23 February 2023
EMA/CHMP/118736/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

LIBTAYO

International non-proprietary name: cemiplimab

Procedure No. EMEA/H/C/004844/II/0028

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

ALK	Anaplastic lymphoma kinase
BCC	Basal cell carcinoma
BOR	Best overall response
CI	Confidence interval
CR	Complete response
CSCC	Cutaneous squamous cell carcinoma
CSR	Clinical study report
CTLA-4	Cytotoxic T lymphocyte-associated antigen
DCR	Disease control rate
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-L13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13
EU	European Union
FAS	Full analysis population
FDA	Food and Drug Administration
FIH	First-in-human
GHS	Global health status
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
IDMC	Independent Data Monitoring Committee
IFU	Instructions for use
IRC	Independent review committee
ICI	Immune checkpoint inhibitor
ITT	Intent-to-treat
laBCC	Locally advanced basal cell carcinoma
laCSCC	Locally advanced cutaneous squamous cell carcinoma

mBCC	Metastatic basal cell carcinoma
mCSCC	Metastatic cutaneous squamous cell carcinoma
mITT	Modified intent-to-treat
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand-1
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient reported outcome
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
Regeneron	Regeneron Pharmaceuticals, Inc.
ROS1	c-ros oncogene 1 receptor tyrosine kinase
SCE	Summary of Clinical Efficacy
SD	Stable disease
SDv	Standard deviation
SEER	Surveillance, Epidemiology, and End Results
TNM	Tumour, nodes, metastases
TPS	Tumour proportion score

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 20 December 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 and IIIB

Extension of indication to include LIBTAYO in combination with platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced NSCLC who are not candidates for definitive chemoradiation or metastatic NSCLC with no EGFR, ALK or ROS1 aberrations; as a consequence, sections 4.1, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted.

Information on paediatric requirements

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

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

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the 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 31 January 2019 (EMEA/H/SA/3225/5/FU/1/2018/II) and on 22 June 2017 (EMEA/H/SA/3225/5/2017/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	20 December 2021
Start of procedure:	23 January 2022
CHMP Rapporteur Assessment Report	17 March 2022
PRAC Rapporteur Assessment Report	24 March 2022
PRAC members comments	30 March 2022
PRAC Outcome	7 April 2022
CHMP members comments	11 April 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	13 April 2022
Request for supplementary information (RSI)	22 April 2022
CHMP Rapporteur Assessment Report	24 June 2022
PRAC Rapporteur Assessment Report	N/A
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	N/A
CHMP members comments	11 July 2022
Updated CHMP Rapporteur Assessment Report	15 July 2022
Request for Supplementary Information	21 July 2022
CHMP Rapporteur Assessment Report	22 November 2022
CHMP members comments	5 December 2022
Updated CHMP Rapporteur Assessment Report	10 December 2022
Request for Supplementary Information	15 December 2022
CHMP Rapporteur Assessment Report	09 February 2023
CHMP members comments	13 February 2023
Updated CHMP Rapporteur Assessment Report	16 February 2023
An Oral explanation took place on:	22 February 2023
CHMP opinion:	23 February 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The claimed indication is for LIBTAYO in combination with platinum-based chemotherapy for the first-line treatment of adult patients with NSCLC with no EGFR, ALK or ROS1 aberrations, who have:

- locally advanced NSCLC who are not candidates for definitive chemoradiation or
- metastatic NSCLC.

The indication as adopted by CHMP is for LIBTAYO in combination with platinum-based chemotherapy for the first-line treatment of adult patients with NSCLC expressing PD-L1 (in ≥ 1% of tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:

- locally advanced NSCLC who are not candidates for definitive chemoradiation, or
- metastatic NSCLC.

Epidemiology and risk factors, screening tools/prevention

Lung cancer was the leading cause of cancer death worldwide in 2020. It represented 11.4% of all new cancer diagnoses with over 2 million new cases and 18.0% of all cancer-related mortality with over 1.8 million deaths (Sung, 2021). The highest incidence rates among males are reported from Micronesia/Polynesia, Eastern Europe, and Eastern Asia, ranging from 51.6 to 48.1 per 100,000 males. Among females, the highest incidence rates are reported from North America, Northern Europe, and Western Europe, ranging from 30.1 to 25.0 per 100,000 females. In 2020, an estimated 235,760 new cases of lung cancer were diagnosed in the US and 131,880 people died from the disease (American Cancer Society, 2021). In the EU an estimated 318,327 new cases of lung cancer were diagnosed and 257,293 people died from the disease (European Cancer Information System (ECIS), 2021).

Biologic features, aetiology and pathogenesis

Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancers and is composed of several histopathological subtypes, the most common of which are adenocarcinoma (40% to 60%) and squamous cell carcinoma (approximately 30%).

Cigarette smoking is estimated to account for approximately 80-90% of all lung cancers.

Clinical presentation, diagnosis and stage/prognosis

At the time of first diagnosis, the majority of patients with NSCLC are found to have advanced disease that is not amenable to surgery with curative intent or that has spread to distant organs outside the thorax (American Cancer Society, 2021).

Until the availability of immunotherapy, systemic therapy with platinum doublet regimens, with or without maintenance therapy, has been the standard of care for first-line treatment of patients with advanced NSCLC whose tumours do not have an EGFR mutation, an ALK mutation, or ROS1 fusion (Besse, 2014) (Ettinger, 2018) (Reck, 2014). These regimens are still the standard of care for patients in countries where anti-PD-1 therapy is not approved, reimbursed, or readily available. Despite optimal treatment, patients have a median overall survival (OS) of approximately 8 to 12 months and a 5-year survival rate of approximately 4-8% (Howlader, 2019), (Siegel, 2016), (American Cancer society).

Management

Locally advanced (definitive chemoradiation not feasible) or metastatic NSCLC is incurable, and therefore is considered a serious and life-threatening condition. The treatment goals in patients with locally advanced (definitive chemoradiation not feasible) or metastatic NSCLC are to reduce tumour burden, slow or delay progression and metastasis, prolong OS, reduce cancer-induced complications, and optimize quality of life (QoL).

In recent years, substantial progress has been made in the field of immuno-oncology and immunotherapy has become part of the standard of care for metastatic NSCLC. Agents that block the immunosuppressive PD-1/PD-L1 axis (often called "immune checkpoint blockade"), such as the anti-PD-1 antibodies cemiplimab, pembrolizumab and nivolumab or the anti PD-L1 antibodies atezolizumab and durvalumab, have collectively shown clinical activity in NSCLC and improvement in patient's outcome in different clinical settings (Tecentriq EPAR,.Keytruda EPAR, Libtayo EPAR, Opdivo EPAR, Imfinzi EPAR)

First line treatment: According to the ESMO guidelines for non-oncogene addicted metastatic NSCLC (Hendricks et al, Ann Onc 2023), the treatment strategy for a patient with a newly diagnosed, metastatic NSCLC without an oncogenic driver includes consideration of histology, tumour genotype, PD-L1 expression, PS, co-morbidities, and the patient's preferences. In general, systemic therapy should be offered to all patients with stage IV NSCLC with an Eastern Cooperative Oncology Group (ECOG) PS of 0-2. A combination of platinum-based ChT plus programmed cell death protein 1 (PD-1)/PD-L1 blockade is the most common treatment approach for a patient with newly-diagnosed stage IV NSCLC (monotherapy ICI for patients with PD-L1 ≥50% is discussed in the "first-line monotherapy immunotherapy" subsection below). Several combination regimens have successfully demonstrated improved overall survival (OS) compared with ChT alone. These have included platinum-based ChT plus: pembrolizumab (non-squamous non-small-cell carcinoma and squamous cell carcinoma), atezolizumab with or without bevacizumab (non-squamous non-small-cell carcinoma only), nivolumab plus ipilimumab (non-squamous non-small-cell carcinoma and squamous cell carcinoma), cemiplimab (non-squamous non-small-cell carcinoma and squamous cell carcinoma), and durvalumab plus tremelimumab (non-squamous non-small-cell carcinoma and squamous cell carcinoma). Of note, at the time of publication of such guidelines, the combination of tremelimumab + durvalumab + chemotherapy and cemiplimab + chemotherapy had not been approved by the EC.

2.1.2. About the product

Cemiplimab (REGN2810) belongs to the pharmacological class of immunomodulatory monoclonal antibodies. Cemiplimab is a recombinant human immunoglobulin G (IgG) 4 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), countering PD-1 mediated inhibition of the immune response, including the anti-tumour immune response.

Cemiplimab 350 mg as an intravenous (IV) infusion over 30 minutes every 3 weeks (Q3W) is approved as monotherapy for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have high (tumour proportion score [TPS] ≥50%) PD-L1 expression in the United States (US) and European Union (EU) (see SmPC section 5.1). It has also received global approvals for the treatment of patients with locally advanced and metastatic basal cell carcinoma (BCC) after treatment with a hedgehog pathway inhibitor (HHI), the treatment of patients with locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC) and the treatment of recurrent or metastatic cervical cancer.

The **proposed dose** of cemiplimab is 350 mg Q3W administered as an intravenous (IV) infusion over 30 minutes until disease progression or unacceptable toxicity.

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

The aspects of the scientific advice are discussed under the clinical efficacy part (section 2.4).

2.1.4. General comments on compliance with GCP

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 Harmonization 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.

However, the MAH identified a violation regarding RECIST evaluation, at the vendor's side, concerning an inborn error in the measurement of lymph node selected as target lesion. This error was investigated, and no influence on the primary endpoint of OS was identified. Though, in future studies, attention should be drawn to the validity of the response assessment system used.

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 submitting 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.

2.2.2. Discussion and conclusion 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.

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

2.3. Clinical aspects

2.3.1. Introduction

Pharmacokinetic (PK), pharmacodynamic, and immunogenicity data for the proposed indication are based on results from the ongoing pivotal Study R2810-ONC-16113 Part 2 (Study 16113 Part 2) per the data cut-off of 14 June 2021. Study 16113 is a two-part study; where Parts 1 and 2 are independent of each other. Study 16113 Part 2 was designed to provide confirmatory evidence for cemiplimab in combination with platinum-based chemotherapy (cemiplimab/chemo) for the treatment of patients with locally advanced and metastatic NSCLC irrespective of PD-L1 expression, who received no prior systemic treatment for their advanced disease. Based on the design difference between Study 16113 Part 1 and study 16113 Part 2, the results of Study 16113 Part 1 are not relevant to this submission.

GCP

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

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

- Tabular overview of clinical studies

Table 1: Overview of clinical studies conducted to evaluate the clinical pharmacology of cemiplimab in patients with NSCLC

Study Number Report Location Study Status Data Cutoff Dates	Study Population	Clinical Pharmacology Objectives PK/Immunogenicity (ADA) Analysis Sets	Study Design PK Sampling Treatment Duration	Cemiplimab Dosing Regimen Number of Patients in the Safety Analysis Set
R2810-ONC-1423 Final CSR Study Complete Study Data cutoff date: 30 Apr 2019	Adult patients with advanced malignancies or that 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. All patients with solid tumors (>6 months treatment) analyzed >18 years of age (204 males, 193 females)	PK and immunogenicity of cemiplimab as monotherapy and in combination with other anti-cancer treatments PK analysis set: 398 patients 71 patients with NSCLC in EXP Cohorts: 20 in EXP1, 33 in EXP2, 6 in EXP17, 6 in EXP21 and 6 in EXP22 ADA analysis set: 337 patients 66 patients with NSCLC in EXP Cohorts: 19 in EXP1, 29 in EXP2, 6 in EXP17, 6 in EXP21 and 6 in EXP22	Phase 1, first in human, open-label, multicenter, repeat-dose, study with cemiplimab as monotherapy and combination therapy. Study phases: ascending-dose escalation phase (DE) and expansion phase (EXP) Dense PK sampling after the first dose in all DE and EXP cohorts 48 weeks (six 56-day [8-week] treatment cycles) with 24 weeks (~ 5.5 months) follow-up	Cemiplimab Monotherapy (1, 3, and 10 mg/kg Q2W or 200 mg Q2W) or Cemiplimab (1 and 3 mg/kg Q2W, or 3 mg/kg Q3W) in combination with radio- and/or chemotherapy 398 patients with solid tumors (71 patients with NSCLC in EXP Cohorts[a])
R2810-ONC-1624 Primary Analysis CSR Study Ongoing Study Data cutoff date: 28 Feb 2020	Adult patients diagnosed with stage IIIB or IIIC or stage IV squamous or non-squamous NSCLC, who are not candidates for definitive chemotherapy and 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	PK and immunogenicity of cemiplimab as monotherapy PK analysis set: 345 patients ADA analysis set: 221 patients	Phase 3, Open-Label Study of REGN2810 (Anti-PD-1 Antibody) Versus Platinum-Based Chemotherapy in First-Line Treatment of Patients with Advanced or Metastatic PD-L1 + Non-Small Cell Lung Cancer	Cemiplimab 350 mg Q3W IV

R2810-ONC-16113 Part 2 Primary Analysis CSR Study Ongoing Study Data cutoff date: 14 Jun 2021	Patients in this study included men and women ≥18 years of age (≥20 years of age for Japanese patients), who were diagnosed with stage IIIB, IIIC, or stage IV non-squamous or squamous NSCLC	PK of cemiplimab when administered in combination with platinum-based doublet chemotherapy. Immunogenicity as measured by anti-drug antibodies (ADAs) for cemiplimab. PK analysis set:295 patients on cemiplimab 350 mg Q3W IV in cemiplimab/chemo ADA analysis set: 273 patients 73 patients received placebo/chemo 200 patients received cemiplimab/chemo	Phase 3, Study of Combinations of Cemiplimab (Anti-PD-1 Antibody) and Platinum-based Doublet Chemotherapy in First-line Treatment of Patients with Advanced or Metastatic Non-Small Cell Lung Cancer. 25 months of study treatment plus 7 months of follow-up	Cemiplimab 350 mg Q3W IV or placebo was administered in combination with platinum-based doublet chemotherapy (administered Q3W for 4 cycles; cemiplimab/chemo or placebo/chemo, respectively)

[a] Study 1423 included 1 patient with NSCLC (reported as "solid tumors" in the PopPK database) at 1 mg/kg Q2W () and 71 patients with NSCLC in the EXP cohorts: 20 patients at 200 mg Q2W monotherapy (EXP1), 33 patients at 3 mg/kg Q2W with radiotherapy (EXP2), 6 patients at 3 mg/kg Q2W with chemotherapy (EXP17), and 6 patients each in EXP21 and EXP 22 at 3 mg/kg Q3W with chemotherapy.
An overview of clinical studies conducted to evaluate the clinical pharmacology of cemiplimab in patients with solid tumors other than NSCLC was provided in the marketing applications for the treatment of advanced BCC (Module 2.7.2 Summary of Clinical Pharmacology BCC Table 3) and advanced NSCLC (Module 2.7.2 Summary of Clinical Pharmacology Monotherapy NSCLC Table 3); Study 16113 Part 2 Primary Analysis CSR.

For all studies, the PK analysis set (PKAS) included patients who received cemiplimab and who had at least 1 non-missing concentration of cemiplimab following the first dose of cemiplimab up to the end of the study.

In Study 16113 Part 2, the PKAS was based on the actual treatment received (as treated) rather than as randomized. For the cemiplimab studies mentioned in the cross-study comparison and included in the population PK analyses sets, blood samples collected for the assessment of cemiplimab concentrations in serum were described in the respective clinical study reports. In brief, dense PK sampling after the first dose followed by sparse PK sampling during treatment and follow-up occurred in the First-in-human (FIH) Study 1423 which included patients with NSCLC, while all the pivotal studies on specific solid tumour types used sparse sampling.

In the FIH Study 1423, where cemiplimab concentration data were assessed using dense PK sampling after the first dose and sparse sampling during the remainder of treatment, noncompartmental analysis (NCA) was used to determine PK parameters after the first dose, and summarized using descriptive statistics. Mean observed cemiplimab C_{trough} and C_{max} during treatment were reported by nominal time with descriptive statistics. Data from Study 1423 included 1 patient with NSCLC (reported as "other" by Papadopoulos, 2020 and as "solid tumors" in the PopPK database) who received cemiplimab 1 mg/kg Q2W, 20 patients with NSCLC at 200 mg Q2W in monotherapy (EXP1), 33 patients at cemiplimab 3 mg/kg Q2W with radiotherapy (EXP2), 6 patients at 3 mg/kg Q2W with chemotherapy (EXP17), and 6 patients each in EXP21 and EXP 22 at 3 mg/kg Q3W with chemotherapy.

Data from patients with NSCLC in pivotal studies included 345 patients from Study 1624 receiving cemiplimab 350 mg Q3W IV as monotherapy, and 295 patients from Study 16113 Part 2 on cemiplimab 350 mg Q3W IV with chemotherapy. In the pivotal studies where only sparse PK sampling was available, observed cemiplimab C_{trough} and C_{max} during treatment were reported by nominal time with descriptive statistics.

2.3.2. Pharmacokinetics

Population Pharmacokinetic Modelling Report R2810-PK-21192-SR-01V1

The objectives of this population pharmacokinetic (PopPK) analysis were to:

- Assess consistency of cemiplimab pharmacokinetics (PK) in NSCLC patients treated with cemiplimab plus chemotherapy in Study R2810-ONC-16113 (referred to as 16113) compared to other cancer types.

- Investigate possible sources of inconsistencies, if any, in the PK of cemiplimab in Study 16113.

Population PK of cemiplimab was described using nonlinear mixed-effects modelling by way of NONMEM, Version 7.4.1 (ICON Development Solutions, Ellicott City, Maryland). Pre- and post-processing of data from each modelling step was conducted using R (Version 4.0.2).

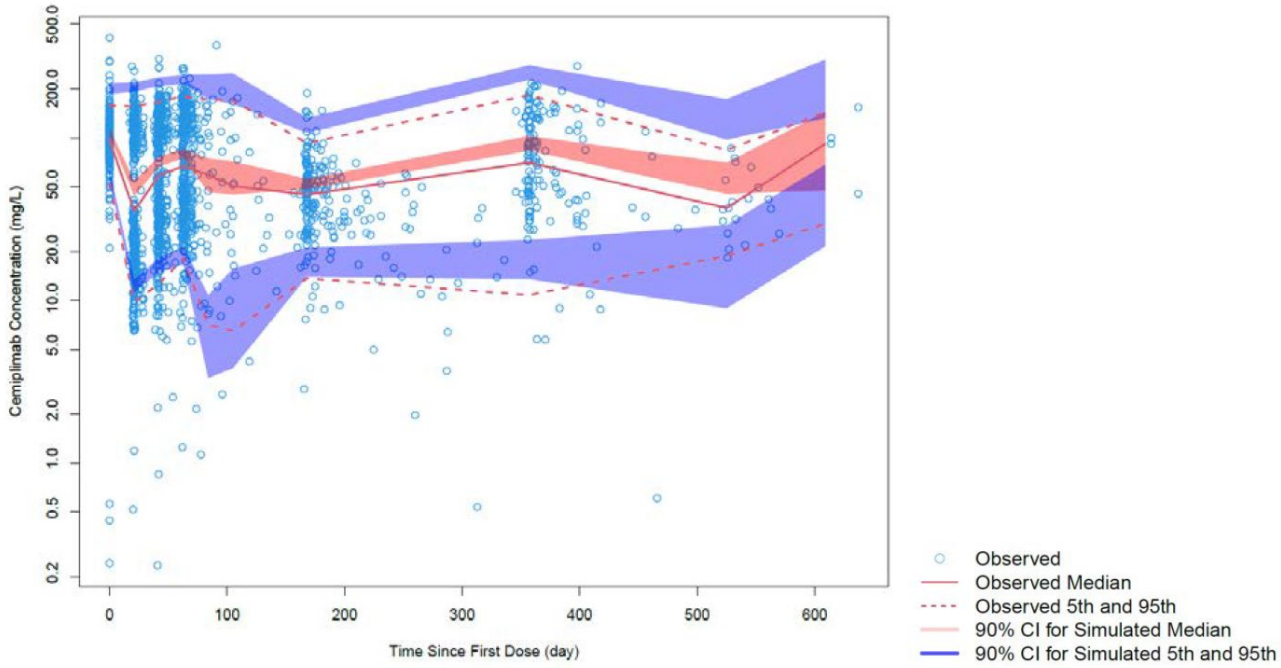
The PopPK model (R2810-PK-20039-SR-01V1) in 1062 patients was updated for cemiplimab in an overall population of 1063 patients from 4 Studies (1423, 1540, 1620 and 1624) to provide support for approval of cemiplimab monotherapy at 350 mg every 3 weeks (Q3W) in patients with advanced cervical cancer using an external validation approach (R2810-PK-21056-SR-01V1). The two-compartment base model, with zero-order IV infusion, a first-order elimination and a sigmoid E_{max} function to empirically describe a time-varying change in clearance, was updated to improve model stability which was demonstrated by 94.8% successful bootstrap runs (compared to 47.6% in the previous model). The major changes made to the previous model involved removing random effects on the maximum change in CL with time (E_{max}), removing random effects on the time for CL to decline by 50% of its maximum value (T_{50}), and only utilizing log additive residual error.

The following covariates were evaluated at their baseline values: body weight, age, sex, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, predicted creatinine clearance, serum creatinine, Eastern Cooperative Oncology Group (ECOG) score, race, ethnicity and tumour types, together with time-varying albumin level. The covariates retained in the final model were baseline body weight, sex, time-varying albumin, baseline ALT, CSCC tumour type, and BCC tumour type on clearance (relative to NSCLC); baseline body weight, sex and baseline albumin on distribution volume; BCC tumour type on E_{max}; and other tumour type on T_{50}. Similar to the model in 1062 patients, cemiplimab demonstrated weight dependent clearance and distribution volume consistent with the PK properties of monoclonal antibodies. Additionally, cemiplimab clearance had an inverse linear relationship with time-varying albumin level, indicating lower clearance as albumin levels increase. Baseline clearance was estimated to be approximately 20% higher in patients with NSCLC compared to patients with CSCC and BCC tumour types. The impact of baseline IgG level (only available in Studies 1423 and 1540) on cemiplimab clearance was assessed in a post-hoc analysis using the updated final model. Consistent with the previous analysis, higher baseline IgG levels were associated with greater cemiplimab clearance and lower exposures compared to patients with lower baseline IgG levels. The updated final model in 1063 patients is the current PopPK model (R2810-PK-21056-SR-01V1) which was used in the external validation analysis.

External Validation for Study 16113

The current final PopPK model (R2810-PK-21056-SR-01V1) was used to evaluate consistency in cemiplimab PK for patients with NSCLC in Study 16113 via an external visual predictive check (VPC). Parameter estimates were fixed to the estimates from the current final model and used to generate datasets (N = 500) which replicated the design, dose regimen, sample size, and covariate distribution for patients with NSCLC in Study 16113. From the 500 simulated datasets conditioned upon the observed study design, 90% confidence intervals (CIs, i.e., 5th and 95th percentiles) were calculated for the median, 5th and 95th percentiles of cemiplimab concentration with nominal time since first dose. The statistical intervals and 90% CIs of simulated concentration data as a function of time were overlaid with the observed cemiplimab concentrations in order to provide a visual assessment of the predictive performance of the current final model for the PK data in patients with NSCLC in Study 16113. If the median, 5th, and 95th percentile of observed concentration data were generally contained within their respective simulated confidence intervals, the PK of cemiplimab in Study 16113 would be considered as comparable to that in previous studies. Result of the external VPC for Study 16113 can be seen in Figure 1.

Figure 1: External visual predictive check for study 16113



90% CI = 90 percent confidence interval

Re-estimation of Model Parameters

Cemiplimab concentration data from Study 16113 were combined with the original dataset consisting of 4 studies (i.e., 1423, 1540, 1620 and 1624) and parameters were re-estimated in the current final PopPK model. PK parameter estimates for the original 4 studies and for the combined 5 studies (i.e., 1423, 1540, 1620, 1624 and 16113) are provided in Table 2. Point estimates for structural model parameters were within 8% for all parameters except T50 with a 20.6% difference. Goodness-of-fit plots for the current final model fit to the data from 5 studies, including Study 16113, are shown in Figure 2.

Table 2: Population pharmacokinetic parameter estimates for the current final model with combined data before and after including study 16113

Parameter (Units)	Current Final Model [a] (4 studies: 1423, 1540, 1620, 1624)			Current Final Model [a] (5 studies: 1423, 1540, 1620, 1624, 16113)		
	Estimate	%RSE	95% CI	Estimate	%RSE	95% CI
Fixed Effects						
TVCL0 (L/day)	0.254	1.56	(0.246, 0.262)	0.274	1.41	(0.266, 0.282)
TVQ (L/day)	0.652	3.65	(0.606, 0.699)	0.643	3.99	(0.593, 0.693)
TVV1 (L)	3.35	1.26	(3.27, 3.44)	3.51	1.15	(3.43, 3.59)
TVV2 (L)	2.52	1.66	(2.44, 2.60)	2.55	1.71	(2.47, 2.64)
TVEMAX	-0.174	4.82	(-0.190, -0.157)	-0.186	4.47	(-0.202, -0.170)
TVT50 (day)	73.7	7.56	(62.8, 84.7)	58.5	7.15	(50.3, 66.7)
HILL	2.50 [b]	-	-	2.50 [b]	-	-
CL_{WGTBL}	0.539	9.19	(0.442, 0.637)	0.523	8.62	(0.434, 0.611)
Vss_{WGTBL}	0.499	10.0	(0.401, 0.597)	0.470	9.64	(0.381, 0.559)
CL_{SEX}	-0.137	13.2	(-0.172, -0.101)	-0.162	10.6	(-0.195, -0.128)
$V1_{SEX}$	-0.0801	23.3	(-0.117, -0.0435)	-0.110	17.2	(-0.147, -0.0729)
$V1_{ALBBL}$	-0.217	28.4	(-0.338, -0.0961)	-0.191	33.0	(-0.314, -0.0674)
CL_{ALB}	-1.11	2.42	(-1.16, -1.06)	-1.07	2.49	(-1.12, -1.02)
CL_{ALTBL}	-0.0729	22.2	(-0.105, -0.0411)	-0.0739	20.5	(-0.104, -0.0442)
CL_{CSCC}	-0.216	9.55	(-0.256, -0.176)	-0.255	7.94	(-0.294, -0.215)
CL_{BCC}	-0.211	12.2	(-0.261, -0.160)	-0.259	10.1	(-0.311, -0.208)
$EMAX_{BCC}$	-0.872	12.6	(-1.09, -0.657)	-0.849	15.7	(-1.11, -0.589)
$T50_{OTHER}$	-0.491	12.1	(-0.608, -0.374)	-0.455	14.9	(-0.588, -0.322)
Residual Variability						
RE	0.241 [c]	0.15	(0.240, 0.242) [c]	0.260 [c]	0.13	(0.261, 0.259) [c]
IIV						
ETA1 – CL_Q	0.0892	4.05	(0.0822, 0.0963)	0.0938	3.75	(0.0869, 0.101)
ETA2 – V1_V2	0.0709	2.03	(0.0681, 0.0737)	0.0766	1.89	(0.0738, 0.0795)

%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; RE = Residual error; IIV = Inter-individual variability

[a] Current final model: R2810-PK-21056-SR-01V1

[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: η-shrinkage values were 7.8% for CL_Q and 8.5% for V1_V2 (4 studies); and 8.6% for CL_Q and 10.1% for V1_V2 (5 studies)

Time dependent clearance was modeled using a sigmoid E_{max} relationship: $TVCL = TVCL0 \cdot exp\left(\frac{Emax \cdot T^{\gamma}}{T50^{\gamma}+T^{\gamma}}\right)$

Model equations:

$$CL_i = TVCL0 \cdot \left(\frac{WGTBL_i}{WGTBL_{REF}}\right)^{CL_{WGTBL}} \cdot \left(\frac{ALB_i}{ALBBL_{REF}}\right)^{CL_{ALB}} \cdot \left(\frac{ALTBL_i}{ALTBL_{REF}}\right)^{CL_{ALTBL}} \cdot (1 + CL_{SEX}) \cdot (1 + CL_{CSCC}) \cdot (1 + CL_{BCC}) \cdot exp\left(\frac{Emax \cdot T^{\gamma}}{T50^{\gamma} + T^{\gamma}}\right) \cdot exp(\eta_{CL\_Q})$$

$$Q_i = TVQ \cdot \left(\frac{WGTBL_i}{WGTBL_{REF}}\right)^{Q_{WGTBL}} \cdot exp(\eta_{CL\_Q})$$

$$V1_i = TVV1 \cdot \left(\frac{WGTBL_i}{WGTBL_{REF}}\right)^{V1_{WGTBL}} \cdot \left(\frac{ALBBL_i}{ALBBL_{REF}}\right)^{V1_{ALBBL}} \cdot (1 + V1_{SEX}) \cdot exp(\eta_{V1\_V2})$$

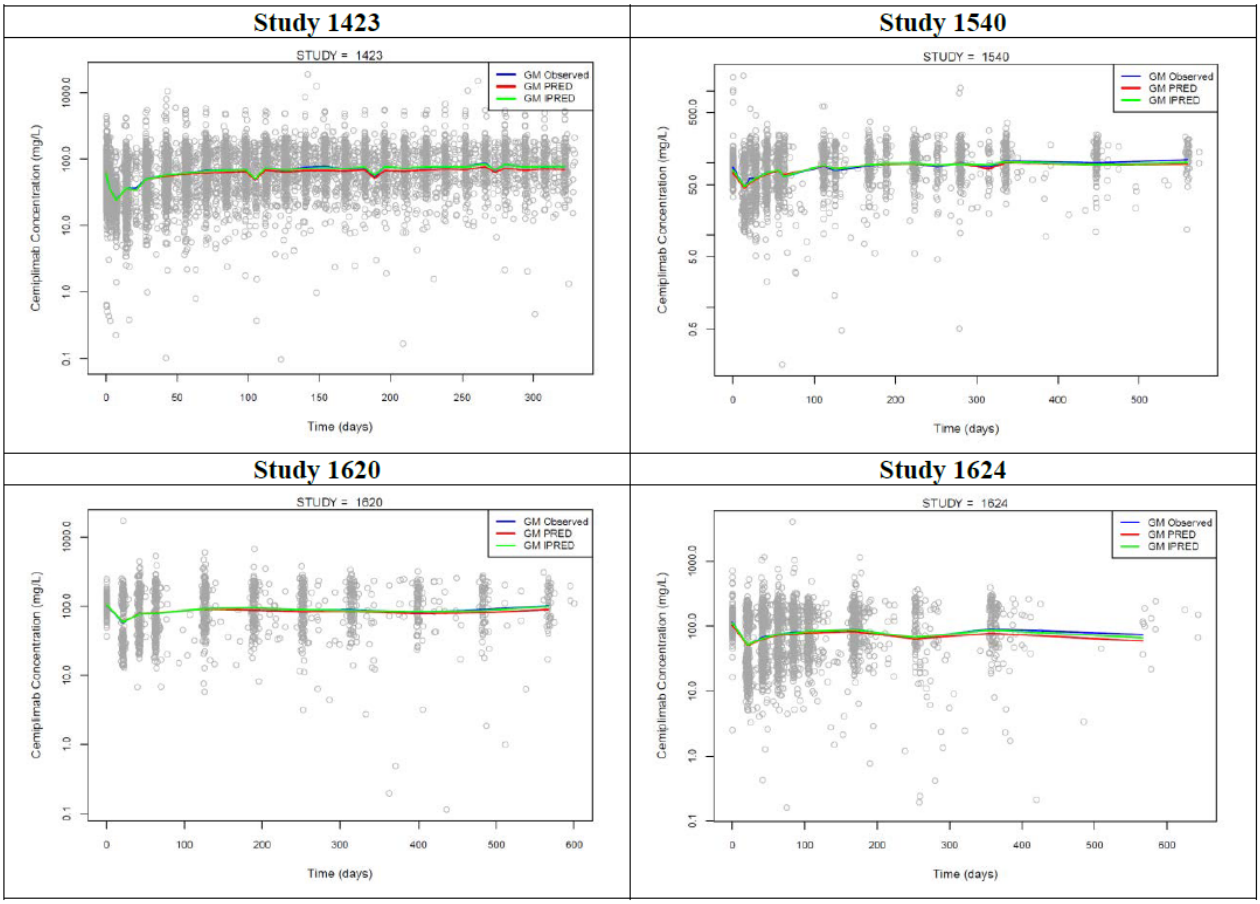
$$V2_i = TVV1 \cdot \left(\frac{WGTBL_i}{WGTBL_{REF}}\right)^{V2_{WGTBL}} \cdot exp(\eta_{V1\_V2})$$

$$T50 = TVT50 \cdot (1 + T50_{OTHER})$$

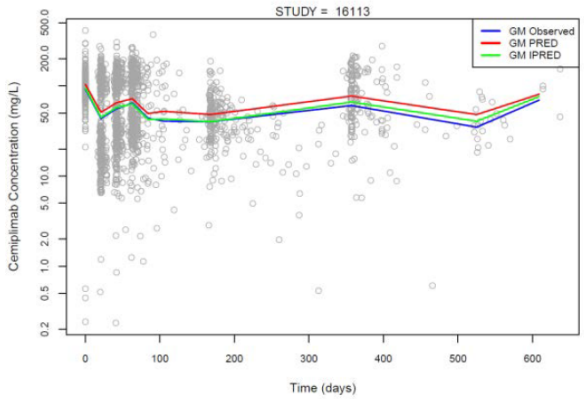
$$EMAX = TVEMAX \cdot (1 + EMAX_{BCC})$$

Note: $CL_{WGTBL} = Q_{WGTBL}$; $Vss_{WGTBL}=V1_{WGTBL}=V2_{WGTBL}$

Figure 2: Goodness-of-Fit plots for the current final model with combined data after including study 16113



Study 16113



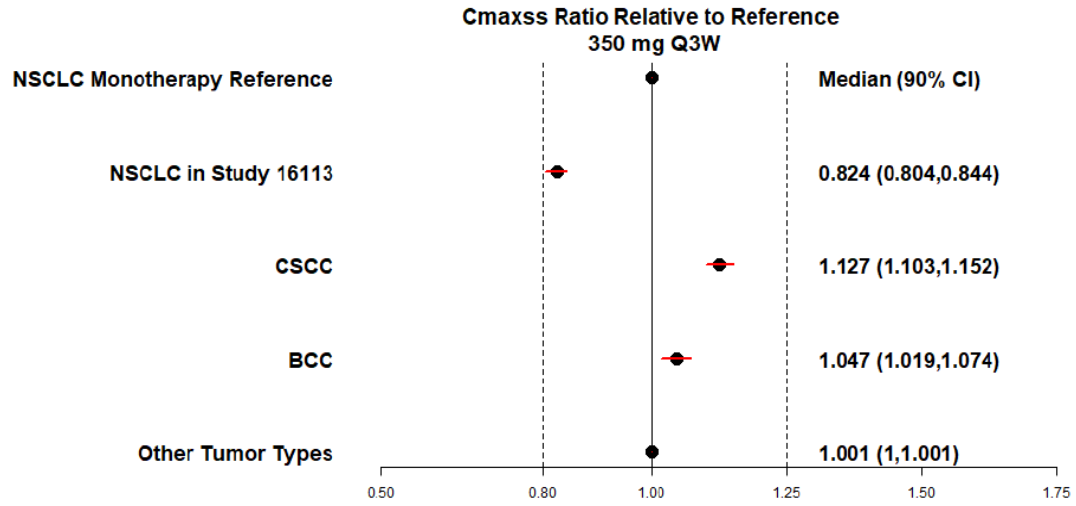
GM = Geometric mean; PRED = Typical individual prediction; IPRED = Individual model prediction
Note: Open gray circles represent individual observed cemiplimab concentrations.

The variation in cemiplimab PK due to study differences was explored by evaluating the distribution of population PK parameters predicted by the current PopPK model with 4 studies (i.e., 1423, 1540, 1620 and 1624) compared to the distribution of parameters from the model after incorporating Study 16113 data. Empirical Bayesian estimates (EBEs) of CL and V1 were derived from the current final model (4 studies) and the model refit with Study 16113 included (5 studies). The histograms showed that the distributions of CL and V1 parameters were essentially unchanged when the model was fit to data from 4 studies (i.e., 1423, 1540, 1620 and 1624) or 5 studies (i.e., 1423, 1540, 1620, 1624 and 16113), suggesting consistency in cemiplimab PK across studies.

Time-varying albumin level and body weight were investigated as potential covariates to account for the variability in Study 16113. These variables may reflect possible differences in disease progression in each study population, which could potentially influence drug clearance. The observed data showed that the time course of albumin levels was identical between NSCLC patients in Study 16113 and Study 1624, and albumin was not explored further. A time-varying body weight covariate was tested on cemiplimab CL in the current final model but did not explain the difference in exposure between studies. Study 16113 covariate effects were subsequently tested on the model parameters CL, V1, T50 and E_{max} using a forward selection procedure, followed by backward elimination. The covariates retained in the model were Study 16113 effects on CL and V1. Simulations were performed to assess the magnitude of Study 16113 covariate effects on post-hoc estimates of area under the curve ($AUC_{3wks,ss}$), peak concentration ($C_{max,ss}$), and minimum concentration ($C_{min,ss}$) over a 3-week dosing interval at steady-state. A reference subject was created with the following conditions: male, NSCLC patient in Study 1624, albumin 38.6 g/L (baseline albumin and time-varying covariate remained unchanged in simulated studies), baseline body weight 75 kg, and baseline alanine aminotransferase (ALT) 19 IU/L. Reference conditions for continuous covariates reflect the approximate median value in the analysis population.

A virtual subject was created for each test condition differing from the reference subject only in tumour type or study. Cemiplimab dosing was simulated as 350 mg every 3 weeks with a full PK profile (PRED) simulated over a dosing interval at steady-state. Each of the virtual subjects were simulated 500 times. A unique set of parameter estimates was utilized for each iteration, drawn randomly from the parameter distributions (mean, variance-covariance matrix) as determined from the current final model with Study 16113 covariates on CL and V1. Relevant exposure metrics were calculated from the steady-state PK profile and the ratio of test-to-reference conditions was calculated and plotted to illustrate the influence of tumour type or study on the exposure metrics in relation to the reference NSCLC patient from Study 1624. Impact of Study 16113-covariate on $C_{max,ss}$ can be seen in Figure 3.

Figure 3: Impact of study 16113 covariates on cemiplimab $C_{max,ss}$



$C_{max,ss}$ = maximum concentration for a 3-week dosing interval at steady-state; Q3W = Once every 3 weeks; NSCLC = Non-small cell lung cancer; BCC = Basal cell carcinoma; CSCC = Cutaneous squamous-cell carcinoma

Note: Black circles show the ratio of the median exposure metric under the test conditions compared to the reference patient. The red line segments represent the corresponding 90% confidence interval. Reference conditions were male, NSCLC patient in Study 1624, albumin 38.6 g/L (baseline albumin and time-varying covariate remained unchanged in simulated studies), baseline body weight 75 kg, and baseline alanine aminotransferase (ALT) 19 IU/L. Test conditions were tumor type or study. Vertical dashed lines indicate the reference interval of 0.8 to 1.25.

Absorption

FIH Study 1423 (Patients with Advanced NSCLC)

The FIH Study 1423 evaluated a range of cemiplimab doses (dose escalation phase: 1 to 10 mg/kg Q2W IV). Patients enrolled in Study 1423 had various tumour types, including CSCC, BCC, NSCLC, and recurrent or metastatic cervical cancer (R/M CC). A total of 72 patients with NSCLC received cemiplimab in Study 1423: 1 patient in the docetaxel cohort received cemiplimab at 1 mg/kg Q2W (Papadopoulos, 2020), and in the expansion cohorts, patients with NSCLC not receiving chemotherapy received cemiplimab at a fixed dose of 200 mg Q2W in monotherapy (EXP1; N=20) or at 3 mg/kg Q2W with radiotherapy (EXP2; N=33), or 3 mg/kg Q2W with chemotherapy (EXP17, N=6), or 3 mg/kg Q3W with chemotherapy (EXP21 and EXP 22, N=6 in each cohort).

The PK of cemiplimab was linear and dose-proportional in Study 1423. Cemiplimab PK was similar across tumour types and regardless of treatment (i.e., as monotherapy or in combination with radiotherapy and/or chemotherapy). Pharmacokinetics in patients with NSCLC in Study 1423 were similar to those in the overall population of patients with various solid tumour types. In the two expansion cohorts of patients with NSCLC (EXP21 and EXP22) AUC was assessed over a 3-week dosing interval with Q3W dosing. Therefore, the AUC3W after Q3W dosing was higher compared the AUC2W assessed over a 2 week dosing interval after Q2W dosing. For the same reasons, C-trough was slightly lower and the half-life was slightly longer when assessed over a 3-week dosing interval compared to a 2-week dosing interval (Table 3).

Table 3: Observed PK parameters of cemiplimab in patients with NSCLC and in all patients who received cemiplimab as monotherapy or in combination therapy (study 1423)

Treatment	Assessment	N	C_{trough} (mg/L) Mean (SD)	C_{max} (mg/L) Mean (SD)	AUC_{2w} (day*mg/L) Mean (SD)	$t_{1/2}$ (days) Mean(SD)
Patients with NSCLC on cemiplimab monotherapy (EXP1)						
200 mg Q2W Monotherapy	After First Dose	20	19.7 (12.4)	61.3 (27.0)	415 (120)	10.6 (3.27)
	At Steady State	20	52.1 (19.3)	105 (26.7)	-	-
Patients with NSCLC on cemiplimab with radiotherapy (EXP2)						
3 mg/kg Q2W + RT (9 Gy × 3)	After First Dose	33	18.9 (9.53)	69.3 (19.1)	466 (166)	10.0 (2.99)
	At Steady State	33	50.7 (21.4)	133 (46.1)	-	-
Patients with NSCLC on cemiplimab with chemotherapy (EXP17, EXP21, EXP22)						
3 mg/kg Q2W + carbo + doce	After First Dose	6	19.2 (5.06)	68.6 (18.5)	430 (106)	11.9 (2.48)
	At Steady State	6	53.8 (4.12)	116 (13.6)	-	-
3 mg/kg Q3W + carbo + pacli	After First Dose	6	15.1 (4.51)	75.3 (26.6)	655 (190)[a]	12.3 (3.34)
	At Steady State	6	30.0 (10.9)	80.1 (23.1)	-	-
3 mg/kg Q3W + carbo + pemex	After First Dose	6	15.9 (5.23)	70.1 (20.1)	607 (73.8)[a]	14.4 (5.93)
	At Steady State	6	29.6 (9.13)	85.1 (17.00)	-	-
Patients with All Tumor Types treated with 3 mg/kg Q2W (DE and EXP)						
All patients at 3 mg/kg Q2W	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)	-	-

[a] AUC_{3W} for cemiplimab administered Q3W
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: Study 1423 Final CSR Appendix 5 (CP Report), Report R2810-ONC-1423-CP-01V2 Table 14 and Table 16

Study 1624 (Patients with Advanced NSCLC)

The pivotal Study 1624 evaluated the efficacy, safety, PK, and immunogenicity of cemiplimab in patients with advanced NSCLC on cemiplimab at 350 mg Q3W IV as monotherapy.

In the overall PK population of patients with advanced NSCLC receiving cemiplimab 350 mg Q3W IV (N=345), and based on observed cemiplimab exposure, steady state was reached by about 18 weeks of treatment. Upon repeated 350 mg Q3W IV dosing, cemiplimab concentrations increased approximately 2-fold compared to the first dose.

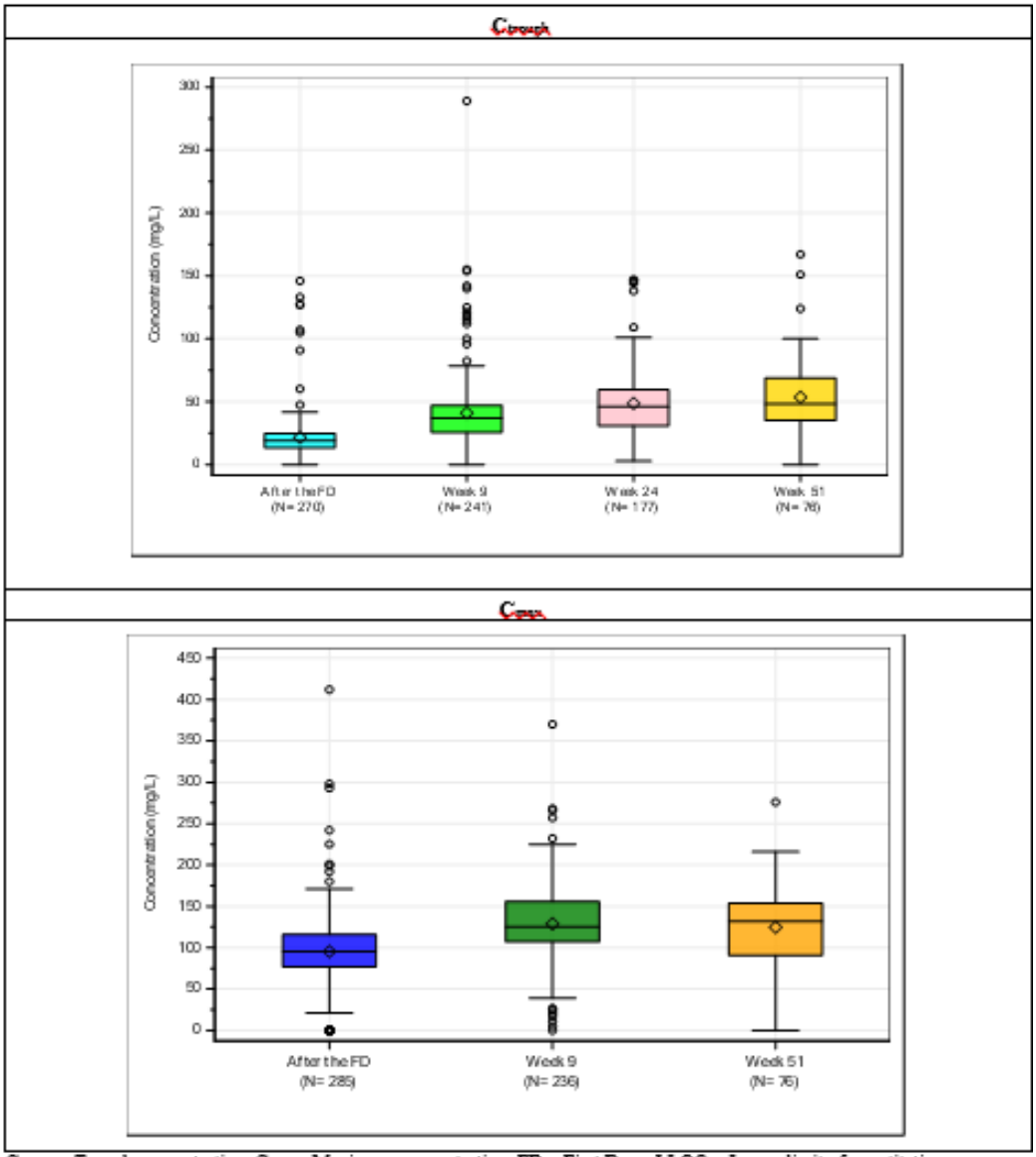
Pivotal Study 16113 Part 2

Concentration-time profiles by tumour histology type (squamous or non-squamous) and by PD-L1 expression level (<1%, 1% to 49%, and ≥50%) overlapped, indicating similar cemiplimab exposure (C_{trough} and C_{max}) regardless of histology type or PD-L1 expression level.

In the overall population of patients with NSCLC receiving cemiplimab included in the PKAS (N = 295), the mean (SD) cemiplimab C_{max} and C_{trough} values after the first dose were 95.3 (48.6) mg/L and 21.5 (18.4) mg/L, respectively. At steady state, mean (SD) C_{max} was 129 (46.9) mg/L (based on week 9; n = 236) and C_{trough} was 48.6 (25.0) mg/L (based on week 24; n = 177). C_{trough} values at steady state were approximately 2-fold of those after the first dose. The C_{max}/C_{trough} ratio (peak to trough) at steady state was approximately 2 to 3. Achievement of steady state for C_{trough} and C_{max} in the overall population is illustrated in the box plots, which indicated similar concentrations from week 9 onwards.

Cemiplimab C_{trough} and C_{max} values were similar regardless of tumour histology type (squamous or non-squamous) and PD-L1 expression level (<1%, 1% to 49%, and ≥50%) (Figure 4).

Figure 4: Boxplot of concentrations (Ctrough and Cmax) of cemiplimab in serum after the first dose and at week 9, week 24 and week 51 in patients with NSCLC receiving cemiplimab plus chemotherapy (PKAS, study R2810-ONC-16113 Part 2)



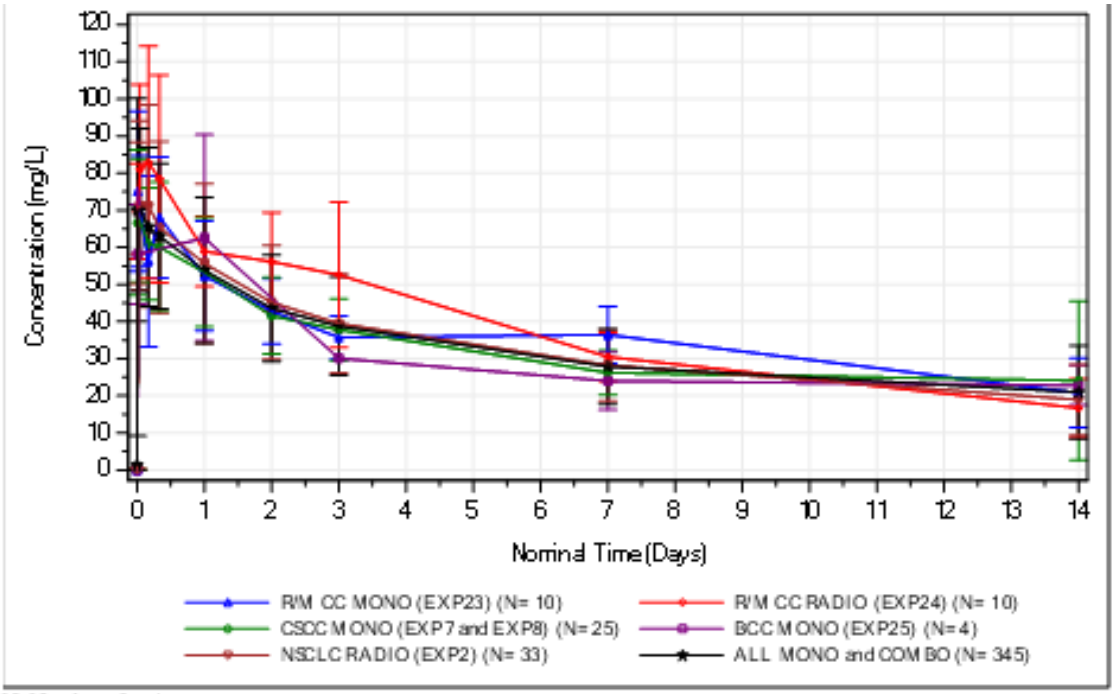
C_{trough} = Trough concentration; C_{max} = Maximum concentration; FD = First Dose; LLOQ = Lower limit of quantitation; N = Number of patients; NSCLC = Non-small cell lung cancer; PT-DC = Platinum-based doublet chemotherapy; Q = Quartile
Notes: After the FD: C_{trough} at Cycle 2 Day 1 pre-infusion. Week 9: C_{trough} at Cycle 4 Day 1. Week 24: C_{trough} at Cycle 9 Day 1. Week 51: C_{trough} at Cycle 18 Day 1.
After the FD: C_{max} at Cycle 1 Day 1 end-of-infusion. Week 9: C_{max} at Cycle 4 Day 1. Week 51: C_{max} at Cycle 18 Day 1.
Patients received cemiplimab 350 mg every 3 weeks plus 4 cycles of PT-DC (cemiplimab/chemo).
Concentrations below the LLOQ were set to 0.

Comparison of Pharmacokinetics Across Studies

Cemiplimab concentrations in serum and pharmacokinetics were similar in patients with different solid tumour types and across studies, as previously described in details based on observed cemiplimab concentrations and population-predicted PK characteristics.

Consistently across tumour types the concentration-time profiles over the first dosing interval was characterized by a brief distribution phase followed by a mono-exponential elimination phase. The overall cemiplimab PK characteristics were similar in patients with different tumour types as shown by the full concentration time profiles within Study 1423 at 3 mg/kg Q2W and across the pivotal studies and tumour types (1540, 1620, 1624, 1676 and 16113 Part 2) at 350 mg Q3W and C_{trough} and C_{max} steady state concentrations. Observed cemiplimab exposure (C_{trough} and C_{max}) during therapy at 350 mg Q3W was also compared between 295 patients with NSCLC in Study 16113 Part 2 and patients with advanced CSCC, BCC, NSCLC and R/M CC in the respective pivotal studies, showing similarity in cemiplimab exposure across tumour types over time and regardless of the treatment; numerical values at steady state are summarized in Table 4.

Figure 5: Observed mean (±SD) cemiplimab concentration-time profiles after the first dose in patients with NSCLC compared to those with other solid tumour types receiving cemiplimab 3 mg/kg Q2W as monotherapy or in combination therapy (FIH study 1423)



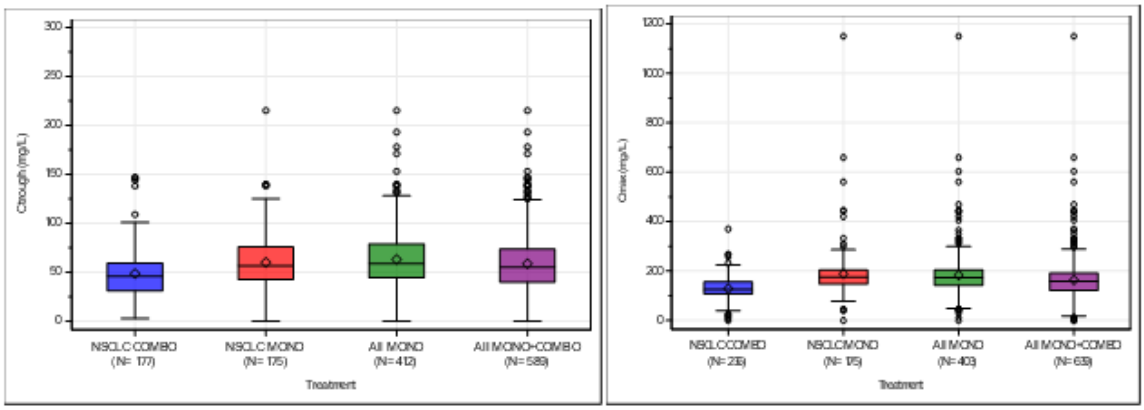
N=Number of patients.
R/M CC=recurrent/metastatic cervical cancer; CSCC=cutaneous squamous cell carcinoma (advanced CSCC); BCC=basal cell carcinoma (advanced BCC); NSCLC=non-small cell lung cancer (advanced NSCLC).
ALL=all solid tumors, MONO=Monotherapy; RADIO=in combination with radiotherapy ; COMBO=in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

Table 4: Observed mean (SD) cemiplimab exposure after the first dose and at steady state (Ctrough and Cmax) in patients with NSCLC compared to All patients receiving cemiplimab 350 mg Q3W in the pivotal studies (PKAS; studies 1540, 1620, 1624, 1676 and 16113 Part 2)

			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	Study	N	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
NSCLC COMBO	16113	295	270	21.5 (18.4)	285	95.3 (48.6)	177	48.6 (25.0)	236	129 (46.9)
NSCLC MONO	1624	345	320	22.8 (16.8)	336	121 (63.3)	175	60.0 (28.7)	175	189 (105)
All MONO	1540, 1620, 1624 and 1676	825	486	25.7 (18.8)	795	124 (77.0)	412	63.1 (29.8)	403	184 (86.7)
All MONO+COMBO	1540, 1620, 1624, 1676 and 16113	1120	756	24.2 (18.8)	1080	116 (71.7)	589	58.8 (29.2)	639	163 (79.1)

N=Number of patients in PK Analysis Set. n=Number of patients for descriptive statistics.
NSCLC=non-small cell lung cancer.
SD: Standard Deviation. Concentrations below the LLOQ were set to 0.
After the First Dose: C_{trough} is Pre-Infusion on Cycle 1 Day 22 (Week 4; 350 mg Q3W; Study 1540 and 1620) and Cycle 2 Day 1 (Week 4; 350 mg Q3W; Study 1624 and 16113 Part 2); C_{max} is at End-of-Infusion at Cycle 1 Day 1 (Week 1).
At Steady State: C_{trough} is Pre-Infusion; C_{max} is End-of-Infusion at Cycle 3 Day 1 (Week 19; Study 1540 and 1620) and at Cycle 9 Day 1 (Week 25; Study 1624) and at Cycle 4 Day 1 (Week 19; Study 1676); For Study 16113, C_{trough} is at Pre-Infusion at Cycle 9 Day 1 (Week 25) and C_{max} is End-of-Infusion at Cycle 4 Day 1 (Week 10).
Data source: Study 1540 Interim CSR Appendix 5 (CP Report), Study 1620 Interim CSR Appendix 5 (CP Report), Study 1624 Primary Analysis CSR Appendix 16.1.15 (CP Report), Study 1676 Primary Analysis CSR Appendix 16.1.15 (CP Report), Study 16113 Part 2 Primary Analysis CSR Appendix 16.1.15 (CP Report).

Figure 6: Boxplot of observed cemiplimab exposure at steady state (C_{trough} and C_{max}) in patients receiving cemiplimab 350 mg Q3W in the pivotal studies (PKAS; studies 1540, 1620, 1624, 1676 and 16113 Part 2)



N = Number of patients.
At Steady State: C_{max} is End-of-Infusion at Cycle 3 Day 1 (Week 19; Study 1540 and 1620) and at Cycle 4 Day 1 (Week 19; Study 1676) and at Cycle 4 Day 1 (Week 10; Study 16113 Part 2). C_{trough} is at Pre-Infusion at Cycle 3 Day 1 (Week 19; Study 1540 and 1620) and at Cycle 4 Day 1 (Week 19; Study 1676) and at Cycle 9 Day 1 (Week 25; Study 1624 and 16113 Part 2).
NSCLC = non-small cell lung cancer. MONO = Monotherapy; COMBO = Combination therapy.
NSCLC MONO (1624); NSCLC COMBO (16113 Part 2); ALL MONO (1540 G3; 1620, 1624, 1676); ALL MONO+COMBO (1540 G3; 1620, 1624, 1676 and 16113 Part 2).
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: Study 1540 Interim CSR Appendix 5 (CP Report), Study 1620 Interim CSR Appendix 5 (CP Report), Study 1624 Primary Analysis CSR Appendix 16.1.15 (CP Report), Study 1676 Primary Analysis CSR Appendix 16.1.15 (CP Report), Study 16113 Part 2 Primary Analysis CSR Appendix 16.1.15 (CP Report)

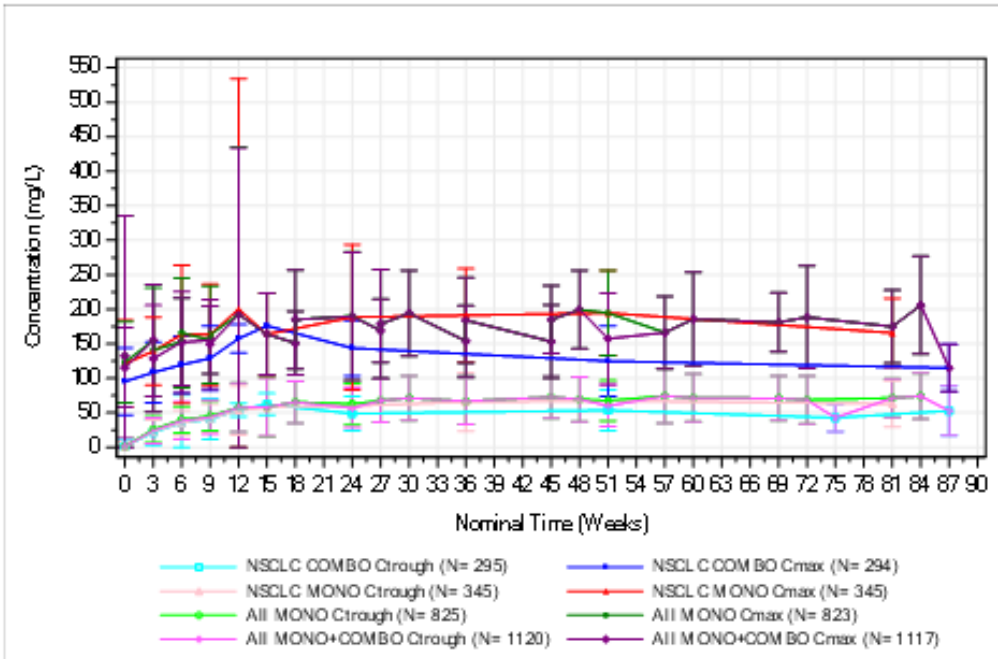
Distribution and elimination

The PK of cemiplimab was characterized using a 2-compartment model with zero-order IV infusion and first-order elimination, that included a sigmoid E_{max} function to empirically describe a time-varying decrease in CL.

Cemiplimab demonstrated a weight-dependent CL and volume of distribution consistent with the PK properties of mAbs.

Dose proportionality and time dependencies

Figure 7: Observed mean (±SD) cemiplimab (Ctrough and Cmax) over time in patients receiving cemiplimab 350 mg Q3W monotherapy (PKAS; studies 1540, 1620, 1624, 1676 and 16113 Part 2)



N=Number of patients. SD=standard deviation.
NSCLC=non-small cell lung cancer (advanced NSCLC).
MONO=Monotherapy; COMBO=in combination with radiotherapy and/or chemotherapy
NSCLC MONO (1624); NSCLC COMBO (16113 Part 2); ALL MONO (1540 G3; 1620, 1624, 1676); ALL MONO+COMBO (1540 G3; 1620, 1624, 1676 and 16113 Part 2).
Concentrations below the LLOQ were set to 0.
Data source: Study 1540 Interim CSR Appendix 5 (CP Report, Study 1620 Interim CSR Appendix 5 (CP Report), Study 1624 Primary Analysis CSR Appendix 16.1.15 (CP Report), Study 1676 Primary Analysis CSR Appendix 16.1.15 (CP Report), Study 16113 Part 2 Primary Analysis CSR Appendix 16.1.15 (CP Report)

Special populations

Cemiplimab CL had an inverse linear relationship with time-varying albumin level, indicating lower CL as albumin levels increase (see Population Pharmacokinetic Modelling Report R2810-PK-21192-SR-01V1). None of the other covariates identified as statistically significant in this model (sex, baseline alanine aminotransferase, tumour type) were considered to have a meaningful impact on cemiplimab exposure. Post-hoc covariate analysis for baseline IgG and baseline PD-L1 expression, available in a limited number of patients and/or studies, indicated no meaningful effect on cemiplimab exposure.

Pharmacokinetic interaction studies

No PK interaction studies were submitted.

2.3.3. Pharmacodynamics

Mechanism of action

Cemiplimab (REGN2810) belongs to the pharmacological class of immunomodulatory monoclonal antibodies (mAbs). Cemiplimab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that

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

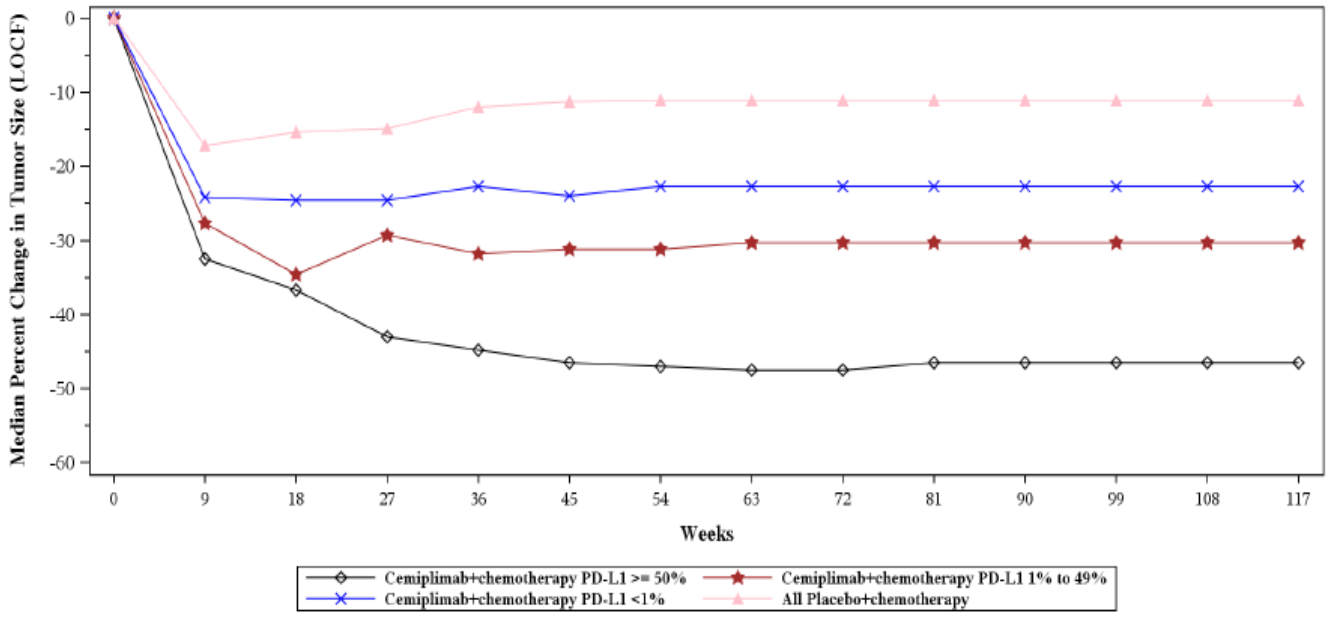
Primary and secondary pharmacology

Pharmacodynamic Results in Patients with NSCLC

In Study 16113 Part 2, the percent change in tumour size in patients with NSCLC on cemiplimab/chemo or placebo/chemo was assessed as a pharmacodynamic marker of efficacy.

Patients with NSCLC in Study 16113 Part 2 were reported by PD-L1 expression category as follow: cemiplimab/chemo PD-L1 expression categories: ≥50%, 1% to 49%, and <1%; placebo/chemo PD-L1 expression category: ≥50%, 1% to 49%, and <1%.

Figure 8: Median percent change in tumour size per independent review committee in patients with NSCLC (FAS; study 16113, Part 2)



Data cutoff as of Jun 14th, 2021. Source: Study 16113 Part 2 Primary Analysis CSR Post-text Figure 14.2.3.4a

Immunogenicity

In clinical studies, serum samples were collected from patients in the cemiplimab group throughout the treatment and post-treatment periods to determine anti-drug antibody (ADA) status.

Immunogenicity assessment was reported for patients with NSCLC who received cemiplimab in Study 16113 Part 2 (200 patients), and reported by dose for a combined total of 1229 patients with solid tumours across studies; 1423 (solid tumours, 337 patients), 1540 (CSCC, 140 patients), 1620 (BCC, 125 patients), 1624 (NSCLC, 221 patients), and 1676 (R/M CC, 206 patients); for a total of 791 patients treated with cemiplimab 350 mg Q3W IV (Table 5, below).

Immunogenicity in Patients with NSCLC in Study 16113 Part 2

Immunogenicity in patients with NSCLC in Study 16113 Part 2 (273 patients; 73 patients receiving placebo/chemo and 200 patients receiving cemiplimab/chemo) was low. Treatment-emergent ADA was observed in a total of 12 patients (4.4%), 5 patients on placebo/chemo (6.8%) and 7 patients on cemiplimab/chemo (3.5%), of which 1 was transient, 6 were indeterminate and all were low titer (<1,000) with no neutralising antibody (Nab) detected. One patient on placebo/chemo had treatment emergent indeterminate ADA at moderate titer (7,290) and a positive NAb response (Table 5).

Cemiplimab concentrations in patients with treatment-emergent ADA-positive response were similar to those in patients with pre-existing or ADA-negative response. No effect of ADA on cemiplimab exposure was observed in patients with NSCLC in this study.

Table 5: Summary of ADA status and category, maximum titer, and Nab status by treatment group in patients with NSCLC (study R2810-ONC-16113 Part 2)

ADA Status and Category	Placebo/chemo n (%)	Cemiplimab/chemo n (%)
Total ADA Patients	73 (100%)	200 (100%)
Negative	65 (89.0%)	187 (93.5%)
Pre-existing	3 (4.1%)	6 (3.0%)
Treatment Boosted Response	0	0
Treatment Emergent Response	5 (6.8%)	7 (3.5%)
TE & TB		
Persistent	0	0
Transient	0	1 (0.5%)
Indeterminate	5 (6.8%)	6 (3.0%)
Maximum Titer		
Low (<1,000)	4 (5.5%)	7 (3.5%)
Moderate (1,000 to 10,000)	1 (1.4%)	0
High (>10,000)	0	0
NAb status		
Pre-existing; NAb-	3 (4.1%)	6 (3.0%)
Pre-existing; NAb+	0	0
TE & TB; NAb-	4 (5.5%)	7 (3.5%)
TE & TB; NAb+	1 (1.4%)	0

ADA = Anti-drug antibodies; n = Number of patients; NAb = Neutralizing antibodies; NAb- = Negative in NAb assay; NAb+ = Positive in NAb assay; NSCLC = Non-small cell lung cancer; TB = Treatment-boosted; TE = Treatment-emergent
Notes: Percentages are based on ADA analysis set. Patients in placebo/chemo received placebo plus 4 cycles of PT DC; patients in cemiplimab/chemo received cemiplimab 350 mg every 3 weeks plus 4 cycles of PT DC.
Data source: Study 16113 Part 2 Primary Analysis CSR Appendix 16.1.15 (CP Report, Table 5, Table 6, and Table 7)

Immunogenicity in All Patients with Solid Tumours

The incidence of treatment-emergent ADA in all patients with solid tumours in the ADA analysis set (n=1229) was low (2.4%) (Table 6). Only 3 patients (0.2%) 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. None of the ADA-positive samples revealed the presence of NAbs.

The incidence of treatment-emergent ADA in the subset of patients who received cemiplimab 350 mg Q3W IV was similarly low (2.5%). The presence of treatment-emergent ADA did not appear to have an effect on cemiplimab concentrations in serum.

Table 6: Summary of the ADA status, category, maximum titer and Nab status in all patients with solid tumours by dose (AAS; studies 1423, 1540, 1620, 1624, 1676 and 16113 Part 2)

ADA Status Max. Titer Category NAb Status	1 mg/kg Q2W n (%)	3 mg/kg Q2W n (%)	3 mg/kg Q3W n (%)	10 mg/kg Q2W n (%)	200 mg Q2W n (%)	350 mg Q3W n (%)	Overall n (%)
Total ADA Patients	24 (100%)	377 (100%)	12 (100%)	6 (100%)	19 (100%)	791 (100%)	1229 (100%)
Negative	22 (91.7%)	364 (96.6%)	12 (100%)	5 (83.3%)	19 (100%)	749 (94.7%)	1171 (95.3%)
Pre-existing	1 (4.2%)	6 (1.6%)	0	0	0	22 (2.8%)	29 (2.4%)
Treatment Boosted Response	0	0	0	0	0	0	0
Treatment Emergent Response	1 (4.2%)	7 (1.9%)	0	1 (16.7%)	0	20 (2.5%)	29 (2.4%)
Persistent	1 (4.2%)	1 (0.3%)	0	0	0	1 (0.1%)	3 (0.2%)
Transient	0	2 (0.5%)	0	0	0	6 (0.8%)	8 (0.7%)
Indeterminate	0	4 (1.1%)	0	1 (16.7%)	0	13 (1.6%)	18 (1.5%)
Maximum Titer							
Low (<1,000)	1 (4.2%)	6 (1.6%)	0	1 (16.7%)	0	20 (2.5%)	28 (2.3%)
Moderate (1,000 to 10,000)	0	1 (0.3%)	0	0	0	0	1 (<0.1%)
High (>10,000)	0	0	0	0	0	0	0
NAb Status							
NAb Negative	24 (100%)	377 (100%)	12 (100%)	6 (100%)	19 (100%)	791 (100%)	1229 (100%)
NAb Positive	0	0	0	0	0	0	0

n=Number of patients with descriptive statistics; ADA=Anti-drug Antibody; NAb=Neutralizing Antibody; R/M CC=recurrent/metastatic cervical cancer; CSCC=cutaneous squamous cell carcinoma; BCC=basal cell carcinoma; NSCLC=non-small cell lung cancer. Patients in ADA data set at 350 mg Q3W dose with CSCC (N=39), BCC (N=125), NSCLC (N=421) and R/M CC (N=206).
Data source: Study 1423 Final CSR Appendix 5 (CP Report), Study 1540 Interim CSR Appendix 5 (CP Report), Study 1620 Interim CSR Appendix 5 (CP Report), Study 1624 Primary Analysis CSR Appendix 16.1.15 (CP Report), Study 1676 Primary Analysis CSR Appendix 16.1.15 (CP Report), Study 16113 Part 2 Primary Analysis CSR Appendix 16.1.15 (CP Report).

2.3.4. PK/PD modelling

See section 2.3.2 for results on population PK modelling.

2.3.5. Discussion on clinical pharmacology

Pharmacokinetic (PK), pharmacodynamic, and immunogenicity data for the proposed indication are based on results from the ongoing pivotal Study R2810-ONC-16113 Part 2 per the data cut-off of 14 June 2021. Limited PK data was collected as part of Study 16113 Part 2, designed to provide confirmatory evidence for cemiplimab in combination with platinum-based chemotherapy (cemiplimab/chemo) for the treatment of patients with locally advanced and metastatic NSCLC irrespective of PD-L1 expression, who received no prior systemic treatment for their advanced disease. However, in the FIH Study 1423 cemiplimab concentration data were assessed using dense PK sampling after the first dose and sparse sampling during the remainder of treatment.

In FIH study 1423, the pharmacokinetics of cemiplimab in patients with NSCLC were found to be similar to those in the overall population of patients with various solid tumour types (see Table 3).

The concentration-time profiles over the first dosing interval is characterized by a brief distribution phase followed by a mono-exponential elimination phase observed consistently across tumour types. Furthermore, the overall cemiplimab PK characteristics are similar in patients with different tumour types.

Observed cemiplimab exposure (C_{trough} and C_{max}) during therapy at 350 mg Q3W was compared between 295 patients with NSCLC in Study 16113 Part 2 and patients with advanced CSCC, BCC, NSCLC and R/M CC in the respective pivotal studies. C_{max} and $C_{through}$ tended to be lower in the NSCLC group that was receiving combination therapy as compared to the NSCLC monotherapy group. However, the numerically lower exposure of cemiplimab in patients with NSCLC by about 20% remained well within the inter-patient variability in exposure (CV of 40%) in the overall patient population and was therefore considered as not being clinically relevant.

Consistent with the incidence of ADA observed across all studies, the incidence of treatment emergent ADA (3.5%) appeared to be low with no persistent ADA observed in patients with NSCLC who received cemiplimab 350 mg Q3W IV with chemotherapy in Study 16113 Part 2.

External validation of the existing PopPK model demonstrated slight model overprediction of cemiplimab concentrations for patients with NSCLC treated with cemiplimab plus chemotherapy in Study 16113. Re-estimation of PK parameters with inclusion of data from Study 16113 were comparable to the existing PopPK model. Differences in cemiplimab PK in patients from Study 16113 were explored but no new covariates could be identified except 'Study 16113' as a covariate effect on CL and V1. Simulations were performed to evaluate the magnitude of the 'Study 16113'-covariate effect on post-hoc estimates of exposure metrics ($AUC_{3wks,ss}$, $C_{max,ss}$ and $C_{min,ss}$) and all exposure metrics were predicted to be approximately 20% lower in NSCLC patients from Study 16113 when compared to a NSCLC monotherapy patient. The numerically lower exposure of cemiplimab in patients with NSCLC by about 20% remains well within the inter-patient variability in exposure (CV of 40%) in the overall patient population and is therefore considered as not being clinically relevant.

No update of the SmPC is required based on the clinical pharmacology data submitted as part of this application.

2.3.6. Conclusions on clinical pharmacology

The PK of cemiplimab in patients with NSCLC receiving cemiplimab 350 mg Q3W IV with chemotherapy in the pivotal Study 16113 Part 2 is similar to the PK previously described in patients with NSCLC based on the data provided from FIH Study 1423 and pivotal Study 1624.

2.4. Clinical efficacy

2.4.1. Main study

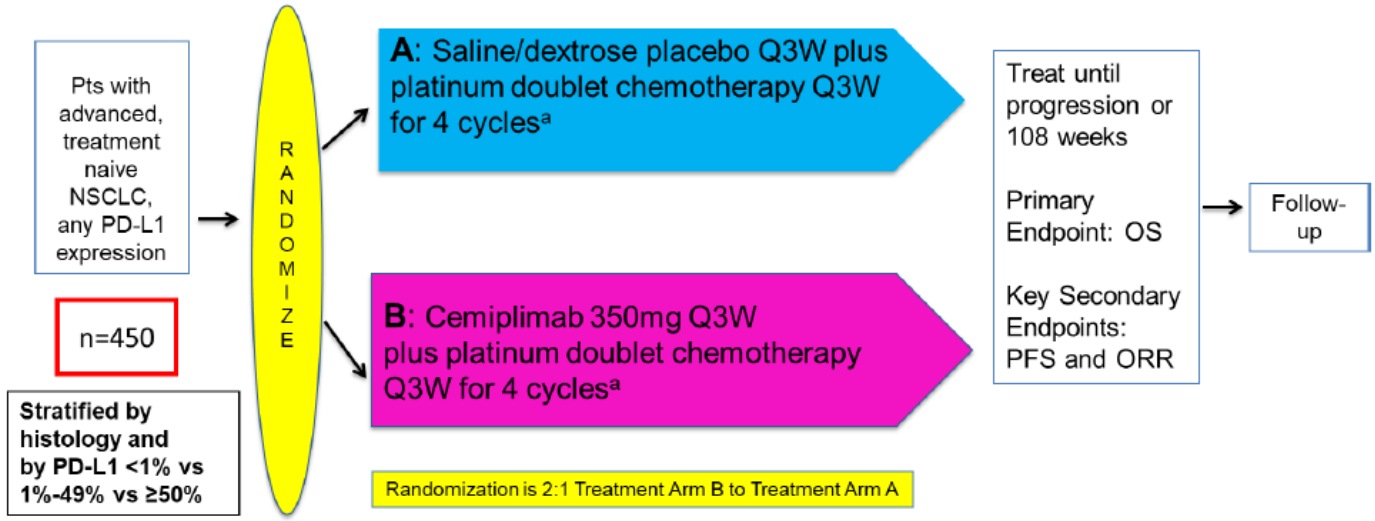
R2810 ONC 16113 Part 2 (EMPOWER-Lung 3) - A Two-Part Randomized, Phase 3 Study of Combinations of Cemiplimab (Anti-PD-1 Antibody) and Platinum-based Doublet Chemotherapy in First-line Treatment of Patients with Advanced or Metastatic Non-Small Cell Lung Cancer

Study 16113 is a 2-part, **randomized, global, phase 3 study** of cemiplimab/ipilimumab /abbreviated platinum-doublet chemotherapy (chemo), and cemiplimab/chemo vs. platinum-doublet chemo (in **Part 1**) or cemiplimab/chemo vs. placebo/chemo (in **Part 2**) in the first line treatment of patients with

advanced squamous or non-squamous NSCLC, regardless of level of PD-L1 expression. Part 2 was **double-blinded**.

Part 2 of the study, which was introduced in Amendment 4, is considered a separate study from Part 1. Patients enrolled in Part 1 do not contribute to the analyses in Part 2 and vice versa. Part 1 and Part 2 have separate randomization schemes, inclusion criteria, and visit/event schedules.

Figure 9: Study flow diagram: Part 2



Abbreviations: NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand 1; PFS=progression-free survival; Q3W=every 3 weeks; Q6W=every 6 weeks; W=weeks

[a] For Treatment Arms A and B: For patients with non-squamous NSCLC for whom the investigator chose a pemetrexed-containing doublet, pemetrexed maintenance was mandatory.

Table 7: Overview of the Clinical Efficacy Study for Cemiplimab plus Chemotherapy in the Treatment of NSCLC

Study / Report Location/ Study Status	Study Population/Analysis Populations	Efficacy Variables	Study Phase, Study Design, and Duration	Treatment: Dose, Route of Administration, Frequency (Number of Patients Treated)
R2810-ONC-16113 Part 2 Study ongoing	Men and women ≥18 years old with histologically or cytologically documented squamous or non-squamous NSCLC with stage IIIB or IIIC disease who are not candidates for curative surgery, definitive chemoradiotherapy, or patients with stage IV disease if they have not received prior systemic treatment for advanced NSCLC.	The primary efficacy variable is OS. The key secondary efficacy variables are: • PFS • ORR Other secondary efficacy variables are: • DOR • DOR	Phase 3 Randomized, multicenter, double blind study	350 mg cemiplimab administered IV over 30 minutes Q3W for up to 108 weeks plus 4 cycles of chemotherapy (**n=312**) or saline placebo administered IV over 30 minutes Q3W for up to 108 weeks plus 4 cycles of chemotherapy (**n=154**)

Study / Report Location/ Study Status	Study Population/Analysis Populations	Efficacy Variables	Study Phase, Study Design, and Duration	Treatment: Dose, Route of Administration, Frequency (Number of Patients Treated)
		• OS rate at 12 months, 18 months, and 24 months • QoL (EORTC QLQ-C30 and EORTC QLQ-L13)		

Abbreviations: DOR, duration of response; EORTC QLQ-C13, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 13; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks

Methods

Study participants

Key inclusion criteria

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

1. Men and women ≥18 years of age (≥20 years of age for Japanese patients).

2. Patients with histologically or cytologically documented squamous or non-squamous NSCLC with stage IIIB or IIIC disease who are not candidates for treatment with definitive concurrent chemoradiation, or patients with stage IV disease if they have not received prior systemic treatment for recurrent or metastatic NSCLC. The histologic diagnosis of NSCLC may be confirmed by a central laboratory.

a. Patients who received adjuvant or neoadjuvant platinum-based doublet chemotherapy (after surgery and/or radiation therapy) and developed recurrent or metastatic disease more than 6 months after completing therapy are eligible.

3. Availability of an archival or on-study obtained formalin-fixed, paraffin-embedded tumor tissue sample.

4. At least 1 radiographically measurable lesion by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST 1.1 criteria (see Appendix 2). Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site.

5. ECOG performance status of ≤1.

6. Adequate organ and bone marrow function.

Key exclusion criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Active or untreated brain metastases or spinal cord compression. Patients are eligible if central nervous system (CNS) metastases are adequately treated and patients have neurologically returned to

baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. Patients must be off (immunosuppressive doses of) corticosteroid therapy (see exclusion criteria 7 for details on timing of discontinuation of steroids).

2. Patients with tumors tested positive for EGFR gene mutations, ALK gene translocations, or ROS1 fusions. All patients will have tumor evaluated for EGFR mutations, ALK rearrangement, and ROS1 fusions confirmed by a central laboratory.

3. Encephalitis, meningitis, or uncontrolled seizures in the year prior to enrollment.

4. History of interstitial lung disease, of active, non-infectious pneumonitis that required immune-suppressive doses of glucocorticoids to assist with management, or of pneumonitis within the last 5 years.

7. Ongoing or recent evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments.

8. Patients with a condition requiring corticosteroid therapy within 14 days of randomization.

9. Another malignancy that is progressing or requires treatment.

10. Known active hepatitis B or known hepatitis C virus (HCV). Uncontrolled infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or HCV infection; or diagnosis of immunodeficiency.

11. Active infection requiring systemic therapy within 14 days prior to randomization.

12. Prior therapy with anti-PD-1 or anti-PD-L1.

13. Treatment-related immune-mediated AEs from immune-modulatory agents that have not resolved to baseline at least 3 months prior to initiation of treatment with study therapy.

Treatments

Patients in Part 2 were randomized to standard of care platinum-doublet chemotherapy plus cemiplimab or platinum-doublet chemotherapy plus saline/dextrose placebo (placebo).

Treatment began within 3 days of randomization. A treatment cycle was defined as 21 days or 3 weeks.

Cemiplimab 350 mg was to be administered as an IV infusion Q3W for up to 108 weeks. Patients treated with cemiplimab were permitted to continue treatment beyond initial RECIST 1.1-defined progressive disease if the investigator perceives the patient to be experiencing clinical benefit, the patient has not completed the 108-week treatment period and the patient meets the following criteria: Investigator assessed no rapid disease progression; Patient continues to meet all other study eligibility criteria; Patient is tolerant of cemiplimab and has a stable performance status; Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression.

Chemotherapy will be administered Q3W as outlined in Table 8 below for 4 cycles or until RECIST 1.1-defined progressive disease or early treatment discontinuation for another reason. Chemotherapy will be administered according to local prescribing information and practice guidelines. The **choice of chemotherapy** will be one of the regimens shown in Table 8 (below). The investigator may choose from one of these regimens provided that it is consistent with the local standard-of-care. Assignment of the chemotherapy choice must be made prior to randomization.

Table 8: Guidelines for Platinum-Based Doublet Chemotherapy Regimens

Option	Chemotherapy Regimen	Dosing Frequency	Maintenance Therapy
1	Paclitaxel 200 mg/m^2 IV plus carboplatin AUC of 5 or 6 mg/mL/minute IV	Day 1 every 21 days (Q3W) for 4 cycles Calculate dose of carboplatin using the Calvert formula.	No maintenance therapy
2	Paclitaxel 200 mg/m^2 IV plus cisplatin 75 mg/m^2 IV	Day 1 every 21 days (Q3W) for 4 cycles	No maintenance therapy
3	Pemetrexed 500 mg/m^2 IV plus carboplatin AUC of 5 or 6 mg/mL/minute IV	Day 1 every 21 days (Q3W) for 4 cycles Calculate dose of carboplatin using the Calvert formula.	Mandatory pemetrexed maintenance 500 mg/m^2 IV day 1 every 21 days; pemetrexed maintenance according to local prescribing information and practice guidelines.
4	Pemetrexed 500 mg/m^2 IV plus cisplatin 75 mg/m^2 IV	Day 1 every 21 days (Q3W) for 4 cycles	Mandatory pemetrexed maintenance 500 mg/m^2 IV day 1 every 21 days; pemetrexed maintenance according to local prescribing information and practice guidelines.

Abbreviations: AUC=area under the curve; IV=intravenous; N/A=not applicable

Radiographic tumour assessments were obtained every 9 weeks (Q9W) beginning at week 9 (day 63 ± 5 days) during year 1, and every 12 weeks (Q12W), beginning at week 55 (first radiographic tumour assessment in year 2 was performed at end of week 54) during year 2, until Independent Review Committee (IRC)-assessed Response Evaluation Criteria in Solid Tumors (RECIST) 1.1-defined progressive disease, withdrawal of consent, death, or initiation of another anti-cancer treatment.

Patients could be **unblinded to treatment** at the time of progressive disease defined by RECIST 1.1 criteria or discontinuation from the study. After completion of the treatment period, patients entered the follow-up period. Patients in Treatment Arm B who experienced RECIST 1.1-defined progressive disease on anti-PD-1 antibody therapy could continue treatment with cemiplimab beyond progression if the investigator judged the patient to be experiencing clinical benefit and if the patient had not completed the 108-week treatment period. Alternatively, patients in either arm of the study who progressed could opt to initiate a new anti-cancer treatment, another clinical trial, or best supportive care. The study protocol also mandated that cemiplimab must be discontinued and other anti-cancer therapy considered in case of further progressive disease, defined as an additional 10% increase in tumour burden from the time of initial progressive disease (including an increase in the sum of all target lesions and/or the development of new lesions).

Objectives

Additional objectives included characterization of PFS, objective tumour responses, patient-reported outcomes, safety, and pharmacokinetics (PK).

Primary objective:

- To determine if cemiplimab/chemo improved overall survival (OS) over placebo/chemo in first line treatment in patients with advanced NSCLC.

Secondary objectives:

- To determine if cemiplimab/chemo improved progression free survival (PFS) over placebo/chemo in first line treatment in patients with advanced NSCLC.
- To compare overall response rate (ORR) from cemiplimab/chemo to that of placebo/chemo
- To compare the duration of response (DOR) from cemiplimab/chemo to that from placebo/chemo
- To compare patient reported quality of life (QoL) when treated with cemiplimab/chemo to when treated with placebo/chemo

Outcomes/endpoints

The primary efficacy endpoint was OS, defined as the date from randomization to the date of death. A patient who had not died was censored at the last known date of contact.

The secondary endpoints are PFS, ORR (and BOR), DoR, QoL (PRO), OS at 12, 18 and 24 months.

- PFS was defined as the time from randomization to the date of the first documented tumor progression or death due to any cause. PFS was assessed by a blinded independent review committee (BIRC) BIRC using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Censoring for PFS: patients with no documented tumor progression or death or no documented tumor progression or death before initiation of new anti-tumor therapy were censored on the date of their last evaluable tumor assessment. Patients who withdrew consent before taking any study treatment or who did not have any evaluable tumor assessments after randomization and did not die were censored on the date of randomization.
- ORR is defined as best overall response (BOR) of confirmed complete response (CR) or partial response (PR) divided by the number of patients in the efficacy analysis set.
- DOR is defined as time from the criteria are first met for CR/PR until the first date of recurrent or progressive disease (radiographic), or death due to any cause.
  Censoring for DOR: patients who never progress while being followed or who do not have a documented tumor progression or death before initiation of new anti-tumor therapy at the last valid tumor measurement.
- QoL was measured using the following questionnaires: EORTC QLQ-C30 and EORTC QLQ-LC13 and defined as change in scores from baseline in the global health status (GHS)/QoL, physical functioning scales, and lung cancer symptoms.

Sample size

Historically, in patients with Stage IIIB or Stage IV NSCLC treated with cisplatin or carboplatin + paclitaxel Q3W, the median PFS has ranged from approximately 2.7 to 6.4 months (El-Shenshawy 2012, Rosell 2002, Scagliotti 2002, Schiller 2002, Shimizu 2013, Socinski 2016); the median OS has ranged from approximately 11.3 to 20.9 months (Socinski 2016, De Lima Lopes 2018, Borghaei 2017, Brahmer 2017, Gandhi 2018, Paz-Ares 2018).

Based on those historical data, the sponsor assumed a median OS of 12 months for patients treated with chemotherapy plus placebo, and a hazard ratio of 0.65 in OS between cemiplimab/chemo arm and placebo/chemo arm.

Patients were to be randomized in a 2:1 ratio to the cemiplimab/chemof arm (Treatment Arm B) versus the placebo/chemo arm (Treatment Arm A). Under these assumptions, 291 deaths were needed

to yield approximately 93% power to detect statistical significance in OS at a 2-sided Type I error level or 0.05 between the two treatment arms.

Considering an enrollment period of 14 months (11 patients per month for the first 4 months, 26 patients per month for month 5 to 8, 50 patients per month afterwards), an approximately 24- month follow-up period for OS after completion of enrollment, and 10% annual dropout, the enrollment of **approximately 450 randomized patients** was needed to obtain 291 deaths for the final analysis of OS.

Based on above historical data, the sponsor assumed a median PFS of 6 months for patients treated with chemotherapy plus placebo, and a hazard ratio of 0.6667 in PFS between the cemiplimab/chemo arm and placebo/chemo arm. With these assumptions and at two-sided 0.05 alpha level, the power for analysis of PFS was to be 90% or more if it was to be performed after 288 or more PFS events was observed. EAST® 6.4.1 was used for sample size calculation.

Randomisation

In Part 2, patients were to be randomized in a 2:1 ratio to the cemiplimab/chemo arm (Treatment Arm B) versus the placebo/chemo-f arm (Treatment Arm A). Stratifications factors were baseline histology [non-squamous versus squamous] and PD-L1 level measured using Ventana SP263 PD-L1 IHC assay [<1% versus 1% to 49% versus ≥ 50%]).

Patients with squamous NSCLC were to be capped at 50% of the total sample size. At least 30% but no more than 40% of patients enrolled must have had tumours that expressed PD-L1 in ≥50% of tumor cells. Enrollment of patients whose tumours expressed PD-L1 in <1% of tumour cells was to be capped at 30% (PD-L1 <50% was capped at 70%). This approach was adopted to mirror the natural distribution of PD-L1 expression levels historically seen in NSCLC.

Blinding (masking)

Treatment for Part 2 of the study was double-blinded with the exception of an unblinded pharmacist at each site. Sites were to receive open label cemiplimab, which will be blinded by the unblinded pharmacist at each site. Patients, the principal investigators, and study site personnel (apart from the unblinded investigative site pharmacist) were to remain blinded to all randomization assignments throughout the study.

Patients in Part 2 were to be unblinded at the time of treatment discontinuation for initial RECIST 1.1-defined progressive disease or discontinuation from the study.

A blinded independent review committee (IRC) composed of members independent from the sponsor and the study investigators was to review all available (de-identified) radiographic tumour assessments to determine tumour response based on RECIST 1.1 criteria. The IRC-determined tumour response was to be used in the analysis of the PFS, ORR, and DOR endpoints.

An independent data monitoring committee (IDMC), composed of members who are independent from the sponsor and the study investigators, was to monitor patient safety by conducting formal reviews of accumulated safety data blinded by treatment arm; if requested, the IDMC may have access to the treatment allocation code, evaluate pre-planned interim analysis results which will be provided by an independent statistician, or any other requested data for the purposes of a risk-benefit assessment. The IDMC was to provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study. The IDMC was to also

institute any measures that may be required for ensuring the integrity of the study results during the study execution.

Statistical methods

The Full Analysis Set (FAS)

The FAS was defined separately for Parts 1 and 2. The FAS included all patients to whom study treatment has been assigned by randomization in each study part. FAS was essentially the intention to treat population (ITT). Per ITT principle, patients were to be analysed according to the treatment and stratification factors they had been assigned to during the randomization. FAS was to be used for all baseline, demographic, and efficacy endpoints.

The Safety Analysis Set (SAF)

The SAF was defined separately for Part 1 and Part 2 of this study. The SAF included all randomized patients who received any study drug; it is based on the treatment received (as treated). Treatment administration and all clinical safety variables were to be analysed using the SAF.

Primary endpoint OS

For the time-to-event endpoints the non-parametric Kaplan-Meier method was to be used to estimate the survival curves. The treatment difference in survival was to be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was to be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate were to be reported. The part specific stratification factors used for randomization per IWRS was to be applied to both the stratified log-rank test and the stratified Cox model. Median OS and PFS along with its 95% CI were to be presented for each treatment arm using Kaplan- Meier method. The Kaplan-Meier curves were to be displayed by treatment arm.

Censoring rules for OS
If a patient is not known to have died or is lost to follow up at the time of analysis cutoff date, the one will be censored at the last date that the patient was known to be alive.

Key secondary endpoint PFS per ICR

The same statistical methods described for OS were used.

Censoring rules for PFS:

• 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 a documented tumour progression or death before initiation of new anti-tumour therapy will be censored on the date of their last evaluable tumour assessment prior to or on the date of new anti-tumour therapy.

• Patients who withdraw consent before taking any study treatment, therefore there is no post baseline tumour assessment, will be censored at the date of randomization.

• Patients who do not have any evaluable tumour assessments after randomization and do not die will be censored on the date of randomization.

Key secondary endpoint ORR by ICR

ORR was to be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by part specific stratification factors at randomization per IWRS. Objective response rate and the corresponding exact 95% CI were to be calculated by Clopper-Pearson method for each treatment arm.

Patient(s) without baseline tumour assessment, or with either unknown or missing BOR were to be included in the denominator and will be counted as non-responder(s).

Interim analyses and type I error control

The analyses of primary endpoint of OS were to be performed as follows: 1) two interim analyses (IA) for OS performed when approximately 146 (50% out of total OS events) and 204 (70% out of total OS events) deaths are observed; 2) final analysis for OS performed when approximately 291 deaths are observed.

The IA was to be reviewed based on a Lan-DeMets approach to the O'Brien-Fleming (OBF) alpha-spending function

If analysis of OS was statistically significant, the key secondary endpoint PFS was to be analyzed using the same statistical method as used in analysis of OS. If analysis of PFS was statistically significant, the ORR was to be analyzed.

The family-wise type I error across the test of primary and key secondary endpoints and the repeated testing of OS in the two interim analyses and final analyses in Part 2 was controlled at two-sided 0.05 level.

The multiplicity between analyses of OS, PFS, and ORR were to be controlled at two-sided 0.05 level by the hierarchical approach.

The type I error for the two interim analyses of OS at 146 (50%) and 204 (70%) and final analysis of OS was controlled at two-sided 0.05 level according to OBF alpha spending function. The exact nominal p-values needed to declare statistical significance at the time of these analyses for OS was to depend on the actual number of OS events at the time of the analyses.

All other statistical comparisons were exploratory in nature and, therefore, not controlled for multiplicity.

Changes to the SAP and to planned analyses

The current SAP is SAP v2, based on the protocol version amendment 5. Changes from version 1 of the SAP included:

Section 1.2.2	Added more details on PRO objective.
Section 3.2	Added clarification on safety analysis set in cases where a patient received partial treatment in the combination treatment group.
Section 4.2	Added brain metastasis and stage of disease as baseline tumor characteristics. Removed mutations status of BRAF, NRAS, C-KIT from baseline tumor characteristics because they are not required per protocol. Added Stage IIIC to cancer stage at screening category as protocol allows enrollment of Stage IIIC patients in both parts.
Section 5.3	Moved Baseline definition to Section 6.1: Definition of Baseline for Efficacy/Safety Variables.
Section 5.7.2	Removed "key" from section title as this section provides statistical methods for all primary and secondary efficacy analyses.
	Further editorial changes were added to separate statistical methods for "primary and key secondary endpoints" (Section 5.7.2.1) and "other secondary endpoints" (Section 5.7.2.2). Added more details on data presentation for the primary and secondary endpoints.
Section 5.7.3	Added brain metastasis, stage of disease, and smoking history as pre-specified subgroup analyses. Added more details on data presentation for subgroup analyses.
Section 5.8.1	Added more details to the definition of TEAE which corrected the typo in TEAE definition in Protocol Amendment 5.
Section 6.1	Added more details on baseline definition of ECOG, tumor assessment, and quality of life.
Section 6.3	Added more details on imputation rule.
Section 7	Added flexible interim analysis timing for Part 1.
Section 3.4, Section 4.8, and Section 5.9.2	Clarified and added more details on ADA analyses
Thoughout this document	Minor editorial changes.

Source: SAP v2, page 13/44

Results

A total of 904 patients were screened for study eligibility in Study 16113 Part 2. 438 patients were screen failures, reasons detailed in Table 10.

At data cut-off for the second interim analysis (IA2) on 14-JUN-2021, 466 patients constitute the full analysis population (FAS), i.e., PD-L1 all-comers. Since the primary endpoint was met at IA2, this is considered the primary analysis. Participant flow is presented in Table 9.

Results for an updated analysis (data cut-off 14-JUN-2022) are also provided in this report.

312 patients were enrolled in the cemiplimab + chemotherapy arm and 154 in the placebo + chemotherapy arm.

Note: The final indication for cemiplimab + chemotherapy in the first line treatment of non-small cell lung cancer includes only patients with tumoural SP263 PD-L1 expression ≥ 1% (n=327, of which 217 in the cemiplimab + chemotherapy arm and 110 in the placebo + chemotherapy arm). Consequently, certain tables present the FAS (PD-L1 all-comers, N=466), while others specify the PD-L1≥1% subgroup (n=327).

Participant flow

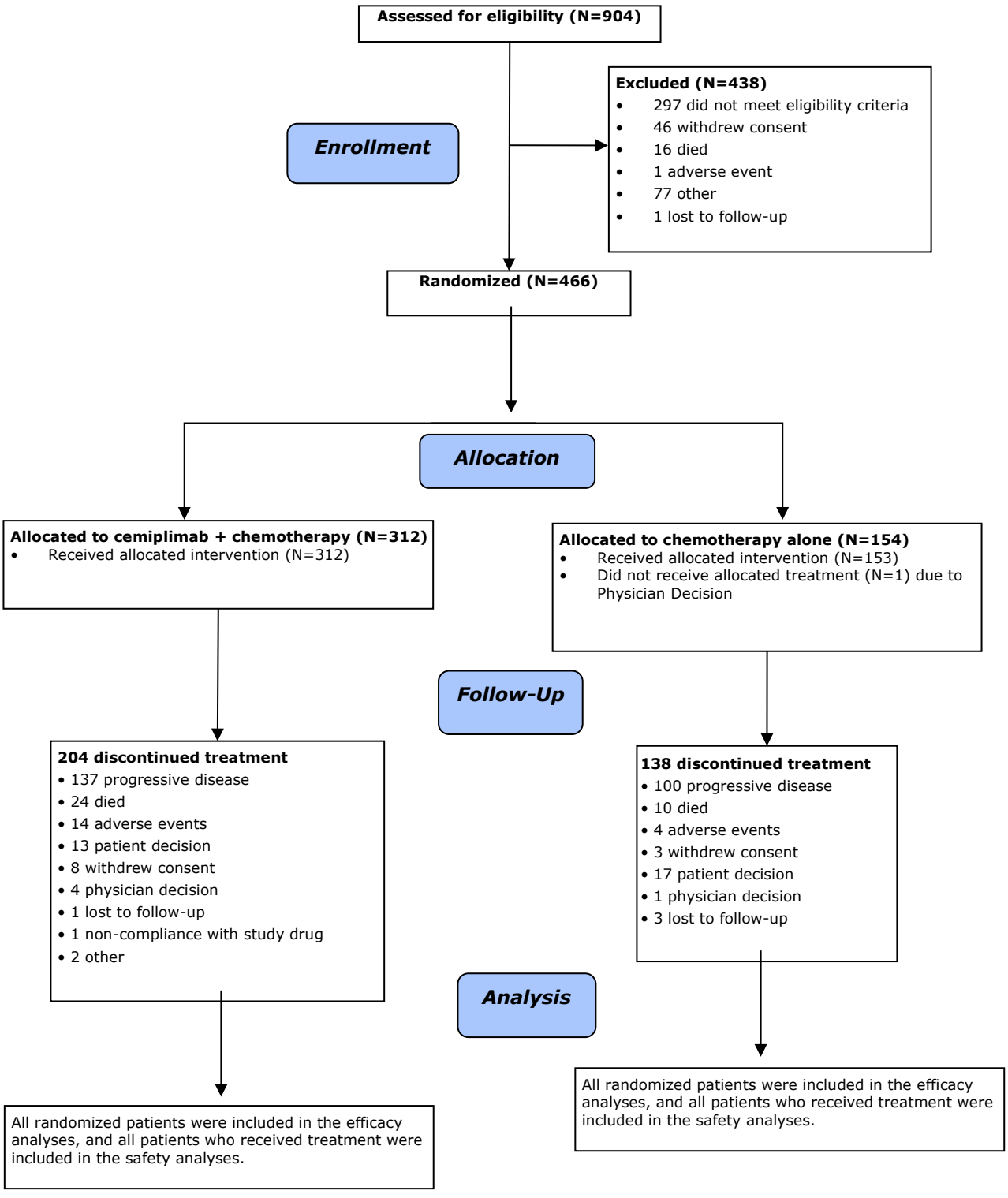


Table 9: Study 16113 Part 2: Patient Disposition (FAS)

	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=154)	Total (N=466)
Randomized and not treated (any study drug), n (%)	0	1 (0.6%)	1 (0.2%)
Treatment ongoing, n (%)	108 (34.6%)	15 (9.7%)	123 (26.4%)
Off treatment, n (%)	204 (65.4%)	138 (89.6%)	342 (73.4%)
Treatment completed	0	0	0
Treatment discontinued	204 (65.4%)	138 (89.6%)	342 (73.4%)
Primary reason for treatment discontinuation			
ADVERSE EVENT	14 (4.5%)	4 (2.6%)	18 (3.9%)
DEATH	24 (7.7%)	10 (6.5%)	34 (7.3%)
LOST TO FOLLOW-UP	1 (0.3%)	3 (1.9%)	4 (0.9%)
NON-COMPLIANCE WITH STUDY DRUG(S)	1 (0.3%)	0	1 (0.2%)
SUBJECT DECISION	13 (4.2%)	17 (11.0%)	30 (6.4%)
PHYSICIAN DECISION	4 (1.3%)	1 (0.6%)	5 (1.1%)
DISEASE PROGRESSION	137 (43.9%)	100 (64.9%)	237 (50.9%)
WITHDRAWAL OF CONSENT	8 (2.6%)	3 (1.9%)	11 (2.4%)
OTHER	2 (0.6%)	0	2 (0.4%)
Study ongoing, n (%)	121 (38.8%)	19 (12.3%)	140 (30.0%)
Off study, n (%)	191 (61.2%)	135 (87.7%)	326 (70.0%)
Study completed	2 (0.6%)	3 (1.9%)	5 (1.1%)
Study discontinued	189 (60.6%)	132 (85.7%)	321 (68.9%)
Primary reason for study discontinuation			
DEATH	70 (22.4%)	40 (26.0%)	110 (23.6%)
LOST TO FOLLOW-UP	6 (1.9%)	3 (1.9%)	9 (1.9%)
NON-COMPLIANCE WITH STUDY DRUG(S)	1 (0.3%)	0	1 (0.2%)
SUBJECT DECISION	13 (4.2%)	18 (11.7%)	31 (6.7%)
PHYSICIAN DECISION	3 (1.0%)	1 (0.6%)	4 (0.9%)
DISEASE PROGRESSION	83 (26.6%)	63 (40.9%)	146 (31.3%)
WITHDRAWAL OF CONSENT	11 (3.5%)	7 (4.5%)	18 (3.9%)
OTHER	2 (0.6%)	0	2 (0.4%)

Data cutoff as of 14 Jun 2021

Recruitment

The first patient (first visit) was enrolled in Part 2 of study R16113 on 31 May 2019. The last patient enrolled in Study 16113 Part 2 was enrolled on 30 September 2020.

Enrollment in Study 16113 Part 2 took place in countries in Central and Eastern Europe, in South-East Asia and in China.

Table 10: Study 16113 Part 2 Enrollment per Site and Country

Country	Total Number Sites by Country	Patients Enrolled Per Country
China	17	26
Georgia	6	171
Greece	6	13
Malaysia	9	21
Poland	9	43
Romania	5	9
Russia	22	141
Thailand	7	11
Turkey	4	22
Ukraine	5	9
TOTAL:	90	466

Conduct of the study

Protocol Amendments

Table 11: Protocol amendments

Amendment/Date	Major Changes
Amendment 5 16 Apr 2020	**Part 2:** • Updated PFS to key secondary endpoint for Part 2 instead of being a primary endpoint. • Added an interim analysis at 50% OS events to Part 2, in addition to the planned interim analysis at 70% OS events. • Added clarification that as a two-sided test is used at interim, the superiority or futility of cemiplimab treatment will be claimed if the statistical boundary is crossed. **Part 1 (original study design):** • Updated primary endpoint of Part 1 from objective response rate (ORR) to overall survival (OS). • Made ORR and progression free survival (PFS) key secondary endpoints, and made characterization of duration of response (DOR), pharmacokinetics (PK), and quality of life (QOL) secondary objectives instead of exploratory objectives. • Added an interim analysis at 83% OS event to Part 1.
Amendment 4 18 Jan 2019	**Part 2:** • Added Part 2 to compare the OS and PFS of cemiplimab/chemo with placebo/chemo in the first-line treatment of patients with advanced squamous or non-squamous NSCLC irrespective of PD-L1 expression. • Never smokers were no longer excluded for Part 2. **Part 1 (original study design):** • Updated study population for Part 1 to approximately 200 but no more than 360 patients, as fewer patients were expected to enroll with the addition of Part 2. • Section for Exploratory Objectives was added to capture many of the objectives for Part 1, which are now descriptive.
Amendment 3 19 Jun 2018	• Removed gemcitabine as an option for platinum doublet. • Duration for chemotherapy was changed from "4 to 6 cycles" to "4 cycles". • Inclusion criterion #2 was revised to include stage IIIC patient eligibility for the study to align with updated American Joint Committee on Cancer (AJCC) staging guidelines that separated stage IIIC from stage IV (no actual change to study population was made). • Clarified that histologic diagnosis of non-small cell lung cancer (NSCLC) may be confirmed by the central laboratory.

Amendment 2 VHP 15 Feb 2018	• Updated key secondary endpoint (OS) from "A patient who has not died will be censored at the last known date of contact" has been revised to "A patient who is lost to follow-up will be censored at the last date that the patient was known to be alive". • Revised the protocol to include regular thyroid function testing for Arm B (cemiplimab + standard of care).
Amendment 2 25 Jan 2018	• Clarified that choice of chemotherapy, including treatment with pemetrexed is chosen by the investigator (patients are not randomized to receive it). • Revised the exclusion criteria concerning human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) to clarify that patients with uncontrolled infection are excluded, but patients with controlled infection are permitted. • Added tuberculosis screening and testing for amylase and lipase.
Amendment 1 06 Oct 2017	• Added stopping rules for Arm C following safety evaluation. • Added DLT criteria (grade 4 anemia and all grade 3 imAEs). • Revised Inclusion criterion #2 to clarify that patients with stage IIIB must not be candidates for treatment with definitive concurrent chemoradiation. • Revised Exclusion criterion #3 to specify that all patients would have tumors evaluated for EGFR mutations, ALK rearrangement, and ROS1 fusions.

A total of 151 important protocol deviations were reported in 112 patients (Table 7) up to IA2 (DCO 14-JUN-2021).

Table 12: Important protocol deviations (FAS)

	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=154)	Total (N=466)
Number of important protocol deviations	82	69	151
Patients with any important protocol deviation, n (%)	69 (22.1%)	43 (27.9%)	112 (24.0%)
Type of important protocol deviations, n (%)			
Entered study even though entry criteria was not satisfied	11 (3.5%)	11 (7.1%)	22 (4.7%)
Inadequate informed consent administration	12 (3.8%)	6 (3.9%)	18 (3.9%)
Other treatment compliance	0	2 (1.3%)	2 (0.4%)
Procedure not performed	25 (8.0%)	11 (7.1%)	36 (7.7%)
Procedure performed outside of window	2 (0.6%)	2 (1.3%)	4 (0.9%)
Randomization error	8 (2.6%)	9 (5.8%)	17 (3.6%)
Received an excluded concomitant treatment	1 (0.3%)	0	1 (0.2%)
Received wrong treatment or incorrect dose	10 (3.2%)	10 (6.5%)	20 (4.3%)
Subject developed withdrawal criteria but were not withdrawn	4 (1.3%)	2 (1.3%)	6 (1.3%)

Data cutoff as of 14 Jun 2021
Source: PTT 14.1.1.6

Treatment beyond progression

In accordance with Study 16113 Part 2 protocol, for 105 patients randomized to the cemiplimab/chemo arm who had BIRC-confirmed disease progression, the Investigators deemed that continuation of the same treatment was the preferred option in the patient's best clinical interest. As per study protocol, this evaluation was based on the consideration that 1) the Investigator assessed no rapid disease progression, 2) the patient continued to meet all other study eligibility criteria, 3) the patient was tolerant of cemiplimab and had a stable performance status, and 4) that treatment beyond progression

would not delay an imminent intervention to prevent serious complications of disease progression. Of note, the further disease progression was assessed locally by the investigators and not centrally reviewed and patient disease was not re-baselined at the time of disease progression. As such, PFS2 was not included among the secondary or exploratory endpoints of the study and was not evaluated for this subgroup of patients and additional post-hoc analysis is not feasible.

Baseline data

Table 13: Study 16113 Part 2: Demographics and Baseline Characteristics (FAS)

	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=154)	Total (N=466)
Age (years)			
n	312	154	466
Mean (SD)	61.8 (9.09)	61.8 (9.21)	61.8 (9.12)
Median	63.0	63.0	63.0
Q1 : Q3	57.0 : 68.0	57.0 : 68.0	57.0 : 68.0
Min : Max	25 : 82	34 : 84	25 : 84
Age Groups (years), n (%)			
<65	184 (59.0%)	94 (61.0%)	278 (59.7%)
≥65	128 (41.0%)	60 (39.0%)	188 (40.3%)
Sex, n (%)			
Male	268 (85.9%)	123 (79.9%)	391 (83.9%)
Female	44 (14.1%)	31 (20.1%)	75 (16.1%)
Race, n (%)			
White	267 (85.6%)	138 (89.6%)	405 (86.9%)
Asian	45 (14.4%)	16 (10.4%)	61 (13.1%)
Ethnicity, n (%)			
Not Hispanic or Latino	311 (99.7%)	149 (96.8%)	460 (98.7%)
Not reported	1 (0.3%)	5 (3.2%)	6 (1.3%)
Geographic region, n (%)			
Europe	270 (86.5%)	138 (89.6%)	408 (87.6%)
Asia	42 (13.5%)	16 (10.4%)	58 (12.4%)
Height (cm)			
n	312	154	466
Mean (SD)	170.41 (8.032)	169.76 (8.331)	170.20 (8.129)
Median	171.00	170.00	170.00
Q1 : Q3	165.00 : 176.00	164.00 : 175.00	165.00 : 176.00
Min : Max	150.0 : 190.0	150.0 : 191.0	150.0 : 191.0
Body Weight (kg)			
n	312	154	466
Mean (SD)	73.14 (16.138)	72.30 (14.499)	72.86 (15.605)
Median	71.00	71.00	71.00
Q1 : Q3	61.50 : 82.00	61.30 : 81.00	61.30 : 82.00
Min : Max	38.5 : 163.2	38.0 : 115.0	38.0 : 163.2
BMI (kg/m2)			
n	312	154	466
Mean (SD)	25.143 (5.0804)	25.064 (4.6361)	25.117 (4.9331)
Median	24.750	24.475	24.555
Q1 : Q3	21.300 : 27.980	21.910 : 27.970	21.470 : 27.970
Min : Max	15.04 : 56.47	14.66 : 38.93	14.66 : 56.47
ECOG performance status, n (%)			
0	51 (16.3%)	18 (11.7%)	69 (14.8%)
1	259 (83.0%)	134 (87.0%)	393 (84.3%)
Missing	2 (0.6%)	2 (1.3%)	4 (0.9%)
Smoking status, n (%)			

	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=154)	Total (N=466)
Current Smoker	173 (55.4%)	75 (48.7%)	248 (53.2%)
Past Smoker	96 (30.8%)	55 (35.7%)	151 (32.4%)
Never Smoked	43 (13.8%)	24 (15.6%)	67 (14.4%)
Pack-year [a], n (%)			
<10	11 (3.5%)	10 (6.5%)	21 (4.5%)
≥10 to <20	27 (8.7%)	14 (9.1%)	41 (8.8%)
≥20 to <30	38 (12.2%)	21 (13.6%)	59 (12.7%)
≥30 to <40	58 (18.6%)	26 (16.9%)	84 (18.0%)
≥40 to <50	57 (18.3%)	25 (16.2%)	82 (17.6%)
≥50	76 (24.4%)	33 (21.4%)	109 (23.4%)
Missing	45 (14.4%)	25 (16.2%)	70 (15.0%)

Data cutoff as of 14 Jun 2021
Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group, max, maximum; min, minimum; Q1, first quartile; Q3, third quartile; SDv, standard deviation
Source: Study 16113 Part 2 Primary Analysis CSR PTT 14.1.2.1

Table 14: Study 16113 Part 2: Baseline Tumour Characteristics (FAS)

	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=154)	Total (N=466)
Histology/Cytology, n(%)			
Squamous	133 (42.6%)	67 (43.5%)	200 (42.9%)
Non-squamous	179 (57.4%)	87 (56.5%)	266 (57.1%)
Adenocarcinoma	168 (53.8%)	81 (52.6%)	249 (53.4%)
Large cell carcinoma	2 (0.6%)	4 (2.6%)	6 (1.3%)
Not otherwise specified	9 (2.9%)	2 (1.3%)	11 (2.4%)
Metastatic sites, n (%)			
Lung	255 (81.7%)	124 (80.5%)	379 (81.3%)
Liver	49 (15.7%)	23 (14.9%)	72 (15.5%)
Bone	59 (18.9%)	41 (26.6%)	100 (21.5%)
Adrenal	66 (21.2%)	28 (18.2%)	94 (20.2%)
Brain	24 (7.7%)	7 (4.5%)	31 (6.7%)
Lymph nodes intrathoracic	235 (75.3%)	124 (80.5%)	359 (77.0%)
Lymph nodes other	82 (26.3%)	45 (29.2%)	127 (27.3%)
Brain metastasis, n (%)			
Yes	24 (7.7%)	7 (4.5%)	31 (6.7%)
No	288 (92.3%)	147 (95.5%)	435 (93.3%)
Mutation status: EGFR, n (%)			
Wildtype	312 (100%)	153 (99.4%)	465 (99.8%)
Mutant	0	1 (0.6%)	1 (0.2%)
Mutation status: ALK Translocation, n (%)			
Not present	311 (99.7%)	154 (100%)	465 (99.8%)
Missing	1 (0.3%)	0	1 (0.2%)
Mutation status: ROS1 Translocation, n (%)			
Not rearranged	312 (100%)	154 (100%)	466 (100%)
Cancer stage at screening, n (%)			
stage IIIB	30 (9.6%)	20 (13.0%)	50 (10.7%)
stage IIIC	15 (4.8%)	4 (2.6%)	19 (4.1%)
stage IV	267 (85.6%)	130 (84.4%)	397 (85.2%)
Cancer stage at screening, n (%)			
Locally advanced	45 (14.4%)	24 (15.6%)	69 (14.8%)
Metastatic	267 (85.6%)	130 (84.4%)	397 (85.2%)
PD-L1 expression levels, n (%)			
<1%	95 (30.4%)	44 (28.6%)	139 (29.8%)
1% to 49%	114 (36.5%)	61 (39.6%)	175 (37.6%)
≥50%	103 (33.0%)	49 (31.8%)	152 (32.6%)

	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=154)	Total (N=466)
T stage at screening, n (%)			
TX	6 (1.9%)	1 (0.6%)	7 (1.5%)
T0	1 (0.3%)	0	1 (0.2%)
T1	13 (4.2%)	5 (3.2%)	18 (3.9%)
T1a	2 (0.6%)	0	2 (0.4%)
T1b	4 (1.3%)	3 (1.9%)	7 (1.5%)
T1c	8 (2.6%)	3 (1.9%)	11 (2.4%)
T2	15 (4.8%)	15 (9.7%)	30 (6.4%)
T2a	19 (6.1%)	7 (4.5%)	26 (5.6%)
T2b	17 (5.4%)	7 (4.5%)	24 (5.2%)
T3	66 (21.2%)	32 (20.8%)	98 (21.0%)
T4	160 (51.3%)	81 (52.6%)	241 (51.7%)
Missing	1 (0.3%)	0	1 (0.2%)
N stage at screening, n (%)			
NX	6 (1.9%)	4 (2.6%)	10 (2.1%)
N0	43 (13.8%)	18 (11.7%)	61 (13.1%)
N1	31 (9.9%)	9 (5.8%)	40 (8.6%)
N2	129 (41.3%)	72 (46.8%)	201 (43.1%)
N3	102 (32.7%)	51 (33.1%)	153 (32.8%)
Missing	1 (0.3%)	0	1 (0.2%)
M stage at screening, n (%)			
M0	45 (14.4%)	23 (14.9%)	68 (14.6%)
M1	266 (85.3%)	131 (85.1%)	397 (85.2%)
M1a	88 (28.2%)	39 (25.3%)	127 (27.3%)
M1b	71 (22.8%)	25 (16.2%)	96 (20.6%)
M1c	105 (33.7%)	66 (42.9%)	171 (36.7%)
M1 non-specified	2 (0.6%)	1 (0.6%)	3 (0.6%)
Missing	1 (0.3%)	0	1 (0.2%)
Time from initial diagnosis to randomization (months) [a]			
n	312	154	466
Mean (SD)	3.324 (10.8427)	2.179 (3.8457)	2.946 (9.1534)
Median	1.480	1.380	1.450
Q1 : Q3	1.035 : 2.070	0.950 : 2.100	1.020 : 2.100
Min : Max	0.03 : 151.95	0.46 : 34.63	0.03 : 151.95
Time from most recent relapse/-recurrence to randomization (months) [b]			
n	26	12	38
Mean (SD)	1.340 (0.8761)	0.588 (0.6946)	1.102 (0.8876)
Median	1.245	0.375	0.740
Q1 : Q3	0.530 : 2.040	0.115 : 0.640	0.390 : 1.940
Min : Max	0.13 : 2.99	0.03 : 2.04	0.03 : 2.99

Data cutoff as of 14 Jun 2021
[a] Time from Initial Diagnosis to Randomization (months) = (Date of randomization - Date of initial diagnosis)/30.4375.
[b] Time from Most Recent Relapse/¬Recurrence to Randomization (months) = (Date of randomization - Date of most recent relapse/¬recurrence)/30.4375.

As per study protocol, patients could have received systemic adjuvant or neo-adjuvant platinum-based chemotherapy, provided that they developed recurrent or metastatic disease more than 6 months after completing such therapy.

Table 15: Study 16113 Part 2: Prior Therapy (FAS)

	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=154)	Total (N=466)
Number of patients with any prior cancer-related therapy, n (%)[a]	55 (17.6%)	16 (10.4%)	71 (15.2%)
Number of patients with any prior cancer-related systemic therapy, n (%)	6 (1.9%)	1 (0.6%)	7 (1.5%)

	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=154)	Total (N=466)
Therapy setting, n (%)			
ADJUVANT	5 (1.6%)	1 (0.6%)	6 (1.3%)
OTHER	1 (0.3%)	0	1 (0.2%)
Regimens, n (%)			
CISPLATIN	6 (1.9%)	1 (0.6%)	7 (1.5%)
ETOPOSIDE	1 (0.3%)	0	1 (0.2%)
GEMCITABINE	1 (0.3%)	1 (0.6%)	2 (0.4%)
VINORELBINE	4 (1.3%)	0	4 (0.9%)
Time from end of last prior regimen to randomization (months)			
n	6	1	7
Mean (SD)	21.96 (11.816)	25.36	22.44 (10.863)
Median	17.68	25.36	19.78
Q1 : Q3	13.54 : 33.84	25.36 : 25.36	13.54 : 33.84
Min : Max	9.9 : 39.1	25.4 : 25.4	9.9 : 39.1
Number of patients with any prior cancer-related surgery, n (%)[b]	17 (5.4%)	5 (3.2%)	22 (4.7%)
Number of patients with any prior cancer-related radiotherapy, n (%)	40 (12.8%)	11 (7.1%)	51 (10.9%)

Data cutoff as of 14 Jun 2021
[a] Any prior cancer-related therapy includes patients who have had systemic therapy, surgery (excluding diagnostic procedures), or radiotherapy.
[b] Prior cancer-related surgery excludes diagnostic procedures.
Source: Study 16113 Part 2 Primary Analysis CSR PTT 14.1.3.1

Analyses excluding PD-L1 <1% patients

Table 16: Demographics and Baseline Characteristics (Full Analysis Set – Excluding PD-L1 <1% patients)

	Cemiplimab + chemotherapy (N=217)	Placebo + chemotherapy (N=110)	Total (N=327)
Age (years)			
n	217	110	327
Mean (SD)	61.2 (9.51)	60.9 (9.21)	61.1 (9.40)
Median	63.0	62.0	62.0
Q1 : Q3	56.0 : 67.0	55.0 : 66.0	56.0 : 67.0
Min : Max	25 : 82	34 : 84	25 : 84
Age Groups (years), n (%)			
<65	129 (59.4%)	74 (67.3%)	203 (62.1%)
>=65	88 (40.6%)	36 (32.7%)	124 (37.9%)
Age Groups (years), n (%)			
<65	129 (59.4%)	74 (67.3%)	203 (62.1%)
>=65 to <75	75 (34.6%)	29 (26.4%)	104 (31.8%)
>=75	13 (6.0%)	7 (6.4%)	20 (6.1%)
Sex, n (%)			
Male	185 (85.3%)	88 (80.0%)	273 (83.5%)
Female	32 (14.7%)	22 (20.0%)	54 (16.5%)
Race, n (%)			
White	185 (85.3%)	101 (91.8%)	286 (87.5%)
Asian	32 (14.7%)	9 (8.2%)	41 (12.5%)
Ethnicity, n (%)			

	Cemiplimab + chemotherapy (N=217)	Placebo + chemotherapy (N=110)	Total (N=327)
Not Hispanic or latino	216 (99.5%)	106 (96.4%)	322 (98.5%)
Not reported	1 (0.5%)	4 (3.6%)	5 (1.5%)
Geographic region, n (%)			
Europe	187 (86.2%)	101 (91.8%)	288 (88.1%)
Asia	30 (13.8%)	9 (8.2%)	39 (11.9%)
Height (cm)			
n	217	110	327
Mean (SD)	170.18 (8.171)	170.33 (8.344)	170.23 (8.217)
Median	170.00	170.00	170.00
Q1 : Q3	165.00 : 176.00	165.00 : 176.00	165.00 : 176.00
Min : Max	150.0 : 190.0	150.0 : 191.0	150.0 : 191.0
Body Weight (kg)			
n	217	110	327
Mean (SD)	72.75 (16.282)	72.86 (14.322)	72.79 (15.628)
Median	70.00	71.00	70.10
Q1 : Q3	61.20 : 81.90	63.00 : 82.00	61.20 : 82.00
Min : Max	38.5 : 134.2	48.5 : 115.0	38.5 : 134.2
BMI (kg/m2)			
n	217	110	327
Mean (SD)	25.059 (4.9943)	25.091 (4.4904)	25.070 (4.8238)
Median	24.540	24.440	24.510
Q1 : Q3	21.190 : 28.610	22.030 : 27.940	21.390 : 28.090
Min : Max	15.04 : 43.44	16.59 : 38.93	15.04 : 43.44
ECOG performance status, n (%)			
0	38 (17.5%)	15 (13.6%)	53 (16.2%)
1	178 (82.0%)	94 (85.5%)	272 (83.2%)
Missing	1 (0.5%)	1 (0.9%)	2 (0.6%)
Smoking status, n (%)			
Current Smoker	114 (52.5%)	53 (48.2%)	167 (51.1%)
Past Smoker	72 (33.2%)	40 (36.4%)	112 (34.3%)
Never Smoked	31 (14.3%)	17 (15.5%)	48 (14.7%)

Data cutoff as of 14 Jun 2021
Source: PTT 14.1.2.1.q20.1

Table 17: Baseline Tumour Characteristics (Full Analysis Set – Excluding PD-L1 <1% patients)

	Cemiplimab + chemotherapy (N=217)	Placebo + chemotherapy (N=110)	Total (N=327)
Histology/Cytology, n(%)			
Squamous	95 (43.8%)	51 (46.4%)	146 (44.6%)
Non-squamous	122 (56.2%)	59 (53.6%)	181 (55.4%)
Adenocarcinoma	116 (53.5%)	55 (50.0%)	171 (52.3%)
Large cell carcinoma	1 (0.5%)	3 (2.7%)	4 (1.2%)
Not otherwise specified	5 (2.3%)	1 (0.9%)	6 (1.8%)
Metastatic sites, n (%)			
Lung	175 (80.6%)	88 (80.0%)	263 (80.4%)
Liver	31 (14.3%)	18 (16.4%)	49 (15.0%)
Bone	39 (18.0%)	32 (29.1%)	71 (21.7%)
Adrenal	42 (19.4%)	22 (20.0%)	64 (19.6%)
Brain	15 (6.9%)	6 (5.5%)	21 (6.4%)
Lymph nodes intrathoracic	162 (74.7%)	91 (82.7%)	253 (77.4%)
Lymph nodes other	66 (30.4%)	34 (30.9%)	100 (30.6%)
Brain metastasis, n (%)			
Yes	15 (6.9%)	6 (5.5%)	21 (6.4%)
No	202 (93.1%)	104 (94.5%)	306 (93.6%)
Histologic grade, n(%)			
Well differentiated	13 (6.0%)	7 (6.4%)	20 (6.1%)
Moderately differentiated	44 (20.3%)	25 (22.7%)	69 (21.1%)
Poorly differentiated	59 (27.2%)	29 (26.4%)	88 (26.9%)
Undifferentiated	1 (0.5%)	1 (0.9%)	2 (0.6%)
Unknown	100 (46.1%)	48 (43.6%)	148 (45.3%)

	Cemiplimab + chemotherapy (N=217)	Placebo + chemotherapy (N=110)	Total (N=327)
Mutation status: EGFR, n (%)			
Wildtype	217 (100%)	109 (99.1%)	326 (99.7%)
Mutant	0	1 (0.9%)	1 (0.3%)
Mutation status: ALK Translocation, n (%)			
Not present	216 (99.5%)	110 (100%)	326 (99.7%)
Missing	1 (0.5%)	0	1 (0.3%)
Mutation status: ROS1 Translocation, n (%)			
Not rearranged	217 (100%)	110 (100%)	327 (100%)
Cancer stage at screening, n (%)			
Stage IIIB	20 (9.2%)	15 (13.6%)	35 (10.7%)
Stage IIIC	10 (4.6%)	2 (1.8%)	12 (3.7%)
Stage IV	187 (86.2%)	93 (84.5%)	280 (85.6%)
Cancer stage at screening, n (%)			
Locally advanced	30 (13.8%)	17 (15.5%)	47 (14.4%)
Metastatic	187 (86.2%)	93 (84.5%)	280 (85.6%)
PD-L1 expression levels, n (%)			
1% to 49%	114 (52.5%)	61 (55.5%)	175 (53.5%)
>=50%	103 (47.5%)	49 (44.5%)	152 (46.5%)
>=50% to <=75%	34 (15.7%)	19 (17.3%)	53 (16.2%)
>75% to <95%	30 (13.8%)	14 (12.7%)	44 (13.5%)
>=95%	39 (18.0%)	16 (14.5%)	55 (16.8%)
T Stage at initial diagnosis, n (%)			
TX	5 (2.3%)	6 (5.5%)	11 (3.4%)
Tis	0	1 (0.9%)	1 (0.3%)
T1	22 (10.1%)	8 (7.3%)	30 (9.2%)
T2	46 (21.2%)	21 (19.1%)	67 (20.5%)
T3	45 (20.7%)	21 (19.1%)	66 (20.2%)
T4	95 (43.8%)	53 (48.2%)	148 (45.3%)
Unknown	4 (1.8%)	0	4 (1.2%)
N Stage at initial diagnosis, n (%)			
NX	9 (4.1%)	10 (9.1%)	19 (5.8%)
N0	24 (11.1%)	9 (8.2%)	33 (10.1%)
N1	27 (12.4%)	5 (4.5%)	32 (9.8%)
N2	90 (41.5%)	56 (50.9%)	146 (44.6%)
N3	63 (29.0%)	30 (27.3%)	93 (28.4%)
Unknown	4 (1.8%)	0	4 (1.2%)
M Stage at initial diagnosis, n (%)			
MX	8 (3.7%)	4 (3.6%)	12 (3.7%)
M0	57 (26.3%)	21 (19.1%)	78 (23.9%)
M1	148 (68.2%)	84 (76.4%)	232 (70.9%)
M1a	48 (22.1%)	29 (26.4%)	77 (23.5%)
M1b	27 (12.4%)	14 (12.7%)	41 (12.5%)
M1c	39 (18.0%)	25 (22.7%)	64 (19.6%)
M1 non-specified	34 (15.7%)	16 (14.5%)	50 (15.3%)
Unknown	4 (1.8%)	0	4 (1.2%)
Missing	0	1 (0.9%)	1 (0.3%)
T Stage at screening, n (%)			
TX	5 (2.3%)	1 (0.9%)	6 (1.8%)
T0	1 (0.5%)	0	1 (0.3%)
T1	11 (5.1%)	3 (2.7%)	14 (4.3%)
T1a	2 (0.9%)	0	2 (0.6%)
T1b	4 (1.8%)	3 (2.7%)	7 (2.1%)
T1c	5 (2.3%)	3 (2.7%)	8 (2.4%)
T2	13 (6.0%)	10 (9.1%)	23 (7.0%)
T2a	11 (5.1%)	4 (3.6%)	15 (4.6%)
T2b	11 (5.1%)	4 (3.6%)	15 (4.6%)
T3	49 (22.6%)	20 (18.2%)	69 (21.1%)

	Cemiplimab + chemotherapy (N=217)	Placebo + chemotherapy (N=110)	Total (N=327)
T4	105 (48.4%)	62 (56.4%)	167 (51.1%)
N Stage at screening, n (%)			
NX	6 (2.8%)	3 (2.7%)	9 (2.8%)
N0	27 (12.4%)	10 (9.1%)	37 (11.3%)
N1	22 (10.1%)	6 (5.5%)	28 (8.6%)
N2	93 (42.9%)	49 (44.5%)	142 (43.4%)
N3	69 (31.8%)	42 (38.2%)	111 (33.9%)
M Stage at screening, n (%)			
M0	30 (13.8%)	16 (14.5%)	46 (14.1%)
M1	187 (86.2%)	94 (85.5%)	281 (85.9%)
M Stage at screening, n (%)			
M1			
M1a	63 (29.0%)	23 (20.9%)	86 (26.3%)
M1b	52 (24.0%)	19 (17.3%)	71 (21.7%)
M1c	71 (32.7%)	51 (46.4%)	122 (37.3%)
M1 non-specified	1 (0.5%)	1 (0.9%)	2 (0.6%)
Time from initial diagnosis to randomization (months) [a]			
n	217	110	327
Mean (SD)	3.811 (12.7979)	2.340 (4.4865)	3.317 (10.7580)
Median	1.480	1.380	1.450
Q1 : Q3	0.990 : 2.100	0.950 : 2.100	0.950 : 2.100
Min : Max	0.56 : 151.95	0.46 : 34.63	0.46 : 151.95
Time from most recent relapse/ recurrence to randomization (months) [b]			
n	17	9	26
Mean (SD)	1.495 (0.8174)	0.481 (0.6089)	1.144 (0.8877)
Median	1.380	0.360	0.855
Q1 : Q3	0.720 : 2.100	0.160 : 0.390	0.390 : 2.040
Min : Max	0.20 : 2.56	0.03 : 2.04	0.03 : 2.56

Data cutoff as of 14 Jun 2021
[a] Time from Initial Diagnosis to Randomization (months) = (Date of randomization – Date of initial diagnosis)/30.4375
[b] Time from Most Recent Relapse/¬Recurrence to Randomization (months) = (Date of randomization – Date of most recent relapse/¬recurrence)/30.4375.

Numbers analysed

Table 18: Analysis population

Analysis Set, n (%)	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=154)	Total (N=466)
Full Analysis Set (FAS)	312 (100%)	154 (100%)	466 (100%)
Safety Analysis Set (SAF)	312 (100%)	153 (99.4%)	465 (99.8%)
Pharmacokinetic Analysis Set (PKA)	295 (94.6%)	0	295 (63.3%)
Anti-drug Antibody Analysis Set (ADA)	200 (64.1%)	73 (47.4%)	273 (58.6%)

Data cutoff as of 14 Jun 2021
Source: PTT 14.1.1.3

Note: the dataset upon which positive opinion (population intended for therapeutic indication) was adopted is constituted by the 327 patients with PD-L1 status ≥1% as per the SP263 assay.

Outcomes and estimation

At IA2, on data cut-off 14-JUN-2021, statistical significance was demonstrated for OS in the FAS (PD-L1 all-comers) and the IDMC recommended that the study be unblinded. The Sponsor then reproduced these analyses and agreed with the IDMC, concluding the study at IA #2 and, as provided in the SAP, designating these data as the primary analysis.

The updated analyses (data cut-off 14-JUN-2022) and efficacy analyses by PD-L1 subgroups are presented in the ancillary analyses section.

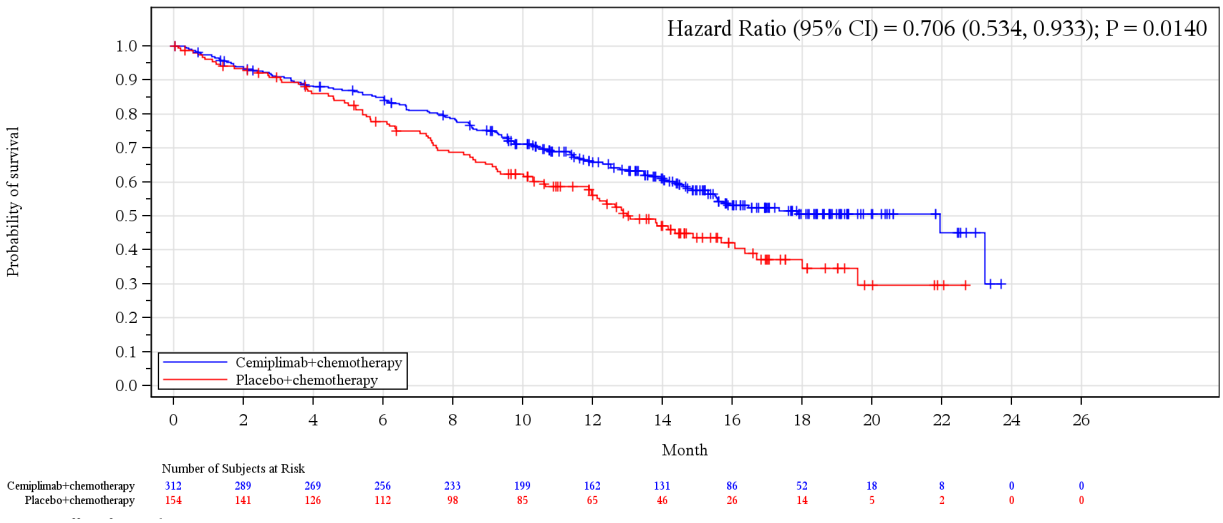
Primary endpoint OS:

Table 19: Study 16113 Part 2: Overall Survival – Primary Analysis (FAS)

	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=154)
Number of deaths, n (%)	132 (42.3%)	82 (53.2%)
Number of censored patients, n (%)	180 (57.7%)	72 (46.8%)
Median (95% CI), (months)[a]	21.9 (15.5, NE)	13.0 (11.9, 16.1)
Stratified log-rank test p-value [b][c]	0.0140	
HR (95% CI) [b][d]	0.706 (0.534, 0.933)	
Estimated Survival Probability , % (95% CI)[a]		
6 months	85.0 (80.5, 88.5)	77.8 (70.2, 83.6)
12 months	65.7 (59.9, 70.9)	56.1 (47.5, 63.8)
18 months	50.6 (43.9, 57.0)	37.2 (27.8, 46.6)
24 months	NE (NE, NE)	NE (NE, NE)

Data cutoff as of 14 Jun 2021
[a] Based on Kaplan-Meier method.
[b] Stratified by histology (squamous, non-squamous) and PD-L1 level (<1%, 1% to 49%, ≥50%) according to IWRS. Significance threshold is set to 0.01631 using O Brien Fleming alpha spending function.
[c] Two-sided p-value.
[d] Based on stratified proportional hazards model (cemiplimab + chemotherapy vs. placebo + chemotherapy).
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, Intent-to-Treat; NE, not evaluable.

Figure 10: Study 16113 Part 2: Kaplan-Meier Curve of Overall Survival



Data cutoff as of 14 Jun 2021
CI, confidence interval;

Secondary endpoints:

Progression Free Survival (PFS)

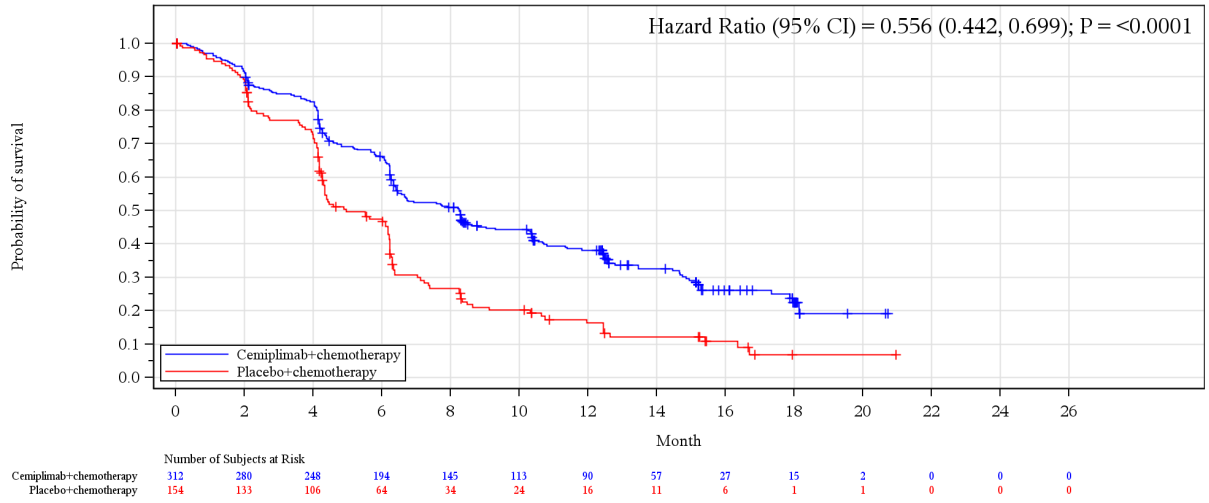
Table 20: Study 16113 Part 2: Progression-Free Survival per IRC (FAS)

	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=154)
Number of events, n (%)	204 (65.4%)	122 (79.2%)
Progressive Disease, n (%)	154 (49.4%)	94 (61.0%)
Number of deaths, n (%)	50 (16.0%)	28 (18.2%)
Number of censored patients, n (%)	108 (34.6%)	32 (20.8%)
Median (95% CI), (months)[a]	8.2 (6.4, 9.3)	5.0 (4.3, 6.2)
Stratified log-rank test p-value [b][c]	<0.0001	
HR (95% CI) [b][d]	0.556 (0.442, 0.699)	
Estimated Event-Free Probability, % (95% CI)[a]		
6 months	66.1 (60.4, 71.1)	47.4 (39.0, 55.3)
12 months	38.1 (32.4, 43.8)	16.4 (10.5, 23.4)
18 months	22.4 (16.3, 29.0)	6.8 (2.4, 14.2)
24 months	NE (NE, NE)	NE (NE, NE)

Data cutoff as of 14 Jun 2021
[a] Based on Kaplan-Meier method.
[b] Stratified by histology (squamous, non-squamous) and PD-L1 level (<1%, 1% to 49%, ≥50%) according to IWRS.
[c] Two-sided p-value.
[d] Based on stratified proportional hazards model (cemiplimab combination therapy vs. chemotherapy).
Abbreviations: CI, confidence interval; HR, hazard ratio; IRC, Independent Review Committee; ITT, intent-to-treat; IWRS, Interactive Web Response System; NE, not evaluable.

Source: Study 16113 Part 2 Primary Analysis CSR PTT 14.2.2.1

Figure 11: Study 16113 Part 2: Kaplan-Meier Curve of Progression Free Survival (FAS)



Data cutoff as of 14 Jun 2021
Source: Study 16113 Part 2 Primary Analysis CSR PTF 14.2.2.1

Overall Response Rate (ORR)

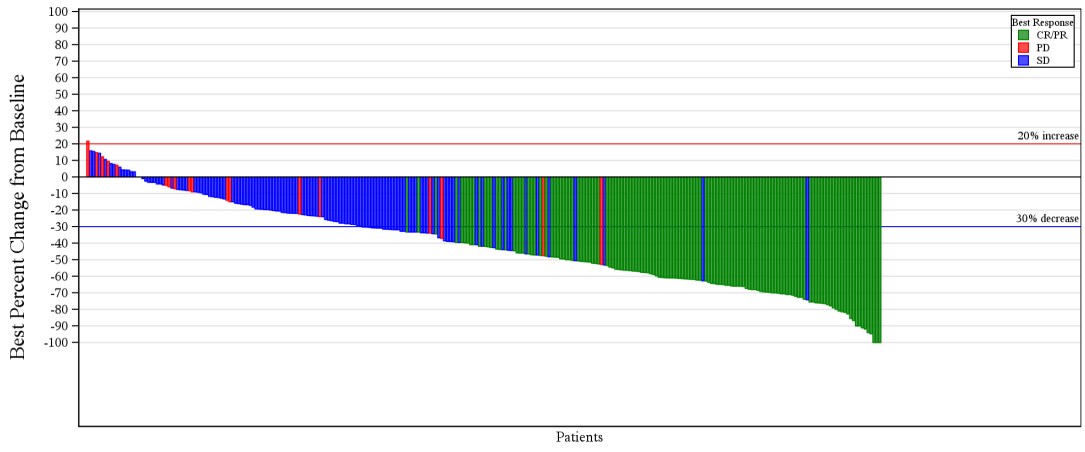
Table 21: Study 16113 Part 2: Best Overall Tumor Response per IRC (FAS)

	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=154)
Best Overall Tumor Response, n (%)		
Complete Response (CR)	8 (2.6%)	0
Partial Response (PR)	127 (40.7%)	35 (22.7%)
Stable Disease (SD)	121 (38.8%)	74 (48.1%)
Non-CR/Non-PD	4 (1.3%)	1 (0.6%)
Progressive Disease (PD)	22 (7.1%)	24 (15.6%)
Not Evaluable (NE)	30 (9.6%)	20 (13.0%)
Response		
Objective Response Rate (ORR:CR+PR)	135 (43.3%)	35 (22.7%)
95% CI for ORR [a]	(37.7%, 49.0%)	(16.4%, 30.2%)
Stratified CMH test p-value [b][c]	<0.0001	
Odds ratio (95% CI) [b][d]	2.682 (1.718, 4.186)	

Data cutoff as of 14 Jun 2021
[a] Clopper-Person exact confidence interval.
[b] Stratified by histology (squamous, non-squamous) and PD-L1 level (<1%, 1% to 49% and ≥50%) according to IWRS.
[c] Two-sided p-value using stratified Cochran-Mantel-Haenszel test.
[d] Based on stratified Cochran-Mantel-Haenszel test (cemiplimab + chemotherapy vs. placebo + chemotherapy).

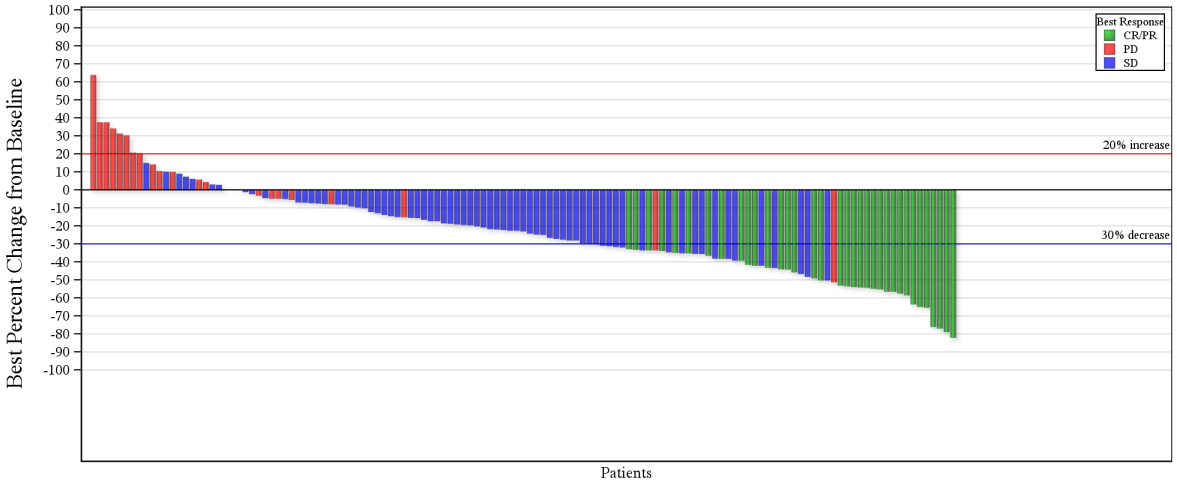
Waterfall plots of best percent change from baseline illustrate depth of responses in target lesions in the cemiplimab/chemo arm (Figure 12) and in the placebo/chemo arm (Figure 13). Each bar represents a patient, and BORs are shown according to the color keys in the figures. Depicted BORs in waterfall plots did not include any tumour assessments obtained after PD.

Figure 12: Study 16113 Part 2 Waterfall Plot by IRC (FAS – Cemiplimab + Chemotherapy Arm)



Data cutoff as of 14 Jun 2021
Abbreviations: CR, complete response; IRC, Independent Review Committee; ITT, intent-to-treat; NE, non-evaluable; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Figure 13: Study 16113 Part 2 Waterfall Plot by IRC (FAS – Placebo + Chemotherapy Arm)



Data cutoff as of 14 Jun 2021
Abbreviations: CR, complete response; IRC, Independent Review Committee; mITT, modified intent-to-treat; NE, non-evaluable; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Duration of Response (DoR)

Table 22: Study 16113 Part 2: Observed Duration of Response per IRC (Patients with Confirmed CR or PR) (FAS)

	Cemiplimab + chemotherapy (N=135)	Placebo + chemotherapy (N=35)
Observed Duration of Response (CR or PR) (months) [a]		
n	135	35
Min : Max	1.7 : 18.7	1.8 : 18.8
Observed Duration of Response (CR or PR), n (%) [a]		
<6 months	25 (18.5%)	22 (62.9%)
≥6 months	110 (81.5%)	13 (37.1%)
≥12 months	43 (31.9%)	7 (20.0%)
≥18 months	1 (0.7%)	1 (2.9%)
≥24 months	0	0

Data cutoff as of 14 Jun 2021

[a] Based on patients with confirmed CR or PR.
Abbreviations: CR, complete response; PR, partial response.
Source: Study 16113 Part 2 Primary Analysis CSR PTT14.2.3.4

Table 23: Study 16113 Part 2: Kaplan-Meier Estimation of Duration of Response per IRC (Confirmed CR or PR) (FAS)

	Cemiplimab + chemotherapy (N=135)	Placebo + chemotherapy (N=35)
KM Estimation of Duration of Response (CR or PR) [a]		
n	135	35
Number of events, n (%)	53 (39.3%)	18 (51.4%)
Number of censored patients, n (%)	82 (60.7%)	17 (48.6%)
Median (95% CI), (months)	15.6 (12.4, NE)	7.3 (4.3, 12.6)
Estimated Event-Free Probability , % (95% CI)[a]		
6 months	86.9 (79.8, 91.7)	53.8 (33.7, 70.3)
12 months	60.2 (50.0, 69.0)	36.4 (18.4, 54.7)
18 months	33.3 (14.2, 53.8)	31.2 (14.2, 50.0)
24 months	NE (NE, NE)	NE (NE, NE)

Data cutoff as of 14 Jun 2021
[a]Based on patients with confirmed CR or PR.
Abbreviations: CR, complete response; NE, not evaluable; PR, partial response.

Quality of Life (QoL), patient reported outcome (PRO)

Baseline completion rates for the EORTC QLQ-C30 and QLQ-LC13 were high, above 97% in all scales. Post-baseline completion rates (adjusted for study attrition) were more than 91% through cycle 21 for those patients expected to complete the PRO assessment.

Figure 14: PRO completion rate on the EORTC QLQ-C30 (Full analysis set) Global Health Status/Quality of Life

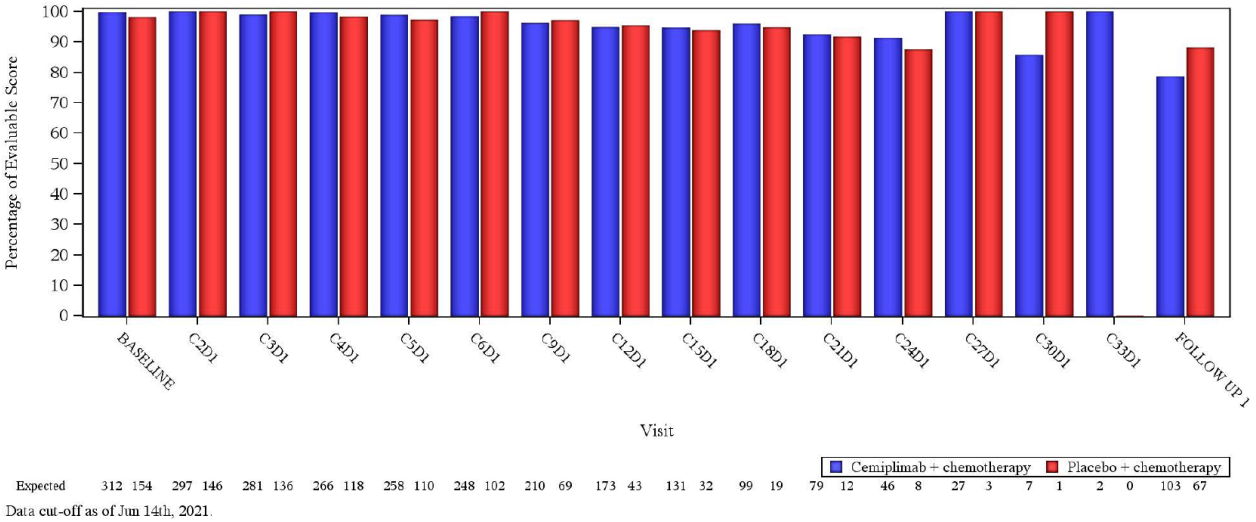
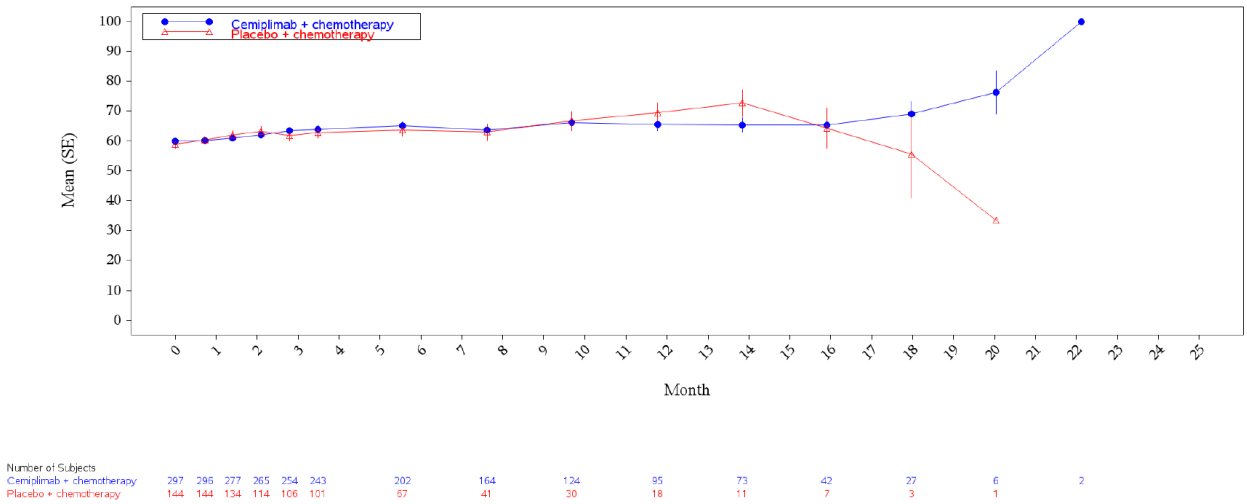


Figure 15: Longitudinal plots of EORTC QLQ-C30 – Observed mean (Full analysis set) Global Health Status/Quality of Life



Data cut-off as of Jun 14th, 2021.

In summary, descriptive analysis of patient reported outcomes per EORTC QLQ-C30 and QLQ-LC13 showed that patients in the cemiplimab/chemo arm had numerically similar GHS/QoL, functions and symptoms scores compared with patients treated with placebo/chemo.

Ancillary analyses

Updated data, additional 12 months follow up of Study 16113, part 2

Table 24: Study 16113 Part 2: Summary of Efficacy Data Based on the Primary Analysis 14 Jun 2021 Data Cut and Based on 14 Jun 2022 Data Cut for the Follow Up

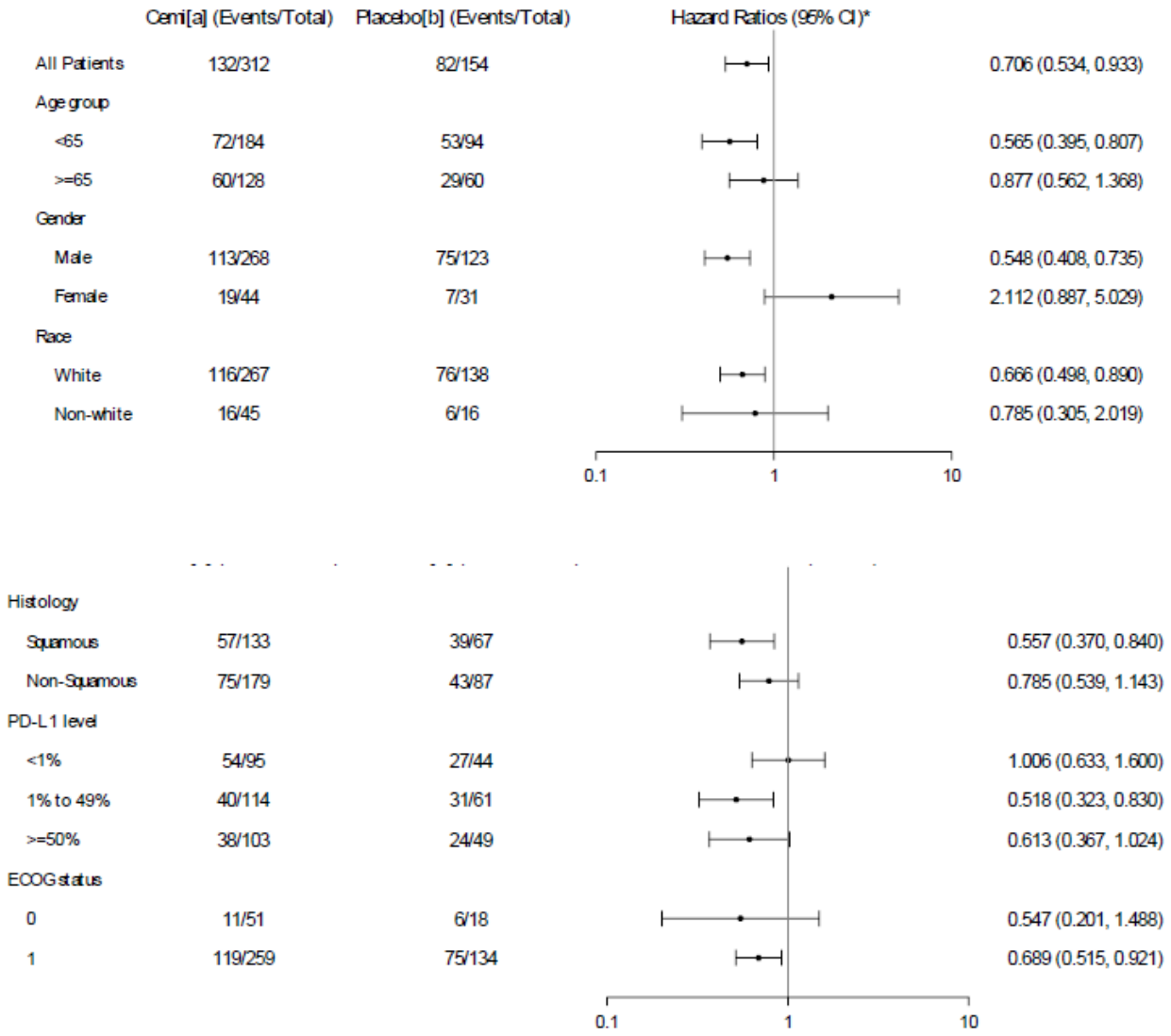
	Initial Data Cut (Follow Up: 16.4 months)			1 Year Follow Up (28.4 months)		
	Events (cemi/chemo vs placebo chemo)	**mOS (months)**	**HR (95% CI)**	**Events (cemi/chemo vs placebo chemo)**	**mOS (months)**	**HR (95% CI)**
OS (N=466)[a, b]	**132/312 vs 82/154**	**21.9 vs 13.0**	**0.706 (0.534, 0.933)**	**180/312 vs 111/154**	**21.1 vs 12.9**	**0.645 (0.507, 0.820)**
PD-L1 <1% (N=139)	54/95 vs 27/44	12.8 vs 14.2	1.006 (0.633, 1.600)	66/95 vs 34/44	12.8 vs 14.2	0.939 (0.619, 1.423)
PD-L1 1-49% (N=175)	40/114 vs 31/61	21.9 vs 12.1	0.518 (0.323, 0.830)	62/114 vs 43/61	23.2 vs 12.0	0.496 (0.335, 0.735)
PD-L1 ≥50% (N=152)	38/103 vs 24/49	17.9 vs 13.8	0.613 (0.367, 1.024)	52/103 vs 34/49	23.5 vs 14.4	0.559 (0.362, 0.862)
		mPFS (months)			**mPFS (months)**	
PFS (N=466)[a, b]	**204/312 vs 122/154**	**8.2 vs 5.0**	**0.566 (0.442, 0.699)**	**234/312 vs 134/154**	**8.2 vs 5.5**	**0.549 (0.441, 0.683)**
PD-L1 <1% (N=139)	70/95 vs 36/44	6.2 vs 4.4	0.764 (0.509, 1.146)	77/95 vs 39/44	6.2 vs 4.4	0.733 (0.496, 1.083)
PD-L1 1-49% (N=175)	77/114 vs 50/61	8.2 vs 5.5	0.474 (0.329, 0.681)	87/114 vs 55/61	8.2 vs 6.1	0.478 (0.339, 0.676)
PD-L1 ≥50% (N=152)	57/103 vs 36/49	12.5 vs 5.0	0.471 (0.309, 0.720)	70/103 vs 39/49	10.8 vs 5.5	0.482 (0.322, 0.721)
ORR (N=466)[c, d]	**43.4% vs. 22.7%**			**43.6% vs 22.1%**		
PD-L1 <1% (N=139)	32.6% vs 22.7%			33.7% vs 20.5%		
PD-L1 1-49% (N=175)	43.0% vs 19.7%			43.0% vs 19.7%		
PD-L1 ≥50% (N=152)	53.4% vs 26.5%			53.4% vs 26.5%		

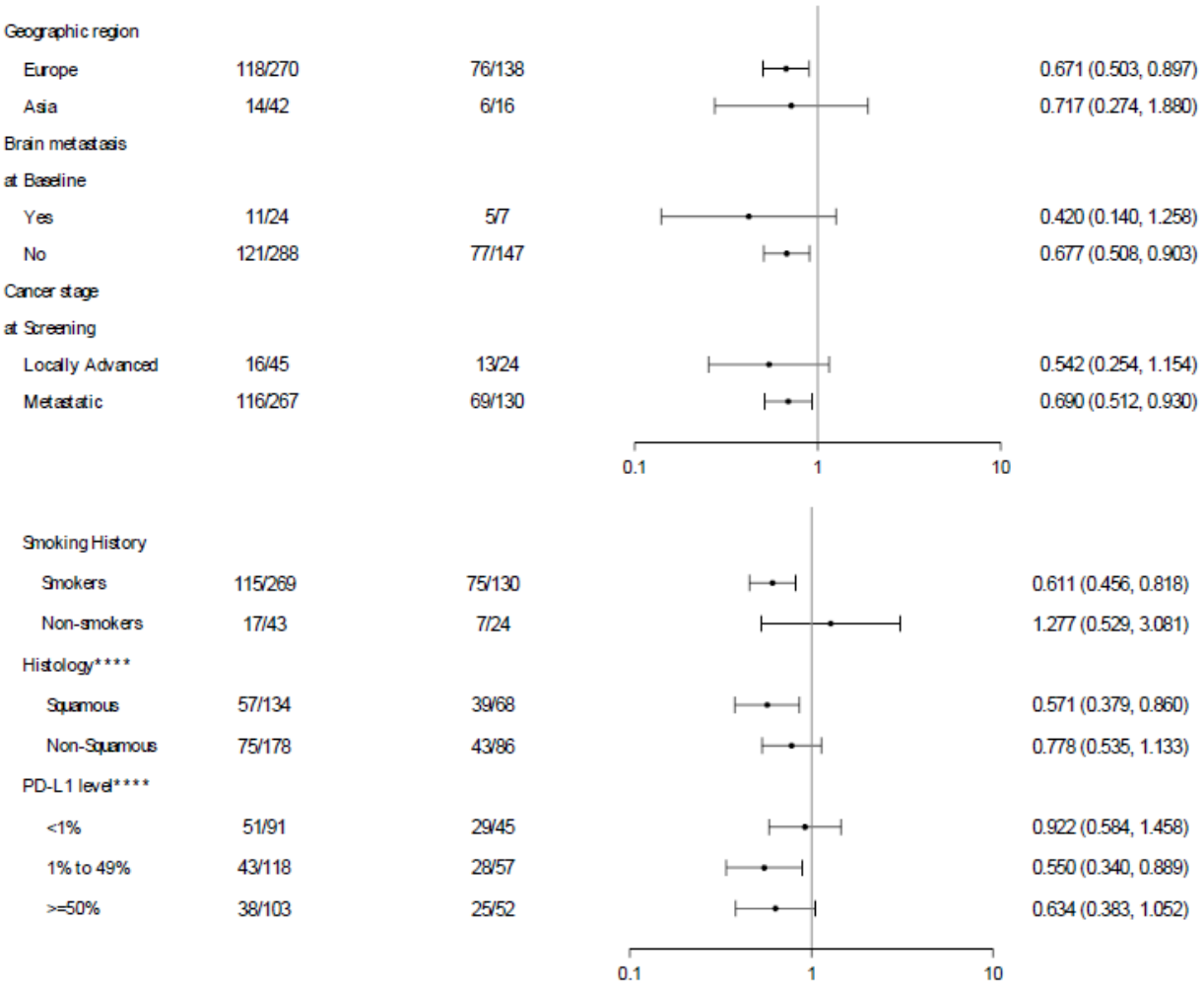
Data cutoff as of 14 Jun 2022 and 14 Jun 2021
Source: Tables 14.2.1.2, 14.2.2.2, Table 14.2.3.2
[a] Based on Kaplan-Meier method.
[b] Based on proportional hazards model (cemiplimab + chemotherapy vs placebo + chemotherapy).
[c] Clopper-Pearson exact confidence interval.
[d] Based on unstratified Cochran-Mantel-Haenszel test (cemiplimab + chemotherapy vs placebo + chemotherapy)

Subgroup analyses

Overall survival

Figure 16: Forest plot for overall survival by subgroup at IA2, DCO 14-JUN-2021

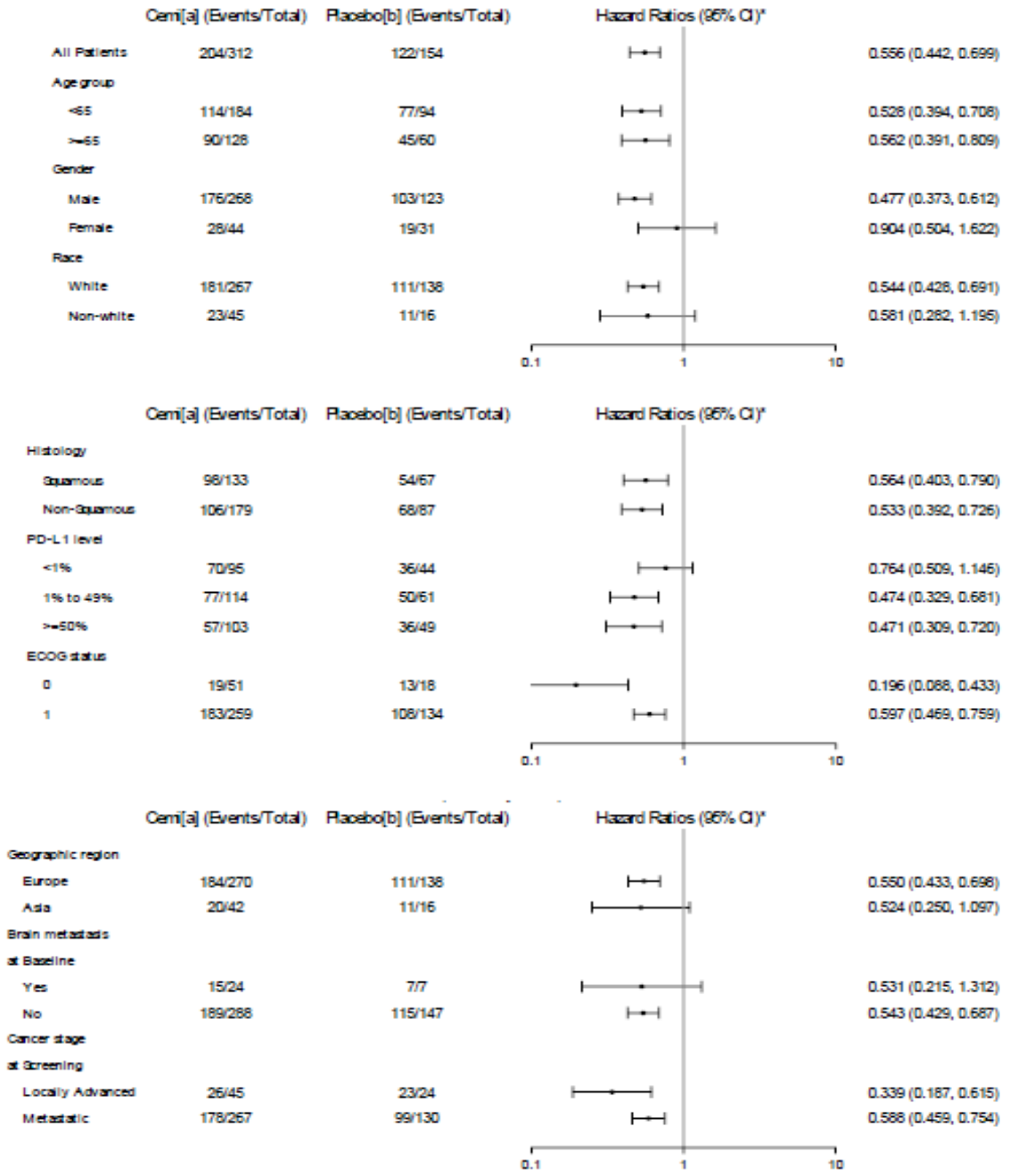


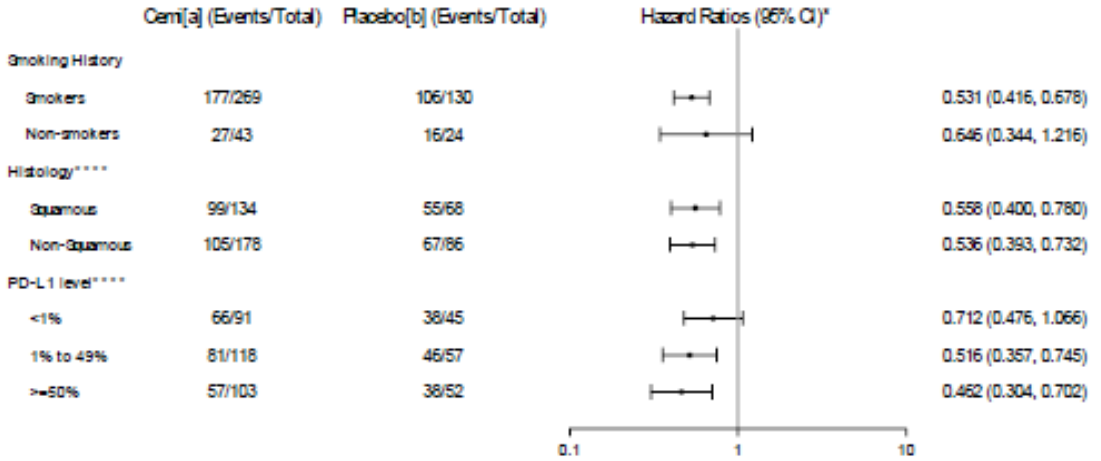


Data cutoff as of 14 Jun 2021
*Stratified by histology and PD-L1 level according to IWRS (cemiplimab + chemotherapy vs placebo + chemotherapy) for ITT population; unstratified for subgroups.
Smokers include current and past smokers; never-smokers is defined as having smoked <100 cigarettes in a lifetime
[a] cemiplimab + chemotherapy
[b] placebo + chemotherapy
PTF 14.2.1.2

Progression free survival

Figure 17: Forest Plot for progression free survival per IRC by subgroup at IA2, DCO 14-JUN-2021





Data cutoff as of 14 Jun 2021
*Stratified by histology and PD-L1 level according to IWRS (cemiplimab + chemotherapy vs placebo + chemotherapy) for ITT population; unstratified for subgroups.
Smokers include current and past smokers; never-smokers is defined as having smoked <100 cigarettes in a lifetime
[a] cemiplimab + chemotherapy
[b] placebo + chemotherapy
PTF 14.2.2.2

Analyses by histology

Table 25: Study 16113 Part 2 (1 year follow up) results for subgroups by histology and PD-L1 expression

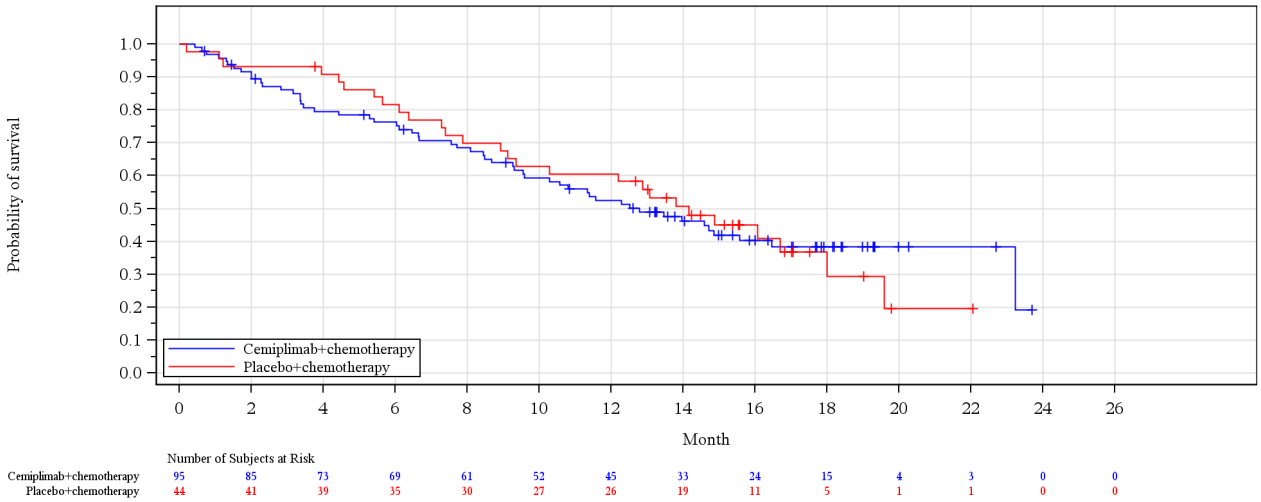
	OS[a, b]			**PFS[a, b]**			**ORR[c, d]**
	Events	mOS	HR (95% CI)	Events	mPFS	HR (95% CI)	
ITT (N=466)	180/312 vs 111/154	21.1m vs 12.9m	0.645 (0.507, 0.820)	234/312 vs 133/154	8.2m vs 5.5m	0.549 (0.441, 0.683)	43.6% vs 22.1%
- Squamous (N=200)	79/133 vs 47/67	22.3m vs 13.8m	0.608 (0.423, 0.874)	109/133 vs 57/67	8.2m vs 4.9m	0.564 (0.407, 0.780)	46.6% vs 26.9%
- Non-Squamous (N=266)	101/179 vs 64/87	19.4m vs 12.4m	0.639 (0.466, 0.875)	125/179 vs 76/87	7.9m vs 5.7m	0.527 (0.394, 0.706)	41.3% vs 18.4%
- Squamous / PD-L1<1% (N=54)	**23/38 vs 13/16**	**21.9m vs 16.7m**	**0.601 (0.301, 1.200)**	31/38 vs 14/16	8.3m vs 6.1m	0.699 (0.369, 1.322)	50.0% vs 31.3%
- Squamous / PD-L1 1-49% (N=81)	31/53 vs 19/28	23.2m vs 8.6m	0.518 (0.291, 0.924)	45/53 vs 25/28	6.7m vs 4.2m	0.548 (0.334, 0.899)	43.4% vs 25.0%
- Squamous / PD-L1 ≥50% (N=65)	25/42 vs 15/23	22.2m vs 15.1m	0.765 (0.403, 1.454)	33/42 vs 18/23	8.3m vs 5.5m	0.506 (0.279, 0.917)	47.6% vs 26.1%
- Non-Squamous / PD-L1<1% (N=85)	**43/57 vs 21/28**	**9.6m vs 13.0m**	**1.255 (0.743, 2.118)**	46/57 vs 25/28	5.2m vs 4.3m	0.794 (0.485, 1.300)	22.8% vs 14.3%
- Non-Squamous / PD-L1 1-49% (N=94)	31/61 vs 24/33	23.2 vs 12.0m	0.476 (0.278, 0.817)	42/61 vs 30/33	8.5m vs 6.2m	0.421 (0.258, 0.688)	42.6% vs 15.2%

	OS[a, b]			PFS[a, b]			ORR[c, d]
- Non-Squamous / PD-L1 ≥50% (N=87)	27/61 vs 19/26	24.8 vs 14.4m	0.418 (0.230, 0.759)	37/61 vs 21/26	12.5m vs 5.2m	0.463 (0.268, 0.800)	57.4% vs 26.9%

Data cutoff as of 14 Jun 2022
HR=hazard ratio; ITT=intention to treat; mOS=median overall survival; mPFS=median progression free survival ORR=objective response rate; OS=overall survival; PFS=progression free survival
Source: Tables 14.2.1.2, 14.2.1.4.nsq, 14.2.1.4.sq, 14.2.2, 14.2.2.5.nsq, 14.2.2.5.sq, 14.2.3.2, 14.2.3.6.nsq, 14.3.2.6.sq
[a] Based on Kaplan-Meier method.
[b] Based on proportional hazards model (cemiplimab + chemotherapy vs placebo + chemotherapy).
[c] Clopper-Pearson exact confidence interval.
[d] Based on unstratified Cochran-Mantel-Haenszel test (cemiplimab + chemotherapy vs placebo + chemotherapy).

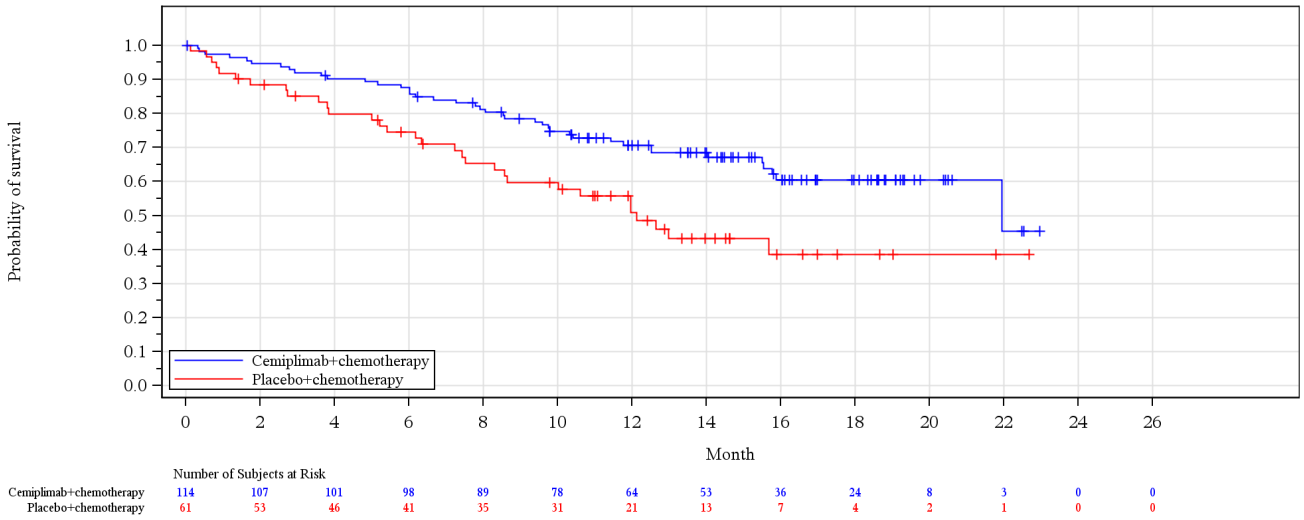
Analyses by PD-L1 expression

Figure 18: Kaplan-Meier Curve of Overall Survival – PD-L1 Level <1% at IA2 (DCO 14-JUN-2021)



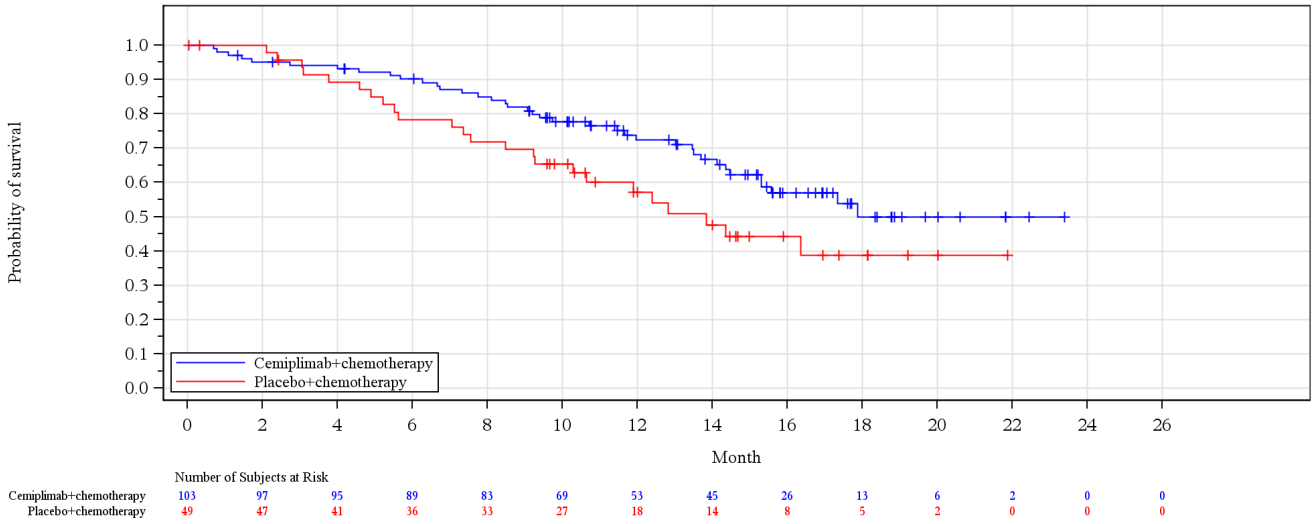
Data cutoff as of 14 Jun 2021
Hazard Ratio (95% CI) = 1.006 (0.633, 1.600)
Source: Study 16113 Part 2 Primary Analysis CSR PTF 14.2.1.1.s91

Figure 19: Kaplan-Meier Curve of Overall Survival – PD-L1 Level 1% to 49% at IA2 (DCO 14-JUN-2021)



Data cutoff as of 14 Jun 2021
Hazard Ratio (95% CI) = 0.518 (0.323, 0.830)
Source: Study 16113 Part 2 Primary Analysis CSR PTF 14.2.1.1.s92

Figure 20: Kaplan-Meier Curve of Overall Survival – PD-L1 Level ≥50% at IA2 (DCO 14-JUN-2021)



Data cutoff as of 14 Jun 2021
Hazard Ratio (95% CI) = 0.613 (0.37067, 1.024)
Source: Study 16113 Part 2 Primary Analysis CSR PTF 14.2.1.1.s93

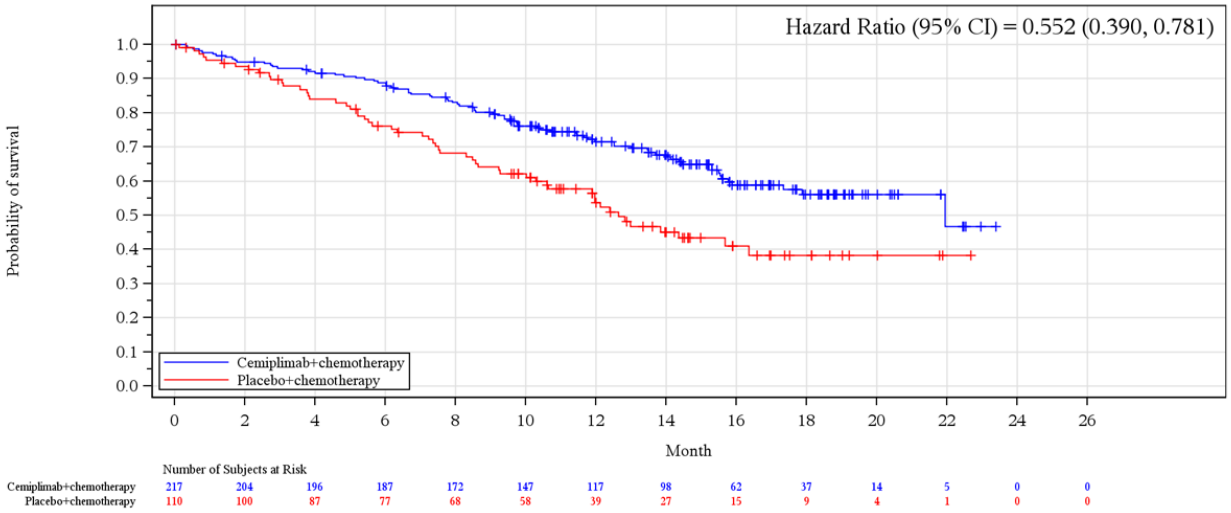
Analyses in PD-L1≥1% patients

Table 26: Overall Survival (PD-L1 ≥1% patients) at IA2 (DCO 14-JUN-2021)

	Cemiplimab + chemotherapy (N=217)	Placebo + chemotherapy (N=110)
Number of deaths, n (%)	78 (35.9%)	55 (50.0%)
Number of censored patients, n (%)	139 (64.1%)	55 (50.0%)
Median (95% CI), (months)[a]	21.9 (17.3, NE)	12.6 (10.3, 16.4)
HR (95% CI) [b][c]	0.552 (0.390, 0.781)	
Estimated Survival Probability , % (95% CI)[a]		
6 months	88.8 (83.7, 92.3)	76.2 (66.8, 83.2)
12 months	71.5 (64.7, 77.3)	53.7 (43.2, 63.1)
18 months	56.1 (47.5, 63.7)	38.2 (26.8, 49.6)
24 months	NE (NE, NE)	NE (NE, NE)

Data cutoff as of 14 Jun 2021
[a] Based on Kaplan-Meier method.
[b] Stratified by histology (squamous, non-squamous) according to IWRS.
[c] Based on stratified hazards model (cemiplimab + chemotherapy vs placebo + chemotherapy).

Figure 21: Kaplan-Meier Curve of Overall Survival (PD-L1 ≥1% patients) at IA2 (DCO 14-JUN-2021)



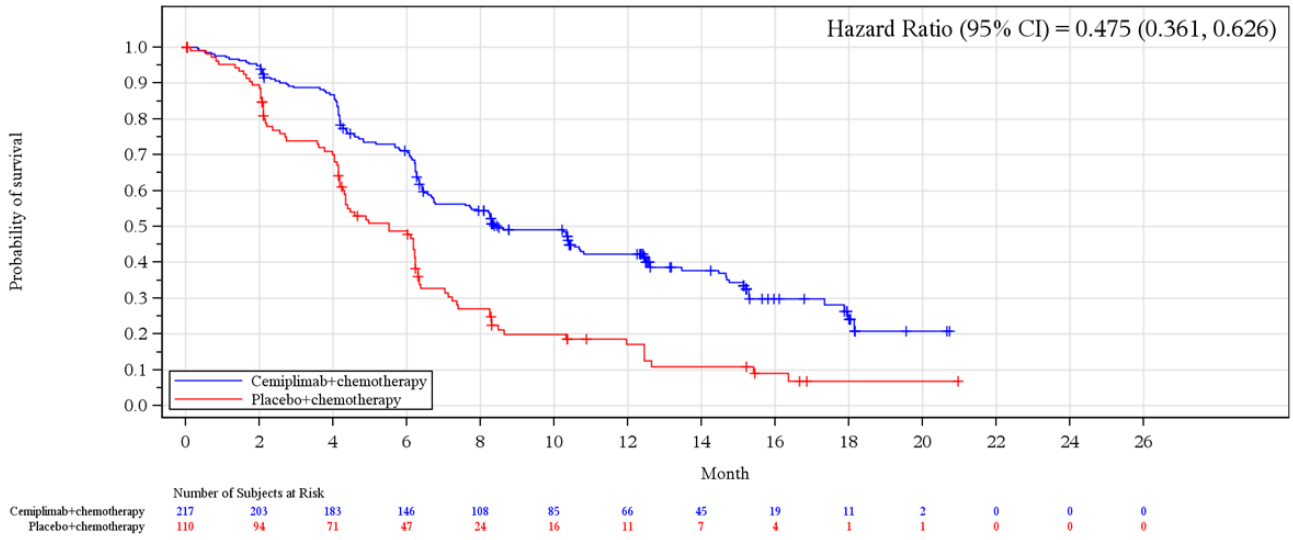
Data cutoff as of 14 Jun 2021
Source PTF 14.2.1.1.q20.1

Table 27: Progression-Free Survival per IRC (PD-L1 ≥1% patients) at IA2 (DCO 14-JUN-2021)

	Cemiplimab + chemotherapy (N=217)	Placebo + chemotherapy (N=110)
Number of events, n (%)	134 (61.8%)	86 (78.2%)
Progressive Disease, n (%)	105 (48.4%)	66 (60.0%)
Number of deaths, n (%)	29 (13.4%)	20 (18.2%)
Number of censored patients, n (%)	83 (38.2%)	24 (21.8%)
Median (95% CI), (months)[a]	8.5 (6.7, 10.7)	5.5 (4.3, 6.2)
HR (95% CI) [b][c]	0.475 (0.361, 0.626)	
Estimated Event-Free Probability , % (95% CI)[a]		
6 months	71.1 (64.4, 76.7)	48.8 (38.7, 58.1)
12 months	42.3 (35.3, 49.2)	17.1 (10.1, 25.7)
18 months	24.2 (16.2, 33.0)	6.8 (2.2, 14.9)
24 months	NE (NE, NE)	NE (NE, NE)

Data cutoff as of 14 Jun 2021
[a] Based on Kaplan-Meier method.
[b] Stratified by histology (squamous,¬ non-squamous) according to IWRS.
[c] Based on stratified hazards model (cemiplimab + chemotherapy vs placebo + chemotherapy).
Source: PTT 14.2.2.1.q20.5

Figure 22: Kaplan-Meier Curve of Progression-Free Survival per IRC (PD-L1 ≥1% patients) at IA2 (DCO 14-JUN-2021)



Data cutoff as of 14 Jun 2021

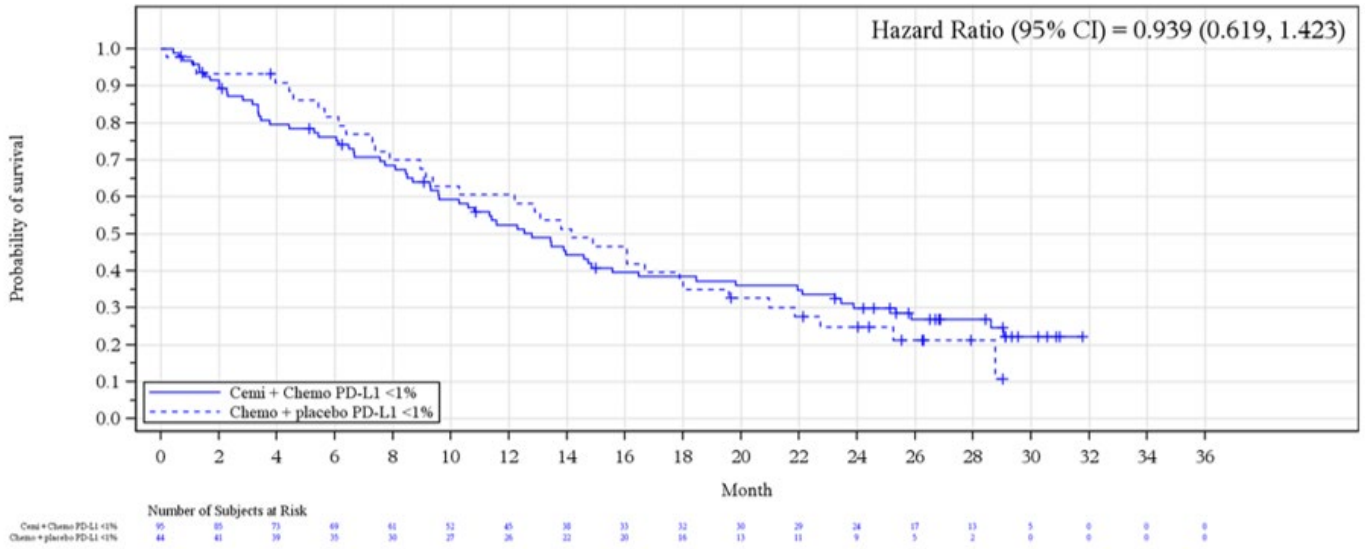
Updated analyses of PD-L1<1% and PD-L1≥1% patient populations

Table 28: Study 16113 Part 2 results for ITT and subgroups by PD-L1<1% and PD-L1 ≥1% expression (follow-up analysis), DCO 14-JUN-2022

	OS			PFS			ORR[c]
	Events	mOS[a]	HR (95% CI)[b]	Events	mPFS[a]	HR (95% CI)[b]	
ITT (N=466)	180/312 vs 111/154	21.1m vs 12.9m	0.645 (0.507, 0.820)	234/312 vs 133/154	8.2m vs 5.5m	0.549 (0.441, 0.683)	43.6% vs 22.1%
PD-L1<1% (N=139)	66/95 vs 34/44	12.8m vs 14.2m	0.939 (0.619, 1.423)	77/95 vs 39/44	6.2m vs 4.4m	0.733 (0.496, 1.083)	33.7% vs 20.5%
PD-L1 ≥1% (N=327)	114/217 vs 77/110	23.5m vs 12.1m	0.519 (0.388, 0.695)	157/217 vs 94/110	8.3m vs 5.5m	0.475 (0.366, 0.617)	47.9% vs 22.7%

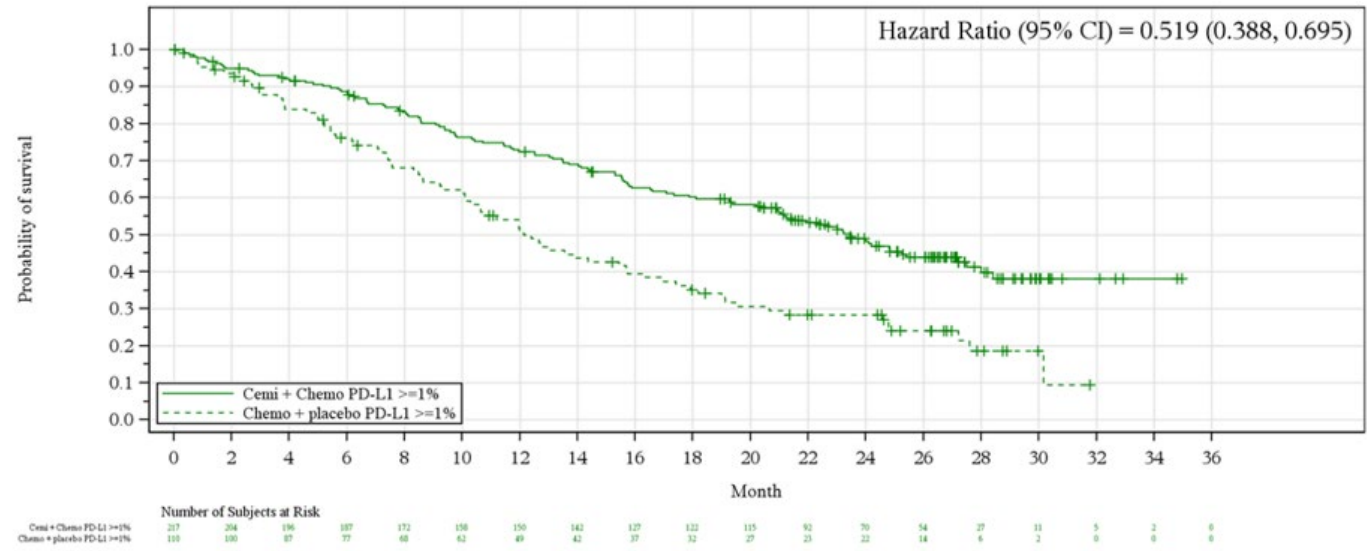
Data cutoff as of 14 Jun 2022
HR=hazard ratio; ITT=intention to treat; mOS=median overall survival; mPFS=median progression free survival ORR=objective response rate; OS=overall survival; PFS=progression free survival
Source: Tables 14.2.1.2c.unspd1, 14.2.2.2c.unspd1, 14.2.3.2c.unspd1
[a] Based on Kaplan-Meier method.
[b] Based on stratified proportional hazards model for ITT population; Unstratified for subgroups.
[c] Clopper-Pearson exact confidence interval.

Figure 23: KM curve: overall survival for Study 16113 Part 2 for PD-L1<1% subgroup (follow-up analysis), DCO 14-JUN-2022



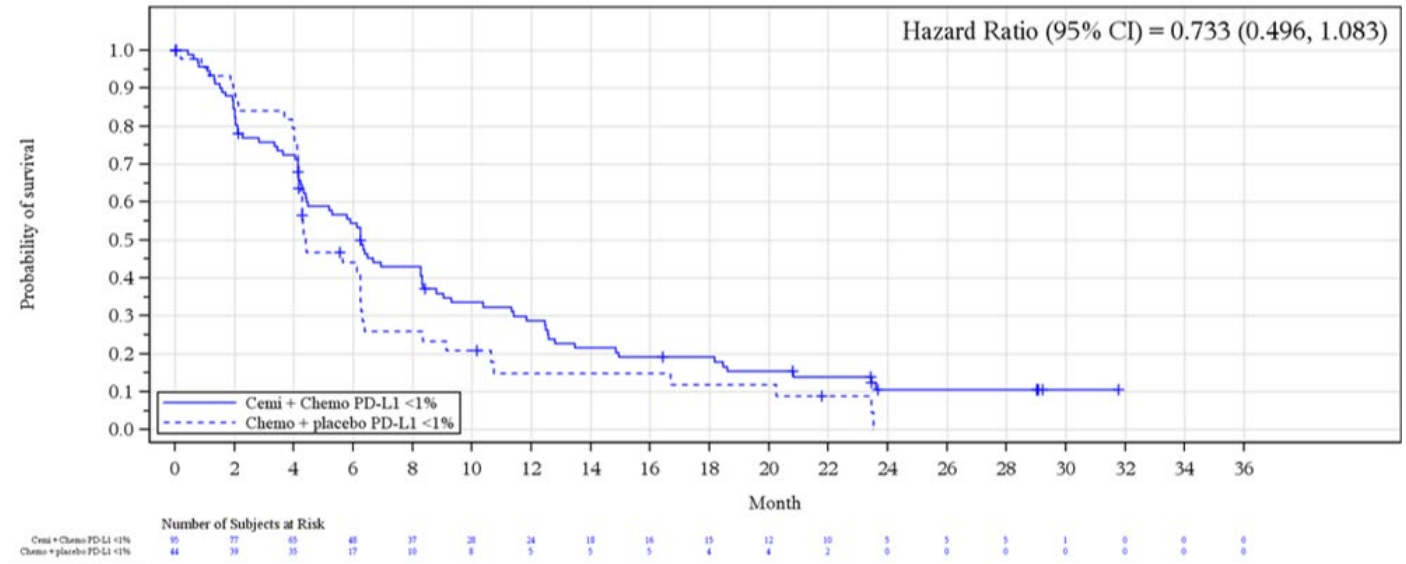
Data cutoff as of 14 Jun 2022

Figure 24: KM curve: overall survival for Study 16113 Part 2 for PD-L1≥1% subgroup (follow-up analysis), DCO 14-JUN-2022



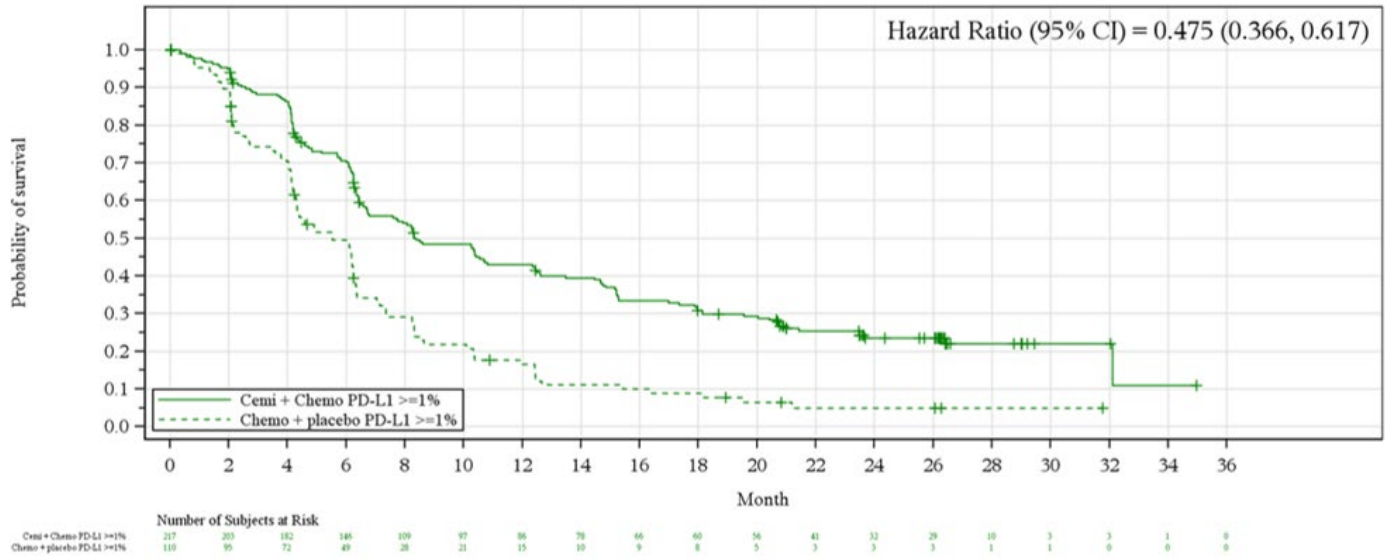
Data cutoff as of 14 Jun 2022

Figure 25: KM curve: progression free survival for Study 16113 Part 2 for PD-L1<1% subgroup (follow-up analysis), DCO 14-JUN-2022



Data cutoff as of 14 Jun 2022

Figure 26: KM curve: progression free survival for Study 16113 Part 2 for PD-L1≥1% subgroup (follow-up analysis), DCO 14-JUN-2022



Data cutoff as of 14 Jun 2022

Summary of main study

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 29: **Summary of Efficacy for trial R2810-ONC-16113 Part 2 (EMPOWER Lung-3)**

Title: A Two-Part Randomized, Phase 3 Study of Combinations of Cemiplimab (Anti-PD-1 Antibody) and Platinum-based Doublet Chemotherapy in First-line Treatment of Patients with Advanced or Metastatic Non-Small Cell Lung Cancer			
Study identifier	IND Number: 134016. EudraCT Number: 2017-001311-36. NCT 03409614		
Design	Phase III, multicentre, open-label, randomised 2:1, placebo controlled double blinded. Cross-over not allowed.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Not applicable Not applicable Not applicable
Hypothesis	Superiority		
Treatments groups	Cemiplimab+investigators choice of chemotherapy		350 mg cemiplimab administered IV over 30 minutes Q3W for up to 108 weeks plus 4 cycles of chemotherapy (**n=312**)
	Placebo+investigators choice of chemotherapy		saline placebo administered IV over 30 minutes Q3W for up to 108 weeks plus 4 cycles of chemotherapy (**n=154**)
Endpoints and definitions	Primary endpoint	IRC-OS	Time from randomization to the date of death. A patient who had not died was censored at the last known date of contact.
	Secondary endpoint	IRC-PFS	Time from randomization to the date of the first documented tumor progression or death due to any cause. PFS was assessed by BIRC using RECIST 1.1.
	Secondary endpoint	IRC-ORR	Best overall response (BOR) of confirmed complete response (CR) or partial response (PR) divided by the number of patients in the efficacy analysis set.
	Secondary endpoint	DoR	Time from the criteria are first met for CR/PR until the first date of recurrent or progressive disease (radiographic), or death due to any cause.
	Secondary endpoint	QoL by PRO	Questionnaires used: EORTC QLQ-C30 and EORTC QLQ-LC13 and defined as change in scores from baseline in the global health status (GHS)/QoL, physical functioning scales, and lung cancer symptoms.
Database lock	14th of June 2021, second prespecified IA.		
Results and Analysis			
Analysis description	**Second prespecified IA, final analysis.** **Data cut-off 14th of June 2021**		
Analysis population and time point description	ITT, n=466. Arm A: 312. Arm B: 154		
Descriptive statistics and estimate variability	Treatment group	Cemiplimab+chemotherapy	Placebo+chemotherapy
	Number of subject	n = 312	n = 154
	IRC-**OS**, patients with event (%)	132 (42.3%)	82 (53.2%)
	Median IRC-OS, months (95% CI)	21.9 (15.5-NE)	13.0 (11.9-16.1)
	IRC-**PFS**, patients with event (%)	204 (65.4%)	122 (79.2%)
	Median IRC-PFS, months (95% CI)	8.2 (6.4-9.3)	5.0 (4.3-6.2)

	ORR (= CR+PR) (%) 95% CI	135 (43.3%) 37.7%-49.0%	35 (22.7%) 16.4%-30.2%
Effect estimate per comparison	OS	Comparison groups	Cemiplimab+chemotherapy vs placebo+chemotherapy
		Stratified HR	0.706
		95% CI	(0.534-0.933)
		P-value	0.0140
	PFS	Comparison groups	Cemiplimab+chemotherapy vs placebo+chemotherapy
		Stratified HR	0.556
		95% CI	(0.442, 0.699)
		P-value	<0.0001
	ORR	Comparison groups	Cemiplimab+chemotherapy vs placebo+chemotherapy
		Stratified OR	2.68
		95% CI	1.72-4.19
		P-value	<0.0001
Analysis description	**Second prespecified IA, final analysis. Data cut-off 14th of June 2021**		
Analysis population and time point description	Patients with PD-L1 expression ⩾ 1%, n=327. Arm A: 217. Arm B: 110		
Descriptive statistics and estimate variability	Treatment group	Cemiplimab+chemotherapy	Placebo+chemotherapy
	Number of subject	n = 217	n = 110
	OS, patients with event (%)	78 (35.9%)	55 (50.0%)
	Median OS, months (95% CI)	21.9 (17.3-NE)	12.6 (10.3-16.4)
	PFS, patients with event (%)	134 (61.8%)	86 (78.2%)
	Median PFS, months (95% CI)	8.5 (6.7-10.7)	5.0 (4.3-6.2)
	ORR (= CR+PR) (%) 95% CI	104 (47.9%) 41.1%-54.8%	25 (22.7%) 15.3%-31.7%

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

Not applicable

Supportive study

As a supplement to the PD-L1 subgroups data, the Applicant presented data that recently became available (data cutoff as of 1 Feb 2022) from Study 16113 Part 1, which was carried out in in patients whose tumors express PD-L1<50%

Study 16113 Part 1 was an open-label three-arm study comparing the efficacy and safety of Arm B (cemiplimab/chemo) and Arm C (cemiplimab/2 cycles of chemotherapy/ipilimumab) versus Arm A (platinum-based doublet chemotherapy) in patients whose tumors express PD-L1 in <50% of tumor cells.

Figure 27: Study 16113 Part 1 design

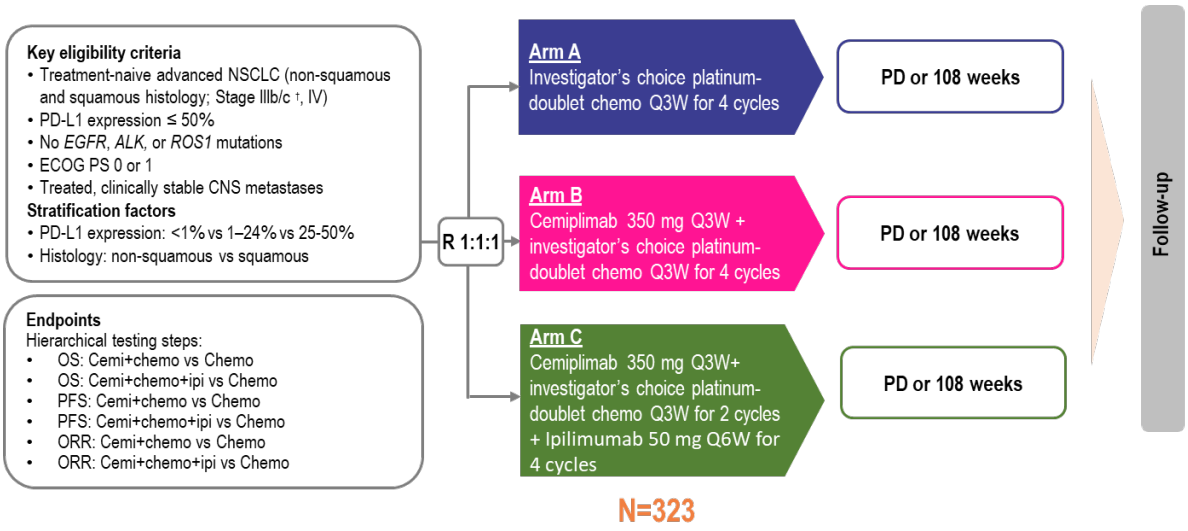


Table 30: Comparison of OS in Study 16113 Part 1 vs Study 16113 Part 2

OS in 16113 Part 1			OS in 16113 Part 2		
	mOS cemiplimab/chemo vs placebo/chemo	HR (95% CI)		mOS cemiplimab/chemo vs placebo/chemo	HR (95% CI)
ITT (N=214) Median duration of follow-up: 35.5 mo	**15.9m vs 13.9m**	**0.800 (0.582, 1.101)**	**ITT (N=466) Median duration of follow-up: 16.4 mo**	**21.9m vs 13.0m**	**0.706 (0.534, 0.933)**
PD-L1 <1% (N=104)	15.5m vs 15.8m	0.863 (0.550, 1.355)	PD-L1 <1% (N=139)	12.8m vs 14.2m	1.006 (0.633, 1.600)
PD-L1 1 to 49% (N=110)	18.0m vs 11.0m	0.746 (0.479, 1.163)	PD-L1 1 to 49% (N=175)	21.9m vs 12.1m	0.518 (0.323, 0.830)
			PD-L1 ≥50% (N=152)	17.9m vs 13.8m	0.613 (0.367, 1.024)

Data cutoff as of 14 Jun 2021 and 1 Feb 2022
Source: Study 16113 Part 1 PTT 14.2.1.2a and Study 16113 Part 2 Primary Analysis CSR PTT 14.2.1.2

Table 31: Study 16113 Part 1 Overall Survival by PD-L1 Subgroups

	Cemiplimab + chemotherapy (N=108)		Chemotherapy (N=106)		
	Event(%)	Median Time (95% CI)[a]	Event(%)	Median Time (95% CI)[a]	HR (95% CI) [b]
PD-L1 expression					
<1%	38/52 (73.1%)	15.5 (10.0, 24.8)	38/52 (73.1%)	15.8 (10.0, 21.2)	0.863 (0.550, 1.355)
1% to 49%	37/56 (66.1%)	18.0 (10.4, 25.5)	42/54 (77.8%)	11.0 (9.1, 17.7)	0.746 (0.479, 1.163)

Data cutoff as of 1 Feb 2022
[a] Based on Kaplan-Meier method.
[b] Based on unstratified proportional hazards model (cemiplimab + chemotherapy vs chemotherapy).

Table 32: Study 16113 Part 1 results for ITT and subgroups by PD-L1 <1% and PD-L1 1-49% expression

	OS			PFS			ORR[c]
	Events	mOS[a]	HR (95% CI)[b]	Events	mPFS[a]	HR (95% CI)[b]	
ITT (N=214)	75/108 vs 80/106	15.9m vs 13.9m	0.800 (0.582, 1.101)	86/108 vs 85/106	6.5m vs 6.3m	0.813 (0.600, 1.102)	39.8% vs 28.3%
PD-L1<1% (N=104)	38/52 vs 38/52	15.5m vs 15.8m	0.863 (0.550, 1.355)	42/52 vs 40/52	6.5m vs 6.2m	0.886 (0.574, 1.368)	42.3% vs 28.8%
PD-L1 1-49% (N=110)	37/56 vs 42/54	18.0m vs 11.0m	0.746 (0.479, 1.163)	44/56 vs 45/54	6.4m vs 6.4m	0.722 (0.472, 1.102)	37.5% vs 27.8%

Data cutoff as of 01 Feb 2022
HR=hazard ratio; ITT=intention to treat; mOS=median overall survival; mPFS=median progression free survival ORR=objective response rate; OS=overall survival; PFS=progression free survival
Source: 14.2.1.2c.unspd1, 14.2.2.2c.unspd1, 14.2.3.2c.unspd1,
[a] Based on Kaplan-Meier method.
[b] Based on stratified proportional hazards model for ITT population; Unstratified for subgroups.
[c] Clopper-Pearson exact confidence interval.

2.4.2. Discussion on clinical efficacy

Based on the results from study R2810-ONC-16113 Part 2 (EMPOWER Lung-3), a phase III, multicentre, double blinded, randomised 2:1, placebo controlled double blinded study of cemiplimab+chemotherapy vs placebo+chemotherapy as first line treatment of patients with metastatic or locally advanced NSCLC, the MAH seeks an extension of indication for this patient group.

The primary endpoint of the trial was OS and the secondary were ICR-PFS, ICR-ORR, ICR-DoR and QoL by PRO. The submitted data was from the second prespecified interim analysis (IA2) and since the primary endpoint was met this is considered the primary analysis. At IA2, on data cut-off 14-JUN-2021, the median follow-up for the total population was 16.43 months (range: 8.5, 24.0). During the procedure, the MAH submitted updated efficacy data (data cut-off 14-JUN-2022), for primary and secondary endpoints, from Study 16113 Part 2 with a follow up of 28.4 months.Design and conduct of clinical studies

A number of other studies have investigated the combination of an immune checkpoint inhibitor with standard chemotherapy for the treatment of metastatic NSCLC in the first line setting and both pembrolizumab and atezolizumab, a PD-1 and a PD-L1 inhibitor respectively, are currently approved for this indication in the EU. However, study 16113 Part 2 was the first study planned to include patients with both locally advanced (not able to receive definitive chemoradiation treatment) and metastatic NSCLC as well as patients with both squamous and non-squamous cell histology, regardless of PD-L1 expression.

The first patient was included in study 16113 at 31st of May 2019. At that timepoint, pembrolizumab+ platin-based chemotherapy had proven superior to chemotherapy alone and had been approved as first line treatment for advanced non-squamous NSCLC in the EU (October 10th 2018) and prior to that (August 2018), for both squamous and non-squamous NSCLC, by the FDA. Therefore, the design of the study, especially the choice of treatment in the comparator arm, was discussed with the MAH at the Scientific Advice (SA) meeting in October 2018. The CHMP considered that pembrolizumab+platin-based chemotherapy was a more appropriate comparator to cemiplimab+platin-based chemotherapy than placebo+platin-based chemotherapy. Still, the MAH chose to continue with placebo+chemotherapy as the comparator, arguing that in the countries study 16113 was conducted in, immune checkpoint inhibitors (ICIs) were not readily available or reimbursed and chemotherapy alone (+placebo) would therefore not be considered an inferior treatment.

Otherwise, study 16113 was well conducted and the results for the overall population were in line with those of Keynote-189 and 407.

Efficacy data and additional analyses

At IA2, the primary endpoint of OS was met in the ITT (PD-L1 all-comers) population (n=466) with a HR of 0.71 (0.53-0.93) and p=0.014, noting 46% of OS maturity (214 events). A remarkable difference was observed in median OS, that was 21.9 months (15.5-NE) in the cemiplimab arm compared to 13 months (11.9-16.1) in the placebo arm. The secondary endpoints of PFS, ORR and DoR were also met in the ITT population. The PFS HR was 0.56 (0.44-0.699) and p<0.0001. Median PFS was 8.2 months (6.4-9.3) vs 5 months (4.3-6.2) in the two arms respectively. A noteworthy difference in ORR with 43.3% (37.7%-49%) in the cemiplimab arm and 22.7% (16.4%-30.2%) in the placebo arm was also registered. Likewise, the difference in median DoR, 15.6 (12.4-NE) vs 7.3 months (4.3-12.6) favours cemiplimab.

These outcomes support the benefit of addition of cemiplimab to standard chemotherapy. Though, from the subgroup analyses the benefit from the addition of cemiplimab to chemotherapy in the PD-L1 negative patients (<1% expression) is uncertain as the cemiplimab arm performed inferior to the placebo arm (OS HR of 1.006 (0.633-1.600), median OS 12.8 months in the cemiplimab arm vs 14.2 months in the placebo arm, PFS HR of 0.764 (0.509-1.146)).

In the supplementary data from Part 1 of study 16113, similar results were observed within the PD-L1 negative patient group with a shorter median OS in the cemiplimab arm than in the placebo arm (OS HR 0.863 (0.550, 1.355), median OS 15.5 months in the cemiplimab arm vs 15.8 months in the placebo arm, PFS HR of 0.886 (0.574-1.368)). Overall, neither in the initially submitted data from Part 2 nor in the subsequently provided data from Part 1 was efficacy from added cemiplimab in the PD-L1 negative patients (PD-L1<1%) considered established and a PD-L1 unrestricted indication was not deemed justified.

During the procedure, the MAH submitted updated results with an additional 12 months of follow up from study 16113 Part 2 (DCO 14-JUN-2022). These results showed consistency over time. For all-comers, with OS maturity of 65% (291 deaths), HR for OS was 0.55 (95% CI 0.44, 0.68). The uncertain treatment effect in the PD-L1 negative patient group was consistently present and with largely unchanged data outcome [OS HR 0.939 (0.62-1.42)], mOS unchanged 12.8 months in the cemiplimab arm vs 14.2 months in the control arm).

Furthermore, the MAH presented OS, PFS and ORR data (tables and K-M plots) for the two PD-L1 subgroups: <1% and ≥1% for both initial and updated data of part 2. With regards to the primary endpoint of OS, the data confirms that in patients with PD-L1 <1%, the median OS was shorter in the cemiplimab arm compared to the placebo arm and that the HRs, and their 95% CI, are reflective (distinctly crossing 1) of this finding. The OS K-M curves, for both initial and updated cut-off, for the PD-L1 negative (<1%) patients, were superposed curves for the cemiplimab arm and the placebo arm, whereas the curves showed a clear separation in the PD-L1 positive (≥1%) patient population.
In the provided data on the PD-L1 positive (≥1%) patients, the baseline patient and tumour characteristics were equivalent to those of the whole ITT population.

At IA2, the HR for OS in patients whose tumours expressed PD-L1 ≥1% was 0.55 (0.39-0.78). The median OS was 21.9 months (17.3-NE) in the cemiplimab arm compared to 12.6 months (10.3-16.4) in the placebo arm. The PFS HR was 0.48 (0.36-0.63) with a median PFS of 8.5 months (6.7-10.7) vs 5.5 months (4.3-6.2) in the two arms respectively. A noteworthy difference in ORR with 47.9% (41.1-54.8) in the cemiplimab arm and 22.7% (15.3-31.7) in the placebo arm was also registered. Likewise, the difference in median DoR, 15.6 (1.7-18.7+) vs 4.9 months (1.9-18.8+) favours cemiplimab.

It was also argued that subgroup analyses from trials Keynote-407, Keynote-189 and IMpower130 did not suggest that overall survival, in similar populations, was driven by PD-L1 expression, and thus the subgroup of PD-L1 <1% patients also showed efficacy benefits in terms of survival. However, published results of the chemotherapy + anti-PD-L1 agent arm from other trials in the same setting, namely IMpower150 (Socinski et al, Journal of Thoracic Oncology 2021) and Poseidon (Johnson et al, JCO 2022) showed outcomes comparable to that of Study 16113 Part 2: HR for OS closely approaching 1 in the PD-L1 <1% subgroup. As discussed above, the external evidence does not consistently show a benefit from the addition of anti PD-1/PD-L1 to chemotherapy in patients with PD-L1 negative tumours and despite the limitations of subgroup analyses, the data available support a restriction of indication to patients with NSCLC expressing PD-L1 (in ≥ 1% of tumour cells).

2.4.3. Conclusions on the clinical efficacy

Cemiplimab in combination with standard chemotherapy for either non-squamous or squamous cell histology showed efficacy in patients with locally advanced (not candidates for definitive chemoradiation) or metastatic NSCLC in first line treatment in the ITT population with regards to the primary endpoint of OS and the secondary endpoints of PFS, ORR and DoR. Nevertheless, within the subgroup of PD-L1 negative patients (<1% expression), the OS and PFS data suggested uncertain benefit from the addition of cemiplimab, also after additional 12 months of follow-up time, justifying that these patients are excluded from the sought indication. Hence, the data did not support an indication statement regardless of PD-L1 expression and despite an oral explanation from the MAH, the CHMP considered by majority that efficacy of cemiplimab as addition to platinum-based chemotherapy was only established in patients whose tumours expressed PD-L1 ≥1%.

2.5. Clinical safety

Introduction

The evaluation of safety is based on data from 465 patients, of which 312 patients were treated with platinum-based doublet chemo and cemiplimab in study 16113 Part 2 per data cut-off of 14 June 2021.

Table 33: Description of Safety Assessment in Clinical Study

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-16113 Part 2 Ongoing 74 centers 10 countries	Adult patients, with histologically or cytologically documented stage IIIB or IIIC squamous or non-squamous NSCLC, who were not eligible for definitive concurrent chemoradiation, or patients with stage IV disease who had not received prior systemic treatment for recurrent or metastatic NSCLC.	Phase 3 Randomized, multicenter, double-blind, placebo controlled, pivotal study	Placebo or cemiplimab 350 mg administered IV over 30 minutes Q3W for 108 weeks, and platinum-based doublet chemo administered intravenously over 30 minutes Q3W for 4 cycles (followed by pemetrexed maintenance for those patients initially assigned to receive a pemetrexed-containing regimen): - Cemiplimab/chemo (N=312) - Placebo/chemo (N=153) Treatment duration: 108 weeks, or until disease progression or unacceptable toxicity.	Safety is assessed through AEs, laboratory data, vital signs, physical examination assessment, ECG results, ECOG performance status, and immunogenicity.

Abbreviations: AE, adverse event; chemo, chemotherapy; CSR, clinical study report; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; IV, intravenously; N, total number of patients (SAF); NSCLC, non-small cell lung cancer; PTT, post-text table; Q3W, every 3 weeks; SAF, Safety Analysis Set
Data cutoff as of 14 Jun 2021.
Source: Study 16113 Part 2 Primary Analysis CSR; Study 16113 Part 2 Primary Analysis CSR PTT 14.1.1.4

Patient exposure

Table 34: Treatment Exposure in Study 16113 Part 2 – SAF

	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=153)
Duration of Exposure (weeks)		
n	312	153
Mean (SD)	41.98 (25.500)	28.31 (20.821)
Median	38.45	21.30
Q1 : Q3	20.65 : 63.85	12.00 : 38.40
Min : Max	1.4 : 102.6	0.6 : 95.0
Duration of Exposure, n (%)		
<6 weeks	22 (7.1%)	12 (7.8%)
6 to 12- weeks	22 (7.1%)	25 (16.3%)
12 to 18- weeks	20 (6.4%)	18 (11.8%)
18 to 36- weeks	69 (22.1%)	52 (34.0%)
36 to 54- weeks	72 (23.1%)	25 (16.3%)
54 to 72- weeks	58 (18.6%)	13 (8.5%)
72 to 96- weeks	45 (14.4%)	8 (5.2%)
96 to 108- weeks	4 (1.3%)	0
≥108 weeks	0	0
Duration of Exposure, n (%)		
≥0 weeks	312 (100%)	153 (100%)
≥6 weeks	290 (92.9%)	141 (92.2%)
≥12 weeks	268 (85.9%)	116 (75.8%)
≥24 weeks	224 (71.8%)	72 (47.1%)
≥36 weeks	179 (57.4%)	46 (30.1%)
≥48 weeks	119 (38.1%)	28 (18.3%)
≥60 weeks	87 (27.9%)	14 (9.2%)
≥72 weeks	49 (15.7%)	8 (5.2%)
≥84 weeks	12 (3.8%)	3 (2.0%)
≥96 weeks	4 (1.3%)	0
≥108 weeks	0	0

Abbreviations: CSR, clinical study report; Max, maximum; Min, minimum; N, number of patients, Q1, quarter 1; Q3, quarter 3; SAF=Safety Analysis Set; SD, standard deviation
Data cutoff as of 14 Jun 2021.
Duration of Exposure (weeks) = [min (date of last dose of any other drug + 20, date of clinical data cutoff, date of death) - date of first dose of any study drug + 1]/7 Source: Study 16113 Part 2 Primary Analysis CSR Table 12

Adverse events

Table 35: **Summary of Treatment-Emergent Adverse Events in Study 16113 Part 2 – SAF**

	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=153)
Number of TEAEs	3095	1086
Number of NCI grade 3/4/5 TEAE	332	107
Number of serious TEAEs	130	49
Number of patients with any TEAE, n (%)	299 (95.8%)	144 (94.1%)
Number of patients with any TEAE, nP (nP/100PY)*	299/30.3 (985.56)	144/13.0 (1107.05)
Number of patients with any NCI grade 3/4/5 TEAE, n (%)	136 (43.6%)	48 (31.4%)
Number of patients with any NCI grade 3/4/5 TEAE, nP (nP/100PY)*	136/198.6 (68.47)	48/66.8 (71.91)
Number of patients with any serious TEAE, n (%)	79 (25.3%)	34 (22.2%)

	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=153)
Number of patients with any serious TEAE, nP (nP/100PY)*	79/225.7 (35.00)	34/75.9 (44.82)
Number of patients with any TEAE leading to permanent treatment discontinuation, n (%)	16 (5.1%)	4 (2.6%)
Number of patients with any TEAE leading to permanent treatment discontinuation, nP (nP/100PY)*	16/249.9 (6.40)	4/83.0 (4.82)
Number of patients with any NCI grade 3/4/5 TEAE leading to permanent treatment discontinuation, n (%)	13 (4.2%)	4 (2.6%)
Number of patients with any NCI grade 3/4/5 TEAE leading to permanent treatment discontinuation, nP (nP/100PY)*	13/250.3 (5.19)	4/83.0 (4.82)
Number of patients with any TEAE leading to a dose delay, n (%)	103 (33.0%)	39 (25.5%)
Number of patients with any TEAE leading to a dose delay, nP (nP/100PY)*	103/200.7 (51.31)	39/64.9 (60.11)
Number of patients with any TEAE leading to an infusion interruption, n (%)	5 (1.6%)	3 (2.0%)
Number of patients with any TEAE leading to a dose modification, n (%)	13 (4.2%)	8 (5.2%)
Number of patients with any TEAE resulting in death, n (%)	19 (6.1%)	12 (7.8%)

Abbreviations: CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; N, number of patients, NCI, National Cancer Institute; nP, number of patients with an event; PY, patient-years; nP/100PY, number of patients with at least one event per 100 patient-year; SAF, Safety Analysis Set; TEAE, treatment-emergent adverse event.
NCI grades were coded using CTCAE Version 4.03.
Data cutoff as of 14 Jun 2021.
A patient is counted only once for multiple occurrences within a category.
*All TEAEs by exposure-adjusted rates are presented in PTTs 14.3.1.2.2.py, 14.3.2.1.2.py, 14.3.1.2.10.py, and 14.3.1.2.6.py.
Source: Study 16113 Part 2 Primary Analysis CSR Table 25

Table 36: Summary of Treatment-Emergent Adverse Events Experienced by ≥5% Patients in Either Arm by System Organ Class, Preferred Term, and NCI Grade in Study 16113 Part 2 – SAF

	Cemiplimab + chemotherapy (N=312)		Placebo + chemotherapy (N=153)	
System Organ Class, n (%) Preferred Term, n (%)	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Number of patients with any TEAE, n (%)	299 (95.8%)	136 (43.6%)	144 (94.1%)	48 (31.4%)
Number of patients with any TEAE, nP (nP/100PY)*	299/30.3 (985.56)	136/198.6 (68.47)	144/13.0 (1107.05)	48/66.8 (71.91)
Blood and lymphatic system disorders	173 (55.4%)	46 (14.7%)	77 (50.3%)	20 (13.1%)
Anaemia	136 (43.6%)	31 (9.9%)	61 (39.9%)	10 (6.5%)
Neutropenia	48 (15.4%)	18 (5.8%)	19 (12.4%)	9 (5.9%)
Thrombocytopenia	41 (13.1%)	8 (2.6%)	19 (12.4%)	2 (1.3%)
Leukopenia	18 (5.8%)	3 (1.0%)	10 (6.5%)	2 (1.3%)
Investigations	161 (51.6%)	32 (10.3%)	64 (41.8%)	8 (5.2%)
Alanine aminotransferase increased	51 (16.3%)	7 (2.2%)	22 (14.4%)	3 (2.0%)
Aspartate aminotransferase increased	46 (14.7%)	1 (0.3%)	18 (11.8%)	3 (2.0%)
Weight decreased	35 (11.2%)	4 (1.3%)	13 (8.5%)	0
Blood creatinine increased	31 (9.9%)	1 (0.3%)	8 (5.2%)	0
Weight increased	24 (7.7%)	0	2 (1.3%)	0
White blood cell count decreased	23 (7.4%)	10 (3.2%)	6 (3.9%)	3 (2.0%)
Amylase increased	22 (7.1%)	3 (1.0%)	5 (3.3%)	0
Blood lactate dehydrogenase increased	22 (7.1%)	0	6 (3.9%)	0
Blood urea increased	21 (6.7%)	0	7 (4.6%)	0
Blood alkaline phosphatase increased	17 (5.4%)	0	14 (9.2%)	0
Platelet count decreased	17 (5.4%)	3 (1.0%)	6 (3.9%)	0

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab + chemotherapy (N=312)		Placebo + chemotherapy (N=153)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Skin and subcutaneous tissue disorders	147 (47.1%)	4 (1.3%)	80 (52.3%)	1 (0.7%)
Alopecia	115 (36.9%)	0	66 (43.1%)	0
Rash	20 (6.4%)	2 (0.6%)	6 (3.9%)	0
Gastrointestinal disorders	139 (44.6%)	11 (3.5%)	55 (35.9%)	3 (2.0%)
Nausea	78 (25.0%)	0	25 (16.3%)	0
Constipation	43 (13.8%)	1 (0.3%)	17 (11.1%)	0
Vomiting	38 (12.2%)	0	15 (9.8%)	0
Diarrhoea	33 (10.6%)	4 (1.3%)	10 (6.5%)	0
Metabolism and nutrition disorders	139 (44.6%)	26 (8.3%)	56 (36.6%)	10 (6.5%)
Hyperglycaemia	55 (17.6%)	6 (1.9%)	18 (11.8%)	0
Decreased appetite	53 (17.0%)	3 (1.0%)	18 (11.8%)	0
Hypoalbuminaemia	32 (10.3%)	2 (0.6%)	9 (5.9%)	0
Hypokalaemia	20 (6.4%)	3 (1.0%)	7 (4.6%)	2 (1.3%)
Hypocalcaemia	19 (6.1%)	1 (0.3%)	11 (7.2%)	1 (0.7%)
General disorders and administration site conditions	111 (35.6%)	24 (7.7%)	44 (28.8%)	3 (2.0%)
Asthenia	38 (12.2%)	6 (1.9%)	18 (11.8%)	2 (1.3%)
Fatigue	38 (12.2%)	7 (2.2%)	11 (7.2%)	1 (0.7%)
Pyrexia	19 (6.1%)	1 (0.3%)	8 (5.2%)	0
Non-cardiac chest pain	14 (4.5%)	1 (0.3%)	9 (5.9%)	0
Respiratory, thoracic and mediastinal disorders	105 (33.7%)	15 (4.8%)	38 (24.8%)	6 (3.9%)
Dyspnoea	39 (12.5%)	7 (2.2%)	10 (6.5%)	1 (0.7%)
Haemoptysis	22 (7.1%)	1 (0.3%)	12 (7.8%)	0
Cough	20 (6.4%)	1 (0.3%)	8 (5.2%)	0
Nervous system disorders	102 (32.7%)	4 (1.3%)	39 (25.5%)	1 (0.7%)
Peripheral sensory neuropathy	28 (9.0%)	0	15 (9.8%)	0
Neuropathy peripheral	18 (5.8%)	0	6 (3.9%)	0
Musculoskeletal and connective tissue disorders	89 (28.5%)	5 (1.6%)	51 (33.3%)	1 (0.7%)
Arthralgia	48 (15.4%)	2 (0.6%)	20 (13.1%)	0
Back pain	15 (4.8%)	0	12 (7.8%)	0
Pain in extremity	15 (4.8%)	0	15 (9.8%)	0
Infections and infestations	69 (22.1%)	20 (6.4%)	27 (17.6%)	8 (5.2%)
Pneumonia	25 (8.0%)	9 (2.9%)	7 (4.6%)	5 (3.3%)
Psychiatric disorders	45 (14.4%)	0	13 (8.5%)	0
Insomnia	34 (10.9%)	0	11 (7.2%)	0
Endocrine disorders	41 (13.1%)	2 (0.6%)	7 (4.6%)	0
Hypothyroidism	28 (9.0%)	1 (0.3%)	4 (2.6%)	0
Hyperthyroidism	18 (5.8%)	1 (0.3%)	4 (2.6%)	0

Abbreviations: CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients, NCI, National Cancer Institute; nP, number of patients with an event; PT, preferred term; PY, patient-years; nP/100PY, number of patients with at least one event per 100 patient-year; SAF, Safety Analysis Set; SOC, system organ class; TEAE, treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 23.1.
NCI grades were coded using CTCAE Version 4.03.
Data cutoff as of 14 Jun 2021.
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 cemiplimab/chemotherapy arm.

Within each SOC, PTs are sorted by decreasing frequency of all grades in the cemiplimab/chemotherapy arm.
*All TEAEs by exposure-adjusted rates are presented in PTT 14.3.1.2.2.py. Source: Study 16113 Part 2 Primary Analysis CSR Table 26

Adverse events of special interest

Infusion-related reactions (IRR)

Table 37: Summary of Sponsor-Identified Infusion Reactions by System Organ Class, Preferred Term, and NCI Grade in Study 16113 Part 2 - SAF

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab + chemotherapy (N=312)	
	All Grades	Grades 3/4/5
Number of Patients with any sponsor-identified infusion reactions, n (%)	7 (2.2%)	0
Gastrointestinal disorders	3 (1.0%)	0
Vomiting	2 (0.6%)	0
Nausea	1 (0.3%)	0
Skin and subcutaneous tissue disorders	2 (0.6%)	0
Pruritus	2 (0.6%)	0
Immune system disorders	1 (0.3%)	0
Hypersensitivity	1 (0.3%)	0
Vascular disorders	1 (0.3%)	0
Flushing	1 (0.3%)	0

Abbreviations: CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients, NCI, National Cancer Institute; PT, preferred term; SAF, Safety Analysis Set; SOC, system organ class; TEAE, treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 23.1.
NCI grades were coded using CTCAE Version 4.03.
Data cutoff as of 14 Jun 2021.
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 cemiplimab/chemotherapy arm.
Within each SOC, PTs are sorted by decreasing frequency of all grades in the cemiplimab/chemotherapy arm.
Source: Study 16113 Part 2 Primary Analysis CSR PTT 14.3.2.8.2

Immune-mediated Adverse events

Table 38: Summary of Treatment-Emergent Sponsor-Identified Immune-Mediated Adverse Events (imAEs Requiring Systemic Corticosteroids and Endocrine-Related imAEs Based on Sponsor-Provided List) in Study 16113 Part 2 - SAF

	Cemiplimab + chemotherapy (N=312)
Number of treatment-emergent sponsor-identified imAEs	98
Number of NCI grade 3/4/5 treatment-emergent sponsor-identified imAE	11
Number of serious treatment-emergent sponsor-identified imAEs	10
Number of patients with any treatment-emergent sponsor-identified imAE, n (%)	59 (18.9%)
Number of patients with any NCI grade 3/4/5 treatment-emergent sponsor-identified imAE, n (%)	9 (2.9%)
Number of patients with any serious treatment-emergent sponsor-identified imAE, n (%)	8 (2.6%)
Number of patients with any treatment-emergent sponsor-identified imAE leading to permanent treatment discontinuation, n (%)	3 (1.0%)
Number of patients with any NCI grade 3/4/5 treatment-emergent sponsor-identified imAE leading to permanent treatment discontinuation, n (%)	3 (1.0%)
Number of patients with any treatment-emergent sponsor-identified imAE leading to a dose delay, n (%)	13 (4.2%)

	Cemiplimab + chemotherapy (N=312)
Number of patients with any treatment-emergent sponsor-identified imAE leading to an infusion interruption, n (%)	0
Number of patients with any treatment-emergent sponsor-identified imAE leading to a dose modification, n (%)	0
Number of patients with any treatment-emergent sponsor-identified imAE resulting in death, n (%)	1 (0.3%)

Abbreviations: CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; imAE, immune-mediated adverse reaction; N, number of patients, NCI, National Cancer Institute; SAF, Safety Analysis Set.
NCI grades were coded using CTCAE Version 4.03.
Data cutoff as of 14 Jun 2021.
A patient is counted only once for multiple occurrences within a category. Source: Study 16113 Part 2 Primary Analysis CSR PTT 14.3.2.7.1

Table 39: Summary of Treatment-Emergent Sponsor-Identified Immune-Mediated Adverse Events by Composite, Preferred Term, and NCI Grade in Study 16113 Part 2 - SAF

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab + chemotherapy (N=312)	
	All Grades	Grades 3/4/5
Number of patients with any treatment-emergent sponsor-identified imAEs, n (%)	59 (18.9%)	9 (2.9%)
Hypothyroidism*	24 (7.7%)	1 (0.3%)
Hypothyroidism	24 (7.7%)	1 (0.3%)
Hyperthyroidism*	16 (5.1%)	0
Hyperthyroidism	16 (5.1%)	0
Immune-mediated pneumonitis*	6 (1.9%)	2 (0.6%)
Pneumonitis	5 (1.6%)	1 (0.3%)
Immune-mediated pneumonitis	1 (0.3%)	1 (0.3%)
Immune-mediated skin reaction*	6 (1.9%)	3 (1.0%)
Dermatitis	2 (0.6%)	0
Rash	2 (0.6%)	1 (0.3%)
Psoriasis	1 (0.3%)	1 (0.3%)
Rash maculo-papular	1 (0.3%)	1 (0.3%)
Immune-mediated hepatitis*	2 (0.6%)	2 (0.6%)
Alanine aminotransferase increased	2 (0.6%)	2 (0.6%)
Aspartate aminotransferase increased	1 (0.3%)	0
Blood bilirubin increased	1 (0.3%)	1 (0.3%)
Gamma-glutamyltransferase increased	1 (0.3%)	1 (0.3%)
Immune-mediated nephritis*	2 (0.6%)	0
Blood creatinine increased	1 (0.3%)	0
Immune-mediated nephritis	1 (0.3%)	0
Pruritus*	2 (0.6%)	0
Pruritus	2 (0.6%)	0
Thyroiditis*	2 (0.6%)	0
Autoimmune thyroiditis	1 (0.3%)	0
Immune-mediated thyroiditis	1 (0.3%)	0
Arthritis*	1 (0.3%)	0
Autoimmune arthritis	1 (0.3%)	0
Immune-mediated colitis*	1 (0.3%)	1 (0.3%)

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab + chemotherapy (N=312)	
	All Grades	Grades 3/4/5
Colitis	1 (0.3%)	1 (0.3%)
Type 1 diabetes mellitus*	1 (0.3%)	0
Diabetes mellitus	1 (0.3%)	0
Other imAEs		
Blood thyroid stimulating hormone increased	13 (4.2%)	0
Blood thyroid stimulating hormone decreased	5 (1.6%)	0
Blood alkaline phosphatase increased	1 (0.3%)	0

Abbreviations: CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; imAE, immune-mediated adverse reaction; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients, NCI, National Cancer Institute; PT, preferred term; SAF, Safety Analysis Set; SOC, system organ class; TEAE, treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 23.1.
NCI grades were coded using CTCAE Version 4.03.
Data cutoff as of 14 Jun 2021.
* Each composite term includes multiple MedDRA preferred terms based on Regeneron defined list.
A patient is counted only once for multiple occurrences within a composite term/PT.
For composite terms, the table is sorted by decreasing frequency of all grades in the cemiplimab/chemotherapy arm. Within each composite term, PTs are sorted by decreasing frequency of all grades in the cemiplimab/chemotherapy arm. Source: Study 16113 Part 2 Primary Analysis CSR PTT 14.3.2.7.6

Table 40: **Treatment-Related Treatment-Emergent Adverse Events Experienced by ≥5% of Patients in Either Arm by System Organ Class, Preferred Term, and NCI Grade in Study 16113 Part 2 – SAF**

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab + chemotherapy (N=312)		Placebo + chemotherapy (N=153)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Number of patients with any treatment-related TEAE, n (%)	275 (88.1%)	90 (28.8%)	129 (84.3%)	28 (18.3%)
Number of patients with any treatment-related TEAE, n (nP/100PY)*	275/39.4 (697.62)	90/209.8 (42.89)	129/17.9 (722.21)	28/69.8 (40.14)
Blood and lymphatic system disorders	161 (51.6%)	45 (14.4%)	68 (44.4%)	20 (13.1%)
Anaemia	127 (40.7%)	30 (9.6%)	52 (34.0%)	10 (6.5%)
Neutropenia	45 (14.4%)	17 (5.4%)	19 (12.4%)	9 (5.9%)
Thrombocytopenia	39 (12.5%)	7 (2.2%)	19 (12.4%)	1 (0.7%)
Leukopenia	18 (5.8%)	3 (1.0%)	10 (6.5%)	2 (1.3%)
Skin and subcutaneous tissue disorders	142 (45.5%)	3 (1.0%)	75 (49.0%)	0
Alopecia	114 (36.5%)	0	65 (42.5%)	0
Rash	16 (5.1%)	1 (0.3%)	4 (2.6%)	0
Investigations	132 (42.3%)	27 (8.7%)	47 (30.7%)	5 (3.3%)
Alanine aminotransferase increased	45 (14.4%)	6 (1.9%)	19 (12.4%)	1 (0.7%)
Aspartate aminotransferase increased	39 (12.5%)	1 (0.3%)	15 (9.8%)	1 (0.7%)
Blood creatinine increased	27 (8.7%)	0	7 (4.6%)	0
White blood cell count decreased	23 (7.4%)	10 (3.2%)	5 (3.3%)	2 (1.3%)
Blood urea increased	21 (6.7%)	0	6 (3.9%)	0
Amylase increased	18 (5.8%)	1 (0.3%)	4 (2.6%)	0
Blood lactate dehydrogenase increased	18 (5.8%)	0	5 (3.3%)	0
Platelet count decreased	16 (5.1%)	3 (1.0%)	6 (3.9%)	0
Weight decreased	16 (5.1%)	0	6 (3.9%)	0
Blood alkaline phosphatase increased	14 (4.5%)	0	10 (6.5%)	0
Gastrointestinal disorders	118 (37.8%)	7 (2.2%)	39 (25.5%)	1 (0.7%)
Nausea	71 (22.8%)	0	25 (16.3%)	0

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab + chemotherapy (N=312)		Placebo + chemotherapy (N=153)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Vomiting	33 (10.6%)	0	14 (9.2%)	0
Constipation	28 (9.0%)	0	12 (7.8%)	0
Diarrhoea	26 (8.3%)	3 (1.0%)	4 (2.6%)	0
Metabolism and nutrition disorders	104 (33.3%)	11 (3.5%)	40 (26.1%)	3 (2.0%)
Decreased appetite	42 (13.5%)	1 (0.3%)	16 (10.5%)	0
Hyperglycaemia	33 (10.6%)	2 (0.6%)	12 (7.8%)	0
Hypoalbuminaemia	18 (5.8%)	0	4 (2.6%)	0
Hypokalaemia	17 (5.4%)	3 (1.0%)	4 (2.6%)	1 (0.7%)
Nervous system disorders	78 (25.0%)	1 (0.3%)	34 (22.2%)	0
Peripheral sensory neuropathy	28 (9.0%)	0	15 (9.8%)	0
Neuropathy peripheral	17 (5.4%)	0	6 (3.9%)	0
General disorders and administration site conditions	65 (20.8%)	8 (2.6%)	23 (15.0%)	2 (1.3%)
Asthenia	28 (9.0%)	2 (0.6%)	10 (6.5%)	1 (0.7%)
Fatigue	26 (8.3%)	3 (1.0%)	9 (5.9%)	1 (0.7%)
Musculoskeletal and connective tissue disorders	53 (17.0%)	3 (1.0%)	26 (17.0%)	1 (0.7%)
Arthralgia	29 (9.3%)	1 (0.3%)	11 (7.2%)	0
Endocrine disorders	36 (11.5%)	1 (0.3%)	5 (3.3%)	0
Hypothyroidism	24 (7.7%)	1 (0.3%)	3 (2.0%)	0
Hyperthyroidism	16 (5.1%)	0	2 (1.3%)	0
Psychiatric disorders	35 (11.2%)	0	8 (5.2%)	0
Insomnia	27 (8.7%)	0	8 (5.2%)	0

Abbreviations: CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients, NCI, National Cancer Institute; nP, number of patients with an event; PT, preferred term; PY, patient-years; nP/100PY, number of patients with at least one event per 100 patient-year; SAF, Safety Analysis Set; SOC, system organ class; TEAE, treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 23.1.
NCI grades were coded using CTCAE Version 4.03.
Data cutoff as of 14 Jun 2021.
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 cemiplimab/chemotherapy arm.
Within each SOC, PTs are sorted by decreasing frequency of all grades in the cemiplimab/chemotherapy arm.
*All TEAEs by exposure-adjusted rates are presented in PTT 14.3.1.3.2.py. Source: Study 16113 Part 2 Primary Analysis CSR Table 28

Adverse drug reactions

Adverse reactions known to occur with cemiplimab or combination therapy components given alone may occur during treatment with these medicinal products in combination.

Table 41: Tabulated list of adverse reactions in patients treated with cemiplimab monotherapy and cemiplimab in combination with chemotherapy

	Cemiplimab Monotherapy			**Cemiplimab in Combination with Chemotherapy**		
System organ class Preferred term	Any Grade %		Grade 3-5 (%)	Any Grade %		Grade 3-5 (%)
Infections and infestations						
Upper respiratory tract infection[a]	Very Common	10.9	0.4			
Urinary tract infection[b]	Common	8.4	2.3			
Blood and lymphatic system disorders						

Anaemia	Very Common	15.0	5.2	Very common	43.6	9.9
Neutropaenia				Very common	15.4	5.8
Thrombocytopaenia				Very common	13.1	2.6
Immune system disorders						
Infusion-related reaction	Common	3.3	< 0.1	Uncommon	0.3	0
Thrombocytopenia[c]	Uncommon	0.9	0			
Sjogren's syndrome	Uncommon	0.2	0			
Solid organ transplant rejection[d]	Not known	--	--			
Endocrine disorders						
Hypothyroidism[e]	Common	6.8	< 0.1	Common	7.7	0.3
Hyperthyroidism	Common	3.0	< 0.1	Common	5.1	0
Thyroiditis[f]	Uncommon	0.6	0	Uncommon	0.6	0
Hypophysitis[g]	Uncommon	0.5	0.2			
Adrenal insufficiency	Uncommon	0.5	0.5			
Type 1 diabetes mellitus[h]	Rare	< 0.1	< 0.1	Uncommon	0.3	0
Nervous system disorders						
Headache	Common	8.0	0.3			
Peripheral neuropathy[i]	Common	1.3	< 0.1	Very common	21.2	0
Meningitis[j]	Rare	< 0.1	< 0.1			
Encephalitis	Rare	< 0.1	< 0.1			
Myasthenia Gravis	Rare	< 0.1	0			
Paraneoplastic encephalomyelitis	Rare	< 0.1	< 0.1			
Chronic inflammatory demyelinating polyradiculoneuropathy	Rare	< 0.1	0			
Eye disorders						
Keratitis	Uncommon	< 0.1	0			
Cardiac disorders						
Myocarditis[k]	Uncommon	0.5	0.3			
Pericarditis[l]	Uncommon	0.3	0.2			
Vascular disorders						
Hypertension[m]	Common	5.7	2.6			
Metabolism and nutrition disorders						
Decreased appetite	Very common	13.0	0.6	Very common	17.0	1.0
Hyperglycaemia				Very common	17.6	1.9
Hypoalbuminaemia				Very common	10.3	0.6
Respiratory, thoracic and mediastinal disorders						
Cough[n]	Very common	10.8	0.2			
Dyspnoea[o]	Common	9.7	1.2	Very common	12.8	2.2
Pneumonitis[p]	Common	3.3	1.1	Common	4.2	0.6
Gastrointestinal disorders						
Nausea	Very common	14.7	0.2	Very common	25.0	0
Diarrhoea	Very common	16.3	0.7	Very common	10.6	1.3
Constipation	Very common	12.3	0.2	Very common	13.8	0.3
Abdominal pain[q]	Very common	11.5	0.7			
Vomiting	Common	9.9	0.2	Very common	12.2	0
Colitis[r]	Common	2.0	0.8	Common	1.0	0.3
Stomatitis	Common	1.8	< 0.1			
Gastritis[s]	Uncommon	0.2	0			
Hepatobiliary disorders						
Hepatitis[t]	Common	2.7	1.8			
Psychiatric Disorders						
Insomnia				Very common	10.9	0
Skin and subcutaneous skin disorders						
Rash[u]	Very common	21.4	1.6	Very common	12.5	1.3

Pruritus[v]	Very common	12.7	0.2	Common	3.5	0
Actinic keratosis	Common	3.7	0			
Alopecia				Very common	36.9	0
Musculoskeletal and connective tissue disorders						
Musculoskeletal pain[w]	Very common	28.3	1.8	Very common	26.9	1.3
Arthritis[x]	Uncommon	0.9	0.2	Common	1.0	0
Myositis[y]	Uncommon	0.3	< 0.1			
Muscular weakness	Uncommon	0.2	0			
Polymyalgia rheumatica	Uncommon	0.2	0			
Renal and urinary disorders						
Nephritis[z]	Common	1.2	0.2	Common	2.6	0
Noninfective cystitis	Not known	--	--			
General disorders and administration site conditions						
Fatigue[aa]	Very common	29.9	2.6	Very common	23.4	3.8
Pyrexia[bb]	Common	8.7	0.2			
Oedema[cc]	Common	7.9	0.4			
Investigations						
Alanine aminotransferase increased	Common	4.6	0.5	Very common	16.3	2.2
Aspartate aminotransferase increased	Common	4.4	0.7	Very common	14.7	0.3
Blood alkaline phosphatase increased	Common	1.9	0.2	Common	4.5	0
Blood creatinine increased	Common	1.6	0	Common	8.7	0
Blood thyroid stimulating hormone increased	Uncommon	0.8	0	Common	4.2	0
Transaminases increased	Uncommon	0.4	< 0.1			
Blood bilirubin increased	Uncommon	0.4	< 0.1	Common	1.6	0.3
Blood thyroid stimulating hormone decreased	Rare	< 0.1	0	Common	1.6	0
Weight decreased				Very common	11.2	1.3
Gamma-glutamyltransferase increased				Uncommon	0.6	0.3

Version 4.03 of NCI CTCAE was used to grade toxicity.

a. Upper respiratory tract infection includes upper respiratory tract infection, nasopharyngitis, sinusitis, respiratory tract infection, rhinitis, viral upper respiratory tract infection, viral respiratory tract infection, pharyngitis, laryngitis, viral rhinitis, acute sinusitis, tonsillitis, and tracheitis.
b. Urinary tract infection includes urinary tract infection, cystitis, pyelonephritis, kidney infection, pyelonephritis acute, urosepsis, bacterial cystitis, escherichia urinary tract infection, pyelocystitis, bacterial urinary tract infection, and urinary tract infection pseudomonal.
c. Thrombocytopenia includes thrombocytopenia and immune thrombocytopenia.
d. Post-marketing event.
e. Hypothyroidism includes hypothyroidism and immune-mediated hypothyroidism.
f. Thyroiditis includes thyroiditis, autoimmune thyroiditis, and immune-mediated thyroiditis.
g. Hypophysitis includes hypophysitis and lymphocytic hypophysitis.
h. Type 1 diabetes mellitus includes diabetic ketoacidosis and Type 1 diabetes mellitus.
i. Peripheral neuropathy includes peripheral sensory neuropathy, peripheral neuropathy, paraesthesia, polyneuropathy, neuritis, and peripheral motor neuropathy.
j. Meningitis includes aseptic meningitis.
k. Myocarditis includes myocarditis, autoimmune myocarditis, and immune-mediated myocarditis.
l. Pericarditis includes autoimmune pericarditis and pericarditis.
m. Hypertension includes hypertension and hypertensive crisis.
n. Cough includes cough, productive cough, and upper-airway cough syndrome.
o. Dyspnea includes dyspnea and dyspnea exertional.
p. Pneumonitis includes pneumonitis, immune-mediated lung disease, interstitial lung disease, and pulmonary fibrosis.
q. Abdominal pain includes abdominal pain, abdominal pain upper, abdominal distension, abdominal pain lower, abdominal discomfort, and gastrointestinal pain.
r. Colitis includes colitis, autoimmune colitis, enterocolitis, and immune-mediated enterocolitis.
s. Gastritis includes gastritis and immune-mediated gastritis.
t. Hepatitis includes autoimmune hepatitis, immune-mediated hepatitis, hepatitis, hepatotoxicity, hyperbilirubinemia, hepatocellular injury, hepatic failure, and abnormal hepatic function.
u. Rash includes rash, rash maculo-papular, dermatitis, erythema, rash pruritic, urticaria, rash erythematous, dermatitis bullous, dermatitis acneiform, rash macular, psoriasis, rash papular, dyshidrotic eczema, pemphigoid, autoimmune dermatitis, dermatitis allergic, atopic dermatitis, drug eruption, erythema nodosum, skin reaction, skin toxicity, dermatitis exfoliative, dermatitis exfoliative generalised, dermatitis psoriasiform, erythema multiforme, exfoliative rash, immune-mediated dermatitis, lichen planus, and parapsoriasis.
v. Pruritus includes pruritus and allergic pruritus.
w. Musculoskeletal pain includes arthralgia, back pain, pain in extremity, myalgia, neck pain, musculoskeletal chest pain, bone pain, musculoskeletal pain, spinal pain, musculoskeletal stiffness, and musculoskeletal discomfort.
x. Arthritis includes arthritis, polyarthritis, autoimmune arthritis, and immune-mediated arthritis.
y. Myositis includes myositis and dermatomyositis.

z. Nephritis includes acute kidney injury, renal impairment, immune-mediated nephritis, nephritis, renal failure, tubulointerstitial nephritis, and nephropathy toxic.
aa. Fatigue includes fatigue, asthenia, and malaise.
bb. Pyrexia includes pyrexia, hyperthermia, and hyperpyrexia.
cc. Edema includes peripheral edema, face edema, peripheral swelling, face swelling, localised edema, generalised edema, and swelling.

Serious adverse event/deaths/other significant events

Table 42: Serious Treatment-Emergent Adverse Events Experienced by Patients (in >1% in Either Arm) by System Organ Class and Preferred Term in Study 16113 Part 2 – SAF

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=153)
Number of patients with any serious TEAE, n (%)	79 (25.3%)	34 (22.2%)
Number of patients with any serious TEAE, nP (nP/100PY)*	79/225.7 (35.00)	34/75.9 (44.82)
Infections and infestations	23 (7.4%)	7 (4.6%)
Pneumonia	9 (2.9%)	3 (2.0%)
Blood and lymphatic system disorders	17 (5.4%)	8 (5.2%)
Anaemia	9 (2.9%)	2 (1.3%)
Febrile neutropenia	4 (1.3%)	4 (2.6%)
General disorders and administration site conditions	11 (3.5%)	3 (2.0%)
Death	5 (1.6%)	0
Respiratory, thoracic and mediastinal disorders	10 (3.2%)	8 (5.2%)
Pulmonary embolism	2 (0.6%)	2 (1.3%)
Respiratory failure	0	2 (1.3%)

Abbreviations: CSR, clinical study report; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients, nP, number of patients with an event; PT, preferred term; PY, patient-years; nP/100PY, number of patients with at least one event per 100 patient-year; SAF, Safety Analysis Set; SOC, system organ class; TEAE, treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 23.1.
Data cutoff as of 14 Jun 2021.
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 cemiplimab/chemotherapy arm.
Within each SOC, PTs are sorted by decreasing frequency of all grades in the cemiplimab/chemotherapy arm.
*All TEAEs by exposure-adjusted rates are presented in PTT 14.3.2.1.2.py. Source: Study 16113 Part 2 Primary Analysis CSR Table 31

Deaths

Table 43: Deaths during on-treatment period (safety analysis set) (data cut-off: 14 June 2021)

	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=153)
Number of Deaths, n (%)	76 (24.4%)	39 (25.5%)
Primary cause of death		
PROGRESSION/RECURRENCE OF DISEASE	56 (17.9%)	27 (17.6%)
ADVERSE EVENT	19 (6.1%)	12 (7.8%)
OTHER	1 (0.3%)	0

Table 44: Summary of Treatment-Emergent Adverse Events Resulting in Death by System Organ Class and Preferred Term in Study 16113 Part 2 – SAF

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=153)
Number of patients with any TEAE resulting in death, n (%)	19 (6.1%)	12 (7.8%)

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=153)
General disorders and administration site conditions	8 (2.6%)	0
Death [a]	5 (1.6%)	0
Sudden death [a]	2 (0.6%)	0
General physical health deterioration	1 (0.3%)	0
Respiratory, thoracic and mediastinal disorders	5 (1.6%)	3 (2.0%)
Acute respiratory distress syndrome	1 (0.3%)	0
Pleural effusion	1 (0.3%)	0
Pneumonitis	1 (0.3%)	0
Pulmonary embolism	1 (0.3%)	2 (1.3%)
Pulmonary haemorrhage	1 (0.3%)	0
Respiratory failure	0	1 (0.7%)
Gastrointestinal disorders	2 (0.6%)	1 (0.7%)
Mesenteric artery thrombosis	1 (0.3%)	0
Thrombosis mesenteric vessel	1 (0.3%)	0
Enterocolitis	0	1 (0.7%)
Infections and infestations	2 (0.6%)	1 (0.7%)
Pneumonia	1 (0.3%)	0
Septic shock	1 (0.3%)	0
COVID-19 pneumonia	0	1 (0.7%)
Cardiac disorders	1 (0.3%)	5 (3.3%)
Atrial fibrillation	1 (0.3%)	0
Acute coronary syndrome	0	1 (0.7%)
Cardiac failure	0	1 (0.7%)
Cardiac failure acute	0	1 (0.7%)
Cardiomyopathy	0	1 (0.7%)
Cardiopulmonary failure	0	1 (0.7%)
Hepatobiliary disorders	1 (0.3%)	0
Hepatitis acute	1 (0.3%)	0
Renal and urinary disorders	0	1 (0.7%)
Acute kidney injury	0	1 (0.7%)
Vascular disorders	0	1 (0.7%)
Embolism	0	1 (0.7%)

Abbreviations: CSR, clinical study report; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients, PT, preferred term; SAF, Safety Analysis Set; SOC, system organ class; TEAE, treatment-emergent adverse event.

[a] For patients experiencing a fatal TEAE of Death or Sudden death, no additional information was available from the investigator.

All adverse events were coded using MedDRA Version 23.1.

Data cutoff as of 14 Jun 2021.

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 plus chemotherapy group. Within each SOC, PTs are sorted by decreasing frequency in the cemiplimab plus chemotherapy group.

Source: Study 16113 Part 2 Primary Analysis CSR Table 29

Table 45: Summary of Treatment-related Treatment-Emergent Adverse Events Resulting in Death by System Organ Class and Preferred Term in Study 16113 Part 2 – SAF

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=153)
Number of patients with any treatment-related TEAE resulting in death, n (%)	4 (1.3%)	1 (0.7%)
General disorders and administration site conditions	2 (0.6%)	0
Death	1 (0.3%)	0
General physical health deterioration	1 (0.3%)	0
Gastrointestinal disorders	1 (0.3%)	1 (0.7%)
Mesenteric artery thrombosis	1 (0.3%)	0
Enterocolitis	0	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	1 (0.3%)	0
Pneumonitis	1 (0.3%)	0

Data cut-off as of Jun 14th, 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 plus chemotherapy group. Within each SOC, PTs are sorted by decreasing frequency in the cemiplimab plus chemotherapy group.

Laboratory findings

Table 46: New or Worsened Laboratory Results by NCI-CTCAE Grade for Hematology in Study 16113 Part 2 - SAF

	Cemiplimab + chemotherapy (N=312)		Placebo + chemotherapy (N=153)	
Parameter (CTCAE Term)	All Grades	Grades 3/4	All Grades	Grades 3/4
Number of patients with at least 1 lab abnormality, n (%)	262/299 (87.6%)	65/299 (21.7%)	120/146 (82.2%)	24/146 (16.4%)
Hemoglobin (Anemia)	204/299 (68.2%)	31/299 (10.4%)	99/146 (67.8%)	10/146 (6.8%)
Hemoglobin (Hemoglobin increased)	8/299 (2.7%)	0/299	0/146	0/146
Leukocytes (White blood cell decreased)	108/299 (36.1%)	19/299 (6.4%)	49/146 (33.6%)	6/146 (4.1%)
Lymphocytes (Lymphocyte count decreased)	106/299 (35.5%)	22/299 (7.4%)	39/146 (26.7%)	11/146 (7.5%)
Lymphocytes (Lymphocyte count increased)	20/299 (6.7%)	0/299	5/146 (3.4%)	0/146
Neutrophils (Neutrophil count decreased)	103/299 (34.4%)	30/299 (10.0%)	48/145 (33.1%)	12/145 (8.3%)
Platelets (Platelet count decreased)	100/299 (33.4%)	14/299 (4.7%)	36/146 (24.7%)	1/146 (0.7%)

Abbreviations: CSR, clinical study repot; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; NCI, National Cancer Institute
NCI grades were coded using CTCAE Version 4.03.
Data cutoff as of 14 Jun 2021.
Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter.
Post-baseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter. Source: Study 16113 Part 2 Primary Analysis CSR Table 38

Table 47: New or Worsened Laboratory Results by NCI-CTCAE Grade for Electrolytes in Study 16113 Part 2 - SAF

	Cemiplimab + chemotherapy (N=312)		Placebo + chemotherapy (N=153)	
Parameter (CTCAE Term)	All Grades	Grades 3/4	All Grades	Grades 3/4
Number of patients with at least 1 lab abnormality, n (%)	255/298 (85.6%)	54/298 (18.1%)	109/146 (74.7%)	27/146 (18.5%)
Calcium (Hypercalcemia [Uncorrected Calcium])	78/298 (26.2%)	5/298 (1.7%)	28/146 (19.2%)	1/146 (0.7%)
Calcium (Hypocalcemia [Uncorrected Calcium])	96/298 (32.2%)	9/298 (3.0%)	36/146 (24.7%)	3/146 (2.1%)
Magnesium (Hypermagnesemia)	41/297 (13.8%)	7/297 (2.4%)	14/144 (9.7%)	4/144 (2.8%)
Magnesium (Hypomagnesemia)	91/297 (30.6%)	2/297 (0.7%)	41/144 (28.5%)	2/144 (1.4%)
Phosphate (Hypophosphatemia)	52/298 (17.4%)	10/298 (3.4%)	18/146 (12.3%)	10/146 (6.8%)
Potassium (Hyperkalemia)	70/298 (23.5%)	8/298 (2.7%)	31/146 (21.2%)	4/146 (2.7%)
Potassium (Hypokalemia)	61/298 (20.5%)	7/298 (2.3%)	20/146 (13.7%)	2/146 (1.4%)
Sodium (Hypernatremia)	22/298 (7.4%)	3/298 (1.0%)	13/146 (8.9%)	0/146
Sodium (Hyponatremia)	80/298 (26.8%)	18/298 (6.0%)	27/146 (18.5%)	6/146 (4.1%)

Abbreviations: CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; N, number of patients; NCI, National Cancer Institute
NCI grades were coded using CTCAE Version 4.03.
Data cutoff as of 14 Jun 2021.
Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter.
Post-baseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter. Source: Study 16113 Part 2 Primary Analysis CSR Table 39

Table 48: New or Worsened Laboratory Results by NCI-CTCAE Grade for Liver Function in Study 16113 Part 2 – SAF

	Cemiplimab + chemotherapy (N=312)		Placebo + chemotherapy (N=153)	
Parameter (CTCAE Term)	All Grades	Grades 3/4	All Grades	Grades 3/4
Number of patients with at least 1 lab abnormality, n (%)	226/299 (75.6%)	15/299 (5.0%)	93/146 (63.7%)	5/146 (3.4%)
Alanine Aminotransferase (Alanine aminotransferase increased)	118/299 (39.5%)	9/299 (3.0%)	49/146 (33.6%)	3/146 (2.1%)
Albumin (Hypoalbuminemia)	90/298 (30.2%)	3/298 (1.0%)	36/146 (24.7%)	0/146
Alkaline Phosphatase (Alkaline phosphatase increased)	80/298 (26.8%)	2/298 (0.7%)	32/146 (21.9%)	1/146 (0.7%)
Aspartate Aminotransferase (Aspartate aminotransferase increased)	120/299 (40.1%)	1/299 (0.3%)	40/146 (27.4%)	3/146 (2.1%)
Bilirubin (Blood bilirubin increased)	40/298 (13.4%)	2/298 (0.7%)	14/146 (9.6%)	1/146 (0.7%)

Abbreviations: CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; N, number of patients; NCI, National Cancer Institute
NCI grades were coded using CTCAE Version 4.03.
Data cutoff as of 14 Jun 2021.

Percentages are based on the number of patients with at least 1 post-baseline value available for that parameter.
Post-baseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter. Source: Study 16113 Part 2 Primary Analysis CSR Table 40

Table 49: Selected Treatment-Emergent Laboratory Abnormalities in ≥15% in All Grades and ≥1% in Grades 3/4 in Study 16113 Part 2 – SAF

	Cemiplimab + chemotherapy (N=312)		Placebo + chemotherapy (N=153)	
Parameter (CTCAE Term)	All Grades	Grades 3/4	All Grades	Grades 3/4
Hematology				
Number of patients with at least 1 lab abnormality, n (%)	262/299 (87.6%)	65/299 (21.7%)	120/146 (82.2%)	24/146 (16.4%)
Hemoglobin (Anemia)	204/299 (68.2%)	31/299 (10.4%)	99/146 (67.8%)	10/146 (6.8%)
Leukocytes (White blood cell decreased)	108/299 (36.1%)	19/299 (6.4%)	49/146 (33.6%)	6/146 (4.1%)
Lymphocytes (Lymphocyte count decreased)	106/299 (35.5%)	22/299 (7.4%)	39/146 (26.7%)	11/146 (7.5%)
Neutrophils (Neutrophil count decreased)	103/299 (34.4%)	30/299 (10.0%)	48/145 (33.1%)	12/145 (8.3%)
Platelets (Platelet count decreased)	100/299 (33.4%)	14/299 (4.7%)	36/146 (24.7%)	1/146 (0.7%)
Electrolytes				
Number of patients with at least 1 lab abnormality, n (%)	255/298 (85.6%)	54/298 (18.1%)	109/146 (74.7%)	27/146 (18.5%)
Calcium (Hypercalcemia (Uncorrected Calcium)	78/298 (26.2%)	5/298 (1.7%)	28/146 (19.2%)	1/146 (0.7%)
Calcium (Hypocalcemia (Uncorrected Calcium)	96/298 (32.2%)	9/298 (3.0%)	36/146 (24.7%)	3/146 (2.1%)
Magnesium (Hypermagnesemia)	41/297 (13.8%)	7/297 (2.4%)	14/144 (9.7%)	4/144 (2.8%)
Magnesium (Hypomagnesemia)	91/297 (30.6%)	2/297 (0.7%)	41/144 (28.5%)	2/144 (1.4%)
Phosphate (Hypophosphatemia)	52/298 (17.4%)	10/298 (3.4%)	18/146 (12.3%)	10/146 (6.8%)
Potassium (Hyperkalemia)	70/298 (23.5%)	8/298 (2.7%)	31/146 (21.2%)	4/146 (2.7%)
Potassium (Hypokalemia)	61/298 (20.5%)	7/298 (2.3%)	20/146 (13.7%)	2/146 (1.4%)
Sodium (Hyponatremia)	80/298 (26.8%)	18/298 (6.0%)	27/146 (18.5%)	6/146 (4.1%)
Liver Function				
Number of patients with at least 1 lab abnormality, n (%)	226/299 (75.6%)	15/299 (5.0%)	93/146 (63.7%)	5/146 (3.4%)
Alanine Aminotransferase (Alanine aminotransferase increased)	118/299 (39.5%)	9/299 (3.0%)	49/146 (33.6%)	3/146 (2.1%)
Albumin (Hypoalbuminemia)	90/298 (30.2%)	3/298 (1.0%)	36/146 (24.7%)	0/146
Alkaline Phosphatase (Alkaline phosphatase increased)	80/298 (26.8%)	2/298 (0.7%)	32/146 (21.9%)	1/146 (0.7%)
Aspartate Aminotransferase (Aspartate aminotransferase increased)	120/299 (40.1%)	1/299 (0.3%)	40/146 (27.4%)	3/146 (2.1%)
Chemistry (Other)				
Number of patients with at least 1 lab abnormality, n (%)	275/298 (92.3%)	17/298 (5.7%)	126/146 (86.3%)	4/146 (2.7%)
Creatinine (Creatinine increased)	254/298 (85.2%)	6/298 (2.0%)	117/146 (80.1%)	2/146 (1.4%)
Fasting Glucose (Hyperglycemia)	141/276 (51.1%)	11/276 (4.0%)	62/134 (46.3%)	2/134 (1.5%)
Coagulation				
Number of patients with at least 1 lab abnormality, n (%)	37/128 (28.9%)	0/128	24/72 (33.3%)	1/72 (1.4%)
Activated Partial Thromboplastin Time (Activated partial thromboplastin time prolonged)	19/122 (15.6%)	0/122	12/70 (17.1%)	0/70
Prothrombin Intl. Normalized Ratio (INR increased)	26/124 (21.0%)	0/124	16/71 (22.5%)	1/71 (1.4%)

Abbreviations: CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients, NCI, National Cancer Institute; PT, preferred term; SAF, Safety Analysis Set; SOC, system organ class; TEAE, treatment-emergent adverse event.

NCI grades were coded using CTCAE Version 4.03.
Data cutoff as of 14 Jun 2021.
Percentages are based on the number of patients with at least one post-baseline value available for that parameter.
Post-baseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.
Source: Study 16113 Part 2 Primary Analysis CSR PTTs 14.3.3.1.1, 14.3.3.2.1, 14.3.3.3.1, 14.3.3.4.1, and 14.3.3.5.1

ECG

Table 50: Shift table of ECG (safety analysis set)

Parameter	Treatment	Baseline	Post-baseline (Worst Grade)			
			Normal	Abnormal NCS	Abnormal CS	Total
Interpretation	Cemiplimab + chemotherapy (N=312)	Normal	2/10 (20.0%)	2/10 (20.0%)	2/10 (20.0%)	6/10 (60.0%)
		Abnormal NCS	0/10	3/10 (30.0%)	0/10	3/10 (30.0%)
		Abnormal CS	0/10	0/10	1/10 (10.0%)	1/10 (10.0%)
		missing	0/10	0/10	0/10	0/10
		Total	2/10 (20.0%)	5/10 (50.0%)	3/10 (30.0%)	10/10 (100%)
	Placebo + chemotherapy (N=153)	Normal	0/5	0/5	0/5	0/5
		Abnormal NCS	2/5 (40.0%)	1/5 (20.0%)	0/5	3/5 (60.0%)
		Abnormal CS	0/5	1/5 (20.0%)	1/5 (20.0%)	2/5 (40.0%)
		missing	0/5	0/5	0/5	0/5
		Total	2/5 (40.0%)	2/5 (40.0%)	1/5 (20.0%)	5/5 (100%)

Data cut-off as of Jun 14th, 2021.
Percentages are based on the number of patients with at least one post-baseline value available.
Baseline value is defined as the last available value before randomization. Post-baseline value is for on-treatment period only.

Table 51: Summary of patients with potential treatment-emergent ECG abnormalities (safety analysis set)

Abnormality Categories	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=153)
Number of patients with at least one abnormality, n (%)	6/10 (60.0%)	1/5 (20.0%)
QTcB (msec)		
>450	2/9 (22.2%)	0/5
>480	1/9 (11.1%)	0/5
>500	0/9	0/5
Increase from baseline>30	3/9 (33.3%)	0/5
Increase from baseline>60	1/9 (11.1%)	0/5
QTcF (msec)		
>450	1/10 (10.0%)	0/5
>480	2/10 (20.0%)	0/5
>500	2/10 (20.0%)	0/5
Increase from baseline>30	4/10 (40.0%)	1/5 (20.0%)
Increase from baseline>60	2/10 (20.0%)	0/5

Data cut-off as of Jun 14th, 2021.
Treatment-Emergent ECG Abnormalities included those developed or worsened during on-treatment peiord.
Percentages are based on the number of patients with at least one post-baseline value available for that parameter.
A patient is counted only once for multiple occurrences for the same category.
/sasdata/Data/Production/BDM/R2810/R2810-ONC/R2810-ONC-16113/Interim_Part2_Combo_NSCLC_sBLA/Analysis_CSR/Programs/TFL/part2/Generated/t_3_4_5_ecgabn.sas (yun.zhang 11NOV2021 21:55 SAS Linux 9.4)

Safety in special populations

Intrinsic factors

Table 52: Distribution of AEs, SAEs, and discontinuations according to aged group (<65, ≥65 to <75, and ≥75 to <85 years) in study 16113 Part 2

	Cemiplimab + chemotherapy (N=312)			Placebo + chemotherapy (N=153)		
	Age: <65 (N=184)	Age: ≥65 to <75 (N=110)	Age: ≥75 to <85 (N=18)	Age: <65 (N=94)	Age: ≥65 to <75 (N=49)	Age: ≥75 to <85 (N=10)
Number of TEAEs	1875	1125	95	667	361	58
Number of NCI grade 3/4/5 TEAEs	199	114	19	55	40	12
Number of Serious TEAEs	73	54	3	25	18	6
Number of Patients with any TEAE, n (%)	179 (97.3%)	103(93.6%)	17 (94.4%)	88 (93.6%)	47 (95.9%)	9 (90.0%)
Number of Patients with any grade 3/4/5 TEAE, n (%)	82 (44.6%)	44 (40.0%)	10 (55.6%)	24 (25.5%)	17 (34.7%)	7 (70.0%)
Number of Patients with any Serious TEAE, n (%)	45 (24.5%)	32 (29.1%)	2 (11.1%)	15 (16.0%)	14 (28.6%)	5 (50.0%)
Fatal	9 (4.9%)	9 (8.2%)	1 (5.6%)	2 (2.1%)	8 (16.3%)	2 (20.0%)
Life-threatening	9 (4.9%)	1 (0.9%)	0	1 (1.1%)	1 (2.0%)	1 (10.0%)
Hospitalization/prolong existing hospitalization	37 (20.1%)	25 (22.7%)	2 (11.1%)	14 (14.9%)	9 (18.4%)	3 (30.0%)
Disability/incapacity	0	0	0	0	0	0
Congenital abnormality or birth defect	0	0	0	0	0	0
Other (medically significant)	4 (2.2%)	3 (2.7%)	0	2 (2.1%)	1 (2.0%)	1 (10.0%)
Number of patients with any TEAE leading to permanent treatment discontinuation, n (%)	13 (7.1%)	2 (1.8%)	1 (5.6%)	1 (1.1%)	2 (4.1%)	1 (10.0%)
Number of patients with any NCI grade 3/4/5 TEAE leading to permanent treatment discontinuation, n (%)	10 (5.4%)	2 (1.8%)	1 (5.6%)	1 (1.1%)	2 (4.1%)	1 (10.0%)
Number of patients with any TEAE leading to a dose delay, n (%)	59 (32.1%)	38 (34.5%)	6 (33.3%)	25 (26.6%)	10 (20.4%)	4 (40.0%)
Number of patients with any TEAE leading to an infusion interruption, n (%)	4 (2.2%)	1 (0.9%)	0	0	3 (6.1%)	0
Number of patients with any TEAE leading to a dose modification, n (%)	6 (3.3%)	6 (5.5%)	1 (5.6%)	5 (5.3%)	3 (6.1%)	0
Number of patients with any TEAE resulting in death, n (%)	9 (4.9%)	9 (8.2%)	1 (5.6%)	2 (2.1%)	8 (16.3%)	2 (20.0%)
Number of Patients with any treatment-emergent sponsor identified imAE, n (%)	33 (17.9%)	23 (20.9%)	3 (16.7%)	0	0	0

Abbreviations: CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; N, number of patients; NCI, National Cancer Institute; TEAE, treatment-emergent adverse events; SAF, safety analysis set
NCI grades were coded using CTCAE Version 4.03.

Data cutoff as of 14 Jun 2021.
A patient is counted only once for multiple occurrences within a category
Source: Study 16113 Part 2 Primary Analysis CSR PTTs 14.3.1.2.1.s2 and 14.3.1.6.7

Gender

Table 53: Summary of treatment-emergent adverse events by gender (safety analysis set)

Gender: Male

	Cemiplimab + chemotherapy (N=268)	Placebo + chemotherapy (N=122)
Number of TEAEs	2574	760
Number of NCI grade 3/4/5 TEAEs	285	77
Number of serious TEAEs	110	41
Number of patients with any TEAE, n (%)	255 (95.1%)	113 (92.6%)
Number of patients with any NCI grade 3/4/5 TEAE, n (%)	117 (43.7%)	35 (28.7%)
Number of patients with any serious TEAE, n (%)	67 (25.0%)	29 (23.8%)
Number of patients with any TEAE leading to permanent treatment discontinuation, n (%)	14 (5.2%)	4 (3.3%)
Number of patients with any NCI grade 3/4/5 TEAE leading to permanent treatment discontinuation, n (%)	11 (4.1%)	4 (3.3%)
Number of patients with any TEAE leading to a dose delay, n (%)	83 (31.0%)	26 (21.3%)
Number of patients with any TEAE leading to an infusion interruption, n (%)	3 (1.1%)	3 (2.5%)
Number of patients with any TEAE leading to a dose modification, n (%)	10 (3.7%)	4 (3.3%)
Number of patients with any TEAE resulting in death, n (%)	16 (6.0%)	12 (9.8%)

Gender: Female

	Cemiplimab + chemotherapy (N=44)	Placebo + chemotherapy (N=31)
Number of TEAEs	521	326
Number of NCI grade 3/4/5 TEAEs	47	30
Number of serious TEAEs	20	8
Number of patients with any TEAE, n (%)	44 (100%)	31 (100%)
Number of patients with any NCI grade 3/4/5 TEAE, n (%)	19 (43.2%)	13 (41.9%)
Number of patients with any serious TEAE, n (%)	12 (27.3%)	5 (16.1%)
Number of patients with any TEAE leading to permanent treatment discontinuation, n (%)	2 (4.5%)	0
Number of patients with any NCI grade 3/4/5 TEAE leading to permanent treatment discontinuation, n (%)	2 (4.5%)	0
Number of patients with any TEAE leading to a dose delay, n (%)	20 (45.5%)	13 (41.9%)
Number of patients with any TEAE leading to an infusion interruption, n (%)	2 (4.5%)	0
Number of patients with any TEAE leading to a dose modification, n (%)	3 (6.8%)	4 (12.9%)
Number of patients with any TEAE resulting in death, n (%)	3 (6.8%)	0

Data cut-off as of Jun 14th, 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.

Race

Table 54: Summary of treatment-emergent adverse events by race (safety analysis set)

Race: White

	Cemiplimab + chemotherapy (N=267)	Placebo + chemotherapy (N=138)
Number of TEAEs	2430	880
Number of NCI grade 3/4/5 TEAEs	234	81
Number of serious TEAEs	88	39
Number of patients with any TEAE, n (%)	256 (95.9%)	130 (94.2%)
Number of patients with any NCI grade 3/4/5 TEAE, n (%)	103 (38.6%)	42 (30.4%)
Number of patients with any serious TEAE, n (%)	57 (21.3%)	28 (20.3%)
Number of patients with any TEAE leading to permanent treatment discontinuation, n (%)	13 (4.9%)	4 (2.9%)
Number of patients with any NCI grade 3/4/5 TEAE leading to permanent treatment discontinuation, n (%)	11 (4.1%)	4 (2.9%)
Number of patients with any TEAE leading to a dose delay, n (%)	84 (31.5%)	34 (24.6%)
Number of patients with any TEAE leading to an infusion interruption, n (%)	3 (1.1%)	0
Number of patients with any TEAE leading to a dose modification, n (%)	9 (3.4%)	7 (5.1%)
Number of patients with any TEAE resulting in death, n (%)	14 (5.2%)	10 (7.2%)

Race: Non-white

	Cemiplimab + chemotherapy (N=45)	Placebo + chemotherapy (N=15)
Number of TEAEs	665	206
Number of NCI grade 3/4/5 TEAEs	98	26
Number of serious TEAEs	42	10
Number of patients with any TEAE, n (%)	43 (95.6%)	14 (93.3%)
Number of patients with any NCI grade 3/4/5 TEAE, n (%)	33 (73.3%)	6 (40.0%)
Number of patients with any serious TEAE, n (%)	22 (48.9%)	6 (40.0%)
Number of patients with any TEAE leading to permanent treatment discontinuation, n (%)	3 (6.7%)	0
Number of patients with any NCI grade 3/4/5 TEAE leading to permanent treatment discontinuation, n (%)	2 (4.4%)	0
Number of patients with any TEAE leading to a dose delay, n (%)	19 (42.2%)	5 (33.3%)
Number of patients with any TEAE leading to an infusion interruption, n (%)	2 (4.4%)	3 (20.0%)
Number of patients with any TEAE leading to a dose modification, n (%)	4 (8.9%)	1 (6.7%)
Number of patients with any TEAE resulting in death, n (%)	5 (11.1%)	2 (13.3%)

Data cut-off as of Jun 14th, 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.

Histology

Table 55: Distribution of AEs, SAEs, and discontinuations according to histology (squamous, non-squamous) in study 16113 Part 2

	Histology: Squamous		Histology: Non-squamous	
	Cemiplimab + chemotherapy (N=133)	Placebo + chemotherapy (N=67)	Cemiplimab + chemotherapy (N=179)	Placebo + chemotherapy (N=86)
Number of TEAEs	1112	373	1983	713
Number of NCI grade 3/4/5 TEAEs	63	18	269	89
Number of serious TEAEs	33	13	97	36
Number of patients with any TEAE, n (%)	129 (97.0%)	63 (94.0%)	170 (95.0%)	81 (94.2%)
Number of patients with any NCI grade 3/4/5 TEAE, n (%)	39 (29.3%)	14 (20.9%)	97 (54.2%)	34 (39.5%)
Number of patients with any serious TEAE, n (%)	25 (18.8%)	11 (16.4%)	54 (30.2%)	23 (26.7%)
Number of patients with any TEAE leading to permanent treatment discontinuation, n (%)	6 (4.5%)	2 (3.0%)	10 (5.6%)	2 (2.3%)
Number of patients with any NCI grade 3/4/5 TEAE leading to permanent treatment discontinuation, n (%)	6 (4.5%)	2 (3.0%)	7 (3.9%)	2 (2.3%)
Number of patients with any TEAE leading to a dose delay, n (%)	29 (21.8%)	11 (16.4%)	74 (41.3%)	28 (32.6%)
Number of patients with any TEAE leading to an infusion interruption, n (%)	3 (2.3%)	2 (3.0%)	2 (1.1%)	1 (1.2%)
Number of patients with any TEAE leading to a dose modification, n (%)	5 (3.8%)	3 (4.5%)	8 (4.5%)	5 (5.8%)
Number of patients with any TEAE resulting in death, n (%)	5 (3.8%)	2 (3.0%)	14 (7.8%)	10 (11.6%)

Abbreviations: CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; N, number of patients; NCI, National Cancer Institute; TEAE, treatment-emergent adverse events; SAF, safety analysis set
NCI grades were coded using CTCAE Version 4.03.
Data cutoff as of 14 Jun 2021.
A patient is counted only once for multiple occurrences within a category

PD-L1 status

Table 56: Distribution of AEs, SAEs, and discontinuations according to PD-L1 expression (<1%, 1% to 49%, ≥50%) in study 16113 Part 2

	PD-L1 Expression: <1%		PD-L1 Expression: 1% to 49%		PD-L1 Expression: ≥50%	
	Cemiplimab + chemotherapy (N=95)	Placebo + chemotherapy (N=44)	Cemiplimab + chemotherapy (N=114)	Placebo + chemotherapy (N=61)	Cemiplimab + chemotherapy (N=103)	Placebo + chemotherapy (N=48)
Number of TEAEs	785	385	1291	370	1019	331
Number of NCI grade 3/4/5 TEAEs	92	50	134	30	106	27
Number of Serious TEAEs	33	16	60	18	37	15
Number of Patients with any TEAE, n (%)	91 (95.8%)	44 (100%)	111 (97.4%)	57 (93.4%)	97 (94.2%)	43 (89.6%)
Number of Patients with any grade 3/4/5 TEAE, n (%)	42 (44.2%)	19 (43.2%)	55 (48.2%)	16 (26.2%)	39 (37.9%)	13 (27.1%)
Number of Patients with any Serious TEAE, n (%)	22 (23.2%)	11 (25.0%)	35 (30.7%)	13 (21.3%)	22 (21.4%)	10 (20.8%)
Fatal	9 (9.5%)	5 (11.4%)	6 (5.3%)	5 (8.2%)	4 (3.9%)	2 (4.2%)
Life-threatening	2 (2.1%)	0	6 (5.3%)	2 (3.3%)	2 (1.9%)	1 (2.1%)
Hospitalization/prolong existing hospitalization	15 (15.8%)	6 (13.6%)	32 (28.1%)	11 (18.0%)	17 (16.5%)	9 (18.8%)
Disability/incapacity	0	0	0	0	0	0
Congenital abnormality or birth defect	0	0	0	0	0	0
Other (medically significant)	2 (2.1%)	3 (6.8%)	2 (1.8%)	1 (1.6%)	3 (2.9%)	0
Number of patients with any TEAE leading to permanent treatment discontinuation, n (%)	4 (4.2%)	2 (4.5%)	7 (6.1%)	1 (1.6%)	5 (4.9%)	1 (2.1%)
Number of patients with any NCI grade 3/4/5 TEAE leading to permanent treatment discontinuation, n (%)	3 (3.2%)	2 (4.5%)	7 (6.1%)	1 (1.6%)	3 (2.9%)	1 (2.1%)
Number of patients with any TEAE leading to a dose delay, n (%)	26 (27.4%)	13 (29.5%)	40 (35.1%)	14 (23.0%)	37 (35.9%)	12 (25.0%)
Number of patients with any TEAE leading to an infusion interruption, n (%)	1 (1.1%)	2 (4.5%)	2 (1.8%)	1 (1.6%)	2 (1.9%)	0
Number of patients with any TEAE leading to a dose modification, n (%)	5 (5.3%)	1 (2.3%)	5 (4.4%)	3 (4.9%)	3 (2.9%)	4 (8.3%)
Number of patients with any TEAE resulting in death, n (%)	9 (9.5%)	5 (11.4%)	6 (5.3%)	5 (8.2%)	4 (3.9%)	2 (4.2%)
Number of Patients with any treatment-emergent sponsor identified imAE, n (%)	11 (11.6%)	0	32 (28.1%)	0	16 (15.5%)	0

Abbreviations: clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; N, number of patients; NCI, National Cancer Institute; PD-L1, Programmed death-ligand 1; TEAE, treatment-emergent adverse events; SAF, safety analysis set
NCI grades were coded using CTCAE Version 4.03.
Data cutoff as of 14 Jun 2021.

ECOG Performance status

Table 57: Shift table of ECOG (safety analysis set)

Treatment	Baseline status	Post-Baseline (Worst Grade) 0	1	2	3	4	5	Total
Cemiplimab + chemotherapy (N=312)	0	27/297 (9.1%)	22/297 (7.4%)	0/297	0/297	1/297 (0.3%)	0/297	50/297 (16.8%)
	1	1/297 (0.3%)	214/297 (72.1%)	24/297 (8.1%)	7/297 (2.4%)	1/297 (0.3%)	0/297	247/297 (83.2%)
	2	0/297	0/297	0/297	0/297	0/297	0/297	0/297
	3	0/297	0/297	0/297	0/297	0/297	0/297	0/297
	4	0/297	0/297	0/297	0/297	0/297	0/297	0/297
	5	0/297	0/297	0/297	0/297	0/297	0/297	0/297
	missing	0/297	0/297	0/297	0/297	0/297	0/297	0/297
	Total	28/297 (9.4%)	236/297 (79.5%)	24/297 (8.1%)	7/297 (2.4%)	2/297 (0.7%)	0/297	297/297 (100%)
Placebo + chemotherapy (N=153)	0	10/144 (6.9%)	7/144 (4.9%)	0/144	1/144 (0.7%)	0/144	0/144	18/144 (12.5%)
	1	1/144 (0.7%)	113/144 (78.5%)	7/144 (4.9%)	5/144 (3.5%)	0/144	0/144	126/144 (87.5%)
	2	0/144	0/144	0/144	0/144	0/144	0/144	0/144
	3	0/144	0/144	0/144	0/144	0/144	0/144	0/144
	4	0/144	0/144	0/144	0/144	0/144	0/144	0/144
	5	0/144	0/144	0/144	0/144	0/144	0/144	0/144
	missing	0/144	0/144	0/144	0/144	0/144	0/144	0/144
	Total	11/144 (7.6%)	120/144 (83.3%)	7/144 (4.9%)	6/144 (4.2%)	0/144	0/144	144/144 (100%)

Data cut-off as of Jun 14th, 2021.
Percentages are based on the number of patients with at least one post-baseline value available.
Baseline value is defined as the last available value before randomization. Post-baseline value is for on-treatment period only.

Extrinsic factors

Region

Table 58: Summary of treatment-emergent adverse events by region (safety analysis set)

Geographic region: Europe

	Cemiplimab + chemotherapy (N=270)	Placebo + chemotherapy (N=138)
Number of TEAEs	2471	880
Number of NCI grade 3/4/5 TEAEs	234	81
Number of serious TEAEs	88	39
Number of patients with any TEAE, n (%)	258 (95.6%)	130 (94.2%)
Number of patients with any NCI grade 3/4/5 TEAE, n (%)	103 (38.1%)	42 (30.4%)
Number of patients with any serious TEAE, n (%)	57 (21.1%)	28 (20.3%)
Number of patients with any TEAE leading to permanent treatment discontinuation, n (%)	13 (4.8%)	4 (2.9%)
Number of patients with any NCI grade 3/4/5 TEAE leading to permanent treatment discontinuation, n (%)	11 (4.1%)	4 (2.9%)
Number of patients with any TEAE leading to a dose delay, n (%)	84 (31.1%)	34 (24.6%)
Number of patients with any TEAE leading to an infusion interruption, n (%)	3 (1.1%)	0
Number of patients with any TEAE leading to a dose modification, n (%)	9 (3.3%)	7 (5.1%)
Number of patients with any TEAE resulting in death, n (%)	14 (5.2%)	10 (7.2%)

Geographic region: Asia

	Cemiplimab + chemotherapy (N=42)	Placebo + chemotherapy (N=15)
Number of TEAEs	624	206
Number of NCI grade 3/4/5 TEAEs	98	26
Number of serious TEAEs	42	10
Number of patients with any TEAE, n (%)	41 (97.6%)	14 (93.3%)
Number of patients with any NCI grade 3/4/5 TEAE, n (%)	33 (78.6%)	6 (40.0%)
Number of patients with any serious TEAE, n (%)	22 (52.4%)	6 (40.0%)
Number of patients with any TEAE leading to permanent treatment discontinuation, n (%)	3 (7.1%)	0
Number of patients with any NCI grade 3/4/5 TEAE leading to permanent treatment discontinuation, n (%)	2 (4.8%)	0
Number of patients with any TEAE leading to a dose delay, n (%)	19 (45.2%)	5 (33.3%)
Number of patients with any TEAE leading to an infusion interruption, n (%)	2 (4.8%)	3 (20.0%)
Number of patients with any TEAE leading to a dose modification, n (%)	4 (9.5%)	1 (6.7%)
Number of patients with any TEAE resulting in death, n (%)	5 (11.9%)	2 (13.3%)

Data cut-off as of Jun 14th, 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.

Safety related to drug-drug interactions and other interactions

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

Discontinuation due to adverse events

Table 59: Treatment-Emergent Adverse Events Resulting in Treatment Discontinuation by System Organ Class and Preferred Term in Study 16113 Part 2 – SAF

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=153)
Number of patients with any TEAE resulting in treatment discontinuation, n (%)	16 (5.1%)	4 (2.6%)
Number of patients with any TEAE resulting in treatment discontinuation, nP (nP/100PY)*	13/250.3 (6.40)	4/83.0 (4.82)
Investigations	5 (1.6%)	0
Alanine aminotransferase increased	2 (0.6%)	0
Activated partial thromboplastin time prolonged	1 (0.3%)	0
Aspartate aminotransferase increased	1 (0.3%)	0
Blood bilirubin increased	1 (0.3%)	0
Blood creatinine increased	1 (0.3%)	0
Weight decreased	1 (0.3%)	0
Infections and infestations	3 (1.0%)	2 (1.3%)
COVID-19 pneumonia	1 (0.3%)	1 (0.7%)
Infection	1 (0.3%)	0
Pneumonia	1 (0.3%)	0
Pneumonia serratia	0	1 (0.7%)
Blood and lymphatic system disorders	2 (0.6%)	1 (0.7%)
Anaemia	2 (0.6%)	0
Pancytopenia	0	1 (0.7%)

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab + chemotherapy (N=312)	Placebo + chemotherapy (N=153)
Gastrointestinal disorders	2 (0.6%)	0
Gastritis	1 (0.3%)	0
Mesenteric artery thrombosis	1 (0.3%)	0
Respiratory, thoracic and mediastinal disorders	2 (0.6%)	0
Pleural effusion	1 (0.3%)	0
Respiratory failure	1 (0.3%)	0
Cardiac disorders	1 (0.3%)	0
Atrial flutter	1 (0.3%)	0
General disorders and administration site conditions	1 (0.3%)	0
Fatigue	1 (0.3%)	0
Immune system disorders	1 (0.3%)	0
Hypersensitivity	1 (0.3%)	0
Musculoskeletal and connective tissue disorders	1 (0.3%)	0
Muscular weakness	1 (0.3%)	0
Renal and urinary disorders	1 (0.3%)	0
Renal failure	1 (0.3%)	0
Skin and subcutaneous tissue disorders	1 (0.3%)	0
Psoriasis	1 (0.3%)	0
Vascular disorders	1 (0.3%)	1 (0.7%)
Hypertension	1 (0.3%)	0
Embolism	0	1 (0.7%)
Reproductive system and breast disorders	0	1 (0.7%)
Prostatitis	0	1 (0.7%)

Abbreviations: CSR, clinical study report; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients, nP, number of patients with an event; PT, preferred term; PY, patient-years; nP/100PY, number of patients with at least one event per 100 patient-year; SAF, Safety Analysis Set; SOC, system organ class; TEAE, treatment-emergent adverse event.
All adverse events were coded using MedDRA Version 23.1.
Data cutoff as of 14 Jun 2021.
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 cemiplimab/chemotherapy arm.
Within each SOC, PTs are sorted by decreasing frequency of all grades in the cemiplimab/chemotherapy arm.
*All TEAEs by exposure-adjusted rates are presented in PTT 14.3.1.2.10.py.

Post marketing experience

Cemiplimab/chemo combination therapy is not yet approved.

Cemiplimab monotherapy is approved in several countries worldwide for the treatment of adult patients with locally advanced or metastatic CSCC who are not candidates for curative surgery or curative radiation. Cemiplimab is also approved in some countries for BCC, first line treatment of NSCLC and cervical cancer. Cumulatively up to 27 Mar 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 Mar 2021, the global cumulative exposure to cemiplimab monotherapy was estimated to be 6484 patient-years.

The list of important identified risks for cemiplimab described 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 ADA and embryo-fetal toxicity. The missing information for cemiplimab are long-term safety data, use in pregnant women and use in breastfeeding women.

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

2.5.1. Discussion on clinical safety

The evaluation of safety is based on data from 465 patients, of which 312 patients were treated with platinum-based doublet chemo and cemiplimab in the pivotal study 16113 Part 2 per data cut-off of 14 June 2021. The provided size of the safety data base is acceptable for an assessment of cemiplimab + platinum-based chemotherapy (n=312) although no other combination therapy regimens have been approved with cemiplimab. The median duration of exposure was 38.5 weeks (10 days to 102.6 weeks) in the cemiplimab/chemo arm compared to 21.3 weeks (4 days to 95 weeks) in the placebo/chemo arm and the majority of the patients in the cemiplimab/chemo arm (71.8%) had been treated for at least 24 weeks while 38.1% had been treated for ≥48 weeks.

Almost all of the patients experienced at least one **adverse event** (AE) in the pivotal study and the most frequently observed events were (cemiplimab/chemo vs placebo/chemo): Anaemia (43.6% vs 39.9%), alopecia (36.9% vs 43.1%), nausea (25.0% vs 16.3%), hyperglycaemia (17.6% vs 11.8%), decreased appetite (17.0% vs 11.8%), alanine aminotransferase increased (16.3% vs 14.4%), neutropenia (15.4% vs 12.4%), and arthralgia (15.4% vs 13.1%). The most commonly observed **grade ≥3 AEs** by PT (≥2% of patients) were: Anaemia (9.9% vs 6.5%), neutropenia (5.8% vs 5.9%), white blood cell count decreased (3.2% vs 2.0%), pneumonia (2.9% vs 3.3%), thrombocytopenia (2.6% vs 1.3%), alanine aminotransferase increased (2.2% vs 2.0%), fatigue (2.2% vs 0.7%), and dyspnoea (2.2% vs 0.7%).

Treatment-related AE's were similar to the AEs observed, and the most commonly observed of all grades were: Anaemia (40.7% vs 34.0%), alopecia (36.5% vs 42.5%), and nausea (22.8% vs 16.3%); while the most common grade ≥3 treatment-related AEs were: Anaemia (9.6% vs 6.5%), neutropenia (5.4% vs 5.9%), and white blood cell count decreased (3.2% vs 1.3%). It is noted that increased haematological toxicity led to a higher incidence of febrile neutropenia in the cemiplimab/chemo arm (1.3% vs 2.6%), but it is within an acceptable level and the ADRs are considered manageable.

Most patients had changes in haematology parameters from baseline and this was slightly more commonly observed for the cemiplimab + chemo group both regarding all grade toxicities (87.6% vs 82.2%) and grade 3 or 4 events (21.7% vs 16.4%), which is acceptable. The incidence of affected electrolytes was also increased in the cemiplimab + chemo groups regarding all grade events (85.6% vs 74.7%); however, the high grade 3-4 events were evenly distributed and the changes are considered manageable. A higher incidence of liver function laboratory abnormalities was observed for the cemiplimab/chemo arm (75.6% vs 63.7%), and grade 3-4 events were also more common (5.0% vs 3.4%). Increased AST of all grades were very commonly observed in both treatment groups (40.1% vs 27.4%), even though it is noted that grade 3-4 events were less common in the cemiplimab arm compared to the placebo arm(0.3% vs 2.1%). The Applicant has clarified that the slightly higher incidence of liver function abnormalities can be attributed to medical history of increased enzymes at baseline; since 4.8% of patients had ALT increased in the cemiplimab/chemo arm compared to 2.0% in

the placebo/chemo arm and 2.9% of patients had AST increased in the cemiplimab/chemo arm at baseline compared to none in the placebo/chemo arm. This is considered plausible. Overall, the differences in laboratory tests are considered manageable and acceptable.

Adverse events of special interest included infusion-related reactions and immune-related adverse events as they are important identified risks with cemiplimab. Only 2.2% of the safety population (n=312) had an infusion-related reactions which is considered acceptable and manageable. Immune-related adverse events were commonly observed (18.9%), but these events were rarely of high grade (≥grade 3: 2.9%) and the most frequently observed were hypothyroidism (7.7%), hyperthyroidism (5.1%), blood thyroid stimulating hormone increased (4.2%) or decreased (1.6%), and pneumonitis (1.6%). Only 1.0% of the patients discontinued treatment due to Immune-Mediated Adverse Events (imAEs) and 1 (0.3%) patient died from pneumonitis. However, the overall incidence of immune-related adverse events is acceptable and considered manageable, considering the underlying lung cancer disease.

Serious adverse events (SAEs) were observed in a quarter of the patients (25.3% vs 22.2%) in the cemiplimab/chemo arm vs the placebo/chemo groups, most often pertaining to pneumonia (2.9 % vs 2.0%) and anaemia (2.9% vs 1.3%), and febrile neutropenia (1.3% vs 2.6%). Hence, there were more serious toxicities observed in the cemiplimab-containing arm compared to the placebo-containing arm but this was within an acceptable range.

Overall, there was an equal fraction of **deaths** in both groups (~25%) and the patients most commonly died due to disease progression (~17%). A similar fraction died due to AEs in both groups and of these, 1.3% (4/312) died of treatment-related AEs (general physical health deterioration, mesenteric artery thrombosis, and pneumonitis) in the cemiplimab/chemo arm compared to 0.7% of the patients in the placebo/chemo arms (enterocolitis). The narratives for these deaths have been reviewed and it is agreed that there was only one death related to treatment with cemiplimab in this safety population; i.e. the one patient (0.3%) who died from pneumonitis.

The overall **discontinuation rate** due to AEs were higher in the cemiplimab + chemo group than for the placebo + cemiplimab group (5.1% vs 2.6%). Hence, the addition of cemiplimab increased the rate of discontinuations, but this is considered within an acceptable range considering the treated and targeted disease of advanced lung cancer.

Subgroup analyses indicating higher toxicity was observed in the >65-year old patients regarding grade 3-4 AEs, SAEs, and AEs leading to death, but the difference was not large and was within an acceptable range. It is noted that there was no clear trend toward more discontinuations due to AEs with age. Moreover, the safety profile according to histology showed that patients with squamous histology, who received cemiplimab + chemo had significantly fewer serious adverse events (SAEs) than patients with non-squamous histology 18.8% vs 30.2%). This can be explained by the use of maintenance pemetrexed in patients with non-squamous histology and increased use of the more toxic cisplatin versus carboplatin-based chemotherapy.

The section 4.8 of the SmPC was updated to reflect the safety profile of cemiplimab in combination with platinum-based chemotherapy. Immune-mediated adverse reactions occurred in 18.9% of patients including Grade 5 (0.3%), Grade 3 (2.6%), and Grade 2 (7.4%). Immune-mediated adverse reactions led to permanent discontinuation of cemiplimab in 1.0% of patients. The most common immune-mediated adverse reactions were hypothyroidism (7.7%), hyperthyroidism (5.1%), increased blood thyroid stimulating hormone (4.2%), immune-mediated skin reaction (1.9%), immune-mediated pneumonitis (1.9%), and decreased blood thyroid stimulating hormone (1.6%).

No changes to the safety concerns and risk minimisation measures in the RMP were deemed necessary.

2.5.2. Conclusions on clinical safety

The addition of cemiplimab to 4 cycles of platinum-based chemotherapy compared to placebo + chemotherapy showed overall increased toxicity, especially haematological, immune-mediated adverse events and more discontinuations due to adverse events. However, no new safety signals were observed, and the safety profile of the combination therapy is acceptable considering the treated and targeted disease of advanced lung cancer.

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 4 is acceptable.

The CHMP endorsed the Risk Management Plan version 4 with the following content:

Safety concerns

Table 60: Summary of Safety Concerns

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

Pharmacovigilance plan

There are no additional pharmacovigilance activities planned for cemiplimab.

Risk minimisation measures

Table 61: 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 PL sections 2 and 4	Routine pharmacovigilance

Safety Concern	Risk Minimisation Activities	Proposed Pharmacovigilance Activities
Immune-mediated adverse reactions **(**immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, immune- mediated skin reactions, nephritis, and other imARs)	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	Use of specific follow-up questionnaire for spontaneous postmarketing reports of imARs
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
Important Potential Risk: Lack of Effect due to Anti-drug Antibodies	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
Long-Term Safety Data	Not applicable	Routine pharmacovigilance

2.7. Update of the Product information

As a consequence of this new indication, 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are being updated to reflect the addition of the new therapeutic indication to include LIBTAYO in combination with platinum - based chemotherapy for the first-line treatment of adult patients with locally advanced NSCLC who are not candidates for definitive chemoradiation or metastatic NSCLC expressing PD-L1 (in $\geqslant$ 1% of tumour cells), with no EGFR, ALK or ROS1 aberrations. The Package Leaflet (PL) is updated accordingly.

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 proposed changes to the package leaflet related to this new indication are minimal and it is consequently agreed that a separate user consultation with target patient groups is not required.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication is for LIBTAYO in combination with platinum-based chemotherapy for the first-line treatment of adult patients with NSCLC expressing PD-L1 (in ≥ 1% of tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:

- locally advanced NSCLC who are not candidates for definitive chemoradiation or
- metastatic NSCLC.

The aim of added cemiplimab in the targeted population is to prolong overall survival (OS) and improve progression-free survival (PFS).

3.1.2. Available therapies and unmet medical need

In the 1st line treatment for the patient group encompassed by the sought indication the recommended treatments are a combination of platinum-based chemotherapy and anti-PD-1/PD-L1 inhibitors, in some cases with added anti-CTLA-4 agents or anti-PD-1/PD-L1 inhibitors as monotherapy for patients with high PD-L1 expression (ESMO 2023). All the approved combinations of platinum-based chemotherapy and immune checkpoint inhibitors for advanced NSCLC encompass the metastatic setting only, so an unmet medical need for patients with locally advanced disease (often stage IIIB) that cannot receive definite chemoradiation exists.

3.1.3. Main clinical studies

The main study for the current application, study R2810 ONC 16113 Part 2 (EMPOWER-Lung 3) is a global, randomised (2:1), phase III, double blinded study aiming to show a difference in OS by the addition of cemiplimab to standard chemotherapy.

3.2. Favourable effects

Study 16113 Part 2 met its primary endpoint of OS in the ITT (PD-L1 unselected) population (n=466) with a HR of 0.71 (95% CI: 0.53-0.93) and p=0.014 at the second pre-planned interim analysis (IA2) with a data cut-off of June 14th 2021 and OS maturity of 46%. The median follow-up for the total population was 16.43 months (range: 8.5, 24.0). There was a clear difference in median OS of 21.9 months (15.5-NE) in the cemiplimab+chemotherapy arm vs 13 months (11.9-16.1) in the placebo+chemotherapy arm. The secondary endpoints of PFS, ORR and DoR were also met in the ITT

population. The PFS HR was 0.56 (95% CI: 0.44-0.699), p<0.0001 and the difference in median PFS of 8.2 months (95% CI: 6.4-9.3) vs 5 months (95% CI: 4.3-6.2) is considered clinically meaningful. The updated efficacy data with a follow up of 28.4 months showed consistency over time. When excluding patients with PD-L1 expression <1%, the median OS was 21.9 months (95% CI: 17.3, NE) in the cemiplimab arm vs 12.6 months (95% CI: 10.3, 16.4) in the placebo arm. The median PFS was 8.5 months (95% CI: 6.7-10.7) in the cemiplimab arm vs 5.5 months (95% CI: 4.3-6.2) in the placebo arm with a HR of 0.48 (95% CI: 0.36-0.63).

3.3. Uncertainties and limitations about favourable effects

Subgroup analyses indicated that patients with PD-L1 expression ≥1% were the main driver of benefit in terms of OS and PFS both in the primary and updated efficacy datasets.

The PD-L1<1% subpopulation was constituted by nearly a third of the ITT (139 patients, 30%), and the benefit from adding cemiplimab to chemotherapy in these patients was uncertain, as a lower median OS was reported in the cemiplimab arm compared to the placebo arm in the primary analysis: OS HR of 1.006 (0.633-1.600), median OS 12.8 months in the cemiplimab arm vs 14.2 months in the placebo arm. Updated results confirmed this trend, noting HR for OS at 0.939 (0.62-1.42) in this subgroup.

3.4. Unfavourable effects

Almost all of the patients experienced at least one **adverse event** (AE) in the pivotal study and the most frequently observed events were (cemiplimab/chemo vs placebo/chemo): Anaemia (43.6% vs 39.9%), alopecia (36.9% vs 43.1%), nausea (25.0% vs 16.3%), hyperglycaemia (17.6% vs 11.8%), decreased appetite (17.0% vs 11.8%), alanine aminotransferase increased (16.3% vs 14.4%), neutropenia (15.4% vs 12.4%), and arthralgia (15.4% vs 13.1%). The most commonly observed **grade ≥3 AEs** by PT (≥2% of patients) were: Anaemia (9.9% vs 6.5%), neutropenia (5.8% vs 5.9%), white blood cell count decreased (3.2% vs 2.0%), pneumonia (2.9% vs 3.3%), thrombocytopenia (2.6% vs 1.3%), alanine aminotransferase increased (2.2% vs 2.0%), fatigue (2.2% vs 0.7%), and dyspnoea (2.2% vs 0.7%).

Treatment-related AEs were similar to the AEs observed, and the most commonly observed of all grades were: Anaemia (40.7% vs 34.0%), alopecia (36.5% vs 42.5%), and nausea (22.8% vs 16.3%); while the most common grade ≥3 treatment-related AEs were: Anaemia (9.6% vs 6.5%), neutropenia (5.4% vs 5.9%), and white blood cell count decreased (3.2% vs 1.3%). It is noted that increased haematological toxicity led to a higher incidence of febrile neutropenia in the cemiplimab/chemo arm (1.3% vs 2.6%).

The incidence of affected electrolytes was also increased in the cemiplimab + chemo groups regarding all grade events (85.6% vs 74.7%); however, the high grade 3-4 events were evenly distributed.

Adverse events of special interest included infusion-related reactions and immune-related adverse events (imAE) as they are important identified risks with cemiplimab. Only 2.2% of the safety population (n=312) had an infusion-related reactions. Immune-related adverse events were commonly observed (18.9%), but these events were rarely of high grade (≥grade 3: 2.9%) and the most frequently observed were hypothyroidism (7.7%), hyperthyroidism (5.1%), blood thyroid stimulating hormone increased (4.2%) or decreased (1.6%), and pneumonitis (1.6%). Only 1.0% of the patients discontinued treatment due to imAEs.

Serious adverse events (SAEs) were observed in a quarter of the patients (25.3% vs 22.2%) in the cemiplimab/chemo arm vs the placebo/chemo groups, most often pertaining to pneumonia (2.9 % vs 2.0%) and anaemia (2.9% vs 1.3%), and as mentioned febrile neutropenia (1.3% vs 2.6%).

Overall, there was an equal fraction of **deaths** in both groups (~25%) and the patients most commonly died due to disease progression (~17%). Importantly, although a similar fraction died due to AE in both groups and of these, 1.3% (4/312) died of treatment-related AEs (general physical health deterioration, mesenteric artery thrombosis, and pneumonitis) in the cemiplimab/chemo arm compared to 0.7% of the patients in the placebo/chemo arms (enterocolitis). The narratives for these deaths have been reviewed and it is agreed that there were only one death related to treatment with cemiplimab in this safety population; i.e. the one patient (0.3%) who died from pneumonitis.

The overall **discontinuation rate** due to AEs were higher in the cemiplimab + chemo group than for the placebo + cemiplimab group (5.1% vs 2.6%).

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 62: **Effects Table for Study 16113 Part 2, PD-L1 in ≥ 1% of tumour cells: *A Two-Part Randomized, Phase 3 Study of Combinations of Cemiplimab (Anti-PD-1 Antibody) and Platinum-based Doublet Chemotherapy in First-line Treatment of Patients with Advanced or Metastatic Non-Small Cell Lung Cancer* (data cut-off: 14 June 2021)**

Effect	Short description	Unit	Treatment Cemiplimab+chemotherapy (n=217)	Control Placebo+chemotherapy (n=110)	Uncertainties / Strength of evidence	
Favourable Effects						
IRC-OS	Median Overall survival	Months (95% CI)	21.9 (17.3-NE)	12.6 (10.3-16.4)	HR 0.55 (0.39-0.78)	
IRC-PFS	Median progression-free survival	Months (95% CI)	8.5 (6.7-10.7)	5.5 (4.3-6.2)	HR 0.48 (0.36-0.63) p<0.0001	
IRC-ORR	Overall response rate	% (n)	47.9 (41.1, 54.8)	22.7 (15.3, 31.7)		
IRC-DoR	Median duration of response	Months (95% CI)	15.6 (1.7, 18.7+)	4.9 (1.9, 18.8+)		
Unfavourable Effects						
Grade ≥3 AEs		%	43.6	31.4		
SAE		%	25.3	22.2		
AEs leading to discontinuation		%	5.1	2.6		
AEs leading to death		%	6.1	7.8		

Abbreviations: IRC – Independent Review Committee; AE – Adverse Event; SAE – Serious AE.
Notes: The median follow-up for the total population was 16.43 months (range: 8.5, 24.0)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Lung cancer is still the leading cause of cancer death worldwide and lung cancer patients in need of treatment options are abundant. It is therefore of great importance, that multiple treatment options exist.

In study 16113 Part 2, the addition of cemiplimab to standard chemotherapy as 1st line treatment of advanced NSCLC proved to prolong overall survival and progression free survival significantly and this is considered clinically relevant.

Study 16113 Part 2 was the first study to include and establish benefit from the addition of cemiplimab (an ICI) to chemotherapy in patients with locally advanced as well as metastatic disease and in patients with both squamous and non-squamous cell histology in one trial. However, in the subgroup of patients who were PD-L1 negative (<1%) the uncertain benefit from the addition of cemiplimab to chemotherapy does not outweigh the added toxicity and this patient group has been excluded from the indication in section 4.1 of the SmPC.

Regarding safety, the addition of cemiplimab to 4 cycles of platinum-based chemotherapy compared to placebo + chemotherapy showed overall increased toxicity, especially haematological, immune-mediated adverse events and more discontinuations due to adverse events. However, no new safety signals are observed, and the safety profile of the combination therapy is acceptable considering the treated and targeted disease of advanced lung cancer.

3.7.2. Balance of benefits and risks

The balance of benefits and risks is positive as the demonstrated gains from the addition of cemiplimab to platinum-based chemotherapy regarding OS and PFS are significant and considered clinically relevant and meaningful.

The overall effect in the ITT population is considered driven by the stratified subgroup of patient with PD-L1 ≥ 1%, for whom a relevant and significant improvement in PFS and OS is observed. in patients with tumoural PD-L1 expression While the overall safety profile of the combination is deemed manageable, the uncertain efficacy in the PD-L1 negative (<1%) population of adding cemiplimab to chemotherapy, does not outweigh the additional toxicity that these patients are exposed to.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of cemiplimab for the intended extension of indication is currently negative due to a major objection that concerns the indication statement.

The overall B/R of Libtayo in combination with platinum - based chemotherapy is positive for the first - line treatment of adult patients with NSCLC expressing PD-L1 (in ⩾ 1% of tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:

- locally advanced NSCLC who are not candidates for definitive chemoradiation, or

- metastatic NSCLC.

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 26 out of 29 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 and IIIB

Extension of indication to include LIBTAYO in combination with platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced NSCLC who are not candidates for definitive chemoradiation or metastatic NSCLC with no EGFR, ALK or ROS1 aberrations; as a consequence, sections 4.1, 4.2, 4.4, 4.8, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted.

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.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Libtayo-H-C-004844-II-28'

APPENDIX

DIVERGENT POSITION DATED 23 February 2023

DIVERGENT POSITION DATED 23 February 2023

LIBTAYO EMEA/H/C/004844/II/0028

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of LIBTAYO indicated for LIBTAYO in combination with platinum - based chemotherapy is indicated for the first - line treatment of adult patients with NSCLC expressing PD-L1 (in ≥ 1% of tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:

- locally advanced NSCLC who are not candidates for definitive chemoradiation or
- metastatic NSCLC.

The reason for divergent opinion was the following:

The restriction of the 1L locally advanced/metastatic NSCLC indication for Libtayo as add-on to chemotherapy, to patients with tumour PD-L1 expression >1% is not agreed.

The 1L NSCLC indication is based on a pivotal study including all-comers with respect to PD-L1 expression. This has robustly demonstrated an OS advantage in its ITT population (HR 0.71; p=0.01)

The most mature data update show that in the subgroup of patients with PD-L1 expression <1% (N=139), the OS HR is 0.94, with a broad 95% confidence interval ranging from 0.61-1.42. Due to the low number of events, no independent inference of efficacy can be made in the PD-L1 <1% subgroup based on the OS metric.

However, in the context of an overall positive study, efficacy in this subgroup is supported by a trend towards a PFS gain (HR 0.73; 95% CI 0.5-1.08) together with an increase in ORR over chemotherapy alone (34% versus 20%). Thus, the antitumoral activity of cemiplimab in low PD-L1 expressors is evident.

Moreover, external evidence supports the benefit of PD-1/PD-L1 targeting drugs as add-on to chemotherapy for the 1L treatment of metastatic NSCLC regardless of the level of PD-L1 expression. Indeed, for none of the other products in this drug class, has the CHMP restricted add-on use in metastatic NSCLC to patients with higher PD-L1 expression.

While the addition of cemiplimab to platinum - based chemotherapy does increase toxicity, this is moderate and manageable.

In summary, available evidence supports efficacy and a positive B/R for Libtayo as add on to chemotherapy in the 1L treatment of locally advanced/metastatic NSCLC, regardless of PD-L1 expression.

Maria Concepcion Prieto Yerro

Kristina Dunder

Sol Ruiz