Clinical trial results:
Atezolizumab in combination with Bevacizumab and Chemotherapy versus Bevacizumab and Chemotherapy in recurrent ovarian cancer – a randomized Phase III trial

Summary

EudraCT number	2017-000202-37
Trial protocol	DE AT BE ES NO DK FI LT EE
Global end of trial date	11 March 2025

Results information

Result version number	v1 (current)
This version publication date	03 April 2026
First version publication date	03 April 2026

Trial information

Trial identification

Sponsor protocol code	AGO-OVAR 2.29

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03353831
WHO universal trial number (UTN)	-
Other trial identifiers	ENGOT: ov-34, EudraCT No.: 2017-000202-37

Notes:

Sponsors

Sponsor organisation name	AGO Research GmbH
Sponsor organisation address	Kaiser-Friedrich-Ring 71, Wiesbaden, Germany, 65185
Public contact	Study Office, AGO Research GmbH, 0049 2019598120, office-essen@ago-ovar.de
Scientific contact	Study Office, AGO Research GmbH, 0049 2019598120, office-essen@ago-ovar.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	26 January 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 March 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of atezolizumab plus bevacizumab and chemotherapy compared with placebo plus bevacizumab and chemotherapy in patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer with 1st or 2nd relapse within 6 months after platinum-based chemotherapy or 3rd relapse.
Co-primary endpoints are overall survival (OS), defined as the time from randomization to death from any cause and progression free survival (PFS), defined as the time from randomization to progressive disease (PD) or death, whichever occurs first. PD is based on investigator assessment using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

Protection of trial subjects:

The study was performed in accordance with ethical principles that had their origin in the Declaration of Helsinki and were consistent with International Council for Harmonisation Good Clinical Practices (ICH-GCP).
Written informed consent was obtained from each participant prior to any study-specific procedures. Participants were informed about potential risks and benefits of participation as well as their right to withdraw from the study at any time without any disadvantage.
Safety was closely monitored throughout the study by regular clinical assessments and laboratory evaluations. Adverse events were documented and graded according to CTCAE criteria.
A predefined safety interim analysis to evaluate tolerability was performed after 24 patients had been randomized. Recruitment was temporarily suspended for the purpose of this safety analysis and was only resumed following review of the safety data by the Independent Data Monitoring Committee (IDMC) and its recommendation to continue the study.

Background therapy:

All patients received standard background therapy:
-- Paclitaxel 80 mg/m² d1, 8,15, 22, q28 days
OR
- Pegylated Liposomal Doxorubicin: 40 mg/m² d1, q28 days

Evidence for comparator:

The combination of chemotherapy with bevacizumab represents a standard treatment option in patients with platinum-resistant ovarian cancer. Therefore, bevacizumab in combination with paclitaxel or pegylated liposomal doxorubicin was selected as the standard comparator arm (Arm A).
Atezolizumab was added to this standard therapy in the experimental arm (Arm B). To ensure a double-blind design and minimise bias, placebo was added to the standard therapy in Arm A.
All patients received active standard treatment. The placebo-controlled design ensured maintenance of blinding and minimised bias in the evaluation of the additional effect of atezolizumab.

Actual start date of recruitment	10 September 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 9
Country: Number of subjects enrolled	Spain: 122
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	Estonia: 1
Country: Number of subjects enrolled	Germany: 231
Country: Number of subjects enrolled	Lithuania: 10
Country: Number of subjects enrolled	France: 144
Country: Number of subjects enrolled	Switzerland: 24
Worldwide total number of subjects	574
EEA total number of subjects	550

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)	338
From 65 to 84 years	235
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Between September 10, 2018, and July 7, 2022, 780 patients were screened. Of these, 574 patients were randomized at 105 sites in 12 European countries (Germany, France, Spain, Denmark, Sweden, Norway, Finland, Estonia, Lithuania, Belgium, Austria, Switzerland).

Pre-assignment

Screening details:

Eligible patients underwent a screening period of up to 28 days including verification of inclusion and exclusion criteria, medical history, concomitant medication, physical examination, ECOG performance status, laboratory tests and baseline tumour assessment according to RECIST. Randomisation was performed after confirmation of eligibility.

Pre-assignment period milestones

Number of subjects started	780[1]
Number of subjects completed	574

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Other: 6
Reason: Number of subjects	Protocol deviation: 105
Reason: Number of subjects	Tissue sample missing: 25
Reason: Number of subjects	General condition: 28
Reason: Number of subjects	Death: 6
Reason: Number of subjects	Consent withdrawn by subject: 25
Reason: Number of subjects	Physician decision: 11

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of subjects who started the pre-assignment period reflects the number of screened subjects (screened = 775). Not all screened subjects were randomized due to screening failures or withdrawal before randomization. Therefore the number differs from the number of subjects enrolled in the trial (randomized = 574).

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Atezolizumab and placebo were double blinded. The study medication was labelled using a unique kit ID number, which was linked to the randomization scheme. The active and placebo kits were presented in the same packaging to ensure blinding of the study medication. The sponsor and its designated representatives (with the exception of personnel responsible for investigational medicinal product supply and randomization procedures) will remain blinded to treatment allocation.

Arms

Are arms mutually exclusive?	Yes

Arm title	Placebo + Bevacizumab + Chemotherapy

Arm description:

Bevacizumab 10 mg/kg administered intravenously every 14 days and matching placebo administered intravenously every 14 days in combination with investigator's choice chemotherapy consisting of either:
• Paclitaxel 80 mg/m² administered intravenously on Days 1, 8, 15 and 22 of each 28-day cycle,
or
• Pegylated liposomal doxorubicin 40 mg/m² administered intravenously on Day 1 of each 28-day cycle.

Study treatment continued until disease progression per RECIST 1.1 or for a maximum of 24 months (whatever occurs first), unacceptable toxicity, or patient or investigator decision to discontinue treatment.

Arm type	Placebo
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab 10 mg/kg administered intravenously as an infusion every 14 days (q2w).

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Matching Placebo administered intravenously as an infusion every 14 days (q2w).

Arm title	Atezolizumab + Bevacizumab + Chemotherapie

Arm description:

Atezolizumab 840 mg administered intravenously every 14 days and bevacizumab 10 mg/kg administered intravenously every 14 days in combination with investigator's choice chemotherapy consisting of either:
• Paclitaxel 80 mg/m² administered intravenously on Days 1, 8, 15 and 22 of each 28-day cycle,
or
• Pegylated liposomal doxorubicin 40 mg/m² administered intravenously on Day 1 of each 28-day cycle.

Study treatment continued until disease progression per RECIST 1.1 or for a maximum of 24 months (whatever occurs first), unacceptable toxicity, or patient or investigator decision to discontinue treatment.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab 10 mg/kg administered intravenously as an infusion every 14 days (q2w).

Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intrauterine use

Dosage and administration details:

Atezolizumab 840 mg administered intravenously as an infusion every 14 days (q2w).

Number of subjects in period 1	Placebo + Bevacizumab + Chemotherapy	Atezolizumab + Bevacizumab + Chemotherapie
Started	289	285
Completed	8	13
Not completed	281	272
Still on treatment	1	4
Patient decision	6	11
Physician decision	2	4
Disease progression	239	219
Adverse Event	15	13
Death (cancer related)	3	11
Did not receive assigned treatment	3	4
Other	4	-
Death (therapy related)	6	6
Lost to follow-up	2	-

Baseline characteristics

Reporting groups

Reporting group title	Placebo + Bevacizumab + Chemotherapy

Reporting group description:

Bevacizumab 10 mg/kg administered intravenously every 14 days and matching placebo administered intravenously every 14 days in combination with investigator's choice chemotherapy consisting of either:
• Paclitaxel 80 mg/m² administered intravenously on Days 1, 8, 15 and 22 of each 28-day cycle,
or
• Pegylated liposomal doxorubicin 40 mg/m² administered intravenously on Day 1 of each 28-day cycle.

Study treatment continued until disease progression per RECIST 1.1 or for a maximum of 24 months (whatever occurs first), unacceptable toxicity, or patient or investigator decision to discontinue treatment.

Reporting group title	Atezolizumab + Bevacizumab + Chemotherapie

Reporting group description:

Atezolizumab 840 mg administered intravenously every 14 days and bevacizumab 10 mg/kg administered intravenously every 14 days in combination with investigator's choice chemotherapy consisting of either:
• Paclitaxel 80 mg/m² administered intravenously on Days 1, 8, 15 and 22 of each 28-day cycle,
or
• Pegylated liposomal doxorubicin 40 mg/m² administered intravenously on Day 1 of each 28-day cycle.

Study treatment continued until disease progression per RECIST 1.1 or for a maximum of 24 months (whatever occurs first), unacceptable toxicity, or patient or investigator decision to discontinue treatment.

Reporting group values	Placebo + Bevacizumab + Chemotherapy	Atezolizumab + Bevacizumab + Chemotherapie	Total
Number of subjects	289	285	574
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)	176	162	338
From 65-84 years	113	122	235
85 years and over	0	1	1
Gender categorical Units: Subjects			
Female	289	285	574
Male	0	0	0
ECOG Performance Status Units: Subjects			
ECOG PS 0	152	163	315
ECOG PS 1	136	120	256
Missing	1	2	3
Histology Units: Subjects			

High-grade serous	230	214	444
Clear cell	16	17	33
Seromucinous	13	19	32
Endometrioid	8	12	20
Low-grade serous	10	8	18
Mucinous	8	7	15
Other	4	8	12
No. of prior lines of therapy Units: Subjects			
1 prior line	70	70	140
2 prior lines	115	112	227
3 prior lines	104	103	207
Prior therapy with bevacizumab Units: Subjects			
Prior bevacizumab	206	210	416
No prior bevacizumab	83	75	158
Planned chemotherapy Units: Subjects			
PLD	135	129	264
Paclitaxel	154	156	310
PD-L1 status at randomization			
PD-L1 status was classified as non-informative in 94 patients included before implementation of central PD-L1 testing			
Units: Subjects			
Positive	68	63	131
Negative	153	153	306
Non-informative	68	69	137
Overall PD-L1 status			
Including PD-L1 status of patients included before implementation of central PD-L1 testing, whose tumors were tested retrospectively.			
Units: Subjects			
Positive	78	70	148
Negative	184	187	371
Non-informative	27	28	55
Prior PARPi therapy Units: Subjects			
Prior PARPi therapy	120	114	234
No prior PARPi	169	171	340

End points

End points reporting groups

Reporting group title	Placebo + Bevacizumab + Chemotherapy

Reporting group description:

Bevacizumab 10 mg/kg administered intravenously every 14 days and matching placebo administered intravenously every 14 days in combination with investigator's choice chemotherapy consisting of either:
• Paclitaxel 80 mg/m² administered intravenously on Days 1, 8, 15 and 22 of each 28-day cycle,
or
• Pegylated liposomal doxorubicin 40 mg/m² administered intravenously on Day 1 of each 28-day cycle.

Study treatment continued until disease progression per RECIST 1.1 or for a maximum of 24 months (whatever occurs first), unacceptable toxicity, or patient or investigator decision to discontinue treatment.

Reporting group title	Atezolizumab + Bevacizumab + Chemotherapie

Reporting group description:

Atezolizumab 840 mg administered intravenously every 14 days and bevacizumab 10 mg/kg administered intravenously every 14 days in combination with investigator's choice chemotherapy consisting of either:
• Paclitaxel 80 mg/m² administered intravenously on Days 1, 8, 15 and 22 of each 28-day cycle,
or
• Pegylated liposomal doxorubicin 40 mg/m² administered intravenously on Day 1 of each 28-day cycle.

Study treatment continued until disease progression per RECIST 1.1 or for a maximum of 24 months (whatever occurs first), unacceptable toxicity, or patient or investigator decision to discontinue treatment.

Primary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

Overall survival (OS) defined as the time from randomization to death from any cause

End point type	Primary

End point timeframe:

time from randomization to death from any cause

End point values	Placebo + Bevacizumab + Chemotherapy	Atezolizumab + Bevacizumab + Chemotherapie		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	285		
Units: months				
median (confidence interval 95%)	13.0 (11.9 to 15.1)	14.2 (13.0 to 16.1)		

Statistical analyses

Statistical analysis title	Hazard ratio for overall survival
Comparison groups	Placebo + Bevacizumab + Chemotherapy v Atezolizumab + Bevacizumab + Chemotherapie

Number of subjects included in analysis	574
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.01

Primary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Progression-free survival (PFS) was defined as the time from randomization to progressive disease (PD) or death, whichever occurred first. Progressive disease was assessed by the investigators according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

End point type	Primary

End point timeframe:

Every 9 weeks during the first year, thereafter every 12 weeks until disease progression

End point values	Placebo + Bevacizumab + Chemotherapy	Atezolizumab + Bevacizumab + Chemotherapie		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	289	285		
Units: months				
median (confidence interval 95%)	6.7 (6.2 to 8.1)	6.4 (6.1 to 7.8)		

Statistical analyses

Statistical analysis title	Hazard ratio for progression-free survival
Comparison groups	Placebo + Bevacizumab + Chemotherapy v Atezolizumab + Bevacizumab + Chemotherapie
Number of subjects included in analysis	574
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.04

Secondary: Duration of response (DoR)

End point title	Duration of response (DoR)

End point description:

Duration of response was defined as the time from first documented complete or partial response to progressive disease or death, whichever occurred first. Tumor response and disease progression were assessed by the investigators according to RECIST version 1.1.

End point type	Secondary

End point timeframe:

from first documented complete or partial response to progressive disease or death, whichever occurs first.

End point values	Placebo + Bevacizumab + Chemotherapy	Atezolizumab + Bevacizumab + Chemotherapie		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	101		
Units: months				
median (confidence interval 95%)	6.1 (5.3 to 7.2)	8.6 (6.9 to 10.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR)

End point title	Objective response rate (ORR)

End point description:

Objective response rate was defined as the proportion of patients with a confirmed complete or partial response. Tumor response was assessed by the investigators according to RECIST version 1.1.

End point type	Secondary

End point timeframe:

Every 9 weeks during the first year, thereafter every 12 weeks until disease progression

End point values	Placebo + Bevacizumab + Chemotherapy	Atezolizumab + Bevacizumab + Chemotherapie		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248	255		
Units: Subjects	108	101		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall survival (OS) in the bevacizumab-pretreated subgroup

End point title	Overall survival (OS) in the bevacizumab-pretreated subgroup

End point description:

Overall survival (OS) analysed according to prior bevacizumab exposure (yes versus no). OS is defined as the time from randomization to death from any cause.

End point type	Other pre-specified

End point timeframe:

time from randomization to death from any cause

End point values	Placebo + Bevacizumab + Chemotherapy	Atezolizumab + Bevacizumab + Chemotherapie		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	210		
Units: months				
median (confidence interval 95%)	12.6 (11.6 to 14.4)	14.9 (13.3 to 18.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Progression-free survival (PFS) in the bevacizumab-pretreated subgroup

End point title	Progression-free survival (PFS) in the bevacizumab-pretreated subgroup

End point description:

Progression-free survival (PFS) analysed according to prior bevacizumab exposure (yes versus no). PFS is defined as the time from randomization to progressive disease (PD) or death from any cause, whichever occurs first. PD was assessed by investigators according to RECIST v1.1 criteria.

End point type	Other pre-specified

End point timeframe:

Every 9 weeks during the first year, thereafter every 12 weeks until disease progression

End point values	Placebo + Bevacizumab + Chemotherapy	Atezolizumab + Bevacizumab + Chemotherapie		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	210		
Units: months				
median (confidence interval 95%)	6.3 (5.8 to 7.4)	6.7 (6.2 to 8.3)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall survival (OS) in the subgroup receiving paclitaxel

End point title	Overall survival (OS) in the subgroup receiving paclitaxel

End point description:

Overall survival (OS) analysed in the subgroup of patients who received paclitaxel as the planned chemotherapy backbone. OS is defined as the time from randomization to death from any cause.

End point type	Other pre-specified

End point timeframe:

time from randomization to death from any cause

End point values	Placebo + Bevacizumab + Chemotherapy	Atezolizumab + Bevacizumab + Chemotherapie		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	156		
Units: months				
median (confidence interval 95%)	14.3 (12.3 to 15.9)	16.2 (13.9 to 20.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Progression-free survival (PFS) in the subgroup receiving paclitaxel

End point title	Progression-free survival (PFS) in the subgroup receiving paclitaxel

End point description:

Progression-free survival (PFS) analysed in the subgroup of patients who received paclitaxel as the planned chemotherapy backbone. PFS is defined as the time from randomization to progressive disease (PD) or death from any cause, whichever occurred first. Progressive disease was assessed by the investigators according to RECIST version 1.1.

End point type	Other pre-specified

End point timeframe:

Every 9 weeks during the first year, thereafter every 12 weeks until disease progression

End point values	Placebo + Bevacizumab + Chemotherapy	Atezolizumab + Bevacizumab + Chemotherapie		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	156		
Units: months				
median (confidence interval 95%)	7.8 (6.7 to 8.4)	8.1 (6.8 to 9.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs occurring after study entry (date of informed consent) will be recorded up to 90 days following the last administration of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	28

Reporting groups

Reporting group title	Placebo + Bevacizumab + Chemotherapy

Reporting group description:

Bevacizumab 10 mg/kg administered intravenously every 14 days and matching placebo administered intravenously every 14 days in combination with investigator's choice chemotherapy consisting of either:
• Paclitaxel 80 mg/m² administered intravenously on Days 1, 8, 15 and 22 of each 28-day cycle,
or
• Pegylated liposomal doxorubicin 40 mg/m² administered intravenously on Day 1 of each 28-day cycle.

Study treatment continued until disease progression per RECIST 1.1 or for a maximum of 24 months (whatever occurs first), unacceptable toxicity, or patient or investigator decision to discontinue treatment.

Reporting group title	Atezolizumab + Bevacizumab + Chemotherapie

Reporting group description:

Atezolizumab 840 mg administered intravenously every 14 days and bevacizumab 10 mg/kg administered intravenously every 14 days in combination with investigator's choice chemotherapy consisting of either:
• Paclitaxel 80 mg/m² administered intravenously on Days 1, 8, 15 and 22 of each 28-day cycle,
or
• Pegylated liposomal doxorubicin 40 mg/m² administered intravenously on Day 1 of each 28-day cycle.

Study treatment continued until disease progression per RECIST 1.1 or for a maximum of 24 months (whatever occurs first), unacceptable toxicity, or patient or investigator decision to discontinue treatment.

Serious adverse events	Placebo + Bevacizumab + Chemotherapy	Atezolizumab + Bevacizumab + Chemotherapie	
Total subjects affected by serious adverse events			
subjects affected / exposed	147 / 286 (51.40%)	179 / 281 (63.70%)	
number of deaths (all causes)	221	197	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Adenocarcinoma gastric			

subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 286 (0.35%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to meninges			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myeloid leukaemia			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	0 / 286 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour ulceration			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 286 (0.70%)	5 / 281 (1.78%)	
occurrences causally related to treatment / all	1 / 2	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	2 / 286 (0.70%)	3 / 281 (1.07%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			

subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (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			
Abdominal operation			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial lesion excision			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheterisation venous			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithotomy			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurodesis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic cavity drainage			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteral catheterisation			

subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Omphalorrhexis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 286 (0.70%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
General physical health deterioration			
subjects affected / exposed	13 / 286 (4.55%)	15 / 281 (5.34%)	
occurrences causally related to treatment / all	6 / 15	6 / 18	
deaths causally related to treatment / all	0 / 2	0 / 5	
Hyperthermia			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Impaired healing			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 286 (0.35%)	3 / 281 (1.07%)	
occurrences causally related to treatment / all	1 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	9 / 286 (3.15%)	5 / 281 (1.78%)	
occurrences causally related to treatment / all	4 / 11	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related hypersensitivity reaction			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Multisystem inflammatory syndrome			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	0 / 286 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic congestion			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal fistula			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	5 / 286 (1.75%)	9 / 281 (3.20%)	
occurrences causally related to treatment / all	2 / 6	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea exertional			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated lung disease			
subjects affected / exposed	0 / 286 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	2 / 286 (0.70%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 286 (1.05%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	3 / 286 (1.05%)	3 / 281 (1.07%)	
occurrences causally related to treatment / all	2 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 286 (1.05%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	3 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 286 (0.35%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 286 (0.00%)	3 / 281 (1.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	

Cholangitis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 286 (0.00%)	3 / 281 (1.07%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated hepatitis			
subjects affected / exposed	1 / 286 (0.35%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			

subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic enzymes increased			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis test positive			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
White blood cell count decreased			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			

subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 286 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Aortic valve disease			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac hypertrophy			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Myocardial infarction			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral haemorrhage			

subjects affected / exposed	1 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cognitive disorder			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (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 / 286 (0.00%)	1 / 281 (0.36%)	
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 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 286 (0.70%)	3 / 281 (1.07%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 286 (0.35%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 286 (0.70%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 286 (0.00%)	3 / 281 (1.07%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thrombotic microangiopathy			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Vestibular disorder			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	8 / 286 (2.80%)	5 / 281 (1.78%)	
occurrences causally related to treatment / all	1 / 8	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute abdomen			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic ulcer perforation			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	2 / 286 (0.70%)	6 / 281 (2.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune pancreatitis			
subjects affected / exposed	0 / 286 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colitis			
subjects affected / exposed	2 / 286 (0.70%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic fistula			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	3 / 286 (1.05%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 286 (1.40%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 286 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocutaneous fistula			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 286 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Female genital tract fistula			

subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 286 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal perforation			
subjects affected / exposed	1 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Ileus			
subjects affected / exposed	4 / 286 (1.40%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 286 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	9 / 286 (3.15%)	3 / 281 (1.07%)	
occurrences causally related to treatment / all	1 / 9	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 0	
Intestinal perforation			

subjects affected / exposed	3 / 286 (1.05%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	2 / 2	0 / 0	
Jejunal perforation			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	4 / 286 (1.40%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	3 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	6 / 286 (2.10%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontal disease			

subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	3 / 286 (1.05%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Subileus			
subjects affected / exposed	13 / 286 (4.55%)	16 / 281 (5.69%)	
occurrences causally related to treatment / all	1 / 15	1 / 19	
deaths causally related to treatment / all	2 / 2	0 / 1	
Volvulus			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	9 / 286 (3.15%)	3 / 281 (1.07%)	
occurrences causally related to treatment / all	1 / 10	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis			

subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis bullous			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis exfoliative generalised			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lichenoid keratosis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 286 (0.70%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	1 / 286 (0.35%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			

subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 286 (1.40%)	5 / 281 (1.78%)	
occurrences causally related to treatment / all	1 / 4	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Autoimmune nephritis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder hypertrophy			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			

subjects affected / exposed	0 / 286 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oliguria			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 286 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Addison's disease			

subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal insufficiency			
subjects affected / exposed	1 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune thyroiditis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	0 / 286 (0.00%)	6 / 281 (2.14%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	0 / 286 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	5 / 286 (1.75%)	18 / 281 (6.41%)	
occurrences causally related to treatment / all	0 / 5	3 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated adrenal insufficiency			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated hypophysitis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated thyroiditis			

subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 286 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Thyroid disorder			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			
subjects affected / exposed	1 / 286 (0.35%)	3 / 281 (1.07%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			

subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sjogren's syndrome			
subjects affected / exposed	1 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergilloma			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
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	3 / 286 (1.05%)	3 / 281 (1.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Citrobacter infection			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 286 (0.35%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 286 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes virus infection			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected lymphocele			

subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (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 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelitis			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 286 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 286 (0.35%)	5 / 281 (1.78%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pneumonia aspiration			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	1 / 286 (0.35%)	4 / 281 (1.42%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyonephrosis			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 286 (0.70%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 286 (0.00%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 286 (1.05%)	5 / 281 (1.78%)	
occurrences causally related to treatment / all	0 / 5	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 286 (0.70%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			

subjects affected / exposed	1 / 286 (0.35%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	2 / 286 (0.70%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 286 (0.35%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 286 (0.35%)	2 / 281 (0.71%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 286 (0.35%)	0 / 281 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 286 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Placebo + Bevacizumab + Chemotherapy	Atezolizumab + Bevacizumab + Chemotherapie	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	285 / 286 (99.65%)	280 / 281 (99.64%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	76 / 286 (26.57%)	70 / 281 (24.91%)	
occurrences (all)	106	116	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	93 / 286 (32.52%)	83 / 281 (29.54%)	
occurrences (all)	136	136	
Fatigue			
subjects affected / exposed	93 / 286 (32.52%)	100 / 281 (35.59%)	
occurrences (all)	110	121	
Mucosal inflammation			
subjects affected / exposed	60 / 286 (20.98%)	74 / 281 (26.33%)	
occurrences (all)	72	99	
Pyrexia			
subjects affected / exposed	38 / 286 (13.29%)	45 / 281 (16.01%)	
occurrences (all)	51	69	

Oedema peripheral			
subjects affected / exposed	37 / 286 (12.94%)	37 / 281 (13.17%)	
occurrences (all)	42	45	
General physical health deterioration			
subjects affected / exposed	11 / 286 (3.85%)	26 / 281 (9.25%)	
occurrences (all)	12	28	
Pain			
subjects affected / exposed	9 / 286 (3.15%)	13 / 281 (4.63%)	
occurrences (all)	10	17	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	90 / 286 (31.47%)	65 / 281 (23.13%)	
occurrences (all)	106	75	
Dyspnoea			
subjects affected / exposed	39 / 286 (13.64%)	52 / 281 (18.51%)	
occurrences (all)	45	62	
Cough			
subjects affected / exposed	40 / 286 (13.99%)	43 / 281 (15.30%)	
occurrences (all)	47	45	
Dysphonia			
subjects affected / exposed	21 / 286 (7.34%)	25 / 281 (8.90%)	
occurrences (all)	25	26	
Oropharyngeal pain			
subjects affected / exposed	9 / 286 (3.15%)	12 / 281 (4.27%)	
occurrences (all)	10	12	
Dyspnoea exertional			
subjects affected / exposed	11 / 286 (3.85%)	9 / 281 (3.20%)	
occurrences (all)	11	9	
Pulmonary embolism			
subjects affected / exposed	7 / 286 (2.45%)	11 / 281 (3.91%)	
occurrences (all)	7	11	
Nasal dryness			
subjects affected / exposed	6 / 286 (2.10%)	11 / 281 (3.91%)	
occurrences (all)	6	11	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	11 / 286 (3.85%)	13 / 281 (4.63%)	
occurrences (all)	11	15	
Anxiety			
subjects affected / exposed	14 / 286 (4.90%)	8 / 281 (2.85%)	
occurrences (all)	14	8	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	22 / 286 (7.69%)	28 / 281 (9.96%)	
occurrences (all)	56	43	
White blood cell count decreased			
subjects affected / exposed	10 / 286 (3.50%)	17 / 281 (6.05%)	
occurrences (all)	30	39	
Lipase increased			
subjects affected / exposed	8 / 286 (2.80%)	16 / 281 (5.69%)	
occurrences (all)	24	34	
Aspartate aminotransferase increased			
subjects affected / exposed	15 / 286 (5.24%)	19 / 281 (6.76%)	
occurrences (all)	23	29	
Blood creatinine increased			
subjects affected / exposed	13 / 286 (4.55%)	20 / 281 (7.12%)	
occurrences (all)	15	22	
Alanine aminotransferase increased			
subjects affected / exposed	13 / 286 (4.55%)	16 / 281 (5.69%)	
occurrences (all)	18	17	
Amylase increased			
subjects affected / exposed	4 / 286 (1.40%)	14 / 281 (4.98%)	
occurrences (all)	8	20	
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 286 (1.75%)	15 / 281 (5.34%)	
occurrences (all)	6	18	
Weight decreased			
subjects affected / exposed	7 / 286 (2.45%)	16 / 281 (5.69%)	
occurrences (all)	7	16	
Blood lactate dehydrogenase increased			

subjects affected / exposed	5 / 286 (1.75%)	12 / 281 (4.27%)	
occurrences (all)	7	13	
Nervous system disorders			
Headache			
subjects affected / exposed	45 / 286 (15.73%)	50 / 281 (17.79%)	
occurrences (all)	60	74	
Neuropathy peripheral			
subjects affected / exposed	44 / 286 (15.38%)	44 / 281 (15.66%)	
occurrences (all)	52	55	
Polyneuropathy			
subjects affected / exposed	34 / 286 (11.89%)	27 / 281 (9.61%)	
occurrences (all)	37	35	
Dysgeusia			
subjects affected / exposed	31 / 286 (10.84%)	27 / 281 (9.61%)	
occurrences (all)	31	30	
Peripheral sensory neuropathy			
subjects affected / exposed	21 / 286 (7.34%)	18 / 281 (6.41%)	
occurrences (all)	29	20	
Neurotoxicity			
subjects affected / exposed	15 / 286 (5.24%)	15 / 281 (5.34%)	
occurrences (all)	19	19	
Paraesthesia			
subjects affected / exposed	13 / 286 (4.55%)	8 / 281 (2.85%)	
occurrences (all)	16	15	
Dizziness			
subjects affected / exposed	12 / 286 (4.20%)	12 / 281 (4.27%)	
occurrences (all)	14	12	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	73 / 286 (25.52%)	93 / 281 (33.10%)	
occurrences (all)	112	150	
Neutropenia			
subjects affected / exposed	55 / 286 (19.23%)	69 / 281 (24.56%)	
occurrences (all)	106	155	
Thrombocytopenia			

subjects affected / exposed	10 / 286 (3.50%)	22 / 281 (7.83%)	
occurrences (all)	20	33	
Leukopenia			
subjects affected / exposed	9 / 286 (3.15%)	13 / 281 (4.63%)	
occurrences (all)	15	19	
Lymphopenia			
subjects affected / exposed	9 / 286 (3.15%)	11 / 281 (3.91%)	
occurrences (all)	12	15	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	8 / 286 (2.80%)	18 / 281 (6.41%)	
occurrences (all)	8	21	
Eye disorders			
Dry eye			
subjects affected / exposed	8 / 286 (2.80%)	9 / 281 (3.20%)	
occurrences (all)	8	11	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	86 / 286 (30.07%)	99 / 281 (35.23%)	
occurrences (all)	141	170	
Nausea			
subjects affected / exposed	102 / 286 (35.66%)	113 / 281 (40.21%)	
occurrences (all)	130	151	
Constipation			
subjects affected / exposed	77 / 286 (26.92%)	75 / 281 (26.69%)	
occurrences (all)	101	92	
Abdominal pain			
subjects affected / exposed	70 / 286 (24.48%)	71 / 281 (25.27%)	
occurrences (all)	82	82	
Vomiting			
subjects affected / exposed	60 / 286 (20.98%)	59 / 281 (21.00%)	
occurrences (all)	79	77	
Abdominal pain upper			
subjects affected / exposed	38 / 286 (13.29%)	40 / 281 (14.23%)	
occurrences (all)	49	50	
Stomatitis			

subjects affected / exposed	37 / 286 (12.94%)	29 / 281 (10.32%)	
occurrences (all)	45	35	
Dyspepsia			
subjects affected / exposed	23 / 286 (8.04%)	19 / 281 (6.76%)	
occurrences (all)	25	20	
Subileus			
subjects affected / exposed	13 / 286 (4.55%)	16 / 281 (5.69%)	
occurrences (all)	14	17	
Gastrooesophageal reflux disease			
subjects affected / exposed	16 / 286 (5.59%)	11 / 281 (3.91%)	
occurrences (all)	16	11	
Ascites			
subjects affected / exposed	10 / 286 (3.50%)	10 / 281 (3.56%)	
occurrences (all)	13	13	
Toothache			
subjects affected / exposed	11 / 286 (3.85%)	12 / 281 (4.27%)	
occurrences (all)	12	13	
Aphthous ulcer			
subjects affected / exposed	10 / 286 (3.50%)	12 / 281 (4.27%)	
occurrences (all)	10	14	
Abdominal distension			
subjects affected / exposed	11 / 286 (3.85%)	9 / 281 (3.20%)	
occurrences (all)	13	10	
Dry mouth			
subjects affected / exposed	3 / 286 (1.05%)	14 / 281 (4.98%)	
occurrences (all)	4	14	
Dysphagia			
subjects affected / exposed	6 / 286 (2.10%)	11 / 281 (3.91%)	
occurrences (all)	6	11	
Haemorrhoids			
subjects affected / exposed	4 / 286 (1.40%)	13 / 281 (4.63%)	
occurrences (all)	4	13	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	56 / 286 (19.58%)	61 / 281 (21.71%)	
occurrences (all)	63	78	

Alopecia			
subjects affected / exposed	62 / 286 (21.68%)	54 / 281 (19.22%)	
occurrences (all)	64	55	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	47 / 286 (16.43%)	45 / 281 (16.01%)	
occurrences (all)	53	49	
Pruritus			
subjects affected / exposed	27 / 286 (9.44%)	32 / 281 (11.39%)	
occurrences (all)	28	40	
Dry skin			
subjects affected / exposed	23 / 286 (8.04%)	26 / 281 (9.25%)	
occurrences (all)	23	28	
Onycholysis			
subjects affected / exposed	22 / 286 (7.69%)	17 / 281 (6.05%)	
occurrences (all)	24	22	
Nail toxicity			
subjects affected / exposed	8 / 286 (2.80%)	16 / 281 (5.69%)	
occurrences (all)	13	24	
Erythema			
subjects affected / exposed	15 / 286 (5.24%)	9 / 281 (3.20%)	
occurrences (all)	17	9	
Nail dystrophy			
subjects affected / exposed	8 / 286 (2.80%)	11 / 281 (3.91%)	
occurrences (all)	8	12	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	44 / 286 (15.38%)	41 / 281 (14.59%)	
occurrences (all)	69	53	
Dysuria			
subjects affected / exposed	9 / 286 (3.15%)	8 / 281 (2.85%)	
occurrences (all)	11	11	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	9 / 286 (3.15%)	39 / 281 (13.88%)	
occurrences (all)	9	43	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	59 / 286 (20.63%)	51 / 281 (18.15%)	
occurrences (all)	72	62	
Back pain			
subjects affected / exposed	40 / 286 (13.99%)	25 / 281 (8.90%)	
occurrences (all)	41	28	
Myalgia			
subjects affected / exposed	31 / 286 (10.84%)	31 / 281 (11.03%)	
occurrences (all)	33	34	
Pain in extremity			
subjects affected / exposed	15 / 286 (5.24%)	15 / 281 (5.34%)	
occurrences (all)	21	21	
Muscle spasms			
subjects affected / exposed	11 / 286 (3.85%)	17 / 281 (6.05%)	
occurrences (all)	15	17	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	40 / 286 (13.99%)	49 / 281 (17.44%)	
occurrences (all)	56	100	
COVID-19			
subjects affected / exposed	23 / 286 (8.04%)	28 / 281 (9.96%)	
occurrences (all)	24	28	
Cystitis			
subjects affected / exposed	18 / 286 (6.29%)	13 / 281 (4.63%)	
occurrences (all)	22	18	
Nasopharyngitis			
subjects affected / exposed	15 / 286 (5.24%)	10 / 281 (3.56%)	
occurrences (all)	18	12	
Rhinitis			
subjects affected / exposed	13 / 286 (4.55%)	8 / 281 (2.85%)	
occurrences (all)	16	8	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	48 / 286 (16.78%)	65 / 281 (23.13%)	
occurrences (all)	57	72	
Hypokalaemia			

subjects affected / exposed	9 / 286 (3.15%)	14 / 281 (4.98%)	
occurrences (all)	11	18	
Hyperkalaemia			
subjects affected / exposed	8 / 286 (2.80%)	12 / 281 (4.27%)	
occurrences (all)	11	16	
Hypomagnesaemia			
subjects affected / exposed	6 / 286 (2.10%)	13 / 281 (4.63%)	
occurrences (all)	9	18	
Hyponatraemia			
subjects affected / exposed	12 / 286 (4.20%)	9 / 281 (3.20%)	
occurrences (all)	14	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 October 2018	- Administrative corrections - Update of the protocol chapter Safety - Update procedure of randomization - Modification of the translational research on blood samples - Implementation of immune-Response Evaluation Criteria of Solid Tumors (iRECIST) - Update of the chapter EDC System (eCRF) and Data Management
22 May 2019	- Administrative corrections - Update of chapter reporting of serious adverse events - Update of guidelines for management of adverse events associated with atezolizumab - Clarification and Update of immune-Response Evaluation Criteria of Solid Tumors (iRECIST) - Update of the chapter EDC System (eCRF) and Data Management
09 January 2020	- Implementation of prospective PD-L1 assessment on tumor samples and PD-L1 tumor status on de novo tumor biopsy (not older than 3 months) as stratification factor for randomization - Updates to align with IB V15 for Atezolizumab to include the diagnostic criteria and management guidelines for HLH and MAS, removal of SIA and inclusion of HLH and MAS as potential risks for atezolizumab
24 April 2020	COVID-19 Addendum
13 July 2021	- Administrative corrections - Update of recruitment timelines - Adding the possibility to perform visits on day 8 and 22 of the first cycle by phone for patients treated with PLD - Addition of exclusion criterion for France - Modification of exclusion criterion - Modification of frequency of LVEF and ECG measurements for patients under treatment - Clarification of frequency of follow-up visits after PD (including follow-up of adverse events) - Modification of the chapter Benefit/Risk and Ethical Assessment to include a more comprehensive benefit-risk section - Update of guidelines for management of adverse events associated with atezolizumab to align with IB V17 for atezolizumab - Addition of possible treatment regime for atezolizumab for patients who has already stopped treatment with bevacizumab and concurrent chemotherapy - Update to implement methods for handling of missing data - Update of the chapter EDC-System (eCRF) and Data Management

04 May 2022	- Update of guidelines for management of adverse events associated with atezolizumab to align with IB V18 for atezolizumab - Change of cap for non-informative tissue PD-L1 status to allow all patients to participate after undergoing a biopsy irrespective of PD-L1 status - Limitation of study treatment to a total duration of 24 months if no other discontinuation criteria are met as there are no data justifying a longer treatment duration and 24 months is in line with similar trials. - Reduction of sample size from 664 to 550 patients and modification of statistical considerations as smaller sample size for recruitment is sufficient for the primary analysis - Modification of timing of the additional survival follow-up (previously eventbased, now time-based at 24 months after LPI) to allow the observation of as much events as possible within a predefined time period. - Deletion of chemotherapy cohort capping as there is no need for a strict capping/uniform distribution of both chemotherapy cohorts. - Modification of reporting period for (S)AEs (90 days instead of 30 days) as the halflife of atezolizumab is given as 27 days and immune-mediated adverse reactions can occur with a latency of several weeks.
11 March 2024	- Update of guidelines for management of adverse events associated with atezoli zumab to align with IB V19 and corresponding addendum 1 and 2 for atezolizumab. - Update toxicity management and dose interruptions attributable to bevacizumab to align with IB V31 of bevacizumab

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/41337696