13 October 2022
EMA/862705/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

LIBTAYO

International non-proprietary name: cemiplimab

Procedure No. EMEA/H/C/004844/II/0026

Note

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

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List of abbreviations

Abbreviation	**Definition**
1L	First line
2L	Second line
AC	Adenocarcinoma
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_{max1}	Maximum concentration after first dose
CPS	Combined proportion score
CR	Complete response
CSCC	Cutaneous squamous cell carcinoma
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
$C_{trough1}$	Trough concentration after first dose
CYP	Cytochrome P450
DCR	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

HHI	Hedgehog (pathway) inhibitor
HPV	Human papilloma virus
IC	Investigator choice
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
imAE	Immune-mediated adverse event (also referred to as irAE)
IRR	Infusion-related reaction
iSAP	Integrated Statistical Analysis Plan
ISS	Integrated Summary of Safety
ITT	Intention-to-treat
IV	Intravenous(ly)
K-M	Kaplan-Meier
MAH	Marketing Authorisation Holder
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-1	Programmed cell death 1
PD-L1, PD-L2	Programmed death-ligand 1, programmed death-ligand 2
PFS	Progression-Free survival
PH	Proportional hazards
PK	Pharmacokinetic(s)
PopPK	Population PK
PPC	Posterior predictive check
PR	Partial response
PRO	Patient reported outcome
PT	Preferred term
Q2W	Every 2 weeks
Q3W	Every 3 weeks
R/M	Recurrent/Metastatic
RECIST	Response Evaluation Criteria in Solid Tumors
QoL	Quality of life

SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SCC	Squamous cell carcinoma
SD	Stable disease
SJS	Stevens-Johnsons syndrome
SMO	Smoothened
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TPS	Tumor proportion score
TTR	Time to response
ULN	Upper limit of normal
US	United States
UV	Ultraviolet
VEGF-A	Vascular endothelial growth factor A
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 8 November 2021 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, II and IIIB

Extension of indication to include monotherapy treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy for Libtayo; sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics, Annex II 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(s) P/0293/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0293/2021 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.

Scientific advice

The MAH received Scientific Advice from the CHMP on 21 April 2017 (EMEA/H/SA/3225/4/2017/II). 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: Aaron Sosa Mejia

Timetable	Actual dates
Submission date	8 November 2020
Start of procedure:	27 November 2020
CHMP Rapporteur Assessment Report	21 January 2021
PRAC Rapporteur Assessment Report	28 January 2021
PRAC Outcome	10 February 2021
CHMP members comments	29 October 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 February 2022
Request for supplementary information (RSI)	24 February 2022
CHMP Rapporteur Assessment Report	24 May 2022
PRAC Rapporteur Assessment Report	27 May 2022
PRAC Outcome	10 June 2022
CHMP members comments	13 June 2022
Updated CHMP Rapporteur Assessment Report	16 June 2022
Request for supplementary information (RSI)	23 June 2022
PRAC Rapporteur Assessment Report	16 September 2022
PRAC members comments	21 September 2022
Updated PRAC Rapporteur Assessment Report	22 September 2022
CHMP Rapporteur Assessment Report	29 September 2022
PRAC Outcome	29 September 2022
CHMP members comments	03 October 2022
Updated CHMP Rapporteur Assessment Report	07 October 2022
An Oral explanation took place on:	12 October 2022
CHMP opinion:	13 October 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Claimed the therapeutic indication

The initially claimed indication was for LIBTAYO as monotherapy for the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after platinum-based chemotherapy.

The recommended indication is for LIBTAYO as monotherapy is indicated for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy.

The recommended dose is 350 mg cemiplimab every 3 weeks (Q3W) administered as an intravenous infusion over 30 minutes.

Treatment may be continued until disease progression or unacceptable toxicity (see SmPC section 4.2).

Epidemiology and risk factors, screening tools/prevention

Cervical cancer is the fourth most frequently diagnosed cancer in women and the fourth highest cause of cancer death in women, with an estimated global incidence of 604,000 new cases and 342,000 deaths globally in 2020 (Sung, 2021). The highest incidence rates are in the Caribbean, Africa, Eastern Europe, and South America (Forman, 2012). In 2018 the world aged-standardized incidence rate (per 100,000 women) ranged from 6.8 in Western Europe to 16.0 in Central-eastern Europe (Arbyn, 2020). The most significant cause of cervical cancer is persistent human papillomavirus (HPV) infection.

Screening with the Papanicolaou (Pap) test since the 1950s, with subsequent incorporation of HPV DNA testing, has been associated with decreased cervical cancer mortality in the US and other developed countries (Wang, 2004). Although vaccination against high risk strains of HPV is projected to gradually decrease the global incidence of cervical cancer in the coming decades, the burden of this disease remains profound (Simms, 2019).

Biologic features

Squamous cell carcinomas account for approximately 70%–80% of cervical cancers and adenocarcinomas for 20%–25% (ESMO Clinical practice guideline on Cervical Cancer).

These histologic subtypes differ substantially in terms of HPV and mutation status (HPV16 for SCC, HPV18 for adenocarcinoma), immune infiltrate, response to therapy, and patient outcome. Several retrospective studies showed that patients with adenocarcinoma have a higher risk of developing metastases, resulting in a poorer prognosis (Rotman J, 2020).

Approximately 5–11% of all cervical cancers are reported to be HPV-negative, which can be attributed to truly negative and false-negative results. The truly HPV-negative cervical cancers are almost all cervical adenocarcinomas with unclear aetiology (Xing B, 2021).

Cervical carcinoma may evade immune response by expression of PD-L1 (programmed-death ligand 1), the ligand for the immune-checkpoint receptor PD-1 (programmed death-1) on T cells (Heeren, 2016). Additionally, analysis of TCGA (The Cancer Genome Atlas) for expression of selected genes (PD-1, PD-L1, CD8A) showed that cervical cancer clusters with other tumour types for which anti-PD-1 therapy improves overall survival (Rischin D, 2020).

Clinical presentation, diagnosis and stage/prognosis

Almost half of the newly diagnosed adult cervical cancer patients have Stage I localized cancer, with a 5-year survival rate of over 90%. Five-year survival rates decrease with stage at diagnosis, becoming as low as 15-17% for metastatic disease (Lorin, 2015; Munich cancer registry 2016; SEER Cervical Cancer).

Following treatment of early-stage cervical cancer, distant metastases or multiple recurrence sites develop in 15% to 61% of patients, usually within the first two years of completing treatment. Recurrent cervical cancer presents as disease isolated to the pelvis (locoregional recurrence) or with disease involving other organs or outside the pelvis. If a vaginal recurrence is suspected, the area of concern should be biopsied to prove recurrent disease. All patients suspected of recurrent disease should undergo positron emission tomography (PET)/computed tomography (CT) for evaluation of local and distant disease.

Management

Treatment options for cervical cancer in adults include surgery (conization, hysterectomy, pelvic exenteration), radiation, and chemotherapy alone or in combination, depending on the stage of the disease (ESMO Guideline). For patients with a local recurrence, surgical resection is recommended, rather than nonsurgical approaches, if they are appropriate surgical candidates based on tumour recurrence, age, and comorbidities. In select patients, surgical resection may present a curative option. However, for patients with a local recurrence who have not received radiation therapy (RT), RT in combination with chemotherapy is an acceptable alternative, and is preferred in those who are not surgical candidates, provided they have not previously undergone pelvic or intravaginal RT. For women with recurrent cervical cancer and who are not surgical candidates, and for those who present with metastatic disease, systemic therapy is recommended.

Cisplatin was the first established systemic therapy for treatment of recurrent or metastatic (R/M) cervical cancer, but single agent activity was modest (Eskander, 2014) (Tewari, 2019). Cisplatin-based doublets with topotecan or paclitaxel have shown superiority to cisplatin monotherapy in terms of response rate and PFS, especially in patients previously exposed to CRT where cisplatin was used as radiosensitizer (Moore, 2004; Long, 2005; ESMO Guideline).

The addition of bevacizumab, a monoclonal directed against vascular endothelial growth factor A (VEGF-A), to doublet chemotherapy study improved overall survival (OS) compared to doublet chemotherapy alone in the GOG-240 study (16.8 vs 13.3 months; hazard ratio [HR 0.77]) (Tewari, 2017; EPAR Avastin).

Carboplatin + paclitaxel was reported to have a more favourable toxicity profile than cisplatin + paclitaxel and was associated with non-inferior OS in a phase 3 study (Kitagawa, 2015). Carboplatin + paclitaxel (with bevacizumab, if appropriate) may be the preferred first line treatment for recurrent/metastatic (R/M) cervical cancer for patients that are not candidates for cisplatin (ESMO Guideline). Topotecan + paclitaxel (with bevacizumab, if appropriate) may also be considered for patients who are not platinum candidates (Tewari, 2014b) (Tewari, 2017).

The role of frontline immunotherapy in cervical cancer has recently been established. Pembrolizumab, a humanized monoclonal antibody that binds to human programmed cell death 1 (PD 1), was recently approved in EU in combination with chemotherapy with or without bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD L1 with a Combined Positive Score (CPS) ≥ 1 (EPAR Keytruda).

In patients progressing following first-line therapy, different cytostatic agents, including vinorelbine, topotecan, gemcitabine or nanoparticle albumin-bound paclitaxel have been evaluated. However, response rates were low and duration of responses was short. Therefore, no ESMO recommendation is given about the most effective second-line treatment (ESMO Guideline). No systemic therapy has been associated with improvement in OS. Patients who progress following 1L chemotherapy and those who are not candidates for combination therapy, might be candidates for single-agent therapy. A choice among active agents must be tailored to the individual patient, with consideration to prior therapies received, residual toxicity, and performance status.

The following response rates have been reported in the literature with single agents:

- Carboplatin - ORR 15% (Weiss, 1990).
- Paclitaxel (175 mg/m^2 IV every three weeks with dose reduction to 135 mg/m^2 if patients received prior RT), ORR 20 to 25% (McGuire, 1996; Curtin, 2001; Kudelka, 1997).
- Topotecan (1.5 mg/m^2 IV daily for five days every 21 days) - ORR 19% (Thigpen, 2003; Bookman, 2000; Muderspach 2001; Abu-Rustum 2000).
- Nanoparticle, albumin-bound paclitaxel (125 mg/m^2 on days 1, 8, and 15 every 28 days) – ORR 29%t (Alberts 2012).
- Vinorelbine (30 mg/m^2 intravenous [IV] push weekly for two weeks every 21 days) – ORR 15% (Morris, 1998; Lacava, 1997; Muggia 2004).
- Pemetrexed (900 mg/m^2 IV every three weeks) – ORR 15% (Miller, 2008; Lorusso 2010).
- Ifosfamide (1.2 g/m^2 IV daily for five days every 28 days) – ORR 22 percent (Thigpen, 2003; Sutton 1996).
- Irinotecan (350 mg/m^2 IV every three weeks, or 125 mg/m^2 weekly for four weeks followed by a two-week washout period) – ORR 15 percent (Look, 1998; Lhommé, 1999).
- Tisotumab vedotin (2 mg/kg intravenously every three weeks) was studied in a single-arm trial of 101 patients with recurrent or metastatic cervical cancer who had received no more than two prior systemic regimens in the recurrent or metastatic setting, including at least one prior platinum-based chemotherapy regimen. ORR to tisotumab was 24% (Coleman, 2021).
- Pembrolizumab (200 mg IV every three weeks) was evaluated in a single-arm trial KEYNOTE-158 including 82 patients from a cohort of patients with advanced, pretreated cervical cancer and PD-L1 expression of 1 percent or more. Pembrolizumab showed ORR of 15% (Chung, 2019; FDA Label for Keytruda). Similar findings were observed in the KEYNOTE-028 trial, in which the ORR was 17% percent and duration of response was 5.4 months (Frenel, 2017).

Tisotumab vedotin and pembrolizumab are not currently approved in EU in the post-chemotherapy setting of cervical cancer.

2.1.2. About the product

Cemiplimab is a monoclonal antibody that binds to programmed cell death 1 (PD-1) and blocks its interaction with programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2). In Europe, cemiplimab is currently approved for the treatment of advanced cutaneous squamous cell carcinoma (CSCC), basal cell carcinoma (BCC) and first line treatment of non-small cell lung cancer (NSCLC) with PD-L1 ≥ 50% and no genetic drivers.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Development program for cemiplimab in cervical cancer:

In the first-in-human (FIH) study with cemiplimab, R2810-ONC-1423, durable anti-tumour responses were observed among patients with advanced cervical cancer. Among the 23 patients combined from the dose escalation and expansion cohorts, ORR was 17% (4/23) by investigator assessment. Durations of the 4 responses were >1 year in 2 patients, and 11.2 months, and 6.4 months, respectively in the other 2 patients. The FIH experience with cemiplimab suggested that PD-1 blockade produces a modest response rate in ≥2L cervical cancer, and that these responses are often durable. Although the ORR of cemiplimab in this setting may be similar to that of chemotherapy, the potential for durable responses with cemiplimab was hypothesized to translate into an OS benefit (versus chemotherapy) in a phase 3 randomized trial. Study R2810-ONC-1676 was designed to test this hypothesis.

The MAH received Scientific advice from the CHMP on 21 April 2017 (EMEA/H/SA/3225/4/2017/II). The overall recommendations from the CHMP were followed along design and conduct of the pivotal trial.

2.1.4. General comments on compliance with GCP

The MAH declared that the clinical studies presented in this application were 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 guidelines for Good Clinical Practice and applicable regulatory requirements. Consultations with health authorities in the US and EU have been conducted regarding the clinical development program and study design. Furthermore, it was stated that no inspections have occurred for trial R2810-ONC-1676 and none are currently planned.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

A claim of exclusion from preparation of environmental risk assessment studies was made according to Section 2 of the 2006 CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (ERA Guideline EMEA/CHMP/SWP/4447/00 corr 2) 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 Applicant concluded that, the claim for ERA exemption was justified and in conformity with the ERA guideline since the marketing authorisation request concerned a monoclonal antibody consisting of naturally occurring amino acids. Cemiplimab is significantly metabolized *in vivo* and is expected to be readily and rapidly degraded in wastewater treatment systems and in the environment. The antibody's structure and mode of action do not indicate any specific risk to the environment.

2.2.2. Discussion on non-clinical aspects

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

2.2.3. Conclusion on the non-clinical aspects

Considering its nature, cemiplimab is not expected to pose a risk to the environment.

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.

Table 1: Tabular overview of clinical studies

Study (NCT and EudraCT Numbers) Study Status	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-1676 (NCT 03257267; EudraCT 2017-000350-19) Study ongoing	Adult patients with recurrent or metastatic cervical cancer	Phase 3 Open-label, randomized, multicenter study	350 mg cemiplimab administered IV over 30 min Q3W Planned treatment duration is up to 96 weeks.	Efficacy data from R/M cervical cancer patients in the FAS (n = 608 patients [477 SCC histology and 131 AC histology]; 304 cemiplimab [239 SCC and 65 AC] and 304 chemotherapy [238 SCC and 66 AC]) Safety data from all patients in the SAF (n = 590 patients [465 SCC and 125 AC]; 300 cemiplimab [234 SCC and 66 AC] and 290 chemotherapy [231 SCC and 59 AC]) PK data from all cemiplimab-treated patients in the PKA set (n = 295 patients [231 SCC and 64 AC]) ADA data from all cemiplimab-treated patients in the ADA analysis set (n = 206 patients [164 SCC and 42 AC histology]) Data cutoff for all data: 04 Jan 2021	Planned study period was up to 96 weeks. Median duration of follow-up was 18.2 months (range:6.0 to 38.2) in the FAS
R2810-ONC-1423 (NCT 02383212; EudraCT 2015-002132-41) Study complete	Adult patients (N = 398) with advanced solid tumor malignancies 20 patients with R/M CC enrolled in Expansion Cohorts 23 and 24	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 20 with R/M CC in Expansion Cohorts 23 and 24 combined]) ADA data from the ADA analysis set (n = 337 patients [including 14 with R/M CC in Expansion Cohorts 23 and 24 combined]) 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.

Study (NCT and EudraCT Numbers) Study Status	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-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.
R2810-ONC-1620 (NCT 02760498; EudraCT 2016-003122-16) 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 = 138 patients) PK data from the PKA set (n = 132 patients) ADA data from the ADA analysis set (n = 125 patients) Data cutoff safety: 30 Jun 2020 Data cutoff for PK/ADA: 17 Feb 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

Study (NCT and EudraCT Numbers) Study Status	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 Data cutoff for PK/ADA: 28 Feb 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: AC, adenocarcinoma; ADA, anti-drug antibody; BCC, basal cell carcinoma; chemo, chemotherapy; CC= cervical cancer, CSCC, cutaneous squamous cell carcinoma; EudraCT, European Clinical Trials Database; FAS, full analysis set; GM-CSF, granulocyte-macrophage colony stimulating factor; ITT, intent-to-treat; IV, intravenous(ly); laBCC, locally advanced basal cell carcinoma; laCSCC, locally advanced mCSCC; mBCC, metastatic basal cell carcinoma; mCSCC, 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; R/M, recurrent or metastatic; SAF, safety analysis set; SCC, squamous cell carcinoma.
Source: Module 2.7.2 Table 1; Module 5.3.5.1 R2810-ONC-1676 Primary Analysis CSR; Module 5.3.5.2 R2810-ONC-1620 Interim CSR; Module 5.3.5.2 R2810-ONC-1423 Final CSR; Module 5.3.5.2 R2810-ONC-1540 Primary Analysis for Groups 2 and 3 CSR; Module 5.3.5.1 R2810-ONC-1624 Primary Analysis CSR

2.3.2. Pharmacokinetics

The proposed dose of cemiplimab is 350 mg Q3W administered as an IV infusion over 30 minutes until disease progression or unacceptable toxicity. This cemiplimab dosing regimen is currently approved for the treatment of advanced CSCC, BCC and first line treatment of NSCLC.

The clinical pharmacology package included data from pharmacokinetics (PK), pharmacodynamics, exposure-response (E-R) for efficacy and safety, and immunogenicity assessment of cemiplimab in the target population. The MAH also submitted PK data assessing consistency across studies in the R/M cervical cancer and by histology (SCC vs AC), as well as PK data in other patient populations (tumour-types) that have been previously reported.

Within the population of patients with R/M cervical cancer, the PK of cemiplimab was assessed across studies (Study 1423 and Study 1676), as well as between patients.

Table 1 provides a summary of the clinical studies that were conducted in patients with R/M cervical cancer.

Study 1676

Study 1676 is an open-label, randomized, multicenter, phase 3 study to compare the OS in patients with R/M cervical cancer that had progressed after platinum-containing chemotherapy, treated with either cemiplimab (REGN2810) as monotherapy at 350 mg Q3W IV or with investigator's choice (IC) chemotherapy. R/M cervical cancer patients with SCC and AC histology were enrolled in this study. All patients underwent screening procedures to determine eligibility within 28 days prior to initial administration of cemiplimab or chemotherapy. After the screening period, patients received up to 96 weeks of treatment, consisting of 16 cycles of 6 weeks each. This study has completed enrollment and is ongoing at the time of this application. The percent change from baseline in tumour target lesions was assessed as a pharmacodynamic marker of efficacy.

Blood samples for assessment of cemiplimab concentrations and detection of immunogenicity in serum were collected at various pre-specified times over the treatment period according to the study schedule. Blood samples for drug concentrations assessment were collected using a sparse sampling schedule: pre-dose and post-dose on day 1 of cycle 1, then pre-dose and post-dose on day 1 of cycles 2 through cycle 6, and cycles 7, 9, 11, 13, and 15. Blood samples were also collected at follow-up visit 1 (approximately 30 days after the last dose of cemiplimab) collection of a blood sample at follow-up visit 2 (approximately 4 months after the last dose of cemiplimab) was optional.

The numbers of patients with R/M cervical cancer in the Study 1676 primary analysis sets are presented in Table 2.

Table 2: Patients with R/M cervical cancer in the primary analysis sets (study 1676)

Analysis Set	SCC 350 mg Q3W N (%)	AC 350 mg Q3W N (%)	Total N (%)
Safety	234 (100%)	66 (100%)	300 (100%)
PK	231 (98.7%)	64 (97.0%)	295 (98.3%)
ADA	164 (70.1%)	42 (63.6%)	206 (68.7%)

N=Number of patients; AC=Adenocarcinoma/adenosquamous carcinoma; ADA=Anti-drug antibody; PK=Pharmacokinetic; Q3W=Every 3 weeks; SCC=Squamous cell carcinoma
Note: Percentages are based on the total in the safety analysis set.
Note: Data cutoff 04 Jan 2021.
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR Appendix 16.1.15 (CP Report) Table 1.

Pharmacokinetic results

Observed cemiplimab PK parameters in patients with R/M cervical cancer in the cemiplimab group in **Study 1676** are summarized in Table 3. Steady state was reached by week 12 in the overall population of patients with R/M cervical cancer upon repeated cemiplimab 350 mg Q3W IV dosing and maintained throughout the period. As such, week 18 was selected as the representative time point to report steady-state concentrations. Cemiplimab exposure (C_{trough} and C_{max}, mean [SD]) at steady state in the overall population of patients with R/M cervical cancer ranged between a C_{trough} of 65.6 (30.0) mg/L and a C_{max} of 186 (60.8) mg/L. Cemiplimab PK parameters were similar in the subpopulations of patients with histology types SCC and AC.

Table 3: Observed cemiplimab exposure (Ctrough and Cmax) after the first dose and at steady state in patients with R/M cervical cancer at 350 mg Q3W monotherapy (study 1676)

		After the First Dose				At Steady State			
		C_{trough} (mg/L)		C_{max} (mg/L)		C_{trough} (mg/L)		C_{max} (mg/L)	
Histology Type	N	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
All	295	NR	NR (NR)	284	134 (58.7)	113	65.6 (30.0)	112	186 (60.8)
SCC	231	NR	NR (NR)	224	135 (61.3)	91	64.8 (31.0)	90	181 (59.0)
AC	64	NR	NR (NR)	60	128 (47.8)	22	68.9 (25.8)	22	204 (65.7)

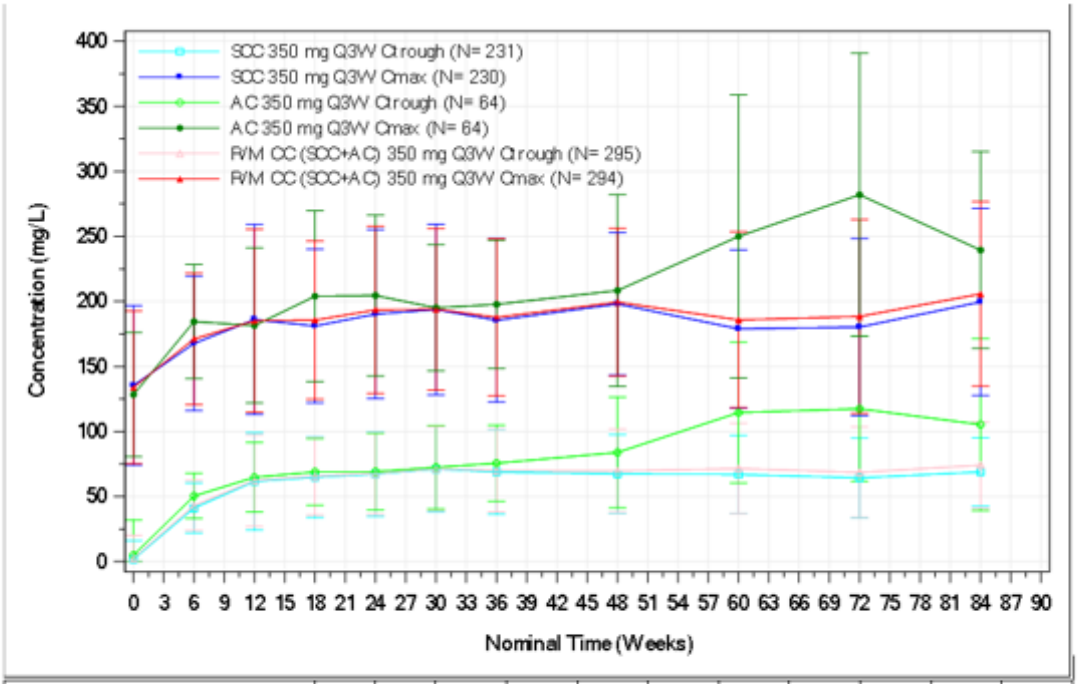
N=Number of patients in PK analysis set; n=Number of patients for descriptive statistics; AC=Adenocarcinoma/adenosquamous carcinoma; C_{max}=Peak concentration; C_{trough}=Trough concentration; LLOQ=Lower limit of quantitation; PK=Pharmacokinetic; Q=Quartile; Q3W=Every 3 weeks; SCC=Squamous cell carcinoma; SD=Standard deviation; NR=Not reported (no PK sample collection at Cycle 1 Day 22).

Week 18 was selected as the representative time point to report steady-state concentrations.

Note: Descriptive statistics included all available PK data in the 295 patients on cemiplimab 350 mg Q3W; although 3 patients who received two doses of cemiplimab showed end-of-infusion concentrations after the first dose that were BLQ, one of them with possible inversion of PK samples between pre-dose (174 mg/L) and end-of-infusion (BLQ). Overall reliable PK data were therefore available from a total of 292 patients in Study 1676. Concentrations below the LLOQ were set to 0. After first dose: C_{max} at Cycle 1 Day 1 end of infusion. At steady state: C_{trough} at Cycle 4 Day 1 pre-infusion; C_{max} at Cycle 4 Day 1 end of infusion.

Data Cutoff: 04 Jan 2021.

Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR Appendix 16.1.15 (CP Report) Table 4.



Treatment Group	WK0	WK6	WK12	WK18	WK24	WK30	WK36	WK48	WK60	WK72	WK84
SCC 350 mg Q3W Ctrough	227	169	116	91	72	60	51	38	28	23	12
SCC 350 mg Q3W Cmax	224	160	115	90	69	59	50	38	28	23	11
AC 350 mg Q3W Ctrough	61	42	31	22	20	17	10	6	3	2	2
AC 350 mg Q3W Cmax	60	41	31	22	20	16	11	6	3	2	2
R/M CC (SCC+AC) 350 mg Q3W Ctrough	288	211	147	113	92	77	61	44	31	25	14
R/M CC (SCC+AC) 350 mg Q3W Cmax	284	201	146	112	89	75	61	44	31	25	13

N=Number of patients; AC=Adenocarcinoma/adenosquamous carcinoma; LLOQ=Lower limit of quantitation; Q3W=Every 3 weeks; SCC=Squamous cell carcinoma; R/M CC=recurrent or metastatic cervical cancer; WK=Week
Data Cutoff: 04 Jan 2021.
Note: Concentrations below the LLOQ were set to 0. Numbers in the table indicate the number of patients at each visit. C_{trough} indicates pre-infusion concentration at each visit; C_{max} indicates end of infusion concentration at each visit. At nominal time 0, pre-dose value is shown instead of C_{trough}. For a graphical representation of these data using a logarithmic scale (log_{10}) for concentration see Figure 15.
Data source: Module 5.3.5.1 Study 1676 Primary Analysis CSR Appendix 16.1.15 (CP Report).

Figure 1: Observed Mean (±SD) Cemiplimab Ctrough and Cmax Over Time and by Histology Type in Patients with R/M Cervical Cancer (Study 1676)

First-in-Human Study 1423 in Patients with Various Tumour Types

The **FIH Study 1423** evaluated a range of cemiplimab doses (dose escalation phase: 1 to 10 mg/kg Q2W IV), included dense sampling for measurement of PK parameters after the first dose, and enrolled patients with multiple solid tumour types (including CSCC, BCC, NSCLC, and R/M cervical cancer), allowing for comparison of PK parameters across tumour types. This study also included comparison of PK parameters for cemiplimab administered as monotherapy or combination therapy (cemiplimab plus radiotherapy and/or chemotherapy).

Study Design

Study 1423 was a FIH, open-label study in patients with advanced solid tumours to evaluate repeat IV dosing with cemiplimab, as monotherapy and as combination therapy (with radiotherapy and/or chemotherapy). The study consisted of both 1a dose escalation phase and a dose expansion phase. Patients were eligible to receive up to 48 weeks of treatment, after which there was a 24-week follow-up period. The 48 weeks of treatment consisted of up to 6 cycles of 8 weeks each. In the dose escalation phase, 60 patients were each assigned to 1 of 3 dose escalation cohorts (1 mg/kg, 3 mg/kg, or 10 mg/kg Q2W administered IV as monotherapy or in combination with other anti-cancer treatments (radiotherapy and/or chemotherapy). During dose escalation, safety was assessed, and no maximum tolerated dose was identified. The expansion phase, which included 24 cohorts, assessed the PK, immunogenicity, safety, and efficacy of cemiplimab in different tumour types after dosing as monotherapy or in combination with other anti-cancer treatments (radiotherapy or chemotherapy).

The descriptive PK of cemiplimab in serum using dense sampling after the first dose was evaluated by Non compartmental analysis (NCA) and during the treatment and follow-up periods.

Pharmacokinetic Results

A total of 23 patients with R/M cervical cancer were enrolled in Study 1423: 3 patients in dose escalation cohorts where tumour type was not specified in the data base and these patients were therefore reported as 'all solid tumours': 2 patients at 1 mg/kg Q2W and 1 patient at 3 mg/kg Q2W (Papadopoulos, 2020), and 20 patients in the expansion cohorts EXP23 and EXP24 that were identified with R/M cervical cancer in the database: 10 patients in expansion cohort 23 (EXP23) who received cemiplimab 3 mg/kg Q2W as monotherapy, and 10 patients in expansion cohort 24 (EXP24), who received cemiplimab 3 mg/kg Q2W with radiotherapy (XRT 9 Gy x 3). The ORR was 10% in EXP23 and 10% in EXP24.

Overall, the PK of cemiplimab was linear and dose-proportional over a dosing range of 1 to 10 mg/kg Q2W IV in Study 1423.

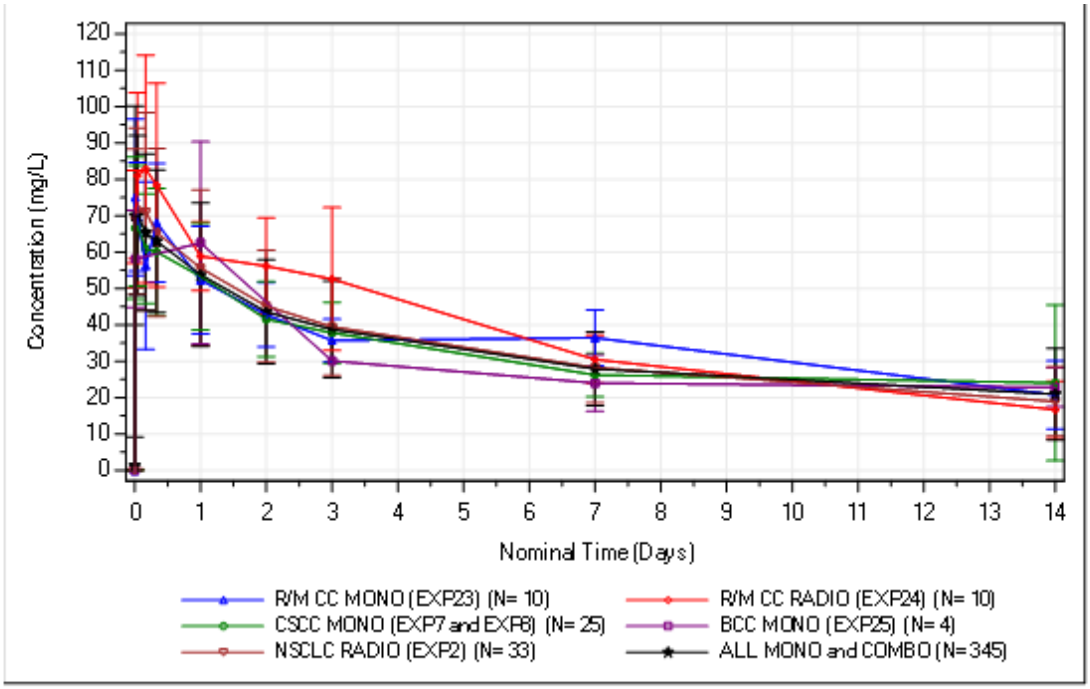
Table 4: Observed Pharmacokinetic Parameters of Cemiplimab in Patients with R/M Cervical Cancer and All Patients Who Received Cemiplimab 3 mg/kg Q2W as Monotherapy or Combination Therapy (Study 1423)

Patients at 3 mg/kg Q2W	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)
R/M CC (EXP23, MONO)	After First Dose	10	20.7 (9.34)	75.1 (21.5)	516 (155)	9.47 (1.82)
	At Steady State	10	61.3 (10.6)	135 (19.4)	NR	NR
R/M CC (EXP24, RADIO)	After First Dose	10	16.7 (7.88)	69.7 (12.8)	446 (187)	8.24 (2.54)
	At Steady State	10	44.3 (10.4)	105 (21.5)	NR	NR
All R/M CC (EXP23+EXP24)	After First Dose	20	18.8 (8.69)	72.4 (17.5)	481 (171)	8.85 (2.15)
	At Steady State	20	52.8 (13.2)	120 (24.8)	NR	NR
All Patients MONO+COMBO	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; C_{max}=concentration at end of infusion; C_{trough}=trough concentration at the end of the dosing interval; 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; R/M CC=recurrent or metastatic cervical cancer; MONO=monotherapy; RADIO=in combination with radiotherapy; COMBO =in combination with radiotherapy and/or chemotherapy; all patients=all patients with solid tumors in Study 1423 at 3 mg/kg Q2W (MONO and COMBO).
Note: Patients with cervical cancer in Study 1423 were in Expansion Cohorts (EXP): EXP23 (MONO) and EXP24 (RADIO).
Data source: Module 5.3.5.2 Study 1423 Final CSR Appendix 5 (CP Report)

COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

This current submission presents the observed and population-predicted cemiplimab concentrations in serum in patients with R/M cervical cancer in the FIH Study 1423 at 3 mg/kg Q2W IV as monotherapy (EXP23, N=10) and in combination with radiotherapy (EXP24, N=10), and in the pivotal Study 1676 at 350 mg Q3W IV as monotherapy (N=295).



N=Number of patients.
R/M CC=recurrent/metastatic cervical cancer; CSCC=cutaneous squamous cell carcinoma (advanced CSCC); BCC=basal cell carcinoma (advanced BCC); NSCLC=non-small cell lung cancer (advanced NSCLC).
ALL=all solid tumors, MONO=Monotherapy; RADIO=in combination with radiotherapy ; COMBO=in combination with radiotherapy and/or chemotherapy
Concentrations below the LLOQ were set to 0.
SD=standard deviation; Q2W=every 2 weeks;
Data source: Module 5.3.5.2 Study 1423 Final CSR Appendix 5 (CP Report)

Figure 2: Observed Mean (±SD) Cemiplimab Concentration-Time Profiles After the First Dose in Patients with R/M Cervical Cancer Compared to Those with Other Solid Tumor Types Receiving Cemiplimab 3 mg/kg Q2W as Monotherapy or in Combination Therapy (FIH Study 1423)

Similarity in the observed cemiplimab exposure (C_{trough} and C_{max}) at 3 mg/kg Q2W after the first dose and at steady state across patients with different tumour types in Study 1423 is presented in Table 5.

Table 5: Observed Cemiplimab Exposure (Ctrough and Cmax) after the First Dose and at Steady State in Patients with R/M Cervical Cancer compared to Patients with Other Solid Tumour Types Receiving Cemiplimab 3 mg/kg Q2W as Monotherapy or in Combination Therapy (Study 1423)

				After the First Dose		At Steady State	
				Ctrough (mg/L)	Cmax (mg/L)	Ctrough (mg/L)	Cmax (mg/L)
Cancer Type	Cohort	Therapy	N	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
R/M CC	EXP23	MONO	10	20.7 (9.34)	75.1 (21.5)	61.3 (10.6)	135 (19.4)
	EXP24	RADIO	10	16.7 (7.88)	69.7 (12.8)	44.3 (10.4)	105 (21.5)
CSCC	EXP7, EXP8	MONO	25	24.1 (21.4)	66.6 (19.6)	63.2 (24.1)	124 (27.8)
BCC	EXP25	MONO	4	22.8 (5.35)	58.1 (13.4)	50.9 (17.4)	106 (55.3)
NSCLC	EXP2	RADIO	33	18.9 (9.53)	69.3 (19.1)	50.7 (21.4)	133 (46.1)
ALL	DE and EXP	MONO	98	20.9 (12.4)	71.3 (42.1)	59.3 (21.8)	122 (35.1)
		RADIO	189	21.5 (13.6)	69.8 (24.4)	61.0 (26.4)	136 (42.0)
ALL	DE and EXP	MONO and COMBO	333	21.0 (12.6)	70.0 (30.3)	60.5 (25.3)	129 (40.1)

All=all solid tumors. DE= dose escalation cohort; EXP=expansion cohort; BCC=basal cell carcinoma; CSCC=cutaneous squamous cell carcinoma; MONO=cemiplimab monotherapy; NSCLC=non-small cell lung cancer; N=number of patients in each analysis set; Q2W=every 2 weeks; Q3W=every 3 weeks; RADIO=cemiplimab + radiotherapy; R/M CC=recurrent or metastatic cervical cancer; SD=standard deviation; N=Number of patients in each Analysis Set. SD=Standard Deviation; mCSCC=metastatic CSCC; laCSCC=locally Q2W=every 2 weeks; Q3W=every 3 weeks;
Steady state is defined at cycle 3 day 1, 4-week cycles.
MONO=monotherapy; RADIO=in combination with radiotherapy; COMBO=in combination with radiotherapy and/or chemotherapy
Data source: Module 5.3.5.2 Study 1423 Final CSR Appendix 5 (CP Report)

As previously demonstrated to support switch of dosing regimens from 3 mg/kg Q2W to 350 mg Q3W, the observed cemiplimab concentrations (C_{trough} and C_{max}) at steady state were similar in patients receiving 350 mg Q3W compared to patients receiving 3 mg/kg Q2W IV as presented in

Table 6 for individual studies and combined data for each dose level across studies.

Observed cemiplimab exposure (C_{trough} and C_{max}) during therapy at 350 mg Q3W was also compared between patients with R/M cervical cancer in Study 1676 and patients with advanced CSCC, BCC, and NSCLC in the respective pivotal studies. Cemiplimab exposure was compared across tumor types over time (Figure 4) and at steady state (

Figure 3); numerical results are summarized in

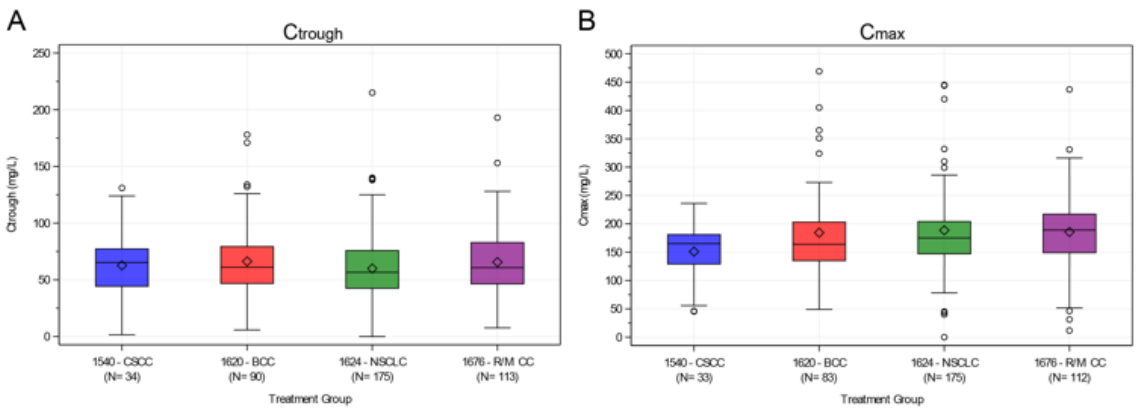
Table 6.

Based on the popPK model, at 350 mg Q3W, the mean cemiplimab concentrations at steady-state ranged between a Ctrough of 59 mg/l and a concentration at end of infusion (Cmax) of 171 mg/l. Steady state exposure is achieved after approximately 4 months of treatment.

Table 6: Observed Mean Cemiplimab Exposure After the First Dose and at Steady State (Ctrough and Cmax) in Patients with R/M CC (Study 1676) Compared to those with Advanced CSCC, Advanced BCC, Advanced NSCLC, and All Patients Receiving Cemiplimab 350 mg Q3W and All Patients Receiving Cemiplimab 3 mg/kg Q2W

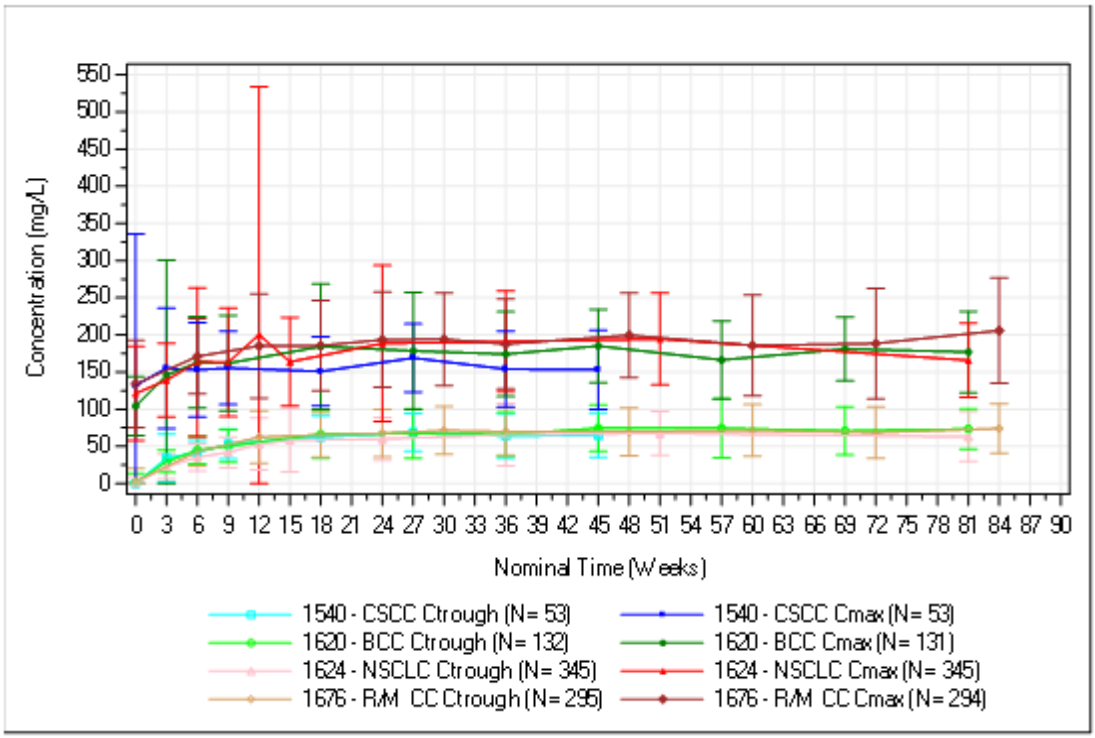
				After the First Dose				At Steady State			
				C_{trough} (mg/L)		C_{max} (mg/L)		C_{trough} (mg/L)		C_{max} (mg/L)	
Cancer Type - Histology	Study	Group - Dose	N	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
All R/M CC		Group 1+2: 350 mg Q3W	295	NR	NR (NR)	284	134 (58.7)	113	65.6 (30.0)	112	186 (60.8)
R/M CC- SCC	1676	Group 1: 350 mg Q3W	231	NR	NR (NR)	224	135 (61.3)	91	64.8 (31.0)	90	181 (59.0)
R/M CC - AC		Group 2: 350 mg Q3W	64	NR	NR (NR)	60	128 (47.8)	22	68.9 (25.8)	22	204 (65.7)
	1540	Group 3: 350 mg Q3W	53	47	34.2 (32.0)	52	132 (203)	34	62.7 (28.3)	33	151 (46.2)
CSCC	1540	Group 1+2: 3 mg/kg Q2W	135	123	24.3 (12.0)	131	88.1 (96.2)	96	68.4 (26.1)	96	150 (79.0)
	1423 and 1540	3 mg/kg Q2W	161	150	24.2 (13.9)	158	90.6 (115)	112	68.1 (25.9)	112	147 (74.7)
BCC	1620	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)
NSCLC	1624	PKAS - 350 mg Q3W	345	320	22.8 (16.8)	336	121 (63.3)	175	60.0 (28.7)	175	189 (105)
Solid Tumors	1423 and 1540	3 mg/kg Q2W	468	438	21.9 (12.5)	463	77.2 (72.2)	232	63.8 (25.9)	227	138 (60.5)
CSCC, BCC, NSCLC, R/M CC	1540, 1620, 1624, and 1676	350 mg Q3W	825	486	25.7 (18.8)	795	124 (77.0)	412	63.1 (29.8)	403	184 (86.7)

N=Number of patients in PK Analysis Set. n=Number of patients for descriptive statistics.
R/M CC=recurrent/metastatic cervical cancer; SCC=squamous cell carcinoma; AC=adenocarcinoma/adenosquamous carcinoma; CSCC=cutaneous squamous cell carcinoma; BCC=basal cell carcinoma; NSCLC=non-small cell lung cancer.
SD: Standard Deviation; Q=Quartile. Concentrations below the LLOQ were set to 0.
After the First Dose: C_{trough} is Pre-Infusion at Cycle 1 Day 15 (3 mg/kg Q2W; Study 1423 and 1540), Cycle 1 Day 22 (350 mg Q3W; Study 1423 and 1540), and Cycle 2 Day 1 (350 mg Q3W; Study 1624); C_{max} is End-of-Infusion at Cycle 1 Day 1.
At Steady State: C_{trough} is Pre-Infusion; C_{max} is End-of-Infusion at Cycle 3 Day 1 (Study 1423, 1540, and 1620), at Cycle 9 Day 1 (Study 1624), and at Cycle 4 Day 1 (Study 1676).
Data source: Module 5.3.5.2 Study 1423 Final CSR Appendix 5 (CP Report), Module 5.3.5.2 Study 1540 Interim CSR Appendix 5 (CP Report), Module 5.3.5.2 Study 1620 Interim CSR Appendix 5 (CP Report), Module 5.3.5.1 Study 1624 Primary Analysis CSR Appendix 16.1.15 (CP Report), Module 5.3.5.1 Study 1676 Primary Analysis CSR Appendix 16.1.15 (CP Report)



N=Number of patients for descriptive statistics.
At Steady State: (A) C_{trough} is at Pre-Infusion at Cycle 3 Day 1 (Study 1540 and 1620) and at Cycle 9 Day 1 (Study 1624) and at Cycle 4 Day 1 (Study 1676); (B)C_{max} is at End-of-Infusion at Cycle 3 Day 1 (Study 1540 and 1620) and at Cycle 9 Day 1 (Study 1624) and at Cycle 4 Day 1 (Study 1676).
R/M CC=recurrent/metastatic cervical cancer; CSCC=cutaneous squamous cell carcinoma; BCC=basal cell carcinoma; NSCLC=non-small cell lung cancer.
Concentrations below the LLOQ were set to 0.
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: Module 5.3.5.2 Study 1540 Interim CSR Appendix 5 (CP Report), Module 5.3.5.2 Study 1620 Interim CSR Appendix 5 (CP Report), Module 5.3.5.1 Study 1624 Primary Analysis CSR Appendix 16.1.15 (CP Report), Module 5.3.5.1 Study 1676 Primary Analysis CSR Appendix 16.1.15 (CP Report)

Figure 3: Box Plot of Observed Cemiplimab Exposure at Steady State (Ctrough and Cmax) in Patients who Received Cemiplimab 350 mg Q3W as Monotherapy in the Pivotal Studies (Studies 1540, 1620, 1624, and 1676)



N=Number of patients in the PK Analysis Set; SD=standard deviation; R/M CC=recurrent/metastatic cervical cancer (SCC+AC histology); CSCC=cutaneous squamous cell carcinoma; BCC=basal cell carcinoma; NSCLC=non-small cell lung cancer. For Study 1676 only, pre-dose value is shown instead of C_{trough} at nominal time 0. Concentrations below the LLOQ were set to 0. For a graphical representation of these data using a logarithmic scale (log_{10}) for concentration see Figure 16.
Data source: Module 5.3.5.2 Study 1540 Interim CSR Appendix 5 (CP Report), Module 5.3.5.2 Study 1620 Interim CSR Appendix 5 (CP Report), Module 5.3.5.1 Study 1624 Primary Analysis CSR Appendix 16.1.15 (CP Report), Module 5.3.5.1 Study 1676 Primary Analysis CSR Appendix 16.1.15 (CP Report)

Figure 4: Observed Mean (±SD) Cemiplimab Ctrough and Cmax Concentrations Over Time in Patients Who Received Cemiplimab 350 mg Q3W Monotherapy in the Pivotal Studies (Studies 1540, 1620, 1624, and 1676)

Population PK analyses

The primary objectives of the population PK analysis were to:

1. Update the existing population PK model for cemiplimab in patients with advanced cutaneous squamous cell carcinoma (CSCC), basal cell carcinoma (BCC), non-small cell lung cancer (NSCLC) or other solid tumour types from studies R2810-ONC-1423, R2810-ONC-1540, R2810-ONC-1620 and R2810-ONC-1624 (referred to as Studies 1423, 1540, 1620 and 1624).
2. Identify and quantify the effects of intrinsic and extrinsic covariates, which may explain variability in PK parameters in the updated model.
3. Perform an external validation of cemiplimab PK patients with cervical cancer (CC) from Study R2810-ONC-1676 (referred to as Study 1676) to assess consistency in cemiplimab PK across various solid tumour types.

The population PK of cemiplimab was previously described by a 2-compartment model with zero-order IV infusion and first-order elimination, which included a sigmoid E_{max} function to describe time-varying change in clearance (CL), and an additive and proportional residual error model. The previous population PK model was based on data from Studies 1423, 1540, 1620 and 1624, which consisted of 1062 patients and 17193 PK samples, whereas the updated model included a total of 1063 patients and 17312 post-dose PK samples. Data summaries of number of patients and post-dose cemiplimab concentrations can be seen across study, dose regimen and tumour type in Table 7 and Table 8.

Table 7: Summary of Populations, Studies and Samples Included in the Population PK Analysis for 1063 Patients

Study Tumor Type	Dose Regimen	Number of Patients	Number of Post-Dose PK Samples[a]
Study 1423 All Solid Tumors (N = 398)	1 mg/kg Q2W	27	899
	10 mg/kg Q2W	6	188
	200 mg Q2W	20	680
	3 mg/kg Q2W	333	7940
	3 mg/kg Q3W	12	293
Study 1540 [b] CSCC (N = 188)	3 mg/kg Q2W	135	1959
	350 mg Q3W	53	512
Study 1620 BCC (N = 132)	350 mg Q3W	132	1621
Study 1624 NSCLC (N = 345)	350 mg Q3W	345	3220
Total		1063	17312

PK = Pharmacokinetic; BCC = Basal cell carcinoma; CSCC = Cutaneous squamous-cell carcinoma; NSCLC = Non-small cell lung cancer; Q2W = Once every 2 weeks; Q3W = Once every 3 weeks

[a] Includes only quantifiable post-dose PK samples

[b] Study 1540 Groups 1-3 only

Table 8: Summary of Population by Tumor Type in the Population PK Analysis for 1063 Patients

Tumor Type	Study ID	Number of Patients	Total Patients	Number of Post-Dose PK Samples[a]	Total Post-Dose PK Samples[a]
BCC	Study 1423	4	136	86	1707
	Study 1620	132		1621	
CSCC	Study 1423	26	214	783	3254
	Study 1540	188		2471	
NSCLC	Study 1423	71	416	1980	5200
	Study 1624	345		3220	
Others	Study 1423	297	297	7151	7151
Total			1063		17312

PK = Pharmacokinetic; BCC = Basal cell carcinoma; CSCC = Cutaneous squamous-cell carcinoma; NSCLC = Non-small cell lung cancer
Note: "Others" includes non-specified in dose escalation cohorts in study 1423.

All cemiplimab post-dose PK samples were included in the master dataset but data below the lower limit of quantification (LLOQ) was omitted from the analysis (M1-method). In total, 81 samples (0.5%) of post-dose concentrations were below the LLOQ and omitted from the analysis. Observations with absolute conditional weighted residuals (CWRES) or absolute individual weighted residuals (IWRES) above 5 were classified as outliers. The dataset did not exclude observations previously identified as concentration outliers. Data excluded from the analysis dataset included (1) inversion samples, (2) duplicated PK samples, (3) missing PK observations and (4) PK observations with unknown or missing sampling information. A total of 1390 PK samples were excluded from the population PK analysis (**Table 9**).

Table 9: Summary of Data Excluded from the Population PK Analysis for 1063 Patients

Reason for Exclusion	Number of PK Samples	Number of Patients
Data Collection Issue	8	4
Inversion[a]	262	104
Post 1st dose concentration < LLOQ	78	70
Pre 1st dose concentration	1003	1003
Pre 1st dose concentration > LLOQ	39	39

PK = Pharmacokinetic; LLOQ = Lower limit of quantification
[a] Inversion is defined as predose concentration higher than the corresponding end of infusion (eoi) concentration (ie, $C_{trough} > C_{eoi}$), and both C_{trough} and C_{eoi} were excluded
Note: 3 of the 262 PK samples classified as 'Inversion' also had concentration < LLOQ; therefore, the total number of post 1st dose concentrations <LLOQ was 81 (78 + 3)

The population PK of cemiplimab were characterized by non-linear mixed-effects modelling using NONMEM (Version 7.4, ICON Development Solutions, Ellicott City, Maryland). Dataset was constructed using SAS (Version 9.4). Statistical software R (Version 4.0.2) was used for data post-processing and figures.

Base model

The population PK base model of cemiplimab was previously described by a 2-compartment model with zero-order intravenous infusion, a first-order elimination, and a sigmoid E_{max} function to describe a time-varying change in CL. However, the updated model did not include body weight on CL, volume of distribution in the central compartment (V_c) on CL or time-varying albumin on CL in the structural model, as these were evaluated in the covariate selection process. The interindividual variability (IIV) terms on E_{max} and T50 from were removed from the updated base model as data could not sufficiently support the estimation of IIV for these parameters. The off-diagonal covariance between inter-individual random effects on inter-compartmental clearance (CLQ) and volume of central compartment/volume of peripheral compartment (V1V2) was also removed. The residual error model was simplified from the previous model to include only a log-additive residual error term. In the base model, the approximate percent coefficient of variation (CV%) were 39.2% and 30.1% and ETA-shrinkage were 5.6% and 7.2% for CLQ and V1V2, respectively.

Covariate model

Potential extrinsic and intrinsic covariates that are predictive of cemiplimab PK variability were tested using a step-wise approach, which included both forward selection and backward elimination. Covariates that improved goodness-of-fit (GOF) as determined by the objective function value (OFV) were retained in the forward selection using: $p < 0.01; \chi^2_{df=1} = \Delta OFV > 6.63$ and in backward elimination: $p < 0.001; \chi^2_{df=1} = \Delta OFV > 10.83$. Furthermore, covariates were also evaluated by successful minimization and covariance step, GOF-plots, plausibility of parameter estimates and their precision, and clinical relevance and significance. Baseline IgG and baseline PDL-1 expression were analysed in a post-hoc covariate analysis. An increase in CL was predicted with increasing baseline IgG, however the exponent of IgG on CL was similar to the previous population PK model and therefore not anticipated to result in a meaningful effect on exposure. PDL-1 expression did not appear to have a meaningful effect on baseline CL or steady-state clearance.

The covariates that were retained in the final covariate model were: body weight, sex, time-varying albumin, baseline ALT, CSCC tumour type, and BCC tumour type on CL; baseline body weight, sex and baseline albumin on V1; BCC tumour type on E_{max}; and other tumour type on T50.

Final model

PK parameter estimates of the updated final model can be seen in Table 10. Parameters in the final model were estimated with percent relative standard errors (%RSE) below 8%. ETA-shrinkage increased slightly from 5.6% and 7.2% to 7.8% and 8.5% for CLQ and V1V2, respectively. IIV terms for CLQ and V1V2 and residual error were reduced as compared to the base model. Cemiplimab clearance had an inverse linear relationship with time-varying albumin level, which indicates lower clearance as albumin levels increase. Also, cemiplimab demonstrated weight-dependent clearance. As with the previous model, NSCLC patients had higher CL, which led to lower exposure than in patients with CSCC or BCC. Estimated exponents for CLQ and V1V2 with body weight were 0.539 and 0.499, respectively.

Table 10: Summary of Parameter Values after Modeling with Analysis Dataset or Bootstrap Datasets for the Updated Final Model (1063 Patients)

Parameter (Units)	Updated Final Model		Bootstrap Datasets (N = 474)[a]		
	Estimate	%RSE	Mean	Median	95% CI
TVCL0 (L/day)	0.254	1.56	0.254	0.254	(0.241, 0.269)
TVQ (L/day)	0.652	3.65	0.650	0.651	(0.581, 0.728)
TVV1 (L)	3.35	1.26	3.35	3.35	(3.27, 3.44)
TVV2 (L)	2.52	1.66	2.52	2.51	(2.29, 2.81)
TVEMAX	-0.174	4.82	-0.181	-0.180	(-0.232, -0.136)
TVT50 (day)	73.7	7.56	90.8	74.4	(46.2, 245)
HILL	2.50 [b]	-	-	-	-
CL_{WGTBL}	0.539	9.19	0.539	0.539	(0.443, 0.639)
Vss_{WGTBL}	0.499	10.0	0.499	0.501	(0.412, 0.569)
CL_{SEX}	-0.137	13.2	-0.133	-0.134	(-0.167, -0.0925)
$V1_{SEX}$	-0.0801	23.3	-0.0798	-0.0794	(-0.115, -0.0471)
$V1_{ALBBL}$	-0.217	28.4	-0.221	-0.225	(-0.361, -0.0870)
CL_{ALB}	-1.11	2.42	-1.12	-1.11	(-1.24, -0.984)
CL_{ALTBL}	-0.0729	22.2	-0.0724	-0.0720	(-0.108, -0.0370)
CL_{CSCC}	-0.216	9.55	-0.219	-0.219	(-0.257, -0.181)
CL_{BCC}	-0.211	12.2	-0.209	-0.209	(-0.261, -0.158)
$EMAX_{BCC}$	-0.872	12.6	-0.841	-0.870	(-1.00, -0.517)
$T50_{OTHER}$	-0.491	12.1	-0.537	-0.518	(-0.987, -0.169)
RE	0.241 [c]	0.15	0.241 [c]	0.240 [c]	(0.227, 0.258) [c]
ETA1 – CL_Q	0.0892	4.05	0.0886	0.0884	(0.0759, 0.101)
ETA2 – V1_V2	0.0709	2.03	0.0692	0.0674	(0.0459, 0.105)

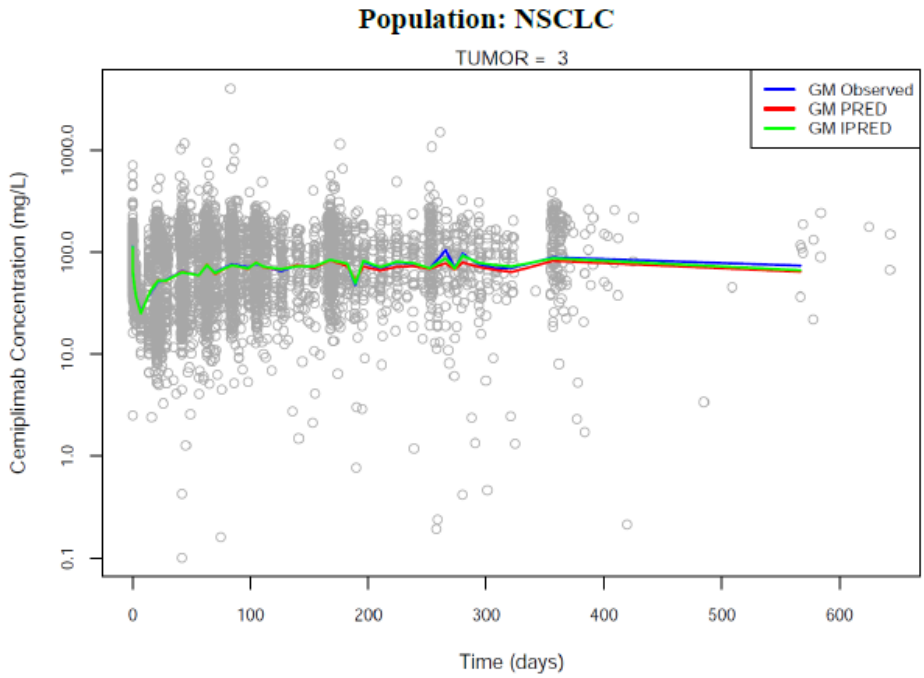
N = Number of patients; %RSE = Percent relative standard error; 95% CI = 95 percent confidence interval; TVCL0 = Typical value of clearance at baseline; TVQ = Typical value of inter-compartmental clearance; TVV1 = Typical value of central volume of distribution; TVV2 = Typical value of peripheral volume of distribution; TVEMAX = Typical value of maximum change in CL with time; TVT50 = Typical value of time to reach 50% of the maximum change in CL; HILL = Hill exponent (γ) in the sigmoid E_{max} function describing the change in CL with time; CL_{WGTBL} = Covariate impact of baseline body weight on CL_Q; Vss_{WGTBL} = Covariate impact of baseline body weight on V1_V2; CL_{SEX} = Covariate impact of female sex on CL; $V1_{SEX}$ = Covariate impact of female sex on V1; $V1_{ALBBL}$ = Covariate impact of baseline albumin on V1; CL_{ALB} = Covariate impact of time-varying albumin on CL; CL_{ALTBL} = Covariate impact of baseline alanine aminotransferase on CL; CL_{CSCC} = Covariate impact of cutaneous squamous-cell carcinoma (CSCC) tumor type on CL; CL_{BCC} = Covariate impact of basal cell carcinoma (BCC) tumor type on CL; $EMAX_{BCC}$ = Covariate impact of BCC tumor type on EMAX; $T50_{OTHER}$ = Covariate impact of OTHER tumor type on T50; RE = Residual error

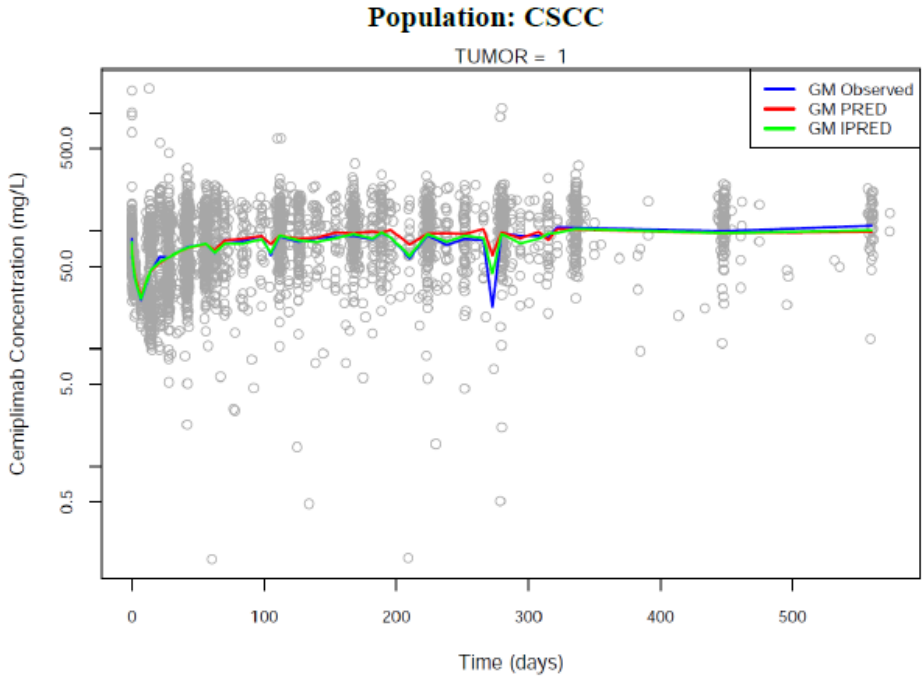
[a] Results are summarized for 474/500 runs that were successful and had condition number <1000

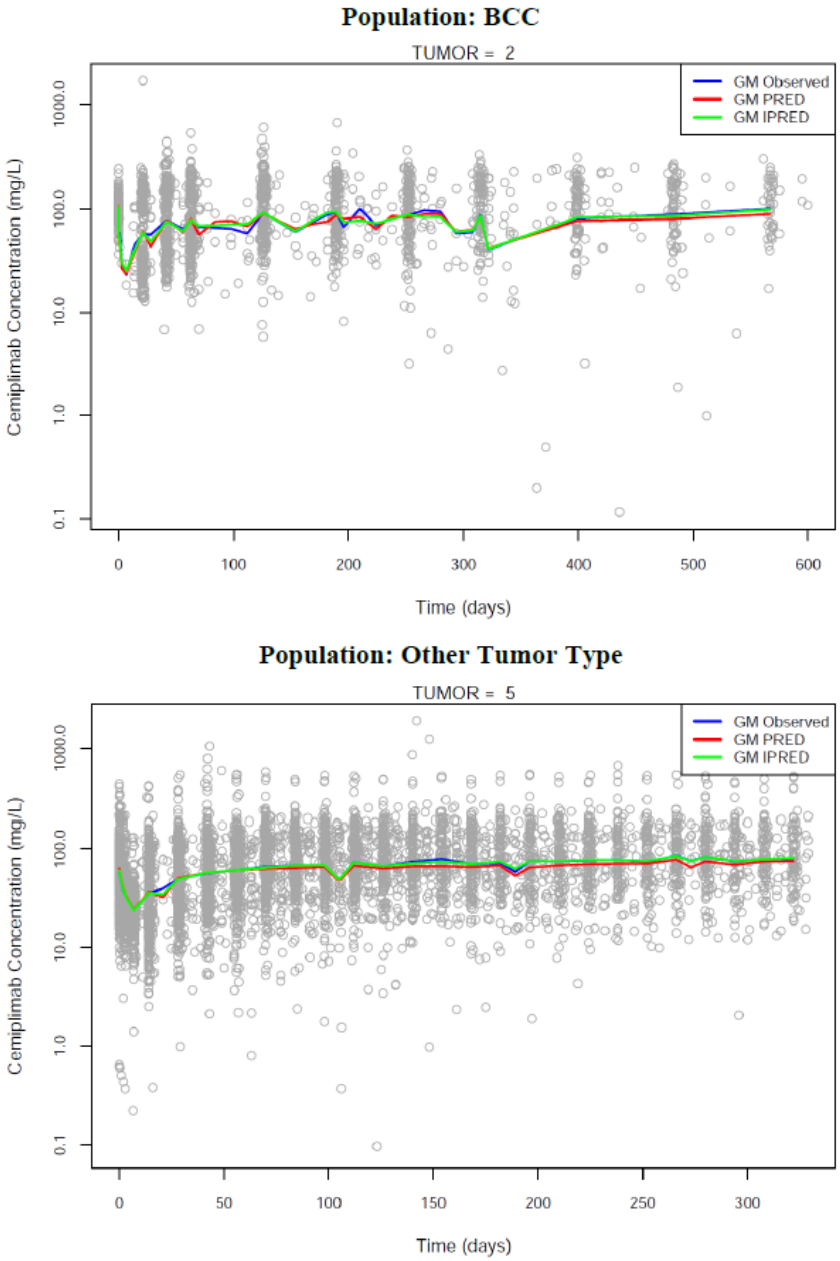
[b] The HILL parameter in the sigmoid E_{max} function for time-varying CL was fixed at 2.50

[c] Residual error is represented as a positive value by calculating the square root of (estimate)^2
Note: 2.5th and 97.5th percentiles are reported as the 95% CI
Time dependent clearance was modeled using a sigmoid E_{max} relationship: $TVCL = TVCL0 \cdot exp\left(\frac{Emax \cdot T^{\gamma}}{T50^{\gamma}+T^{\gamma}}\right)$

The final model was evaluated by means of bootstrap analysis, GOF-plots and visual predictive checks (VPCs). GOF-plots of the final model across tumour types (NSCLC, CSCC, BCC and other tumour type) can be seen in Figure 5. Model stability was evaluated using bootstrap analysis. 474/500 (94.8%) model runs converged successfully with a condition number under 1000.





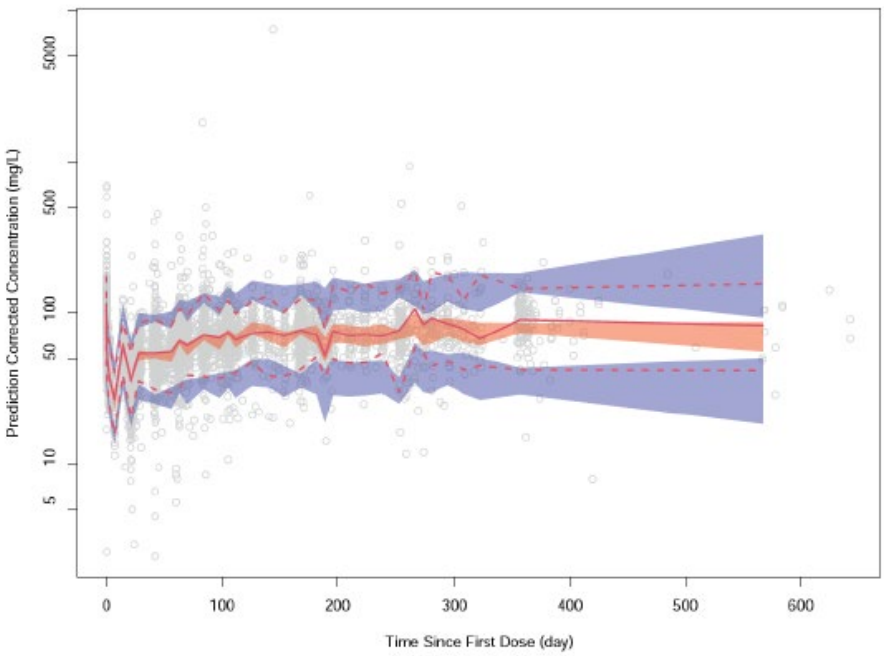


GM = Geometric mean; PRED = Typical individual prediction; IPRED = Individual model prediction; NSCLC = Non-small cell lung cancer; CSCC = Cutaneous squamous-cell carcinoma; BCC = Basal cell carcinoma

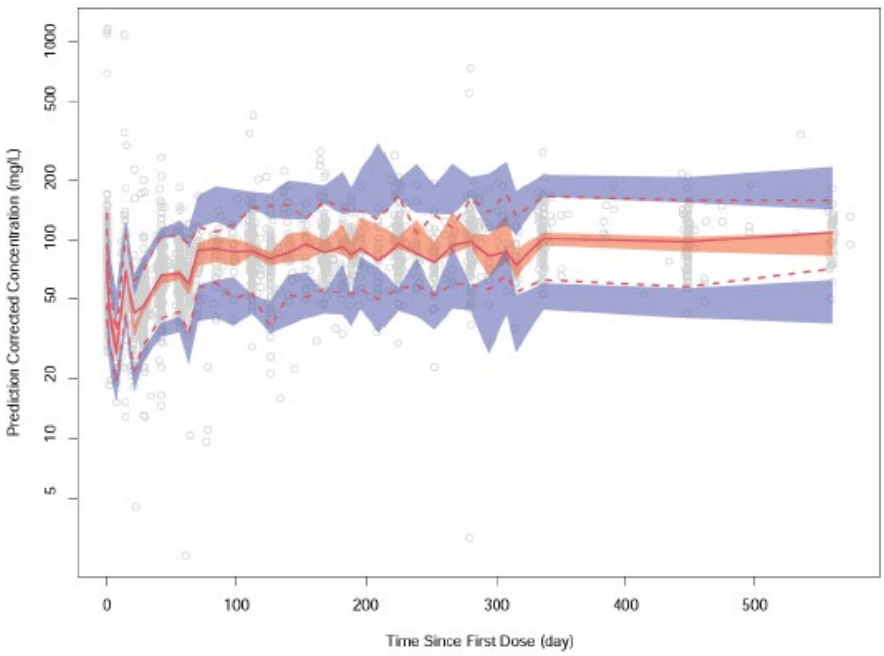
Figure 5: Final Model Goodness-of-Fit Plots (1063 Patients)

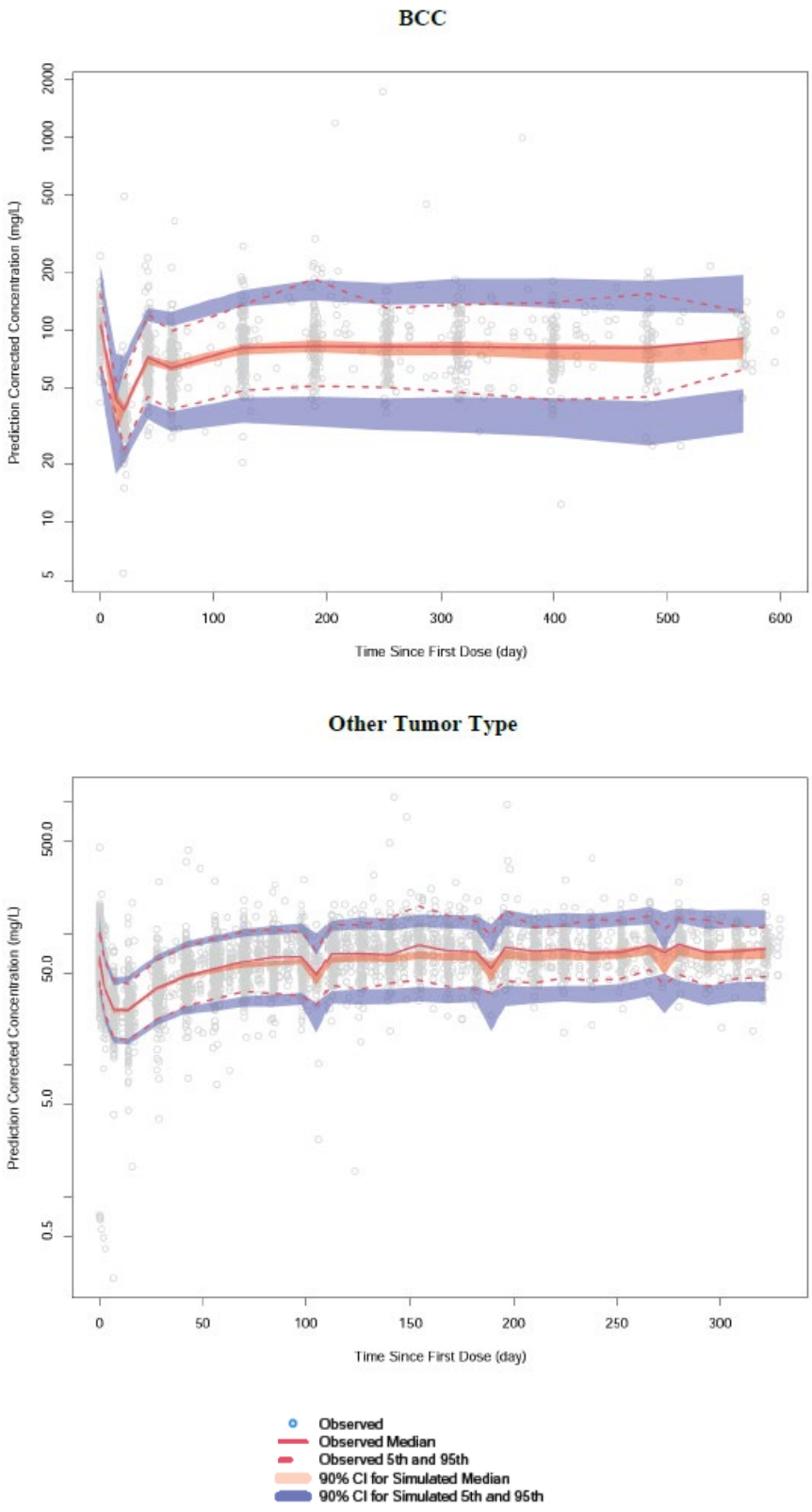
The updated final model was evaluated in each tumour type (NSCLC, CSCC, BCC and other tumour type) by prediction-corrected VPCs (pcVPCs), which can be seen in Figure 6.

NSCLC


Prediction Corrected Concentration (mg/L)
5000
500
100
50
10
5
0
100
200
300
400
500
600
Time Since First Dose (day)

CSCC


Prediction Corrected Concentration (mg/L)
1000
500
200
100
50
20
10
5
0
100
200
300
400
500
Time Since First Dose (day)



NSCLC = Non-small cell lung cancer; CSCC = Cutaneous squamous-cell carcinoma; BCC = Basal cell carcinoma;
90% CI = 90 percent confidence interval

Figure 6: Prediction-Corrected Visual Predictive Check Plots for the Final Model (1063 Patients)

External validation of Study 1676

The updated population PK model was used to externally validate cemiplimab PK in 295 patients from Study 1676 by means of posterior predictive check (PPC). Study 1676 (data cut-off date: 4th of January 2021) consisted of adult females ≥ 18 years old with recurrent, persistent, and/or metastatic CC who received cemiplimab as monotherapy, administered 350 mg IV once every 3 weeks (Q3W). 3 patients had no quantifiable concentrations and were not included in the external validation. Study 1676 therefore comprised of 292 patients with 2030 PK samples. Summary of data exclusion in the external validation can be seen in Table 11.

Table 11: Summary of Data Excluded from the Population PK External Validation

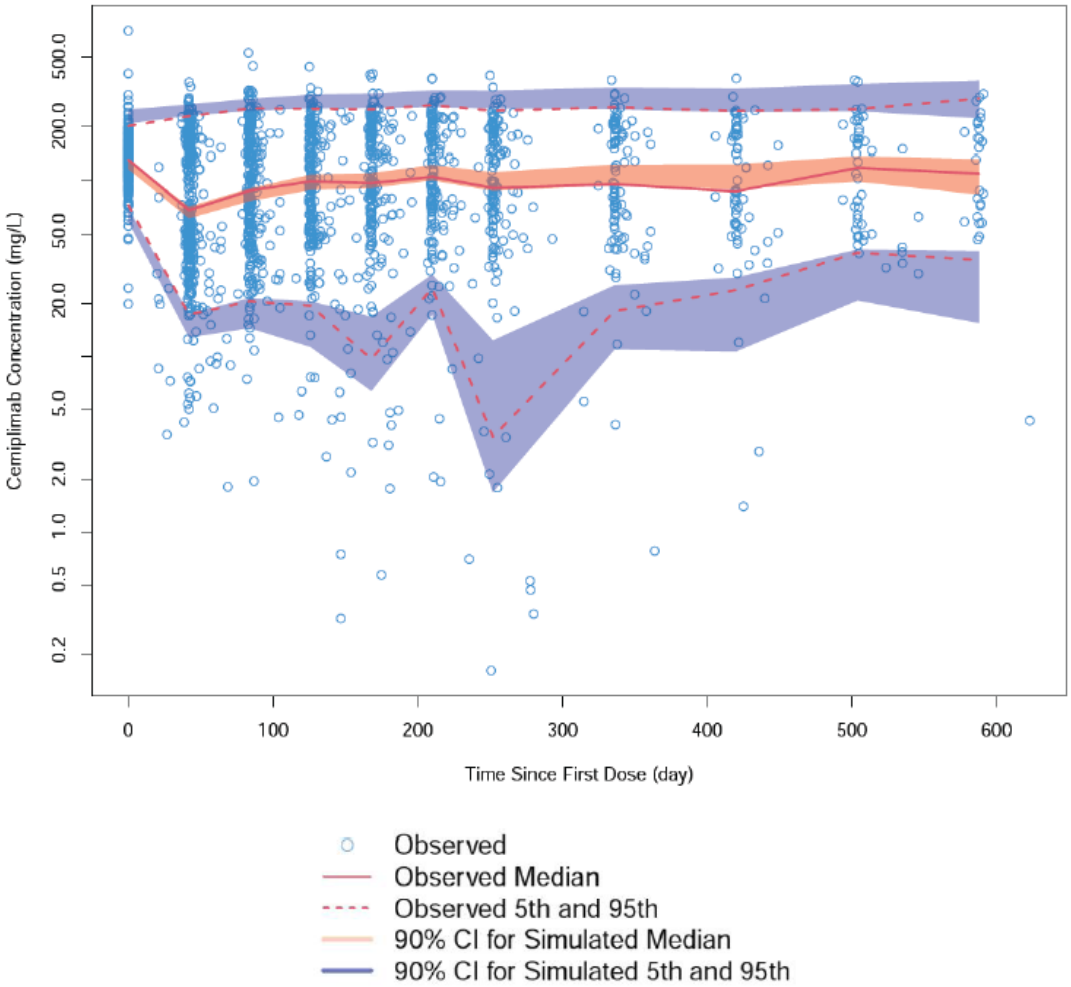
Reason for Exclusion	Number of PK Samples	Number of Patients
Data Collection Issue	0	0
Inversion[a]	54	21
No post 1st dose concentration > LLOQ	7	3
Post 1st dose concentration < LLOQ	11	11
Pre 1st dose concentration	276	276
Pre 1st dose concentration > LLOQ	6	6

PK = Pharmacokinetic; LLOQ = Lower limit of quantification

[a] Inversion is defined as predose concentration higher than the corresponding end of infusion (eoi) concentration (ie, $C_{trough} > C_{eoi}$), and both C_{trough} and C_{eoi} were excluded

Note: 2 of the 54 PK samples classified as 'Inversion' also had concentration < LLOQ; therefore, the total number of post 1st dose concentrations < LLOQ was 13 (11 + 2)

A smoothed parametric bootstrap procedure was utilised to incorporate uncertainty in parameter estimates. Parameter estimates from the updated final model was assumed to have a multivariate normal distribution with the mean vector set to the population parameter estimates and the covariance matrix set to the covariance matrix of the estimates from the updated model. The multivariate normal distribution was utilised as an approximate posterior distribution to generate 500 sets of population parameter values, which were then used to simulate datasets that replicated the design, subject population, dose regimen, sample size and covariate distribution for Study 1676. From the simulated datasets conditioned upon the observed study design, 90% confidence intervals were calculated and overlaid for the 5th, 50th and 95th percentiles of observed cemiplimab concentrations. The result of the PPC can be seen in Figure 7.



90% CI = 90 percent confidence interval

Figure 7: External Posterior Predictive Check for Study 1676 including Cervical Cancer Patients

Post-hoc PK parameter estimates were generated for CC patients and are summarized in Table 12.

Table 12: Descriptive Statistics for Post-Hoc Cemiplimab PK Parameters in the PopPK Patient Population (N = 292) with Cervical Cancer in Study 1676 Estimated Using the Updated Final PopPK Model

Parameter	Mean (CV%)	SD
Clearance at the first dose (L/day)	0.208 (22.4)	0.0467
Clearance at steady-state (L/day)	0.191 (29.4)	0.0560
Percent change in clearance (%)	-7.8	18.7
Half-life at the first dose (day)	19.0 (14.5)	2.76
Half-life at steady-state (day)	21.0 (19.4)	4.07
Accumulation Index	1.96 (17.2)	0.336
V_{ss} (L) †	5.16 (12.2)	0.629
Percent AUC_{3wks} after the 5th dose	93.5 (14.8)	13.8

† V_{ss} = V1 + V2
N = Number of patients; CV = Coefficient of variation; SD = Standard deviation; V_{ss} = Volume of distribution; V1 = Volume of the central compartment; V2 = Volume of the peripheral compartment; AUC_{3wks} = Area under the concentration time curve for a 3-week dosing interval; AUC_{3wks} = Area under the concentration time curve for a 3-week dosing interval

Exposure predictions for Study 1676

The final population PK model was used to generate exposure metrics after first dose (Table 13) and steady-state concentration in patients with CC from Study 1676 with Q3W.

Table 13: Summary of Individual Predicted Estimates of Exposure of Cemiplimab for the 350 mg Q3W Regimen After the First Dose and at Steady-State for Patients with Cervical Cancer in Study 1676 (N = 292)

Tumor Type (Study)	N	Mean (CV%) Exposure Metric					
		First Dose			Steady-State		
		AUC_{3wks} (mg·day/L)	C_{max} (mg/L)	C_{min} (mg/L)	$AUC_{3wks,ss}$ (mg·day/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
CC (Study 1676)	292	993 (13.6)	125 (11.9)	27.3 (18.3)	1949 (22.6)	185 (14.7)	60.1 (30.2)

Q3W = Every 3 weeks; N = Number of patients; CV = Coefficient of variation; AUC_{3wks} = Area under the concentration time curve for a 3-week dosing interval; C_{max} = Maximum concentration; C_{min} = Minimum concentration; SS = Steady-state; CC = Cervical cancer

Absorption

Please refer to the description of individual studies and comparison across studies above.

Distribution

Study 1676 based on the external validation of the PopPK model (PopPK 21056), PK parameters are similar and best described by a 2-compartment model. Please refer description of individual studies and

comparison across studies above. Volume (Vd) after the first dose could only be assessed by NCA in 4/10 patients in EXP23 and in 3/10 patients in EXP24 in study 1423 and ranged from 3.1 L to 5.3 L.

Based on the PopPK model, cemiplimab is primarily distributed in the vascular system with a volume of distribution at steady-state (Vss) of 5.35.9 l. Median Tmax occurs at the end of the 30-minute infusion.

Elimination

Linear elimination and with a time varying decrease in clearance was described. Please refer description of individual studies and comparison across studies above.

Clearance after the first dose could only be assessed by NCA in 4/10 patients in EXP23 and in 3/10 patients in EXP24 in study 1423 and ranged from 0.24 L/day to 0.37 L/day.

Based on the popPK model, 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 0.25 l/day. The total clearance appears to decrease by approximately 11% over time, resulting in a steady state clearance (CLss) of 0.22 l/day; the decrease in CL is not considered clinically relevant. The within dosing interval half-life at steady state is 22 days.

Dose proportionality and time dependencies

Please refer to the description of individual studies and comparison across studies above.

Table 14: Percent of steady state AUC_{3wks} achieved during 5th and 6th dosing periods in patients with solid tumours (studies 1423, 1540, 1620, and 1624) and in patients with R/M cervical cancer in study 1676

Patient Population	Number of Patients	Parameter	Time Since First Dose (Weeks)	Mean (CV%)	SD
Solid Tumor Patients (Studies 1423, 1540, 1620, 1624)	1062	Percent Individual Predicted AUC_{3wks} after the 5th dose	12 to 15	92.1 (11.6)	10.7
		Percent Individual Predicted AUC_{3wks} after the 6th dose	15 to 18	95.0 (10.4)	9.9
CC Patients (Study 1676)	292	Percent Typical Predicted AUC_{3wks} after the 5th dose	12 to 15	93.5 (14.8)	13.8
		Percent Typical Predicted AUC_{3wks} after the 6th dose	15 to 18	96.1 (13.9)	13.3

CV = Coefficient of variation; SD = Standard deviation; AUC_{3wks} = Area under the concentration time curve for a 3-week dosing interval; CC = Cervical carcinoma

Special populations

Table 15: Summary of Individual Predicted Estimates of Exposure of Cemiplimab for the 350 mg Q3W Regimen at Steady-State in Patients with CC Categorized by Age Group (Study 1676)

Age (years)	N	Mean (CV%) Age (years)	Mean (CV%) Exposure Metric at Steady-State		
			$AUC_{3wks,ss}$ (mg·day/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
<65	258	48.6 (20.1)	1953 (22.6)	185 (14.8)	60.3 (30.1)
≥65	34	70.1 (6.15)	1918 (22.7)	185 (14.1)	58.2 (30.6)
<65	258	48.6 (20.1)	1953 (22.6)	185 (14.8)	60.3 (30.1)
[65, 75)	29	68.8 (4.21)	1904 (24.5)	184 (15.1)	57.8 (32.6)
≥75	5	78.0 (2.72)	1996 (9.48)	194 (4.99)	60.2 (17.6)
<65	258	48.6 (20.1)	1953 (22.6)	185 (14.8)	60.3 (30.1)
[65, 75)	29	68.8 (4.21)	1904 (24.5)	184 (15.1)	57.8 (32.6)
[75, 85)	5	78.0 (2.72)	1996 (9.48)	194 (4.99)	60.2 (17.6)
≥85	0	NA	NA	NA	NA

Q3W = Every 3 weeks; N = Number of patients; CV = Coefficient of variation; $AUC_{3wks,ss}$ = Steady-state area under the concentration time curve for a 3-week dosing interval; $C_{max,ss}$ = Steady-state maximum concentration; $C_{min,ss}$ = Steady-state minimum concentration; NA = not applicable
Source: PopPK report R2810-PK-21056-SR-01V1 Table 35

Table 16: Summary of Individual Predicted Estimates of Exposure of Cemiplimab for the 350 mg Q3W Regimen at Steady-State in the Overall Patient Population with Solid Tumors Categorized by Age (Studies 1423, 1540, 1620, and 1624)

Age (years)	N	Mean (CV%) Age (years)	Mean (CV%) Exposure Metric at Steady-State		
			$AUC_{3wks,ss}$ (mg·day/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
<65	517	54.8 (13.8)	1843 (38.3)	170 (27.3)	57.7 (49.4)
≥65	545	73.2 (8.52)	1885 (35.9)	171 (26.9)	59.6 (45.0)
<65	517	54.8 (13.8)	1843 (38.3)	170 (27.3)	57.7 (49.4)
[65, 75)	343	69.2 (3.91)	1831 (38.2)	169 (28.3)	57.3 (48.0)
≥75	202	79.9 (5.56)	1977 (31.7)	176 (24.5)	63.3 (39.6)
<65	517	54.8 (13.8)	1843 (38.3)	170 (27.3)	57.7 (49.4)
[65, 75)	343	69.2 (3.91)	1831 (38.2)	169 (28.3)	57.3 (48.0)
[75, 85)	168	78.4 (3.62)	1963 (32.9)	175 (25.4)	62.8 (40.9)
≥85	34	87.5 (3.34)	2045 (25.9)	180 (19.9)	66.1 (33.4)

Q3W = Every 3 weeks; N = Number of patients; CV = Coefficient of variation; $AUC_{3wks,ss}$ = Steady-state area under the concentration time curve for a 3-week dosing interval; $C_{max,ss}$ = Steady-state maximum concentration; $C_{min,ss}$ = Steady-state minimum concentration

Note: One subjection from Study 1423, was excluded from the summary of exposure metrics due to extremely high predicted V_{ss} of 183.6 L that is inconsistent with the typical distribution volume for monoclonal antibodies (also excluded in the prior PopPK analysis). Therefore, exposure predictions are reported for a total of N = 1062 subjects.

Source: PopPK report R2810-PK-21056-SR-01V1 Table 29

Table 17: Summary of Individual Predicted Estimates of Exposure of Cemiplimab for the 350 mg Q3W Regimen at Steady-State and Relevant Covariates in Patients with CC Categorized by Baseline Creatinine Clearance (Study 1676)

Renal Function Category (Baseline CRCL)	N	Mean (CV%) Baseline CRCL (mL/min)	Mean (CV%) Baseline Body Weight (kg)	Mean (CV%) Exposure Metric at Steady-State		
				$AUC_{3wks,ss}$ (mg·day/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
Normal CRCL ≥90 mL/min	85	119 (23.5)	75.7 (23.6)	1797 (24.9)	171 (16.5)	55.4 (32.6)
Mild Impairment CRCL 60 to 89 mL/min	124	74.4 (11.5)	62.8 (21.8)	2023 (20.5)	189 (12.4)	63.0 (28.0)
Moderate Impairment CRCL 30 to 59 mL/min	83	47.6 (16.2)	55.6 (19.7)	1995 (22.0)	193 (13.4)	60.4 (30.0)

Q3W = Every 3 weeks; N = Number of patients; CV = Coefficient of variation; CRCL = Creatinine clearance; $AUC_{3wks,ss}$ = Steady-state area under the concentration time curve for a 3-week dosing interval; $C_{max,ss}$ = Steady-state maximum concentration; $C_{min,ss}$ = Steady-state minimum concentration

Source: PopPK report R2810-PK-21056-SR-01V1 Table 37

Table 18: Summary of Individual Predicted Estimates of Exposure of Cemiplimab for the 350 mg Q3W Regimen at Steady-State and Relevant Covariates in the Overall Patient Population with Solid Tumors Categorized by Baseline Creatinine Clearance (Studies 1423, 1540, 1620, and 1624)

Renal Function Category (Baseline CRCL)	N	Mean (CV%) Baseline CRCL (mL/min)	Mean (CV%) Baseline Body Weight (kg)	Mean (CV%) Exposure Metric at Steady-State		
				$AUC_{3wks,ss}$ (mg·day/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
Normal CRCL ≥90 mL/min	497	120 (25.6)	82.5 (23.1)	1731 (36.9)	161 (25.8)	54.0 (48.2)
Mild Impairment CRCL 60 to 89 mL/min	391	74.8 (11.3)	72.2 (20.9)	1929 (34.7)	174 (24.7)	61.2 (44.3)
Moderate Impairment CRCL 30 to 59 mL/min	167	49.5 (14.7)	65.1 (20.3)	2084 (35.5)	189 (27.3)	66.0 (44.4)
Severe Impairment CRCL 15 to 29 mL/min	7	25.3 (10.1)	49.7 (24.4)	2488 (67.0)	243 (54.3)	75.9 (79.8)

Q3W = Every 3 weeks; CRCL = Creatinine clearance; N = Number of patients; CV = Coefficient of variation; $AUC_{3wks,ss}$ = Steady-state area under the concentration time curve for a 3-week dosing interval; $C_{max,ss}$ = Steady-state maximum concentration; $C_{min,ss}$ = Steady-state minimum concentration
Note: One subject from Study 1423, was excluded from the summary of exposure metrics due to extremely high predicted V_{ss} of 183.6 L that is inconsistent with the typical distribution volume for monoclonal antibodies (also excluded in the prior PopPK analysis). Therefore, exposure predictions are reported for a total of N = 1062 subjects.
Source: PopPK report R2810-PK-21056-SR-01V1 Table 31

Table 19: Summary of Individual Predicted Estimates of Exposure of Cemiplimab for the 350 mg Q3W Regimen at Steady-State and Relevant Covariates in Patients with CC Categorized by Baseline Total Bilirubin (Study 1676)

Hepatic Function (Baseline Total Bilirubin)	N	Mean (CV%) Baseline Value				Mean (CV%) Exposure Metric at Steady-State		
		Total Bilirubin (µmol/L)	Body Weight (kg)	AST (IU/L)	ALT (IU/L)	$AUC_{3wks,ss}$ (mg·day/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
Normal (TB ≤1x ULN)	283	7.19 (48.0)	64.6 (25.5)	23.7 (73.6)	18.5 (77.1)	1944 (22.6)	185 (14.7)	59.8 (30.1)
Mild Impairment (TB >1 to ≤1.5x ULN)	6	22.9 (6.71)	61.5 (17.9)	28.1 (44.6)	31.3 (43.9)	2264 (23.9)	201 (14.0)	73.8 (32.1)
Moderate Impairment (TB >1.5 to ≤3x ULN)	1	35.9 (NA)	58.9 (NA)	40.0 (NA)	57.0 (NA)	1765 (NA)	173 (NA)	52.1 (NA)
NA	2[a]	6.84 (NA)	60.4 (NA)	19.0 (NA)	14.0 (NA)	1887 (NA)	184 (NA)	56.7 (NA)

Q3W = Every 3 weeks; N = Number of patients; CV = Coefficient of variation; TB = Total bilirubin; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; $AUC_{3wks,ss}$ = Steady-state area under the concentration time curve for a 3-week dosing interval; $C_{max,ss}$ = Steady-state maximum concentration; $C_{min,ss}$ = Steady-state minimum concentration; NA = Not applicable

[a] ULN values were not available for 2 patients

Source: PopPK report R2810-PK-21056-SR-01V1 Table 38

Table 20: Summary of Individual Predicted Estimates of Exposure of Cemiplimab for the 350 mg Q3W Regimen at Steady-State and Relevant Covariates in the Overall Patient Population with Solid Tumors Categorized by Baseline Total Bilirubin (Studies 1423, 1540, 1620, and 1624)

Hepatic Function (Baseline Total Bilirubin)	N	Mean (CV%) Baseline Value				Mean (CV%) Exposure Metric at Steady-State		
		Total Bilirubin (µmol/L)	Body Weight (kg)	AST (IU/L)	ALT (IU/L)	$AUC_{3wks,ss}$ (mg·day/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
Normal (TB ≤1x ULN)	1023	8.58 (44.4)	75.6 (23.9)	25.3 (70.6)	23.9 (86.3)	1868 (36.9)	171 (27.0)	58.8 (47.0)
Mild Impairment (TB >1 to ≤1.5x ULN)	22	23.9 (17.3)	79.7 (26.3)	42.0 (85.1)	25.4 (76.1)	1723 (36.6)	164 (30.0)	52.4 (44.1)
Moderate Impairment (TB >1.5 to ≤3x ULN)	3	43.1 (15.5)	85.5 (35.6)	42.0 (47.6)	38.7 (60.1)	1584 (11.0)	144 (13.4)	48.6 (21.1)
NA	14	8.43 (2.02)	77.5 (24.5)	21.1 (24.9)	19.0 (12.7)	1894 (47.3)	163 (32.2)	62.2 (58.0)

Q3W = Every 3 weeks; N = Number of patients; CV = Coefficient of variation; TB = Total bilirubin; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; $AUC_{3wks,ss}$ = Steady-state area under the concentration time curve for a 3-week dosing interval; $C_{max,ss}$ = Steady-state maximum concentration; $C_{min,ss}$ = Steady-state minimum concentration

Note: one subject from Study 1423 was excluded from the summary of exposure metrics due to extremely high predicted V_{ss} of 183.6 L that is inconsistent with the typical distribution volume for monoclonal antibodies (also excluded in the prior PopPK analysis). Therefore, exposure predictions are reported for a total of N = 1062 subjects.

Source: PopPK report R2810-PK-21056-SR-01V1 Table 32

Table 21: Summary of Individual Predicted Estimates of Exposure of Cemiplimab for the 350 mg Q3W Regimen at Steady-State in Patients with CC Categorized by Baseline Albumin (Study 1676)

Baseline Albumin (g/L)	N	Mean (CV%) Baseline Albumin (g/L)	Mean (CV%) Exposure Metric at Steady-State		
			$AUC_{3wks,ss}$ (mg·day/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
<5th percentile [20, 28.2]	15	24.9 (11.8)	1345 (22.9)	154 (14.2)	34.2 (33.1)
5-95th percentile (28.2, 47]	269	39.3 (11.8)	1972 (21.5)	186 (14.2)	61.1 (28.4)
>95th percentile (47, 50.7]	8	48.8 (2.81)	2303 (12.3)	204 (10.7)	75.4 (14.6)
≤30	26	26.9 (12.2)	1509 (27.5)	161 (16.0)	41.4 (39.3)
(30, 35]	46	33.3 (4.21)	1670 (23.7)	171 (15.0)	48.1 (32.8)
>35	220	41.4 (8.58)	2060 (19.1)	191 (13.1)	64.8 (24.9)

Q3W = Every 3 weeks; N = Number of patients; CV = Coefficient of variation; $AUC_{3wks,ss}$ = Steady-state area under the concentration time curve for a 3-week dosing interval; $C_{max,ss}$ = Steady-state maximum concentration; $C_{min,ss}$ = Steady-state minimum concentration
Source: PopPK report R2810-PK-21056-SR-01V1 Table 34

Table 22: Summary of Individual Predicted Estimates of Exposure of Cemiplimab for the 350 mg Q3W Regimen at Steady-State in the Overall Patient Population with Solid Tumors Categorized by Baseline Albumin (Studies 1423, 1540, 1620, and 1624)

Baseline Albumin (g/L)	N	Mean (CV%) Baseline Albumin (g/L)	Mean (CV%) Exposure Metric at Steady-State		
			$AUC_{3wks,ss}$ (mg·day/L)	$C_{max,ss}$ (mg/L)	$C_{min,ss}$ (mg/L)
<5th percentile [20, 29.3]	55	26.6 (8.48)	1397 (46.5)	146 (27.1)	39.4 (67.4)
5-95th percentile (29.3, 46]	965	38.4 (10.3)	1870 (35.9)	171 (26.6)	58.9 (45.5)
>95th percentile (46, 93]	42	49.7 (15.2)	2341 (35.4)	199 (27.6)	78.5 (41.8)
≤30	76	27.5 (8.90)	1404 (42.5)	147 (24.9)	39.6 (62.3)
(30, 35]	217	33.3 (4.08)	1661 (36.2)	157 (25.1)	50.5 (47.3)
>35	769	40.6 (9.51)	1967 (35.2)	177 (26.8)	62.9 (44.0)

Q3W = Every 3 weeks; N = Number of patients; CV = Coefficient of variation; $AUC_{3wks,ss}$ = Steady-state area under the concentration time curve for a 3-week dosing interval; $C_{max,ss}$ = Steady-state maximum concentration; $C_{min,ss}$ = Steady-state minimum concentration
Note: one subject from Study 1423, was excluded from the summary of exposure metrics due to extremely high predicted V_{ss} of 183.6 L that is inconsistent with the typical distribution volume for monoclonal antibodies (also excluded in the prior PopPK analysis). Therefore, exposure predictions are reported for a total of N = 1062 subjects.
Source: PopPK report R2810-PK-21056-SR-01V1 Table 25

2.3.3. Pharmacodynamics

Primary and secondary pharmacology

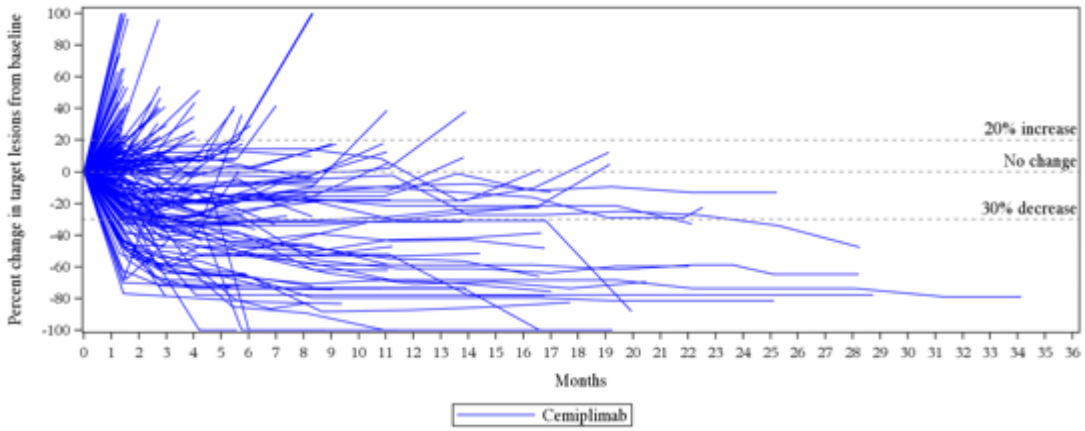
Pharmacodynamic Results in Patients with R/M Cervical Cancer

Due to the insufficient number of patients with R/M cervical cancer in the FIH Study 1423 (2 responders out of 20 patients total in EXP23 and EXP24), pharmacodynamic analysis was performed exclusively in patients with R/M cervical cancer in the pivotal Study 1676. Data for patients on cemiplimab therapy are presented here for all patients with R/M cervical cancer (N=304) and the subgroup with SCC histology (N=239) on cemiplimab 350 mg Q3W.

In Study 1676, the percent change from baseline in target lesions was assessed as a pharmacodynamic marker of efficacy using radiologic imaging according to RECIST 1.1. Patients with confirmed response status of CR or PR according to RECIST 1.1 contributed to ORR (50 responders in the total patient population and 42 in the subgroup with SCC histology).

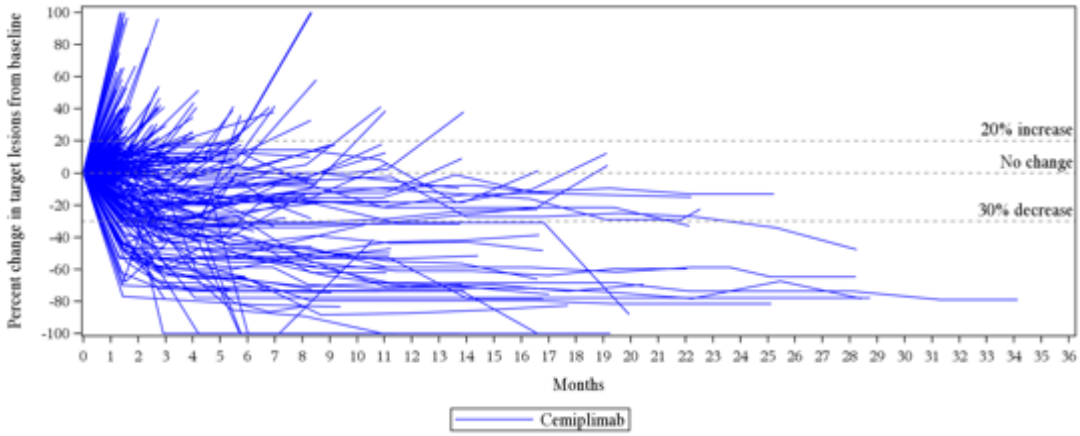
Spider plots provide a comprehensive perspective regarding the depth and kinetics of responses, illustrating the percent changes in target lesion measurements over time for individual patients. Spider plots for changes in target lesions relative to baseline were provided for patients who received cemiplimab 350 mg Q3W in the SCC subgroup **(**Figure 8**)** and the total population **(**Figure 9**).**

In the SCC histology subgroup, as well as in the total population, the estimated median DOR was 16.4 months in patients receiving cemiplimab 350 mg Q3W.



N= 42 responders (CR or PR) out of 239 patients in the subgroup with SCC histology on cemiplimab 350 mg Q3W. Data cutoff as of Jan 4th, 2021. Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR Post-text Figure 14.2.3.2scc

Figure 8: Spider Plot for Change in Target Lesions Relative to Baseline over Time in R/M Cervical Cancer Patients with SCC Histology who Received Cemiplimab 350 mg Q3W in Study 1676



N= 50 responders (CR or PR) out of 304 patients in the total population of patients with R/M cervical cancer on cemiplimab 350 mg Q3W. Data cutoff as of Jan 4th, 2021. Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR Post-text Figure 14.2.3.2all

Figure 9: Spider Plot for Change in Target Lesions Relative to Baseline over Time in All Patients with R/M Cervical Cancer who Received Cemiplimab 350 mg Q3W in Study 1676

Exposure-Response Relationships in Patients with R/M Cervical Cancer in the Pivotal Study 1676

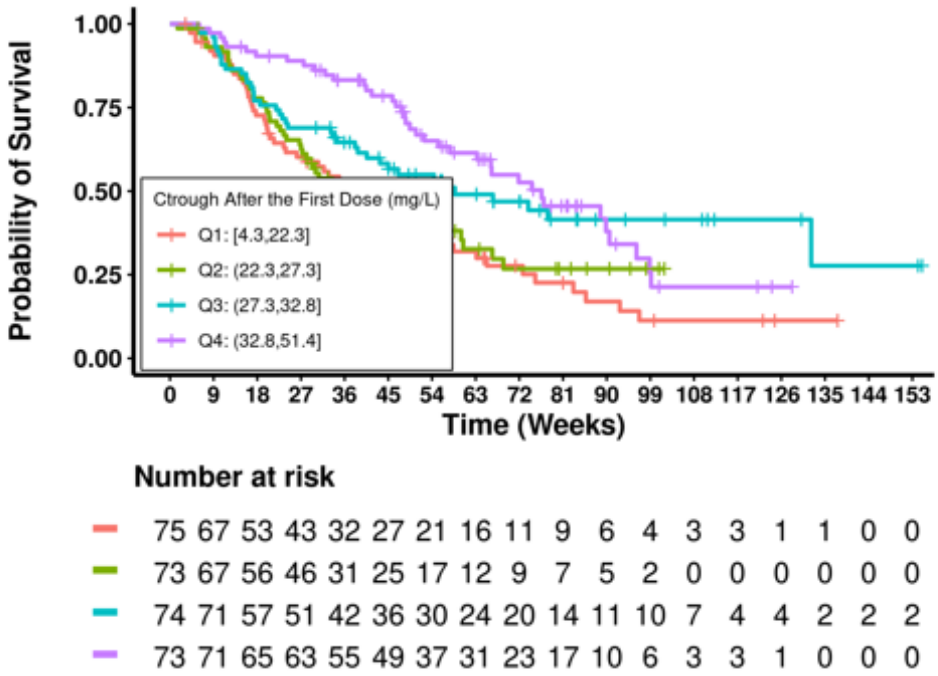
Descriptive and model-based E-R relationships analyses were conducted for efficacy and safety endpoints using post-hoc estimates of exposure metrics C_{trough}, C_{max}, and average concentration (C_{av}) after the first dose, with emphasis on C_{trough} for efficacy endpoints and on C_{max} for safety endpoints, as considered to be the most sensitive exposure metrics for these clinical assessments.

E-R relationship analyses for efficacy were conducted on OS as primary endpoint, and PFS, ORR (based on BOR), and DOR as secondary endpoints, while E-R relationships for safety were conducted on immune-mediated adverse event (irAEs) (all and grade ≥3) as safety endpoints.

E-R relationship analyses for efficacy and safety, performed on patients with R/M cervical cancer from Study 1676 who received cemiplimab 350 mg Q3W are presented in this section.

Exposure-Response Relationship Analyses for Efficacy

In the descriptive exposure-efficacy analysis, Kaplan-Meier curves of OS by quartile of C_{trough} after the first dose (C_{trough},1) is presented in Figure 10 .



Number at risk

	75	67	53	43	32	27	21	16	11	9	6	4	3	3	1	1	0	0
	73	67	56	46	31	25	17	12	9	7	5	2	0	0	0	0	0	0
	74	71	57	51	42	36	30	24	20	14	11	10	7	4	4	2	2	2
	73	71	65	63	55	49	37	31	23	17	10	6	3	3	1	0	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 cutoff 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 cutoff date.
Source: Module 5.3.3.5 R2810-PK-21058-SR-01V1 Figure 1

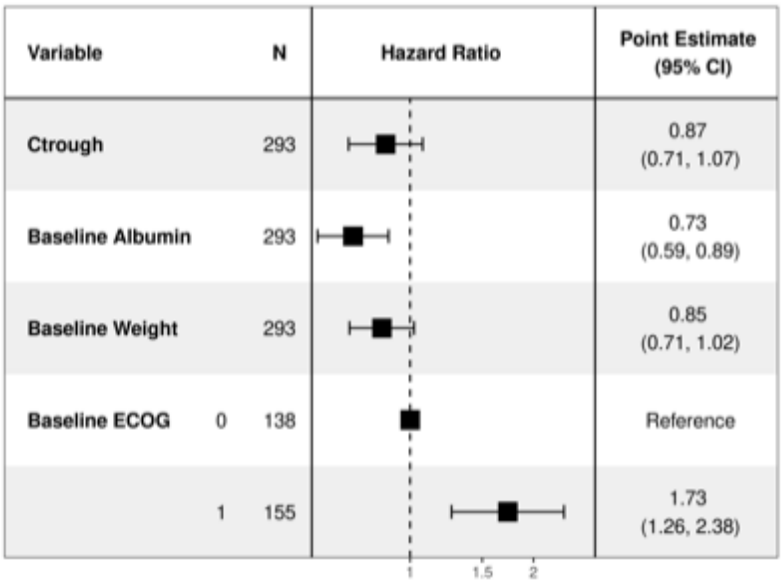
Figure 10: Kaplan-Meier Curves of OS Stratified by Quartiles of Individual Predicted Cemiplimab Ctrough After the First Dose in Patients with R/M Cervical Cancer

To address the limitations associated with the descriptive E-R analysis (K-M analysis of OS by C_{trough},1), a Cox proportional hazards (PH) model was implemented. This Cox PH modelling showed that C_{trough},1 was a significant predictor of OS hazard when it was the sole predictor in the model (Table 23), but after adjusting for baseline values of albumin, weight, and ECOG performance status, C_{trough},1 was no longer significant since the 95% confidence interval for the hazard ratio (HR) contains 1 (Figure 11).

Table 23: Summary of Results from Cox PH Models of OS Fit with Predicted Exposure Metrics and Baseline Covariates as the Only Individual Predictor in Each Model in Patients with R/M Cervical Cancer

Exposure Metric	AIC	BIC	P-Value
Baseline PD-L1 (%)	591	593	2.09e-01
Baseline Albumin (g/L)	1718	1721	4.93e-10
Baseline ECOG Score	1757	1760	1.23e-05
C_{trough} After the First Dose (mg/L)	1758	1761	1.68e-05
C_{ss} After the First Dose (mg/L)	1768	1771	3.64e-03
Baseline Weight (kg)	1773	1776	6.80e-02
C_{max} After the First Dose (mg/L)	1776	1779	6.44e-01

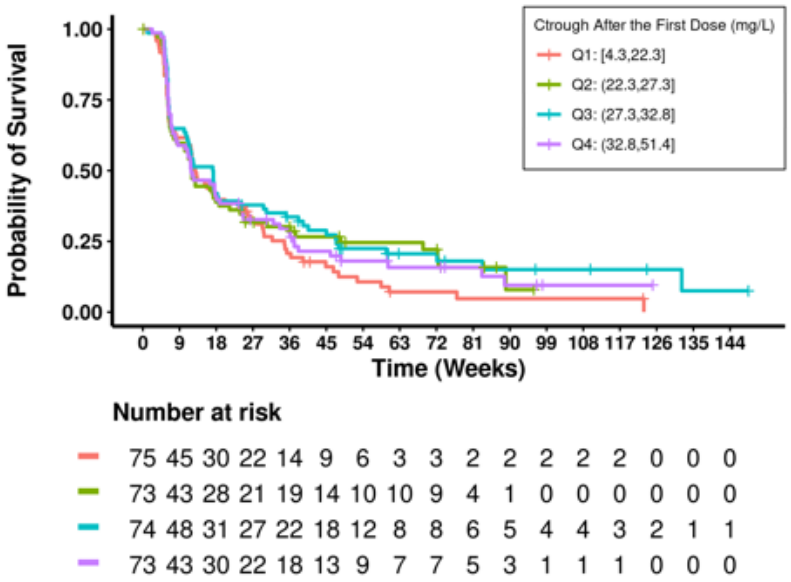
Lower AIC or BIC values indicate better model fits. In general, a difference of more than 10 in AIC between the best model and the next best model provides evidence that the model with the lowest AIC is the best model. Models where the difference in AIC is 4 or less suggests that either model would be appropriate.
Source: Module 5.3.3.5 R2810-PK-21058-SR-01V1 Table 1



Note: C_{trough} was fit based on after first dose values in this model. Point estimates are interpreted in terms of an increase in one unit of SD from the mean value of the variable.
Source: Module 5.3.3.5 R2810-PK-21058-SR-01V1 Figure 2

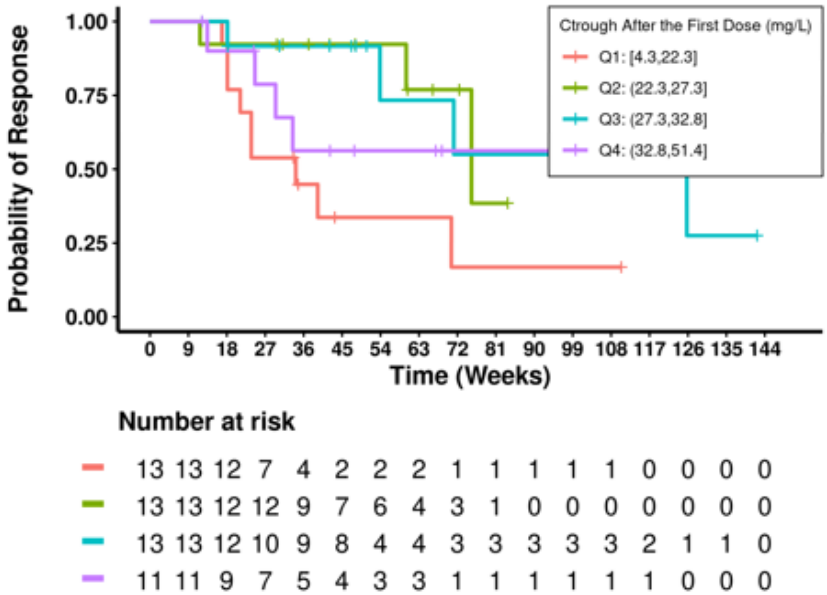
Figure 11: Forest Plot of Cox PH Model of OS with Individual Predicted Cemiplimab Ctrough After the First Dose and Baseline Covariates as Model Predictors in Patients with R/M Cervical Cancer

Kaplan-Meier (K-M) curves of PFS (Figure 12) and DOR (Figure 13) are presented below.



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 R2810-PK-21058-SR-01V1 Figure 3

Figure 12: Kaplan-Meier Curves of PFS Stratified by Quartiles of Individual Predicted Cemiplimab Ctrough After the First Dose in Patients with R/M Cervical Cancer



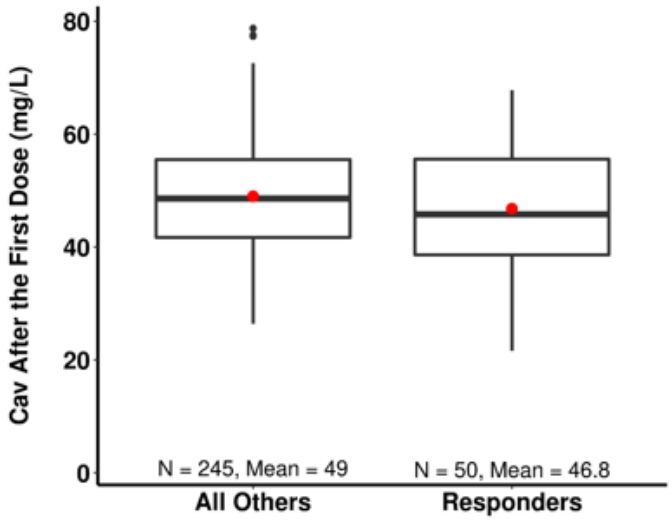
The vertical hatches through the Kaplan-Meier curves indicate the last known date where the patient is still alive and has not experienced progressive or recurrent disease.
Source: Module 5.3.3.5 R2810-PK-21058-SR-01V1 Figure 6

Figure 13: Kaplan-Meier Curves of DOR Stratified by Quartiles of Individual Predicted Cemiplimab Ctrough After the First Dose in Patients with R/M Cervical Cancer

Exposure metrics between "responders" and "all others" were unlikely to differ from one another due to the overlapping distribution of values and comparable mean and median values (

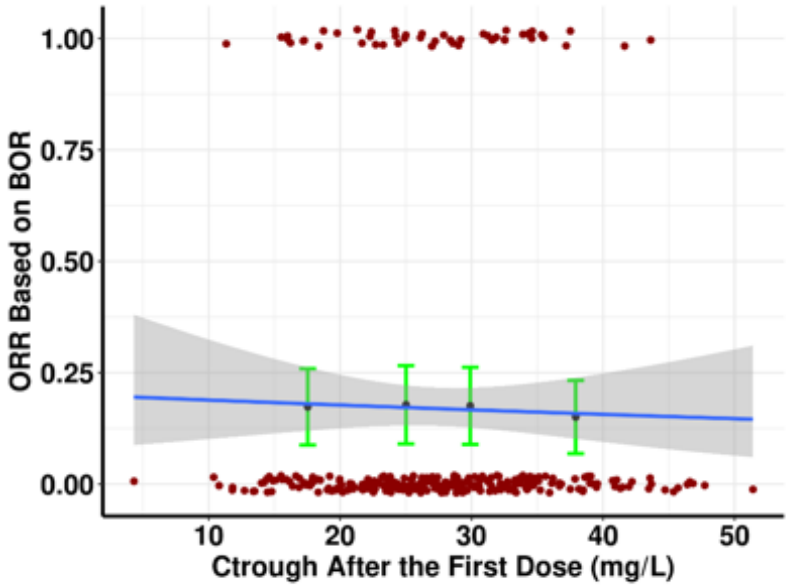
Figure **14**). Logistic regression models with BOR as the response and continuous exposure metric as the independent variable showed a flat relationship in both the fitted model and in the trend of observed data (Figure 15). Additionally, univariate logistic regression models compared to the intercept-only model did not reveal any advantage over the intercept-only model (

Table 24).



The lower and upper hinges correspond to the first and third quartiles (the 25th and 75th percentiles). The upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge (where IQR is the inter-quartile range, or distance between the first and third quartiles). The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. Data beyond the end of the whiskers are called 'outlying' points and are plotted individually. Note: 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, who were not able to be classified as CR or PR, who were not evaluable, or who had stable disease, were considered as 'all others' for these analyses. BOR was determined by the investigator.
Source: Module 5.3.3.5 R2810-PK-21058-SR-01V1 Figure 4

Figure 14: Boxplot of Individual Predicted Cemiplimab Ctrough After the First Dose by BOR in Patients with R/M Cervical Cancer



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. Refer to Table 9 for descriptive statistics of quartiles.
Source: Module 5.3.3.5 R2810-PK-21058-SR-01V1 Figure 5

Figure 15: Logistic Regression of ORR based on BOR versus Individual Predicted Cemiplimab Ctrough After the First Dose with ORR (Mean of Best Overall Response) by Quartiles of Exposure in Patients with Cervical Carcinoma

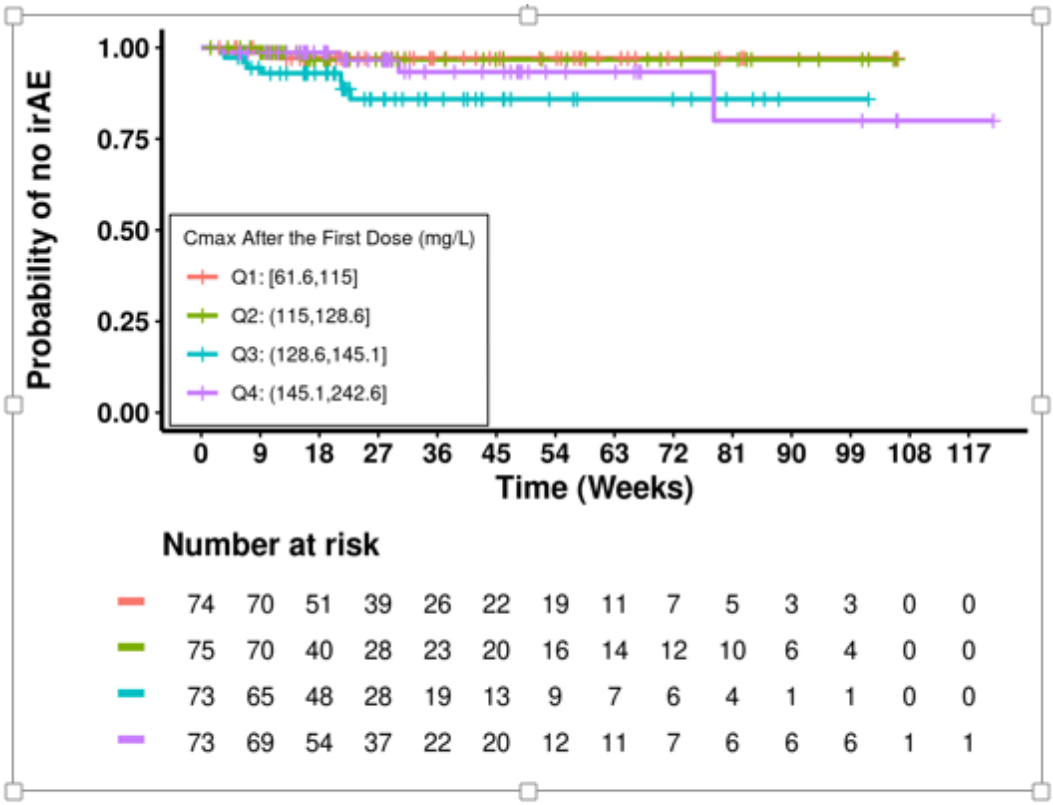
Table 24: Summary of Results from Logistic Regression Models of BOR Fit with Individual Predicted Exposure Metrics After the First Dose and Baseline Covariates as the Only Predictor in Each Model in Patients with R/M Cervical Cancer

Exposure Metric	AIC	BIC	P-Value
C_{max} After the First Dose (mg/L)	266	273	1.44e-02
Intercept-Only Model	270	274	1.29e-24
Baseline Weight (kg)	269	276	4.64e-02
Baseline ECOG Score	269	277	8.32e-02
C_{av} After the First Dose (mg/L)	271	278	1.85e-01
Baseline Albumin (g/L)	271	279	4.84e-01
C_{trough} After the First Dose (mg/L)	272	280	7.00e-01

Lower AIC or BIC values indicate better model fits. In general, a difference of more than 10 in AIC between the best model and the next best model provides evidence that the model with the lowest AIC is the best model. Models where the difference in AIC is 4 or less suggests that either model would be appropriate. Models are compared to the intercept-only model. Source: Module 5.3.3.5 R2810-PK-21058-SR-01V1 Table 2

Exposure-Response Relationships for Safety

The exposure-safety relationship analyses for all irAEs and irAEs grade ≥3 with C_{max} after the first dose (C_{max},1) as the representative exposure metric for safety were conducted in all patients with R/M cervical cancer in Study 1676. In addition, average concentration after the first dose (C_{av},1) and C_{trough} after the first dose (C_{trough},1) were also evaluated.



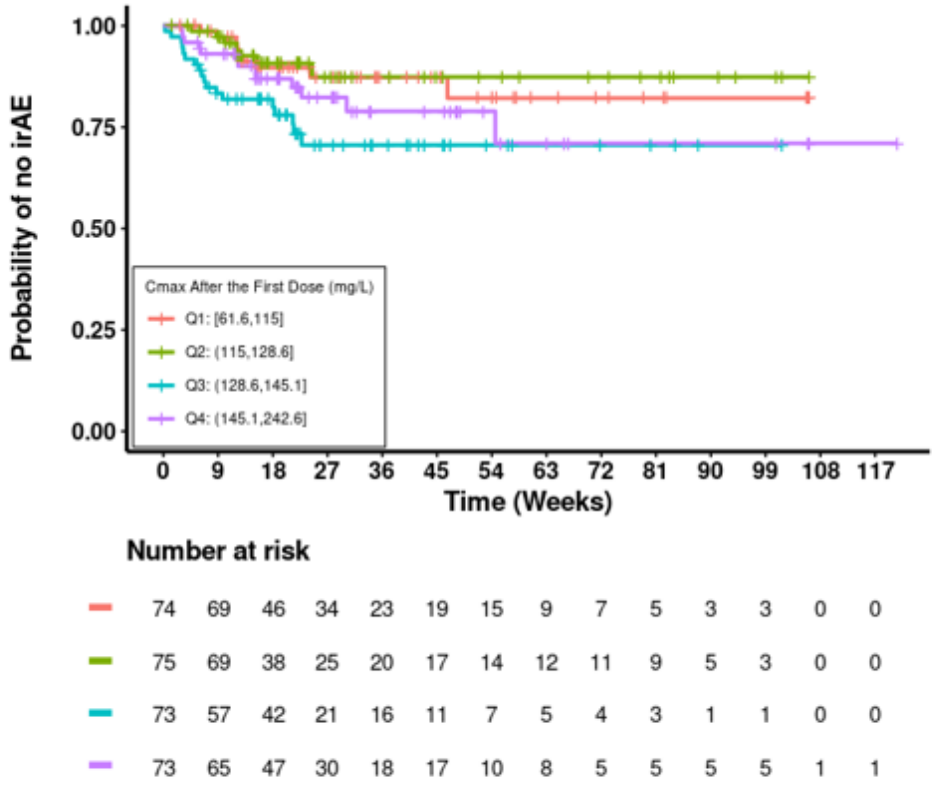
A drop in the Kaplan-Meier curves indicates the time in which the patient experiences an irAE grade ≥3, and the censored events describe the last known date where the patient has not experienced any irAEs grade ≥3. The table provided underneath the plot describes the number of patients who have not experienced irAE grade ≥3 in each quartile at each time point.
Source: Module 5.3.3.5 R2810-PK-21058-SR-01V1 Figure 7

Figure 16: Kaplan-Meier Curves of Grade 3 or Higher irAEs Stratified by Quartiles of Individual Predicted Cemiplimab Cmax After the First Dose in Patients with R/M Cervical Cancer

Table 25: Summary of Results from Cox PH Models of Grade 3 or Higher irAEs Fit with Predicted Exposure Metrics and Baseline Covariates as the Only Individual Predictor in Each Model in Patients with R/M Cervical Cancer

Exposure Metric	AIC	BIC	P-Value
Baseline ECOG Score	170	171	0.333
C_{av} After the First Dose (mg/L)	171	172	0.755
C_{max} After the First Dose (mg/L)	171	172	0.586
C_{trough} After the First Dose (mg/L)	171	172	0.450
Baseline Weight (kg)	171	172	0.793
Baseline Albumin (g/L)	171	172	0.967

Lower AIC or BIC values indicate better model fits. In general, a difference of more than 10 in AIC between the best model and the next best model provides evidence that the model with the lowest AIC is the best model. Models where the difference in AIC is 4 or less suggests that either model would be appropriate.
Source: Module 5.3.3.5 R2810-PK-21058-SR-01V1 Table 3



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 R2810-PK-21058-SR-01V1 Figure 8

Figure 17: Kaplan-Meier Curves of irAEs Stratified by Quartiles of Individual Predicted Cemiplimab Cmax After the First Dose in Patients with R/M Cervical Cancer

Table 26: Summary of Results from Cox PH Models of irAEs Fit with Predicted Exposure Metrics and Baseline Covariates as the Only Individual Predictor in Each Model in Patients with R/M Cervical Cancer

Exposure Metric	AIC	BIC	P-Value
Baseline Weight (kg)	504	506	0.339
Baseline Albumin (g/L)	504	506	0.451
C_{av} After the First Dose (mg/L)	505	507	0.780
C_{max} After the First Dose (mg/L)	505	507	0.676
C_{trough} After the First Dose (mg/L)	505	507	0.536
Baseline ECOG Score	505	507	0.601

Lower AIC or BIC values indicate better model fits. In general, a difference of more than 10 in AIC between the best model and the next best model provides evidence that the model with the lowest AIC is the best model. Models where the difference in AIC is 4 or less suggests that either model would be appropriate. Models are compared to the intercept-only model.
Source: Module 5.3.3.5 R2810-PK-21058-SR-01V1 Table 4

SPECIAL STUDIES

Immunogenicity

Immunogenicity assessments were presented for Study 1676 in patients with R/M cervical cancer and across all clinical studies in patients with solid tumors (Studies 1423, 1540, 1620, 1624, and 1676).

Immunogenicity

Study 1676

Immunogenicity in patients with R/M cervical cancer in the anti-drug antibody (ADA) data set (N=206) was low with no apparent difference in the occurrence of immunogenicity (ADA) in patients with SCC and AC. Pre-existing ADA occurred in 6 patients with R/M cervical cancer (2.9%). Treatment-emergent ADA (1.9% in total) was observed in 4 patients with SCC, 1 was transient and 3 were indeterminate; all were low titers (<1,000). None of the ADA-positive samples revealed the presence of neutralizing antibody. No effect of immunogenicity/ADA on exposure was observed in patients with R/M cervical cancer in this study.

Study 1423

Among 337 patients in the ADA Analysis Set in Study 1423, ADA incidence was low, with treatment-emergent ADA in 9 patients (2.7%). Treatment-emergent ADA was reported in 9 patients (1 patient at 1 mg/kg Q2W, 7 patients at 3 mg/kg Q2W, and 1 patient at 10 mg/kg Q2W): persistent ADA was observed in 2 patients (1 at 1 mg/kg Q2W and 1 at 3 mg/kg Q2W), transient ADA was observed in 2 patients (both at 3 mg/kg Q2W) and indeterminate ADA was observed in 5 patients (4 at 3 mg/kg Q2W and 1 at 10 mg/kg Q2W). The ADA titers were generally low with only 1 patient exhibiting moderate ADA titer. No patients were positive for NAbs. No relationship was observed between ADA status and cemiplimab exposure in the few cases of treatment-emergent ADA.

Of the patients with R/M cervical cancer in the ADA Analysis Set in Study 1423, 1 patient at 10 mg/kg Q2W of the 3 patients in the dose escalation cohorts, and none of the patients in EXP 23 (n=7) and EXP 24 (n=7) at 3 mg/kg Q3W showed a positive ADA response.

Immunogenicity in Patients with R/M Cervical Cancer from Study 1676

Immunogenicity in patients with R/M cervical cancer in Study 1676 (206 patients, including 164 patients with SCC histology and 42 patients with AC histology), was low with no apparent difference in the

occurrence of immunogenicity (ADA) based on histology. Pre-existing ADA occurred in 6 patients with R/M cervical cancer (2.9%). Treatment-emergent ADA (1.9% in total) was observed in 4 patients with SCC, 1 was transient and 3 were indeterminate; all were low titers (<1,000). None of the ADA-positive samples revealed the presence of neutralizing antibodies. No effect of immunogenicity/ADA on cemiplimab exposure was observed in patients with R/M cervical cancer in this study.

Immunogenicity in All Patients with Solid Tumours

In the overall population of patients with solid tumours, immunogenicity was assessed in patients with solid tumours, including patients with R/M cervical cancer, after cemiplimab administration as monotherapy (Studies 1423, 1540, 1620, 1624 and 1676) or in combination with radiotherapy and/or chemotherapy (Study 1423).

The incidence of treatment-emergent ADA in all patients with solid tumours in the ADA analysis set (n=1029) was low (2.1%). Only 3 patients (0.3%) had a persistent ADA response: 1 patient at 1 mg/kg Q2W IV, 1 patient at 3 mg/kg Q2W IV, and 1 patient at 350 mg Q3W IV. The ADA titers were generally low. No patients were positive for NAbs. The incidence of treatment-emergent ADA in the subset of patients (n=591) who received cemiplimab 350 mg Q3W IV was similarly low (2.2%).

2.3.4. Discussion on clinical pharmacology

The clinical pharmacology data package submitted in support of the proposed indication for cemiplimab in patients with R/M cervical cancer included data on PK, PD, E-R relationships for efficacy and safety, and immunogenicity of cemiplimab in the target population. The PK was also assessed for consistency across studies in the R/M cervical cancer and by histology (SCC vs. AC), as well as in other patient populations (tumour-types) that have been previously reported. Within the population of patients with R/M cervical cancer, the PK of cemiplimab was assessed across studies (Study 1423 and Study 1676), as well as between patients.

The previous population PK model for cemiplimab in patients with CSCC, BCC, NSCLC and other solid tumours was updated with data from Study 1423, 1540, 1620 and 1624, which comprised of 17312 samples from 1063 patients.

Consistent with the initial population PK model, the pharmacokinetics of cemiplimab could be described by a 2-compartment model with zero-order intravenous infusion, a first-order elimination, and a sigmoid E_{max} function to describe a time-varying change in CL. Interindividual variability terms on E_{max} and T_{50} were removed, the proportional error model was refined to a log-additive error model and the off-diagonal covariance between interindividual random effects on CLQ and V1V2 was removed. The population PK model was evaluated adequately by means of GOF-plots, bootstrap analysis and VPCs. Model stability was significantly improved (94.8% successful convergence rate in the bootstrap analysis). The suitability of the updated final population PK model in predicting cemiplimab concentrations in patients with CC was evaluated through an external PPC, which indicated that the updated model adequately described cemiplimab concentrations in patients with cervical cancer.

Descriptive analyses at the study level showed that the PK of cemiplimab in patients with R/M cervical cancer receiving 3 mg/kg Q2W IV in the FIH Study 1423 was comparable to that observed in patients with R/M cervical cancer receiving 350 mg Q3W IV in the pivotal Study 1676. Within Study 1676, the PK was also observed to be similar between patients with SCC and AC histology types.

Consistently across tumour types the concentration-time profiles over the dosing interval was characterized by initial brief distribution phase followed by a mono-exponential elimination phase.

Attainment of steady-state was determined by inspection of the concentration-time profiles and attainment of a plateau of C_{trough}. From history it was expected for a monoclonal antibody (mAb) directed against PD-1 with observed linear kinetics at the defined dose level and dosing interval, steady-state was achieved by week 18 (i.e., after approximately 4 months of cemiplimab IV administration). Furthermore, predicted AUC3W after the fifth and sixth 350 mg every 3 weeks (Q3W) intravenous (IV) doses of cemiplimab showed that >90% and >95% of the exposure at plateau were reached after the fifth and sixth cemiplimab Q3W IV dose, respectively. The PopPK approach supported the selection of week 18 to report descriptive cemiplimab concentrations at steady state in the clinical pharmacology report of Study REGN2810-ONC-1676 (Study 1676).

Cemiplimab exposure data in special populations were also presented. Exposure at steady state in special populations between the target population of patients with R/M cervical cancer (292 patients in Study 1676) vs. the PopPK population (1062 patients) was compared for age, renal function, hepatic function, and baseline albumin, respectively.

No additional information or impact on exposures was observed on age, moderate or severe renal impairment, and/or moderate or severe hepatic impairment, in the target population in Study 1676 that would have an impact on the dosing profile for special populations.

In the descriptive exposure-efficacy analysis, Kaplan-Meier curves of OS by quartile of Ctrough after the first dose (Ctrough,1) were performed. An apparent E-R was suggested by MAH with improved OS in the higher quartile of exposures. However, this univariate analysis was confounded by the correlation of Ctrough,1 with baseline levels of albumin, which itself was correlated with baseline ECOG performance status. Given these underlying confounding factors, it is difficult to conclude on the significance of the E-R relationship results, especially over such a narrow exposure range, as these confounding factors cannot be completely eliminated from the analysis with the available data.

Kaplan-Meier (K-M) curves of PFS and DOR did not reveal any trends, and the rank order of the quartiles was not preserved. Therefore, further analyses with Cox PH modelling were not deemed necessary for these endpoints.

Logistic regression analyses conducted on ORR showed no significant relationship with cemiplimab exposure as indicated by the flat E-R for ORR.

In the exposure-safety relationship analysis, Kaplan-Meier plots for irAEs grade ≥3 and for all irAEs suggested a trend where higher exposure quantiles (Cmax) were correlated with higher probabilities of experiencing irAEs. However, univariate Cox PH modelling for irAEs grade ≥3 and for all irAEs showedd that exposure metrics were not significant predictors of irAE hazard. Therefore, it is unlikely that an E-R relationship for all irAEs and irAEs grade ≥3 exists in patients with R/M cervical cancer in Study 1676. Similar results were observed for Ctrough and Cav.

Overall, no E-R relationships for both efficacy and safety endpoints were found in R/M patients with cervical cancer in Study 1676 who received cemiplimab 350 mg Q3W IV. These results are consistent with the knowledge gained from prior E-R relationship analyses of cemiplimab in patients with advanced CSCC, advanced BCC, and advanced NSCLC.

Consistent with the incidence of ADA observed across all studies, in patients with R/M cervical cancer who received cemiplimab 350 mg Q3W IV in Study 1676, the incidence of treatment emergent ADA (1.9%) and of persistent ADA (0%) was estimated to be low.

Since cemiplimab is a human monoclonal antibody and hence cleared from the circulation through catabolism, and not subject to protein transporters, no metabolic drug-drug interactions are expected. Hence it is acceptable that no formal pharmacokinetic drug interaction studies were submitted.

No changes to section 5.2 of the SmPC are required since the results from the popPK analysis were already updated as part of variation EMEA/H/C/004844/II/31.

2.3.5. Conclusions on clinical pharmacology

The presented clinical pharmacology data for cemiplimab support the approvability of cemiplimab 350 mg Q3W IV for the treatment of patients with R/M cervical cancer.

2.4. Clinical efficacy

2.4.1. Main study

- **Main study – R2810-ONC-1676**

Study 1676 is an ongoing open-label, randomised 1:1, multicentre, pivotal phase III trial that evaluates the efficacy and safety of cemiplimab monotherapy vs. investigator's choice of chemotherapy

(pemetrexed or topotecan or irinotecan or gemcitabine or vinorelbine) in women with recurrent or metastatic cervical cancer after progression to platinum-containing chemotherapy with or without bevacizumab. Patients were enrolled regardless of PD-L1 status. Figure 18 provides an overview of the key features of Study 1676.

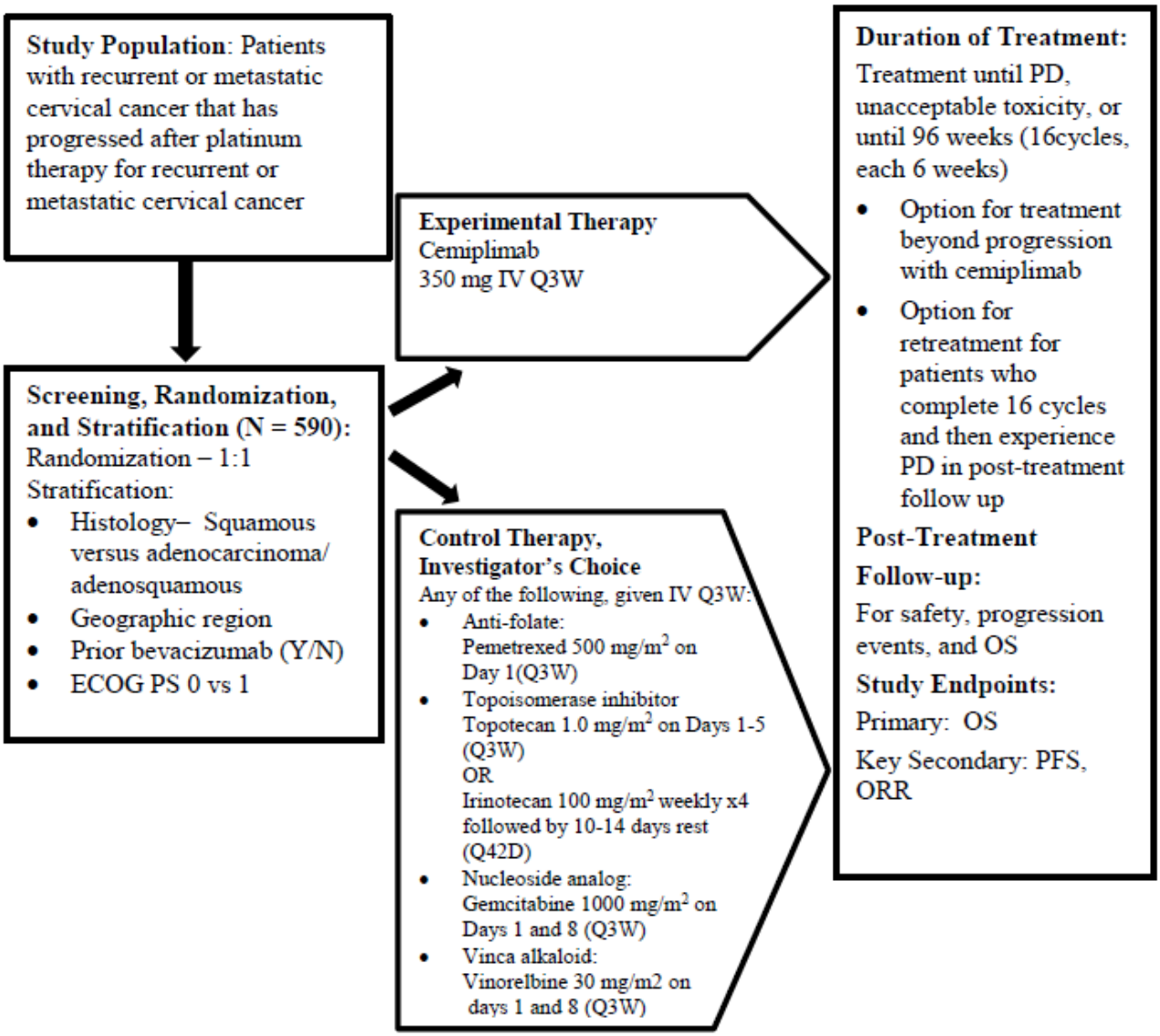


Figure 18: Design scheme of Study 1676

The study included 3 periods: screening, treatment, and follow-up. The screening period began with the signing of the informed consent form (ICF). Cycle length was 6 weeks, and tumour imaging (efficacy assessment) was at the end of cycles 1 through 4, 6, 8, 10, 12, 14, and 16. Imaging was also performed during follow-up visit 1 (30 ±10 days from last dose of cemiplimab or IC of chemotherapy) and follow-up visit 2 (90 ±10 days after follow-up visit 1). The investigator decided whether imaging was done by CT or MRI, but subsequent assessments should have been made using the same modality.

Cross-over treatment at progression was not allowed.

An independent data monitoring committee (IDMC) composed of members who were independent from the sponsor and the study investigators monitored patient safety by conducting formal reviews of accumulated safety data. At prespecified interim analyses only, the IDMC also monitored and reviewed the interim primary efficacy analyses for OS in the SCC population. If requested, the IDMC could have access to the treatment allocation code or any other requested data for the purposes of a risk-benefit assessment. The IDMC acted in an advisory capacity to the sponsor.

Methods

Study participants

Key inclusion criteria:

1. Recurrent, persistent, and/or metastatic cervical cancer with squamous cell histology, for which there is not a curative-intent option (surgery or radiation therapy with or without chemotherapy).
   a. Patients with the following histologies: squamous carcinoma, adenocarcinoma, and adenosquamous carcinoma, were to be enrolled from the original protocol through protocol Amendment 4. For the purpose of this study, adenosquamous carcinoma was to be stratified as adenocarcinoma.
   b. Starting with protocol Amendment 5, only patients with squamous cell histology are eligible to enrol.
2. Tumour progression or recurrence after treatment with platinum therapy (must have been used to treat metastatic, persistent, or recurrent cervical cancer). NOTE: Platinum-therapy given in other settings (e.g., concurrent with radiation therapy as part of curative-intent therapy, after radiation [or chemoradiation] as adjuvant treatment in a patient with no evidence of disease) does not satisfy the eligibility requirement regarding prior platinum therapy.
3. Patient must have measurable disease as defined by RECIST 1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least 1 dimension (longest dimension to be recorded). Each lesion must be ≥10 mm when measured by computed tomography (CT), magnetic resonance imaging (MRI), or caliper measurement by clinical exam or must be ≥20 mm when measured by chest x-ray. Lymph nodes must be >15 mm in short axis when measured by CT or MRI.

   Tumours within a previously irradiated field will be designated as non-measurable lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.
4. Eastern Cooperative Oncology Group (ECOG) performance status ≤1
5. ≥18 years old
6. Hepatic function:

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

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

c. Alkaline phosphatase ≤2.5x ULN (or ≤5.0x ULN, if liver or bone metastases)

7. Renal function: Serum creatinine ≤1.5x ULN or estimated creatinine clearance >45 mL/min

8. Bone marrow function:

a. Hemoglobin ≥9.0 g/dL

b. Absolute neutrophil count (ANC) ≥1.5x 10^9/L

c. Platelet count ≥75 x 10^9/L

9. Anticipated life expectancy >12 weeks

10. At least one of the following criteria regarding prior bevacizumab therapy:

a. Received prior bevacizumab-containing therapy, which was discontinued due to progression of disease or toxicity

b. Was deemed unsuitable for prior bevacizumab therapy for one of the following reasons: (i) unacceptable risk of fistula formation; (ii) poorly controlled hypertension; (iii) "low risk" disease according to the Moore Criteria (Tewari 2015).

c. Refused prior bevacizumab therapy.

d. Did not have access to bevacizumab therapy due to logistical reasons (e.g., lived in a region in which bevacizumab was not commercially available for patients with cervical cancer, or did not have insurance coverage for bevacizumab).

11. At least one of the following criteria regarding prior paclitaxel therapy:

a. Received prior paclitaxel-containing therapy, which was discontinued due to progression of disease or toxicity.

b. Was deemed unsuitable for prior paclitaxel therapy for one of the following reasons: (i) neuropathy (ii) allergy to paclitaxel or its components.

c. Refused prior paclitaxel therapy.

<u>Key exclusion criteria:</u>

1. Ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest higher risk for severe irAEs. The following are not exclusionary: vitiligo, childhood asthma that hasresolved, type 1 diabetes, residual hypothyroidism that required only hormone replacement, or psoriasis that does not require systemic treatment.

2. Prior treatment with an agent that blocks the PD-1/PD-L1 pathway.

3. Prior treatment with other systemic immune-modulating agents that was (a) within fewer than 4 weeks (28 days) of the enrollment date, or (b) associated with irAEs of any grade within 90 days prior to enrollment, or (c) associated with toxicity that resulted in discontinuation of the immune-modulating agent. Examples of immune-modulating include therapeutic vaccines, cytokine

treatments (other than granulocyte colony stimulating factor or erythropoietin), or agents that target cytotoxic T-lymphocyte antigen 4 (CTLA-4), 4-1BB (CD137), PI 3-K-delta, LAG3, or OX-40.

4. Known history of brain metastasis(es) that may be considered active (screening imaging of brain is not required unless there is clinical suspicion of brain metastases). Patients with previously treated brain metastases may participate provided that the lesions are stable (without evidence of progression for at least 6 weeks on imaging obtained during the screening period), there is no evidence of new or enlarging brain metastases, and the patient does not require any immunosuppressive doses of systemic corticosteroids for management of brain metastases within 4 weeks of the first dose of study drug (cemiplimab or IC chemo).

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

6. Active bacterial, viral, fungal or mycobacterial infection requiring therapy, including known infection with human immunodeficiency virus (HIV), or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).

7. Pneumonitis (interstitial pneumonitis, non-infectious pneumonia, interstitial lung disease) within the last 5 years.

8. History of documented allergic reactions or acute hypersensitivity reaction attributed to antibody treatments

9. Concurrent malignancy other than cervical cancer and/or history of malignancy other than cervical cancer within 3 years of date of first planned dose of study drug (cemiplimab or IC chemo), except for tumors with negligible risk of metastasis or death, such as adequately treated cutaneous squamous cell carcinoma or basal cell carcinoma of the skin or ductal carcinoma in situ of the breast. Patients with hematologic malignancies (eg, chronic lymphocytic leukemia) are excluded.

10. Any acute or chronic psychiatric problems that, in the opinion of the investigator, make the patient ineligible for participation.

11. Patients with a history of solid organ transplant (patients with prior corneal transplant(s) may be allowed to enroll after discussion with and approval from the medical monitor).

12. Any medical co-morbidity, physical examination finding, or metabolic dysfunction, or clinical laboratory abnormality that, in the opinion of the investigator, renders 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.

13. Pregnant or breastfeeding women.

14. Women of childbearing potential who are unwilling to practice highly effective contraception prior to the initial study drug treatment, during the study, and for at least 6 months after the last dose.

15. Prior treatment with idelalisib

16. Prior treatment with live vaccines within 30 days of initial administration of study drug (cemiplimab or IC chemo). Patients must not be treated with live vaccines during the study and up to 5 half-lives following the last dose of study drug

Treatments

Experimental arm: Cemiplimab at a flat dose of 350 mg Q3W IV, the currently approved dose and schedule.

Control arm: Investigator's choice (IC) chemotherapy agents were of 4 classes:

- Antifolate: pemetrexed (500 mg/m^2 IV on day 1, Q3W)
- Topoisomerase 1 inhibitor: topotecan (1.0 mg/m^2 on days 1 to 5, Q3W) or irinotecan (100 mg/m^2 weekly X 4, followed by 10 to 14 days rest, every 6 weeks [Q6W])
- Nucleoside analogue: gemcitabine (1000 mg/m^2 IV on days 1 and 8, Q3W)
- Vinca alkaloid: vinorelbine (30 mg/m^2 on days 1 and 8, Q3W).

The study design did not allow cross over between treatment arms.

Planned treatment for both arms was up to 96 weeks (up to 16 cycles of 6 weeks each), disease progression, unacceptable toxicity, or withdrawal of consent. For patients in the cemiplimab arm, there was an option for treatment past progression. Patients who experienced progressive disease on cemiplimab were permitted to continue treatment with cemiplimab, as long as they had not presented cemiplimab-related safety concerns and their disease was not rapidly progressive.

According to the protocol, treatment with cemiplimab beyond progression was permitted in patients who fulfilled the following conditions:

- Stable performance status
- The patient does not have rapid progression of disease
- The patient has not experienced adverse events that would require permanent discontinuation of cemiplimab
- The patient provides written informed consent prior to resuming treatment by signing the current version of the ICF (eg, the patient repeats the written informed consent that was done prior to initial study enrollment).
- It is understood that, if there is further progression after resumption of treatment (≥30% increase in tumor burden from the time of initial progressive disease by RECIST criteria; this includes an increase in the sum of all target lesions and/or the development of new lesions), that cemiplimab will be discontinued.

Objectives

Primary objective: To compare overall survival (OS) for patients with recurrent or metastatic cervical cancer who have histology of squamous cell carcinoma (SCC) and who have any eligible histology, treated with either cemiplimab or investigator's choice chemotherapy.

Secondary objectives (performed among SCC patients and among all eligible histologies [(SCC and adenocarcinoma/adenosquamous carcinoma]) were :

• To compare progression-free survival (PFS) of cemiplimab versus IC chemotherapy.

- To compare objective response rate (ORR) (partial response [PR] + complete response [CR]) of cemiplimab versus IC chemotherapy per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1.
- To compare the duration of response (DOR) of cemiplimab versus IC chemotherapy.
- To compare the safety profiles of cemiplimab versus IC chemotherapy by describing adverse events (AE).
- To compare quality of life (QOL) for patients treated with cemiplimab versus IC chemotherapy using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30).

Exploratory Objectives:

- To measure concentrations of cemiplimab in serum and characterize the pharmacokinetics (PK) of cemiplimab.
- To assess the immunogenicity of cemiplimab.
- To explore associations between the clinical efficacy of cemiplimab and molecular features in pretreatment tumour samples.
- To explore the pharmacodynamic activity of cemiplimab on the immune system in peripheral blood samples

Outcomes/endpoints

Primary efficacy endpoint: OS, defined as the time from randomisation to the date of death. For patients who did not have a death date at the time of data cutoff, OS was censored at last known alive date.

Secondary endpoints:

- PFS by investigator: defined as the time from randomisation to the date of the first documented tumour progression using RECIST 1.1 per investigator assessment, or death due to any cause. Patients who do not have a documented tumour progression or death will be censored on the date of their last evaluable tumour assessment. Patients who do not have any evaluable tumour assessments after randomization and do not die were to be censored on the date of randomization.
- ORR by investigator: defined as the number of patients with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) using RECIST 1.1 per investigator assessment divided by the number of patients in the efficacy analysis set. Best overall response was defined as the BOR between the date of randomization and the date of the first objectively documented progression or the date of subsequent anti-cancer therapy, whichever came first.

Other endpoints included duration of response (DOR) and patient reported outcomes (PRO). Duration of response was defined as the time between the date of first response (CR or PR) to the date of the first documented tumour progression (per RECIST 1.1) or death due to any cause.

Patients with recurrent or metastatic cervical carcinoma were given the opportunity to report on their symptoms, functioning and overall QoL in Study 1676 using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) PRO instrument, version 3.

Patient safety was to be assessed through the collection of reported adverse events (AEs), clinical laboratory data, vital signs, ECG and physical exam. Unless otherwise noted, the baseline value was defined as the last available value before the first dose of study treatment.

Sample size

The primary endpoint was overall survival among patients treated with cemiplimab versus IC of chemotherapy. The median OS has been reported in range of 6.5 months to 8.1 months in the phase 2 setting. The sponsor assumed a median OS of 7 months for SCC patients treated with IC chemotherapy and a median OS of 10 months for SCC patients treated with cemiplimab. The assumptions corresponded to an approximately 42.8% increase in median OS and a hazard ratio (HR) of 0.7 if OS is distributed exponentially in both treatment groups.

Two interim efficacy analyses were planned using Lan-DeMets (O'Brien-Fleming) spending function at 70% and 85% of the total OS events, respectively. A total of 340 OS events in SCC patients was to yield approximately 90% power to detect an HR of 0.7 with an overall type I error of 0.025 (1-sided).

Considering the enrollment rate (2 patients/month for months 1 to 5, 9 patients/month for months 6 to 16, 20 patients/month for months 17 to 23, and 22 patients/month for month 24 and beyond) and 10% dropout rate per year, enrollment of 460 randomized SCC patients was to yield 340 OS events for analysis of OS around 42 months after the first SCC patient is randomized.

At the time when 460 SCC patients were enrolled in the study, a total enrollment in the study of approximately 590 patients was projected (SCC plus non-SCC). The actual number of patients to be enrolled was to depend on the proportion of adenocarcinoma patients in the patient population and the time when Amendment 5 was implemented at each of the study sites. If the HR was 0.7, the power for testing OS in the overall population was to be higher than 90%.

Randomisation

Randomization was stratified according to:

1. Histology (squamous cell carcinoma vs. adenocarcinoma). Adenosquamous histology was considered adenocarcinoma for the purpose of stratification.

2. Geographic Region: North America (Canada, USA) vs. Asia (Japan, South Korea, Taiwan) vs. Rest of World (ROW) (Australia, Brazil, Poland, Russia, Spain, Belgium, Italy, Greece, UK)

3. Prior bevacizumab (yes/no)

4. ECOG performance status (0,1)

The stratification factors of "prior bevacizumab use" and "ECOG performance status" were used for balancing treatment assignment only and were not included in the statistical model for analysis of the primary endpoint.

Blinding (masking)

This was an open-label study.

Statistical methods

Efficacy analysis population

The full analysis set (FAS) included all randomized patients. This was the intention to treat population. The FAS was based on the treatment allocated (as randomized). All efficacy endpoints were analysed using the FAS.

Primary efficacy endpoint OS

The primary endpoint of OS was to be analysed in SCC patients by stratified log-rank test using geographic region (North America versus Asia-Pacific versus ROW) as a stratification factor. The HR and its 95% CI were to be estimated by a stratified Cox regression model with Efron's method for tie handling and using the treatment as covariate. The distribution of OS was to be estimated using the Kaplan-Meier method.

If the analysis of OS was statistically significant in the SCC patients, then the analysis of OS was to be performed in the overall population by stratified log-rank test using the following stratification factors (histology and geographic region). The HR and its 95% CI were to be estimated by a stratified Cox regression model with Efron's method for tie handling and using the treatment as covariate. The Kaplan-Meier estimate of median OS with its 95% CI and the estimates with the 95% CIs at specific time points were to be summarized by treatment group.

Censoring rules for OS

A patient who has not died was to be censored at the last known alive date.

Sensitivity analyses were to be performed for OS

- The first sensitivity analysis was to be performed using the stratification information (i.e., histology) collected in the clinical database.
- The second sensitivity analysis was to be performed using the Rank Preserving Structural Failure Time (RPSFT) model to account for the effect of the PD-1/PD-L1 treatments after disease progression in the chemotherapy arm
- The third sensitivity analysis was to be performed to account for the effect of the posttreatment immune check-point inhibitors (including PD1/PDL1, and others) in both arms after primary study period. Patients who received post-treatment immune checkpoint inhibitors were to be censored on the start date of post-treatment immune checkpoint inhibitors.

Key secondary efficacy endpoints PFS and ORR

PFS

The analysis of PFS was to be analysed using the same statistical method as described for the primary analysis of OS with regard to SCC and overall population.

Censoring rules for PFS

Patients who do not have a documented tumour progression or death were to be censored on the date of their last evaluable tumour assessment. Patients who do not have any evaluable tumour assessments after randomization and do not die were to be censored on the date of randomization.

Sensitivity analyses will be performed for PFS

The first sensitivity analysis was the same as the main analysis except that it considered initiation of new anti-cancer therapy as a progressive disease event for patients without documented radiological PD or death on or prior to initiation of new anticancer treatment.

The second sensitivity analysis was the same as the main analysis except that it considered clinical progression as a progressive disease event for patients without documented radiological PD or death on or prior to clinical progression.

ORR

The ORR was to be analysed using Cochran-Mantel-Haenszel test stratified by the same stratification factors used in analysis of OS with regard to the SCC and overall population. ORR and the corresponding 95% exact CI will be calculated by Clopper-Pearson method for each treatment arm.

Patients with the best overall response of NE will be considered as non-responder.

One sensitivity analysis will be performed using the same method as above in ORR eligible patients, defined as all randomized patients who had baseline and at least one valid post-baseline tumor evaluation.

Multiplicity considerations

The multiplicity was controlled at one-sided 0.025 level by group sequential design for interim and final analyses for OS in SCC patients and a hierarchical testing procedure for OS, PFS, QoL and ORR in SCC and overall population.

Type I error control for interim and final analyses of OS in SCC patients using group sequential design

Two interim efficacy analyses were planned for the primary endpoint of OS in SCC patients using Lan-DeMets (O'Brien-Fleming) spending function at 70% and 85% of the total OS, respectively.

The first interim efficacy analysis was to be performed after observing approximately 238 OS events in SCC patients (70% of total OS events). The second interim efficacy analysis was to be performed after observing approximately 289 OS events in SCC patients (85% of total OS events). The final efficacy analysis was to be performed after observing approximately 340 OS events in SCC patients. The actual alpha spending was to be based on the actual number of OS events included in the analyses and determined.

Type I error control for OS, PFS, QoL and ORR in SCC and overall population using hierarchical testing procedure

Table 27: statistical testing for efficacy results (listed in hierarchical order as pre-specified in SAP)

Endpoint	
1.	OS in SCC population
2.	OS in total population (also called the overall population)
3.	PFS in SCC population
4.	Overall mean change from baseline in GHS/QoL scale in SCC population
5.	Overall mean change from baseline in physical functioning scale in SCC population
6.	ORR in SCC population
7.	PFS in total population
8.	ORR in total population
9.	Mean change from baseline to cycle 2 in GHS/QoL scale in SCC population
10.	Mean change from baseline to cycle 2 in physical functioning scale in SCC population
11.	Overall mean change from baseline in GHS/QoL scale in total population
12.	Overall mean change from baseline in physical functioning scale in total population
13.	Mean change from baseline to cycle 2 in GHS/QoL scale in total population
14.	Mean change from baseline to cycle 2 in physical functioning scale in total population

GHS/QoL=global health status/quality of life; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; SAP=statistical analysis plan; SCC=squamous cell carcinoma.

Source: CSR, page 37/135.

Changes to the SAP and to the planned analyses

All changes in the planned analyses for the study were implemented by SAP amendment(s), as described in the SAP, see under study conduct, protocol amendments.

Results

Participant flow

A total of 752 patients were screened for study eligibility.

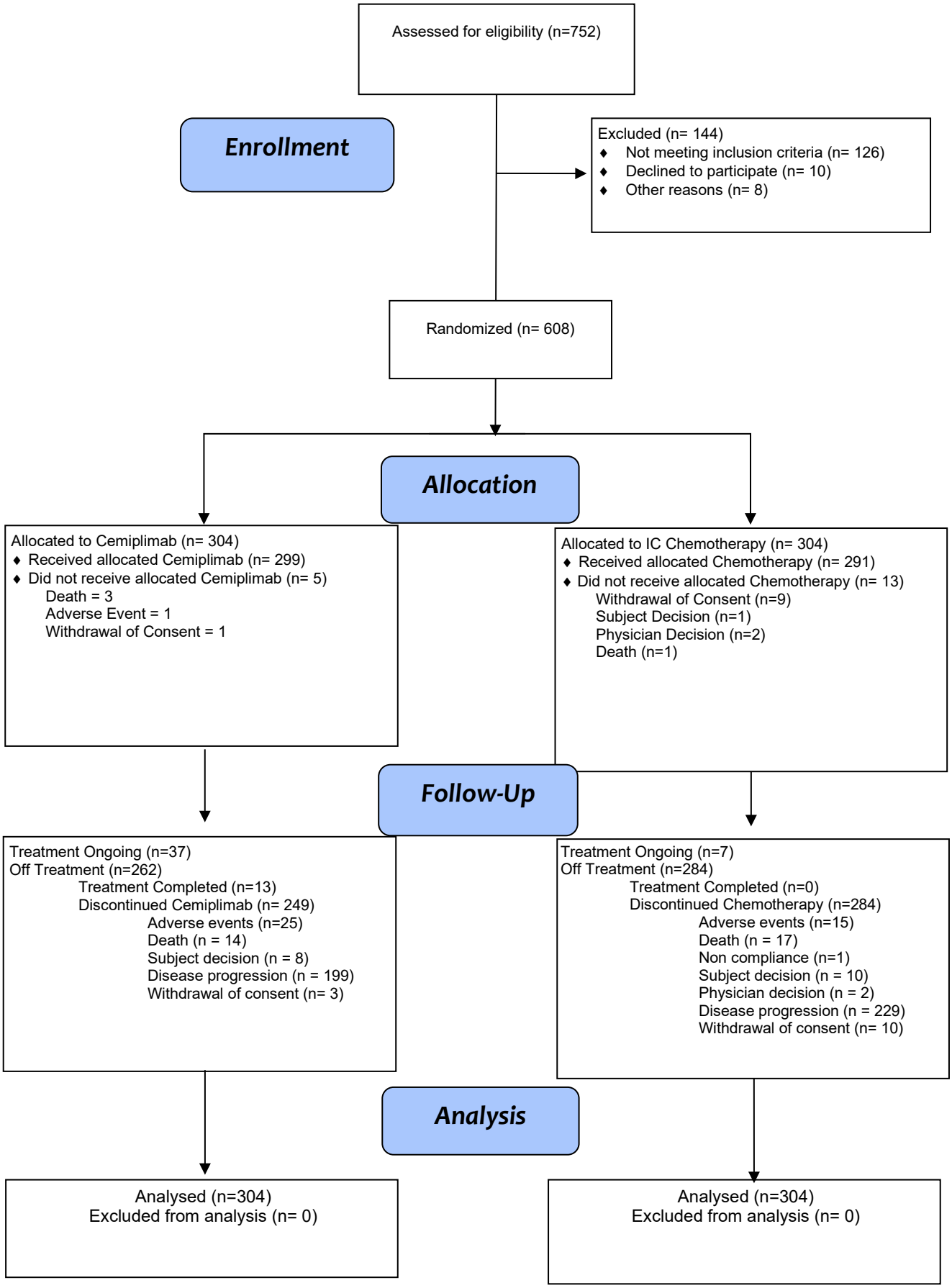


Figure 19: Participant Flow - Study 1676

Of the patients screened, 608 were randomized, 304 patients to the cemiplimab arm and 304 patients to the investigator's choice of chemotherapy arm. Table 28 shows patient disposition for the intention-to-treat (ITT) population of the pivotal trial.

As of the data cut-off for the CSR (04 January 2021), the median follow-up duration (from randomisation to data cutoff date) for the total population was 18.18 months (range: 6.0 to 38.2 months).

Table 28: Study 1676 – Patient disposition (ITT)

	SCC and AC	
	Cemiplimab (N=304)	**Chemotherapy (N=304)**
Randomized but Never Treated, n (%)	5 (1.6%)	13 (4.3%)
Treatment Ongoing, n (%)	37 (12.2%)	7 (2.3%)
Off Treatment, n (%)	262 (86.2%)	284 (93.4%)
Treatment completed	13 (4.3%)	0
Treatment discontinued	249 (81.9%)	284 (93.4%)
Primary reason for treatment discontinuation		
Adverse event	25 (8.2%)	15 (4.9%)
Death	14 (4.6%)	17 (5.6%)
Noncompliance with study drug(s)	0	1 (0.3%)
Subject decision	8 (2.6%)	10 (3.3%)
Physician decision	0	2 (0.7%)
Disease progression	199 (65.5%)	229 (75.3%)
Withdrawal of consent	3 (1.0%)	10 (3.3%)
Study ongoing, n (%)	53 (17.4%)	11 (3.6%)
Off study, n (%)	251 (82.6%)	293 (96.4%)
Study completed	7 (2.3%)	0
Study discontinued	244 (80.3%)	293 (96.4%)
Primary reason for study discontinuation		
Adverse event	9 (3.0%)	7 (2.3%)
Death	92 (30.3%)	95 (31.3%)
Lost to follow-up	2 (0.7%)	2 (0.7%)
Noncompliance with study drug(s)	0	1 (0.3%)
Subject decision	34 (11.2%)	42 (13.8%)
Physician decision	1 (0.3%)	3 (1.0%)
Disease progression	98 (32.2%)	117 (38.5%)
Withdrawal of consent	8 (2.6%)	26 (8.6%)

Data cut-off as of 04 Jan 2021.
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTT 14.1.1.5.1all

Table 29: Study 1676 – Actual treatment among randomised patients (ITT)

	Assigned Treatment per IWRS						
Actual Treatment Status	Cemiplimab (N=304)	Chemotherapy Pemetrexed (N=111)	Chemotherapy Topotecan (N=21)	Chemotherapy Irinotecan (N=19)	Chemotherapy Gemcitabine (N=121)	Chemotherapy Vinorelbine (N=32)	Chemotherapy All (N=304)
Randomized but never treated	5 (1.6%)	2 (1.8%)	5 (23.8%)	0	3 (2.5%)	3 (9.4%)	13 (4.3%)
Treated as assigned	299 (98.4%)	109 (98.2%)	16 (76.2%)	19 (100%)	118 (97.5%)	28 (87.5%)	290 (95.4%)
Treated but not as assigned	0	0	0	0	0	1 (3.1%)	1 (0.3%)
Cemiplimab	NA	0	0	0	0	1 (3.1%)	1 (0.3%)
Pemetrexed	0	NA	0	0	0	0	0
Topotecan	0	0	NA	0	0	0	0
Irinotecan	0	0	0	NA	0	0	0
Gemcitabine	0	0	0	0	NA	0	0
Vinorelbine	0	0	0	0	0	NA	0

Source: Post-text tables, page 55/1482

Protocol deviations

Table 30: Study 1676 – Important protocol deviations (ITT)

	Cemiplimab (N=304)	Chemotherapy (N=304)	Total (N=608)
Number of important protocol deviations	39	20	59
Patients with any important protocol deviation, n (%)	33 (10.9%)	19 (6.3%)	52 (8.6%)
Type of important protocol deviations, n (%)			
Exclusion criteria met but subject enrolled	5 (1.6%)	1 (0.3%)	6 (1.0%)
Inadequate informed consent administration	1 (0.3%)	1 (0.3%)	2 (0.3%)
Inclusion criteria not met but subject enrolled	5 (1.6%)	4 (1.3%)	9 (1.5%)
Other	13 (4.3%)	5 (1.6%)	18 (3.0%)
Procedure not performed	0	2 (0.7%)	2 (0.3%)
Treatment deviation	11 (3.6%)	6 (2.0%)	17 (2.8%)

Data cutoff as of 04 Jan 2021.
AC=adenocarcinoma/adenosquamous histology; SCC=squamous cell carcinoma.
Source: PTT 14.1.1.6all.

Recruitment

The first patient was randomised on 30 October 2017 and the last patient was randomised on 7 July 2020.

Enrollment took place in 14 countries. The leading countries for patient enrollment were Brazil (89 patients), Russia (85 patients), and South Korea (76 patients). Enrollment included 172 patients from Europe (Spain, Poland, Italy, Belgium, Greece, United Kingdom), 56 patients from Japan, 34 patients from Taiwan, 30 patients from Australia, and 66 patients from North America (US, Canada).

Conduct of the study

At the time of data cutoff (04 January 2021), Study 1676 had 7 protocol amendments. Only the study conduct reflected in the latest protocol amendment prior to the database lock date was presented in this application. The major protocol amendments are presented in the following table.

Table 31: Study 1676 - Major protocol amendments along study conduct

Amendment/Date	Major Changes
Amend. 6 26 May 2020	• Added 2 interim analyses to provide early efficacy assessment in the unmet-need population. Increased sample size to maintain 90% power with 2 protocol-specified interim analyses. Interim efficacy analyses to be reviewed by an IDMC. • Added language to meet a requirement under the guidance of EU and the US authorities to address considerations related to conduct of a study during the COVID-19 pandemic, including statistical analysis language.
Amend. 5 8 Mar 2019	• Updated study population to cap enrollment of patients with adenocarcinoma histology to mimic real world distribution. Updated the statistical plan to hierarchically analyze SCC population prior to total study population. SCC patient enrollment was increased to maintain statistical power. • Removed interim futility rule because the OS benefit of immune checkpoint blockers in oncology studies may not be evident in an early event analysis.
Amend. 4 16 Aug 2018	• Removed the requirement for patients to be platinum-refractory, defined as progression of disease within 6 months of last dose of platinum therapy. The term 'platinum-refractory' used to describe the patient population was removed from the protocol. • Revised inclusion requiring platinum-therapy. Patients must have had disease progression after prior platinum therapy in recurrent or metastatic disease setting, but without the requirement for progression within 6 months of last dose.
Amend. 3 JP 27 Apr 2018	• Inclusion criterion #5 clarified to include the following statement: For patients enrolling in Japan who are ≥18 and <20 years old, both the patient and parent/legal representative must provide signed informed consent. • Per standard of care in Japan, for patients enrolling in Japan, there were to be at least 14 days of rest before subsequent irinotecan administration. • GCP Statement section clarified to include the following text: "The clinical study will be conducted in compliance with Pharmaceutical and Medical Device Act, Japanese GCP, and other relevant laws in Japan".
Amend. 3 21 Mar 2018	• Updated the monitoring needed for IC chemotherapy of vinorelbine treatment, to align with the standard of care. • Subgroup analyses of patients from Japan were included. • MedDRA-derived PT for potential imAEs list was updated as per MedDRA version 20.1.
Amend. 2 3 Nov 2017	• Revised exclusion criteria per request from the South Korean Ministry of Food and Drug Safety. • Added ECOG performance status as a stratification factor for randomization to balance treatment assignment, per request from the US FDA. The ECOG performance status was not to be included in the primary analysis model for efficacy.
Amend. 1 14 Jul 2017	• An exclusion criterion was added to exclude patients who had previously been treated with idelalisib from being treated with REGN2810. • Additional safety guidance language was added for the management of patients developing stomatitis or mucositis. • An AESI was added to the list of AESIs that require accelerated reporting to the Sponsor. • An imAE of any grade in a patient previously treated with a PI-3-K inhibitor was added to the list of events that require accelerated reporting to the Sponsor.

Source: CSR, page. 28/135.

SAP amendments

Table 32: Modifications from the approved statistical analysis plan

SAP vesion	Changes
SAP v3.0	This SAP was updated to include additional PRO endpoints: 1. Section 5.8.3, the adjusted mean estimates at cycle 2 was added. 2. Section 7.2, the PRO endpoints will be tested in SCC and then in overall population in the hierarchy.
SAP v2.0	This SAP was updated according to R2810-ONC-1676 all Protocol Amendements, up to Amendement 6. The major changes include: 1. Section 2.2, updated sample size with interim analysis, targeted population and enrollement rate. 2. Section 5.8.1, the primary efficacy analysis will be performed with a hierarchical order of SCC patients, then overall population. 3. Sections 7 and 8, added multiplicity control to reflect interim analyses using Lan-DeMets O'Brien-Fleming alpha spending function, and hierarchical order in testing the primary endpoints and secondary endpoints.
SAP v0.2	This is the original version of SAP

Source: SAP v3.0, page 10/38.

Baseline data

Table 33: Study 1676 – Demographics and baseline characteristics (ITT)

	Cemiplimab (N=304)	Chemotherapy (N=304)	Total (N=608)
Age (years)			
n	304	304	608
Mean (SDv)	51.1 (11.59)	51.2 (11.77)	51.1 (11.67)
Median	51.0	50.0	51.0
Q1 : Q3	42.0 : 60.0	43.0 : 59.0	43.0 : 59.0
Min : Max	22 : 81	24 : 87	22 : 87
Age Groups (years), n (%)			
<65	269 (88.5%)	264 (86.8%)	533 (87.7%)
≥65	35 (11.5%)	40 (13.2%)	75 (12.3%)
Age Groups (years), n (%)			
<65	269 (88.5%)	264 (86.8%)	533 (87.7%)
≥65 and <75	30 (9.9%)	29 (9.5%)	59 (9.7%)
≥75	5 (1.6%)	11 (3.6%)	16 (2.6%)
Race, n (%)			
White	193 (63.5%)	192 (63.2%)	385 (63.3%)
Black or African American	9 (3.0%)	12 (3.9%)	21 (3.5%)
Asian	88 (28.9%)	88 (28.9%)	176 (28.9%)
American Indian or Alaska native	2 (0.7%)	1 (0.3%)	3 (0.5%)
Other	8 (2.6%)	4 (1.3%)	12 (2.0%)
Unknown	1 (0.3%)	1 (0.3%)	2 (0.3%)
Not reported	3 (1.0%)	6 (2.0%)	9 (1.5%)
Ethnicity, n (%)			
Not Hispanic or Latino	251 (82.6%)	250 (82.2%)	501 (82.4%)
Hispanic or Latino	47 (15.5%)	44 (14.5%)	91 (15.0%)
Not reported	6 (2.0%)	10 (3.3%)	16 (2.6%)
Geographic region, n (%)			
North America	32 (10.5%)	34 (11.2%)	66 (10.9%)
Asia	83 (27.3%)	83 (27.3%)	166 (27.3%)
Rest of World	189 (62.2%)	187 (61.5%)	376 (61.8%)
Height (cm)			
n	304	304	608
Mean (SDv)	160.73 (6.639)	159.99 (6.628)	160.36 (6.638)
Median	160.15	159.05	160.00
Q1 : Q3	155.90 : 165.10	155.35 : 164.50	155.65 : 165.00
Min : Max	147.0 : 178.0	137.0 : 181.0	137.0 : 181.0
Body Weight (kg)			
n	304	304	608
Mean (SDv)	64.14 (16.166)	63.60 (16.140)	63.87 (16.142)
Median	61.80	61.20	61.55
Q1 : Q3	51.90 : 73.00	52.00 : 73.20	52.00 : 73.00
Min : Max	35.9 : 128.7	35.0 : 120.0	35.0 : 128.7
BMI (kg/m^2)			
n	304	304	608
Mean (SDv)	24.779 (5.9095)	24.783 (5.8057)	24.781 (5.8530)
Median	23.480	23.720	23.595
Q1 : Q3	20.740 : 27.870	20.510 : 28.305	20.645 : 28.250
Min : Max	14.17 : 49.00	14.20 : 46.62	14.17 : 49.00
ECOG performance status, n (%)			
0	142 (46.7%)	141 (46.4%)	283 (46.5%)
1	162 (53.3%)	163 (53.6%)	325 (53.5%)

Data cut-off as of 04 Jan 2021.

AC, adenocarcinoma/adenosquamous histology; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; Max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile SCC, squamous cell carcinoma; SDv, standard deviation.

Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTT 14.1.2.1.1all

Table 34: Study 1676 – Baseline tumour characteristics (ITT)

	Cemiplimab (N=304)	Chemotherapy (N=304)	Total (N=608)
Histology/cytology per EDC n(%)			
AC Histology	64 (21.1%)	71 (23.4%)	135 (22.2%)
Adenocarcinoma	54 (17.8%)	62 (20.4%)	116 (19.1%)
Adenosquamous cell carcinoma	10 (3.3%)	9 (3.0%)	19 (3.1%)
SCC Histology	240 (78.9%)	233 (76.6%)	473 (77.8%)
Histology/cytology per IWRS n(%)			
AC Histology	65 (21.4%)	66 (21.7%)	131 (21.5%)
SCC Histology	239 (78.6%)	238 (78.3%)	477 (78.5%)
Histologic grade, n(%)			
Moderately differentiated	81 (26.6%)	93 (30.6%)	174 (28.6%)
Poorly differentiated	64 (21.1%)	67 (22.0%)	131 (21.5%)
Undifferentiated	4 (1.3%)	2 (0.7%)	6 (1.0%)
Unknown	123 (40.5%)	118 (38.8%)	241 (39.6%)
Well differentiated	32 (10.5%)	24 (7.9%)	56 (9.2%)
FIGO stage at initial diagnosis, n(%)			
Stage I	2 (0.7%)	1 (0.3%)	3 (0.5%)
Stage IA	2 (0.7%)	2 (0.7%)	4 (0.7%)
Stage IA1	1 (0.3%)	2 (0.7%)	3 (0.5%)
Stage IA2	0	2 (0.7%)	2 (0.3%)
Stage IB	14 (4.6%)	6 (2.0%)	20 (3.3%)
Stage IB1	24 (7.9%)	24 (7.9%)	48 (7.9%)
Stage IB2	16 (5.3%)	24 (7.9%)	40 (6.6%)
Stage II	12 (3.9%)	7 (2.3%)	19 (3.1%)
Stage IIA	7 (2.3%)	9 (3.0%)	16 (2.6%)
Stage IIA1	0	2 (0.7%)	2 (0.3%)
Stage IIA2	5 (1.6%)	4 (1.3%)	9 (1.5%)
Stage IIB	60 (19.7%)	65 (21.4%)	125 (20.6%)
Stage III	15 (4.9%)	10 (3.3%)	25 (4.1%)
Stage IIIA	2 (0.7%)	6 (2.0%)	8 (1.3%)
Stage IIIB	50 (16.4%)	55 (18.1%)	105 (17.3%)
Stage IVA	15 (4.9%)	15 (4.9%)	30 (4.9%)
Stage IVB	72 (23.7%)	63 (20.7%)	135 (22.2%)
Unknown	7 (2.3%)	7 (2.3%)	14 (2.3%)
Time from initial diagnosis to randomization (months) [a]			
n	304	304	608
Mean (SDv)	39.145 (38.0589)	39.580 (38.8464)	39.363 (38.4236)
Median	27.695	26.020	26.910
Q1 : Q3	16.115 : 47.050	16.475 : 46.505	16.315 : 46.520
Min : Max	3.81 : 283.33	3.68 : 296.41	3.68 : 296.41
Extent of Disease at screening, n(%)			
Metastatic	284 (93.4%)	290 (95.4%)	574 (94.4%)
Recurrent/Persistent	20 (6.6%)	14 (4.6%)	34 (5.6%)
Number of Target Lesions			
n	304	303	607
Mean (SD)	2.34 (1.269)	2.25 (1.194)	2.29 (1.232)
Median	2.00	2.00	2.00
Q1 : Q3	1.00 : 3.00	1.00 : 3.00	1.00 : 3.00
Min : Max	1.0 : 5.0	1.0 : 5.0	1.0 : 5.0
Sum of Target Lesions (mm)			
n	304	303	607
Mean (SD)	77.17 (52.511)	70.23 (47.701)	73.71 (50.246)

	Cemiplimab (N=304)	Chemotherapy (N=304)	Total (N=608)
Median	68.00	58.00	62.00
Q1 : Q3	37.00 : 102.00	35.00 : 97.00	35.20 : 100.00
Min : Max	10.1 : 359.0	10.0 : 278.0	10.0 : 359.0
Metastatic Sites, n(%)			
Bone	26 (8.6%)	34 (11.2%)	60 (9.9%)
Breast	2(0.7%)	1 (0.3%)	3 (0.5%)
Kidney	2 (0.7%)	3 (1.0%)	5 (0.8%)
Liver	78 (25.7%)	65 (21.4%)	143 (23.5%)
Lung	107 (35.2%)	94 (30.9%)	201 (33.1%)
Lymph node	196 (64.5%)	182 (59.9%)	378 (62.2%)
Other	154 (50.7%)	180 (59.2%)	334 (54.9%)
Ovary	7 (2.3%)	5 (1.6%)	12 (2.0%)
Parametrium	6 (2.0%)	6 (2.0%)	12 (2.0%)
Pericardium	0	3 (1.0%)	3 (0.5%)
Pleural effusion	11 (3.6%)	7 (2.3%)	18 (3.0%)
Rectum	4 (1.3%)	0	4 (0.7%)
Skin	1 (0.3%)	2 (0.7%)	3 (0.5%)
Small intestine	1 (0.3%)	1 (0.3%)	2 (0.3%)
Spleen	1 (0.3%)	6 (2.0%)	7 (1.2%)
Stomach	0	1 (0.3%)	1 (0.2%)

Data cut-off as of 04 Jan 2021.
AC, adenocarcinoma/adenosquamous histology; EDC, electronic data capture; IWRS, Interactive voice response system; Max, maximum; Min, minimum; SCC, squamous cell carcinoma; SDv, standard deviation.
[a] Time from Initial Diagnosis to Randomization (months) = (Date of randomization - Date of initial diagnosis)/30.4375.
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTT 14.1.1.8, 14.1.2.2.1all

Table 35: Study 1676 – Summary of prior cancer systemic therapy by setting (ITT)

	Cemiplimab (N=304)	Chemotherapy (N=304)	Total (N=608)
Number of patients with any prior cancer-related systemic therapy, n (%)	304 (100%)	304 (100%)	608 (100%)
Therapy setting, n (%)			
Concurrent with radiotherapy	139 (45.7%)	159 (52.3%)	298 (49.0%)
Recurrent, persistent, and/or metastatic	301 (99.0%)	304 (100%)	605 (99.5%)
Adjuvant	16 (5.3%)	14 (4.6%)	30 (4.9%)
Neo-adjuvant	19 (6.3%)	20 (6.6%)	39 (6.4%)
Other	1 (0.3%)	4 (1.3%)	5 (0.8%)
Number of prior lines (any setting), n (%)			
1	81 (26.6%)	66 (21.7%)	147 (24.2%)
2	126 (41.4%)	128 (42.1%)	254 (41.8%)
3	54 (17.8%)	72 (23.7%)	126 (20.7%)
4	26 (8.6%)	21 (6.9%)	47 (7.7%)
5	9 (3.0%)	12 (3.9%)	21 (3.5%)
6	4 (1.3%)	3 (1.0%)	7 (1.2%)
7	3 (1.0%)	1 (0.3%)	4 (0.7%)
8	1 (0.3%)	1 (0.3%)	2 (0.3%)
Number of prior lines (any setting)			
n	304	304	608
Mean (SD)	2.3 (1.24)	2.4 (1.15)	2.3 (1.20)
Median	2.0	2.0	2.0
Q1 : Q3	1.0 : 3.0	2.0 : 3.0	2.0 : 3.0
Min : Max	1 : 8	1 : 8	1 : 8
Number of prior lines of systemic therapy for recurrent or metastatic disease, n (%)			
1	177 (58.2%)	169 (55.6%)	346 (56.9%)
2	70 (23.0%)	83 (27.3%)	153 (25.2%)
3	31 (10.2%)	36 (11.8%)	67 (11.0%)
4	14 (4.6%)	9 (3.0%)	23 (3.8%)
5	7 (2.3%)	5 (1.6%)	12 (2.0%)
6	0	1 (0.3%)	1 (0.2%)
7	2 (0.7%)	1 (0.3%)	3 (0.5%)
Number of prior lines of systemic therapy for recurrent or metastatic disease			
n	301	304	605
Mean (SD)	1.7 (1.08)	1.7 (0.99)	1.7 (1.04)
Median	1.0	1.0	1.0
Q1 : Q3	1.0 : 2.0	1.0 : 2.0	1.0 : 2.0
Min : Max	1 : 7	1 : 7	1 : 7
Number of patients with prior bevacizumab, n (%)	148 (48.7%)	149 (49.0%)	297 (48.8%)
Number of patients with prior paclitaxel, n (%)	273 (89.8%)	287 (94.4%)	560 (92.1%)
Progressed after prior platinum therapy, n (%)			
<=6 months	266 (87.5%)	268 (88.2%)	534 (87.8%)
>6 months	33 (10.9%)	30 (9.9%)	63 (10.4%)
Missing*	5 (1.6%)	6 (2.0%)	11 (1.8%)
Prior Platinum Agent, n(%)			
CARBOPLATIN	192 (63.2%)	200 (65.8%)	392 (64.5%)
CISPLATIN	245 (80.6%)	250 (82.2%)	495 (81.4%)
NEDAPLATIN	8 (2.6%)	3 (1.0%)	11 (1.8%)
PLATINUM COMPOUNDS [a]	1 (0.3%)	0	1 (0.2%)

Data cutoff as of 04 Jan 2021.
*Eleven patients had a PD date as an incomplete date; therefore, they cannot be included into any of the categories above (<=6 or >6 clarify)
AC=adenocarcinoma/adenosquamous histology; Max=maximum; Min=minimum; SCC=squamous cell carcinoma; SD=standard deviation.
Source: PTT 14.1.3.1.1all., PTT14.1.3.3.1all.

Table 36. Summary of Prior Cancer Systemic Therapy by Setting – Longest Duration: Using the Longest Duration when Patients had Multiple Lines (FAS) – Patients with SCC and non-SCC Histology

	Cemiplimab (N=304)		Chemotherapy (N=304)		Total (N=608)	
Progressed after prior platinum therapy, n (%)						
<=1 month	120	(39.5%)	114	(37.5%)	234	(38.5%)
>1 month and <=6 months	102	(33.6%)	113	(37.2%)	215	(35.4%)
> 6 months and <=12 months	50	(16.4%)	45	(14.8%)	95	(15.6%)
> 12 months	27	(8.9%)	26	(8.6%)	53	(8.7%)
Missing	5	(1.6%)	6	(2.0%)	11	(1.8%)

Data cut off as of Jan 4th 2022
Source: Table 14.1.3.1.1all.ema.exp2

Table 37: Study 1676 – Treatment compliance (ITT)

		Chemotherapy					
	Cemiplimab (N=300)	**Pemetrexed (N=109)**	**Topotecan (N=16)**	**Irinotecan (N=19)**	**Gemcitabine (N=118)**	**Vinorelbine (N=28)**	**Total (N=290)**
Treatment Compliance [a], n (%)							
< 60%	3 (1.0%)	0	0	0	5 (4.2%)	0	5 (1.7%)
≥ 60% - < 80%	39 (13.0%)	21 (19.3%)	2 (12.5%)	1 (5.3%)	13 (11.0%)	3 (10.7%)	40 (13.8%)
≥ 80% - ≤ 100%	258 (86.0%)	88 (80.7%)	14 (87.5%)	18 (94.7%)	96 (81.4%)	23 (82.1%)	239 (82.4%)
> 100%	0	0	0	0	4 (3.4%)	2 (7.1%)	6 (2.1%)

Data cut-off as of 04 Jan 2021.
[a] Treatment Compliance = (Number of doses of study administered during treatment period/Number of doses of study drug planned to be administered during treatment period) *100%.
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTT 14.1.4.4all

Numbers analysed

Table 38: Study 1676 – Analysis sets (ITT)

Analysis Set, n	Cemiplimab	Chemotherapy	Total
Full Analysis Set (FAS)	304	304	608
Safety Analysis Set (SAF)	300	290	590
Pharmacokinetic Analysis Set (Cemiplimab only)	295	NA	NA
Anti-drug Antibody Analysis Set (Cemiplimab only)	206	NA	NA
PD-L1 status available	182	189	371

Data cutoff as of Jan 4th, 2021
Source: Table 14.1.1.3all.ema.ir1.q17

Outcomes and estimation

Overview of hierarchical testing of primary and secondary endpoints as per SAP:

Endpoint	One-sided P-Value
Primary Endpoints	
1. OS in squamous cell carcinoma patients	**0.00306**
2. OS in total population	**0.00011**
Secondary Endpoints	
3. PFS in SCC patients	**0.00026**
4. Overall mean change from baseline in GHS/QoL scale in SCC patients	**0.00025**
5. Overall mean change from baseline in physical functioning scale in SCC patients	**0.00008**
6. ORR in SCC patients	**0.00014**
7. PFS in total population	**0.00048**
8. ORR in total population	**0.00004**

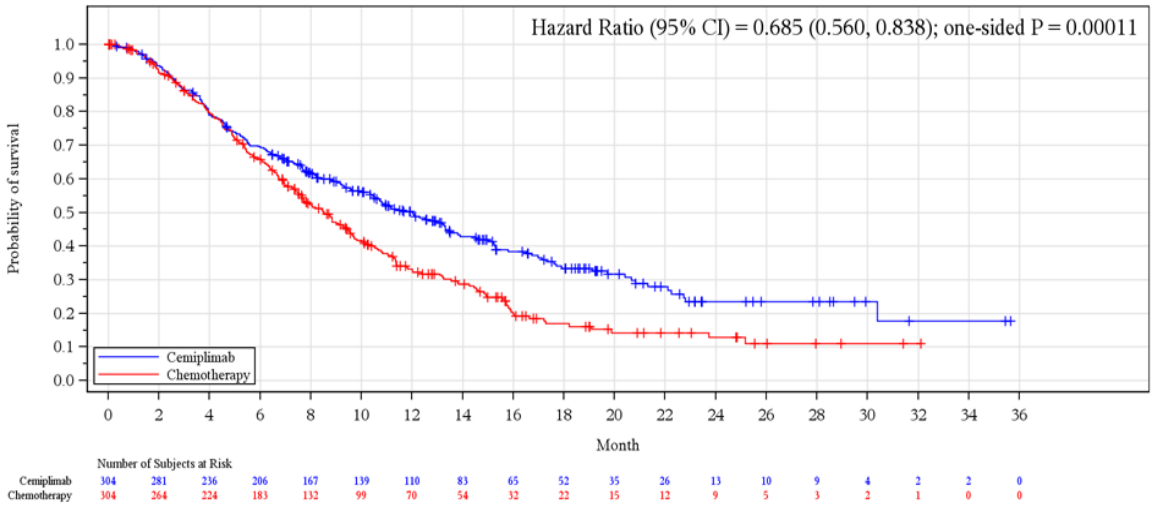
Note: This overview only includes endpoints with a statistically significant result.
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR

Primary endpoint – OS:

Table 39: Study 1676 – Overall survival (ITT)

	SCC		AC		Total	
	Cemiplimab (N=239)	**Chemotherapy (N=238)**	**Cemiplimab (N=65)**	**Chemotherapy (N=66)**	**Cemiplimab (N=304)**	**Chemotherapy (N=304)**
Number of deaths, n (%)	143 (59.8%)	161 (67.6%)	41 (63.1%)	50 (75.8%)	184 (60.5%)	211 (69.4%)
Number of censored patients, n (%)	96 (40.2%)	77 (32.4%)	24 (36.9%)	16 (24.2%)	120 (39.5%)	93 (30.6%)
Median (95% CI), (months)[a]	11.1 (9.2, 13.4)	8.8 (7.6, 9.8)	13.3 (9.6, 17.6)	7.0 (5.1, 9.7)	12.0 (10.3, 13.5)	8.5 (7.5, 9.6)
Stratified log-rank test one-sided p-value [b][c]	0.00306				0.00011	
HR (95% CI) [b][d]	0.727 (0.579, 0.914)		0.556 (0.363, 0.853)		0.685 (0.560, 0.838)	
Estimated Survival Probability , % (95% CI)[a]						
6 months	69.6 (63.3, 75.0)	68.5 (61.9, 74.1)	69.6 (56.5, 79.4)	57.7 (44.4, 68.9)	69.6 (64.0, 74.5)	66.1 (60.3, 71.3)
12 months	48.2 (41.3, 54.7)	35.3 (28.6, 42.1)	57.4 (43.9, 68.7)	26.0 (15.5, 37.8)	50.2 (44.1, 56.0)	33.2 (27.4, 39.0)
18 months	33.4 (26.3, 40.6)	16.1 (10.4, 22.8)	34.2 (21.5, 47.3)	17.7 (8.9, 29.0)	33.4 (27.2, 39.7)	16.9 (11.9, 22.6)
24 months	25.3 (17.8, 33.5)	13.6 (8.1, 20.4)	19.5 (8.4, 34.1)	10.1 (2.7, 23.3)	23.6 (17.1, 30.6)	12.8 (8.0, 18.8)
30 months	25.3 (17.8, 33.5)	10.8 (5.2, 18.8)	NE (NE, NE)	NE (NE, NE)	23.6 (17.1, 30.6)	11.0 (6.1, 17.5)
36 months	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Data cut-off as of 04 Jan 2021.
[a] Based on Kaplan-Meier method.
[b] Stratified by geographic region (North America versus Asia versus ROW) for SCC and AC. Stratified by geographic region (North America versus Asia versus ROW) and Histology (SCC versus AC) according to IWRS for Total.
[c] One-sided p-value converted from stratified log-rank test two-sided p-value. Significant threshold is set to 0.01508 using O'Brien Fleming alpha spending function.
[d] Based on stratified proportional hazards model (cemiplimab vs IC chemotherapy).
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTTs 14.2.1.1all, 14.2.1.1scc, and 14.2.1.1ade



Data cut-off as of 04 Jan 2021.
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTF 14.2.1.1all

Figure 20: Study 1676 –Kaplan-Meier curve of overall survival (ITT)

Table 40: Study 1676 – Summary of patients censored in overall survival (ITT)

	Cemiplimab (N=304)	**Chemotherapy (N=304)**
Number of patients without event, n (%)	120 (39.5%)	93 (30.6%)
Reason for censoring, n (%)		
Alive at the cut-off date	102 (33.6%)	65 (21.4%)
Alive before the cut-off date	1 (0.3%)	0
Withdrew consent	9 (3.0%)	25 (8.2%)
Lost to follow-up	8 (2.6%)	3 (1.0%)
Time from last known alive date to cut-off date (months)		
n	18	28
Mean (SDv)	15.25 (10.826)	21.11 (7.655)
Median	15.10	23.13
Q1 : Q3	3.68 : 25.89	15.02 : 26.22
Min : Max	0.7 : 30.6	6.6 : 34.0
Time from last known alive date to cut-off date (class)		
n	18	28
>2 months	17 (94.4%)	28 (100%)
>4 months	13 (72.2%)	28 (100%)
>6 months	12 (66.7%)	28 (100%)
>8 months	12 (66.7%)	26 (92.9%)
>10 months	11 (61.1%)	24 (85.7%)
>12 months	10 (55.6%)	24 (85.7%)
>14 months	9 (50.0%)	22 (78.6%)
>16 months	9 (50.0%)	20 (71.4%)

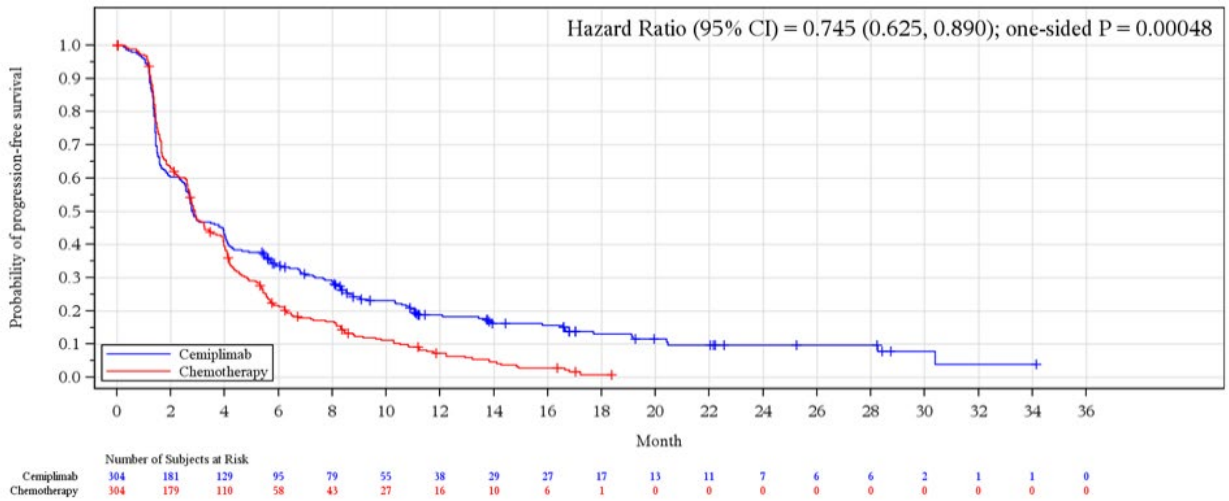
Data cut-off as of 04 Jan 2021.
Q1, first quartile; Q3, third quartile; SDv, standard deviation.
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTT 14.2.1.8all

Secondary endpoint – PFS:

Table 41: Study 1676 – Progression free survival by investigator (ITT)

	Total		SCC		AC	
	Cemiplimab (N=304)	**Chemotherapy (N=304)**	**Cemiplimab (N=239)**	**Chemotherapy (N=238)**	**Cemiplimab (N=65)**	**Chemotherapy (N=66)**
Number of events, n (%)	253 (83.2%)	269 (88.5%)	197 (82.4%)	214 (89.9%)	56 (86.2%)	55 (83.3%)
Progressive Disease, n (%)	212 (69.7%)	215 (70.7%)	163 (68.2%)	172 (72.3%)	49 (75.4%)	43 (65.2%)
Number of deaths, n (%)	41 (13.5%)	54 (17.8%)	34 (14.2%)	42 (17.6%)	7 (10.8%)	12 (18.2%)
Number of censored patients, n (%)	51 (16.8%)	35 (11.5%)	42 (17.6%)	24 (10.1%)	9 (13.8%)	11 (16.7%)
Median (95% CI), (months)[a]	2.8 (2.6, 3.9)	2.9 (2.7, 3.4)	2.8 (2.6, 4.0)	2.9 (2.7, 3.9)	2.7 (2.3, 4.0)	2.8 (2.0, 3.2)
Stratified log-rank test one-sided p-value [b][c]	0.00048		0.00026			
HR (95% CI) [b][d]	0.745 (0.625, 0.890)		0.705 (0.578, 0.861)		0.912 (0.623, 1.335)	
Estimated Event-Free Probability , % (95% CI)[a]						
6 months	33.5 (28.2, 38.9)	21.7 (17.1, 26.7)	34.5 (28.5, 40.5)	22.1 (16.9, 27.8)	30.1 (19.3, 41.6)	20.4 (11.2, 31.7)
12 months	18.8 (14.4, 23.6)	7.3 (4.6, 11.0)	21.0 (15.8, 26.6)	7.3 (4.2, 11.4)	10.6 (4.4, 20.0)	8.2 (2.7, 17.6)
18 months	13.0 (9.0, 17.8)	0.8 (0.1, 3.6)	14.5 (9.7, 20.1)	0.0 (NE, NE)	8.5 (3.0, 17.6)	4.1 (0.8, 12.2)
24 months	9.7 (6.0, 14.6)	NE (NE, NE)	10.3 (5.9, 16.0)	0.0 (NE, NE)	8.5 (3.0, 17.6)	NE (NE, NE)
30 months	7.8 (3.8, 13.6)	NE (NE, NE)	7.7 (3.2, 14.8)	0.0 (NE, NE)	NE (NE, NE)	NE (NE, NE)
36 months	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	0.0 (NE, NE)	NE (NE, NE)	NE (NE, NE)

Data cut-off as of 04 Jan 2021.
[a] Based on Kaplan-Meier method.
[b] Stratified by geographic region (North America versus Asia versus ROW) for SCC and AC. Stratified by geographic region (North America versus Asia versus ROW) and Histology (SCC versus AC) according to IWRS for Total.
[c] One-sided p-value converted from stratified log-rank test two-sided p-value.
[d] Based on stratified proportional hazards model (cemiplimab vs IC chemotherapy).
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTT 14.2.2.1all, 14.2.2.1scc, 14.2.2.1ade



Data cut-off as of 04 Jan 2021.
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTF 14.2.2.1all

Figure 21: Study 1676 – Kaplan-Meier curve of progression free survival by investigator (ITT)

Secondary endpoint – ORR by investigator:

Table 42: Study 1676 – Best overall tumour response rate by investigator (ITT)

	Total		SCC		AC	
	Cemiplimab (N=304)	**Chemotherapy (N=304)**	**Cemiplimab (N=239)**	**Chemotherapy (N=238)**	**Cemiplimab (N=65)**	**Chemotherapy (N=65)**
Best Overall Tumor Response, n (%)						
Complete Response (CR) [a]	10 (3.3%)	3 (1.0%)	7 (2.9%)	2 (0.8%)	3 (4.6%)	1 (1.5%)
Partial Response (PR) [a]	40 (13.2%)	16 (5.3%)	35 (14.6%)	14 (5.9%)	5 (7.7%)	2 (3.0%)
Stable Disease (SD) [b]	125 (41.1%)	148 (48.7%)	93 (38.9%)	116 (48.7%)	32 (49.2%)	32 (48.5%)
Progressive Disease (PD)	105 (34.5%)	88 (28.9%)	86 (36.0%)	71 (29.8%)	19 (29.2%)	17 (25.8%)
Not Evaluable (NE)	24 (7.9%)	49 (16.1%)	18 (7.5%)	35 (14.7%)	6 (9.2%)	14 (21.2%)
Response						
Objective Response Rate (ORR:CR+PR)	50 (16.4%)	19 (6.3%)	42 (17.6%)	16 (6.7%)	8 (12.3%)	3 (4.5%)
95% CI for ORR [c]	(12.5%, 21.1%)	(3.8%, 9.6%)	(13.0%, 23.0%)	(3.9%, 10.7%)	(5.5%, 22.8%)	(0.9%, 12.7%)
Stratified CMH test one-sided p-value [d]	0.00004		0.00014			
Odds ratio (95% CI) [d]	2.984 (1.707, 5.215)		3.002 (1.629, 5.530)		2.894 (0.732, 11.445)	

Data cut-off as of 04 Jan 2021.
[a] CR/PR must be confirmed by repeated assessments no less than 4 weeks apart
[b] SD criteria must be met at least once for a minimum duration of 4 weeks after first dose date
[c] Clopper-Person exact confidence interval.
[d] One-sided p-value and odds ratio using geographic region stratified Cochran-Mantel-Haenszel test for SCC and AC; One-sided p-value and odds ratio using geographic region and histology stratified Cochran-Mantel-Haenszel test for Total. Due to the low response rate in the IC chemitherapy arm, the results from CMH test should be interpreted with caution.
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTT 14.2.3.1all, 14.2.3.1scc, 14.2.3.1ade

Secondary endpoint – DOR by investigator:

Table 43: Study 1676 – Kaplan-Meier estimation of duration of response by investigator (responders in ITT)

	Cemiplimab (N=50)	Chemotherapy (N=19)
KM Estimation of Duration of Response (CR or PR) [a]		
n	50	19
Number of events, n (%)	20 (40.0%)	16 (84.2%)
Number of censored patients, n (%) [b]	30 (60.0%)	3 (15.8%)
Median (95% CI), (months)[a]	16.4 (12.4, NE)	6.9 (5.1, 7.7)
Estimated Event-Free Probability , % (95% CI)[a]		
6 months	79.0 (64.4, 88.1)	59.6 (33.1, 78.5)
12 months	69.0 (53.1, 80.4)	0.0 (NE, NE)
18 months	41.4 (20.7, 61.0)	0.0 (NE, NE)
24 months	41.4 (20.7, 61.0)	0.0 (NE, NE)
30 months	20.7 (1.8, 54.0)	0.0 (NE, NE)
36 months	NE (NE, NE)	0.0 (NE, NE)

Data cut-off as of 04 Jan 2021.
[a] Based on patients with confirmed CR or PR.
[b] Censored patients were patients who did not die, were lost to follow up, or had withdrawn consent censored at the last known date of contact.
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTT 14.2.3.5all

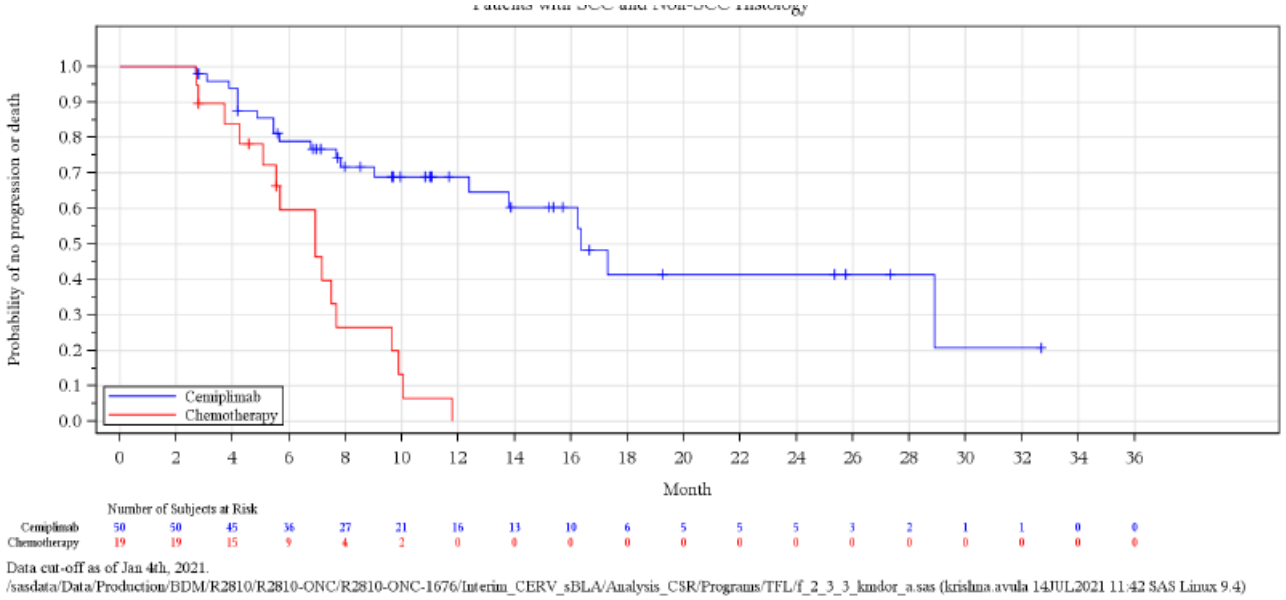
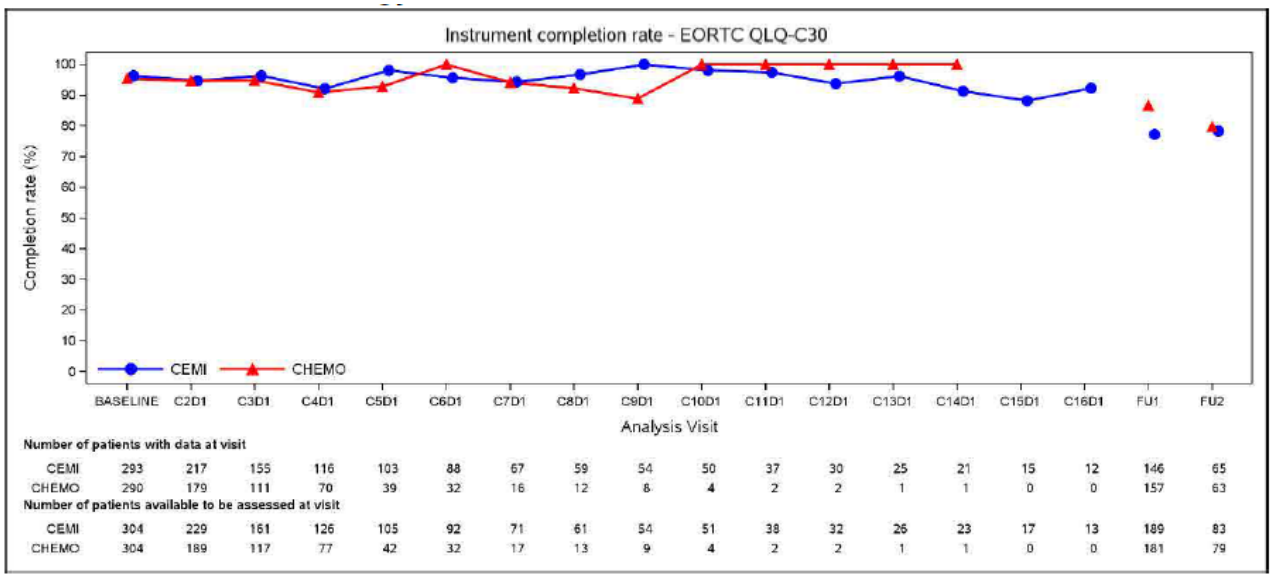


Figure 22: Study 1676 – Kaplan-Meier curve of duration of response by investigator (responders in ITT)

Secondary endpoint – PROs:



Source: Figure 1.1.2 in Appendix B

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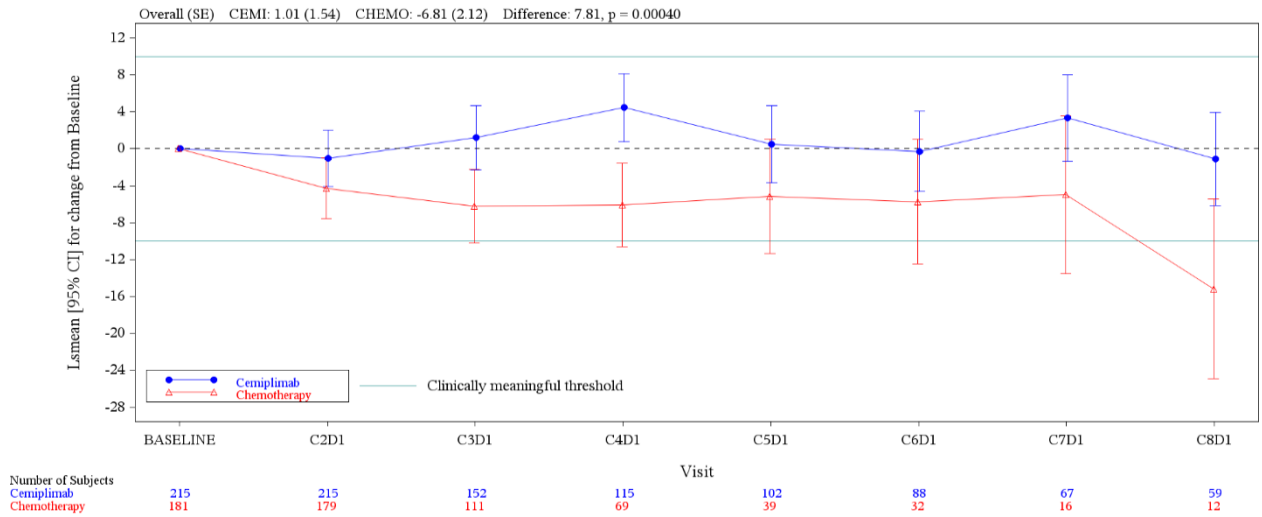
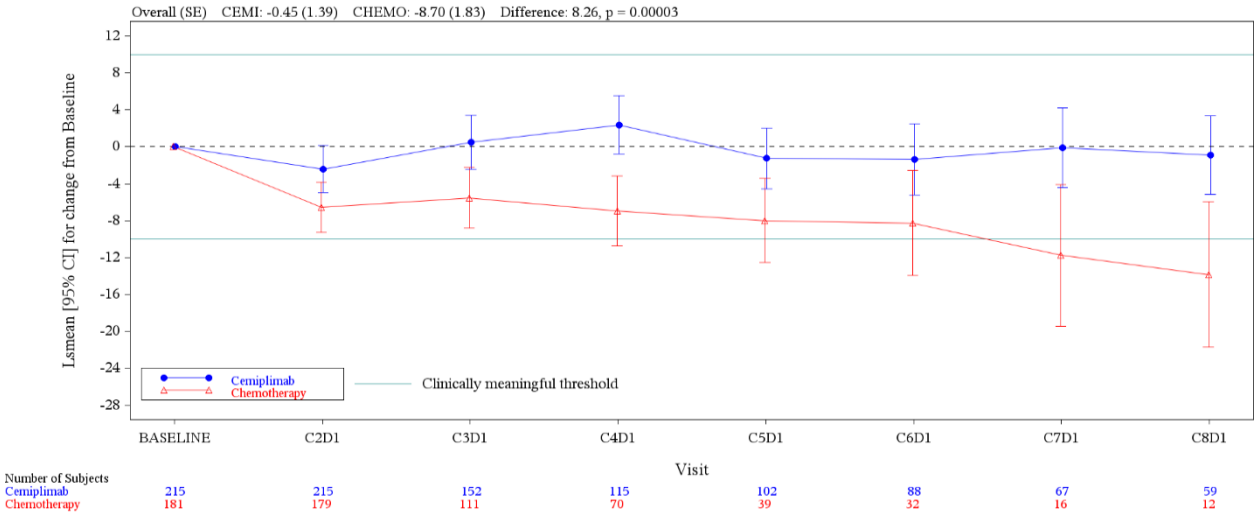
Figure 23: Instrument completion rate – EORTC-QLQ-C30



Data cut-off as of 04 Jan 2021.
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTF 14.2.4.6all

Figure 24: Longitudinal plots of change from baseline EORTC-QLQ-C30 – GHS/QoL



Data cut-off as of 04 Jan 2021.

Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTF 14.2.4.7all

Figure 25: Longitudinal plots of change from baseline EORTC-QLQ-C30 – physical functioning

Exploratory endpoint – Post treatment anticancer therapy:

Table 44: Study 1676 – Summary of post-trial anticancer systemic therapy (ITT)

	Cemiplimab (N=304)	Chemotherapy (N=304)
Number of patients received any post treatment anti-cancer systemic therapy, n (%)	110 (36.2%)	144 (47.4%)
Number of patients received any post treatment immune check-point inhibitors, n (%)	6 (2.0%)	47 (15.5%)
Number of patients received any post treatment Anti PD-L1 [1], n (%)	4 (1.3%)	46 (15.1%)

Data cut-off as of 04 Jan 2021.
[1] The remaining 3 patients received ipilimumab.
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTT 14.2.5.4all

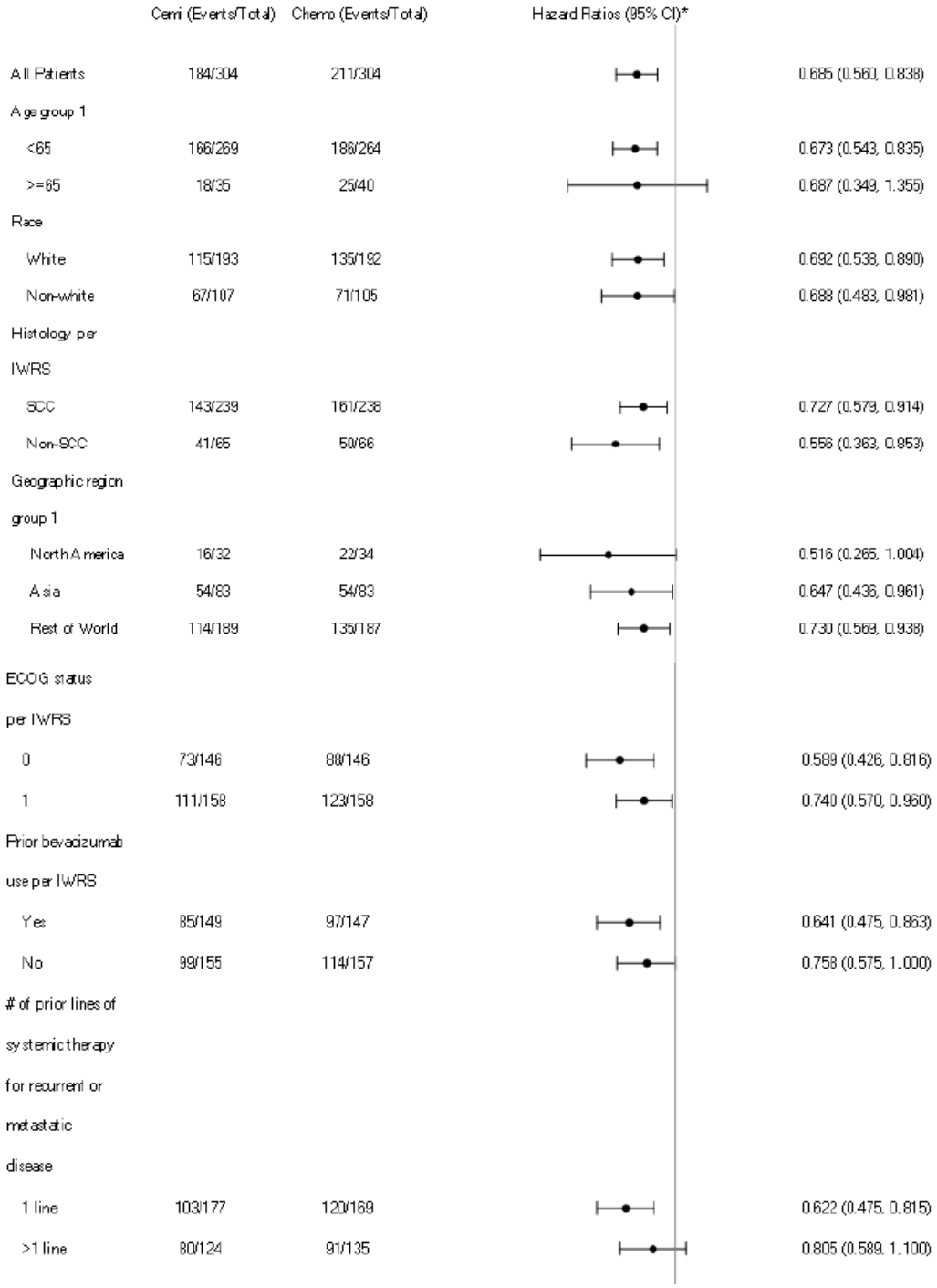
Table 45: Study 1676 – Detailed post treatment anticancer systemic therapy (ITT)

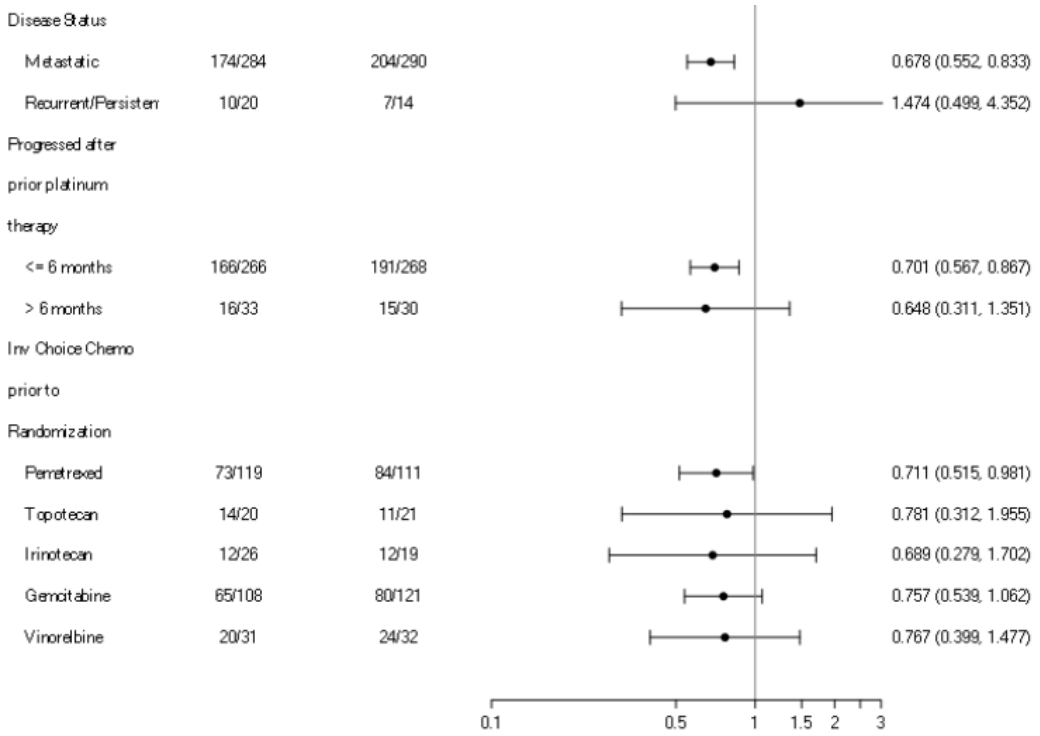
ATC Level 2, n (%) ATC Level 4, n (%)	Cemiplimab (N=304)	Chemotherapy (N=304)
Number of patients received any post treatment anti-cancer systemic therapy, n (%)	110 (36.2%)	144 (47.4%)
ANTINEOPLASTIC AGENTS	110 (36.2%)	144 (47.4%)
PYRIMIDINE ANALOGUES	31 (10.2%)	31 (10.2%)
PLATINUM COMPOUNDS	28 (9.2%)	39 (12.8%)
TAXANES	27 (8.9%)	28 (9.2%)
COMBINATIONS OF ANTINEOPLASTIC AGENTS	22 (7.2%)	16 (5.3%)
OTHER ANTINEOPLASTIC AGENTS	22 (7.2%)	26 (8.6%)
MONOCLONAL ANTIBODIES	17 (5.6%)	60 (19.7%)
VINCA ALKALOIDS AND ANALOGUES	12 (3.9%)	16 (5.3%)
ANTHRACYCLINES AND RELATED SUBSTANCES	4 (1.3%)	3 (1.0%)
FOLIC ACID ANALOGUES	4 (1.3%)	3 (1.0%)
ATC4 CODE NOT AVAILABLE	3 (1.0%)	4 (1.3%)
PODOPHYLLOTOXIN DERIVATIVES	2 (0.7%)	0
PROTEIN KINASE INHIBITORS	2 (0.7%)	0
NITROGEN MUSTARD ANALOGUES	1 (0.3%)	5 (1.6%)
ALL OTHER THERAPEUTIC PRODUCTS	1 (0.3%)	0
DETOXIFYING AGENTS FOR ANTINEOPLASTIC TREATMENT	1 (0.3%)	0
DRUGS FOR TREATMENT OF BONE DISEASES	1 (0.3%)	0
BISPHOSPHONATES	1 (0.3%)	0
IMMUNOSTIMULANTS	1 (0.3%)	0
ATC4 CODE NOT AVAILABLE	1 (0.3%)	0

Source: Post text tables, page 1464-5/1482

Ancillary analyses

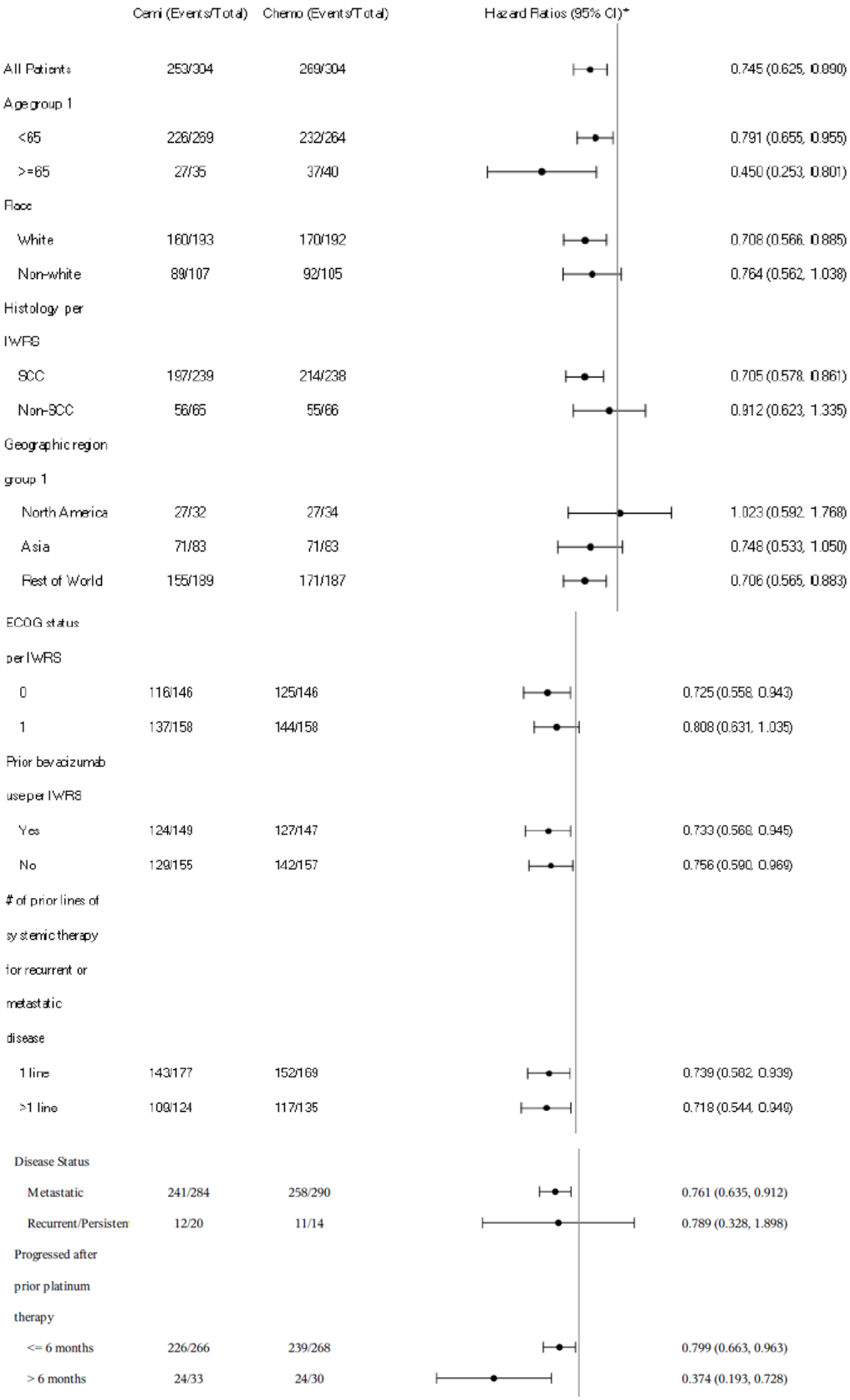
Subgroup analyses:

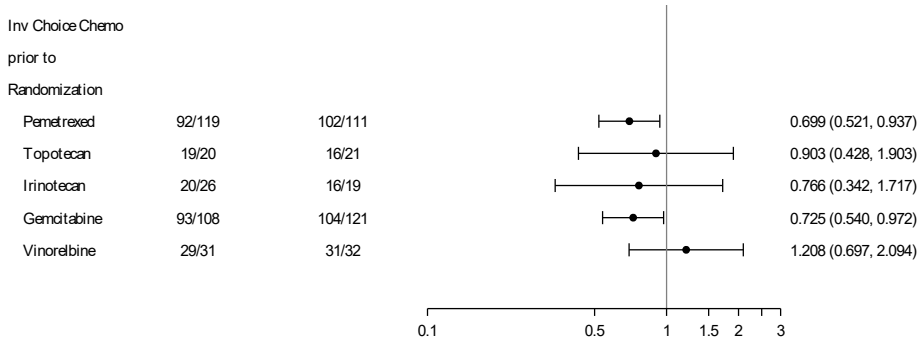




Data cut-off as of 04 Jan 2021.
*Stratified by geographic region (North America versus ROW per IWRS) and Histology (SCC versus adenocarcinoma per IWRS) except for Geographics region (cemiplimab vs chemotherapy)
For Geographical region subgroups stratified by Histology (SCC versus adenocarcinoma IWRS) (Cemiplimab vs chemotherapy)
Source: Figure 14.2osall7.ema

Figure 26: Study 1676 – Forest plot for overall survival by subgroup (ITT)


Cemi (Events/Total)
Chemo (Events/Total)
Hazard Ratios (95% CI)*
All Patients 253/304 269/304 0.745 (0.625, 0.890)
Age group 1
<65 226/269 232/264 0.791 (0.655, 0.955)
>=65 27/35 37/40 0.450 (0.253, 0.801)
Race
White 160/193 170/192 0.708 (0.566, 0.885)
Non-white 89/107 92/105 0.764 (0.562, 1.038)
Histology per IWRS
SCC 197/239 214/238 0.705 (0.578, 0.861)
Non-SCC 56/65 55/66 0.912 (0.623, 1.335)
Geographic region group 1
North America 27/32 27/34 1.023 (0.592, 1.768)
Asia 71/83 71/83 0.748 (0.533, 1.050)
Rest of World 155/189 171/187 0.706 (0.565, 0.883)
ECOG status per IWRS
0 116/146 125/146 0.725 (0.558, 0.943)
1 137/158 144/158 0.808 (0.631, 1.035)
Prior bevacizumab use per IWRS
Yes 124/149 127/147 0.733 (0.568, 0.945)
No 129/155 142/157 0.756 (0.590, 0.969)
# of prior lines of systemic therapy for recurrent or metastatic disease
1 line 143/177 152/169 0.739 (0.582, 0.939)
>1 line 109/124 117/135 0.718 (0.544, 0.949)
Disease Status
Metastatic 241/284 258/290 0.761 (0.635, 0.912)
Recurrent/Persisten 12/20 11/14 0.789 (0.328, 1.898)
Progressed after prior platinum therapy
<= 6 months 226/266 239/268 0.799 (0.663, 0.963)
> 6 months 24/33 24/30 0.374 (0.193, 0.728)



Data cut-off as of 04 Jan 2021.
*Stratified by geographic region (North America versus ROW per IWRS) and Histology (SCC versus adenocarcinoma per IWRS) except for Geographics region (cemiplimab vs chemotherapy)
For Geographical region subgroups stratified by Histology (SCC versus adenocarcinoma IWRS) (Cemiplimab vs chemotherapy)
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTF 14.2pfs.all7

Figure 27: Study 1676 – Forest plot for progression free survival according to investigator by subgroup (ITT)

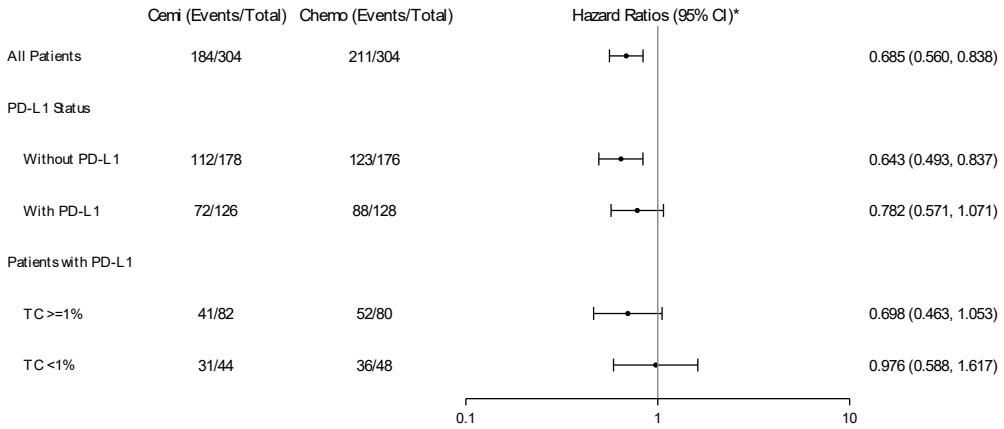
Subgroup analyses – Efficacy by PD-L1 status:

Patients were recruited regardless of PD-L1 status. Exploratory analysis of tumour cell PD-L1 expression in available archival tumour samples was performed using the analytically validated immunohistochemistry (IHC) assay. The PD-L1 assay was performed by a third-party vendor (Roche, Ventana) using the SP263 antibody clone. Based on the assay vendor instructions for use, 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 to be outside the optimal testing window.

Table 46: Study 1676 – Baseline PD-L1 status per Ventana SP263 (ITT)

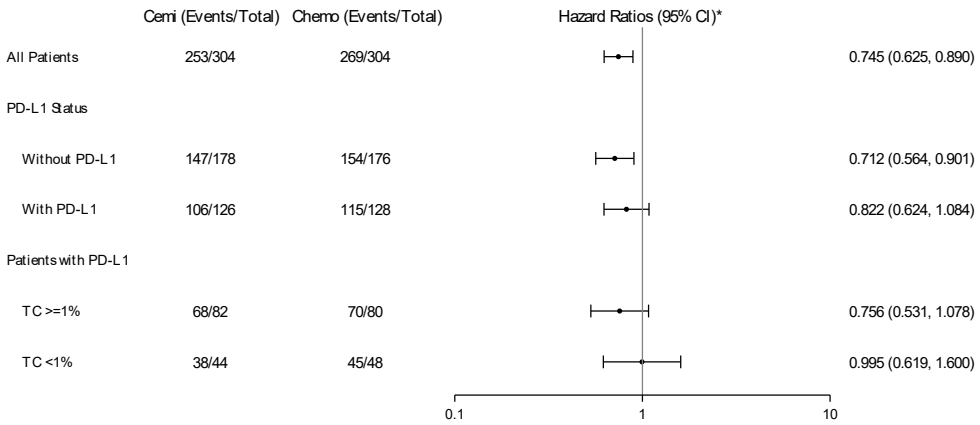
	Cemiplimab (N=304)	Chemotherapy (N=304)	Total (N=608)
Total Population			
Without PD-L1	178 (58.6%)	176 (57.9%)	354 (58.2%)
With PD-L1	126 (41.4%)	128 (42.1%)	254 (41.8%)
TC ≥1%	82 (27.0%)	80 (26.3%)	162 (26.6%)
TC <1%	44 (14.5%)	48 (15.8%)	92 (15.1%)

Data cut-off as of 04 Jan 2021.
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTT 14.1.2.5all, 14.1.2.5scc, 14.1.2.5.ade



Data cut-off as of 04 Jan 2021.
*Stratified by geographical region (North America vs Asia vs ROW per IWRS) and Histology (SCC vs AC IWRS) (cemiplimab vs chemotherapy).
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTF 14.2.1.5all

Figure 28: Study 1676 – Forest plot of overall survival by PD-L1 expression (ITT)



Data cut-off as of 04 Jan 2021.
*Stratified by geographical region (North America vs Asia vs ROW per IWRS) and Histology (SCC vs AC IWRS) (cemiplimab vs chemotherapy).
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTF 14.2.2.4all

Figure 29: Study 1676 – Forest plot of progression free survival according to investigator by PD-L1 expression (ITT)

Table 47: Updated Overall Survival by PD-L1 expression in patients with SCC and Non-SCC histology (Full Analysis Set [N=254][1])

	Primary Analysis (datacut January 2021)					1-year update Analysis (datacut January 2022)				
	Cemiplimab (N=304)		Chemotherapy (N=304)			Cemiplimab (N=304)		Chemotherapy (N=304)		
	Event (%)	Median Time (95% CI)[a]	Event (%)	Median Time (95% CI)[a]	HR (95% CI) [b]	Event (%)	Median Time (95% CI)[a]	Event (%)	Median Time (95% CI)[a]	HR (95% CI) [b]
All Patients	184/304 (60.5%)	12.0 (10.3, 13.5)	211/304 (69.4%)	8.5 (7.5, 9.6)	0.685 (0.560, 0.838)	216/304 (71.1%)	11.7 (9.6, 13.4)	249/304 (81.9%)	8.5 (7.5, 9.6)	0.656 (0.545, 0.790)
PD-L1 Status										
Without PD-L1[2]	112/178 (62.9%)	12.7 (9.6, 14.5)	123/176 (69.9%)	8.7 (7.4, 9.7)	0.643 (0.493, 0.837)	130/178 (73.0%)	11.7 (9.2, 13.5)	143/176 (81.3%)	8.7 (7.4, 9.7)	0.649 (0.509, 0.828)
With PD-L1[3]	72/126 (57.1%)	11.2 (8.0, 15.0)	88/128 (68.8%)	8.2 (6.7, 10.8)	0.782 (0.571, 1.071)	86/126 (68.3%)	12.0 (8.1, 14.9)	106/128 (82.8%)	8.2 (6.7, 11.0)	0.732 (0.548, 0.978)
PD-L1 Expression Levels										
TC ≥1%	41/82 (50.0%)	13.9 (9.6, NE)	52/80 (65.0%)	9.3 (7.0, 11.4)	0.698 (0.463, 1.053)	53/82 (64.6%)	13.9 (9.6, 17.4)	63/80 (78.8%)	9.3 (7.0, 11.4)	0.699 (0.482, 1.014)
TC <1%	31/44 (70.5%)	7.7 (4.3, 12.3)	36/48 (75.0%)	6.7 (3.9, 9.5)	0.976 (0.588, 1.617)	33/44 (75.0%)	8.2 (4.3, 12.3)	43/48 (89.6%)	6.7 (3.9, 11.8)	0.846 (0.527, 1.357)

1. Biomarker set with samples that were within stability window (n=254)
2. Patients without PD-L1 samples
3. Patients with PD-L1 samples

[a] Based on Kaplan-Meier method.
[b] Based on geographic region (North America versus Asia versus ROW per IWRS) and Histology (SCC versus adenocarcinoma per IWRS) stratified proportional hazards model (cemiplimab vs chemotherapy).
SSC, Squamous cell carcinoma; PD-L1, Programmed death-ligand 1; CI , Confidence Interval
Source: PTT 14.2.1.6all (datacut 4 January 2022) and Study 1676 Primary Analysis CSR PTT 14.2.1.6all (datacut 4 January 2021)

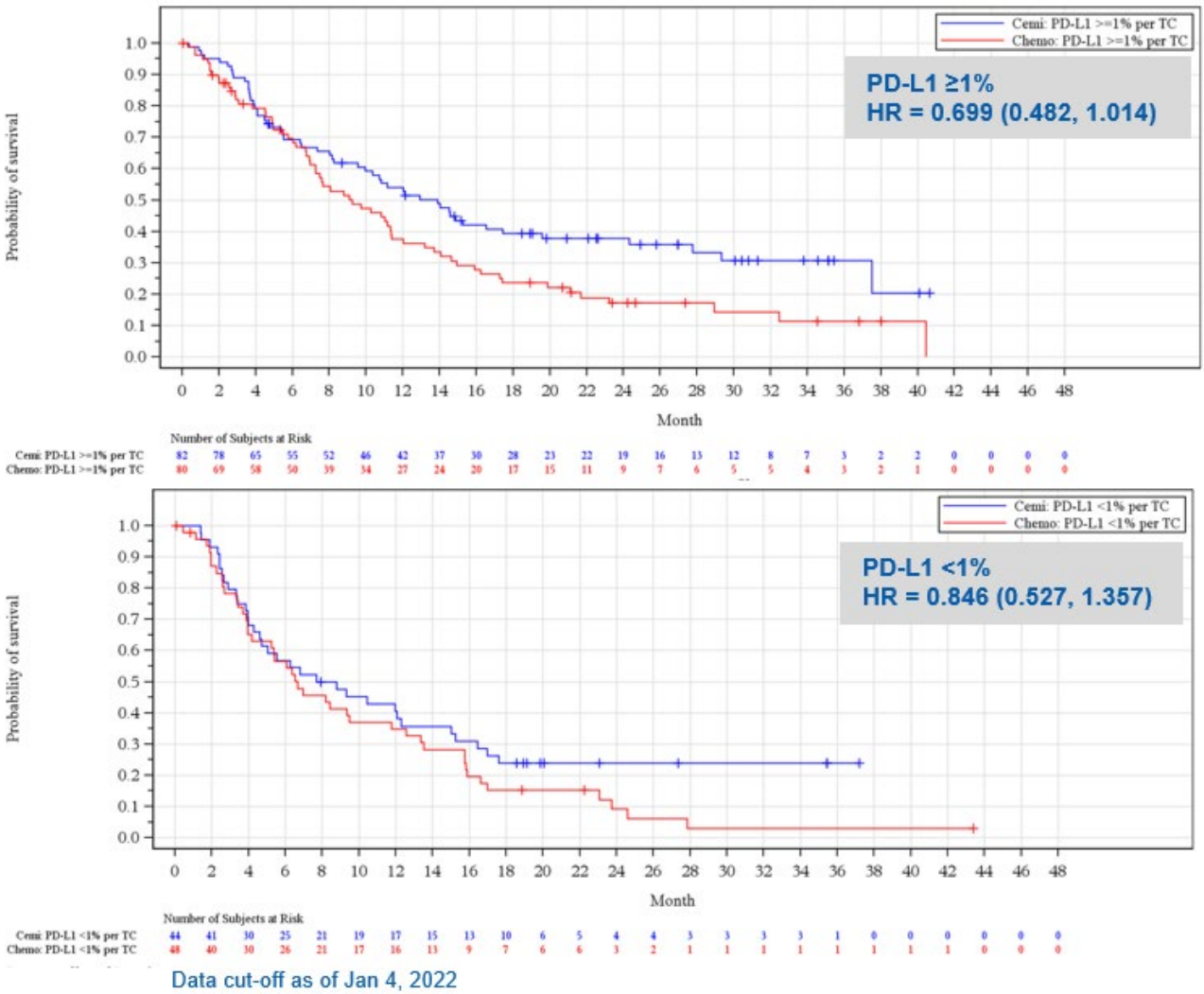


Figure 30: Study 1676 – Kaplan-Meier Curve of Overall Survival by PD-L1 Expression per Tumor Cell Method, (n=254, Biomarker Available Set): 1 Year Update Analysis

Subgroup analyses – Efficacy in patients treated with cemiplimab beyond PD

70 patients form the cemiplimab arm (70 out of 304, 23%) fulfilled the conditions for treatment with cemiplimab beyond documentation of PD.

Table 48: Overall Survival (FAS) – Patients Treated Beyond Progression Versus Those Who Were Not (Patients with SCC and non-SCC Histology)

	Cemiplimab treated beyond progression (N=70)	Cemiplimab not treated beyond progression (N=234)
Number of deaths, n (%)	42 (60.0%)	142 (60.7%)
Number of censored patients, n (%)	28 (40.0%)	92 (39.3%)
Median (95% CI), (months)[a]	13.9 (11.7, 17.9)	10.5 (8.2, 12.9)
HR (95% CI) [b][c]	0.798 (0.559, 1.141)	
Estimated Survival Probability , % (95% CI)[a]		
6 months	79.8 (68.3, 87.5)	66.5 (60.0, 72.2)
12 months	62.6 (49.8, 73.1)	46.4 (39.5, 53.0)
18 months	36.7 (24.0, 49.5)	32.8 (25.7, 40.0)
24 months	24.7 (13.0, 38.5)	23.9 (16.2, 32.3)
30 months	NE (NE, NE)	23.9 (16.2, 32.3)
36 months	NE (NE, NE)	NE (NE, NE)

Data cut-off as of Jan 4th, 2021.
[a] Based on Kaplan-Meier method.
[b] Stratified by geographic region (North America versus Asia versus ROW) and Histology (SCC versus adenocarcinoma) according to IWRS.
[c] Based on stratified proportional hazards model (cemiplimab vs chemotherapy).
Source: Table 14.2.1.1all.ema.ir1.q8

Sensitivity analyses:

Table 49: Study 1676 – Sensitivity analysis of OS by censoring patients with any post-treatment immune checkpoint inhibitors

	Cemiplimab (N=304)	Chemotherapy (N=304)
Number of deaths, n (%)	180 (59.2%)	184 (60.5%)
Number of censored patients, n (%)	124 (40.8%)	120 (39.5%)
Median (95% CI), (months)[a]	12.1 (10.3, 13.8)	8.5 (7.5, 9.6)
Stratified log-rank test one-sided p-value [b][c]	0.00018	
HR (95% CI) [b][d]	0.684 (0.554, 0.844)	
Estimated Survival Probability , % (95% CI)[a]		
6 months	69.9 (64.3, 74.7)	66.5 (60.4, 71.9)
12 months	50.6 (44.5, 56.4)	32.6 (26.4, 39.0)
18 months	33.7 (27.3, 40.1)	15.9 (10.6, 22.3)
24 months	24.4 (17.8, 31.7)	10.5 (5.0, 18.2)
30 months	24.4 (17.8, 31.7)	NE (NE, NE)
36 months	NE (NE, NE)	NE (NE, NE)

Source: Post text-tables, page 1197/1482

Data cut-off as of Jan 4th, 2021

The purpose of prespecifying a rank preserving structural failure time (RPSFT) sensitivity analysis on OS was to remove the crossover treatment benefit in the chemotherapy arm in the case that many patients in the chemotherapy arm crossed over to PD-1/PD-L1 treatment outside of this study. Given only 15.1% patients in the chemotherapy arm received post-progression PD-L1 treatment outside of the study, this analysis was not performed after database lock. Nevertheless, the MAH provided the results of this analysis upon request.

Table 50: Sensitivity Analysis of OS Using RPSFT Method (FAS) Patients with SCC and non-SCC Histology

	Cemiplimab (N=304)	Reconstructed Chemotherapy (N=304)
Psi	-0.3705	
Exp(Psi)	0.6904	
Number of deaths, n (%)	184 (60.5%)	181 (59.5%)
Number of censored patients, n (%)	120 (39.5%)	123 (40.5%)
Median (95% CI), (months)[a]	12.0 (10.3, 13.5)	8.4 (7.5, 9.4)
Stratified log-rank test one-sided p-value [b][c]	0.00010	
HR (95% CI) [b][d]	0.670 (0.542, 0.829)	
Estimated Survival Probability , % (95% CI)[a]		
6 months	69.6 (64.0, 74.5)	65.3 (59.4, 70.6)
12 months	50.2 (44.1, 56.0)	30.8 (24.6, 37.2)
18 months	33.4 (27.2, 39.7)	15.8 (9.5, 23.5)
24 months	23.6 (17.1, 30.6)	NE (NE, NE)
30 months	23.6 (17.1, 30.6)	NE (NE, NE)
36 months	NE (NE, NE)	NE (NE, NE)

Data cut-off as of Jan 4th, 2021.
[a] Based on Kaplan-Meier method.

	Cemiplimab (N=304)	Reconstructed Chemotherapy (N=304)

[b] Stratified by geographic region (North America versus Asia versus ROW) and Histology (SCC versus adenocarcinoma) according to IWRS.
[c] One-sided p-value converted from stratified log-rank test two-sided p-value.
[d] Based on stratified proportional hazards model (cemiplimab vs chemotherapy).
Source: Table 14.2.1.1all.rpsft

Table 51: Study 1676 – Sensitivity analysis of PFS including subsequent anticancer therapy as PFS event

	Cemiplimab (N=304)	Chemotherapy (N=304)
Number of events, n (%)	254 (83.6%)	276 (90.8%)
Progressive Disease, n (%)	211 (69.4%)	209 (68.8%)
Number of deaths, n (%)	31 (10.2%)	42 (13.8%)
Subsequent Anti-Cancer Therapy, n (%)	12 (3.9%)	25 (8.2%)
Number of censored patients, n (%)	50 (16.4%)	28 (9.2%)
Median (95% CI), (months)[a]	2.8 (2.6, 3.8)	2.8 (2.6, 3.0)
Stratified log-rank test one-sided p-value [b][c]	0.00004	
HR (95% CI) [b][d]	0.706 (0.592, 0.841)	
Estimated Event-Free Probability , % (95% CI)[a]		
6 months	31.1 (25.9, 36.4)	18.3 (14.0, 23.0)
12 months	18.5 (14.2, 23.4)	5.5 (3.2, 8.8)
18 months	12.7 (8.7, 17.5)	1.2 (0.3, 3.5)
24 months	10.2 (6.4, 15.1)	NE (NE, NE)
30 months	8.1 (4.1, 14.0)	NE (NE, NE)
36 months	NE (NE, NE)	NE (NE, NE)

Source: Post text-tables, page 1237/1482

Data cut-off as of Jan 4th, 2021

Table 52: Study 1676 – Sensitivity analysis of PFS including clinical progression as PFS event

	Cemiplimab (N=304)	Chemotherapy (N=304)
Number of events, n (%)	254 (83.6%)	275 (90.5%)
Progressive Disease - Radiographic, n (%)	210 (69.1%)	211 (69.4%)
Progressive Disease - Clinical, n (%)	19 (6.3%)	34 (11.2%)
Number of deaths, n (%)	25 (8.2%)	30 (9.9%)
Number of censored patients, n (%)	50 (16.4%)	29 (9.5%)
Median (95% CI), (months)[a]	2.7 (2.5, 3.4)	2.8 (2.6, 3.0)
Stratified log-rank test one-sided p-value [b][c]	0.00010	
HR (95% CI) [b][d]	0.719 (0.603, 0.857)	
Estimated Event-Free Probability , % (95% CI)[a]		
6 months	31.4 (26.3, 36.7)	19.7 (15.3, 24.5)
12 months	18.6 (14.2, 23.4)	5.2 (3.0, 8.5)
18 months	13.3 (9.2, 18.1)	0.9 (0.1, 3.7)
24 months	9.9 (6.1, 14.8)	NE (NE, NE)
30 months	7.9 (3.9, 13.8)	NE (NE, NE)
36 months	NE (NE, NE)	NE (NE, NE)

Source: Post-text tables, page 1240/1482

Data cut-off as of Jan 4th, 2021

Summary of main study(ies)

The following table summarises the efficacy results from the main study 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 21: Summary of Efficacy for Study 1676

R2810-ONC-1676: An open-label, randomised, phase III clinical trial of cemiplimab vs. investigator's choice of chemotherapy in recurrent or metastatic cervical carcinoma				
Study identifier	EudraCT number 2017-000350-19; IND number 133224; NCT03257267			
Design	Phase III, multicentre, open-label, randomised 1:1, active control. Cross-over not allowed.			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Not applicable, event driven Not applicable Not applicable	
Hypothesis	Superiority			
Treatment groups	Cemiplimab arm		Cemiplimab 350 mg IV Q3W for up to 96W n=304	
	Investigator's choice chemotherapy arm		Investigator's choice chemotherapy, for up to 96W; n=304 • Pemetrexed 500 mg/m^2 Q3W; n=111 • Topotecan 1.0 mg/m^2 on days 1-5 Q3W; n=21 • Irinotecan 100 mg/m^2 weekly x4 followed by 10-14 days rest Q42D; n=19 • Gemcitabine 1000 mg/m^2 on days 1 and 8 Q3W; n=121 • Vinorelbine 30 mg/m^2 on days 1 and 8 Q3W; n=32	
Endpoints and definitions	Primary	OS	Time from randomisation to the date of death by any cause.	
	Secondary	INV-PFS	Time from randomisation to the date of the first documented tumour progression using RECIST 1.1 per investigator assessment, or death due to any cause.	
	Secondary	INV-ORR	Number of patients with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) using RECIST 1.1 per investigator assessment divided by the number of patients in the efficacy analysis set.	
Database lock	18-FEB-2021			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT (N=608) at data cutoff 04-JAN-2021			
Descriptive statistics and estimate variability	Treatment group		Cemiplimab arm	Investigator's choice chemotherapy arm
	Number of subjects		304	304
	OS, patients with event (%)		184 (60.5)	211 (69.4)
	Median OS[a], months		12.0	8.5
	95% CI		10.3, 13.5	7.5, 9.6
	INV-PFS, patients with event (%)		253 (83.2)	269 (88.5)
	Median INV-PFS[a], months		2.8	2.9
	95% CI		2.6, 3.9	2.7, 3.4
	INV-ORR (n)		16.4 (50)	6.3 (19)
	95% CI		12.5, 21.1	3.8, 9.6
Effect estimate per comparison	OS	Comparison groups	Cemiplimab arm vs. investigator's choice chemotherapy arm	
		Stratified HR[b]	0.685	
		95% CI	0.560, 0.838	
		P-value[c]	0.00011	
	INV-PFS	Comparison groups	Cemiplimab arm vs. investigator's choice chemotherapy arm	

		Stratified HR[b]	0.745
		95% CI	0.625, 0.890
		P-value[c]	0.00048
	INV-ORR	Comparison groups	Cemiplimab arm vs. investigator's choice chemotherapy arm
		Odds ratio[d]	2.984
		95% CI[e]	1.707, 5.215
		P-value	0.00004

Notes:
[a] Based on Kaplan-Meier method
[b] Based on stratified proportional hazards model (cemiplimab vs. chemotherapy), stratification by geographic region (North America vs Asia vs. ROW) and histology (SCC vs. AC) according to IWRS
[c] 1-sided p-value converted from stratified log-rank test two-sided p-value
[d] Using geographic region and histology stratified Cochran-Mantel-Haenszel test
[e] Clopper-Pearson exact confidence interval

Supportive study – Study 1423

Study 1423 was the first-in-human (FIH) study of cemiplimab. Planned treatment duration was 48 weeks, followed by a post-treatment follow-up period of approximately 5.5 months. The protocol contained a dose escalation portion and 25 expansion cohorts. The three cervical cancer patients in the dose escalation portion were not discussed as they received different doses of cemiplimab to the dose used in the expansion phase. Expansion cohorts 23 and 24 (EXP23 and EXP24) were designed to obtain additional clinical experience with cemiplimab in patients with relapsed/metastatic cervical cancer. Ten patients were enrolled in EXP23 and received 3 mg/kg cemiplimab IV every 2 weeks (Q2W) and 10 patients enrolled in EXP24 and received 3 mg/kg cemiplimab IV Q2W + radiation therapy (RT).

Disposition, Demographics, and Baseline Characteristics

In EXP23, 9 out of 10 patients discontinued treatment prior to the analysis cut-off date with the main reason being disease progression/recurrence. The median age of the patients in EXP23 was 51.5 years (range: 31 to 76 years), 90% were white, all patients had an ECOG performance status of 0 (40.0%) or 1 (60.0%), and all patients had received prior cancer-related systemic therapy.

In EXP24, all 10 patients discontinued treatment prior to (or by) analysis cut-off date with the main reason being disease progression/recurrence. The median age of the patients in EXP24 was 48.6 years (range: 29 to 65 years), 8 patients were white, 1 black or African American and 1 Asian. All patients had an ECOG performance status of 0 (20.0%) or 1 (80.0%), and all patients had received prior cancer-related systemic therapy and 8 out of 10 had prior cancer-related radiotherapy.

Efficacy Results

The data cut-off date for this efficacy analysis was 30 April 2019. All efficacy results were per investigator assessment. Patients were not tested for PD-L1 status prior to being randomized on the study.

The ORR for patients in EXP23 was 10.0% (1/10) and in EXP24 was 10.0% (1/10), partial responses in both cases.

The observed estimated DOR was 11.2 months for the responder in EXP23 and 6.4 months for the responder in EXP24.

The KM estimation of median PFS by investigator assessment was 1.9 months (95% CI [1.0, 9.0]) for EXP23 and 3.6 months (95% CI [0.6, 5.7]) for EXP24.

The KM estimation of median OS for EXP23 was 10.3 (2.1, NE) months; median OS for EXP24 was 8.0 (1.7, NE).

Combining the dose escalation portion of the study, in which objective responses were observed in 2 of 3

cervical cancer patients per investigator assessment with cervical cancer EXP23 and EXP24, there were 4 responses among 23 cervical cancer patients. All 4 responses were in patients with squamous tumor histology.

2.4.2. Discussion on clinical efficacy

The MAH for cemiplimab, an anti-PD-1 immune checkpoint inhibitor, seeks an extension of indication to treat *adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy*. The application is based on results from Study 1676, an open-label, randomised 1:1, phase III trial that compared cemiplimab monotherapy vs. investigator's choice of chemotherapy (pemetrexed or topotecan or irinotecan or gemcitabine or vinorelbine) in women with recurrent or metastatic cervical cancer after progression to platinum-based chemotherapy with or without bevacizumab.

In study 1676, 608 patients were randomised between November 2017 and July 2020. Subjects were recruited regardless of PD-L1 expression status, but only squamous cell carcinoma (SCC) or adenocarcinoma/adenosquamous carcinoma (AC) histologies were allowed. The primary endpoint was overall survival (OS). Secondary endpoints were PFS, ORR, DOR and QoL.

Design and conduct of clinical studies

The design of this pivotal trial was discussed with the CHMP via a scientific advice (SA) procedure in April 2017. Given the diverse treatment options in the control arm, the open-label nature of the trial was considered acceptable, as were the primary and secondary endpoints, frequency of response assessments, stratification factors and statistical analysis plan (SAP). ECOG PS was added as a stratification factor as of Amendment 2, but it was not to be included in the primary analysis model for efficacy. A cap on enrollment of AC histology was added as of Amendment 5 and sample size was changed accordingly.

Study participants: Inclusion/exclusion criteria appropriately reflect the population intended for treatment with cemiplimab.

As of Amendment 4 of the protocol (16-AUG-2018), the term "platinum-refractory", defined as progressive disease within 6 months of last dose of platinum therapy, was removed from the protocol. Subsequently, the eligibility requirement regarding prior platinum therapy (inclusion criterion #2) stated that tumour progression or recurrence should have occurred *after* treatment with cisplatin or carboplatin. Nevertheless, the applicant clarified that 55% (331 out of 608) of patients recruited in Study 1676 discontinued platinum-based chemotherapy due to progression while on treatment, which justifies the proposed indication. No other important amendments to inclusion/exclusion criteria that would alter the B/R of cemiplimab in the intended indication were done along conduct of the pivotal study. Treatments: All five choices of chemotherapy in the control arm are deemed acceptable. The regimen of cemiplimab in the experimental arm corresponds to the currently authorised dose and schedule and is considered acceptable (see discussion on clinical pharmacology). The fact that crossover was not allowed to avoid confounding survival is reasonable, noting that a sensitivity analysis of OS that censored patients who had received post-treatment immune checkpoint inhibitors was consistent with the primary analysis.

Endpoints: The objectives and endpoints of Study 1676 are deemed adequate for the targeted setting. Despite the open-label nature of the trial, considering the unmet medical need of the intended population (≥2L, low response rates from other products) and the fact that the primary endpoint is OS, response assessment by investigator is considered reasonable. The fact that PROs were collected is acknowledged, but since their clinical relevance in an open-label trial remains questionable, inclusion of their results in section 5.1 of the SmPC is not endorsed.

Statistical methods: Sample size calculations are endorsed. The stratification factors (histology, geographic region, prior bevacizumab and ECOG PS) are clinically relevant and thus acceptable. Since prior bevacizumab and ECOG PS were not included in the statistical tests of OS and PFS, sensitivity analyses were provided (data not shown), along with the planned RPSFT analysis for OS. In both cases, results were concordant with those from the primary analysis. The statistical approach to control type I error due to multiple looks (2 IAs + final analysis) and testing of diverse hypotheses is endorsed. The SCC subpopulation (n=477) was prioritised over the ITT (N=608) across testing of all efficacy endpoints (OS, PFS, ORR). The requested indication does not specify histology, but this is acceptable when considering favourable results across both ITT and SCC. Changes to the SAP followed major amendments of the protocol which is acceptable.

Regarding the recruitment of patients with adenocarcinoma (AC) histology, capped as of Amendment 5 (08-MAR-2019), the MAH clarified that these patients have longer follow-up than those with SCC. There were no major changes in standard of care for AC patients after March 2019 and therefore patients with AC recruited before March 2019 are expected to be representative of those recruited afterwards.

Participant flow and recruitment: A total of 752 patients were screened for eligibility. Most of screen failures (87% out of 144) were due to not meeting inclusion/exclusion criteria. The screen failure rate (19%) is acceptable. 304 patients were randomised to cemiplimab and 304 to chemotherapy. 3% of patients from the ITT were randomised but never treated. It is not expected that this low proportion will impact the interpretation of efficacy endpoints. The unbalance among arms (13 in the chemotherapy arm vs 5 in cemiplimab) is understandable due to the open-label nature of the trial. From the patients randomised to chemotherapy, the preferred agents in decreasing order were: gemcitabine (40%), pemetrexed (37%), vinorelbine (10%), topotecan (7%) and irinotecan (6%). Median follow-up since randomisation (~18 months) was balanced between arms. At data cutoff date (4-JAN-2021), 78% of patients had been followed up for ≥12 months since randomisation.

Conduct of the study: Major protocol violations were scant and treatment-related: lack or reconsenting for continuing treatment beyond PD in the cemiplimab arm or SAEs reported ≥24h were the most frequent causes. Regarding major protocol amendments, the rationale to cap enrolment of patients with AC is not entirely followed. However, the overall proportions of SCC and AC in Study 1676 were consistent with global distribution of cervical cancer histologies and no significant differences in efficacy according to histology were seen. Two interim analyses were introduced late (06-MAY-2020) compared to the start of the study (05-SEP-2017) and close to the database lock (18-FEB-2021), apparently to provide an opportunity for an early efficacy analysis, but they were performed by an independent statistician prior to review by the IDMC.

Baseline data: Median age was 51 years (22 to 87 years); 63% were white, 29% asian, 3.5% black; 92% had received previous paclitaxel, while 49% had received prior bevacizumab; 47% had ECOG PS 0; 78% had SCC histology and 22% AC. Regarding the extent of disease at randomisation, 94% of patients had metastatic disease, while the remaining 6% had recurrent or persistent disease. The overall burden and distribution of disease according to RECIST 1.1 data is balanced between both arms of the trial. 43% had >1 prior line of treatment in the recurrent or metastatic setting.

Patients from both arms seem to be balanced according to the period after prior platinum (≤6 months vs. >6 months) and specific platinum compound (i.e., carboplatin, cisplatin). About 88% of patients had a platinum-free interval (PFI) ≤6 months. Tables that detail the platinum-free interval (PFI) by longest and shortest duration (some of them were re-treated with platinum) showed a balanced distribution between both arms of Study 1676. An ad hoc analysis of efficacy in terms of OS/PFS/ORR/DOR according to PFI (not presented in this report) suggest that the benefit of cemiplimab over chemotherapy seems to be maintained regardless of the time interval to progression after prior platinum therapy, even in the ≥12 months subgroup (for which retreatment with platinum could potentially be a choice).

Discordances between stratification factors according to IWRS and clinical database were scarce (data not shown) and thus not expected to impact interpretation of efficacy results.

Overall, the baseline demographic and disease characteristics were consistent with inclusion/exclusion criteria and reflect the targeted population for treatment with cemiplimab.

Efficacy data and additional analyses

OS: At data cutoff 04-JAN-2021 and with a median follow-up of 18.2 months, 395 deaths had occurred (65% of OS maturity) in the ITT population of Study 1676. The study met its primary endpoint, since the HR for OS showed superiority of cemiplimab over investigator's choice of chemotherapy in both SCC population [HR for OS 0.73 (95% CI 0.58, 0.91), p-value 0.00306] and ITT [HR for OS 0.68 (95% CI 0.56, 0.84), p-value 0.00011], as prespecified in hierarchical testing. The AC histology population representing 22% of the ITT population also exhibited a survival benefit, with an exploratory HR of 0.56 (95% CI 0.36, 0.85). For the ITT, K-M estimates of median OS were 12.0 months in the cemiplimab arm and 8.5 months in the chemotherapy arm. A median survival improvement of 4.5 months is considered a clinically relevant achievement of cemiplimab in the targeted advanced cervical cancer population.

In an updated exploratory OS analysis (data cut-off 04-JAN-2022) with median follow-up of 30.2 months and 76% of event maturity, the survival benefit from cemiplimab over chemotherapy was maintained (HR: 0.66, 95% CI 0.55, 0.79).

INV-assessed PFS: At considerable event maturity (86%) in the ITT, PFS was also statistically improved in the cemiplimab vs. the chemotherapy arm: HR 0.745 (95% CI 0.625, 0.89), p-value 0.00048. K-M estimates of PFS were almost equivalent in both arms (2.8 months in cemiplimab, 2.9 months in chemotherapy) as curves separated after the third month. This pattern of "delayed" PFS benefit (i.e. less pronounced PFS improvement than OS improvement) has been seen with other immune checkpoint inhibitors, particularly for tumour types that exhibit high aggressiveness, e.g. extensive-stage small cell lung cancer (IMpower133, Horn et al, NEJM 2018; CASPIAN, Paz-Ares et al, Lancet 2019). Considering one third of patients from the cemiplimab arm and almost half from the chemotherapy arm received post-trial treatment anticancer systemic therapy, a PFS2 analysis would have been of value. However, time-to-event data for a PFS2 analysis are not available according to the MAH. Cytotoxic agents constituted the majority of post-trial treatments in both arms, although, expectably, a higher proportion of monoclonal antibodies (almost all immune checkpoint inhibitors) was used in the chemotherapy arm (60 patients, 20%) as compared to the cemiplimab arm (17 patients, 6%).

INV-assessed ORR/DOR: Acknowledging the advanced post-platinum setting, low response rates were observed in both arms: 16.4% in the cemiplimab arm vs. 6.3% in the chemotherapy arm, although a statistically significant CMH test was observed. Likewise, the few responses were more durable in the cemiplimab arm (mDOR 16.4 months, vs. 6.9 in the chemotherapy arm).

Ancillary analyses: OS and PFS advantage from cemiplimab over chemotherapy was observed across almost all the prespecified subgroups. Although the HR for OS in the recurrent/persistent subgroup exceeded 1, this subpopulation consisted of only 34 patients with 17 events.

Efficacy by PD-L1 status: An exploratory analysis on the relationship between PD-L1 expression according to the SP263 IHC assay and efficacy in terms of OS, PFS and ORR was done for a subgroup of the population of Study 1676. Evaluable samples were available for 254 patients (42%) from the ITT and balanced between arms.

Among these samples, 64% were PD-L1≥1% and 36% were PD-L1<1%. At the updated exploratory OS analysis on 04-JAN-2022, the hazard ratio for the PD-L1≥ 1% group was 0.70 (95% CI: 0.48, 1.01) and 0.85 (95% CI: 0.53, 1.36) for the PD-L1<1% group. Upon these data, it appears that the efficacy estimate is also compatible with benefit in the underpowered PD-L1<1% subgroup; moreover, given what

is known about PD-1 inhibitors, a detrimental effect of cemiplimab in the present treatment setting is not considered likely.

The evaluation of efficacy in subgroups is generally fraught with difficulty given that these will generally not be large enough for independent efficacy inferences. In an overall positive study, it is considered acceptable to use the most mature –and therefore statistically powerful– dataset to evaluate the impact of treatment in subgroups. While the pivotal study was overall positive, the magnitude of efficacy in subgroups indicate that also in this treatment setting PD-L1 expression is a relevant effect modifier.

Recognising that efficacy will increase with increasing PD-L1 expression, this is understood as a continuum, and it seems reasonable not to restrict use based on PD-L1 expression levels. OS by PD-L1 status, however, will be presented in section 5.1 of the SmPC, as an integral part of the description of the performance characteristics of cemiplimab in the intended treatment setting.

Treatment with cemiplimab beyond progression: Efficacy data presented for the subgroup of 70 patients (23% of the cemiplimab arm) who continued cemiplimab beyond progression as allowed per protocol suggest that they continued to derive an efficacy benefit. However, considering the fact that these patients are highly selected, these data will not be presented in the SmPC.

Supportive data from Study 1423: 20 patients from two advanced cervical cancer cohorts were treated in this FIH trial. Although data were clearly limited, efficacy signals (10% ORR) served to support the design of Study 1676.

2.4.3. Conclusions on the clinical efficacy

Study 1676 showed an advantage of cemiplimab vs. investigator's choice of chemotherapy choices in the treatment of patients with recurrent or metastatic cervical cancer with disease progression after platinum-based chemotherapy. While the pivotal study was overall positive, the magnitude of efficacy in subgroups indicate that PD-L1 expression is a relevant effect modifier, although a restricted indication is not deemed necessary.

2.5. Clinical safety

2.5.1. Introduction

The safety profile of cemiplimab has been characterised in patients with advanced solid malignancies who received cemiplimab monotherapy in 4 clinical studies. The toxicity profile of cemiplimab is characterised by immune-related mediated adverse reactions including hypothyroidism, hyperthyroidism pneumonitis, hepatitis, colitis and skin adverse reactions. Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with cemiplimab treatment.

The summary of clinical safety (SCS) submitted by the MAH presented safety data from 5 studies: Study 1676 (confirmatory study for the cervical cancer indication), and studies 1423, 1540, 1620 and 1624, in patients who received at least 1 dose of cemiplimab as monotherapy. The following table summarises the studies included in the safety data pools.

Table 53: Description of safety assessments on clinical studies

Study Number Study Status Total Number of Centers With Treated Patients Country(ies)	Study Population	Study Phase Study Design	Dose and Schedule	Safety Assessments and Objectives / Endpoints
R2810-ONC-1676 Ongoing 97 centers 14 countries	Adult patients with recurrent, persistent or metastatic cervical cancer for which there is no curative intent option, and who have progressed or had recurrence after treatment with platinum therapy. (N = 608; with 590 patients in the safety analysis set [SAF])	Phase 3 Randomized, multicenter, open-label, pivotal study	350 mg cemiplimab administered intravenously over 30 minutes Q3W for up to 96 weeks (N=300) or investigator choice (IC) chemotherapy for up to 96 weeks (N=290)	Safety is assessed through AEs, laboratory data, vital signs, and Eastern Cooperative Oncology Group (ECOG) performance status.
R2810-ONC-1423 Complete 38 centers 3 countries	Adult patients with advanced malignancies or who are incurable and have failed to respond to or showed tumor progression despite standard therapy, or patients who are not candidates for standard therapy, or for whom no available therapy is expected to convey clinical benefit, or for whom PD-1 blockade has been shown to be at least equivalent to standard of care. (N = 398 [FAS and SAF]; 130 patients received cemiplimab monotherapy)	Phase 1 first-in-human (FIH), open-label, multicenter, repeat-dose study	Cemiplimab administered intravenously over 30 min every 2 weeks (Q2W) at: -3 mg/kg (n = 333) -1 mg/kg (n = 27) -10 mg/kg (n = 6) -200 mg (n = 20) Cemiplimab 3 mg/kg Q3W (n=12) Treatment duration: 48 weeks	Safety is assessed through AEs, laboratory data, vital signs, and ECOG performance status.

Study Number Study Status Total Number of Centers With Treated Patients Country(ies)	Study Population	Study Phase Study Design	Dose and Schedule	Safety Assessments and Objectives / Endpoints
R2810-ONC-1540 Ongoing 35 centers 3 countries	Adult patients with mCSCC (Group 1 and Group 3) and locally advanced cutaneous squamous cell carcinoma (laCSCC) (Group 2) (N = 193 [FAS and SAF]; 59 in Group 1, 78 in Group 2, and 56 in Group 3)	Phase 2 nonrandomized, 3-group, multicenter study	Cemiplimab administered intravenously over 30 min at: -3 mg/kg Q2W (Groups 1 and 2) -350 mg Q3W (Group 3) Treatment duration: up to 96 weeks for Groups 1 and 2 and up to 54 weeks in Group 3	Safety is assessed through AEs, laboratory data, vital signs, and ECOG performance status.
R2810-ONC-1620 Ongoing 49 centers 10 countries	Adult patients with mBCC (Group 1) and unresectable laBCC (Group 2) (N = 138 [SAF]; 48 in Group 1 and 84 in Group 2)	Phase 2 nonrandomized, 2-group, multicenter study	Cemiplimab administered intravenously over 30 min at 350 mg Q3W Treatment duration: 93 weeks	Safety is assessed through AEs, laboratory data, vital signs, and ECOG performance status.
R2810-ONC-1624 Ongoing[a] 138 centers 24 countries	Adult patients, diagnosed with stage IIIB, IIIC, or stage IV squamous or non-squamous NSCLC, who are not eligible for definitive chemo/radiation, whose tumors express PD-L1 in ≥50% of tumor cells (using the PD-L1 IHC 22C3 pharmDx assay), and who have received no prior systemic treatment for their advanced disease. (N=710; including 697 in the SAF)	Phase 3 Randomized, multicenter, open-label, pivotal study	350 mg cemiplimab administered intravenously over 30 minutes Q3W for up to 108 weeks (N=355) or standard of care chemotherapy for 4 to 6 cycles (N=342)	Safety is assessed through AEs, laboratory data, vital signs, and ECOG performance status.

Abbreviations: AE, adverse event; BCC, basal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; FAS, Full analysis set; IC, investigator choice; laBCC, locally advanced basal cell carcinoma; laCSCC, locally advanced cutaneous squamous cell carcinoma; mBCC, metastatic basal cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; N, total number of patients; n, number of patients in subgroups; NSCLC, non-small cell lung cancer; PD-1, programmed death-1 (receptor); PD-L1, programmed death ligand 1; Q2W, every 2 weeks; Q3W, every 3 weeks; SAF, safety analysis set

[a] This study met endpoints. Study patients are being followed for long term survival

Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR, Module 5.3.5.2 Study 1423 Final CSR, Module 5.3.5.2 Study 1540 Interim CSR, Module 5.3.5.2 Study 1620 Interim CSR, BCC ISS Table 14.1.1.1.p0, 30Jun2020, Module 5.3.5.1 Study 1624 Primary Analysis CSR.

Data from two safety data pools were presented as described below:

- **Safety Pool 1** (Cervical Cancer population): All patients who received at least 1 dose of cemiplimab monotherapy in Study 1676. This pool included 300 patients. This is the primary pool for the analysis of safety of cemiplimab in patients with recurrent/metastatic cervical cancer.
- **Safety Pool 2** (cemiplimab monotherapy population): All patients (n=1116) who received at least 1 dose of cemiplimab as monotherapy across Study 1676 (n=300), Study 1423 (n=130), Study 1540 (Groups 1, 2, and 3, n=193), Study 1620 (n=138) and Study 1624 (excluding crossover cemiplimab treatment, n=355). This pool is used to evaluate the frequency and characteristics of important risks of cemiplimab (imAEs and IRRs) and allows a broader assessment of the safety profile of cemiplimab monotherapy across dose levels and solid tumor indications.

Table 2 summarises the studies contained in each safety pool and the data cutoff dates.

Table 54: Integrated Databases by Each Pool

Studies/Patients	Database Cutoff	Safety Pool 1	Safety Pool 2
Study 1676 (cervical): All patients who received cemiplimab monotherapy (N = 300)	04 Jan 2021	x	x
Study 1423 (FIH): All patients who received cemiplimab monotherapy (N = 130)	30 Apr 2019		x
Study 1540 (CSCC): Patients in Group 1, Group 2, and Group 3 (N = 193)	20 Sep 2018 (Groups 1 and 3); 10 Oct 2018 (Group 2)		x
Study 1620 (BCC): All patients (N = 138)	30 Jun 2020		x
Study 1624 (NSCLC): Cemiplimab monotherapy (N = 355)	01 Mar 2020		x

2.5.2. Patient exposure

Table 55: Patient Disposition in Study 1676 (Safety Analysis Set) -Total Population

	Cemiplimab (N=300)	Chemotherapy (N=290)
Treatment ongoing, n (%)	37 (12.3%)	7 (2.4%)
Off treatment, n (%)	263 (87.7%)	283 (97.6%)
Treatment completed	13 (4.3%)	0
Treatment discontinued	250 (83.3%)	283 (97.6%)
Primary reason for treatment discontinuation		
Adverse event	25 (8.3%)	15 (5.2%)
Death	14 (4.7%)	17 (5.9%)
Non-compliance with study drug(s)	1 (0.3%)	0
Subject decision	8 (2.7%)	10 (3.4%)
Physician decision	0	2 (0.7%)
Disease progression	199 (66.3%)	229 (79.0%)
Withdrawal of consent	3 (1.0%)	10 (3.4%)
Study ongoing, n (%)	53 (17.7%)	11 (3.8%)
Off study, n (%)	247 (82.3%)	279 (96.2%)
Study completed	7 (2.3%)	0
Study discontinued	240 (80.0%)	279 (96.2%)
Primary reason for study discontinuation		
Adverse event	8 (2.7%)	7 (2.4%)
Death	89 (29.7%)	94 (32.4%)
Lost to follow-up	2 (0.7%)	2 (0.7%)
Non-compliance with study drug(s)	1 (0.3%)	0
Subject decision	34 (11.3%)	41 (14.1%)
Physician decision	1 (0.3%)	1 (0.3%)
Disease progression	98 (32.7%)	117 (40.3%)
Withdrawal of consent	7 (2.3%)	17 (5.9%)

Abbreviation: N, number of patients
Data cutoff as of 04 Jan 2021 for all patients in Study 1676.
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTT 14.1.1.5.2all

Table 56: Treatment Exposure in Study 1676 (Safety Analysis Set) - Total Population

	Cemiplimab (N = 300)	Chemotherapy (N = 290)
Duration of Exposure (weeks)		
n	300	290
Mean (SD)	26.49 (26.033)	14.37 (13.038)
Median	15.15	10.05
Q1 : Q3	6.50 : 36.10	5.10 : 19.00
Min-Max	1.4 : 100.7	1.0 : 81.9
Duration of Exposure, n (%)		
≥ 3 weeks	298 (99.3%)	270 (93.1%)
≥ 6 weeks	266 (88.7%)	204 (70.3%)
≥ 12 weeks	185 (61.7%)	125 (43.1%)
≥ 18 weeks	141 (47.0%)	79 (27.2%)
≥ 24 weeks	111 (37.0%)	49 (16.9%)
≥ 36 weeks	81 (27.0%)	21 (7.2%)
≥ 48 weeks	58 (19.3%)	10 (3.4%)
≥ 72 weeks	28 (9.3%)	1 (0.3%)
≥ 96 weeks	8 (2.7%)	0
Duration of Exposure, n (%)		
0 - < 3 weeks	2 (0.7%)	20 (6.9%)
3 - < 6 weeks	32 (10.7%)	66 (22.8%)
6 - < 12 weeks	81 (27.0%)	79 (27.2%)
12 - < 24 weeks	74 (24.7%)	76 (26.2%)
24 - < 36 weeks	30 (10.0%)	28 (9.7%)
36 - < 48 weeks	23 (7.7%)	11 (3.8%)
48 - < 72 weeks	30 (10.0%)	9 (3.1%)
72 - < 96 weeks	20 (6.7%)	1 (0.3%)
≥ 96 weeks	8 (2.7%)	0

Abbreviation: SD, standard deviation.
Data cutoff as of 04 Jan 2021 for all patients in Study 1676.
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTT 14.1.4.1all

Table 57: Treatment Exposure for Cemiplimab Pooled Data Sets (Safety Analysis Set)

	Pool 1 All Cervical Patients (N = 300)	Pool 2 All Monotherapy Patients (N =1116)
Duration of Exposure (weeks)[a]		
n	300	1116
Mean (SD)	26.49 (26.033)	34.08 (28.099)
Median	15.15	26.90
Q1: Q3	6.50: 36.10	10.75: 48.80
Min-Max	1.4: 100.7	0.3: 144.4
Duration of Exposure, n (%)		
≥ 0 weeks	300 (100%)	1116 (100%)
≥ 6 weeks	266 (88.7%)	1010 (90.5%)
≥ 12 weeks	185 (61.7%)	817 (73.2%)
≥ 24 weeks	111 (37.0%)	591 (53.0%)
≥ 36 weeks	81 (27.0%)	448 (40.1%)
≥ 48 weeks	58 (19.3%)	321 (28.8%)
≥ 60 weeks	41 (13.7%)	196 (17.6%)
≥ 72 weeks	28 (9.3%)	150 (13.4%)
≥ 84 weeks	17 (5.7%)	102 (9.1%)
≥ 96 weeks	8 (2.7%)	35 (3.1%)
≥ 108 weeks	0	6 (0.5%)
≥ 120 weeks	0	2 (0.2%)
≥ 132 weeks	0	1 (<0.1%)
≥ 144 weeks	0	1 (<0.1%)
≥ 156 weeks	0	0

[a] Duration of exposure (weeks) = minimum of [last dose date - first dose date + (14 or 21 based on Q2W or Q3W dosing schedule)]/7 and (data cutoff date or death date - first dose date + 1) / 7.

Abbreviations: Max, maximum; Min, minimum; Q1, quarter 1; Q2W, every 2 weeks; Q3, quarter 3; Q3W, every 3 weeks; SD, standard deviation

Data cutoff as of 04 Jan 2021 for all patients in Study 1676; data cutoff as of 30 Jun 2020 for Study 1620; data cutoff as of 01 Mar 2020 for Study 1624; data cutoff as of 30 Apr 2019 for Study 1423; data cutoff as of 20 Sep 2018 for Group 1 and Group 3 patients in Study 1540; and data cutoff as of 10 Oct 2018 for Group 2 patients in Study 1540.

Source: ISS Table 14.1.4.1

2.5.3. Adverse events

Summary of AEs in Study 1676 and cemiplimab monotherapy pool:

Table 58: Summary of treatment-emergent adverse events in study 1676 total population (safety analysis set) and pool 2

	Cemiplimab (N=300)	Chemotherapy (N=290)	All Cemiplimab Monotherapy Patients (N=1116)
Number of TEAEs	1969	2356	8435
Number of NCI grade 3/4/5 TEAEs	299	385	1029
Number of serious TEAEs	147	133	587
Number of patients with any TEAE, n (%)	265 (88.3%)	265 (91.4%)	1030 (92.3%)
Number of patients with any NCI grade 3/4/5 TEAE, n (%)	135 (45.0%)	155 (53.4%)	472 (42.3%)
Number of patients with any serious TEAE, n (%)	89 (29.7%)	78 (26.9%)	335 (30.0%)
Number of patients who discontinued study treatment due to TEAEs, n (%)	26 (8.7%)	15 (5.2%)	92 (8.2%)
Number of patients with any TEAE leading to a dose interruption/delay, n (%)	75 (25.0%)	114 (39.3%)	331 (29.7%)
Number of patients with any TEAE leading to a dose reduction, n (%)	0	58 (20.0%)	6 (0.5%)
Number of patients with any TEAE resulting in death, n (%)	5 (1.7%)	2 (0.7%)	54 (4.8%)

Data cut-off as of 04 Jan 2021.
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.

All-grade and high-grade (≥G3) AEs in Study 1676 and cemiplimab monotherapy pool:

Table 59: Treatment-emergent adverse events by SOC, PT, and NCI Grade in Study 1676 (All Grades in >5% of patients in any treatment arm or Grade ≥3 in >2% of patient in any treatment arm in study 1676) (Safety analysis set) and pool 2

	Cemiplimab (N=300)		Chemotherapy (N=290)		All Cemiplimab Monotherapy Patients (N=1116)	
System Organ Class, n (%) Preferred Term, n (%)	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Number of patients with any TEAE, n (%)	265 (88.3%)	135 (45.0%)	265 (91.4%)	155 (53.4%)	1030 (92.3%)	472 (42.3%)
Gastrointestinal disorders						
Nausea	55 (18.3%)	1 (0.3%)	97 (33.4%)	6 (2.1%)	155 (13.9%)	2 (0.2%)
Vomiting	48 (16.0%)	2 (0.7%)	68 (23.4%)	7 (2.4%)	108 (9.7%)	3 (0.3%)
Constipation	45 (15.0%)	0	59 (20.3%)	1 (0.3%)	133 (11.9%)	2 (0.2%)
Diarrhoea	32 (10.7%)	3 (1.0%)	39 (13.4%)	4 (1.4%)	168 (15.1%)	7 (0.6%)
Abdominal pain	29 (9.7%)	3 (1.0%)	33 (11.4%)	3 (1.0%)	83 (7.4%)	6 (0.5%)
Stomatitis	12 (4.0%)	1 (0.3%)	22 (7.6%)	3 (1.0%)	30 (2.7%)	1 (<0.1%)
General disorders and administration site conditions						
Fatigue	50 (16.7%)	4 (1.3%)	45 (15.5%)	4 (1.4%)	235 (21.1%)	18 (1.6%)
Pyrexia	35 (11.7%)	1 (0.3%)	61 (21.0%)	0	89 (8.0%)	2 (0.2%)
Asthenia	33 (11.0%)	7 (2.3%)	44 (15.2%)	3 (1.0%)	80 (7.2%)	12 (1.1%)
General disorders and administration site conditions						
Oedema peripheral	19 (6.3%)	1 (0.3%)	16 (5.5%)	0	65 (5.8%)	1 (<0.1%)
Infections and infestations						
Urinary tract infection	35 (11.7%)	15 (5.0%)	25 (8.6%)	8 (2.8%)	79 (7.1%)	23 (2.1%)
Metabolism and nutrition disorders						
Decreased appetite	45 (15.0%)	1 (0.3%)	46 (15.9%)	2 (0.7%)	147 (13.2%)	6 (0.5%)
Hypoalbuminaemia	21 (7.0%)	4 (1.3%)	18 (6.2%)	4 (1.4%)	60 (5.4%)	8 (0.7%)
Hypokalaemia	18 (6.0%)	8 (2.7%)	17 (5.9%)	7 (2.4%)	55 (4.9%)	17 (1.5%)
Hyperglycaemia	4 (1.3%)	1 (0.3%)	16 (5.5%)	3 (1.0%)	39 (3.5%)	8 (0.7%)
Blood and lymphatic system disorders						
Anaemia	75 (25.0%)	36 (12.0%)	129 (44.5%)	78 (26.9%)	181 (16.2%)	63 (5.6%)
Neutropenia	6 (2.0%)	3 (1.0%)	44 (15.2%)	26 (9.0%)	14 (1.3%)	5 (0.4%)
Blood and lymphatic system disorders						
Leukopenia	4 (1.3%)	1 (0.3%)	13 (4.5%)	7 (2.4%)	10 (0.9%)	3 (0.3%)
Thrombocytopenia	2 (0.7%)	1 (0.3%)	16 (5.5%)	9 (3.1%)	18 (1.6%)	1 (<0.1%)
Musculoskeletal and connective tissue disorders						
Back pain	33 (11.0%)	4 (1.3%)	25 (8.6%)	2 (0.7%)	99 (8.9%)	5 (0.4%)
Arthralgia	31 (10.3%)	1 (0.3%)	8 (2.8%)	0	137 (12.3%)	3 (0.3%)
Pain in extremity	18 (6.0%)	2 (0.7%)	7 (2.4%)	2 (0.7%)	65 (5.8%)	6 (0.5%)
Investigations						
Blood creatinine increased	20 (6.7%)	4 (1.3%)	17 (5.9%)	1 (0.3%)	73 (6.5%)	7 (0.6%)
Alanine aminotransferase increased	13 (4.3%)	2 (0.7%)	20 (6.9%)	2 (0.7%)	69 (6.2%)	9 (0.8%)
Aspartate aminotransferase increased	12 (4.0%)	2 (0.7%)	19 (6.6%)	0	66 (5.9%)	15 (1.3%)
Neutrophil count decreased	2 (0.7%)	1 (0.3%)	26 (9.0%)	12 (4.1%)	8 (0.7%)	2 (0.2%)
Investigations						
White blood cell count decreased	2 (0.7%)	0	14 (4.8%)	6 (2.1%)	10 (0.9%)	0
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	26 (8.7%)	5 (1.7%)	17 (5.9%)	1 (0.3%)	104 (9.3%)	16 (1.4%)
Cough	20 (6.7%)	1 (0.3%)	20 (6.9%)	1 (0.3%)	113 (10.1%)	2 (0.2%)
Skin and subcutaneous tissue disorders						
Rash	18 (6.0%)	3 (1.0%)	19 (6.6%)	0	88 (7.9%)	6 (0.5%)
Pruritus	16 (5.3%)	0	15 (5.2%)	1 (0.3%)	122 (10.9%)	1 (<0.1%)
Nervous system disorders						
Headache	22 (7.3%)	1 (0.3%)	17 (5.9%)	0	85 (7.6%)	4 (0.4%)

Renal and urinary disorders						
Hydronephrosis	9 (3.0%)	7 (2.3%)	4 (1.4%)	2 (0.7%)	11 (1.0%)	7 (0.6%)
Reproductive system and breast disorders						
Pelvic pain	14 (4.7%)	1 (0.3%)	16 (5.5%)	3 (1.0%)	20 (1.8%)	1 (<0.1%)
Psychiatric disorders						
Insomnia	19 (6.3%)	0	16 (5.5%)	1 (0.3%)	64 (5.7%)	0
Endocrine disorders						
Hypothyroidism	18 (6.0%)	1 (0.3%)	0	0	85 (7.6%)	1 (<0.1%)

Data cut-off as of 04 Jan 2021.
TEAE: Treatment-emergent adverse event.
All adverse events were coded using the MedDRA Version 23.1. NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a system organ class/preferred term.
For SOCs, the table is sorted by decreasing frequency of all grades in the cemiplimab group. Within each SOC, PTs are sorted by decreasing frequency of all grades in the cemiplimab group.

2.5.4. Serious adverse event/deaths/other significant events

2.5.4.1. SAEs in Study 1676 and cemiplimab monotherapy pool

Table 60: Serious Treatment-Emergent Adverse Events by SOC and PT in Study 1676 (in ≥1% of Patients in Any Treatment Arm in Study 1676) (Safety Analysis Set) and Pool 2

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab (N=300)	Chemotherapy (N=290)	All Cemiplimab Monotherapy Patients (N=1116)
Number of patients with any serious TEAE, n (%)	89 (29.7%)	78 (26.9%)	335 (30.0%)
Infections and infestations			
Urinary tract infection	12 (4.0%)	10 (3.4%)	21 (1.9%)
Pneumonia	4 (1.3%)	3 (1.0%)	31 (2.8%)
Pyelonephritis	3 (1.0%)	3 (1.0%)	4 (0.4%)
Gastrointestinal disorders			
Vomiting	1 (0.3%)	3 (1.0%)	1 (<0.1%)
General disorders and administration site conditions			
Pyrexia	4 (1.3%)	5 (1.7%)	9 (0.8%)
Renal and urinary disorders			
Acute kidney injury	5 (1.7%)	3 (1.0%)	9 (0.8%)
Haematuria	3 (1.0%)	1 (0.3%)	5 (0.4%)
Hydronephrosis	3 (1.0%)	0	3 (0.3%)
Hepatobiliary disorders			
Autoimmune hepatitis	4 (1.3%)	0	8 (0.7%)
Immune-mediated hepatitis	3 (1.0%)	0	6 (0.5%)
Respiratory, thoracic and mediastinal disorders			
Pneumonitis	3 (1.0%)	1 (0.3%)	20 (1.8%)
Blood and lymphatic system disorders			
Febrile neutropenia	3 (1.0%)	5 (1.7%)	4 (0.4%)
Anaemia	2 (0.7%)	14 (4.8%)	8 (0.7%)
Thrombocytopenia	0	3 (1.0%)	0
Investigations			
Blood creatinine increased	3 (1.0%)	1 (0.3%)	5 (0.4%)

Data cut-off as of 04 Jan 2021.
TEAE: Treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 23.1.
A patient is counted only once for multiple occurrences within a system organ class/preferred term.
For SOCs, the table is sorted by decreasing frequency in the cemiplimab group. Within each SOC, PTs are sorted by decreasing frequency in the cemiplimab group.

2.5.4.2. AEs resulting in death in Study 1676

Table 61: Summary of Treatment-Emergent Adverse Events Resulting in Death by System Organ Class and Preferred Term in Study 1676 (Safety Analysis Set) - Total Population

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab (N=300)	Chemotherapy (N=290)
Number of patients with any TEAE resulting in death, n (%)	5 (1.7%)	2 (0.7%)
General disorders and administration site conditions	2 (0.7%)	2 (0.7%)
Death	1 (0.3%)	0
Sudden death	1 (0.3%)	0
Multiple organ dysfunction syndrome	0	1 (0.3%)
Performance status decreased	0	1 (0.3%)
Nervous system disorders	2 (0.7%)	0
Cerebrovascular accident	1 (0.3%)	0
Ischaemic stroke	1 (0.3%)	0
Infections and infestations	1 (0.3%)	1 (0.3%)
Pneumonia	1 (0.3%)	0
Neutropenic sepsis	0	1 (0.3%)

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event
All AEs were coded using MedDRA Version 23.1. A patient is counted only once for multiple occurrences within a SOC/PT.
For SOCs, the table is sorted by decreasing frequency in the cemiplimab group. Within each SOC, PTs are sorted by decreasing frequency in the cemiplimab group.
Data cutoff as of 04 Jan 2021 for all patients in Study 1676.
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTT 14.3.2.3.1all

2.5.4.3. Adverse events of special interest

Adverse events of special interest for this study included the following:

- Grade ≥2 infusion related reactions
- Grade ≥2 allergic/hypersensitivity reaction
- Grade ≥3 immune-mediated AEs
- An immune-mediated AE of any grade in a patient previously treated with a PI3-K inhibitor

Table 62: Summary of Treatment-Emergent Adverse Events of Special Interest (based on AESI Question in CRF) (Safety Analysis Set) - Patients with SCC and AC Histology

	Cemiplimab (N=300)	Chemotherapy (N=290)
Number of treatment-emergent AESIs	41	0
Number of NCI grade 3/4/5 treatment-emergent AESIs	34	0
Number of serious treatment-emergent AESIs	14	0
Number of patients with any treatment-emergent AESI, n (%)	34 (11.3%)	0
Number of patients with any NCI grade 3/4/5 treatment-emergent AESI, n (%)	29 (9.7%)	0
Number of patients with any serious treatment-emergent AESI, n (%)	14 (4.7%)	0
Number of patients who discontinued study treatment due to treatment-emergent AESIs, n (%)	12 (4.0%)	0
Number of patients with any treatment-emergent AESI leading to a dose interruption/delay, n (%)	14 (4.7%)	0
Number of patients with any treatment-emergent AESI leading to a dose reduction, n (%)	0	0
Number of patients with any treatment-emergent AESI resulting in death, n (%)	0	0

Data cutoff as of 04 Jan 2021.
AC=adenocarcinoma/adenosquamous histology; AESI=Adverse event of special interest; SCC=squamous cell carcinoma.
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.
Source: PTT 14.3.2.6.1all

Infusion-Related Reactions

Table 63: Summary of Infusion Reactions (Safety Analysis Set) - Patients with SCC and AC Histology

	Cemiplimab (N=300)	Chemotherapy (N=290)
Number of infusion reactions	8	38
Number of NCI grade 3/4/5 infusion reactions	0	1
Number of serious infusion reactions	0	0
Number of patients with any infusion reaction, n (%)	8 (2.7%)	13 (4.5%)
Number of patients with any NCI grade 3/4/5 infusion reaction, n (%)	0	1 (0.3%)
Number of patients with any serious infusion reaction, n (%)	0	0
Number of patients who discontinued study treatment due to infusion reactions, n (%)	0	2 (0.7%)
Number of patients with any infusion reaction leading to a dose interruption/delay, n (%)	5 (1.7%)	9 (3.1%)
Number of patients with any infusion reaction leading to a dose reduction, n (%)	0	0
Number of patients with any infusion reaction resulting in death, n (%)	0	0

Data cutoff as of 04 Jan 2021.
AC=adenocarcinoma/adenosquamous histology; NCI=National Cancer Institute; SCC=squamous cell carcinoma.
Infusion reaction: any AE that occurs during the infusion or within 2 hours after the infusion is completed.
NCI grades were coded using CTCAE Version 4.03.
Source: PTT 14.3.2.7.1all.

Table 64: Summary of Sponsor-Identified Infusion Reactions by System Organ Class, Preferred Term, and NCI Grade (Safety Analysis Set)

	Pool 1 All Cervical Patients (N=300)		Pool 2 All Monotherapy Patients (N=1116)	
System Organ Class				
Preferred Term, n (%)	**All Grades**	**Grades 3/4/5**	**All Grades**	**Grades 3/4/5**
Number of infusion reactions (based on sponsor definition)	22	-	105	1
Number of patients with any infusion reaction (based on sponsor definition), n (%)	20 (6.7%)	0	83 (7.4%)	1 (<0.1%)
Injury, poisoning and procedural complications	8 (2.7%)	0	33 (3.0%)	0
Infusion-related reaction	8 (2.7%)	0	33 (3.0%)	0
Gastrointestinal disorders	9 (3.0%)	0	23 (2.1%)	0
Nausea	6 (2.0%)	0	14 (1.3%)	0
Vomiting	4 (1.3%)	0	8 (0.7%)	0
Abdominal pain	1 (0.3%)	0	4 (0.4%)	0

System Organ Class Preferred Term, n (%)	Pool 1 All Cervical Patients (N=300)		Pool 2 All Monotherapy Patients (N=1116)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
General disorders and administration site conditions	3 (1.0%)	0	15 (1.3%)	0
Pyrexia	3 (1.0%)	0	12 (1.1%)	0
Chills	0	0	4 (0.4%)	0
Skin and subcutaneous tissue disorders	0	0	7 (0.6%)	0
Rash	0	0	6 (0.5%)	0
Erythema	0	0	1 (<0.1%)	0
Respiratory, thoracic and mediastinal disorders	0	0	5 (0.4%)	1 (<0.1%)
Dyspnoea	0	0	4 (0.4%)	1 (<0.1%)
Wheezing	0	0	1 (<0.1%)	0
Immune system disorders	0	0	3 (0.3%)	0
Hypersensitivity	0	0	2 (0.2%)	0
Drug hypersensitivity	0	0	1 (<0.1%)	0
Musculoskeletal and connective tissue disorders	0	0	3 (0.3%)	0
Back pain	0	0	3 (0.3%)	0
Vascular disorders	0	0	2 (0.2%)	0
Flushing	0	0	2 (0.2%)	0

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute; PT, preferred term; SOC, system organ class
All AEs were coded using MedDRA Version 23.1. NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a SOC/PT.
For SOCs, the table is sorted by decreasing frequency of all grades in the total group. Within each SOC, PTs are sorted by decreasing frequency in the total group.
Data cutoffs: 04 Jan 2021 in Study 1676; 01 Mar 2020 for patients in Study 1624; 30 Apr 2019 for patients in Study 1423; 20 Sep 2018 for all patients in Group 1 and Group 3 and 10 Oct 2018 for Group 2 in Study 1540; and 30 Jun 2020 for all patients in Study 1620.
Source: ISS Table 14.3.2.5.1 and ISS Table 14.3.2.5.4

Treatment-Emergent Sponsor Identified Immune-Mediated Adverse Events

Table 65: Summary of Treatment-Emergent Sponsor-Identified Immune-Mediated Adverse Events (imAEs Requiring Systemic Corticosteroids and Endocrine-Related imAEs Based on Sponsor-Provided List; Safety Analysis Set)

	Chemotherapy (n=290)	Pool 1 All Cervical Patients (N=300)	Pool 2 All Monotherapy Patients (N=1116)
Number of treatment-emergent sponsor-identified imAEs	2	63	328[a]
Number of NCI grade 3/4/5 treatment-emergent sponsor-identified imAEs	2	18	82[a]
Number of serious treatment-emergent sponsor-identified imAEs	2	15	69[a]
Number of patients with any treatment-emergent sponsor-identified imAE, n (%)	2 (0.7%)	47 (15.7%)	229 (20.5%)
Number of patients with any NCI grade 3/4/5 treatment-emergent sponsor-identified imAE, n (%)	2 (0.7%)	16 (5.3%)	71 (6.4%)
Number of patients with any serious treatment-emergent sponsor-identified imAE, n (%)	2 (0.7%)	15 (5.0%)	61 (5.5%)
Number of patients who discontinued study treatment due to treatment-emergent sponsor-identified imAE, n (%)	2 (0.7%)	15 (5.0%)	51 (4.6%)[a]
Number of patients with any treatment-emergent sponsor-identified imAE leading to a drug interruption/delay, n (%)	0	8 (2.7%)	80 (7.2%)
Number of patients with any treatment-emergent sponsor-identified imAE leading to a dose reduction, n (%)	0	0	3 (0.3%)
Number of patients with any treatment-emergent sponsor-identified imAE leading to both a drug interruption/delay and a dose reduction, n (%)	0	0	3 (0.3%)
Number of patients with any treatment-emergent sponsor-identified imAE resulting in death, n (%)	0	0	4 (0.4%)[a]

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; imAE, immune-mediated adverse event; NCI, National Cancer Institute

NCI grades were coded using CTCAE Version 4.03.

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

Data cutoffs: 04 Jan 2021 in Study 1676; 01 Mar 2020 for patients in Study 1624; 30 Apr 2019 for patients in Study 1423; 20 Sep 2018 for all patients in Group 1 and Group 3 and 10 Oct 2018 for Group 2 in Study 1540; and 30 Jun 2020 for all patients in Study 1620.

Source: ISS Table 14.3.2.4.1 and R2810-ONC-1624 Primary Analysis CSR Erratum

[a] Two additional identified imAEs of Myocarditis (grade 5) and Immune-mediated hepatitis (grade 4) were identified by the sponsor during medical review of cases and added to **Table 65** (R2810-ONC-1624 Primary Analysis CSR Erratum).

Table 66: Treatment-Emergent Sponsor Identified Immune-Mediated Adverse Events by System Organ Class, Preferred Term and NCI Grade (ImAEs Requiring Systemic Corticosteroids or Immunosuppressants, or Endocrine-related ImAEs Based on Sponsor Provided List (Safety Analysis Set) -Patients with SCC and AC Histology

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab (N=300)		Chemotherapy (N=290)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Number of patients with any treatment-emergent sponsor identified imAE, n (%)	47 (15.7%)	16 (5.3%)	2 (0.7%)	2 (0.7%)
Endocrine disorders	24 (8.0%)	1 (0.3%)	0	0
Hypothyroidism	18 (6.0%)	1 (0.3%)	0	0
Hyperthyroidism	9 (3.0%)	0	0	0
Thyroiditis	1 (0.3%)	0	0	0
Hepatobiliary disorders	10 (3.3%)	10 (3.3%)	0	0
Immune-mediated hepatitis	4 (1.3%)	4 (1.3%)	0	0
Autoimmune hepatitis	3 (1.0%)	3 (1.0%)	0	0
Hepatic function abnormal	1 (0.3%)	1 (0.3%)	0	0
Hepatitis	1 (0.3%)	1 (0.3%)	0	0
Hepatotoxicity	1 (0.3%)	1 (0.3%)	0	0
Skin and subcutaneous tissue disorders	5 (1.7%)	1 (0.3%)	0	0
Rash	3 (1.0%)	1 (0.3%)	0	0
Dermatitis	1 (0.3%)	0	0	0
Rash pruritic	1 (0.3%)	0	0	0
Gastrointestinal disorders	4 (1.3%)	1 (0.3%)	0	0
Colitis	2 (0.7%)	1 (0.3%)	0	0
Diarrhoea	2 (0.7%)	0	0	0
Respiratory, thoracic, and mediastinal disorders	4 (1.3%)	2 (0.7%)	1 (0.3%)	1 (0.3%)
Pneumonitis	4 (1.3%)	2 (0.7%)	1 (0.3%)	1 (0.3%)
Investigations	2 (0.7%)	1 (0.3%)	0	0
Alanine aminotransferase increased	1 (0.3%)	1 (0.3%)	0	0
Blood thyroid stimulating hormone increased	1 (0.3%)	0	0	0
Musculoskeletal and connective tissue disorders	2 (0.7%)	1 (0.3%)	0	0
Arthritis	1 (0.3%)	0	0	0
Polyarthritis	1 (0.3%)	1 (0.3%)	0	0
Renal and urinary disorders	2 (0.7%)	0	1 (0.3%)	1 (0.3%)
Acute kidney injury	1 (0.3%)	0	0	0
Nephritis	1 (0.3%)	0	0	0
Renal failure	0	0	1 (0.3%)	1 (0.3%)
Cardiac disorders	1 (0.3%)	0	0	0
Autoimmune pericarditis	1 (0.3%)	0	0	0

Data cutoff as of 4 Jan 2021.
AC=adenocarcinoma/adenosquamous histology; imAE=Immune-mediated Adverse Event; SCC=squamous cell carcinoma.
All adverse events were coded using the MedDRA Version 23.1. NCI grade were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurences within a system organ class/preferred term.
For SOCs, the table is sorted by decreasing frequency of all grades in the cemiplimab group. Within each SOC, PTs are sorted by decreasing frequency of all grades in the cemiplimab group.
Source: PTT 14.3.2.5.4all.

Table 67: Summary of Treatment-Emergent Sponsor-Identified Immune-Mediated Adverse Events by Composite/Preferred Term and NCI Grade (Safety Analysis Set)

	Pool 1 All Cervical Patients (N=300)		Pool 2 All Monotherapy Patients (N=1116)	
Composite*/Preferred Term, n (%)	**All Grades**	**Grades 3/4/5**	**All Grades**	**Grades 3/4/5**
Number of patients with any treatment-emergent sponsor identified imAE, n (%)	47 (15.7%)	16 (5.3%)	229 (20.5%)	71 (6.4%)
Hypothyroidism*	18 (6.0%)	1 (0.3%)	79 (7.1%)	1 (<0.1%)
Hyperthyroidism*	9 (3.0%)	0	36 (3.2%)	0
Immune-mediated pneumonitis*	4 (1.3%)	2 (0.7%)	30 (2.7%)	10 (0.9%)
Immune-mediated hepatitis*	10 (3.3%)	10 (3.3%)	27 (2.4%)[a]	24 (2.2%)[a]
Immune-mediated colitis*	4 (1.3%)	1 (0.3%)	23 (2.1%)	9 (0.8%)
Immune-mediated skin reaction*	5 (1.7%)	1 (0.3%)	18 (1.6%)	8 (0.7%)
Arthralgia	0	0	10 (0.9%)	0
Blood thyroid stimulating hormone increased	1 (0.3%)	0	7 (0.6%)	0
Immune-mediated nephritis*	2 (0.7%)	0	7 (0.6%)	2 (0.2%)
Arthritis*	2 (0.7%)	1 (0.3%)	6 (0.5%)	2 (0.2%)
Thyroiditis*	1 (0.3%)	0	6 (0.5%)	0
Myocarditis*	0	0	5 (0.4%)[a]	4 (0.4%)[a]
Adrenal insufficiency*	0	0	3 (0.3%)	3 (0.3%)
Immune-mediated hypophysitis*	0	0	3 (0.3%)	2 (0.2%)
Neuropathy peripheral*	0	0	3 (0.3%)	1 (<0.1%)
Pericarditis*	1 (0.3%)	0	3 (0.3%)	2 (0.2%)
Pruritus*	0	0	3 (0.3%)	1 (<0.1%)
Stomatitis	0	0	3 (0.3%)	0
Myositis*	0	0	2 (0.2%)	0
Autoimmune demyelinating disease*	0	0	1 (<0.1%)	0
Blood alkaline phosphatase increased	0	0	1 (<0.1%)	0
Blood thyroid stimulating hormone decreased	0	0	1 (<0.1%)	0
Encephalitis*	0	0	1 (<0.1%)	1 (<0.1%)
Immune-mediated thrombocytopenia*	0	0	1 (<0.1%)	0
Meningitis*	0	0	1 (<0.1%)	1 (<0.1%)
Muscular weakness	0	0	1 (<0.1%)	0
Myalgia	0	0	1 (<0.1%)	1 (<0.1%)
Paraneoplastic encephalomyelitis	0	0	1 (<0.1%)	1 (<0.1%)
Polymyalgia rheumatica	0	0	1 (<0.1%)	0
Sjogren's syndrome	0	0	1 (<0.1%)	0
Type 1 diabetes mellitus*	0	0	1 (<0.1%)	1 (<0.1%)

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; imAE, immune-mediated adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute; PT, preferred term; Regeneron, Regeneron Pharmaceuticals, Inc.
All AEs were coded using MedDRA Version 23.1. NCI grades were coded using CTCAE Version 4.03.
* Each composite term includes multiple MedDRA PTs based on Regeneron defined list. Refer to ISS Table 14.3.2.4.11.
[a] Two additional identified imAEs of Myocarditis (grade 5) and Immune-mediated hepatitis (grade 4) were identified by the sponsor during medical review of cases and added to Table 67 (R2810-ONC-1624 Primary Analysis CSR Erratum).
A patient is counted only once for multiple occurrences within a composite term/PT.
The table is sorted by decreasing frequency of all grades in the total group.
Data cutoffs: 04 Jan 2021 in Study 1676; 01 Mar 2020 for patients in Study 1624; 30 Apr 2019 for patients in Study 1423; 20 Sep 2018 for all patients in Group 1 and Group 3 and 10 Oct 2018 for Group 2 in Study 1540; and 30 Jun 2020 for all patients in Study 1620.
Source: ISS Table 14.3.2.4.1, ISS Table 14.3.2.4.10, and R2810-ONC-1624 Primary Analysis CSR Erratum

2.5.4.4. Adverse drug reactions

The adverse drug reaction (ADR) table is based on safety data from Study 1676 (Pool 1) and from integrated safety data (Pool 2). Adverse drug reactions were defined as AEs that met at least 1 of the following criteria:

- TEAEs that occurred in at least 10% of patients in either Pool 1 or Pool 2
- Identified imAEs occurring in at least 1 patient in Pool 2
- Infusion-related reactions occurring in at least 1 patient (using the PT IRR) in Pool 2

Table 68: Adverse Drug Reactions Occurring in At Least 10% of Patients in the Cemiplimab Arm in Study 1676 (Safety Analysis Set) - Total Population

Adverse Reactions	Cemiplimab (N=300)		Chemotherapy (N=290)	
SOC PT	All Grades N (%)	Grade 3/4 N (%)	All Grades N (%)	Grade 3/4 N (%)
Number of patients with any TEAE, n (%)	265 (88.3%)	135 (45.0%)	265 (91.4%)	155 (53.4%)
Gastrointestinal disorders	151 (50.3%)	23 (7.7%)	185 (63.8%)	28 (9.7%)
Nausea	55 (18.3%)	1 (0.3%)	97 (33.4%)	6 (2.1%)
Vomiting	48 (16.0%)	2 (0.7%)	68 (23.4%)	7 (2.4%)
Constipation	45 (15.0%)	0	59 (20.3%)	1 (0.3%)
Diarrhoea	32 (10.7%)	3 (1.0%)	39 (13.4%)	4 (1.4%)
General disorders and administration site conditions	124 (41.3%)	19 (6.3%)	152 (52.4%)	11 (3.8%)
Fatigue	50 (16.7%)	4 (1.3%)	45 (15.5%)	4 (1.4%)
Pyrexia	35 (11.7%)	1 (0.3%)	61 (21.0%)	0
Asthenia	33 (11.0%)	7 (2.3%)	44 (15.2%)	3 (1.0%)
Infections and infestations	107 (35.7%)	30 (10.0%)	87 (30.0%)	30 (10.3%)
Urinary tract infection	35 (11.7%)	15 (5.0%)	25 (8.6%)	8 (2.8%)
Metabolism and nutrition disorders	92 (30.7%)	20 (6.7%)	88 (30.3%)	14 (4.8%)
Decreased appetite	45 (15.0%)	1 (0.3%)	46 (15.9%)	2 (0.7%)
Blood and lymphatic system disorders	87 (29.0%)	41 (13.7%)	157 (54.1%)	101 (34.8%)
Anaemia	75 (25.0%)	36 (12.0%)	129 (44.5%)	78 (26.9%)
Musculoskeletal and connective tissue disorders	83 (27.7%)	10 (3.3%)	65 (22.4%)	6 (2.1%)
Back pain	33 (11.0%)	4 (1.3%)	25 (8.6%)	2 (0.7%)
Arthralgia	31 (10.3%)	1 (0.3%)	8 (2.8%)	0

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute PT, preferred term; SOC, system organ class
All AEs coded using the MedDRA Version 23.1. NCI grade were coded using CTCAE Version 4.03.
Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03
A patient is counted only once for multiple occurrences within a system organ class/preferred term.
For system organ class, the table was sorted by decreasing frequency of all grades in the cemiplimab arm. Within each system organ class, preferred terms are sorted by decreasing frequency in the cemiplimab arm.
Data cutoff as 04 Jan 2021 in Study 1676.
a. Fatigue is a composite term that includes Fatigue, Asthenia, and Malaise
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTT 14.3.1.2.4all

Table 69: Adverse Drug Reactions Occurring in At Least 10% of Cemiplimab-Treated Patients in Study 1676 (Pool 1) or Pool 2 (Safety Analysis Set)

System organ class	Pool 1 All Cervical Patients (N=300)		Pool 2 All Monotherapy Patients (N=1116)	
Composite/Preferred term	**All Grades**	**Grades 3/4/5**	**All Grades**	**Grades 3/4/5**
Number of patients with any TEAE, n (%)	265 (88.3%)	135 (45.0%)	1030 (92.3%)	472 (42.3%)
Gastrointestinal disorders	151 (50.3%)	23 (7.7%)	506 (45.3%)	58 (5.2%)
Nausea	55 (18.3%)	1 (0.3%)	155 (13.9%)	2 (0.2%)
Vomiting	48 (16.0%)	2 (0.7%)	108 (9.7%)	3 (0.3%)
Abdominal pain*	45 (15.0%)	4 (1.3%)	124 (11.1%)	9 (0.8%)
Constipation	45 (15.0%)	0	133 (11.9%)	2 (0.2%)
Diarrhoea*	32 (10.7%)	3 (1.0%)	168 (15.1%)	7 (0.6%)
General disorders and administration site conditions	124 (41.3%)	19 (6.3%)	484 (43.4%)	57 (5.1%)
Fatigue*	83 (27.7%)	11 (3.7%)	312 (28.0%)	30 (2.7%)
Pyrexia*	40 (13.3%)	1 (0.3%)	95 (8.5%)	2 (0.2%)
Infections and infestations	107 (35.7%)	30 (10.0%)	427 (38.3%)	122 (10.9%)
Urinary tract infection*	49 (16.3%)	19 (6.3%)	99 (8.9%)	28 (2.5%)
Upper respiratory tract infection*	24 (8.0%)	0	112 (10.0%)	3 (0.3%)
Metabolism and nutrition disorders	92 (30.7%)	20 (6.7%)	365 (32.7%)	82 (7.3%)
Decreased appetite	45 (15.0%)	1 (0.3%)	147 (13.2%)	6 (0.5%)
Blood and lymphatic system disorders	87 (29.0%)	41 (13.7%)	246 (22.0%)	84 (7.5%)
Anaemia	75 (25.0%)	36 (12.0%)	181 (16.2%)	63 (5.6%)
Musculoskeletal and connective tissue disorders	83 (27.7%)	10 (3.3%)	367 (32.9%)	32 (2.9%)
Musculoskeletal pain*	72 (24.0%)	6 (2.0%)	315 (28.2%)	19 (1.7%)
Respiratory, thoracic and mediastinal disorders	62 (20.7%)	8 (2.7%)	331 (29.7%)	64 (5.7%)
Cough*	24 (8.0%)	1 (0.3%)	126 (11.3%)	2 (0.2%)
Skin and subcutaneous tissue disorders	60 (20.0%)	5 (1.7%)	374 (33.5%)	20 (1.8%)
Rash*	37 (12.3%)	5 (1.7%)	223 (20.0%)	18 (1.6%)
Pruritus*	16 (5.3%)	0	123 (11.0%)	1 (<0.1%)

Abbreviations: PT, preferred term; SOC, system organ class
* Each composite term includes multiple MedDRA preferred terms based on Regeneron defined list.
All AEs were coded using MedDRA Version 23.1. NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a SOC/PT.
For SOCs, the table is sorted by decreasing frequency of all grades in the total group. Within each SOC, PTs are sorted by decreasing frequency in the total group.
Data cutoffs: 04 Jan 2021 in Study 1676;01 Mar 2020 for patients in Study 1624; 30 Apr 2019 for patients in Study 1423; 20 Sep 2018 for all patients in Group 1 and Group 3 and 10 Oct 2018 for Group 2 in Study 1540; and 30 Jun 2020 for all patients in Study 162
Source: ISS Table 14.3.2.7.2.

2.5.5. Laboratory findings

Summary of laboratory findings

Table 70: Selected Treatment-Emergent Laboratory Abnormalities in ≥15% in All Grades in Study 1676 (Safety Analysis Set) – Total Population

Parameter (CTCAE Term)	Cemiplimab (N=300)		Chemotherapy (N=290)	
	All Grades n/N (%)	Grades ¾ n/N (%)	All Grades n/N (%)	Grades ¾ n/N (%)
Liver Function				
Number of patients with at least one lab abnormality	209/294 (71.1%)	27/294 (9.2%)	187/271 (69.0%)	24/271 (8.9%)
Alanine aminotransferase increased	71/294 (24.1%)	10/294 (3.4%)	97/271 (35.8%)	4/271 (1.5%)
Hypoalbuminemia	115/293 (39.2%)	9/293 (3.1%)	98/271 (36.2%)	12/271 (4.4%)
Alkaline phosphatase increased	103/293 (35.2%)	10/293 (3.4%)	81/269 (30.1%)	5/269 (1.9%)
Aspartate aminotransferase increased	87/294 (29.6%)	12/294 (4.1%)	84/271 (31.0%)	3/271 (1.1%)
Electrolytes				
Number of patients with at least one lab abnormality	199/294 (67.7%)	42/294 (14.3%)	154/271 (56.8%)	32/271 (11.8%)
Hypercalcemia (Uncorrected Calcium)	45/294 (15.3%)	3/294 (1.0%)	27/271 (10.0%)	2/271 (0.7%)
Hypocalcemia (Uncorrected Calcium)	76/294 (25.9%)	5/294 (1.7%)	69/271 (25.5%)	4/271 (1.5%)
Hyperkalemia	40/294 (13.6%)	7/294 (2.4%)	41/271 (15.1%)	2/271 (0.7%)
Hypokalemia	58/294 (19.7%)	14/294 (4.8%)	52/271 (19.2%)	11/271 (4.1%)
Hyponatremia	93/294 (31.6%)	18/294 (6.1%)	71/271 (26.2%)	15/271 (5.5%)
Hematology				
Number of patients with at least one lab abnormality	210/293 (71.7%)	83/293 (28.3%)	254/278 (91.4%)	137/278 (49.3%)
Anemia	156/293 (53.2%)	49/293 (16.7%)	212/278 (76.3%)	83/278 (29.9%)
White blood cell decreased	45/293 (15.4%)	4/293 (1.4%)	151/277 (54.5%)	38/277 (13.7%)
Lymphocyte count decreased	107/293 (36.5%)	42/293 (14.3%)	154/278 (55.4%)	61/278 (21.9%)
Neutrophil count decreased	20/293 (6.8%)	7/293 (2.4%)	115/278 (41.4%)	44/278 (15.8%)
Platelet count decreased	38/293 (13.0%)	6/293 (2.0%)	78/278 (28.1%)	19/278 (6.8%)
Other Chemistry				
Number of patients with at least one lab abnormality	237/294 (80.6%)	12/294 (4.1%)	210/272 (77.2%)	10/272 (3.7%)
Creatinine (Creatinine increased)	200/294 (68.0%)	9/294 (3.1%)	188/272 (69.1%)	8/272 (2.9%)
Fasting Glucose (Hyperglycemia)	91/228 (39.9%)	2/228 (0.9%)	72/193 (37.3%)	3/193 (1.6%)
Coagulation				
Number of patients with at least one lab abnormality	5/18 (27.8%)	0/18	4/23 (17.4%)	0/23
Activated Partial Thromboplastin Time (Activated partial thromboplastin time prolonged)	5/18 (27.8%)	0/18	4/23 (17.4%)	0/23

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute
NCI grades were coded using CTCAE Version 4.03.
Percentages are based on the number of patients with at least 1 postbaseline value available for that parameter.
Postbaseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.
Data cutoff as of 04 Jan 2021 for all patients in Study 1676.
Sources: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTTs 14.3.3.1.1all, 14.3.3.2.1all, 14.3.3.3.1all, 14.3.3.4.1all, and 14.3.3.5.1all.

2.5.6. Safety in special populations

Intrinsic factors:

Incidence of AEs according to age subgroups:

Table 71: Distribution of AEs, SAEs, and Discontinuations According to Age Group (Safety Analysis Set) – Pool 2

	Age: <65 years (N=640)	Age: 65 to 74 years (N=289)	Age: 75 to 84 years (N=154)	Age: ≥85 years (N=33)	Total (N=1116)
Number of TEAEs	4575	2223	1275	362	8435
Number of patients with any TEAE, n (%)	575 (89.8%)	270 (93.4%)	152 (98.7%)	33 (100%)	1030 (92.3%)
Number of serious TEAEs	282	146	113	46	587
Number of patients with any serious TEAE, n (%)	172 (26.9)	87 (30.1%)	57 (37.0%)	19 (57.6%)	335 (30.0%)
Fatal	28 (4.4%)	19 (6.6%)	3 (1.9%)	4 (12.1%)	54 (4.8%)
Life-threatening	13 (2.0%)	10 (3.5%)	7 (4.5%)	4 (12.1%)	34 (3.0%)
Hospitalization/prolonged existing hospitalization	160 (25.0%)	75 (26.0%)	55 (35.7%)	19 (57.6%)	309 (27.7%)
Disability/incapacity	9 (1.4%)	0	2 (1.3%)	1 (3.0%)	12 (1.1%)
Congenital abnormality or birth defect	0	0	0	0	0
Other (medically significant)	5 (0.8%)	6 (2.1%)	5 (3.2%)	2 (6.1%)	18 (1.6%)
Number of patients who discontinued study treatment due to TEAE, n (%)	47 (7.3%)	22 (7.6%)	16 (10.4%)	7 (21.2%)	92 (8.2%)

Abbreviations: TEAE, treatment-emergent adverse event.
Data cutoffs: 04 Jan 2021 in Study 1676; 01 Mar 2020 for patients in Study 1624; 30 Apr 2019 for patients in Study 1423; 20 Sep 2018 for all patients in Group 1 and Group 3 and 10 Oct 2018 for Group 2 in Study 1540; and 30 Jun 2020 for all patients in Study 1620.
A patient is only counted once for multiple occurrences within a category.
Source: ISS Table 14.3.2.8.1.p2

Incidence of AEs according to PD-L1 subgroups:

Table 72: Summary of Treatment-Emergent Adverse Events by PD-L1 Status in Study 1676 (Safety Analysis Set) – Patients with SCC and non-SCC Histology

	Cemiplimab				Chemotherapy			
	PD-L1 ≥1%	PD-L1 <1%	PD-L1 Unknown	Total	PD-L1 ≥1%	PD-L1 <1%	PD-L1 Unknown	Total
	(N=115)	(N=67)	(N=118)	(N=300)	(N=117)	(N=65)	(N=108)	(N=290)
Number of TEAEs	795	453	721	1969	975	624	757	2356
Number of NCI grade 3/4/5 TEAEs	111	57	131	299	144	82	159	385
Number of serious TEAEs	48	38	61	147	50	39	44	133
Number of patients with any TEAE, n (%)	105 (91.3%)	58 (86.6%)	102 (86.4%)	265 (88.3%)	110 (94.0%)	60 (92.3%)	95 (88.0%)	265 (91.4%)
Number of patients with any NCI grade 3/4/5 TEAE, n (%)	53 (46.1%)	33 (49.3%)	49 (41.5%)	135 (45.0%)	66 (56.4%)	34 (52.3%)	55 (50.9%)	155 (53.4%)
Number of patients with any serious TEAE, n (%)	30 (26.1%)	26 (38.8%)	33 (28.0%)	89 (29.7%)	31 (26.5%)	21 (32.3%)	26 (24.1%)	78 (26.9%)
Number of patients who discontinued study treatment due to TEAEs, n (%)	10 (8.7%)	4 (6.0%)	12 (10.2%)	26 (8.7%)	5 (4.3%)	6 (9.2%)	4 (3.7%)	15 (5.2%)
Number of patients with any TEAE leading to a dose interruption/delay, n (%)	24 (20.9%)	19 (28.4%)	32 (27.1%)	75 (25.0%)	42 (35.9%)	28 (43.1%)	44 (40.7%)	114 (39.3%)
Number of patients with any TEAE leading to a dose reduction, n (%)	0	0	0	0	31 (26.5%)	12 (18.5%)	15 (13.9%)	58 (20.0%)
Number of patients with any TEAE resulting in death, n (%)	3 (2.6%)	0	2 (1.7%)	5 (1.7%)	2 (1.7%)	0	0	2 (0.7%)

Data cut-off as of 04 Jan 2021.
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.

Table 73: Treatment-Emergent Adverse Events of Special Interest by PD-L1 Status in Study 1676 Based on CRF Collected Criteria (Safety Analysis Set) – Patients with SCC and non-SCC Histology

	Cemiplimab				Chemotherapy
	PD-L1 ≥1%	PD-L1 <1%	PD-L1 Unknown	Total	Total
	(N=115)	(N=67)	(N=118)	(N=300)	(N=290)
Number of patients with any treatment-emergent AESI, n (%)	14 (12.2%)	6 (9.0%)	14 (11.9%)	34 (11.3%)	0
Grade 2 or greater infusion-related reactions	3 (2.6%)	0	1 (0.8%)	4 (1.3%)	0
Grade 2 or greater allergic reactions	0	0	2 (1.7%)	2 (0.7%)	0
Grade 3 or greater immune-related toxicities	11 (9.6%)	6 (9.0%)	12 (10.2%)	29 (9.7%)	0
An irAE of any grade in a patient previously treated with a PI 3-K inhibitor	0	0	0	0	0

Data cut-off as of 04 Jan 2021.
AESI: Adverse event of special interest.
A patient is counted only once for multiple occurrences within a CRF reported criteria.

2.5.7. Safety related to drug-drug interactions and other interactions

No pharmacokinetic drug-drug interaction studies were submitted which was considered acceptable (see discussion on clinical pharmacology).

2.5.8. Discontinuation due to adverse events

Table 74: Summary of Treatment-Emergent Adverse Events Resulting in Treatment Discontinuation by System Organ Class and Preferred Term in Study 1676 (Safety Analysis Set) -Total Population

	Cemiplimab (N=300)		Chemotherapy (N=290)	
System Organ Class, n (%) Preferred Term, n (%)	**n (%)**	**Rate per 100 PY**	**n (%)**	**Rate per 100 PY**
Number of patients with any TEAE resulting in treatment discontinuation, n (%)	26 (8.7%)	17.09	15 (5.2%)	18.95
Hepatobiliary disorders	8 (2.7%)	5.25	0	0.00
Autoimmune hepatitis	3 (1.0%)	1.97	0	0.00
Immune-mediated hepatitis	3 (1.0%)	1.97	0	0.00
Hepatic function abnormal	1 (0.3%)	0.66	0	0.00
Hepatitis	1 (0.3%)	0.66	0	0.00
Respiratory, thoracic and mediastinal disorders	5 (1.7%)	3.28	1 (0.3%)	1.25
Pneumonitis	5 (1.7%)	3.28	1 (0.3%)	1.25
Infections and infestations	4 (1.3%)	2.63	1 (0.3%)	1.25
COVID-19 pneumonia	1 (0.3%)	0.66	0	0.00
Gastroenteritis	1 (0.3%)	0.66	0	0.00
Pelvic abscess	1 (0.3%)	0.66	0	0.00
Peritonitis	1 (0.3%)	0.66	1 (0.3%)	1.25
Pneumonia	1 (0.3%)	0.66	0	0.00
Pyomyositis	1 (0.3%)	0.66	0	0.00
Gastrointestinal disorders	3 (1.0%)	1.97	2 (0.7%)	2.52
Colitis	1 (0.3%)	0.66	0	0.00
Gastritis	1 (0.3%)	0.66	0	0.00
Pancreatic mass	1 (0.3%)	0.66	0	0.00
Pancreatitis chronic	1 (0.3%)	0.66	0	0.00
Diverticular perforation	0	0.00	1 (0.3%)	1.25
Nausea	0	0.00	1 (0.3%)	1.26
Vomiting	0	0.00	1 (0.3%)	1.26
Blood and lymphatic system disorders	2 (0.7%)	1.31	2 (0.7%)	2.51
Anaemia	1 (0.3%)	0.66	1 (0.3%)	1.25
Disseminated intravascular coagulation	1 (0.3%)	0.66	0	0.00
Febrile neutropenia	1 (0.3%)	0.66	0	0.00
Neutropenia	0	0.00	1 (0.3%)	1.25
Thrombocytopenia	0	0.00	1 (0.3%)	1.25
Endocrine disorders	2 (0.7%)	1.31	0	0.00
Hypothyroidism	2 (0.7%)	1.31	0	0.00
Investigations	2 (0.7%)	1.31	0	0.00
Alanine aminotransferase increased	1 (0.3%)	0.66	0	0.00
Amylase increased	1 (0.3%)	0.66	0	0.00
Platelet count decreased	1 (0.3%)	0.66	0	0.00
Cardiac disorders	1 (0.3%)	0.66	1 (0.3%)	1.25
Autoimmune pericarditis	1 (0.3%)	0.66	0	0.00
Cardiac failure	0	0.00	1 (0.3%)	1.25
General disorders and administration site conditions	1 (0.3%)	0.66	2 (0.7%)	2.51
Non-cardiac chest pain	1 (0.3%)	0.66	0	0.00
Fatigue	0	0.00	1 (0.3%)	1.25
Malaise	0	0.00	1 (0.3%)	1.25
Injury, poisoning and procedural complications	1 (0.3%)	0.66	2 (0.7%)	2.51
Spinal compression fracture	1 (0.3%)	0.66	0	0.00
Infusion-related reaction	0	0.00	2 (0.7%)	2.51
Metabolism and nutrition disorders	1 (0.3%)	0.66	1 (0.3%)	1.25
Decreased appetite	1 (0.3%)	0.66	1 (0.3%)	1.25
Musculoskeletal and connective tissue disorders	1 (0.3%)	0.66	1 (0.3%)	1.25
Polyarthritis	1 (0.3%)	0.66	0	0.00
Muscular weakness	0	0.00	1 (0.3%)	1.25
Renal and urinary disorders	1 (0.3%)	0.66	1 (0.3%)	1.25
Acute kidney injury	1 (0.3%)	0.66	0	0.00
Renal failure	0	0.00	1 (0.3%)	1.25
Vascular disorders	1 (0.3%)	0.66	1 (0.3%)	1.25
Superior vena cava syndrome	1 (0.3%)	0.66	0	0.00
Deep vein thrombosis	0	0.00	1 (0.3%)	1.25
Immune system disorders	0	0.00	1 (0.3%)	1.25

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab (N=300) n (%)	Rate per 100 PY	Chemotherapy (N=290) n (%)	Rate per 100 PY
Anaphylactic reaction	0	0.00	1 (0.3%)	1.25
Nervous system disorders	0	0.00	3 (1.0%)	3.77
Headache	0	0.00	1 (0.3%)	1.26
Neurotoxicity	0	0.00	1 (0.3%)	1.25
Transient ischaemic attack	0	0.00	1 (0.3%)	1.25
Psychiatric disorders	0	0.00	1 (0.3%)	1.25
Agoraphobia	0	0.00	1 (0.3%)	1.25

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; PY, patient-years; SOC, system organ class; TEAE, treatment-emergent adverse event
All AEs were coded using MedDRA Version 23.1.
A patient is counted only once for multiple occurrences within a SOC/PT.
For SOCs, the table is sorted by decreasing frequency in the total group. Within each SOC, PTs are sorted by decreasing frequency in the total group.
Data cutoff as of 04 Jan 2021 for all patients in Study 1676.
Source: Module 5.3.5.1 Study 1676 Primary Analysis CSR PTTs 14.3.1.2.9all and 14.3.1.2.16all

Table 75: Patient disposition (safety analysis set)

	Pool 1 All Cervical Patients (N=300)	Pool 2 All Monotherapy Patients (N=1116)
Treatment Ongoing, n (%)	37 (12.3%)	260 (23.3%)
Off Treatment, n (%)	263 (87.7%)	856 (76.7%)
Treatment Completed	13 (4.3%)	110 (9.9%)
Treatment Discontinued	250 (83.3%)	746 (66.8%)
Primary Reason for Treatment Discontinuation		
ADVERSE EVENT	25 (8.3%)	89 (8.0%)
PREGNANCY	0	0
DEATH	14 (4.7%)	57 (5.1%)
LOST TO FOLLOW-UP	0	6 (0.5%)
NON-COMPLIANCE	1 (0.3%)	5 (0.4%)
SUBJECT DECISION	8 (2.7%)	32 (2.9%)
SPONSOR DECISION	0	0
PHYSICIAN DECISION	0	17 (1.5%)
PROGRESSIVE DISEASE	199 (66.3%)	507 (45.4%)
WITHDRAWAL OF CONSENT	3 (1.0%)	17 (1.5%)
CR OR PR OR SD	0	0
CONFIRMED CR	0	2 (0.2%)
OTHER	0	14 (1.3%)

Data cut-off as of 04 Jan 2021 for Study 1676; Data cut-off as of 30 Jun 2020 for Study 1620; Data cut-off as of 01 Mar 2020 for Study 1624; Data cut-off as of 30 Apr 2019 for Study 1423; Data cut-off as of 20 Sep 2018 for Group 1 and Group 3 patients in Study 1540; Data cut-off as of 10 Oct 2018 for Group 2 patients in Study 1540.

The most frequent reasons for discontinuations in the **cemiplimab arm** were primarily immune-mediated events: hepatobiliary disorders in 8 (2.7%) patients (autoimmune/immune-mediate/other hepatitis, abnormal hepatic function) and respiratory disorders in 5 (1.7%) (pneumonitis).

Less frequent reasons for discontinuing cemiplimab were: infections 4 (1.3%) patients (pneumonias, various abdominal infections), gastrointestinal disorders 3 (1%) patients (colitis, gastritis, pancreatitis), blood and lymphatic disorders 2 (0.7%) patients (anaemia, febrile neutropenia) and endocrine disorders 2 (0.7%) patients (hypothyroidism).

In the **chemotherapy arm**, the reasons for discontinuations were more varied, the most frequent being: gastrointestinal disorders 2 (0.7%) patients, blood and lymphatic disorders 2 (0.7%) patients, general disorders (fatigue, malaise) 2 (0.7%) patients, infusion-related reactions 2 (0.7%) patients and nervous system disorders 3 (1%) patients.

2.5.9. Post marketing experience

Cemiplimab is approved in several countries for the treatment of adult patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation. Cemiplimab is also approved in some countries for BCC and first line treatment of NSCLC with high PD-L1 expression. Cumulatively up to 27 March 2021, a total of 3945 patients (3349 patients from Regeneron studies and 596 patients from non-Regeneron sponsored studies) have been treated with investigational cemiplimab monotherapy, combination therapy, or comparator product in multiple clinical trials. The cumulative exposure to cemiplimab in clinical studies is estimated to be 97,072 patient weeks (82,266 patient-weeks in Regeneron studies and 14,806 patient-weeks in non-Regeneron studies).

Based on the sales figures through 31 March 2021, the global cumulative exposure to cemiplimab was estimated to be 6484 patient-years.

The list of important identified risks for cemiplimab discussed in the Periodic Safety Update Report are Immune-related adverse reactions and Infusion-related reactions. The important potential risks for cemiplimab are lack of effect due to anti-drug antibodies and embryo-fetal toxicity (not a risk in the EU risk management plan). The missing information for cemiplimab are long-term safety data (risk management plan safety concern), use in pregnant women and use in breast-feeding women.

Since initial approval in the US in September 2018, no new safety concerns/important risks were identified from post marketing data.

2.5.10. Discussion on clinical safety

For the safety assessment, the MAH has provided data from the safety dataset (n=300 in the cemiplimab arm and n=290 in the chemotherapy arm) at the second interim analysis (~65% of OS events observed) of the ongoing study 1676 in patients with cervical cancer with progression after prior platinum treatment. The safety data cutoff (DCO) for this submission was 04 January 2021.

Also, pooled safety data from 5 studies was submitted: 1676 (current study), 1423, 1540, 1620 and 1624 in patients who received at least 1 dose of cemiplimab as monotherapy, the majority of whom received the currently authorised dose of 350 mg Q3W. Data from the cemiplimab arm of study 1676 represented safety pool 1 (n=300) and data from the 5 monotherapy studies comprised the safety pool 2 (n=1116). The size of safety data pools is considered sufficient for a meaningful safety assessment.

Exposure: By the DCO, 87.7% patients in the cemiplimab arm and 97.6% in the chemotherapy arm were off treatment and 82.3% and 96.2% respectively were off study. In both arms most patients discontinued treatment primarily due to disease progression, only 4.3% in the cemiplimab arm completed the maximum allowed treatment (96 weeks). The main reasons for being off study in both arms were either death, 29.7% and 32.4%, or disease progression, 32.7% and 40.3%. The extent of on-treatment and on-study is considered sufficient for a meaningful safety assessment. The median and mean duration of treatment exposure were higher in the cemiplimab arm (15 and 26.5 (26) weeks) compared to the chemotherapy arm (10 and 14.4 (13) weeks) in study 1676. In the cemiplimab arm vs the chemotherapy arm, 61.7% vs 43.1% were on treatment ≥12 weeks, 37% vs 16.9% more than 24 weeks and 19.3% vs 3.4% more than 48 weeks. Patients were on treatment longer in the cemiplimab arm compared to the chemotherapy arm, which suggests better tolerability of cemiplimab.

Exposure for patients with known PD-L1 status (updated n=371 biomarker dataset) across both arms appeared slightly longer for those with PD-L1≥1% in both arms.

AEs: Most patients experienced an AE of any grade in the pivotal trial, 88.3% in the cemiplimab arm and 91.4% in the chemotherapy arm, and 45% vs 53.4% experienced AEs of grade ≥3. In both categories, frequencies were higher in the chemotherapy arm.

SAEs and AEs resulting in death were observed in 29.7% vs 26.9% and 1.7% vs 0.7% in the cemiplimab vs the chemotherapy arm respectively. Discontinuation due to AEs was observed in 8.7% vs 5.2%. In these 3 categories, the observed frequencies were higher in the cemiplimab arm, and were comparable to those observed in the cemiplimab monotherapy pool.

High-grade AEs: With regards to **AEs ≥grade 3**, the five most frequent in the cemiplimab arm were: anaemia 12%, urinary tract infection 5%, hypokalaemia 2.7%, asthenia 2.3% and hydronephrosis 2.3%. In the chemotherapy arm the five most frequent were: anaemia 26.9%, neutropenia 9%, thrombocytopenia 3.1%, urinary tract infection 2.8% and vomiting 2.4%.
The observed frequencies and categories of high-grade (≥G3) AEs were as expected. The overall incidence of high-grade events between the cemiplimab arm of Study 1676 and the cemiplimab monotherapy pool were overall comparable.

SAEs occurred in 29.7% of patients from the cemiplimab arm and in 26.9% of the chemotherapy arm. The most frequent SAE in both arms was infections: 10.7% vs, 11.4%, respectively. The most frequent infections were urinary tract infections (4% vs 3.4%), pneumonia (1.3% vs 1%) and pyelonephritis (1% in both arms). Gastrointestinal disorders (4.3% vs 4.8%) were equally frequent. Autoimmune/immune-mediated hepatitis, a known imAE with incidence of 2.6%, only occurred in the cemiplimab arm. Pneumonitis was also more frequent in the cemiplimab arm (1% vs 0.3%) whereas haematologic SAEs (1.7% vs 6.9%) occurred with a higher frequency in the chemotherapy arm, with febrile neutropenia (1% vs 1.7%), anaemia (0.7% vs 4.8%) and thrombocytopenia (0% vs 1%) being the most frequent. The pattern in the distribution, frequency and type of the SAEs in the two arms was reflective of immunotherapy and chemotherapy, respectively, and were as expected.

AEs resulting in death: In study 1676, from the narratives of the patients with AEs resulting in death in the cemiplimab arm it is agreed that in 4 out of 5 patients, the deaths do not seem to be treatment related. In the case of a 39-year-old patient that died from pneumonia, not enough data could be obtained to rule out the possibility of immune-related pneumonitis. In the chemotherapy arm, 2 patients experienced TEAEs resulting in death, both incidences considered as treatment-related by the investigator.

AESIs: In the study protocol, 4 types of events were defined as AESIs whereof data only on 2 of these 4 have been presented in the dossier (CSR): infusion related reactions (IRR) and imAEs. The data presented was sponsor-identified and not investigator-identified.

IRRs: As expected, the incidence of IRRs was higher in the chemotherapy arm (4.5%) compared to the cemiplimab arm (2.7%). 0 vs 1 (0.3%) in the cemiplimab arm and chemotherapy arm respectively were grade ≥3, no patient in either arm experienced serious IRRs, 0 vs 2 (0.7%) patients discontinued treatment due to IRRs and 5 (1.7%) vs 9 (3.1%) had dose interruptions/delay due to IRRs. The frequencies of IRRs were similar between safety pool 1 and 2, 2.7 % vs 3% respectively. The symptoms were mostly gastro-intestinal (nausea 2% vs 1.3%, vomiting 1.3% vs 0.7%, abdominal pain 0.3% vs 0.4%) and pyrexia (1% vs 1.1%) and were as expected similar between the 2 pools.

imAEs: As expected, the incidence of imAEs was higher in the cemiplimab arm (15.7%) than in the chemotherapy arm (0.7%). About a third of imAEs were high-grade and/or serious, and the same proportion discontinued cemiplimab because of imAEs. Slightly fewer patients (15.7%) in pool 1 had any imAE compared to pool 2 (20.5%). Any grade ≥3 imAEs (5.3% vs 6.4%), serious imAEs (5% vs 5.5%) or discontinuations due to imAEs (5% vs 4.6%) were comparable between pool 1 and 2. The most frequent imAEs in the cemiplimab arm were endocrine disorders 8%, hepatobiliary disorders 3.3% and skin and subcutaneous disorders 1.7%, same as in pool 2. No new or unexpected frequencies of known IRRs or imAEs were registered in study 1676.

ADRs:

The ADRs nausea, vomiting and abdominal pain together with urinary tract infections occurred with a higher frequency in the cemiplimab arm of study 1676 compared to the chemotherapy arm and to pool 2. This could be explained by the pattern of dissemination and location of cervical cancer.

General disorders (fatigue, pyrexia and asthenia), infections (except for urinary tract infections that occurred with a higher frequency), metabolic and nutrition disorders (decreased appetite) and musculoskeletal disorders (musculoskeletal pain) all occurred with **similar frequencies** in the 2 pools.

Respiratory and skin disorders occurred with **lower frequencies** in pool 1 compared to pool 2.

Patients with cervical cancer exhibited higher rates of ADR anaemia across both cemiplimab and chemotherapy arms, noting nearly double risk of any-grade and ≥G3 anaemia from chemotherapy. Of note, anaemia was part of the medical history of 37% of patients from the cemiplimab arm and 36% of the chemotherapy arm. All ADRs are appropriately listed in Table 2 from section 4.8 of the SmPC.

The incidences of ADRs have already been updated in the SmPC section 4.8 based on a larger safety dataset (N=1198) as part of the recently approved renewal application (see EMEA/H/C/004844/R/0029). Hence no further update of section 4.8 of the SmPC is warranted.

Laboratory findings: The laboratory findings in study 1676 were as expected and in line with the higher rate of haematological toxicity in the chemotherapy arm and hepatotoxicity in the cemiplimab arm.

Incidence of AEs according to age subgroups: As expected, the largest differences were in general observed between the group of <65 years and ≥85 years, but not considered to require a specific warning.

AEs according to PD-L1 expression subgroups: Particularly concerning the cemiplimab arm, there does not seem to be a specific pattern of toxicity that would indicate higher rates of all-grade, high-grade, G5 AEs, imAEs and AEs leading to discontinuation in the PD-L1<1% vs. PD-L1≥1% subpopulations. Of note, although SAEs occurred in 39% vs. 28% of patients (PD-L1<1% and PD-L1≥1% subgroups, respectively), it cannot be concluded that this difference would be attributable to PD-L1% expression per se taking into account that absolute numbers of patients in these subgroups were low.

Discontinuation due to AEs: The discontinuation rate of 8.7% in the cemiplimab arm was higher than in the chemotherapy arm (5.2%) and was also slightly higher than what was seen with cemiplimab for 1L advanced NSCLC (6.5%, study 1624), noting that in the current study the treatment was given in second

or ulterior lines in a heavily pretreated population. Also, compared to other PD-1 inhibitors, the current discontinuation rate is at the same/low end level.

2.5.11. Conclusions on clinical safety

In conclusion, chemotherapy exhibited a more toxic profile regarding AEs and grade ≥3 AEs compared to the PD-1 inhibitor cemiplimab in Study 1676. The opposite pattern was seen with regards to SAEs, treatment discontinuation and AEs associated with death, in which, treatment with cemiplimab resulted in higher frequencies compared to chemotherapy. This pattern is what would be expected from treatment with a PD-1 inhibitor bearing in mind that immune-mediated AEs –although relatively infrequent– can have fatal outcomes. Overall, toxicity from cemiplimab is considered manageable.

No new events or concerning high frequencies of any known events were reported in study 1676. Importantly, the incidence of AEs across categories of any-grade, high-grade, SAEs, G5 AEs and AEs leading to discontinuation does not seem to exhibit a relationship to known PD-L1 status.

2.5.12. 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 to submit 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 3.0 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 3.0 with the following content:

Safety concerns

Table 76: Summary of Safety Concerns

Summary of Safety Concerns	
Important Identified Risks	imARs IRRs
Important Potential Risks	Lack of effect due to anti-drug antibodies
Missing Information	Long-term safety data

Pharmacovigilance plan

Risk minimisation measures

Table 77: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Activities	Proposed Pharmacovigilance Activities
Important Identified Risk: Immune-mediated Adverse Reactions	Routine risk communication messages: SmPC sections 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 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 postmarketing reports of imARs 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 sections 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

Safety Concern	Risk Minimisation Activities	Proposed Pharmacovigilance Activities
		Squamous Cell Carcinoma (Group 6)
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 and 5.1 of the SmPC have been updated. The MAH has taken the opportunity to make minor changes to the product information.

2.7.1. 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:

The current Type II variation is in relation to an addition of a new therapeutic indication. The application is not related to a change in legal status or to a new presentation, and no particular critical safety issues

have been identified with Libtayo. Proposed changes to the package leaflet are thus minimal and it is consequently agreed that a separate user consultation with target patient groups is not required.

3. Benefit-Risk Balance

3.1.1. Disease or condition

The indication is for the t*reatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy.*

The aim of such therapy is to improve overall survival (OS) and progression free survival (PFS).

3.1.2. Available therapies and unmet medical need

The preferred first line (1L) approach for persistent, recurrent or metastatic cervical cancer in Europe involves platinum-based chemotherapy, often with paclitaxel, and in some cases, adding bevacizumab, or pembrolizumab (if tumour PD-L1 expression CPS ≥1). When progressive disease occurs, single-agent chemotherapy –topotecan, vinorelbine, pemetrexed, irinotecan, ifosfamide, among others– can be considered in second or ulterior lines, although none of the available choices has shown significant survival improvements (median OS <9 months).

3.1.3. Main clinical studies

The current application is based on results from Study 1676, an open-label, randomised 1:1, phase III trial that compared cemiplimab monotherapy vs. investigator's choice of chemotherapy (pemetrexed or topotecan or irinotecan or gemcitabine or vinorelbine) in women with recurrent or metastatic cervical cancer after progression to platinum-based chemotherapy with or without bevacizumab. 608 patients were recruited between November 2017 and July 2020, regardless of PD-L1 expression status, but only squamous cell carcinoma (SCC) or adenocarcinoma/adenosquamous carcinoma (AC) histologies were allowed. The primary endpoint was overall survival (OS). Secondary endpoints were PFS, ORR, DOR and QoL.

3.2. Favourable effects

- The study met its primary endpoint. After 65% of OS events and with a median follow-up of 18.2 months on data cut-off 04-JAN-2021, improved survival from cemiplimab (mOS 12.0 months) over investigator's choice of chemotherapy (mOS 8.5 months) was shown: HR for OS 0.68 (95% CI 0.56, 0.84), p-value 0.00011. The survival benefit was evident across both SCC and AC subpopulations of the trial, all prespecified subgroups and sensitivity analyses. In an updated exploratory OS analysis (data cut-off 04-JAN-2022) with median follow-up of 30.2 months and 76% of event maturity, the survival benefit from cemiplimab over chemotherapy was maintained (HR: 0.66, 95% CI 0.55, 0.79).
- PFS at 86% of event maturity was also statistically improved in the cemiplimab arm [HR 0.745 (95% CI 0.625, 0.89), p-value 0.00048], although K-M estimates of median PFS were almost equivalent in both arms: 2.8 for cemiplimab and 2.9 for chemotherapy.
- Albeit responses were scant (16% from cemiplimab and 6% from chemotherapy), ORR was also statistically improved for cemiplimab vs. chemotherapy.

- An exploratory OS analysis of the 254 patients with known PD-L1 status (i.e., biomarker-available population, 42% of the ITT) was presented. Among these samples, 64% were PD-L1≥1% and 36% were PD-L1<1%. At the most updated exploratory OS analysis on 04-JAN-2022, the hazard ratio for the PD-L1≥ 1% group was 0.70 (95% CI: 0.48, 1.01) and 0.85 (95% CI: 0.53, 1.36) for the PD-L1<1% group.

3.3. Uncertainties and limitations about favourable effects

- The magnitude of efficacy in subgroups indicate that PD-L1 expression might act as a relevant effect modifier. Recognising that efficacy will increase with increasing PD-L1 expression, this is understood as a continuum

3.4. Unfavourable effects

- Most patients in both arms of Study 1676 experienced an AE of any grade. The most frequent AEs in the cemiplimab arm were: anaemia 25%, nausea 18.3%, fatigue 16.7% and vomiting 16%. The most frequent AEs in the chemotherapy arm were: anaemia 44.5%, nausea 33.4%, vomiting 23.4%, pyrexia 21%. AEs and AEs of grade ≥3 were more frequent in the chemotherapy arm.
- The most prevalent grade ≥3 AEs were as expected: anaemia, urinary tract infection and hypokalaemia in the cemiplimab arm, while all events in the chemotherapy arm fall within the category of blood & lymphatic disorders.
- SAEs, AEs resulting in death and discontinuation due to AEs were slightly more frequent in the cemiplimab arm.
- SAEs were registered in 29.7% (cemiplimab) vs 26.9% (chemotherapy). The most frequent SAEs in both arms were infections (10.7%/11.4%) and gastrointestinal disorders (4.3%/4.8%). Autoimmune/immune-mediated hepatitis (1.3%/1%) only occurred in the cemiplimab arm. Of note, the incidence of hepatitis as a composite term (including autoimmune hepatitis, immune-mediated hepatitis, hepatic function abnormal, hepatitis, hepatotoxicity, hepatic failure and hepatocellular injury) is 2.6%. Pneumonitis was more frequent in the cemiplimab arm (1%/0.3%) whereas haematologic SAEs (1.7%/6.9%) were more frequent in the chemotherapy arm.
- AEs resulting in death in the cemiplimab arm (1.7%) occurred in 4 out of 5 patients, not considered to be treatment-related. In the chemotherapy arm (0.7%, 2 patients), both fatalities were considered treatment-related.
- 15.7% of patients in the cemiplimab arm vs 0.7% in the chemotherapy arm experienced any imAE, grade ≥3 5.3% vs 0.7%, serious imAEs and discontinuation 5% vs 0.7%. Fewer patients in pool 1 (15.7%) had any imAE compared to pool 2 (20.5%). In line with the established imAEs profile of cemiplimab, the most frequent imAEs were endocrine disorders 8%, hepatobiliary disorders 3.3% and skin & subcutaneous disorders 1.7%.
- Particularly in the cemiplimab arm, no specific pattern of toxicity that would indicate higher rates of all-grade, high-grade, G5 AEs, imAEs and AEs leading to discontinuation in the PD-L1<1% vs. PD-DL1 ≥1% subpopulations seems present although SAEs occurred in 39% vs. 28% of patients (PD-L1<1% and PD-DL1≥1% subgroups).

3.5. Uncertainties and limitations about unfavourable effects

Not applicable.

3.6. Effects Table

Table 78: Effects Table for cemiplimab in the treatment of patients with recurrent or metastatic cervical cancer and disease progression after chemotherapy (Study 1676, data cut-off: 04-JAN-2021)

Effect	Short description	Unit	Treatment Cemiplimab n=304	Control Chemotherapy n=304	Uncertainties / Strength of evidence	References
Favourable Effects						
OS	Median overall survival	Months (95% CI)	12.0 (10.3, 13.5)	8.5 (7.5, 9.6)	Stratified HR 0.685 (95% CI 0.56, 0.84), p-value 0.00011	Table 25/ CSR
PFS-INV	Median progression free survival by investigator	Months (95% CI)	2.8 (2.6, 3.9)	2.9 (2.7, 3.4)	Stratified HR 0.745 (95% CI 0.62, 0.89), p-value 0.00048	Table 26/ CSR
ORR-INV	Overall response rate by investigator	% (n)	16.4 (50)	6.3 (19)	Odds ratio 2.984 (95% CI 1.71, 5.22) p-value 0.00004	Table 28/ CSR
Unfavourable Effects – study 1676						
	Description	**%**	**Cemiplimab (n=300)**	**Chemotherapy (n=290)**		
	AEs	%	88	91		
	AEs ≥grade 3	%	45	53		
	SAEs	%	30	27		
	imAEs	%	16	0.7		
	AEs leading to discontinuation	%	9	5		
	AEs with outcome of death	% (n)	1.7 (5)	0.7 (2)		

Abbreviations: OS overall survival; PFS progression free survival; ORR overall response rate; HR hazard ratio; CI confidence interval; CSR clinical study report; AE adverse event;
Notes: Stratification for the OS and PFS analyses was based on 2 out of 4 stratification factors: region of the world and histology.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Cervical cancer still represents a major public health problem in Europe despite availability of HPV vaccines and widespread screening programs, noting five-year relative survival of ~62% between 2000–2007. Surgery and chemoradiotherapy constitute the mainstay of treatment for local/locoregional disease, while systemic therapy with cisplatin plus paclitaxel and bevacizumab remains the preferred approach to recurrent or metastatic disease, regardless of histology. While the addition of bevacizumab was supported by a survival benefit shown at the GOG 240 study (Tewari et al, NEJM 2014), the role of added immunotherapy in first line has been recently established (Keytruda EPAR).

Diverse single-agent approaches assayed beyond progression to initial systemic treatment have shown modest response rates, although none has proved a significant survival advantage.

Upon this major unmet medical need, and considering promising efficacy data from phase I Study 1423, the MAH for Libtayo designed and successfully conducted Study 1676, which compared cemiplimab vs. investigator's choice of chemotherapy (among gemcitabine, pemetrexed, vinorelbine, topotecan or irinotecan) in the targeted population of women with recurrent or metastatic cervical cancer with progressive disease after initial chemotherapy.

While a positive outcome favouring cemiplimab was seen across the primary (OS) and secondary efficacy endpoints, the magnitude of efficacy in subgroups indicate that PD-L1 expression might act as a relevant effect modifier in this setting: data from the exploratory survival analysis in patients from the trial with available PD-L1 samples suggests that efficacy improves with increasing PD-L1 expression.

Regarding safety, the overall toxicity profile of cemiplimab is in line with its anti-PD-1 mechanism of action, and compares favourably with chemotherapy in Study 1676. Immune-mediated AEs occurred in a substantial proportion of patients treated with cemiplimab, albeit mostly of low-grade and thus manageable. Overall, safety results from cemiplimab in Study 1676 (n=300) are similar to those of the safety pool from the cemiplimab monotherapy trials (n=1116). Of note, no new events or concerningly high frequencies of any known events were registered in the cited pivotal trial.

3.7.2. Balance of benefits and risks

Ultimately, a median survival improvement of ~4 months is considered a clinically relevant achievement of cemiplimab for women with advanced cervical cancer after progression to first line chemotherapy with platinum compounds.

The observed safety profile of cemiplimab appears consistent with the one expected for its pharmacological class. Toxicity is considered manageable and acceptable with no new events or concerningly high frequencies of any known events registered in study 1676.

3.7.3. Additional considerations on the benefit-risk balance

Acknowledging that exploratory data suggest that PD-L1 expression is a relevant effect modifier, efficacy estimates indicate that survival benefits were also observed in the underpowered PD-L1<1% subgroup. Overall, it was deemed reasonable not to restrict the therapeutic indication (see section 4.1 of SmPC) based on PD-L1 expression levels.

3.8. Conclusions

The overall B/R of cemiplimab as monotherapy for the treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy, is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by a majority of 29 out of 30 votes, 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 monotherapy treatment of adult patients with recurrent or metastatic cervical cancer and disease progression on or after platinum-based chemotherapy for Libtayo; sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The MAH has taken the opportunity to make minor changes to the product information. Version 3.0 of the RMP is approved.

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 and IIIB and to the Risk Management Plan are recommended.

Divergent position to the majority recommendation is appended to this report.

APPENDIX

DIVERGENT POSITION DATED 13 OCTOBER 2022

DIVERGENT POSITION DATED 13 OCTOBER 2022

LIBTAYO EMEA/H/C/004844/II/0026

The undersigned member of the CHMP did not agree with the CHMP's positive opinion recommending the variation to the terms of the marketing authorisation of LIBTAYO.

The reason for divergent opinion was the following:

Study 1676 demonstrated a benefit in overall survival for cemiplimab compared to investigators' choice of chemotherapy. PD-L1 is a possible predictor of response, based on the mechanism of action and on external data with other immunotherapies, and therefore it is considered of interest to investigate and scrutinize the relative sub-groups. Yet, the trial recruited patients irrespective of PD-L1 status but PD-L1 status was not routinely collected and it is missing or not sufficiently reliable in about 60% of the population and based on a non-validated assay, limiting the interpretation of the results in relevant sub-groups. This is regarded as a relevant limitation of the study design, preventing a thorough assessment of the B/R in the overall population.

Notwithstanding the above-mentioned limitations, taking into account the totality of evidence, a positive B/R could be agreed in the PD-L1-positive subgroup. On the contrary, the absence of external data backing a benefit in the PD-L1 low expressors/negative population and a hazard ratio for overall survival of 0.846 (0.527; 1.357) in this sub-population versus comparators with undemonstrated efficacy on this end-point make the data/trial inadequate and insufficiently robust to inform on a benefit in the PD-L1 negative population.

Armando Genazzani