



Clinical trial results:

A phase II trial evaluating the safety and efficacy of the addition of concurrent anti-PD-1 nivolumab to standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B Non-Small Cell Lung Carcinoma.

Summary

EudraCT number	2014-005097-11
Trial protocol	BE ES DE NL
Global end of trial date	14 August 2019

Results information

Result version number	v1 (current)
This version publication date	05 May 2021
First version publication date	05 May 2021

Trial information

Trial identification

Sponsor protocol code	ETOP6-14
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02434081
WHO universal trial number (UTN)	-
Other trial identifiers	BMS number: CA209-208

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	14 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 August 2019
Global end of trial reached?	Yes
Global end of trial date	14 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and efficacy of the concurrent nivolumab administration with standard first-line chemotherapy and radiotherapy in locally advanced stage IIIA/B NSCLC, as defined by the rate of grade ≥ 3 pneumonitis (CTCAE V4.0) 6 months post-radiotherapy and, if safety is proven, to assess the progression-free survival.

Protection of trial subjects:

Informed consent for each patient was obtained prior to initiating any trial procedures. Patients have the right to withdraw consent for further trial participation at any time without having to specify the reason. Patients may only start nivolumab treatment if all adverse events from previous chemotherapy have resolved to grade <2 (with a few exceptions specified in the protocol). Because of the potential for clinically meaningful nivolumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected AEs of selected categories. Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab). Also, specific criteria for treatment discontinuation apply, and instructions on how to deal with AEs according to their severity are provided. If a patient inadvertently becomes pregnant while on treatment with nivolumab, trial treatment will be stopped immediately for the patient and the event reported immediately. The trial may be discontinued early in parts or completely if the information on the product leads to doubt as to the benefit/risk ratio, by decision of ETOP or Trial Steering Committee, or at the suggestion of the IDMC based on the interim safety evaluations. The trial can be terminated at any time if the authorization and approval to conduct the trial is withdrawn by ethics committee or regulatory authority decision, insufficient accrual, emerging new data impacting the scientific value of the trial or ethical grounds.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	33 Months
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: 29
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Switzerland: 11

Worldwide total number of subjects	79
EEA total number of subjects	68

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)	44
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

82 eligible patients enrolled in the trial (79 patients in concurrent and 3 in sequential treatment). One of the patients enrolled under the protocol amendment, was initially under the original protocol, but was reconsidered and allowed to switch (assigned to the sequential treatment schedule).

Pre-assignment

Screening details:

A total of 95 patients, registered under the protocol amendment, were captured in iBiobank from 30th of September 2016 (enrollment of 1st patient) until the 6th of August 2018 (accrual suspension). Out of these, 13 were labeled with "Ineligible" or "Error" or "Draft" status.

Period 1

Period 1 title	Concurrent CRT-Nivo (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This is a single arm, open-label trial.

Arms

Arm title	Concurrent CRT-Nivo
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Arm description:

Concurrent administration of chemoradiotherapy (CRT) and nivolumab (nivo)

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	BMS-936558
Other name	MDX-1106
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The initial 4 doses of nivolumab were administered at 360 mg as intravenous infusion (approx. 30 minutes) every 3-weeks. The first 2 doses were administered concurrently with the last two chemotherapy cycles. Nivolumab was administered first and the infusion was promptly followed by a saline flush to clear the line of nivolumab before starting the chemotherapy infusion, no sooner than 30 minutes after completion of the nivolumab infusion. From dose 5 on, nivolumab was administered at 480 mg every 4 weeks for up to 1 year from start of nivolumab treatment, unless nivolumab treatment stopped earlier due to unacceptable toxicity, disease progression, withdrawal of consent or the trial is terminated by the sponsor. Dose 5 started 3 weeks after dose 4. Dose reductions or dose escalations of nivolumab were not permitted.

Number of subjects in period 1	Concurrent CRT-Nivo
Started	79
Completed	31
Not completed	48
Physician decision	2
Consent withdrawn by subject	1
Toxicity	20

Death	2
Progression	20
Protocol deviation	1
Patient died before start of treatment	2

Baseline characteristics

Reporting groups

Reporting group title	Concurrent CRT-Nivo
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Reporting group description: -

Reporting group values	Concurrent CRT-Nivo	Total	
Number of subjects	79	79	
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			
Age at enrolment			
Units: years			
median	62		
full range (min-max)	41 to 78	-	
Gender categorical			
Units: Subjects			
Female	26	26	
Male	53	53	
Smoking history			
Units: Subjects			
Current	22	22	
Former	54	54	
Never	3	3	
ECOG PS at enrolment			
Units: Subjects			
Zero	37	37	
One	41	41	
Unkown/Missing	1	1	
Histology			
Units: Subjects			
Non-squamous	47	47	
Squamous	28	28	
Missing	4	4	
Stage			
Units: Subjects			
IIIA	28	28	
IIIB	50	50	

Missing	1	1	
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Subject analysis sets

Subject analysis set title	Concurrent CRT-Nivo
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Subject analysis set type	Intention-to-treat
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Subject analysis set description:

All patients enrolled to the concurrent chemo-radio-nivo treatment.

Subject analysis set title	Safety population
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Subject analysis set type	Safety analysis
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Subject analysis set description:

All patients who started the concurrent chemo-radio-nivo treatment.

Subject analysis set title	Primary efficacy cohort
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

The primary efficacy analysis cohort included the first 74 assessable patients on concurrent chemoradiotherapy who either completed 1 year of follow-up without an event or had a PFS event up to the 1-year time-point. This cohort did not take into consideration the two patients who died before the treatment started, one who withdrew 2.6 months after enrolment, and the last two enrolled patients who reached a 1-year follow-up at a later timepoint.

Reporting group values	Concurrent CRT-Nivo	Safety population	Primary efficacy cohort
Number of subjects	79	77	74
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age at enrolment			
Units: years			
median	62	62	62
full range (min-max)	41 to 78	41 to 78	41 to 78
Gender categorical Units: Subjects			
Female	26	26	23
Male	53	51	51
Smoking history Units: Subjects			
Current	22	22	21
Former	54	52	50
Never	3	3	3

ECOG PS at enrolment			
Units: Subjects			
Zero	37	37	34
One	41	39	39
Unkown/Missing	1	1	1
Histology			
Units: Subjects			
Non-squamous	47	45	43
Squamous	28	28	27
Missing	4	4	4
Stage			
Units: Subjects			
IIIA	28	27	25
IIIB	50	49	48
Missing	1	1	1

End points

End points reporting groups

Reporting group title	Concurrent CRT-Nivo
Reporting group description:	
Concurrent administration of chemoradiotherapy (CRT) and nivolumab (nivo)	
Subject analysis set title	Concurrent CRT-Nivo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients enrolled to the concurrent chemo-radio-nivo treatment.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who started the concurrent chemo-radio-nivo treatment.	
Subject analysis set title	Primary efficacy cohort
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The primary efficacy analysis cohort included the first 74 assessable patients on concurrent chemoradiotherapy who either completed 1 year of follow-up without an event or had a PFS event up to the 1-year time-point. This cohort did not take into consideration the two patients who died before the treatment started, one who withdrew 2.6 months after enrolment, and the last two enrolled patients who reached a 1-year follow-up at a later timepoint.	

Primary: PFS (primary efficacy cohort)

End point title	PFS (primary efficacy cohort) ^[1]
End point description:	
The censoring date for PFS was the date of the last tumour assessment without event.	
Estimates refer to 1-year PFS.	
End point type	Primary
End point timeframe:	
Progression-free survival (PFS) is defined at the time from first chemotherapy cycle until a documented progression of disease or death if no documented progression had occurred.	
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: Based on the Kaplan-Meier method, the PFS at 1-year was 50.0% (95% CI: 39.9% – 60.1%).	
Thus, the null hypothesis of a 1-year PFS rate of less than or equal to 45% could not be rejected (exact binomial test p=0.23).	

End point values	Primary efficacy cohort			
Subject group type	Subject analysis set			
Number of subjects analysed	74			
Units: Percentage				
number (confidence interval 95%)	50 (39.9 to 60.1)			

Statistical analyses

No statistical analyses for this end point

Primary: Rate of pts without grade \geq 3 pneumonitis 6-months post-RT

End point title	Rate of pts without grade \geq 3 pneumonitis 6-months post-RT ^[2]
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End point description:

End point type	Primary
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End point timeframe:

Grade \geq 3 pneumonitis (CTCAE V4.0) observed any time during 6 months from end of radiotherapy.

Notes:

[2] - 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: This endpoint provides the number of patients (rate) without grade \geq 3 pneumonitis 6-months post-radiotherapy. These were 71 out of 77, thus a rate of 92.2%. The corresponding safety hypothesis has been tested in an interim analysis and safety of the treatment was proven there.

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	77			
Units: Pts w/o grade \geq 3 pneumonitis 6-m post-RT	71			

Statistical analyses

No statistical analyses for this end point

Secondary: TFP3

End point title	TFP3
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End point description:

End point type	Secondary
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End point timeframe:

Time to first pneumonitis of grade \geq 3 (TFP3) is defined as time from the first chemotherapy cycle until first documented pneumonitis of grade \geq 3.

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	77			
Units: Percentage				
number (confidence interval 95%)	87.0 (76.4 to 93.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR

End point title ORR

End point description:

End point type Secondary

End point timeframe:

For the calculation of objective response rate (ORR) the time from first chemotherapy cycle until partial or complete response was considered.

End point values	Concurrent CRT-Nivo			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: No. of subjects with objective response	58			

Statistical analyses

No statistical analyses for this end point

Secondary: TTF

End point title TTF

End point description:

End point type Secondary

End point timeframe:

Time to treatment failure (TTF) is defined as time from first chemotherapy cycle to discontinuation of treatment for any reason, including disease progression, toxicity, withdrawal, lost to follow-up or death.

End point values	Concurrent CRT-Nivo			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Months				
median (confidence interval 95%)	9.2 (6.4 to 12.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: OS

End point title	OS
End point description:	
End point type	Secondary
End point timeframe:	
Overall survival (OS) is defined as time from first chemotherapy cycle until death from any cause.	

End point values	Concurrent CRT-Nivo			
Subject group type	Reporting group			
Number of subjects analysed	79 ^[3]			
Units: Months				
median (confidence interval 95%)	38.8 (26.8 to 9999)			

Notes:

[3] - Upper 95%CI is Not Estimable (NE). Since letters are not accepted, a value of "9999" is entered.

Statistical analyses

No statistical analyses for this end point

Secondary: Toxicity

End point title	Toxicity
End point description:	
Adverse events classified according to CTCAE version 4.	
End point type	Secondary
End point timeframe:	
Time from first chemotherapy cycle until 100 days after the final dose of nivolumab (regardless of whether the adverse events were considered related to the trial treatment).	

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	77			
Units: No. of adverse events	780			

Statistical analyses

No statistical analyses for this end point

Secondary: PFS (full concurrent CRT-Nivo cohort)

End point title	PFS (full concurrent CRT-Nivo cohort)
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End point description:

The censoring date for PFS was the date of the last tumour assessment without event.

Estimates refer to 1-year PFS.

End point type	Secondary
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End point timeframe:

Progression-free survival (PFS) is defined at the time from first chemotherapy cycle until a documented progression of disease or death if no documented progression had occurred.

End point values	Concurrent CRT-Nivo			
Subject group type	Reporting group			
Number of subjects analysed	79			
Units: Percentage				
number (confidence interval 95%)	53.7 (42.0 to 64.0)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected up to 100 days after the final dose of nivolumab, regardless of whether they were considered related to the trial treatment.

Adverse event reporting additional description:

After the last dose, only AEs considered possibly related to nivolumab by the Investigator had to be reported.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	4.0
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Reporting groups

Reporting group title	Safety cohort
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Reporting group description: -

Serious adverse events	Safety cohort		
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 77 (48.05%)		
number of deaths (all causes)	37		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelodysplastic syndrome			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Cardiac disorders			
Heart failure			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocarditis			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pericarditis			

subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Stroke			
subjects affected / exposed	3 / 77 (3.90%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 1		
Ataxia			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	4 / 77 (5.19%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	3 / 77 (3.90%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Malaise			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Autoimmune disorder	Additional description: The main cause of death is not certain. Immune-mediated myocarditis vs pulmonary embolism are not excluded.		
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Gastrointestinal disorders			
Esophagitis			
subjects affected / exposed	3 / 77 (3.90%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	3 / 77 (3.90%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		
Esophageal fistula			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Esophageal varices hemorrhage			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	13 / 77 (16.88%)		
occurrences causally related to treatment / all	13 / 13		
deaths causally related to treatment / all	1 / 1		
Dyspnea			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchopulmonary hemorrhage			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchial stricture			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary fibrosis			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchial infection			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Upper respiratory infection			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	2 / 77 (2.60%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter related infection			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 77 (1.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety cohort		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 77 (98.70%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	38 / 77 (49.35%)		
occurrences (all)	38		
Fever			
subjects affected / exposed	15 / 77 (19.48%)		
occurrences (all)	15		
Pain			
subjects affected / exposed	13 / 77 (16.88%)		
occurrences (all)	13		
Flu like symptoms			
subjects affected / exposed	6 / 77 (7.79%)		
occurrences (all)	6		
Non-cardiac chest pain			
subjects affected / exposed	5 / 77 (6.49%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	34 / 77 (44.16%)		
occurrences (all)	34		
Productive cough			
subjects affected / exposed	31 / 77 (40.26%)		
occurrences (all)	31		
Dyspnea			
subjects affected / exposed	26 / 77 (33.77%)		
occurrences (all)	26		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	13 / 77 (16.88%)		
occurrences (all)	13		
Anxiety			
subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	4		

Investigations			
Lipase increased			
subjects affected / exposed	9 / 77 (11.69%)		
occurrences (all)	9		
Lymphocyte count decreased			
subjects affected / exposed	9 / 77 (11.69%)		
occurrences (all)	9		
Platelet count decreased			
subjects affected / exposed	9 / 77 (11.69%)		
occurrences (all)	9		
White blood cell decreased			
subjects affected / exposed	9 / 77 (11.69%)		
occurrences (all)	9		
Creatinine increased			
subjects affected / exposed	8 / 77 (10.39%)		
occurrences (all)	8		
Serum amylase increased			
subjects affected / exposed	8 / 77 (10.39%)		
occurrences (all)	8		
Alanine aminotransferase increased			
subjects affected / exposed	6 / 77 (7.79%)		
occurrences (all)	6		
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 77 (6.49%)		
occurrences (all)	5		
Weight gain			
subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	4		
Injury, poisoning and procedural complications			
Dermatitis radiation			
subjects affected / exposed	5 / 77 (6.49%)		
occurrences (all)	5		
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 77 (14.29%)		
occurrences (all)	11		

Headache subjects affected / exposed occurrences (all)	6 / 77 (7.79%) 6		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	5 / 77 (6.49%) 5		
Tremor subjects affected / exposed occurrences (all)	4 / 77 (5.19%) 4		
Stroke subjects affected / exposed occurrences (all)	4 / 77 (5.19%) 4		
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all)	37 / 77 (48.05%) 37		
Neutrophil count decreased subjects affected / exposed occurrences (all)	27 / 77 (35.06%) 27		
Febrile neutropenia subjects affected / exposed occurrences (all)	7 / 77 (9.09%) 7		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	4 / 77 (5.19%) 4		
Gastrointestinal disorders Dysphagia subjects affected / exposed occurrences (all)	26 / 77 (33.77%) 26		
Diarrhea subjects affected / exposed occurrences (all)	12 / 77 (15.58%) 12		
Vomiting subjects affected / exposed occurrences (all)	10 / 77 (12.99%) 10		
Esophageal pain			

subjects affected / exposed	7 / 77 (9.09%)		
occurrences (all)	7		
Constipation			
subjects affected / exposed	8 / 77 (10.39%)		
occurrences (all)	8		
Mucositis oral			
subjects affected / exposed	5 / 77 (6.49%)		
occurrences (all)	5		
Esophagitis			
subjects affected / exposed	24 / 77 (31.17%)		
occurrences (all)	24		
Nausea			
subjects affected / exposed	20 / 77 (25.97%)		
occurrences (all)	20		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	12 / 77 (15.58%)		
occurrences (all)	12		
Dry skin			
subjects affected / exposed	10 / 77 (12.99%)		
occurrences (all)	10		
Rash acneiform			
subjects affected / exposed	6 / 77 (7.79%)		
occurrences (all)	6		
Rash maculo-papular			
subjects affected / exposed	5 / 77 (6.49%)		
occurrences (all)	5		
Alopecia			
subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	4		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 77 (5.19%)		
occurrences (all)	4		
Endocrine disorders			

Hypothyroidism subjects affected / exposed occurrences (all)	6 / 77 (7.79%) 6		
Hyperthyroidism subjects affected / exposed occurrences (all)	5 / 77 (6.49%) 5		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	9 / 77 (11.69%) 9		
Infections and infestations Bronchial infection subjects affected / exposed occurrences (all) Upper respiratory infection subjects affected / exposed occurrences (all) Lung infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	8 / 77 (10.39%) 8 7 / 77 (9.09%) 7 6 / 77 (7.79%) 6 5 / 77 (6.49%) 5		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all) Hypomagnesaemia subjects affected / exposed occurrences (all)	14 / 77 (18.18%) 14 6 / 77 (7.79%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 June 2016	Under first amendment there would still be two treatment schedules in the trial, a concurrent and a sequential, as in the original protocol. The amendment differed from the original in the sense that, under both treatment schedules, administration of nivolumab would start together with radiotherapy.
04 July 2017	Under second amendment there would be only the concurrent treatment schedule in the trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported