



Clinical trial results:

A phase II study of the anti-PDL1 antibody atezolizumab, bevacizumab and acetylsalicylic acid to investigate safety and efficacy of this combination in recurrent platinum-resistant ovarian, fallopian tube or primary peritoneal adenocarcinoma

Summary

EudraCT number	2015-004601-17
Trial protocol	ES FR NL GB
Global end of trial date	16 February 2022

Results information

Result version number	v1 (current)
This version publication date	03 February 2023
First version publication date	03 February 2023

Trial information

Trial identification

Sponsor protocol code	1508-GCG
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02659384
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	EORTC
Sponsor organisation address	Avenue E. Mounier 83, Brussels, Belgium, 1200
Public contact	Clinical Operations Unit, European Organisation For Research and Treatment of Cancer (EORTC), 32 2774 10 15, regulatory@eortc.be
Scientific contact	Clinical Operations Unit, European Organisation For Research and Treatment of Cancer (EORTC), 32 2774 10 15, regulatory@eortc.be

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 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 February 2022
Global end of trial reached?	Yes
Global end of trial date	16 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the efficacy and safety of 5 different treatments involving atezolizumab, bevacizumab and/or acetylsalicylic acid in advanced recurrent platinum-resistant ovarian, fallopian tube or primary peritoneal cancer patients in order to select the optimal treatments for further development in phase III.

Protection of trial subjects:

The study is conducted in agreement with the Declaration of Helsinki (available on the World Medical Association web site (<http://www.wma.net>)) and/or the laws and regulations of the participating countries, whichever provides the greatest protection of the patient. The protocol has been written, and the study conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice. The protocol was approved by the competent ethics committee(s) as required by the applicable national legislation. Safety data were reviewed within the EORTC Headquarters on a regular basis as part of the Medical Review process. Safety information was included in trial status reports which served as a basis of discussion during EORTC Group meetings.

Background therapy:

None.

Evidence for comparator:

Work from Coukos et al. as well as other groups has provided evidence that ovarian tumors are spontaneously recognized and attacked by the immune system in many patients, and that the presence of tumor-infiltrating lymphocytes (TILs) is associated with improved outcome. This suggests that immune therapy could produce substantial clinical benefits in ovarian cancer, which is supported by pilot clinical data.

It has been demonstrated that increased levels of intratumoral VEGF are associated with absence of TILs in human ovarian cancer. Tumor endothelial cells express Fas ligand (FasL), killing activated lymphocytes and in particular effector cells while immune-suppressive regulatory T cells (Tregs) seem to be resistant to FasL induced cell death. In addition, expression of FasL on tumor endothelial cells was induced by prostaglandin E2 (PGE2) produced at high levels by tumor cells expressing COX1. The effect of PGE2 on FasL expression was further amplified by vascular endothelial growth factor A (VEGF-A), also produced by tumor cells. In several mouse tumor models the administration of acetylsalicylic acid (ASA) to irreversibly inhibit the constitutively expressed COX1 as well as the inducible COX2 combined with anti-VEGF antibody resulted in reduced tumor growth, which was associated and mediated by increased T cell infiltration. Thus, blockade of VEGF and PGE2 in ovarian cancer can reverse the endothelial barrier and allow T cell infiltration, which is expected to synergize with T cell activation by PD-L1 blockade. In the EORTC 1508 trial we propose to combine an anti-PDL1 antibody atezolizumab, to relieve suppression of effector T cells, with bevacizumab and the irreversible COX1/2 inhibitor ASA (acetylsalicylic acid), with the goal to downregulate the expression of FasL on tumor endothelial cells, ablating the barrier that keeps effector lymphocytes out of the tumor.

Actual start date of recruitment	14 October 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Switzerland: 26
Country: Number of subjects enrolled	Netherlands: 36
Worldwide total number of subjects	122
EEA total number of subjects	66

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)	66
From 65 to 84 years	56
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 22 December 2016 and 27 February 2020, 122 patients were recruited by 12 centers from 5 countries (Netherlands, United Kingdom, Switzerland, France and Spain).

Pre-assignment

Screening details:

Recurrent, histologically proven, platinum-resistant, epithelial ovarian cancer, fallopian tube and primary peritoneal cancer in advanced or metastatic stage. Age ≥ 18 years. Life expectancy of ≥ 12 weeks. Adequate hematologic and end organ function. Written informed consent must be given according to ICH/GCP, and national/local regulations.

Period 1

Period 1 title	Overall study period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The trial design is partially blind. Only the ASA administration is masked from the patient and local staff through placebo use. The clinical trial administrative personnel (not at the local hospital) remains aware of the actual treatment arm allocation. Allocation of bevacizumab and atezolizumab is not blinded. This blinding system was implemented as ASA can be purchased by patients outside of the trial. Therefore blinding of ASA allocation was enforced to avoid self-medication by the patient.

Arms

Are arms mutually exclusive?	Yes
Arm title	bevacizumab mono

Arm description:

Bevacizumab 15 mg/kg q3w will be administered as bevacizumab monotherapy treatment and discontinued upon RECISTv1.1-documented progression or upon treatment withdrawal, whichever occurs first. Patients will cross-over to the combination of bevacizumab and atezolizumab upon progression as long as they meet cross-over criteria.

Arm type	Active comparator
Investigational medicinal product name	bevacizumab
Investigational medicinal product code	rhuMAb VEGF
Other name	Avastin
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Parenteral use

Dosage and administration details:

Bevacizumab 15 mg/kg q3w will be administered as bevacizumab monotherapy treatment and discontinued upon RECISTv1.1-documented progression or upon treatment withdrawal, whichever occurs first.

Arm title	atezolizumab + placebo
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Arm description:

atezolizumab 1200 mg flat dose q3w will be administered together with placebo 320 mg/d as combination treatment and discontinued upon RECISTv1.1-documented progression or upon treatment withdrawal, whichever occurs first. Patients will cross-over to the combination of bevacizumab and atezolizumab upon progression as long as they meet cross-over criteria

Arm type	Active comparator
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	MPDL3280A
Other name	Tecentriq
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

atezolizumab 1200 mg flat dose q3w will be administered and discontinued upon RECISTv1.1-documented progression or upon treatment withdrawal, whichever occurs first.

Arm title	atezolizumab + ASA
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Arm description:

atezolizumab 1200 mg flat dose q3w will be administered together with ASA 320 mg/d as combination treatment and discontinued upon RECISTv1.1-documented progression or upon treatment withdrawal, whichever occurs first. Patients will cross-over to the combination of bevacizumab and atezolizumab upon progression as long as they meet cross-over criteria

Arm type	Active comparator
Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	MPDL3280A
Other name	Tecentriq
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

atezolizumab 1200 mg flat dose q3w will be administered and discontinued upon RECISTv1.1-documented progression or upon treatment withdrawal, whichever occurs first.

Arm title	atezolizumab + bevacizumab + placebo
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Arm description:

atezolizumab 1200 mg flat dose q3w will be administered together with bevacizumab 15 mg/kg q3w and placebo 320 mg/d as combination treatment and discontinued upon treatment failure or upon treatment withdrawal, whichever occurs first. Patients then go off protocol treatment and further treatment is left to the investigator's decision.

Arm type	Active comparator
Investigational medicinal product name	bevacizumab
Investigational medicinal product code	rhumaB VEGF
Other name	Avastin
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Parenteral use

Dosage and administration details:

Bevacizumab 15 mg/kg q3w will be administered as bevacizumab monotherapy treatment and discontinued upon RECISTv1.1-documented progression or upon treatment withdrawal, whichever occurs first.

Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	MPDL3280A
Other name	Tecentriq
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

atezolizumab 1200 mg flat dose q3w will be administered and discontinued upon RECISTv1.1-documented progression or upon treatment withdrawal, whichever occurs first.

Arm title	atezolizumab + bevacizumab + ASA
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Arm description:

atezolizumab 1200 mg flat dose q3w will be administered together with bevacizumab 15 mg/kg q3w and ASA 320 mg/d as combination treatment and discontinued upon treatment failure or upon treatment withdrawal, whichever occurs first. Patients then go off protocol treatment and further treatment is left to the investigator's decision.

Arm type	Active comparator
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Investigational medicinal product name	bevacizumab
Investigational medicinal product code	rhuMAb VEGF
Other name	Avastin
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Parenteral use

Dosage and administration details:

Bevacizumab 15 mg/kg q3w will be administered as bevacizumab monotherapy treatment and discontinued upon RECISTv1.1-documented progression or upon treatment withdrawal, whichever occurs first.

Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	MPDL3280A
Other name	Tecentriq
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

atezolizumab 1200 mg flat dose q3w will be administered and discontinued upon RECISTv1.1-documented progression or upon treatment withdrawal, whichever occurs first.

Number of subjects in period 1	bevacizumab mono	atezolizumab + placebo	atezolizumab + ASA
Started	33	11	13
Completed	33	11	13

Number of subjects in period 1	atezolizumab + bevacizumab + placebo	atezolizumab + bevacizumab + ASA
Started	32	33
Completed	32	33

Baseline characteristics

Reporting groups

Reporting group title	bevacizumab mono
Reporting group description: Bevacizumab 15 mg/kg q3w will be administered as bevacizumab monotherapy treatment and discontinued upon RECISTv1.1-documented progression or upon treatment withdrawal, whichever occurs first. Patients will cross-over to the combination of bevacizumab and atezolizumab upon progression as long as they meet cross-over criteria.	
Reporting group title	atezolizumab + placebo
Reporting group description: atezolizumab 1200 mg flat dose q3w will be administered together with placebo 320 mg/d as combination treatment and discontinued upon RECISTv1.1-documented progression or upon treatment withdrawal, whichever occurs first. Patients will cross-over to the combination of bevacizumab and atezolizumab upon progression as long as they meet cross-over criteria	
Reporting group title	atezolizumab + ASA
Reporting group description: atezolizumab 1200 mg flat dose q3w will be administered together with ASA 320 mg/d as combination treatment and discontinued upon RECISTv1.1-documented progression or upon treatment withdrawal, whichever occurs first. Patients will cross-over to the combination of bevacizumab and atezolizumab upon progression as long as they meet cross-over criteria	
Reporting group title	atezolizumab + bevacizumab + placebo
Reporting group description: atezolizumab 1200 mg flat dose q3w will be administered together with bevacizumab 15 mg/kg q3w and placebo 320 mg/d as combination treatment and discontinued upon treatment failure or upon treatment withdrawal, whichever occurs first. Patients then go off protocol treatment and further treatment is left to the investigator's decision.	
Reporting group title	atezolizumab + bevacizumab + ASA
Reporting group description: atezolizumab 1200 mg flat dose q3w will be administered together with bevacizumab 15 mg/kg q3w and ASA 320 mg/d as combination treatment and discontinued upon treatment failure or upon treatment withdrawal, whichever occurs first. Patients then go off protocol treatment and further treatment is left to the investigator's decision.	

Reporting group values	bevacizumab mono	atezolizumab + placebo	atezolizumab + ASA
Number of subjects	33	11	13
Age categorical			
Age categorical			
Units: Subjects			
Adults (18-64 years)	18	2	8
From 65-84 years	15	9	5
Age continuous			
Age continuous			
Units: years			
median	64	70	60
full range (min-max)	36 to 75	47 to 80	43 to 78
Gender categorical			
Gender categorical			
Units: Subjects			
Female	33	11	13
Male	0	0	0

WHO PS			
WHO performance status			
Units: Subjects			
WHO PS 0	14	5	7
WHO PS 1	19	6	5
WHO PS 2	0	0	1
Primary tumour site			
Primary tumour site			
Units: Subjects			
ovary	25	9	10
fallopian tube	3	1	1
peritoneum	5	1	2
other	0	0	0
FIGO stage			
FIGO stage			
Units: Subjects			
FIGO I	1	1	1
FIGO II	1	0	0
FIGO III	22	6	7
FIGO IV	9	4	5
Unknown	0	0	0
Months since initial diagnosis			
Time in months between initial diagnosis of the primary cancer and date of randomization			
Units: months			
median	44.0	52.5	41.9
full range (min-max)	9.5 to 117.8	26.8 to 131.9	27.0 to 74.2

Reporting group values	atezolizumab + bevacizumab + placebo	atezolizumab + bevacizumab + ASA	Total
Number of subjects	32	33	122
Age categorical			
Age categorical			
Units: Subjects			
Adults (18-64 years)	20	18	66
From 65-84 years	12	15	56
Age continuous			
Age continuous			
Units: years			
median	59.5	63	
full range (min-max)	40 to 80	40 to 82	-
Gender categorical			
Gender categorical			
Units: Subjects			
Female	32	33	122
Male	0	0	0
WHO PS			
WHO performance status			
Units: Subjects			
WHO PS 0	13	23	62
WHO PS 1	19	10	59
WHO PS 2	0	0	1

Primary tumour site			
Primary tumour site			
Units: Subjects			
ovary	30	26	100
fallopian tube	2	4	11
peritoneum	0	2	10
other	0	1	1
FIGO stage			
FIGO stage			
Units: Subjects			
FIGO I	1	0	4
FIGO II	2	1	4
FIGO III	21	19	75
FIGO IV	7	13	38
Unknown	1	0	1
Months since initial diagnosis			
Time in months between initial diagnosis of the primary cancer and date of randomization			
Units: months			
median	44.8	39.8	
full range (min-max)	23.9 to 133.7	17.4 to 135.0	-

Subject analysis sets

Subject analysis set title	ITT set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All randomized patients according to allocated treatment arm	
Subject analysis set title	PFS6 analysis set
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The primary endpoint was the progression free survival rate at 6 months (PFS-6) defined as the number of patients who are alive and without confirmed progression at month 6 + 1 week after randomization divided by the number of patients known to be alive or dead at month 6 + 1 week after randomization per treatment arm. Two randomized patients with incomplete follow-up prior to month 6 are excluded from the PFS-6 endpoint: one patient withdrew consent at the time of randomization and received no protocol treatment. A second patient received an immunosuppressor (tocilizumab) due to toxicity, which is a medication prohibited by the protocol. This patient was lost-to-follow-up shortly thereafter. Patients included in the Atezolizumab+ASA and Atezolizumab+Placebo arms are excluded as these arms were closed prematurely due to inefficiency.

Reporting group values	ITT set	PFS6 analysis set	
Number of subjects	122	96	
Age categorical			
Age categorical			
Units: Subjects			
Adults (18-64 years)	66		
From 65-84 years	56		
Age continuous			
Age continuous			
Units: years			
median	62.5		
full range (min-max)	36 to 82		

Gender categorical			
Gender categorical			
Units: Subjects			
Female	122		
Male	0		
WHO PS			
WHO performance status			
Units: Subjects			
WHO PS 0	62	49	
WHO PS 1	59	47	
WHO PS 2	1	0	
Primary tumour site			
Primary tumour site			
Units: Subjects			
ovary	100	79	
fallopian tube	11	9	
peritoneum	10	7	
other	1	1	
FIGO stage			
FIGO stage			
Units: Subjects			
FIGO I	4	2	
FIGO II	4	4	
FIGO III	75	61	
FIGO IV	38	28	
Unknown	1	1	
Months since initial diagnosis			
Time in months between initial diagnosis of the primary cancer and date of randomization			
Units: months			
median	43.3	43.3	
full range (min-max)	9.5 to 135.0	15.6 to 135.0	

End points

End points reporting groups

Reporting group title	bevacizumab mono
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Reporting group description:

Bevacizumab 15 mg/kg q3w will be administered as bevacizumab monotherapy treatment and discontinued upon RECISTv1.1-documented progression or upon treatment withdrawal, whichever occurs first. Patients will cross-over to the combination of bevacizumab and atezolizumab upon progression as long as they meet cross-over criteria.

Reporting group title	atezolizumab + placebo
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Reporting group description:

atezolizumab 1200 mg flat dose q3w will be administered together with placebo 320 mg/d as combination treatment and discontinued upon RECISTv1.1-documented progression or upon treatment withdrawal, whichever occurs first. Patients will cross-over to the combination of bevacizumab and atezolizumab upon progression as long as they meet cross-over criteria

Reporting group title	atezolizumab + ASA
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Reporting group description:

atezolizumab 1200 mg flat dose q3w will be administered together with ASA 320 mg/d as combination treatment and discontinued upon RECISTv1.1-documented progression or upon treatment withdrawal, whichever occurs first. Patients will cross-over to the combination of bevacizumab and atezolizumab upon progression as long as they meet cross-over criteria

Reporting group title	atezolizumab + bevacizumab + placebo
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Reporting group description:

atezolizumab 1200 mg flat dose q3w will be administered together with bevacizumab 15 mg/kg q3w and placebo 320 mg/d as combination treatment and discontinued upon treatment failure or upon treatment withdrawal, whichever occurs first. Patients then go off protocol treatment and further treatment is left to the investigator's decision.

Reporting group title	atezolizumab + bevacizumab + ASA
-----------------------	----------------------------------

Reporting group description:

atezolizumab 1200 mg flat dose q3w will be administered together with bevacizumab 15 mg/kg q3w and ASA 320 mg/d as combination treatment and discontinued upon treatment failure or upon treatment withdrawal, whichever occurs first. Patients then go off protocol treatment and further treatment is left to the investigator's decision.

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

All randomized patients according to allocated treatment arm

Subject analysis set title	PFS6 analysis set
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

The primary endpoint was the progression free survival rate at 6 months (PFS-6) defined as the number of patients who are alive and without confirmed progression at month 6 + 1 week after randomization divided by the number of patients known to be alive or dead at month 6 + 1 week after randomization per treatment arm. Two randomized patients with incomplete follow-up prior to month 6 are excluded from the PFS-6 endpoint: one patient withdrew consent at the time of randomization and received no protocol treatment. A second patient received an immunosuppressor (tocilizumab) due to toxicity, which is a medication prohibited by the protocol. This patient was lost-to-follow-up shortly thereafter.

Patients included in the Atezolizumab+ASA and Atezolizumab+Placebo arms are excluded as these arms were closed prematurely due to inefficiency.

Primary: PFS at 6 months

End point title	PFS at 6 months
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End point description:

The primary endpoint is PFS at 6 months (PFS-6) as assessed by the local investigator according to RECIST 1.1. This is defined as the number of patients who are alive and without confirmed progression at month 6 + 1 week after randomization divided by the number of patients known to be alive or dead at month 6 + 1 week after randomization per treatment arm. Patients with incomplete follow-up prior to month 6 are not included.

End point type	Primary
End point timeframe:	
6 months after randomization	

End point values	bevacizumab mono	atezolizumab + placebo	atezolizumab + ASA	atezolizumab + bevacizumab + placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	11	13	32
Units: patients				
Alive without progression	7	1	3	8
Dead or progressed	25	10	10	24

End point values	atezolizumab + bevacizumab + ASA	PFS6 analysis set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	32	96		
Units: patients				
Alive without progression	8	23		
Dead or progressed	24	73		

Statistical analyses

Statistical analysis title	A'hern test for bevacizumab mono
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Statistical analysis description:

In order to consider a treatment arm successful, an increase from 30% to 50% PFS-6 would need to be observed within that arm. An A'hern design will first be applied within each arm independently which would require at least 12 out of 29 patients alive and progression-free at month 6.

Comparison groups	bevacizumab mono v PFS6 analysis set
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	< 0.15 ^[2]
Method	binary decision rule
Parameter estimate	proportion
Point estimate	24.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.3
upper limit	43.5

Notes:

[1] - In order to consider a treatment arm successful, an increase from 30% to 50% PFS-6 would need to be observed within that arm. An A'hern design will first be applied within each arm independently which would require at least 12 out of 29 patients alive and progression-free at month 6. This decision rule was applied to the first 29 patients in each arm.

[2] - An A'hern design was applied within each arm independently to test the null hypothesis (H_0 : PFS-6 = 30%) against the alternative (H_1 : PFS-6 = 50%) at 1-sided 15% significance level and 85% power.

Statistical analysis title	A'hern test for Bevacizumab+Atezolizumab+Placebo
Statistical analysis description:	
In order to consider a treatment arm successful, an increase from 30% to 50% PFS-6 would need to be observed within that arm. An A'hern design will first be applied within each arm independently which would require at least 12 out of 29 patients alive and progression-free at month 6.	
Comparison groups	atezolizumab + bevacizumab + placebo v PFS6 analysis set
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	< 0.15 ^[4]
Method	binary decision rule
Parameter estimate	proportion
Point estimate	20.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	8
upper limit	39.7

Notes:

[3] - In order to consider a treatment arm successful, an increase from 30% to 50% PFS-6 would need to be observed within that arm. An A'hern design will first be applied within each arm independently which would require at least 12 out of 29 patients alive and progression-free at month 6. This decision rule was applied to the first 29 patients in each arm.

[4] - An A'hern design was applied within each arm independently to test the null hypothesis (H_0 : PFS-6 = 30%) against the alternative (H_1 : PFS-6 = 50%) at 1-sided 15% significance level and 85% power.

Statistical analysis title	A'hern test for Bevacizumab+Atezolizumab+ASA
Statistical analysis description:	
In order to consider a treatment arm successful, an increase from 30% to 50% PFS-6 would need to be observed within that arm. An A'hern design will first be applied within each arm independently which would require at least 12 out of 29 patients alive and progression-free at month 6.	
Comparison groups	atezolizumab + bevacizumab + ASA v PFS6 analysis set
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	other ^[5]
P-value	< 0.15 ^[6]
Method	binary decision rule
Parameter estimate	proportion
Point estimate	27.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.7
upper limit	47.2

Notes:

[5] - In order to consider a treatment arm successful, an increase from 30% to 50% PFS-6 would need to be observed within that arm. An A'hern design will first be applied within each arm independently which would require at least 12 out of 29 patients alive and progression-free at month 6. This decision rule was applied to the first 29 patients in each arm.

[6] - An A'hern design was applied within each arm independently to test the null hypothesis (H0: PFS-6 = 30%) against the alternative (H1: PFS-6 = 50%) at 1-sided 15% significance level and 85% power.

Secondary: PFS

End point title	PFS
End point description:	
Progression-free survival (PFS) is defined as the time between the date of randomization and the date of first documented progression or death (whatever the cause), whichever occurs first. For patients who remain alive and whose disease has not recurred, PFS will be censored on the date of last visit/contact with disease assessments. PFS will be based on the disease assessment or date of death provided by the local investigator.	
End point type	Secondary
End point timeframe:	
From randomization to end of trial completion.	

End point values	bevacizumab mono	atezolizumab + placebo	atezolizumab + ASA	atezolizumab + bevacizumab + placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	11	13	32
Units: months				
median (confidence interval 95%)	2.3 (2.0 to 4.1)	2.1 (0.9 to 2.5)	2.2 (1.5 to 4.2)	4.1 (2.2 to 5.4)

End point values	atezolizumab + bevacizumab + ASA			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: months				
median (confidence interval 95%)	4.0 (2.3 to 5.7)			

Statistical analyses

Statistical analysis title	PFS: Bev mono vs Bev+Ate+Pbo
Statistical analysis description:	
Comparison of the progression free survival in the Bevacizumab + Atezolizumab + Placebo arm to the Bevacizumab monotherapy arm.	
Comparison groups	bevacizumab mono v atezolizumab + bevacizumab + placebo
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.801 ^[8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.38

Notes:

[7] - Comparison of the progression free survival in the Bevacizumab + Atezolizumab + Placebo arm to the Bevacizumab monotherapy arm.

[8] - Logrank test

Statistical analysis title	PFS: Bev mono vs Bev+Ate+ASA
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Statistical analysis description:

Comparison of the progression free survival in the Bevacizumab + Atezolizumab + ASA arm to the Bevacizumab monotherapy arm.

Comparison groups	atezolizumab + bevacizumab + ASA v bevacizumab mono
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.561 ^[10]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81

Confidence interval

level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.34

Notes:

[9] - Comparison of the progression free survival in the Bevacizumab + Atezolizumab + ASA arm to the Bevacizumab monotherapy arm.

[10] - Logrank test

Secondary: Overall survival

End point title	Overall survival
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End point description:

Overall survival (OS) is defined as the time from the date of randomization to the date of death, whatever the cause. The follow-up of patients still alive will be censored at the moment of last visit/contact.

End point type	Secondary
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End point timeframe:

From randomization until end of trial completion

End point values	bevacizumab mono	atezolizumab + placebo	atezolizumab + ASA	atezolizumab + bevacizumab + placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	11	13	32
Units: months				
median (confidence interval 95%)	10.4 (5.6 to 13.0)	9.6 (2.4 to 21.7)	16.2 (1.8 to 31.1)	12.1 (6.0 to 14.1)

End point values	atezolizumab + bevacizumab + ASA			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: months				
median (confidence interval 95%)	11.6 (8.8 to 24.7)			

Statistical analyses

Statistical analysis title	OS: Bev mono vs Bev+Ate+Pbo
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Statistical analysis description:

Comparison of the overall survival in the Bevacizumab + Atezolizumab + Placebo to the Bevacizumab monotherapy arm.

Comparison groups	bevacizumab mono v atezolizumab + bevacizumab + placebo
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	= 0.752 ^[12]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.6

Notes:

[11] - Comparison of the overall survival in the Bevacizumab + Atezolizumab + Placebo to the Bevacizumab monotherapy arm.

[12] - Logrank test

Statistical analysis title	OS: Bev mono vs Bev+Ate+ASA
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Statistical analysis description:

Comparison of the overall survival in the Bevacizumab + Atezolizumab + ASA to the Bevacizumab monotherapy arm.

Comparison groups	bevacizumab mono v atezolizumab + bevacizumab + ASA
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	= 0.2 ^[14]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.32

Notes:

[13] - Comparison of the overall survival in the Bevacizumab + Atezolizumab + ASA to the Bevacizumab monotherapy arm.

[14] - Logrank test

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded as they occur and graded according to the CTCAE version 4.0 from time of first protocol treatment administration until 30 days after last protocol treatment or if deemed related to study participation.

Adverse event reporting additional description:

AEs are evaluated using CTCAE v4 grading, SAEs using MedDra. AEs were also derived from laboratory toxicities if grade ≥ 3 and all laboratory toxicities that triggered a treatment modification, if not reported on an AE form, were added.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Safety population Bev mono arm
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Reporting group description:

All patients who have started their allocated treatment (at least one dose) in the Bevacizumab monotherapy arm.

Reporting group title	Safety population Bev+Ate+ASA
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Reporting group description:

All patients who have started their allocated treatment (at least one dose) in the Bevacizumab + Atezolizumab + ASA arm.

Reporting group title	Safety population Bev+Ate+Pbo
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Reporting group description:

All patients who have started their allocated treatment (at least one dose) in the Bevacizumab + Atezolizumab + Placebo arm.

Serious adverse events	Safety population Bev mono arm	Safety population Bev+Ate+ASA	Safety population Bev+Ate+Pbo
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 31 (48.39%)	14 / 33 (42.42%)	12 / 31 (38.71%)
number of deaths (all causes)	22	22	21
number of deaths resulting from adverse events	2	0	2
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 24			

subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLOOD BILIRUBIN INCREASED			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLATELET COUNT DECREASED			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WHITE BLOOD CELL COUNT DECREASED			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
FRACTURE			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ATRIAL FIBRILATION			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC ARREST			
alternative dictionary used: MedDRA 24			

subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
CARDIAC DISORDER, OTHER : CORONARY SPASM			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEART FAILURE			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOCARDITIS			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
DEPRESSED LEVEL OF CONSCIOUSNESS			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ENCEPHALOPATHY			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
ANAEMIA			
alternative dictionary used: MedDRA 24			

subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
FATIGUE			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEVER			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FLU LIKE SYMPTOMS			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
AUTOIMMUNE DISORDER			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
AUTOIMMUNE TOXICITY			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHECKPOINT INHIBITOR IMMUNE INDUCED ENCEPHALITIS			
alternative dictionary used: MedDRA 24			

subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CYTOKINE RELEASE SYNDROME			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	2 / 33 (6.06%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAL HAEMORRHAGE			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BOWEL OBSTRUCTION			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLITIS			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLONIC PERFORATION			
alternative dictionary used: MedDRA 24			

subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLONIC ULCER			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONSTIPATION			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHEA			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRIC HEMORRHAGE			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
GASTRITIS			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL DISORDER, OTHER: COPROSTASIS			
alternative dictionary used: MedDRA 24			

subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL DISORDER, OTHER: SMALL BOWEL PERFORATION			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL DISORDER, OTHER: SMALL INTESTINAL OBSTRUCTION			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL DISORDERS, OTHER : GASTROENTERITIS			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROINTESTINAL FISTULA			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ILEAL PERFORATION			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA			
alternative dictionary used: MedDRA 24			

subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL PAIN			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SMALL INTESTINAL STENOSIS			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
DYSPNEA			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	2 / 31 (6.45%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURITIC PAIN			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONITIS			
alternative dictionary used: MedDRA 24			

subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EDEMA			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal and urinary disorders			
ACUTE KIDNEY INJURY			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYDRONEPHROSIS			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINAY RETENTION			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
BACK PAIN			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
ABDOMINAL INFECTION			
alternative dictionary used: MedDRA 24			

subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 INFECTION			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
FLU LIKE SYMPTOMS			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTIOUS PNEUMONITIS			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG INFECTION			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PELVIC INFECTION			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERITONEAL INFECTION			
alternative dictionary used: MedDRA 24			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

SEPSIS alternative dictionary used: MedDRA 24 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 31 (9.68%) 0 / 3 0 / 0	0 / 33 (0.00%) 0 / 0 0 / 0	0 / 31 (0.00%) 0 / 0 0 / 0
STOMA SITE INFECTION alternative dictionary used: MedDRA 24 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 31 (3.23%) 0 / 1 0 / 0	0 / 33 (0.00%) 0 / 0 0 / 0	0 / 31 (0.00%) 0 / 0 0 / 0
URINARY TRACT INFECTION alternative dictionary used: MedDRA 24 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 31 (3.23%) 0 / 1 0 / 0	1 / 33 (3.03%) 0 / 1 0 / 0	4 / 31 (12.90%) 1 / 4 0 / 0
VAGINAL INFECTION alternative dictionary used: MedDRA 24 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 31 (0.00%) 0 / 0 0 / 0	1 / 33 (3.03%) 1 / 1 0 / 0	0 / 31 (0.00%) 0 / 0 0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety population Bev mono arm	Safety population Bev+Ate+ASA	Safety population Bev+Ate+Pbo
Total subjects affected by non-serious adverse events subjects affected / exposed	31 / 31 (100.00%)	33 / 33 (100.00%)	31 / 31 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) NEOPLASMS BENIGN - OTHER, BILATERAL BREAST NODULES alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	1 / 33 (3.03%) 1	0 / 31 (0.00%) 0
NEOPLASMS BENIGN - OTHER, PITUITARY CYSTIC LESION alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
TUMOR PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	2 / 31 (6.45%)
occurrences (all)	0	1	2
TUMOUR PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
FINGERS PERIPHERAL VASOCONSTRICTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
HEMATOMA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
HOT FLASHES			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	3 / 31 (9.68%)
occurrences (all)	2	0	4
HYPERTENSION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	11 / 31 (35.48%)	10 / 33 (30.30%)	9 / 31 (29.03%)
occurrences (all)	23	37	23
LYMPHEDEMA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
OCCLUSIVE SYNDROME			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
THROMBOEMBOLIC EVENT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
VASCULAR DISORDERS - OTHER, CYANOSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
VASCULAR DISORDERS - OTHER, PROMINENT CHEST VEINS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
ABDOMINAL PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	3	0	0
ASTENIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
ASTHENIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
EDEMA LIMBS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 31 (12.90%)	4 / 33 (12.12%)	6 / 31 (19.35%)
occurrences (all)	4	4	7
EDEMA RIGHT LOWER LIMB			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
FATIGUE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	21 / 31 (67.74%)	16 / 33 (48.48%)	17 / 31 (54.84%)
occurrences (all)	33	26	24
FEVER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	6 / 31 (19.35%)	12 / 33 (36.36%)	5 / 31 (16.13%)
occurrences (all)	10	20	6
FLU LIKE SYMPTOMS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 31 (16.13%)	7 / 33 (21.21%)	4 / 31 (12.90%)
occurrences (all)	6	11	5
GAIT DISTURBANCE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
GENERAL DISORDERS - OTHER, ARM DISCOMFORT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
GENERAL DISORDERS - OTHER, NIGHT SWEATS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
INFUSION RELATED REACTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	2 / 31 (6.45%)
occurrences (all)	2	0	2
INFUSION SITE EXTRAVASATION			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
INGUINAL PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
INJECTION SITE REACTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
LOCALIZED EDEMA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
MALAISE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	2	0	1
NIGHT SWEAT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
NON-CARDIAC CHEST PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 31 (9.68%)	1 / 33 (3.03%)	2 / 31 (6.45%)
occurrences (all)	3	1	2
PERIPHERAL EDEMA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0

SHIVERING alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all) WEIGHT GAIN alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all) WEIGHT LOSS alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
	1	0	0
	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
	0	0	1
	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
	1	0	0
Immune system disorders ALLERGIC REACTION alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all) AUTOIMMUNE DISORDER alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all) AUTOIMMUNE TOXICITY alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all) CHECKPOINT INHIBITOR IMMUNE INDUCED ENCEPHALITIS alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all) CYTOKINE RELEASE SYNDROME alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	2 / 31 (6.45%)	1 / 33 (3.03%)	2 / 31 (6.45%)
	3	1	3
	1 / 31 (3.23%)	3 / 33 (9.09%)	1 / 31 (3.23%)
	1	6	1
	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
	0	0	1
	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
	0	1	0
	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
	0	0	1
Reproductive system and breast disorders			

BREAST DISORDERS - OTHER, THICKNESS OF L BREAST alternative dictionary used: CTCAE 4			
	subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)
	occurrences (all)	0	1
BREAST DISORDERS, OTHER - BREAST HARDENING (L) alternative dictionary used: CTCAE 4			
	subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)
	occurrences (all)	1	0
REPRODUCTIVE SYSTEM DISORDERS - OTHER, VULVAR MUCOSITIS alternative dictionary used: CTCAE 4			
	subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)
	occurrences (all)	0	1
UTERINE HEMORRHAGE alternative dictionary used: CTCAE 4			
	subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)
	occurrences (all)	0	2
VAGINAL DISCHARGE alternative dictionary used: CTCAE 4			
	subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)
	occurrences (all)	1	0
VAGINAL DRYNESS alternative dictionary used: CTCAE 4			
	subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)
	occurrences (all)	0	0
VAGINAL HEMORRHAGE alternative dictionary used: CTCAE 4			
	subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)
	occurrences (all)	0	1
VAGINAL HEMORRHAGE alternative dictionary used: CTCAE 4			
	subjects affected / exposed	2 / 31 (6.45%)	1 / 33 (3.03%)
	occurrences (all)	2	3
Respiratory, thoracic and mediastinal disorders			

ALLERGIC RHINITIS				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	2 / 31 (6.45%)	
occurrences (all)	0	1	2	
ATELECTASIS				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	0	1	
BREATHLESSNESS				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	0	2	
COUGH				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	7 / 31 (22.58%)	5 / 33 (15.15%)	4 / 31 (12.90%)	
occurrences (all)	7	5	6	
DYSPNEA				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	13 / 31 (41.94%)	8 / 33 (24.24%)	8 / 31 (25.81%)	
occurrences (all)	16	9	8	
EPISTAXIS				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	4 / 31 (12.90%)	1 / 33 (3.03%)	2 / 31 (6.45%)	
occurrences (all)	4	3	2	
HICCUPS				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)	
occurrences (all)	0	1	0	
HOARSENESS				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	3 / 31 (9.68%)	8 / 33 (24.24%)	6 / 31 (19.35%)	
occurrences (all)	3	8	6	
INFECTION UPPER RESPIRATORY				
alternative dictionary used: CTCAE 4				

subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
LARYNGEAL INFLAMMATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
NASAL CONGESTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
PLEURAL EFFUSION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
PLEURITIC PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	3 / 31 (9.68%)
occurrences (all)	0	0	3
PNEUMONITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	3	0	0
PRODUCTIVE COUGH			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
PULMONARY EDEMA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
'RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1

<p>RHINORRHEA</p> <p>alternative dictionary used: CTCAE 4</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>SORE THROAT</p> <p>alternative dictionary used: CTCAE 4</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>			
	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
	0	1	0
	2 / 31 (6.45%)	2 / 33 (6.06%)	0 / 31 (0.00%)
	2	2	0
<p>Psychiatric disorders</p> <p>ANXIETY</p> <p>alternative dictionary used: CTCAE 4</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>CONFUSION</p> <p>alternative dictionary used: CTCAE 4</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>DEPRESSION</p> <p>alternative dictionary used: CTCAE 4</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>HALLUCINATIONS</p> <p>alternative dictionary used: CTCAE 4</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>INSOMNIA</p> <p>alternative dictionary used: CTCAE 4</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>			
	3 / 31 (9.68%)	2 / 33 (6.06%)	0 / 31 (0.00%)
	3	2	0
	1 / 31 (3.23%)	0 / 33 (0.00%)	2 / 31 (6.45%)
	2	0	2
	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
	1	0	0
	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
	1	0	0
	4 / 31 (12.90%)	0 / 33 (0.00%)	1 / 31 (3.23%)
	4	0	1
<p>Investigations</p> <p>ALANINE AMINOTRANSERASE INCREASED</p> <p>alternative dictionary used: CTCAE 4</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ALANINE AMINOTRANSFERASE</p>			
	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
	0	0	1

INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	4 / 33 (12.12%)	3 / 31 (9.68%)
occurrences (all)	4	4	4
ALKALINE PHOSPHATASE INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 31 (9.68%)	4 / 33 (12.12%)	0 / 31 (0.00%)
occurrences (all)	9	5	0
ALP INCREASE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
ALT INCREASE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	2
AMYLASE INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
APTT INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	4 / 33 (12.12%)	5 / 31 (16.13%)
occurrences (all)	3	6	5
AST INCREASE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
BLOOD BILIRUBIN INCREASED			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
CARDIAC TROPONIN T INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
CREATININE INCREASE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	2	0	1
CREATININE INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	1 / 33 (3.03%)	1 / 31 (3.23%)
occurrences (all)	4	1	1
CRP INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
FOLATE DEFICIT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
GGT INCREASE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	3
GGT INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	4	3	0
HYPERKALEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0

INVESTIGATION OTHER: WHITE BLOOD CELL INCREASED				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	0	1	
INVESTIGATIONS - OTHER, PT DECREASED				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)	
occurrences (all)	0	1	0	
LDH INCREASED				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)	
occurrences (all)	0	1	0	
LIPASE INCREASED				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	2 / 31 (6.45%)	5 / 33 (15.15%)	3 / 31 (9.68%)	
occurrences (all)	3	6	5	
LYMPHOCYTE COUNT DECREASED				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	2 / 31 (6.45%)	5 / 33 (15.15%)	1 / 31 (3.23%)	
occurrences (all)	3	13	2	
LYMPHOCYTES COUNT DECREASE				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)	
occurrences (all)	0	1	0	
LYMPHOPENIA				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	0	2	
NEUTROPHIL COUNT DECREASE				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	0	2	
PLATELET COUNT DECREASE				
alternative dictionary used: CTCAE 4				

subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	3
NEUTROPHIL COUNT DECREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	3 / 33 (9.09%)	2 / 31 (6.45%)
occurrences (all)	1	5	7
PLATELET COUNT DECREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	5 / 33 (15.15%)	6 / 31 (19.35%)
occurrences (all)	2	7	9
WEIGH LOSS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
SERUM AMYLASE INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	5 / 33 (15.15%)	4 / 31 (12.90%)
occurrences (all)	3	6	5
WEIGHT GAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	4 / 31 (12.90%)
occurrences (all)	1	1	6
WEIGHT LOSS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	12 / 31 (38.71%)	7 / 33 (21.21%)	11 / 31 (35.48%)
occurrences (all)	16	16	17
WHITE BLOOD CELL COUNT DECREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
WHITE BLOOD CELLS DECREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1

WHITE BLOOD CELL DECREASED alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	4 / 33 (12.12%) 7	3 / 31 (9.68%) 5
Injury, poisoning and procedural complications BRUISING alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all) FRACTURE alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1 0 / 31 (0.00%) 0	2 / 33 (6.06%) 2 0 / 33 (0.00%) 0	0 / 31 (0.00%) 0 1 / 31 (3.23%) 1
Cardiac disorders ATRIAL FIBRILATION alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all) CARDIAC ARREST alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all) CARDIAC DISORDER, OTHER : CORONARY SPASM alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all) HEART FAILURE alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all) MYOCARDITIS alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0 0 / 31 (0.00%) 0 0 / 31 (0.00%) 0 0 / 31 (0.00%) 0 0 / 31 (0.00%) 0	0 / 33 (0.00%) 0 0 / 33 (0.00%) 0 0 / 33 (0.00%) 0 0 / 33 (0.00%) 0 1 / 33 (3.03%) 1	1 / 31 (3.23%) 1 1 / 31 (3.23%) 1 1 / 31 (3.23%) 1 2 / 31 (6.45%) 2 0 / 31 (0.00%) 0

<p>PALPITATIONS</p> <p>alternative dictionary used: CTCAE 4</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>SINUS TACHYCARDIA</p> <p>alternative dictionary used: CTCAE 4</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>SUPRAVENTRICULAR TACHYCARDIA</p> <p>alternative dictionary used: CTCAE 4</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>TACHYCARDIA</p> <p>alternative dictionary used: CTCAE 4</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>VENTRICULAR ARRHYTHMIA</p> <p>alternative dictionary used: CTCAE 4</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>			
	2 / 31 (6.45%)	1 / 33 (3.03%)	2 / 31 (6.45%)
	2	1	2
	2 / 31 (6.45%)	1 / 33 (3.03%)	1 / 31 (3.23%)
	2	1	1
	1 / 31 (3.23%)	1 / 33 (3.03%)	0 / 31 (0.00%)
	1	4	0
	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
	0	0	1
	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
	0	1	0
<p>Nervous system disorders</p> <p>DEPRESSED LEVEL OF CONSCIOUSNESS</p> <p>alternative dictionary used: CTCAE 4</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>DIZZINESS</p> <p>alternative dictionary used: CTCAE 4</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>DYSESTHESIA</p> <p>alternative dictionary used: CTCAE 4</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>DYSGEUSIA</p> <p>alternative dictionary used: CTCAE</p>			
	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
	0	0	1
	3 / 31 (9.68%)	2 / 33 (6.06%)	2 / 31 (6.45%)
	4	2	3
	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
	1	0	0

4			
subjects affected / exposed	2 / 31 (6.45%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	2	1	0
DYSGUEUSIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
ENCEPHALOPATHY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
HEADACHE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 31 (16.13%)	4 / 33 (12.12%)	8 / 31 (25.81%)
occurrences (all)	9	4	10
HEADACHES			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
HEADEACHE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
MUSCLE SPASTICITY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
NEURALGIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
PARESTHESIA			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
PERIPHAL SENSORY NEUROPATHY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
PERIPHERAL MOTOR NEUROPATHY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
PERIPHERAL NEUROPATHY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
PERIPHERAL SENSORY NEUROPATHY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	3 / 33 (9.09%)	1 / 31 (3.23%)
occurrences (all)	1	3	1
SOMNOLENCE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
SPASTICITY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
SYNCOPE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
THORACIC NEUROGENIC PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0

TREMOR alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	1 / 33 (3.03%) 1	0 / 31 (0.00%) 0
Blood and lymphatic system disorders ANAEMIA alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 33 (0.00%) 0	2 / 31 (6.45%) 3
ANEMIA alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	8 / 31 (25.81%) 17	7 / 33 (21.21%) 10	10 / 31 (32.26%) 17
HEMOLYTIC UREMIC SYNDROME alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	1 / 33 (3.03%) 1	0 / 31 (0.00%) 0
PLATELET COUNT DECREASED alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	1 / 33 (3.03%) 1	0 / 31 (0.00%) 0
Ear and labyrinth disorders EAR PAIN alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0
HEARING IMPAIRED alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0
HEARING LOSS alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 33 (0.00%) 0	1 / 31 (3.23%) 1
TINNITUS			

alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	1 / 33 (3.03%)	1 / 31 (3.23%)
occurrences (all)	2	1	1
VERTIGO			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
BLURRED VISION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	2 / 31 (6.45%)
occurrences (all)	2	0	2
CATARACT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
CONJUNCTIVITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
DRY EYE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	1	2	0
EYE DISORDERS - OTHER, PUFFY EYES			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
EYE DISORDERS, OTHER: DETERIORATION OF VISUAL ACUITY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
WATERING EYES			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
ABDOMINAL DISCOMFORT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
ABDOMINAL DISTENSION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
ABDOMINAL PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	10 / 31 (32.26%)	7 / 33 (21.21%)	9 / 31 (29.03%)
occurrences (all)	23	10	12
ADDOMINAL PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
ANAL HAEMORRHAGE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
ANAL HEMORRHAGE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
ASCITES			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	2 / 33 (6.06%)	0 / 31 (0.00%)
occurrences (all)	2	2	0
BLOATING			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	1 / 31 (3.23%)
occurrences (all)	1	1	1
BOWEL OBSTRUCTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
COLITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	3	0	1
COLONIC PERFORATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	2
COLONIC ULCER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	3	0	0
CONSTIPATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	9 / 31 (29.03%)	16 / 33 (48.48%)	8 / 31 (25.81%)
occurrences (all)	12	18	9
DIARRHEA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	12 / 31 (38.71%)	7 / 33 (21.21%)	8 / 31 (25.81%)
occurrences (all)	23	10	11
DIARRHEOA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
DRY MOUTH			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	4 / 33 (12.12%)	1 / 31 (3.23%)
occurrences (all)	2	10	1

DYSPEPSIA				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	2 / 31 (6.45%)	
occurrences (all)	0	1	3	
DYSPHAGIA				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	2 / 31 (6.45%)	2 / 33 (6.06%)	0 / 31 (0.00%)	
occurrences (all)	2	3	0	
ESOPHAGEAL PAIN				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	1	0	0	
ESOPHAGITIS				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	0	1	
FLATULENCE				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	0	2	
GASTRIC HEMORRHAGE				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	0	1	
GASTRITIS				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	0	1	
GASTROESOPHAGEAL REFLUX DISEASE				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	2 / 31 (6.45%)	2 / 33 (6.06%)	1 / 31 (3.23%)	
occurrences (all)	3	4	1	
GASTROINTESTINAL - OTHER: SMALL INTESTINAL OBSTRUCTION				
alternative dictionary used: CTCAE 4				

subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
GASTROINTESTINAL DISORDER, OTHER: COPROSTASIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
GASTROINTESTINAL DISORDER, OTHER: COPROSTATIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
GASTROINTESTINAL DISORDER, OTHER: SMALL BOWEL PERFORATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	2
GASTROINTESTINAL DISORDERS - OTHER, AEROPHAGIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
GASTROINTESTINAL DISORDERS - OTHER, GUM BLEEDING			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
GASTROINTESTINAL DISORDERS - OTHER, PYROSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
GASTROINTESTINAL DISORDERS - OTHER: GASTROENTERITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
GASTROINTESTINAL DISORDERS,			

OTHER : GASTROENTERITIS				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	0	1	
GASTROINTESTINAL FISTULA				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	1	0	0	
GASTROINTESTINAL PAIN				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	2 / 31 (6.45%)	1 / 33 (3.03%)	0 / 31 (0.00%)	
occurrences (all)	2	1	0	
GASTROPARESIS				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	1	0	0	
HAEMARRHOIDS				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	0	1	
HEMORRHOIDS				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)	
occurrences (all)	1	0	0	
ILEAL PERFORATION				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	0 / 31 (0.00%)	
occurrences (all)	1	2	0	
ILEUS				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	2	0	1	
INTESTINAL OCCLUSION				
alternative dictionary used: CTCAE 4				

subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
LIP PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
LOWER GASTROINTESTINAL HEMORRHAGE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
MELENA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
MUCOSITIS ORAL			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 31 (16.13%)	4 / 33 (12.12%)	2 / 31 (6.45%)
occurrences (all)	5	5	2
MUCOSITIS ORAL (EVENTHOUGH NOT AS ACCURATE AS TONSILOLITH)			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
NAUSEA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	10 / 31 (32.26%)	6 / 33 (18.18%)	9 / 31 (29.03%)
occurrences (all)	19	9	12
ORAL HEMORRHAGE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	1 / 31 (3.23%)
occurrences (all)	0	2	1
ORAL MUSCOSITIS			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
ORAL PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
OTHER - EPIGASTRIC PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
PANCREATITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
RECTAL FISTULA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
RECTAL HEMORRHAGE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	0 / 31 (0.00%)
occurrences (all)	0	3	0
RECTAL MUCOSITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
RECTAL PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	8	0	0
SMALL INTESTINAL STENOSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0

STOMACH PAIN alternative dictionary used: CTCAE 4	subjects affected / exposed	2 / 31 (6.45%)	2 / 33 (6.06%)	0 / 31 (0.00%)
	occurrences (all)	2	3	0
	TOOTHACHE alternative dictionary used: CTCAE 4			
	subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
	occurrences (all)	0	0	1
UPPER GASTROINTESTINAL HEMORRHAGE alternative dictionary used: CTCAE 4	subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
	occurrences (all)	0	1	0
	VOMINTING alternative dictionary used: CTCAE 4			
VOMINTING alternative dictionary used: CTCAE 4	subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	0 / 31 (0.00%)
	occurrences (all)	2	0	0
	VOMITING alternative dictionary used: CTCAE 4			
VOMITING alternative dictionary used: CTCAE 4	subjects affected / exposed	12 / 31 (38.71%)	8 / 33 (24.24%)	5 / 31 (16.13%)
	occurrences (all)	27	14	6
Hepatobiliary disorders HEPATIC INFECTION alternative dictionary used: CTCAE 4	subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
	occurrences (all)	0	0	1
	HEPATITIS alternative dictionary used: CTCAE 4			
	subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
	occurrences (all)	1	0	0
	HEPATITIS VIRAL alternative dictionary used: CTCAE 4			
	subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
	occurrences (all)	1	0	0
	HEPATOBIILIARY DISORDERS - OTHER, HEPATITIS			

alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
ALLERGIC RASH CUTANEOUS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
ALOPECIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
DRY SKIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 31 (16.13%)	4 / 33 (12.12%)	3 / 31 (9.68%)
occurrences (all)	5	4	3
ERYTHEMA MULTIFORME			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
NAIL DISCOLORATION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
NAIL LOSS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
PAIN OF SKIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	1	2	0
PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
PALMAR-PLANTAR ERYTHRODYSETHESIA SYNDROME			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
PLAMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
PRURITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
PRURITUS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 31 (12.90%)	3 / 33 (9.09%)	1 / 31 (3.23%)
occurrences (all)	5	3	1
RASH			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
RASH ACNEIFORM			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	2 / 31 (6.45%)
occurrences (all)	0	2	2
RASH MACULAR			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
RASH MACULO PAPULAR			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
RASH MACULO-PAPULAR			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 31 (9.68%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	3	0	0
SCALP PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
SKIN AND SUBCUT. TISSUE DISORDERS - OTHER, REDNESS LEFT FOOT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
SKIN AND SUBCUTANEOUS DISORDERS, OTHER : ZONA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, RASH			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, XEROSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS: OTHER, RASH			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
SKIN OTHER: SKIN ABRASION LEFT FOREARM			

alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0
SKIN ULCERATION alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	2 / 33 (6.06%) 3	0 / 31 (0.00%) 0
URTICARIA alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	1 / 33 (3.03%) 1	0 / 31 (0.00%) 0
Renal and urinary disorders ACUTE KIDNEY INJURY alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0
BLADDER SPASM alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2	0 / 33 (0.00%) 0	0 / 31 (0.00%) 0
CHRONIC KIDNEY DISEASE alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	1 / 33 (3.03%) 2	0 / 31 (0.00%) 0
CYSTITIS NONINFECTIVE alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	1 / 33 (3.03%) 1	1 / 31 (3.23%) 2
HEMATURIA alternative dictionary used: CTCAE 4 subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	0 / 33 (0.00%) 0	1 / 31 (3.23%) 5
HYDRONEPHROSIS alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
PROTEINURIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	6 / 31 (19.35%)	4 / 33 (12.12%)	1 / 31 (3.23%)
occurrences (all)	10	17	2
RENAL AND URINARY DISORDERS - OTHER, DYSURIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	2
RENAL AND URINARY DISORDERS - OTHER, HYDRONEPHROSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
RENAL AND URINARY DISORDERS - OTHER, NOCTURIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
RENAL AND URINARY DISORDERS - OTHER, RENAL IMPAIRMENT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
RENAL AND URINARY DISORDERS, OTHER, LEUKOCYTURIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
RENAL AND URINARY DISORDERS: LEUKOCYTURIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
URINARY FREQUENCY			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
URINARY INCONTINENCE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
URINAY RETENTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
ENDOCRINE DISORDER; OTHER: TSH INCREASED			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
ENDOCRINE DISORDERS - OTHER, INCREASED TSH			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
HYPOTHYROIDISM			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
HYPERTHYROIDISM			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	4 / 33 (12.12%)	0 / 31 (0.00%)
occurrences (all)	0	5	0
HYPOTHYROIDISM			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	3 / 33 (9.09%)	3 / 31 (9.68%)
occurrences (all)	1	3	4
Musculoskeletal and connective tissue disorders			

ARTHRALGIA				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	3 / 31 (9.68%)	4 / 33 (12.12%)	4 / 31 (12.90%)	
occurrences (all)	3	5	4	
ARTHRITIS				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	0 / 31 (0.00%)	
occurrences (all)	0	5	0	
BACK PAIN				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	4 / 31 (12.90%)	5 / 33 (15.15%)	2 / 31 (6.45%)	
occurrences (all)	6	6	2	
CHEST WALL PAIN				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	2 / 31 (6.45%)	
occurrences (all)	1	1	3	
FLANK PAIN				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	4 / 31 (12.90%)	0 / 33 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	4	0	1	
GENERALIZED MUSCLE WEAKNESS				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)	
occurrences (all)	0	1	0	
JOINT RANGE OF MOTION DECREASED				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)	
occurrences (all)	0	0	1	
LEG CRAMPS				
alternative dictionary used: CTCAE 4				
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)	
occurrences (all)	0	1	0	
MUSCLE SPASM				
alternative dictionary used: CTCAE 4				

subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
MUSCLE WEAKNESS LOWER LIMB alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	3
MUSCLE WEAKNESS LOWER LIMBS alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
MUSCLE WEAKNESS UPPER LIMB alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
MUSCLE WEAKNESS UPPER LIMBS alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
MUSCULAR OTHER, LEGS CRAMPS alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
MUSCULOSKELETAL - OTHER, TORSION RIGHT TOE WITH PAIN alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
MUSCULOSKELETAL AND CONNECTIVE TISS. DIS.- OTHER, BODY ACHES alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
MUSCULOSKELETAL DEFORMITY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
MUSCULOSKELETAL DISORDER - OTHER: CRAMP INFERIOR LIMB			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
MUSCULOSKELETAL DISORDERS - OTHER, MYOCLONUS SUPERIOR LIMBS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
MYALGIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	5 / 31 (16.13%)	7 / 33 (21.21%)	1 / 31 (3.23%)
occurrences (all)	5	10	1
MYOSITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	1 / 31 (3.23%)
occurrences (all)	1	1	1
NECK PAIN			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 31 (9.68%)	1 / 33 (3.03%)	2 / 31 (6.45%)
occurrences (all)	4	1	3
OSTEOPOROSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	1 / 31 (3.23%)
occurrences (all)	0	2	1
PAIN EXTREMITY			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
PAIN IN EXTREMITY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	4 / 31 (12.90%)	1 / 33 (3.03%)	1 / 31 (3.23%)
occurrences (all)	4	1	1
Infections and infestations			
ABDOMINAL INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	5	0
CATHETER RELATED INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
COVID-19 INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	4	0	0
FLU LIKE SYMPTOMS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	1	1	0
GUM INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	2
INFECTION - OTHER: STAPHYLOCOCCUS EPIDERMIDIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
INFECTIONS AND INFESTATIONS - OTHER, SHINGLES			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
INFECTIONS AND INFESTATIONS- OTHER: ORAL THRUSH			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
INFECTIONS AND INFESTATIONS, OTHER : VARICELLA ZOSTER			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
INFECTIOUS PNEUMONITIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
LIP INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
LUNG INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
MUCOSAL INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	4	0
PELVIC INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
PERITONEAL INFECTION			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0
RHINITIS INFECTIVE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	1 / 33 (3.03%)	1 / 31 (3.23%)
occurrences (all)	3	1	1
RHINITUS INFECTIVE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
SEPSIS			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 31 (9.68%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	3	0	0
SKIN INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
STOMA SITE INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
TOOTH INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
UPPER RESPIRATORY INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 31 (9.68%)	4 / 33 (12.12%)	1 / 31 (3.23%)
occurrences (all)	3	4	1
URINARY TRACT INFECTION			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	8 / 31 (25.81%)	5 / 33 (15.15%)	6 / 31 (19.35%)
occurrences (all)	9	9	11

URINARY TRACT INFECTION/KLEBSIELLA PNEUMONIAE alternative dictionary used: CTCAE 4 subjects affected / exposed 0 / 31 (0.00%) occurrences (all) 0				0 / 33 (0.00%)	0	1 / 31 (3.23%)	1
VAGINAL INFECTION alternative dictionary used: CTCAE 4 subjects affected / exposed 0 / 31 (0.00%) occurrences (all) 0				1 / 33 (3.03%)	1	0 / 31 (0.00%)	0
VULVAL INFECTION alternative dictionary used: CTCAE 4 subjects affected / exposed 0 / 31 (0.00%) occurrences (all) 0				0 / 33 (0.00%)	0	1 / 31 (3.23%)	1
WOUND INFECTION alternative dictionary used: CTCAE 4 subjects affected / exposed 0 / 31 (0.00%) occurrences (all) 0				1 / 33 (3.03%)	1	0 / 31 (0.00%)	0
Metabolism and nutrition disorders ANOREXIA alternative dictionary used: CTCAE 4 subjects affected / exposed 12 / 31 (38.71%) occurrences (all) 16				10 / 33 (30.30%)	10	7 / 31 (22.58%)	13
DEHYDRATION alternative dictionary used: CTCAE 4 subjects affected / exposed 0 / 31 (0.00%) occurrences (all) 0				1 / 33 (3.03%)	1	1 / 31 (3.23%)	1
HYPERCALCEMIA alternative dictionary used: CTCAE 4 subjects affected / exposed 2 / 31 (6.45%) occurrences (all) 5				0 / 33 (0.00%)	0	0 / 31 (0.00%)	0
HYPERGLYCAEMIA alternative dictionary used: CTCAE 4 subjects affected / exposed 0 / 31 (0.00%) occurrences (all) 0				0 / 33 (0.00%)	0	1 / 31 (3.23%)	1
HYPERGYLCEMIA							

alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
HYPERGLYCEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	3
HYPERKALEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
HYPOALBUMINEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	1 / 33 (3.03%)	2 / 31 (6.45%)
occurrences (all)	2	2	2
HYPERPHOSPHATEMIA INTERMITTENT			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
HYPOKALAEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
HYPOCALCEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	1	0	1
HYPOKALEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	3 / 31 (9.68%)
occurrences (all)	2	0	3
HYPOMAGNESAEMIA			
alternative dictionary used: CTCAE 4			

subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	1 / 31 (3.23%)
occurrences (all)	0	2	2
HYPOMAGNESEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	2 / 31 (6.45%)	3 / 33 (9.09%)	3 / 31 (9.68%)
occurrences (all)	4	15	3
HYPOMAGNESMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	0 / 31 (0.00%)
occurrences (all)	0	1	0
HYPONATREMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	3 / 31 (9.68%)	1 / 33 (3.03%)	2 / 31 (6.45%)
occurrences (all)	3	1	3
HYPOPHOSPHATEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	2 / 33 (6.06%)	1 / 31 (3.23%)
occurrences (all)	1	2	3
METABOLISM AND NUTRITION DISORDERS: HYPOREALBUMINEMIA			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
NUTRITION DISORDERS - OTHER, EARLY SATIETY			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	0 / 31 (0.00%)	0 / 33 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
REDUCED APETITE			
alternative dictionary used: CTCAE 4			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	0 / 31 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 February 2019	This amendment resulted in a major impact on the study design. The original study design was composed of 5 arms. Following amendment 7 (protocol version 5.0), the 2 Atezolizumab monotherapy arms (+ ASA/placebo) were closed. The amendment was motivated by the results of the Javelin 200 trial casting doubts on the efficacy of the Atezolizumab + ASA/Placebo arms (arms 2 and 3). The results from this phase III study showed that the efficacy of this PD-L1 inhibitor alone in resistant/refractory ovarian cancer failed to achieve the required efficacy criteria for both primary endpoints (OS & PFS). Keeping the Atezolizumab + ASA/Placebo arms open to recruitment, given the Javelin results, would be unethical to the patients as it would put them at risk of being exposed to potentially ineffective yet toxic therapy. At the time of this amendment (18/02/2019), 57 patients had been randomized in the 5 arms, of which 24 in the now defunct arms. The objectives, statistical methodology and sample size for the three remaining arms did not change requiring 32 patients in each of arms 1, 4 and 5. In addition to the closure of the 2 Atezolizumab monotherapy arms, amendment 7 also formalized the change in study coordinator whereby the original study coordinator, Anita Wolfer (Centre Hospitalier Universitaire Vaudois – Lausanne, Switzerland) was replaced by the current study coordinator Susana Banerjee (The Royal Marsden NHS Foundation Trust, London).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Two of the 5 initial treatment arms were discontinued during the course of the study. See amendment section for more details.

Notes: