Clinical trial results:
A Randomized, Phase 3, Open-Label Study of Combinations of REGN2810 (Cemiplimab, Anti-PD-1 Antibody), Platinum based Doublet Chemotherapy, and Ipilimumab (Anti-CTLA-4 Antibody) Versus Pembrolizumab Monotherapy in First-Line Treatment of Patients With Advanced or Metastatic Non-Small Cell Lung Cancer With Tumors Expressing PD-L1 50%

Summary

EudraCT number	2017-001041-27
Trial protocol	NL LT GB AT IT
Global end of trial date	29 July 2021

Results information

Result version number	v1 (current)
This version publication date	12 August 2022
First version publication date	12 August 2022

Trial information

Trial identification

Sponsor protocol code	R2810-ONC-16111

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03515629
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Road, Tarrytown, NY, 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	02 August 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 July 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to compare the progression-free survival (PFS) of cemiplimab plus ipilimumab combination therapy (hereinafter referred to as cemiplimab/ipi) and cemiplimab plus 2 cycles only of platinum-based doublet chemotherapy plus ipilimumab combination therapy (hereinafter referred to as "cemiplimab/chemo/ipi") with standard-of-care pembrolizumab monotherapy in the first line treatment of patients with advanced squamous or non-squamous non-small cell lung cancer (NSCLC) whose tumors express programmed 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 ICH guidelines for GCP and applicable regulatory requirements.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	02 July 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	Italy: 1
Country: Number of subjects enrolled	Lithuania: 1
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	5
EEA total number of subjects	2

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)	4
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 3 centers that randomized 5 participants in the United States, Lithuania, and Italy.

Pre-assignment

Screening details:

Due to program de-prioritization, the sponsor decided to cease enrollment at which time only 5 participants were randomized to 2 of 3 treatment arms (i.e. no participants were randomized to receive pembrolizumab).

Period 1

Period 1 title	Overall Study (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 + ipilimumab 50 mg Q6W

Arm description:

Cemiplimab was administered at 350 mg as an intravenous (IV) infusion every 3 weeks (Q3W) for 108 weeks in combination with ipilimumab administered IV over approximately 90 minutes at 50 mg Q6W for up to 4 doses.

Arm type	Experimental
Investigational medicinal product name	ipilimumab
Investigational medicinal product code	
Other name	Yervoy
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV ipilimumab 50 mg Q6W

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:

IV cemiplimab 350 mg Q3W

Arm title	Cemiplimab 350 mg Q3W + chemotherapy + ipilimumab 50 mg Q6W

Arm description:

Cemiplimab was administered at 350 mg as an IV infusion Q3W for 108 weeks in combination with platinum-based doublet chemotherapy administered IV Q3W for 2 cycles and with ipilimumab administered IV over approximately 90 minutes at 50 mg Q6W for up to 4 doses.

Arm type	Experimental
Investigational medicinal product name	carboplatin
Investigational medicinal product code	
Other name	Platinum-based doublet chemotherapy
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details: IV carboplatin 10 mg/mL	
Investigational medicinal product name	paclitaxel
Investigational medicinal product code	
Other name	Platinum-based doublet chemotherapy
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: IV paclitaxel	
Investigational medicinal product name	pemetrexed
Investigational medicinal product code	
Other name	Platinum-based doublet chemotherapy
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: IV pemetrexed 1 mg/mL	
Investigational medicinal product name	cisplatin
Investigational medicinal product code	
Other name	Platinum-based doublet chemotherapy
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: IV cisplatin 1 mg/mL	

Number of subjects in period 1	Cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W	Cemiplimab 350 mg Q3W + chemotherapy + ipilimumab 50 mg Q6W
Started	3	2
Completed	1	1
Not completed	2	1
Adverse event, serious fatal	1	1
Progressive disease	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W
Reporting group description:	
Cemiplimab was administered at 350 mg as an intravenous (IV) infusion every 3 weeks (Q3W) for 108 weeks in combination with ipilimumab administered IV over approximately 90 minutes at 50 mg Q6W for up to 4 doses.	
Reporting group title	Cemiplimab 350 mg Q3W + chemotherapy + ipilimumab 50 mg Q6W
Reporting group description:	
Cemiplimab was administered at 350 mg as an IV infusion Q3W for 108 weeks in combination with platinum-based doublet chemotherapy administered IV Q3W for 2 cycles and with ipilimumab administered IV over approximately 90 minutes at 50 mg Q6W for up to 4 doses.	

Reporting group values	Cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W	Cemiplimab 350 mg Q3W + chemotherapy + ipilimumab 50 mg Q6W	Total
Number of subjects	3	2	5
Age categorical Units: Subjects			
Adults (18-64 years)	2	2	4
From 65-84 years	1	0	1
Age Continuous Units: Years			
arithmetic mean	61.7	56.5	
standard deviation	± 9.29	± 4.95	-
Sex: Female, Male Units: Participants			
Female	3	0	3
Male	0	2	2
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	3	2	5
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	3	2	5
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W

Reporting group description:

Cemiplimab was administered at 350 mg as an intravenous (IV) infusion every 3 weeks (Q3W) for 108 weeks in combination with ipilimumab administered IV over approximately 90 minutes at 50 mg Q6W for up to 4 doses.

Reporting group title	Cemiplimab 350 mg Q3W + chemotherapy + ipilimumab 50 mg Q6W

Reporting group description:

Cemiplimab was administered at 350 mg as an IV infusion Q3W for 108 weeks in combination with platinum-based doublet chemotherapy administered IV Q3W for 2 cycles and with ipilimumab administered IV over approximately 90 minutes at 50 mg Q6W for up to 4 doses.

Primary: Progression-Free Survival (PFS) as assessed by a blinded Independent Review Committee (IRC) based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) assessments

End point title	Progression-Free Survival (PFS) as assessed by a blinded Independent Review Committee (IRC) based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) assessments[1]

End point description:

Per protocol, the final analysis of PFS was to be performed after observing 142 PFS events in the pembrolizumab treatment arm. PFS was not assessed due to insufficient data collected.

End point type	Primary

End point timeframe:

Up to 32 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: Due to ceasing enrollment early, no participants were randomized to receive pembrolizumab.

End point values	Cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W	Cemiplimab 350 mg Q3W + chemotherapy + ipilimumab 50 mg Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[2] - PFS was not assessed due to insufficient data collected.

[3] - PFS was not assessed due to insufficient data collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Per protocol, if the final analysis of PFS was statistically significant for both cemiplimab combination therapy versus pembrolizumab treatment, the analysis of OS for cemiplimab combinations-versus-pembrolizumab comparison was to be performed at the time of PFS analysis, 12 months, and 18 months after analysis of PFS using the same method as used in the analysis of PFS; however, OS was not assessed due to insufficient data collected.

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W	Cemiplimab 350 mg Q3W + chemotherapy + ipilimumab 50 mg Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[4] - OS was not assessed due to insufficient data collected.

[5] - OS was not assessed due to insufficient data collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

Per protocol, the ORR for each cemiplimab combination-versus-pembrolizumab comparison was to be analyzed using the Cochran-Mantel-Haenszel test stratified by histological status (non-squamous versus squamous).

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W	Cemiplimab 350 mg Q3W + chemotherapy + ipilimumab 50 mg Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: Not Applicable				
number (not applicable)				

Notes:

[6] - OS was not assessed due to insufficient data collected.

[7] - OS was not assessed due to insufficient data collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Treatment-Emergent Adverse Events (TEAEs)

End point description:

Safety analysis set (SAF), defined as all enrolled participants who received any amount of study treatment.

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W	Cemiplimab 350 mg Q3W + chemotherapy + ipilimumab 50 mg Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	2		
Units: Events	68	91		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Dose-Limiting Toxicities (DLTs)

End point title	Number of Participants with Dose-Limiting Toxicities (DLTs)

End point description:

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W	Cemiplimab 350 mg Q3W + chemotherapy + ipilimumab 50 mg Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	2		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Any Serious TEAEs

End point title	Number of Participants with Any Serious TEAEs

End point description:

Safety analysis set (SAF), defined as all enrolled participants who received any amount of study treatment.

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W	Cemiplimab 350 mg Q3W + chemotherapy + ipilimumab 50 mg Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	2		
Units: Participants	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Deaths

End point title	Number of Deaths

End point description:

Safety analysis set (SAF), defined as all enrolled participants who received any amount of study treatment.

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W	Cemiplimab 350 mg Q3W + chemotherapy + ipilimumab 50 mg Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	2		
Units: Participants	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Laboratory Abnormalities

End point title	Number of Participants with Laboratory Abnormalities

End point description:

Safety analysis set (SAF), defined as all enrolled participants who received any amount of study treatment.

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W	Cemiplimab 350 mg Q3W + chemotherapy + ipilimumab 50 mg Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	2		
Units: Participants	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) at 12 months

End point title	Overall Survival (OS) at 12 months

End point description:

Per protocol, if the final analysis of PFS was statistically significant for both cemiplimab combination therapy versus pembrolizumab treatment, the analysis of OS for cemiplimab combinations-versus-pembrolizumab comparison was to be performed at the time of PFS analysis, 12 months, and 18 months after analysis of PFS using the same method as used in the analysis of PFS.

End point type	Secondary

End point timeframe:

At 12 months

End point values	Cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W	Cemiplimab 350 mg Q3W + chemotherapy + ipilimumab 50 mg Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: Not Applicable				
number (not applicable)				

Notes:

[8] - OS was not assessed due to insufficient data collected.

[9] - OS was not assessed due to insufficient data collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) at 18 months

End point title	Overall Survival (OS) at 18 months

End point description:

Per protocol, if the final analysis of PFS was statistically significant for both cemiplimab combination therapy versus pembrolizumab treatment, the analysis of OS for cemiplimab combinations-versus-pembrolizumab comparison was to be performed at the time of PFS analysis, 12 months, and 18 months after analysis of PFS using the same method as used in the analysis of PFS.

End point type	Secondary

End point timeframe:

At 18 months

End point values	Cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W	Cemiplimab 350 mg Q3W + chemotherapy + ipilimumab 50 mg Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: Not Applicable				
number (not applicable)				

Notes:

[10] - OS was not assessed due to insufficient data collected.

[11] - OS was not assessed due to insufficient data collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life (Core 30 Questionnaire)

End point title	Quality of Life (Core 30 Questionnaire)

End point description:

Quality of Life (QoL) as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) four-point scale, with 1 as "not at all" and 4 as "very much." Per protocol, the change in EORTC QLQ-C30 scores from the first assessment to the end of the study were to be summarized descriptively at each post-baseline time point and compared using a mixed effects model, if appropriate.

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W	Cemiplimab 350 mg Q3W + chemotherapy + ipilimumab 50 mg Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: Not Applicable				
number (not applicable)				

Notes:

[12] - The EORTC QLQ-C30 was not assessed due to insufficient data collected.

[13] - The EORTC QLQ-C30 was not assessed due to insufficient data collected.

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life (Lung Cancer 13 Questionnaire)

End point title	Quality of Life (Lung Cancer 13 Questionnaire)

End point description:

QoL as measured by the Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13) to assess lung cancer-associated symptoms and treatment-related side effects among lung cancer patients. The scale for EORTC-QLQ-LC13 is 1-4 for most outcome measures of systems, with 1 rated as "not at all" and 4 rated as "very much." Per protocol, the change in EORTC QLQ-LC13 scores from the first assessment to the end of the study were to be summarized descriptively at each post-baseline time point and compared using a mixed effects model, if appropriate.

End point type	Secondary

End point timeframe:

Up to 32 months

End point values	Cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W	Cemiplimab 350 mg Q3W + chemotherapy + ipilimumab 50 mg Q6W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[14]	0[15]		
Units: Not Applicable				
number (not applicable)				

Notes:

[14] - The EORTC QLQ-LC13 was not assessed due to insufficient data collected.

[15] - The EORTC QLQ-LC13 was not assessed due to insufficient data collected.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dose of study drug to end of study (up to 32 months)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Cemiplimab 350 mg Q3W + chemotherapy+ ipilimumab 50 mg Q6W
Reporting group description: -	
Reporting group title	Cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W
Reporting group description: -	

Serious adverse events	Cemiplimab 350 mg Q3W + chemotherapy+ ipilimumab 50 mg Q6W	Cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	2 / 3 (66.67%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events			
Cardiac disorders			
Pericarditis			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Enterocolitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Secondary adrenocortical insufficiency			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cemiplimab 350 mg Q3W + chemotherapy+ ipilimumab 50 mg Q6W	Cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)	3 / 3 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Tumour pseudoprogression			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 2 (100.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Hypotension			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Aortic arteriosclerosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 2 (100.00%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Fatigue			
subjects affected / exposed	2 / 2 (100.00%)	2 / 3 (66.67%)	
occurrences (all)	2	4	
Asthenia			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Pain			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	3	
Influenza like illness			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Suprapubic pain			

subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 3 (66.67%)	
occurrences (all)	0	3	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Haemoptysis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Dyspnoea exertional			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Pulmonary oedema			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Pneumonitis			
subjects affected / exposed	0 / 2 (0.00%)	2 / 3 (66.67%)	
occurrences (all)	0	2	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Insomnia			

subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Investigations			
Liver function test increased			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 2 (100.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Thermal burn			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	2	
Palpitations			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 2 (100.00%)	1 / 3 (33.33%)	
occurrences (all)	3	1	
Balance disorder			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	
occurrences (all)	3	4	
Dysgeusia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Paraesthesia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 2 (100.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Leukopenia			
subjects affected / exposed	2 / 2 (100.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Neutropenia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 2 (100.00%)	1 / 3 (33.33%)	
occurrences (all)	4	1	
Abdominal pain			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 2 (100.00%)	1 / 3 (33.33%)	
occurrences (all)	7	2	
Constipation			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Dyspepsia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	

Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	
occurrences (all)	2	3	
Gastritis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Immune-mediated hepatitis			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 2 (100.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Erythema			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Hair colour changes			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Rash			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Skin reaction			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Renal and urinary disorders			

Dysuria			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Oliguria			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Hypothyroidism			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Secondary adrenocortical insufficiency			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Hyperthyroidism			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	2 / 2 (100.00%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Arthralgia			
subjects affected / exposed	1 / 2 (50.00%)	2 / 3 (66.67%)	
occurrences (all)	1	2	
Back pain			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Muscle spasms			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Fungal oesophagitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	

Oral candidiasis			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Otitis media acute			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	0 / 2 (0.00%)	2 / 3 (66.67%)	
occurrences (all)	0	2	
Urinary tract infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 2 (100.00%)	1 / 3 (33.33%)	
occurrences (all)	5	1	
Hypokalaemia			
subjects affected / exposed	2 / 2 (100.00%)	1 / 3 (33.33%)	
occurrences (all)	3	1	
Hyperglycaemia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Hypochloraemia			
subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Hypomagnesaemia			
subjects affected / exposed	1 / 2 (50.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Hypoglycaemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Hyponatraemia			

subjects affected / exposed	1 / 2 (50.00%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Metabolic acidosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 November 2017	The redesigned study is a phase 3, randomized, global, open-label, pivotal, study of the efficacy and safety of REGN2810/ipilimumab versus REGN2810/chemotherapy/ipilimumab versus pembrolizumab monotherapy in patients with stage IIIB or stage IV squamous or non squamous NSCLC whose tumors express PD L1 in ≥50% of tumor cells and who have received no prior systemic treatment for their advanced disease. In the redesigned study, the study arms A and C remain the same; arm B will evaluate REGN2810 in combination with ipilimumab instead of chemotherapy. Rationale revised to reflect the new study design. Due to a new statistical design, enrollment of approximately 585 subjects is needed to generate enough progression free survival (PFS) events. Therefore, the approximate number of planned subjects is reduced to 585 from 675. An interim analysis for secondary endpoint of OS will be performed at the time of primary analysis for PFS
23 February 2018	The current text of Key Secondary Endpoint "A patient who has not died will be censored at the last known date of contact" has been revised to "A patient who is lost to follow-up will be censored at the last date that the patient was known to be alive", following European Union (EU) regulatory review; Revised the exclusion criteria concerning human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) to clarify that patients with uncontrolled infection are excluded, but patients with controlled infection are permitted, as requested following EU regulatory review; The current text: "REGN2810 C2P1 drug product is supplied as a sterile liquid solution of 5.6 or 7.4 mL in a 10 or 20 mL glass vial for IV administration." is revised to "REGN2810 C2P1 drug product is supplied as a sterile liquid solution of 5.6 mL in a 10 mL glass vial for IV administration." as requested following EU regulatory review.
16 March 2018	The following text added to exclusion criterion #10 "patients with HIV or hepatitis must have their disease reviewed by the specialist (e.g., infectious disease or hepatologist) managing this disease prior to commencing and throughout the duration of their participation in the trial" following European Union (EU) regulatory review.

14 May 2018	Clarified: Patients on treatment Arm C, pemetrexed maintenance is not allowed; Clarified: Patients in follow-up may be offered retreatment up to an additional 108 wks; Revised secondary endpoint text: To assess predictive utility of baseline PD L1 tumor expression levels on clinical response; Clarified list of Other Secondary Objectives; Inclusion criterion revised to add stage IIIC patient eligibility & clarified histologic diagnosis of NSCLC may be confirmed by central lab; Gemcitabine options for platinum-based doublet deleted; Chemotherapy cycles changed to 4 cycles; Text deleted regarding brain scans during treatment & follow-up periods; PK/ADA sample collection time points revised; Clarified: If possible, a tumor biopsy should be collected at time of progressive disease; Clarified exclusion criteria #3, #23; Exclusion criteria #24 & #25 added based on a health authority feedback; Clarified: Tumor tissue samples will also be tested for EGFR mutations & ALK translocations as well as for ROS1 fusions by a central lab, unless testing already performed & results available from other Regeneron NSCLC immunotherapy studies; Text deleted from Biomarker procedures; Text revised in screening visit assessments; Electrocardiogram text revised; Text added on request by regulatory authority: If necessary, samples may also be used for ADA assessments of ipilimumab; Text revised: Each vial will contain withdrawable cemiplimab at a concentration of 50 mg/mL; Clarified: Pre-medications are not required prior to first administration of cemiplimab & pre-treatment with vitamin supplementation is to start within 3 days of randomization for patients with non-squamous NSCLC; Text added: Pemetrexed maintenance therapy should be given according to local prescribing information & practice guidelines; Deleted "standard-of-care" in regard to platinum-based chemotherapy(ies); Changed REGN2810 to cemiplimab & other minor editorial changes made throughout protocol.

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.

At the time of administrative close of study, a total of 5 patients were randomized to 2 treatment arms. With limited data, only important demographic and safety parameters were summarized.

Notes: