



Clinical trial results:

A randomized phase II study evaluating efficacy and safety of 2nd or 3rd line treatment by Nivolumab monotherapy or Nivolumab plus Ipilimumab, for unresectable Malignant Pleural Mesothelioma (MPM) patients

Summary

EudraCT number	2015-004475-75
Trial protocol	FR
Global end of trial date	22 June 2019

Results information

Result version number	v1 (current)
This version publication date	11 February 2022
First version publication date	11 February 2022

Trial information

Trial identification

Sponsor protocol code	IFCT-1501
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02716272
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IFCT
Sponsor organisation address	10 rue de la Grange-Batelière, PARIS, France, 75009
Public contact	Contact, IFCT, 33 156811045, contact@ifct.fr
Scientific contact	Contact, IFCT, 0156811046 156811045, contact@ifct.fr

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	01 August 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	22 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

We raise the hypothesis that inhibition of immune PD-1+/- CTLA-4 check-point(s) would delay tumor progression in patients with unresectable MPM, experiencing disease progression after one or two lines of chemotherapy including at least first-line with pemetrexed and platinum, without altering significantly the quality of life of patients.

Protection of trial subjects:

Algorithms for management of adverse events were provided in the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 March 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 125
Worldwide total number of subjects	125
EEA total number of subjects	125

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)	27
From 65 to 84 years	94
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

A total of 125 subjects (63 in the nivolumab arm and 62 in the nivolumab plus ipilimumab arm) were randomized in 21 centers, 124 subjects (63 in the nivolumab arm and 61 in the nivolumab plus ipilimumab arm) received at least one dose of the allocated treatment.

Pre-assignment

Screening details:

Eligible patients were aged 18 years or older with an Eastern Cooperative Oncology Group performance status of 0–1, histologically proven malignant pleural mesothelioma progressing after first-line or second-line pemetrexed and platinum based treatments, measurable disease by CT, and life expectancy greater than 12 weeks.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Monotherapy arm

Arm description:

Nivolumab was administered IV over 60 minutes at 3 mg/kg every 2 weeks

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

Dosage and administration details:

3 mg/kg every 2 weeks over 60 minutes

Arm title	Combination arm
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Arm description:

Nivolumab was administered IV over 60 minutes at 3 mg/kg every 2 weeks combined with ipilimumab administered IV over 90 minutes at 1 mg/kg every 6 weeks.

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

Dosage and administration details:

3 mg/kg every 2 weeks over 60 minutes

Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1 mg/kg every 6 weeks over 90 minutes

Number of subjects in period 1	Monotherapy arm	Combination arm
Started	63	62
Completed	3	1
Not completed	60	61
Adverse event, serious fatal	1	6
Patient's choice	1	-
Adverse event, non-fatal	3	14
Intercurrent disease	1	1
Other	-	1
Second cancer	1	-
Disease progression and toxicity	2	-
Lack of efficacy	51	39

Baseline characteristics

Reporting groups

Reporting group title	Monotherapy arm
Reporting group description:	
Nivolumab was administered IV over 60 minutes at 3 mg/kg every 2 weeks	
Reporting group title	Combination arm
Reporting group description:	
Nivolumab was administered IV over 60 minutes at 3 mg/kg every 2 weeks combined with ipilimumab administered IV over 90 minutes at 1 mg/kg every 6 weeks.	

Reporting group values	Monotherapy arm	Combination arm	Total
Number of subjects	63	62	125
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	71.23	70.36	
standard deviation	± 9.46	± 8.99	-
Gender categorical			
Units: Subjects			
Female	16	9	25
Male	47	53	100
Smoking status			
Units: Subjects			
Never smoker	28	24	52
Smoker	35	38	73
Histology			
Units: Subjects			
Biphasic/mixed	11	5	16
Sarcomatoid	0	4	4
Epithelioid	52	53	105
ECOG Performance status			
Units: Subjects			
PS = 0	20	24	44
PS = 1	43	37	80
PS = 2	0	1	1
Number of prior line			
Units: Subjects			

1 prior line	44	42	86
2 prior lines	17	19	36
3 prior lines	1	1	2
4 prior lines	1	0	1
Chemosensitivity to cisplatin/pemetrexed Units: Subjects			
Progression before 3 months	21	18	39
Progression after 3 months	42	44	86
PD-L1 class 1 Units: Subjects			
< 1%	31	27	58
≥1%	19	22	41
MISSING	13	13	26
PD-L1 class 2 Units: Subjects			
<50%	50	46	96
≥50%	0	3	3
MISSING	13	13	26
Tumour-node-metastasis classification Units: Subjects			
Stage I-II	7	11	18
Stage III-IV	56	51	107
Leucocytes Units: Subjects			
< 8.3 x10 ⁹ per L	43	41	84
≥ 8.3 x10 ⁹ per L	20	21	41
Hemoglobin Units: Subjects			
≤ 12 g/L	30	25	55
> 12 g/L	33	37	70
Platelets Units: Subjects			
< 350 x 10 ⁹ per L	46	43	89
≥ 350 x 10 ⁹ per L	17	19	36
Weight Units: kilogram(s)			
arithmetic mean	72.92	73.68	
standard deviation	± 13.58	± 14.82	-
Number of pack-years Units: Pack-years			
arithmetic mean	23.47	22.82	
standard deviation	± 15.64	± 22.11	-

End points

End points reporting groups

Reporting group title	Monotherapy arm
Reporting group description: Nivolumab was administered IV over 60 minutes at 3 mg/kg every 2 weeks	
Reporting group title	Combination arm
Reporting group description: Nivolumab was administered IV over 60 minutes at 3 mg/kg every 2 weeks combined with ipilimumab administered IV over 90 minutes at 1 mg/kg every 6 weeks.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: Patient who received at least one dose of the allocated treatment	
Subject analysis set title	Efficacy population
Subject analysis set type	Per protocol
Subject analysis set description: Patients with no major deviation from the inclusion and exclusion criteria	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intention-to-treat population	

Primary: Disease Control Rate at 12 weeks assessed by the Investigator

End point title	Disease Control Rate at 12 weeks assessed by the
End point description:	
End point type	Primary
End point timeframe: 12 weeks after randomization	

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: Non comparative study

End point values	Monotherapy arm	Combination arm	Efficacy population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	63	62	118	
Units: percent				
number (confidence interval 95%)	50.0 (36.7 to 63.3)	57.4 (44.2 to 70.6)	53.7 (44.3 to 63.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate at 12 weeks assessed by the Blinded Independent Review Committee

End point title	Disease Control Rate at 12 weeks assessed by the Blinded Independent Review Committee
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks after randomization	

End point values	Monotherapy arm	Combination arm	Efficacy population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	54 ^[2]	54 ^[3]	108 ^[4]	
Units: percent				
number (confidence interval 95%)	44.4 (31.2 to 57.7)	50.0 (36.7 to 63.3)	47.2 (37.8 to 56.6)	

Notes:

[2] - The first 108 eligible patients were analysed as planned in the protocol

[3] - The first 108 eligible patients were analysed as planned in the protocol

[4] - The first 108 eligible patients were analysed as planned in the protocol

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate at 12 weeks assessed by the Blinded Independent Review Committee

End point title	Overall Response Rate at 12 weeks assessed by the Blinded Independent Review Committee
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks after randomization	

End point values	Monotherapy arm	Combination arm	Efficacy population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	54 ^[5]	54 ^[6]	108 ^[7]	
Units: percent				
number (confidence interval 95%)	18.5 (8.2 to 28.9)	27.8 (15.8 to 39.7)	23.2 (15.2 to 31.1)	

Notes:

[5] - The first 108 eligible patients were analysed as planned in the protocol

[6] - The first 108 eligible patients were analysed as planned in the protocol

[7] - The first 108 eligible patients were analysed as planned in the protocol

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate at 12 weeks assessed by the Investigator

End point title	Overall Response Rate at 12 weeks assessed by the Investigator
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks after randomization	

End point values	Monotherapy arm	Combination arm	Efficacy population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	54 ^[8]	54 ^[9]	108 ^[10]	
Units: Percent				
number (confidence interval 95%)	13.0 (4.0 to 21.9)	18.5 (8.2 to 28.9)	15.7 (8.9 to 22.6)	

Notes:

[8] - The first 108 eligible patients were analysed as planned in the protocol

[9] - The first 108 eligible patients were analysed as planned in the protocol

[10] - The first 108 eligible patients were analysed as planned in the protocol

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free survival

End point title	Progression Free survival
End point description:	
End point type	Secondary
End point timeframe:	
Time from date of inclusion to the earliest date of disease progression. The median follow-up was 18.40 months in both arms.	

End point values	Monotherapy arm	Combination arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	62		
Units: Months				
median (confidence interval 95%)	3.97 (2.79 to 5.68)	5.44 (3.06 to 8.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival
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End point description:

End point type	Secondary
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End point timeframe:

Time from date of inclusion to the date of death due to any cause. The median follow-up was 37.48 months in both arms.

End point values	Monotherapy arm	Combination arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	62		
Units: Months				
median (confidence interval 95%)	11.86 (6.73 to 17.44)	15.93 (10.68 to 22.21)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The timeframe events extends from the date of signature of the informed consent until 100 days after the last day of study treatment except for adverse events related to study drug.

Adverse event reporting additional description:

The maximal grade of adverse events was collected by cycle of treatment.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21
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Reporting groups

Reporting group title	Safety Population
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Reporting group description: -

Reporting group title	Arm A Safety population
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Reporting group description: -

Reporting group title	Arm B safety population
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Reporting group description: -

Serious adverse events	Safety Population	Arm A Safety population	Arm B safety population
Total subjects affected by serious adverse events			
subjects affected / exposed	61 / 124 (49.19%)	25 / 63 (39.68%)	36 / 61 (59.02%)
number of deaths (all causes)	107	55	52
number of deaths resulting from adverse events	24	13	10
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	1 / 124 (0.81%)	1 / 63 (1.59%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to peritoneum			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Neoplasm progression			
subjects affected / exposed	8 / 124 (6.45%)	4 / 63 (6.35%)	4 / 61 (6.56%)
occurrences causally related to treatment / all	0 / 8	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 8	0 / 4	0 / 4
Vascular disorders			

Pulmonary embolism			
subjects affected / exposed	1 / 124 (0.81%)	1 / 63 (1.59%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 124 (0.81%)	1 / 63 (1.59%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	2 / 124 (1.61%)	1 / 63 (1.59%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 124 (0.81%)	1 / 63 (1.59%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
General physical health deterioration			
subjects affected / exposed	17 / 124 (13.71%)	11 / 63 (17.46%)	6 / 61 (9.84%)
occurrences causally related to treatment / all	0 / 17	0 / 11	0 / 6
deaths causally related to treatment / all	0 / 10	0 / 6	0 / 4
Hyperthermia malignant			
subjects affected / exposed	2 / 124 (1.61%)	1 / 63 (1.59%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 124 (1.61%)	1 / 63 (1.59%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cough			
subjects affected / exposed	2 / 124 (1.61%)	1 / 63 (1.59%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	9 / 124 (7.26%)	5 / 63 (7.94%)	4 / 61 (6.56%)
occurrences causally related to treatment / all	0 / 10	0 / 6	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Lung disorder			
subjects affected / exposed	2 / 124 (1.61%)	0 / 63 (0.00%)	2 / 61 (3.28%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	4 / 124 (3.23%)	2 / 63 (3.17%)	2 / 61 (3.28%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 124 (0.81%)	1 / 63 (1.59%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	3 / 124 (2.42%)	1 / 63 (1.59%)	2 / 61 (3.28%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0

Respiratory failure			
subjects affected / exposed	1 / 124 (0.81%)	1 / 63 (1.59%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	4 / 124 (3.23%)	1 / 63 (1.59%)	3 / 61 (4.92%)
occurrences causally related to treatment / all	4 / 4	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis chemical			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 124 (0.81%)	1 / 63 (1.59%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	4 / 124 (3.23%)	1 / 63 (1.59%)	3 / 61 (4.92%)
occurrences causally related to treatment / all	3 / 4	1 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			

subjects affected / exposed	3 / 124 (2.42%)	1 / 63 (1.59%)	2 / 61 (3.28%)
occurrences causally related to treatment / all	1 / 3	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	1 / 124 (0.81%)	1 / 63 (1.59%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 124 (0.81%)	1 / 63 (1.59%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	2 / 124 (1.61%)	1 / 63 (1.59%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 124 (0.81%)	1 / 63 (1.59%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Acute polyneuropathy			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal artery occlusion			
subjects affected / exposed	1 / 124 (0.81%)	1 / 63 (1.59%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Autoimmune colitis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	2 / 124 (1.61%)	1 / 63 (1.59%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	2 / 2	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 124 (1.61%)	0 / 63 (0.00%)	2 / 61 (3.28%)
occurrences causally related to treatment / all	2 / 2	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	2 / 124 (1.61%)	1 / 63 (1.59%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Gastritis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal obstruction			
subjects affected / exposed	2 / 124 (1.61%)	0 / 63 (0.00%)	2 / 61 (3.28%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 124 (0.81%)	1 / 63 (1.59%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Hepatobiliary disorders			

Hepatitis fulminant			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Budd-Chiari syndrome			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular injury			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis toxic			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis bullous			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriasis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pemphigoid			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 124 (1.61%)	0 / 63 (0.00%)	2 / 61 (3.28%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1

Pleurisy			
subjects affected / exposed	1 / 124 (0.81%)	1 / 63 (1.59%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hypophysitis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 124 (0.81%)	1 / 63 (1.59%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 124 (0.81%)	1 / 63 (1.59%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyarthrititis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 124 (0.81%)	1 / 63 (1.59%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection			
subjects affected / exposed	1 / 124 (0.81%)	0 / 63 (0.00%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			

subjects affected / exposed	1 / 124 (0.81%)	1 / 63 (1.59%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mediastinal abscess			
subjects affected / exposed	1 / 124 (0.81%)	1 / 63 (1.59%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pneumonia			
subjects affected / exposed	3 / 124 (2.42%)	2 / 63 (3.17%)	1 / 61 (1.64%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 124 (0.81%)	1 / 63 (1.59%)	0 / 61 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	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	Safety Population	Arm A Safety population	Arm B safety population
Total subjects affected by non-serious adverse events			
subjects affected / exposed	124 / 124 (100.00%)	63 / 63 (100.00%)	61 / 61 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 124 (6.45%)	3 / 63 (4.76%)	5 / 61 (8.20%)
occurrences (all)	13	6	7
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	94 / 124 (75.81%)	48 / 63 (76.19%)	46 / 61 (75.41%)
occurrences (all)	406	210	196
Chest pain			
subjects affected / exposed	70 / 124 (56.45%)	34 / 63 (53.97%)	36 / 61 (59.02%)
occurrences (all)	198	90	108
Pyrexia			

subjects affected / exposed	31 / 124 (25.00%)	10 / 63 (15.87%)	21 / 61 (34.43%)
occurrences (all)	45	14	31
Oedema peripheral			
subjects affected / exposed	23 / 124 (18.55%)	13 / 63 (20.63%)	10 / 61 (16.39%)
occurrences (all)	42	21	21
General physical health deterioration			
subjects affected / exposed	28 / 124 (22.58%)	15 / 63 (23.81%)	13 / 61 (21.31%)
occurrences (all)	37	17	20
Mucosal inflammation			
subjects affected / exposed	12 / 124 (9.68%)	6 / 63 (9.52%)	6 / 61 (9.84%)
occurrences (all)	25	19	6
Chills			
subjects affected / exposed	9 / 124 (7.26%)	3 / 63 (4.76%)	6 / 61 (9.84%)
occurrences (all)	16	9	7
Pain			
subjects affected / exposed	6 / 124 (4.84%)	1 / 63 (1.59%)	5 / 61 (8.20%)
occurrences (all)	6	1	5
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	90 / 124 (72.58%)	48 / 63 (76.19%)	42 / 61 (68.85%)
occurrences (all)	306	155	151
Cough			
subjects affected / exposed	63 / 124 (50.81%)	33 / 63 (52.38%)	30 / 61 (49.18%)
occurrences (all)	165	79	86
Productive cough			
subjects affected / exposed	14 / 124 (11.29%)	8 / 63 (12.70%)	6 / 61 (9.84%)
occurrences (all)	30	15	15
Pleural effusion			
subjects affected / exposed	7 / 124 (5.65%)	4 / 63 (6.35%)	3 / 61 (4.92%)
occurrences (all)	23	6	17
Psychiatric disorders			
Anxiety			
subjects affected / exposed	7 / 124 (5.65%)	4 / 63 (6.35%)	3 / 61 (4.92%)
occurrences (all)	10	6	4
Insomnia			

subjects affected / exposed occurrences (all)	6 / 124 (4.84%) 8	5 / 63 (7.94%) 6	2 / 61 (3.28%) 2
Investigations			
Weight decreased			
subjects affected / exposed	23 / 124 (18.55%)	15 / 63 (23.81%)	18 / 61 (29.51%)
occurrences (all)	67	22	45
Gamma-glutamyltransferase increased			
subjects affected / exposed	13 / 124 (10.48%)	8 / 63 (12.70%)	5 / 61 (8.20%)
occurrences (all)	62	11	51
Blood creatinine increased			
subjects affected / exposed	13 / 124 (10.48%)	6 / 63 (9.52%)	7 / 61 (11.48%)
occurrences (all)	51	29	22
Alanine aminotransferase increased			
subjects affected / exposed	13 / 124 (10.48%)	3 / 63 (4.76%)	10 / 61 (16.39%)
occurrences (all)	31	3	28
Aspartate aminotransferase increased			
subjects affected / exposed	14 / 124 (11.29%)	5 / 63 (7.94%)	9 / 61 (14.75%)
occurrences (all)	29	9	20
Lipase increased			
subjects affected / exposed	8 / 124 (6.45%)	4 / 63 (6.35%)	4 / 61 (6.56%)
occurrences (all)	16	9	7
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 124 (5.65%)	1 / 63 (1.59%)	6 / 61 (9.84%)
occurrences (all)	16	3	13
Blood thyroid stimulating hormone increased			
subjects affected / exposed	6 / 124 (4.84%)	4 / 63 (6.35%)	2 / 61 (3.28%)
occurrences (all)	10	8	2
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	5 / 124 (4.03%)	1 / 63 (1.59%)	4 / 61 (6.56%)
occurrences (all)	6	1	5
Tachycardia			
subjects affected / exposed	4 / 124 (3.23%)	0 / 63 (0.00%)	4 / 61 (6.56%)
occurrences (all)	5	0	5
Nervous system disorders			

Neuralgia			
subjects affected / exposed	7 / 124 (5.65%)	3 / 63 (4.76%)	4 / 61 (6.56%)
occurrences (all)	24	7	17
Headache			
subjects affected / exposed	9 / 124 (7.26%)	3 / 63 (4.76%)	6 / 61 (9.84%)
occurrences (all)	22	3	19
Paraesthesia			
subjects affected / exposed	6 / 124 (4.84%)	2 / 63 (3.17%)	4 / 61 (6.56%)
occurrences (all)	12	4	8
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	60 / 124 (48.39%)	27 / 63 (42.86%)	33 / 61 (54.10%)
occurrences (all)	296	164	132
Thrombocytopenia			
subjects affected / exposed	6 / 124 (4.84%)	4 / 63 (6.35%)	2 / 61 (3.28%)
occurrences (all)	37	18	19
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	10 / 124 (8.06%)	5 / 63 (7.94%)	5 / 61 (8.20%)
occurrences (all)	13	6	7
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	31 / 124 (25.00%)	11 / 63 (17.46%)	20 / 61 (32.79%)
occurrences (all)	71	20	51
Constipation			
subjects affected / exposed	36 / 124 (29.03%)	20 / 63 (31.75%)	16 / 61 (26.23%)
occurrences (all)	61	33	28
Nausea			
subjects affected / exposed	29 / 124 (23.39%)	15 / 63 (23.81%)	14 / 61 (22.95%)
occurrences (all)	52	32	20
Dry mouth			
subjects affected / exposed	11 / 124 (8.87%)	4 / 63 (6.35%)	7 / 61 (11.48%)
occurrences (all)	29	16	13
Abdominal pain			
subjects affected / exposed	16 / 124 (12.90%)	8 / 63 (12.70%)	8 / 61 (13.11%)
occurrences (all)	27	13	14
Dysphagia			

subjects affected / exposed occurrences (all)	13 / 124 (10.48%) 25	7 / 63 (11.11%) 15	6 / 61 (9.84%) 10
Abdominal pain upper subjects affected / exposed occurrences (all)	14 / 124 (11.29%) 23	6 / 63 (9.52%) 9	8 / 61 (13.11%) 14
Vomiting subjects affected / exposed occurrences (all)	12 / 124 (9.68%) 17	5 / 63 (7.94%) 6	7 / 61 (11.48%) 11
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	21 / 124 (16.94%) 107	6 / 63 (9.52%) 20	15 / 61 (24.59%) 87
Rash subjects affected / exposed occurrences (all)	15 / 124 (12.10%) 76	6 / 63 (9.52%) 34	9 / 61 (14.75%) 42
Dry skin subjects affected / exposed occurrences (all)	12 / 124 (9.68%) 36	3 / 63 (4.76%) 12	9 / 61 (14.75%) 24
Hyperhidrosis subjects affected / exposed occurrences (all)	8 / 124 (6.45%) 10	5 / 63 (7.94%) 6	3 / 61 (4.92%) 4
Erythema subjects affected / exposed occurrences (all)	6 / 124 (4.84%) 6	1 / 63 (1.59%) 1	5 / 61 (8.20%) 5
Renal and urinary disorders			
Renal failure subjects affected / exposed occurrences (all)	11 / 124 (8.87%) 31	6 / 63 (9.52%) 21	5 / 61 (8.20%) 10
Acute kidney injury subjects affected / exposed occurrences (all)	5 / 124 (4.03%) 6	0 / 63 (0.00%) 0	5 / 61 (8.20%) 6
Endocrine disorders			
Hyperthyroidism subjects affected / exposed occurrences (all)	8 / 124 (6.45%) 37	2 / 63 (3.17%) 13	6 / 61 (9.84%) 24
Hypothyroidism			

subjects affected / exposed occurrences (all)	9 / 124 (7.26%) 25	4 / 63 (6.35%) 6	5 / 61 (8.20%) 19
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	28 / 124 (22.58%)	15 / 63 (23.81%)	13 / 61 (21.31%)
occurrences (all)	58	23	35
Arthralgia			
subjects affected / exposed	20 / 124 (16.13%)	9 / 63 (14.29%)	11 / 61 (18.03%)
occurrences (all)	54	21	33
Musculoskeletal chest pain			
subjects affected / exposed	24 / 124 (19.35%)	12 / 63 (19.05%)	12 / 61 (19.67%)
occurrences (all)	48	15	33
Musculoskeletal pain			
subjects affected / exposed	14 / 124 (11.29%)	5 / 63 (7.94%)	9 / 61 (14.75%)
occurrences (all)	41	13	28
Pain in extremity			
subjects affected / exposed	12 / 124 (9.68%)	7 / 63 (11.11%)	5 / 61 (8.20%)
occurrences (all)	15	8	7
Muscle spasms			
subjects affected / exposed	8 / 124 (6.45%)	5 / 63 (7.94%)	3 / 61 (4.92%)
occurrences (all)	13	9	4
Myalgia			
subjects affected / exposed	9 / 124 (7.26%)	4 / 63 (6.35%)	5 / 61 (8.20%)
occurrences (all)	11	5	6
Neck pain			
subjects affected / exposed	5 / 124 (4.03%)	1 / 63 (1.59%)	4 / 61 (6.56%)
occurrences (all)	5	1	4
Infections and infestations			
Rhinitis			
subjects affected / exposed	12 / 124 (9.68%)	7 / 63 (11.11%)	5 / 61 (8.20%)
occurrences (all)	15	7	8
Bronchitis			
subjects affected / exposed	12 / 124 (9.68%)	5 / 63 (7.94%)	7 / 61 (11.48%)
occurrences (all)	14	6	8
Oral candidiasis			

subjects affected / exposed occurrences (all)	11 / 124 (8.87%) 13	5 / 63 (7.94%) 6	6 / 61 (9.84%) 7
Influenza subjects affected / exposed occurrences (all)	5 / 124 (4.03%) 7	1 / 63 (1.59%) 1	4 / 61 (6.56%) 6
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	42 / 124 (33.87%) 95	23 / 63 (36.51%) 47	19 / 61 (31.15%) 48
Hypoalbuminaemia subjects affected / exposed occurrences (all)	5 / 124 (4.03%) 15	5 / 63 (7.94%) 15	0 / 61 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 April 2016	Clarification of inclusion criteria, adding stratification criteria and amendment of the patient information letter.

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.

The phase 2 nature of this trial was a conservative choice aimed solely to detect early efficacy (and tolerance) signals of two different immunotherapy regimens at the same time, with no preconceptions, and to select at least one of these regimens.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30660609>