20 May 2021
EMA/319413/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

LIBTAYO

International non-proprietary name: cemiplimab

Procedure No. EMEA/H/C/004844/II/0011

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

Abbreviation	Definition
5-FU	fluorouracil
13cRA	13-*cis*-retinoic acid
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BA	Bioavailability
BCC	Basal cell carcinoma
BOR	Best objective response
CI	Confidence interval
CLcr	Creatinine clearance
C_{max}	Peak concentration
CNS	Central Nervous System
CR	Complete response
CSCC	Cutaneous squamous cell carcinoma
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte antigen-4
C_{trough}	Trough concentration at the end of the dosing interval
CV	Coefficient of variation
CYP	Cytochrome P450
DCR	Disease control rate
DDCR	Durable disease control rate
DOR	Duration of response
DP	Drug product
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EudraCT	European Clinical Trials Database
FAS	Full analysis set
FDA	Food and Drug Administration
FIH	First-in-Human
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICR	Independent central review
ICRC	Independent Composite Review Committee
IDMC	Independent Data Monitoring Committee
IFNα	Interferon alpha
IFU	Instructions for use
IgG	Immunoglobulin G
imAE	Immune-mediated adverse event (also referred to as immune-related adverse event [irAE])
IPRC	Independent Photographic Review Committee
irAE	Immune-related adverse event (also referred to as imAE)
IRR	Infusion-related reaction
IRRC	Independent Radiology Review Committee
iSAP	Integrated Statistical Analysis Plan
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intention-to-treat
IV	Intravenous(ly)

Abbreviation	Definition
K-M	Kaplan-Meier
laBCC	Locally advanced basal cell carcinoma
laCSCC	Locally advanced cutaneous squamous cell carcinoma
MAH	Marketing authorisation holder
mBCC	Metastatic basal cell carcinoma
mCSCC	Metastatic cutaneous squamous cell carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
n	Total number of patients in the group
N	Total number of patients
NAb	Neutralizing antibody
NCT	National Clinical Trial
NE	Not evaluable
NSCLC	Non-small cell lung cancer
NTL	Non-target lesion
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1, PD-L2	Programmed death-ligand 1, programmed death-ligand 2
PF	Platinum + 5-fluorouracil
PFS	Progression-free survival
PI3K	Phosphatidylinositol 3-kinase
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic
PR	Partial response
PT	Preferred term
Q2W	Every 2 weeks
Q3W	Every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Stable disease
SDv	Standard deviation
SEER	Surveillance, Epidemiology, and End Results Program
SJS	Stevens-Johnsons syndrome
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TEN	Toxic epidermal necrolysis
TL	Target lesion
TLR-7	Toll-Like Receptor-7
TMB	Tumor mutation burden
TTR	Time to response
ULN	Upper limit of normal
US	United States
UV	Ultraviolet
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Regeneron Ireland Designated Activity Company (DAC) submitted to the European Medicines Agency on 21 August 2020 an application for a variation.

The following variation was requested:

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

Extension of indication for LIBTAYO as monotherapy indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:

- locally advanced NSCLC and who are not candidates for surgical resection or definitive chemoradiation, or have progressed after treatment with definitive chemoradiation, or
- metastatic NSCLC.

The PL is revised accordingly. A revised RMP is submitted.

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

Information on paediatric requirements

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

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

MAH request for additional market protection

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

Scientific advice

The MAH received scientific advice (SA) from the CHMP in November 2016 and follow-up SA in January 2019.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Sinan B. Sarac Co-Rapporteur: Johanna Lähteenvuo

Timetable	Actual dates
Submission date	21 August 2020
Start of procedure:	12 September 2020
CHMP Co-Rapporteur Assessment Report	6 November 2020
CHMP Rapporteur Assessment Report	13 November 2020
PRAC Rapporteur Assessment Report	13 November 2020
PRAC Outcome	26 November 2020
CHMP members comments	30 November 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	4 December 2020
Request for supplementary information (RSI)	10 December 2020
CHMP Rapporteur Assessment Report	24 February 2021
PRAC Outcome	11 March 2021
Updated PRAC Rapporteur Assessment Report	18 March 2021
Updated CHMP Rapporteur Assessment Report	18 March 2021
Request for supplementary information (RSI)	25 March 2021
CHMP Rapporteur Assessment Report	05 May 2021
CHMP members comments	10 May 2021
Updated CHMP Rapporteur Assessment Report	12 May 2021
Opinion	20 May 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The MAH proposed the following indication:

LIBTAYO as monotherapy is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:

• locally advanced NSCLC and who are not candidates for surgical resection or definitive chemoradiation, or have progressed after treatment with definitive chemoradiation, or

• metastatic NSCLC.

Epidemiology

Lung cancer is the main cause of malignancy-related mortality worldwide (Bray F et al. CA Cancer J Clin. 2018), accounting for 1.80 million of deaths globally per year as estimated by the World Health Organization (WHO) (GLOBOCAN 2020). 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%) (Principles and Practice of Oncology. 9th Edition. 2011).

Biologic features, Aetiology and pathogenesis

Historically, NSCLC has been considered a non-immunogenic disease (Brahmer 2013). However, emerging evidence has demonstrated that the lack of an effective immune response is, in fact, often the result of specific, active immune-evasive mechanisms. These mechanisms, if understood, can be overcome therapeutically with meaningful clinical efficacy (Carbone et al 2016). The most significant advances in NSCLC immunotherapy have been made in metastatic setting by targeting the PD-1/PD-L1 immune checkpoint (Shu and Rizvi 2016). The PD-1/PD-L1 checkpoint inhibitors shift the balance of immune activity from a tumour-induced immune suppressive state toward an active antitumor immune response.

Clinical presentation, diagnosis and 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, 2020).

Histological diagnosis of NSCLC is crucial to many treatment decisions and should be as exact and detailed as the samples and available technology allow.

Despite optimal treatment, patients have a median overall survival (OS) of approximately 8 to 12 months, and a 5-year survival rate of approximately 18% (Siegel, 2016).

Management

The majority of patients diagnosed with NSCLC are unsuitable for curative treatment. Systemic therapy with platinum-based doublet regimens, with or without maintenance therapy was until recently the standard first-line treatment for patients with locally advanced or metastatic NSCLC whose tumors do not have an EGFR mutation, an ALK mutation, or a ROS1 fusion (Besse, 2014) (Ettinger, 2016) (Reck, 2014).

Over the past decade, however, substantial progress has been made in the field of immuno-oncology, a treatment approach based on inducing host anti-tumor immune responses that lead to clinical responses. Agents that block the immunosuppressive PD-1/PD-L1 axis (often called "immune checkpoint blockade"), have collectively demonstrated clinical activity in numerous solid tumor indications, including NSCLC.

The phase III KEYNOTE-024 study has established the role for pembrolizumab as first-line treatment in patients with untreated, advanced NSCLC and tumour characterised by PD-L1 expression ≥ 50%, in absence of EGFR mutation or ALK translocations. In KEYNOTE-024, 1934 patients were screened to identify 500 patients (30%) with tumour PD-L1 expression ≥ 50%. Of these patients, 305 patients were randomised to receive 200 mg pembrolizumab every 3 weeks (up to 2 years) or 4–6 cycles of standard platinum-doublet ChT. All efficacy measures favoured pembrolizumab, including objective response rate (ORR 45% versus 28%), progression-free survival (HR 0.5, 95% CI 0.37–0.68, p<0.001)] and overall survival (HR 0.6, 95% CI 0.41–0.89, p=0.005) (Reck, 2016). According to the ESMO 2020 guidelines, pembrolizumab is considered a standard first-line option for patients with advanced NSCLC and PD-L1 expression ≥ 50% who do not otherwise have contraindications to use of immunotherapy (such as severe autoimmune disease or organ transplantation).

2.1.2. About the product

Cemiplimab (LIBTAYO) 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-tumor immune response.

In June 2019, the EMA granted cemiplimab a conditional marketing authorisation (CMA) for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma (mCSCC or laCSCC) who are not candidates for curative surgery or curative radiation.

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

The current type II variation application is primarily based on the pivotal Study 1624 in NSCLC. The design aspects of the study were first presented to the CHMP in a SA procedure in November 2016, when the study was still at the planning stage. In January 2019, the MAH's plans for potential changes in the nature of endpoints and planned statistical analyses were discussed in a follow-up procedure. Pertinent items within the procedure include:

- Elevation of OS from a key secondary to a co-primary endpoint was accepted by CHMP.

- As the protocol had been amended to allow patients in the cemiplimab arm to receive chemotherapy in combination with cemiplimab at the time of progression, the CHMP advised that due consideration should be given to the potential confounding effect of the post-study treatments on OS. Therefore, when such a strategy is pursued, the Applicant is strongly recommended to carefully collect data after progression during the study, including PFS2. Moreover, adequate measures according to available guidelines should be implemented/pre-planned in order to capture potential impact of the crossover/post study therapies on the OS results. In particular, the activity/benefit of continuation of a checkpoint inhibitor (in this case cemiplimab) after progression with addition of chemotherapy hasn't been previously tested, but a potential confounding effect on OS (with potential inflation of the OS effect) cannot be excluded.
- Regarding the proposed testing analysis of the PFS and OS endpoints, the CHMP emphasised that in case OS and PFS are tested as co-primary endpoints, both endpoints would be required to be significant at the required alpha level. In the situation where the alpha is split, the study could be considered successful if either one of the two endpoints reaches significance. This is not the preferred approach for CHMP. Alternatively, a hierarchical testing strategy (similar to the strategy proposed for the add-on setting, first OS then PFS) could be considered acceptable.
- The proposed interim analysis for OS at the time of the final PFS analysis was acceptable to CHMP. However, a more detailed revised protocol would be needed for the CHMP to provide more specific advice on this aspect. The MAH was advised to ensure that a sufficient number of events have been observed at the time of the analysis to allow adequate evaluation of the treatment benefits.
- The non-proportional hazard of the study was discussed with the MAH as well as the inadequacy of conducting a log-rank test as primary analysis. Even though, in contrast to the Cox-proportional hazard model, the log-rank test is often incorrectly considered to make no assumption on the hazard it is not correct to assume that it will not be affected by the presence of a violation of that assumption. The MAH was invited to consider additional analyses that would allow the assessment of the impact of the violation of the proportionality assumption. Several methods have been described in the literature, with landmark analyses and restricted mean being the most often considered, but given the focus on this problem, an increasing number of additional methods are developed. According to CHMP, the MAH should consider pre-planning for such analyses, but is advised to explore all available options to address the needs of this specific setting. In addition, the MAH should provide analyses to explore whether the assumption is actually violated or not.

Some CHMP recommendations have not been followed within the submission, and the MAH has provided the following justifications:

- The MAH deemed collection of PFS2 data as not feasible as many patients would be moving to other studies where their data would no longer be available. Furthermore, the changed focus to OS in the MAH's opinion made the addition of PFS2 to substantiate a PFS advantage less relevant.
- According to the MAH, both alpha split and alpha reallocation are valid statistical methods to control overall type I error rate. The MAH chose to split alpha between OS and PFS to allow opportunity to test OS and PFS independently.
- According to the MAH, log-rank test is a nonparametric test which is valid with or without the existence of non-proportional hazard. The MAH increased study sample size to accommodate the loss of study power if non-proportional hazard exists in the study. Given that most of sensitivity analyses dealing with non-proportional hazard may inflate treatment effect, the MAH determined no additional sensitivity analysis is needed for this study.

Subsequent to the follow-up procedure, the MAH implemented further significant changes in its statistical analytical approach, including a substantial change in the interim analysis strategy

(discussed in further detail in section "Clinical efficacy"). This change and thus the final study design (per Protocol Amendment 8) was not the subject of a SA procedure.

2.1.4. General comments on compliance with GCP

No GCP inspections have occurred to the date of submission of the Marketing Authorisation Application (MAA). No critical audit findings were observed for Study R2810-ONC-1624.

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

Cemiplimab is an IgG4 monoclonal antibody consisting of linked naturally occurring amino acids being extensively degraded in the patient's body by regular proteolytic mechanisms before excretion, cemiplimab is unlikely to result in a significant environmental exposure. Cemiplimab is expected to biodegrade in the environment and does not pose a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), cemiplimab is exempt from the submission of Environmental Risk Assessment studies as the product and excipients do not pose a significant risk to the environment.

2.2.2. Discussion and conclusion on non-clinical aspects

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.

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of cemiplimab.

Considering the above data, cemiplimab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1. List of clinical studies in patients with solid tumours, including NSCLC, where pharmacokinetics and anti-drug antibodies were collected

Study Number Phase Data Cutoff/Status	Study Title (N = Number Enrolled)	Total Patients with solid tumors Evaluated for PK, PD, and ADA	Patients with NSCLC Evaluated for PK, PD, and ADA	Patients dosed with 350 mg Q3W Evaluated for PK, PD, and ADA
R2810-ONC-1423 Phase 1 30 Apr 2019/complete	A First-In-Human Study of Repeat Dosing with REGN2810, A Monoclonal, Fully Human Antibody to Programmed Death-1 (PD-1), As Single Therapy and In Combination with Other Anti-Cancer Therapies, In Patients with Advanced Malignancies (N = 398)	PK: 398 ADA: 337	PK: 71 ADA: 66	-
R2810-ONC-1540 Phase 2 20 Sep 2018 (Groups 1 + 3); 10 Oct 2018 (Group 2)/ongoing	A Phase 2 Study of REGN2810, A Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), In Patients with Advanced Cutaneous Squamous Cell Carcinoma (N = 193)	PK: 188 ADA: 140	-	PK: 53 ADA: 39
R2810-ONC-1620 Phase 2 17 Feb 2020/ongoing	A Phase 2 Study of REGN2810, A Fully Human Monoclonal Antibody to Programmed Death-1, In Patients with Advanced Basal Cell Carcinoma Who Experienced Progression of Disease on Hedgehog Pathway Inhibitor Therapy, Or Were Intolerant of Prior Hedgehog Pathway Inhibitor Therapy (N = 132)	PK: 132 ADA: 125	-	PK: 132 ADA: 125
R2810-ONC-1624 Phase 3 01 Mar 2020/ongoing Pivotal study for the NSCLC indication	A Global, Randomized, Phase 3, Open-Label Study of REGN2810 (Anti-PD-1 Antibody) Versus Platinum-Based Chemotherapy in First-Line Treatment of Patients with Advanced or Metastatic PD-L1 + Non-Small Cell Lung Cancer (N = 710 [356 randomized to cemiplimab])	PK: 345 PD: 283 ADA: 221	PK: 345 PD: 283 ADA: 221	PK: 345 PD: 283 ADA: 221
TOTAL		PK: 1063 PD: 283 ADA: 823	PK: 416 PD: 283 ADA: 287	PK: 530 PD: 283 ADA: 385

ADA = anti-drug antibody; NSCLC = non-small cell lung cancer; PD = pharmacodynamics; PK = pharmacokinetics; REGN2810 = cemiplimab.
Note: Although cemiplimab 350 mg Q3W dosing was not implemented in Study 1624 until Protocol Amendment 3, patient enrollment did not commence at any site until after approval of this amendment by the relevant health authorities and independent ethics committees.

The pharmacokinetics, pharmacodynamics, and immunogenicity of cemiplimab were assessed in four clinical studies: 1) the completed FIH Study 1423 conducted in adult patients with various types of advanced solid tumours, including patients with NSCLC, treated with cemiplimab as monotherapy or in combination therapy, with dense sampling for pharmacokinetics (PK) and anti-drug antibody (ADA) assessment; 2) two ongoing pivotal phase 2 studies with cemiplimab monotherapy in adult patients with skin cancer: Study R2810-ONC-1540 (referred to as Study 1540) in patients with advanced CSCC and Study R2810-ONC-1620 (referred to as Study 1620) in patients with advanced basal cell carcinoma (BCC); and 3) one ongoing pivotal phase 3 monotherapy study in adult patients with advanced NSCLC: R2810-ONC-1624 (Study 1624) in patients with stage IIIB, IIIC, or stage IV squamous or non-squamous NSCLC, whose tumours express ≥50% PD-L1.

2.3.2. Pharmacokinetics

Bioanalytical methods

For all four studies, serum samples for quantitation of functional cemiplimab were analysed using a validated enzyme-linked immunosorbent assay with a lower limit of quantitation (LLOQ) of 78 ng/mL cemiplimab in neat serum.

The validated method for detecting ADA is a non-quantitative, titer-based, electrochemiluminescent bridging immunoassay for screening, confirmation and titer determination. The ADA method was amended with established long-term stability of 12 months for the positive control. The method determined a drug tolerance of 415 µg/mL cemiplimab at a sensitivity of 100 ng/mL ADA positive control, which is adequate to cover the C_{min} drug contents anticipated at steady-state in NSCLC patients (about 60 µg/mL at 350 mg (once every 3 weeks (Q3W)). However, in the bioanalytical reports, the drug tolerance limit is given as 734 µg/mL cemiplimab at a sensitivity of 500 ng/mL ADA positive control. The determined drug tolerance seems adequate and should be given at the 100 ng/mL sensitivity level. Cut-off points in the immunogenicity assay were determined using baseline samples from Study 1423, which also included NSCLC patients.

The NAb method is an electrochemiluminescence-based competitive ligand binding assay. The drug tolerance level of the NAb method is 330 ng/mL cemiplimab with a sensitivity of 500 ng/mL NAb positive control, which is not adequate to cover the anticipated drug levels in the samples.

In general, the number of failed plates were low indicating the conducted bioanalyses were robust.

In Study 1624 (NSCLC), 240 out of 3671 samples analysed were tested for incurred sample reanalysis (ISR) with a 98.8% pass-rate. 634 samples were evaluated ADA and 17 confirmed ADA+ samples were tested for NAbs. All tested negative. In Study 1620 (BCC), 1783 samples were analysed while 638 samples were evaluated for ADA. ISR was conducted on 148 samples with a pass rate of 100%. In Study 1423, 10540 samples were analysed in total, while 1151 samples were evaluated for ADA. ISR was conducted of 579 samples with a pass rate of 91%. In Study 1540, 2708 samples were analysed (data cut-off 20 Sep 2018), 262 samples were evaluated for ADA and ISR was conducted of 199 samples (7%) with a 75% pass-rate.

All samples for determination of cemiplimab concentration were stored at -80°C prior to analysis and analysed within 24 months of collection within the established 24-month long-term storage stability.

Population PK analyses

The final Pop PK model for cemiplimab in patients with solid tumours was based on a model developed for cutaneous squamous cell carcinoma (CSCC). The initial model was updated with data from Studies 1423, 1540, 1620 and 1624 in patients with basal cell carcinoma (BCC), CSCC, NSCLC and other solid tumours who received cemiplimab 350 mg Q3W. The Pop PK population contained 17193 data points from 1062 patients (Table 2).

Table 2. Summary of Population and PK samples included in the Pop PK in analysis dataset

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

N = Number of patients; Q2W = Once every 2 weeks; Q3W = Once every 3 weeks

The final structural model (BASE006) was a two-compartment model with zero-order IV infusion, linear elimination with a time-dependent clearance (sigmoid E_{max} function with fixed Hill factor), time-varying albumin and effect of baseline body weight allometric scaled with fixed exponents of 0.75 (CL) and 1.0 (V). The final covariate model included four covariates: weight, albumin, immunoglobulin G (IgG) (only applicable to studies 1423 and 1540) and disease type (NSCLC relative to CSCC) on the elimination clearance CL.

Compared to the previous model, the following covariate changes are present: Previously, "Black" race was a predictor of delay of clearance change (T_{50}), indicating a slower decrease in clearance than what is observed for other ethnicities. This covariate relationship is no longer present. Also, the covariate effect of alanine aminotransferase on clearance has disappeared. A new covariate effect to describe association between NSCLC and clearance is included. The covariate effect of albumin on clearance is essentially unchanged, and so is the effect of IgG on clearance. Regarding size, body weight was previously included as an empirical covariate, and clearance was proportional to weight to the power of 0.45. Steady-state volume of distribution (Vd) was previously proportional to weight to the power of 0.935 and proportional to body-mass index (BMI) to the power of -0.553. In the current model, fixed allometry has been used to set the clearance proportional to weight to the power of 0.75, and Vd proportional to weight to the power of 1.0. Plots of Empirical Bayes Estimates versus covariates from the final population PK model reveal a slight trend of decreasing random effect values versus weight for both clearance and steady-state volume of distribution, however the magnitude of the trend is small compared to the extent of overall inter-individual variability. The fixed allometric exponents are considered to sufficiently capture the cemiplimab weight-PK covariate relationships. No other significant trends could be observed in plots of Empirical Bayes Estimates versus covariates.

The final model was evaluated by Bootstrap analysis, goodness of fit (GoF) plots and visual predictive checks (VPCs). All diagnostic plots and VPCs indicated the PK model could describe the PK of cemiplimab. The final parameters were estimated with adequate precision (%RSE). Nonparametric bootstrap was performed on 500 replicate datasets and resulted in 95% CIs for population PK parameter estimates. The bootstrap estimates matched well to the final parameter estimates and none of the 95% CI contained the null (Table 3).

Inter-individual variability was included for the parameters describing the T_{50} and the maximal extent of clearance change (Emax). This is appropriate to ensure that a unique time-varying clearance profile

is estimated for each subject, and the resulting individual exposure parameters are informative for the exposure-response analyses.

Eta shrinkage ranged from 18.5 to 30.4%. The shrinkage was high for Emax and T_{50}, hence the information for these effects are limited. The conditional number was <10, indicating that the model was not over-parameterised. Less than half of the 500 bootstrap runs (238 (~47.6%)) converged, which might indicate lack of robustness in the model structure. The CV% of population PK parameter estimates from the final model ranged from 49%-97.5% with the non-linear clearance parameters Emax and T_{50} having the highest CV% of 63.3% and 97.5%. These parameters were also the main reason for the large proportion of failed bootstrap runs due to inadequate data to describe the time-dependent clearance.

Clearance decreased over time of treatment with cemiplimab. The change in clearance is larger in patients who were considered responders to cemiplimab (35.3% decrease).

Table 3. Summary of parameter values after modelling with analysis dataset or bootstrap datasets for the final model

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

*HILL was fixed at 2.50.

It is noted that at steady state, the NSCLC population have marked increased CL, shorter half-life and thus lower exposure, in non-responders ("all others") compared to responders. This is not seen to the same extent for the other solid tumour types (Figure 1).

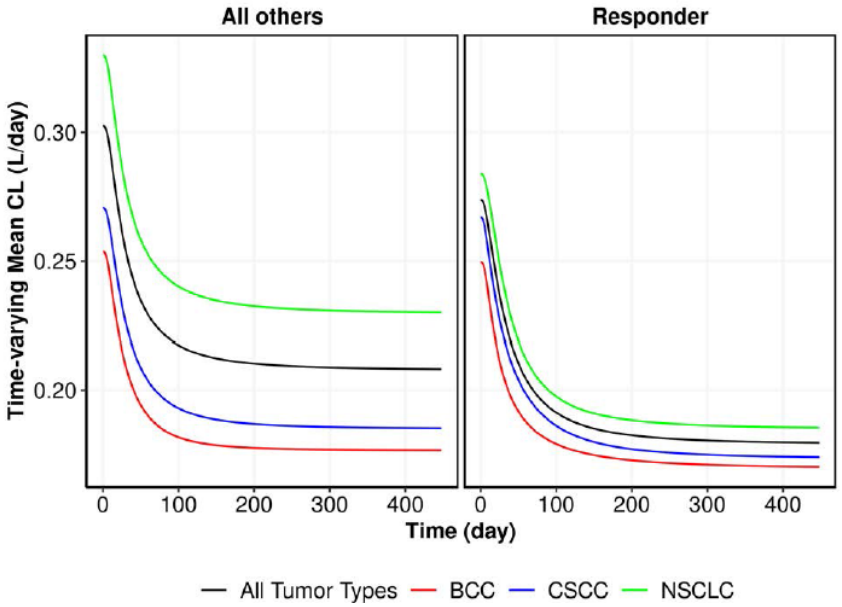

Figure 1. Clearance over time in responders vs all others in patients with BCC, CSCC or NSCLC compared to the overall patients
Abbreviations: CSCC= cutaneous squamous-cell carcinoma; BCC= basal cell carcinoma; NSCLC= non-small-cell lung cancer. Note: All tumour types=In the overall PopPK population (n=1062), including advanced BCC: All others (n=106), Responders (n=30); CSCC= All others (n=118), Responders (n= 96); NSCLC = All others (n= 279), Responders (n=137).

The Pop PK model for cemiplimab was refined which improved robustness and gave a better fit for NSCLC patients. The model structure was maintained. Estimation of inter-individual variability on Emax and T_{50} were removed, the proportional error model was changed to a log-additive error model and the off-diagonal covariance between inter-individual random effects on CLQ and V_{SS} was also removed. A covariate effect of NSCLC on T_{50} was included which improved the model notably. The original model was not stable. Model stability of the updated model was evaluated using bootstrap (n=500) and all runs converged successfully. The provided GoF plots and pc-VPCs indicated the model could adequately describe the observed concentrations of cemiplimab in non-NSCLC and NSCLC patients.

A sensitivity analysis of outliers defined as |CWRES|>5 or |IWRES|>5 (n=85) indicated inclusion/exclusion of these observations did not have relevant impact on the parameter estimates.

Simulation of exposure metrics

The final population PK model was used to generate post-hoc estimates of individual PK parameters and simulate exposure metrics for each subject in the analysis population. Descriptive statistics of summary exposure metrics were presented after the first dose and at steady-state stratified for dose or solid tumour type and responder/all others (data not shown).

Absorption

Cemiplimab was administered intravenous (IV) as a 30-minute infusion and peak concentrations (Cmax) are typically reached at the end of infusion.

Similar absorption and distribution profiles after the first dose were noted in patients with advanced NSCLC and in all patients with solid tumours (Table 4).

Table 4. Cemiplimab exposure (Ctrough and Cmax) after the first dose and at steady state in patients with CSCC, in patients with BCC, in patients with NSCLC, in all patients receiving 350 mg Q3W and in all patients receiving 3 mg/kg Q2W on cemiplimab monotherapy

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

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

In the first-in-human study 1423, rich PK sampling occurred after the first dose, allowing to assess Tmax, while in the pivotal phase 2/3 Studies 1540, 1620 and 1624, sparse PK sample collection was applied at pre-dose and end-of-infusion during treatment and at selected time points during follow up. Except for Study 1423, where Cmax could be estimated, concentrations at the end-of-infusion were referred to as 'Cmax'. While maximal cemiplimab concentrations are expected to be reached at the end of the 30-minute IV infusion, as anticipated for a monoclonal antibody with a slow clearance, very similar concentrations within the bioanalytical range of variability are observed at 1-hour and occasionally at 4-hours post-end-of-infusion. As a result, the median value for Tmax in the FIH Study 1423 is reported as 0.5 hours, with a range of 0.033 hours to 4.0 hours.

Population predicted Ctrough and Cmax values in the overall PopPK population of 1062 patients at 350 mg Q3W are presented in Table 5. These data indicate that cemiplimab exposure in the overall PopPK population of patients with solid tumours is similar to that observed in patients with advanced NSCLC and that the population model predicted values in the overall population of patients with solid tumours are representative of patients with advanced NSCLC in the pivotal Study 1624.

Table 5. Population PK estimates of cemiplimab exposure in patients with solid tumours in the overall PopPK population and patients with advanced NSCLC receiving 350 mg Q3W

After first Dose			At Steady State		
Parameter	**Units**	**Mean (CV%)**	**Parameter**	**Units**	**Mean (CV%)**
All Patients with Solid Tumors (N=1062)					
$C_{max,3wk}$	mg/L	112(25.9%)	$C_{max,ss}$	mg/L	171(27.5%)
$C_{trough,3wk}$	mg/L	22.1(34.0%)	$C_{trough,ss}$	mg/L	60.9(44.9%)
AUC_{3wk}	mg*day/L	885(26.6%)	$AUC_{3wk,ss}$	mg*day/L	1940(35.5%)
Patients with NSCLC (N=345)					
$C_{max,3wk}$	mg/L	118(24.1%)	$C_{max,ss}$	mg/L	169(25.3%)
$C_{trough,3wk}$	mg/L	20.0(32.8%)	$C_{trough,ss}$	mg/L	53.0(43.5%)
AUC_{3wk}	mg*day/L	876(24.9%)	$AUC_{3wk,ss}$	mg*day/L	1800(33.2%)

Overall PopPK population (N=1062 patients). The last dose in the simulations is at week 48
Source: Population PK Report R2810-PK-20039-SR-01V1 Table 29 and Table 37.

Distribution

As is typical for monoclonal antibodies, cemiplimab is primarily distributed in the vascular system. Based on PopPK analysis, the total volume of distribution at steady state is 5.3 L (Table 6).

Elimination

Specific metabolism studies were not conducted because cemiplimab is a protein. Cemiplimab is expected to be degraded into small peptides and individual amino acids. Additionally, given their molecular weight and hydrodynamic size, mAbs are also not subject to renal elimination.

The clearance of cemiplimab is independent of dose for the regimens studied (1 mg/kg to 10 mg/kg Q2W) and linear elimination was confirmed by PopPK analysis. Descriptive statistics for individual cemiplimab PK parameters in PopPK patient population are summarized in (Table 6).

Table 6. Descriptive statistics for individual cemiplimab PK parameters in PopPK patient population with solid tumours estimated using the final PK population model

Parameter	Mean (CV%)	SD
Clearance after the first dose (L/day)	0.293(33.1%)	0.0972
Clearance at steady state (L/day)	0.203(40.2%)	0.0814
Reduction in clearance (%)	29.4(49.2%)	14.5
Half-life at first dose (day)	13.9(22.5%)	3.12
Half-life at steady state (day)	20.3(29.2%)	5.94
Volume of distribution at steady state (L)	5.26(26.0%)	1.37
Overall PopPK Population (N=1062 Patients) CV% = percent coefficient of variation; SD = standard deviation.		
Source: Population PK Report R2810-PK-20039-SR-01V1 Table 31 and Table 32.		

The time-dependent decrease in clearance in clearance for "responders" versus "all other" patients with BCC appears to be similar (Figure 2).

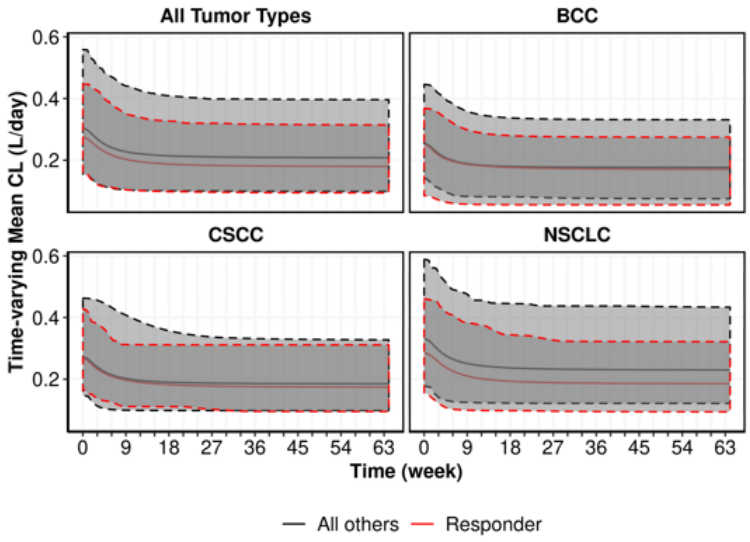

Figure 2. Clearance over time (with 95% CI) in patients with advanced BCC, advanced CSCC, or advanced NSCLC, compared to overall PopPK patient population with solid tumours, by responder category.
Abbreviations: CSCC= cutaneous squamous-cell carcinoma; BCC= basal cell carcinoma; NSCLC= non-small-cell lung cancer. Note: All tumour types=In the overall PopPK population (n=1062), including advanced BCC= All others (n=106), Responders (n=30); CSCC= All others (n=118), Responders (n= 96); NSCLC = All others (n= 279), Responders (n=137). Solid coloured lines are for median CL for the corresponding tumour types, the dashed lines and shaded gray area represent 95% CI.

Dose proportionality and time dependencies

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

Cemiplimab exposure in patients with solid tumours reach steady state by 4 months (16 weeks) of cemiplimab dosing (>90% of plateau) (Figure 3). The accumulation index upon Q3W dosing is 2.2, indicating an accumulation upon repeated dosing of approximately 2-fold.

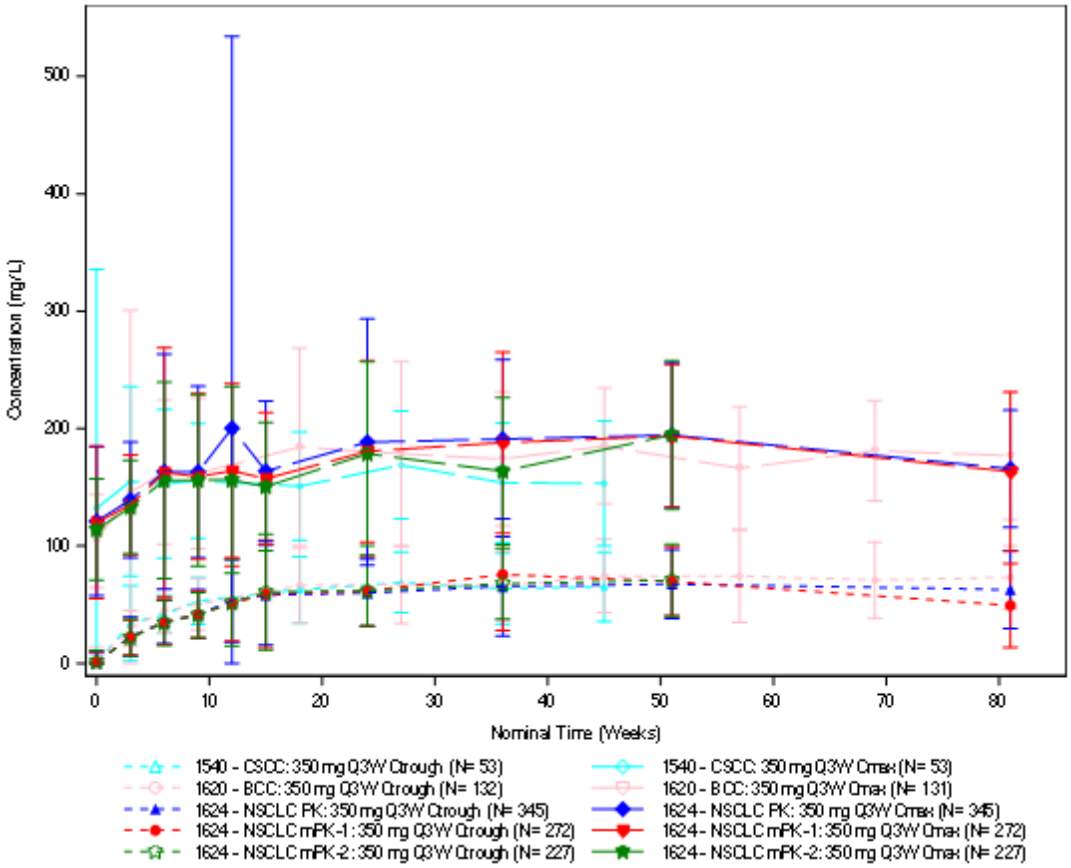

Figure 3. Observed mean (±SD) cemiplimab Ctrough and Cmax concentrations by time in patients with advanced CSCC (Study 1540), advanced BCC (Study 1620), and advanced NSCLC (Study 1624) receiving 350 mg Q3W
Abbreviations: BCC= basal cell carcinoma; CSCC= cutaneous squamous cell carcinoma; la= locally advanced; m= metastatic; N= Number of patients in PK analysis set; n= number of patients; NSCLC= non-small-cell lung cancer; Q= quartile; SD= standard deviation; mPK-1= modified PK-1 analysis set; mPK-2= modified PK-2 analysis set.
Note: Concentrations below the LLOQ were set to 0.

Special populations

In the PopPK analysis, the main identified intrinsic sources of PK variability were body weight, as well as baseline albumin and baseline IgG concentrations. No other tested covariates, including demographics (e.g., age) and baseline PD-L1 expression, had a statistically significant effect on cemiplimab exposure. The effect of all covariates combined on the post-hoc estimations of exposure (C_{max}, C_{min}, and AUC) was relatively small (<25%), and within the typical PK variability observed of

approximately 30%. While tumour type (NSCLC) was found as one of the statistically significant covariates, the resulting exposure across tumour types including advanced CSCC, advanced BCC, and advanced NSCLC was comparable (differences <10%).

Consistent with other monoclonal antibodies, cemiplimab is not subject to elimination through the renal or hepatic pathways; no specific studies for renal or hepatic impairment were conducted. The impact of renal and hepatic impairment on cemiplimab PK was assessed through PopPK analysis. No difference in cemiplimab exposure due to mild to severe renal impairment or mild to moderate hepatic impairment was identified.

Table 7. Summary of individual predicted estimates of cemiplimab exposure for the 350mg Q3W regimen after the first dose and at steady state in the overall PopPK population of patients with solid tumours, by key covariates and study number

Covariate	Value	N	First Dose			Steady-state		
			AUC_{3wks} (day*mg/L)	C_{max} (mg/L)	C_{min} (mg/L)	AUC_{3wks} (day*mg/L)	C_{max} (mg/L)	C_{min} (mg/L)
Reference exposure		1062	885(26.6%)	112(25.9%)	22.1(34.0%)	1940(35.5%)	171(27.5%)	60.9(44.9%)
Baseline Albumin (g/L)	<5th [20,29.3]	55	715(25.9%)	111(24.3%)	13.6(38.9%)	1310(30.8%)	143(23.8%)	33.6(42.4%)
	5-95th (29.3-46]	965	887(25.9%)	111(26.0%)	22.2(32.0%)	1950(33.3%)	171(26.7%)	61.1(41.6%)
	>95th (46,93]	42	1050(25.3%)	119(25.6%)	30.0(29.0%)	2660(39.8%)	208(31.5%)	91.5(48.1%)
Best overall response	0	798	874(28.0%)	111(26.9%)	21.7(35.9%)	1890(36.8%)	168(28.8%)	58.8(46.5%)
	1	264	917(21.9%)	114(22.7%)	23.1(27.8%)	2100(30.5%)	179(23.1%)	67.4(39.5%)
Concomitant Medication Flag	0	800	890(26.7%)	112(26.0%)	22.2(34.1%)	1950(35.8%)	172(27.8%)	61.3(45.3%)
	1	262	868(25.9%)	110(25.3%)	21.5(33.6%)	1900(34.4%)	168(26.6%)	59.7(43.8%)
Baseline ECOG Status	0	405	902(25.2%)	109(25.2%)	23.5(31.6%)	2070(35.5%)	175(27.4%)	67.0(44.7%)
	1	657	874(27.3%)	113(26.2%)	21.2(35.0%)	1860(34.7%)	168(27.5%)	57.1(43.7%)
Baseline IgG (g/L)	<5th [1.24,5.31]	31	961(23.1%)	113(21.7%)	26.1(29.6%)	2370(32.0%)	191(24.7%)	80.2(39.2%)
	5-95th (5.31, 17.1]	525	881(27.8%)	108(26.9%)	22.6(33.5%)	1980(34.3%)	170(28.1%)	63.2(41.6%)
	>95th (17.1,27.9]	29	746(31.0%)	107(32.0%)	15.5(35.3%)	1400(31.7%)	143(30.1%)	37.8(36.9%)
	NA	477	892(24.9%)	116(24.3%)	21.6(33.5%)	1910(36.0%)	172(26.5%)	58.5(47.3%)
Cancer stage at screening	Locally Advanced	231	939(27.3%)	114(26.9%)	24.6(33.3%)	2130(36.3%)	181(28.9%)	68.8(44.8%)
	Metastatic	460	879(23.9%)	114(24.4%)	21.2(31.0%)	1890(32.6%)	170(24.7%)	58.1(42.7%)
	NA	371	857(28.6%)	107(26.7%)	21.5(36.2%)	1890(37.1%)	165(29.3%)	59.5(45.8%)
Monotherapy or not	0	267	863(28.5%)	108(26.6%)	21.6(36.5%)	1900(37.5%)	166(29.2%)	59.9(46.8%)
	1	795	892(25.9%)	113(25.6%)	22.2(33.2%)	1950(34.8%)	172(26.9%)	61.2(44.3%)
Baseline PD-L1	<5th [0-50%]	249	895(29.6%)	111(29.9%)	22.9(35.1%)	1990(37.9%)	172(30.8%)	63.2(47.0%)
	5-95th [50%-70%)	103	869(23.8%)	114(24.8%)	20.4(29.2%)	1830(30.6%)	168(24.7%)	55.1(39.2%)
	>95th [70%-90%)	101	878(25.1%)	116(22.8%)	20.5(34.4%)	1870(33.1%)	171(24.7%)	56.7(42.8%)
	[90%-100%]	95	859(25.2%)	117(24.2%)	19.5(34.3%)	1750(34.4%)	166(25.6%)	51.2(45.9%)
	NA	514	889(26.0%)	110(24.7%)	22.8(33.2%)	1990(35.1%)	171(27.2%)	63.6(43.8%)
Study ID	Study 1423	397	856(28.2%)	107(26.5%)	21.6(35.6%)	1890(36.4%)	165(28.8%)	59.6(45.1%)
	Study 1540	188	927(26.6%)	111(27.5%)	24.4(30.4%)	2140(31.1%)	179(26.6%)	69.7(37.3%)
	Study 1620	132	934(24.2%)	109(23.7%)	25.6(28.8%)	2200(36.8%)	180(28.6%)	73.2(45.2%)
	Study 1624	345	876(24.9%)	118(24.1%)	20.0(32.8%)	1800(33.2%)	169(25.3%)	53.0(43.5%)
Baseline Weight (kg)	<5th [30.9,50.1]	54	1190(29.4%)	153(25.9%)	28.8(39.6%)	2590(38.5%)	231(29.6%)	80.2(48.5%)
	5-95th (50.1,107]	956	881(24.2%)	111(23.2%)	22.0(32.3%)	1930(33.7%)	170(25.1%)	60.6(43.6%)
	>95th (107,172]	52	649(19.7%)	79.4(22.3%)	16.7(25.2%)	1440(29.8%)	124(21.9%)	45.9(39.4%)

Note: Summary data are presented as Mean (CV%). Post-hoc estimates in the overall PopPK population of patients with solid tumours (N= 1062). CV%= percent coefficient of variation; NA= not available or missing. Baseline weight was selected as a covariate due to high correlation found between WGTBL, BMIBL and BSABL.

Body Weight

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

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

Age

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

Sex

The complete patient population with solid tumours on cemiplimab treatment included 750 males and 312 females. Sex was not identified as a statistically significant covariate of cemiplimab exposure.

Race and Ethnicity

Race and ethnicity were not identified as statistically significant covariates on CL. The population predicted estimates of cemiplimab exposure by race or ethnicity are comparable.

Baseline Albumin Level

Baseline albumin seemed directly correlated to exposure. The higher albumin the higher exposure (Figure 4). Albumin was shown to have a statistically significant effect on the clearance of cemiplimab. In patients with advanced NSCLC and in the overall patient population, lower albumin levels were associated with increased clearance of cemiplimab.

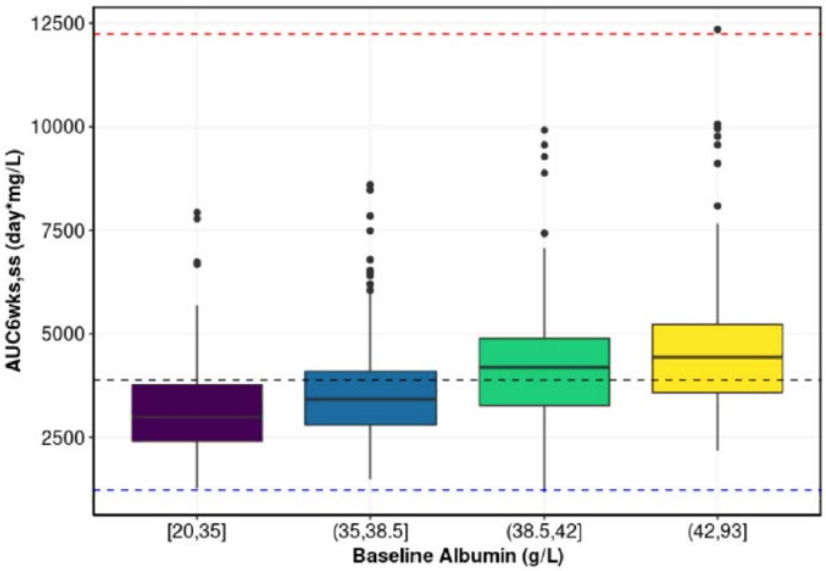

Figure 4. Boxplot of individual post-hoc estimates of $AUC_{6wks,ss}$ by quartiles of baseline albumin for 350 mg Q3W

Baseline Immunoglobulin Level

Baseline IgG levels did not have large effect on exposure (Figure 5). Boxplots of steady state exposure metrics AUC and Ctrough indicated a lower exposure for NSCLC patients in general compared to patients with BCC and CSCC. This is also evident from the simulated concentration-time profile for NSCLC vs. all other tumour types. However, in the current PopPK model, covariate analysis showed that IgG at baseline is a statistically significant covariate in that cemiplimab clearance was greater in patients with higher IgG levels.

Baseline IgG levels were not collected in Study 1620 in patients with advanced BCC and in Study 1624 in patients with advanced NSCLC. Thus, the effect of high IgG on cemiplimab efficacy cannot be assessed in patients with advanced NSCLC. However, clinical efficacy was observed in patients with advanced CSCC with extremely high baseline IgG levels.

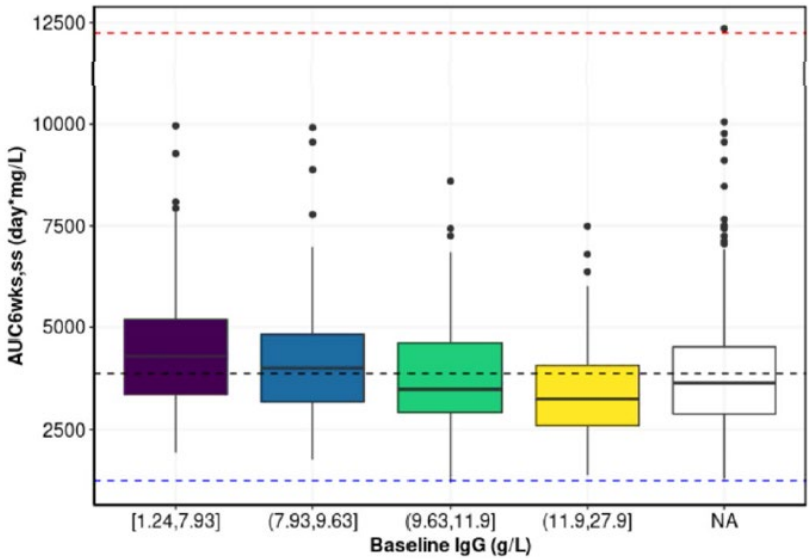

Figure 5. Boxplot of individual post-hoc estimates of $AUC_{6wks,ss}$ by quartiles of baseline IgG for 350 mg Q3W

Tumour Type

Boxplots of steady state exposure metrics AUC and Ctrough indicated a lower exposure for NSCLC patients in general compared to patients with BCC and CSCC (Figure 6, Figure 7). This is also evident from the simulated concentration-time profile for NSCLC vs. all other tumour types (figure not shown).

Tumour type (NSCLC) was found to be a statistically significant covariate; exposures in patients with NSCLC were approximately 10% lower than in patients with CSCC or BCC at 350 mg Q3W, which is within the overall range of variability in exposure.

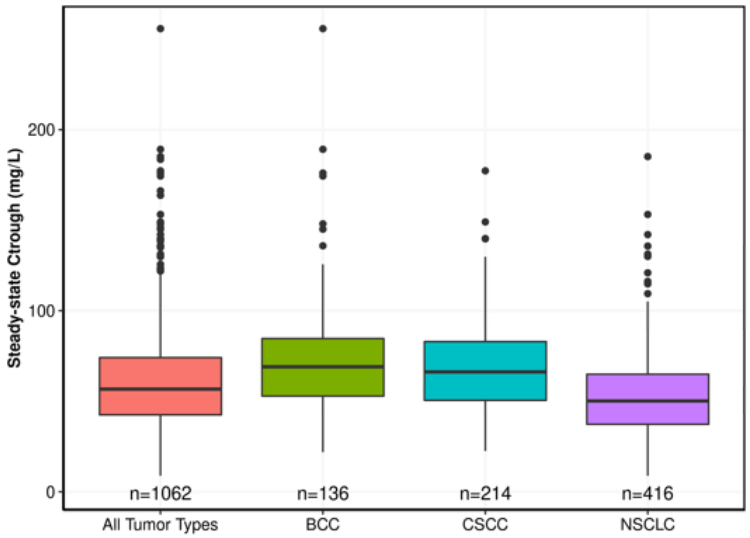

Figure 6. Boxplot of individual predicted cemimplimab $C_{trough,ss}$ by tumour type in the overall PopPK population of patients with solid tumours receiving 350 mg Q3W

Abbreviations: BCC= basal cell carcinoma; CSCC= cutaneous squamous cell carcinoma; n= number of patients; NSCLC= non-small-cell lung cancer; Q= quartile; SD= standard deviation; mPK-1= modified PK-1 analysis set; mPK-2= modified PK-2 analysis set. Note: Post-hoc estimates in the overall population of patients with solid tumours (N= 1062)

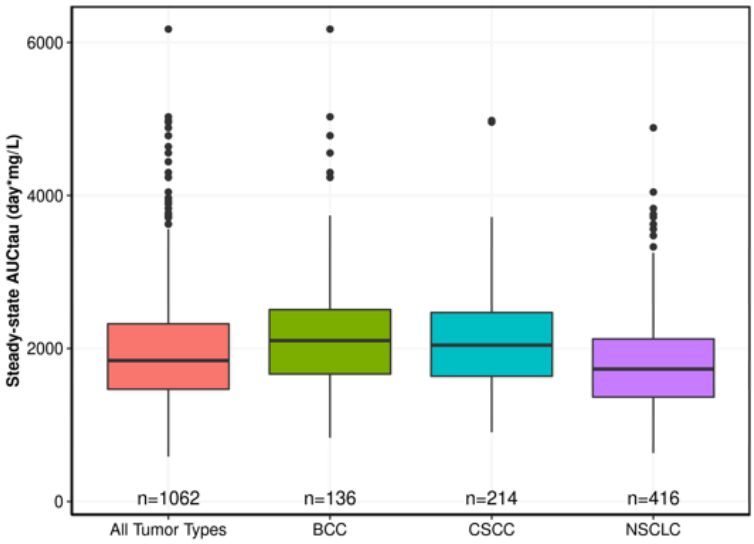

Figure 7. Boxplot of individual predicted cemimplimab $AUC_{tau,ss}$ by tumour type in the overall PopPK population of patients with solid tumours receiving 350 mg Q3W

Abbreviations: BCC= basal cell carcinoma; CSCC= cutaneous squamous cell carcinoma; n= number of patients; NSCLC= non-small-cell lung cancer; Q= quartile; SD= standard deviation; mPK-1= modified PK-1 analysis set; mPK-2= modified PK-2 analysis set. Note: Post-hoc estimates in the overall population of patients with solid tumours (N= 1062)

PD-L1 Expression

By PopPK covariate analysis, PD-L1 expression at baseline was not identified as a statistical covariate of cemiplimab exposure.

Responders versus All Others

Post-hoc analysis of cemiplimab concentrations over time to week 63 with 350 mg Q3W dosing indicated that patients who responded to cemiplimab treatment tend to have a slightly higher exposure than all other patients. An observed higher exposure in the 'responders' is consistent with the

difference in baseline CL. This observation in the overall population is largely driven by the patients from the NSCLC population, as the exposure in the 'responders' versus 'all others' is quite similar in patients with advanced CSCC and advanced BCC, given the similarity in baseline CL in these two populations.

Similar cemiplimab exposure across tumour types and within one tumour type, in 'responders' (1) compared to 'all others' (0), within the variability in exposure, was observed (Table 8). In addition, no difference in covariate levels were observed between 'responders' and 'all others'.

Table 8. Summary of individual predicted estimates of exposure of cemiplimab at 350 mg Q3W by tumour type, for 'responders' and 'all others'

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

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

Baseline Performance Status

Baseline ECOG status was not identified as a statistically significant covariate.

Renal Impairment

The effect of renal impairment on the exposure of cemiplimab was evaluated by a population PK analysis in patients with mild (CLcr 60 to 89 ml/min; n= 396), moderate (CLcr 30 to 59 ml/min; n= 166), or severe (CLcr 15 to 29 ml/min; n= 7) renal impairment.

Renal impairment is not expected to affect the PK of cemiplimab. Consistent with this, renal function was not identified as a significant covariate in the PopPK model. However, the individual predicted exposure at steady-state was observed to increase with increasing severity of renal impairment.

Hepatic Impairment

By PopPK covariate analysis, hepatic impairment was not identified as a statistically significant covariate. Additionally, no differences in the exposure of cemiplimab were found between patients with mild ((n= 22) (total bilirubin [TB] greater than 1.0 to 1.5 times the upper limit of normal [ULN] and any aspartate aminotransferase [AST])) or moderate ((n=3) (total bilirubin >1.5 times ULN up to 3.0 times ULN) and any AST) hepatic impairment and patients with normal hepatic function. No patients with severe hepatic impairment were included.

Extrinsic Factors

The magnitude of covariate effects on cemiplimab exposure and PK in the PopPK analysis model was used to assess the potential effect of extrinsic factors on cemiplimab exposure. Extrinsic covariates tested included treatment (monotherapy versus combination therapies with radiation and/or chemotherapy) and country (site, region).

Treatment (Monotherapy versus Combination Therapy)

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

Country

Overall, there was no apparent difference (<20%) in cemiplimab exposure ($AUC_{6wk,ss}$ or $C_{trough,ss}$) across patients from the different countries where Studies 1423, 1540, 1620, and 1624 were conducted.

Effect of ADAs on exposure

In the overall Pop PK population (N=1062), 803 patients tested ADA negative, 18 patients were ADA-positive and 241 were "NA". In Study 1624, out of 221 NSCLC patients, 6 were pre-treatment ADA positive while 5 were post-treatment ADA positive. All 11 patients were NAb negative. A spaghetti plot of individual concentration profiles indicates that ADA status do not affect exposure.

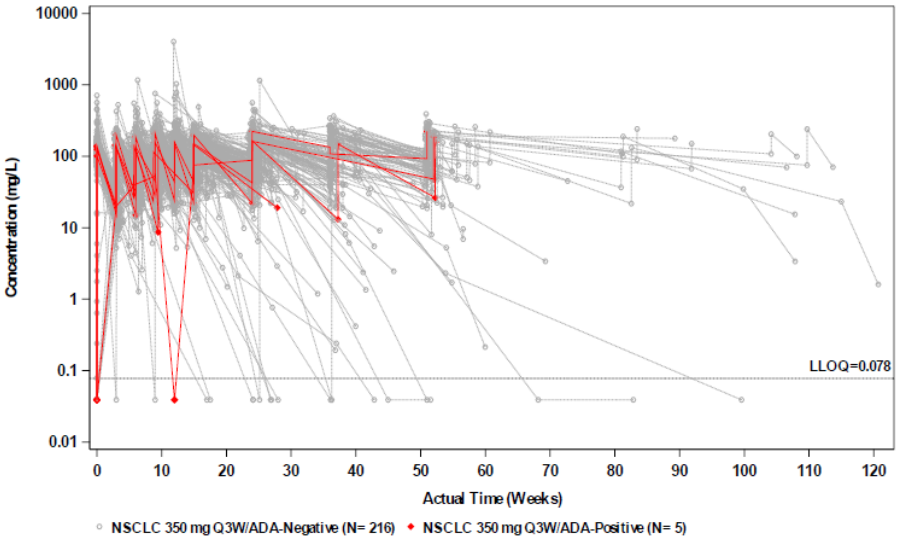

Figure 8. Individual concentrations of cemiplimab in serum vs. time by ADA status in patients with NSCLC treated with cemiplimab in the overall population
Abbreviations: N= number of patients; NSCLC= non-small-cell lung cancer. Note: Concentration below the LLOQ were set to LLOQ/2 for log scale. Source: Study R2810-ONC-1424, log-scaled

Pharmacokinetic interaction studies

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

2.3.3. Pharmacodynamics

Median percent change in tumor size after cemiplimab or chemotherapy treatment was used as a pharmacodynamics marker in the mITT-1 population (N=563), as this comprises all patients with tumor PD-L1 expression ≥50% as determined using a test performed according to instructions for use (Figure 9). The decrease in tumour size was more pronounced for higher levels of PD L1 expression, with the highest median percent of change observed in patients treated with cemiplimab who expressed PD-L1 ≥90%.

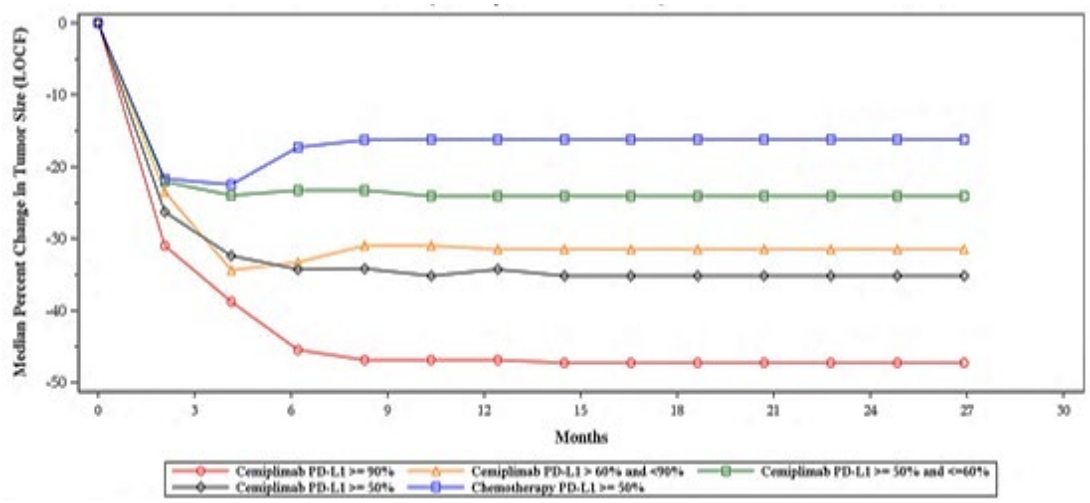

Figure 9. Median percent change in tumour size per IRC after cemiplimab or chemotherapy treatment – mITT-1 Population (N=563)
Abbreviations: IRC= independent review committee; mITT-1= intent-to-treat; LOCF= Last observation carried forward; PD-L1= programmed cell death ligand 1. Note: In the mITT-1 population, patients were divided per treatment arm and by level of PD-L1 expression (cemiplimab PD-L1 expression categories: ≥90%, >60% and <90%, ≥50% and ≤60%, and ≥50%; chemotherapy PD-L1 expression category: ≥50%).

Mechanism of action

Cemiplimab is a high affinity, fully human, hinge stabilized immunoglobulin G4 (IgG4) antibody directed to the PD-1 receptor that blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2.

Primary and secondary pharmacology

Exposure-Response Relationships

Descriptive and model-based E-R relationship analyses were conducted for efficacy and safety endpoints using post-hoc estimates of exposure metrics (C_{max}, C_{trough}, and AUC) after the first dose and at steady state, with emphasis on C_{trough} for efficacy endpoints and on C_{max} for safety endpoints. In addition, the relationships between efficacy endpoints and clearance of cemiplimab at baseline and steady state were also investigated.

Exposure-Response (E-R) analyses for efficacy were conducted on the primary efficacy endpoints OS and PFS, and also ORR (based on BOR). Analysis by the Cox proportional model indicated that the exposure metrics (after the first dose and at steady state), clearance of cemiplimab at baseline and steady state, and baseline PD-L1 were consistently significant predictors (Figure 10, Figure 11, Figure 12), with clearance of cemiplimab being the most significant predictor of both PFS and OS.

Univariate and multivariable models which included terms for the exposure metrics, indicated that baseline PD-L1 status has a significant effect on PFS and drug concentration.

No meaningful E-R relationships for safety variables (immune-related adverse event (imAEs) all grades and imAEs ≥ grade 3) were observed in patients with NSCLC on cemiplimab monotherapy in Study 1624 (Pool 1), patients on cemiplimab monotherapy (Pool 2), or all patients receiving cemiplimab as monotherapy and/or combination therapy (Pool 3).

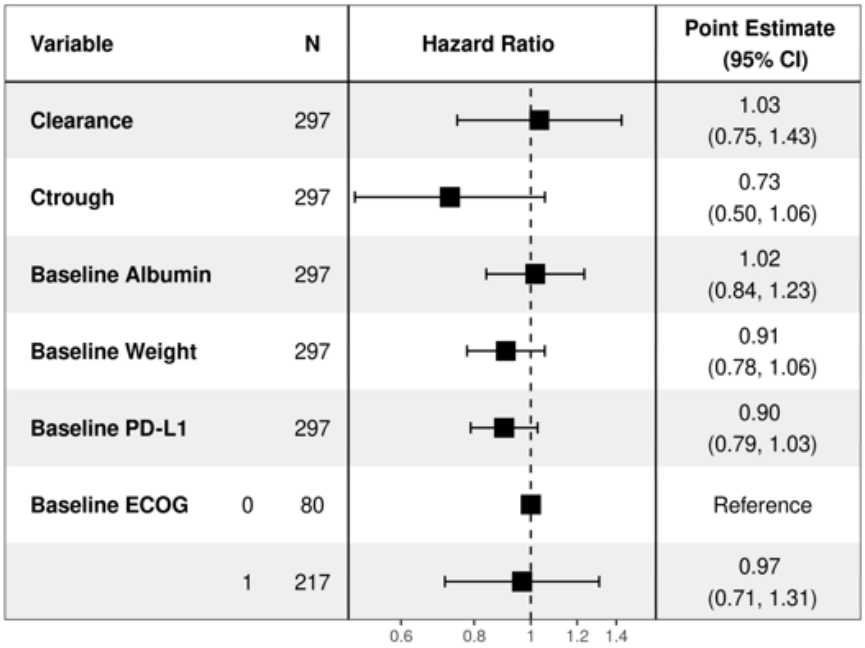

Figure 10. Forest plot of Cox proportional hazards model of duration of response with individual predicted exposure metrics after the first dose and baseline covariates in patients with NSCLC in the ITT population.
Note: Clearance and Ctrough are fit based on their baseline/after first dose values in this model. Point estimates are interpreted in terms of an increase in one unit of SD from the mean value of the variable.

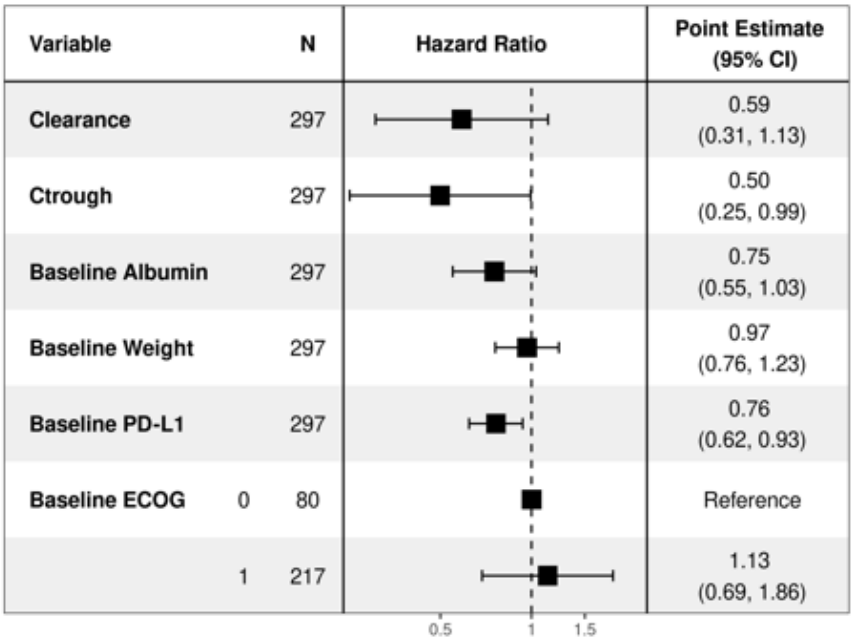

Figure 11. Forest plot of Cox proportional hazards model of overall survival with individual predicted exposure metrics after the first dose and baseline covariates in patients with NSCLC in the ITT population.
Note: Clearance and Ctrough are fit based on their baseline/after first dose values in this model. Point estimates are interpreted in terms of an increase in one unit of SD from the mean value of the variable.

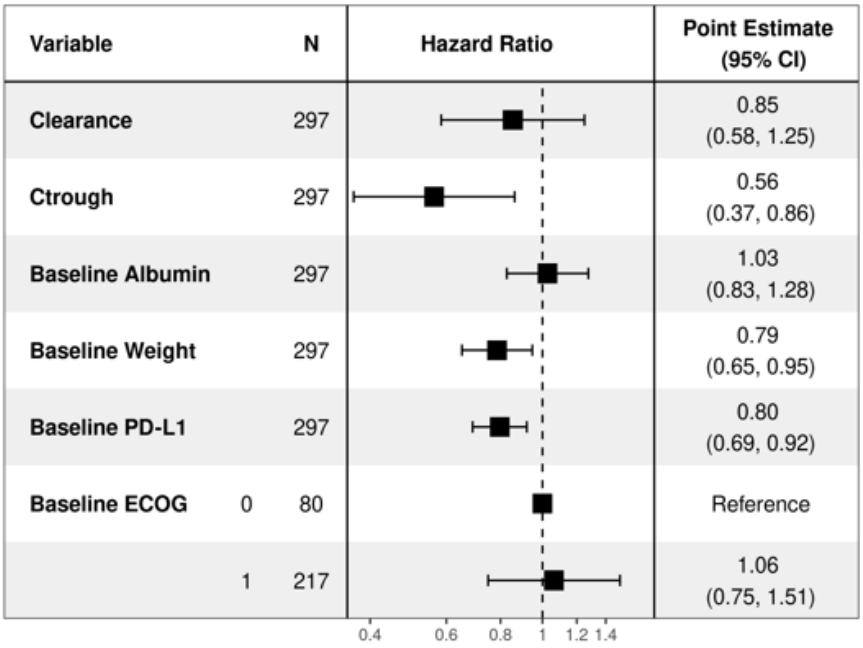

Figure 12. Forest plot of Cox proportional hazards model of progression free survival with individual predicted exposure metrics after the first dose and baseline covariates in patients with NSCLC in the ITT population.
Note: Clearance and Ctrough are fit based on their baseline/after first dose values in this model. Point estimates are interpreted in terms of an increase in one unit of SD from the mean value of the variable.

Immunogenicity

The incidence of treatment-emergent ADA was 2.3% in all patients receiving cemiplimab 350 mg Q3W. Antibody titers were all low. Of the patients who developed treatment emergent antibodies to cemiplimab, none developed NAb. The incidence of persistent ADA was 0.4% in all patients receiving cemiplimab. The incidence of treatment-emergent ADA in patients with advanced NSCLC in Study 1624 (2.3%) was consistent with the incidence observed across all studies. The presence of ADA was not associated with significant AEs or imAEs.

Dose Selection

In Study 1624, the selected dosing regimen of 350 mg Q3W IV in patients with advanced NSCLC was supported by preliminary efficacy data in the FIH Study 1423, the evolving efficacy data in the treatment of advanced CSCC (Study 1540), as well as the combined safety data in 1078 patients across the cemiplimab program.

2.3.4. Discussion on clinical pharmacology

Pharmacokinetics

The bioanalytical methods used to determine the concentration of functional cemiplimab and to assess immunogenicity in human serum samples are the same assays assessed in the original marketing authorisation application for CSCC.

The pharmacokinetics, pharmacodynamics, and immunogenicity of cemiplimab were assessed in four clinical studies and were further analysed by Population PK/PD models. The drug tolerance level of the NAb method is 330 ng/mL cemiplimab with a sensitivity of 500 ng/mL NAb positive control, which is

not adequate to cover the anticipated drug levels in the samples. The Applicant is recommended to improve drug tolerance in the NAb assay.

Consistent with the initial Pop PK assessments in support of the initial marketing authorisation application, the kinetics of cemiplimab in the overall population could be described by a two-compartment model with a time-varying component on clearance and of baseline albumin. Less than half of 500 bootstrap runs converged. The main reason for the failed runs was inadequate data to describe the time-dependent clearance parameters Emax and T_{50}.

The Pop PK model was updated. Estimation of inter-individual variability on Emax and T_{50} were removed, the proportional error model was changed to a log-additive error model and the off-diagonal covariance between inter-individual random effects on CLQ and V_{SS} was also removed. A covariate effect of NSCLC on T_{50} was included which improved the model notably. The updated model was evaluated using bootstrap (n=500) and all runs converged successfully. The provided GoF plots and pc-VPCs indicated the model could adequately describe the observed concentrations of cemiplimab in non-NSCLC and NSCLC patients. The fixed allometric exponents are considered to sufficiently capture the cemiplimab weight-PK covariate relationships. No other significant trends could be observed in plots of Empirical Bayes Estimates versus covariates. Exclusion of outlier concentrations did not change the population PK parameter estimates in a relevant manner.

Concentration data from 1062 patients with various solid tumours who received cemiplimab were combined in a population PK analysis. At 350 mg Q3W, the mean cemiplimab concentrations at steady-state ranged between a Ctrough of 61 mg/l and a concentration at end of infusion (Cmax) of 171 mg/l. Steady state exposure is achieved after approximately 4 months of treatment (see section 5.2 of the SmPC).

Cemiplimab is administered via the intravenous route and hence is completely bioavailable. As is typical for monoclonal antibodies, Cemiplimab is primarily distributed in the vascular system with a volume of distribution at steady state (Vss) of 5.3 l. Median Tmax occurs at the end of the 30-minute infusion. Specific metabolism studies were not conducted because cemiplimab is a protein. Cemiplimab is expected to degrade to small peptides and individual amino acids (see section 5.2 of the SmPC).

At the dosing regimens of 1 mg/kg to 10 mg/kg every two weeks, pharmacokinetics of cemiplimab were linear and dose proportional, suggesting saturation of the systemic target mediated pathway (see section 5.2 of the SmPC). Cemiplimab clearance after the first dose is approximately 0.29 l/day. The total clearance appears to decrease by approximately 29% over time, resulting in a steady state clearance (CLss) of 0.20 l/day. However, the decrease in CL is not considered clinically relevant. The within dosing interval half-life at steady state is 20.3 days (see section 5.2 of the SmPC).

The time-varying change in clearance is accounted for by a sigmoid-Emax function with a fixed Hill factor in the population PK model. The hypothesis that cachexia is the cause of time-varying clearance of cemiplimab would be supported by the result that albumin was able to explain some, but not all of the trends in clearance. If cachexia causes the degradation rates of albumin and cemiplimab to be proportional to each other at any given time, then it follows that current albumin concentrations are a "delayed" biomarker of cachexia, as it takes some time for a new albumin concentration equilibrium to be reached after a change in clearance.

A difference in time dependent decrease for responders vs. all others patients in patients with BCC and NSCLC was observed. However, due to relatively wide confidence intervals in baseline clearance and change in clearance over time in addition to the considerable overlap between 'responders and 'all others' across tumour types, further interpretation and conclusions cannot be made at the individual level to predict clinical effect based on cemiplimab clearance.

Cemiplimab exposure in patients with solid tumours reach steady-state by 4 months (16 weeks) of cemiplimab dosing. The accumulation index upon Q3W dosing is 2.2, indicating an accumulation upon repeated dosing of approximately 2-fold.

The significant covariates identified in the Pop PK population were body weight, albumin, baseline IgG (only applicable to studies 1423 and 1540), and tumour type.

Baseline albumin seemed directly correlated to exposure. The association between low albumin and increased clearance for a monoclonal antibody is well known, and may be related to the altered neonatal fragment crystallizable receptor-mediated recirculation of monoclonal antibodies or the fact that the elimination or turnover of proteins including mAbs and albumin is higher in cachectic patients. The magnitude of increasing/decreasing exposure (25%) associated with high/low albumin levels is within the typical variability in exposure in the patient population at 350 mg Q3W. In light of the sparse data, it is agreed that in the absence of a noticeable effect of low baseline albumin levels on cemiplimab exposure and efficacy, no changes to the SmPC are needed. Also, it is acknowledged that the observed levels of exposure remained within the variability in exposure in the overall PopPK population of 1062 patients.

Tumour type (NSCLC) was found to be a statistically significant covariate; exposures in patients with NSCLC were approximately 10% lower than in patients with CSCC or BCC at 350 mg Q3W, which is within the overall range of variability in exposure. Furthermore, the lower (-<10%) cemiplimab exposure in patients with advanced NSCLC compared to patients with advanced CSCC or advanced BCC is possibly related to their slightly higher baseline clearance.

A population PK analysis suggests that the following factors have no clinically significant effect on the exposure of cemiplimab: age, gender, body weight, race, cancer type, albumin level, renal impairment, and mild to moderate hepatic impairment (see section 5.2 of the SmPC).

Renal function was not identified as a significant covariate in the PopPK model. However, the individual predicted exposure at steady-state was observed to increase with increasing severity of renal impairment. It was noted that patients with severe renal impairment have lower body weights and thus higher exposure of cemiplimab.

No clinically important differences in the exposure of cemiplimab were found between patients with renal impairment and patients with normal renal function. Cemiplimab has not been studied in patients with CLcr <21 ml/min. No clinically important differences in the exposure of cemiplimab were found compared to patients with normal hepatic function. Cemiplimab has not been studied in patients with severe hepatic impairment. There are insufficient data in patients with severe hepatic impairment for dosing recommendations (see section 5.2 of the SmPC).

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

Pharmacodynamics

The decrease in tumour size was more pronounced for higher levels of PD-L1 expression, with the highest median percent of change observed in patients treated with cemiplimab who expressed PD-L1 ≥90%. The MAH is conducting a phase 3 clinical trial (R2810-ONC-16113, EudraCT Number: 2017-001311-36) of cemiplimab in combination with platinum-doublet chemotherapy in which patients with PD-L1 expression of <50% are eligible.

There was evidence of an E-R relationship across all efficacy endpoints (ORR/BOR, DOR, and for the primary endpoints OS and PFS), with exposure metrics (after the first dose and at steady state) in patients with advanced NSCLC treated with 350 mg Q3W.

Clearance of cemiplimab at baseline and steady state and baseline PD-L1 were consistently significant predictors of PFS. Since CL is a strong covariate of exposure, it is a confounding factor in the interpretation of the E-R relationship. The differences in CL between 'responders' and 'non-responders' leading to this apparent E-R relationship likely reflect other patient characteristics that affect the tumour response to cemiplimab.

There are no clinically meaningful relationships between cemiplimab exposure (C_{max}, C_{trough}, and AUC) and imAEs in patients with advanced NSCLC and in the overall population of patients with solid tumours.

Cemiplimab has low immunogenicity potential. The incidence of anti cemiplimab antibodies in patients with advanced NSCLC (2.3%) treated with cemiplimab 350 mg Q3W is low. Of the patients who developed treatment-emergent antibodies to cemiplimab, none developed NAbs. There was no effect of anti-cemiplimab antibodies on the PK of cemiplimab.

The proposed posology 350 mg Q3W in Study 1540 is based on the initial MAA approval in advanced CSCC. Cemiplimab demonstrated comparable PK properties in patients with CSCC and NSCLC. Furthermore, the 350 mg Q3W dose was intentionally selected to saturate the target mediated pathway over the dosing interval, leading to the observed linear PK. Having saturated the target mediated pathway and at concentrations sufficient to account for inter-patient variability in exposure, changes in drug concentrations are not expected to lead to any further pharmacological effect from the perspective of safety or efficacy. The selected dosing strategy is accepted.

2.3.5. Conclusions on clinical pharmacology

Overall, the clinical pharmacology of cemiplimab has been adequately described for patients with NSCLC.

2.4. Clinical efficacy

2.4.1. Dose response study

No additional dose-response study was performed (see Section 2.3.3. Pharmacodynamics and discussion on clinical pharmacology). A fixed dose of cemiplimab 350 mg Q3W (same regimen authorised for CSCC) was used in Study 1624.

2.4.2. Main study – Study 1624

Study 1624 is a randomised, multicentre, global, open-label, pivotal phase 3 study of cemiplimab monotherapy versus platinum-based doublet chemotherapy in patients with stage IIIB, stage IIIC, or stage IV squamous or non-squamous NSCLC who were not candidates for treatment with definitive chemoradiotherapy, whose tumours expressed PD-L1 in ≥50% of tumour cells, with no EGFR, ALK, or ROS1 aberrations, and who had received no prior systemic treatment for their advanced disease.

The study design is summarised in Figure 13. Eligible patients were randomised equally to either cemiplimab monotherapy or platinum-based doublet chemotherapy. Randomisation was stratified by histology (squamous versus non-squamous) and geographic region (Europe, Asia, or rest of the world (ROW)).

Patients assigned to the cemiplimab arm received cemiplimab on day 1 of every treatment cycle (Q3W) for up to 108 weeks or until Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1)

defined progressive disease, unacceptable toxicity, death, or withdrawal of consent. Patients assigned to the chemotherapy arm received a platinum-based doublet chemotherapy (with or without maintenance therapy) for four to six cycles and according to the local prescribing information and practice guidelines, or until disease progression, unacceptable toxicity, death, or withdrawal of consent.

The first radiographic tumour assessment occurred after nine weeks of study treatment and was repeated every nine weeks thereafter. To decrease bias in the assessment of disease progression in the open-label study, an Independent Review Committee (IRC) that is blinded to treatment assignment was used to adjudicate tumour responses.

The study will end when the survival analysis is complete; according to the study protocol, 476 deaths were expected at final analysis of OS. The last patient last visit will be 48 months from the enrolment of the last patient. The duration of the study for each patient is approximately 48 months.

Table 9. Overview of the Clinical Efficacy Study for Cemiplimab 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-1624 Study ongoing	Adult patients, diagnosed with stage IIIB, IIIC, or IV squamous or non-squamous NSCLC, who are not eligible for definitive chemo/radiation, whose tumours express PD-L1 in ≥50% of tumour cells (using the PD-L1 IHC 22C3 pharmDx assay), and who have received no prior systemic treatment for their advanced disease.	The primary efficacy variable is OS and PFS assessed by IRC. The key secondary efficacy variable is ORR by IRC. Other secondary efficacy variables are: • DOR • patient-reported quality of life as measured by the EORTC QLQ-C30 and EORTC QLQ-C13	Phase 3 Randomized, multicenter, open-label, pivotal study	350 mg cemiplimab administered intravenously over 30 minutes Q3W for up to 108 weeks (N=356) or standard of care chemotherapy for 4 to 6 cycles (N=354)

Abbreviations: CSR, clinical study report; 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
Source: Study 1624 Primary Analysis CSR

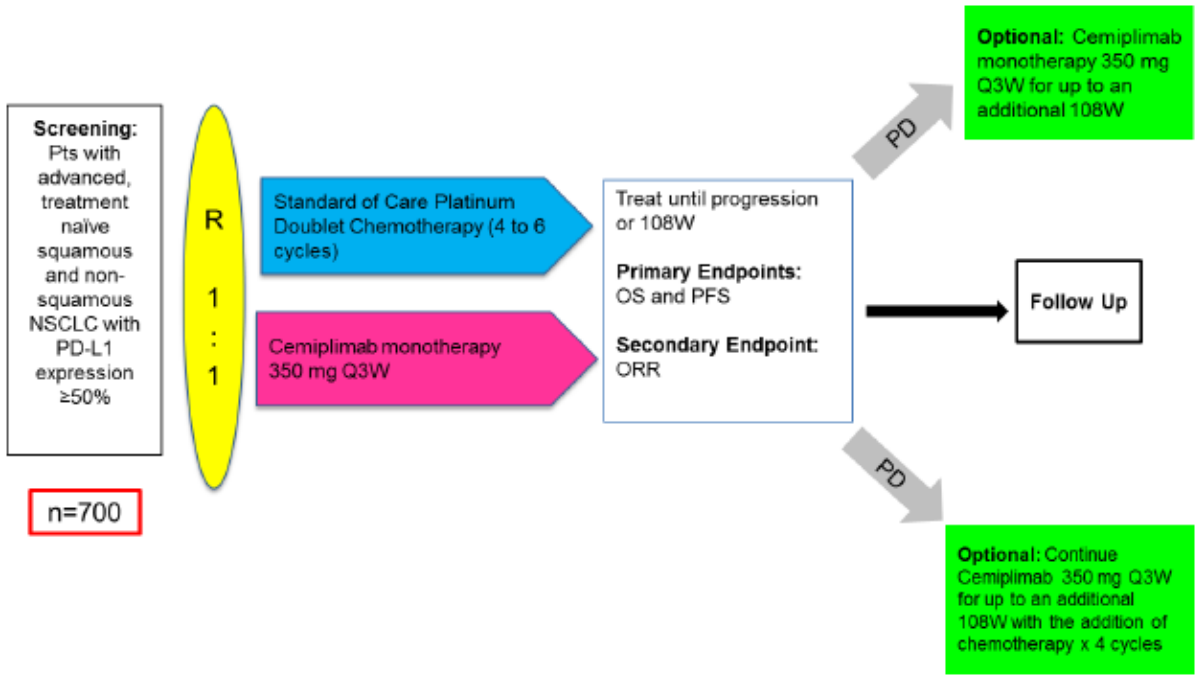

Figure 13. Study flow diagram – Utilized prior to pre-specified interim analysis 2 through protocol amendment 8
Note: This figure depicts the study design in effect during protocol amendment 8 when the primary endpoint was reached. Abbreviations: NSCLC= non-small cell lung cancer; OOR= objective response rate; OS= overall survival; PD= progressive disease; PD-L1= programmed cell death ligand 1; PFS= progression-free survival; Pts= patients; Q3W= every 3 weeks; R= randomization; W= week.

Methods

Study participants

Main inclusion criteria

1. Men and women ≥18 years of age

2. Patients with histologically or cytologically documented squamous or non-squamous NSCLC with stage IIIB or stage IIIC disease who are not candidates for treatment with definitive concurrent chemoradiation or patients with stage IV disease who received no prior systemic treatment for recurrent or metastatic NSCLC.

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

3. Archival or newly obtained formalin-fixed tumour tissue from a metastatic/recurrent site, which has not previously been irradiated

    a. Tissue may be obtained from the primary site if it is still in place and the other metastatic sites are either not accessible (i.e., brain), cannot be used (i.e., bone), or the biopsy would put the patient at undue risk

    b. If an archival biopsy is used, it must be less than 5 months old

4. Tumour cells expressing PD-L1 in ≥50% of tumour cells by IHC performed by the central laboratory

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

6. ECOG performance status of ≤1

7. Anticipated life expectancy of at least 3 months

8. Adequate organ and bone marrow function

Main exclusion criteria

1. Patients that have never smoked, defined as smoking ≤100 cigarettes in a lifetime

2. 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 randomization. Patients must be off (immunosuppressive doses of) corticosteroid therapy.

3. Patients with tumours tested positive for EGFR gene mutations, ALK gene translocations, or ROS1 fusions. All patients should have tumour evaluations for EGFR mutations, ALK rearrangement, and ROS1 fusions confirmed by a central laboratory.

4. Encephalitis, meningitis, or uncontrolled seizures in the year prior to randomization.

5. History of interstitial lung disease (e.g., idiopathic pulmonary fibrosis, organizing pneumonia) or active, noninfectious pneumonitis that required immune-suppressive doses of glucocorticoids to assist with management. A history of radiation pneumonitis in the radiation field is permitted as long as pneumonitis resolved ≥6 months prior to randomization.

6. Patients with active, known, or suspected autoimmune disease that has required systemic therapy in the past 2 years. Patients with vitiligo, type I diabetes mellitus, and hypothyroidism (including hypothyroidism due to autoimmune thyroiditis) only requiring hormone replacement are permitted to be randomized.

7. Patients with a condition requiring corticosteroid therapy (>10 mg prednisone/day or equivalent) within 14 days of randomization. Physiologic replacement doses are allowed even if they are >10 mg of prednisone/day or equivalent, as long as they are not being administered for immunosuppressive intent. Inhaled or topical steroids are permitted, provided that they are not for treatment of an autoimmune disorder.

8. Another malignancy that is progressing or requires treatment, with the exception of non-melanomatous skin cancer that has undergone potentially curative therapy, or in situ cervical carcinoma or any other tumour that has been treated, and the patient is deemed to be in complete remission for at least 2 years prior to randomization, and no additional therapy is required during the study period.

9. Uncontrolled infection with hepatitis B or hepatitis C or human immunodeficiency virus; or diagnosis of immunodeficiency.

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

11. Prior therapy with anti-PD-1 or anti-PD-L1. Prior exposure to other immunomodulatory or vaccine therapy such as anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibodies is permitted, but the last dose of such an antibody should have been at least 3 months prior to the first dose of study drug.

12. Treatment-related immune-mediated AEs from immune-modulatory agents (including but not limited to anti-PD1/PD-L1 mAbs, anti-CTLA4 mAbs, and phosphoinositol 3- kinase [PI 3-K]-δ inhibitors) that have not resolved to baseline at least 3 months prior to initiation of treatment with study therapy. Patients are excluded from treatment with cemiplimab if they experienced immune-mediated AEs related to prior treatment with a blocker of the PD-1/PD-L1 pathway that were grade 3 or 4 in severity and/or required discontinuation of the agent, regardless of time of occurrence.

13. Receipt of an investigational drug or device within 30 days of screening or within 5 half-lives of the investigational drug (whichever is longer).

14. Receipt of a live vaccine within 30 days of planned start of study medication.

15. Major surgery or significant traumatic injury within 4 weeks prior to first dose.

16. Documented allergic or acute hypersensitivity reaction attributed to antibody treatments.

17. Known psychiatric or substance abuse disorder that would interfere with participation with the requirements of the study, including current use of any illicit drugs.

18. Pregnant or breastfeeding women.

19. Women of childbearing potential or men who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose.

20. Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities will be excluded from this study.

21. Prior treatment with idelalisib.

22. Member of the clinical site study team and/or his/her immediate family, unless prior approval granted by the Sponsor.

23. Recipients of organ transplants.

24. Active or latent tuberculosis.

Treatments

Cemiplimab

The dose level of cemiplimab in Study 1624 was 350 mg administered by IV infusion every 3 weeks (Q3W) for up to total of 108 weeks or until progression, unacceptable toxicity, death or withdrawal of consent.

As of protocol amendment 6 (22-AUG-2018), patients randomized to receive cemiplimab 350 mg who experience RECIST 1.1-defined progression during cemiplimab monotherapy were given the option to continue cemiplimab treatment with the addition of four cycles of histology-specific platinum-based doublet chemotherapy until further progression is observed, provided, the patient has not completed the 108-week treatment period and protocol-specified criteria were met.

Chemotherapy

Platinum-based doublet chemotherapy (with or without maintenance therapy), administered for four to six cycles as outlined in Table 10 and according to the local prescribing information and practice guidelines, or until disease progression, unacceptable toxicity, death, or withdrawal of consent. The investigators were permitted to choose from several alternatives; these regimens were consistent with

clinical treatment guidelines for chemotherapy options in NSCLC at the time the trial was designed (Table 10).

Table 10. Guidelines for platinum-based doublet chemotherapy regimens

Option	Chemotherapy Regimen	Dosing Frequency	Maintenance Therapy
1	Pemetrexed 500 mg/m^2 IV plus cisplatin 75 mg/m^2 IV	Day 1 every 21 days for 4 to 6 cycles	Optional pemetrexed 500 mg/m^2 IV day 1 every 21 days
2	Pemetrexed 500 mg/m^2 IV plus carboplatin AUC of 5 or 6 mg/mL/minute IV	Day 1 every 21 days for 4 to 6 cycles	Optional pemetrexed 500 mg/m^2 IV day 1 every 21 days
3	Paclitaxel 200 mg/m^2 IV plus cisplatin 75 mg/m^2 IV	Day 1 every 21 days for 4 to 6 cycles	No maintenance
4	Paclitaxel 200 mg/m^2 IV plus carboplatin AUC of 5 or 6 mg/mL/minute IV	Day 1 every 21 days for 4 to 6 cycles	No maintenance
5	Gemcitabine 1250 mg/m^2 IV plus cisplatin 100 mg/m^2 IV	Day 1 and day 8 (gemcitabine only) every 21 days for 4 to 6 cycles	No maintenance
6	Gemcitabine 1250 mg/m^2 IV plus carboplatin AUC of 5 or 6 mg/mL/minute IV	Day 1 and day 8 (gemcitabine only) every 21 days for 4 to 6 cycles	No maintenance

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

Cross-over

Patients who experience disease progression while on, or after completion of chemotherapy were offered the option to crossover to cemiplimab at the time of IRC confirmed progression to receive cemiplimab 350 mg Q3W for up to 108 weeks, provided they met the following criteria:

- IRC confirms investigator assessment of disease progression
- Investigator assesses use of a PD-1 inhibitor as an appropriate second-line treatment
- Patient continues to meet all other study eligibility criteria, as defined in the inclusion/exclusion criteria

Within Interim Analysis 2 that was conducted per Protocol Amendment 8 (database lock [DBL] date: 14 Apr 2020) and defined to be conducted when approximately 50% of expected OS events are observed, the primary endpoint of OS was reached. Subsequent to this, Protocol Amendment 9 was implemented to allow patients randomised to chemotherapy to crossover with cemiplimab for up to 108 weeks. Patients eligible to crossover to cemiplimab included the following:

- Patients who were actively being treated with chemotherapy
- Patients who had completed chemotherapy and were in the follow-up phase, but whose disease had not yet progressed
- Patients who had discontinued chemotherapy and had progressed, but had not yet crossed over to cemiplimab for any reason and had not started any other systemic therapy

Dose modifications

Dose modifications of cemiplimab are not permitted per protocol. Dose modification/reduction or temporary cessation of a given chemotherapy was to be managed in accordance with regional standard-of-care and guidelines.

Objectives

According to the Protocol dated 23 Oct 2019 (Protocol Amendment 8), the objectives of the study were:

Primary Objective:

- To compare the overall survival (OS) of cemiplimab versus platinum-based doublet chemotherapies in the first-line treatment of patients with advanced or metastatic NSCLC whose tumours express PD-L1 in ≥50% of tumour cells
- To compare the progression-free survival (PFS) of cemiplimab versus platinum-based doublet chemotherapies in the first-line treatment of patients with advanced or metastatic NSCLC whose tumours express PD-L1 in ≥50% of tumour cells

Key Secondary Objectives:

- To compare the objective response rate (ORR) of cemiplimab versus platinum-based chemotherapies

Secondary Objectives:

- To compare the duration of response (DOR) of cemiplimab versus platinum-based chemotherapies
- To assess the quality of life (QoL) of patients treated with cemiplimab versus patients receiving platinum-based chemotherapies as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQC30) and EORTC QLQ Lung Cancer 13 (LC13)
- To evaluate the safety and tolerability of cemiplimab versus platinum-based chemotherapies
- To measure concentrations of cemiplimab in serum and characterise the PK of cemiplimab
- To assess immunogenicity (anti-drug antibodies /neutralising antibodies [ADAs/NAbs]) to cemiplimab and any relationship with drug concentrations, efficacy, and safety
- To conduct exposure-response analyses on efficacy endpoints and safety

Exploratory Objectives:

- To assess correlation between the level of PD-L1 expression at baseline and efficacy of study treatment
- To assess time to new anti-tumour therapy
- To assess pharmacodynamic (PD) changes in putative serum biomarkers (which could include but were not limited to cytokines, circulating tumour nucleic acids, etc)
- To conduct PK/PD analyses on exploratory biomarkers, as appropriate

Outcomes/endpoints

Primary efficacy endpoints

- OS, defined as the date from randomisation to the date of death. A patient who has not died was censored at the last known date of contact.
- PFS, defined as the time from randomisation to the date of the first documented tumour progression or death due to any cause. PFS was assessed by a blinded independent review committee (IRC) using Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Patients were censored according to the following rules:
    - Patients who did not have a documented tumour progression or death were censored on the date of their last evaluable tumour assessment.

- Patients who did not have a documented tumour progression or death before initiation of new anti-tumour therapy were censored on the date of their last evaluable tumour assessment prior to or on the date of new anti-tumour therapy.
- Patients who withdrew consent before taking any study treatment (therefore there was no post-baseline tumour assessment) were censored on the date of randomisation.
- Patients who did not have any evaluable tumour assessments after randomisation and did not die were censored on the date of randomisation.

Key secondary endpoint

ORR was defined as the number of patients with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR). The BOR is defined as the best response, as determined by the blinded IRC per RECIST 1.1, between the date of randomisation and the date of the first documented tumour progression or the date of subsequent anti-cancer therapy, whichever came first.

Other secondary endpoints

- The DOR determined for patients with BOR of CR or PR. DOR is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date of recurrent or progressive disease (radiographic), or death due to any cause. Patients who never progress while being followed will be censored at the last valid tumour measurement. 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.
- Patient-reported quality of life, measured by the EORTC QLQ-C30 and EORTC QLQ-C13.

Sample size

Enrolment of 700 patients was assumed to occur over 38 months. The patients were randomized at 1:1 ratio to cemiplimab arm or platinum-based chemotherapy arm. A dropout rate of 10% per year was assumed.

Overall Survival

The MAH assumed without crossover effect a median OS of 13 months for patients treated with chemotherapy alone, and a non-proportional HR between cemiplimab and chemotherapy, with an HR of 1.05 for the first 6 months and an HR of 0.58 after 6 months.

With 5 interim analysis planned using Lan-DeMets O'Brien-Fleming alpha spending function, and with 476 deaths at final analysis of OS, the study had approximately 86% power for detecting a significant OS effect at 2-sided α of 0.04 and approximately 88% power for detecting a significant OS effect at 2-sided α of 0.05.

Progression-Free Survival

The MAH assumed a median PFS of 6.4 months for patients treated with chemotherapy alone, and a HR between cemiplimab and chemotherapy, with an HR of 1.3 for the first 3 months and an HR of 0.5 after 3 months.

With 525 PFS events, the study had approximately 76% power for detecting a significant PFS effect at 2-sided α of 0.01 and approximately 90% power for detecting a significant PFS effect at 2-sided α of 0.05.

Randomisation

Patients were planned for randomization in a 1:1 ratio (experimental to control arm)

- Arm 1 (experimental arm): cemiplimab monotherapy
- Arm 2 (control arm): platinum doublet chemotherapy

Randomization was planned to be stratified by the following factors:

- Status of histology (squamous, non-squamous)
- Geographic region (Europe, Asia, ROW)

Blinding (masking)

This was an open-label study. To reduce bias in the assessment of disease progression, endpoint assessments were performed by an IRC blinded to treatment assignment.

Statistical methods

Analysis Populations

Full Analysis population (Intent-to-Treat (ITT])): this includes all randomized patients (N=710). The ITT population was based on the treatment allocated (as randomized). All efficacy endpoints were analysed using the ITT population by treatment group.

Modified Intent-to-Treat 1 (mITT-1) population: This includes all randomized patients who were enrolled based on tests performed after August 2018 whose tumours expressed PD-L1 in ≥50% of tumour cells based on a PD-L1 assay at entry performed in accordance with approved labelling, including assay IFU (n=475), as well as patients who were tested before August 2018, but whose PD-L1 samples required retesting due to PD-L1 quality testing issues and, upon retest, were confirmed as having PD-L1 tumour expression in ≥50% of tumour cells based on a PD-L1 assay performed in accordance with approved labelling, including assay IFU (n=88) as described in Section 3.6.4. The mITT-1 population (N=563) was described in the SAP as the population to be used for a sensitivity analyses requested by a health authority for the primary endpoints (OS and PFS).

Modified Intent-to-Treat 2 (mITT-2) population: This includes all randomized patients who were tested after August 2018 whose tumours expressed PD-L1 in ≥50% of tumour cells based on a PD-L1 assay at entry performed in accordance with approved labelling, including assay IFU (N=475). The mITT-2 population was based on the treatment allocated (as randomized). Although the mITT-2 population was not pre-specified in the study protocol or SAP, the Sponsor defined this cohort based on pre-submission interactions with a health authority and a request for the Sponsor to address if there was a need to impute PD-L1 expression for the 91 patients whose samples were not available for re-testing as described above. This mITT-2 population represents a meaningful randomized cohort that was not affected by the PD-L1 testing issues that occurred prior to August 2018. As it avoids any need for imputation of PD-L1 expression, it serves to check whether the analyses of the mITT-1 population accurately represents the results expected in patients whose tumours express PD-L1 in ≥50% of tumour cells based on the 22C3 IHC assay performed in accordance with its approved labelling, including assay IFU.

Primary endpoint

Overall survival

OS will be analysed by stratified log-rank test using status of histology (non-squamous versus squamous) as stratification factor. The HR and its 95% CI will be estimated by a stratified Cox regression model with Ephron's method for tie handling and using the treatment as covariate. The stratification factor used in Cox model will be the same factor used in stratified log-rank test. The distribution of OS will be estimated using the Kaplan-Meier method.

Censoring rules: A patient who has not died will be censored at last known date of contact.

Table 11. Reasons for censoring in overall survival (full analysis set)

	Cemiplimab (N=356)	Chemotherapy (N=354)
Number of censored patients, n (%)	248 (69.7%)	213 (60.2%)
Ongoing study or in survival follow-up	212 (85.5%)	165 (77.5%)
Lost to follow-up	6 (2.4%)	5 (2.3%)
Withdrew consent	28 (11.3%)	40 (18.8%)
Other	2 (0.8%)	3 (1.4%)

Data cut-off as of Mar 01, 2020

/sasdata/Data/Production/BDM/R2810/R2810-ONC/R2810-ONC-1624/Interim_NSCLC_sBLA/Analysis_CSR/Programs/TFL/Generated/t_2_1_2_os_cn_rs.sas (baole.fan 17AUG2020 18:37 SAS Linux 9.4)

Sensitivity analyses may be performed for OS. The first sensitivity analysis may be performed using the Rank Preserving Structural Failure Time (RPSFT) model to account for the effect of the additional treatments after disease progression, since patients in the control arm are allowed cemiplimab treatment after progressive disease and patients in the cemiplimab arm are allowed cemiplimab plus chemotherapy treatment after progressive disease. The second sensitivity analysis using the Restricted Mean Survival Time (RMST) method may be conducted to account for the possible non-proportional hazards effect.

Progression free survival

The primary endpoint of IRC-PFS will be analysed by stratified log-rank test using status of histology (non-squamous versus squamous) as stratification factors. The HR and its 95% confidence interval will be estimated by a stratified Cox regression model using the treatment as covariate and status of histology as stratification factor. The distribution of IRC-PFS will be estimated using the Kaplan-Meier method.

Censoring rules: 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 on 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.

Three sensitivity analyses will be performed for IRC-PFS. The first sensitivity analysis is the same as the primary analysis except that it considers initiation of new anti-tumour treatment as a progressive disease event for patients without documented progressive disease or death prior to initiation of new anti-tumour treatment. The second sensitivity analysis is the same as the primary analysis except that for the second sensitivity analysis, a patient who has progressive disease or death after missing ≥2 tumour assessments will be censored at the last evaluable tumour assessment prior to missing ≥ 2 tumour assessments. The third sensitivity analysis will be performed based on investigator-determined progressive disease events.

Key secondary efficacy variable ORR

The ORR will be analyzed using Cochran-Mantel-Haenszel test stratified by status of histology (non-squamous versus squamous). ORR and the corresponding 95% exact CI will be calculated by Clopper-Pearson method for each treatment arm. Not evaluated response includes the missing and unknown response. Patients with the best overall response of NE will be considered as non-responder (CR/PR). Two sensitivity analyses will be performed for ORR. The first sensitivity analysis will be performed based on randomized patients who had at least one valid post-baseline tumour evaluation, except those who had an early disease progression/death. The second sensitivity analysis will be performed based on investigator-assessed responses.

Type I error control

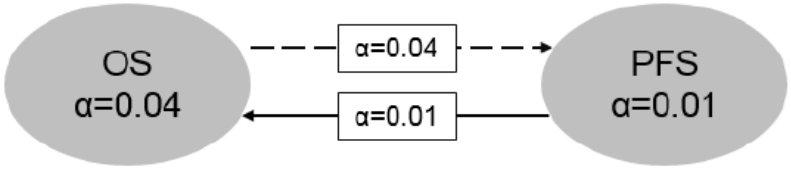

Figure 14. α reallocation strategy between primary endpoints of PFS and OS

Five interim analyses for OS are planned in addition to the final analysis. The OS hypothesis will be tested at overall 2-sided α of 0.04. If IRC-PFS analysis is significant, the OS hypothesis will be tested at overall 2-sided α of 0.05 (re-allocated α). The Lan-DeMets O'Brien-Fleming spending function will be used for analysis of OS. For the key secondary endpoint of ORR, the type I error rate is controlled by hierarchical testing procedure, that is, ORR will only be tested if both analyses of OS and IRC-PFS are statistically significant. All other statistical comparisons will be exploratory in nature and, therefore, not controlled for multiplicity and should be interpreted accordingly.

Table 12. Plan for interim and final analyses of primary endpoints

Analysis in this study	Analyses to be conducted	Timing
Interim Analysis 1	Interim analysis of OS only	When approximately 1/3 of OS events are observed (~159 deaths)
Interim Analysis 2	Interim analysis of OS only	When approximately 50% of OS events are observed (~238 deaths)
Interim Analysis 3	Interim analysis of OS only	When approximately 60% of OS events are observed (~286 deaths)
Interim Analysis 4	Final analysis of PFS Interim analysis of OS	When approximately 525 PFS events are observed. 308 deaths are expected, which is ~64.7% OS information time.
Interim Analysis 5	Interim analysis of OS only	When approximately 75% of OS events are observed (~357 deaths)
Final Analysis	Final analysis of OS	When approximately 476 deaths are observed

Results

Participant flow

A total of 3.662 patients were screened for study eligibility. Of the patients screened, 710 were randomised (356 patients to cemiplimab and 354 patients to chemotherapy) and 697 were treated (355 patients in the cemiplimab arm and 342 patients in the chemotherapy arm) at 137 sites in 24 countries.

Among the 2.952 patients failing screening, the most common reason for screen failure was non-eligibility per inclusion criterion 4 (tumour cells expressing PD-L1 in ≥50% of tumour cells); this was reported for 2.270 patients (76.9%) failing screening.

Patient disposition of the ITT population (N=710) at the date of data cutoff on 01-MAR-2020 is summarised in Table 13.

Table 13. Patient disposition (ITT population)

	Cemiplimab (N=356)	Chemotherapy (N=354)	Total (N=710)
Randomized and Not Treated (any study drug), n (%)	1 (0.3)	12 (3.4)	13 (1.8)
Treatment Ongoing, n (%)	139 (39.0)	45 (12.7)	184 (25.9)
Off Treatment, n (%)	216 (60.7)	297 (83.9)	513 (72.3)
Treatment Completed	6 (1.7)	149 (42.1)	155 (21.8)
Treatment Discontinued	210 (59.0)	148 (41.8)	358 (50.4)
Primary Reason for Treatment Discontinuation			
Adverse event	23 (6.5)	14 (4.0)	37 (5.2)
Death	29 (8.1)	25 (7.1)	54 (7.6)
Lost to follow-up	3 (0.8)	4 (1.1)	7 (1.0)
Patient decision	9 (2.5)	7 (2.0)	16 (2.3)
Physician decision	5 (1.4)	5 (1.4)	10 (1.4)
Disease progression	133 (37.4)	84 (23.7)	217 (30.6)
Withdrawal of consent	8 (2.2)	9 (2.5)	17 (2.4)
Study Ongoing, n (%)	193 (54.2)	146 (41.2)	339 (47.7)
Off Study, n (%)	163 (45.8)	208 (58.8)	371 (52.3)
Study Completed	3 (0.8)	1 (0.3)	4 (0.6)
Primary Reason for Study Discontinuation			
Death	96 (27.0)	111 (31.4)	207 (29.2)
Lost to follow-up	5 (1.4)	6 (1.7)	11 (1.5)
Patient decision	17 (4.8)	16 (4.5)	33 (4.6)
Sponsor decision	1 (0.3)	1 (0.3)	2 (0.3)
Physician decision	1 (0.3)	3 (0.8)	4 (0.6)
Disease progression	12 (3.4)	21 (5.9)	33 (4.6)
Withdrawal of consent	28 (7.9)	45 (12.7)	73 (10.3)
Other	0	4 (1.1)	4 (0.6)

ITT, intent-to-treat; mITT, modified intent-to-treat.
Source: PTT 14.1.1.5

Table 14. Duration of follow-up from randomization to cut-off date of 01 March 2020 (ITT population)

	Cemiplimab (N=356)	Chemotherapy (N=354)	Total (N=710)
Duration of follow-up between randomization and cutoff date (months)			
n	356	354	710
Mean (SDv)	14.04 (7.568)	14.04 (7.572)	14.04 (7.565)
Median	13.09	13.08	13.08
Q1, Q3	8.57, 20.21	8.67, 20.14	8.64, 20.17
Min, Max	0.1, 31.9	0.2, 32.4	0.1, 32.4
Duration of follow-up between randomization and cutoff date, n (%)			
≥6 months	297 (83.4)	296 (83.6)	593 (83.5)
≥12 months	199 (55.9)	197 (55.6)	396 (55.8)
≥18 months	113 (31.7)	113 (31.9)	226 (31.8)
≥24 months	43 (12.1)	41 (11.6)	84 (11.8)
≥30 months	3 (0.8)	4 (1.1)	7 (1.0)

ITT, intent-to-treat; max, maximum; min, minimum; SDv, standard deviation.
Source: PTT 14.1.1.11

Recruitment

The original version of the protocol was dated 01-November-2016. Enrolment of the first patient occurred under Protocol Amendment 3 dated 15-March-2017; first patient first visit took place on 29-May-2017.

The study is being conducted at 138 Investigator sites across 24 participating countries. The highest numbers of patients have been enrolled in Turkey (212 patients at 15 sites), Russia (93 patients at 21 sites), Ukraine (79 patients at 11 sites), Georgia (69 patients at 6 sites), Poland (37 patients at 9 sites) and Brazil (34 patients at 13 sites). Patients from United States were not included since pembrolizumab monotherapy was already approved as 1L treatment for NSCLC.

Conduct of the study

Protocol amendments

The protocol was amended on eight occasions. Table 15 outlines the major changes per amendment.

Protocol amendments 1-5, and 9 did not include changes that could impact on the study results. However, protocol amendments 6, 7 and 8 may have had significant impact on the study results:

- Amendment 6 (22-AUG-2018) increased the enrolment target from 300 to 700 and radically changed initial planned treatment: for patients in the chemotherapy arm who progressed the option of crossover to cemiplimab was added, whereas for patients in the cemiplimab arm who progressed, the option to continue cemiplimab with the addition of chemotherapy was added.
- Amendment 7 (28-MAY-2019) elevated OS as the second primary endpoint and implemented an interim analysis for OS.
- Amendment 8 (23-OCT-2019) implemented four additional interim analyses.

Table 15. Protocol amendments

Amendment/Date	Major Changes
Amendment 8 23 Oct 2019	• Added 4 additional time points for interim analyses and updated the alpha spending function under the originally specified O'Brien-Fleming alpha spending framework.
Amendment 7 28 May 2019	• Changed OS to a primary objective and endpoint (from secondary) to provide more robust support for a registration application. • Added an interim analysis for OS based on the Lan-DeMets O'Brien-Fleming alpha spending function.
Amendment 6 Admin 06 Sep 2018	• A typographical error in Amendment 6, which incorrectly stated that the sample size for this study was 300, was corrected to reflect the actual sample size of 700.
Amendment 6 22 Aug 2018	• Increased enrollment from 300 to 700 patients to account for a possible smaller effect size as suggested by the KEYNOTE-042 study. • Added option to crossover to cemiplimab after initial disease progression on chemotherapy. • Added option to continue cemiplimab with the addition of 4 cycles of histology-specific chemotherapy after initial disease progression on cemiplimab monotherapy; remove option for patients randomized to cemiplimab monotherapy to continue cemiplimab monotherapy until further progression.
Amendment 5 06 Sep 2017	• A 12-lead ECG should be acquired prior to obtaining any blood samples. • Added: The partial pressure of carbon dioxide test is an acceptable test at centers where this is commonly used instead of the bicarbonate test.
Amendment 4 17 Jul 2017	• Other secondary objectives added: To assess immunogenicity (ADA/NAbs) to REGN2810 and any relationship with drug concentrations, efficacy and safety); To conduct Exposure-Response analyses on efficacy endpoints, safety, and relevant exploratory biomarkers, as appropriate. • Exploratory Objectives added: To assess PD changes in putative serum biomarkers (which may include but are not limited to cytokines, circulating tumor nucleic acids, etc; To conduct PK/PD analyses on exploratory biomarkers, as appropriate. • An exclusion criterion was added: Patients who have previously been treated with idelalisib will be excluded from treatment with REGN2810. • An AESI was added to the list of AESIs: An irAE of any grade in a patient previously treated with a PI 3-K inhibitor.
Amendment 3 15 Mar 2017	**Subjects were first enrolled to the study under this amendment** • Updated dose to 350 mg Q3W from 250 mg Q3W and provided rationale for dose change. • ADA sample collection added at day 1 cycle 1, preinfusion on day 1 of cycle 3, day 1 of cycle 9, and day 1 of cycle 18. • Clarified all infusions reactions are to be recorded as an AE.
Amendment 2 19 Jan 2017	• Added Asia to the geographical stratification.
Amendment 1 29 Nov 2016	• Removed the US and Japan as study site locations.

ADA, anti-drug antibody; AE, adverse event; AESI, adverse event of special interest; CO_2, carbon dioxide; ECG, electrocardiogram; irAE, immune-related adverse event; IRC, Independent Review Committee; NAb, neutralizing anti-drug antibody; NSCLC, non-small cell lung cancer; OS, overall survival; PD, pharmacodynamic; PI 3-K, phosphatidylinositol 3 kinase; PK, pharmacokinetic; US, United States.

Changes to the planned analyses (SAP Amendments)

Version / Date	Major Changes
Version 3.0/12 Mar 2020	• Added Section 5.8.5 for PD-L1 sensitivity analysis; this corresponds to the mITT-1 population described in this report. • Added details of exploratory biomarker analysis in Section 5.10.3. • Clarified the OS sensitivity analyses may be performed to account for the effect of the additional treatments after disease progression.
Version 2.0/23 Oct 2019	• Promoted OS as a primary objective and primary endpoint (instead of key secondary objective/endpoint) in addition to the existing primary objective/endpoint of PFS. • Added interim OS analyses using the previously specified Lan-DeMets O'Brien-Fleming alpha spending function. • Updated section of multiplicity control to reflect the addition of OS primary endpoints and OS interim analyses.
Version 1.0 / 26 Oct 2016	Original version.

OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival.

Inadvertent Aggregation

An inadvertent aggregation of investigator-determined ORR data by treatment arm, performed by a student intern, came to Sponsor's attention in September 2019. This included data only from the first 361 patients enrolled and investigator-assessed responses of the open-label study.

Nevertheless, corrective actions were immediately pursued: all paper and electronic copies were destroyed, the medical monitors who had access to the response data were no longer in charge of the medical monitoring, and a different medical director took over guidance of the study. The IDMC chair was notified. The Sponsor concluded that the study had not been compromised and would continue: the information did not compromise equipoise and involved only 51% of the patients enrolled. However, the Sponsor determined that the information could be considered potentially material and needed to be disclosed as part of its obligations under securities regulations. This was done in the form of a press release on 05 Nov 2019.

The Sponsor also determined that, to provide balance in the press release, it would ask the IDMC to perform an interim analysis of OS using the Lan-DeMets approach already pre-specified in the protocol. The OS data were independently statistically analyzed and presented to the IDMC in a closed session. The IDMC recommended to continue the study; at that time, proof of efficacy had not been reached yet. The protocol was then amended (see Appendix 16.1.1 Amendment 8) to increase the number of planned interim analyses from the one previously specified, at time of final IRC-PFS, to a total number of 5, with the first analysis at approximately 1/3 of OS events coinciding with the timing of the interim analysis described above at the time of the inadvertent aggregation of the partial response data.

Changes Following Study Unblinding/Database Lock and Post-hoc Analyses

The following were added:

- Additional subgroup analyses (brain metastasis at baseline: Y/N; stage of cancer at baseline: locally advanced/metastatic)
- Post-hoc analyses (mITT-1 population) for the key secondary endpoint of ORR by IRC and other secondary efficacy variables.
- Post-hoc analyses (mITT-2 population) for the primary endpoints of OS and IRC-PFS and for the key secondary endpoint of ORR by IRC and other secondary efficacy variables.

Protocol deviations

Table 16. Important protocol deviations

	Cemiplimab (N=356)	Chemotherapy (N=354)	Total (N=710)
Number of important protocol deviations	91	86	177
Patients with any important protocol deviation, n (%)	58 (16.3)	54 (15.3)	112 (15.8)
Type of important protocol deviations, n (%)			
Entered study even though entry criteria was not satisfied	11 (3.1)	11 (3.1)	22 (3.1)
Inadequate informed consent administration	1 (0.3)	9 (2.5)	10 (1.4)
Other treatment compliance	0	1 (0.3)	1 (0.1)
Procedure not performed	34 (9.6)	33 (9.3)	67 (9.4)
Procedure performed outside of window	10 (2.8)	5 (1.4)	15 (2.1)
Received an excluded concomitant treatment	0	2 (0.6)	2 (0.3)
Received wrong treatment or incorrect dose	6 (1.7)	1 (0.3)	7 (1.0)
Patient developed withdrawal criteria but was not withdrawn	2 (0.6)	0	2 (0.3)

Source: PTT 14.1.1.6

Baseline data

Table 17. Demographics and baseline characteristics (ITT population)

	Cemiplimab (N=356)	Chemotherapy (N=354)	Total (N=710)
Age (years)			
n	356	354	710
Mean (SDv)	63.0 (8.17)	63.3 (8.56)	63.1 (8.36)
Median	63.0	64.0	63.0
Q1, Q3	58.0, 69.0	57.0, 69.0	57.0, 69.0
Min, Max	31, 79	40, 84	31, 84
Age groups (years), n (%)			
<65	200 (56.2)	190 (53.7)	390 (54.9)
≥65	156 (43.8)	164 (46.3)	320 (45.1)
Sex, n (%)			
Male	312 (87.6)	294 (83.1)	606 (85.4)
Female	44 (12.4)	60 (16.9)	104 (14.6)
Race, n (%)			
White	308 (86.5)	305 (86.2)	613 (86.3)
Black or African American	1 (0.3)	3 (0.8)	4 (0.6)
Asian	39 (11.0)	38 (10.7)	77 (10.8)
American Indian or Alaska native	6 (1.7)	8 (2.3)	14 (2.0)
Other	2 (0.6)	0	2 (0.3)
Ethnicity, n (%)			
Not Hispanic or Latino	320 (89.9)	327 (92.4)	647 (91.1)
Hispanic or Latino	36 (10.1)	26 (7.3)	62 (8.7)
Not reported	0	1 (0.3)	1 (0.1)
Geographic region, n (%)			
Europe	275 (77.2)	278 (78.5)	553 (77.9)
Asia	39 (11.0)	38 (10.7)	77 (10.8)
ROW	42 (11.8)	38 (10.7)	80 (11.3)
Height (cm)			
n	352	353	705
Mean (SDv)	168.96 (8.391)	168.86 (9.241)	168.91 (8.820)
Median	170.00	169.00	170.00
Q1, Q3	164.00, 175.00	163.00, 175.00	164.00, 175.00
Min, Max	143.0, 194.0	143.0, 197.0	143.0, 197.0
Body weight (kg)			
n	356	353	709
Mean (SDv)	70.74 (15.124)	70.11 (14.724)	70.42 (14.919)
Median	69.30	69.70	69.60
Q1, Q3	61.00, 78.00	60.00, 79.50	60.00, 78.70
Min, Max	37.6, 138.0	39.5, 125.0	37.6, 138.0
BMI (kg/m^2)			
n	352	353	705
Mean (SDv)	24.713 (4.5693)	24.484 (4.2558)	24.599 (4.4134)
Median	24.265	24.170	24.220
Q1, Q3	21.485, 27.210	21.340, 26.790	21.450, 27.040
Min, Max	15.53, 43.07	15.62, 37.66	15.53, 43.07
ECOG performance status, n (%)			
0	96 (27.0)	96 (27.1)	192 (27.0)
1	260 (73.0)	258 (72.9)	518 (73.0)
Smoking status, n (%)			
Current smoker	133 (37.4)	120 (33.9)	253 (35.6)
Past smoker	223 (62.6)	234 (66.1)	457 (64.4)

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; max, maximum; min, minimum; ROW; rest of the world; SDv, standard deviation.
Source: PTT 14.1.2.1

Disease characteristics

Table 18. Baseline tumour characteristics (Full analysis set)

Table 14.1.2.2 Baseline Tumor Characteristics
(Full Analysis Set)

	Cemiplimab (N=356)	Chemotherapy (N=354)	Total (N=710)
Histology/Cytology, n (%)			
SQUAMOUS	159 (44.7%)	152 (42.9%)	311 (43.8%)
NON-SQUAMOUS	197 (55.3%)	202 (57.1%)	399 (56.2%)
ADENOCARCINOMA	180 (50.6%)	185 (52.3%)	365 (51.4%)
LARGE CELL CARCINOMA	3 (0.8%)	5 (1.4%)	8 (1.1%)
NOT OTHERWISE SPECIFIED	14 (3.9%)	12 (3.4%)	26 (3.7%)
Metastatic sites, n (%)			
Lung	227 (63.8%)	243 (68.6%)	470 (66.2%)
Liver	54 (15.2%)	54 (15.3%)	108 (15.2%)
Bone	80 (22.5%)	97 (27.4%)	177 (24.9%)
Adrenal	76 (21.3%)	71 (20.1%)	147 (20.7%)
Brain	44 (12.4%)	39 (11.0%)	83 (11.7%)
Lymph nodes intrathoracic	252 (70.8%)	244 (68.9%)	496 (69.9%)
Lymph nodes other	74 (20.8%)	76 (21.5%)	150 (21.1%)
Mutation status: EGFR, n (%)			
WILDTYPE	356 (100%)	354 (100%)	710 (100%)
Mutation status: ALK Translocation, n (%)			
NOT PRESENT	356 (100%)	354 (100%)	710 (100%)
Mutation status: ROS1 Translocation, n (%)			
NOT REARRANGED	356 (100%)	354 (100%)	710 (100%)
Cancer stage at screening, n (%)			
STAGE IIIA	0	1 (0.3%)	1 (0.1%)
STAGE IIIB	52 (14.6%)	39 (11.0%)	91 (12.8%)
STAGE IIIC	11 (3.1%)	12 (3.4%)	23 (3.2%)
STAGE IV	293 (82.3%)	302 (85.3%)	595 (83.8%)
Cancer stage at screening, n (%)			
Locally Advanced	63 (17.7%)	52 (14.7%)	115 (16.2%)
Metastatic	293 (82.3%)	302 (85.3%)	595 (83.8%)
PD-L1 expression levels, n (%)			
0%	3 (0.8%)	3 (0.8%)	6 (0.8%)
1-49%	26 (7.3%)	24 (6.8%)	50 (7.0%)
>=50%	283 (79.5%)	280 (79.1%)	563 (79.3%)
>=90%	98 (27.5%)	94 (26.6%)	192 (27.0%)
>60% and <90%	89 (25.0%)	90 (25.4%)	179 (25.2%)
>=50% and <=60%	96 (27.0%)	96 (27.1%)	192 (27.0%)
Unknown	44 (12.4%)	47 (13.3%)	91 (12.8%)

Data cut-off as of Mar 01, 2020
[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.

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Table 19. Prior therapy (ITT population)

	Cemiplimab (N=356)	Chemotherapy (N=354)	Total (N=710)
Number of patients with any prior cancer-related therapy[a], n (%)	83 (23.3)	81 (22.9)	164 (23.1)
Number of patients with any prior cancer-related systemic therapy, n (%)	13 (3.7)	20 (5.6)	33 (4.6)
Therapy setting, n (%)			
Adjuvant	9 (2.5)	15 (4.2)	24 (3.4)
Neo-adjuvant	4 (1.1)	7 (2.0)	11 (1.5)
Time from end of last prior regimen to randomization (months)			
n	12	20	32
Mean (SDv)	18.69 (19.515)	34.77 (46.736)	28.74 (39.197)
Median	12.40	23.62	14.71
Q1, Q3	9.50, 17.09	13.32, 34.58	11.27, 28.67
Min, Max	7.1, 77.8	7.8, 221.7	7.1, 221.7
Number of patients with any prior cancer-related surgery[b], n (%)	33 (9.3)	36 (10.2)	69 (9.7)
Number of patients with any prior cancer-related radiotherapy, n (%)	63 (17.7)	59 (16.7)	122 (17.2)

[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.
ITT, intent-to-treat; max, maximum; min, minimum; SDv, standard deviation.
Source: PTT 14.1.3.1

Demographic and baseline characteristics were balanced between the treatment groups; 85% of patients were male, and median age was 63 years. Reflecting inclusion/exclusion criteria, all the patients were current or previous smokers. Non-squamous histology was observed in 56% of patients, and the disease stage at screening was metastatic (Stage IV) in 84% of patients. About 23% of patients had received some prior therapy, most commonly radiotherapy, for their disease.

Numbers analysed

Due to irregularities in the PD-L1 testing process, a total of 235 patients enrolled before August 2018 had an initial PD-L1 test result that was considered unreliable. These patients were retested when possible, with the retest results used to delineate two modified ITT populations as outlined in Figure 15 and Table 20.

The irregularities in PD-L1 testing led to the necessity of defining modified ITT populations for statistical analysis purposes. The ITT population represents the whole sample randomised into the study, and presentation of results for this population is considered essential. While it can be agreed that the mITT-1 is in a strict sense not a randomised population, there is no reason to assume that the possibility of systematic bias needs to be considered when evaluating results in this subpopulation.

The assessment of efficacy results will focus on baseline data for the ITT population (n=710), which is the primary population. Results obtained from the two modified ITT populations, i.e. mITT-1 and mITT-2, are considered supportive.

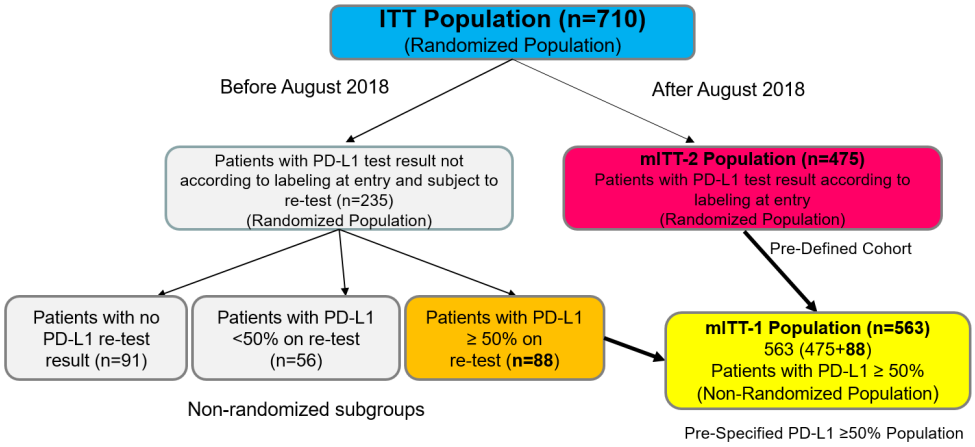

Figure 15. Patient Disposition by PD-L1 Testing Status and Retest
Abbreviations: ITT, Intent-to-Treat; mITT, modified intent-to-treat; Neo, NeoGenomics; PD-L1, programmed cell death ligand-1; pts, patients; Q2, Q2 Laboratories. Source: Study 1624 Primary Analysis CSR Figure 3

Table 20. Analysis populations

Analysis Population, n (%)	Cemiplimab (N=356)	Chemotherapy (N=354)	Total (N=710)
Full Analysis Population (ITT)	356 (100)	354 (100)	710 (100)
Modified Intent-To-Treat-1 Population (mITT-1)	283 (79.5)	280 (79.1)	563 (79.3)
Modified Intent-To-Treat-2 Population (mITT-2)	238 (66.9)	237 (66.9)	475 (66.9)
Safety Analysis Population (SAF)	355 (99.7)	342 (96.6)	697 (98.2)
Pharmacokinetic Analysis Population (PKA)	345 (96.9)	0	345 (48.6)
Anti-drug Antibody Analysis Population (ADA)	221 (62.1)	0	221 (31.1)

Source: PTT 14.1.1.3

Outcomes and estimation

Primary endpoints: OS and IRC-PFS

According to the eighth amendment of the protocol on 23-OCT-2019, the second interim analysis (IA2) was planned when approximately 50% of 476 planned OS events at final analysis (~238 deaths) had occurred across both arms. After 249 OS events (35% of ITT), on data cut-off date 01-MAR-2020, the study met its OS primary endpoint by showing a statistically significant increase in survival with cemiplimab monotherapy vs. platinum-based chemotherapy in the targeted population.

Table 21. Study 1624: Overall Survival – Primary Analysis

	ITT Population (n=710)	
	Cemiplimab (N=356)	**Chemotherapy (N=354)**
Number of deaths, n (%)	108 (30.3)	141 (39.8)
Number of censored patients, n (%)	248 (69.7)	213 (60.2)
Median (95% CI), (months)[a]	22.1 (17.7, NE)	14.3 (11.7, 19.2)
Stratified log-rank test p-value[b]	0.0022[c]	
HR (95% CI)[d]	0.676 (0.525, 0.870)	
Estimated Survival Probability, % (95% CI)		
6 months	81.2 (76.4, 85.1)	76.2 (71.0, 80.6)
12 months	70.3 (64.4, 75.4)	55.7 (49.2, 61.7)
18 months	56.1 (48.1, 63.3)	43.3 (35.8, 50.4)
24 months	48.6 (39.2, 57.3)	29.7 (18.8, 41.4)
30 months	45.5 (35.0, 55.4)	NE (NE, NE)

[a] Based on Kaplan-Meier method.
[b] Stratified by histology (squamous, non-squamous) according to IWRS.
[c] Two-sided p-value. Significance threshold is population to 0.0025 using the O'Brien-Fleming alpha spending function.
[d] Based on stratified proportional hazards model (cemiplimab versus chemotherapy).
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, Intent-to-Treat; NE, not evaluable. Sources: Study 1624 Primary Analysis CSR Table 19, Table 20, and Table 21

Table 22. Reasons for censoring in overall survival (Full analysis set)

	Cemiplimab (N=356)	Chemotherapy (N=354)
Number of censored patients, n (%)	248 (69.7%)	213 (60.2%)
Ongoing study or in survival follow-up	212 (85.5%)	165 (77.5%)
Lost to follow-up	6 (2.4%)	5 (2.3%)
Withdrew consent	28 (11.3%)	40 (18.8%)
Other	2 (0.8%)	3 (1.4%)

Data cut-off as of Mar 01, 2020

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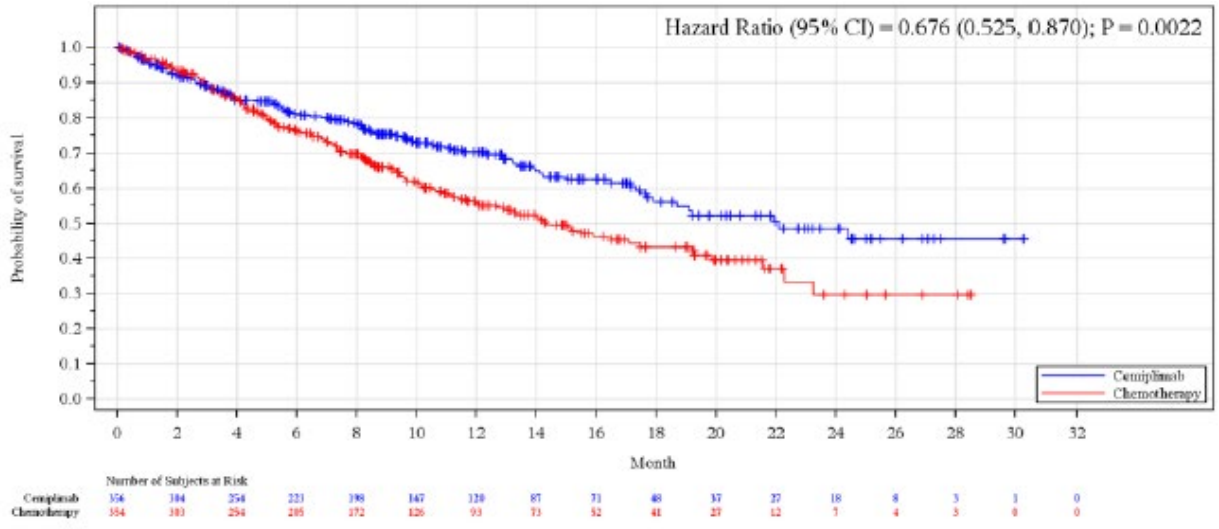

Figure 16. Kaplan-Meier curve of overall survival (ITT population)
Abbreviations: CI= confidence interval; ITT= intent-to-treat. Source: PTF 14.2.1.1

Table 23. Study 1624: Progression-Free Survival per IRC – Primary Analysis

	ITT Population (n=710)	
	Cemiplimab (N=356)	**Chemotherapy (N=354)**
Number of events, n (%)	201 (56.5)	262 (74.0)
Progressive disease, n (%)	158 (44.4)	203 (57.3)
Death, n (%)	43 (12.1)	59 (16.7)
Number of censored patients, n (%)	155 (43.5)	92 (26.0)
Median (95% CI), (months)[a]	6.2 (4.5, 8.3)	5.6 (4.5, 6.1)
Stratified log-rank test p-value[b, c]	<0.0001	
HR (95% CI)[d]	0.593 (0.491, 0.718)	
Estimated Survival Probability, % (95% CI)		
6 months	53.1 (47.4, 58.5)	48.0 (42.2, 53.6)
12 months	37.8 (31.9, 43.6)	7.2 (4.3, 11.2)
18 months	28.0 (21.7, 34.7)	3.9 (1.8, 7.5)
24 months	21.7 (14.7, 29.7)	NE (NE, NE)
30 months	0.0 (NE, NE)	NE (NE, NE)

[a] Based on Kaplan-Meier method.

[b] Stratified by histology (squamous, non-squamous) according to IWRS.
[c] Two-sided p-value.
[d] Based on stratified proportional hazards model (cemiplimab versus 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 1624 Primary Analysis CSR Table 22, Table 23, and Table 24

Table 24. Summary of events and reasons for censoring in PFS analysis per IRC (full analysis set)

	Cemiplimab (N=356)	Chemotherapy (N=354)
Number of events, n (%)	201 (56.5%)	262 (74.0%)
Progressive Disease, n (%)	158 (78.6%)	203 (77.5%)
Death, n (%)	43 (21.4%)	59 (22.5%)
Number of censored patients, n (%)	155 (43.5%)	92 (26.0%)
Without event and are ongoing study	116 (74.8%)	47 (51.1%)
Without event and are off study	10 (6.5%)	10 (10.9%)
Initiation of new anticancer therapy	4 (2.6%)	4 (4.3%)
No post-baseline tumor assessment	25 (16.1%)	31 (33.7%)

Data cut-off as of Mar 01, 2020

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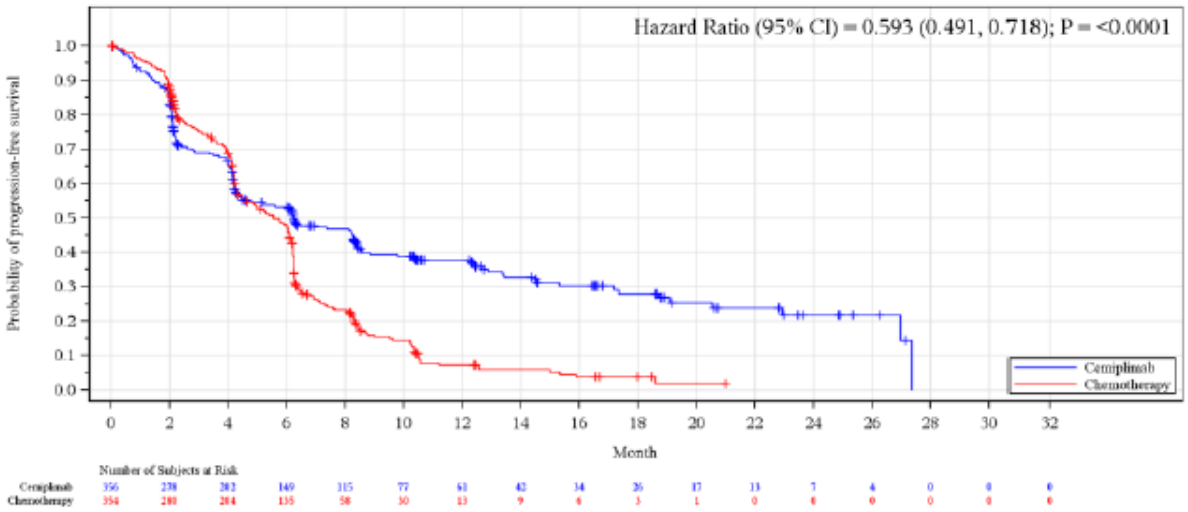

Figure 17. Kaplan-Meier curve of progression-free survival per IRC (ITT population)
Abbreviations: CI= confidence interval; IRC= independent review committee; ITT= intent-to-treat. Source: PTF 14.2.1.1

Secondary endpoints: IRC-ORR and IRC-DOR

Table 25. Study 1624: Best Overall Tumour Response per IRC

	ITT Population (n=710)	
	Cemiplimab (N=356)	**Chemotherapy (N=354)**
Best Overall Tumour Response, n (%)		
Complete Response (CR)	11 (3.1)	3 (0.8)
Partial Response (PR)	119 (33.4)	70 (19.8)
Stable Disease (SD)	101 (28.4)	168 (47.5)
Non-CR/Non-PD	2 (0.6)	4 (1.1)
Progressive Disease (PD)	68 (19.1)	52 (14.7)
Not Evaluable (NE)	55 (15.4)	57 (16.1)
Response		

	ITT Population (n=710)	
	Cemiplimab (N=356)	**Chemotherapy (N=354)**
Objective Response Rate (ORR: CR + PR)	130 (36.5)	73 (20.6)
95% CI for ORR[a]	31.5, 41.8	16.5, 25.2
Stratified CMH test p-value[b]	<0.0001	
Odds ratio (95% CI)[b]	2.214 (1.582, 3.098)	

[a] Clopper-Person exact CI.
[b] Two-sided p-value using stratified Cochran-Mantel-Haenszel test.
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; ITT, intent-to-treat; mITT, Modified Intent-to-Treat; ORR, objective response rate
Source: Study 1624 Primary Analysis CSR Table 31, Table 32, and Table 33

Table 26. Best overall tumour response rate per investigator assessment (ITT population)

	Cemiplimab (N=356)	Chemotherapy (N=354)
Best Overall Tumor Response, n (%)		
Complete Response (CR)	5 (1.4)	0
Partial Response (PR)	131 (36.8)	72 (20.3)
Stable Disease (SD)	121 (34.0)	174 (49.2)
Progressive Disease (PD)	47 (13.2)	50 (14.1)
Not Evaluable (NE)	52 (14.6)	58 (16.4)
Response		
Objective Response Rate (ORR: CR + PR), n (%)	136 (38.2)	72 (20.3)
95% CI for ORR[a]	33.1, 43.5	16.3, 24.9
Stratified CMH test p-value[b]	<0.0001	
Odds ratio (95% CI)[b]	2.421 (1.731, 3.387)	

[a] Clopper-Person exact CI.
[b] Two-sided p-value using stratified Cochran-Mantel-Haenszel test.
CI, confidence interval; CMH, Cochran-Mantel-Haenszel; IRC, Independent Review Committee; ITT, intent-to-treat; ORR, objective response rate.
Source: PTT 14.2.3.6

Table 27. Study 1624: Observed Duration of Response per IRC (ITT Population, Patients with Confirmed CR or PR)

	ITT Population (n=710)	
	Cemiplimab (N=130)	**Chemotherapy (N=73)**
Observed Duration of Response (CR or PR) (months)[a]		
n	130	73
Min, Max	1.9, 23.3	1.3, 16.5
Observed Duration of Response (CR and PR), n (%)[a]		
<6 months	40 (30.8)	43 (58.9)
≥6 months	90 (69.2)	30 (41.1)
≥12 months	36 (27.7)	5 (6.8)
≥18 months	15 (11.5)	0
≥24 months	0	0

[a] Based on patients with confirmed CR or PR.

Abbreviations: CR, complete response; ITT, intent-to-treat; max, maximum; min, minimum; mITT, modified intent-to-treat; PR, partial response.
Source: Study 1624 Primary Analysis CSR Table 37, Table 38, and Table 39

Table 28. Study 1624: Kaplan-Meier Estimation of Duration of Response (Confirmed CR or PR) per IRC

	ITT Population (n=710)	
	Cemiplimab (N=130)	**Chemotherapy (N=73)**
n	130	73
Number of events (PD or death), n (%)	37 (28.5)	49 (67.1)
Median (95% CI), (months)	21.0 (14.9, NE)	6.0 (4.3, 6.4)
6 months	88.3 (80.7, 93.0)	50.5 (37.5, 62.1)
12 months	66.4 (54.6, 75.8)	16.4 (7.4, 28.5)
18 months	54.0 (40.0, 66.1)	NE (NE, NE)
24 months	NE (NE, NE)	NE (NE, NE)
30 months	NE (NE, NE)	NE (NE, NE)

[a] Based on patients with confirmed CR or PR.
Abbreviations: CR, complete response; ITT, Intent-to-Treat; mITT, modified intent-to-treat; NE, not evaluable; NR, not reported; PR, partial response. Source: Study 1624 Primary Analysis CSR Table 40, Table 41, and Table 42

Secondary endpoints: Patient-Reported Quality of Life

Mean (SD) baseline scores for General Health Status / QoL on the EORTC QLQ-C30 scale were 59.0 (21.5) and 59.7 (20.8) in the cemiplimab and chemotherapy treatment groups, respectively, indicating impaired QoL. For functioning scores, mean baseline scores generally indicated moderate to high levels of functioning; of a possible score of 100, mean baseline functioning scale scores were similar between the treatment groups and ranged from 74.0 for physical functioning to 88.5 for cognitive functioning in the cemiplimab group, and from 74.6 for physical functioning to 89.3 for cognitive functioning in the chemotherapy group.

In the cemiplimab group, an improvement of 5.2 points for mean GHS / QoL was seen by cycle 2; mean improvement further increased to above 9 points by cycle 6 (N=230) and above 10 points by cycle 18 (N=72). In the chemotherapy arm, mean improvement for GHS / QoL was less than 3 points up to cycle 12; at cycle 12, data in the chemotherapy group was only available for 27 patients.

There were generally few changes exceeding the threshold of clinically meaningful improvement (≥10 points) on functioning scales. For emotional functioning, a mean improvement exceeding 11 points was seen at cycle 15 (N=92) for cemiplimab; at the corresponding time point, mean change was 1.5 points in the chemotherapy group, although data was only available for 11 patients.

Mean baseline scores for the 9 symptom scales/items on EORTC-QLQ-C30 were similar between patients in the cemiplimab and chemotherapy treatment groups, generally indicating low to moderate symptom burden. In the cemiplimab arm, a meaningful improvement of ≥10 points was achieved by cycle 9 in fatigue, pain, dyspnoea, insomnia, and appetite loss. Few changes indicating meaningful improvement were observed in the chemotherapy arm.

Mean baseline symptom scores on the lung cancer-specific EORTC-QLQ-LC13 scale were similar between the treatment groups. For lung cancer symptoms, mean improvements of ≥10 points were seen in the cemiplimab arm for dyspnoea (cycles 12 [N=139] and 30 [N=16]), pain in chest (from cycle 6 [N=230] onward) and pain in other parts (cycles 18 [N=72], 21 [N=44], and 33 [N=9]); in the chemotherapy arm, pain in chest improved by ≥10 points at cycle 6 (N=176) and pain in other parts at cycles 21 (N=3), 24 (N=2), and 27 (N=1). For cough, mean improvements often exceeding ≥10 points were seen from

cycle 4 onward in both treatment groups. Comparable small improvements (generally <10 points) were seen in both treatment groups for haemoptysis and pain in arm or shoulder.

For treatment-related side effects such as sore mouth, dysphagia, peripheral neuropathy, and alopecia, mean scores remained consistent as compared to baseline among patients in the cemiplimab arm. Similar results were observed in the chemotherapy arm, with the exception of significant worsening in alopecia as early as cycle 2 and peripheral neuropathy at cycles 5 and 6.

Ancillary analyses

Subsequent anticancer treatments

Table 29. Subsequent anticancer therapies (full analysis set)

	Cemiplimab (N=356)	Chemotherapy (N=354)
Number of patients received any subsequent anticancer therapies, n (%)	71 (19.9%)	157 (44.4%)
Radiotherapy [a]	0	0
Surgery	0	1 (0.3%)
Systemic therapy	71 (19.9%)	156 (44.1%)
Cemiplimab as crossover treatment	0	150 (42.4%)
Cemiplimab plus chemotherapy as extended treatment	51 (14.3%)	0
Other systemic therapies	23 (6.5%)	18 (5.1%)
CARBOPLATIN	12 (3.4%)	10 (2.8%)
PACLITAXEL	9 (2.5%)	5 (1.4%)
CISPLATIN	6 (1.7%)	1 (0.3%)
PEMETREXED	5 (1.4%)	1 (0.3%)
GEMCITABINE	3 (0.8%)	4 (1.1%)
VINORELBINE	3 (0.8%)	2 (0.6%)
DOCETAXEL	2 (0.6%)	4 (1.1%)
AFATINIB	1 (0.3%)	0
BEVACIZUMAB	1 (0.3%)	0
ETOPOSIDE	1 (0.3%)	3 (0.8%)
NINTEDANIB ESILATE	1 (0.3%)	1 (0.3%)
PEMBROLIZUMAB	0	2 (0.6%)

Data cut-off as of Mar 01, 2020
[a] Subsequent anticancer radiotherapy excludes radiotherapies with palliative intent
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About 20% (71 out of 356) of patients in the cemiplimab arm vs. 45% (157 out of 354) in the chemotherapy arm received any subsequent anticancer therapies Table 29. Of note, from the patients in the cemiplimab arm who received other therapies, 70% (51 out of 71) received cemiplimab plus chemotherapy as extended treatment, as allowed by Amendment 6 of the protocol.

In the chemotherapy arm, 156 out of 203 progressors by data cut-off (77%) went on to 2L, most of them to crossover cemiplimab.

Subgroup analysis of OS and IRC-PFS in the ITT population

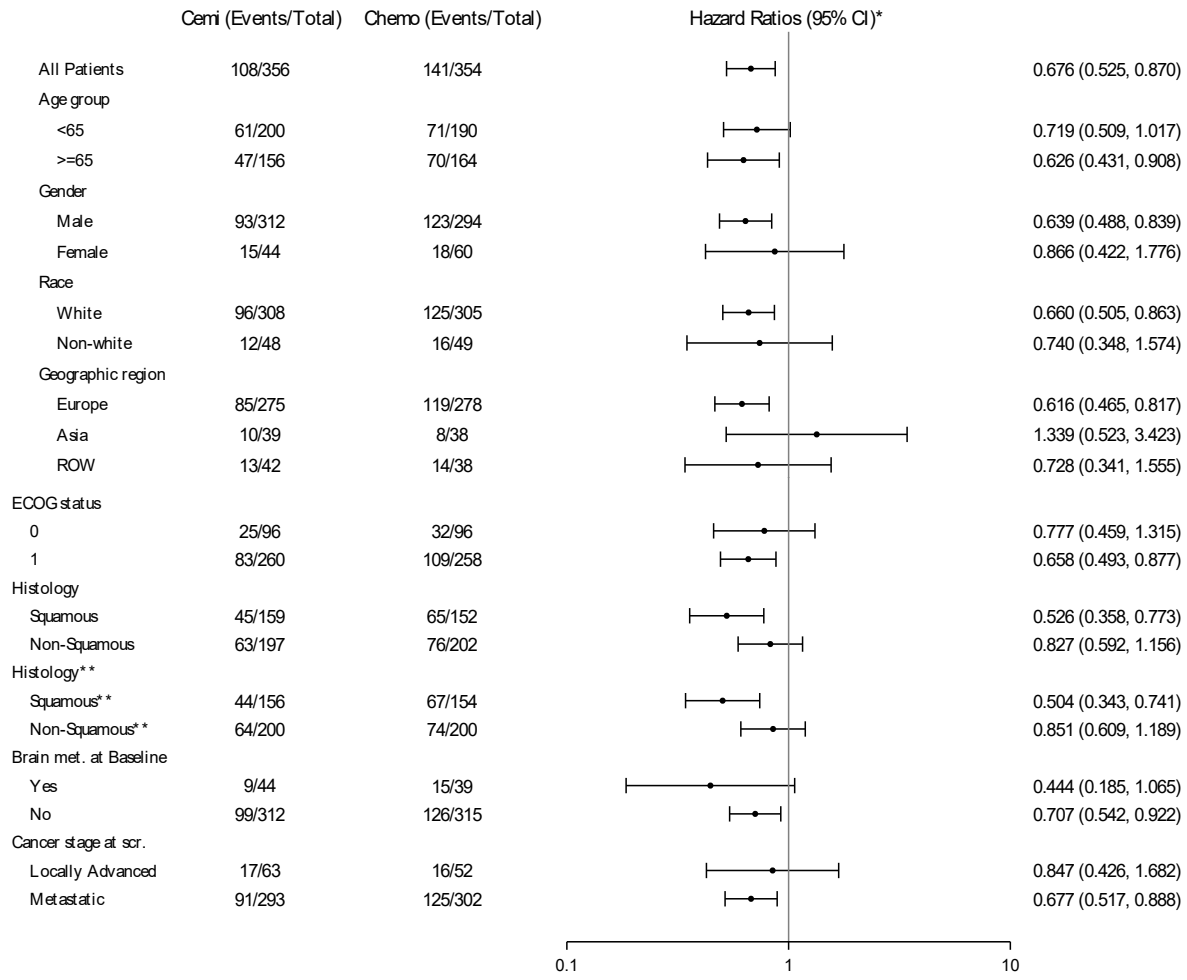

Figure 18. Study 1624: Forest Plot for Overall Survival by Subgroup (ITT Population)
*Stratified by histology (squamous, non-squamous) accordingly to IWRS except for Histology subgroups.
** According to IWRS.
Abbreviations: CI= confidence interval; ECOG= Eastern Cooperative Oncology Group; HR= hazard ratio; ITT= intent-to-treat; IWRS= Interactive Web Response System; ROW= rest of the world.
Source: Study 1624 Primary Analysis CSR Figure 14.2.1.2.a

Table 30. Overall survival by age groups (<65, >=65 to <75, >=75) (full analysis set)

	Cemiplimab (N=356)		Chemotherapy (N=354)		
	Event(%)	Median Time (95% CI)[a]	Event(%)	Median Time (95% CI)[a]	HR (95% CI) [b]
All Patients	108/356 (30.3%)	22.1 (17.7, NE)	141/354 (39.8%)	14.3 (11.7, 19.2)	0.676 (0.525, 0.870)
Age group					
<65	61/200 (30.5%)	24.4 (17.3, NE)	71/190 (37.4%)	17.1 (12.1, 23.3)	0.719 (0.509, 1.017)
>=65 to <75	36/123 (29.3%)	NR (13.4, NE)	52/127 (40.9%)	14.3 (10.6, 22.3)	0.715 (0.466, 1.097)
>=75	11/33 (33.3%)	19.2 (17.7, NE)	18/37 (48.6%)	8.5 (5.4, 14.2)	0.300 (0.125, 0.722)

Data cut-off as of Mar 01, 2020
[a] Based on Kaplan-Meier method.
[b] Based on stratified proportional hazards model (cemiplimab vs chemotherapy).
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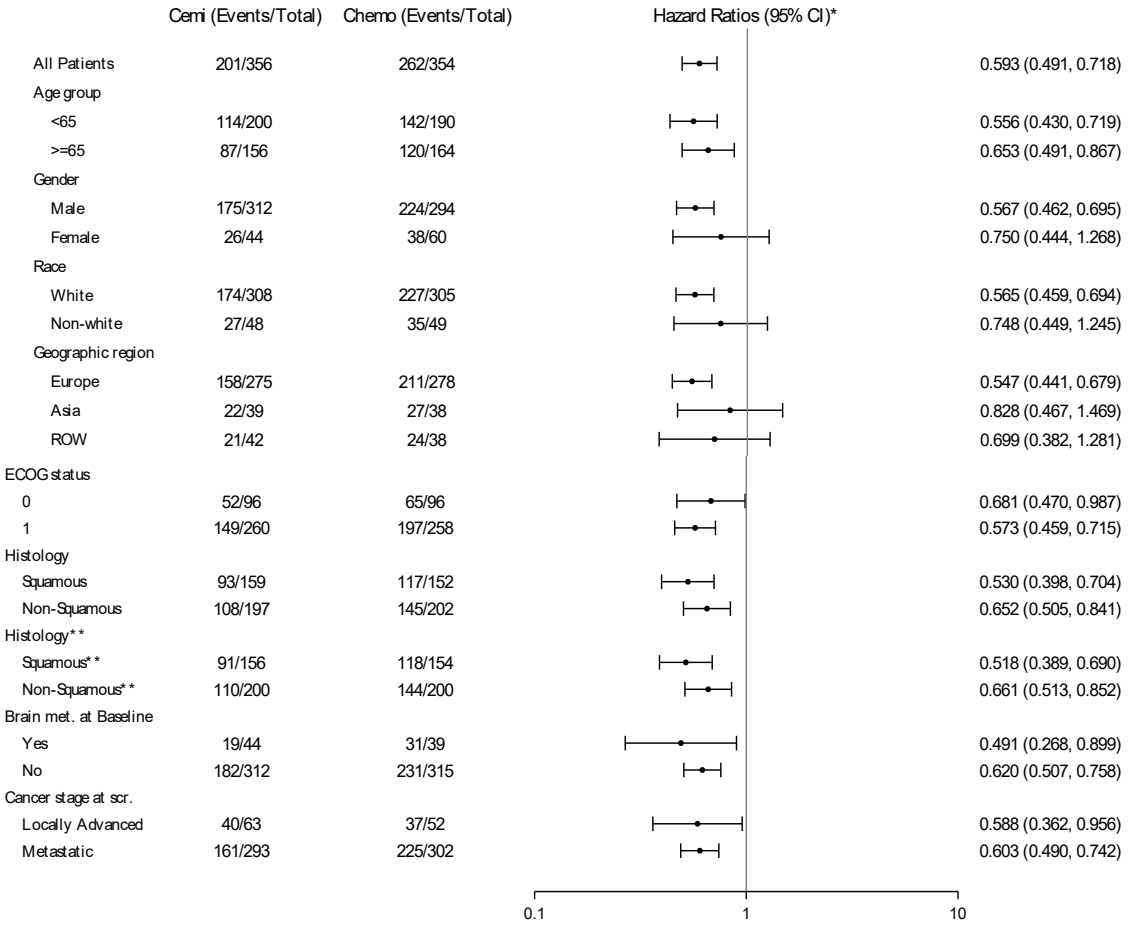

Figure 19. Study 1624: Forest Plot for Progression-Free Survival per IRC by Subgroup (ITT Population)
*Stratified by histology (squamous, non-squamous) accordingly to IWRS except for Histology subgroups.
** According to IWRS.
Abbreviations: Cemi= cemiplimab; Chemo= chemotherapy; CI= confidence interval; ECOG= European Cooperative Oncology Group; IRC= Independent Review Committee; ITT= intent-to-treat; IWRS= Interactive Web Response System; ROW= rest of the world.
Source: Study 1624 Primary Analysis CSR Figure 14.2.2.3.a

In the analyses of OS and PFS by patient subgroup, point estimates generally favour cemiplimab. While there are several subgroups with small sample sizes, and consequently the confidence intervals remain wide, the effects are consistent e.g. across age groups and are observable with both histologies and among patients with treated brain metastases at baseline.

IRC-PFS analyses in the ITT population show a consistent benefit of cemiplimab vs. chemotherapy across the investigated subgroups. Overall, the subgroup analyses of the primary endpoints of IRC-PFS and OS are in line with the primary analysis.

Sensitivity analysis of OS and PFS using RMST

The sensitivity analyses using restricted mean survival time method were conducted for OS and PFS in the ITT population. In the ITT population, mean survival times were 18.9 (95% CI: 17.5 to 20.3) months in cemiplimab arm and 15.8 (95% CI: 14.4 to 17.3) months in chemotherapy arm; p-value=0.0011; mean PFS time were 9.6 (95% CI: 8.7 to 10.6) months in cemiplimab arm and 6.0 (95% CI: 5.5 to 6.5) months in chemotherapy arm; p-value< 0.0001.

Sensitivity analysis of OS using RPSFT

The sensitivity analyses using rank preserved structural failure time method were conducted for OS in ITT population to account for crossover effects. The treatment effect, ψ, is estimated by balancing counter-factual event times (that would be observed if no treatment were received) between treatment groups. Value of ψ is estimated such that a test statistic $Z(\psi) = 0$. This is the test statistic used in the primary analysis, i.e., log rank test statistic stratified by histology. Re-censoring was applied to the chemotherapy arm at minimum possible censoring time $min\,(Ci\ ,\ Ciexp(\psi))$, where Ci is the potential censoring time for patient i, to remove the potential dependency between the reconstructed survival time and Ci (White, 1999).

In the ITT population, HR=0.580 (0.438, 0.770); p=0.0001; median OS 22.1 (17.7, NE) months for cemiplimab vs 12.0 (9.7, 14.2) months for chemotherapy (Table 31).

Table 31. Overall survival – sensitivity analysis using RPSFT method (full analysis set)

	Cemiplimab (N=356)	Reconstructed Chemotherapy (N=354)
Psi	-0.5051	
Exp(Psi)	0.6035	
Number of deaths, n (%)	108 (30.3%)	111 (31.4%)
Number of censored patients, n (%)	248 (69.7%)	243 (68.6%)
Median (95% CI), (months)[a]	22.1 (17.7, NE)	12.0 (9.7, 14.2)
Stratified log-rank test p-value [b][c]	0.0001	
HR (95% CI) [b][d]	0.580 (0.438, 0.770)	
Estimated Survival Probability , % (95% CI)[a]		
6 months	81.2 (76.4, 85.1)	75.5 (70.0, 80.1)
12 months	70.3 (64.4, 75.4)	48.8 (40.4, 56.7)
18 months	56.1 (48.1, 63.3)	NE (NE, NE)
24 months	48.6 (39.2, 57.3)	NE (NE, NE)
30 months	45.5 (35.0, 55.4)	NE (NE, NE)

Data cutoff as of 01 Mar 2020
[a] Based on Kaplan-Meier method.
[b] Stratified by histology (squamous,¬ non-squamous) according to IWRS.
[c] Two-sided p-value.
[d] Based on stratified proportional hazards model (cemiplimab vs reconstructed chemotherapy).
Source: Post-text Table 14.2.1.8

Sensitivity analysis – Efficacy in the mITT-1 population

Table 32. Study 1624: Overall Survival – mITT-1

	mITT-1 Population (n=563)	
	Cemiplimab (N=283)	**Chemotherapy (N=280)**
Number of deaths, n (%)	70 (24.7)	105 (37.5)
Number of censored patients, n (%)	213 (75.3)	175 (62.5)
Median (95% CI), (months)[a]	NR (17.9, NE)	14.2 (11.2, 17.5)
Stratified log-rank test p-value[b]	0.0002	
HR (95% CI)[c]	0.566 (0.418, 0.767)	

[a] Based on Kaplan-Meier method.
[b] Stratified by histology (squamous, non-squamous) according to IWRS.
[c] Two-sided p-value. Significance threshold is population to 0.0025 using the O'Brien-Fleming alpha spending function.
[d] Based on stratified proportional hazards model (cemiplimab versus chemotherapy).

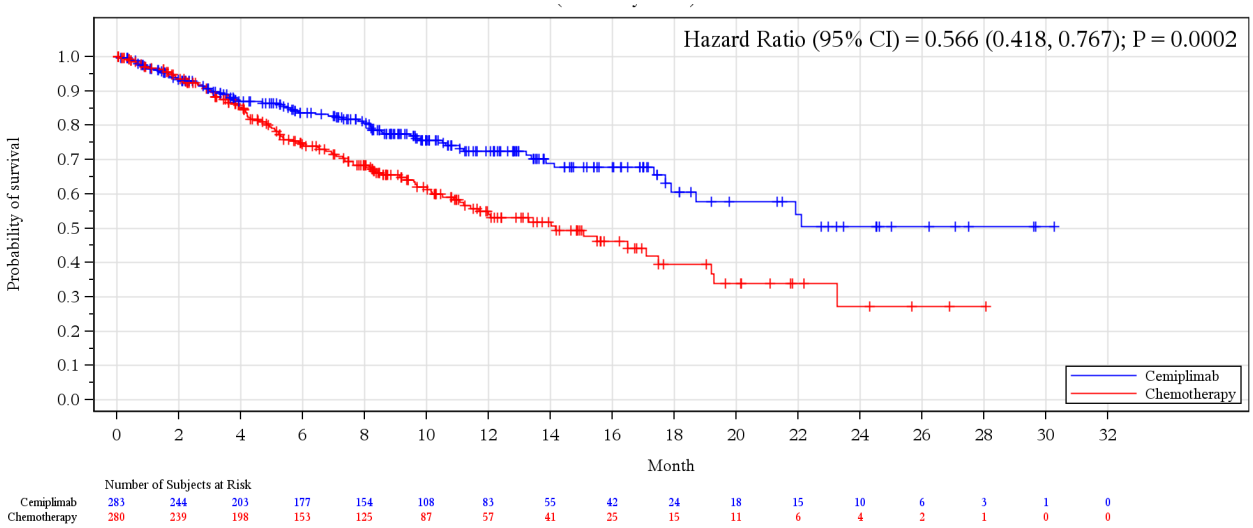

Figure 20. Kaplan-Meier plot of OS in mITT-1 Population

Table 33. Study 1624: Progression-Free Survival per IRC – mITT-1 population

	mITT-1 Population (n=563)	
	Cemiplimab (N=283)	**Chemotherapy (N=280)**
Number of events, n (%)	147 (51.9)	197 (70.4)
Progressive disease, n (%)	119 (42.0)	150 (53.6)
Death, n (%)	28 (9.9)	47 (16.8)
Number of censored patients, n (%)	136 (48.1)	83 (29.6)
Median (95% CI), (months)[a]	8.2 (6.1, 8.8)	5.7 (4.5, 6.2)
Stratified log-rank test p-value[b, c]	<0.0001	
HR (95% CI)[d]	0.541 (0.433, 0.675)	

[a] Based on Kaplan-Meier method.
[b] Stratified by histology (squamous, non-squamous) according to IWRS.
[c] Two-sided p-value.
[d] Based on stratified proportional hazards model (cemiplimab versus chemotherapy).

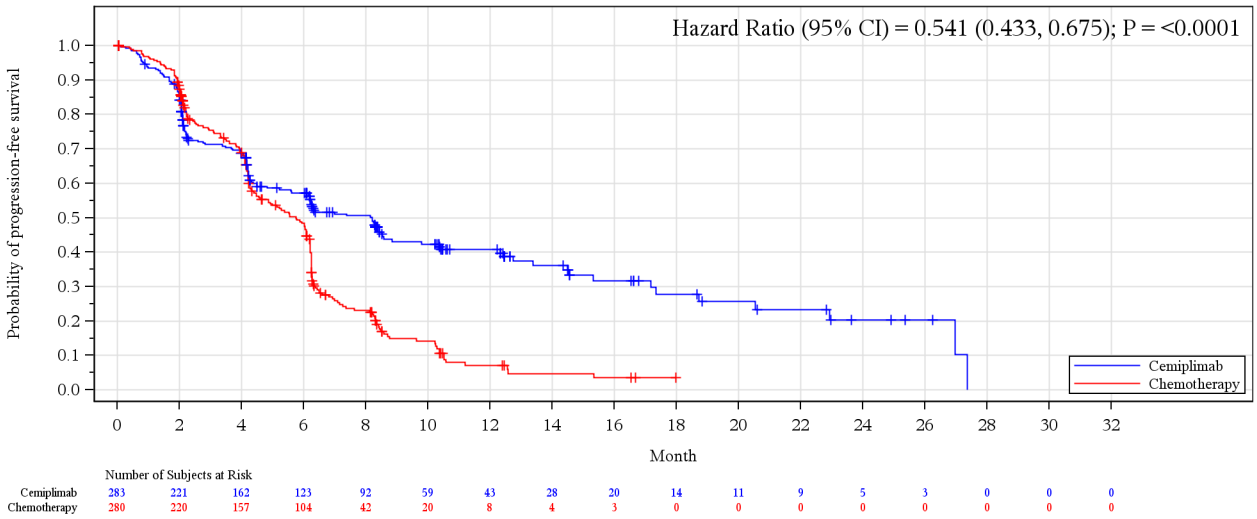

Figure 21. Kaplan-Meier plot of PFS-IRC in mITT-1 Population

Analysis of OS and IRC-PFS by level of PD-L1 expression

The role of PD-L1 expression as a quantitative variable to predict the survival benefit of cemiplimab was investigated. Patients in the mITT-1 and mITT-2 populations were further categorised into 3 subgroups by the level of PD-L1 expression (high tertile [≥90%], medium tertile >60% and <90%], and low tertile [≥50% and ≤60%]). This analysis was not performed for the ITT population, which included patients with unknown results and PD-L1 values <50%.

Results for median OS and PFS in the mITT-1 population are displayed in Table 34. Corresponding Kaplan-Meier curves for OS and PFS by PD-L1 expression in the mITT-1 population are displayed in Figure 22 and Figure 23, respectively. Median percent change in tumour size after cemiplimab or chemotherapy treatment was also used as a pharmacodynamic marker in the mITT-1 population (Figure 24).

Table 34. Overall survival and progression-free survival by PD-L1 expression (mITT-1 population)

	Cemiplimab (N=283)		Chemotherapy (N=280)		
	Event (%)	Median Time (95% CI)[b]	Event (%)	Median Time (95% CI)[b]	Hazard Ratio (95% CI)[a]
OS	70/283 (24.7)	NR (17.9, NE)	105/280 (37.5)	14.2 (11.2, 17.5)	0.566 (0.418, 0.767)
PD-L1 high[c]	16/98 (16.3)	NR (17.3, NE)	29/94 (30.9)	15.1 (11.1, NE)	0.457 (0.246, 0.849)
PD-L1 medium[d]	22/89 (24.7)	22.1 (17.9, NE)	36/90 (40.0)	12.0 (9.6, 19.2)	0.466 (0.271, 0.800)
PD-L1 low[e]	32/96 (33.3)	21.9 (13.2, NE)	40/96 (41.7)	14.0 (9.4, 19.3)	0.774 (0.486, 1.234)
PFS	147/283 (51.9)	8.2 (6.1, 8.8)	197/280 (70.4)	5.7 (4.5, 6.2)	0.541 (0.433, 0.675)
PD-L1 high[c]	29/98 (29.6)	15.3 (10.4, 18.7)	54/94 (57.4)	5.9 (4.3, 6.2)	0.280 (0.170, 0.461)
PD-L1 medium[d]	56/89 (62.9)	6.2 (4.2, 8.4)	68/90 (75.6)	4.2 (4.1, 5.7)	0.553 (0.383, 0.799)
PD-L1 low[e]	62/96 (64.6)	4.3 (2.8, 6.3)	75/96 (78.1)	6.2 (5.0, 6.2)	0.793 (0.560, 1.123)

[a] Based on Kaplan-Meier method.
[b] Based on stratified proportional hazards model (cemiplimab versus chemotherapy).
[c] PD-L1 expression ≥90%.
[d] PD-L1 expression >60% and <90%.
[e] PD-L1 expression ≥50% and ≤60%.
CI, confidence interval; mITT, modified intent-to-treat; NE, not evaluable; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival.
Sources: PTT 14.2.1.1m1, PTT 14.2.1.5m1, PTT 14.2.2.1m1, and PTT 14.2.2.8m1

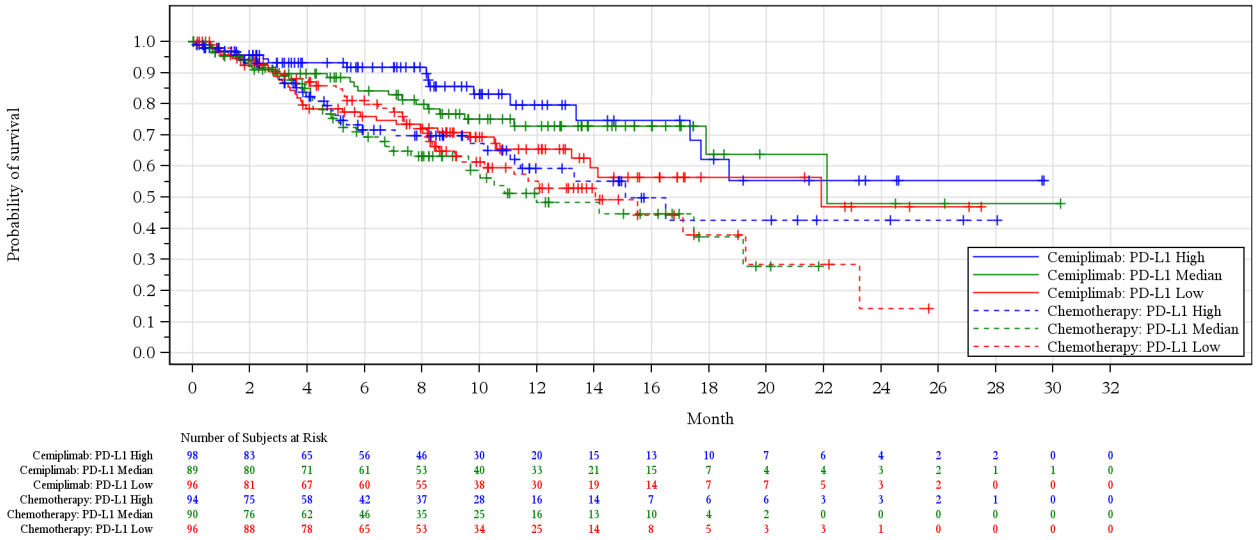

Figure 22. Study 1624: Kaplan-Meier Curve of Overall Survival by PD-L1 Expression (mITT-1 Population)

Abbreviations: mITT= modified intent-to treat; PD-L1= programmed death ligand-1.
Source: Study 1624 Primary Analysis CSR Figure 14.2.1.3m1

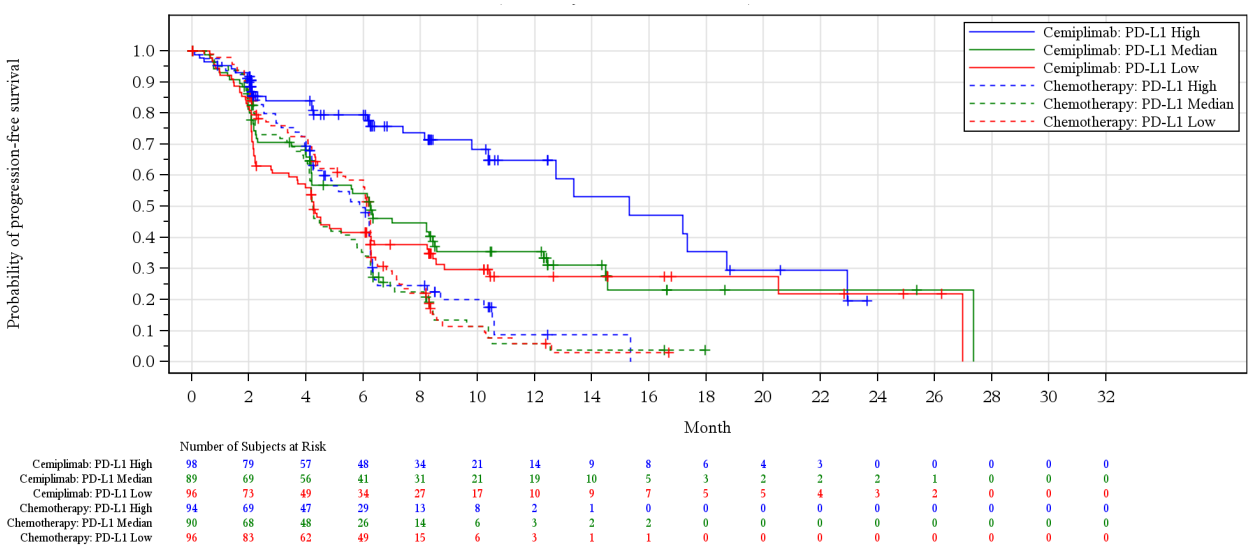

Figure 23. Study 1624: Kaplan-Meier Curve of Progression-Free Survival per IRC by PD-L1 Expression (mITT-1 Population)

Abbreviations: IRC= Independent Review Committee; mITT= modified intent-to treat; PD-L1= programmed death ligand-1. Source: Study 1624 Primary Analysis CSR Figure 14.2.2.4m

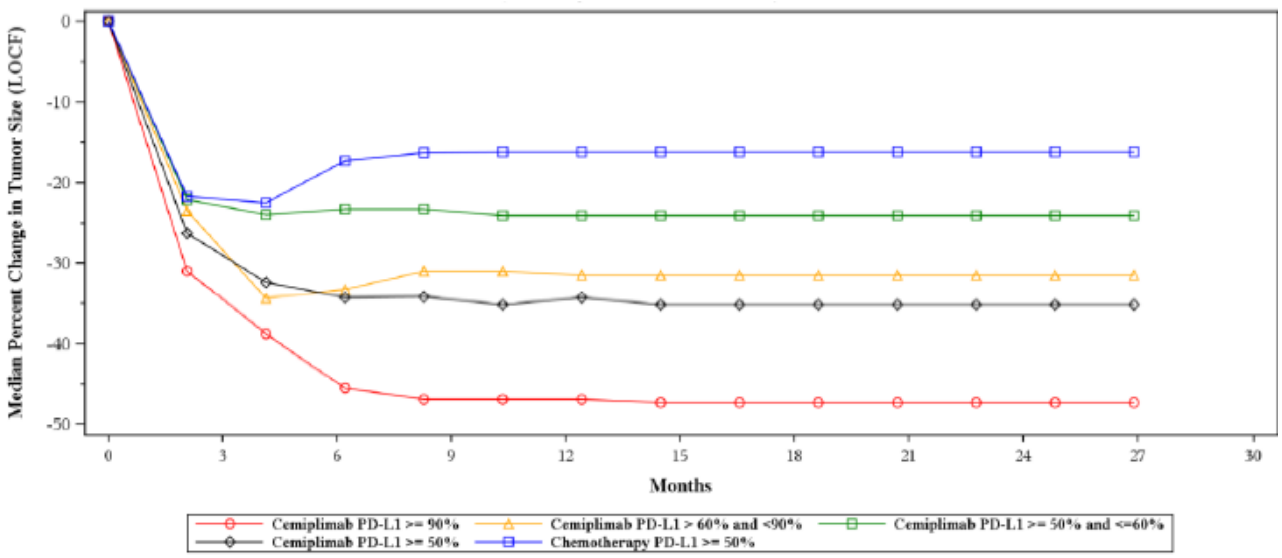

Figure 24. Percent change in tumour size per IRC (mITT-1 population)

Abbreviations: IRC= Independent Review Committee; mITT-1= modified intent-to treat; LOCF= last observation carried forward; PD-L1= programmed death ligand-1. Source: PTF 14.2.3.4ml

In exploratory survival analyses by level of PD-L1 expression, the greatest survival benefits in the cemiplimab group were seen among patients with high expression levels, and the change in tumour size also correlated with expression level. There was no correlation of PD-L1 expression level and survival in the chemotherapy group. This provides further evidence of PD-L1 expression level as a potential quantitative biomarker to predict a favourable treatment effect with checkpoint inhibition through PD-1.

Anti-drug Antibodies

ADAs were analysed among 62% (n=221) of the patients in the cemiplimab arm (n=356). While some changes in the sampling schedule were implemented during the study, samples appear to have been consistently obtained pre-dose at cycles 9 and 18.

ADAs to cemiplimab were reported in 11 patients with NSCLC receiving cemiplimab 350 mg Q3W (6 pre-existing, 5 treatment-emergent or boosted); all were at low titer (<1,000). No NAb were detected in the patients with a positive response in the ADA assay. Patients with treatment-emergent ADA showed similar cemiplimab exposure in serum compared to the overall population of patients with NSCLC who had an ADA-negative response.

Table 35. Summary of ADA status, ADA category, maximum titer and NAb status in the ITT population of patients with NSCLC treated with cemiplimab (Study 1624)

ADA Status and Category	NSCLC 350 mg Q3W n (%)
Total ADA Subjects	221 (100%)
Negative	210 (95.0%)
Pre-existing	6 (2.7%)
Treatment Boosted Response	0
Treatment Emergent Response	5 (2.3%)
Treatment Emergent and Treatment Boosted	
Persistent	1 (0.5%)
Transient	2 (0.9%)
Indeterminate	2 (0.9%)
Treatment Emergent and Treatment Boosted Maximum Titer Category	
Low (<1,000)	5 (2.3%)
Moderate (1,000 to 10,000)	0
High (>10,000)	0
Treatment Emergent and Treatment Boosted NAb Status	
NAb negative	5 (2.3%)
NAb positive	0

ADA = anti-drug antibody; n = number; NAb = neutralizing antibody; NSCLC = non-small cell lung cancer; Q3W = every 3 weeks.

Summary of main study

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

Table 36. Summary of Efficacy for Study 1624

Title: A global, randomised, 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			
Study identifier	R2810-ONC-1624, NCT 03088540, EudraCT number: 2016-004407-31		
Design	Phase III, multicentre, randomized, open label study comparing cemiplimab monotherapy versus platinum doublet chemotherapy		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Up to 108 weeks of treatment Up to 28 days (screening phase) not applicable
Hypothesis	Superiority of cemiplimab monotherapy vs platinum doublet chemotherapy		
Treatments groups	Cemiplimab arm		Cemiplimab 350 mg Q3W up to 108 weeks until PD or toxicity, n=356
	Chemotherapy arm		Platinum doublet chemotherapy treatment until PD or toxicity, n=354
Endpoints and definitions	Primary endpoint	Overall survival (OS)	Time from randomisation to the date of death

	Primary endpoint	Progression free survival (PFS) by IRC	Time from randomisation to the date of the first documented tumour progression, as determined by the IRC (using RECIST 1.1) or death due to any cause
	Key Secondary	Objective response rate (ORR) by IRC	Number of patients with a best overall response of confirmed complete response or partial response as determined by the IRC (using RECIST 1.1) divided by the number of patients in the efficacy analysis population
Data cut-off	01-MAR-2020		
Database lock	14-APR-2020		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intention to treat; n=710 patients Interim analysis # 2 for OS		
Descriptive statistics and estimate variability	Treatment group	Cemiplimab	Chemotherapy
	Number of subjects	356	354
	Median OS (months)	22.1	14.3
	95% Confidence Interval (CI)	(17.7, NE*)	(11.7, 19.2)
	PFS (months)	6.2	5.6
	95% CI	(4.5, 8.3)	(4.5, 6.1)
	ORR (%) 95% CI	36.5 (31.5, 41.8)	20.6 (16.5, 25.2)
Effect estimate per comparison	OS	Comparison groups	Cemiplimab vs. chemo
		Hazard ratio (HR)	0.676
		95% CI	(0.525, 0.870)
		P-value	0.0022
	PFS	Comparison groups	Cemiplimab vs. chemo
		HR	0.593
		95% CI	(0.491, 0.718)
		P-value	<0.0001
	ORR	Comparison groups	Cemiplimab vs. chemo
		Odds ratio	2.214
		95% CI	(1.582, 3.098)
		P-value	<0.0001
Notes	According to the MAH, full analysis of primary endpoints, key secondary endpoint and all other secondary and exploratory endpoints was conducted upon positive outcome for OS at IA #2. However, according to the SAP, only OS was to be analysed at IA #2 and all other analyses should therefore be considered descriptive. * Not evaluable		

Clinical studies in special populations

Not applicable.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical study

The MAH has submitted data from the second interim analysis of Study 1624 as the grounds to support the addition of the following proposed therapeutic indication:

LIBTAYO as monotherapy is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:

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

Study 1624 is a phase III, randomised, open-label, multicentre trial, comparing cemiplimab monotherapy versus platinum doublet chemotherapy in patients with locally advanced NSCLC not eligible for definite chemoradiation, or metastatic NSCLC, with tumours expressing PD-L1 50≥%, with no EGFR, ALK, or ROS1 aberrations.

The primary endpoints of the study are OS and IRC-PFS, intending to show superiority of cemiplimab over platinum doublet regimen for patients with advanced NSCLC and PD-L1 expression ≥ 50%. Although the chosen comparator is no longer the standard-of-care (SOC) treatment for this high PD-L1 expressing population, it was considered appropriate at the time the study was discussed at a scientific advice (SA) procedure with the CHMP in November 2016. Of note, based on the primary analysis from study KEYNOTE-24, pembrolizumab as monotherapy was approved by EMA for the first line treatment of patients with metastatic NSCLC and PD-L1 expression ≥50% as of December 2016. In March 2021 the CHMP granted an indication for atezolizumab in a similar patient population based on results from the IMpower110 study (Herbst et al, NEJM 2020), although the definition of PD-L1 positivity is based on a different SP142– PD-L1 assay.

The primary endpoints of OS and IRC-PFS are considered appropriate for confirmatory studies in the CHMP Guideline on the clinical evaluation of anticancer medicinal products (EMA/CHMP/205/95 Rev.6). The secondary endpoints (ORR and DOR) and the exploratory endpoint of time to new anti-tumour treatment are considered appropriate for the targeted disease and patient population, PFS2 was not selected as an exploratory endpoint – even when this had been recommended by the CHMP in two SA procedures.

Crossover was allowed, so that patients into the chemotherapy arm could also benefit from second line immunotherapy with cemiplimab, particularly since the first patient was randomised in May 2017. As of protocol amendment 6, patients randomized to receive cemiplimab 350 mg who experience RECIST 1.1-defined progression during cemiplimab monotherapy were permitted to continue cemiplimab treatment with the addition of 4 cycles of histology-specific chemotherapy until further progression is observed, provided, the patient has not completed the 108-week treatment period and protocol-specified criteria were met. This amendment was based on results from the KEYNOTE-042, KEYNOTE-189 and KEYNOTE-407 studies. Before amendment 6, a considerable number of progressors from the cemiplimab arm continued cemiplimab -as allowed by the protocol- without adding chemotherapy: 17 out of 24.

Inclusion and exclusion criteria seem to appropriately reflect the targeted population and match the currently proposed therapeutic indication. Several important features of the target population were agreed beforehand within a CHMP Scientific Advice procedure in 2016; these include the threshold of PD-L1 expression in over 50% of tumour cells; the exclusion of patients with no smoking history; and the inclusion of patients with an ECOG performance status of 0 to 1 only.

Selection of the geographical placement of study 1624 was influenced by the approval of pembrolizumab as monotherapy first-line treatment of metastatic NSCLC in patients whose tumours expressed a high level of PD-L1. The trial design could therefore have been considered unethical in countries where pembrolizumab was considered as standard of care for these patients. Consequently, countries where patients were enrolled were countries where anti-PD-1 agents were not approved, not reimbursed, or not readily available.

The subpopulation of patients with locally advanced stage (n=115) is highly heterogenous, but few of these patients had received previous treatments for their disease. Progression to concurrent chemoradiotherapy was not strictly defined within inclusion criteria, but only 3 patients with these characteristics were recruited. Inclusion criteria did not suffer significant amendments along study conduct.

The main efficacy analysis population is the FAS (N=710), which included all randomised subjects. Enrolment was limited to patients whose tumours expressed PD-L1 in ≥50%. A central commercial laboratory was used to analyse PD-L1 expression (IHC 22C3 pharmDx assay), with no EGFR, ALK, and ROS1 aberrations in tumour samples. The 22C3 pharmDX assay is FDA-approved in the United States for use with pembrolizumab and is CE-marked in the EU. During the course of the study, the MAH became aware that PD-L1 testing of samples from Study 1624 at the central commercial laboratory (NeoGenomics Laboratories) had a number of quality issues. These issues included (but were not limited to): absence of batch controls (negative and positive), cell line control failures being discovered more than 2 weeks after the sample results had been reported, and staining inconsistencies causing unreliable PD-L1 scoring. Even though corrective and preventative actions were implemented in the original testing facility, in November 2018, the MAH initiated transition of PD-L1 testing to Q2 Solutions Laboratories where the Dako PD-L1 IHC 22C3 pharmDx IUO assay was used in accordance with the FDA-approved labelling instruction and the assay IFU was performed under Dako/Agilent supervision. The transition of PD-L1 central laboratory to Q2 Laboratories was completed in March 2019. As recommended by the FDA, retesting of the samples from study 1624 was performed (for those patient samples which were still available). Since not all patients had remaining samples suitable for re-testing and not all of the re-tested patients were categorised as PD-L1 ≥50% with the new assay, two additional populations were defined: mITT1 (n=563) and mITT-2 (n=475). Since the efficacy analyses of these subpopulations were not defined in the SAP, their results are considered as supportive, but not suitable for publication at the SmPC.

The INV-ORR for 50% of the enrolled patients was analysed accidentally and published via a press release on 05-NOV-2019 while the study was still recruiting. The degree of influence of data disclosure on patients' behaviour remains uncertain, but its overall impact on B/R is expected to be minimal. On the account of complicated access to anti-PD-1/PD-L1 treatment in the countries where Study 1624 took place, it seems unlikely that awareness of results led to a significantly increased number of consent withdrawals from patients in the chemotherapy arm.

The sample size was based on the results observed in clinical studies with other anti-PD-1 treatments, assuming non-proportional hazards, but not the crossover effect. Historically, in patients with stage IIIB, stage IIIC, or stage IV NSCLC treated with cisplatin or carboplatin + paclitaxel Q3W, the median OS and the median PFS ranged from approximately 11.3 to 14.2 months and 4.8 to 6.4 months, respectively. For anti-PD-1 monotherapy, a delayed treatment effect in OS and PFS has been observed in KEYNOTE-042 and CheckMate 026. In these studies, during the first 6 months of treatment, anti-PD-1 monotherapies had either no treatment effect or worse treatment effect in OS when compared to treatment with chemotherapy, especially in the patient population with PD-L1 expression <50%. During the first 3 months of treatment, PD-1 monotherapies had either no treatment effect or worse treatment effect in PFS when compared to treatment with chemotherapy, especially in the patient population with PD-L1 expression <50%.

The randomisation strategy and block size (4) are acceptable. It is noted that the study design included two stratification factors: region of the world and histology, but only histology was considered in the log-rank and Cox model. In the EMA guideline on adjustment for baseline covariates in clinical trials (EMA/CHMP/295050/2013) it is stated that the primary analysis should reflect the restriction on randomization implied by the stratification. A sensitivity analysis that considered both stratification factors (only histology had been used) was concordant with the primary analysis. Further sensitivity analyses raised from concerns upon the censoring rules were also consistent with the primary analysis. The MAH has also presented an additional simulation of OS data based on a model accounting for the non-proportional hazards, which is consistent with the primary analysis.

OS and IRC-PFS were primary endpoints. To control for multiplicity, the MAH implemented an alpha-allocation strategy. The study has stopped at interim for OS prior to the primary PFS analysis. It is noteworthy that the MAH has planned for five interim analyses for OS and none for PFS with three of the OS interim analyses before the planned primary PFS analysis, though PFS per definition matures faster than OS.

Overall, the baseline characteristics of age, sex, race/ethnicity, ECOG PS, disease aspects and prior cancer-related therapy were evenly distributed between the treatment arms. 85% of patients were male, and median age was 63 years. A non-squamous histology was observed in 56% of patients, and the disease stage at screening was metastatic (Stage IV) in 84% of patients. About 23% of patients had received some prior therapy, most commonly radiotherapy, for their disease.

A slightly higher dropout rate in the control arm is attributable to the open-label nature of the trial.

Efficacy data and additional analyses

According to the eight amendment of the protocol on 23-OCT-2019, the second interim analysis (IA2) was planned when approximately 50% of 476 planned OS events at final analysis (~238 deaths) had occurred across both arms.

At the time of the primary analysis for study 1624, treatment was still ongoing for 184 patients (26%). Study treatment had been completed in 42% patients from the chemotherapy arm vs. 2% in the cemiplimab arm; the large difference between the groups is due to the different duration of treatment.

With a median follow-up of 13 months and after 249 OS events (35% of ITT) on data cut-off date 01-MAR-2020, the study met its OS primary endpoint by showing a statistically significant increase in survival with cemiplimab monotherapy vs. platinum-based chemotherapy in the targeted population: HR 0.68; 95%CI 0.53, 0.87, p=0.0022. The median OS for the cemiplimab was 22.1 months vs 14.3 months for the chemotherapy arm, an improvement of 7.8 months. The Kaplan-Meier curves of OS start separating after 4 months of therapy. As the primary endpoint was met, IA2 was considered the primary analysis, without any further interim analyses planned. As seen in other studies with anti-PD1/PD-L1 agents in similar settings, non-proportional hazards were evidenced, but an RMST analysis that accounts for this issue is concordant with the primary analysis results.

The apparent OS benefit in the cemiplimab arm is considered clinically relevant, even when several uncertainties hamper interpretation of OS results. From the 461 censored patients, 19% in the chemotherapy arm and 11% in the cemiplimab arm have withdrawn consent to be followed for survival. Follow-up is limited and insufficient to fully characterise OS, especially when considering non-proportional hazards. Moreover, the effect of crossover on OS is unknown, noticing that after the cut-off date at 1 March 2020, Amendment 9 was added, allowing all patients in the chemotherapy arm to crossover to the cemiplimab arm, even without having progressed on chemotherapy. The influence of crossover in OS is considered of major importance. The difference observed in OS could be attributed

to the first line treatment (cemiplimab monotherapy) or to ulterior treatment lines. Since all patients could receive cemiplimab and chemotherapy, interpretation of the OS results is challenging, with the additional difficulty that PFS2 was not captured. To partially address this uncertainty, the MAH provided a RPSFT sensitivity analysis to account for crossover effects. Nevertheless, a RPFST sensitivity analysis to account for the effects of crossover and a simulation of OS based on a model that accounts for non-proportional hazards are consistent with the primary analysis results.

After 463 PFS events (65%), a trend for benefit of the cemiplimab arm is observed (mPFS 6.2 months vs. 5.6 in the chemotherapy arm), although a net advantage of 0.6 months may not be clinically relevant. Similar to OS, an effect on PFS is not observed immediately; for PFS, the curve initially favours chemotherapy and the curves only cross at about 4 months. It is noted that future updates of PFS will not provide an unbiased estimate because of the allowed crossover of chemotherapy patients to cemiplimab even before PD (Amendment 9). This lesser magnitude of PFS benefit has also been observed in akin immunotherapy trials (IMpower133; Horn et al, NEJM 2018).

It seemed that less patients in the cemiplimab arm had received subsequent anticancer therapies (20% vs. 45% in the chemotherapy arm). However, if the number of patients who received subsequent treatments in the cemiplimab arm is relativized to the number of progressors by data cut-off, the proportion of patients who went on to 2L therapies becomes 45%, in line with the control arm and current clinical practice.

Results from secondary endpoints ORR and DOR support the benefit of cemiplimab over chemotherapy in the targeted population. However, relatively large proportions of patients in both treatment groups are indicated as being not evaluable for overall tumour response. The major reasons for non-evaluability were "first time point not yet reached" and "death". Overall frequencies are quite comparable between treatment groups.

The results on quality of life measures are impacted by decreasing sample sizes and consequently very large standard deviations at the later time points. Notable differences between the treatment groups include a significant worsening of alopecia and peripheral neuropathy with chemotherapy, which is entirely in line with its known adverse effect profile.

Subgroup analysis of OS in the ITT suggest consistent benefit of cemiplimab over chemotherapy across most subgroups, although the degree of benefit is highly variable. For instance, with usual caution regarding subgroup sizes, it is noted that the highly heterogeneous subgroup of 115 patients with locally advanced disease report a borderline OS benefit from cemiplimab vs. chemotherapy (HR 0.85, 95% CI 0.43, 1.68) as compared to their metastatic counterparts (HR 0.68, 95% CI 0.52, 0.89). The forest plot of IRC-PFS shows a consistent benefit of cemiplimab vs. chemotherapy across the investigated subgroups.

OS and PFS-IRC results from the mITT-1 population evidence a higher degree of benefit in the cemiplimab arm, but these analyses were not type-1-error-controlled, and hence considered as supportive.

Given low incidence of ADAs to cemiplimab, it is not considered that they had a major impact on efficacy or safety.

2.4.4. Conclusions on the clinical efficacy

Interim analysis of Study 1624 has shown statistically significant OS benefit in favour of cemiplimab vs. chemotherapy in the treatment of patients with locally advanced and metastatic NSCLC and PD-L1 ≥50%. This advantage is clinically meaningful, as the sensitivity analyses conducted to address remaining uncertainties (non-proportional hazards, crossover effect, censoring rules) are consistent

with the primary analysis. The PFS advantage provided by cemiplimab in the experimental arm is marginal and not type-1-error-controlled, although concordant with results of akin anti-PD-1/PD-L1 monotherapy trials in the 1L setting of advanced NSCLC.

2.5. Clinical safety

Introduction

Libtayo as monotherapy is indicated for the treatment of adult patients with metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC). For the initial approval, the safety of cemiplimab was evaluated in 591 patients from studies 1423 (advanced solid malignancies, n=372) and 1540 (advanced CSCC, n=219).

The most commonly reported adverse drug reactions are rash (23.3%), fatigue (21.5%), diarrhoea (13.2%) and pruritus (12.3%) (Libtayo SmPC).

Immune-related adverse reactions occurred in 20.3% of patients treated with cemiplimab in clinical trials including Grade 5 (0.7%), Grade 4 (1.2%) and Grade 3 (6.3%). The most common immune-related adverse reactions were hypothyroidism (7.1%), pneumonitis (3.7%), cutaneous adverse reactions (2.0%), hyperthyroidism (1.9%) and hepatitis (1.9%). Immune-related adverse reactions led to permanent discontinuation of cemiplimab in 4.4% of patients. Immune-related pneumonitis led to permanent discontinuation of cemiplimab in 11 (1.9%) of 591 patients.

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

The study population in this application included patients with advanced NSCLC and ≥50% PD-L1 expression in tumour cells and limited to previous and current smokers. Patients with EGFR, ALK or ROS1 aberrations were excluded.

The evaluation of safety of cemiplimab for the treatment of advanced NSCLC is based on data from both arms of the safety dataset of Study 1624 (N=697).

Safety Pool 2 (monotherapy population): As supportive data, the MAH has also provided pooled safety results from cemiplimab monotherapy across 4 studies (N=816), summarised in Table 1. All patients who received at least 1 dose of cemiplimab as monotherapy in Study 1624 (n=355), Study 1423 (n=130), Study 1540 (n=193), and Study 1620 (n=138) were included in this pool.

Table 37: Description of Safety Assessments in Clinical Studies

Study Number Study Status Total Number of Centers With Treated Patients Country(ies)	Study Population	Study Phase Study Design	Dose and Schedule	Safety Assessments and Objectives / Endpoints
R2810-ONC-1624 Ongoing 138 centers 24 countries	Adult patients, diagnosed with stage IIIB, IIIC, or stage IV squamous or non-squamous NSCLC, who are not eligible for definitive chemo/radiation, whose tumors express PD-L1 in ≥50% of tumor cells (using the PD-L1 IHC 22C3 pharmDx assay), and who have received no prior systemic	Phase 3 Randomized, multicenter, open-label, pivotal study	350 mg cemiplimab administered intravenously over 30 minutes Q3W for up to 108 weeks (N=355) or standard of care chemotherapy for 4 to 6 cycles (N=342)	Safety is assessed through AEs, laboratory data, vital signs, and ECOG performance status.

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
	treatment for their advanced disease.			
R2810-ONC-1423 Complete 38 centers 3 countries	Adult patients with advanced malignancies or who are incurable and have failed to respond to or showed tumor progression despite standard therapy, or patients who are not candidates for standard therapy, or for whom no available therapy is expected to convey clinical benefit, or for whom PD-1 blockade has been shown to be at least equivalent to standard of care. (N = 398; 130 patients received cemiplimab monotherapy)	Phase 1 first-in-human, open-label, multicenter, repeat-dose study	Cemiplimab administered intravenously over 30 min Q2W at: -3 mg/kg (n = 333) -1 mg/kg (n = 27) -10 mg/kg (n = 6) -200 mg (n = 20) Cemiplimab 3 mg/kg Q3W (n=12) Treatment duration: 48 weeks	Safety is assessed through AEs, laboratory data, vital signs, and ECOG performance status.
R2810-ONC-1540 Ongoing 35 centers 3 countries	Adult patients with mCSCC (Group 1 and Group 3) and laCSCC (Group 2) (N = 193)	Phase 2 nonrandomized, 3-group, multicenter study	Cemiplimab administered intravenously over 30 min at: -3 mg/kg Q2W (Groups 1 and 2) -350 mg Q3W (Group 3) Treatment duration: up to 96 weeks for Groups 1 and 2 and up to 54 weeks in Group 3	Safety is assessed through AEs, laboratory data, vital signs, and ECOG performance status.
R2810-ONC-1620 Ongoing 49 centers 10 countries	Adult patients with mBCC (Group 1) and unresectable laBCC (Group 2) (N = 138)	Phase 2 nonrandomized, 2-group, multicenter study	Cemiplimab administered intravenously over 30 min at 350 mg Q3W Treatment duration: 93 weeks	Safety is assessed through AEs, laboratory data, vital signs, and ECOG performance status.

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; BCC, basal cell carcinoma; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; laBCC, locally advanced basal cell carcinoma; laCSCC, locally advanced cutaneous squamous cell carcinoma; mBCC, metastatic basal cell carcinoma; mCSCC, metastatic cutaneous squamous cell carcinoma; N, total number of patients; n, number of patients in subgroups; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressive disease; PD-1, programmed death-1 (receptor); PD-L1, programmed death ligand 1; PFS, progression free survival; Q2W, every 2 weeks; Q3W, every 3 weeks; w, weeks
Source: Study 1423 Final CSR, Study 1540 Interim CSR, Study 1620 Interim CSR, Study 1624 Primary Analysis CSR

Patient exposure

Table 38: Treatment exposure for each study treatment (safety analysis set)

		Chemotherapy (N=342)				
	Cemiplimab (N=355)	Cisplatin (N=74)	Carboplatin (N=271)	Pemetrexed (N=137)	Paclitaxel (N=140)	Gemcitabine (N=68)
Duration of Exposure (weeks)						
n	355	74	271	137	140	68
Mean (SD)	32.94 (26.369)	13.48 (5.636)	14.15 (5.951)	22.19 (16.733)	14.31 (5.660)	14.19 (6.923)
Median	27.30	13.70	16.30	17.90	17.70	16.35
Q1 : Q3	12.00 : 46.40	9.10 : 18.00	10.60 : 18.30	10.60 : 32.90	10.95 : 18.30	8.65 : 18.75
Min : Max	0.3 : 115.0	0.7 : 24.3	0.6 : 29.0	0.6 : 86.7	0.6 : 29.0	0.7 : 27.9
Duration of Exposure, n (%)						
< 6 weeks	39 (11.0%)	7 (9.5%)	33 (12.2%)	15 (10.9%)	15 (10.7%)	11 (16.2%)
6 to 12- weeks	49 (13.8%)	20 (27.0%)	45 (16.6%)	25 (18.2%)	24 (17.1%)	10 (14.7%)
12 to 18- weeks	41 (11.5%)	20 (27.0%)	85 (31.4%)	30 (21.9%)	41 (29.3%)	16 (23.5%)
18 to 36- weeks	87 (24.5%)	27 (36.5%)	108 (39.9%)	36 (26.3%)	60 (42.9%)	31 (45.6%)
36 to 54- weeks	72 (20.3%)	0	0	23 (16.8%)	0	0
54 to 72- weeks	31 (8.7%)	0	0	5 (3.6%)	0	0
72 to 96- weeks	24 (6.8%)	0	0	3 (2.2%)	0	0
96 to 108- weeks	8 (2.3%)	0	0	0	0	0
>= 108 weeks	4 (1.1%)	0	0	0	0	0
Number of Doses Administered						
n	355	74	271	137	140	68
Mean (SD)	10.84 (8.607)	4.39 (1.719)	4.49 (1.738)	7.09 (5.277)	4.62 (1.732)	8.34 (3.835)
Median	9.00	5.00	5.00	5.00	6.00	10.00
Q1 : Q3	4.00 : 15.00	3.00 : 6.00	3.00 : 6.00	3.00 : 10.00	3.00 : 6.00	5.00 : 12.00
Min : Max	1.0 : 36.0	1.0 : 8.0	1.0 : 6.0	1.0 : 29.0	1.0 : 6.0	1.0 : 12.0
Number of Doses Administered, n (%)						
< 6	125 (35.2%)	43 (58.1%)	143 (52.8%)	69 (50.4%)	66 (47.1%)	18 (26.5%)
6 to 12-	91 (25.6%)	31 (41.9%)	128 (47.2%)	40 (29.2%)	74 (52.9%)	27 (39.7%)
12 to 24-	100 (28.2%)	0	0	26 (19.0%)	0	23 (33.8%)
24 to 36-	33 (9.3%)	0	0	2 (1.5%)	0	0
>= 36	6 (1.7%)	0	0	0	0	0
Cumulative Dose [a]						
n	355	74	271	137	140	68
Mean (SD)	3793.31 (3012.936)	334.16 (137.314)	22.73 (9.461)	3480.59 (2628.378)	891.21 (344.267)	9297.72 (4482.093)
Median	3150.00	343.25	24.15	2511.64	1037.71	10059.21
Q1 : Q3	1400.00 : 5250.00	223.29 : 449.31	15.68 : 30.00	1516.24 : 4972.27	606.14 : 1195.63	5946.20 : 12903.97
Min : Max	350.0 : 12600.0	74.5 : 617.1	3.6 : 44.0	490.8 : 14522.6	15.0 : 1236.4	978.3 : 15488.3
Actual Dose Intensity [b]						
n	355	74	271	137	140	68
Mean (SD)	339.55 (21.119)	73.80 (10.804)	4.81 (0.728)	465.11 (45.195)	185.44 (23.545)	2060.04 (449.569)
Median	348.81	74.05	4.89	477.77	194.23	1991.20
Q1 : Q3	337.50 : 350.00	68.50 : 75.50	4.34 : 5.14	449.56 : 496.37	174.70 : 200.06	1755.64 : 2370.87
Min : Max	229.7 : 363.0	46.2 : 103.0	2.6 : 7.4	270.4 : 524.9	15.0 : 209.9	1278.2 : 3642.1
Relative Dose Intensity, %						
n	355	74	271	137	140	68
Mean (SD)	97.01 (6.034)	92.44 (10.527)	92.29 (12.265)	93.02 (9.039)	93.58 (11.580)	88.32 (16.096)
Median	99.66	97.07	95.68	95.55	98.01	89.94
Q1 : Q3	96.43 : 100.00	86.61 : 99.58	85.70 : 100.00	89.91 : 99.27	88.36 : 100.04	78.84 : 98.57
Min : Max	65.6 : 103.7	61.6 : 106.7	46.6 : 147.8	54.1 : 105.0	7.5 : 105.2	51.4 : 145.7

Data cut-off as of Mar 01, 2020
[a] Cumulative dose is total dose of drug taken during treatment phase - cemiplimab, mg; carboplatin, mg/mL/min; other chemo, mg/m2.
[b] Actual dose intensity is the average dose per cycle - cemiplimab, mg/cycle; carboplatin, mg/mL/min/cycle; other chemo, mg/m2/cycle.

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Table 39: Treatment exposure for cemiplimab (safety analysis set)

	Pool 1 All NSCLC Patients (N=355)	Pool 2 All Monotherapy Patients (N=810)	Pool 3 All Patients (N=1078)
Duration of Exposure (weeks)[a]			
n	355	810	1078
Mean (SD)	32.94 (26.369)	36.55 (27.984)	32.54 (26.353)
Median	27.30	30.65	25.00
Q1 : Q3	12.00 : 46.40	12.10 : 52.10	10.60 : 48.00
Min : Max	0.3 : 115.0	0.3 : 144.4	0.3 : 144.4
Duration of Exposure, n (%)			
>=0 weeks	355 (100%)	810 (100%)	1078 (100%)
>=6 weeks	316 (89.0%)	737 (91.0%)	975 (90.4%)
>=12 weeks	267 (75.2%)	624 (77.0%)	797 (73.9%)
>=24 weeks	197 (55.5%)	477 (58.9%)	567 (52.6%)
>=36 weeks	139 (39.2%)	364 (44.9%)	416 (38.6%)
>=48 weeks	84 (23.7%)	263 (32.5%)	298 (27.6%)
>=60 weeks	51 (14.4%)	153 (18.9%)	153 (14.2%)
>=72 weeks	36 (10.1%)	114 (14.1%)	114 (10.6%)
>=84 weeks	22 (6.2%)	75 (9.3%)	75 (7.0%)
>=96 weeks	12 (3.4%)	26 (3.2%)	26 (2.4%)
>=108 weeks	4 (1.1%)	6 (0.7%)	6 (0.6%)
>=120 weeks	0	2 (0.2%)	2 (0.2%)
>=132 weeks	0	1 (0.1%)	1 (<0.1%)
>=144 weeks	0	1 (0.1%)	1 (<0.1%)
>=156 weeks	0	0	0
Number of Doses Administered			
n	355	810	1078
Mean (SD)	10.8 (8.61)	13.7 (11.26)	12.7 (10.54)
Median	9.0	10.5	9.0
Q1 : Q3	4.0 : 15.0	4.0 : 21.0	4.0 : 19.0
Min : Max	1 : 36	1 : 72	1 : 72
Actual Dose Intensity (mg/wk)[c]			
n	355	563	563
Mean (SD)	113.18 (7.040)	112.07 (10.603)	112.07 (10.603)
Median	116.27	116.34	116.34
Q1 : Q3	112.50 : 116.67	110.65 : 116.67	110.65 : 116.67
Min : Max	76.6 : 121.0	39.1 : 163.3	39.1 : 163.3
Relative Dose Intensity[d]			
n	355	810	1078
Mean (SD)	0.97 (0.060)	0.96 (0.093)	0.96 (0.093)
Median	1.00	0.99	0.99
Q1 : Q3	0.96 : 1.00	0.95 : 1.00	0.95 : 1.00
Min : Max	0.7 : 1.0	0.3 : 1.4	0.3 : 1.4

Data cut-off as of Feb 17, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624. Data cut-off as of Apr 30, 2019 for Study 1423; Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients in Study 1540; Data cut-off as of Oct 10, 2018 for Group 2 patients in Study 1540.

[a] Duration of Exposure (weeks) = Minimum of [last dose date - first dose date + (14 or 21 based on Q2W or Q3W dosing schedule)]/7 AND (data cut-off date or death date - first dose date + 1)/7.

[b] Actual Dose Intensity (mg/kg/week) = Total dose received per kg (mg/kg) / Duration of exposure (weeks).

[c] Actual Dose Intensity (mg/week) = Total dose received (mg) / Duration of exposure (weeks) for the 200 mg Q2W and 350 mg Q3W dosing schedules.

[d] Relative Dose Intensity = Actual dose intensity / Planned dose intensity. Planned dose intensity (mg/kg/week) = Planned dose (mg/kg) / (2 or 3 weeks based on Q2W or Q3W dosing schedule). Planned dose intensity (mg /week) = Planned dose (mg) / (2 or 3 weeks based on Q2W or Q3W dosing schedule).

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Table 40: Patient disposition in study 1624 – safety population

	Cemiplimab (N=355)	Chemotherapy (N=342)
Randomized, not treated (any study drug), n (%)	0	0
Treatment ongoing, n (%)	139 (39.2)	45 (13.2)
Off treatment, n (%)	216 (60.8)	297 (86.8)
Treatment completed	6 (1.7)	149 (43.6)
Treatment discontinued	210 (59.2)	148 (43.3)
Primary reason for treatment discontinuation		
Adverse event	23 (6.5)	14 (4.1)
Death	29 (8.2)	25 (7.3)
Lost to follow-up	3 (0.8)	4 (1.2)
Patient decision	9 (2.5)	7 (2.0)
Physician decision	5 (1.4)	5 (1.5)
Disease progression	133 (37.5)	84 (24.6)
Withdrawal of consent	8 (2.3)	9 (2.6)

Abbreviation: N, number of patients
Data cutoff as 01 Mar 2020 for all patients in Study 1624.
Source: Study 1624 Primary Analysis CSR PTT 14.1.1.5a

Adverse events

Table 41: Summary of Treatment-Emergent Adverse Events in Study 1624 – Safety Population

	Cemiplimab (N=355)	Chemotherapy (N=342)
Number of TEAEs	1976	2610
Number of NCI grade 3/4/5 TEAEs	255	458
Number of serious TEAEs	165	177
Number of patients with any TEAE, n (%)	313 (88.2)	322 (94.2)
Number of patients with any NCI grade 3/4/5 TEAE, n (%)	132 (37.2)	166 (48.5)
Number of patients with any serious TEAE, n (%)	100 (28.2)	94 (27.5)
Number of patients who discontinued study treatment due to TEAE, n (%)	23 (6.5)	14 (4.1)
Number of patients with any TEAE leading to a dose delay/ infusion interruption, n (%)	100 (28.2)	106 (31.0)
Number of patients with any TEAE leading to a dose reduction, n (%)	0	51 (14.9)
Number of patients with any TEAE resulting in death, n (%)	34 (9.6)	31 (9.1)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; N, number of patients; NCI, National Cancer Institute; TEAE, treatment-emergent adverse event
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.
Data cutoff as 01 Mar 2020 for all patients in Study 1624.
Source: Study 1624 Primary Analysis CSR PTT 14.3.1.2.1

Table 42: Summary of treatment-emergent adverse events (safety analysis set)

	Pool 1 All NSCLC Patients (N=355)	Pool 2 All Monotherapy Patients (N=810)	Pool 3 All Patients (N=1078)
Number of TEAEs	1976	6351	8898
Number of NCI grade 3/4/5 TEAEs	255	721	1045
Number of serious TEAEs	165	433	570
Number of Patients with any TEAE, n (%)	313 (88.2%)	756 (93.3%)	1022 (94.8%)
Number of Patients with any NCI grade 3/4/5 TEAE, n (%)	132 (37.2%)	333 (41.1%)	472 (43.8%)
Number of Patients with any serious TEAE, n (%)	100 (28.2%)	243 (30.0%)	323 (30.0%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	23 (6.5%)	64 (7.9%)	81 (7.5%)
Number of Patients with any TEAE leading to a drug interruption/delay, n (%)	100 (28.2%)	256 (31.6%)	344 (31.9%)
Number of Patients with any TEAE leading to a dose reduction, n (%)	0	6 (0.7%)	9 (0.8%)
Number of Patients with any TEAE leading to both a drug interruption/delay and a dose reduction, n (%)	0	5 (0.6%)	8 (0.7%)
Number of Patients with any TEAE resulting in death, n (%)	34 (9.6%)	47 (5.8%)	50 (4.6%)

Data cut-off as of Feb 17, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624. Data cut-off as of Apr 30, 2019 for Study 1423; Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients in Study 1540; Data cut-off as of Oct 10, 2018 for Group 2 patients in Study 1540.
TEAE: Treatment Emergent Adverse Events
NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a category.
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Table 43: Summary of Common (>5% of Any Grade or >2% of Grade 3/4/5 in Any Group) Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and NCI Grade in Study 1624 – Safety Population

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab (N=355)		Chemotherapy (N=342)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Number of patients with any TEAE, n (%)	**313 (88.2)**	**132 (37.2)**	**322 (94.2)**	**166 (48.5)**
General disorders and administration site conditions	**113 (31.8)**	**13 (3.7)**	**130 (38.0)**	**13 (3.8)**
Fatigue	36 (10.1)	4 (1.1)	58 (17.0)	5 (1.5)
Pyrexia	24 (6.8)	0	15 (4.4)	0
Non-cardiac chest pain	18 (5.1)	0	11 (3.2)	3 (0.9)
Asthenia	14 (3.9)	0	30 (8.8)	2 (0.6)
Gastrointestinal disorders	**106 (29.9)**	**6 (1.7)**	**176 (51.5)**	**17 (5.0)**
Constipation	27 (7.6)	0	52 (15.2)	0
Diarrhoea	25 (7.0)	1 (0.3)	32 (9.4)	7 (2.0)
Nausea	22 (6.2)	0	97 (28.4)	4 (1.2)
Vomiting	15 (4.2)	0	49 (14.3)	4 (1.2)
Investigations	**102 (28.7)**	**20 (5.6)**	**129 (37.7)**	**36 (10.5)**
Alanine aminotransferase increased	29 (8.2)	5 (1.4)	18 (5.3)	1 (0.3)
Aspartate aminotransferase increased	27 (7.6)	8 (2.3)	15 (4.4)	1 (0.3)
Blood creatinine increased	21 (5.9)	1 (0.3)	24 (7.0)	1 (0.3)
Blood alkaline phosphatase increased	19 (5.4)	3 (0.8)	10 (2.9)	1 (0.3)
Weight decreased	16 (4.5)	2 (0.6)	22 (6.4)	0
Platelet count decreased	5 (1.4)	0	36 (10.5)	12 (3.5)

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab (N=355)		Chemotherapy (N=342)	
	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
White blood cell count decreased	5 (1.4)	0	28 (8.2)	13 (3.8)
Neutrophil count decreased	2 (0.6)	1 (0.3)	42 (12.3)	18 (5.3)
Metabolism and nutrition disorders	**102 (28.7)**	**23 (6.5)**	**122 (35.7)**	**20 (5.8)**
Decreased appetite	42 (11.8)	2 (0.6)	63 (18.4)	1 (0.3)
Hypoalbuminaemia	23 (6.5)	2 (0.6)	24 (7.0)	3 (0.9)
Hyperglycaemia	18 (5.1)	1 (0.3)	14 (4.1)	0
Hyponatraemia	14 (3.9)	9 (2.5)	18 (5.3)	8 (2.3)
Hypomagnesaemia	8 (2.3)	0	29 (8.5)	2 (0.6)
Respiratory, thoracic and mediastinal disorders	**102 (28.7)**	**28 (7.9)**	**88 (25.7)**	**21 (6.1)**
Cough	34 (9.6)	0	26 (7.6)	1 (0.3)
Dyspnoea	34 (9.6)	7 (2.0)	22 (6.4)	6 (1.8)
Haemoptysis	18 (5.1)	2 (0.6)	18 (5.3)	1 (0.3)
Pulmonary embolism	10 (2.8)	9 (2.5)	5 (1.5)	3 (0.9)
Musculoskeletal and connective tissue disorders	**96 (27.0)**	**4 (1.1)**	**99 (28.9)**	**6 (1.8)**
Back pain	35 (9.9)	0	21 (6.1)	2 (0.6)
Arthralgia	25 (7.0)	0	32 (9.4)	1 (0.3)
Pain in extremity	18 (5.1)	1 (0.3)	22 (6.4)	1 (0.3)
Infections and infestations	**93 (26.2)**	**32 (9.0)**	**86 (25.1)**	**30 (8.8)**
Pneumonia	33 (9.3)	17 (4.8)	37 (10.8)	19 (5.6)
Skin and subcutaneous tissue disorders	**86 (24.2)**	**5 (1.4)**	**118 (34.5)**	**3 (0.9)**
Pruritus	27 (7.6)	0	12 (3.5)	0
Rash	23 (6.5)	3 (0.8)	11 (3.2)	0
Alopecia	4 (1.1)	0	82 (24.0)	2 (0.6)
Blood and lymphatic system disorders	**71 (20.0)**	**17 (4.8)**	**207 (60.5)**	**93 (27.2)**
Anaemia	52 (14.6)	12 (3.4)	171 (50.0)	56 (16.4)
Thrombocytopenia	7 (2.0)	0	52 (15.2)	28 (8.2)
Neutropenia	6 (1.7)	2 (0.6)	63 (18.4)	35 (10.2)
Leukopenia	4 (1.1)	1 (0.3)	31 (9.1)	9 (2.6)
Febrile neutropenia	1 (0.3)	1 (0.3)	8 (2.3)	8 (2.3)
Nervous system disorders	**58 (16.3)**	**12 (3.4)**	**108 (31.6)**	**13 (3.8)**
Headache	18 (5.1)	1 (0.3)	5 (1.5)	0
Neuropathy peripheral	3 (0.8)	1 (0.3)	37 (10.8)	1 (0.3)
Endocrine disorders	**38 (10.7)**	**0**	**8 (2.3)**	**0**
Hypothyroidism	23 (6.5)	0	0	0
Psychiatric disorders	**32 (9.0)**	**3 (0.8)**	**29 (8.5)**	**2 (0.6)**
Insomnia	21 (5.9)	0	18 (5.3)	0

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; NCI, National Cancer Institute; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event
All AEs were coded using MedDRA Version 22.1. NCI grades were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a SOC/PT.

For SOCs, the table is sorted by decreasing frequency of all grades in the total group. Within each SOC, PTs are sorted by decreasing frequency in the total group.
Data cutoff as 01 Mar 2020 for all patients in Study 1624.

Table 44: Treatment-Emergent Adverse Events by preferred term and NCI grade (Safety analysis set)

	Pool 1 All NSCLC Patients (N=355)		Pool 2 All Monotherapy Patients (N=810)		Pool 3 All Patients (N=1078)	
Preferred Term, n (%)	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5	All Grades	Grades 3/4/5
Number of Patients with any TEAE, n (%)	313 (88.2%)	132 (37.2%)	756 (93.3%)	333 (41.1%)	1022 (94.8%)	472 (43.8%)
Fatigue	36 (10.1%)	4 (1.1%)	182 (22.5%)	13 (1.6%)	275 (25.5%)	19 (1.8%)
Nausea	22 (6.2%)	0	98 (12.1%)	1 (0.1%)	188 (17.4%)	4 (0.4%)
Diarrhoea	25 (7.0%)	1 (0.3%)	130 (16.0%)	4 (0.5%)	180 (16.7%)	7 (0.6%)
Decreased appetite	42 (11.8%)	2 (0.6%)	102 (12.6%)	5 (0.6%)	156 (14.5%)	7 (0.6%)
Anaemia	52 (14.6%)	12 (3.4%)	106 (13.1%)	27 (3.3%)	149 (13.8%)	46 (4.3%)
Constipation	27 (7.6%)	0	87 (10.7%)	2 (0.2%)	148 (13.7%)	4 (0.4%)
Cough	34 (9.6%)	0	92 (11.4%)	1 (0.1%)	125 (11.6%)	2 (0.2%)
Pruritus	27 (7.6%)	0	106 (13.1%)	1 (0.1%)	122 (11.3%)	1 (<0.1%)
Arthralgia	25 (7.0%)	0	79 (9.8%)	2 (0.2%)	118 (10.9%)	4 (0.4%)
Dyspnoea	34 (9.6%)	7 (2.0%)	77 (9.5%)	11 (1.4%)	113 (10.5%)	17 (1.6%)
Back pain	35 (9.9%)	0	66 (8.1%)	1 (0.1%)	103 (9.6%)	7 (0.6%)
Vomiting	15 (4.2%)	0	58 (7.2%)	1 (0.1%)	102 (9.5%)	5 (0.5%)
Pyrexia	24 (6.8%)	0	54 (6.7%)	1 (0.1%)	97 (9.0%)	2 (0.2%)
Headache	18 (5.1%)	1 (0.3%)	61 (7.5%)	3 (0.4%)	95 (8.8%)	5 (0.5%)
Rash	23 (6.5%)	3 (0.8%)	68 (8.4%)	3 (0.4%)	90 (8.3%)	4 (0.4%)
Abdominal pain	15 (4.2%)	0	53 (6.5%)	3 (0.4%)	84 (7.8%)	7 (0.6%)
Hypothyroidism	23 (6.5%)	0	66 (8.1%)	0	83 (7.7%)	1 (<0.1%)
Asthenia	14 (3.9%)	0	47 (5.8%)	5 (0.6%)	81 (7.5%)	7 (0.6%)
Insomnia	21 (5.9%)	0	44 (5.4%)	0	75 (7.0%)	0
Alanine aminotransferase increased	29 (8.2%)	5 (1.4%)	56 (6.9%)	7 (0.9%)	74 (6.9%)	12 (1.1%)
Aspartate aminotransferase increased	27 (7.6%)	8 (2.3%)	53 (6.5%)	13 (1.6%)	73 (6.8%)	21 (1.9%)
Dizziness	9 (2.5%)	0	46 (5.7%)	1 (0.1%)	73 (6.8%)	1 (<0.1%)
Oedema peripheral	12 (3.4%)	0	45 (5.6%)	0	73 (6.8%)	0
Pneumonia	33 (9.3%)	17 (4.8%)	50 (6.2%)	29 (3.6%)	70 (6.5%)	39 (3.6%)
Urinary tract infection	5 (1.4%)	0	43 (5.3%)	8 (1.0%)	69 (6.4%)	13 (1.2%)
Pain in extremity	18 (5.1%)	1 (0.3%)	46 (5.7%)	4 (0.5%)	67 (6.2%)	5 (0.5%)
Rash maculo-papular	5 (1.4%)	1 (0.3%)	48 (5.9%)	4 (0.5%)	65 (6.0%)	4 (0.4%)
Hypokalaemia	11 (3.1%)	3 (0.8%)	37 (4.6%)	9 (1.1%)	64 (5.9%)	14 (1.3%)
Blood creatinine increased	21 (5.9%)	1 (0.3%)	53 (6.5%)	3 (0.4%)	58 (5.4%)	3 (0.3%)
Upper respiratory tract infection	11 (3.1%)	0	47 (5.8%)	0	58 (5.4%)	0
Weight decreased	16 (4.5%)	2 (0.6%)	41 (5.1%)	5 (0.6%)	57 (5.3%)	9 (0.8%)
Hypoalbuminaemia	23 (6.5%)	2 (0.6%)	39 (4.8%)	4 (0.5%)	54 (5.0%)	5 (0.5%)
Myalgia	5 (1.4%)	0	31 (3.8%)	1 (0.1%)	51 (4.7%)	1 (<0.1%)
Hypertension	14 (3.9%)	3 (0.8%)	44 (5.4%)	16 (2.0%)	49 (4.5%)	18 (1.7%)
Blood alkaline phosphatase increased	19 (5.4%)	3 (0.8%)	36 (4.4%)	3 (0.4%)	48 (4.5%)	11 (1.0%)
Dry mouth	9 (2.5%)	0	33 (4.1%)	0	46 (4.3%)	0
Hyperglycaemia	18 (5.1%)	1 (0.3%)	35 (4.3%)	7 (0.9%)	46 (4.3%)	12 (1.1%)
Hyponatraemia	14 (3.9%)	9 (2.5%)	30 (3.7%)	19 (2.3%)	46 (4.3%)	30 (2.8%)

Data cut-off as of Feb 17, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624. Data cut-off as of Apr 30, 2019 for Study 1423; Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients in Study 1540; Data cut-off as of Oct 10, 2018 for Group 2 patients in Study 1540.
TEAE: Treatment-emergent adverse event
All adverse events were coded using the MedDRA Version 22.1. NCI grade were coded using CTCAE Version 4.03.
A patient is counted only once for multiple occurrences within a preferred term.
The table is sorted by decreasing frequency in the total group.

Adverse events of special interest

Immune-mediated adverse events (imAEs)

Treatment-related AEs included in the MAH´s list of immune-mediated PTs were considered potential imAEs. Potential imAEs requiring treatment with systemic corticosteroid or other immunosuppressants or events that were immune-mediated endocrinopathies are defined as identified imAEs. High-dose corticosteroids in the following sections are defined as ≥40 mg prednisone per day, or equivalent.

Table 45: Summary of Treatment-Emergent Sponsor-Identified Immune-Mediated Adverse Events by Composite/Preferred Term and NCI Grade (imAEs Requiring Systemic Corticosteroids and Endocrine-Related imAEs Based on Sponsor-Provided List; Safety Population)

	Pool 1 - All Cemiplimab NSCLC Patients (N=355)		Pool 2 - All Cemiplimab Monotherapy Patients (N=810)		Pool 3 - All Cemiplimab Patients (N=1078)	
Composite*/Preferred Term, n (%)	**All Grades**	**Grades 3/4/5**	**All Grades**	**Grades 3/4/5**	**All Grades**	**Grades 3/4/5**
Total number of treatment-emergent sponsor-identified imAEs	87	14	253	59	306	82
Number of patients with any treatment-emergent sponsor-identified imAE, n (%)	62 (17.5)	13 (3.7)	177 (21.9)	53 (6.5)	217 (20.1)	72 (6.7)
Hypothyroidism*	20 (5.6)	0	60 (7.4)	0	74 (6.9)	1 (<0.1)
Immune-related pneumonitis*	8 (2.3)	2 (0.6)	26 (3.2)	8 (1.0)	32 (3.0)	12 (1.1)
Hyperthyroidism*	15 (4.2)	0	26 (3.2)	0	31 (2.9)	1 (<0.1)
Immune-related hepatitis*	6 (1.7)	5 (1.4)	16 (2.0)	13 (1.6)	20 (1.9)	17 (1.6)
Immune-related colitis*	4 (1.1)	1 (0.3)	18 (2.2)	7 (0.9)	19 (1.8)	8 (0.7)
Immune-related skin adverse reaction*	6 (1.7)	3 (0.8)	13 (1.6)	7 (0.9)	19 (1.8)	10 (0.9)
Arthralgia	0	0	9 (1.1)	0	11 (1.0)	0
Blood thyroid stimulating hormone increased	2 (0.6)	0	5 (0.6)	0	7 (0.6)	0
Immune-related nephritis*	3 (0.8)	1 (0.3)	5 (0.6)	2 (0.2)	6 (0.6)	3 (0.3)
Adrenal insufficiency*	0	0	3 (0.4)	3 (0.4)	5 (0.5)	3 (0.3)
Thyroiditis*	2 (0.6)	0	5 (0.6)	0	5 (0.5)	0
Arthritis*	2 (0.6)	0	4 (0.5)	1 (0.1)	4 (0.4)	1 (<0.1)
Type 1 diabetes mellitus*	0	0	1 (0.1)	1 (0.1)	4 (0.4)	4 (0.4)
Hypophysitis	1 (0.3)	0	3 (0.4)	2 (0.2)	3 (0.3)	2 (0.2)
Neuropathy peripheral*	2 (0.6)	1 (0.3)	3 (0.4)	1 (0.1)	3 (0.3)	1 (<0.1)
Pruritus*	0	0	3 (0.4)	1 (0.1)	3 (0.3)	1 (<0.1)
Stomatitis	1 (0.3)	0	3 (0.4)	0	3 (0.3)	0
Encephalitis*	0	0	1 (0.1)	1 (0.1)	2 (0.2)	2 (0.2)
Meningitis*	0	0	1 (0.1)	1 (0.1)	2 (0.2)	2 (0.2)
Myocarditis*	1 (0.3)	0	2 (0.2)	1 (0.1)	2 (0.2)	2 (0.2)
Pericarditis*	0	0	2 (0.2)	1 (0.1)	2 (0.2)	1 (<0.1)
Blood alkaline phosphatase increased	1 (0.3)	0	1 (0.1)	0	1 (<0.1)	0
Blood thyroid stimulating hormone decreased	0	0	1 (0.1)	0	1 (<0.1)	0
Chronic inflammatory demyelinating polyradiculoneuropathy	0	0	1 (0.1)	0	1 (<0.1)	0
Guillain-Barre syndrome	0	0	0	0	1 (<0.1)	1 (<0.1)
Immune thrombocytopenic purpura	0	0	1 (0.1)	0	1 (<0.1)	0
Muscular weakness	0	0	1 (0.1)	0	1 (<0.1)	0
Myalgia*	0	0	1 (0.1)	1 (0.1)	1 (<0.1)	1 (<0.1)
Myositis*	1 (0.3)	0	1 (0.1)	0	1 (<0.1)	0
Paraneoplastic encephalomyelitis	0	0	1 (0.1)	1 (0.1)	1 (<0.1)	1 (<0.1)
Polymyalgia rheumatica	0	0	1 (0.1)	0	1 (<0.1)	0
Sjogren's syndrome	0	0	1 (0.1)	0	1 (<0.1)	0
Vasculitis	0	0	0	0	1 (<0.1)	0

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; imAE, immune-mediated adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; NCI, National Cancer Institute; PT, preferred term; Regeneron, Regeneron Pharmaceuticals, Inc.

All AEs were coded using MedDRA Version 22.1. NCI grades were coded using CTCAE Version 4.03.
* Each composite term includes multiple MedDRA PTs based on Regeneron defined list. Refer to ISS Table 14.3.2.4.11.p0.
A patient is counted only once for multiple occurrences within a composite term/PT.
The table is sorted by decreasing frequency of all grades in the total group.
Data cutoffs: 01 Mar 2020 for patients in Study 1624; 30 Apr 2019 for patients in Study 1423; 20 Sep 2018 for all patients in Group 1 and Group 3 and 10 Oct 2018 for Group 2 in Study 1540; and 17 Feb 2020 for all patients in Study 1620.

Infusion-related reactions (IRRs)

6.5% of patients experienced an IRR, based on sponsor definition, with 1 patient with a serious infusion reaction and 1 patient discontinuing the treatment due to an IRR. 3.7% of patients had a dose delay or dose interruption due to an IRR. There were no fatal IRRs.

Serious adverse event/deaths

SAEs

Table 46: Summary of Common (>1% by PT in Any Group) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in Study 1624 – Safety Population

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab (N=355)	Chemotherapy (N=342)
Number of patients with any serious TEAE, n (%)	**100 (28.2)**	**94 (27.5)**
Infections and infestations	**30 (8.5)**	**32 (9.4)**
Pneumonia	17 (4.8)	17 (5.0)
Septic shock	4 (1.1)	2 (0.6)
Respiratory, thoracic, and mediastinal disorders	**28 (7.9)**	**18 (5.3)**
Pneumonitis	6 (1.7)	0
Pulmonary embolism	6 (1.7)	2 (0.6)
Dyspnoea	4 (1.1)	4 (1.2)
Pleural effusion	4 (1.1)	3 (0.9)
Respiratory failure	4 (1.1)	2 (0.6)
General disorders and administration site conditions	**12 (3.4)**	**8 (2.3)**
Death	5 (1.4)	1 (0.3)
Gastrointestinal disorders	**8 (2.3)**	**10 (2.9)**
Vomiting	0	4 (1.2)
Blood and lymphatic system disorders	**6 (1.7)**	**24 (7.0)**
Anaemia	3 (0.8)	13 (3.8)
Febrile neutropenia	1 (0.3)	8 (2.3)
Neutropenia	1 (0.3)	4 (1.2)
Thrombocytopenia	0	6 (1.8)

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event
All AEs were coded using MedDRA Version 20.0.
A patient is counted only once for multiple occurrences within a SOC/PT.
For SOCs, the table is sorted by decreasing frequency in the total group. Within each SOC, PTs are sorted by decreasing frequency in the total group.
Data cutoff as 01 Mar 2020 for all patients in Study 1624.

Table 47: Serious treatment-emergent adverse events by preferred term (safety analysis set)

Preferred Term, n (%)	Pool 1 All NSCLC Patients (N=355)	Pool 2 All Monotherapy Patients (N=810)	Pool 3 All Patients (N=1078)
Number of Patients with any serious TEAE, n (%)	100 (28.2%)	243 (30.0%)	323 (30.0%)
Pneumonia	17 (4.8%)	27 (3.3%)	36 (3.3%)
Pneumonitis	6 (1.7%)	17 (2.1%)	22 (2.0%)
Pulmonary embolism	6 (1.7%)	7 (0.9%)	10 (0.9%)
Pyrexia	2 (0.6%)	5 (0.6%)	10 (0.9%)
Urinary tract infection	0	9 (1.1%)	10 (0.9%)
Cellulitis	1 (0.3%)	8 (1.0%)	8 (0.7%)
Dyspnoea	4 (1.1%)	6 (0.7%)	8 (0.7%)
Sepsis	1 (0.3%)	6 (0.7%)	8 (0.7%)
Anaemia	3 (0.8%)	6 (0.7%)	7 (0.6%)
Death	5 (1.4%)	7 (0.9%)	7 (0.6%)
Pleural effusion	4 (1.1%)	6 (0.7%)	7 (0.6%)
Colitis	1 (0.3%)	5 (0.6%)	6 (0.6%)
Fall	0	4 (0.5%)	6 (0.6%)
Hypercalcaemia	1 (0.3%)	4 (0.5%)	6 (0.6%)
Respiratory failure	4 (1.1%)	5 (0.6%)	6 (0.6%)
Acute kidney injury	0	4 (0.5%)	5 (0.5%)
Atrial fibrillation	0	2 (0.2%)	5 (0.5%)
Deep vein thrombosis	0	2 (0.2%)	5 (0.5%)
Myocardial infarction	2 (0.6%)	5 (0.6%)	5 (0.5%)
Skin infection	0	5 (0.6%)	5 (0.5%)
Autoimmune hepatitis	0	4 (0.5%)	4 (0.4%)
Back pain	1 (0.3%)	2 (0.2%)	4 (0.4%)
Dehydration	0	2 (0.2%)	4 (0.4%)
Fatigue	3 (0.8%)	4 (0.5%)	4 (0.4%)
Hyponatraemia	0	1 (0.1%)	4 (0.4%)
Hypotension	0	3 (0.4%)	4 (0.4%)
Hypoxia	1 (0.3%)	3 (0.4%)	4 (0.4%)
Infusion related reaction	1 (0.3%)	2 (0.2%)	4 (0.4%)
Ischaemic stroke	3 (0.8%)	3 (0.4%)	4 (0.4%)
Respiratory tract infection	3 (0.8%)	3 (0.4%)	4 (0.4%)
Septic shock	4 (1.1%)	4 (0.5%)	4 (0.4%)
Adrenal insufficiency	0	2 (0.2%)	3 (0.3%)
Alanine aminotransferase increased	1 (0.3%)	2 (0.2%)	3 (0.3%)
Aspartate aminotransferase increased	1 (0.3%)	2 (0.2%)	3 (0.3%)
Cholecystitis	2 (0.6%)	2 (0.2%)	3 (0.3%)
Clostridium difficile infection	1 (0.3%)	2 (0.2%)	3 (0.3%)
Delirium	0	2 (0.2%)	3 (0.3%)

Data cut-off as of Feb 17, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624. Data cut-off as of Apr 30, 2019 for Study 1423; Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients in Study 1540; Data cut-off as of Oct 10, 2018 for Group 2 patients in Study 1540.
TEAE: Treatment-emergent adverse event
All adverse events were coded using the MedDRA Version 22.1
A patient is counted only once for multiple occurrences within a preferred term.
The table is sorted by decreasing frequency in the total group.

Deaths

Table 48: All deaths (safety analysis set)

	Cemiplimab (N=355)	Chemotherapy (N=342)
Number of Deaths, n (%)	107 (30.1%)	139 (40.6%)
Primary cause of death		
PROGRESSION/RECURRENCE OF DISEASE	64 (18.0%)	93 (27.2%)
ADVERSE EVENT	36 (10.1%)	41 (12.0%)
OTHER	7 (2.0%)	5 (1.5%)

Table 49: Summary of Treatment-Emergent Adverse Events Resulting in Death by System Organ Class and Preferred Term in Study 1624 – Safety Population

System Organ Class Preferred Term	Cemiplimab (N=355)	Chemotherapy (N=342)
Number of patients with any TEAE resulting in death, n (%)	**34 (9.6)**	**31 (9.1)**
Respiratory, thoracic, and mediastinal disorders	**11 (3.1)**	**6 (1.8)**
Respiratory failure	4 (1.1)	2 (0.6)
Pulmonary embolism	3 (0.8)	2 (0.6)
Bronchospasm	1 (0.3)	0

System Organ Class Preferred Term	Cemiplimab (N=355)	Chemotherapy (N=342)
Dyspnoea	1 (0.3)	1 (0.3)
Hypoxia	1 (0.3)	0
Pulmonary haemorrhage	1 (0.3)	1 (0.3)
Cardiac disorders	**6 (1.7)**	**9 (2.6)**
Acute myocardial infarction	1 (0.3)	0
Autoimmune myocarditis	1 (0.3)	0
Cardiac failure	1 (0.3)	0
Cardio-respiratory arrest	1 (0.3)	2 (0.6)
Cardiopulmonary failure	1 (0.3)	0
Myocardial infarction	1 (0.3)	2 (0.6)
Cardiac arrest	0	3 (0.9)
Cardiac failure acute	0	1 (0.3)
Myocardial ischaemia	0	1 (0.3)
General disorders and administration site conditions	**6 (1.7)**	**3 (0.9)**
Death	5 (1.4)	1 (0.3)
Multiple organ dysfunction syndrome	1 (0.3)	1 (0.3)
Sudden death	0	1 (0.3)
Infections and infestations	**4 (1.1)**	**2 (0.6)**
Septic shock	2 (0.6)	1 (0.3)
Pneumonia	1 (0.3)	0
Sepsis	1 (0.3)	1 (0.3)
Bronchitis	0	1 (0.3)
Lung abscess	0	1 (0.3)
Pulmonary tuberculosis	0	1 (0.3)
Nervous system disorders	**2 (0.6)**	**12 (3.5)**
Cerebral infarction	1 (0.3)	1 (0.3)
Cerebral ischaemia	1 (0.3)	8 (2.3)
Cerebrovascular accident	0	1 (0.3)
Ischaemic cerebral infarction	0	1 (0.3)
Vascular disorders	**2 (0.6)**	**1 (0.3)**
Embolism	1 (0.3)	1 (0.3)
Shock haemorrhagic	1 (0.3)	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.3)**	**1 (0.3)**
Tumour hyperprogression	1 (0.3)	2 (0.6)
Psychiatric disorders	**1 (0.3)**	**0**
Completed suicide	1 (0.3)	0
Renal and urinary disorders	**1 (0.3)**	**1 (0.3)**
Nephritis	1 (0.3)	1 (0.3)

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event
All AEs were coded using MedDRA Version 20.0. A patient is counted only once for multiple occurrences within a SOC/PT.
For SOCs, the table is sorted by decreasing frequency in the total group. Within each SOC, PTs are sorted by decreasing frequency in the total group.
Data cutoff as 01 Mar 2020 for all patients in Study 1624.

Table 50: Summary of all deaths (safety analysis set)

	Pool 1 All NSCLC Patients (N=355)	Pool 2 All Monotherapy Patients (N=810)	Pool 3 All Patients (N=1078)
Number of Deaths, n (%)	107 (30.1%)	221 (27.3%)	393 (36.5%)
Primary cause of death			
PROGRESSION/RECURRENCE OF DISEASE	64 (18.0%)	151 (18.6%)	306 (28.4%)
ADVERSE EVENT	36 (10.1%)	49 (6.0%)	52 (4.8%)
OTHER	7 (2.0%)	21 (2.6%)	35 (3.2%)

Data cut-off as of Feb 17, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624. Data cut-off as of Apr 30, 2019 for Study 1423; Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients in Study 1540; Data cut-off as of Oct 10, 2018 for Group 2 patients in Study 1540.

Table 51: Treatment-Emergent Adverse Events Resulting in Death by System Organ Class and Preferred Term (Safety analysis set)

System Organ Class, n (%) Preferred Term, n (%)	Pool 1 All NSCLC Patients (N=355)	Pool 2 All Monotherapy Patients (N=810)	Pool 3 All Patients (N=1078)
Number of Patients with any TEAE resulting in death, n (%)	34 (9.6%)	47 (5.8%)	50 (4.6%)
Respiratory, thoracic and mediastinal disorders	11 (3.1%)	13 (1.6%)	15 (1.4%)
Pulmonary embolism	3 (0.8%)	4 (0.5%)	4 (0.4%)
Respiratory failure	4 (1.1%)	4 (0.5%)	4 (0.4%)
Pneumonitis	0	0	2 (0.2%)
Acute respiratory distress syndrome	0	1 (0.1%)	1 (<0.1%)
Bronchospasm	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Dyspnoea	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Hypoxia	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Pulmonary haemorrhage	1 (0.3%)	1 (0.1%)	1 (<0.1%)
General disorders and administration site conditions	6 (1.7%)	8 (1.0%)	8 (0.7%)
Death	5 (1.4%)	7 (0.9%)	7 (0.6%)
Multiple organ dysfunction syndrome	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Cardiac disorders	6 (1.7%)	6 (0.7%)	6 (0.6%)
Acute myocardial infarction	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Autoimmune myocarditis	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Cardiac failure	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Cardio-respiratory arrest	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Cardiopulmonary failure	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Myocardial infarction	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Infections and infestations	4 (1.1%)	6 (0.7%)	6 (0.6%)
Pneumonia	1 (0.3%)	2 (0.2%)	2 (0.2%)
Septic shock	2 (0.6%)	2 (0.2%)	2 (0.2%)
Pneumonia staphylococcal	0	1 (0.1%)	1 (<0.1%)
Sepsis	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3%)	2 (0.2%)	3 (0.3%)
Brain neoplasm malignant	0	1 (0.1%)	1 (<0.1%)
Myelodysplastic syndrome	0	0	1 (<0.1%)
Tumour hyperprogression	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Nervous system disorders	2 (0.6%)	3 (0.4%)	3 (0.3%)
Cerebral infarction	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Cerebral ischaemia	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Paraneoplastic encephalomyelitis	0	1 (0.1%)	1 (<0.1%)
Renal and urinary disorders	1 (0.3%)	3 (0.4%)	3 (0.3%)
Acute kidney injury	0	2 (0.2%)	2 (0.2%)
Nephritis	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Vascular disorders	2 (0.6%)	3 (0.4%)	3 (0.3%)
Arterial haemorrhage	0	1 (0.1%)	1 (<0.1%)
Embolism	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Shock haemorrhagic	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Hepatobiliary disorders	0	1 (0.1%)	1 (<0.1%)
Hepatic failure	0	1 (0.1%)	1 (<0.1%)
Metabolism and nutrition disorders	0	1 (0.1%)	1 (<0.1%)
Cachexia	0	1 (0.1%)	1 (<0.1%)
Psychiatric disorders	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Completed suicide	1 (0.3%)	1 (0.1%)	1 (<0.1%)

Data cut-off as of Feb 17, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624. Data cut-off as of Apr 30, 2019 for Study 1423; Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients in Study 1540; Data cut-off as of Oct 10, 2018 for Group 2 patients in Study 1540.
TEAE: Treatment-emergent adverse event.
All adverse events were coded using the MedDRA Version 22.1.
A patient is counted only once for multiple occurrences within a system organ class/preferred term.
For SOCs, the table is sorted by decreasing frequency in the total group. Within each SOC, PTs are sorted by decreasing frequency in the total group.

Laboratory findings

Haematology

Table 52: Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade for Haematology in Study 1624 – Safety Population

	Cemiplimab (N=355)		Chemotherapy (N=342)	
Parameter (CTCAE Term)	**All Grades**	**Grades 3/4**	**All Grades**	**Grades 3/4**
Number of patients with at least 1 postbaseline laboratory abnormality, n (%)	197/336 (58.6)	31/336 (9.2)	291/324 (89.8)	104/324 (32.1)
Hemoglobin (Anemia)	109/336 (32.4)	9/336 (2.7)	245/324 (75.6)	52/324 (16.0)
Hemoglobin (Hemoglobin increased)	15/336 (4.5)	0/336	1/324 (0.3)	0/324
Leukocytes (White blood cell decreased)	27/335 (8.1)	1/335 (0.3)	144/324 (44.4)	30/324 (9.3)
Lymphocytes (Lymphocyte count decreased)	79/335 (23.6)	22/335 (6.6)	116/324 (35.8)	29/324 (9.0)
Lymphocytes (Lymphocyte count increased)	18/335 (5.4)	0/335	17/324 (5.2)	0/324
Neutrophils (Neutrophil count decreased)	17/336 (5.1)	3/336 (0.9)	127/324 (39.2)	44/324 (13.6)
Platelets (Platelet count decreased)	46/336 (13.7)	1/336 (0.3)	121/323 (37.5)	25/323 (7.7)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; N, number of patients; NCI, National Cancer Institute
NCI grades were coded using CTCAE Version 4.03.
Percentages are based on the number of patients with at least 1 postbaseline value available for that parameter.
Postbaseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.
Data cutoff as of 01 Mar 2020 for patients in Study 1624.

Table 53: Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade for Haematology (safety analysis set)

	Pool 1 All NSCLC Patients (N=355)		Pool 2 All Monotherapy Patients (N=810)		Pool 3 All Patients (N=1078)	
Parameter (CTCAE Term)	All Grades	Grades 3/4	All Grades	Grades 3/4	All Grades	Grades 3/4
Number of pts. with at least one post-baseline lab abnormality, n (%)	197/336 (58.6%)	31/336 (9.2%)	539/786 (68.6%)	89/786 (11.3%)	779/1053 (74.0%)	175/1053 (16.6%)
Hemoglobin (Anemia)	109/336 (32.4%)	9/336 (2.7%)	311/786 (39.6%)	25/786 (3.2%)	472/1053 (44.8%)	46/1053 (4.4%)
Hemoglobin (Hemoglobin increased)	15/336 (4.5%)	0/336	24/786 (3.1%)	0/786	28/1053 (2.7%)	0/1053
Leukocytes (White blood cell decreased)	27/335 (8.1%)	1/335 (0.3%)	94/785 (12.0%)	2/785 (0.3%)	176/1052 (16.7%)	16/1052 (1.5%)
Lymphocytes (Lymphocyte count decreased)	79/335 (23.6%)	22/335 (6.6%)	274/785 (34.9%)	67/785 (8.5%)	445/1052 (42.3%)	133/1052 (12.6%)
Lymphocytes (Lymphocyte count increased)	18/335 (5.4%)	0/335	31/785 (3.9%)	0/785	33/1052 (3.1%)	0/1052
Neutrophils (Neutrophil count decreased)	17/336 (5.1%)	3/336 (0.9%)	52/785 (6.6%)	4/785 (0.5%)	102/1052 (9.7%)	18/1052 (1.7%)
Platelets (Platelet count decreased)	46/336 (13.7%)	1/336 (0.3%)	108/786 (13.7%)	1/786 (0.1%)	174/1053 (16.5%)	3/1053 (0.3%)

Data cut-off as of Feb 17, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624. Data cut-off as of Apr 30, 2019 for Study 1423; Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients in Study 1540; Data cut-off as of Oct 10, 2018 for Group 2 patients in Study 1540.
NCI grades were coded using CTCAE Version 4.03.
Percentages are based on the number of patients with at least one post-baseline value available for that parameter.
Post-baseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.

Electrolytes

Table 54: Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade for Electrolytes in Study 1624 – Safety Population

	Cemiplimab (N=355)		Chemotherapy (N=342)	
Parameter (CTCAE Term)	**All Grades**	**Grades 3/4**	**All Grades**	**Grades 3/4**
Number of patients with at least 1 postbaseline laboratory abnormality, n (%)	248/336 (73.8)	57/336 (17.0)	241/321 (75.1)	56/321 (17.4)
Calcium (Hypercalcemia [uncorrected calcium])	60/333 (18.0)	4/333 (1.2)	47/320 (14.7)	7/320 (2.2)
Calcium (Hypocalcemia [uncorrected calcium])	87/333 (26.1)	13/333 (3.9)	83/320 (25.9)	11/320 (3.4)
Magnesium (Hypermagnesemia)	28/334 (8.4)	7/334 (2.1)	23/318 (7.2)	5/318 (1.6)
Magnesium (Hypomagnesemia)	55/334 (16.5)	0/334	100/318 (31.4)	5/318 (1.6)
Phosphate (Hypophosphatemia)	53/334 (15.9)	8/334 (2.4)	52/317 (16.4)	13/317 (4.1)
Potassium (Hyperkalemia)	74/336 (22.0)	14/336 (4.2)	65/321 (20.2)	6/321 (1.9)
Potassium (Hypokalemia)	34/336 (10.1)	5/336 (1.5)	43/321 (13.4)	7/321 (2.2)
Sodium (Hypernatremia)	25/336 (7.4)	0/336	21/321 (6.5)	2/321 (0.6)
Sodium (Hyponatremia)	101/336 (30.1)	21/336 (6.3)	99/321 (30.8)	24/321 (7.5)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; N, number of patients; NCI, National Cancer Institute
NCI grades were coded using CTCAE Version 4.03.
Percentages are based on the number of patients with at least 1 postbaseline value available for that parameter.
Postbaseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.
Data cutoff as of 01 Mar 2020 for patients in Study 1624.

Table 55: Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade for Electrolytes (safety analysis set)

	Pool 1 All NSCLC Patients (N=355)		Pool 2 All Monotherapy Patients (N=810)		Pool 3 All Patients (N=1078)	
Parameter (CTCAE Term)	All Grades	Grades 3/4	All Grades	Grades 3/4	All Grades	Grades 3/4
Number of pts. with at least one post-baseline lab abnormality, n (%)	248/336 (73.8%)	57/336 (17.0%)	580/785 (73.9%)	104/785 (13.2%)	801/1052 (76.1%)	156/1052 (14.8%)
Calcium (Hypercalcemia (Uncorrected Calcium))	60/333 (18.0%)	4/333 (1.2%)	107/782 (13.7%)	9/782 (1.2%)	130/1049 (12.4%)	12/1049 (1.1%)
Calcium (Hypocalcemia (Uncorrected Calcium))	87/333 (26.1%)	13/333 (3.9%)	188/782 (24.0%)	13/782 (1.7%)	305/1049 (29.1%)	15/1049 (1.4%)
Magnesium (Hypermagnesemia)	28/334 (8.4%)	7/334 (2.1%)	49/653 (7.5%)	9/653 (1.4%)	61/920 (6.6%)	11/920 (1.2%)
Magnesium (Hypomagnesemia)	55/334 (16.5%)	0/334	104/653 (15.9%)	0/653	159/920 (17.3%)	2/920 (0.2%)
Phosphate (Hypophosphatemia)	53/334 (15.9%)	8/334 (2.4%)	126/651 (19.4%)	23/651 (3.5%)	197/917 (21.5%)	42/917 (4.6%)
Potassium (Hyperkalemia)	74/336 (22.0%)	14/336 (4.2%)	154/785 (19.6%)	17/785 (2.2%)	179/1052 (17.0%)	18/1052 (1.7%)
Potassium (Hypokalemia)	34/336 (10.1%)	5/336 (1.5%)	115/785 (14.6%)	9/785 (1.1%)	174/1052 (16.5%)	15/1052 (1.4%)
Sodium (Hypernatremia)	25/336 (7.4%)	0/336	54/785 (6.9%)	0/785	71/1052 (6.7%)	0/1052
Sodium (Hyponatremia)	101/336 (30.1%)	21/336 (6.3%)	229/785 (29.2%)	42/785 (5.4%)	331/1052 (31.5%)	69/1052 (6.6%)

Data cut-off as of Feb 17, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624. Data cut-off as of Apr 30, 2019 for Study 1423; Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients in Study 1540; Data cut-off as of Oct 10, 2018 for Group 2 patients in Study 1540.
NCI grades were coded using CTCAE Version 4.03.
Percentages are based on the number of patients with at least one post-baseline value available for that parameter.
Post-baseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.

Liver parameters

Table 56: Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade for Liver Function in Study 1624 – Safety Population

	Cemiplimab (N=355)		Chemotherapy (N=342)	
Parameter (CTCAE Term)	**All Grades**	**Grades 3/4**	**All Grades**	**Grades 3/4**
Number of patients with at least 1 postbaseline laboratory abnormality, n (%)	226/336 (67.3)	26/336 (7.7)	185/321 (57.6)	9/321 (2.8)
Alanine aminotransferase (Alanine aminotransferase increased)	86/336 (25.6)	9/336 (2.7)	73/321 (22.7)	1/321 (0.3)
Albumin (Hypoalbuminemia)	110/336 (32.7)	6/336 (1.8)	84/320 (26.3)	4/320 (1.3)
Alkaline phosphatase (Alkaline phosphatase increased)	86/335 (25.7)	8/335 (2.4)	74/321 (23.1)	1/321 (0.3)
Aspartate aminotransferase (Aspartate aminotransferase increased)	92/336 (27.4)	13/336 (3.9)	76/321 (23.7)	4/321 (1.2)
Bilirubin (Blood bilirubin increased)	46/336 (13.7)	7/336 (2.1)	23/321 (7.2)	1/321 (0.3)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; N, number of patients; NCI, National Cancer Institute
NCI grades were coded using CTCAE Version 4.03.
Percentages are based on the number of patients with at least 1 postbaseline value available for that parameter.
Postbaseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.
Data cutoff as of 01 Mar 2020 for patients in Study 1624.

Table 57: Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade for Liver Function (safety analysis set)

	Pool 1 All NSCLC Patients (N=355)		Pool 2 All Monotherapy Patients (N=810)		Pool 3 All Patients (N=1078)	
Parameter (CTCAE Term)	All Grades	Grades 3/4	All Grades	Grades 3/4	All Grades	Grades 3/4
Number of pts. with at least one post-baseline lab abnormality, n (%)	226/336 (67.3%)	26/336 (7.7%)	518/785 (66.0%)	49/785 (6.2%)	728/1052 (69.2%)	84/1052 (8.0%)
Alanine Aminotransferase (Alanine aminotransferase increased)	86/336 (25.6%)	9/336 (2.7%)	182/785 (23.2%)	13/785 (1.7%)	248/1052 (23.6%)	26/1052 (2.5%)
Albumin (Hypoalbuminemia)	110/336 (32.7%)	6/336 (1.8%)	264/785 (33.6%)	10/785 (1.3%)	398/1052 (37.8%)	15/1052 (1.4%)
Alkaline Phosphatase (Alkaline phosphatase increased)	86/335 (25.7%)	8/335 (2.4%)	165/784 (21.0%)	14/784 (1.8%)	259/1051 (24.6%)	24/1051 (2.3%)
Aspartate Aminotransferase (Aspartate aminotransferase increased)	92/336 (27.4%)	13/336 (3.9%)	216/784 (27.6%)	26/784 (3.3%)	303/1051 (28.8%)	40/1051 (3.8%)
Bilirubin (Blood bilirubin increased)	46/336 (13.7%)	7/336 (2.1%)	100/785 (12.7%)	15/785 (1.9%)	129/1052 (12.3%)	23/1052 (2.2%)

Data cut-off as of Feb 17, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624. Data cut-off as of Apr 30, 2019 for Study 1423; Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients in Study 1540; Data cut-off as of Oct 10, 2018 for Group 2 patients in Study 1540.
NCI grades were coded using CTCAE Version 4.03.
Percentages are based on the number of patients with at least one post-baseline value available for that parameter.
Post-baseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.

Other chemistry

Table 58: Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade for Chemistry (Other) in Study 1624 – Safety Population

	Cemiplimab (N=355)		Chemotherapy (N=342)	
Parameter (CTCAE Term)	**All Grades**	**Grades 3/4**	**All Grades**	**Grades 3/4**
Number of patients with at least 1 postbaseline laboratory abnormality, n (%)	273/336 (81.3)	4/336 (1.2)	250/321 (77.9)	5/321 (1.6)
Creatinine (Creatinine increased)	267/336 (79.5)	4/336 (1.2)	246/321 (76.6)	5/321 (1.6)
Glucose (Hypoglycemia)	39/335 (11.6)	0/335	23/321 (7.2)	0/321

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; N, number of patients; NCI, National Cancer Institute
NCI grades were coded using CTCAE Version 4.03.
Percentages are based on the number of patients with at least 1 postbaseline value available for that parameter.
Postbaseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.
Data cutoff as of 01 Mar 2020 for patients in Study 1624.

Table 59: Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade for Chemistry (Other) (safety analysis set)

	Pool 1 All NSCLC Patients (N=355)		Pool 2 All Monotherapy Patients (N=810)		Pool 3 All Patients (N=1078)	
Parameter (CTCAE Term)	All Grades	Grades 3/4	All Grades	Grades 3/4	All Grades	Grades 3/4
Number of pts. with at least one post-baseline lab abnormality, n (%)	273/336 (81.3%)	4/336 (1.2%)	644/785 (82.0%)	10/785 (1.3%)	855/1052 (81.3%)	11/1052 (1.0%)
Creatinine (Creatinine increased)	267/336 (79.5%)	4/336 (1.2%)	630/785 (80.3%)	10/785 (1.3%)	836/1052 (79.5%)	11/1052 (1.0%)
Glucose (Hypoglycemia)	39/335 (11.6%)	0/335	85/777 (10.9%)	0/777	113/1044 (10.8%)	0/1044

Data cut-off as of Feb 17, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624. Data cut-off as of Apr 30, 2019 for Study 1423; Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients in Study 1540; Data cut-off as of Oct 10, 2018 for Group 2 patients in Study 1540.
NCI grades were coded using CTCAE Version 4.03.
Percentages are based on the number of patients with at least one post-baseline value available for that parameter.
Post-baseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.
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Coagulation

Table 60: Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade for Coagulation in Study 1624 – Safety Population

	Cemiplimab (N=355)		Chemotherapy (N=342)	
Parameter (CTCAE Term)	**All Grades**	**Grades 3/4**	**All Grades**	**Grades 3/4**
Number of patients with at least 1 postbaseline laboratory abnormality, n (%)	28/180 (15.6)	0/180	20/150 (13.3)	1/150 (0.7)
Activated partial thromboplastin time (Activated partial thromboplastin time prolonged)	28/180 (15.6)	0/180	20/150 (13.3)	1/150 (0.7)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; INR, international normalized ratio; N, number of patients; NCI, National Cancer Institute
NCI grades were coded using CTCAE Version 4.03.
Percentages are based on the number of patients with at least 1 postbaseline value available for that parameter.
Postbaseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.
Data cutoff as of 01 Mar 2020 for patients in Study 1624.

Table 61: Summary of New or Worsened Laboratory Results by NCI-CTCAE Grade for Coagulation (safety analysis set)

	Pool 1 All NSCLC Patients (N=355)		Pool 2 All Monotherapy Patients (N=810)		Pool 3 All Patients (N=1078)	
Parameter (CTCAE Term)	All Grades	Grades 3/4	All Grades	Grades 3/4	All Grades	Grades 3/4
Number of pts. with at least one post-baseline lab abnormality, n (%)	28/180 (15.6%)	0/180	104/497 (20.9%)	9/497 (1.8%)	166/688 (24.1%)	15/688 (2.2%)
Activated Partial Thromboplastin Time (Activated partial thromboplastin time prolonged)	28/180 (15.6%)	0/180	83/475 (17.5%)	4/475 (0.8%)	129/658 (19.6%)	7/658 (1.1%)
Prothrombin Intl. Normalized Ratio (INR increased)	0/0	0/0	40/297 (13.5%)	5/297 (1.7%)	68/488 (13.9%)	8/488 (1.6%)

Data cut-off as of Feb 17, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624. Data cut-off as of Apr 30, 2019 for Study 1423; Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients in Study 1540; Data cut-off as of Oct 10, 2018 for Group 2 patients in Study 1540.
NCI grades were coded using CTCAE Version 4.03.
Percentages are based on the number of patients with at least one post-baseline value available for that parameter.
Post-baseline value is for on-treatment period only.
A patient is counted only once for multiple occurrences for the same parameter.

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Thyroid functions tests (TSH and T4)

Table 62: Abnormal laboratory results for TSH and T4

	Cemiplimab (N=355)	Chemotherapy (N=342)
Number of patients with TSH increased, n (%)	49 (13.8%)	7 (2.0%)
Number of patients with T4 decreased, n (%)	29 (8.2%)	4 (1.2%)
Number of patients with concurrent TSH increased and T4 decreased, n (%)	21 (5.9%)	1 (0.3%)

Data cutoff as of 01 Mar 2020
Post-baseline value is for on-treatment period only
A patient is counted only once for multiple occurrences for the same parameter

Safety in special populations

Age:

Table 63: Distribution of AEs, SAEs according to age group for study 1624 (n=710)

	Cemiplimab			Chemotherapy		
	Age: <65 years	Age: 65 to 74 years	Age: ≥75	Age: <65 years	Age: 65 to 74 years	Age: ≥75
	(N=199)	(N=123)	(N=33)	(N=185)	(N=123)	(N=34)
Number of Patients with any TEAE, n (%)	173 (86.9%)	109 (88.6%)	31 (93.9%)	174 (94.1%)	116 (94.3%)	32 (94.1%)
Number of Patients with any Grade 3/4/5 TEAE, n (%)	70 (35.2%)	47 (38.2%)	15 (45.5%)	83 (44.9%)	61 (49.6%)	22 (64.7%)
Number of Serious TEAEs	87	57	21	95	58	24
Number of Patients with any Serious TEAE, n (%)	53 (26.6%)	38 (30.9%)	9 (27.3%)	52 (28.1%)	29 (23.6%)	13 (38.2%)
Fatal	19 (9.5%)	14 (11.4%)	1 (3.0%)	14 (7.6%)	12 (9.8%)	5 (14.7%)
Life-threatening	7 (3.5%)	6 (4.9%)	1 (3.0%)	11 (5.9%)	9 (7.3%)	2 (5.9%)
Hospitalization/prolong existing hospitalization	45 (22.6%)	27 (22.0%)	9 (27.3%)	45 (24.3%)	23 (18.7%)	12 (35.3%)
Disability/incapacity	3 (1.5%)	0	1 (3.0%)	0	1 (0.8%)	0
Other (medically significant)	0	2 (1.6%)	0	2 (1.1%)	0	1 (2.9%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	10 (5.0%)	9 (7.3%)	4 (12.1%)	4 (2.2%)	8 (6.5%)	2 (5.9%)
Number of Patients with any treatment-emergent sponsor identified imAE, n (%)	31 (15.6%)	25 (20.3%)	6 (18.2%)	4 (2.2%)	3 (2.4%)	1 (2.9%)

Source: 14.3.1.2.12

Gender:

Table 64: Distribution of AEs, SAEs according to gender group for study 1624 (n=710)

	Cemiplimab		Chemotherapy	
	Male	Female	Male	Female
	(N=312)	(N=43)	(N=286)	(N=56)
Number of Patients with any TEAE, n (%)	275 (88.1%)	38 (88.4%)	270 (94.4%)	52 (92.9%)
Number of Patients with any Grade 3/4/-5 TEAE, n (%)	116 (37.2%)	16 (37.2%)	133 (46.5%)	33 (58.9%)
Number of Serious TEAEs	148	17	158	19
Number of Patients with any Serious TEAE, n (%)	88 (28.2%)	12 (27.9%)	80 (28.0%)	14 (25.0%)
Fatal	30 (9.6%)	4 (9.3%)	25 (8.7%)	6 (10.7%)
Life-threatening	13 (4.2%)	1 (2.3%)	21 (7.3%)	1 (1.8%)
Hospitalization/prolong existing hospitalization	72 (23.1%)	9 (20.9%)	68 (23.8%)	12 (21.4%)
Disability/incapacity	4 (1.3%)	0	1 (0.3%)	0
Other (medically significant)	2 (0.6%)	0	3 (1.0%)	0
Number of Patients who discontinued study treatment due to TEAE, n (%)	20 (6.4%)	3 (7.0%)	13 (4.5%)	1 (1.8%)
Number of Patients with any treatment-emergent sponsor identified imAE, n (%)	49 (15.7%)	13 (30.2%)	8 (2.8%)	0

Source: 14.3.1.2.13

Race:

Table 65: Distribution of AEs, SAEs according to race group for study 1624 (n=710)

	Cemiplimab		Chemotherapy	
	White	Non-white	White	Non-white
	(N=307)	(N=48)	(N=295)	(N=47)
Number of Patients with any TEAE, n (%)	267 (87.0%)	46 (95.8%)	277 (93.9%)	45 (95.7%)
Number of Patients with any Grade 3/4/5 TEAE, n (%)	107 (34.9%)	25 (52.1%)	136 (46.1%)	30 (63.8%)
Number of Serious TEAEs	138	27	130	47
Number of Patients with any Serious TEAE, n (%)	83 (27.0%)	17 (35.4%)	72 (24.4%)	22 (46.8%)
Fatal	30 (9.8%)	4 (8.3%)	25 (8.5%)	6 (12.8%)
Life-threatening	12 (3.9%)	2 (4.2%)	16 (5.4%)	6 (12.8%)
Hospitalization/prolong existing hospitalization	65 (21.2%)	16 (33.3%)	60 (20.3%)	20 (42.6%)
Disability/incapacity	3 (1.0%)	1 (2.1%)	0	1 (2.1%)
Other (medically significant)	2 (0.7%)	0	1 (0.3%)	2 (4.3%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	19 (6.2%)	4 (8.3%)	11 (3.7%)	3 (6.4%)
Number of Patients with any treatment-emergent sponsor identified imAE, n (%)	51 (16.6%)	11 (22.9%)	7 (2.4%)	1 (2.1%)

Source: 14.3.1.2.14

Region:

Table 66: Distribution of AEs, SAEs according to region group for study 1624 (n=710)

	Cemiplimab			Chemotherapy		
	Europe	Asia	ROW	Europe	Asia	ROW
	(N=274)	(N=39)	(N=42)	(N=268)	(N=37)	(N=37)
Number of Patients with any TEAE, n (%)	237 (86.5%)	37 (94.9%)	39 (92.9%)	252 (94.0%)	37 (100%)	33 (89.2%)
Number of Patients with any Grade 3/4/5 TEAE, n (%)	95 (34.7%)	18 (46.2%)	19 (45.2%)	122 (45.5%)	22 (59.5%)	22 (59.5%)
Number of Serious TEAEs	117	21	27	118	36	23
Number of Patients with any Serious TEAE, n (%)	73 (26.6%)	12 (30.8%)	15 (35.7%)	64 (23.9%)	16 (43.2%)	14 (37.8%)
Fatal	26 (9.5%)	3 (7.7%)	5 (11.9%)	24 (9.0%)	2 (5.4%)	5 (13.5%)
Life-threatening	10 (3.6%)	2 (5.1%)	2 (4.8%)	15 (5.6%)	4 (10.8%)	3 (8.1%)
Hospitalization/prolong existing hospitalization	57 (20.8%)	11 (28.2%)	13 (31.0%)	53 (19.8%)	15 (40.5%)	12 (32.4%)
Disability/incapacity	3 (1.1%)	1 (2.6%)	0	0	0	1 (2.7%)
Other (medically significant)	1 (0.4%)	0	1 (2.4%)	1 (0.4%)	1 (2.7%)	1 (2.7%)
Number of Patients who discontinued study treatment due to TEAE, n (%)	14 (5.1%)	3 (7.7%)	6 (14.3%)	11 (4.1%)	3 (8.1%)	0
Number of Patients with any treatment-emergent sponsor identified imAE, n (%)	49 (17.9%)	8 (20.5%)	5 (11.9%)	6 (2.2%)	1 (2.7%)	1 (2.7%)

Source: 14.3.1.2.15

ECOG PS status:

Table 67: Distribution of AEs, SAEs according to ECOG group for study 1624 (n=710)

	Cemiplimab		Chemotherapy	
	ECOG: 0	ECOG: 1	ECOG: 0	ECOG: 1
	(N=96)	(N=259)	(N=92)	(N=250)
Number of Patients with any TEAE, n (%)	82 (85.4%)	231 (89.2%)	88 (95.7%)	234 (93.6%)
Number of Patients with any Grade 3/4/5 TEAE, n (%)	27 (28.1%)	105 (40.5%)	46 (50.0%)	120 (48.0%)
Number of Serious TEAEs	41	124	60	117
Number of Patients with any Serious TEAE, n (%)	23 (24.0%)	77 (29.7%)	28 (30.4%)	66 (26.4%)
Fatal	8 (8.3%)	26 (10.0%)	8 (8.7%)	23 (9.2%)
Life-threatening	3 (3.1%)	11 (4.2%)	9 (9.8%)	13 (5.2%)
Hospitalization/prolong existing hospitalization	20 (20.8%)	61 (23.6%)	23 (25.0%)	57 (22.8%)
Disability/incapacity	0	4 (1.5%)	0	1 (0.4%)
Other (medically significant)	0	2 (0.8%)	2 (2.2%)	1 (0.4%)

Safety related to drug-drug interactions and other interactions

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

Discontinuation due to adverse events

Table 68: Summary of Treatment-Emergent Adverse Events Resulting in Treatment Discontinuation (At Least 2 Patients in Any Arm) by System Organ Class and Preferred Term in Study 1624 – Safety Population

System Organ Class, n (%) Preferred Term, n (%)	Cemiplimab (N=355)	Chemotherapy (N=342)
Number of patients with any TEAE resulting in treatment discontinuation, n (%)	**23 (6.5)**	**14 (4.1)**
Respiratory, thoracic and mediastinal disorders	**5 (1.4)**	**0**
Pneumonitis	4 (1.1)	0
Nervous system disorders	**4 (1.1)**	**2 (0.6)**
Ischaemic stroke	2 (0.6)	1 (0.3)
Investigations	**3 (0.8)**	**2 (0.6)**
Aspartate aminotransferase increased	2 (0.6)	0
Blood and lymphatic system disorders	**0**	**6 (1.8)**
Anaemia	0	2 (0.6)
Thrombocytopenia	0	3 (0.9)

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event
All AEs were coded using MedDRA Version 20.0.
A patient is counted only once for multiple occurrences within a SOC/PT.
For SOCs, the table is sorted by decreasing frequency in the total group. Within each SOC, PTs are sorted by decreasing frequency in the total group.
Data cutoff as 01 Mar 2020 for all patients in Study 1624.

Table 69: Treatment-Emergent Adverse Events Resulting in Treatment Discontinuation by System Organ Class and Preferred Term (Safety analysis set)

System Organ Class, n (%) Preferred Term, n (%)	Pool 1 All NSCLC Patients (N=355)	Pool 2 All Monotherapy Patients (N=810)	Pool 3 All Patients (N=1078)
Number of Patients with any TEAE resulting in treatment discontinuation, n (%)	23 (6.5%)	64 (7.9%)	81 (7.5%)
Respiratory, thoracic and mediastinal disorders	5 (1.4%)	15 (1.9%)	20 (1.9%)
Pneumonitis	4 (1.1%)	11 (1.4%)	15 (1.4%)
Cough	0	2 (0.2%)	2 (0.2%)
Pleural effusion	0	1 (0.1%)	2 (0.2%)
Pulmonary embolism	1 (0.3%)	1 (0.1%)	1 (<0.1%)
Hepatobiliary disorders	3 (0.8%)	9 (1.1%)	10 (0.9%)
Autoimmune hepatitis	1 (0.3%)	4 (0.5%)	5 (0.5%)
Hepatitis	1 (0.3%)	2 (0.2%)	2 (0.2%)
Immune-mediated hepatitis	1 (0.3%)	2 (0.2%)	2 (0.2%)
Hepatic failure	0	1 (0.1%)	1 (<0.1%)
Infections and infestations	2 (0.6%)	7 (0.9%)	10 (0.9%)
Pneumonia	1 (0.3%)	2 (0.2%)	3 (0.3%)
Bronchitis	0	1 (0.1%)	1 (<0.1%)
Embolic pneumonia	1 (0.3%)	1 (0.1%)	1 (<0.1%)

Data cut-off as of Feb 17, 2020 for Study 1620; Data cut-off as of Mar 1, 2020 for Study 1624. Data cut-off as of Apr 30, 2019 for Study 1423; Data cut-off as of Sep 20, 2018 for Group 1 and Group 3 patients in Study 1540; Data cut-off as of Oct 10, 2018 for Group 2 patients in Study 1540.
TEAE: Treatment-emergent adverse event.
All adverse events were coded using the MedDRA Version 22.1.
A patient is counted only once for multiple occurrences within a system organ class/preferred term.
For SOCs, the table is sorted by decreasing frequency in the total group. Within each SOC, PTs are sorted by decreasing frequency in the total group.

Treatment-Emergent Adverse Events Leading to Dose Delays or Interruptions

In Study 1624, 100 (28.2%) patients who received cemiplimab and 106 (31.0%) patients who received chemotherapy had AEs resulting in delay or interruption of study drug. The most frequently reported AEs resulting in dose delay or interruption of study drug were pneumonia in the cemiplimab arm and myelotoxicity in the chemotherapy arm.

The rates of infections and infestations leading to dose interruption or delay were similar in both treatment arm (7.9% for cemiplimab and 7.6% for chemotherapy). In both treatment arms pneumonia led to dose delay or interruption at a similar frequency (4.2% in cemiplimab-arm vs 4.4% in chemotherapy-arm).

Endocrine disorders leading to dose delay or interruption were more frequent in cemiplimab-arm (2.5%) than in the chemotherapy arm (0%). Of these, hypothyroidism was the most frequent (1.4%). Also, disorders affecting skin and subcutis leading to dose delay or interruption were more frequent in the cemiplimab-treatment (2.5% vs 0%), rash being the most frequent of these.

Dose reductions

As per protocol no dose modifications for cemiplimab were permitted. In the chemotherapy arm, 14.9% of patients had an AE of any grade leading to dose reduction.

Post marketing experience

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

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

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

2.5.1. Discussion on clinical safety

Cemiplimab received a conditional marketing authorisation from EMA in June 2019, for the treatment of locally advanced and metastatic CSCC. Its safety profile had been initially characterised with results from 591 patients recruited in Studies 1423 (advanced solid malignancies, n=372) and 1540 (advanced CSCC, n=219). Considering its anti-PD-1 mechanism of action, the frequency of immune-related ADRs was about 20%, with the most frequent being hypothyroidism (7.1%), pneumonitis (3.7%), cutaneous adverse reactions (2.0%), hyperthyroidism (1.9%) and hepatitis (1.9%). Most events were clinically manageable as well as expectable with this class of immunotherapy.

The MAH has submitted data from the two arms of Study 1624 (N=697) seeking indication of cemiplimab in the first line treatment of advanced NSCLC. As supportive data, the MAH has also provided pooled safety results from cemiplimab monotherapy across 4 studies (Pool 2, N=816). All patients who received at least 1 dose of cemiplimab as monotherapy in Study 1624 (NSCLC, n=355), Study 1423 (advanced solid malignancies, n=130), Study 1540 (CSCC, n=193), and Study 1620 (BCC, n=138) were included in this pool.

Study 1624

As expected from the design of the trial, **exposure** was longer in the cemiplimab arm (median number of doses 9, median duration 27 weeks) as compared to the chemotherapy arm (median number of

cisplatin or carboplatin doses 5, median duration 18 weeks). Conversely, treatment was discontinued in a greater number of patients in the cemiplimab arm (59%) than in the chemotherapy arm (43%). A greater proportion of progressors led to discontinuation in cemiplimab arm (37%) than in chemotherapy arm (25%). These conflicting data are probably related to different lengths of treatment and different durations of responses (median 21.0 months for cemiplimab vs. 6.0 months for chemotherapy in the ITT population), as well as diverse overall safety profiles.

At data cut-off, 39.2% of patients in the cemiplimab-arm were still on cemiplimab-treatment and only 1.7% had completed the treatment reaching the planned 108 weeks. At this point it is not possible to draw conclusions of the safety of cemiplimab in the proposed 2-year long treatment for patients with advanced NSCLC, particularly when considering its immune-activating mechanism of action.

Surprisingly, carboplatin was selected as platinum agent for a higher than expected percentage of patients (80%). Out of the 134 patients with non-squamous NSCLC who received pemetrexed as part of their chemotherapy, 52 (39%) received >6 doses pemetrexed. Assuming that some of these patients only did 4 or 5 platinum cycles before starting pemetrexed maintenance, the proportion would be slightly higher. This compares to clinical practice and published literature.

The elevated number of patients (n=22) who withdrew from the cemiplimab arm because of patient/physician decision was partially substantiated by the MAH. Differences in exposure from the locally advanced and metastatic subpopulations are not major.

As expected, most of the patients from both arms presented **AEs.** The proportion of high-grade (G≥3) AEs was numerically higher in the chemotherapy arm (48%) as compared to the cemiplimab arm (37%). The incidence of SAEs (~28%) and G5 AEs (~9%) was almost identical in both arms. The proportion of patients who discontinued treatment permanently because of an AEs was slightly higher in the cemiplimab arm (6.5%) as compared to the chemotherapy arm (4.1%).

The **profile of AEs** was notably different in the chemotherapy arm vs. the cemiplimab arm. Patients in the chemotherapy arm presented higher incidence and severity of myelotoxicity, alopecia, nausea, constipation, decreased appetite, neuropathy and fatigue. On the contrary, immune-mediated AEs (imAEs) and related endocrine disorders were more prevalent in the cemiplimab arm.

The three most common **G≥3 AEs** in the cemiplimab arm were pneumonia 4.8%, anaemia 3.4%, pulmonary embolism and hyponatraemia (both 2.5%). In the chemotherapy arm, the three most common G≥AEs were anaemia 16.4%, neutropenia 10.2% and thrombocytopenia 8.2%.The incidence of **imAEs** in patients from the cemiplimab arm of Study 1624 (17.5%) was comparable to that of previous studies of cemiplimab and to that seen with other anti-PD-1/anti-PD-1 agents used in clinical practice. The most frequent imAEs were hypothyroidism (5.6%), hyperthyroidism (4.2%), pneumonitis (2.3%), hepatitis (1.7%), rash (1.7%) and colitis (1.1%). About 80% of all imAEs were G1/2 events and were clinically manageable.

The frequency of **infusion-related reactions** (6.5%) was in line with what had been previously reported at the SmPC (9.1%).

SAEs occurred in a similar proportion of patients from the chemotherapy (27.5%) and the cemiplimab (28.2%) arms, although the causality varied according to arm. Pneumonia was the most common SAE and equally prevalent in both arms: 17 cases in each. Other respiratory SAEs were much more frequent in the cemiplimab arm: pneumonitis and pulmonary embolism occurred in 12 patients, as compared to 2 in the chemotherapy arm. On the other hand, myelotoxic effects such as anaemia and febrile neutropenia prevailed in the chemotherapy arm (24 vs. 6 cases).

Deaths: About two thirds of patients from Study 1624 died from progressive or recurrent disease, while the other third died from causes directly or indirectly related to AEs. The proportion of patients

who died from respiratory events is higher in the cemiplimab arm (11 out of 34, 32%) as compared to the chemotherapy arm (6 out of 31, 19%). Conversely, more patients in the chemotherapy arm died from nervous system AEs (12 out of 31, 39%) and cardiac AEs (9 out of 31, 29%). Despite the considerable proportion of patients from the chemotherapy arm who experienced haematological AEs, high-grade AEs and SAEs, none of them died from causes attributable to myelotoxicity. There were six deaths, in which the MAH changed the Investigator´s causality assessment from related to cemiplimab to not related. After careful consideration, a reasonable possibility is that cemiplimab might have contributed to the fatal outcome of at least 4, if not 5 of these cases. The MAH acknowledges that altering the causality deductions carried out by the Investigator by the study sponsor should be avoided, unless there is clear evidence. The MAH has further informed that in the future they will consider this approach for causal assessments.

Haematology, electrolytes, liver function tests and coagulation **laboratory values** do not show unexpected findings. Despite the low reported incidence of immune-related hypothyroidism (5.6%), it is estimated that a considerable amount of patients might experience subclinical hypothyroidism (increased TSH reported in 13.8% and decreased T4 in 8.2% of patients from the cemiplimab arm), thus leading to an underestimation of the real proportion of patients who might need further endocrine assessment.

Regarding the safety performance of cemiplimab in **special populations**, consistent proportions of overall AEs, G≥3 AEs, SAEs and AEs leading to discontinuation is observed across gender, race, region and ECOG PS status. Conversely, the proportion of SAEs and discontinuations in the elderly is slightly higher, which prompts the need for specific disclosure at the SmPC.

A similar proportion of patients from each arm **discontinued treatment because of AEs** (6.5% in the cemiplimab arm vs. 4.1% in the chemotherapy arm), although the causalities differed according to arm. In the cemiplimab arm, 5 patients discontinued because of respiratory AEs, most of them pneumonitis. In the chemotherapy arm, 6 patients discontinued because of haematological toxicity events.

Monotherapy pool (N=816)

Exposure patterns in the monotherapy pool were overall comparable to those in Study 1624: median duration of treatment is 30.5 weeks and median number of doses is 10.5.

Regarding AEs, incidence and severity of the diverse AE categories in the monotherapy pool was also comparable to those from the cemiplimab arm of Study 1624, although AEs that resulted in death were half as prevalent (5.8% vs. 9.6%).

Incidence of imAEs was 22%, the most frequent being hypothyroidism, pneumonitis, hyperthyroidism, colitis, hepatitis and immune-mediated rash. Only 1 death in the entire pool is attributable to an imAE of hepatitis. This pattern is comparable to other anti-PD-1/anti-PD-L1 checkpoint inhibitors used in clinical practice.

SAEs occurred in a similar proportion as in patients from the cemiplimab arm of Study 1624, but the specific incidence of SAEs of infections in the monotherapy pool was higher.

The main cause of treatment discontinuation from an AE was pneumonitis, in 15 patients. Immune-related hepatitis was the second most prevalent cause of discontinuation of cemiplimab in (8 patients).

2.5.2. Conclusions on clinical safety

Overall, the safety performance of cemiplimab in Study 1624 is as expected from an anti-PD-1 checkpoint inhibitor in a population of patients with advanced NSCLC, noting a considerable proportion

of SAEs and G5 AEs from associated respiratory/mediastinal/thoracic entities. Importantly, the incidence, distribution and severity of imAEs compares to previous experience with cemiplimab and other checkpoint inhibitors: most immune-mediated events are of low grade and clinically manageable with corticosteroid treatment.

Although similar proportion of SAEs, G5 AEs and AEs leading to treatment discontinuation were seen in both cemiplimab and chemotherapy arms, it overall seems that cemiplimab is well tolerated and compares favourably in relationship to bothersome chemotherapy-related AEs.

No major safety concerns arise from results in the cemiplimab arm of Study 1624 (N=355) or the monotherapy pool containing it (N=816).

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 2 with this application.

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

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

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

Safety concerns

Table 68: Summary of Safety Concerns

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

Pharmacovigilance plan

Table 69: On-going and Planned Additional Pharmacovigilance Activities

Study **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
R2810-ONC-1540 A Phase 2 Study of REGN2810, A Fully Human	To confirm the clinical efficacy and safety of cemiplimab	• irARs (ir pneumonitis, colitis, hepatitis, endocrinopathies,	Protocol submitted	09/07/2019

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Monoclonal Antibody to Programmed Cell Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Group 6) Ongoing	monotherapy for patients with advanced CSCC (metastatic or unresectable locally advanced) treated with cemiplimab 350 mg Q3W IV.	skin adverse reactions, nephritis, and other irARs) • Infusion related reactions • Long-term safety data • Lack of effect due to ADA	FPFV	31/01/2020
			LPLV	28/02/2022
			Interim report	31/03/2023
R2810-ONC-1540 A Phase 2 Study of REGN2810, A Fully Human Monoclonal Antibody to Programmed Cell Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Group 1, 2 and 3) Ongoing	To estimate the clinical efficacy and safety of cemiplimab monotherapy for patients with advanced CSCC (metastatic or unresectable locally advanced) treated with cemiplimab 350 mg Q3W IV. The study will provide additional safety data up to approximately 3.5 years of safety data for patients in Groups 1 and 2, and approximately 2.5 years of safety data for patients in Group 3.	Long-term safety data	Protocol completion	23/11/2015
			FPFV	07/04/2016
			LPLV	31/10/2021
			Final report	31/10/2022

Risk minimisation measures

Table 70: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Activities	Proposed Pharmacovigilance Activities
Important Identified Risk: Immune-related Adverse Reactions Immune-related adverse reactions **(**immune-related pneumonitis, colitis, hepatitis, endocrinopathies, immune-related skin adverse reactions, nephritis, and other irARs)	Routine risk communication messages: SmPC section 4.4 and 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: See SmPC sections 4.2 and 4.4 See PL section 2 and 3	Routine pharmacovigilance Use of specific follow-up questionnaire for spontaneous postmarketing reports of irARs Additional pharmacovigilance activities:

Safety Concern	Risk Minimisation Activities	Proposed Pharmacovigilance Activities
	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	Study short name and title: R2810-ONC-1540: A Phase 2 Study of REGN2810, A Fully Human Monoclonal Antibody to Programmed Cell Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Group 6)
Important Identified Risk: Infusion-related Reactions	Routine communication messages: SmPC section 4.4 and 4.8 PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC sections 4.2, 4.3, and 4.4. PL sections 2 and 3 Other routine risk minimisation measures beyond the Product Information: Legal status: Cemiplimab is supplied subject to restricted medical prescription and treatment must be initiated and supervised by physicians experienced in the treatment of cancer. Additional risk minimisation measures: Patient Guide and Alert Card	Routine pharmacovigilance Use of specific follow-up questionnaire for spontaneous post-authorisation reports of infusion-related reactions Additional pharmacovigilance activities: Study short name and title: R2810-ONC-1540: A Phase 2 Study of REGN2810, A Fully Human Monoclonal Antibody to Programmed Cell Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Group 6)
Important Potential Risk: Lack of Effect due to Anti-drug Antibodies	Routine communication messages SmPC section 4.8 Other routine risk minimisation measures beyond the Product Information: Legal status: Cemiplimab is subject to restricted medical prescription and treatment must be initiated and supervised by physicians experienced in the treatment of cancer.	Routine pharmacovigilance Additional pharmacovigilance activities: Study short name and title: R2810-ONC-1540: A Phase 2 Study of REGN2810, A Fully Human Monoclonal Antibody to Programmed Cell Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma (Group 6)
Long-Term Safety Data	Not applicable	Routine pharmacovigilance Additional pharmacovigilance activities: Study short name and title: R2810-ONC-1540: A Phase 2 Study of REGN2810, A Fully Human Monoclonal Antibody to Programmed Cell Death-1 (PD-1), in Patients with Advanced Cutaneous

Safety Concern	Risk Minimisation Activities	Proposed Pharmacovigilance Activities
		Squamous Cell Carcinoma (Groups 1, 2, 3 and 6)

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are being updated to reflect the addition of the new therapeutic indication in Non-Small Cell Lung Cancer (NSCLC).

The Package Leaflet has been 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:

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication agreed by the CHMP is:

Libtayo as monotherapy is indicated for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:

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

3.1.2. Available therapies and unmet medical need

The majority of patients diagnosed with NSCLC are unsuitable for curative treatment. Over the past decade, however, substantial progress has been made in the field of immuno-oncology, a treatment approach based on inducing host anti-tumor immune responses that lead to clinical responses. Agents that block the immunosuppressive PD-1/PD-L1 immune checkpoint blockade, have collectively demonstrated clinical activity in numerous solid tumour indications, including NSCLC.

According to the ESMO 2020 guidelines, pembrolizumab is considered a standard first-line option for patients with advanced NSCLC and PD-L1 expression ≥ 50% (22C3 assay) who do not otherwise have contraindications to the use of immunotherapy (such as severe autoimmune disease or organ transplantation), while atezolizumab represents a promising option in these patients, although identified by the TC/IC-based SP142 assay.

An unmet need can be identified in the locally advanced subpopulation of NSCLC as no specific indication involving an immune checkpoint inhibitor in monotherapy exists.

3.1.3. Main clinical study

Study R2810-ONC-1624 (Study 1624) is a phase III, open-label, randomised, multicentre trial designed to compare the efficacy and safety of cemiplimab monotherapy vs. platinum doublet chemotherapy in patients with locally advanced or metastatic NSCLC as first line treatment. In total, 710 patients were randomised, 356 patients to the cemiplimab monotherapy arm and 354 patients to the chemotherapy arm.

The MAH has submitted efficacy and safety results from the second interim analysis of Study 1624, which is considered the primary analysis. Additionally, pooled safety data from studies where cemiplimab was used in monotherapy were provided.

The primary endpoints of Study 1624 were OS and IRC-PFS and the key secondary endpoint was ORR. Other secondary endpoints were DOR and PROs.

3.2. Favourable effects

With a median follow-up of 13 months and after 249 OS events (35% of ITT) up to data cut-off 01 March 2020, results from the second interim analysis of Study 1624 show that the primary OS endpoint was met.

OS showed a statistically significant difference between the two arms in favour of the cemiplimab arm (HR 0.68; 95% CI 0.53, 0.87; p-value 0.0022), with median OS of 22.1 months in the cemiplimab arm and 14.3 in the chemotherapy arm. Subgroup analysis of OS suggest benefit of cemiplimab over chemotherapy across most subgroups. Sensitivity analyses that account for the effect of crossover (RPSFT) and non-proportional hazards (RMST) are concordant with the primary analysis results.

PFS results also favour the cemiplimab arm (median IRC-PFS 6.2 months vs 5.6 months in the chemotherapy arm).

ORR (36% vs. 21% in the cemiplimab and chemotherapy arms, respectively) and median DOR results (21 vs. 6 months in the cemiplimab and chemotherapy arms, respectively) support the benefit observed in OS and IRC-PFS.

3.3. Uncertainties and limitations about favourable effects

Issues with PD-L1 testing were discovered when over half of the planned population had been recruited, creating the need for re-testing of the 235 randomised patients at that point, but not all of them had remaining tissue samples (38%) and not all the re-tested samples proved PD-L1 ≥50% (24%). As a result of this, two subpopulations from the ITT were created (mITT-1 and mITT-2), whose results were consistent with the primary analysis, and hence served as supportive data.

3.4. Unfavourable effects

Most patients from both arms of Study 1624 presented AEs, but the toxicity profile was notably different in the chemotherapy arm vs. the cemiplimab arm. Patients in the chemotherapy arm presented higher incidence and severity of myelotoxicity, alopecia, nausea, constipation, decreased

appetite, neuropathy and fatigue. On the contrary, immune-mediated AEs (imAEs) were more prevalent in the cemiplimab arm.

The proportion of high-grade (G≥3) AEs was numerically higher in the chemotherapy arm (48%) as compared to the cemiplimab arm (37%).

The incidence of SAEs (~28%) and G5 AEs (~9%) was almost identical in both arms. Pneumonia was the most common SAE. The proportion of patients who discontinued treatment permanently because of an AE was slightly higher in the cemiplimab arm (6.5%) as compared to the chemotherapy arm (4.1%).

The incidence of imAEs in patients from the cemiplimab arm of Study 1624 (17.5%) was comparable to that of previous studies of cemiplimab and to that seen with other anti-PD-1/anti-PD-L1 agents used in clinical practice. The most frequent imAEs were hypothyroidism (5.6%), hyperthyroidism (4.2%), pneumonitis (2.3%), hepatitis (1.7%), rash (1.7%) and colitis (1.1%). About 80% of all imAEs were G1/2 events and were clinically manageable.

The reported incidence of immune-related hypothyroidism in the cemiplimab arm (5.6%) might underestimate subclinical hypothyroidism: the proportion of patients with increased TSH is 13.8% and with decreased T4 is 8.2%.

The overall safety performance of cemiplimab in the NSCLC population of Study 1624 (Pool 1, N=355) is comparable to the cemiplimab monotherapy pool (Pool 2, N=816).

3.5. Uncertainties and limitations about unfavourable effects

Not applicable

3.6. Effects Table

Table 71: **Effects Table for cemiplimab monotherapy vs. platinum doublet chemotherapy in the first line treatment of adult patients with locally advanced and metastatic non-small cell lung cancer (NSCLC) and PD-L1 expression ≥50%, data cut-off 01-MAR-2020**

Effect	Unit	Cemiplimab monotherapy (experimental) n=356	Platinum doublet chemotherapy (control) n=354	Uncertainties / Strength of evidence
Favourable Effects				
*OS ITT	Months	22.1	14.3	HR 0.676 (95% CI 0.525, 0.870) p=0.0022
*IRC-PFS ITT	Months	6.2	5.6	HR 0.59 (95% CI 0.49, 0.72) p<0.0001
§ORR ITT	%	36.5	20.6	Odds ratio 2.214 p<0.0001
Unfavourable Effects				
AEs	%	88.2	94.2	
G≥3 AEs	%	37.2	48.5	
SAEs	%	28.2	27.5	
imAEs	%	17.5	-	
AEs leading to permanent treatment discontinuation	%	6.5	4.1	
G5 AEs	% (n)	9.6 (34)	9.1 (31)	

* Primary endpoint
§ Key secondary endpoint

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

According to the CHMP Guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev.5), convincingly demonstrated favourable effects on survival are, from both a clinical and methodological perspective, the most persuasive outcome of a clinical trial. At its second interim analysis, Study 1624 met its primary OS endpoint, showing superiority of cemiplimab vs. chemotherapy in the treatment of patients with advanced NSCLC, no targetable genetic aberrations and PD-L1 expression ≥ 50%. The PFS data from Study 1624 could be considered to favour cemiplimab over chemotherapy upon a modest advantage.

Regarding safety, cemiplimab exhibited an acceptable toxicity profile, as expected from an anti-PD-1 checkpoint inhibitor. The incidence and severity of imAEs was within reasonable ranges, with comparable results between the cemiplimab arm from both Study 1624 and the cemiplimab monotherapy pool.

3.7.2. Balance of benefits and risks

In terms of OS and IRC-PFS, cemiplimab showed an efficacy advantage as compared to chemotherapy in the treatment of patients with locally advanced and metastatic NSCLC with high-expression of PD-L1 and not targetable genetic aberrations. This benefit is consistent across most sensitivity analyses and most of the analysed subgroups. The toxicity profile of cemiplimab is acceptable and compares favourably to chemotherapy.

3.7.3. Additional considerations on the benefit-risk balance

Issues on PD-L1 testing along conduct of the study led to the definition of a modified ITT population (mITT-1) that only contained patients for which high PD-L1 status had been confirmed. OS and PFS-IRC results from this population evidence a slightly higher degree of benefit from the cemiplimab arm, but their analysis was not predefined in the SAP. Subsequently, and in respect of the ITT principle, these data are only considered supportive evidence.

3.8. Conclusions

The overall B/R of Libtayo is positive.

4. Recommendations

Outcome

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

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition	Type II	I and IIIB

	of a new therapeutic indication or modification of an approved one		

Extension of indication for LIBTAYO as monotherapy indicated for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) expressing PD-L1 (in ≥ 50% tumour cells), with no EGFR, ALK or ROS1 aberrations based on the results of study R2810-ONC-1624 comparing cemiplimab monotherapy to platinum doublet chemotherapy. The PL is revised accordingly. RMP version 2.0 has been agreed.

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

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.