Clinical trial results:
A Randomized, Open-Label Study of Combinations of Standard and High Dose REGN2810 (Cemiplimab; Anti-PD-1 Antibody) and Ipilimumab (Anti CTLA-4 Antibody) in the Second-Line Treatment of Patients with Advanced Non-Small Cell Lung Cancer

Summary

EudraCT number	2017-003684-35
Trial protocol	DE BE GB FR PL ES
Global end of trial date	27 October 2021

Results information

Result version number	v1 (current)
This version publication date	26 October 2022
First version publication date	26 October 2022

Trial information

Trial identification

Sponsor protocol code	R2810-ONC-1763

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03430063
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Road, Tarrytown, United States, 10591
Public contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., 001 844-734-6643, clinicaltrials@regeneron.com
Scientific contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., 001 844-734-6643, clinicaltrials@regeneron.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 October 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to compare the objective response rate (ORR) of high dose cemiplimab and standard dose cemiplimab plus ipilimumab combination therapy to the ORR of standard dose cemiplimab in the second-line treatment of subjects with advanced squamous or non-squamous non-small cell lung cancer (NSCLC), in subjects whose tumors express programmed cell death ligand 1 (PD-L1) in <50% of tumor cells.

Protection of trial subjects:

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 May 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Korea, Republic of: 10
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	28
EEA total number of subjects	10

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	10
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Due to early enrollment cessation, only 28 participants were randomized and 27 participants received study treatment in this study. One participant was randomized but not treated.

Pre-assignment

Screening details:

Of the 27 participants treated, four participants completed the study. The most common reason for study discontinuation was death (8 participants) followed by withdrawal of consent (6 participants), and progressive disease (4 participants).

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cemiplimab 350 mg Q3W

Arm description:

Participants received 350 mg of cemiplimab IV infusion on Day 1 of Q3W for up to 108 weeks or until progression of disease or unacceptable toxicity, withdrawal of consent, death, initiation of another anti-cancer treatment.

Arm type	Experimental
Investigational medicinal product name	cemiplimab
Investigational medicinal product code	REGN2810
Other name	LIBTAYO®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cemiplimab 350 mg Q3W for 108 weeks as an intravenous (IV) infusion

Arm title	Cemiplimab 350 mg Q3W + Ipilimumab 50 mg Q6W

Arm description:

Participants received 350 mg of cemiplimab IV infusion on Day 1 of Q3W for up to 108 weeks followed by ipilimumab 50 mg flat dose administered IV on Day 1 of every other treatment cycle (every 42 days or every 6 weeks [Q6W]) for up to 4 doses or until progression of disease or unacceptable toxicity, withdrawal of consent, death, initiation of another anti-cancer treatment

Arm type	Experimental
Investigational medicinal product name	ipilimumab
Investigational medicinal product code	
Other name	YERVOY®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab 50 mg Q6W for up to 4 doses as an IV infusion

Investigational medicinal product name	cemiplimab
Investigational medicinal product code	REGN2810
Other name	LIBTAYO®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cemiplimab 350 mg Q3W for 108 weeks as an intravenous (IV) infusion

Arm title	Cemiplimab 1050 mg Q3W

Arm description:

Participants received 1050 mg of cemiplimab IV infusion on Day 1 of Q3W for up to 108 weeks or until progression of disease or unacceptable toxicity, withdrawal of consent, death, initiation of another anti-cancer treatment.

Arm type	Experimental
Investigational medicinal product name	cemiplimab
Investigational medicinal product code	REGN2810
Other name	LIBTAYO®
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cemiplimab 1050 mg Q3W for 108 weeks as an IV infusion

Number of subjects in period 1[1]	Cemiplimab 350 mg Q3W	Cemiplimab 350 mg Q3W + Ipilimumab 50 mg Q6W	Cemiplimab 1050 mg Q3W
Started	8	11	8
Completed	0	3	1
Not completed	8	8	7
Adverse event, serious fatal	3	2	3
Consent withdrawn by subject	3	1	2
Adverse event, non-fatal	-	1	-
Un-specified	1	1	-
Withdrawal by Subject	-	-	1
Progressive disease	1	2	1
Lost to follow-up	-	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 28 participants were enrolled and randomized, out of which 27 participants received study treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Cemiplimab 350 mg Q3W
Reporting group description:	
Participants received 350 mg of cemiplimab IV infusion on Day 1 of Q3W for up to 108 weeks or until progression of disease or unacceptable toxicity, withdrawal of consent, death, initiation of another anti-cancer treatment.	
Reporting group title	Cemiplimab 350 mg Q3W + Ipilimumab 50 mg Q6W
Reporting group description:	
Participants received 350 mg of cemiplimab IV infusion on Day 1 of Q3W for up to 108 weeks followed by ipilimumab 50 mg flat dose administered IV on Day 1 of every other treatment cycle (every 42 days or every 6 weeks [Q6W]) for up to 4 doses or until progression of disease or unacceptable toxicity, withdrawal of consent, death, initiation of another anti-cancer treatment	
Reporting group title	Cemiplimab 1050 mg Q3W
Reporting group description:	
Participants received 1050 mg of cemiplimab IV infusion on Day 1 of Q3W for up to 108 weeks or until progression of disease or unacceptable toxicity, withdrawal of consent, death, initiation of another anti-cancer treatment.	

Reporting group values	Cemiplimab 350 mg Q3W	Cemiplimab 350 mg Q3W + Ipilimumab 50 mg Q6W	Cemiplimab 1050 mg Q3W
Number of subjects	8	11	8
Age categorical Units: Participants			
Age continuous Units: years			
arithmetic mean	62.4	68.5	68.1
standard deviation	± 7.91	± 8.72	± 12.08
Gender categorical Units: Participants			
Female	2	4	1
Male	6	7	7
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	6	7	6
Unknown or Not Reported	2	4	2
Race Units: Subjects			
Asian	6	3	3
White	0	5	3
Unknown or Not Reported	2	3	2

Reporting group values	Total		
Number of subjects	27		
Age categorical Units: Participants			

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Participants			
Female	7		
Male	20		
Ethnicity Units: Subjects			
Hispanic or Latino	0		
Not Hispanic or Latino	19		
Unknown or Not Reported	8		
Race Units: Subjects			
Asian	12		
White	8		
Unknown or Not Reported	7		

End points

End points reporting groups

Reporting group title	Cemiplimab 350 mg Q3W
Reporting group description:	
Participants received 350 mg of cemiplimab IV infusion on Day 1 of Q3W for up to 108 weeks or until progression of disease or unacceptable toxicity, withdrawal of consent, death, initiation of another anti-cancer treatment.	
Reporting group title	Cemiplimab 350 mg Q3W + Ipilimumab 50 mg Q6W
Reporting group description:	
Participants received 350 mg of cemiplimab IV infusion on Day 1 of Q3W for up to 108 weeks followed by ipilimumab 50 mg flat dose administered IV on Day 1 of every other treatment cycle (every 42 days or every 6 weeks [Q6W]) for up to 4 doses or until progression of disease or unacceptable toxicity, withdrawal of consent, death, initiation of another anti-cancer treatment	
Reporting group title	Cemiplimab 1050 mg Q3W
Reporting group description:	
Participants received 1050 mg of cemiplimab IV infusion on Day 1 of Q3W for up to 108 weeks or until progression of disease or unacceptable toxicity, withdrawal of consent, death, initiation of another anti-cancer treatment.	

Primary: Objective Response Rate (ORR) in Participants whose Tumors Express Programmed Cell Death Ligand 1 (PD-L1) in <50% of Tumor Cells

End point title	Objective Response Rate (ORR) in Participants whose Tumors Express Programmed Cell Death Ligand 1 (PD-L1) in <50% of Tumor Cells[1]
End point description:	
ORR was defined as the number of participants with a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the number of participants in the efficacy analysis set. BOR was defined as the best response recorded, as determined by a blinded Independent Review Committee (IRC) based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) between the date of randomization and the date of the first objectively documented progression or date of subsequent anti-cancer therapy, whichever came first. CR was defined as disappearance of all target lesions (Any pathological lymph nodes [whether target or non-target] must have reduction in short axis to <10 mm [<1 cm]). PR was defined as having at least a 30% decrease in sum of diameters of target lesions, taking as reference the baseline sum diameters. Safety analysis set (SAF): all randomized participants who received any study drug; it is based on the treatment received (as treated).	
End point type	Primary
End point timeframe:	
From date of randomization up to 41 months	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical and comparison analysis were performed for this endpoint.	

End point values	Cemiplimab 350 mg Q3W	Cemiplimab 350 mg Q3W + Ipilimumab 50 mg Q6W	Cemiplimab 1050 mg Q3W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	11	8	
Units: Percentage of participants				
number (confidence interval 95%)	0 (0.0 to 36.9)	45.5 (16.7 to 76.6)	0 (0.0 to 36.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate

End point title	Overall Response Rate

End point description:

Overall Response Rate was defined as the number of participants with a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the number of participants in the efficacy analysis set. BOR was defined as the best response recorded, as determined by a blinded Independent Review Committee (IRC) RECIST 1.1 between the date of randomization and the date of the first objectively documented progression or the date of subsequent anti-cancer therapy, whichever came first. CR was defined as the disappearance of all target lesions (Any pathological lymph nodes [whether target or non-target] must have reduction in short axis to <10 mm [<1 cm]). PR was defined as having at least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. SAF included all randomized subjects who received any study drug; it is based on the treatment received (as treated).

End point type	Secondary

End point timeframe:

From date of randomization up to 41 months

End point values	Cemiplimab 350 mg Q3W	Cemiplimab 350 mg Q3W + Ipilimumab 50 mg Q6W	Cemiplimab 1050 mg Q3W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	11	8	
Units: Percentage of participants				
number (not applicable)				
Complete Response	0	0	0	
Partial Response	0	45.5	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in Participants with Tumor PD-L1 Expression Levels <50% of Tumor Cells

End point title	Overall Survival (OS) in Participants with Tumor PD-L1 Expression Levels <50% of Tumor Cells

End point description:

OS was defined as the time from randomization to the date of death due to any cause. A participant who lost to follow-up was censored at the last date that the participant was known to be alive. OS was measured using Kaplan-Meier method. SAF included all randomized participants who received any study

drug; it is based on the treatment received (as treated). Here, 99999 indicates data could not be estimated due to higher number (> 50%) of censored participants.

End point type	Secondary

End point timeframe:

Time from randomization to the date of death (up to 41 months)

End point values	Cemiplimab 350 mg Q3W	Cemiplimab 350 mg Q3W + Ipilimumab 50 mg Q6W	Cemiplimab 1050 mg Q3W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	11	8	
Units: Months				
median (confidence interval 95%)	5.1 (1.7 to 99999)	99999 (2.2 to 99999)	8.4 (1.4 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) in Participants With Tumor PD-L1 Expression Levels <50% of Tumor Cells

End point title	Progression Free Survival (PFS) in Participants With Tumor PD-L1 Expression Levels <50% of Tumor Cells

End point description:

PFS was defined as the time from randomization to the date of the first documented tumor progression, as determined by the IRC (based on RECIST 1.1 assessments) or death due to any cause, whichever occurred earlier. PFS was measured using Kaplan-Meier method. SAF included all randomized participants who received any study drug; it is based on the treatment received (as treated). Here, 99999 indicates that upper limit of 95% CI was not estimable due to low number of events.

End point type	Secondary

End point timeframe:

Time from randomization up to the date of the first documented tumor progression or death (up to 41 months)

End point values	Cemiplimab 350 mg Q3W	Cemiplimab 350 mg Q3W + Ipilimumab 50 mg Q6W	Cemiplimab 1050 mg Q3W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	11	8	
Units: Months				
median (confidence interval 95%)	2.0 (0.7 to 8.3)	20.8 (1.2 to 99999)	1.8 (1.1 to 2.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment Emergent Adverse Events (TEAEs), Serious TEAEs, and TEAEs Resulting in Death

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAEs), Serious TEAEs, and TEAEs Resulting in Death

End point description:

Adverse event (AE): any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug. Serious AE: an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. TEAE: AE with onset after start of treatment or with onset date before the treatment start date but worsening after the treatment start date. TEAEs included both serious and non-serious TEAEs. Number of participants with TEAEs, Serious TEAEs and TEAEs leading to death were reported. SAF included all randomized participants who received any study drug; it is based on the treatment received (as treated).

End point type	Secondary

End point timeframe:

Up to 41 months

End point values	Cemiplimab 350 mg Q3W	Cemiplimab 350 mg Q3W + Ipilimumab 50 mg Q6W	Cemiplimab 1050 mg Q3W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	11	8	
Units: Count of participants				
Participants with any TEAE	7	11	8	
Participants with any serious TEAE	1	7	4	
Participants with any TEAE resulting in death	0	2	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Laboratory Test Abnormalities of Grade 2 or Higher Severity Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grading System

End point title	Number of Participants With Laboratory Test Abnormalities of Grade 2 or Higher Severity Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grading System

End point description:

The laboratory measurements included hematology, chemistry, electrolytes and liver function. NCI-CTCAE was graded according to the following scale: Grade 1 (Mild): Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; Grade 2 (Moderate): Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL); Grade 3 (Severe): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL; Grade 4 (Life–threatening): Life-threatening consequences; urgent intervention indicated; Grade 5

(Death): Death related to AE. Safety Analysis Set included all randomized subjects who received any study drug; it is based on the treatment received (as treated). SAF included all randomized participants who received any study drug; it is based on the treatment received (as treated).

End point type	Secondary

End point timeframe:

Up to 41 months

End point values	Cemiplimab 350 mg Q3W	Cemiplimab 350 mg Q3W + Ipilimumab 50 mg Q6W	Cemiplimab 1050 mg Q3W	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	11	8	
Units: Count of participants				
Hematology	2	3	5	
Electrolytes	3	3	1	
Liver Function	2	3	1	
Chemistry	1	1	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dose up to 41 months	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	Cemiplimab 350 mg Q3W
Reporting group description: Participants received 350 mg of cemiplimab IV infusion on Day 1 of Q3W for up to 108 weeks or until progression of disease or unacceptable toxicity, withdrawal of consent, death, initiation of another anti-cancer treatment.	
Reporting group title	Cemiplimab 1050 mg Q3W
Reporting group description: Participants received 1050 mg of cemiplimab IV infusion on Day 1 of Q3W for up to 108 weeks or until progression of disease or unacceptable toxicity, withdrawal of consent, death, initiation of another anti-cancer treatment.	
Reporting group title	Cemiplimab 350 mg Q3W + Ipilimumab 50 mg Q6W
Reporting group description: Participants received 350 mg of cemiplimab IV infusion on Day 1 of Q3W for up to 108 weeks followed by ipilimumab 50 mg flat dose administered IV on Day 1 of every other treatment cycle (every 42 days or every 6 weeks [Q6W]) for up to 4 doses or until progression of disease or unacceptable toxicity, withdrawal of consent, death, initiation of another anti-cancer treatment.	

Serious adverse events	Cemiplimab 350 mg Q3W	Cemiplimab 1050 mg Q3W	Cemiplimab 350 mg Q3W + Ipilimumab 50 mg Q6W
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	4 / 8 (50.00%)	7 / 11 (63.64%)
number of deaths (all causes)	3	4	3
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vascular disorders			
Cyanosis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain stem embolism			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradypnoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	3 / 11 (27.27%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperkalaemia			

subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cemiplimab 350 mg Q3W	Cemiplimab 1050 mg Q3W	Cemiplimab 350 mg Q3W + Ipilimumab 50 mg Q6W
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)	8 / 8 (100.00%)	11 / 11 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin cancer			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Vascular disorders			
Lymphoedema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	3 / 11 (27.27%)
occurrences (all)	0	0	5
Asthenia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 8 (0.00%)	2 / 11 (18.18%)
occurrences (all)	2	0	5
Non-cardiac chest pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 11 (9.09%)
occurrences (all)	0	1	2
Infusion site extravasation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	0 / 11 (0.00%)
occurrences (all)	1	2	0
Pain			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Oedema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Contrast media reaction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Pruritus genital			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Pelvic pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 8 (25.00%)	2 / 8 (25.00%)	3 / 11 (27.27%)
occurrences (all)	2	2	4
Haemoptysis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
Productive cough			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	2 / 11 (18.18%)
occurrences (all)	0	1	2
Dysphonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Epistaxis			

subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Wheezing			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Respiratory failure			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	0 / 11 (0.00%)
occurrences (all)	1	5	0
Pulmonary embolism			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	2 / 11 (18.18%)
occurrences (all)	1	0	2
Nervousness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	3
Anxiety			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	2 / 11 (18.18%)
occurrences (all)	0	1	2
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Blood lactate dehydrogenase increased			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Blood lactic acid increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	1 / 11 (9.09%)
occurrences (all)	1	1	1
Blood urea increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	0 / 8 (0.00%)	2 / 8 (25.00%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Lipase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Transaminases increased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Platelet count decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			

Arthropod bite			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Limb injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Infusion related reaction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Head injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Headache			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	2 / 11 (18.18%)
occurrences (all)	1	0	4
Presyncope			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Dysgeusia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Dysarthria			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	1
Cauda equina syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Neuropathy peripheral			

subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 8 (25.00%)	1 / 11 (9.09%)
occurrences (all)	1	2	1
Pancytopenia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Leukocytosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 8 (0.00%)	2 / 8 (25.00%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Ear pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Vestibular disorder			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Eye disorders			
Cataract			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Eyelid ptosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Vision blurred			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 8 (25.00%)	1 / 8 (12.50%)	3 / 11 (27.27%)
occurrences (all)	2	1	3
Constipation			
subjects affected / exposed	3 / 8 (37.50%)	1 / 8 (12.50%)	2 / 11 (18.18%)
occurrences (all)	3	1	5
Vomiting			
subjects affected / exposed	3 / 8 (37.50%)	0 / 8 (0.00%)	2 / 11 (18.18%)
occurrences (all)	3	0	2
Nausea			
subjects affected / exposed	2 / 8 (25.00%)	1 / 8 (12.50%)	2 / 11 (18.18%)
occurrences (all)	2	1	2
Dry mouth			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Dysphagia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Haemorrhoids			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Oral lichen planus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0
Oral lichenoid reaction			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2

Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	3 / 11 (27.27%)
occurrences (all)	2	1	3
Pruritus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
Dry skin			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Eczema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Hyperhidrosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Lichen planus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Urticaria			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Umbilical erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Skin odour abnormal			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	3 / 11 (27.27%)
occurrences (all)	0	0	3
Hyperthyroidism			
subjects affected / exposed	0 / 8 (0.00%)	2 / 8 (25.00%)	2 / 11 (18.18%)
occurrences (all)	0	2	2
Hypophysitis			

subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	3 / 11 (27.27%)
occurrences (all)	2	0	3
Bone pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	2 / 11 (18.18%)
occurrences (all)	0	0	2
Back pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 8 (12.50%)	3 / 11 (27.27%)
occurrences (all)	1	1	3
Musculoskeletal pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	2 / 11 (18.18%)
occurrences (all)	1	0	2
Myalgia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Flank pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Arthritis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Fasciitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			

Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	3 / 11 (27.27%)
occurrences (all)	0	0	3
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Conjunctivitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	2
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Cellulitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hyperphosphataemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 8 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Decreased appetite			
subjects affected / exposed	4 / 8 (50.00%)	3 / 8 (37.50%)	3 / 11 (27.27%)
occurrences (all)	4	4	6
Hypercalcaemia			

subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Hypomagnesaemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Hyponatraemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 8 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Tumour lysis syndrome			
subjects affected / exposed	0 / 8 (0.00%)	1 / 8 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 May 2018	• Changed the study population enrollment criteria from NSCLC patients with PD-L1 expression in <50% of tumor cells to include those with PD-L1 expression in ≥50% of tumor cells. • Updated the planned patient enrollment number from approximately 201 to approximately 252. • Specified that serum samples collected for cemiplimab ADA assessment may be used for evaluation of ipilimumab ADA, if in the future it becomes necessary to evaluate ipilimumab ADA. • Added inclusion of NSCLC patients with stage IIIc disease • Removed from Inclusion Criteria patients with 'anticipated life expectancy of at least 3 months' • Modified exclusion criteria to be defined as occurring 'prior to randomization' rather than 'prior to informed consent,' 'prior to enrollment,' or prior to study entry.' • Added an exclusion criterion to prohibit enrollment of patients with 'prior treatment with an anti-CTLA-4 antibody or anti-PD1/PDL1 for advanced disease.' • Specified that patients who continue treatment beyond the initial determination of progressive disease would be required to re-consent using a separate ICF • Changed and updated stratification of patients at randomization by PD-L1 expression in tumor cells from '<1% versus 1% to <50%' to '<1% versus 1% to 49% versus ≥50%'. • Revised sampling times for PK and ADA analyses • Changed the definition of acute infusion reactions window from 'within 2 hours after the infusion' to 'within 1 day after the infusion' • Changed adverse events reporting requirement window from 'within 105 days after the last study treatment' to 'within 90 days after the last study treatment' • Added text specifying the primary endpoint applies to patients whose tumors express PD-L1 in <50% of tumor cells • Added a secondary objective to compare the ORR in patients with PD-L1 in ≥50% of tumor cells and in all patients and a corresponding secondary endpoint to evaluate ORR in all patients • Revised, added, or removed text, including redundant text, for clarity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

All participants' tumors had PD-L1 expression levels of <50% at baseline. Therefore, the results do not present efficacy for participants with PD-L1 expression levels of ≥50% of tumor cells versus all participants.

Notes: