Clinical trial results:
A randomised open-label phase II trial of consolidation with nivolumab and ipilimumab in limited-stage SCLC after chemo-radiotherapy

Summary

EudraCT number	2013-002609-78
Trial protocol	BE ES FR DE NL GB
Global end of trial date	03 June 2021

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	ETOP/IFCT 4-12/CA184-310

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02046733
WHO universal trial number (UTN)	-
Other trial identifiers	IFCT: IFCT 4-12

Notes:

Sponsors

Sponsor organisation name	European Thoracic Oncology Platform
Sponsor organisation address	Effingerstr. 40, Bern, Switzerland, 3008
Public contact	ETOP Coordinating Office, ETOP, +41 31 511 94 00, regulatoryoffice@etop-eu.org
Scientific contact	ETOP Coordinating Office, ETOP, +41 31 511 94 00, regulatoryoffice@etop-eu.org

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	25 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 May 2020
Global end of trial reached?	Yes
Global end of trial date	03 June 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to evaluate if patients treated with chemo-radiotherapy and prophylactic cranial irradiation followed by consolidation treatment (nivolumab plus ipilimumab) have a better outcome in terms of progression-free survival and overall survival, compared to patients treated with chemo-radiotherapy and prophylactic cranial irradiation without consolidation treatment.

Protection of trial subjects:

The Investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997) or with local law if it affords greater protection to the patient. For studies conducted in the EU/EEA countries, the Investigator will ensure compliance with the EU Clinical Trial Directive (2001/20/EC). All protocols and the patient informed consent forms must have the approval of a properly constituted committee or committees responsible for approving clinical trials. Once approved or acknowledged by the appropriate ERB/IRB and by the Health Authorities (if required), the investigator shall implement the protocol modifications. Protocol modifications for urgent safety matters may be directly implemented following the instructions of ETOP.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 February 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	Spain: 61
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	France: 78
Country: Number of subjects enrolled	Germany: 36
Country: Number of subjects enrolled	Switzerland: 10
Country: Number of subjects enrolled	Australia: 6
Worldwide total number of subjects	222
EEA total number of subjects	197

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)	139
From 65 to 84 years	83
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From December 2015 to April 2019, a total of 222 patients were enrolled to the chemotherapy phase under protocol AM1 coming from 52 centers of 8 countries. Overall, 153 patients were randomized under AM1 and constitute the ITT cohort of the efficacy analysis (145 of those were enrolled under AM1 and 8 were enrolled under the original protocol).

Pre-assignment

Screening details:

302 patients registered in ETOP iBiobank up to 30 April 2019. Of note, these patients are not all assessed for eligibility, since it was not mandatory to enter in database all patients assesses. Out of 302 patients, 38 did not enrolled (23 ineligible, 15 error). In total 222 patients enrolled under protocol AM1 and of them 153 randomized under AM1.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab and Ipilimumab

Arm description:

Induction phase: Nivolumab followed (on the same day) by Ipilimumab, for 4 cycles.
Maintenance phase: Nivolumab, for a maximum of 12 months from the start of the maintenance phase.

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	BMS-936558
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Induction phase (to start within 6-8 weeks (42-56 days) after the start of chemotherapy cycle 4, and not more than 2 weeks (14 days) after the date of randomisation): Nivolumab at a dose of 1 mg/kg i.v. over a period of 30 minutes, for 4 cycles.
Maintenance phase (to start 3 weeks (21days) after the last IMP doses of induction phase): Nivolumab at a dose of 240 mg i.v. over a period of 30 minutes, once every 2 weeks (+/- 2 days, without dosing delay), for a maximum of 12 months from the start of maintenance. Patients should not be dosed less than 12 days from the previous dose of nivolumab.

Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Induction phase (to start within 6-8 weeks (42-56 days) after the start of chemotherapy cycle 4, and not more than 2 weeks (14 days) after the date of randomisation): Ipilimumab at a dose of 3 mg/kg i.v. over a period of 90 minutes once every 3 weeks (+/- 3 days, without dosing delay), for 4 cycles

Arm title	Observation

Arm description:

No further treatment after chemo-radiotherapy and PCI.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1[1]	Nivolumab and Ipilimumab	Observation
Started	78	75
Completed	8	33
Not completed	70	42
On treatment	5	-
Physician decision	4	-
Patient decision	7	-
On 'treatment'	-	4
Adverse event, non-fatal	36	-
Death	3	-
Progression	15	31
Never initiated 'treatment visits'	-	6
unspecified reason	-	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: Of the 222 patients enrolled under protocol AM1, 145 patients were eligible for randomization under AM1. In total 153 patients were randomized under protocol AM1 (145 enrolled under AM1 and 8 enrolled under original protocol) (78 in experimental arm and 75 in observation arm).

Baseline characteristics

Reporting groups	
Reporting group title	Nivolumab and Ipilimumab
Reporting group description:	
Induction phase: Nivolumab followed (on the same day) by Ipilimumab, for 4 cycles. Maintenance phase: Nivolumab, for a maximum of 12 months from the start of the maintenance phase.	
Reporting group title	Observation
Reporting group description:	
No further treatment after chemo-radiotherapy and PCI.	

Reporting group values	Nivolumab and Ipilimumab	Observation	Total
Number of subjects	78	75	153
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	57	48	105
From 65-84 years	21	27	48
85 years and over	0	0	0
Age continuous			
Age (years at enrolment)			
Units: years			
median	61.1	61.9	
full range (min-max)	37.7 to 83.2	38.6 to 77.3	-
Gender categorical Units: Subjects			
Female	28	33	61
Male	50	42	92
Smoking history Units: Subjects			
Current	27	25	52
Former (≥100 cigarettes in the past/whole life)	51	49	100
Never (0-99 cigarettes/whole life)	0	1	1
ECOG performance status (at randomization)			
Measure Description: 0: Fully active, able to carry on all pre-disease performance without restriction, 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work, 2: Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours, 3: Capable of only limited self-care; confined to bed or chair more than 50% of waking hours, 4: Completely disabled; cannot carry on any self-care; totally confined to bed or chair, 5: Dead			
Units: Subjects			
zero	25	23	48

one	50	51	101
two	3	1	4
Stage			
Measure Description: based on the 7th TNM classification (IASLC classification for SCLC proposal)			
Units: Subjects			
IA	0	2	2
IB	2	1	3
IIA	3	5	8
IIB	6	2	8
IIIA	26	27	53
IIIB	40	36	76
Missing	1	2	3
Response to chemo-radiotherapy (before randomization) Units: Subjects			
Complete response	9	11	20
Partial response	65	60	125
Stable disease	4	3	7
Not evaluable	0	1	1
Number of radiotherapy fractions per day Units: Subjects			
One	48	49	97
Two	30	26	56
PEC-CT Units: Subjects			
Done	25	26	51
Not done	53	49	102

End points

End points reporting groups

Reporting group title	Nivolumab and Ipilimumab

Reporting group description:

Induction phase: Nivolumab followed (on the same day) by Ipilimumab, for 4 cycles.
Maintenance phase: Nivolumab, for a maximum of 12 months from the start of the maintenance phase.

Reporting group title	Observation

Reporting group description:

No further treatment after chemo-radiotherapy and PCI.

Primary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Defined as the time from the date of randomisation until documented progression or death, if progression is not documented. Censoring for PFS occurs at the last tumor assessment.
Assessment of Progressive Disease (PD) based on Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1):
Target lesions: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on the study (this includes the baseline sum if that is the smallest on the study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Non-target lesions: Unequivocal progression of existing non-target lesions. To achieve 'unequivocal progression', there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently.
The appearance of one or more new lesions is also considered as progression.

End point type	Primary

End point timeframe:

From the date of randomisation until documented progression or death, assessed up to 4.5 years after the enrolment of the last patient.

End point values	Nivolumab and Ipilimumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[1]	75[2]		
Units: months				
median (confidence interval 95%)	10.7 (7.0 to 9999)	14.5 (8.2 to 9999)		

Notes:

[1] - The upper 95% CI is not estimable. Since letters are not accepted, a value of "9999" is entered.

[2] - The upper 95% CI is not estimable. Since letters are not accepted, a value of "9999" is entered.

Statistical analyses

Statistical analysis title	Primary efficacy analysis of PFS

Statistical analysis description:

The trial is designed to test the hypotheses that treatment with chemoradiotherapy and PCI followed by consolidation treatment (nivolumab plus ipilimumab) will lead to an increase in median PFS to 22.8 months, from 13.1 months under treatment with chemoradiotherapy and PCI without consolidation treatment. According to the study design, this corresponds to a PFS HR of 0.57. Using 80% power and a one-sided type I error of 5%, a total of 81 PFS events are needed.

Comparison groups	Observation v Nivolumab and Ipilimumab
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.93 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.58

Notes:

[3] - In the frame of final efficacy analysis, the formal comparison of the PFS between the two treatment arms, will be based on stratified log-rank test (with number of fractions of radiotherapy [1/2] and administration of FDG-PET-CT [Yes/No] being the stratification factors).

[4] - The statistical significance of trial treatment will be tested at the 5% significance level.

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Defined as the time from the date of randomisation until death from any cause. Censoring for OS occurs at the last follow-up date.

End point type	Secondary

End point timeframe:

From date of randomisation until death from any cause, assessed up to 4.5 years after the enrolment of the last patient.

End point values	Nivolumab and Ipilimumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[5]	75[6]		
Units: months				
median (confidence interval 95%)	9999 (24.1 to 9999)	32.1 (26.1 to 9999)		

Notes:

[5] - The median is not reached and the upper 95% CI is not estimable. A value of "9999" is entered.

[6] - The upper 95% CI is not estimable. Since letters are not accepted, a value of "9999" is entered.

Statistical analyses

Statistical analysis title	Secondary efficacy analysis of OS
Comparison groups	Nivolumab and Ipilimumab v Observation
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83 [7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.52

Notes:

[7] - The statistical significance of trial treatment will be tested at the 5% significance level.

Secondary: Objective response (OR)

End point title	Objective response (OR)

End point description:

Objective response is defined as the best overall response (complete or partial response) according to RECIST 1.1 criteria across all assessment time-points during the period from randomisation to termination of trial treatment. Of note, the determination of OR is restricted to patients who have not attained a CR during the chemo-radiotherapy phase.
Complete Response (CR): Disappearance of all target lesions, Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum of diameters, Progression (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum recorded on the trial. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm., Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters recorded on the trial.

End point type	Secondary

End point timeframe:

From randomisation to termination of trial treatment, for a maximum of 12 months from start of maintenance phase.

End point values	Nivolumab and Ipilimumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69[8]	64[9]		
Units: subjects				
Complete response	6	8		
Partial response	20	22		
Stable disease	28	22		
Progressive disease	9	10		
Non-evaluable	6	2		

Notes:

[8] - 9 patients in experimental arm who have attained a CR during chemo-radiotherapy are excluded

[9] - 11 patients in observation arm who have attained a CR during chemo-radiotherapy are excluded

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-treatment Failure (TTF)

End point title	Time-to-treatment Failure (TTF)

End point description:

Defined as the time from the date of randomisation to discontinuation of treatment for any reason (including progression of disease, treatment toxicity, refusal, lost to follow-up, and death). Censoring for TTF occurs at the last follow-up date.

End point type	Secondary

End point timeframe:

From date of randomisation until discontinuation of treatment for any reason, assessed up to 4.5 years after the enrolment of the last patient.

End point values	Nivolumab and Ipilimumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	75		
Units: months				
median (confidence interval 95%)	1.7 (1.2 to 2.5)	14.5 (8.2 to 24.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity

End point title	Toxicity

End point description:

Adverse events graded according to NCI CTCAE V4.0.

End point type	Secondary

End point timeframe:

Toxicity was assessed across all time-points during randomization phase until 100 days after the final dose of investigational medical product (IMP).

End point values	Nivolumab and Ipilimumab	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[10]	75[11]		
Units: Subjects				
Patients experienced AEs/SAEs	77	65		
Patients not experienced AEs/SAEs	1	10		
Number of total AEs/SAEs	633	242		

Notes:

[10] - Safety cohort

[11] - Safety cohort

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were assessed across all time-points during randomization phase until 100 days after the final dose of investigational medical product (IMP).

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Nivolumab and Ipilimumab

Reporting group description:

Induction phase: Nivolumab followed (on the same day) by Ipilimumab, for 4 cycles.
Maintenance phase: Nivolumab, for a maximum of 12 months from the start of the maintenance phase.

Reporting group title	Observation

Reporting group description:

No further treatment after chemo-radiotherapy and PCI.

Serious adverse events	Nivolumab and Ipilimumab	Observation	
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 78 (61.54%)	12 / 75 (16.00%)	
number of deaths (all causes)	34	37	
number of deaths resulting from adverse events	4	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	0 / 78 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melanoma			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboembolic event			

subjects affected / exposed	1 / 78 (1.28%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death NOS			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fever			
subjects affected / exposed	3 / 78 (3.85%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	2 / 11	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flu like symptoms			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 78 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	2 / 78 (2.56%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Autoimmune disorder			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			

subjects affected / exposed	1 / 78 (1.28%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 13	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	9 / 78 (11.54%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	8 / 22	0 / 4	
deaths causally related to treatment / all	2 / 2	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusion			
subjects affected / exposed	0 / 78 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
White blood cell decreased			
subjects affected / exposed	0 / 78 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	2 / 78 (2.56%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial nerve disorder			
subjects affected / exposed	3 / 78 (3.85%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neuralgia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinopathy			
subjects affected / exposed	2 / 78 (2.56%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	2 / 78 (2.56%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 15	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	8 / 78 (10.26%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	8 / 22	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nausea			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 19	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pancreatitis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 21	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 78 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)			
subjects affected / exposed	0 / 78 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			

subjects affected / exposed	3 / 78 (3.85%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	3 / 22	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 13	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchial infection			
subjects affected / exposed	2 / 78 (2.56%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral meningitis			
subjects affected / exposed	0 / 78 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	6 / 78 (7.69%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	4 / 10	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 78 (1.28%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	2 / 78 (2.56%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 25	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Nivolumab and Ipilimumab	Observation	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 78 (92.31%)	62 / 75 (82.67%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 78 (7.69%)	1 / 75 (1.33%)	
occurrences (all)	6	1	
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 78 (6.41%)	1 / 75 (1.33%)	
occurrences (all)	5	1	
Platelet count decreased			
subjects affected / exposed	4 / 78 (5.13%)	5 / 75 (6.67%)	
occurrences (all)	4	5	
Weight loss			
subjects affected / exposed	7 / 78 (8.97%)	2 / 75 (2.67%)	
occurrences (all)	7	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 78 (11.54%)	8 / 75 (10.67%)	
occurrences (all)	9	8	
Headache			
subjects affected / exposed	11 / 78 (14.10%)	2 / 75 (2.67%)	
occurrences (all)	11	2	
Peripheral sensory neuropathy			
subjects affected / exposed	7 / 78 (8.97%)	2 / 75 (2.67%)	
occurrences (all)	8	2	
Blood and lymphatic system disorders			

Anemia			
subjects affected / exposed	7 / 78 (8.97%)	13 / 75 (17.33%)	
occurrences (all)	7	13	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	5 / 78 (6.41%)	1 / 75 (1.33%)	
occurrences (all)	5	1	
Fatigue			
subjects affected / exposed	38 / 78 (48.72%)	21 / 75 (28.00%)	
occurrences (all)	38	21	
Fever			
subjects affected / exposed	8 / 78 (10.26%)	1 / 75 (1.33%)	
occurrences (all)	11	1	
Pain			
subjects affected / exposed	9 / 78 (11.54%)	9 / 75 (12.00%)	
occurrences (all)	9	9	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 78 (8.97%)	1 / 75 (1.33%)	
occurrences (all)	7	1	
Constipation			
subjects affected / exposed	14 / 78 (17.95%)	3 / 75 (4.00%)	
occurrences (all)	15	3	
Diarrhea			
subjects affected / exposed	14 / 78 (17.95%)	6 / 75 (8.00%)	
occurrences (all)	22	6	
Dry mouth			
subjects affected / exposed	6 / 78 (7.69%)	0 / 75 (0.00%)	
occurrences (all)	6	0	
Dysphagia			
subjects affected / exposed	4 / 78 (5.13%)	2 / 75 (2.67%)	
occurrences (all)	4	2	
Mucositis oral			
subjects affected / exposed	5 / 78 (6.41%)	0 / 75 (0.00%)	
occurrences (all)	5	0	
Nausea			

subjects affected / exposed	18 / 78 (23.08%)	6 / 75 (8.00%)	
occurrences (all)	19	6	
Vomiting			
subjects affected / exposed	20 / 78 (25.64%)	5 / 75 (6.67%)	
occurrences (all)	21	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	20 / 78 (25.64%)	5 / 75 (6.67%)	
occurrences (all)	20	5	
Dyspnea			
subjects affected / exposed	12 / 78 (15.38%)	5 / 75 (6.67%)	
occurrences (all)	13	6	
Pneumonitis			
subjects affected / exposed	13 / 78 (16.67%)	3 / 75 (4.00%)	
occurrences (all)	22	4	
Productive cough			
subjects affected / exposed	5 / 78 (6.41%)	0 / 75 (0.00%)	
occurrences (all)	5	0	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	4 / 78 (5.13%)	0 / 75 (0.00%)	
occurrences (all)	4	0	
Pruritus			
subjects affected / exposed	19 / 78 (24.36%)	0 / 75 (0.00%)	
occurrences (all)	19	0	
Rash acneiform			
subjects affected / exposed	4 / 78 (5.13%)	1 / 75 (1.33%)	
occurrences (all)	4	1	
Rash maculo-papular			
subjects affected / exposed	10 / 78 (12.82%)	0 / 75 (0.00%)	
occurrences (all)	10	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	5 / 78 (6.41%)	2 / 75 (2.67%)	
occurrences (all)	5	2	
Insomnia			

subjects affected / exposed	5 / 78 (6.41%)	1 / 75 (1.33%)	
occurrences (all)	5	1	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	19 / 78 (24.36%)	0 / 75 (0.00%)	
occurrences (all)	22	0	
Hypothyroidism			
subjects affected / exposed	12 / 78 (15.38%)	0 / 75 (0.00%)	
occurrences (all)	13	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 78 (5.13%)	3 / 75 (4.00%)	
occurrences (all)	5	3	
Back pain			
subjects affected / exposed	4 / 78 (5.13%)	7 / 75 (9.33%)	
occurrences (all)	4	7	
Myalgia			
subjects affected / exposed	5 / 78 (6.41%)	1 / 75 (1.33%)	
occurrences (all)	5	1	
Infections and infestations			
Lung infection			
subjects affected / exposed	4 / 78 (5.13%)	2 / 75 (2.67%)	
occurrences (all)	10	4	
Upper respiratory infection			
subjects affected / exposed	4 / 78 (5.13%)	2 / 75 (2.67%)	
occurrences (all)	4	2	
Urinary tract infection			
subjects affected / exposed	7 / 78 (8.97%)	3 / 75 (4.00%)	
occurrences (all)	8	3	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	23 / 78 (29.49%)	12 / 75 (16.00%)	
occurrences (all)	25	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 September 2015	ETOP/IFCT 4-12 STIMULI trial was activated in December 2013 (under original protocol). The low accrual rate experienced in the first few months of the STIMULI study, along with presented results showing significant benefits with Nivolumab treatment with or without Ipilimumab (Antonia S.J. et.al., 2015; Larkin J. et.al., 2015; Postow M.A. et.al, 2017), led the protocol team to decide to proceed to a protocol amendment. The main modifications introduced by the amendment were: • the addition of Nivolumab to consolidation therapy • the addition of carboplatin to standard therapy as an alternative to cisplatin • the addition of PFS as co-primary endpoint • the option of contrast enhanced CT of the brain as an alternative to MRI at screening • allowing one cycle of chemotherapy before enrolment of a patient.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 April 2019	Because of the low accrual rate of STIMULI trial, as well as additional internal strategic considerations unrelated to the scientific rational or trial design, BMS decided not to continue funding the STIMULI trial. Thus, the trial Steering Committee decided to close the accrual of the trial permanently as of April 30, 2019. Patients who had already consented were still allowed to be enrolled until April 30, 2019. After this date, no new patients were allowed to be enrolled into the trial. Treatment and follow-up for all included patients continued as per protocol. Patients in the chemo-radiotherapy phase who met the criteria were still allowed to be randomised.	-

Notes:

Limitations and caveats

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

After premature accrual closure, the statistical design was modified and the primary endpoint of the trial was finally defined as only the PFS (previous: co-primary PFS and OS).

Notes: