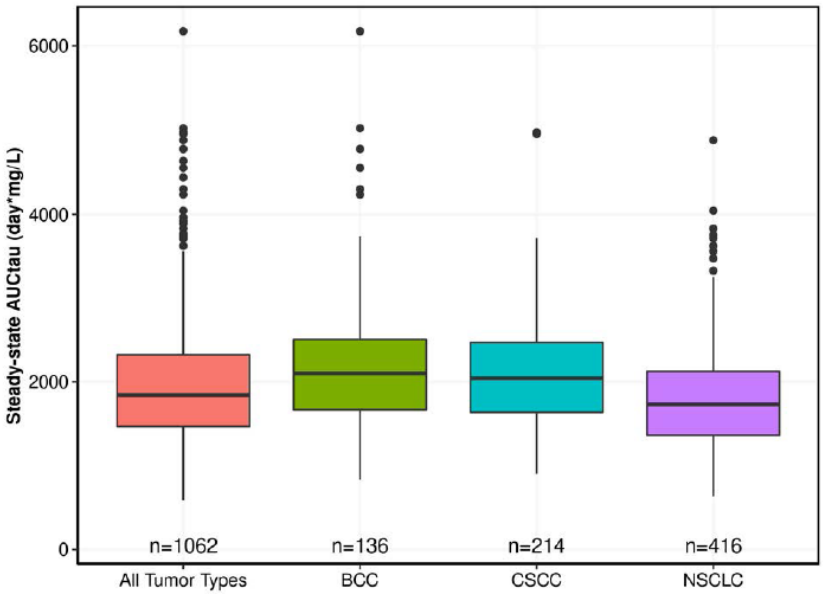
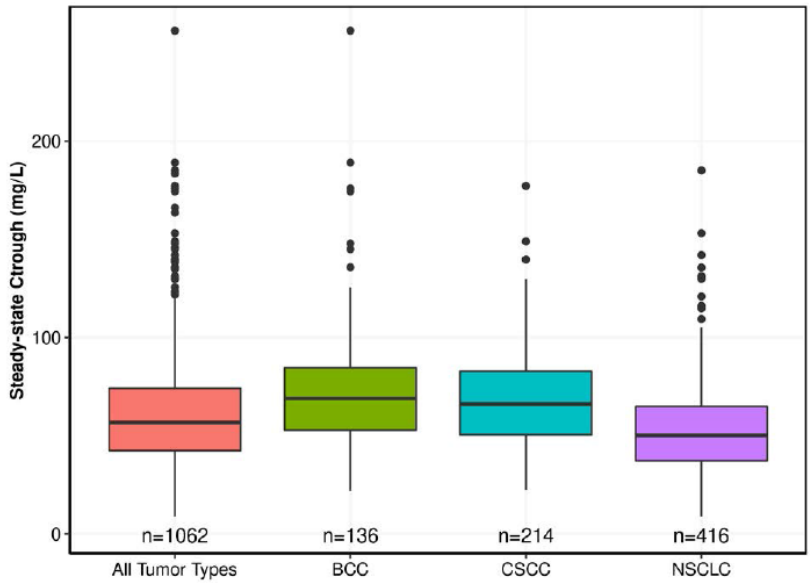


Figure 18: **Boxplot of Individual Predicted Cemiplimab $AUC_{tau,ss}$ for the 350 mg Q3W Regimen by Tumor Type in PopPK Patient Population (N=1062) with Solid Tumors**



N = Number of patients; CSCC = Cutaneous squamous cell carcinoma; BCC = Advanced basal cell carcinoma, NSCLC = Non-small cell lung cancer
Note: Bottom and top edges of box are 25th and 75th percentiles, respectively; Horizontal line is Median (50th percentile); Diamond is Mean; Vertical lines extending from top to bottom are the upper and lower fence, respectively; black dots are outliers defined by the '1.5 rule' namely when less than [Q1 - 1.5*IQR] or greater than [Q3 + 1.5*IQR], with IQR = Q3 - Q1.

Figure 17: Boxplot of Individual Predicted Cemiplimab $C_{trough,ss}$ for the 350 mg Q3W Regimen by Tumor Type in PopPK Patient Population (N=1062) with Solid Tumors



N = Number of patients; CSCC = Cutaneous squamous cell carcinoma; BCC = Advanced basal cell carcinoma; NSCLC = Non-small cell lung cancer
Note: Bottom and top edges of box are 25th and 75th percentiles, respectively; Horizontal line is Median (50th percentile); Diamond is Mean; Vertical lines extending from top to bottom are the upper and lower fence, respectively; black dots are outliers defined by the '1.5 rule' namely when less than [Q1 - 1.5*IQR] or greater than [Q3 + 1.5*IQR], with IQR = Q3 - Q1.

Absorption

Cemiplimab was administered IV as a 30-minute infusion and peak concentrations (C_{max}) is typically reached at the end of infusion. Similar distribution profiles were observed in patients with advanced BCC (N=136 [132 patients in Study 1620 and 4 patients in Expansion Cohort 25 in Study 1423 and in the overall PopPK population (N=1062). In the FIH study 1423, rich PK sampling occurred after the first dose, allowing to assess Tmax, while in the pivotal phase 2/3 Studies 1540, 1620 and 1624, sparse PK sample collection was applied at pre-dose and end-of-infusion during treatment and at selected time points during follow up. Except for the FIH Study 1423, where Cmax could be estimated, concentrations at the end-of-infusion were referred to as 'Cmax'. While maximal cemiplimab concentrations are expected to be reached at the end of the 30-minute IV infusion, as anticipated for a monoclonal antibody with a slow clearance, very similar concentrations within the bioanalytical range of variability are observed at 1-hour and occasionally at 4-hours post-end-of-infusion. As a result, the median value for Tmax in the FIH Study 1423 is reported as 0.5 hours, with a range of 0.033 hours to 4.0 hours. Assessed by PopPK analysis in the overall PopPK population at 350 mg Q3W steady state Ctrough,ss and Cmax,ss were 60.9 mg/L (44.9%) and 171 mg/L (27.5%), respectively. In patients with advanced BCC in Study 1620, mean (CV%) values of cemiplimab exposure at steady state determined by population PK analysis were $C_{trough,ss}$ of 73.2 mg/L (45.2%) and C_{max} of 180 mg/L (28.6%).

Table 6 Observed PK parameters in patients with advanced BCC compared to all patients on cemiplimab monotherapy 3 mg/kg Q2W (study 1423)

Patients on 3 mg/kg Q2W Monotherapy	Assessment	N	C_{trough} (mg/L)	C_{max} (mg/L)	AUC_{2w} (day*mg/L)	$t_{1/2}$* (days)
			Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
BCC (EXP 25)	After First Dose	4	22.8 (5.35)	58.1 (13.4)	488 (158)	12.5 (2.00)
	At Steady State	4	50.9 (17.4)	106 (55.3)	NR	NR
All Patients	After First Dose	333	21.0 (12.6)	70.0 (30.3)	443 (168)	11.2 (5.19)
	At Steady State	333	60.5 (25.3)	129 (40.1)	NR	NR

AUC_{2w} = area under the concentration-time curve for 2 weeks; BCC = basal cell carcinoma; C_{max} = concentration at end of infusion; C_{trough} = trough concentration at the end of the dosing interval; EXP 25 = Expansion Cohort 25; N = number of patients; NR = not reported; Q2W = every 2 weeks; SD = standard deviation; $t_{1/2}$* = estimated elimination half-life is underestimated as assessed over a dosing interval.
All patients = all patients in Study 1423 at 3 mg/kg Q2W (monotherapy and combination therapy). Patients with advanced BCC were in Study 1423 EXP 25.

Table 7 Observed cemiplimab exposure (Ctrough and Cmax) after the first dose and at steady state in patients with advanced BCC at 350 mg Q3W monotherapy (study 1620)

Group	After the First Dose						At Steady State					
	C_{trough} (mg/L)			C_{max} (mg/L)			C_{trough} (mg/L)			C_{max} (mg/L)		
	n	Mean (SD)	Median (Q1:Q3)	n	Mean (SD)	Median (Q1:Q3)	n	Mean (SD)	Median (Q1:Q3)	n	Mean (SD)	Median (Q1:Q3)
mBCC (N=48)	41	30.0 (19.9)	26.1 (21.5: 33.2)	42	104 (26.4)	98.8 (83.3: 122)	24	59.8 (29.6)	55.9 (46.2: 78.8)	22	163 (56.0)	160 (132: 196)
laBCC (N=84)	78	29.8 (12.0)	27.9 (22.5: 35.2)	81	104 (45.5)	102 (83.2: 130)	66	68.6 (32.8)	62.3 (46.8: 79.3)	61	192 (91.6)	165 (139: 203)
Total (N=132)	119	29.8 (15.1)	27.6 (22.0: 35.0)	123	104 (39.9)	102 (83.2: 127)	90	66.2 (32.1)	61.1 (46.8: 79.3)	83	184 (84.3)	164 (135: 203)

laBCC = Locally advanced BCC; mBCC = Metastatic BCC; n = Number of patients; Q = Quartile; SD = standard deviation.
After first dose: C_{trough} at cycle 1 day 22 pre-infusion, C_{max} at cycle 1 day 1 end of infusion.
Steady state: C_{trough} at cycle 3 day 1 pre-infusion, C_{max} at cycle 3 day 1 end of infusion.
Note: Two patients (Patient 276024002 with mBCC and Patient 840008001 with laBCC) had no end-of-infusion PK sample taken on cycle 1 day 1 and no PK samples taken on cycle 1 day 22 and on cycle 3 day 1.
PK analysis set: 48 patients with mBCC; 84 patients with laBCC; 132 patients total (advanced BCC).

Table 8 Population PK estimates of cemiplimabexposure in patients with solid tumours in the overall popPK population and patients with advanced BCC receiving 350 mg Q3W

After first Dose			At Steady State		
Parameter	**Units**	**Mean (CV%)**	**Parameter**	**Units**	**Mean (CV%)**
All Patients with Solid Tumors (N=1062)					
$C_{max,3wk}$	mg/L	112(25.9%)	$C_{max,ss}$	mg/L	171(27.5%)
$C_{trough,3wk}$	mg/L	22.1(34.0%)	$C_{trough,ss}$	mg/L	60.9(44.9%)
AUC_{3wk}	mg*day/L	885(26.6%)	$AUC_{3wk,ss}$	mg*day/L	1940(35.5%)
Patients with Advanced BCC (N=132; Study 1620)					
$C_{max,3wk}$	mg/L	109(23.7%)	$C_{max,ss}$	mg/L	180(28.6%)
$C_{trough,3wk}$	mg/L	25.6(28.8%)	$C_{trough,ss}$	mg/L	73.2(45.2%)
AUC_{3wk}	mg*day/L	934(24.2%)	$AUC_{3wk,ss}$	mg*day/L	2200(36.8%)
Overall PopPK population (N=1062 patients). The last dose in the simulations is at week 48 Data Source: Module 5.3.3.5 Population PK Report R2810-PK-20039-SR-01V1 Table 29 and Table 37					

Distribution

Based on PopPK analysis, the mean (CV%) total volume of distribution at steady state is 5.3 L.

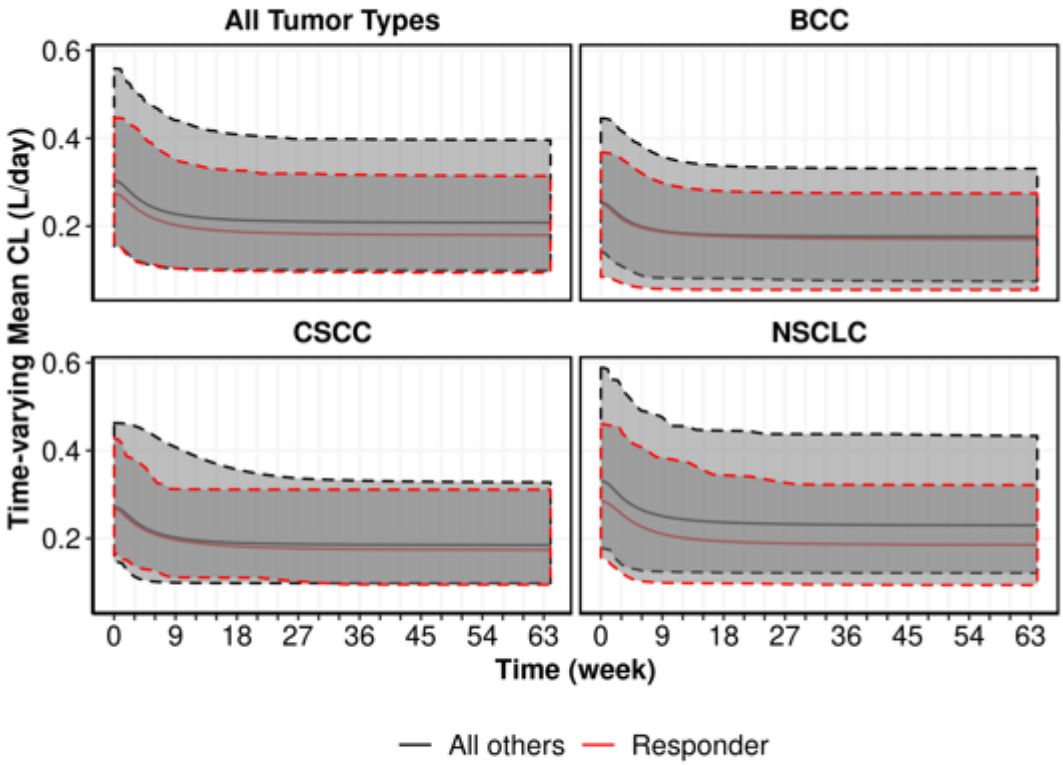
Elimination

The clearance of cemiplimab is independent of dose for the regimens studied (1 mg/kg to 10 mg/kg every 2 weeks [Q2W]. Due to study design and the need for continued treatment (where appropriate) limited data were available to fully characterize cemiplimab PK in the off-treatment period.

Clearance (mean CV%) of cemiplimab after the first dose is approximately 0.293 L/day (33.1%). After repeated dosing, total clearance (CL) appeared to decrease by approximately 29.4% over the first 4 to 5 months of treatment, resulting in a CL at steady state of 0.203 L/day (40.2%). The mean (CV%) within-treatment interval half-life at steady state as is 20.3 days (29.2%).

The clearance at baseline and the time-dependent decrease in clearance over time in 'responders' and 'all others' across different tumour types (advanced BCC, advanced CSCC, and advanced NSCLC) is shown below.

Figure 6: Clearance over Time in Patients with Advanced BCC, Advanced CSCC, or Advanced NSCLC, Compared to the Overall PopPK Population of Patients with Solid Tumors, by Responder Category



Notes: Post-hoc estimates in the Overall Population of Patients with Solid Tumors (N=1062). All Tumor types = In the overall PopPK patient population (n=1062), including advanced BCC: All Others (n=106), Responders (n=30); CSCC: All Others (n=118), Responders (n=96); NSCLC: All Others (n=279), Responders (n=137).
BCC = basal cell carcinoma; CSCC = cutaneous squamous-cell carcinoma; NSCLC = non-small-cell lung cancer.
Source: Source: Module 5.3.3.5 Population PK Report R2810-PK-20039-SR-01V1 Figure 10

In the overall PopPK population (N=1062; below) after repeated dosing, the total clearance of cemiplimab appears to decrease over time by about 29.4% from a baseline value of 0.293 L/day (33.1%) down to 0.203 L/day (40.2%; below). The decrease in clearance was somewhat larger in patients who were considered "responders" to cemiplimab (-35.3%) compared with "all others" (-26.7%)

Table 9: Summary of the overall population PK and PK analysis set

Table 7: Summary of the Overall PopPK Population and PK Analysis Set

Study	Dose	Number of Patients	Number of Post-dose PK Samples
Study 1423 (N = 397)	1 mg/kg Q2W	27	897
	10 mg/kg Q2W	6	188
	200 mg Q2W	20	676
	3 mg/kg Q2W	332	7899
	3 mg/kg Q3W	12	292
Study 1540 (N = 188)	3 mg/kg Q2W	135	1937
	350 mg Q3W	53	505
Study 1620 (N = 132)	350 mg Q3W	132	1614
Study 1624 (N = 345)	350 mg Q3W	345	3185
Overall PopPK population		1062	17193

N = number of patients; Q2W = every 2 weeks; Q3W = every 3 weeks.
Source: Module 5.3.3.5 Population PK Report R2810-PK-20039-SR-01V1 Table 13.

Table 10: Descriptive Statistics for Individual Cemiplimab PK Parameters in the Overall PopPK Population of Patients with All Solid Tumors Estimated by the PopPK Model

Parameter	Mean (CV%)	SD
Clearance after the first dose (L/day)	0.293(33.1%)	0.0972
Clearance at steady state (L/day)	0.203(40.2%)	0.0814
Reduction in clearance (%)	29.4(49.2%)	14.5
Half-life at first dose (day)	13.9(22.5%)	3.12
Half-life at steady state (day)	20.3(29.2%)	5.94
Volume of distribution at steady state (L)	5.26(26.0%)	1.37

Overall PopPK Population (N=1062)
CV% = percent coefficient of variation; SD = standard deviation.
Source: Module 5.3.3.5 Population PK Report R2810-PK-20039-SR-01V1 Tables 31 and 32.

This observed difference in the time-varying clearance between "responders" and "all other" patients in the overall population is largely driven by the effect in patients with NSCLC; as the time-variant decrease). This time dependent decrease in clearance for "responders" versus "all other" patients with BCC was quite similar (29.6% versus 26.0%, respectively).

Based on the PopPK analysis, the between dose-interval mean half-life of cemiplimab at steady state in patients with solid tumors is 20.3 days (29.2%); in patients with advanced BCC it was 22.5 days (24.1%). As a result of the differences in change in clearance over time between patients with solid tumors considered "responders" and "all others", it was observed that patients who responded to cemiplimab treatment exhibit longer half-life at steady state than 'all others' with mean (CV%) values of 22.2 days [25.9%] and 19.5 days [29.9%], respectively. However, in patients with advanced BCC, where this is a very comparable time-variant change in clearance, the half-life between "responders" and "all other" patients were also quite similar, with a mean (CV%) elimination half-life at steady state of 23.8 days (21.0%) in "responders" and 22.1 days (25.0%) in "all others".

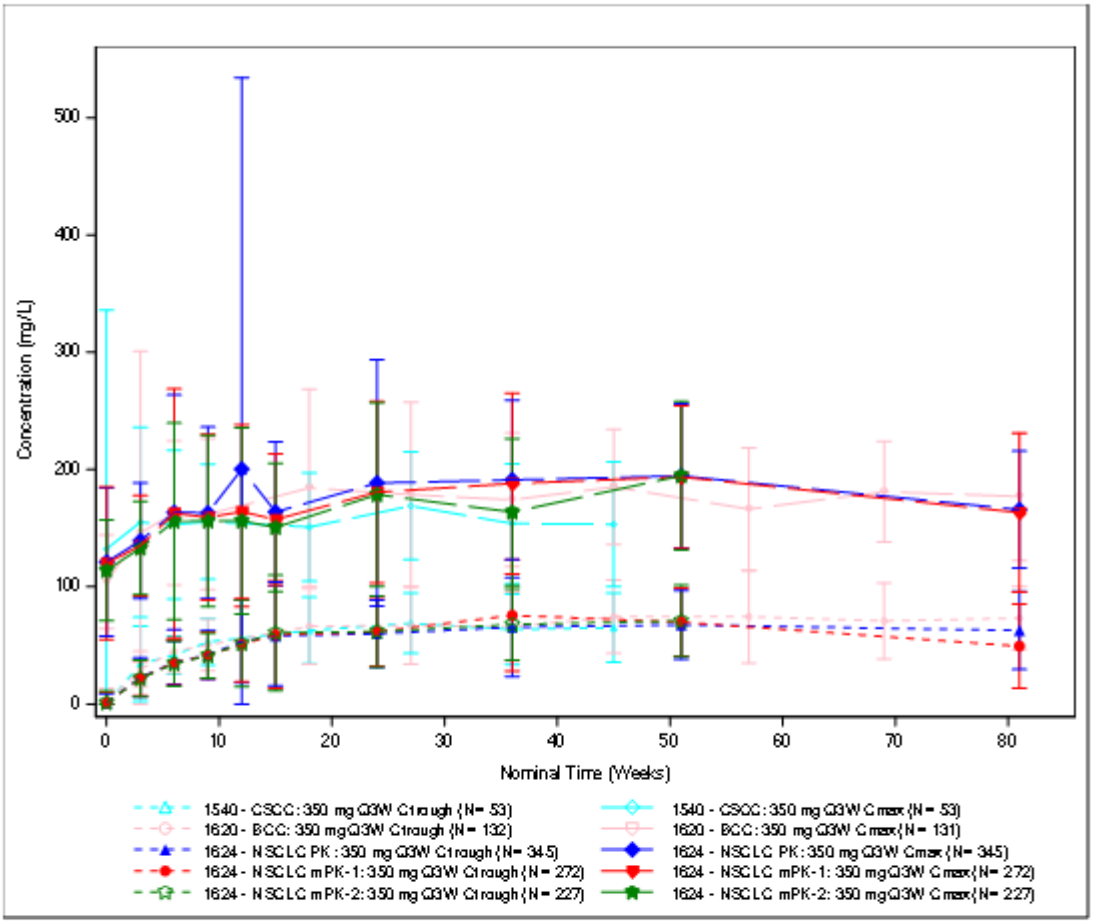
Dose proportionality and time dependencies

As described in the initial application, the mean exposure of cemiplimab generally increased in a dose proportional manner over the studied dosing regimens (1 mg/kg to 10 mg/kg Q2W); with a subtle signal of an enhanced deviation from dose proportionality in the C_{trough} at the end of the dosing interval for the lowest dose studied of 1 mg/kg (CSCC Submission). Typically, the observation of systemic linear PK is associated with saturation of the target-mediated pathway.

Linearity and dose proportionality of cemiplimab exposure was observed over a dose range of 1 mg/kg to 10 mg/kg Q2W in the FIH Study 1423, including both monotherapy and combination therapy, and different solid tumor types, including 4 patients with BCC in the expansion cohorts. This was further confirmed by PopPK analysis using integrated data of the overall PopPK population (1062 patients) of the 4 studies combined. In patients with advanced BCC treated with cemiplimab at 350 mg Q3W, systemic concentrations of cemiplimab were identified by PopPK analysis to reside within the linear dose-proportional range.

Cemiplimab exposure in patients with solid tumors reach steady state by 4 months (16 weeks) of cemiplimab dosing (>90% of plateau). This was assessed by PopPK analysis and illustrated by observed concentrations in patients with advanced BCC, advanced CSCC, and advanced NSCLC at 350 mg Q3W (Figure 3, below). The accumulation index upon Q3W dosing is 2.18, indicating an accumulation upon repeated dosing of approximately 2-fold. The PopPK model estimated that 90% the plateau of the AUC_{3wks} exposure is reached by week 16 (after 5 Q3W doses, and 97% of the plateau of AUC_{3wks} exposure is reached by week 25 (after 8 Q3W doses).

Figure 3: Observed Mean (±SD) Cemiplimab Ctrough and Cmax Concentrations by Time in Patients with Advanced CSCC (Study 1540), Advanced BCC (Study 1620), and Advanced NSCLC (Study 1624) Receiving 350 mg Q3W



Concentrations below the LLOQ were set to 0.
BCC = basal cell carcinoma; CSCC = cutaneous squamous cell carcinoma; laBCC = locally advanced BCC; laCSCC = locally advanced CSCC; mBCC = metastatic BCC; mCSCC= metastatic CSCC; N = number of patients in PK Analysis Set; n = number of patients; NSCLC= non-small cell lung cancer; Q = quartile; SD = Standard Deviation.
mPK-1 = modified PK-1 analysis set; mPK-2 = modified PK-2 analysis set.
Data Source: Study 1540 Final CSR Appendix 5 Clinical Pharmacology Report R2810-ONC-1540-CP-01V1; Study 1620 Interim CSR Appendix 5 Clinical Pharmacology Report R2810-ONC-1620-CP-01V1; Study 1624 Primary Analysis CSR Appendix 5 Clinical Pharmacology Report R2810-ONC-1624-CP-01V1

Special populations

Of all the covariates investigated in the overall PopPK population in 1062 patients across 4 studies, statistically significant intrinsic sources of PK variability were body weight, albumin, tumor type (NSCLC relative to CSCC), and baseline IgG levels (limited to Studies 1423 and 1540; Table 11 below).

While tumor type (NSCLC) was one of the statistically significant covariates, the resulting exposure across tumor types, including advanced CSCC, advanced BCC, and advanced NSCLC, was comparable (~10%).

No other tested covariates, including demographics (ie, age) and baseline PD-L1 level, had a statistically significant effect on cemiplimab exposure. The effect of all covariates combined on the post-hoc estimations of exposure (C_{max}, C_{min}, and AUC) was relatively small (<25%) and within the typical PK variability observed of approximately 30%.

Table 10: Summary of individual predicted estimates of cemiplimab exposure for the 350 Q3W after 1st dose and at steady state in the overall popPK population of patients with solid tumours by key covariates

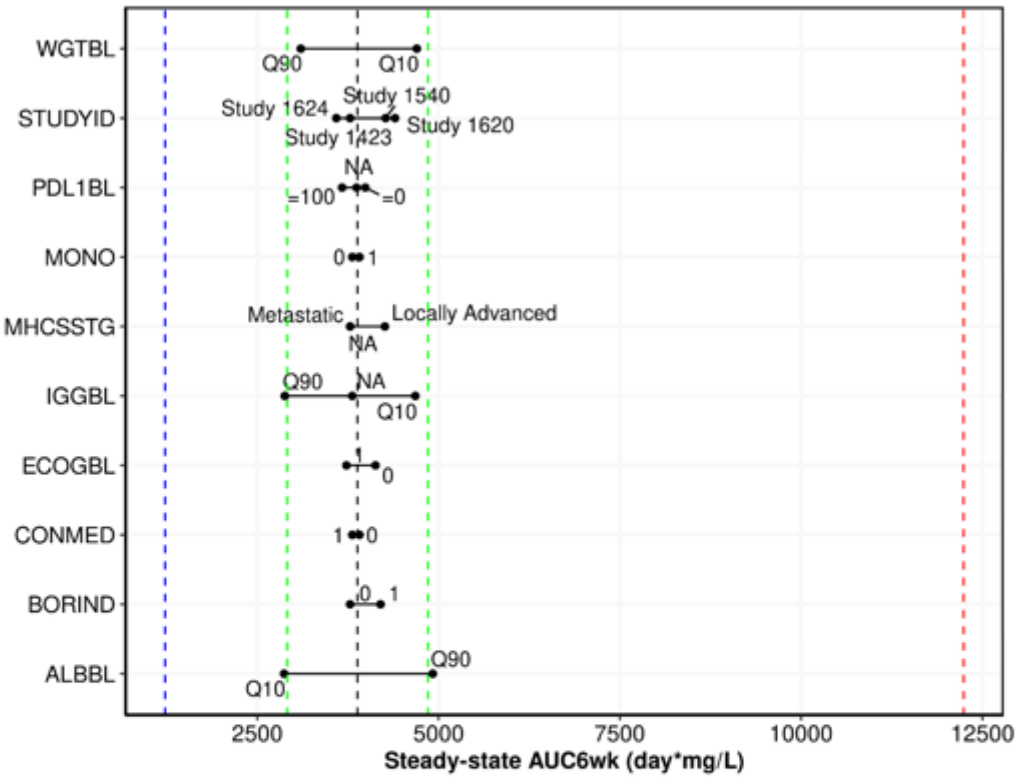
Covariate	Value	N	First Dose			Steady-state		
			AUC3wks (day*mg/L)	Cmax (mg/L)	Cmin (mg/L)	AUC3wks (day*mg/L)	Cmax (mg/L)	Cmin (mg/L)
Reference exposure		**1062**	**885 (26.6%)**	**112 (25.9%)**	**22.1 (34.0%)**	**1940 (35.5%)**	**171 (27.5%)**	**60.9 (44.9%)**
Baseline albumin (g/L)	<5th [20,29.3]	55	715(25.9%)	111(24.3%)	13.6(38.9%)	1310(30.8%)	143(23.8%)	33.6(42.4%)
	5-95th (29.3,46]	965	887(25.9%)	111(26.0%)	22.2(32.0%)	1950(33.3%)	171(26.7%)	61.1(41.6%)
	>95th (46,93]	42	1050(25.3%)	119(25.6%)	30.0(29.0%)	2660(39.8%)	208(31.5%)	91.5(48.1%)
Best overall response	0	798	874(28.0%)	111(26.9%)	21.7(35.9%)	1890(36.8%)	168(28.8%)	58.8(46.5%)
	1	264	917(21.9%)	114(22.7%)	23.1(27.8%)	2100(30.5%)	179(23.1%)	67.4(39.5%)
Concomitant medication flag	0	800	890(26.7%)	112(26.0%)	22.2(34.1%)	1950(35.8%)	172(27.8%)	61.3(45.3%)
	1	262	868(25.9%)	110(25.3%)	21.5(33.6%)	1900(34.4%)	168(26.6%)	59.7(43.8%)
Baseline ECOG status	0	405	902(25.2%)	109(25.2%)	23.5(31.6%)	2070(35.5%)	175(27.4%)	67.0(44.7%)
	1	657	874(27.3%)	113(26.2%)	21.2(35.0%)	1860(34.7%)	168(27.5%)	57.1(43.7%)
Baseline IgG (g/L)	<5th [1.24,5.31]	31	961(23.1%)	113(21.7%)	26.1(29.6%)	2370(32.0%)	191(24.7%)	80.2(39.2%)
	5-95th (5.31,17.1]	525	881(27.8%)	108(26.9%)	22.6(33.5%)	1980(34.3%)	170(28.1%)	63.2(41.6%)
	>95th (17.1,27.9]	29	746(31.0%)	107(32.0%)	15.5(35.3%)	1400(31.7%)	143(30.1%)	37.8(36.9%)

Covariate	Value	N	First Dose			Steady-state		
			AUC3wks (day*mg/L)	Cmax (mg/L)	Cmin (mg/L)	AUC3wks (day*mg/L)	Cmax (mg/L)	Cmin (mg/L)
Reference exposure		**1062**	**885 (26.6%)**	**112 (25.9%)**	**22.1 (34.0%)**	**1940 (35.5%)**	**171 (27.5%)**	**60.9 (44.9%)**
	NA	477	892(24.9%)	116(24.3%)	21.6(33.5%)	1910(36.0%)	172(26.5%)	58.5(47.3%)
Cancer Stage at Screening	Locally Advanced	231	939(27.3%)	114(26.9%)	24.6(33.3%)	2130(36.3%)	181(28.9%)	68.8(44.8%)
	Metastatic	460	879(23.9%)	114(24.4%)	21.2(31.0%)	1890(32.6%)	170(24.7%)	58.1(42.7%)
	NA	371	857(28.6%)	107(26.7%)	21.5(36.2%)	1890(37.1%)	165(29.3%)	59.5(45.8%)
Monotherapy Flag	0	267	863(28.5%)	108(26.6%)	21.6(36.5%)	1900(37.5%)	166(29.2%)	59.9(46.8%)
	1	795	892(25.9%)	113(25.6%)	22.2(33.2%)	1950(34.8%)	172(26.9%)	61.2(44.3%)
Baseline PD-L1	[0-50%]	249	895(29.6%)	111(29.9%)	22.9(35.1%)	1990(37.9%)	172(30.8%)	63.2(47.0%)
	[50%-70%)	103	869(23.8%)	114(24.8%)	20.4(29.2%)	1830(30.6%)	168(24.7%)	55.1(39.2%)
	[70%-90%)	101	878(25.1%)	116(22.8%)	20.5(34.4%)	1870(33.1%)	171(24.7%)	56.7(42.8%)
	[90%-100%]	95	859(25.2%)	117(24.2%)	19.5(34.3%)	1750(34.4%)	166(25.6%)	51.2(45.9%)
	NA	514	889(26.0%)	110(24.7%)	22.8(33.2%)	1990(35.1%)	171(27.2%)	63.6(43.8%)
STUDYID	Study 1423	397	856(28.2%)	107(26.5%)	21.6(35.6%)	1890(36.4%)	165(28.8%)	59.6(45.1%)
	Study 1540	188	927(26.6%)	111(27.5%)	24.4(30.4%)	2140(31.1%)	179(26.6%)	69.7(37.3%)
	Study 1620	132	934(24.2%)	109(23.7%)	25.6(28.8%)	2200(36.8%)	180(28.6%)	73.2(45.2%)
	Study 1624	345	876(24.9%)	118(24.1%)	20.0(32.8%)	1800(33.2%)	169(25.3%)	53.0(43.5%)
Baseline body weight (kg)	<5th [30.9,50.1]	54	1190(29.4%)	153(25.9%)	28.8(39.6%)	2590(38.5%)	231(29.6%)	80.2(48.5%)

Covariate	Value	N	First Dose			Steady-state		
			AUC3wks (day*mg/L)	Cmax (mg/L)	Cmin (mg/L)	AUC3wks (day*mg/L)	Cmax (mg/L)	Cmin (mg/L)
Reference exposure		**1062**	**885 (26.6%)**	**112 (25.9%)**	**22.1 (34.0%)**	**1940 (35.5%)**	**171 (27.5%)**	**60.9 (44.9%)**
	5-95th (50.1,107]	956	881(24.2%)	111(23.2%)	22.0(32.3%)	1930(33.7%)	170(25.1%)	60.6(43.6%)
	>95th (107,172]	52	649(19.7%)	79.4(22.3%)	16.7(25.2%)	1440(29.8%)	124(21.9%)	45.9(39.4%)

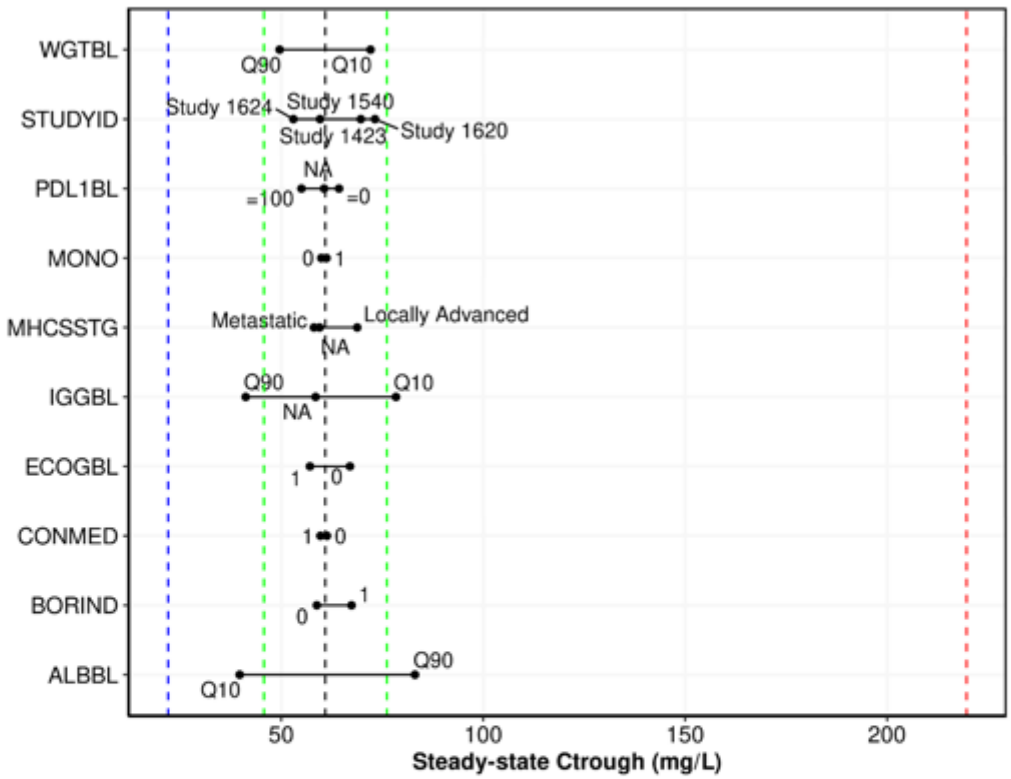
Note: Summary data are presented as mean (CV%). Post-hoc estimates in the overall PopPK population of patients with solid tumors (N=1062).
CV% = percent coefficient of variation; NA = not available or missing.
Baseline weight was selected as a covariate due to high correlation found between WGTBL, BMIBL and BSABL.
Source: Module 5.3.3.5 Population PK Report R2810-PK-20039-SR-01V1 Table 37.

Figure 7: Effect of Relevant Intrinsic Factors on Individual Predicted Steady-State Cemiplimab Exposure –$AUC_{6wk,ss}$ in the Overall PopPK Population of Patients with Solid Tumors (N=1062)



Notes: Post-hoc estimates in the Overall Population of Patients with Solid Tumors (N=1062).
WGTBL: baseline body weight; STUDYID: study ID; PDL1BL: baseline PD-L1; MONO: Monotherapy Flag, MHCSSTG: Cancer Stage at Screening (metastatic or local advanced; IGGBL: baseline IgG, ECOGBL: baseline ECOG status, CONMED: Concomitant Medication Flag, ALBBL: baseline albumin.
The black dashed reference line represents the median steady-state AUC6wk (3880 day*mg/L) at 350 mg Q3W. 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, or sub-population indicated by categorical variables. The length of bar from the dashed reference line represents the deviation from the reference exposure at 350 mg Q3W. The blue line and red line represent the median exposures of 1230 day*mg/L and 12200 day*mg/L at 1 mg/kg Q2W and 10 mg/kg Q2W, respectively. The green lines represent the 75% or 125% of the reference exposure. A typical patient in this patient population is a 65-year-old white male weighing 75 kg, albumin level (ALB) of 38 g/L, lactate dehydrogenase (LDH) of 250 IU/L, alkaline phosphatase (ALP) of 85 IU/L, alanine aminotransferase (ALT) of 20 IU/L, creatinine (CREAT) of 78 µmol/L, immunoglobulin G (IgG) of 10 g/L.
Source: Module 5.3.3.5 Population PK Report R2810-PK-20039-SR-01V1 Figure 11.

Figure 8: Effect of Relevant Intrinsic Factors on Individual Predicted Steady-State Cemiplimab Exposure – $C_{trough,ss}$ in the Overall PopPK Population of Patients with Solid Tumors (N=1062)



Notes: Post-hoc estimates in the Overall Population of Patients with Solid Tumors (N=1062).
WGTBL: baseline body weight; STUDYID: study ID; PDL1BL: baseline PD-L1; MONO: Monotherapy Flag, MHCSSTG: Cancer Stage at Screening (metastatic or local advanced; IGGBL: baseline IgG, ECOGBL: baseline ECOG status, CONMED: Concomitant Medication (ie, corticosteroids), ALBBL: baseline albumin.
The black dashed reference line represents the median steady-state Ctrough (60.9 mg/L) at 350 mg Q3W. 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, or 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 deviation from the reference exposure at 350 mg Q3W. The blue line and red line represent the median concentrations of 22.0 mg/L and 220 mg/L at 1 mg/kg Q2W and 10 mg/kg Q2W, respectively. The green lines represent the 75% or 125% of the reference exposure. A typical patient in this patient population is a 65-year-old white male weighing 75 kg, albumin level (ALB) of 38 g/L, lactate dehydrogenase (LDH) of 250 IU/L, alkaline phosphatase (ALP) of 85 IU/L, alanine aminotransferase (ALT) of 20 IU/L, creatinine (CREAT) of 78 µmol/L, immunoglobulin G (IgG) of 10 g/L.
Source: Module 5.3.3.5 Population PK Report R2810-PK-20039-SR-01V1 Figure 12.

Body Weight

Typical of monoclonal antibodies and other large protein therapeutic agents for which the central compartment largely comprises the systemic volume, drug exposure is correlated with body weight and body mass index (BMI). Consistent with these findings, the PopPK analysis in the overall patient population with a mean body weight of 75.8 kg and ranging from 30.9 kg to 172 kg showed a modest decrease in cemiplimab exposure with increasing body weight with this fixed dosing regimen.

Given the small variation in C_{min} due to body weight, systemic concentrations of cemiplimab remain sufficient to maintain linear kinetics over the dosing intervals.

In mBCC patients, 5 patients had a BMI ≥30 kg/m2 and in this group no responses were noted, in laBCC patients with a BMI ≥30 kg/m2, ORR was 33.3% (7 of 21; 95% CI 14.6% to 57.0%) with a KM estimated median duration of response that has not been reached.

Patients with advanced BCC (n=132) on cemiplimab 350 mg Q3W therapy in the PopPK population, comprised 22 moderately obese (BMI 30 to 34.9 kg/m2), 8 severely obese (BMI 35 to 39.9 kg/m2) and 2 extremely obese (BMI ≥ 40 kg/m2) patients. Predicted cemiplimab exposure at steady state in moderately and severely obese patients was within the variability of exposure, although slightly lower (<-30%) than the population exposure. In very severely obese patients, exposure was slightly lower (-50%) compared to the overall patient population and with Cmin values >20 mg/L, thus still exceeding systemic target saturation.

Individual observed cemiplimab concentrations in patients with advanced BCC who received cemiplimab 350 mg Q3W with BMI ≥ 30 kg/m2 for laBCC patients (n=21) and for mBCC patients (n=11), in relation to their response based on Best Overall Response (BOR), showed that the 7 patients with laBCC (6 obese and 1 severely obese) responded to cemiplimab therapy.

Age

In the overall population of patients with solid tumors, age was 65 years on average, and ranged from 27 to 96 years. Based on the PopPK analysis, age did not affect the PK of cemiplimab in the overall PopPK population of patients with solid tumours; the same applies to the patients with advanced BCC.

Table 14: Summary of Individual Predicted Estimates of Cemiplimab Exposure in the Overall PopPK Population of Patients with Solid Tumors Receiving 350 mg Q3W, by Age Group

Age Groups	Age (years)	N	First Dose			Steady State		
			AUC_{tau} (day*mg/L)	C_{max} (mg/L)	C_{min} (mg/L)	AUC_{tau} (day*mg/L)	C_{max} (mg/L)	C_{min} (mg/L)
Group1	<65	517	878(26.9%)	112(25.9%)	21.6(35.3%)	1920(37.8%)	170(28.4%)	59.8(48.8%)
	>=65	545	891(26.3%)	111(25.8%)	22.5(32.8%)	1970(33.2%)	171(26.6%)	62.0(41.2%)
Group2	<65	517	878(26.9%)	112(25.9%)	21.6(35.3%)	1920(37.8%)	170(28.4%)	59.8(48.8%)
	>=65 to <75	343	879(27.6%)	111(27.2%)	21.8(34.2%)	1920(34.3%)	169(27.8%)	60.1(42.5%)
	>=75	202	912(23.9%)	112(23.5%)	23.5(30.1%)	2040(31.0%)	175(24.5%)	65.2(38.7%)
Group-3	<65	517	878(26.9%)	112(25.9%)	21.6(35.3%)	1920(37.8%)	170(28.4%)	59.8(48.8%)
	>=65 to <75	343	879(27.6%)	111(27.2%)	21.8(34.2%)	1920(34.3%)	169(27.8%)	60.1(42.5%)
	>=75 to <85	168	904(24.5%)	112(24.0%)	23.2(31.1%)	2020(32.4%)	174(25.4%)	64.4(40.4%)
	>=85	34	949(20.5%)	115(20.9%)	24.8(25.1%)	2130(23.8%)	182(19.4%)	68.6(30.0%)

Note: Summary data are presented as Mean (CV%). Post-hoc estimates in the overall PopPK population of patients with solid tumors (N=1062).
CV% = percent coefficient of variation; N = number of patients
Source: Module 5.3.3.5 Population PK Report R2810-PK-20039-SR-01V1 Table 47.

Sex

The complete patient population with solid tumors on cemiplimab treatment included 750 males and 312 females. Sex was not identified as a statistically significant covariate of cemiplimab exposure. A post-hoc analysis indicates that female patients tend to have higher exposure at 350 mg Q3W. This is caused by a

lower body weight in females compared to males in the studied population (i.e. 66 kg for females versus 76 kg for males).

Table 15: Summary of Individual Predicted Estimates of Cemiplimab Exposure in the Overall PopPK Population of Patients with Solid Tumors Receiving 350 mg Q3W, by Gender

Gender	N	First Dose			Steady State		
		AUC_{tau} (day*mg/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)	AUC_{tau} (day*mg/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
F	312	1000(25.7%)	125(24.5%)	25.3(33.8%)	2240(35.8%)	194(27.0%)	71.2(45.7%)
M	750	837(24.7%)	106(24.7%)	20.7(31.7%)	1820(32.6%)	161(25.3%)	56.6(41.7%)

Note: Summary data are presented as Mean (CV%). Post-hoc estimates in the overall PopPK population of patients with solid tumors (N=1062).
CV% = percent coefficient of variation; F = female; M = male; N = number of patients.
Source: Module 5.3.3.5 Population PK Report R2810-PK-20039-SR-01V1 Table 47.

Race and Ethnicity

Table 11 Summary of individual predicted estimates of cemiplimab exposure in the overall popPK population pf patients with solid tumours receiving 350 mg Q3W by race and ethnicity.

Group	Population	N	First Dose			Steady State		
			AUC_{tau} (day*mg/L)	C_{max} (mg/L)	C_{min} (mg/L)	AUC_{tau} (day*mg/L)	C_{max} (mg/L)	C_{min} (mg/L)
RACE	Missing	53	887(20.3%)	106(21.8%)		2020(28.3%)	170(22.0%)	65.7(35.7%)
	Other	78	939(27.0%)	127(23.9%)	21.6(37.4%)	1970(37.5%)	183(27.4%)	58.6(48.9%)
	White	931	880(26.8%)	111(25.9%)	22.0(34.2%)	1930(35.7%)	170(27.7%)	60.8(45.1%)
ETHNIC	HISPANIC OR LATINO	75	838(25.0%)	112(23.1%)	19.3(35.5%)	1760(36.7%)	163(25.5%)	53.1(49.5%)
	MISSING	33	918(18.9%)	107(20.5%)	25.1(22.7%)	2170(27.7%)	178(21.1%)	72.1(34.6%)
	NOT HISPANIC OR LATINO	938	889(27.0%)	112(26.3%)	22.2(34.2%)	1950(35.7%)	171(27.9%)	61.2(45.0%)
	NOT REPORTED	16	810(17.4%)	97.3(16.3%)	21.3(23.3%)	1810(23.0%)	154(17.5%)	58.1(29.1%)

Note: Summary data are presented as Mean (CV%). Post-hoc estimates in the overall PopPK population of patients with solid tumors (N=1062).
CV% = percent coefficient of variation; N = number of patients.

Baseline Albumin Level

Table 12 Summary of individual predicted estimates of cemiplimab exposure in the overall popPK population pf patients with solid tumours receiving 350 mg Q3W by baseline albumin levels

Baseline Albumin (g/L)	N	Baseline Albumin (g/L)	Baseline Body Weight (kg)	Baseline IgG (g/L)	$AUC_{3wks,ss}$ (day*mg/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
<30	76	27.5 (8.90%)	72.4 (26.2%)	11.2 (42.3%)	1360 (29.9%)	144 (22.6%)	35.9 (43.0%)
(30,35]	217	33.3 (4.08%)	75.9 (27.5%)	10.1 (42.0%)	1670 (32.9%)	155 (25.7%)	49.6 (42.3%)
>35	769	40.6 (9.51%)	76.0 (22.7%)	10.2 (33.3%)	2080 (33.4%)	178 (27.0%)	66.6 (41.3%)

Note: Summary data are presented as Mean (CV%). Post-hoc estimates in the overall PopPK population of patients with solid tumors (N=1062).
CV% = percent coefficient of variation; IgG = immunoglobulin G; N = number of patients.

Baseline Immunoglobulin Level

Table 13 Summary of individual predicted estimates of cemiplimab exposure in the overall popPK population pf patients with solid tumours receiving 350 mg Q3W by baseline IgG level

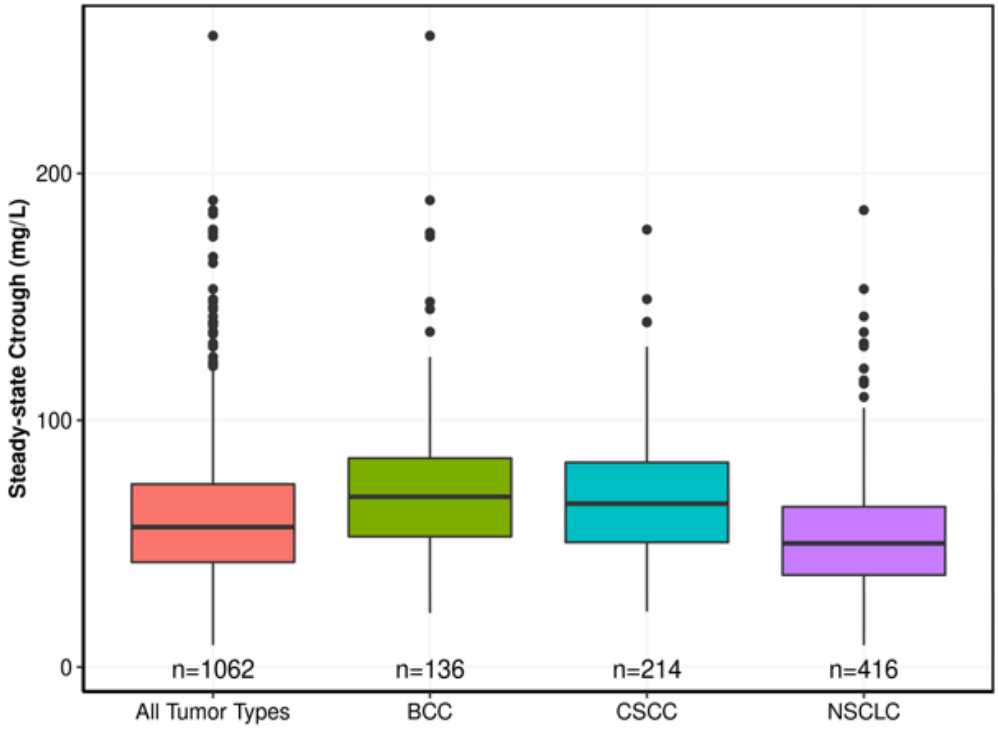
Quantile	Baseline IgG (g/L)	N	Baseline IgG (g/L)	Baseline Body Weight (kg)	Baseline Albumin (g/L)	$AUC_{3wks,ss}$ (day*mg/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
$<5^{th}$	[1.24, 5.31]	31	3.92 (29.4%)	76.5 (20.9%)	36.5 (12.7%)	2370 (32.0%)	191 (24.7%)	80.2 (39.2%)
$5\text{-}95^{th}$	(5.31, 17.1]	525	10.0 (25.1%)	78.5 (24.3%)	37.6 (12.6%)	1980 (34.3%)	170 (28.1%)	63.2 (41.6%)
$>95^{th}$	(17.1, 27.9]	29	20.9 (14.3%)	78.1 (26.3%)	34.9 (11.8%)	1400 (31.7%)	143 (30.1%)	37.8 (36.9%)
NA	NA	477	NA	72.6 (22.9%)	39.3 (15.1%)	1910 (36.0%)	172 (26.5%)	58.5 (47.3%)

Note: Summary data are presented as Mean (CV%). Post-hoc estimates in the overall PopPK population of patients with solid tumors (N=1062).
CV% = percent coefficient of variation; IgG = immunoglobulin G; N = number of patients; NA = not available.

Tumour Type

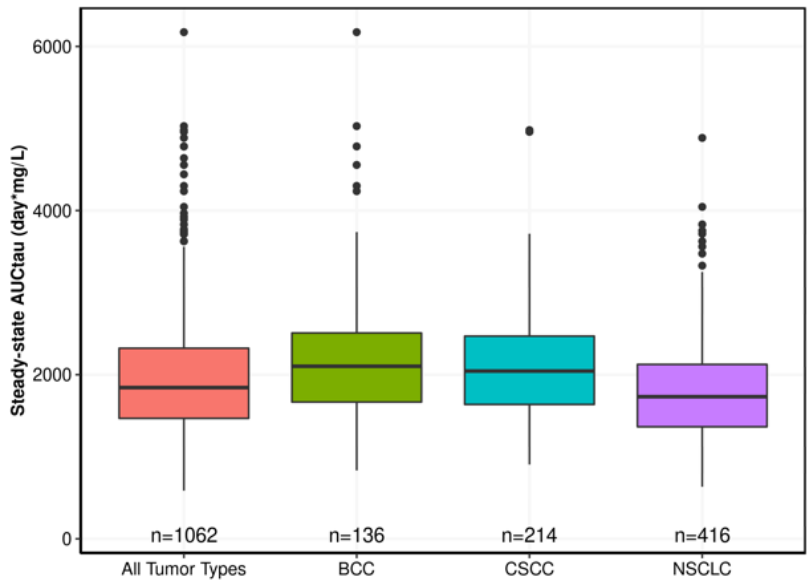
Exposures in patients with NSCLC were approximately 10% lower than in patients with CSCC or BCC, which is within the overall range of variability in exposure.

Figure 3 Box plots of $C_{trough,ss}$ by tumour type in patients with solid tumors, 350 mg Q3W.



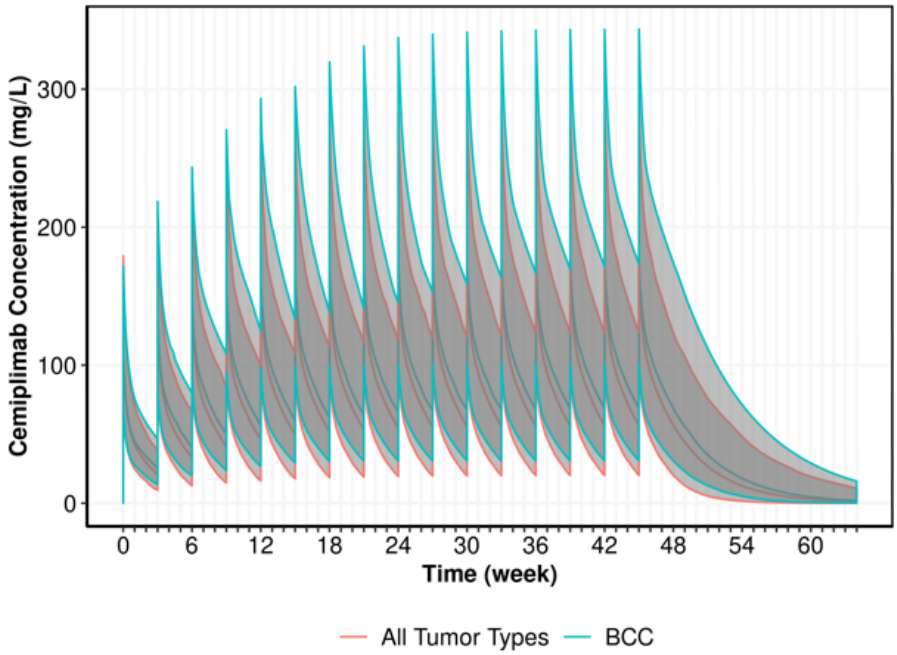
Post-hoc estimates in the Overall Population of Patients with Solid Tumors (N=1062)
Note, n = Number of patients; CSCC = advanced cutaneous squamous cell carcinoma, BCC = advanced basal cell carcinoma, NSCLC = Non-small cell lung cancer; Bottom and top edges of box are 25th and 75th percentiles, respectively; Horizontal line is Median (50th percentile); Diamond is Mean; Vertical lines extending from top to bottom are the upper and lower fence, respectively; black dots are outliers defined by the '1.5 rule' namely when less than [Q1 – 1.5*IQR] or greater than [Q3 + 1.5*IQR], with IQR = Q3 – Q1.

Figure 4 Box plots of $AUC_{3wks,ss}$ by tumour type in patients with solid tumors, 350 mg Q3W



Post-hoc estimates in the Overall Population of Patients with Solid Tumors (N=1062)
Note, n = Number of patients; CSCC = advanced cutaneous squamous cell carcinoma, BCC = advanced Basal cell carcinoma, NSCLC = Non-small cell lung cancer.
Bottom and top edges of box are 25th and 75th percentiles, respectively; Horizontal line is Median (50th percentile); Diamond is Mean; Vertical lines extending from top to bottom are the upper and lower fence, respectively; black dots are outliers defined by the '1.5 rule' namely when less than [Q1 – 1.5*IQR] or greater than [Q3 + 1.5*IQR], with IQR = Q3 – Q1.

Figure 12: Simulated Mean (±95% Confidence Interval) Concentration-Time Profiles for Cemiplimab 350 mg Q3W in Patients with Advanced BCC Compared to the Overall PopPK Population of Patients with Solid Tumors

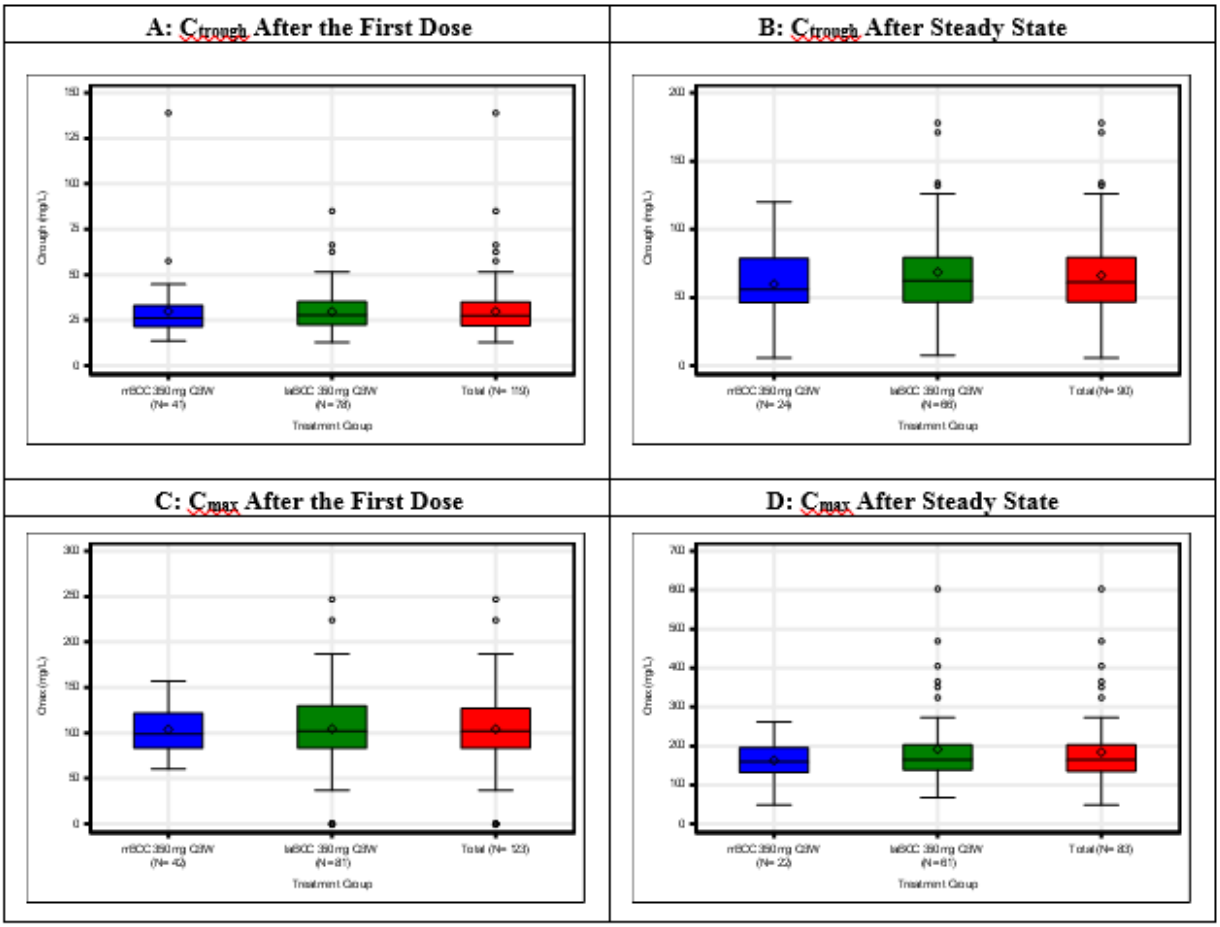


Post-hoc estimates in the Overall Population of Patients with Solid Tumors (N=1062)
Note, All tumor types (N=1062); BCC = Basal cell carcinoma (N=136)
Source: Module 5.3.3.5 Population PK Report R2810-PK-20039-SR-01V1 Figure 14.

Locally Advanced versus Metastatic

From the observed data of C_{max} and C_{trough} following the first dose, as well as after achieving steady state, there was no apparent difference in the exposure to cemiplimab in patients with laBCC or mBCC. Consistently, the PopPK covariate analysis did not identify laBCC versus mBCC as a statistical covariate.

Figure 5 Box plots of observed concentration ($C_{trough,ss}$ and C_{max}) of cemiplimab in serum after the first dose and at steady state in patients with laBCC and mBCC, receiving 350 mg Q3W



N = Number of patients; mBCC = Metastatic BCC; laBCC = Locally advanced BCC. Note: Concentrations below the LLOQ were set to 0.
Source: Module 5, Study R2810-ONC-1620 Appendix 5 Figure 9.

PD-L1 Expression

By PopPK covariate analysis, PD-L1 expression at baseline was not identified as a statistical covariate of cemiplimab exposure. In the overall population of patients with solid tumors, cemiplimab exposure was similar regardless of the level of PD-L1 expression.

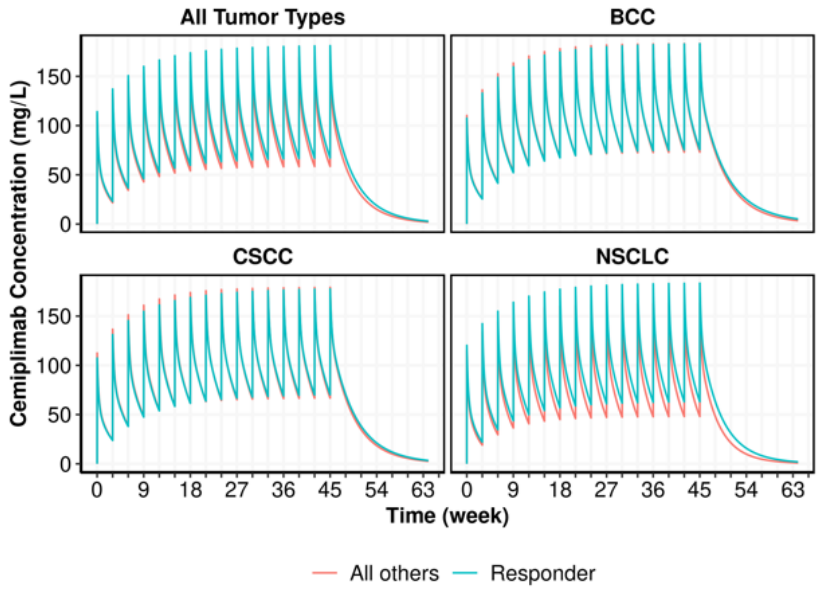
Table 19: Summary of Individual Predicted Estimates of Cemiplimab Exposure in the Overall PopPK Population of Patients with Solid Tumors Receiving 350 mg Q3W, by PD-L1 Expression at Baseline

Value	N	First Dose			Steady-state		
		AUC_{3wks} (day*mg/L)	C_{max} (mg/L)	C_{min} (mg/L)	AUC_{3wks} (day*mg/L)	C_{max} (mg/L)	C_{min} (mg/L)
[0-50%]	249	895(29.6%)	111(29.9%)	22.9(35.1%)	1990(37.9%)	172(30.8%)	63.2(47.0%)
[50%-70%)	103	869(23.8%)	114(24.8%)	20.4(29.2%)	1830(30.6%)	168(24.7%)	55.1(39.2%)
[70%-90%)	101	878(25.1%)	116(22.8%)	20.5(34.4%)	1870(33.1%)	171(24.7%)	56.7(42.8%)
[90%-100%]	95	859(25.2%)	117(24.2%)	19.5(34.3%)	1750(34.4%)	166(25.6%)	51.2(45.9%)
NA	514	889(26.0%)	110(24.7%)	22.8(33.2%)	1990(35.1%)	171(27.2%)	63.6(43.8%)

Note: Summary data are presented as Mean (CV%). Post-hoc estimates in the overall PopPK population of patients with solid tumors (N=1062).
CV% = percent coefficient of variation; N = number of patients; NA = not available.
Source: Module 5.3.3.5 Population PK Report R2810-PK-20039-SR-01V1 Table 37.

Responders versus All Others

Figure 6 Simulated mean concentration time- profiles for cemiplimab 350 mg Q3W by tumour type in "Responders" versus "All Others"



Post-hoc estimates in the Overall Population of Patients with Solid Tumors (N=1062)
Note, CSCC: Cutaneous squamous-cell carcinoma, BCC: Basal cell carcinoma , NSCLC: Non-small cell lung cancer. All tumor types (N=1062); including advanced BCC: All Others (n=106), Responders (n=30); CSCC: All Others (n=118), Responders (n=96); NSCLC: All Others (n=279), Responders (n=137)

Table 14 Summary of individual predicted estimates for cemiplimab 350 mg Q3W by tumour type in "Responders" versus "All Others"

Tumor Type	Responder/ All others	N	First Dose			Steady-state		
			$AUC_{3wk,ss}$ (day*mg/L)	C_{max} (mg/L)	C_{min} (mg/L)	$AUC_{3wk,ss}$ (day*mg/L)	C_{max} (mg/L)	C_{min} (mg/L)
BCC	0	106	975(26.9%)	113(27.4%)	27.0(29.8%)	2310(35.6%)	188(29.8%)	77.0(41.7%)
	1	30	917(18.6%)	106(16.1%)	25.2(28.1%)	2240(42.1%)	180(28.1%)	75.7(55.3%)
CSCC	0	118	917(26.8%)	111(27.1%)	24.1(31.8%)	2100(31.4%)	177(26.3%)	68.3(38.0%)
	1	96	886(20.4%)	105(21.1%)	23.5(23.8%)	2140(27.1%)	175(21.4%)	71.5(33.9%)
NSCLC	0	279	838(25.7%)	112(25.2%)	19.3(33.5%)	1690(33.9%)	160(26.0%)	49.7(44.7%)
	1	137	939(23.0%)	120(23.0%)	22.7(29.0%)	2100(29.1%)	184(23.1%)	65.8(36.8%)
OTHERS	0	295	861(29.0%)	106(26.9%)	22.0(36.5%)	1940(36.8%)	166(29.6%)	61.8(44.7%)
	1	1	888(0%)	105(0%)	23.9(0%)	1830(0%)	161(0%)	57.2(0%)

Note: Summary data are presented as Mean (CV%). Post-hoc estimates in the overall PopPK population of patients with solid tumors (N=1062).
BCC = Basal cell carcinoma; CSCC: Cutaneous squamous-cell carcinoma; CV% = percent coefficient of variation; N = number of patients; NSCLC: Non-small cell lung cancer.
Others includes non-specified in dose escalation (DE) cohorts, HCC (Hepatocellular cancer); ST (Solid tumors); CRC (colorectal cancer); CC (Cervical cancer), etc. in study 1423.
Responder: 1, All others: 0.
There is only one responder patient (R2810-ONC-1423-840-004-003, 1 mg/kg Q2W) whose tumor type is classified as "Others".

Baseline Performance Status

By PopPK covariate analysis, baseline ECOG status was not identified as a statistically significant covariate. Consistently, in the post-hoc assessment of ECOG status, there is no apparent difference in exposure with the differences in $C_{trough,ss}$, and $AUC_{3wk,ss}$ being <25% after cemiplimab 350 mg Q3W, with respect to the baseline ECOG status.

Renal impairment

The effect of renal impairment on the exposure of cemiplimab was evaluated in patients with mild (CLCr 60 to 89 mL/min; n=396), moderate (CLCr 30 to <59 mL/min; n=166), or severe (CLCr 15 to 29 mL/min; n=7) renal impairment and were compared to patients with normal renal (CLCr ≥90 mL/min; n=493).

Consistent with other monoclonal antibodies, cemiplimab elimination by the renal route is likely to be insignificant as its large size prevents efficient filtration through the glomerulus. Therefore, renal impairment is not expected to affect the PK of cemiplimab.

Consistent with this, renal function was not identified as a significant covariate in the PopPK model.

Table 21: Summary of Individual Predicted Estimates of Cemiplimab Exposure in the Overall PopPK Population of Patients with Solid Tumors Receiving 350 mg Q3W, Categorized by Renal Function, with Baseline Creatinine Clearance and Body Weight

Renal Function	Baseline Creatinine Clearance (mL/min)	N	Baseline Creatinine Clearance (mL/min)	Baseline Body Weight (kg)	$AUC_{3wks,ss}$ (day*mg/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
Normal	>=90	493	120 (25.8%)	82.3 (23.2%)	1800 (34.3%)	160 (26.0%)	55.8 (44.1%)
Mild	60-89	396	75.0 (11.3%)	72.5 (21.1%)	2010 (34.8%)	175 (25.9%)	63.5 (44.8%)
Moderate	30-59	166	49.5 (14.7%)	65.2 (20.3%)	2200 (33.7%)	191 (26.8%)	69.5 (41.9%)
Severe	15-29	7	25.3 (10.1%)	49.7 (24.4%)	2560 (48.2%)	244 (46.1%)	74.5 (51.9%)

Note: Summary data are presented as Mean (CV%). Post-hoc estimates in the overall PopPK population of patients with solid tumors (N=1062).
CRCLBL = baseline creatinine clearance; CV% = percent coefficient of variation; N = number of patients; WGTBL = baseline body weight.
Creatinine Clearance determined by Cockroft- Gault equation
Source: Module 5.3.3.5 Population PK Report R2810-PK-20039-SR-01V1 Table 40

Hepatic Impairment

By PopPK covariate analysis, hepatic impairment was not identified as a statistically significant covariate. The effect of baseline total bilirubin on the exposure of cemiplimab was evaluated and the results are presented with summary statistics by hepatic impairment categories based on total bilirubin (expressed as [value/ULN], where ULN is the upper limit of normal range) and any AST and ALT levels. In patients (n=22) with mild hepatic impairment (total bilirubin greater than 1.0 to 1.5 times the ULN) and 3 patients with moderate (total bilirubin >1.5 ULN) hepatic impairment, no differences in the exposure of cemiplimab were found between patients with mild/moderate hepatic impairment and patients with normal hepatic function.

Table 22: Summary of Individual Predicted Cemiplimab Exposure in the Overall PopPK Population of Patients with Solid Tumors Receiving 350 mg Q3W, Categorized by Hepatic Function, with Total Bilirubin, Body Weight, and ALT and AST Levels

Hepatic Function	Total Bilirubin (ULN)	N	Total Bilirubin (µmol/L)	Baseline Body Weight (kg)	Baseline AST (IU/L)	Baseline ALT (IU/L)	$AUC_{3wks,ss}$ (day*mg/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
Normal	<1.0 ULN	1023	8.58 (44.4%)	75.6 (23.9%)	25.3 (70.6%)	23.9 (86.3%)	1940 (35.3%)	171 (27.4%)	61.0 (44.8%)
Mild	1-1.5 ULN	22	23.9 (17.3%)	79.7 (26.3%)	42.0 (85.1%)	25.4 (76.1%)	1820 (34.6%)	162 (28.8%)	56.1 (42.3%)
Moderate	≥1.5-3 ULN	3	43.1 (15.5%)	85.5 (35.6%)	42.0 (47.6%)	38.7 (60.1%)	1820 (12.4%)	155 (19.6%)	58.0 (8.26%)

Hepatic Function	Total Bilirubin (ULN)	N	Total Bilirubin (µmol/L)	Baseline Body Weight (kg)	Baseline AST (IU/L)	Baseline ALT (IU/L)	$AUC_{3wks,ss}$ (day*mg/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
NA	NA	14	8.43 (2.02%)	77.5 (24.5%)	21.1 (24.9%)	19.0 (12.7%)	1880 (49.4%)	163 (34.2%)	60.3 (63.0%)

Notes: Post-hoc estimates in the Overall Population of Patients with Solid Tumors (N=1062). All data are mean (CV%).
CV% = coefficient of variation; NA: not available.
Source: Module 5.3.3.5 Population PK Report R2810-PK-20039-SR-01V1 Table 41

Extrinsic Factors

Extrinsic covariates tested included treatment (monotherapy versus combination therapies with radiation and/or chemotherapy) and country (site, region).

Treatment (Monotherapy versus Combination Therapy)

There is no apparent difference (<25%) in cemiplimab exposure ($AUC_{tau,ss}$ or Ctrough,ss) in patients treated with cemiplimab as monotherapy compared with patients treated with cemiplimab in combination therapies, including radiotherapy and chemotherapy with cyclophosphamide, carboplatin, docetaxel, paclitaxel, or GM-CSF (Table 23).

Table 23: Summary of Individual Predicted Estimates of Cemiplimab Exposure in Patients with Solid Tumors Receiving 350 mg Q3W as Monotherapy or in Combination Therapy

Covariate	Value	N	First Dose			Steady-state		
			AUC3wks (day*mg/L)	Cmax (mg/L)	Cmin (mg/L)	AUC3wks(day*mg/L)	Cmax (mg/L)	Cmin (mg/L)
Monotherapy	No	267	863 (28.5%)	108 (26.6%)	21.6 (36.5%)	1900 (37.5%)	166 (29.2%)	59.9 (46.8%)
	Yes	795	892 (25.9%)	113 (25.6%)	22.2 (33.2%)	1950 (34.8%)	172 (26.9%)	61.2 (44.3%)

Note: Summary data are presented as Mean (CV%). Post-hoc estimates in the overall PopPK population of patients with solid tumors (N=1062).
CV% = percent coefficient of variation; N = number of patients.
YES = Monotherapy
NO = Combination therapy with radiation and/or chemotherapy
Source: Module 5.3.3.5 Population PK Report R2810-PK-20039-SR-01V1 Table 37

Pharmacokinetic interaction studies

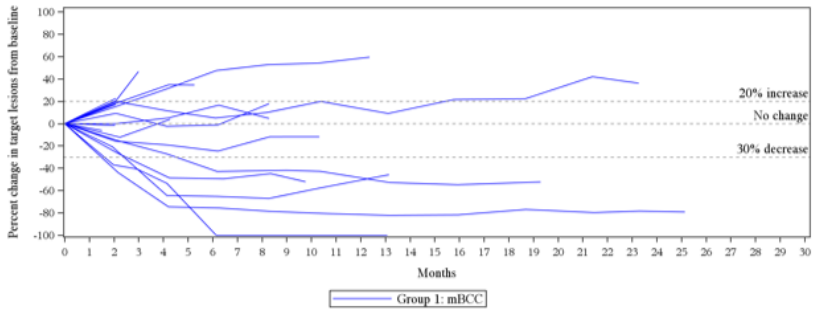
No PK interaction studies have been submitted (see discussion on Clinical Pharmacology).

2.3.3. Pharmacodynamics

Change in tumor size is used as a measure of pharmacodynamic effect of cemiplimab and provides a pharmacodynamic perspective of the biological response (decrease in tumor size) per the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, which describes a standard approach to solid tumor measurement and definitions for objective assessment of change in tumor size in adult and paediatric clinical studies (Eisenhauer, 2009).

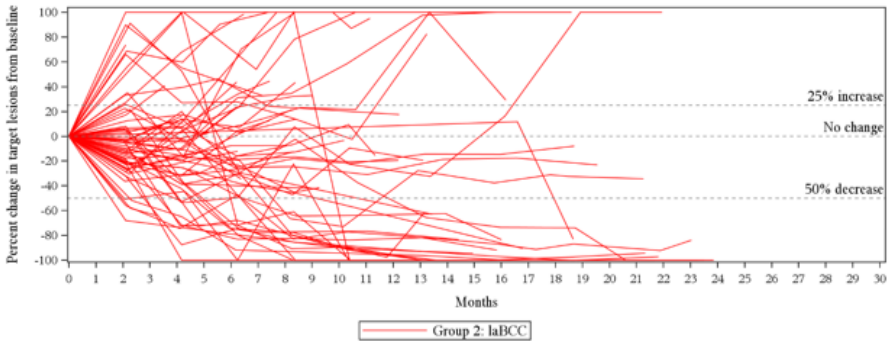
Spider plots provide a comprehensive perspective regarding the kinetics of responses, illustrating the percent changes in target lesion measurements over time for individual patients described in Study 1620. In addition to displaying the emerging durability of responses among patients with locally advanced BCC and metastatic BCC, spider plots also show that many of the responses deepen over time. Spider plots for percent changes in target lesions were provided in 17 patients with mBCC (Figure 15) and in 64 patients with laBCC Figure 16). Inspection of the spider plot for locally advanced BCC patients reveals several patients in which there were apparent increases in tumor measurements, followed by subsequent reductions according to ICR

Figure 15: Spider Plot of Percent of Change from Baseline in Target Lesions Over Time per RECIST 1.1 by Independent Central Review – Group 1 (mBCC); Full Analysis Set)



N = 17 out of 28 patients with mBCC
Source: R2810-ONC-1620 CSR Figure 6

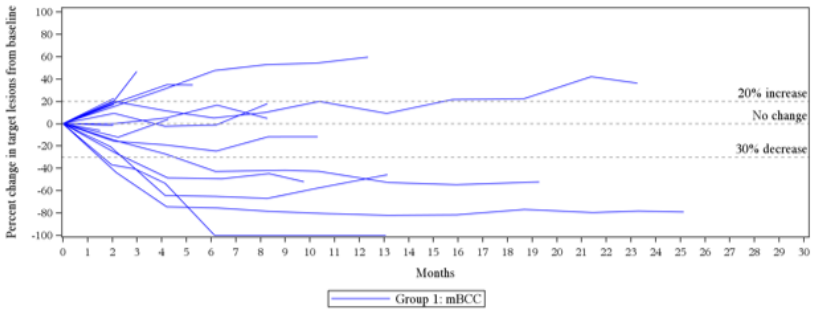
Figure 16: Spider Plot of Percent of Change from Baseline in Target Lesions Over Time per WHO Criteria by Independent Central Review – Group 2 (laBCC; Full Analysis Set)



N = 64 out of 84 patients with laBCC
Source: R2810-ONC-1620 CSR Figure 5

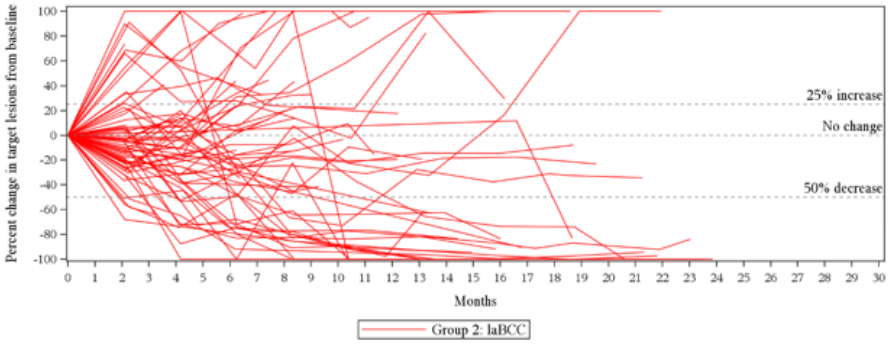
Change in tumor size is presented as a measure of pharmacodynamic effect of cemiplimab. Change in tumor size provides a pharmacodynamic perspective of the biological response (decrease in tumor size). Assessment of tumor size is a component of the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, which describes a standard approach to solid tumor measurement and definitions for objective assessment of change in tumor size in adult and paediatric clinical studies (Eisenhauer, 2009). Spider plots provide a comprehensive perspective regarding the kinetics of responses, illustrating the percent changes in target lesion measurements over time for individual patients described in Study 1620. In addition to displaying the emerging durability of responses among patients with locally advanced BCC and metastatic BCC, spider plots also show that many of the responses deepen over time. Spider plots for percent changes in target lesions were provided in 17 patients with mBCC (Figure 15) and in 64 patients with laBCC Figure 16).

Figure 15: Spider Plot of Percent of Change from Baseline in Target Lesions Over Time per RECIST 1.1 by Independent Central Review – Group 1 (mBCC); Full Analysis Set)



N = 17 out of 28 patients with mBCC
Source: R2810-ONC-1620 CSR Figure 6

Figure 16: Spider Plot of Percent of Change from Baseline in Target Lesions Over Time per WHO Criteria by Independent Central Review – Group 2 (laBCC; Full Analysis Set)



N = 64 out of 84 patients with laBCC
Source: R2810-ONC-1620 CSR Figure 5

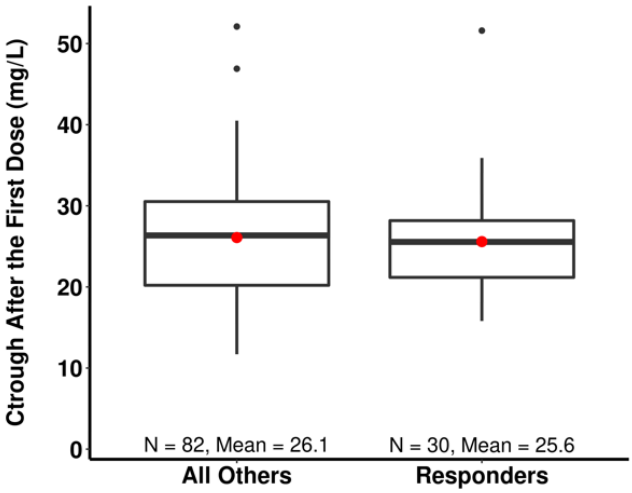
Mechanism of action

Cemiplimab is a high affinity, fully human, hinge stabilized IgG4P antibody directed to the PD 1 receptor that blocks the interaction of PD 1 with its ligands, PD L1 and PD L2.

Primary and secondary pharmacology

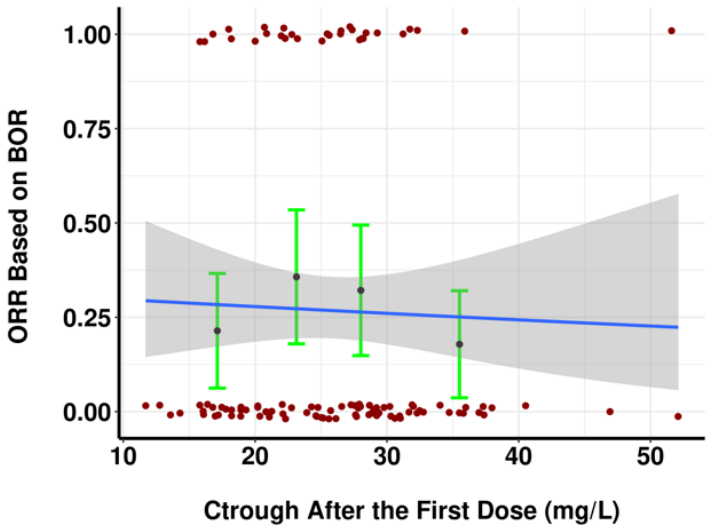
Exposure-response assessments are provided for efficacy and safety. The relationship between cemiplimab exposure in serum and efficacy endpoints in patients with advanced BCC was assessed for objective response rate (ORR) by logistic regression analysis. In addition, the relationship between cemiplimab exposure and the primary efficacy endpoints were investigated using Kaplan Meier analysis. Exposure-response relationships are displayed in figure 17-21 below. For safety, the integrated database for this application includes 3 safety pools: 1) patients with advanced BCC from Study 1620 who received cemiplimab 350 mg Q3W as monotherapy [Safety Pool 1]; 2) all patients from Studies 1423, 1540, 1620, and 1624 who received cemiplimab as monotherapy (at any dose) [Safety Pool 2]; and 3) all patients from Studies 1423, 1540, 1620, and 1624 who received cemiplimab as monotherapy or in combination with radiotherapy and/or with chemotherapy [Safety Pool 3]. These safety pools are used in the E-R analysis of safety. Exposure-Safety relationships are displayed in figure 22-25 below.

Figure 17: Boxplot of Individual Predicted Cemiplimab C_{trough} After the First Dose by Best Overall Response in Patients with Advanced BCC



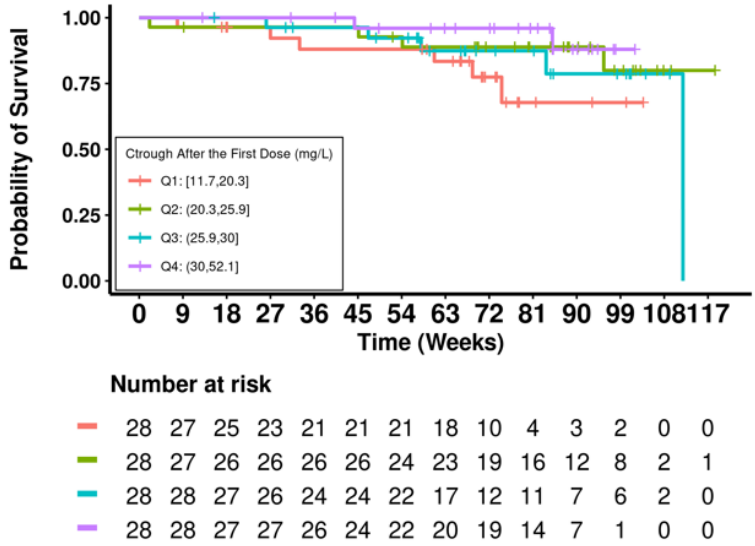
The lower and upper hinges correspond to the first and third quartiles (the 25th and 75th percentiles), respectively. The upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge (where IQR is the interquartile range, or the distance between the first and third quartiles). The lower whisker extends from the hinge to the smallest at most 1.5 * IQR of the hinge. Data beyond the end of the whiskers are called 'outlying' points and are plotted individually. Using a conservative approach, only patients who achieved PR or CR were considered 'responders.' The rest of the patient population, including patients who did not achieve CR or PR, were not able to be classified as CR or PR, were not evaluable, or had stable disease, were considered as 'all others' for these analyses.
Source: Module 5.3.3.5 Exposure-Response Report R2810-PK-20043-SR-01V1 Figure 1

Figure 18: Logistic Regression of Best Overall Response versus Individual Predicted Cemiplimab C_{trough} After the First Dose with Objective Response Rate (Mean of Best Overall Response) by Quartiles of Exposure in Patients with Advanced BCC



Note: The blue line and grey shaded area represent the fitted logistic regression model and 95% confidence band, where the entire range of exposure was used as a predictor in the model. The dark red jittered points represent individual patient values of BOR. The four black points represent mean BOR in quartiles of exposure, and the vertical green lines are the 95% confidence interval derived from the normal approximation of the binomial proportional confidence interval.
Source: Module 5.3.3.5 Exposure-Response Report R2810-PK-20043-SR-01V1 Figure 2

Figure 19: Kaplan-Meier Curves of Overall Survival Stratified by Quartiles of Individual Predicted Cemiplimab C_{trough} After the First Dose in Patients with Advanced BCC

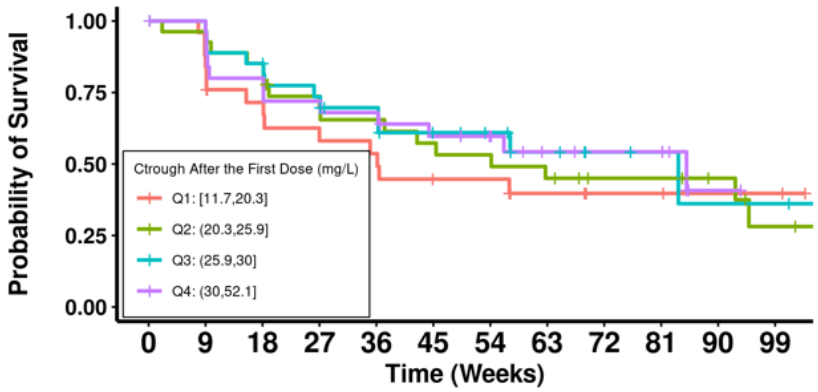


Number at risk

28	27	25	23	21	21	21	18	10	4	3	2	0	0
28	27	26	26	26	26	24	23	19	16	12	8	2	1
28	28	27	26	24	24	22	17	12	11	7	6	2	0
28	28	27	27	26	24	22	20	19	14	7	1	0	0

The vertical hatches through the Kaplan-Meier curves represent the last documented times that patients were observed to be alive. These censored patients may have dropped out of the study, or, since not all patients were enrolled in the study at the same time, they may have been censored at the time that the data cut-off occurred for this analysis. A drop in the Kaplan-Meier curve indicates the time of death due to any cause. The table provided underneath the Kaplan-Meier plot describes the number of patients alive in each quartile at each time point, which, for those patients, occurred before the data cut-off date.
Source: Module 5.3.3.5 Exposure-Response Report R2810-PK-20043-SR-01V1 Figure 3

Figure 20: Kaplan-Meier Curves of Progression-Free Survival Stratified by Quartiles of Individual Predicted Cemiplimab C_{trough} After the First Dose in Patients with Advanced BCC

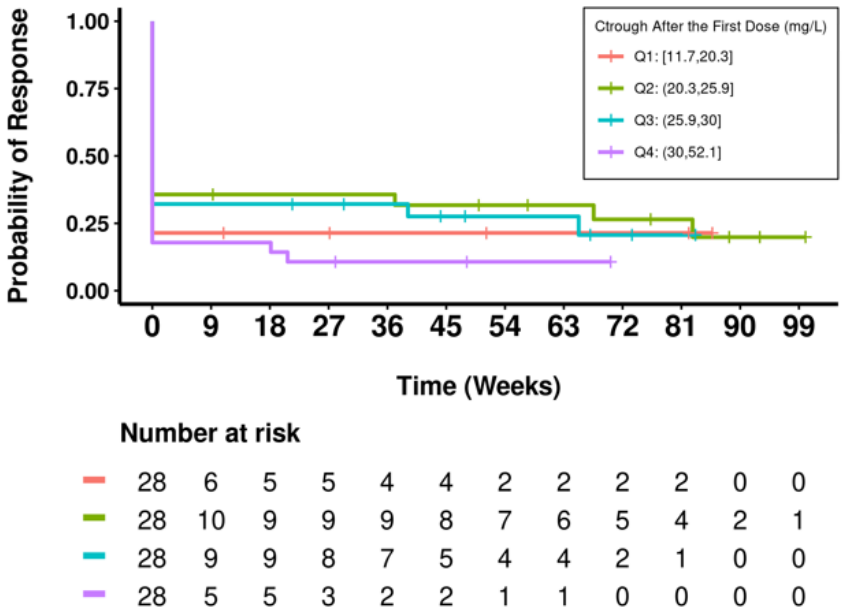


Number at risk

28	22	16	14	12	9	9	6	3	3	2	2
28	26	23	18	16	14	13	11	8	8	6	3
28	27	23	19	16	12	10	7	4	3	2	2
28	25	20	18	17	14	12	8	7	7	1	0

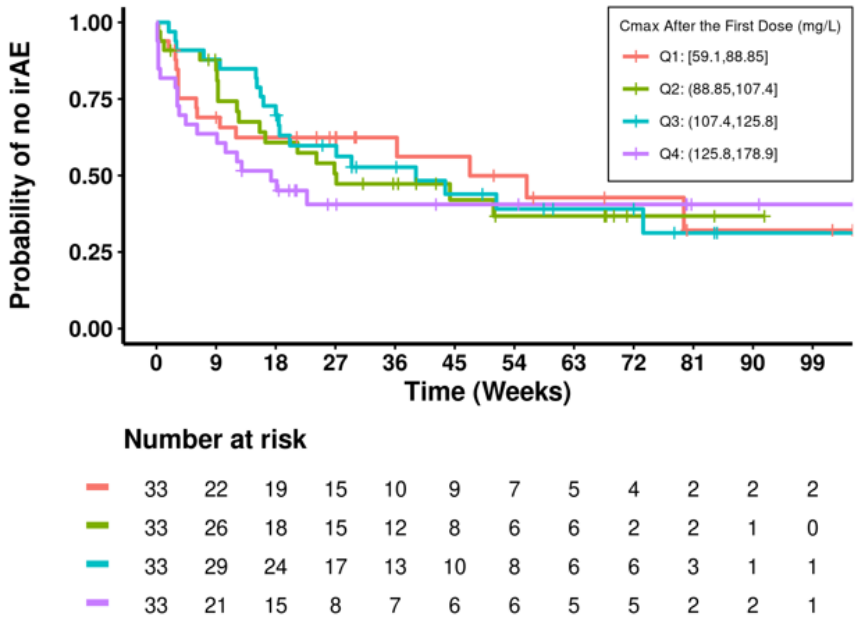
The vertical hatches through the Kaplan-Meier curves represent the last documented times that patients were observed to be alive with no disease progression. A drop in the Kaplan-Meier curves indicates the time of disease progression or death due to any cause. The table provided underneath the plot describes the number of patients alive with no disease progression in each quartile at each time point.
Source: Module 5.3.3.5 Exposure-Response Report R2810-PK-20043-SR-01V1 Figure 4

Figure 21: Kaplan-Meier Curves of Duration of Response Stratified by Quartiles of Individual Predicted Cemiplimab C_{trough} After the First Dose in Patients with Advanced BCC



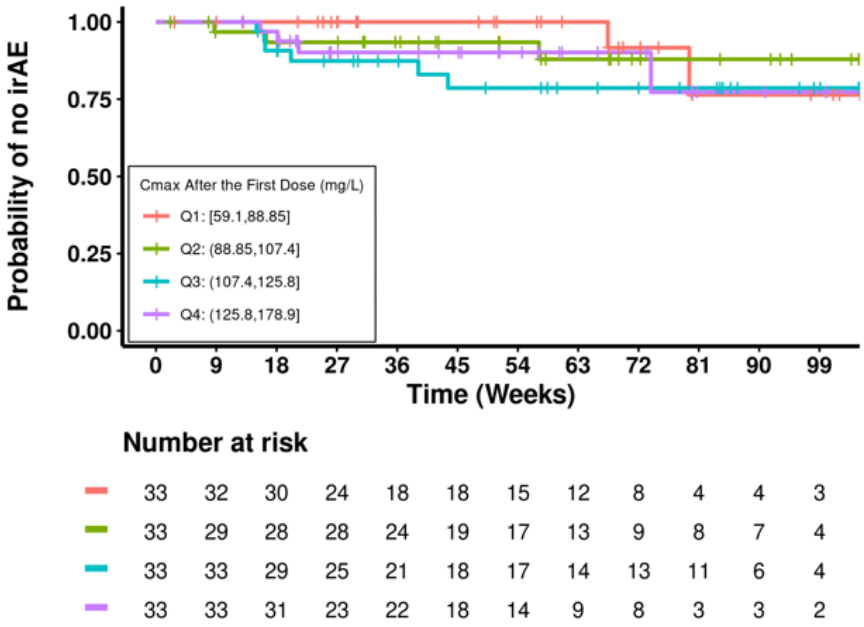
Note, the value at time zero represents the proportion of responders (ORR) within each quartile of exposure. A drop in the Kaplan-Meier curve after time zero indicates the time of recurrent or progressive disease or death due to any cause. The vertical hatches through the Kaplan-Meier curves indicate the last known date where the patient is still alive and has not experienced progressive or recurrent disease.
Source: Module 5.3.3.5 Exposure-Response Report R2810-PK-20043-SR-01V1 Figure 5

Figure 22: Kaplan-Meier Curves of All Immune-Mediated Treatment-Emergent Adverse Events Across Quartiles of Predicted Cemiplimab Cmax After the First Dose in Patients with Advanced BCC



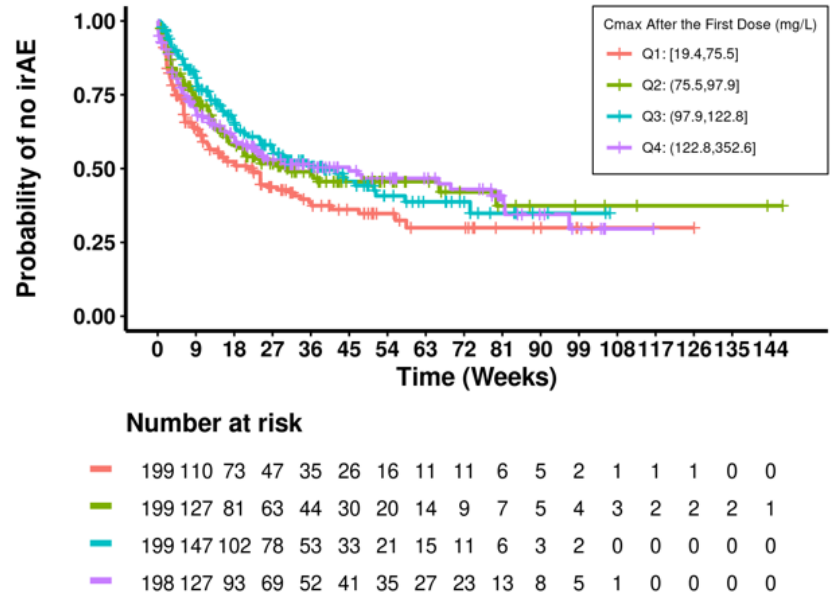
A drop in the Kaplan-Meier curves indicates the time in which the patient experiences an irAE > grade 3, and the censored events describe the last known date where the patient has not experienced any irAEs > grade 3. The table provided underneath the plot describes the number of patients who have not experienced irAE > grade 3 in each quartile at each time point.
Source: Module 5.3.3.5 Exposure-Response Report R2810-PK-20043-SR-01V1 Figure 6

Figure 23: Kaplan-Meier Curves of Grade 3 or Higher Immune-Mediated Treatment-Emergent Adverse Events Across Quartiles of Predicted Cemiplimab C_{max} at After the First Dose in Patients with Advanced BCC



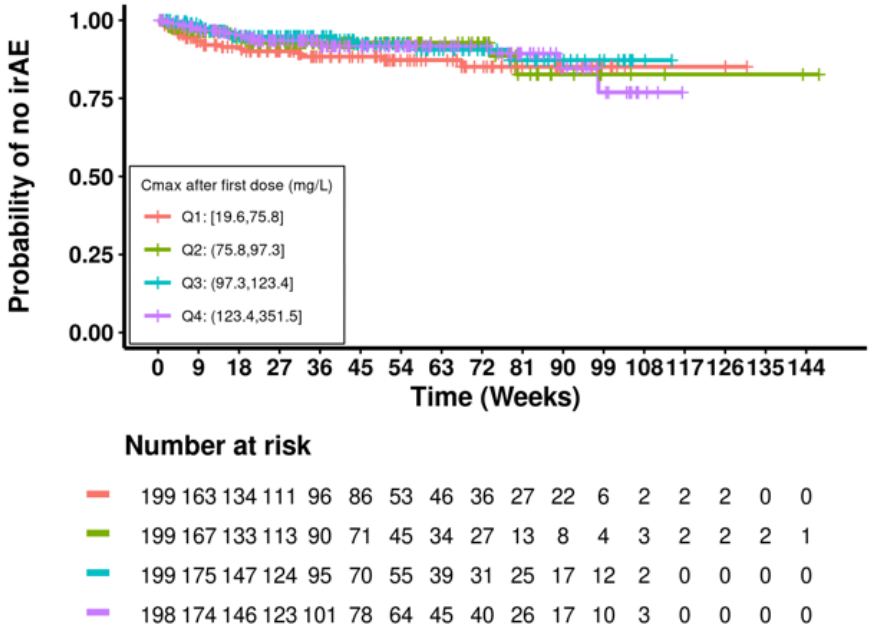
A drop in the Kaplan-Meier curves indicates the time in which the patient experiences an irAE ≥ grade 3, and the censored events describe the last known date where the patient has not experienced any irAEs ≥ grade 3. The table provided underneath the plot describes the number of patients who have not experienced irAE ≥ grade 3 in each quartile at each time point.
Source: Module 5.3.3.5 Exposure-Response Report R2810-PK-20043-SR-01V1 Figure 7

Figure 24: Kaplan-Meier Curves of All Immune-Mediated Treatment-Emergent Adverse Events Across Quartiles of Predicted Cemiplimab C_{max} After the First Dose in Patients on Cemiplimab Monotherapy



A drop in the Kaplan-Meier curves indicates the time in which the patient experiences any irAE, and the censored events describe the last known date where the patient has not experienced any irAEs. The table provided underneath the plot describes the number of patients who have not experienced any irAEs in each quartile at each time point.
Source: Module 5.3.3.5 Exposure-Response Report R2810-PK-20043-SR-01V1 Figure 8

Figure 25: Kaplan-Meier Curves of Grade 3 or Higher Immune-Mediated Treatment-Emergent Adverse Events Stratified by Quartiles of Individual Predicted Cemiplimab C_{max} After the First Dose in Patients on Cemiplimab Monotherapy



Number at risk

199	163	134	111	96	86	53	46	36	27	22	6	2	2	2	0	0
199	167	133	113	90	71	45	34	27	13	8	4	3	2	2	2	1
199	175	147	124	95	70	55	39	31	25	17	12	2	0	0	0	0
198	174	146	123	101	78	64	45	40	26	17	10	3	0	0	0	0

A drop in the Kaplan-Meier curves indicates the time in which the patient experiences an irAE ≥ grade 3, and the censored events describe the last known date where the patient has not experienced any irAEs ≥ grade 3. The table provided underneath the plot describes the number of patients who have not experienced irAE ≥ grade 3 in each quartile at each time point.
Source: Module 5.3.3.5 Exposure-Response Report R2810-PK-20043-SR-01V1 Figure 9

Immunogenicity

Immunogenicity was assessed in all 4 studies. Samples for ADA assessment were collected prior to dosing at several time points. The incidence of treatment-emergent immunogenicity was low (2.2%) in all patients (N = 823) receiving cemiplimab at any dose and regimen and was low (2.3%) in all patients (N = 385) receiving cemiplimab 350 mg Q3W. Antibody titers were all low with the exception of 1 patient who exhibited moderate ADA titers. Of the patients who developed treatment emergent antibodies to cemiplimab, none developed NAb. The incidence of persistent ADA was low (0.4%) in all patients receiving cemiplimab.

Neither of the 2 patients with advanced BCC who were included in the ADA analysis set in Study 1423 tested positive for ADA. The immunogenicity results in patients with advanced BCC from Study 1620 (125 patients, including 44 patients with mBCC and 81 patients with laBCC), showed 4 of 125 patients (3.2%) with a treatment-emergent ADA response; 2 were transient and 2 were indeterminate, all with a low titer (titer<1000). No neutralizing antibodies (NAb) were detected in the patients with a positive response in the ADA assay.

Table 15 Summary of ADA status in solid tumours patients by dose in studies 1423, 1540, 1620, 1624

ADA Status Max. Titer Category NAb Status	Cemiplimab Treatment Regimen						
	1mg/kg Q2W n (%)	3 mg/kg Q2W n (%)	3 mg/kg Q3W n (%)	10mg/kg Q2W n (%)	200mg Q2W n (%)	350mg Q3W n (%)	Overall n (%)
Total ADA Patients	24 (100%)	377 (100%)	12 (100%)	6 (100%)	19 (100%)	385 (100%)	823 (100%)
Negative	22 (91.7%)	364 (96.6%)	12 (100%)	5 (83.3%)	19 (100%)	366 (95.1%)	788 (95.7%)
Pre-existing	1 (4.2%)	6 (1.6%)	0	0	0	10 (2.6%)	17 (2.1%)
Treatment Boosted Response	0	0	0	0	0	0	0
Treatment Emergent Response	1 (4.2%)	7 (1.9%)	0	1 (16.7%)	0	9 (2.3%)	18 (2.2%)
Persistent	1 (4.2%)	1 (0.3%)	0	0	0	1 (0.3%)	3 (0.4%)
Transient	0	2 (0.5%)	0	0	0	4 (1.0%)	6 (0.7%)
Indeterminate	0	4 (1.1%)	0	1 (16.7%)	0	4 (1.0%)	9 (1.1%)
Maximum Titer							
Low (<1,000)	1 (4.2%)	6 (1.6%)	0	1 (16.7%)	0	9 (2.3%)	17 (2.1%)
Moderate (1,000 to 10,000)	0	1 (0.3%)	0	0	0	0	1 (0.1%)
High (>10,000)	0	0	0	0	0	0	0
NAb Status							
NAb Negative	24 (100%)	377 (100%)	12 (100%)	6 (100%)	19 (100%)	385 (100%)	823 (100%)
NAb Positive	0	0	0	0	0	0	0

ADA=anti-drug antibody; n = Number of patients; NAb=neutralizing antibody

Table 16 Summary of ADA status in BCC patients in study 1620

ADA Status and Category	mBCC 350 mg Q3W n (%)	laBCC 350 mg Q3W n (%)	Total n (%)
Total ADA Patients	44 (100%)	81 (100%)	125 (100%)
Negative	42 (95.5%)	75 (92.6%)	117 (93.6%)
Pre-existing	2 (4.5%)	2 (2.5%)	4 (3.2%)
Treatment Boosted Response	0	0	0
Treatment Emergent Response	0	4 (4.9%)	4 (3.2%)
Treatment Emergent and Treatment Boosted			
Persistent	0	0	0
Transient	0	2 (2.5%)	2 (1.6%)
Indeterminate	0	2 (2.5%)	2 (1.6%)
Treatment Emergent and Treatment Boosted Maximum Titer Category			
Low (<1,000)	0	4 (4.9%)	4 (3.2%)
Moderate (1,000 to 10,000)	0	0	0
High (>10,000)	0	0	0
Treatment Emergent and Treatment Boosted NAb Status			
NAb negative	0	4 (4.9%)	4 (3.2%)
NAb positive	0	0	0

ADA = anti-drug antibody; BCC = basal cell carcinoma; laBCC = locally advanced BCC; mBCC = metastatic BCC; n = number; NAb = neutralizing antibody; Q3W = every 3 weeks.

Dose Selection

Table 17

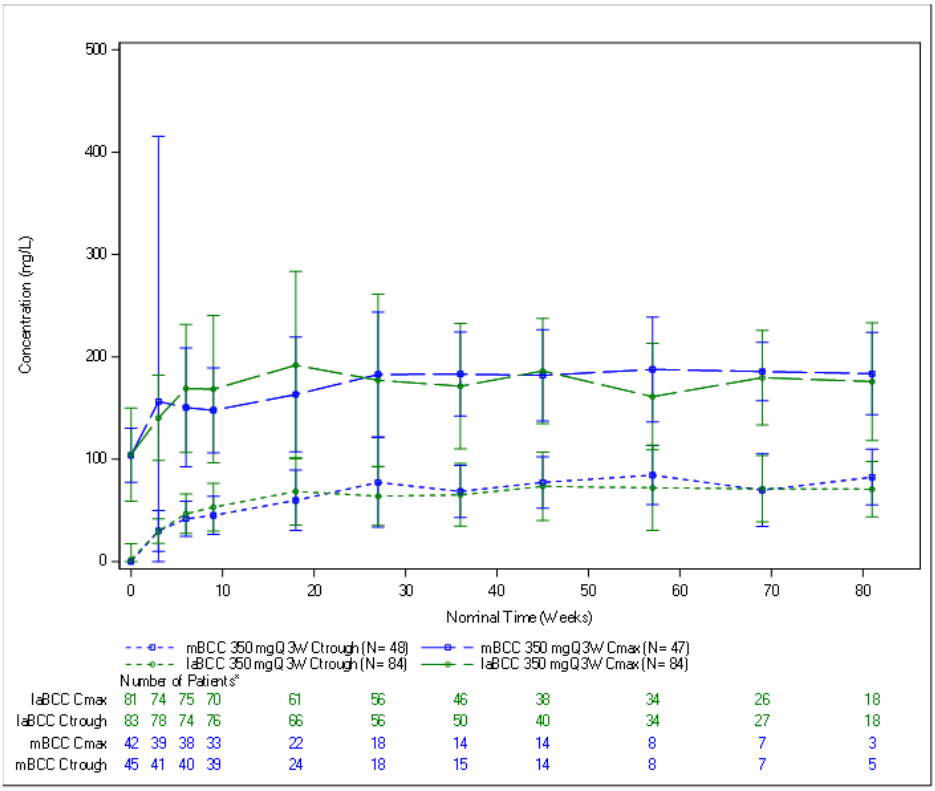
Table 6: Observed Cemiplimab Exposure (C_{trough} and C_{max}) after the First Dose and at Steady State in Patients with Advanced BCC at 350 mg Q3W monotherapy (Study 1620)

Group	After the First Dose						At Steady State					
	C_{trough} (mg/L)			C_{max} (mg/L)			C_{trough} (mg/L)			C_{max} (mg/L)		
	n	Mean (SD)	Median (Q1:Q3)	n	Mean (SD)	Median (Q1:Q3)	n	Mean (SD)	Median (Q1:Q3)	n	Mean (SD)	Median (Q1:Q3)
mBCC (N=48)	41	30.0 (19.9)	26.1 (21.5: 33.2)	42	104 (26.4)	98.8 (83.3: 122)	24	59.8 (29.6)	55.9 (46.2: 78.8)	22	163 (56.0)	160 (132: 196)
laBCC (N=84)	78	29.8 (12.0)	27.9 (22.5: 35.2)	81	104 (45.5)	102 (83.2: 130)	66	68.6 (32.8)	62.3 (46.8: 79.3)	61	192 (91.6)	165 (139: 203)
Total (N=132)	119	29.8 (15.1)	27.6 (22.0: 35.0)	123	104 (39.9)	102 (83.2: 127)	90	66.2 (32.1)	61.1 (46.8: 79.3)	83	184 (84.3)	164 (135: 203)

laBCC = Locally advanced BCC; mBCC = Metastatic BCC; n = Number of patients; Q = Quartile; SD = standard deviation.
After first dose: C_{trough} at cycle 1 day 22 pre-infusion, C_{max} at cycle 1 day 1 end of infusion.
Steady state: C_{trough} at cycle 3 day 1 pre-infusion, C_{max} at cycle 3 day 1 end of infusion.
Note: Two patients (Patient 276024002 with mBCC and Patient 840008001 with laBCC) had no end-of-infusion PK sample taken on cycle 1 day 1 and no PK samples taken on cycle 1 day 22 and on cycle 3 day 1.
PK analysis set: 48 patients with mBCC; 84 patients with laBCC; 132 patients total (advanced BCC).
Source: Study 1620 Interim CSR, Appendix 5, Clinical Pharmacology Report R2810-ONC-1620-CP-01V1

Figure 7

Figure 1: Observed Mean (±SD) Cemiplimab C_{trough} and C_{max} by Time in Patients with mBCC and laBCC Receiving 350 mg Q3W (Study 1620)



BCC = basal cell carcinoma; mBCC=metastatic BCC; laBCC=locally advanced BCC; N = number of patients.
Note: Concentrations below the LLOQ were set to 0.
*Ctrough: Pre-infusion concentration at each visit; Cmax: End of infusion concentration at each visit.
Source: Study 1620 Interim CSR, Appendix 5, Clinical Pharmacology Report R2810-ONC-1620-CP-01V1 Figure 5.

Figure 8

Figure 2: Observed Mean (±SD) Cemiplimab Concentration-Time Profiles After the First Dose in Patients with Advanced CSCC, Advanced BCC, Advanced NSCLC, and in All Patients with Solid Tumors, by Dose (Study 1423)

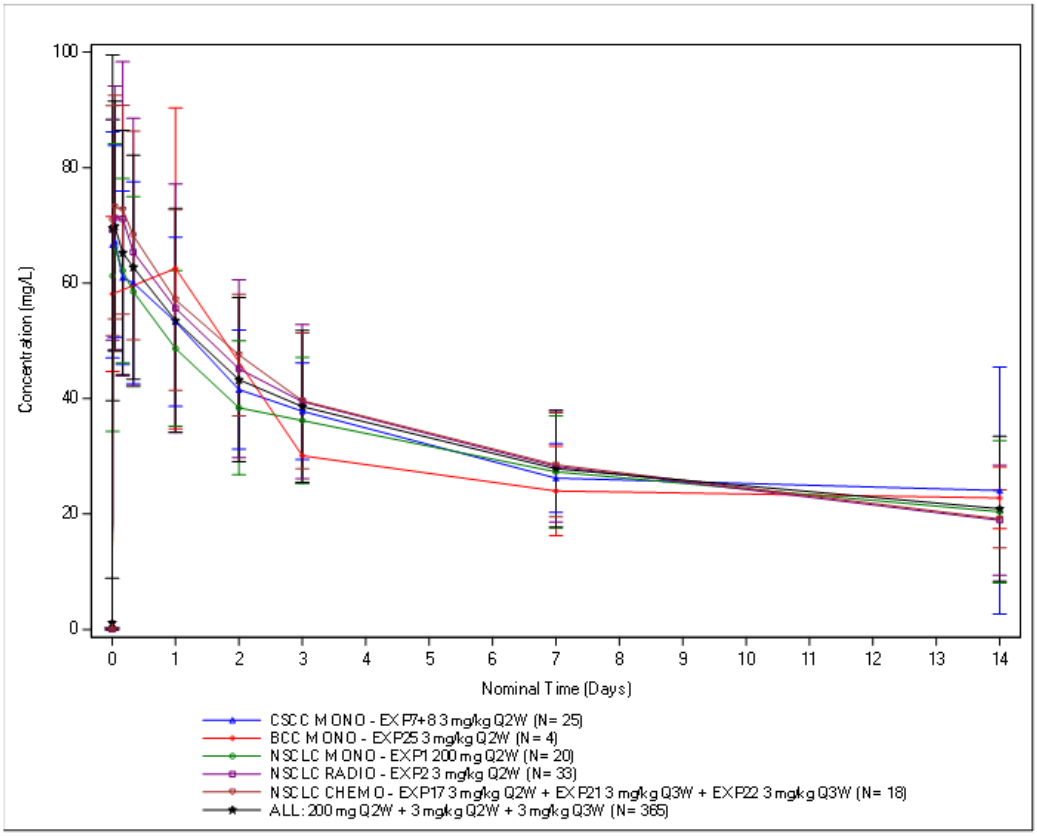


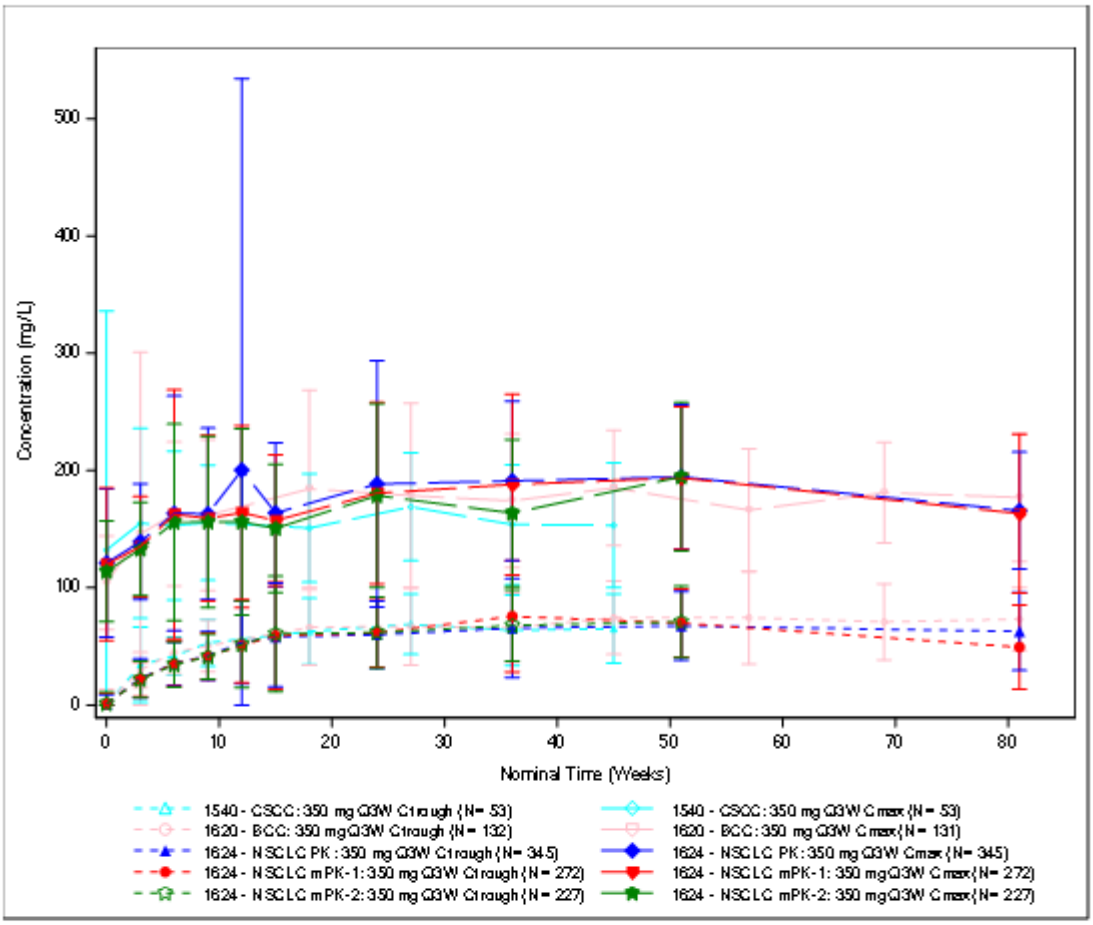
Table 18

Table 8: Cemiplimab Exposure (C_{trough} and C_{max}) after the First Dose and at Steady State in Patients with CSCC (PKAS; Study 1540), in Patients with BCC (PKAS; Study 1620), in Patients with NSCLC (PKAS, mPK1AS and mPK2AS) (Study 1624), in All Patients Receiving 350 mg Q3W and in All Patients Receiving 3 mg/kg Q2W on Cemiplimab Monotherapy (Studies 1423, 1540, 1620, and 1624)

				After the First Dose				At Steady State			
				C_{trough} (mg/L)		C_{max} (mg/L)		C_{trough} (mg/L)		C_{max} (mg/L)	
Study	Cancer Type	Group - Dose	N	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
1540	mCSCC	Group 1 - 3 mg/kg Q2W	59	53	21.5 (7.12)	58	108 (147)	38	69.9 (19.3)	38	151 (83.7)
	laCSCC	Group 2 - 3 mg/kg Q2W	76	71	26.3 (14.3)	74	85.3 (105)	58	67.5 (29.8)	58	148 (76.6)
	CSCC	Group 1+2 - 3 mg/kg Q2W	135	124	24.2 (12.0)	132	95.1 (125)	96	68.4 (26.1)	96	150 (79.0)
	mCSCC	Group 3 - 350 mg Q3W	53	47	34.2 (32.0)	52	132 (203)	34	62.7 (28.3)	33	151 (46.2)
1620	mBCC	Group 1 - 350 mg Q3W	48	41	30.0 (19.9)	42	104 (26.4)	24	59.8 (29.6)	22	163 (56.0)
	laBCC	Group 2 - 350 mg Q3W	84	78	29.8 (12.0)	81	104 (45.5)	66	68.6 (32.8)	61	192 (91.6)
	BCC	Group 1+2 - 350 mg Q3W	132	119	29.8 (15.1)	123	104 (39.9)	90	66.2 (32.1)	83	184 (84.3)
1624	NSCLC	PKAS - 350 mg Q3W	345	320	22.8 (16.8)	336	121 (63.3)	175	60.0 (28.7)	175	189 (105)
	NSCLC	mPK-1 - 350 mg Q3W	272	257	22.1 (14.8)	264	120 (65.0)	136	61.7 (29.4)	136	181 (77.3)
	NSCLC	mPK-2 - 350 mg Q3W	227	212	21.9 (15.6)	222	114 (43.1)	105	61.8 (30.2)	105	179 (78.4)
1423 and 1540	Solid Tumors	3 mg/kg Q2W	468	438	21.9 (12.5)	463	77.2 (72.2)	232	63.8 (25.9)	227	138 (60.5)
1540, 1620 and 1624	CSCC, BCC and NSCLC	350 mg Q3W	530	486	25.7 (18.8)	511	118 (85.0)	299	62.2 (29.7)	291	183 (94.9)

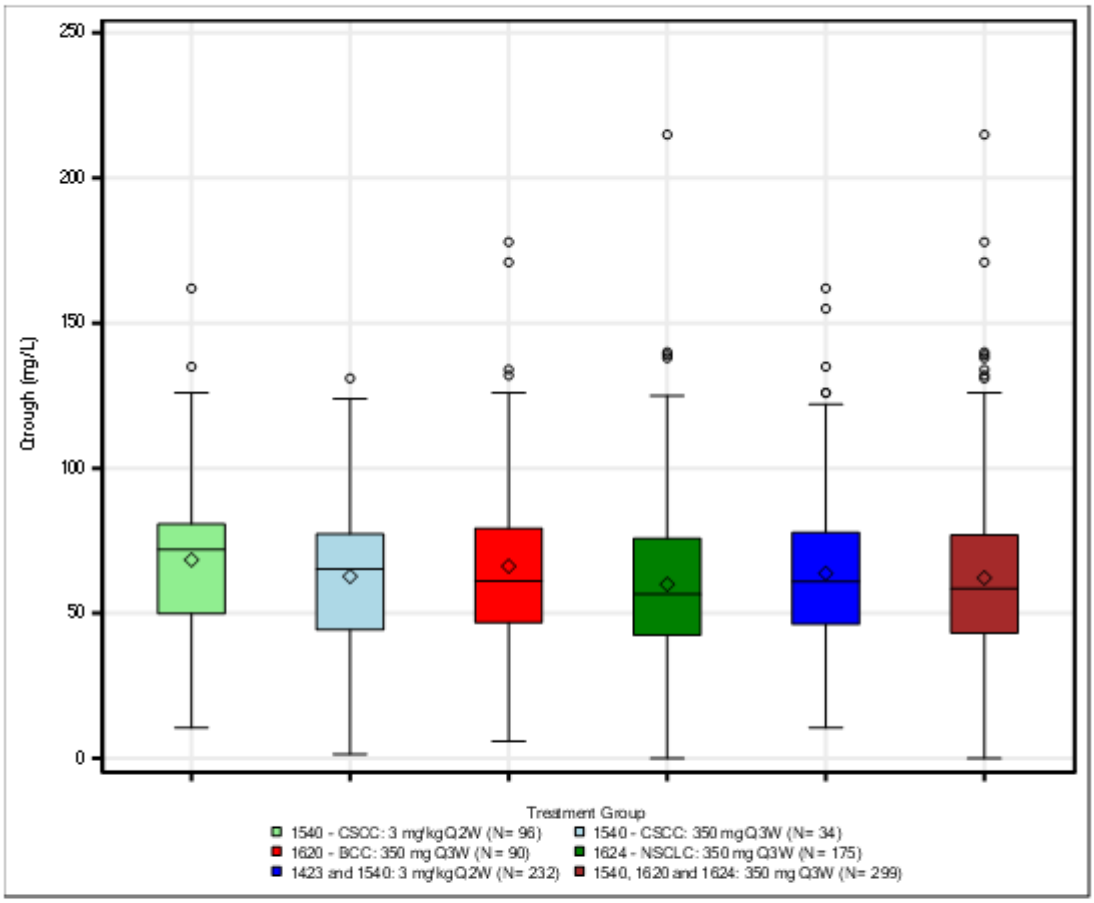
N= Number of patients in PK Analysis Set for Study 1423, 1540 and 1620. N= Number of patients in each Analysis Set for Study 1624. n= Number of patients. mPK1AS: modified PK-1 Analysis Set; mPK2AS: modified PK-2 Analysis Set. mPK-1: modified PK-1; mPK-2: modified PK-2. SD: Standard Deviation. mCSCC= metastatic CSCC; laCSCC= locally advanced CSCC; mBCC= metastatic BCC; laBCC= locally advanced BCC; NSCLC= non-small cell lung cancer. After the First dose: C_{trough} is Pre-Infusion at Cycle 1 Day 15 (CSCC Q2W) and at Cycle 1 Day 22 (CSCC Q3W and BCC) and at Cycle 2 Day 1 (NSCLC) and C_{max} is End of Infusion at Cycle 1 Day 1 (CSCC, BCC and NSCLC). At Steady State: C_{trough} is Pre-Infusion and C_{max} is End-of-Infusion at Cycle 3 Day 1 (CSCC and BCC) and at Cycle 9 Day 1 (NSCLC).
Data Source: Study 1540 Final CSR Appendix 5 Clinical Pharmacology Report R2810-ONC-1540-CP-01V1; Study 1620 Interim CSR Appendix 5 Clinical Pharmacology Report R2810-ONC-1620-CP-01V1; Study 1624 Primary Analysis CSR Appendix 5 Clinical Pharmacology Report R2810-ONC-1624-CP-01V1

Figure 3: Observed Mean (±SD) Cemiplimab Ctrough and Cmax Concentrations by Time in Patients with Advanced CSCC (Study 1540), Advanced BCC (Study 1620), and Advanced NSCLC (Study 1624) Receiving 350 mg Q3W



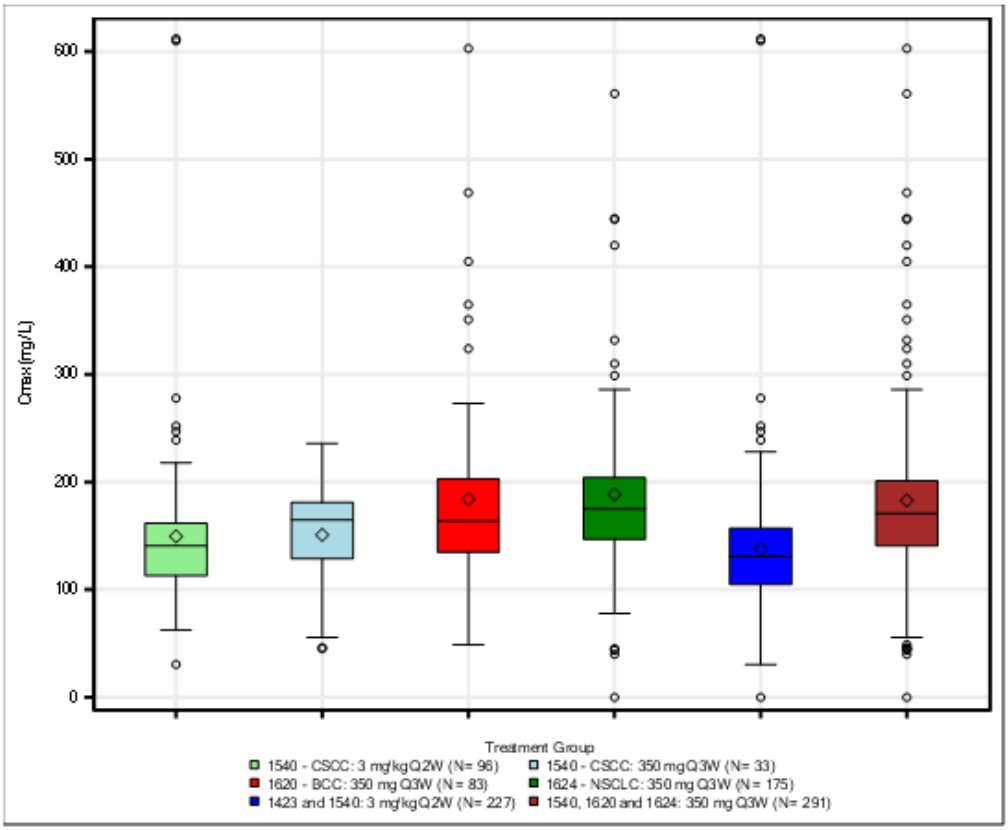
Concentrations below the LLOQ were set to 0.
BCC = basal cell carcinoma; CSCC = cutaneous squamous cell carcinoma; laBCC = locally advanced BCC; laCSCC = locally advanced CSCC; mBCC = metastatic BCC; mCSCC= metastatic CSCC; N = number of patients in PK Analysis Set; n = number of patients; NSCLC= non-small cell lung cancer; Q = quartile; SD = Standard Deviation.
mPK-1 = modified PK-1 analysis set; mPK-2 = modified PK-2 analysis set.
Data Source: Study 1540 Final CSR Appendix 5 Clinical Pharmacology Report R2810-ONC-1540-CP-01V1; Study 1620 Interim CSR Appendix 5 Clinical Pharmacology Report R2810-ONC-1620-CP-01V1; Study 1624 Primary Analysis CSR Appendix 5 Clinical Pharmacology Report R2810-ONC-1624-CP-01V1

Figure 4: Box Plot of Observed Cemiplimab Exposure at Steady State (C_{trough}) in Patients with Advanced CSCC (Study 1540), Advanced BCC (Study 1620), Advanced NSCLC (Study 1624), and Advanced Malignancies (Study 1423) Receiving 3 mg/kg Q2W or 350 mg Q3W



N = Number of patients in PK Analysis Set.
At Steady State: C_{trough} is Pre-Infusion at Cycle 3 Day 1 (CSCC and advanced BCC) and at Cycle 9 Day 1 (NSCLC).
Concentrations below the LLOQ were set to 0.
mCSCC = metastatic CSCC; laCSCC = locally advanced CSCC; mBCC = metastatic BCC; laBCC = locally advanced BCC; NSCLC= non-small cell lung cancer.
Bottom and top edges of box are 25th and 75th percentiles, respectively; Horizontal line is Median (50th percentile); Diamond is Mean; Vertical lines extending from top to bottom are the maximum value below upper fence and minimum value above lower fence respectively; circles are outliers defined by the '1.5 rule' namely when less than [Q1 - 1.5*IQR] or greater than [Q3 + 1.5*IQR], with IQR = Q3 - Q1.
Data Source: Study 1540 Final CSR Appendix 5 Clinical Pharmacology Report R2810-ONC-1540-CP-01V1; Study 1620 Final CSR Appendix 5 Clinical Pharmacology Report R2810-ONC-1620-CP-01V1; Study 1624 Final CSR Appendix 5 Clinical Pharmacology Report R2810-ONC-1624-CP-01V1

Figure 5: Box Plot of Observed Cemiplimab Exposure at Steady State (C_{max}) in Patients with Advanced CSCC (Study 1540), Advanced BCC (Study 1620), Advanced NSCLC (1624), and Advanced Malignancies (Study 1423) Receiving 3 mg/kg Q2W or 350 mg Q3W



N = Number of patients in PK Analysis Set.
At Steady State: C_{max} is End-of-Infusion at Cycle 3 Day 1 (CSCC and advanced BCC) and at Cycle 9 Day 1 (NSCLC). Concentrations below the LLOQ were set to 0.
mCSCC = metastatic CSCC; laCSCC = locally advanced CSCC; mBCC = metastatic BCC; laBCC = locally advanced BCC; NSCLC = non-small cell lung cancer.
Bottom and top edges of box are 25th and 75th percentiles, respectively; Horizontal line is Median (50th percentile); Diamond is Mean; Vertical lines extending from top to bottom are the maximum value below upper fence and minimum value above lower fence respectively; circles are outliers defined by the '1.5 rule' namely when less than [Q1 - 1.5*IQR] or greater than [Q3 + 1.5*IQR], with IQR = Q3 - Q1.
Data Source: Study 1540 Final CSR Appendix 5 Clinical Pharmacology Report R2810-ONC-1540-CP-01V1; Study 1620 Final CSR Appendix 5 Clinical Pharmacology Report R2810-ONC-1620-CP-01V1; Study 1624 Final CSR Appendix 5 Clinical Pharmacology Report R2810-ONC-1624-CP-01V1

2.3.4. Discussion on clinical pharmacology

The PK and immunogenicity of cemiplimab were assessed in 4 clinical studies: Study 1620 (advanced BCC), Study 1423 (FIH), Study 1540 (advanced CSCC), and Study 1624 (advanced NSCLC).

Spider plots for percent changes in target lesions in patients with advanced BCC in 17 patients with advanced mBCC and in 64 patients with advanced laBCC were provided. Inspection of the spider plot for locally advanced BCC patients reveals several patients in which there were apparent increases in tumor measurements, followed by subsequent reductions according to ICR. In one case there was an initial increase in tumor measurements by photography, followed by tumor reduction with -48% reduction in product of diameters at the third tumor assessment. Per the ICRC, the best overall response for this patient was PD. Other patients in which dimensions of externally visible tumors fluctuated over time were a patient who had best response of SD per the ICRC, and another patient who had best response of PR per ICRC. These cases illustrate the varied kinetics of changes in tumor measurements for some

advanced BCC patients treated with cemiplimab and underscore that prolonged tumor treatment may be required for some patients to achieve maximal tumor regressions.

Consistent with the initial PopPK assessments in support of the initial marketing application, the kinetics of cemiplimab in the overall population could be described by a two-compartment model with a time-varying component on clearance and of baseline albumin. The model was not stable as less than half of 500 bootstrap runs converged. The PopPK model was updated. Estimation of inter-individual variability on Emax and T50 were removed, the proportional error model was changed to a log-additive error model and the off-diagonal covariance between inter-individual random effects on CLQ and VSS was also removed. A covariate effect of NSCLC on T50 was included which improved the model notably. The updated model was evaluated using bootstrap (n=500) and all runs converged successfully. The provided GoF plots and pc-VPCs indicated the model could adequately describe the observed concentrations of cemiplimab in non-NSCLC and NSCLC patients. The fixed allometric exponents are considered to sufficiently capture the cemiplimab weight-PK covariate relationships. No other significant trends could be observed in plots of Empirical Bayes Estimates versus covariates. Exclusion of outlier concentrations did not change the population PK parameter estimates in a relevant manner.

With continuous treatment of 350 mg Q3W steady state was reached by approximately 16 weeks, with an accumulation ratio of approximately 2-fold. Cemiplimab is primarily distributed in the vascular system with a volume of distribution at steady-state (V_{ss}) of 5.3 l. Median T_{max} occurs at the end of the 30-minute infusion (see SmPC section 5.2.).

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 0.293 l/day. The total clearance appears to decrease by approximately 29.4% over time, resulting in a steady state clearance (CLss) of 0.201 l/day; the decrease in CL is not considered clinically relevant. The within dosing interval half-life at steady state is 20.3 days.

At the dosing regimens of 1 mg/kg to 10 mg/kg every two weeks, pharmacokinetics of cemiplimab were observed to be linear and dose proportional, suggesting saturation of the systemic target mediated pathway.

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, renal impairment, and mild to moderate hepatic impairment and renal impairment.

Consistent with other monoclonal antibodies, cemiplimab as a monoclonal antibody, is not subject to elimination through the renal or hepatic pathways as such no specific studies for renal or hepatic impairment were conducted. The impact of renal and hepatic impairment on cemiplimab PK was assessed through PopPK analysis. No difference in cemiplimab exposure due to renal impairment or mild to moderate hepatic impairment was identified. However, the individual predicted exposure at steady-state ($AUC_{3wks,ss}$) was observed to increase with increasing severity of renal impairment. Notably, the increase in severity of renal impairment was also associated with a consistent reduction in body weight. As body weight is a known covariate of exposure for monoclonal antibodies in general as well as for cemiplimab this difference in exposure is most likely explained by the indirect effect of body weight and is unlikely to reflect a direct effect of renal function on cemiplimab PK.

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 21 ml/min (see SmPC section 4.2 and 5.2).

The effect of hepatic impairment on the exposure of cemiplimab was evaluated by population PK analysis. In patients with mild hepatic impairment (n= 225) (total bilirubin [TB] greater than 1.0 to 1.5 times the upper limit of normal [ULN] and any aspartate aminotransferase [AST]) and patients with moderate hepatic impairment (n=3) (total bilirubin >1.5 times ULN up to 3.0 times ULN) and any 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 orsevere hepatic impairment. There are insufficient data in patients with moderate or severe hepatic impairment for dosing recommendations (see SmPC section 4.2).

Based on PopPK analysis of the overall population, the initial mean total clearance of cemiplimab decreased by about 29.4% over the first 4 to 5 months. This decrease in clearance in the overall population is larger in patients who were classified as responders. However, in patients with BCC the decrease in clearance was similar in patients between "responders" and "all other" patients (29.6% versus 26.0%). Consistently, the difference in half-life between "responders" and "all other" patients was also unremarkable in patients with BCC (23.8 days versus 22.1 days, respectively).

The identified intrinsic sources of PK variability are body weight, albumin, tumor type (NSCLC) and baseline IgG. Baseline PD-L1 and BCC tumor type were not identified as statistically significant covariates.

The effect of the all covariates combined on the post hoc estimations of exposure (C_{max}, C_{min}, and AUC) was relatively small (<25%), and within the typical PK variability observed of approximately 30%. None of the other baseline demographic characteristics tested (eg, age, race, or gender) or extrinsic covariates (eg, monotherapy versus combination therapy, country, or study) were found to be statistically significant. Data are limited in patients ≥75 years on cemiplimab monotherapy (see SmPC section 4.2).

Clinical efficacy has been observed in patients with advanced BCC who have moderate or severe obesity. However, exposure at steady state in moderately and severely obese patients was lower (<-30%) than the population exposure. In very severely obese patients, exposure was slightly lower (-50%) compared to the overall patient population.

Cemiplimab is not anticipated to interact directly or indirectly with cytochrome P450 (CYP) enzymes therefore no specific drug-drug interaction studies of cemiplimab with other drugs were conducted.

No meaningful E-R relationships were observed for all explored efficacy endpoints (ORR based on best objective response [BOR], DOR, overall survival [OS], and PFS) and for the explored safety endpoints (imAEs of all grades and imAEs of grade ≥3) with exposure metrics (after the first dose and at steady state) in patients with advanced BCC receiving cemiplimab (350 mg Q3W) as monotherapy (Safety Pool 1), patients in all 4 studies receiving cemiplimab monotherapy (Safety Pool 2), or patients in all 4 studies receiving cemiplimab monotherapy or combination therapy (Safety Pool 3).

The selected dosing regimen of 350 mg Q3W IV in patients with advanced BCC was supported by preliminary efficacy data in the FIH Study 1423, the evolving efficacy data in the treatment of advanced CSCC (Study 1540), as well as the combined safety data in 1078 patients across the cemiplimab program. In Study 1423, cemiplimab demonstrated comparable PK properties in patients with CSCC and BCC. However, the Applicant has not been able to demonstrate any E-R relationships. Therefore, it is difficult to evaluate whether the proposed dose of 350 mg Q3W is the most optimal dose in patients with advanced BCC.

Based on the mechanism of action of cemiplimab as an anti-PD1 agent acting at the level of the T-cells, considering that drug concentrations at the clinical doses 1) exceed systemic target saturation, as demonstrated by linear pharmacokinetics and elimination. and 2) are similar regardless of the tumor types, 3) that efficacy has been demonstrated in multiple tumor types (including advanced CSCC, BCC and NSCLC) and that E-R relationships for efficacy were flat in patients with advanced BCC over the exposure range studied at the clinical dose, it is reasonable to conclude that the 350 mg Q3W dosing strategy is an acceptable therapeutic dose in patients with BCC and across multiple tumor types. An evaluation of the lacking E-R relationships should consider that cemiplimab concentrations at the clinical doses exceed systemic target saturation, as demonstrated by linear pharmacokinetics and elimination. In addition, drug concentrations are similar regardless of the tumor types, and it is therefore reasonable to

conclude that the 350 mg Q3W dosing strategy is an acceptable therapeutic dose in patients with BCC and across multiple tumor types.

2.3.5. Conclusions on clinical pharmacology

Overall the clinical pharmacology of cemiplimab have been adequately described for patients with advanced or metastatic BCC. The 350 mg Q3W is considered an acceptable therapeutic dose in patients with BCC and across multiple tumour types.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

See clinical pharmacology.

2.4.2. Main study(ies)

R2810-ONC-1620 (Study 1620): A Phase 2 Study of REGN2810 (cemiplimab) in Patients With Advanced Basal Cell Carcinoma Who Experienced Progression of Disease on Hedgehog Pathway Inhibitor Therapy, or Were Intolerant of Prior Hedgehog Pathway Inhibitor Therapy

Study 1620 is an ongoing phase 2, non-randomized, 2 group, multicenter pivotal study of cemiplimab (REGN2810) monotherapy for patients with locally advanced BCC (Group 2) and metastatic BCC (Group 1) after first-line HHI therapy. For group 2, patients must be deemed to have unresectable disease and this is defined by any of the following:

a) Lack of response to prior HHI therapy

b) Response to prior HHI therapy, but currently unresectable.

These data are from the primary analysis of patients with locally advanced BCC (group 2) and an interim analysis of patients with metastatic BCC (group 1). Baseline and efficacy analyses for Study 1620 are based on the FAS, with a data cutoff date of 17 Feb 2020.

The analyses include data from all patients in Study 1620 who received their first dose of cemiplimab on or before 07 Jan 2019, which is the date Group 2 completed enrollment (N=84).

Methods

Study participants

Inclusion Criteria

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

1. Histologically confirmed diagnosis of invasive BCC

Note for clarification: The following were acceptable histologic subtypes of BCC: nodular, morpheaform, metatypical, superficial, micronodular, infiltrative, mixed, basosquamous, keratotic, desmoplastic

2. Patients must have been deemed unlikely to benefit from further therapy with an HHI due to any of the following:

a. Prior progression of disease on HHI therapy, or

b. Intolerance of prior HHI therapy defined as:

(i) any Grade 3 or 4 AE deemed related to HHI

(ii) Or any of the following HHI-related events in patients with at least 3 months of exposure to HHI therapy (exclusive of treatment breaks):

- Grade 2 muscle spasms or myalgias (iia)
- Grade 2 dysgeusia or anorexia, if accompanied by ≥Grade 1 weight loss (iib)
- Grade 2 nausea or diarrhea despite medical management (iic)

c. No better than a stable disease after 9 months on HHI therapy (exclusive of treatment breaks)

3. 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 could be followed as non-target lesions if there was at least 1 other measurable target lesion.

Group 1: At baseline, there must have been at least 1 measurable lesion ≥10 mm in maximal diameter (1.5 cm in short axis for lymph nodes) according to RECIST 1.1 criteria.

Group 2: At baseline, there must have been at least 1 measurable baseline lesion in which the longest diameter and the perpendicular diameter are both ≥10 mm if measured by digital medical photography. Non-measurable disease for Group 2 was defined as either unidimensionally measurable lesions, tumors with margins that were not clearly defined, or lesions with maximum perpendicular diameters <10 mm. Patients without measurable disease at baseline were not eligible for the study.

4. Eastern Cooperative Oncology Group (ECOG) performance status ≤1
5. At least 18 years old
6. Hepatic function:

a. Total bilirubin ≤1.5x upper limit of normal (ULN) (or ≤3x ULN, if liver metastases).

Patients with Gilbert's Disease and total bilirubin up to 3x ULN may have been eligible after communication with and approval from the medical monitor

b. Transaminases ≤3x ULN (or ≤5x ULN, if liver metastases)

c. Alkaline phosphatase (ALP) ≤2.5x ULN (or ≤5x ULN, if liver or bone metastases)

Note regarding patients with hepatic metastases being considered for enrollment in Group 1: If transaminase levels (AST and/or ALT) are >3x but ≤5x ULN, total bilirubin must have been ≤1.5x ULN. If total bilirubin was >1.5x but ≤3x ULN, both transaminases (AST and ALT) must have been ≤3x ULN.

7. Renal function: Serum creatinine ≤2x ULN or estimated creatinine clearance >35 mL/min (according the method of Cockcroft and Gault)
8. Creatine phosphokinase (CPK) (also known as CK [creatine kinase]) elevation ≤ grade 2
9. Bone marrow function:

a. Hemoglobin ≥9.0 g/dL

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

c. Platelet count ≥75 x 109/L

10. Anticipated life expectancy >12 weeks

11. All patients in either group must have consented to provide archived or newly obtained tumor material (either formalin-fixed, paraffin-embedded [FFPE] block or 10 unstained or stained slides) for central pathology review for confirmation of diagnosis of BCC. This material must have been confirmed as received by the central laboratory prior to enrollment.

12. **Group 2 only (unresectable laBCC)**: Patients must have consented to undergo biopsies of externally visible BCC lesions at baseline, cycle 1 day 22 (±3 business days), at time of tumor progression, and at other time points that were clinically indicated in the opinion of the investigator

13. We are willing and able to comply with clinic visits and study-related procedures

14. Provided signed informed consent prior to any screening procedures (with the exception of brain MRI which was allowed to be obtained within 60 days of enrollment).

15. **Group 2 only:** laBCC patients must have been deemed to have unresectable disease. Surgery must have been deemed contraindicated in the opinion of a Mohs dermatologic surgeon, a head and neck surgeon, or plastic surgeon. A copy of the surgeon's consultation note (surgeon may be site PI) from a clinical visit within 60 days of enrollment must have been submitted.

    Acceptable contraindications in the surgeon's note included:

    a. BCC that had recurred in the same location after 2 or more surgical procedures and curative resection was deemed unlikely

    b. BCCs with significant local invasion that precluded complete resection

    c. BCCs in anatomically challenging locations for which surgery might have resulted in severe disfigurement or dysfunction (eg, removal of all or part of a facial structure, such as nose, ear, or eye; or requirement for limb amputation)

    Other conditions deemed to be contraindicating for surgery must have been discussed with the medical monitor before enrolling the patient.

16. **Group 2 Only**: laBCC patients must have been deemed as not appropriate for radiation therapy. Specifically, patients must meet at least 1 of the following criteria:

    a. A patient previously received radiation therapy for BCC, such that further radiation therapy would exceed 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, must have been submitted.

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

    c. A clinic note from the investigator indicating that an individualized benefit:risk assessment was performed by a multidisciplinary team (consisting of, at minimum, a radiation oncologist and either a medical oncologist with expertise in cutaneous malignancies OR a dermato-oncologist, or a head and neck surgeon) within 60 days prior to enrollment in the proposed study, and the radiation therapy was deemed to be contraindicated. Acceptable contraindications to radiation therapy in the investigator's note for patients who had not received any prior radiation included:

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

Exclusion Criteria

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

1. Ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may have suggested risk for immune-related adverse events (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 did not require systemic treatment.
2. Prior treatment with an agent that blocks the PD-1/PD-L1 pathway
3. Prior treatment with other systemic immune-modulating agents within fewer than 28 days prior to the first dose of REGN2810. Examples of immune-modulating agents included therapeutic vaccines, cytokine treatments, or agents that target cytotoxic T-lymphocyte antigen 4 (CTLA-4), 4-1BB (CD137), or OX-40.

   Note in clarification: Prior treatment with imiquimod or other topical or intralesional immune modulators were not exclusionary
4. Untreated brain metastasis(es) that may have been considered active. (Note: patients with brain involvement of BCC due to direct extension of invading tumor, rather than metastasis, may have been allowed to enroll if they did not require >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 patients did not require any immunosuppressive doses of systemic corticosteroids for management of brain metastasis(es) within 28 days of the first dose of REGN2810.
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 positive tests for human immunodeficiency virus (HIV)-1 or HIV-2 serum antibody, hepatitis B virus (HBV), or hepatitis C virus (HCV)
7. History of pneumonitis within the last 5 years
8. Any anticancer treatment other than radiation therapy (chemotherapy, targeted systemic therapy, imiquimod, photodynamic therapy), investigational or standard of care, within 30 days of the initial administration of cemiplimab or planned to occur during the study period (patients receiving bisphosphonates or denosumab were allowed because these were not considered anticancer treatments in this protocol)
9. History of documented allergic reactions or acute hypersensitivity reaction attributed to antibody treatments
10. 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.

Trace components of doxycycline were present in earlier clinical trial material, but are not present in the cell lines used to make later clinical trial or commercial materials.

11. Concurrent malignancy other than BCC and/or history of malignancy other than BCC within 3 years of date of first planned dose of REGN2810, except for tumors with negligible risk of metastasis or death, such as adequately treated CSCC of the skin, carcinoma in situ of the cervix, or ductal carcinoma in situ of the breast, or low-risk early stage prostate adenocarcinoma (T1-T2a N0M0 and Gleason score <6 and PSA <10 ng/mL) for which the management plan is active surveillance, or prostate adenocarcinoma with biochemical-only recurrence with documented PSA doubling time of >12 months for which the management plan was active surveillance (D'Amico, 2005) (Pham, 2016). Patients with hematologic malignancies (eg, chronic lymphocytic leukemia) were excluded.
12. Any acute or chronic psychiatric problems that, in the opinion of the investigator, made the patient ineligible for participation
13. Patients with a history of solid organ transplant (patients with prior corneal transplants could be allowed to enroll after discussion with and approval from the medical monitor)
14. 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
15. Inability to undergo any contrast-enhanced radiologic response assessment
16. Breastfeeding
17. 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)
18. Receipt of live vaccines (including attenuated) within 30 days of first study treatment
19. Women of childbearing potential who were unwilling to practice highly effective contraception prior to the start of the first treatment, during the study, and for at least 6 months after the last dose. Highly effective contraceptive measures included stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomized partner; and or sexual abstinence.
20. Prior treatment with idelalisib

Treatments

In both groups, the treatment regimen is 350 mg cemiplimab IV Q3W and the patients will receive up to twelve 56-day (8-week) treatment cycles for up to 93 weeks of treatment.

Objectives

Primary Objective

The primary objective of the study was to estimate the ORR for mBCC (Group 1) or unresectable laBCC (Group 2), according to central review, when treated with cemiplimab monotherapy in patients who had progressed on HHI therapy, or were intolerant of prior HHI therapy.

Secondary Objectives

The secondary objectives for all groups were to:

- Estimate ORR according to investigator review
- Estimate the duration of response (DOR), progression-free survival (PFS) by central and investigator review, and overall survival (OS)

Exploratory Objectives (Group 2 Only)

As specified in the protocol, these exploratory objectives were only planned for Group 2, given the expected accessibility of lesions in the locally advanced group. The exploratory objectives were to explore the pharmacodynamic effects of cemiplimab in tumor biopsies obtained at baseline, during treatment, and at progression in BCC patients treated with cemiplimab, and to assess predictive potential and correlation to clinical response for biomarkers of interest including but not limited to:

- Tumor RNA expression
- Number and distribution of tumor-infiltrating lymphocytes (TILs) (CD8+ T cells, CD4+ T cells, T regulatory cells, and tissue permitting, other subtypes such as B cells, myeloid-derived cells, natural killer [NK] cells, etc.)
- Expression levels (mRNA and/or protein) of programmed death ligand 1(PD-L1), glucocorticoid-induced TNFR family related gene (GITR), and lymphocyte activation gene-3 (LAG-3), and possibly other check-point modulators
- Mutations in known oncogenes and potential tumor neoantigens
- Tumor mutational burden
- 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) and Skindex-16

Outcomes/endpoints

- Primary endpoint: ORR based on ICR evaluation using RECIST 1.1 or by composite review criteria for patients with laBCC
- ORR based on investigator review using RECIST 1.1 or by composite review criteria for patients with laBCC
- DOR
- Progression-free survival (PFS)
- OS
- TTR
- CR rate
- Disease control rate (DCR)
- Durable disease control rate (dDCR)

Sample size

50 patients were planned to be enrolled in group 1 and 80 patients in group 2 (to provide at least 85% power to reject a null hypothesis of an ORR of 20% at a 2-sided significance level of 5% if the true ORR is 35%). At the time of data cut off as of 17 Feb 2020 where an interim analysis was conducted with a subsequent new data cut off as of 30 Jun 2020, 138 patients were included in the study 1620 FAS (84 patients with locally advanced BCC and 54 patients with metastatic BCC. All patients but 26 patients in the mBCC group (in total 112 patients) had the opportunity to be followed from onset of response for at least 6 months.

Randomisation

This a non-randomised phase 2 study.

Blinding (masking)

This is an open-label study.

Statistical methods

For continuous variables, descriptive statistics included 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 is provided.

For categorical or ordinal data, frequencies and percentages were displayed for each category. The denominator was determined by the analysis population used for the summary.

For time-to-event variables, median time-to-event (and the survival rate at a fixed time point) and its 2-sided 95% confidence intervals were summarized by the Kaplan-Meier method, unless otherwise specified.

Statistical analysis for efficacy in mBCC and laBCC was conducted independently.

In order to describe ORR and DOR, the data cut for primary efficacy analysis allowed responding patients to be followed from onset of response for at least 6 months. For primary analysis, the last patient in a group had the opportunity to be followed for approximately 57 weeks, including 27 weeks (cycles 1 to 3) for response, plus an additional 30 weeks (cycles 4 to 6) for DOR. If the last patient(s) had early EOS, the timing of data cut was determined by the enrollment date of the last enrolled patient who remained on study (first dose + approximately 57 weeks).

An interim analysis of mBCC patients was performed at the time of the primary analysis for laBCC patients.

An updated analysis of the response duration will be performed after all responding patients have been followed for a minimum of 12 months from onset of response.

Interim Analysis

An interim analysis of mBCC patients was performed at the time of the primary analysis for laBCC patients. All mBCC patients enrolled on or prior to the cutoff date were included in the safety analysis. All mBCC patients who had the opportunity to be followed from onset of response for at least 6 months were included in the efficacy analysis (that is, mBCC patients who had the opportunity to be followed for

approximately 57 weeks – including 27 weeks (cycles 1 to 3) for response, plus an additional 30 weeks [cycles 4 to 6] for DOR).

For regions where, alpha spending was not required: For this interim analysis on mBCC patients, the ORR and associated 95% confidence interval were summarized. As the primary objective of this interim analysis was point estimation on ORR and characterizing the precision of point estimation, there was no hypothesis testing associated with this interim analysis. Also, no decisions were made regarding study conduct associated with the interim analysis. Therefore, Type I error adjustment was not applicable for this planned interim analysis. At the time of the final analysis for mBCC patients, 95% exact confidence intervals will be reported.

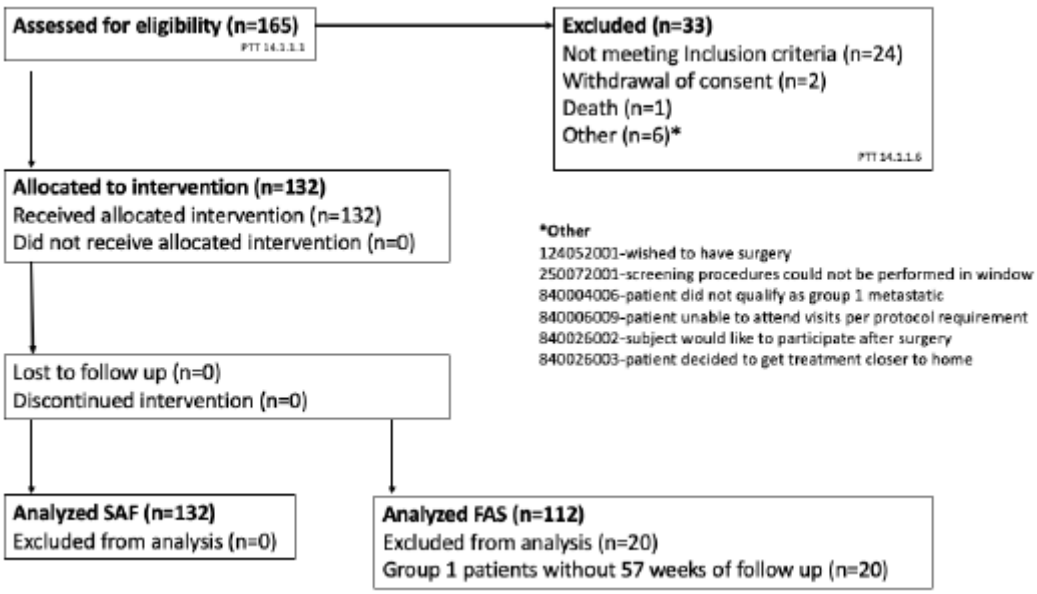
For regions where, alpha spending is required: For this interim analysis on mBCC patients, a 2-sided alpha of 0.0001 was allocated for interim analysis, and a 2-sided alpha of 0.0499 was preserved for the final analysis. Correspondingly, for the interim analysis of the primary endpoint of ORR in mBCC patients, the precision of ORR was estimated by an adjusted and 2-sided 99.99% exact confidence interval. The unadjusted and 2-sided 95% exact confidence interval was also reported at the time of interim analysis. At the time of the final analysis for mBCC patients, both adjusted 95.01% and unadjusted 95% exact confidence intervals will be reported.

For other efficacy endpoints in mBCC patients, only a 2-sided 95% exact confidence interval was presented at the interim and will also be presented at the final analysis.

Results

Participant flow

Figure 9 Participant flow - as of the 17 Feb 2020 data cut.



As of the data cutoff for this interim CSR, a total of 170 patients were screened with 32 screen-failures at 49 sites in 10 countries. In the 134-day interval between 17 Feb 2020 to 30 Jun 2020 group 1 (mBCC) completed enrollment of 54 patients (53 planned), with 6 additional patients enrolled in this period (in total 138 patients). The data cut for the primary analysis for Group 1 is projected to occur on 20 May

2021, which represents 57 weeks from cycle 1/day 1 for the 54th patient enrolled in Group 1. As of the 30 Jun 2020 data cutoff, treatment was ongoing for 40 patients (29.0%). The most common reason for premature treatment discontinuation was disease progression (40.6% [56/138]), followed by AEs in 17 patients (12.3%). Death was reported as the reason for discontinuation in 3 (2.2%) patients.

Recruitment

The analyses include data from all patients in study 1620 who received their first dose of cemiplimab on or before 07 January 2019, which is the date that group 2 (locally advanced BCC) completed enrolment (N=84) and the interim analysis was conducted for group 2.

As of the data cutoff sites from Austria, Belgium, Canada, France, Germany, Greece, Italy, Spain, Switzerland, and the United States (US) participated in this study.

Conduct of the study

The original protocol was amended 4 times. The rationale for each amendment is summarized below:

Table 19 Summary of main protocol amendments

Amendment / Date	Major Changes
Amendment 1 / 28 Nov 2016	• Noted regional laboratory testing for bicarbonate • Added a window for the duration of the cemiplimab infusion • Updated the contraception language in the exclusion criteria
Amendment 2 / 23 Mar 2017	• The dose of cemiplimab was changed from 250 mg Q3W to 350 mg Q3W to achieve greater consistency in exposure with the 3 mg/kg Q2W dose used in the FIH study. The dose selection was supported by modeling of exposure. • Updated the length of treatment period to 9 cycles
Amendment 3 / 03 Jul 2017	• Added an eligibility criterion to exclude patients who had previously been treated with idelalisib. • Added safety guidance language for the management of patients developing stomatitis or mucositis. • Added an irAE of any grade in a patient previously treated with a PI3-K inhibitor to the list of AESIs.
Amendment 4 / 21 Jul 2019	• Clarified the details of the timing of the data cut for the primary analysis for laBCC and added an interim analysis for mBCC. • Clarified eligibility for re-treatment • Extended post-treatment follow-up for an additional year, for a total of approximately 1.5 years after completion of the treatment at the end of the extended follow-up (unless the patient enters re-treatment) • NAb analysis was added to the ADA analysis

ADA=anti-drug antibody; AESI=adverse event of special interest; FIH=first in human; irAE=immune-related adverse event; PI 3-K= phosphatidylinositol 3 kinase; PK=pharmacokinetic; Q2W=every 2 weeks; Q3W=every 3 weeks; TEAE=treatment-emergent adverse event.

Protocol deviations

Thirty-four important protocol deviations were reported in 25 patients in the Safety Analysis Set.

Table 20 Summary of important protocol deviations (Safety Analysis Set).

	Group 1: mBCC (N=48)	Group 2: laBCC (N=84)	Total (N=132)
Number of Important Protocol Deviations	5	29	34
Patients with Any Important Protocol Deviation, n (%)	5 (10.4%)	20 (23.8%)	25 (18.9%)
Type of Important Protocol Deviations, n (%)			
EXCLUSION CRITERIA MET BUT SUBJECT ENROLLED	2 (4.2%)	3 (3.6%)	5 (3.8%)
INADEQUATE INFORMED CONSENT ADMINISTRATION	0	1 (1.2%)	1 (0.8%)
INCLUSION CRITERIA NOT MET BUT SUBJECT ENROLLED	2 (4.2%)	13 (15.5%)	15 (11.4%)
OTHER	0	2 (2.4%)	2 (1.5%)
SAES/AESIS NOT REPORTED WITHIN 24 HOURS TO PVRM	0	1 (1.2%)	1 (0.8%)
TREATMENT DEVIATION	1 (2.1%)	2 (2.4%)	3 (2.3%)

Data cutoff as of 17 Feb17 Feb 2020

Table 1: Important Deviations Related to Inclusion Criteria

Inclusion Criteria	Group 1 (mBCC)	Group 2 (laBCC)
Inclusion 3: No measurable lesion	1	2
Inclusion 6: Hepatic Function not meeting protocol criteria for alkaline phosphatase levels that were higher than the 2.5x upper limit of normal (ULN) on both Screening and C1D1	0	1
Inclusion 8: Creatine phosphokinase (CPK) (also known as CK [creatine kinase]) not performed on both Screening and C1D1	1	6
Inclusion 11: Archival or newly obtained tumor material for central pathology review for confirmation of BCC was not confirmed as received by central laboratory prior to enrollment	0	7

Several patients reported more than one deviation (276061001: Incl 8 and 11, 276061002 Incl 3, 8 and 11)
The total number of patients with at least one deviation in group 1 is 2 and in group 2 is 13.
Source: Table 10 Study 1620 Interim CSR, post-text listing 16.2.2.1 and 16.2.4.4

Baseline data

Table 14.1.2.1f Demographics and Baseline Characteristics
(Full Analysis Set)

	Group 1: mBCC (N=54)	Group 2: laBCC (N=84)	Total (N=138)
Age (years)			
n	54	84	138
Mean (SD)	63.8 (11.09)	69.1 (12.84)	67.0 (12.42)
Median	63.5	70.0	68.0
Q1 : Q3	57.0 : 73.0	60.5 : 79.0	57.0 : 77.0
Min : Max	38 : 90	42 : 89	38 : 90
Age Groups (years), n (%)			
<65	27 (50.0%)	31 (36.9%)	58 (42.0%)
>=65	27 (50.0%)	53 (63.1%)	80 (58.0%)
Age Groups (years), n (%)			
<65	27 (50.0%)	31 (36.9%)	58 (42.0%)
>=65 to <75	18 (33.3%)	19 (22.6%)	37 (26.8%)
>=75	9 (16.7%)	34 (40.5%)	43 (31.2%)
Age Groups (years), n (%)			
<75	45 (83.3%)	50 (59.5%)	95 (68.8%)
>=75	9 (16.7%)	34 (40.5%)	43 (31.2%)
Sex, n (%)			
Male	38 (70.4%)	56 (66.7%)	94 (68.1%)
Female	16 (29.6%)	28 (33.3%)	44 (31.9%)
Race, n (%)			
White	47 (87.0%)	57 (67.9%)	104 (75.4%)
Not Reported	1 (1.9%)	0	1 (0.7%)
Missing	6 (11.1%)	27 (32.1%)	33 (23.9%)
Ethnicity, n (%)			
Not Hispanic or Latino	46 (85.2%)	56 (66.7%)	102 (73.9%)
Hispanic or Latino	2 (3.7%)	1 (1.2%)	3 (2.2%)
Missing	6 (11.1%)	27 (32.1%)	33 (23.9%)
Height (cm)			
n	53	83	136
Mean (SD)	173.04 (8.621)	170.13 (9.519)	171.27 (9.257)
Median	173.00	170.00	170.60
Q1 : Q3	167.00 : 179.00	163.00 : 177.00	165.00 : 178.00
Min : Max	156.0 : 194.0	147.0 : 192.0	147.0 : 194.0
Body Weight (kg)			
n	54	84	138
Mean (SD)	79.10 (20.727)	75.70 (17.512)	77.03 (18.835)
Median	75.50	72.95	73.55
Q1 : Q3	62.90 : 89.60	64.45 : 86.50	63.50 : 88.00
Min : Max	48.0 : 129.9	44.6 : 134.8	44.6 : 134.8
BMI (kg/m2)			
n	53	83	136
Mean (SD)	26.157 (5.6258)	26.166 (5.4696)	26.162 (5.5102)
Median	25.600	24.490	25.030
Q1 : Q3	21.870 : 29.600	22.460 : 30.300	22.255 : 29.675
Min : Max	16.81 : 42.91	17.50 : 42.74	16.81 : 42.91
ECOG Performance Status, n (%)			
0	36 (66.7%)	51 (60.7%)	87 (63.0%)
1	18 (33.3%)	33 (39.3%)	51 (37.0%)
BMI (kg/m2)			
n	47	83	130
Mean (SD)	26.151 (5.8728)	26.166 (5.4696)	26.160 (5.5960)
Median	25.590	24.490	24.815
Q1 : Q3	21.740 : 29.940	22.460 : 30.300	22.230 : 29.940
Min : Max	16.81 : 42.91	17.50 : 42.74	16.81 : 42.91
ECOG Performance Status, n (%)			
0	31 (64.6%)	51 (60.7%)	82 (62.1%)
1	17 (35.4%)	33 (39.3%)	50 (37.9%)

†This information was not reported for patients enrolled in countries that preclude the collection or reporting of patient race/ethnicity, and this information was documented as "missing."

Data cutoff 17 Feb 2020
Source: PTT 14.1.2.1

Table 21 Baseline tumour characteristics (safety analysis set)

	Group 1: mBCC (N=54)	Group 2: laBCC (N=84)	Total (N=138)
Primary Site of Tumor, n (%)			
Head and Neck	22 (40.7%)	75 (89.3%)	97 (70.3%)
Extremity	6 (11.1%)	2 (2.4%)	8 (5.8%)
Trunk	25 (46.3%)	7 (8.3%)	32 (23.2%)
Anogenital	1 (1.9%)	0	1 (0.7%)
Time from Initial Diagnosis to First Dose (months) [a]			
n	54	83	137
Mean (SD)	117.5 (110.52)	143.2 (123.74)	133.1 (118.95)
Median	74.3	96.9	96.0
Q1 : Q3	39.1 : 151.8	46.2 : 212.0	44.1 : 183.7
Min : Max	10 : 424	10 : 513	10 : 513
Stage at Initial Diagnosis, n (%)			
Stage I	1 (2.1%)	7 (8.3%)	8 (6.1%)
Stage II	3 (6.3%)	5 (6.0%)	8 (6.1%)
Stage III	3 (6.3%)	10 (11.9%)	13 (9.8%)
Stage IIIa	0	1 (1.2%)	1 (0.8%)
Stage IIIb	0	2 (2.4%)	2 (1.5%)
Stage IIIc	0	1 (1.2%)	1 (0.8%)
Stage IIa	1 (2.1%)	1 (1.2%)	2 (1.5%)
Stage IIb	0	1 (1.2%)	1 (0.8%)
Stage IIc	0	1 (1.2%)	1 (0.8%)
Stage IV	11 (22.9%)	1 (1.2%)	12 (9.1%)
Stage IVb	2 (4.2%)	0	2 (1.5%)
Stage Ia	1 (2.1%)	0	1 (0.8%)
Unknown	26 (54.2%)	53 (63.1%)	79 (59.8%)
Missing	0	1 (1.2%)	1 (0.8%)

Data cut-off as of Feb 17th, 2020.
[a] Time from Initial Diagnosis to First Dose (months) = (Date of first dose of Cemiplimab - Date of initial diagnosis)/30.4375.
[b] Time from Most Recent Relapse/Recurrence to First Dose (months) = (Date of first dose of Cemiplimab - Date of most recent relapse/recurrence)/30.4375.
[c] Unknown includes missing values

/sasdata/Data/Production/BDM/R2810/R2810-ONC/R2810-ONC-1620/Interim_BCC_sBLA/Analysis_CSR/Programs/TFL/Generated/t_1_2_2_tumorchar_saf.sas (michael.klingler 17AUG2020 16:33 SAS Linux 9.4)

Table 22 Summary of prior HHI therapy by setting (Full Analysis Set)

	Group 1: mBCC (N=54)	Group 2: laBCC (N=84)	Total (N=138)
Number of Patients with prior HHI therapy, n (%)	54 (100%)	84 (100%)	138 (100%)
Sonidegib	9 (16.7%)	14 (16.7%)	23 (16.7%)
Vismodegib	52 (96.3%)	79 (94.0%)	131 (94.9%)
Both Vismodegib and Sonidegib	7 (13.0%)	9 (10.7%)	16 (11.6%)

Table 14.1.2.4 Reasons for Discontinuation of Prior HHI Therapy
(Safety Analysis Set)

	Group 1: mBCC (N=54)	Group 2: laBCC (N=84)	Total (N=138)
Progression of Disease on HHI, n (%)	41 (75.9%)	60 (71.4%)	101 (73.2%)
Intolerant of prior HHI therapy, n (%)	18 (33.3%)	32 (38.1%)	50 (36.2%)
Intolerant to Vismodegib, n (%)	19 (35.2%)	32 (38.1%)	51 (37.0%)
Intolerant to Sonidegib, n (%)	5 (9.3%)	4 (4.8%)	9 (6.5%)
No better than a stable disease after 9 months on HHI therapy, n (%)	7 (13.0%)	7 (8.3%)	14 (10.1%)
Progression of Disease vs Other			
Progression of Disease on HHI, n (%)	41 (75.9%)	60 (71.4%)	101 (73.2%)
Other than Progression of Disease on HHI, n (%)	13 (24.1%)	24 (28.6%)	37 (26.8%)
Intolerant of prior HHI therapy, n (%)	10 (18.5%)	22 (26.2%)	32 (23.2%)
Intolerant to Vismodegib, n (%)	9 (16.7%)	20 (23.8%)	29 (21.0%)
Intolerant to Sonidegib, n (%)	3 (5.6%)	2 (2.4%)	5 (3.6%)
No better than a stable disease after 9 months on HHI therapy, n (%)	5 (9.3%)	3 (3.6%)	8 (5.8%)
Progression or Lack of Response vs Intolerance			
Progression or lack of response, n (%)	46 (85.2%)	63 (75.0%)	109 (79.0%)
Intolerance, n (%)	8 (14.8%)	21 (25.0%)	29 (21.0%)

Data cut-off as of Jun 30th, 2020.

Numbers analysed

Table 11: Analysis Sets

Analysis Set, n (%)	Group 1 (N = 48)	Group 2 (N = 84)	Total (N = 132)
Full Analysis Set (FAS)	28 (58.3%)	84 (100%)	112 (84.8%)
Safety Analysis Set (SAF)	48 (100%)	84 (100%)	132 (100%)
Pharmacokinetic Analysis Set (PKA)	48 (100%)	84 (100%)	132 (100%)
Anti-drug Antibody Analysis Set (ADA)	44 (91.7%)	81 (96.4)	125 (94.7%)

Data cutoff as of 17 Feb 2020
Source: PTT 14.1.1.3

Table 14.1.1.3f Analysis Sets
(Full Analysis Set)

Analysis Set, n (%)	Group 1: mBCC (N=54)	Group 2: laBCC (N=84)	Total (N=138)
Full Analysis Set (FAS)	54 (100%)	84 (100%)	138 (100%)
Safety Analysis Set (SAF)	54 (100%)	84 (100%)	138 (100%)

Data cutoff as of 30 June 2020

A total of 138 patients who met criteria as of the data cutoff date were included in the FAS, and 138 patients who met criteria as of the data cutoff were included in the SAF (data cutoff 30.06.2020). A total of 132 and 125 patients who met criteria were included in the PK and ADA analysis sets, respectively (data cutoff 17.02.2020).

The full analysis set (FAS) includes all enrolled patients for each group who passed screening and were deemed to be eligible for this study. All efficacy endpoints were analyzed using FAS by group.

At the time of data cutoff as of 17 Feb 2020, the median duration of follow-up in the FAS was 15.06 months (range: 0.5 to 25.1 months) for locally advanced BCC patients, 9.46 months (range: 1.5 to 27.2 months) for metastatic BCC patients, and 13.26 months (range: 0.5 to 27.2 months) for the combined total of advanced BCC patients.

Group 1 is the mBCC cohort for Study 1620 and reached its planned total enrollment of 54 patients as of 09 April 2020 and has been closed to enrollment.

On 30 June 2020, a new data cut was performed for the purpose of confirming responses for 2 laBCC patients who had BOR (per central review) of "unconfirmed response" at the 17 February data cut; investigator-assessed efficacy data have been extracted from that data cut off.

Per protocol, efficacy data are considered mature when a patient has opportunity for at least 57 weeks of follow up. Therefore, the mBCC interim analysis for efficacy in the initial submission was also comprised of those patients (N = 28) who had opportunity or at least 57 weeks of follow up at the 17 February 2020 data cut.

Outcomes and estimation

Primary endpoint – ORR- by Independent Central Review

Table 6: Study 1620: Best Overall Tumor Response Rate by Independent Central Review (Full Analysis Set)

	Group 1 mBCC (N = 28)	Group 2 laBCC (N = 84)	Total (N = 112)
Best Overall Tumor Response, n (%)			
Complete response (CR)[a]	0	5 (6.0%)	5 (4.5%)
Partial response (PR)[a]	6 (21.4%)	19 (22.6%)	25 (22.3%)
Stable disease (SD)[b]	10 (35.7%)	43 (51.2%)	53 (47.3%)
Non-CR/non-PD[c]	3 (10.7%)	0	3 (2.7%)
Progressive disease (PD)	7 (25.0%)	9 (10.7%)	16 (14.3%)
Not evaluable (NE)[d]	2 (7.1%)	8 (9.5%)	10 (8.9%)
Response			
Objective response rate (ORR: CR + PR)	6 (21.4%)	24 (28.6%)	30 (26.8%)
95% CI for ORR[e]	(8.3%, 41.0%)	(19.2%, 39.5%)	(18.9%, 36.0%)
99.99% CI for ORR[e]	(2.4%, 59.3%)		
CR rate[a]	0	5 (6.0%)	5 (4.5%)
95% CI for CR rate[e]	(0.0%, 12.3%)	(2.0%, 13.3%)	(1.5%, 10.1%)
Disease control rate (DCR: CR + PR + SD + non-CR/non-PD)[f]	19 (67.9%)	67 (79.8%)	86 (76.8%)
95% CI for DCR[e]	(47.6%, 84.1%)	(69.6%, 87.7%)	(67.9%, 84.2%)
Durable DCR[g]	13 (46.4%)	50 (59.5%)	63 (56.3%)
95% CI for durable DCR[e]	(27.5%, 66.1%)	(48.3%, 70.1%)	(46.6%, 65.6%)

[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 the first dose date.
[c] Non-CR/non-PD is for patients with nonmeasurable disease only.
[d] Not evaluable response includes the missing and unknown tumor response.
[e] Clopper-Person exact confidence interval.
[f] DCR is the proportion of patients with first evaluable tumor assessment of CR, PR, SD, or non-CR/non-PD occurring no sooner than first scheduled tumor assessment at 9 weeks (measured from Day 56 to account for visit windows).
[g] Durable DCR is the proportion of patients with CR, PR, SD, or non-CR/non-PD for at least 27 weeks (measured from Day 182 to account for visit windows) without PD.
Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; CR, complete response; DCR, disease control rate; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
Data cutoff date was 17 Feb 2020. Only patients who started treatment on or prior to 07 Jan 2019 are included in Group 1 (mBCC).
Source: ISE Table 14.2.1.1af.

Table 2: Best Overall Tumor Response Rate by Independent Central Review (Full Analysis Set) – laBCC Patients

	Group 2: laBCC (N=84)
Best Overall Tumor Response, n (%)	
Complete Response (CR) [a]	6 (7.1%)
Partial Response (PR) [a]	21 (25.0%)
Stable Disease (SD) [b]	40 (47.6%)
Non-CR/Non-PD [c]	0
Progressive Disease (PD)	9 (10.7%)
Not Evaluable (NE) [d]	8 (9.5%)
Response	
Objective Response Rate (ORR: CR+PR)	27 (32.1%)
95% CI for ORR [e]	(22.4%, 43.2%)
Complete Response Rate (CR) [a]	6 (7.1%)
95% CI for CR Rate [e]	(2.7%, 14.9%)
Disease Control Rate (DCR: CR+PR+SD+Non-CR/Non-PD)	67 (79.8%)
95% CI for DCR [e]	(69.6%, 87.7%)
Durable DCR [f]	50 (59.5%)
95% CI for Durable DCR [e]	(48.3%, 70.1%)

Data cutoff as of 30 Jun 2020.

Table 3: Study1620: Best Overall Tumor Response in Patients with Advanced BCC by Independent Central Review: Updated to Include Confirmatory Assessments for Two Patients After Data Cutoff (Full Analysis Set)

	Study 1620 mBCC (N = 28)	Study 1620 laBCC (N = 84)	Study 1620 Total (N =112)
Best Overall Tumor Response, n (%)			
Complete Response (CR) [a]	0	5 (6.0%)	5 (4.5%)
Partial Response (PR) [a]	6 (21.4%)	21 (25.0%) [h]	27 (24.1%)
Stable Disease (SD) [b]	10 (35.7%)	41 (48.8%)	51 (45.5%)
Non-CR/Non-PD [c]	3 (10.7%)	0	3 (2.7%)
Progressive Disease (PD)	7 (25.0%)	9 (10.7%)	16 (14.3%)
Not Evaluable (NE) [d]	2 (7.1%)	8 (9.5%)	10 (8.9%)
Response			
Objective Response Rate (ORR: CR+PR)	6 (21.4%)	26 (31.0%) [h]	32 (28.6%)
95% CI for ORR [e]	(8.3%, 41.0%)	(21.3%, 42.0%)	(20.4%, 37.9%)
99.99% CI for ORR [e]	(2.4%, 59.3%)		
Complete Response Rate (CR) [a]	0	5 (6.0%)	5 (4.5%)
95% CI for CR Rate [e]	(0.0%, 12.3%)	(2.0%, 13.3%)	(1.5%, 10.1%)
Disease Control Rate [f] (DCR: CR+PR+SD+Non-CR/Non-PD)	19 (67.9%)	67 (79.8%)	86 (76.8%)
95% CI for DCR [e]	(47.6%, 84.1%)	(69.6%, 87.7%)	(67.9%, 84.2%)
Durable DCR [g]	13 (46.4%)	50 (59.5%)	63 (56.3%)
95% CI for Durable DCR [e]	(27.5%, 66.1%)	(48.3%, 70.1%)	(46.6%, 65.6%)

Data cutoff was 17 Feb 2020. Patients with mBCC are only included if they started treatment on or prior to 07 Jan 2019.
[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-Pearson exact confidence interval.
[f] DCR: proportions of patients with CR, PR, SD, or Non-CR/Non-PD at the first evaluable tumor assessment occurring no sooner than 9 weeks (measured from day 56 to account for treatment windows).
[g] Durable DCR: proportion of patients with CR, PR, or SD for at least 27 weeks (measured from day 182 to account for treatment windows) without PD
[h] The ORR result for locally advanced BCC includes two patients who first met the criteria for PR (per ICR) at the last tumor assessment prior to the data cut and the confirmatory assessments were obtained after data cutoff. Both patients are counted as PR in the analysis because their responses were confirmed per ICR in tumor assessments done after data cut.
Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; CR, complete response; DCR, disease control rate; ICR, independent central review; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease
Source: ISE Table 14.2.1.1afm

Table 1: Best Overall Tumor Response Rate by Investigator Assessment in mBCC patients (Study 1620 Group 1)

	Group 1: mBCC (N=35)
Best Overall Tumor Response, n (%)	
Complete Response (CR) [a]	1 (2.9%)
Partial Response (PR) [a]	9 (25.7%)
Stable Disease (SD) [b]	14 (40.0%)
Progressive Disease (PD)	9 (25.7%)
Not Evaluable (NE) [c]	2 (5.7%)
Response	
Objective Response Rate (ORR:CR+PR)	10 (28.6%)
95% CI for ORR [d]	(14.6%, 46.3%)
Complete Response Rate (CR) [a]	1 (2.9%)
95% CI for CR Rate [d]	(0.1%, 14.9%)
Disease Control Rate (DCR: CR+PR+SD)	24 (68.6%)
95% CI for DCR [d]	(50.7%, 83.1%)
Durable DCR [e]	15 (42.9%)
95% CI for Durable DCR [d]	(26.3%, 60.6%)

Data cut-off as of Jun 30th, 2020. Only patients who started treatment on or prior to May 21st, 2019 are included in Group 1 (mBCC).
[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-Pearson exact confidence interval.
[e] Durable DCR: proportion of patients with CR, PR or SD for at least 182 days without PD.
Source: Table 14.2.1.2f

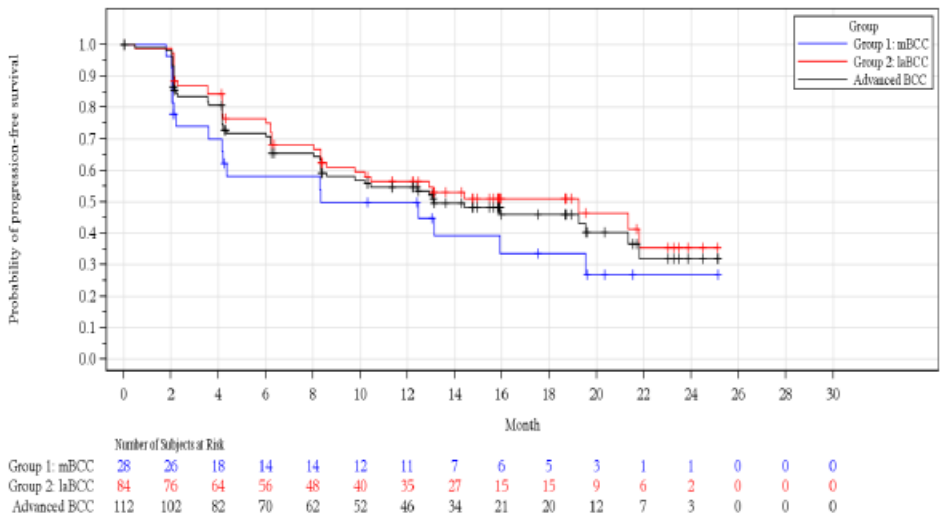
Secondary endpoints – PFS

Table 11: Study 1620: Kaplan-Meier Estimation of Progression-Free Survival by Independent Central Review (Full Analysis Set)

	Group 1: mBCC (N = 28)	Group 2: laBCC (N = 84)	Total (N = 112)
K-M estimation of Progression-Free Survival			
Number of events, n (%)	17 (60.7%)	38 (45.2%)	55 (49.1%)
Progressive disease, n (%)	14 (50.0%)	33 (39.3%)	47 (42.0%)
Death, n (%)	3 (10.7%)	5 (6.0%)	8 (7.1%)
Number of censored patients, n (%)	11 (39.3%)	46 (54.8%)	57 (50.9%)
Median (95% CI) (months)	8.3 (3.6, 19.5)	19.3 (8.6, NE)	13.1 (8.3, 21.3)
Estimated Event-Free Probability, % (95% CI)			
4 months	70.0 (48.8, 83.7)	84.4 (74.1, 90.8)	80.6 (71.6, 87.1)
6 months	58.1 (37.1, 74.3)	76.3 (65.1, 84.4)	71.7 (61.8, 79.4)
8 months	58.1 (37.1, 74.3)	68.1 (56.3, 77.4)	65.5 (55.4, 73.9)
12 months	49.8 (29.5, 67.1)	56.5 (44.3, 67.0)	54.7 (44.4, 64.0)
16 months	33.6 (15.2, 53.2)	51.0 (38.6, 62.1)	46.0 (35.2, 56.1)
20 months	26.9 (10.0, 47.3)	46.4 (32.2, 59.4)	40.2 (28.4, 51.8)
24 months	26.9 (10.0, 47.3)	35.3 (19.1, 52.0)	32.0 (18.8, 46.0)

Abbreviations: CI, confidence interval; K-M, Kaplan-Meier; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma.
Data cutoff as of 17 Feb 2020. Only patients who started treatment on or prior to 07 Jan 2019 are included in Group 1 (mBCC).
Source: ISE Table 14.2.2.1af.

Figure 1: Study 1620: Kaplan-Meier Curve for Progression-Free Survival by Independent Central Review - All Patients with BCC (Full Analysis Set)



Abbreviation: BCC, basal cell carcinoma; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma.
Data cutoff date was 17 Feb 2020. Only patients who started treatment on or prior to 07 Jan 2019 are included in Group 1 (mBCC).
Source: ISE Figure 14.2.2.1a.

Table 3: Kaplan-Meier Estimation of PFS by Investigator Assessment in mBCC Patients (Study 1620 – Group 1)

	Group 1: mBCC (N=35)
KM estimation of Progression Free Survival	
Number of events, n (%)	26 (74.3%)
Progressive Disease, n (%)	25 (71.4%)
Death, n (%)	1 (2.9%)
Number of censored patients, n (%)	9 (25.7%)
Median (95% CI), (months)	6.6 (4.2, 8.3)
Estimated Event-Free Probability, % (95% CI)	
4 months	70.4 (51.9, 82.8)
6 months	60.8 (42.1, 75.1)
8 months	41.6 (24.6, 57.7)
12 months	28.8 (14.5, 44.8)
16 months	21.6 (9.2, 37.3)
20 months	21.6 (9.2, 37.3)
24 months	14.4 (3.6, 32.4)

Data cut-off as of Jun 30th, 2020. Only patients who started treatment on or prior to May 21st, 2019 are included in Group 1 (mBCC).
Source: Table 14.2.2.2f

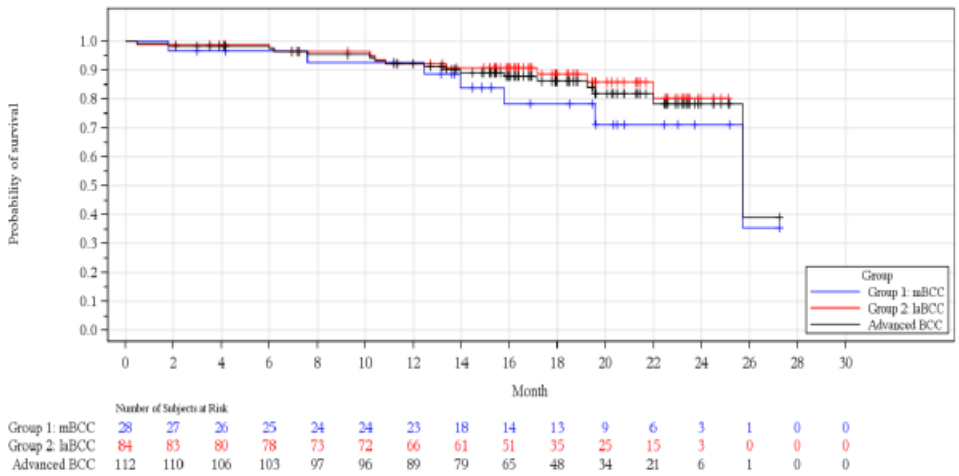
Secondary endpoints - OS

Table 12: Summary of Overall Survival (Full Analysis Set)

	Group 1: mBCC (N = 28)	Group 2: laBCC (N = 84)	Total (N = 112)
K-M estimation of Overall Survival			
Number of deaths, n (%)	7 (25.0%)	10 (11.9%)	17 (15.2%)
Number of censored patients, n (%)	21 (75.0%)	74 (88.1%)	95 (84.8%)
Median (95% CI) (months)	25.7 (19.5, NE)	NR (NE, NE)	25.7 (25.7, NE)
Estimated Probability of Survival, % (95% CI)			
4 months	96.4 (77.2, 99.5)	98.8 (91.8, 99.8)	98.2 (93.0, 99.6)
6 months	96.4 (77.2, 99.5)	98.8 (91.8, 99.8)	98.2 (93.0, 99.6)
8 months	92.6 (73.4, 98.1)	96.3 (88.9, 98.8)	95.3 (89.1, 98.0)
12 months	92.6 (73.4, 98.1)	92.3 (83.6, 96.5)	92.3 (85.3, 96.1)
16 months	78.3 (54.7, 90.5)	90.8 (81.7, 95.5)	87.8 (79.4, 92.9)
20 months	71.2 (45.1, 86.5)	85.7 (73.2, 92.6)	82.0 (70.9, 89.1)
24 months	71.2 (45.1, 86.5)	80.3 (62.6, 90.3)	78.2 (64.6, 87.1)

Abbreviations: CI, confidence interval; K-M, Kaplan-Meier; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma.
Data cutoff as of 17 Feb 2020. Only patients who started treatment on or prior to 07 Jan 2019 are included in Group 1 (mBCC).
Source: ISE Table 14.2.3.1af.

Figure 2: Study 1620: Kaplan-Meier Curve for Overall Survival - All Patients with BCC (Full Analysis Set)



Abbreviation: BCC, basal cell carcinoma; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma.
Data cutoff date was 17 Feb 2020. Only patients who started treatment on or prior to 07 Jan 2019 are included in Group 1 (mBCC).
Source: ISE Figure 14.2.3.1a

Table 4: Summary of Overall Survival in mBCC patients (Study 1620 Group 1)

	Group 1: mBCC (N=35)
KM estimation of Overall Survival	
Number of deaths, n (%)	9 (25.7%)
Number of censored patients, n (%)	26 (74.3%)
Median (95% CI), (months)	NR (25.7, NE)
Estimated Probability of Survival, % (95% CI)	
4 months	97.1 (81.4, 99.6)
6 months	97.1 (81.4, 99.6)
8 months	87.7 (70.5, 95.2)
12 months	87.7 (70.5, 95.2)
16 months	77.4 (58.2, 88.6)
20 months	72.6 (51.9, 85.5)
24 months	72.6 (51.9, 85.5)

Data cut-off as of Jun 30th, 2020. Only patients who started treatment on or prior to May 21st, 2019 are included in Group 1 (mBCC).

Source: Table 14.2.3.1f

Secondary endpoints – TTR

Table 13: Study 1620: Summary of Time to Response by Independent Central Review - Patients with Confirmed CR or PR (Full Analysis Set)

	Group 1: mBCC (N = 6)	Group 2: laBCC (N = 24)	Total (N = 30)
Observed Time to Response (CR or PR) (months)			
n	6	24	30
Mean (SD)	4.54 (3.338)	5.17 (2.598)	5.04 (2.709)
Median	3.17	4.21	4.17
Q1 : Q3	2.14 : 6.21	4.14 : 6.62	2.83 : 6.31
Min : Max	2.1 : 10.5	2.1 : 13.4	2.1 : 13.4
Observed Time to Response (CR or PR), n (%)[a]			
<2 months	0	0	0
2 to 4 months	3 (50.0%)	5 (20.8%)	8 (26.7%)
4 to 6 months	1 (16.7%)	12 (50.0%)	13 (43.3%)
≥6 months	2 (33.3%)	7 (29.2%)	9 (30.0%)

[a] Percentages are based on the number of patients with confirmed CR or PR

Abbreviations: CR, complete response; laBCC, locally advanced basal cell carcinoma; max, maximum; mBCC, metastatic basal cell carcinoma; min, minimum; PR, partial response; Q1, first quartile; Q3, third quartile.

Data cutoff as of 17 Feb 2020. Only patients who started treatment on or prior to 07 Jan 2019 are included in Group 1 (mBCC).

Source: ISE Table 14.2.1.7af

Secondary endpoints – DOR

Table 17: Summary of Duration of Response by Independent Central Review (Full Analysis Set - Patients with Confirmed CR or PR)

	Group 1: mBCC (N=6)	Group 2: laBCC (N=24)
KM Estimation of Duration of Response (CR or PR)		
n	6	24
Number of events, n (%) [a]	2 (33.3%)	6 (25.0%)
Number of censored patients, n (%) [a]	4 (66.7%)	18 (75.0%)
Median (95% CI), (months)	NR (9.0, NE)	NR (15.0, NE)
Observed Duration of Response (CR or PR) (months)		
n	6	24
Min : Max	9.0 : 23.0+	2.1:21.4+
Observed Duration of Response (CR or PR), n (%) [a]		
≥4 months	6 (100%)	22 (91.7%)
≥6 months	6 (100%)	19 (79.2%)
≥8 months	6 (100%)	16 (66.7%)
≥12 months	2 (33.3%)	11 (45.8%)
≥16 months	1 (16.7%)	9 (37.5%)
≥20 months	1 (16.7%)	2 (8.3%)
≥24 months	0	0

Data cut-off as of 17 Feb 2020. Only patients who started treatment on or prior to Jan 7th, 2019 are included in Group 1 (mBCC).
[a] Events include progressive disease or deaths. Percentages are based on number of patients with confirmed CR or PR.
Source: PTT 14.2.1.3fand PTT 14.2.1.5f

Table 18: Kaplan-Meier Estimation of Duration of Response by Independent Central Review (Full Analysis Set - Patients with Confirmed CR or PR)

	Group 1: mBCC (N=6)	Group 2: laBCC (N=24)
Estimated Event-Free Probability, % (95% CI)		
4 months	100 (NE, NE)	100 (NE, NE)
6 months	100 (NE, NE)	90.9 (68.3, 97.6)
8 months	100 (NE, NE)	90.9 (68.3, 97.6)
12 months	66.7 (19.5, 90.4)	85.2 (60.5, 95.0)
16 months	66.7 (19.5, 90.4)	69.7 (40.3, 86.7)

Data cut-off as of 17 Feb 2020. Only patients who started treatment on or prior to Jan 7th, 2019 are included in Group 1 (mBCC).
[a] Events include progressive disease or deaths. Percentages are based on number of patients with confirmed CR or PR.
Source: PTT 14.2.1.13f

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

	Group 2: laBCC (N=27)	
KM Estimation of Duration of Response (CR or PR)		
n	27	
Number of events, n (%) [a]	7 (25.9%)	
Number of censored patients, n (%) [a]	20 (74.1%)	
Median (95% CI), (months)	NR (15.5, NE)	
Estimated Event-Free Probability, % (95% CI)		
4 months	100 (NE, NE)	
6 months	91.7 (70.6, 97.8)	
8 months	91.7 (70.6, 97.8)	
12 months	86.3 (62.8, 95.4)	
16 months	71.9 (43.6, 87.7)	
20 months	52.4 (22.6, 75.5)	
24 months	52.4 (22.6, 75.5)	
28 months	NE (NE, NE)	
Observed Duration of Response (CR or PR) (months)		
n	27	
Min : Max	1.9 : 25.8	
Observed Duration of Response (CR or PR), n (%) [a]		
>=4 months	24	(88.9%)
>=6 months	21	(77.8%)
>=8 months	18	(66.7%)
>=12 months	13	(48.1%)
>= 16 months	10	(37.0%)
>= 20 months	5	(18.5%)
>= 24 months	1	(3.7%)
>= 28 months	0	

Data cutoff as of 30 Jun 2020

Table 2: Kaplan-Meier Estimation of Duration of Response by Investigator Assessment in mBCC (Study 1620 Group 1) – Patients with Confirmed CR or PR)

	Group 1: mBCC (N=10)
KM Estimation of Duration of Response (CR or PR)	
n	10
Number of events, n (%) [a]	4 (40.0%)
Number of censored patients, n (%) [a]	6 (60.0%)
Median (95% CI), (months)	NR (4.3, NE)
Estimated Event-Free Probability, % (95% CI)	
4 months	100 (NE, NE)
6 months	90.0 (47.3, 98.5)
8 months	90.0 (47.3, 98.5)
12 months	64.3 (24.5, 87.1)
16 months	51.4 (16.0, 78.6)
20 months	51.4 (16.0, 78.6)
24 months	51.4 (16.0, 78.6)

Data cut-off as of Jun 30th, 2020. Only patients who started treatment on or prior to May 21st, 2019 are included in Group 1 (mBCC).
[a] Events include progressive disease or deaths. Percentages are based on number of patients with confirmed CR or PR.
Source: Table 14.2.1.4f

Ancillary analyses

PD-L1 expression in tumor cells by IHC in pretreatment tumor samples was done on an exploratory basis, without formal validation. The PD-L1 assay was performed by a third-party vendor (Ventana) using the SP263 antibody clone. Based on previous experience in other indications, to preserve antigenicity, slides should have been stained within 6 months from the date that sections were mounted on slides. Slides that were >6 months old were considered unevaluable.

Pretreatment tumor samples were available for PD-L1 IHC testing in 50 of 84 laBCC patients (Appendix 16). Table 26 presents centrally reviewed ORR data and PD-L1 tumor proportion score (TPS) at 4 different cutoffs (<1%, ≥1% to <5%, ≥5% to <50%, ≥50%). Responses are noted at all PD-L1 cutoffs.

Among 35 patients in the PD-L1 negative subgroup in Group 2 (TPS <1%), ORR was 25.7% (9/35 patients). The samples of the remaining 34 patients were excluded from PD-L1 analysis because the slides were expired (>6 months since slide cut date) or because there were an insufficient number of cells.

Table 26: Best Overall Tumor Response Rate by Independent Central Review (Group 2 patients who had samples evaluable for PD-L1 assay)

	PD-L1<1% (N=35)	PD-L1>=1% to <5% (N=11)	PD-L1>=5% to <50% (N=4)	PD-L1>=50% (N=0)
Best Overall Tumor Response, n (%)				
Complete Response (CR) [a]	2 (5.7%)	2 (18.2%)	0	
Partial Response (PR) [a]	7 (20.0%)	1 (9.1%)	1 (25.0%)	
Stable Disease (SD) [b]	18 (51.4%)	7 (63.6%)	2 (50.0%)	
Non-CR/Non-PD [c]	0	0	0	
Progressive Disease (PD)	5 (14.3%)	1 (9.1%)	0	
Not Evaluable (NE) [d]	3 (8.6%)	0	1 (25.0%)	
Response				
Objective Response Rate (ORR: CR+PR)	9 (25.7%)	3 (27.3%)	1 (25.0%)	
95% CI for ORR [e]	(12.5%, 43.3%)	(6.0%, 61.0%)	(0.6%, 80.6%)	
Complete Response Rate (CR) [a]	2 (5.7%)	2 (18.2%)	0	
95% CI for CR Rate [e]	(0.7%, 19.2%)	(2.3%, 51.8%)	(0.0%, 60.2%)	
Disease Control Rate (DCR: CR+PR+SD+Non-CR/Non-PD)	27 (77.1%)	10 (90.9%)	3 (75.0%)	
95% CI for DCR [e]	(59.9%, 89.6%)	(58.7%, 99.8%)	(19.4%, 99.4%)	
Durable DCR [f]	18 (51.4%)	6 (54.5%)	2 (50.0%)	
95% CI for Durable DCR [e]	(34.0%, 68.6%)	(23.4%, 83.3%)	(6.8%, 93.2%)	

ORR for the remaining 34 patients excluded from this table was 32.4% (95% CI: 17.4%, 50.5%) (PTT 14.2.1.21f)
Data cutoff as of 17 Feb 2020
[a] CR/PR must be confirmed by repeated assessments no less than 4 weeks apart.
[b] SD criteria must be met at least once after a minimum duration of 39 days after first dose date.
[c] Non-CR/Non-PD is for patients with non-measurable disease only.
[d] Not evaluable response includes the missing and unknown tumor response.
[e] Clopper-Person exact confidence interval.
[f] Durable DCR: proportion of patients with CR, PR, SD or Non-CR/Non-PD for at least 182 days without PD.
Source: PTT 14.2.1.17f

Table 4.4.2.14 TMB by Best Overall Tumor Response by Independent Central Review

	Responders (N=18)	Non-responders (N=38)	Total (N=56)
Mutations / Mb			
n	18	38	56
Mean (SD)	65.60 (58.684)	49.39 (64.044)	54.60 (62.306)
Median	58.23	23.49	34.55
Q1 : Q3	21.97 : 77.07	9.63 : 63.42	12.67 : 70.84
Min : Max	2.3 : 246.8	0.8 : 326.3	0.8 : 326.3

Data Cutoff as of 17 Feb 2020
Source: PTT 14.2.1.24f

Table 12: Best Overall Tumor Response Rate by Independent Central Review (Full Analysis Set - Group 2 Patients)

	Evaluable PD-L1 (N=50)	No Evaluable PD-L1 (N=34)
Best Overall Tumor Response, n (%)		
Complete Response (CR) [a]	4 (8.0%)	2 (5.9%)
Partial Response (PR) [a]	9 (18.0%)	12 (35.3%)
Stable Disease (SD) [b]	27 (54.0%)	13 (38.2%)
Non-CR/Non-PD [c]	0	0
Progressive Disease (PD)	6 (12.0%)	3 (8.8%)
Not Evaluable (NE) [d]	4 (8.0%)	4 (11.8%)
Response		
Objective Response Rate (ORR: CR+PR)	13 (26.0%)	14 (41.2%)
95% CI for ORR [e]	(14.6%, 40.3%)	(24.6%, 59.3%)
Complete Response Rate (CR) [a]	4 (8.0%)	2 (5.9%)
95% CI for CR Rate [e]	(2.2%, 19.2%)	(0.7%, 19.7%)
Disease Control Rate (DCR: CR+PR+SD+Non-CR/Non-PD)	40 (80.0%)	27 (79.4%)
95% CI for DCR [e]	(66.3%, 90.0%)	(62.1%, 91.3%)
Durable DCR [f]	26 (52.0%)	24 (70.6%)
95% CI for Durable DCR [e]	(37.4%, 66.3%)	(52.5%, 84.9%)

Data cut-off as of 30 Jun 2020.

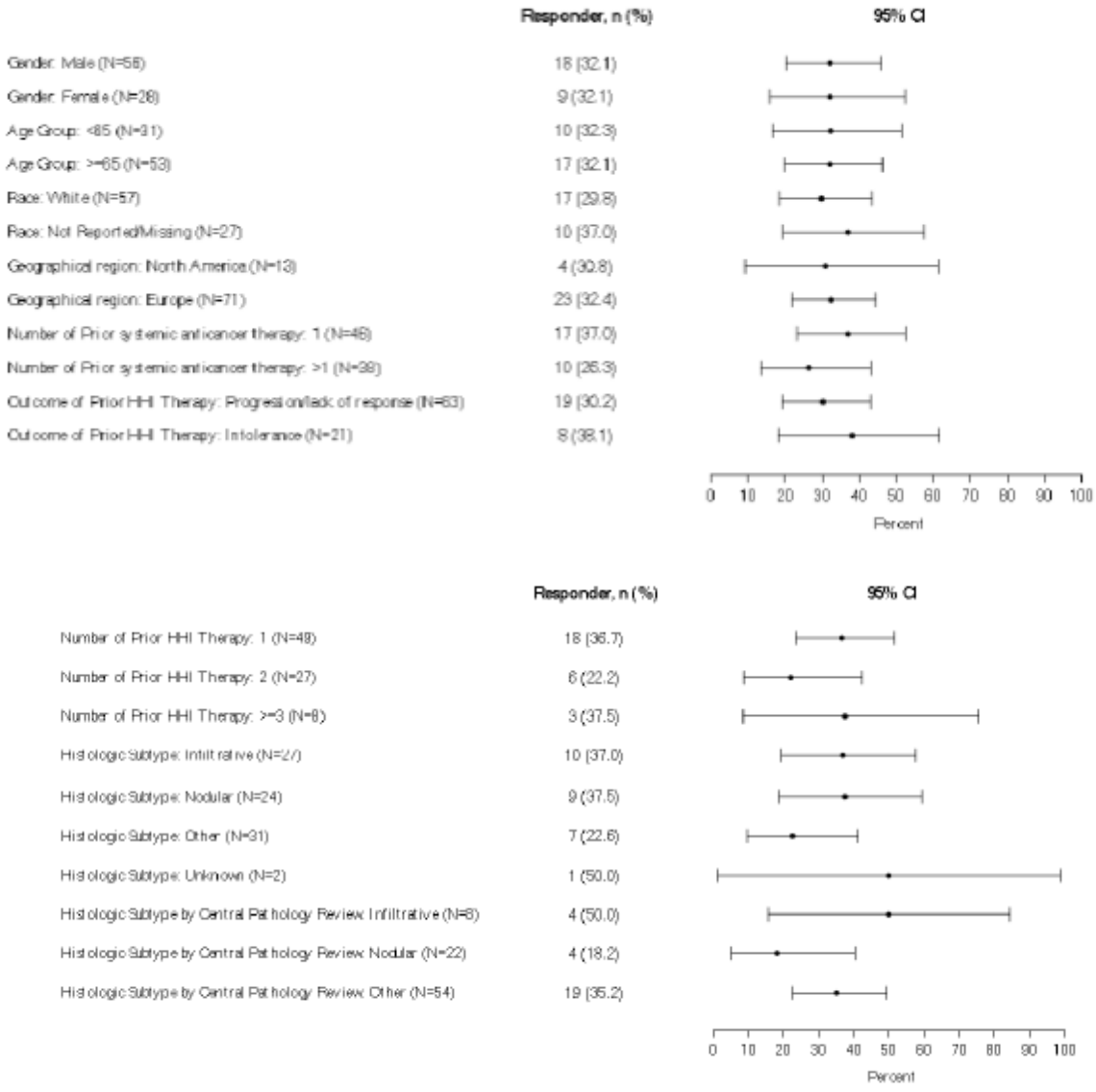
Subgroup Efficacy Analyses

Subgroup exploratory analyses were performed based on the following factors for each group, separately:

- gender (Male, Female)
- age group (<65, ≥65)
- race (White, Non-White)
- geographical region (North American, Europe and Rest of World)
- the number of prior systemic therapies
- reason for discontinuation of HHI (Progression/Lack of Response, Intolerant).

Figure 10

Figure 5: Forest Plot by Independent Central Review by Subgroup (Full Analysis Set – laBCC Patients



Data cut-off as of Jun 30th, 2020.

Summary of main study

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 1. Summary of Efficacy for trial R2810-ONC-1620

Title: A Phase 2 Study of REGN2810, a Fully Human Monoclonal Antibody to Programmed Death-1, in Patients with Advanced Basal Cell Carcinoma who Experienced Progression of Disease on Hedgehog Pathway Inhibitor Therapy, or Were Intolerant of Prior Hedgehog Pathway Inhibitor Therapy			
Study identifier	R2810-ONC-1620, NCT03132636, EudraCT 2016-003112-16		
Design	Ongoing Phase 2, single arm study, 2-group, multicenter		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		93 weeks Up to 28 days (screening) N/A
Hypothesis	Exploratory: Improved ORR		
Treatments groups	Group 1(mBCC)		Cemiplimab 350 mg Q3W for 93 weeks. 53 mBCC patients included, results available for 28 patients.
	Group 2 (laBCC)		Cemiplimab 350 mg Q3W for 93 weeks. 84 laBCC patients included, results available for 84 patients.
Endpoints and definitions	Primary endpoint	IRC-assessed ORR	Objective response rate (ORR) based on a centrally reviewed evaluation. ORR was defined as the proportion of patients with best overall response of complete or partial response by group.
	Secondary endpoint	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)
		PFS	Progression Free Survival
		OS	Overall Survival
		DCR	Disease control rate and durable disease control rate
		Median Duration of follow up	Median duration of follow-up
Database lock	20 Apr 2019		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Primary Analysis for laBCC patients and interim analysis for mBCC patients Primary analysis for 84/84 patients of Group 2 Interim analysis for 28/53 patients of Group 1		
Descriptive statistics and estimate variability	Treatment group	Group 1	Group 2*
	Number of subject	54	84
	IRC-assessed ORR, %	286	32.1
	95% CI, %	8.3, 41.0	19.2, 39.5
	IRC-assessed median DoR, months	Not Reached	Not Reached
	95% CI, months	9.0, NE	15.0, NE**
	IRC-assessed median PFS, months 95% CI, months	8.3 3.6, 19.5	19.3 8.6, NE**
	Median OS (estimated) months 95% CI, months	25.7 19.5, NE	NR*** NE, NE
Notes	*The MAH was initially applying for the indication for laBCC, results of the interim data from mBCC included in the application. mDoR has not been reached for any group. **Non evaluable *** Not Reached		

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

Not applicable.

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	0/0	0/0	0/0
Non-Controlled trials-Study 1620 Group 1(mBCC)	9/28	5/28	1/28
Non-Controlled trials-Study 1620 Group 2 (laBCC)	19/84	23/84	11/84

Supportive study

Supportive efficacy is provided for 6 patients with advanced BCC from Study 1423, which is a completed basket dose-finding phase 1 study (FIH). The efficacy data were not pooled or integrated with the Study 1620 data as the small BCC data set in Study 1423 would not have a meaningful impact on the efficacy analyses for Study 1620.

- Estimate the complete response (CR) rate by central review
- Assess the safety and tolerability of cemiplimab
- Assess the PK of cemiplimab (at select sites only)
- Assess the immunogenicity of cemiplimab

The efficacy data were not pooled or integrated with the Study 1620 data as the small BCC data set in Study 1423 would not have a meaningful impact on the efficacy analyses for Study 1620.

2.4.3. Discussion on clinical efficacy

LIBTAYO (cemiplimab) 350 mg as an IV infusion over 30 minutes Q3W was first approved in the US on 28 September 2018 and in the EU on 28 June 2019 for the treatment of patients with metastatic CSCC or patients with locally advanced CSCC who are not candidates for curative surgery or curative radiation.

Design and conduct of clinical studies

Study 1620 is an ongoing phase 2, non-randomized, open-label, 2 group, multicenter pivotal study of cemiplimab (REGN2810) monotherapy for patients with locally advanced BCC (Group 2) and metastatic BCC (Group 1) after first-line HHI therapy. For group 2, patients must be deemed to have unresectable disease and this is defined by any of the following: Lack of response to prior HHI therapy or Response to prior HHI therapy, but currently unresectable. The prevalence of such advanced disease is very low and hence a confirmatory randomized controlled trial may not be feasible.

In both groups, the treatment regimen is 350 mg cemiplimab IV Q3W and the patients will receive up to twelve 56-day (8-week) treatment cycles for up to 93 weeks of treatment. A total of 132 patients with advanced BCC (84 patients with locally advanced BCC, 48 patients with metastatic BCC) are included in

the Study 1620 FAS but only 28/48 patients with mBCC (in total 112 patients) had enough follow-up time to assert any efficacy. Patients were enrolled at clinical sites in North America (N = 27) and the EU (N = 85).

In the cemiplimab treated patients the majority had either progression of disease on HHI therapy or were intolerant of prior HHI therapy. As many as 71.4% (60/84) of the laBCC patients in Group 2 had experienced disease progression on prior HHI, and only 2 patients had SD after 9 months of HHI therapy. Patients having progressed after HHI represent a patient population of a high unmet medical need.

The inclusion/exclusion criteria clearly define a second line patient population but it is though somehow controversial that patients with "no better than a stable disease after 9 months on HHI therapy" could be enrolled in the study. One could argue that there was not an unmet medical need for these patients. On the other hand, subsequent responses were not seen in a patient with SD on HHI after 6 months treatment. It is therefore not likely that an eventually subsequent response on cemiplimab could have been obtained from the treatment with an HHI.

Patients excluded from clinical studies are described under 4.4 of the SmPC as patients that had active infections, or that were immunocompromised, had a history of autoimmune diseases, ECOG PS $\geqslant$2 or a history of interstitial lung disease were not included in the main study. A detailed list of patients excluded from clinical trials is given in section 5.1 of the SmPC.

The currently applied indication was for the treatment of adult patients with locally advanced basal cell carcinoma (BCC) previously treated with a hedgehog pathway inhibitor (HHI). However, the CHMP considered that the wording should define only the patients with prior unsuccessful treatment with HHI, and at the same time, a patient population consistent with the one included in the pivotal Study 1620. The wording was revised to include patients who have progressed on or are intolerant to a HHI.

The primary endpoint (ORR according to central review) is fully acceptable in a second line setting and is a clinically relevant endpoint in this cutaneous malignancy. DOR, PFS, CR and OS are important secondary endpoints. The MAH has formulated multiple clinically secondary and exploratory endpoints.

It could be argued that demonstration of direct anti-tumour activity alone would not be considered to represent a patient benefit per se if not accompanied by other clinically relevant effects. However, the endpoint of ORR could still be acceptable in the advanced BCC, as it is assumed that it isolates the drug effect. Further, ORR itself can be considered to provide clinical benefit (even in the absence of demonstrated PFS/OS gain) to these advanced BCC patients, with very invasive, disfiguring tumours. Therefore, overall, it is acceptable that in this pivotal study, the primary endpoint was ORR and the time to event endpoints are not yet mature.

In total 170 patients were screened for enrolment with 138 patients participating in this study.

Main reasons for discontinuation was PD and AE. AE were more profound in the laBCC group (15.5% vs 6.3%). Otherwise, there were no clinically relevant differences between the two treatment groups.

There were several protocol amendments. The dose of cemiplimab was changed from 250 mg Q3W to 350 mg Q3W and the length of treatment was extended, but no patients in the study were dosed with cemiplimab 250 mg Q3W.

The number of important protocol deviations were not balanced between the two treatment groups (29 in group 2 and 5 in group 1). In group 2 the inclusion criteria were not met in 13 patients while it was the case in only 2 patients in group 1. None of these deviations jeopardized the integrity of the data. It is acknowledged that the Study 1620 is not a randomized study and therefore the 2 groups would not be expected to be balanced. Group 2 enrolled more rapidly than Group 1. Therefore Group 1 was less impacted by this imbalance. The imbalance is as expected largely due to confirmation of receipt of archival material not being received prior to enrolment for both groups. The patients were enrolled prior

to the establishment of an enrolment checklist that addressed this issue. This shows that in the period of initiating the study there has been a logistic problem with the local pathology apartments.

All patients in the FAS received prior HHI therapy and the reason for discontinuation of HHI is mainly due to progression of disease and intolerance to HHI. "No better than SD after 9 months of HHI therapy" is the reason in 3/35 in mBCC and 2/84 in laBCC. From a clinical point of view disease characteristics and prognosis of patients with stable disease might differ from patients with PD on HHI-therapy, as this is the truly second-line population. The indication was revised as discussed above to focus on "patients who have progressed on or are intolerant to a HHI.

Efficacy data and additional analyses

The effect observed in the laBCC population (ORR 28.6%, (6/28); 95% CI 19.2, 39.5%; 6% CR; and with notably long duration of response, i.e. 85.2% for 12 months, 69.7% for 16 months) and a mPFS of 19.3 months can be considered clinically meaningful, even when pre-specified success criteria for the primary endpoint were formally missed in the primary analysis (95% CI for ORR excludes 20%). For 2 laBCC patients the responses of SD were subsequently confirmed as PR per ICR at tumour assessment after the data cut-off.

The MAH provided a new data update as of 30 June 2020 during this assessment procedure; the updated ORR for the laBCC group is 32.1% (27/84).

These results are encouraging in a small patient population in the second line setting with limited treatment possibilities.

BOR by ICR with an updated ORR for laBCC patients was 32.1% (27/84). Twenty-one (21) responses were PRs and 6 were CRs. This includes the 2 patients who had unconfirmed PRs at the 17 February 2020 data cut. Both responses are confirmed in the new data cut. An additional responder in this data cut is a laBCC patient whose BOR previous to 17 February 2020 was SD. Based on tumour assessments between 17 February 2020 and 30 June 2020, the patient achieved a confirmed CR first response (CR) on 25 February 2020 (confirmation response date: 23 April 2020). For two laBCC patients the responses of SD were subsequently confirmed as PR per ICR at tumour assessment after the data cut-off.

Responses in laBCC can develop over a wide and long range of time. Median time to response for laBCC was 4.21 months (range: 2.1 to 13.4 months) with evidence that responses deepen over time in the spider plots. However, as the responses can develop over a long period of time, clinical benefit can be achieved even in patients who do not fulfil response criteria, and no clear cut-off can be defined beyond which responses would not be expected, it is acceptable that it can be left to the treating physician to decide if continuation of the treatment is warranted. In the SmPC the current recommendation to continue treatment until disease progression or unacceptable toxicity applies for the BCC indication too.

Group 1 is the mBCC cohort for Study 1620 and reached its planned total enrolment of 54 patients as of 09 Apr 2020 and has been closed for enrolment. However, the MAH has after request from the CHMP updated the efficacy data for mBBC patients with a new cut-off date as of 30 June 2020. The median duration of follow up for mBCC patients (N = 35) was 8.54 months at this data cut-off. The data show that treatment of 35 mBCC patients with cemiplimab resulted in an objective response rate (ORR) of 28.6%, including 1 patient who had a complete response and 9 patients who had partial responses (PR). The response rates in mBCC are comparable and consistent with that seen in laBCC (ORR of 32.1%). The mPFS is 6.6 months with an estimated PFS at 12 months of 28.8%.

Without a randomisation it is not possible to draw any conclusion on the time to event data because of underlying/not measured selection bias in this single-arm study. For all patients with advanced BCC the mOS was not reached as of data cut-off 30 Jun 2020. The estimated median is unstable due to small number of events.

Duration of Response (DOR) (Investigator Assessment) by Kaplan Meier method has not been reached for mBCC patients as of 30 June 2020 data cut-off. The estimated event-free probability was 90% at 6 months (95% CI: 47.3% to 98.5%). Longer follow-up will eventually be available in the final study reports as the MAH is being requested by the CHMP to submit the final CSR for study 1620 (see Annex II.D).

PFS and OS are challenging to assess without a comparator group and are of supportive evidence only. For all patients with advanced BCC the mOS was 25.7 months as of data cut-off. The estimated median is unstable due to small number of events. The mPFS is 19.3 months for the laBCC group and with the new data as of 30 June 2020 cut-off 6.6 months for the mBCC group. The estimated PFS at 12 months was 28.8%. Median OS was not reached for mBCC patients at time of 30 June 2020 data cutoff. The results are encouraging in a second line setting in a patient group with a very poor prognosis and limited treatment possibilities but no confirmatory conclusions can be drawn in terms of OS in the absence of a comparator group.

It is notable that the disease control rate (DCR) and durable disease control rate are high, 79.8% and 59.5% respectively. The DCR and dDCR results observed in Study 1620 provide further evidence of the clinical benefit of cemiplimab.

Biomarker data is only presented for the 50/84 laBCC patients. The remaining 34 patients had an unknown PD-L1 status. The best ORR by ICR for the 50 patients is 26.0% and 41.2% for the PD-L1 not evaluable group within the laBCC cohort. No biomarker data is available for the mBCC group. Cemiplimab appeared active against advanced BCC in all PD-L1 strata. The relationship between PD-L1 status and efficacy was analyzed post-hoc in patients with available samples. Based on the limited number of patients with tumour samples, clinical activity seems to be observed regardless of tumour PD-L1 expression status. Thus, the data do not support a restriction of the indication based on the PD-L1 expression.

There is a major unmet medical need in this late line treatment, after HHI-therapies and when radiation/ surgery is not possible, with no remaining treatment options for these patients. The prevalence of such advanced disease is very low and hence a confirmatory randomized controlled trial may not be feasible. However, the product has been already licenced and shown to provide benefit in patients with CCSC, which is a very similar disease with BCC, with shared lineage with epidermal keratinocytes, providing further support and plausibility for efficacy in the currently sought indication.

The results in the mBCC demonstrated an important benefit in this population, in addition to the laBCC, and the CHMP considered that the indication should be revised to reflect this. The final wording of the indication included locally advanced or metastatic basal cell carcinoma.

At the time of this report the primary analysis for the metastatic population has not been completed; the data cut for the primary analysis for Group 1 is projected to occur on 20 May 2021, which represents 57 weeks from cycle 1/day 1 for the 54th patient enrolled in Group 1. Data lock would occur in July 2021. The MAH anticipates that the updated CSR for mBCC will be completed in September 2021 and committed to provide the primary and final analysis of the mBCC population post-approval (see Annex II.D).

2.4.4. Conclusions on the clinical efficacy

The pivotal study 1620 (REGN2810) showed clinically relevant results for Libtayo monotherapy in the treatment of adult patients with locally advanced or metastatic basal cell carcinoma (laBCC or mBCC) who have progressed on or are intolerant to a hedgehog pathway inhibitor (HHI).

The following measures are considered necessary to address issues related to efficacy:

Submission of the report from clinical study 1620 to further confirm clinical efficacy and safety of cemiplimab in patients with mBCC who experienced progression of disease on hedgehog pathway inhibitor therapy or were intolerant of prior hedgehog pathway inhibitor therapy.

Submission of Report on primary analysis in Q1 2022 and submission of the final study report after 36 months of follow up, in Q2 2024 (see Annex II.D).

2.5. Clinical safety

Introduction

The evaluation of safety for the advanced BCC application is based on data from 3 additional studies of cemiplimab that were pooled with study 1620: Study 1423 (FIH for various solid advanced tumours), Study 1540 (advanced CSCC), and Study 1624 (advanced NSCLC as first-line therapy). The primary focus is on data from the SAF for Safety Pool 1 who included 138 advanced BCC (84 laBCC and 54 mBCC) patients who had received at least 1 dose cemiplimab as monotherapy in Study 1620 and Safety Pool 2 including 816 subjects who also had received at least 1 dose of cemiplimab as monotherapy in Studies 1620 (138), 1423 (130), 1540 (193) and 1624 (355).

Patient exposure

Table 14.1.4.1 Treatment Exposure
(Safety Analysis Set)

	Group 1: mBCC (N=54)	Group 2: laBCC (N=84)	Total (N=138)
Duration of Exposure (weeks)[a]			
n	54	84	138
Mean (SD)	35.94 (27.723)	55.28 (30.985)	47.71 (31.123)
Median	26.80	47.15	39.10
Q1 : Q3	15.10 : 48.40	27.00 : 88.50	18.40 : 84.00
Min : Max	3.0 : 98.0	2.1 : 94.0	2.1 : 98.0
Duration of Exposure, n (%)			
>=0 weeks	54 (100%)	84 (100%)	138 (100%)
>=6 weeks	51 (94.4%)	83 (98.8%)	134 (97.1%)
>=12 weeks	47 (87.0%)	79 (94.0%)	126 (91.3%)
>=24 weeks	28 (51.9%)	67 (79.8%)	95 (68.8%)
>=36 weeks	21 (38.9%)	55 (65.5%)	76 (55.1%)
>=48 weeks	14 (25.9%)	42 (50.0%)	56 (40.6%)
>=60 weeks	10 (18.5%)	39 (46.4%)	49 (35.5%)
>=72 weeks	8 (14.8%)	34 (40.5%)	42 (30.4%)
>=84 weeks	7 (13.0%)	28 (33.3%)	35 (25.4%)
>=96 weeks	1 (1.9%)	0	1 (0.7%)
Number of Doses Administered			
n	54	84	138
Mean (SD)	11.3 (8.38)	17.4 (10.03)	15.0 (9.85)
Median	7.5	15.0	13.0
Q1 : Q3	5.0 : 16.0	8.0 : 27.5	6.0 : 25.0
Min : Max	1 : 31	1 : 31	1 : 31
Number of Doses Administered, n (%)			
>=0	54 (100%)	84 (100%)	138 (100%)
>=3	51 (94.4%)	81 (96.4%)	132 (95.7%)
>=6	38 (70.4%)	73 (86.9%)	111 (80.4%)
>=12	21 (38.9%)	52 (61.9%)	73 (52.9%)
>=18	11 (20.4%)	40 (47.6%)	51 (37.0%)
>=24	7 (13.0%)	31 (36.9%)	38 (27.5%)
>=30	2 (3.7%)	17 (20.2%)	19 (13.8%)
>=36	0	0	0
>=42	0	0	0
>=48	0	0	0
Cumulative Dose Administered (mg)			
n	54	84	138
Mean (SD)	3934.3 (2934.57)	6056.3 (3510.85)	5225.9 (3446.67)
Median	2625.0	5250.0	4375.0
Q1 : Q3	1750.0 : 5600.0	2800.0 : 9450.0	2100.0 : 8750.0
Min : Max	350 : 10850	350 : 10850	350 : 10850
Actual Dose Intensity (mg/wk) [b]			
n	54	84	138
Mean (SD)	111.99 (12.589)	110.21 (12.472)	110.91 (12.503)
Median	116.67	115.23	115.95
Q1 : Q3	105.05 : 117.37	106.69 : 116.67	106.31 : 116.67
Min : Max	66.5 : 137.4	69.6 : 163.3	66.5 : 163.3
Relative Dose Intensity [c]			
n	54	84	138
Mean (SD)	0.96 (0.108)	0.94 (0.107)	0.95 (0.107)
Median	1.00	0.99	0.99
Q1 : Q3	0.90 : 1.01	0.91 : 1.00	0.91 : 1.00
Min : Max	0.6 : 1.2	0.6 : 1.4	0.6 : 1.4

Data cut-off as of Jun 30th, 2020.

Table 14.1.1.4 Patient Disposition
(Safety Analysis Set)

	Group 1: mBCC (N=54)	Group 2: laBCC (N=84)	Total (N=138)
Treatment Ongoing, n (%)	13 (24.1%)	8 (9.5%)	21 (15.2%)
Off Treatment, n (%)	41 (75.9%)	76 (90.5%)	117 (84.8%)
Treatment Completed	5 (9.3%)	21 (25.0%)	26 (18.8%)
Treatment Discontinued	36 (66.7%)	55 (65.5%)	91 (65.9%)
Primary Reason for Treatment Discontinuation			
ADVERSE EVENT	3 (5.6%)	14 (16.7%)	17 (12.3%)
PREGNANCY	0	0	0
DEATH	2 (3.7%)	1 (1.2%)	3 (2.2%)
LOST TO FOLLOW-UP	1 (1.9%)	2 (2.4%)	3 (2.2%)
NONCOMPLIANCE WITH PROTOCOL BY THE SUBJECT	1 (1.9%)	1 (1.2%)	2 (1.4%)
SUBJECT DECISION	0	5 (6.0%)	5 (3.6%)
SPONSOR DECISION	0	0	0
PHYSICIAN DECISION	0	0	0
PROGRESSIVE DISEASE	26 (48.1%)	30 (35.7%)	56 (40.6%)
WITHDRAWAL OF CONSENT	2 (3.7%)	0	2 (1.4%)
CONFIRMED CR	1 (1.9%)	1 (1.2%)	2 (1.4%)
OTHER	0	1 (1.2%)	1 (0.7%)
Number of patients entered follow-up, n (%)	4 (7.4%)	28 (33.3%)	32 (23.2%)
Study Ongoing, n (%)	17 (31.5%)	23 (27.4%)	40 (29.0%)
Off Study, n (%)	37 (68.5%)	61 (72.6%)	98 (71.0%)
Study Completed	1 (1.9%)	6 (7.1%)	7 (5.1%)
Study Discontinued	36 (66.7%)	55 (65.5%)	91 (65.9%)
Primary Reason for Study Discontinuation			
ADVERSE EVENT	1 (1.9%)	2 (2.4%)	3 (2.2%)
PREGNANCY	0	0	0
DEATH	3 (5.6%)	7 (8.3%)	10 (7.2%)
LOST TO FOLLOW-UP	1 (1.9%)	2 (2.4%)	3 (2.2%)
NONCOMPLIANCE WITH PROTOCOL BY THE SUBJECT	1 (1.9%)	1 (1.2%)	2 (1.4%)
SUBJECT DECISION	1 (1.9%)	6 (7.1%)	7 (5.1%)
SPONSOR DECISION	0	1 (1.2%)	1 (0.7%)
PHYSICIAN DECISION	0	0	0
PROGRESSIVE DISEASE	27 (50.0%)	30 (35.7%)	57 (41.3%)
WITHDRAWAL OF CONSENT	2 (3.7%)	4 (4.8%)	6 (4.3%)
CONFIRMED CR	0	0	0
OTHER	0	2 (2.4%)	2 (1.4%)

Data cut-off as of Jun 30th, 2020.

Adverse events

Table 14.3.1.2.1 Summary of Treatment-Emergent Adverse Events
(Safety Analysis Set)

	Group 1: mBCC (N=54)	Group 2: laBCC (N=84)	Total (N=138)
Number of TEAEs	515	1024	1539
Number of NCI grade 3/4/5 TEAE	46	100	146
Number of Serious TEAEs	35	58	93
Number of Patients with any TEAE, n (%)	51 (94.4%)	83 (98.8%)	134 (97.1%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	19 (35.2%)	44 (52.4%)	63 (45.7%)
Number of Patients with any Serious TEAE, n (%)	14 (25.9%)	31 (36.9%)	45 (32.6%)
Number of Patients who discontinued study treatment due to TEAEs, n (%)	4 (7.4%)	15 (17.9%)	19 (13.8%)
Number of Patients with any TEAE leading to a dose delay, n (%)	14 (25.9%)	31 (36.9%)	45 (32.6%)
Number of Patients with any TEAE leading to a drug interruption, n (%)	4 (7.4%)	3 (3.6%)	7 (5.1%)
Number of Patients with any TEAE leading to dose reduction, n (%)	0	1 (1.2%)	1 (0.7%)
Number of Patients with any TEAE resulting in death, n (%)	2 (3.7%)	4 (4.8%)	6 (4.3%)

Table 14.3.1.2.1.p0 Summary of Treatment-Emergent Adverse Events
(Safety Analysis Set)

	Pool 1 All BCC Patients (N=132)	Pool 2 All Monotherapy Patients (N=810)	Pool 3 All Patients (N=1078)
Number of TEAEs	1424	6351	8898
Number of NCI grade 3/4/5 TEAEs	137	721	1045
Number of serious TEAEs	86	433	570
Number of Patients with any TEAE, n (%)	125 (94.7%)	756 (93.3%)	1022 (94.8%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	59 (44.7%)	333 (41.1%)	472 (43.8%)
Number of Patients with any serious TEAE, n (%)	42 (31.8%)	243 (30.0%)	323 (30.0%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	17 (12.9%)	64 (7.9%)	81 (7.5%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	50 (37.9%)	256 (31.6%)	344 (31.9%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	1 (0.8%)	6 (0.7%)	9 (0.8%)
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	1 (0.8%)	5 (0.6%)	8 (0.7%)
Number of Patients with any TEAE resulting in death, n (%)	4 (3.0%)	47 (5.8%)	50 (4.6%)

Data cut-off as of Feb 17, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624. Data cut-off as of Apr 30, 2019 for Study 1423; Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients in Study 1540; Data cut-off as of Oct 10, 2018 for Group 2 patients in Study 1540.
TEAE: Treatment Emergent Adverse Events
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.

/sasdata/Data/Production/BDM/R2810/R2810-ONC/R2810-ONC-BCC-NSCLC-ISS/Interim_BCC_NSCLC_sBLA/Analysis_CSR/Programs/TFL/BCC/Generated/t_3_1_2_1_aeprof_p0.sas
(yun.zhang 18AUG2020 18:16 SAS Linux 9.4)

The table above has not been updated as of 30 June 2020.

Table 14.3.1.2.2 Summary of Treatment-Emergent Adverse Events by System Organ Class
(Safety Analysis Set)

System Organ Class, n (%)	Group 1: mBCC (N=54)	Group 2: laBCC (N=84)	Total (N=138)
Total number of TEAEs	515	1024	1539
Number of Patients with any TEAE, n (%)	51 (94.4%)	83 (98.8%)	134 (97.1%)
General disorders and administration site conditions	31 (57.4%)	51 (60.7%)	82 (59.4%)
Gastrointestinal disorders	33 (61.1%)	44 (52.4%)	77 (55.8%)
Infections and infestations	28 (51.9%)	47 (56.0%)	75 (54.3%)
Skin and subcutaneous tissue disorders	25 (46.3%)	43 (51.2%)	68 (49.3%)
Investigations	27 (50.0%)	39 (46.4%)	66 (47.8%)
Musculoskeletal and connective tissue disorders	21 (38.9%)	35 (41.7%)	56 (40.6%)
Nervous system disorders	16 (29.6%)	34 (40.5%)	50 (36.2%)
Metabolism and nutrition disorders	14 (25.9%)	31 (36.9%)	45 (32.6%)
Respiratory, thoracic and mediastinal disorders	16 (29.6%)	26 (31.0%)	42 (30.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (16.7%)	32 (38.1%)	41 (29.7%)
Blood and lymphatic system disorders	7 (13.0%)	23 (27.4%)	30 (21.7%)
Eye disorders	6 (11.1%)	21 (25.0%)	27 (19.6%)
Injury, poisoning and procedural complications	11 (20.4%)	14 (16.7%)	25 (18.1%)
Vascular disorders	10 (18.5%)	13 (15.5%)	23 (16.7%)
Renal and urinary disorders	9 (16.7%)	13 (15.5%)	22 (15.9%)
Endocrine disorders	7 (13.0%)	12 (14.3%)	19 (13.8%)
Psychiatric disorders	5 (9.3%)	13 (15.5%)	18 (13.0%)
Cardiac disorders	6 (11.1%)	11 (13.1%)	17 (12.3%)
Ear and labyrinth disorders	3 (5.6%)	7 (8.3%)	10 (7.2%)
Hepatobiliary disorders	2 (3.7%)	4 (4.8%)	6 (4.3%)
Reproductive system and breast disorders	1 (1.9%)	4 (4.8%)	5 (3.6%)
Congenital, familial and genetic disorders	0	2 (2.4%)	2 (1.4%)
Immune system disorders	1 (1.9%)	1 (1.2%)	2 (1.4%)
Product issues	0	1 (1.2%)	1 (0.7%)

Data cut-off as of 30 June 2020

Table 14.3.1.4.4 Summary of Treatment-Related Treatment-Emergent Adverse Events (in >=5% of Patients in Any Group) by System Organ Class, Preferred Term and NCI Grade (Safety Analysis Set)

System Organ Class, n (%) Preferred Term, n (%)	Group 1: mBCC (N=54)		Group 2: laBCC (N=84)		Total (N=138)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Total number of treatment-related TEAEs	160	14	301	19	461	33
Number of Patients with any treatment-related TEAE, n (%)	39 (72.2%)	7 (13.0%)	66 (78.6%)	18 (21.4%)	105 (76.1%)	25 (18.1%)
General disorders and administration site conditions	24 (44.4%)	3 (5.6%)	35 (41.7%)	3 (3.6%)	59 (42.8%)	6 (4.3%)
Fatigue	18 (33.3%)	0	21 (25.0%)	2 (2.4%)	39 (28.3%)	2 (1.4%)
Asthenia	3 (5.6%)	1 (1.9%)	12 (14.3%)	1 (1.2%)	15 (10.9%)	2 (1.4%)
Skin and subcutaneous tissue disorders	12 (22.2%)	0	30 (35.7%)	1 (1.2%)	42 (30.4%)	1 (0.7%)
Pruritus	7 (13.0%)	0	12 (14.3%)	0	19 (13.8%)	0
Rash maculo-papular	4 (7.4%)	0	5 (6.0%)	1 (1.2%)	9 (6.5%)	1 (0.7%)
Gastrointestinal disorders	13 (24.1%)	2 (3.7%)	27 (32.1%)	4 (4.8%)	40 (29.0%)	6 (4.3%)
Diarrhoea	6 (11.1%)	0	11 (13.1%)	0	17 (12.3%)	0
Nausea	1 (1.9%)	0	9 (10.7%)	0	10 (7.2%)	0
Colitis	3 (5.6%)	2 (3.7%)	2 (2.4%)	2 (2.4%)	5 (3.6%)	4 (2.9%)

Data cut-off as of Jun 30th, 2020.

Table 14.3.1.4.4 Summary of Treatment-Related Treatment-Emergent Adverse Events (in >=5% of Patients in Any Group) by System Organ Class, Preferred Term and NCI Grade (Safety Analysis Set)

System Organ Class, n (%) Preferred Term, n (%)	Group 1: mBCC (N=54)		Group 2: laBCC (N=84)		Total (N=138)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Gastrointestinal disorders						
Constipation	3 (5.6%)	0	0	0	3 (2.2%)	0
Musculoskeletal and connective tissue disorders	7 (13.0%)	0	14 (16.7%)	0	21 (15.2%)	0
Arthralgia	5 (9.3%)	0	6 (7.1%)	0	11 (8.0%)	0
Myalgia	3 (5.6%)	0	2 (2.4%)	0	5 (3.6%)	0
Endocrine disorders	7 (13.0%)	0	12 (14.3%)	3 (3.6%)	19 (13.8%)	3 (2.2%)
Hypothyroidism	4 (7.4%)	0	8 (9.5%)	0	12 (8.7%)	0
Hyperthyroidism	4 (7.4%)	0	2 (2.4%)	0	6 (4.3%)	0
Metabolism and nutrition disorders	5 (9.3%)	0	13 (15.5%)	1 (1.2%)	18 (13.0%)	1 (0.7%)
Decreased appetite	1 (1.9%)	0	8 (9.5%)	0	9 (6.5%)	0
Hyperglycaemia	3 (5.6%)	0	0	0	3 (2.2%)	0

Table 14.3.1.4.4 Summary of Treatment-Related Treatment-Emergent Adverse Events (in >=5% of Patients in Any Group) by System Organ Class, Preferred Term and NCI Grade (Safety Analysis Set)

System Organ Class, n (%) Preferred Term, n (%)	Group 1: mBCC (N=54)		Group 2: laBCC (N=84)		Total (N=138)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Nervous system disorders	5 (9.3%)	1 (1.9%)	7 (8.3%)	0	12 (8.7%)	1 (0.7%)
Headache	3 (5.6%)	1 (1.9%)	3 (3.6%)	0	6 (4.3%)	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	6 (11.1%)	2 (3.7%)	5 (6.0%)	0	11 (8.0%)	2 (1.4%)
Pneumonitis	3 (5.6%)	1 (1.9%)	0	0	3 (2.2%)	1 (0.7%)
Injury, poisoning and procedural complications	4 (7.4%)	0	1 (1.2%)	0	5 (3.6%)	0
Infusion related reaction	4 (7.4%)	0	0	0	4 (2.9%)	0

Table 14.3.1.2.2 Summary of Treatment-Emergent Adverse Events by System Organ Class
(Safety Analysis Set)

System Organ Class, n (%)	Group 1: mBCC (N=54)	Group 2: laBCC (N=84)	Total (N=138)
Total number of TEAEs	515	1024	1539
Number of Patients with any TEAE, n (%)	51 (94.4%)	83 (98.8%)	134 (97.1%)
General disorders and administration site conditions	31 (57.4%)	51 (60.7%)	82 (59.4%)
Gastrointestinal disorders	33 (61.1%)	44 (52.4%)	77 (55.8%)
Infections and infestations	28 (51.9%)	47 (56.0%)	75 (54.3%)
Skin and subcutaneous tissue disorders	25 (46.3%)	43 (51.2%)	68 (49.3%)
Investigations	27 (50.0%)	39 (46.4%)	66 (47.8%)
Musculoskeletal and connective tissue disorders	21 (38.9%)	35 (41.7%)	56 (40.6%)
Nervous system disorders	16 (29.6%)	34 (40.5%)	50 (36.2%)
Metabolism and nutrition disorders	14 (25.9%)	31 (36.9%)	45 (32.6%)
Respiratory, thoracic and mediastinal disorders	16 (29.6%)	26 (31.0%)	42 (30.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (16.7%)	32 (38.1%)	41 (29.7%)
Blood and lymphatic system disorders	7 (13.0%)	23 (27.4%)	30 (21.7%)
Eye disorders	6 (11.1%)	21 (25.0%)	27 (19.6%)
Injury, poisoning and procedural complications	11 (20.4%)	14 (16.7%)	25 (18.1%)
Vascular disorders	10 (18.5%)	13 (15.5%)	23 (16.7%)
Renal and urinary disorders	9 (16.7%)	13 (15.5%)	22 (15.9%)
Endocrine disorders	7 (13.0%)	12 (14.3%)	19 (13.8%)
Psychiatric disorders	5 (9.3%)	13 (15.5%)	18 (13.0%)

Data cut-off as of Jun 30th, 2020.

Table 14.3.1.2.2 Summary of Treatment-Emergent Adverse Events by System Organ Class
(Safety Analysis Set)

System Organ Class, n (%)	Group 1: mBCC (N=54)	Group 2: laBCC (N=84)	Total (N=138)
Cardiac disorders	6 (11.1%)	11 (13.1%)	17 (12.3%)
Ear and labyrinth disorders	3 (5.6%)	7 (8.3%)	10 (7.2%)
Hepatobiliary disorders	2 (3.7%)	4 (4.8%)	6 (4.3%)
Reproductive system and breast disorders	1 (1.9%)	4 (4.8%)	5 (3.6%)
Congenital, familial and genetic disorders	0	2 (2.4%)	2 (1.4%)
Immune system disorders	1 (1.9%)	1 (1.2%)	2 (1.4%)
Product issues	0	1 (1.2%)	1 (0.7%)

Adverse events of special interest (AESI)

Table 20: Summary of Treatment-Emergent Sponsor-Identified Immune-Mediated Adverse Events by Composite/Preferred Term and NCI Grade (Safety Analysis Set)

	Safety Pool 1 - BCC Pool (N = 132)		Safety Pool 2 - Monotherapy Pool (N = 810)		Safety Pool 3 - All Patients Pool (N = 1078)	
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 imAEs	50	11	253	59	306	82
Number of Patients with any treatment-emergent identified imAE, n (%)	33 (25.0)	11 (8.3)	177 (21.9)	53 (6.5)	217 (20.1)	72 (6.7)
Hypothyroidism[a]	12 (9.1)	0	60 (7.4)	0	74 (6.9)	1 (<0.1)
Immune related pneumonitis[a]	2 (1.5)	0	26 (3.2)	8 (1.0)	32 (3.0)	12 (1.1)
Hyperthyroidism[a]	5 (3.8)	0	26 (3.2)	0	31 (2.9)	1 (<0.1)
Immune related hepatitis[a]	3 (2.3)	1 (0.8)	16 (2.0)	13 (1.6)	20 (1.9)	17 (1.6)
Immune related colitis[a]	8 (6.1)	5 (3.8)	18 (2.2)	7 (0.9)	19 (1.8)	8 (0.7)
Immune related skin adverse reaction[a]	1 (0.8)	1 (0.8)	13 (1.6)	7 (0.9)	19 (1.8)	10 (0.9)
Arthralgia	3 (2.3)	0	9 (1.1)	0	11 (1.0)	0
Blood thyroid stimulating hormone increased	2 (1.5)	0	5 (0.6)	0	7 (0.6)	0
Immune related nephritis[a]	0	0	5 (0.6)	2 (0.2)	6 (0.6)	3 (0.3)
Adrenal insufficiency[a]	2 (1.5)	2 (1.5)	3 (0.4)	3 (0.4)	5 (0.5)	3 (0.3)
Thyroiditis[a]	2 (1.5)	0	5 (0.6)	0	5 (0.5)	0
Arthritis[a]	0	0	4 (0.5)	1 (0.1)	4 (0.4)	1 (<0.1)
Type 1 diabetes mellitus[a]	0	0	1 (0.1)	1 (0.1)	4 (0.4)	4 (0.4)
Hypophysitis	1 (0.8)	1 (0.8)	3 (0.4)	2 (0.2)	3 (0.3)	2 (0.2)
Neuropathy peripheral[a]	0	0	3 (0.4)	1 (0.1)	3 (0.3)	1 (<0.1)
Pruritus[a]	1 (0.8)	0	3 (0.4)	1 (0.1)	3 (0.3)	1 (<0.1)
Stomatitis	0	0	3 (0.4)	0	3 (0.3)	0
Encephalitis[a]	0	0	1 (0.1)	1 (0.1)	2 (0.2)	2 (0.2)
Meningitis[a]	0	0	1 (0.1)	1 (0.1)	2 (0.2)	2 (0.2)
Myocarditis[a]	0	0	2 (0.2)	1 (0.1)	2 (0.2)	1 (<0.1)
Pericarditis[a]	1 (0.8)	1 (0.8)	2 (0.2)	2 (0.2)	2 (0.2)	2 (0.2)
Blood alkaline phosphatase increased	0	0	1 (0.1)	0	1 (<0.1)	0
Blood thyroid stimulating hormone decreased	1 (0.8)	0	1 (0.1)	0	1 (<0.1)	0
Chronic inflammatory demyelinating polyradiculoneuropathy	0	0	1 (0.1)	0	1 (<0.1)	0
Guillain-Barre syndrome	0	0	0	0	1 (<0.1)	1 (<0.1)
Immune thrombocytopenic purpura	0	0	1 (0.1)	0	1 (<0.1)	0
Muscular weakness	0	0	1 (0.1)	0	1 (<0.1)	0
Myalgia	0	0	1 (0.1)	1 (0.1)	1 (<0.1)	1 (<0.1)
Myositis[a]	0	0	1 (0.1)	0	1 (<0.1)	0
Paraneoplastic encephalomyelitis	0	0	1 (0.1)	1 (0.1)	1 (<0.1)	1 (<0.1)
Polymyalgia rheumatica	0	0	1 (0.1)	0	1 (<0.1)	0
Sjogren's syndrome	0	0	1 (0.1)	0	1 (<0.1)	0
Vasculitis	0	0	0	0	1 (<0.1)	0

[a] Each composite term includes multiple MedDRA PTs based on Regeneron-defined list. Refer to ISS Table 14.3.2.4.11.p0.

Abbreviations: AE, adverse event; BCC, basal cell carcinoma; CTCAE, Common Terminology Criteria for Adverse Events; imAE, immune-mediated adverse event; ISS, Integrated Summary of Safety; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; n, number of events; NCI, National Cancer Institute; PT, preferred term; Regeneron, Regeneron Pharmaceuticals, Inc.

Data cutoff as of 30 Apr 2019 for patients in Study 1423; data cutoff as of 20 Sep 2018 for all patients in Group 1 and Group 3 and 10 Oct 2018 for Group 2 in Study 1540; data cutoff as of 17 Feb 2020 for all patients in Study 1620; and data cutoff as of 01 Mar 2020 for all patients in Study 1624.

All AEs were coded using MedDRA Version 22.1. NCI grades were coded using CTCAE Version 4.03.

A patient was 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.

Source: ISS Table 14.3.2.4.1.p0 and Table 14.3.2.4.10.p0

Table 14.3.2.4.6 Summary of Treatment-Emergent Immune-Related Adverse Events Based on Investigator Assessment by Preferred Term and NCI Grade (Safety Analysis Set)

	Group 1: mBCC (N=54)		Group 2: laBCC (N=84)		Total (N=138)	
Preferred Term, n (%)	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Total number of immune-related TEAEs	88	10	131	11	219	21
Number of Patients with any immune-related TEAE, n (%)	31 (57.4%)	5 (9.3%)	49 (58.3%)	11 (13.1%)	80 (58.0%)	16 (11.6%)
Pruritus	6 (11.1%)	0	12 (14.3%)	0	18 (13.0%)	0
Fatigue	5 (9.3%)	0	7 (8.3%)	0	12 (8.7%)	0
Hypothyroidism	4 (7.4%)	0	8 (9.5%)	0	12 (8.7%)	0
Diarrhoea	4 (7.4%)	0	7 (8.3%)	0	11 (8.0%)	0
Rash maculo-papular	4 (7.4%)	0	5 (6.0%)	1 (1.2%)	9 (6.5%)	1 (0.7%)
Arthralgia	2 (3.7%)	0	4 (4.8%)	0	6 (4.3%)	0
Hyperthyroidism	4 (7.4%)	0	2 (2.4%)	0	6 (4.3%)	0
Colitis	3 (5.6%)	2 (3.7%)	2 (2.4%)	2 (2.4%)	5 (3.6%)	4 (2.9%)
Rash	2 (3.7%)	0	3 (3.6%)	0	5 (3.6%)	0
Autoimmune colitis	1 (1.9%)	0	2 (2.4%)	2 (2.4%)	3 (2.2%)	2 (1.4%)
Blood thyroid stimulating hormone increased	1 (1.9%)	0	2 (2.4%)	0	3 (2.2%)	0
Dermatitis	0	0	3 (3.6%)	0	3 (2.2%)	0
Pneumonitis	3 (5.6%)	1 (1.9%)	0	0	3 (2.2%)	1 (0.7%)
Actinic keratosis	0	0	2 (2.4%)	0	2 (1.4%)	0
Adrenal insufficiency	0	0	2 (2.4%)	2 (2.4%)	2 (1.4%)	2 (1.4%)

Data cut-off as of Jun 30th, 2020.

Serious adverse event/deaths/other significant events

Deaths

In Study 1620, 6 (4.3%) patients experienced TEAEs resulting in death; 2 had mBCC, and 4 had laBCC. The causes of death were as follows: 1 Pneumonia staphylococcal in mBCC patient, and 1 Cachexia, 1 Brain neoplasm malignant, and 1 Acute kidney injury in patients with laBCC). None of the TEAEs resulting in death was considered by the investigator as related to cemiplimab.

Table 14.3.2.3.1 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 (%)	Group 1: mBCC (N=54)	Group 2: laBCC (N=84)	Total (N=138)
Total number of TEAEs resulting in death	2	4	6
Number of Patients with any TEAE resulting in death, n (%)	2 (3.7%)	4 (4.8%)	6 (4.3%)
Respiratory, thoracic and mediastinal disorders	1 (1.9%)	1 (1.2%)	2 (1.4%)
Haemoptysis	1 (1.9%)	0	1 (0.7%)
Pulmonary oedema	0	1 (1.2%)	1 (0.7%)
Infections and infestations	1 (1.9%)	0	1 (0.7%)
Pneumonia staphylococcal	1 (1.9%)	0	1 (0.7%)
Metabolism and nutrition disorders	0	1 (1.2%)	1 (0.7%)
Cachexia	0	1 (1.2%)	1 (0.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (1.2%)	1 (0.7%)
Brain neoplasm malignant	0	1 (1.2%)	1 (0.7%)
Renal and urinary disorders	0	1 (1.2%)	1 (0.7%)
Acute kidney injury	0	1 (1.2%)	1 (0.7%)

Data cut-off as of Jun 30th, 2020.

Table 14.3.2.3.3 Summary of Death during On-Treatment Period
(Safety Analysis Set)

	Group 1: mBCC (N=54)	Group 2: laBCC (N=84)	Total (N=138)
Number of Deaths, n (%)	4 (7.4%)	6 (7.1%)	10 (7.2%)
Primary cause of death			
ADVERSE EVENT	2 (3.7%)	4 (4.8%)	6 (4.3%)
PROGRESSION/RECURRENCE OF DISEASE	2 (3.7%)	0	2 (1.4%)
OTHER	0	2 (2.4%)	2 (1.4%)

Serious adverse events

Table 14: Study 1620: Summary of Common (≥1% in Any Group) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	mBCC (N = 48)	laBCC (N = 84)	Total BCC (N = 132)
Number of Patients with any serious TEAE, n (%)	13 (27.1)	29 (34.5)	42 (31.8)
Infections and infestations	**7 (14.6)**	**11 (13.1)**	**18 (13.6)**
Urinary tract infection	1 (2.1)	4 (4.8)	5 (3.8)
Arthritis bacterial	1 (2.1)	0	1 (0.8)
Atypical pneumonia	1 (2.1)	0	1 (0.8)
Clostridium difficile colitis	1 (2.1)	0	1 (0.8)
Clostridium difficile infection	1 (2.1)	0	1 (0.8)
Hepatitis C[a]	0	1 (1.2)	1 (0.8)
Infection	1 (2.1)	0	1 (0.8)
Influenza	0	1 (1.2)	1 (0.8)
Lower respiratory tract infection	0	1 (1.2)	1 (0.8)
Oral candidiasis	0	1 (1.2)	1 (0.8)
Pneumonia	1 (2.1)	0	1 (0.8)
Pneumonia staphylococcal	1 (2.1)	0	1 (0.8)
Skin infection	1 (2.1)	0	1 (0.8)

System Organ Class Preferred Term	mBCC (N = 48)	laBCC (N = 84)	Total BCC (N = 132)
Soft tissue infection	0	1 (1.2)	1 (0.8)
Subcutaneous abscess	0	1 (1.2)	1 (0.8)
Wound infection staphylococcal	0	1 (1.2)	1 (0.8)
Nervous system disorders	**3 (6.3)**	**5 (6.0)**	**8 (6.1)**
Somnolence	1 (2.1)	1 (1.2)	2 (1.5)
Brain oedema	0	1 (1.2)	1 (0.8)
Cerebrospinal fluid leakage	0	1 (1.2)	1 (0.8)
Cerebrovascular accident	0	1 (1.2)	1 (0.8)
Dizziness	0	1 (1.2)	1 (0.8)
Facial paralysis	1 (2.1)	0	1 (0.8)
Haemorrhage intracranial	0	1 (1.2)	1 (0.8)
Headache	1 (2.1)	0	1 (0.8)
Gastrointestinal disorders	**2 (4.2)**	**5 (6.0)**	**7 (5.3)**
Colitis	2 (4.2)	2 (2.4)	4 (3.0)
Autoimmune colitis	0	1 (1.2)	1 (0.8)
Constipation	0	1 (1.2)	1 (0.8)
Gastritis erosive	0	1 (1.2)	1 (0.8)
Cardiac disorders	**3 (6.3)**	**2 (2.4)**	**5 (3.8)**
Atrial fibrillation	1 (2.1)	0	1 (0.8)
Autoimmune myocarditis	1 (2.1)	0	1 (0.8)
Autoimmune pericarditis	1 (2.1)	0	1 (0.8)
Immune-mediated myocarditis	1 (2.1)	0	1 (0.8)
Myocardial infarction	0	1 (1.2)	1 (0.8)
Supraventricular tachycardia	0	1 (1.2)	1 (0.8)
Injury, poisoning and procedural complications	**4 (8.3)**	**1 (1.2)**	**5 (3.8)**
Fall	1 (2.1)	0	1 (0.8)
Infusion related reaction	1 (2.1)	0	1 (0.8)
Multiple fractures	1 (2.1)	0	1 (0.8)
Procedural pain	1 (2.1)	0	1 (0.8)
Radial head dislocation	0	1 (1.2)	1 (0.8)
Tibia fracture	1 (2.1)	0	1 (0.8)
Upper limb fracture	0	1 (1.2)	1 (0.8)
Wound haemorrhage	1 (2.1)	0	1 (0.8)

System Organ Class Preferred Term	mBCC (N = 48)	laBCC (N = 84)	Total BCC (N = 132)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**1 (2.1)**	**4 (4.8)**	**5 (3.8)**
Infected neoplasm	0	2 (2.4)	2 (1.5)
Brain neoplasm malignant	0	1 (1.2)	1 (0.8)
Lymphoproliferative disorder	1 (2.1)	0	1 (0.8)
Meningioma	0	1 (1.2)	1 (0.8)
Blood and lymphatic system disorders	**2 (4.2)**	**2 (2.4)**	**4 (3.0)**
Anaemia	0	2 (2.4)	2 (1.5)
Lymphadenopathy mediastinal	1 (2.1)	0	1 (0.8)
Pancytopenia	1 (2.1)	0	1 (0.8)
Endocrine disorders	**0**	**3 (3.6)**	**3 (2.3)**
Adrenal insufficiency	0	2 (2.4)	2 (1.5)
Hypophysitis	0	1 (1.2)	1 (0.8)
Renal and urinary disorders	**1 (2.1)**	**2 (2.4)**	**3 (2.3)**
Acute kidney injury	0	2 (2.4)	2 (1.5)
Urinary retention	1 (2.1)	0	1 (0.8)
Vascular disorders	**0**	**3 (3.6)**	**3 (2.3)**
Hypertensive crisis	0	1 (1.2)	1 (0.8)
Hypotension	0	1 (1.2)	1 (0.8)
Phlebitis	0	1 (1.2)	1 (0.8)
General disorders and administration site conditions	**2 (4.2)**	**0**	**2 (1.5)**
General physical health deterioration	1 (2.1)	0	1 (0.8)
Pyrexia	1 (2.1)	0	1 (0.8)
Hepatobiliary disorders	**1 (2.1)**	**1 (1.2)**	**2 (1.5)**
Autoimmune hepatitis	1 (2.1)	0	1 (0.8)
Immune-mediated hepatitis	0	1 (1.2)	1 (0.8)
Musculoskeletal and connective tissue disorders	**0**	**2 (2.4)**	**2 (1.5)**
Back pain	0	1 (1.2)	1 (0.8)
Dupuytren's contracture	0	1 (1.2)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	**2 (4.2)**	**0**	**2 (1.5)**

System Organ Class Preferred Term	mBCC (N = 48)	laBCC (N = 84)	Total BCC (N = 132)
Pleural effusion	1 (2.1)	0	1 (0.8)
Pneumonitis	1 (2.1)	0	1 (0.8)
Ear and labyrinth disorders	**0**	**1 (1.2)**	**1 (0.8)**
Ear disorder	0	1 (1.2)	1 (0.8)
Immune system disorders	**0**	**1 (1.2)**	**1 (0.8)**
Sarcoidosis	0	1 (1.2)	1 (0.8)
Metabolism and nutrition disorders	**0**	**1 (1.2)**	**1 (0.8)**
Cachexia	0	1 (1.2)	1 (0.8)
Psychiatric disorders	**0**	**1 (1.2)**	**1 (0.8)**
Delirium	0	1 (1.2)	1 (0.8)
Skin and subcutaneous tissue disorders	**0**	**1 (1.2)**	**1 (0.8)**
Dermal cyst	0	1 (1.2)	1 (0.8)

[a] Not a new HCV infection but worsening of liver tests/fibrosis attributed to an ongoing infection.
Abbreviations: AE, adverse event; BCC, basal cell carcinoma; CSR, clinical study report; laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event
Data cutoff as of 17 Feb 2020 for all patients in Study 1620.
All AEs were coded using MedDRA Version 22.1.
A patient was counted only once for multiple occurrences within an 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.
Source: Study 1620 Interim CSR PTT 14.3.2.1.3

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Protocol: R2810-BCC-Pool

Page 1 of 1

Table 14.3.2.1.1.p0 Summary of Serious Treatment-Emergent Adverse Events
(Safety Analysis Set)

	Pool 1 All BCC Patients (N=132)	Pool 2 All Monotherapy Patients (N=810)	Pool 3 All Patients (N=1078)
Number of serious TEAEs	86	433	570
Number of NCI grade 3/4/5 serious TEAEs	59	340	441
Number of Patients with any serious TEAE, n (%)	42 (31.8%)	243 (30.0%)	323 (30.0%)
Number of Patients with any NCI grade 3/4/5 serious TEAE, n (%)	34 (25.8%)	205 (25.3%)	271 (25.1%)
Number of Patients who discontinued study treatment due to serious TEAE, n (%)	10 (7.6%)	41 (5.1%)	51 (4.7%)
Number of Patients with any serious TEAE leading to a drug interruption/delay, n (%)	20 (15.2%)	89 (11.0%)	127 (11.8%)
Number of Patients with any serious TEAE leading to a dose reduction, n (%)	1 (0.8%)	2 (0.2%)	4 (0.4%)
Number of Patients with any serious TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	1 (0.8%)	2 (0.2%)	4 (0.4%)
Number of Patients with any serious TEAE resulting in death, n (%)	4 (3.0%)	47 (5.8%)	50 (4.6%)

Data cut-off as of Feb 17, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624. Data cut-off as of Apr 30, 2019 for Study 1423; Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients in Study 1540; Data cut-off as of Oct 10, 2018 for Group 2 patients in Study 1540.
TEAE: Treatment Emergent Adverse Events
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.

/sasdata/Data/Production/BDM/R2810/R2810-ONC/R2810-ONC-BCC-NSCLC-ISS/Interim_BCC_NSCLC_sBLA/Analysis_CSR/Programs/TFL/BCC/Generated/t_3_2_1_1_saeprof_p0.sas (yun.zhang 18AUG2020 18:18 SAS Linux 9.4)

Table 14.3.2.1.1 Summary of Serious Treatment-Emergent Adverse Events
(Safety Analysis Set)

	Group 1: mBCC (N=54)	Group 2: laBCC (N=84)	Total (N=138)
Number of serious TEAEs	35	58	93
Number of NCI grade 3/4/5 serious TEAE	27	38	65
Number of Patients with any serious TEAE, n (%)	14 (25.9%)	31 (36.9%)	45 (32.6%)
Number of Patients with any NCI grade 3/4/5 serious TEAE, n (%)	13 (24.1%)	24 (28.6%)	37 (26.8%)
Number of Patients who discontinued study treatment due to serious TEAEs, n (%)	3 (5.6%)	8 (9.5%)	11 (8.0%)
Number of Patients with any serious TEAE leading to a dose delay, n (%)	9 (16.7%)	11 (13.1%)	20 (14.5%)
Number of Patients with any serious TEAE leading to a drug interruption, n (%)	1 (1.9%)	0	1 (0.7%)
Number of Patients with any serious TEAE leading to dose reduction, n (%)	0	1 (1.2%)	1 (0.7%)
Number of Patients with any serious TEAE resulting in death, n (%)	2 (3.7%)	4 (4.8%)	6 (4.3%)

Data cut-off as of Jun 30th, 2020.

Laboratory findings

Haematology

Table 14.3.3.1.1 Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade for Hematology
(Safety Analysis Set)

	Group 1:mBCC (N=54)		Group 2:laBCC (N=84)		Total (N=138)	
Parameter (CTCAE Term)	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Number of patients with at least one lab abnormality, n (%)	37/54 (68.5%)	2/54 (3.7%)	55/83 (66.3%)	2/83 (2.4%)	92/137 (67.2%)	4/137 (2.9%)
Hemoglobin (Anemia)	26/54 (48.1%)	0/54	31/83 (37.3%)	0/83	57/137 (41.6%)	0/137
Hemoglobin (Hemoglobin increased)	0/54	0/54	3/83 (3.6%)	0/83	3/137 (2.2%)	0/137
Leukocytes (White blood cell decreased)	2/54 (3.7%)	0/54	4/83 (4.8%)	0/83	6/137 (4.4%)	0/137
Lymphocytes (Lymphocyte count decreased)	21/54 (38.9%)	2/54 (3.7%)	26/83 (31.3%)	1/83 (1.2%)	47/137 (34.3%)	3/137 (2.2%)
Lymphocytes (Lymphocyte count increased)	2/54 (3.7%)	0/54	5/83 (6.0%)	0/83	7/137 (5.1%)	0/137
Neutrophils (Neutrophil count decreased)	2/54 (3.7%)	0/54	3/83 (3.6%)	1/83 (1.2%)	5/137 (3.6%)	1/137 (0.7%)
Platelets (Platelet count decreased)	4/54 (7.4%)	0/54	7/83 (8.4%)	0/83	11/137 (8.0%)	0/137

Data cut-off as of Jun 30th, 2020.

Table 14.3.1.2.3.p0 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(Safety Analysis Set)

System Organ Class, n (%) Preferred Term, n (%)	Pool 1 All BCC Patients (N=132)	Pool 2 All Monotherapy Patients (N=810)	Pool 3 All Patients (N=1078)
Blood and lymphatic system disorders			
Neutropenia	0	8 (1.0%)	21 (1.9%)
Thrombocytopenia	1 (0.8%)	16 (2.0%)	19 (1.8%)
Leukocytosis	8 (6.1%)	11 (1.4%)	13 (1.2%)
Lymphadenopathy	1 (0.8%)	6 (0.7%)	8 (0.7%)
Leukopenia	0	6 (0.7%)	6 (0.6%)
Thrombocytosis	4 (3.0%)	5 (0.6%)	5 (0.5%)
Iron deficiency anaemia	2 (1.5%)	4 (0.5%)	4 (0.4%)
Eosinophilia	0	3 (0.4%)	3 (0.3%)
Pancytopenia	1 (0.8%)	3 (0.4%)	3 (0.3%)
Febrile neutropenia	0	1 (0.1%)	2 (0.2%)
Neutrophilia	1 (0.8%)	2 (0.2%)	2 (0.2%)
Normocytic anaemia	0	0	2 (0.2%)
Coagulopathy	0	1 (0.1%)	1 (<0.1%)
Haemorrhagic diathesis	1 (0.8%)	1 (0.1%)	1 (<0.1%)
Immune thrombocytopenic purpura	0	1 (0.1%)	1 (<0.1%)
Lymph node pain	0	1 (0.1%)	1 (<0.1%)
Lymphadenitis	0	1 (0.1%)	1 (<0.1%)
Lymphadenopathy mediastinal	1 (0.8%)	1 (0.1%)	1 (<0.1%)
Microcytic anaemia	0	1 (0.1%)	1 (<0.1%)

Data cut-off as of Feb 17, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624. Data cut-off as of Apr 30, 2019 for Study 1423; Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients in Study 1540; Data cut-off as of Oct 10, 2018 for Group 2 patients in Study 1540.
TEAE: Treatment-emergent adverse event.
All adverse events were coded using the MedDRA Version 22.1.
A patient is counted only once for multiple occurrences within a system organ class/preferred term.
For SOCs, the table is sorted by decreasing frequency in the total group. Within each SOC, PTs are sorted by decreasing frequency in the total group.
/sasdata/Data/Production/BDM/R2810/R2810-ONC/R2810-ONC-BCC-NSCLC-ISS/Interim_BCC_NSCLC_sBLA/Analysis_CSR/Programs/TFL/BCC/Generated/t_3_1_2_3_aesocpt_p0.sas (yun.zhang 18AUG2020 18:16 SAS Linux 9.4)

Chemistry

Table 14.3.3.2.1 Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade for Electrolytes
(Safety Analysis Set)

	Group 1:mBCC (N=48)		Group 2:laBCC (N=84)		Total (N=132)	
Parameter (CTCAE Term)	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Number of patients with at least one lab abnormality, n (%)	21/47 (44.7%)	2/47 (4.3%)	65/83 (78.3%)	4/83 (4.8%)	86/130 (66.2%)	6/130 (4.6%)
Calcium (Hypercalcemia (Uncorrected Calcium))	3/47 (6.4%)	0/47	11/83 (13.3%)	0/83	14/130 (10.8%)	0/130
Calcium (Hypocalcemia (Uncorrected Calcium))	3/47 (6.4%)	0/47	20/83 (24.1%)	0/83	23/130 (17.7%)	0/130
Potassium (Hyperkalemia)	6/47 (12.8%)	0/47	24/83 (28.9%)	0/83	30/130 (23.1%)	0/130
Potassium (Hypokalemia)	5/47 (10.6%)	1/47 (2.1%)	12/83 (14.5%)	1/83 (1.2%)	17/130 (13.1%)	2/130 (1.5%)
Sodium (Hypernatremia)	1/47 (2.1%)	0/47	8/83 (9.6%)	0/83	9/130 (6.9%)	0/130
Sodium (Hyponatremia)	10/47 (21.3%)	1/47 (2.1%)	27/83 (32.5%)	3/83 (3.6%)	37/130 (28.5%)	4/130 (3.1%)

Data cut-off as of Feb 17th, 2020.
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.

/sasdata/Data/Production/BDM/R2810/R2810-ONC/R2810-ONC-1620/Interim_BCC_sBLA/Analysis_CSR/Programs/TFL/Generated/t_3_3_2_1_lbelcgrdsum_saf.sas (michael.klingler 17AUG2020 16:35 SAS Linux 9.4)

Table 4.5.9 Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade (≥15% in All Grades) (Safety Pool 1)

	Safety Pool 1 (N=132)	
Parameter (CTCAE Term)	**All Grades n/N (%)**	**Grades 3/4 n/N (%)**
Chemistry (Other)		
Creatinine increased[a]	42/130 (32.3)	0/130
Liver function		
Alanine aminotransferase increased	29/130 (22.3)	1/130 (0.8)
Aspartate aminotransferase increased	43/130 (33.1)	1/130 (0.8)
Alkaline phosphatase increased	20/130 (15.4)	1/130 (0.8)
Hypoalbuminemia	35/130 (26.9)	1/130 (0.8)
Electrolytes		
Hyponatremia	37/130 (28.5)	4/130 (3.1)
Hyperkalemia	30/130 (23.1)	0/130
Hypocalcemia	23/130 (17.7)	0/130
Hematology		
Anaemia	52/130 (40.0)	0/130
Lymphocyte count decreased	44/130 (33.8)	3/130 (2.3)

[a] For Creatinine, NCI grades were coded using CTCAE Version 5.0. All other NCI grades were coded using CTCAE Version 4.03.
Abbreviations: ISS, Integrated Summary of Safety; N, number of patients.
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.
Data cutoff as of 17 Feb 2020 for all patients in Safety Pool 1 (Study 1620).
Sources: ISS Table 14.3.3.1.1.p0, Table 14.3.3.2.1.p0, Table 14.3.3.3.1.p0, and Table 14.3.3.4.1a.p0.

Safety in special populations

Table 1: Treatment Exposure by Age Group, Gender And Renal Impairment In Patients that Received Cemiplimab Monotherapy (Pool 2)

Age group	Mild renal impairment		Moderate renal impairment		Severe renal impairment	
	Number of patients	Median exposure duration in weeks	Number of patients	Median exposure duration in weeks	Number of patients	Median Exposure duration in weeks
< 65 years	110	36.3	20	37.1	0	0
65 to74 years	119	38.0	32	30.2	1	4.1
75 to 84 years	68	35.0	61	27.0	3	12.9
≥ 85 years	10	46.9	21	20.9	2	64.5
Male	254	39.0	96	30.1	1	72
Female	53	26.9	38	28.7	5	12.9
Total patients	307		134		6	

Source: Table 14.1.4.1.4.p2.s1 and Table 14.1.4.1.4.p2.s3

Table 2: Treatment Exposure by Age Group, Gender and Hepatic Impairment in Patients with Cemiplimab Monotherapy (Pool 2).

Age group	Mild hepatic impairment		Moderate hepatic impairment		Severe hepatic impairment	
	Number of patients	Median exposure duration in weeks	Number of patients	Median exposure duration in weeks	Number of patients	Median exposure duration in weeks
< 65 years	9	29.1	2	24.9	0	0
65 to 74 years	5	48.0	1	18.1	0	0
75 to 84 years	3	8.0	0	0	0	0
≥ 85 years	1	41.4	0	0	0	0
Male	13	30.0	3	18.1	0	0
Female	5	12.9	0	0	0	0
Total patients	18		3		0	

Source: Table 14.1.4.1.4.p2.s2 and Table 14.1.4.1.4.p2.s4

Safety related to drug-drug interactions and other interactions

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

Please see the assessment of clinical pharmacology.

Discontinuation due to adverse events

Table 14.3.2.3.5 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 (%)	Group 1: mBCC (N=54)	Group 2: laBCC (N=84)	Total (N=138)
Total number of TEAEs resulting in treatment discontinuation	8	19	27
Number of Patients with any TEAE resulting in treatment discontinuation, n (%)	4 (7.4%)	15 (17.9%)	19 (13.8%)
Gastrointestinal disorders	0	4 (4.8%)	4 (2.9%)
Colitis	0	2 (2.4%)	2 (1.4%)
Autoimmune colitis	0	1 (1.2%)	1 (0.7%)
Enterocolitis	0	1 (1.2%)	1 (0.7%)
Endocrine disorders	1 (1.9%)	2 (2.4%)	3 (2.2%)
Adrenal insufficiency	0	1 (1.2%)	1 (0.7%)
Hypophysitis	0	1 (1.2%)	1 (0.7%)
Immune-mediated hypothyroidism	1 (1.9%)	0	1 (0.7%)
General disorders and administration site conditions	2 (3.7%)	1 (1.2%)	3 (2.2%)
General physical health deterioration	1 (1.9%)	1 (1.2%)	2 (1.4%)
Asthenia	0	1 (1.2%)	1 (0.7%)
Pain	1 (1.9%)	0	1 (0.7%)

Table 14.3.2.3.5 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 (%)	Group 1: mBCC (N=54)	Group 2: laBCC (N=84)	Total (N=138)
Nervous system disorders	0	3 (3.6%)	3 (2.2%)
Cerebrovascular accident	0	1 (1.2%)	1 (0.7%)
Haemorrhage intracranial	0	1 (1.2%)	1 (0.7%)
Somnolence	0	1 (1.2%)	1 (0.7%)
Hepatobiliary disorders	1 (1.9%)	1 (1.2%)	2 (1.4%)
Autoimmune hepatitis	1 (1.9%)	0	1 (0.7%)
Immune-mediated hepatitis	0	1 (1.2%)	1 (0.7%)
Renal and urinary disorders	0	2 (2.4%)	2 (1.4%)
Acute kidney injury	0	1 (1.2%)	1 (0.7%)
Renal failure	0	1 (1.2%)	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	1 (1.9%)	1 (1.2%)	2 (1.4%)
Cough	0	1 (1.2%)	1 (0.7%)
Pleural effusion	1 (1.9%)	0	1 (0.7%)
Cardiac disorders	1 (1.9%)	0	1 (0.7%)
Autoimmune pericarditis	1 (1.9%)	0	1 (0.7%)
Immune-mediated myocarditis	1 (1.9%)	0	1 (0.7%)

Table 14.3.2.3.5 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 (%)	Group 1: mBCC (N=54)	Group 2: laBCC (N=84)	Total (N=138)
Infections and infestations	0	1 (1.2%)	1 (0.7%)
Bronchitis	0	1 (1.2%)	1 (0.7%)
Investigations	0	1 (1.2%)	1 (0.7%)
Ejection fraction decreased	0	1 (1.2%)	1 (0.7%)
Metabolism and nutrition disorders	0	1 (1.2%)	1 (0.7%)
Cachexia	0	1 (1.2%)	1 (0.7%)
Musculoskeletal and connective tissue disorders	1 (1.9%)	0	1 (0.7%)
Neck pain	1 (1.9%)	0	1 (0.7%)
Vascular disorders	0	1 (1.2%)	1 (0.7%)
Peripheral ischaemia	0	1 (1.2%)	1 (0.7%)

Data cut-off as of Jun 30th, 2020.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity with cemiplimab. Immunogenicity was assessed by monitoring ADAs to cemiplimab. Samples for ADA assessment were collected prior to dosing at several time points.

Among all patients in the ADA analysis set of Safety Pool 3, 2.2% (18/823) of patients developed treatment-emergent antibodies to cemiplimab. Maximum antibody titers were all low with the exception of 1 moderate titer. No patient developed NAbs. Persistent antibody responses, defined as having at least 2 consecutive positive post baseline samples separated by at least 16 weeks, occurred in 0.4% (3/823) of patients overall.

The incidence of treatment-emergent ADA in Safety Pool 1 (Study 1620 in BCC) was 3.2%, with 4 patients with treatment emergent ADA (0 persistent, 2 transient, and 2 indeterminate treatment-emergent ADA responses); all had low titers (<1,000). Pre-existing ADA occurred in 4 patients (3.2%). No NAb were detected in the patients with a positive response in the ADA assay.

In the patients who developed anti-cemiplimab antibodies, there was no evidence of altered exposure to cemiplimab.

The presence of ADA was not associated with significant TEAEs or imAEs.

Post marketing experience

Cemiplimab is approved in several countries worldwide for the treatment of adult patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation. Cumulatively up to 27 Mar 2020, a total of 3547 patients have been treated with investigational cemiplimab monotherapy, combination therapy, or comparator in multiple clinical trials.

The international birth date (IBD) for cemiplimab is 28 September 2018 (date of first-ever approval in any country). Using the sales data and assuming that all vials sold were administered to patients at the approved dose of 350 mg Q3W, the estimated post marketing exposure from the IBD up to 27 March 2020 is 2576.3 patient-years.

Since the initial approval of cemiplimab, 2 identified risks (immune-related myositis and solid organ transplant rejection) have been confirmed. These risks are part of well-known immune related adverse events associated with this class of drug. Review of post marketing safety data did not identify any new unexpected safety findings.

2.5.1. Discussion on clinical safety

The most relevant safety database for this application is the monotherapy patients (Safety Pool 2), comprising 816 patients, where 2/3 of patients have received the proposed dosing regimen of 350 mg Q3W (n=549). Median duration of exposure in the pivotal Study 1640 is 26.8 weeks for the mBCC group and 47.15 weeks for the laBCC group. A comprehensive safety profile of cemiplimab in the proposed dose is sufficiently characterized and endorsed. Importantly, however, the number of patients with advanced BCC (138 patients) was limited and the study 1620 (pivotal study for BCC) was an open-label single arm study.

According to the SmPC, the safety of cemiplimab has been evaluated in 591 patients with advanced solid malignancies including 219 advanced CSCC. Severe and fatal immune-related adverse reactions (irADRs) have been observed and these immune-related reactions may involve any organ system. Most of these

adverse reactions, including severe reactions, have resolved following initiation of appropriate medical therapy or withdrawal of cemiplimab.

Almost all monotherapy patients had at least one AE (97.1%) and more than a third (45.7%) had high-grade (≥3grade) AE. Two thirds of the patients had treatment-emergent AEs most frequently fatigue (28.3%), diarrhoea (12.3%), pruritus (13.8%) and hypothyroidism (8.7%) in pool 1, and that was consistent with the patients in pool 2 in the updated version as of 17 Feb 2020. Thyroiditis can present with or without an alteration in thyroid function tests. Hypothyroidism can follow hyperthyroidism (see section 4.4 of the SmPC).

Adverse events of special interest include immune-related events and the most commonly identified overall grade irAEs in pool 1 were hypothyroidism (8.7%), colitis (3.6%), hyperthyroidism (4.3%) and arthralgia (4.3%) but ≥grade 3 events rarely occurred. 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 although the proportion of patients experiencing serious TEAEs increased with age in Study 1620 (Safety Pool 1) as well as in Safety Pool 3.

As of the data cut-off, 4.3% (6/138) of patients in Study 1620 experienced TEAEs resulting in death. According to the narratives the 3/4 patients had substantial co-morbidities. Four additional patients were noted to have died during the on-study period due to disease progression; the relevant narratives have been updated.

Serious TEAEs as well as treatment discontinuations are clearly more common in the elderly population than in the younger patients (24,5% vs 57.6% and 5,4% vs 21,2% respectively). Also, SAEs related to cemiplimab treatment are more common in the elderly (5,9% in patients <65 years and 21,2% in patients ≥85 years). The SmPC section 5.1 reflects the higher frequency of serious adverse events and discontinuations due to adverse events in patients 65 years and older compared with patients aged less than 65 years.

Patients in the monotherapy pool (Pool 2, n=441) were presented according to mild, moderate and severe renal impairment; 307 patients had mild and 134 patients had moderate renal impairment. Only 6 patients with severe renal impairment were treated with monotherapy cemiplimab. Review of safety data in these patients did not identify any significant differences compared to patients with normal renal function. In the monotherapy pool (Pool 2), a total of 21 patients with mild (18 patients) and moderate (3 patients) hepatic impairment were treated with cemiplimab. Here again a review of safety data in these patients did not identify any significant differences compared to patients with normal hepatic function. The existing text in the SmPC regarding patients with renal and hepatic impairment is adequate.

Most treatment discontinuations in the BCC group were due to gastrointestinal, endocrine and nervous system disorders but the numbers are very small (2-4 patients in each disorder). 19.6% of the patients in the BCC group (pool 1) discontinued the treatment. Based on data presented, it can be concluded, that the overall frequency of TEAEs, severe TEAS of grade 3/4/5 and serious TEAEs in the laBCC group was roughly similar to other patients treated with cemiplimab, especially when compared to study 1540 (193 patients with CSCC). However, discontinuations due to TEAEs were more common in laBCC patients than in any other patient group treated with cemiplimab. The frequency of discontinuations due to TEAEs was 17,9% in laBCC patients and 6,5%, 7,8% and 6,5% in studies 1423, 1540 and 1624 respectively. The frequency of adverse events resulting in treatment discontinuation was higher in the laBCC group than in mBCC group, 17.9% and 7.4% respectively. The most common reason for discontinuations of treatment in the laBCC group were gastrointestinal disorders including colitis, autoimmune colitis and enterocolitis. There seems not to be any differences between pool 1 and pool 2. However, again the numbers are small making a comparison difficult.

Following the CHMP request to use Pool 2 in the ADR table in section 4.8 of the SmPC, the table was revised to include patients treated with cemiplimab monotherapy (n=810 in total), which included BCC safety data from the Feb 2020 data cut (n=132, laBCC: n=84 and mBCC: n=48). Inclusion of June 2020 data resulted in 6 additional mBCC patients so n=816 as pooled safety data. The ADR table in section 4.8 was updated in both NSCLC and BCC variations for consistency. (see section 4.8 of the SmPC).

The incidence of anti-cemiplimab antibodies (ADAs) in patients with advanced BCC treated with cemiplimab 350 mg Q3W was 3.2%. Of the patients who developed treatment-emergent antibodies to cemiplimab, none developed NAbs. Thus, cemiplimab had low immunogenicity potential, consistent with patients with advanced CSCC.

2.5.2. Conclusions on clinical safety

The safety profile of cemiplimab is as expected for a PD-1 inhibitor, and considering the elderly patient population. There are no new safety findings nor any major concerns.

The relevant SmPC Sections have been revised, to reflect the safety profile of pool 2 and the safety in relation to age of patients treated with cemiplimab monotherapy. Further safety data will be submitted in the context of the Annex II.D PAES (see clinical efficacy section) i.e. submission of the final CSR for study 1620.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2 is acceptable.

The CHMP endorsed the Risk Management Plan version 2 with the following content:

Safety concerns

*Table 23**: Summary of Safety Concerns***

Summary of Safety Concerns	
Important Identified Risks	irARs (pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis, and other irARs) IRRs
Important Potential Risks	Lack of effect due to anti-drug antibodies
Missing Information	Long-term safety data

Pharmacovigilance plan

*Table 24: **On-going and Planned Additional Pharmacovigilance Activities***

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 REGN2810, A Fully Human Monoclonal Antibody to Programmed Cell Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Group 6) Ongoing	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 submitted	09/07/2019
			FPFV	31/01/2020
			LPLV	28/02/2022
			Interim report	31/03/2023
R2810-ONC-1540: A Phase 2 Study of REGN2810, A Fully Human Monoclonal Antibody to Programmed Cell Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Group 1, 2 and 3) 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

Risk minimisation measures

Table : 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 4.4 and 4.8 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 irARs Additional pharmacovigilance activities: Study short name and title: R2810-ONC-1540: A Phase 2 Study of REGN2810, A Fully Human Monoclonal Antibody to Programmed Cell Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Group 6)
Important Identified Risk: Infusion-related Reactions	Routine communication messages: SmPC section 4.4 and 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: R2810-ONC-1540: A Phase 2 Study of REGN2810, A Fully Human Monoclonal Antibody to Programmed Cell Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Group 6)

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: R2810-ONC-1540: A Phase 2 Study of REGN2810, A Fully Human Monoclonal Antibody to Programmed Cell Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Group 6)
Long-Term Safety Data	Not applicable	Routine pharmacovigilance Additional pharmacovigilance activities: Study short name and title: R2810-ONC-1540: A Phase 2 Study of REGN2810, A Fully Human Monoclonal Antibody to Programmed Cell Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Groups 1, 2, 3 and 6)

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. Particularly, a new warning with regard to thyroiditis has been added to the product information. The Package Leaflet has been updated accordingly. Annex IID has been revised.

User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

There are no changes in legal status or introduction of a new presentation, and no particular critical safety issues have been identified with Libtayo.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Disease or condition

Treatment of adult patients with locally advanced or metastatic basal cell carcinoma (laBCC or mBCC) who have progressed on or are intolerant to a hedgehog pathway inhibitor (HHI).

Available therapies and unmet medical need

Advanced BCC is a serious condition that includes potentially life-threatening disease for metastatic patients and persistent invasive and disfiguring tumours for patients with locally advanced BCC. Despite the practice-changing efficacy observed with the HHIs vismodegib and sonidegib for first-line therapy for advanced BCC, the limitations of HHIs are that approximately half of patients do not experience objective responses, most responses are partial, and side effect profiles of these agents can create difficulties for long-term therapy.

For advanced BCC patients (laBCC+mBCC), who no longer benefit from first-line HHI therapy, there are no approved or efficacious second-line therapies. There is major unmet medical need in this late line treatment, after HHI-therapies and when radiation/ surgery is not possible, with no remaining treatment options for these patients.

Main clinical studies

The pivotal study for this application regarding efficacy and safety is the 1620 (REGN2810) study, which is an ongoing, international, multicentre, non-randomized, open-label, two-group phase 2 study of cemiplimab monotherapy for patients with mBCC and laBCC, and who have discontinued prior HHI therapy due to disease progression, no better than stable disease after 9 months, or intolerance. As of the data cut-off date (30 Jun 2020), there were 138 patients enrolled in the study (54 in the mBCC group and 84 in the laBCC group).

3.2. Favourable effects

Primary results of the laBCC group and interim results and updated efficacy results of the mBCC group from the pivotal Study 1620 (REGN2810) in the efficacy target population showed an ORR per ICR-assessed (RECIST 1.1) of 32.1% in the laBCC group and 28.6% in the mBCC group.

The disease control rate in the laBCC group was 79.8% (95%CI 69.6, 87.7), and durable disease control rate 59.5% (95% CI 48.3, 70.1).

The K-M estimated percentages of responses ongoing in patients with locally advanced BCC at 6 months and 12 months per ICR were 90.9% (95% CI: 68.3%, 97.6%) and 85.2% (95% CI: 60.5%, 95.0), respectively. For the mBCC group at 6 months it was 90%.

For all patients with advanced BCC the mOS was 25.7 months as of data cut-off. The estimated median is unstable due to small number of events. The mPFS is 19.3 months for the laBCC group and 6.6 months for the mBCC group which is clinically meaningful considering that this is a second line setting in a patient group with a very poor prognosis and limited treatment options.

3.3. Uncertainties and limitations about favourable effects

The efficacy of cemiplimab in mBCC is based on interim data on a limited number of patients from a non-randomised, open-label study. The data cut for the primary analysis for Group 1 is projected to occur on 20 May 2021, which represents 57 weeks from cycle 1/day 1 for the 54th patient enrolled in Group 1. Data lock would occur in July 2021. The MAH anticipates that the updated CSR for mBCC will be completed in September 2021 and committed to provide the primary and final analysis of the mBCC population from study 1620post-approval (see Annex II.D).

3.4. Unfavourable effects

Most patients in study 1620 (97,1%) had at least one AE and 45,7% had high-grade events (≥3 grade). The latter was distributed with 35.3% in the mBCC group and 52.4% in the laBCC group and this is probably because of the longer treatment duration in the laBCC group. In pool 2 it was respectively 93.3% and 41.1%. Most common high-grade AE in the BCC group were colitis (2.9%), fatigue 1.4%) and asthenia (1.4%).

Adverse events of special interest included immune-related AEs (irAEs) and were reported as identified events (required steroids or were endocrinopathies) and overall grade irAEs occurred frequently in approximately a quarter of the patients but ≥grade 3 events rarely occurred (11.6% and 6.5% in pool 1 and 2 respectively).

Serious adverse events were common during treatment (any grades 32.6% in pool 1 and 30.0% in pool 2) and most often related to infections (13.6% in pool 1 and 11.1% in pool 2), again this may due to the underlying disease and the elderly patient population.

Most treatment discontinuations in the BCC group were due to gastrointestinal, endocrine and nervous system disorders. 19.6% of the patients in the BCC group (pool 1) discontinued the treatment.

3.5. Uncertainties and limitations about unfavourable effects

In the BCC group the numbers in each disorder concerning discontinuation are very small (2-4 patients in each disorders). Safety findings from other safety pools (Pool 2 and Pool 3) were used to provide supportive information particularly concerning imAEs, but the Pool 2 (monotherapy pool) includes even patients with other than existing or sought indications i.e. off-label indications and patients in Pool 3 (used primary to discuss imAEs) have also received combination treatments and an essential part of other patients have received different dosing regimen (3 mg/kg cemiplimab Q2W IV), so there are several confounding factors in these safety evaluations.

Further safety data, the primary analysis of group 1, as well as a 18 months follow up from study 1620 will be submitted for CHMP review post authorisation (see Annex II.D).

3.6. Effects Table

Table 2. Effects Table for LIBTAYO as monotherapy for the treatment of adult patients with advanced basal cell carcinoma (laBCC+mBCC) previously treated with a hedgehog pathway inhibitor (HHI) (30 Jun 2020 cutoff)

Effect	Short description	Unit	Treatment Cemiplimab N=132	Control NA	Uncertainties / Strength of evidence	References
Favourable Effects						
Primary endpoint						
ORR (laBCC)	Overall response rate	N (%)	27 (32.1%)		interim data - limited number of patients - non-randomised - open-label	
ORR (mBCC)	Overall response rate	N (%)	10 (28.6%)			
Secondary endpoints						
OS (all)	Overall survival	Months	25.7			
DOR	Duration of response	Months	NA			
PFS (laBCC)	Progression free survival	Months	19.3			
PFS (mBCC)	Progression free survival	Months	6.6			
Unfavourable Effects						
≥AE	AE	%	97.1%			
≥Grade 3	AE (ADR)	%	45.7%			
SAEs	AE (ADR)	%	32.6%			
AEs leading to discount.	AE (ADR)	%	19.6%			
Fatigue	ADR	%	28.3			
Diarrhea	ADR	%	12.3			
Hypothyreoidism	ADR	%	8.7			
Pruritus	ADR	%	13.8			

3.7. Benefit-risk assessment and discussion

Importance of favourable and unfavourable effects

Advanced BCC is a serious condition and despite the efficacy observed with the HHIs vismodegib and sonidegib for first line therapy, the limitations of HHIs are that approximately half of patients do not experience objective responses and the side effect profiles can create difficulties for long-term therapy. There is currently no approved treatment for these patients in the second-line, thus there is an unmet medical need in this setting.

There is a major unmet medical need in this late line treatment, after HHI-therapies and when radiation/ surgery is not possible, with no remaining treatment options for these patients. The prevalence of such advanced disease is very low and hence a confirmatory randomized controlled trial may not be feasible. Although cemiplimab is explored in a non-randomized study without a comparator the observed ORR of 28.6-32.1% and the PFS of 6.6-19.3 months in the mBCC and laBCC group respectively, are considered clinically meaningful in this palliative setting.

Further, the product has been already licenced and shown to provide benefit in patients with CCSC, which is a very similar disease with BCC, with shared lineage with epidermal keratinocytes, providing further support and plausibility for efficacy in the currently sought indication.

Balance of benefits and risks

The observed clinical benefit in terms of ORR and PFS in the mBCC and laBCC group respectively, outweighs the risks which are considered manageable in this condition.

Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Libtayo is positive provided the final CSR for the mBCC cohort is submitted post authorisation.

The following measures are considered necessary to address issues related to efficacy and safety:

Submission of the report from clinical study 1620 to further confirm clinical efficacy and safety of cemiplimab in patients with mBCC who experienced progression of disease on hedgehog pathway inhibitor therapy or were intolerant of prior hedgehog pathway inhibitor therapy.

Submission of Report on primary analysis: Q1 2022; Submission of Final report after 36 months of follow up: Q2 2024

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include : LIBTAYO as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic basal cell carcinoma (laBCC or mBCC) who have progressed on or are intolerant to a hedgehog pathway inhibitor (HHI).SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 have been revised. The PL has been updated accordingly. Version 2.0 of the RMP has been submitted. Annex IID has been revised.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

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

Risk management plan (RMP)

The Marketing authorisation holder (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.

In addition, 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.

Obligation to conduct post-authorisation measures

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

Description	Due date
In order to further characterise the efficacy and safety of cemiplimab in mBCC, the MAH should submit the primary analysis for mBCC and the final study report from clinical study 1620 evaluating objective response rate and duration of response of cemiplimab in patients with mBCC who experienced progression of disease on hedgehog pathway inhibitor therapy or were intolerant of prior hedgehog pathway inhibitor therapy. Submission of Final study report	30/06/2024

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 1).