Clinical trial results:
A randomized, double-blinded, phase III study of atezolizumab versus placebo in patients with late relapse of epithelial ovarian, fallopian tube, or peritoneal cancer treated by platinum-based chemotherapy and bevacizumab

Summary

EudraCT number	2015-005471-24
Trial protocol	FR ES AT DE BE CZ
Global end of trial date	22 February 2024

Results information

Result version number	v1 (current)
This version publication date	10 April 2025
First version publication date	10 April 2025

Trial information

Trial identification

Sponsor protocol code	GINECO-OV236b

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02891824
WHO universal trial number (UTN)	-
Other trial identifiers	ENGOT-ov29: ENGOT

Notes:

Sponsors

Sponsor organisation name	ARCAGY-GINECO
Sponsor organisation address	8 rue Lamennais, Paris, France, 75008
Public contact	Marina Gomes, projet manager, ARCAGY-GINECO, +33 184852020, contact@arcagy.org
Scientific contact	Marina Gomes, projet manager, ARCAGY-GINECO, +33 184852020, contact@arcagy.org

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2024
Global end of trial reached?	Yes
Global end of trial date	22 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of combining atezolizumab with carboplatin-based chemotherapy and bevacizumab compared to placebo with carboplatin-based chemotherapy and bevacizumab in patients with late (platinum-sensitive) relapse of epithelial ovarian, fallopian tube, or peritoneal cancer.
Co-Primary outcomes will be the Progression Free Survival (PFS1) in the ITT population and in the PD-L1 positive subpopulation (PD-L1 expression ≥ 1%).
The primary endpoint measure is progression free survival (PFS1), where the date of progression is based on investigator assessment using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).

Protection of trial subjects:

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and are consistent with International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements. Informed consent was obtained before inclusion in the study.
All patients were treated with the standard of care for patients with a relapse from ovarian cancer and placebo or atezolizumab was added. Disease progression was a criterion for study end, so patients not correctly treated by the study treatment exited the study and were treated with other options.

Background therapy:

Platinum-based chemotherapy either :
- Carboplatin (AUC = 4, d1) combined with gemcitabine (1000 mg/m2, d1 & d8) and bevacizumab (15mg/kg, d1) + placebo (1200mg, d1) x 6 cycles q3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w or
- Carboplatin (AUC = 5, d1) combined with paclitaxel (175 mg/m², d1) and bevacizumab (15mg/kg, d1) + placebo (1200mg, d1) x 6 cycles every 3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w or
- Carboplatin (AUC = 5, d1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², d1) and bevacizumab (10mg/kg, d1 & 15) + placebo (800mg, d1& 15) x 6 cycles every 4wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w.

Evidence for comparator:

Atezolizumab was compared to a placebo. In both groups patients were also treated with bevacizumab and a platinum-based chemotherapy.

Actual start date of recruitment	28 September 2016
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: 67
Country: Number of subjects enrolled	Austria: 24

Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Czechia: 8
Country: Number of subjects enrolled	France: 441
Country: Number of subjects enrolled	Germany: 70
Country: Number of subjects enrolled	Israel: 1
Worldwide total number of subjects	614
EEA total number of subjects	613

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)	342
From 65 to 84 years	272
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

787 patients were included from 25/09/2016 to 04/10/2019 and 614 patients were randomized from 07/10/2016 to 15/10/2019.

Pre-assignment

Screening details:

787 patients were screened and 173 were excluded before randomization(n=93 for not meeting the inclusion criteria, n=27 for tumor block unavailability, n=7 for adverse events, n= 21 withdrew their consent, n= 2 were lost to follow-up and n= 23 for other reasons).

Period 1

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

Blinding implementation details:

Atezolizumab and placebo treatment 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.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo + bevacizumab & platinum-based chemotherapy
The placebo arm included one of 3 following regimens up to investigator choice (chosen prior to randomization)
d) Carboplatin (AUC = 4, d1) combined with gemcitabine (1000 mg/m2, d1 & d8) and bevacizumab (15mg/kg, d1) + placebo (1200mg, d1) x 6 cycles q3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w or
e) Carboplatin (AUC = 5, d1) combined with paclitaxel (175 mg/m², d1) and bevacizumab (15mg/kg, d1) + placebo (1200mg, d1) x 6 cycles every 3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w or
f) Carboplatin (AUC = 5, d1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², d1) and bevacizumab (10mg/kg, d1 & 15) + placebo (800mg, d1& 15) x 6 cycles every 4wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w.

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

Dosage and administration details:

The fixed dose of 1200 mg (equivalent to an average body weight−based dose of 15 mg/kg) was selected based on both nonclinical studies and available clinical data. This atezolizumab/placebo 1200mg dose was delivered every 3 weeks before bevacizumab infusion and prior to the carboplatin-gemcitabine or paclitaxel regimen and in all the maintenance schedule. The atezolizumab/placebo dose was 800mg every 2 weeks when delivered with carboplatin-PLD chemotherapy.

Arm title	Atezolizumab

Arm description:

Atezolizumab + bevacizumab & platinum-based chemotherapy
The atezolizumab arm included one of 3 following regimens up to investigator choice (chosen prior to randomization)

a) Carboplatin (AUC = 4, d1) combined with gemcitabine (1000 mg/m2, d1 & d8) and bevacizumab (15mg/kg, d1) + atezolizumab (1200mg, d1) x 6 cycles q3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w or
b) Carboplatin (AUC = 5, d1) combined with paclitaxel (175 mg/m², d1) and bevacizumab (15mg/kg, d1) + atezolizumab (1200mg, d1) x 6 cycles every 3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w or
c) Carboplatin (AUC = 5, d1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², d1) and bevacizumab (10mg/kg, d1 & 15) + atezolizumab (800mg, d1& 15) x 6 cycles every 4wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w.

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

Dosage and administration details:

The fixed dose of 1200 mg (equivalent to an average body weight−based dose of 15 mg/kg) was selected based on both nonclinical studies and available clinical data. This atezolizumab/placebo 1200mg dose was delivered every 3 weeks before bevacizumab infusion and prior to the carboplatin-gemcitabine or paclitaxel regimen and in all the maintenance schedule. The atezolizumab/placebo dose was 800mg every 2 weeks when delivered with carboplatin-PLD chemotherapy.

Number of subjects in period 1	Placebo	Atezolizumab
Started	204	410
Completed	204	410

Baseline characteristics

Reporting groups	
Reporting group title	Placebo

Reporting group description:

Placebo + bevacizumab & platinum-based chemotherapy
The placebo arm included one of 3 following regimens up to investigator choice (chosen prior to randomization)
d) Carboplatin (AUC = 4, d1) combined with gemcitabine (1000 mg/m2, d1 & d8) and bevacizumab (15mg/kg, d1) + placebo (1200mg, d1) x 6 cycles q3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w or
e) Carboplatin (AUC = 5, d1) combined with paclitaxel (175 mg/m², d1) and bevacizumab (15mg/kg, d1) + placebo (1200mg, d1) x 6 cycles every 3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w or
f) Carboplatin (AUC = 5, d1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², d1) and bevacizumab (10mg/kg, d1 & 15) + placebo (800mg, d1& 15) x 6 cycles every 4wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w.

Reporting group title	Atezolizumab

Reporting group description:

Atezolizumab + bevacizumab & platinum-based chemotherapy
The atezolizumab arm included one of 3 following regimens up to investigator choice (chosen prior to randomization)
a) Carboplatin (AUC = 4, d1) combined with gemcitabine (1000 mg/m2, d1 & d8) and bevacizumab (15mg/kg, d1) + atezolizumab (1200mg, d1) x 6 cycles q3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w or
b) Carboplatin (AUC = 5, d1) combined with paclitaxel (175 mg/m², d1) and bevacizumab (15mg/kg, d1) + atezolizumab (1200mg, d1) x 6 cycles every 3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w or
c) Carboplatin (AUC = 5, d1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², d1) and bevacizumab (10mg/kg, d1 & 15) + atezolizumab (800mg, d1& 15) x 6 cycles every 4wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w.

Reporting group values	Placebo	Atezolizumab	Total
Number of subjects	204	410	614
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 Units: years			
median	62.54	61.76	
standard deviation	± 10.82	± 10.75	-
Gender categorical Units: Subjects			
Female	204	410	614
Male	0	0	0

ECOG Units: Subjects			
score of 0	131	277	408
score of 1	72	131	203
score of 2	0	2	2
score of 3	0	0	0
score of 4	0	0	0
NA	1	0	1
CA125 dosage before treatment administration Units: Subjects			
Anormal <100 kU/L	48	88	136
Anormal >=100 kU/L	113	227	340
Normal	43	92	135
NA	0	3	3
Blood Pressure Units: Subjects			
High (SBP > 140 and DPB >90)	9	12	21
Normal	193	395	588
NA	2	3	5
PDL1 expression			
PD-L1–positive status was defined as tumor-infiltrating immune cell (IC) PD-L1 expression on ≥1% of tumor area using the Ventana SP142 immunohistochemistry assay (Ventana Medical Systems, Tucson, AZ), as in previous atezolizumab trials (Moore et al. 2021; Schmid et al. 2018; Mittendorf et al. 2020; Miles et al. 2021).			
Units: Subjects			
Positive	77	156	233
Negative	102	196	298
Inconclusive	25	58	83
Primary cancer site Units: Subjects			
Ovary	191	369	560
Fallopian tube	5	27	32
Peritoneal	8	14	22
Adenocarcinoma type Units: Subjects			
Serous High Grade (a)	169	346	515
Serous Low Grade (b)	8	32	40
Endometrioid Grade 2/3 (c)	11	12	23
Endometrioid Grade 1 (d)	0	1	1
Clear cell	9	8	17
Mucinous	0	0	0
Undifferentiated	4	4	8
Other	1	1	2
Carcinosarcoma	1	4	5
Mixed tumor	0	2	2
Brenner	1	0	1
FIGO Units: Subjects			
Stage I	5	18	23
Stage II	8	18	26
Stage III	117	261	378

Stage IV	49	73	122
Unknown	25	40	65
BRCA mutation status Units: Subjects			
Germline or somatic mutation	32	40	72
Inconclusive	54	129	183
No mutation	118	241	359
Debulking surgery Units: Subjects			
No	21	27	48
Yes	183	383	566
Number of previous lines of treatment Units: Subjects			
1 line	147	307	454
2 lines	56	103	159
3 lines	1	0	1
Tumor size Units: millimetre(s)			
median	38.5	47	
inter-quartile range (Q1-Q3)	24 to 68	28 to 82.75	-
BMI			
kg/cm2			
Units: kilogram(s)/square centimetre			
median	24.27	24.67	
inter-quartile range (Q1-Q3)	21.62 to 27.99	21.61 to 28.23	-
Time between relapse before entering the sutyd and randomization Units: day			
median	57	59	
inter-quartile range (Q1-Q3)	41 to 78	42 to 82	-

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo + bevacizumab & platinum-based chemotherapy
The placebo arm included one of 3 following regimens up to investigator choice (chosen prior to randomization)
d) Carboplatin (AUC = 4, d1) combined with gemcitabine (1000 mg/m2, d1 & d8) and bevacizumab (15mg/kg, d1) + placebo (1200mg, d1) x 6 cycles q3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w or
e) Carboplatin (AUC = 5, d1) combined with paclitaxel (175 mg/m², d1) and bevacizumab (15mg/kg, d1) + placebo (1200mg, d1) x 6 cycles every 3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w or
f) Carboplatin (AUC = 5, d1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², d1) and bevacizumab (10mg/kg, d1 & 15) + placebo (800mg, d1& 15) x 6 cycles every 4wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w.

Reporting group title	Atezolizumab

Reporting group description:

Atezolizumab + bevacizumab & platinum-based chemotherapy
The atezolizumab arm included one of 3 following regimens up to investigator choice (chosen prior to randomization)
a) Carboplatin (AUC = 4, d1) combined with gemcitabine (1000 mg/m2, d1 & d8) and bevacizumab (15mg/kg, d1) + atezolizumab (1200mg, d1) x 6 cycles q3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w or
b) Carboplatin (AUC = 5, d1) combined with paclitaxel (175 mg/m², d1) and bevacizumab (15mg/kg, d1) + atezolizumab (1200mg, d1) x 6 cycles every 3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w or
c) Carboplatin (AUC = 5, d1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², d1) and bevacizumab (10mg/kg, d1 & 15) + atezolizumab (800mg, d1& 15) x 6 cycles every 4wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w.

Subject analysis set title	PD-L1 positive Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PD-L1 expression was assessed by immunochemistry on immune cells of the tumor de novo biopsy obtained before entry in ATALANTE. PD-L1 positivity was defined as ≥1% of immune cells (ICs) expressing PD-L1 which was referred to IC1/2/3 according to PD-L1 scoring algorithm.

Subject analysis set title	PD-L1 positive Atzolizumab
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PD-L1 expression was assessed by immunochemistry on immune cells of the tumor de novo biopsy obtained before entry in ATALANTE. PD-L1 positivity was defined as ≥1% of immune cells (ICs) expressing PD-L1 which was referred to IC1/2/3 according to PD-L1 scoring algorithm.

Primary: Progression free survival

End point title	Progression free survival

End point description:

The co-primary endpoints were not reached and therefore the statistics for the secondary endpoints are not detailed here.

End point type	Primary

End point timeframe:

Progression free survival was assessed over the entire duration of the study from 25/09/2016 to 15/10/2023.

End point values	Placebo	Atezolizumab	PD-L1 positive Placebo	PD-L1 positive Atzolizumab
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	204	410	77	156
Units: month				
median (confidence interval 95%)	11.27 (11.04 to 13.50)	13.60 (12.32 to 14.29)	13.08 (11.40 to 16.49)	15.24 (13.14 to 17.02)

Statistical analyses

Statistical analysis title	Cox model results in ITT population
Comparison groups	Placebo v Atezolizumab
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	0.98

Statistical analysis title	Cox model in PD-L1 positive population
Comparison groups	PD-L1 positive Placebo v PD-L1 positive Atzolizumab
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	Cox model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.18

Secondary: Treatment exposure

End point title	Treatment exposure

End point description:

End point type	Secondary

End point timeframe:

From start of trial until date of data cut-off (10/15/2023)

End point values	Placebo	Atezolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	202	407		
Units: month				
median (inter-quartile range (Q1-Q3))	11.2 (8.41 to 16.74)	11.33 (7.06 to 18.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

Over the whole duration of the study.

End point values	Placebo	Atezolizumab	PD-L1 positive Placebo	PD-L1 positive Atzolizumab
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	204	410	77	156
Units: percent				
number (confidence interval 95%)	30.62 (27.79 to 33.15)	35.75 (32.89 to 41.00)	33.68 (30.62 to 50.76)	42.97 (38.05 to 50.23)

Statistical analyses

Statistical analysis title	Cox model results in ITT population

Statistical analysis description:

The proportional hazard assumption was tested using Likelihood ratio test on time-dependent coefficient. The test statistic for the likelihood ratio test between the time independent and time dependent models was 1.422. With one degree of freedom, the corresponding p value is equal to 0.233, therefore the time dependent coefficient is non-significant. Based on this result, an adjusted Cox model without time varying effect of treatment was used for the analysis on the ITT population.

Comparison groups	Placebo v Atezolizumab

Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	0.98

Statistical analysis title	Cox model results in PD-L1 positive population
Comparison groups	PD-L1 positive Placebo v PD-L1 positive Atzolizumab
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.17

Secondary: Time to first subsequent therapy

End point title	Time to first subsequent therapy

End point description:

End point type	Secondary

End point timeframe:

Over the whole duration of the trial

End point values	Placebo	Atezolizumab	PD-L1 positive Placebo	PD-L1 positive Atzolizumab
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	204	410	77	156
Units: month				
median (confidence interval 95%)	12.42 (11.83 to 14.42)	14.36 (13.67 to 15.64)	14.16 (12.02 to 18.43)	17.12 (14.36 to 19.98)

Statistical analyses

Statistical analysis title	Cox model results in ITT population
Comparison groups	Placebo v Atezolizumab
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	0.99

Statistical analysis title	Cox model in PD-L1 positive population
Comparison groups	PD-L1 positive Placebo v PD-L1 positive Atzolizumab
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.19

Secondary: Time to second subsequent therapy	
End point title	Time to second subsequent therapy
End point description:	

End point type	Secondary
End point timeframe:	
Endpoint was assessed over the entire duration of the study from 25/09/2016 to 15/10/2023.	

End point values	Placebo	Atezolizumab	PD-L1 positive Placebo	PD-L1 positive Atzolizumab
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	204	410	77	156
Units: month				
median (confidence interval 95%)	20.99 (18.63 to 23.75)	23.72 (22.60 to 25.72)	25.26 (21.62 to 31.18)	27.14 (24.61 to 33.08)

Statistical analyses

Statistical analysis title	Cox model results in ITT population
Comparison groups	Placebo v Atezolizumab
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	0.99

Statistical analysis title	Cox model in PD-L1 positive population
Comparison groups	PD-L1 positive Placebo v PD-L1 positive Atzolizumab
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.32

Secondary: Time to RECIST progression or CA125 deterioration	
End point title	Time to RECIST progression or CA125 deterioration
End point description:	

End point type	Secondary
End point timeframe:	
Was assessed over the entire duration of the study from 25/09/2016 to 15/10/2023.	

End point values	Placebo	Atezolizumab	PD-L1 positive Placebo	PD-L1 positive Atzolizumab
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	204	410	77	156
Units: month				
median (confidence interval 95%)	10.81 (10.38 to 11.17)	11.56 (11.07 to 12.88)	11.17 (10.64 to 12.45)	13.70 (12.62 to 16.39)

Statistical analyses

Statistical analysis title	Cox model results in ITT population
Comparison groups	Placebo v Atezolizumab
Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	0.95

Statistical analysis title	Cox model in PD-L1 positive population
Comparison groups	PD-L1 positive Placebo v PD-L1 positive Atzolizumab
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.98

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events will be collected from time of signature of informed consent, throughout the treatment period and up to and including the 30-day follow-up period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26

Reporting groups

Reporting group title	Safety population

Reporting group description:

The safety was described on the safety set population (N=609), including only patients who had at least one dose of study treatment. 5 patients (3 in the atezolizumab group and 2 in the placebo group) did not start bevacizumab nor atezolizumab after randomization.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	444 / 609 (72.91%)		
number of deaths (all causes)	443		
number of deaths resulting from adverse events	19		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute megakaryocytic leukaemia			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Acute myeloid leukaemia			
subjects affected / exposed	3 / 609 (0.49%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	2 / 3		
Adrenal metastases			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			

subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cancer pain				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphangitis carcinomatosis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myelodysplastic syndrome				
subjects affected / exposed	4 / 609 (0.66%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Paraneoplastic syndrome				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Aortic stenosis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	190 / 609 (31.20%)			
occurrences causally related to treatment / all	173 / 190			
deaths causally related to treatment / all	0 / 0			
Hematoma				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombosis				

subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Orthostatic hypotension				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Embolism				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematoma				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant hypertension				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Phlebitis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Intervertebral disc operation				

subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary catheter insertion				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Stomatitis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Catheter infection				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Drug intolerance				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				

subjects affected / exposed	10 / 609 (1.64%)			
occurrences causally related to treatment / all	4 / 10			
deaths causally related to treatment / all	0 / 0			
Inflammation				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza like illness				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mucositis				
subjects affected / exposed	3 / 609 (0.49%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Multi organ failure				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pain				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	8 / 609 (1.31%)			
occurrences causally related to treatment / all	1 / 8			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Hypersensitivity				
subjects affected / exposed	7 / 609 (1.15%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Anaphylactic reaction				

subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Anaphylactic shock				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Drug hypersensitivity				
subjects affected / exposed	7 / 609 (1.15%)			
occurrences causally related to treatment / all	5 / 7			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Rectovaginal fistula				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute pulmonary oedema				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnea				
subjects affected / exposed	5 / 609 (0.82%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Embolism pulmonary				
subjects affected / exposed	19 / 609 (3.12%)			
occurrences causally related to treatment / all	12 / 19			
deaths causally related to treatment / all	1 / 2			
Laryngeal spasm				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Pleural effusion				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	4 / 609 (0.66%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary infarction				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Confusional state				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	4 / 609 (0.66%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Alkaline phosphatase increased				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	7 / 609 (1.15%)			
occurrences causally related to treatment / all	6 / 7			
deaths causally related to treatment / all	0 / 0			

CSF white blood cell count decreased				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
GGT increased				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Left ventricular ejection fraction decreased				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	10 / 609 (1.64%)			
occurrences causally related to treatment / all	2 / 10			
deaths causally related to treatment / all	0 / 0			
Renal biopsy				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transaminases increased				
subjects affected / exposed	3 / 609 (0.49%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
White blood cell decreased				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Cat bite				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Eye burns			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fracture vertebral			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			
subjects affected / exposed	3 / 609 (0.49%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Intraoperative hemorrhage			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post biopsy bleeding			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural pneumothorax			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tendon achilles rupture			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			

Aplasia			
subjects affected / exposed	2 / 609 (0.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	5 / 609 (0.82%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Acute heart failure			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Cardiac disorder			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac dysfunction			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac failure			
subjects affected / exposed	4 / 609 (0.66%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Coronary artery stenosis			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			

subjects affected / exposed	4 / 609 (0.66%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Myocarditis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Non ST segment elevation myocardial infarction				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Palpitations				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cephalgia				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral ischaemia				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebral venous thrombosis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dizziness				

subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Encephalopathy			
subjects affected / exposed	2 / 609 (0.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Epileptic seizure			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Headache aggravated			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hemorrhagic stroke			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hypercapnic coma			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Cerebrovascular accident			
subjects affected / exposed	3 / 609 (0.49%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Ischemic stroke			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Meningismus			

subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Meningorrhagia				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neurologic disorder NOS				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Posterior reversible encephalopathy syndrome				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Stroke				
subjects affected / exposed	3 / 609 (0.49%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Transient ischemic attack				
subjects affected / exposed	3 / 609 (0.49%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Tremor				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Blood and lymphatic system disorders				
Anaemia				

subjects affected / exposed	10 / 609 (1.64%)		
occurrences causally related to treatment / all	2 / 10		
deaths causally related to treatment / all	0 / 0		
Aplasia bone marrow			
subjects affected / exposed	2 / 609 (0.33%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Febrile aplasia			
subjects affected / exposed	8 / 609 (1.31%)		
occurrences causally related to treatment / all	2 / 8		
deaths causally related to treatment / all	0 / 1		
Evans syndrome			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	30 / 609 (4.93%)		
occurrences causally related to treatment / all	6 / 30		
deaths causally related to treatment / all	0 / 0		
Hemolytic anemia			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperviscosity syndrome			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune thrombocytopenic purpura			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			

subjects affected / exposed	42 / 609 (6.90%)			
occurrences causally related to treatment / all	10 / 42			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	17 / 609 (2.79%)			
occurrences causally related to treatment / all	8 / 17			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	68 / 609 (11.17%)			
occurrences causally related to treatment / all	12 / 68			
deaths causally related to treatment / all	0 / 0			
Thrombotic microangiopathy				
subjects affected / exposed	9 / 609 (1.48%)			
occurrences causally related to treatment / all	9 / 9			
deaths causally related to treatment / all	0 / 0			
Thrombotic thrombocytopenic purpura				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Splenic haematoma				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bone marrow failure				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Eosinophilia				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Labyrinthine hydrops				

subjects affected / exposed	2 / 609 (0.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Blurred vision			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Posterior vitreous detachment			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal bleeding			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Uveitis			
subjects affected / exposed	3 / 609 (0.49%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Vitreous hemorrhage			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	8 / 609 (1.31%)		
occurrences causally related to treatment / all	1 / 8		
deaths causally related to treatment / all	0 / 0		
Acute abdomen			

subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Autoimmune colitis				
subjects affected / exposed	4 / 609 (0.66%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Autoimmune pancreatitis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bloody stool				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bowel perforation				
subjects affected / exposed	3 / 609 (0.49%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	1 / 1			
Colitis				
subjects affected / exposed	7 / 609 (1.15%)			
occurrences causally related to treatment / all	7 / 7			
deaths causally related to treatment / all	0 / 0			
Colonic fistula				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal motility disorder				

subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	22 / 609 (3.61%)			
occurrences causally related to treatment / all	15 / 22			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocutaneous fistula				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epigastric pain				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal fistula				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Glossitis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hemorrhoids				

subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hernial eventration				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	4 / 609 (0.66%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	11 / 609 (1.81%)			
occurrences causally related to treatment / all	1 / 11			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				
subjects affected / exposed	4 / 609 (0.66%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Intestinal subobstruction				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mechanical ileus				
subjects affected / exposed	3 / 609 (0.49%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				

subjects affected / exposed	4 / 609 (0.66%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Perforation gastrointestinal				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal pain				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal perforation				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reflux oesophagitis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small bowel obstruction				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Small intestinal perforation				

subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Stagnation of intestinal contents				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	11 / 609 (1.81%)			
occurrences causally related to treatment / all	3 / 11			
deaths causally related to treatment / all	0 / 0			
Subocclusive syndrome				
subjects affected / exposed	3 / 609 (0.49%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal hemorrhage				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	11 / 609 (1.81%)			
occurrences causally related to treatment / all	5 / 10			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Acute cholecystitis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Autoimmune hepatitis				
subjects affected / exposed	3 / 609 (0.49%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Bile duct stenosis				

subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Biliary colic				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Calculus biliary				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cholestasis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic cytolysis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gallbladder rupture				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis				
subjects affected / exposed	3 / 609 (0.49%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Liver disorder				

subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis acute				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatocellular injury				
subjects affected / exposed	5 / 609 (0.82%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Cutaneous lupus erythematosus				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dermatitis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dermatitis bullous				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dermatomyositis				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Drug eruption				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Erythroderma				

subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Exanthema				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gallbladder perforation				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hidradenitis suppurativa				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Itching and rash				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Leg ulcer				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Macular rash				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Maculopapular rash				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Palmar-plantar erythrodysesthesia syndrome				

subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin rash				
subjects affected / exposed	21 / 609 (3.45%)			
occurrences causally related to treatment / all	19 / 21			
deaths causally related to treatment / all	0 / 0			
Skin toxicity				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stevens-Johnson syndrome				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney failure				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Proteinuria				
subjects affected / exposed	22 / 609 (3.61%)			
occurrences causally related to treatment / all	19 / 22			
deaths causally related to treatment / all	0 / 0			
Acute renal insufficiency				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Acute renal failure				
subjects affected / exposed	5 / 609 (0.82%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Glomerulonephritis				

subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Macroscopic haematuria				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nephrotic syndrome				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvicaliectasis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Renal insufficiency				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Renal impairment				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Adrenal insufficiency				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Autoimmune thyroid disorder				

subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Autoimmune thyroiditis				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hyperthyroidism				
subjects affected / exposed	15 / 609 (2.46%)			
occurrences causally related to treatment / all	12 / 15			
deaths causally related to treatment / all	0 / 0			
Hypophysitis				
subjects affected / exposed	3 / 609 (0.49%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Hypothyroidism				
subjects affected / exposed	72 / 609 (11.82%)			
occurrences causally related to treatment / all	70 / 72			
deaths causally related to treatment / all	0 / 0			
Panhypopituitarism				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thyroiditis				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bone pain				

subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Joint pain				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Myalgia				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myositis				
subjects affected / exposed	4 / 609 (0.66%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Rhizomelic pseudopolyarthritis				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abscess				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Abscess dental				
subjects affected / exposed	5 / 609 (0.82%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	0 / 0			
Abscess gum				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Anal abscess				

subjects affected / exposed	2 / 609 (0.33%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Acute upper respiratory tract infection			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites infection			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aspergillosis			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial sepsis			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	4 / 609 (0.66%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
CMV infection			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	6 / 609 (0.99%)		
occurrences causally related to treatment / all	3 / 6		
deaths causally related to treatment / all	0 / 0		
COVID-19			

subjects affected / exposed	3 / 609 (0.49%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Encephalitis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Enterococcus faecalis infection				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia urinary tract infection				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Flu syndrome				

subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infected lymphocele				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Influenza A virus infection				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
H1N1 influenza				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Groin abscess				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Papulopustular rash				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic abscess				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Perianal abscess				

subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Periorbital cellulitis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Peritoneal infection				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	3 / 609 (0.49%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	1 / 1			
Pyelitis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	10 / 609 (1.64%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 0			
Respiratory infection				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	4 / 609 (0.66%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Septic arthritis				

subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Septicaemia due to Escherichia coli (E. coli)				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stoma site infection				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tooth abscess				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory infection				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary infection				
subjects affected / exposed	8 / 609 (1.31%)			
occurrences causally related to treatment / all	1 / 8			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vertebral abscess				

subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Arthritis bacterial				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Osteonecrosis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetes				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetes with ketoacidosis				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Electrolyte disturbance				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperamylasemia				
subjects affected / exposed	1 / 609 (0.16%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercalcemia				
subjects affected / exposed	2 / 609 (0.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hypercreatininaemia				

subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalemia			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperlipasemia			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalemia			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatremia			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatremia aggravated			
subjects affected / exposed	1 / 609 (0.16%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	609 / 609 (100.00%)		
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	231 / 609 (37.93%)		
occurrences (all)	451		
Blood and lymphatic system disorders			

Anemia subjects affected / exposed occurrences (all) NEUTROPENIA subjects affected / exposed occurrences (all) THROMBOCYTOPENIA subjects affected / exposed occurrences (all) LEUKOPENIA subjects affected / exposed occurrences (all)	353 / 609 (57.96%) 1042 354 / 609 (58.13%) 1166 304 / 609 (49.92%) 1026 133 / 609 (21.84%) 416		
General disorders and administration site conditions ASTHENIA subjects affected / exposed occurrences (all) FATIGUE subjects affected / exposed occurrences (all)	 327 / 609 (53.69%) 817 175 / 609 (28.74%) 377		
Gastrointestinal disorders NAUSEA subjects affected / exposed occurrences (all) DIARRHOEA subjects affected / exposed occurrences (all) CONSTIPATION subjects affected / exposed occurrences (all)	 382 / 609 (62.73%) 852 239 / 609 (39.24%) 476 237 / 609 (38.92%) 411		
Respiratory, thoracic and mediastinal disorders EPISTAXIS subjects affected / exposed occurrences (all)	 226 / 609 (37.11%) 326		
Renal and urinary disorders PROTEINURIA			

subjects affected / exposed occurrences (all)	184 / 609 (30.21%) 480		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 July 2016	Modified protocol to include clarifications of subject selection criteria. Clarification of exploratory objectives. Amended of stratification factor. Clarifications of the use of corticosteroids. Clarifications of the collection of auto-immune disease. Amended management of bevacizumab and atezolizumab specific adverse event. Modification of the frequency of questionnaires collection. Added of data sharing.
20 October 2016	Amended management of atezolizumab specific adverse event.
07 April 2017	Modified protocol to add secondary objective. Modification of statistical analysis. Clarification of inclusion criteria.
18 December 2017	Amended management of atezolizumab specific adverse events. Clarification of exclusion criteria.
26 November 2018	Increase of the number of patients (from 405 to 600), update of the study calendar, addition of a co-primary outcome, update of secondary objectives, modification of statistical methods and sample size determination, modification of the management of atezolizumab specific adverse events (addition of renal events) and suppression of PRO sub-study.
17 May 2019	Change of sponsor's address and phone number, precision regarding study treatment duration, precision of estimated date of end of study, addition of a secondary objective (PK and ADA analysis), addition of an exploratory objective, modification of statistical part, addition of a possible Blinded Independent Scan Review, precision regarding the necessity of the additional CT scan after detection of disease progression, modification of the management of atezolizumab specific adverse events (addition of immune-related Myositis), clarification regarding the unblinded treatment, clarification to make the difference between patient study treatment withdrawal and patient study withdrawal, clarification of the definition of SAE, list of AESI updated.
04 May 2020	Amended management of atezolizumab specific adverse events, list of AESI of atezolizumab updated.
06 November 2020	Modifications of statistical part and amended management of atezolizumab specific adverse events
08 March 2021	Amended management of atezolizumab specific adverse events (MAS/HLH added).
26 November 2021	Addition of secondary objective (PFS1 and OS will be evaluated according to PD-L1 and/or CD8 status) with related modifications in the chapters of Translational Research, statistical analysis and references. Alignment of the statistical test for the co-primary efficacy endpoint with Statistical Analysis Plan. Replacement of new GCIG logo and correction of minor typo. Update of the Trial Manager name.

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/37643382