# 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 |

### 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 |

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 |

Reporting group description: -

| Reporting group values | Concurrent CRT-Nivo | Total | |
|---|---|---|---|
| Number of subjects | 79 | 79 | |
| Age categorical<br>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<br>Units: Subjects | | | |
| Female | 26 | 26 | |
| Male | 53 | 53 | |
| Smoking history<br>Units: Subjects | | | |
| Current | 22 | 22 | |
| Former | 54 | 54 | |
| Never | 3 | 3 | |
| ECOG PS at enrolment<br>Units: Subjects | | | |
| Zero | 37 | 37 | |
| One | 41 | 41 | |
| Unkown/Missing | 1 | 1 | |
| Histology<br>Units: Subjects | | | |
| Non-squamous | 47 | 47 | |
| Squamous | 28 | 28 | |
| Missing | 4 | 4 | |
| Stage<br>Units: Subjects | | | |
| IIIA | 28 | 28 | |
| IIIB | 50 | 50 | |

| | | | |
|---|---|---|---|
| Missing | 1 | 1 | |

**Subject analysis sets**

| | |
|---|---|
| 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.

| **Reporting group values** | Concurrent CRT-Nivo | Safety population | Primary efficacy cohort |
|---|---|---|---|
| Number of subjects | 79 | 77 | 74 |
| Age categorical<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>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<br>Units: Subjects | | | |
| Female | 26 | 26 | 23 |
| Male | 53 | 51 | 51 |
| Smoking history<br>Units: Subjects | | | |
| Current | 22 | 22 | 21 |
| Former | 54 | 52 | 50 |
| Never | 3 | 3 | 3 |

| | | | |
|---|---|---|---|
| ECOG PS at enrolment<br>Units: Subjects | | | |
| Zero | 37 | 37 | 34 |
| One | 41 | 39 | 39 |
| Unkown/Missing | 1 | 1 | 1 |
| Histology<br>Units: Subjects | | | |
| Non-squamous | 47 | 45 | 43 |
| Squamous | 28 | 28 | 27 |
| Missing | 4 | 4 | 4 |
| Stage<br>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.<br><br>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.<br>Justification: Based on the Kaplan-Meier method, the PFS at 1-year was 50.0% (95% CI: 39.9% – 60.1%).<br>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≥3 pneumonitis 6-months post-RT

| End point title | Rate of pts without grade≥3 pneumonitis 6-months post-RT[2] |
|---|---|

End point description:

| End point type | Primary |
|---|---|

End point timeframe:

Grade ≥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≥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≥3 pneumonitis 6-m post-RT | 71 | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: TFP3

| End point title | TFP3 |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Time to first pneumonitis of grade ≥3 (TFP3) is defined as time from the first chemotherapy cycle until first documented pneumonitis of grade ≥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) |
|---|---|

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 |
|---|---|

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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 4.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Safety cohort |

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

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

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