Clinical trial results:
AtTEnd: Atezolizumab Trial in Endometrial cancer - Phase III double-blind randomized placebo controlled trial of atezolizumab in combination with paclitaxel and carboplatin in women with advanced/recurrent endometrial cancer.

Summary

EudraCT number	2018-001072-37
Trial protocol	GB AT ES DE IT
Global end of trial date	20 January 2025

Results information

Result version number	v1 (current)
This version publication date	18 February 2026
First version publication date	18 February 2026

Trial information

Trial identification

Sponsor protocol code	IRFMN-EN-7556

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03603184
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IRCCS Istituto di Ricerche Farmacologiche Mario Negri IRCCS
Sponsor organisation address	Via Mario Negri 2, Milan, Italy, 20156
Public contact	Laboratorio Metodologia per la rice, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, 0039 0239014648, attend@marionegri.it
Scientific contact	Laboratorio Metodologia per la rice, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, 0039 0239014648, attend@marionegri.it

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	05 August 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 January 2025
Global end of trial reached?	Yes
Global end of trial date	20 January 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy in terms of PFS and OS of first-line atezolizumab versus placebo in combination with carboplatin and paclitaxel in patients with advanced stage III/IV or recurrent endometrial cancer.

Protection of trial subjects:

The protection of trial subjects was ensured by a favorable risk/benefit assessment and by conducting the study in accordance with the Declaration of Helsinki, ICH Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements. Written informed consent was obtained from all participants prior to any study-related procedures. Subject confidentiality was maintained in compliance with GDPR through data anonymization and/or pseudonymization. Subject safety was closely monitored throughout the study, including appropriate management and reporting of adverse events. Participants were free to withdraw from the study at any time without prejudice. The study was approved by a competent Ethics Committee and covered by appropriate insurance.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 July 2018
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	Spain: 81
Country: Number of subjects enrolled	United Kingdom: 54
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Italy: 219
Country: Number of subjects enrolled	Japan: 80
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 21
Country: Number of subjects enrolled	Switzerland: 19
Country: Number of subjects enrolled	Australia: 44
Country: Number of subjects enrolled	New Zealand: 4
Worldwide total number of subjects	549
EEA total number of subjects	325

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)	231
From 65 to 84 years	314
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Between October 3rd, 2018 and January 7th, 2022, 672 patients were screened for eligibility, and 551 patients from 89 centres were randomized (189 in Arm A and 360 in Arm B). Two patients were excluded from all analyses because of a lack of consent to use their data.

Pre-assignment

Screening details:

A total of 672 subjects were assessed for eligibility. Of these, 121 subjects were excluded prior to randomization: 86 subjects did not meet the eligibility criteria, 28 subjects withdrew informed consent, and 7 subjects were excluded for other reasons

Period 1

Period 1 title	Overall Trial - ITT
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Blinding implementation details:

Blinding was ensured by identically packaged active and placebo IMP kits labeled with unique medication IDs. Emergency unblinding was managed through sealed envelopes stored securely at each site and opened only in case of medical emergency. Blinding was maintained after disease progression to allow unbiased assessment. Non-emergency unblinding required Sponsor approval and was considered a protocol deviation.

Arms

Are arms mutually exclusive?	Yes
Arm title	ARM A

Arm description:

paclitaxel 175 mg/m2 + carboplatin AUC 6 or AUC 5 will be administered every 21 days for 6-8 cycles or PD. Placebo will be administered as I.V. infusion every 21 days until objective radiological disease progression as assessed by the investigator if they do not meet any other discontinuation criteria (patient refusal, toxicity).

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Placebo was administered every 3 weeks prior to carboplatin–paclitaxel and during the maintenance phase. The placebo was delivered by intravenous infusion in 250-mL 0.9% NaCl bags via PVC or polyolefin lines with 0.2 µm in-line filters. The first infusion was administered over 60 minutes, and if well tolerated, subsequent infusions were given over 30 minutes. Prepared solutions were used immediately or stored under specified conditions prior to infusion.

Arm title	ARM B

Arm description:

paclitaxel 175 mg/m2 + carboplatin AUC 5 or 6 will be administered every 21 days for 6-8 cycles or PD. Atezolizumab will be administered as I.V. infusion at a fixed dose of 1200 mg, every 21 days until objective radiological disease progression as assessed by the investigator if they do not meet any other discontinuation criteria (patient refusal, toxicity).

Arm type	Experimental

Investigational medicinal product name	atezolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Atezolizumab was administered at a fixed dose of 1200 mg every 3 weeks, corresponding to an average weight-based dose of 15 mg/kg, prior to carboplatin–paclitaxel and during the maintenance phase. The drug was delivered by intravenous infusion in 250-mL 0.9% NaCl bags via PVC or polyolefin lines with 0.2 µm in-line filters. The first infusion was administered over 60 minutes, and if well tolerated, subsequent infusions were given over 30 minutes. Prepared solutions were used immediately or stored under specified conditions prior to infusion.

Number of subjects in period 1	ARM A	ARM B
Started	189	360
Completed	108	197
Not completed	81	163
Consent withdrawn by subject	16	16
Lost to follow-up	2	6
Treatment never administered	4	4
Study closure	59	137

Period 2

Period 2 title	ITT-dMMR
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	ARM A - dMMR

Arm description:

paclitaxel 175 mg/m2 + carboplatin AUC 6 or AUC 5 will be administered every 21 days for 6-8 cycles or PD. Placebo will be administered as I.V. infusion every 21 days until objective radiological disease progression as assessed by the investigator if they do not meet any other discontinuation criteria (patient refusal, toxicity).

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Placebo was administered every 3 weeks prior to carboplatin–paclitaxel and during the maintenance

phase. The placebo was delivered by intravenous infusion in 250-mL 0.9% NaCl bags via PVC or polyolefin lines with 0.2 µm in-line filters. The first infusion was administered over 60 minutes, and if well tolerated, subsequent infusions were given over 30 minutes. Prepared solutions were used immediately or stored under specified conditions prior to infusion.

Arm title	ARM B - dMMR

Arm description:

paclitaxel 175 mg/m2 + carboplatin AUC 5 or 6 will be administered every 21 days for 6-8 cycles or PD. Atezolizumab will be administered as I.V. infusion at a fixed dose of 1200 mg, every 21 days until objective radiological disease progression as assessed by the investigator if they do not meet any other discontinuation criteria (patient refusal, toxicity).

Arm type	Experimental
Investigational medicinal product name	atezolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Atezolizumab was administered at a fixed dose of 1200 mg every 3 weeks, corresponding to an average weight-based dose of 15 mg/kg, prior to carboplatin–paclitaxel and during the maintenance phase. The drug was delivered by intravenous infusion in 250-mL 0.9% NaCl bags via PVC or polyolefin lines with 0.2 µm in-line filters. The first infusion was administered over 60 minutes, and if well tolerated, subsequent infusions were given over 30 minutes. Prepared solutions were used immediately or stored under specified conditions prior to infusion.

Number of subjects in period 2[1]	ARM A - dMMR	ARM B - dMMR
Started	44	81
Completed	25	29
Not completed	19	52
Consent withdrawn by subject	3	3
Lost to follow-up	1	3
Study closure	15	46

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The period option was used solely to define the analysis population for one of the primary endpoints. The periods do not represent consecutive study phases; therefore, the number of subjects starting this period is not expected to match the number completing the preceding period.

Baseline characteristics

Reporting groups	
Reporting group title	ARM A
Reporting group description:	
paclitaxel 175 mg/m2 + carboplatin AUC 6 or AUC 5 will be administered every 21 days for 6-8 cycles or PD. Placebo will be administered as I.V. infusion every 21 days until objective radiological disease progression as assessed by the investigator if they do not meet any other discontinuation criteria (patient refusal, toxicity).	
Reporting group title	ARM B
Reporting group description:	
paclitaxel 175 mg/m2 + carboplatin AUC 5 or 6 will be administered every 21 days for 6-8 cycles or PD. Atezolizumab will be administered as I.V. infusion at a fixed dose of 1200 mg, every 21 days until objective radiological disease progression as assessed by the investigator if they do not meet any other discontinuation criteria (patient refusal, toxicity).	

Reporting group values	ARM A	ARM B	Total
Number of subjects	189	360	549
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
The age will be calculated as: Age(years)=year of randomization-year of birth,			
Units: years			
arithmetic mean	64.9	66.4	
standard deviation	± 9.5	± 8.8	-
Gender categorical			
Units: Subjects			
Female	189	360	549

Subject analysis sets	
Subject analysis set title	ITT-dMMR
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT-dMMR Analysis Set is defined as all participants with MSI/dMMR tumor who are included in the ITT Analysis set.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Analysis Set is defined as all participants who provide informed consent and are randomized in the study. Patients will be analysed according to the randomization arm, regardless the treatment actually received. The ITT Analysis Set is defined as all participants who provide informed consent and are randomized in the study. Patients will be analysed according to the randomization arm, regardless the treatment actually received.

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set is defined as all patients included of the ITT Analysis Set, who receive at least one dose of study treatment, whether withdrawn prematurely or not. Patients will be considered in the treatment arm they actually received.

Reporting group values	ITT-dMMR	ITT	Safety
Number of subjects	125	549	541
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
The age will be calculated as: Age(years)=year of randomization-year of birth,			
Units: years			
arithmetic mean	64.1	65.9	65.8
standard deviation	± 9.7	± 9.1	± 9.1
Gender categorical Units: Subjects			
Female	125	549	541

End points

End points reporting groups

Reporting group title	ARM A

Reporting group description:

paclitaxel 175 mg/m2 + carboplatin AUC 6 or AUC 5 will be administered every 21 days for 6-8 cycles or PD. Placebo will be administered as I.V. infusion every 21 days until objective radiological disease progression as assessed by the investigator if they do not meet any other discontinuation criteria (patient refusal, toxicity).

Reporting group title	ARM B

Reporting group description:

paclitaxel 175 mg/m2 + carboplatin AUC 5 or 6 will be administered every 21 days for 6-8 cycles or PD. Atezolizumab will be administered as I.V. infusion at a fixed dose of 1200 mg, every 21 days until objective radiological disease progression as assessed by the investigator if they do not meet any other discontinuation criteria (patient refusal, toxicity).

Reporting group title	ARM A - dMMR

Reporting group description:

paclitaxel 175 mg/m2 + carboplatin AUC 6 or AUC 5 will be administered every 21 days for 6-8 cycles or PD. Placebo will be administered as I.V. infusion every 21 days until objective radiological disease progression as assessed by the investigator if they do not meet any other discontinuation criteria (patient refusal, toxicity).

Reporting group title	ARM B - dMMR

Reporting group description:

paclitaxel 175 mg/m2 + carboplatin AUC 5 or 6 will be administered every 21 days for 6-8 cycles or PD. Atezolizumab will be administered as I.V. infusion at a fixed dose of 1200 mg, every 21 days until objective radiological disease progression as assessed by the investigator if they do not meet any other discontinuation criteria (patient refusal, toxicity).

Subject analysis set title	ITT-dMMR
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT-dMMR Analysis Set is defined as all participants with MSI/dMMR tumor who are included in the ITT Analysis set.

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT Analysis Set is defined as all participants who provide informed consent and are randomized in the study. Patients will be analysed according to the randomization arm, regardless the treatment actually received. The ITT Analysis Set is defined as all participants who provide informed consent and are randomized in the study. Patients will be analysed according to the randomization arm, regardless the treatment actually received.

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set is defined as all patients included of the ITT Analysis Set, who receive at least one dose of study treatment, whether withdrawn prematurely or not. Patients will be considered in the treatment arm they actually received.

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

The PFS is defined as the time from randomization to the date of first progression or death from any cause, whichever occurs first. The censored patients are patients alive and progression free at the time of statistical analysis (e.g. last tumor assessment without documented progression) or without information on the status (e.g. patients lost to follow-up without documented progression or death). For progressed or dead patients, the PFS time (months) is the time between the date of randomization and the date of first progression or death, whichever occurs first:
PFS time(months)=(Date of progression or death -Date of randomization+1)/30.4

End point type	Primary
End point timeframe: overall trial	

End point values	ARM A	ARM B	ARM A - dMMR	ARM B - dMMR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	189	360	44	81
Units: month				
median (confidence interval 95%)	8.9 (8.1 to 9.6)	9.9 (9.3 to 12.0)	6.9 (6.2 to 9.0)	0.0 (0.0 to 0.0)

Statistical analyses

Statistical analysis title	Logrank test ITT
Comparison groups	ARM A v ARM B
Number of subjects included in analysis	549
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0055
Method	Logrank
Parameter estimate	Mean difference (final values)
Point estimate	2.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	4.22

Statistical analysis title	Logrank test ITT-dMMR
Comparison groups	ARM A - dMMR v ARM B - dMMR
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.55

Primary: Overall survival

End point title	Overall survival

End point description:

The OS time (months) is the time between the date of randomization and the date of death or the last date in which the patient is known to be still alive:
OS time(months)=(Date of death or Last followup-Date of randomization+1)/30.4

End point type	Primary

End point timeframe:

overall trial

End point values	ARM A	ARM B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	189	360		
Units: month				
median (confidence interval 95%)	30.5 (25.0 to 41.8)	36.0 (30.0 to 45.2)		

Statistical analyses

Statistical analysis title	Logrank test ITT
Comparison groups	ARM A v ARM B
Number of subjects included in analysis	549
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0824
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and serious adverse events will be recorded from time of signature of first informed consent, throughout the treatment period and including the safety follow-up period (135 days after the last study drug administration).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26

Reporting groups

Reporting group title	ARM A
Reporting group description: -	
Reporting group title	ARM B

Reporting group description: -

Serious adverse events	ARM A	ARM B	
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 185 (34.05%)	137 / 356 (38.48%)	
number of deaths (all causes)	108	196	
number of deaths resulting from adverse events	5	11	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer stage 0			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal carcinoma			

subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
High-grade B-cell lymphoma			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 185 (0.00%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Paraneoplastic syndrome			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary tumour benign			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			

subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Lymphadenectomy			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device removal			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 185 (0.00%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mucosal inflammation			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 185 (0.54%)	7 / 356 (1.97%)	
occurrences causally related to treatment / all	0 / 1	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 185 (0.00%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 185 (0.54%)	3 / 356 (0.84%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Genital pain			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermenstrual bleeding			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	1 / 185 (0.54%)	3 / 356 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Female genital tract fistula			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 185 (0.54%)	3 / 356 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 185 (0.00%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated lung disease			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 185 (0.00%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Laryngeal inflammation			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 185 (0.54%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 185 (0.54%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 185 (1.08%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			

subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteroides test positive			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	2 / 185 (1.08%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femur fracture			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	2 / 185 (1.08%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			

subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac tamponade			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 185 (0.00%)	3 / 356 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinus node dysfunction			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			

subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dural arteriovenous fistula			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 185 (0.00%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			

subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensorimotor neuropathy			
subjects affected / exposed	0 / 185 (0.00%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 185 (2.70%)	6 / 356 (1.69%)	
occurrences causally related to treatment / all	0 / 6	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	5 / 185 (2.70%)	16 / 356 (4.49%)	
occurrences causally related to treatment / all	0 / 7	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 185 (0.54%)	4 / 356 (1.12%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	1 / 185 (0.54%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 185 (0.00%)	4 / 356 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 185 (1.08%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 185 (0.54%)	4 / 356 (1.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 185 (0.00%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	3 / 185 (1.62%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 185 (0.54%)	4 / 356 (1.12%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolonic fistula			

subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocutaneous fistula			
subjects affected / exposed	0 / 185 (0.00%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ileus			
subjects affected / exposed	1 / 185 (0.54%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	5 / 185 (2.70%)	4 / 356 (1.12%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 1	
Mechanical ileus			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	1 / 185 (0.54%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 185 (0.00%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 185 (0.54%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 185 (0.54%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 185 (0.54%)	6 / 356 (1.69%)	
occurrences causally related to treatment / all	0 / 1	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			

subjects affected / exposed	1 / 185 (0.54%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 185 (0.00%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
rash			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria papular			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 185 (0.54%)	4 / 356 (1.12%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 185 (0.00%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular disorder			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal vein thrombosis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 185 (0.00%)	3 / 356 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Adrenal insufficiency			
subjects affected / exposed	0 / 185 (0.00%)	3 / 356 (0.84%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopituitarism			
subjects affected / exposed	0 / 185 (0.00%)	3 / 356 (0.84%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 185 (0.00%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myositis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 185 (0.00%)	4 / 356 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cellulitis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 185 (1.08%)	3 / 356 (0.84%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			

subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematological infection			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph gland infection			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 185 (0.54%)	0 / 356 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	2 / 185 (1.08%)	3 / 356 (0.84%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	1 / 1	1 / 1	
Pyelonephritis			
subjects affected / exposed	1 / 185 (0.54%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
SARS-CoV-2 sepsis			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 185 (0.54%)	4 / 356 (1.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site infection			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	9 / 185 (4.86%)	4 / 356 (1.12%)	
occurrences causally related to treatment / all	0 / 12	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	2 / 185 (1.08%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 185 (1.08%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	1 / 185 (0.54%)	2 / 356 (0.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 185 (0.00%)	1 / 356 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ARM A	ARM B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	185 / 185 (100.00%)	351 / 356 (98.60%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 185 (6.49%)	30 / 356 (8.43%)	
occurrences (all)	14	37	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	13 / 185 (7.03%)	17 / 356 (4.78%)	
occurrences (all)	18	25	
Fatigue			
subjects affected / exposed	76 / 185 (41.08%)	139 / 356 (39.04%)	
occurrences (all)	107	209	
Oedema peripheral			
subjects affected / exposed	14 / 185 (7.57%)	12 / 356 (3.37%)	
occurrences (all)	15	13	
Pyrexia			
subjects affected / exposed	20 / 185 (10.81%)	55 / 356 (15.45%)	
occurrences (all)	29	73	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	8 / 185 (4.32%)	26 / 356 (7.30%)	
occurrences (all)	11	28	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	7 / 185 (3.78%)	18 / 356 (5.06%)	
occurrences (all)	8	22	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 185 (5.95%)	27 / 356 (7.58%)	
occurrences (all)	11	32	
Dyspnoea			

subjects affected / exposed	23 / 185 (12.43%)	20 / 356 (5.62%)	
occurrences (all)	33	23	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 185 (5.95%)	31 / 356 (8.71%)	
occurrences (all)	13	31	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 185 (5.41%)	31 / 356 (8.71%)	
occurrences (all)	13	43	
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 185 (4.86%)	25 / 356 (7.02%)	
occurrences (all)	12	30	
Blood creatinine increased			
subjects affected / exposed	9 / 185 (4.86%)	26 / 356 (7.30%)	
occurrences (all)	13	36	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	8 / 185 (4.32%)	29 / 356 (8.15%)	
occurrences (all)	10	36	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	10 / 185 (5.41%)	28 / 356 (7.87%)	
occurrences (all)	12	28	
Headache			
subjects affected / exposed	16 / 185 (8.65%)	28 / 356 (7.87%)	
occurrences (all)	20	34	
Paraesthesia			
subjects affected / exposed	24 / 185 (12.97%)	44 / 356 (12.36%)	
occurrences (all)	30	64	
Peripheral sensory neuropathy			
subjects affected / exposed	73 / 185 (39.46%)	138 / 356 (38.76%)	
occurrences (all)	81	156	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	65 / 185 (35.14%)	147 / 356 (41.29%)	
occurrences (all)	92	228	
Febrile neutropenia			
subjects affected / exposed	7 / 185 (3.78%)	23 / 356 (6.46%)	
occurrences (all)	9	23	
Leukopenia			
subjects affected / exposed	13 / 185 (7.03%)	49 / 356 (13.76%)	
occurrences (all)	25	122	
Neutropenia			
subjects affected / exposed	73 / 185 (39.46%)	145 / 356 (40.73%)	
occurrences (all)	145	332	
Thrombocytopenia			
subjects affected / exposed	50 / 185 (27.03%)	102 / 356 (28.65%)	
occurrences (all)	69	203	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	15 / 185 (8.11%)	35 / 356 (9.83%)	
occurrences (all)	17	40	
Constipation			
subjects affected / exposed	50 / 185 (27.03%)	98 / 356 (27.53%)	
occurrences (all)	66	127	
Diarrhoea			
subjects affected / exposed	35 / 185 (18.92%)	80 / 356 (22.47%)	
occurrences (all)	46	122	
Nausea			
subjects affected / exposed	69 / 185 (37.30%)	121 / 356 (33.99%)	
occurrences (all)	114	193	
Stomatitis			
subjects affected / exposed	17 / 185 (9.19%)	36 / 356 (10.11%)	
occurrences (all)	19	43	
Vomiting			
subjects affected / exposed	15 / 185 (8.11%)	51 / 356 (14.33%)	
occurrences (all)	23	70	
Skin and subcutaneous tissue disorders			
Alopecia			

subjects affected / exposed	67 / 185 (36.22%)	112 / 356 (31.46%)	
occurrences (all)	67	116	
Pruritus			
subjects affected / exposed	9 / 185 (4.86%)	44 / 356 (12.36%)	
occurrences (all)	10	51	
Rash			
subjects affected / exposed	8 / 185 (4.32%)	28 / 356 (7.87%)	
occurrences (all)	13	41	
Rash maculo-papular			
subjects affected / exposed	9 / 185 (4.86%)	32 / 356 (8.99%)	
occurrences (all)	9	48	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	6 / 185 (3.24%)	21 / 356 (5.90%)	
occurrences (all)	8	35	
Hypothyroidism			
subjects affected / exposed	10 / 185 (5.41%)	48 / 356 (13.48%)	
occurrences (all)	19	67	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	51 / 185 (27.57%)	94 / 356 (26.40%)	
occurrences (all)	81	140	
Back pain			
subjects affected / exposed	20 / 185 (10.81%)	23 / 356 (6.46%)	
occurrences (all)	22	27	
Myalgia			
subjects affected / exposed	16 / 185 (8.65%)	48 / 356 (13.48%)	
occurrences (all)	19	69	
Pain in extremity			
subjects affected / exposed	16 / 185 (8.65%)	27 / 356 (7.58%)	
occurrences (all)	24	32	
Infections and infestations			
COVID-19			
subjects affected / exposed	19 / 185 (10.27%)	37 / 356 (10.39%)	
occurrences (all)	21	38	
Urinary tract infection			

subjects affected / exposed	28 / 185 (15.14%)	40 / 356 (11.24%)	
occurrences (all)	37	58	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	23 / 185 (12.43%)	39 / 356 (10.96%)	
occurrences (all)	26	47	
Hypomagnesaemia			
subjects affected / exposed	15 / 185 (8.11%)	35 / 356 (9.83%)	
occurrences (all)	22	47	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 July 2018	To include immune-related nephritis as an atezolizumab adverse reaction and its management guidelines, previously not addressed in the protocol, in line with updated safety information.
20 February 2019	To include immune-related myositis as an atezolizumab adverse reaction and its management guidelines. Additional updates were implemented to align clinical management with the current Investigator's Brochure, formalize operational procedures in EDC/IVRS/IWRS, and extend the safety follow-up period to 135 days after last study drug administration, as requested by the German competent authority.
09 March 2020	To introduce exploratory analyses on PK, ADA and ct-DNA and to clarify eligibility criteria. Additional changes were made to update adverse reaction management per the current Investigator's Brochure, allow surgery for patients becoming operable during the study, and better specify data collection and assessment timing.
10 February 2021	To update accrual duration and study timelines, introduce a revised statistical design anticipating PFS analysis at OS interim analysis, and add two futility analyses. Additional updates aligned adverse reaction management with the current Investigator's Brochure and clarified procedures for AE reporting and emergency unblinding.
03 May 2022	To update clinical management guidelines for atezolizumab adverse reactions according to the latest Investigator's Brochure and Dear Investigator Letters, and to update the study background and Statistical Analysis Plan.
23 April 2024	To update the protocol according to the evolving clinical and regulatory landscape, including new data on immune checkpoint inhibitors, updated approvals and safety information for atezolizumab, results of final PFS and interim OS analyses, post-trial access provisions, and updated scientific references.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/39102832

http://www.ncbi.nlm.nih.gov/pubmed/40590326