# Clinical trial results:
# A phase II trial of nivolumab in combination with ipilimumab to evaluate efficacy and safety in relapsed lung cancer and to evaluate biomarkers predictive for response to immune checkpoint inhibition

## Summary

| | |
|---|---|
| EudraCT number | 2016-003334-25 |
| Trial protocol | DE |
| Global end of trial date | 20 November 2023 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 21 February 2025 |
| First version publication date | 21 February 2025 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | Uni-Koeln-2785 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03083691 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | University of Cologne |
| Sponsor organisation address | Albertus-Magnus-Platz, Cologne, Germany, 50923 |
| Public contact | Inken Terjung, University of Cologne, +49 22147898766, inken.terjung@uk-koeln.de |
| Scientific contact | Dr. Rieke Fischer, University of Cologne, +49 22147842672, rieke.fischer@uk-koeln.de |

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 | 20 November 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 31 August 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 November 2023 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Cohort 1:
To assess ORR when ipilimumab is added to nivolumab after progression on nivolumab monotherapy in patients relapsed with non-squamous NSCLC (second line).
Note: Cohort 1 was closed for enrollment. Subjects who started screening for cohort 1 prior to stop of recruitment initiated by Coordinating PI on April 25 2019 continue to receive treatment. SCLC subjects eligible for BIOLUMA are enrolled in cohort 2b after TMB-Prescreening from October 29 2018 on.

Cohort 2a:
To assess ORR of the combination therapy of ipilimumab and nivolumab in patients with relapsed SCLC and non-discriminated TMB (second line).
Note: Cohort 2a was closed for enrollment. SCLC Subjects eligible for BIOLUMA are enrolled in Cohort 2b after TMB-Prescreening from October 29 2018 on.

Cohort 2b:
To assess ORR of the combination therapy of ipilimumab and nivolumab in patients with relapsed SCLC and high TMB (second line).

Protection of trial subjects:

The trial data including study procedures, safety results and efficacy results were extensively reviewed by the participating DMSC members on a regular basis.
In the initial cohort 2 (SCLC, not TMB-discriminated), two treatment-related deaths occurred. One patient died from pneumonitis, one patient experienced a fatal course of encephalitis. Both patients did have a good tumor response within the trial. As during that time new data were presented, which indicated that the combination therapy of nivolumab and ipilimumab in SCLC patients only has beneficial effects in patients with high tumor mutation burden (23), a risk-benefit consideration lead to stop of recruitment in cohort 2. The remaining SCLC patients in the trial were treated analogous to the NSCLC patients in cohort 1.
The cohort was re-opened for patients with high tumor mutation burden only (cohort 2b) and the former cohort 2 was renamed to cohort 2a for clarification reasons.
In cohort 2b, one patient died due to study-procedure related complications: in order to gain a tumor biopsy, a bronchoscopy had been performed. During the procedure, the patient died from a cardiogenic shock. The patient had achieved a partial response to the study treatment. As a consequence of that fatal event, the protocol was amended (protocol amendment no.4) for cohort 2b to change tumor biopsy before study treatment from mandatory to optional.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 05 April 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Germany: 90 |
| Worldwide total number of subjects | 90 |
| EEA total number of subjects | 90 |

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) | 47 |
| From 65 to 84 years | 42 |
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment cohort 1: 05/04/2017 - 25/04/2019
Recruitment cohort 2a: 05/04/2017 - 15/12/2017
Recruitment cohort 2b: 24/10/2018 - 28/07/2022

Last Patient Out: 20/11/2023

### Pre-assignment

Screening details:

Screenings: 127 patients

Screening failures: 37 patients (cohort 1: 20; cohort 2a: 10; cohort 2b: 7)

Reasons for screening failures:
- non-fulfillment of inclusion criterion: 17 patients
- fulfillment of exclusion criterion: 18 patients
- withdrawal of ICF during screening: 2 patients

Pre-screeenings (for cohort 2b only): 297 patients

### Period 1

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

Blinding implementation details:

As this was a single-arm, non-randomized open-label study, blinding did not apply.

### Arms

| | |
|---|---|
| **Arm title** | Single arm |

Arm description:

Cohort 1 (non-squamous NSCLC):
Treatment Part A: nivolumab 240 mg IV q2w as monotherapy; at the time of disease progression another re-biopsy; then Treatment Part B: combination therapy (nivolumab in a dose of 3 mg/kg q2w together with ipilimumab 1 mg/kg IV q6w (with a 12 days gap between last dose of nivolumab and nivolumab + ipilimumab).
In case of occurrence of intolerable toxicity attributed to the combination therapy, treatment was continued with nivolumab 240 mg q2w monotherapy only.

Cohort 2a (SCLC all-comer) + 2b (SCLC TMB high):
Treatment Part A: nivolumab 1 mg/kg q3w together with ipilimumab 3 mg/kg q3w for a total of four doses, in case of occurrence of an AE and if AE was attributed to combination therapy, it was possible to continue treatment with Part B without completion of the four combined doses.
Treatment Part B: another optional rebiopsy, then nivolumab 240 mg q2w monotherapy until disease progression or inacceptable toxicity

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Nivolumab |
| Investigational medicinal product code | |
| Other name | OPDIVO |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Cohort 1:
- Part A: nivolumab (monotherapy) 240 mg as a 30 minute IV-infusion, every 2 weeks
- Part B: nivolumab (in combination with ipilimumab) dose = 3 mg/kg as a 30 minute IV-infusion, every 2 weeks

Cohort 2a and 2b:
- Part A: 4 doses of nivolumab (in combination with ipilimumab), dose = 1 mg/kg as a 30 minute IV-infusion, every 3 weeks
- Part B: nivolumab (monotherapy) 240 mg as a 30 minute IV-infusion every 2 weeks

For combination therapy with ipilimumab: Nivolumab should be administered as a 30 minute infusion, followed by Ipilimumab as a 90 minutes infusion (in between 30 min break)

| | |
|---|---|
| Investigational medicinal product name | Ipilimumab |
| Investigational medicinal product code | |
| Other name | YERVOY |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Cohort 1:
- Part A: no administration of ipilimumab
- Part B: ipilimumab (in combination with nivolumab) dose = 1 mg/kg as a 90 minute IV-infusion, every 6 weeks

Cohort 2a and 2b:
-Part A: four doses of ipilimumab (in combination with nivolumab) dose = 3 mg/kg as a 90 minute IV-infusion, every 3 weeks
-Part B: no administration of ipilimumab

For combination therapy of nivolumab + ipilimumab: nivolumab should be administered as a 30 minute infusion, followed by ipilimumab as a 90 minute infusion (in between 30 min break)

| **Number of subjects in period 1** | Single arm |
|---|---|
| Started | 90 |
| Completed | 90 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Overall trial |
|---|---|

Reporting group description: -

| Reporting group values | Overall trial | Total | |
|---|---|---|---|
| Number of subjects | 90 | 90 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 47 | 47 | |
| From 65-84 years | 42 | 42 | |
| 85 years and over | 1 | 1 | |
| Age continuous<br>Units: years | | | |
| median | 63.0 | | |
| full range (min-max) | 38 to 85 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 41 | 41 | |
| Male | 49 | 49 | |

### Subject analysis sets

| Subject analysis set title | Response-evaluable population - cohort 1 |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

The response-evaluable population includes all patients who received at least one dose of study medication and who had at least one follow-up tumor assessment (except patients with a switch of tumor histology (all cohorts) and patients who received additional tumor treatment within the trial).
The response-evaluable population was the primary population for the efficacy endpoints ORR, DCR, DR, TTR, PFS and OS. Subjects who continued treatment beyond initial investigator-assessed, RECIST 1.1-defined progression were considered to have investigator-assessed progressive disease at the time of the initial progression event.

| Subject analysis set title | Response-evaluable population - cohort 2b |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

The response-evaluable population includes all patients who received at least one dose of study medication and who had at least one follow-up tumor assessment (except patients with a switch of tumor histology (all cohorts)).
The response-evaluable population was the primary population for the efficacy endpoints ORR, DCR, DR, TTR, PFS and OS. Subjects who continued treatment beyond initial investigator-assessed, RECIST 1.1-defined progression were considered to have investigator-assessed progressive disease at the time of the initial progression event.

| Subject analysis set title | Response-evaluable population - cohort 2a |
|---|---|

| | |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

The response-evaluable population includes all patients who received at least one dose of study medication and who had at least one follow-up tumor assessment (except patients with a switch of tumor histology (all cohorts) patients in cohort 2a treated analogously to cohort 1).
The response-evaluable population was the primary population for the efficacy endpoints ORR, DCR, DR, TTR, PFS and OS. Subjects who continued treatment beyond initial investigator-assessed, RECIST 1.1-defined progression were considered to have investigator-assessed progressive disease at the time of the initial progression event. Subjects in cohort 2a, who were treated analogous to cohort 1 for safety reasons after two treatmentrelated deaths occurred, were only included in the response-evaluable population, if they received at least one dose of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg + follow-up assessment before switch.

| | |
|---|---|
| Subject analysis set title | Safety analysis population - cohort 1 |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety analysis population includes all enrolled patients who received at least one dose of study medication. It is the primary population for evaluating patient characteristics, treatment compliance, toxicity and AEs.

| | |
|---|---|
| Subject analysis set title | Safety analysis population - cohort 2b |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The safety analysis population includes all enrolled patients who received at least one dose of study medication. It is the primary population for evaluating patient characteristics, treatment compliance, toxicity and AEs.

| | |
|---|---|
| Subject analysis set title | Safety analysis population - cohort 2a |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The safety analysis population includes all enrolled patients who received at least one dose of study medication. It is the primary population for evaluating patient characteristics, treatment compliance, toxicity and AEs.

| **Reporting group values** | Response-evaluable population - cohort 1 | Response-evaluable population - cohort 2b | Response-evaluable population - cohort 2a |
|---|---|---|---|
| Number of subjects | 25 | 45 | 15 |
| Age categorical<br>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) | 12 | 26 | 7 |
| From 65-84 years | 13 | 19 | 8 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| median | 66.0 | 62.0 | 65.0 |
| full range (min-max) | 42 to 79 | 38 to 79 | 46 to 80 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 12 | 23 | 5 |
| Male | 13 | 22 | 10 |

| **Reporting group values** | Safety analysis population - cohort 1 | Safety analysis population - cohort 2b | Safety analysis population - cohort 2a |
|---|---|---|---|
| Number of subjects | 27 | 45 | 18 |
| 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) | 13 | 26 | 8 |
| From 65-84 years | 13 | 19 | 10 |
| 85 years and over | 1 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| median | 66.0 | 62.0 | 65.5 |
| full range (min-max) | 42 to 85 | 38 to 79 | 64 to 80 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 12 | 23 | 6 |
| Male | 15 | 22 | 12 |

## End points

### End points reporting groups

| Reporting group title | Single arm |
|---|---|

Reporting group description:

Cohort 1 (non-squamous NSCLC):
Treatment Part A: nivolumab 240 mg IV q2w as monotherapy; at the time of disease progression another re-biopsy; then Treatment Part B: combination therapy (nivolumab in a dose of 3 mg/kg q2w together with ipilimumab 1 mg/kg IV q6w (with a 12 days gap between last dose of nivolumab and nivolumab + ipilimumab).
In case of occurrence of intolerable toxicity attributed to the combination therapy, treatment was continued with nivolumab 240 mg q2w monotherapy only.

Cohort 2a (SCLC all-comer) + 2b (SCLC TMB high):
Treatment Part A: nivolumab 1 mg/kg q3w together with ipilimumab 3 mg/kg q3w for a total of four doses, in case of occurrence of an AE and if AE was attributed to combination therapy, it was possible to continue treatment with Part B without completion of the four combined doses.
Treatment Part B: another optional rebiopsy, then nivolumab 240 mg q2w monotherapy until disease progression or inacceptable toxicity

| Subject analysis set title | Response-evaluable population - cohort 1 |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

The response-evaluable population includes all patients who received at least one dose of study medication and who had at least one follow-up tumor assessment (except patients with a switch of tumor histology (all cohorts) and patients who received additional tumor treatment within the trial).
The response-evaluable population was the primary population for the efficacy endpoints ORR, DCR, DR, TTR, PFS and OS. Subjects who continued treatment beyond initial investigator-assessed, RECIST 1.1-defined progression were considered to have investigator-assessed progressive disease at the time of the initial progression event.

| Subject analysis set title | Response-evaluable population - cohort 2b |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

The response-evaluable population includes all patients who received at least one dose of study medication and who had at least one follow-up tumor assessment (except patients with a switch of tumor histology (all cohorts)).
The response-evaluable population was the primary population for the efficacy endpoints ORR, DCR, DR, TTR, PFS and OS. Subjects who continued treatment beyond initial investigator-assessed, RECIST 1.1-defined progression were considered to have investigator-assessed progressive disease at the time of the initial progression event.

| Subject analysis set title | Response-evaluable population - cohort 2a |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

The response-evaluable population includes all patients who received at least one dose of study medication and who had at least one follow-up tumor assessment (except patients with a switch of tumor histology (all cohorts) patients in cohort 2a treated analogously to cohort 1).
The response-evaluable population was the primary population for the efficacy endpoints ORR, DCR, DR, TTR, PFS and OS. Subjects who continued treatment beyond initial investigator-assessed, RECIST 1.1-defined progression were considered to have investigator-assessed progressive disease at the time of the initial progression event. Subjects in cohort 2a, who were treated analogous to cohort 1 for safety reasons after two treatmentrelated deaths occurred, were only included in the response-evaluable population, if they received at least one dose of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg + follow-up assessment before switch.

| Subject analysis set title | Safety analysis population - cohort 1 |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety analysis population includes all enrolled patients who received at least one dose of study medication. It is the primary population for evaluating patient characteristics, treatment compliance, toxicity and AEs.

| Subject analysis set title | Safety analysis population - cohort 2b |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

The safety analysis population includes all enrolled patients who received at least one dose of study medication. It is the primary population for evaluating patient characteristics, treatment compliance, toxicity and AEs.

| Subject analysis set title | Safety analysis population - cohort 2a |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

The safety analysis population includes all enrolled patients who received at least one dose of study medication. It is the primary population for evaluating patient characteristics, treatment compliance, toxicity and AEs.

## Primary: Overall response rate (ORR)

| End point title | Overall response rate (ORR) |
|---|---|

End point description:

ORR per RECIST 1.1 with 95% confidence interval was calculated based on all patients in the response-evaluable population. ORR was defined as proportion of subjects whose best confirmed objective response is a CR or PR as assessed by RECIS v1.1, relative to the evaluable population.

Cohort 1:
ORR according to investigator-assessed RECIST 1.1 criteria of the combination of nivolumab and ipilimumab after progression on nivolumab monotherapy in patients re-lapsed with non-squamous NSCLC.
Cohort 2a:
ORR according to investigator-assessed RECIST 1.1 criteria of the combination of nivolumab and ipilimumab in patients with relapsed SCLC and non-discriminated TMB.
Cohort 2b:
ORR according to investigator-assessed RECIST 1.1 criteria of the combination of nivolumab and ipilimumab in patients with relapsed SCLC and high TMB.

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

End point timeframe:

05/04/2017 to 31/08/2022

| **End point values** | Response-evaluable population - cohort 1 | Response-evaluable population - cohort 2b | Response-evaluable population - cohort 2a | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 12[1] | 43[2] | 15 | |
| Units: patients | 1 | 4 | 4 | |

Notes:

[1] - Only 12 patients were treated in treatment part B. ORR of treatment part B is the primary endpoint

[2] - 2 pts are not included in per protocol analysis due to add. tumor treatment or staging too early

## Statistical analyses

| **Statistical analysis title** | Cohort 1, Cohort 2a, Cohort 2b |
|---|---|
| Comparison groups | Response-evaluable population - cohort 2b v Response-evaluable population - cohort 1 v Response-evaluable population - cohort 2a |

| | |
|---|---|
| Number of subjects included in analysis | 70 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0 [3] |
| Method | p not applicable |

Notes:

[3] - No comparison was performed between the 3 cohorts

| **Statistical analysis title** | Cohort 1, Cohort 2a, Cohort 2b |
|---|---|
| Comparison groups | Response-evaluable population - cohort 2a v Response-evaluable population - cohort 1 v Response-evaluable population - cohort 2b |
| Number of subjects included in analysis | 70 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0 [4] |
| Method | p not applicable |

Notes:

[4] - No comparison between the 3 cohorts was performed

| **Statistical analysis title** | Cohort 1, Cohort 2a, Cohort 2b |
|---|---|
| Comparison groups | Response-evaluable population - cohort 2b v Response-evaluable population - cohort 2a v Response-evaluable population - cohort 1 |
| Number of subjects included in analysis | 70 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0 [5] |
| Method | p not applicable |

Notes:

[5] - No comparison was done between the 3 cohorts

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first intake of study drug (or if adverse events related to study procedures, after signature of informed consent), and for a minimum of 100 days following the last intake of study drug (or for serious adverse events until end of survival follow-up)

Adverse event reporting additional description:

Frequent study visits with laboratory assessments.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 26.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Cohort 1 |

Reporting group description:

NSCLC

| | |
|---|---|
| Reporting group title | Cohort 2a |

Reporting group description:

SCLC all-comer

| | |
|---|---|
| Reporting group title | Cohort 2b |

Reporting group description:

SCLC TMB high

| Serious adverse events | Cohort 1 | Cohort 2a | Cohort 2b |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 25 / 27 (92.59%) | 18 / 18 (100.00%) | 43 / 45 (95.56%) |
| number of deaths (all causes) | 18 | 16 | 37 |
| number of deaths resulting from adverse events | 18 | 16 | 37 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 14 / 27 (51.85%) | 9 / 18 (50.00%) | 25 / 45 (55.56%) |
| occurrences causally related to treatment / all | 0 / 15 | 0 / 10 | 0 / 28 |
| deaths causally related to treatment / all | 0 / 14 | 0 / 9 | 0 / 27 |
| Metastases to meninges | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cancer pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Small cell lung cancer | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour pseudoprogression | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Cancer surgery | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheterisation venous | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 1 / 18 (5.56%) | 5 / 45 (11.11%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 5 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | 2 / 45 (4.44%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 2 / 18 (11.11%) | 3 / 45 (6.67%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| Injection site inflammation | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 27 (14.81%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 2 / 5 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Aspiration | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 2 / 45 (4.44%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| Dyspnoea | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 27 (14.81%) | 2 / 18 (11.11%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 2 / 18 (11.11%) | 3 / 45 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 3 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 1 / 1 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |

| | | | |
|---|---|---|---|
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic enzymes increased | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Femur fracture | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Aphasia | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Diabetic hyperosmolar coma | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disorientation | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Facial paralysis | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Polyneuropathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sensory loss | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphadenitis | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Immune-mediated enterocolitis | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Autoimmune colitis | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Autoimmune pancreatitis | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 1 / 18 (5.56%) | 2 / 45 (4.44%) |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 1 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Faecaloma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric perforation | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune-mediated pancreatitis | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaundice | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prerenal failure | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelocaliectasis | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |

| | | | |
|---|---|---|---|
| Hyperthyroidism | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 2 / 18 (11.11%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune-mediated hyperthyroidism | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis aseptic | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Pneumonia | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 2 / 18 (11.11%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia necrotising | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | 2 / 45 (4.44%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vestibular neuronitis | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 1 / 18 (5.56%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 3 / 18 (16.67%) | 2 / 45 (4.44%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Cohort 1 | Cohort 2a | Cohort 2b |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 25 / 27 (92.59%) | 16 / 18 (88.89%) | 39 / 45 (86.67%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 18 (5.56%) | 6 / 45 (13.33%) |
| occurrences (all) | 1 | 4 | 15 |
| Amylase increased | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 3 / 18 (16.67%) | 6 / 45 (13.33%) |
| occurrences (all) | 3 | 3 | 8 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 3 / 18 (16.67%) | 5 / 45 (11.11%) |
| occurrences (all) | 1 | 5 | 11 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 18 (5.56%) | 7 / 45 (15.56%) |
| occurrences (all) | 2 | 1 | 8 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 4 / 18 (22.22%) | 3 / 45 (6.67%) |
| occurrences (all) | 1 | 6 | 3 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 2 / 18 (11.11%) | 1 / 45 (2.22%) |
| occurrences (all) | 3 | 2 | 1 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 2 / 18 (11.11%) | 6 / 45 (13.33%) |
| occurrences (all) | 13 | 3 | 14 |
| Lipase increased | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 3 / 18 (16.67%) | 9 / 45 (20.00%) |
| occurrences (all) | 4 | 5 | 16 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 0 / 18 (0.00%) | 9 / 45 (20.00%) |
| occurrences (all) | 0 | 0 | 18 |
| Platelet count decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 27 (3.70%) | 2 / 18 (11.11%) | 4 / 45 (8.89%) |
| occurrences (all) | 2 | 2 | 5 |
| Weight decreased | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 0 / 18 (0.00%) | 4 / 45 (8.89%) |
| occurrences (all) | 2 | 0 | 4 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 2 / 18 (11.11%) | 2 / 45 (4.44%) |
| occurrences (all) | 11 | 2 | 2 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 7 / 27 (25.93%) | 3 / 18 (16.67%) | 5 / 45 (11.11%) |
| occurrences (all) | 10 | 4 | 7 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 5 / 45 (11.11%) |
| occurrences (all) | 1 | 0 | 5 |
| Chest pain | | | |
| subjects affected / exposed | 6 / 27 (22.22%) | 1 / 18 (5.56%) | 0 / 45 (0.00%) |
| occurrences (all) | 6 | 1 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 6 / 27 (22.22%) | 9 / 18 (50.00%) | 17 / 45 (37.78%) |
| occurrences (all) | 8 | 10 | 18 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 18 (5.56%) | 5 / 45 (11.11%) |
| occurrences (all) | 1 | 1 | 6 |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 3 / 18 (16.67%) | 0 / 45 (0.00%) |
| occurrences (all) | 4 | 3 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 0 / 18 (0.00%) | 4 / 45 (8.89%) |
| occurrences (all) | 1 | 0 | 5 |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 27 (18.52%) | 8 / 18 (44.44%) | 15 / 45 (33.33%) |
| occurrences (all) | 7 | 13 | 21 |

| | | | |
|---|---|---|---|
| Nausea | | | |
| subjects affected / exposed | 9 / 27 (33.33%) | 5 / 18 (27.78%) | 9 / 45 (20.00%) |
| occurrences (all) | 10 | 6 | 9 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 18 (5.56%) | 3 / 45 (6.67%) |
| occurrences (all) | 1 | 1 | 4 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 9 / 27 (33.33%) | 4 / 18 (22.22%) | 4 / 45 (8.89%) |
| occurrences (all) | 11 | 4 | 6 |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 2 / 18 (11.11%) | 3 / 45 (6.67%) |
| occurrences (all) | 3 | 2 | 5 |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 3 / 18 (16.67%) | 4 / 45 (8.89%) |
| occurrences (all) | 2 | 4 | 4 |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 1 / 18 (5.56%) | 4 / 45 (8.89%) |
| occurrences (all) | 2 | 1 | 4 |
| Pruritus | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 4 / 18 (22.22%) | 13 / 45 (28.89%) |
| occurrences (all) | 4 | 4 | 18 |
| Rash | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 3 / 18 (16.67%) | 8 / 45 (17.78%) |
| occurrences (all) | 2 | 3 | 12 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | 3 / 18 (16.67%) | 3 / 45 (6.67%) |
| occurrences (all) | 0 | 3 | 3 |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 4 / 18 (22.22%) | 4 / 45 (8.89%) |
| occurrences (all) | 2 | 4 | 4 |
| Hypothyroidism | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 27 (7.41%) | 2 / 18 (11.11%) | 1 / 45 (2.22%) |
| occurrences (all) | 2 | 2 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 5 / 18 (27.78%) | 3 / 45 (6.67%) |
| occurrences (all) | 2 | 6 | 6 |
| Back pain | | | |
| subjects affected / exposed | 2 / 27 (7.41%) | 2 / 18 (11.11%) | 4 / 45 (8.89%) |
| occurrences (all) | 5 | 4 | 4 |
| Infections and infestations | | | |
| Infection | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 1 / 18 (5.56%) | 3 / 45 (6.67%) |
| occurrences (all) | 6 | 1 | 4 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 1 / 18 (5.56%) | 3 / 45 (6.67%) |
| occurrences (all) | 1 | 1 | 3 |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 4 / 18 (22.22%) | 3 / 45 (6.67%) |
| occurrences (all) | 5 | 4 | 5 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 4 / 27 (14.81%) | 0 / 18 (0.00%) | 7 / 45 (15.56%) |
| occurrences (all) | 5 | 0 | 8 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 27 (3.70%) | 2 / 18 (11.11%) | 5 / 45 (11.11%) |
| occurrences (all) | 1 | 4 | 5 |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 27 (11.11%) | 2 / 18 (11.11%) | 10 / 45 (22.22%) |
| occurrences (all) | 3 | 3 | 13 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 22 January 2018 | Protocol Amendment 1 comprised replacement of deep rectal swabs by stool samples for microbiome analysis, as this sample modality was more feasibly for patients to perform and a higher return flow for samples was expected. Some clarifications of reporting period for SAEs related to study drug or to study-related procedures were included as well as specification of SAE reporting of SAEs related to disease progression. Other changes in amendment 1 concerned new safety data on nivolumab and ipilimumab. |
| 30 October 2018 | With Protocol Amendment 2, cohort 2 was modified to include SCLC patients with high tumor mutation burden only and TMB pre-screening was implemented for SCLC patients. This amendment was necessary as in December 2017, two treatment-related had occured. As new data were presented, which indicated that the combination therapy of nivolumab and ipilimumab in SCLC patients only had beneficial effects in patients with high tumor mutation burden, a risk-benefit consideration lead to stop of recruitment in cohort 2. The remaining SCLC patients in the trial were treated analogous to the NSCLC patients in cohort 1 for safety reasons. |
| 18 December 2019 | Protocol Amendment 4: The original cohort 2 was subdivided in cohort 2a for the terminated cohort of SCLC patients who were not TMB discriminated and in cohort 2b for patients with high tumor mutation burden. The renaming was performed in order to have a clear separation of the biologically different patient groups. Additionally, the initial mandatory rebiopsy before study treatment was changed to optional in cohort 2b. This decision was made after one procedure-related death had occurred for bronchoscopic tumor biopsy in a trial subject who had responded well to study drug treatment.<br><br>Protocol amendment 3 was rejected by EC, but approved by CA. Rrecruitment for NSCLC patients (cohort 1) was closed. This decision had been made as a high dropout rate from treatment part A to part B was observed. Thus, due to lack of feasibility, enrolment to this cohort was terminated early. Subjects enrolled into this cohort prior to the amendment continued to receive treatment with study drugs per protocol.<br>For the SCLC cohort, the amendment included expansion of the patient number to a total of 79 trial subjects<br>(TMB high plus TMB non-discriminated SCLC patients). |
| 05 June 2020 | Protocol Amendment 5 comprised a modification of inclusion criteria for SCLC patients in cohort 2b. Given the fact, that some patients receive rechallenge treatment with a platinum-based therapy instead of topotecan, enrolment after 2nd line therapy was allowed independent of the drug used in 2.line (with exception to monotherapy with anti-PD-1/-PD-L1/-CTLA-4 antibodies) to allow a more realistic treatment setting. Additionally, the interval between radiation of brain metastases and start of study treatment was eliminated as data indicated that both can be performed simultaneously without increase of toxicity. This indicated that delay of study treatment would be potentially more harmful to the patient, given the rapid growth of this tumor entity. |

| | |
|---|---|
| 15 October 2021 | Protocol Amendment 6 was performed for adjustment of statistical plan for cohort 2b. The original plan was a one-stage A'Hern design with response proportions 0 = 0.075 and 1 = 0.2,  = 0.1 and  = 0.10. Here, 51 evaluable patients were required, the null hypothesis 0:  ≤ 0.075 would have been rejected if at least 7 responses in 51 patients were observed. By the same assumptions and expectation as described above, 59 (≈ 51/0.9) patients would be needed to be enrolled, thus 563 patients were expected to be screened in total to include 59 TMB high patients. As recruitment into the trial was slower than anticipated, the patient number was reduced within a modified statistic which still provided sufficient power for primary endpoint analysis. Additionally, some clarifications concerning the screening biopsy in cohort 2b were provided. |
| 19 December 2022 | With Protocol Amendment 7, timelines for conduct of the trial were modified and enrolment for cohort 2b was closed, as the cohort was fully recruited. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial?  Yes

| Date | Interruption | Restart date |
|---|---|---|
| 15 December 2017 | The cohort 2a (SCLC all-comer) was stopped for recruitment after eighteen patients had been enrolled as two treatment-related deaths had occurred.<br>Cohort 2b was opened for SCLC patients with high tumor mutation burden in October 2018. | 30 October 2018 |
| 25 April 2019 | The cohort 1 (NSCLC) had to be terminated early due to lack of feasibility as there was a high dropout rate (50%) from treatment part A to part B. This was partially due to either rapid disease progression which led to physicians' decision of performing treatment outside the trial and partially due to immune-related adverse events in treatment part A that would not allow therapy-escalation by adding ipilimumab. Furthermore, during the course of the trial the anti-PD-1 antibody pembrolizumab was approved in 1st line treatment of NSCLC, either alone or in combination with chemotherapy. This approval altered the basic conditions for the conduct of the trial as only immunotherapy-naïve were allowed to be enrolled into this cohort. | - |

Notes:

## Limitations and caveats

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

Cohort 1: terminated early
Cohort 2a: terminated early

Notes:

## Online references

http://www.ncbi.nlm.nih.gov/pubmed/26762738

http://www.ncbi.nlm.nih.gov/pubmed/15117980

http://www.ncbi.nlm.nih.gov/pubmed/7738624

http://www.ncbi.nlm.nih.gov/pubmed/10080612

http://www.ncbi.nlm.nih.gov/pubmed/27718847

http://www.ncbi.nlm.nih.gov/pubmed/29658856

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