



Clinical trial results:

Open-label first line, single-arm phase II study of CisGem combined with pembrolizumab in patients with advanced or metastatic biliary tract cancer

Summary

EudraCT number	2017-003323-30
Trial protocol	GB ES
Global end of trial date	31 August 2023

Results information

Result version number	v1 (current)
This version publication date	25 September 2024
First version publication date	25 September 2024

Trial information

Trial identification

Sponsor protocol code	EORTC-1607-GITCG
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03260712
WHO universal trial number (UTN)	-
Other trial identifiers	NCRI-UK Upper GI CSG (HB): ABC-09

Notes:

Sponsors

Sponsor organisation name	European Organisation for the Research and treatment of Cancer (EORTC)
Sponsor organisation address	Avenue Emmanuel Mounier 83/11, Brussels, Belgium, 1200
Public contact	Regulatory Affairs Department, European Organisation for the Research and treatment of Cancer (EORTC), +32 27741072, murielle.mauer@gmail.com
Scientific contact	Regulatory Affairs Department, European Organisation for the Research and treatment of Cancer (EORTC), 0471693363 27741072, murielle.mauer@gmail.com

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	01 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2023
Global end of trial reached?	Yes
Global end of trial date	31 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this single-arm phase II trial is to detect an increase in progression-free survival (PFS) rate at 6 months (according to RECIST version 1.1) in patients with BTC treated with CisGem combined with pembrolizumab as compared to historical controls when treated with standard chemotherapy approach.

Protection of trial subjects:

The responsible investigator had to ensure that this study was conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (<http://www.wma.net>)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol had been written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at https://www.ema.europa.eu/documents/scientific-guideline/ich-e6-r1-guideline-good-clinicalpractice_en.pdf).

The protocol was approved by the competent ethics committee(s) as required by the applicable national

Background therapy:

No control arm is available in this study. Historical controls treated with standard CisGem chemotherapy are used as benchmark.

All patients will receive CisGem [25mg/m² intravenous (IV) cisplatin + 1000mg/m² IV gemcitabine, on days 1 and 8 of a 21-day cycle] as backbone chemotherapy regimen plus 200 mg intravenous pembrolizumab 200 mg on day 1 of a 21-day cycle up to 2 years from enrolment until disease progression or the early occurrence of a withdrawal.

Evidence for comparator:

Valle et al. conducted randomized phase III study, the ABC-02 trial with a total of 410 patients (including the ABC-01 cohort) with locally advanced or metastatic CCA, GBC, or ampullary cancer randomly assigned to treatment either with cisplatin (25 mg/m² on days 1 and 8), followed by gemcitabine (1000 mg/m² on days 1 and 8 every 3 weeks) or gemcitabine (1000 mg/m² on days 1, 8 and 15 every 4 weeks) alone (Ref. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362(14):1273-1281).

With a median overall survival of 11.7 months in the CisGem group, as compared to 8.1 months in the gemcitabine group (hazard ratio, 0.64; 95% confidence interval (CI), 0.52 to 0.80; P<0.001), the CisGem combination demonstrated a significant survival benefit.

Actual start date of recruitment	07 January 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	Germany: 10
Worldwide total number of subjects	50
EEA total number of subjects	19

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)	26
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 07/01/2020 and 27/04/2021, 50 patients with advanced or metastatic biliary tract cancer were enrolled at 7 medical centres in 3 countries (Germany, Spain and UK).

Pre-assignment

Screening details:

Upon signing the informed consent and after verification of eligibility, patients were centrally enrolled using the electronic platform available on the EORTC website. Patients were not randomized as this was a single arm study.

Period 1

Period 1 title	From enrollment (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Experimental arm
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Arm description:

CisGem [25mg/m² intravenous (IV) cisplatin + 1000mg/m² IV gemcitabine, on days 1 and 8 of a 21-day cycle] plus 200 mg intravenous pembrolizumab 200 mg on day 1 of a 21-day cycle up to 2 years from enrolment until progressive disease or the early occurrence of a withdrawal.

Arm type	Experimental
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

25mg/m² intravenous (IV) cisplatin, on days 1 and 8 of a 21-day cycle up to 2 years from enrolment until progressive disease or the early occurrence of a withdrawal.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000mg/m² IV gemcitabine, on days 1 and 8 of a 21-day cycle up to 2 years from enrolment until progressive disease or the early occurrence of a withdrawal.

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	MK 3475
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

On day 1 of each cycle, pembrolizumab will be administered before the chemotherapies. All patients will receive 200 mg intravenous pembrolizumab on day 1 of a 21-day cycle up to 2 years from enrolment until progressive disease or the early occurrence of a withdrawal.

Number of subjects in period 1	Experimental arm
Started	50
Completed	3
Not completed	47
Adverse event, serious fatal	2
Adverse event, non-fatal	3
Death not due to malignant disease or toxicity	2
Other malignancy	1
Patient's or investigator's decision (no AE)	3
Progression of disease/death due to PD	32
Deterioration of health status/clinical PD	4

Baseline characteristics

Reporting groups

Reporting group title	From enrollment
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Reporting group description: -

Reporting group values	From enrollment	Total	
Number of subjects	50	50	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
median	63		
inter-quartile range (Q1-Q3)	52 to 70	-	
Gender categorical			
Units: Subjects			
Female	31	31	
Male	19	19	
ECOG performance status			
Units: Subjects			
ECOG 0	32	32	
ECOG 1	18	18	
Histopathological diagnosis of BTC			
Units: Subjects			
Intra-hepatic biliary tract cancer	29	29	
Extra-hepatic biliary tract cancer	8	8	
Both intra- and extra-hepatic biliary tract cancer	2	2	
Gallbladder carcinoma	11	11	
Type of biliary tract cancer			
Units: Subjects			
Non-resectable biliary tract cancer	21	21	
Recurrent/metastatic biliary tract cancer	18	18	
Missing	11	11	
Measurable disease by CT/MRI (RECIST 1.1)			
Units: Subjects			
Yes	50	50	

Lead ECG			
Units: Subjects			
Normal	36	36	
Abnormal, not clinically significant	14	14	
Any prior systemic chemotherapy for locally advanced or metastatic disease			
Units: Subjects			
No	50	50	
Prior adjuvant therapy			
Units: Subjects			
No	48	48	
Yes, without Cisplatin or Gemcitabine	2	2	
Prior adjuvant therapy			
Units: Subjects			
No	48	48	
Yes, stopped for more than 6 months	2	2	
Prior non-curative surgery for disease under study			
Units: Subjects			
No	48	48	
Yes, R2 resection	2	2	
Prior curative surgery with clear evidence of non-resectable disease relapse after surgery			
Units: Subjects			
No	46	46	
Yes	4	4	
Prior radiotherapy for localised disease with PD/relapse after radiotherapy			
Units: Subjects			
No	48	48	
Yes	2	2	
Primary site			
Units: Subjects			
Intrahepatic bile duct cancer	30	30	
Distal bile duct cancer	2	2	
Ampulla of Vater cancer	2	2	
Proximal or perihilar bile duct cancer	3	3	
Gallbladder cancer	11	11	
Extrahepatic cholangiocarcinoma	1	1	
Hilar cholangiocarcinoma	1	1	
AJCC stage at initial diagnosis			
Units: Subjects			
Stage II	4	4	
Stage IIIA	3	3	
Stage IIIB	11	11	
Stage IV	27	27	
Stage IVB	4	4	
Missing	1	1	
AJCC stage at study entry			
Units: Subjects			

Stage II	1	1	
Stage IIIA	1	1	
Stage IIIB	9	9	
Stage IV	33	33	
Stage IVB	5	5	
Missing	1	1	

End points

End points reporting groups

Reporting group title	Experimental arm
Reporting group description: CisGem [25mg/m ² intravenous (IV) cisplatin + 1000mg/m ² IV gemcitabine, on days 1 and 8 of a 21-day cycle] plus 200 mg intravenous pembrolizumab 200 mg on day 1 of a 21-day cycle up to 2 years from enrolment until progressive disease or the early occurrence of a withdrawal.	

Primary: Progression free survival rate at 6 months according to RECIST 1.1

End point title	Progression free survival rate at 6 months according to RECIST 1.1 ^[1]
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End point description:

In this single-arm phase II trial, the primary objective was to detect an increase in PFS rate at 6 months (according to RECIST 1.1) from 60% (assumption based on historical controls) to 75% in patients with BTC when treated with CT combined with pembrolizumab using a one-sided type I error of 10%. PFS rate at 6 months and its two-sided 80% confidence interval was estimated using the log-log transformation of the Kaplan-Meier estimate and the standard deviation of the Kaplan Meier estimate based on the Greenwood formula. If the lower bound of the two-sided 80% CI was above 60%, the null hypothesis of a PFS rate at 6 months equal or lower than 60% in the experimental arm could be rejected. Given that the lower bound of the two-sided 80% CI is 51.7% and therefore below 60% and the two-sided 80% CI includes 60%, the hypothesis testing could not reject a PFS rate at 6 months equal or lower than 60%.

End point type	Primary
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End point timeframe:

Progression free survival (PFS) rate at 6 months was defined as the rate of patients alive and progression free at 6 months. PFS rate at 6 months was estimated using the Kaplan Meier technique to take into account possible loss to follow-up

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is a single-arm early phase II study with an hypothesis testing in the experimental arm to reject a PFS rate at 6 months equal to or lower than 60% (assumption based on historical controls) using a one-sided type I error of 10%. No formal comparative statistical analysis was foreseen and no comparison groups could be specified.

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	49 ^[2]			
Units: Percentage				
number (confidence interval 80%)	61.2 (51.7 to 69.5)			

Notes:

[2] - 1 patient was not evaluable for efficacy as WBC was very high and considered as active infection.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS) according to RECIST 1.1.

End point title	Progression free survival (PFS) according to RECIST 1.1.
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End point description:

Progression free survival (PFS) according to RECIST 1.1 was computed from the date of enrollment to the date of first progression according to the RECIST criteria (version 1.1) or death, whatever came first. Patients alive and free of progression prior to the analysis cut-off date are censored at the date of the most recent assessment.

End point type	Secondary
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End point timeframe:

Disease evaluation was to be performed every 12 weeks (within 7 days prior to dosing) during treatment and every 3 months \pm 7days after the end of treatment (in the absence of progression) until progression or 2 years after start of treatment.

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	49 ^[3]			
Units: Months				
median (confidence interval 95%)	8.28 (5.59 to 10.58)			

Notes:

[3] - 1 patient was not evaluable for efficacy as WBC was very high and considered as active infection.

Attachments (see zip file)	Progression free survival according to RECIST v1.
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Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS) according to iRECIST

End point title	Progression free survival (PFS) according to iRECIST
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End point description:

Progression free survival (iPFS) according to iRECIST was computed from the date of enrollment to the date of first progression according to the iRECIST criteria or death, whatever came first. Patients alive and free of progression prior to the analysis cut-off date were censored at the date of the most recent assessment.

End point type	Secondary
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End point timeframe:

Disease evaluation was to be performed every 12 weeks (within 7 days prior to dosing) during treatment and every 3 months \pm 7days after the end of treatment (in the absence of progression) until progression or 2 years after start of treatment.

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	49 ^[4]			
Units: Months				
median (confidence interval 95%)	8.34 (5.62 to 11.10)			

Notes:

[4] - 1 patient was not evaluable for efficacy as WBC was very high and considered as active infection.

Attachments (see zip file)	Progression free survival according to
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Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate according to RECIST 1.1

End point title	Overall response rate according to RECIST 1.1
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End point description:

Overall response rate according to RECIST v1.1 was computed as the rate of complete response (CR) or partial response (PR) as best overall response according to the RECIST v1.1 criteria.

End point type	Secondary
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End point timeframe:

All patients had their BEST OVERALL RESPONSE assessed according to RECIST 1.1 from the start of study treatment until progression or the start of further anticancer therapy or maximum 2 years after the start of study treatment whatever came first.

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	49 ^[5]			
Units: Patients				
Complete response (CR)	0			
Partial response (PR)	20			
Stable disease (SD)	18			
Progressive disease (PD)	6			
Early death	5			

Notes:

[5] - 1 patient was not evaluable for efficacy as WBC was very high and considered as active infection.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate according to iRECIST

End point title	Overall response rate according to iRECIST
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End point description:

Overall response rate according to iRECIST was computed as the rate of complete response (iCR) or partial response (iPR) as best overall response according to the iRECIST criteria.

End point type	Secondary
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End point timeframe:

All patients had their BEST OVERALL IMMUNE RESPONSE assessed from the start of study treatment until confirmed progression according to iRECIST or the start of further anticancer therapy or maximum

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	49 ^[6]			
Units: Patients				
Complete response (iCR)	0			
Partial response (iPR)	20			
Stable disease (iSD)	18			
Progressive disease (iUPD/iCPD)	6			
Early death	5			

Notes:

[6] - 1 patient was not evaluable for efficacy as WBC was very high and considered as active infection.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival rate at 6 months according to iRECIST

End point title	Progression free survival rate at 6 months according to iRECIST
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End point description:

This was a supportive analysis for the primary endpoint PFS rate at 6 months according to RECIST v1.1 in which PFS rate at 6 months was evaluated using the iRECIST criteria instead of the RECIST v1.1 criteria. Given that the lower bound of the two-sided 80% CI is 53.7% and therefore below 60% and the two-sided 80% CI includes 60%, the hypothesis testing could not reject a PFS rate at 6 months equal or lower than 60%.

End point type	Secondary
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End point timeframe:

Progression free survival (PFS) rate at 6 months was defined as the rate of patients alive and progression free at 6 months. PFS rate at 6 months was estimated using the Kaplan Meier technique to take into account possible loss to follow-up.

End point values	Experimental arm			
Subject group type	Reporting group			
Number of subjects analysed	49 ^[7]			
Units: Percentage				
number (confidence interval 80%)	63.3 (53.7 to 71.4)			

Notes:

[7] - 1 patient was not evaluable for efficacy as WBC was very high and considered as active infection.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from day 1 of study treatment (after the "screening" period) till then end of the follow-up period for safety.

Adverse event reporting additional description:

AEs are evaluated using CTC grading, SAEs using MedDra. Non-SAEs has not been collected specifically, all AEs will be reported in non-SAE section.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25
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Reporting groups

Reporting group title	Experimental Arm
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Reporting group description:

CisGem [25mg/m² intravenous (IV) cisplatin + 1000mg/m² IV gemcitabine, on days 1 and 8 of a 21-day cycle] plus 200 mg intravenous pembrolizumab 200 mg on day 1 of a 21-day cycle up to 2 years from enrolment until progressive disease or the early occurrence of a withdrawal.

Serious adverse events	Experimental Arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 50 (50.00%)		
number of deaths (all causes)	37		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
METASTASES TO CENTRAL NERVOUS SYSTEM			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
EMBOLISM			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
PYREXIA			

alternative dictionary used: MedDRA 25			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences causally related to treatment / all	4 / 6		
deaths causally related to treatment / all	0 / 0		
CONDITION AGGRAVATED			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
CHILLS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
PULMONARY HYPERTENSION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HYPOXIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
COUGH			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
BLOOD CREATININE INCREASED			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
PLATELET COUNT DECREASED			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
FALL			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
HUMERUS FRACTURE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SUBDURAL HAEMATOMA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
ATRIAL SEPTAL DEFECT			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
CARDIOVASCULAR DISORDER			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
ATRIAL FIBRILLATION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
LEFT VENTRICULAR FAILURE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
SUPRAVENTRICULAR TACHYCARDIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
PERICARDITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MYOCARDIAL INFARCTION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
HEADACHE			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
PERIPHERAL SENSORY NEUROPATHY			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
SYNCOPE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
FEBRILE NEUTROPENIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
ANAEMIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
ASCITES			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
ABDOMINAL PAIN UPPER			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	2 / 50 (4.00%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
UPPER GASTROINTESTINAL HAEMORRHAGE				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
OESOPHAGEAL VARICES HAEMORRHAGE				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MELAENA				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
LARGE INTESTINAL HAEMORRHAGE				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
INTESTINAL OBSTRUCTION				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
CONSTIPATION				
alternative dictionary used: MedDRA 25				

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
GALLBLADDER RUPTURE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
CHOLESTASIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
CHOLECYSTITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
CHOLANGITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
TUBULOINTERSTITIAL NEPHRITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
AUTOIMMUNE NEPHRITIS			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
ACUTE KIDNEY INJURY			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
HYPERTHYROIDISM			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
FLANK PAIN			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
JOINT EFFUSION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
ABSCCESS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
BILIARY SEPSIS			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
BILIARY TRACT INFECTION				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
CLOSTRIDIUM DIFFICILE INFECTION				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PNEUMONIA				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
PERITONITIS BACTERIAL				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
LOWER RESPIRATORY TRACT INFECTION				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
INFECTION				
alternative dictionary used: MedDRA 25				

subjects affected / exposed	4 / 50 (8.00%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
HEPATOBIILIARY INFECTION				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
COVID-19 PNEUMONIA				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
COVID-19				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SEPSIS				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	4 / 50 (8.00%)			
occurrences causally related to treatment / all	5 / 7			
deaths causally related to treatment / all	0 / 1			
URINARY TRACT INFECTION				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
HYPERCALCAEMIA				
alternative dictionary used: MedDRA 25				

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
HYPONATRAEMIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Experimental Arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 50 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED -OTHER, CYST alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
TUMOR PAIN alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Vascular disorders			
HOT FLASHES alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
FLUSHING alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
HEMATOMA alternative dictionary used: AECTC 5.0			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
HYPERTENSION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	12 / 50 (24.00%)		
occurrences (all)	73		
HYPOTENSION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
VASCULAR DISORDERS - OTHER, VARICOSE VEIN PAIN			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
THROMBOEMBOLIC EVENT			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	7		
VASCULAR DISORDERS - OTHER, CIRCULATORY DISORDER			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
PHLEBITIS			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
INFUSION RELATED REACTION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
CHILLS			
alternative dictionary used: AECTC 5.0			

subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
DISEASE PROGRESSION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
EDEMA FACE			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
EDEMA LIMBS			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	20 / 50 (40.00%)		
occurrences (all)	24		
FATIGUE			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	35 / 50 (70.00%)		
occurrences (all)	93		
FEVER			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	11 / 50 (22.00%)		
occurrences (all)	15		
FLU LIKE SYMPTOMS			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
GAIT DISTURBANCE			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER			
alternative dictionary used: AECTC 5.0			

<p>subjects affected / exposed</p> <p>3 / 50 (6.00%)</p> <p>occurrences (all)</p> <p>5</p> <p>INFUSION SITE EXTRAVASATION</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>1</p> <p>LOCALIZED EDEMA</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>2 / 50 (4.00%)</p> <p>occurrences (all)</p> <p>2</p> <p>MALAISE</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>1</p> <p>NON-CARDIAC CHEST PAIN</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>2 / 50 (4.00%)</p> <p>occurrences (all)</p> <p>2</p> <p>PAIN</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>5 / 50 (10.00%)</p> <p>occurrences (all)</p> <p>7</p>			
<p>Immune system disorders</p> <p>IMMUNE SYSTEM DISORDERS - OTHER, HAYFEVER</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>Respiratory, thoracic and mediastinal disorders</p> <p>POSTNASAL DRIP</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>1</p> <p>ALLERGIC RHINITIS</p> <p>alternative dictionary used: AECTC 5.0</p>			

subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
COUGH			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	9 / 50 (18.00%)		
occurrences (all)	11		
DYSPNEA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	10 / 50 (20.00%)		
occurrences (all)	16		
EPISTAXIS			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	3		
HICCUPS			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
HOARSENESS			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
HYPOXIA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
LARYNGEAL INFLAMMATION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
LUNG INFECTION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		

NASAL CONGESTION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
PRODUCTIVE COUGH			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDER, OTHER EMBOLI			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER LRTI			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER, PFO			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - OTHER, LRTI			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
RESPIRATORY, THORACIC, MEDIASTINAL DISORDER-OTHER, HAEMOPTYSIS			
alternative dictionary used: AECTC			

5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
SORE THROAT			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
PULMONARY HYPERTENSION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Psychiatric disorders			
AGITATION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
ANXIETY			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
DEPRESSION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
HALLUCINATIONS			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
INSOMNIA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
RESTLESSNESS			
alternative dictionary used: AECTC 5.0			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	8 / 50 (16.00%)		
occurrences (all)	27		
ALKALINE PHOSPHATASE INCREASED			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	4		
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	8 / 50 (16.00%)		
occurrences (all)	11		
BLOOD BILIRUBIN INCREASED			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	8		
CREATININE INCREASED			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
GGT INCREASED			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	4		
INVESTIGATIONS - OTHER, CREATININE CLEARANCE DECREASED			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
INVESTIGATIONS - OTHER, DECREASED GFR			

alternative dictionary used: AECTC 5.0			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
INVESTIGATIONS - OTHER, INCREASED D-DIMER			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
INVESTIGATIONS - OTHER, THROMBOCYTOSIS			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
LYMPHOCYTE COUNT DECREASED			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
NEUTROPHIL COUNT DECREASED			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	24 / 50 (48.00%)		
occurrences (all)	141		
PLATELET COUNT DECREASED			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	16 / 50 (32.00%)		
occurrences (all)	86		
THYROID STIMULATING HORMONE INCREASED			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
WEIGHT GAIN			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	12		
WEIGHT LOSS			
alternative dictionary used: AECTC 5.0			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>WHITE BLOOD CELL DECREASED</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 50 (8.00%)</p> <p>6</p> <p>1 / 50 (2.00%)</p> <p>1</p>		
<p>Injury, poisoning and procedural complications</p> <p>FRACTURE</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>SYNCOPE</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>FALL</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 50 (4.00%)</p> <p>4</p> <p>1 / 50 (2.00%)</p> <p>1</p> <p>2 / 50 (4.00%)</p> <p>2</p>		
<p>Cardiac disorders</p> <p>ATRIAL FIBRILLATION</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>CARDIAC DISORDERS - OTHER, SPECIFY PATENT FORAMEN OVALE</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>CARDIAC DISORDERS - OTHER, DYSPNEA</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>CHEST PAIN - CARDIAC</p> <p>alternative dictionary used: AECTC 5.0</p>	<p>1 / 50 (2.00%)</p> <p>1</p> <p>1 / 50 (2.00%)</p> <p>1</p> <p>1 / 50 (2.00%)</p> <p>1</p>		

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
MYOCARDIAL INFARCTION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
PAROXYSMAL ATRIAL TACHYCARDIA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
PERICARDITIS			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
SINUS TACHYCARDIA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	3		
SUPRAVENTRICULAR TACHYCARDIA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Nervous system disorders			
PRESYNCOPE			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
DIZZINESS			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	4		
DYSGEUSIA			
alternative dictionary used: AECTC 5.0			

subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	9		
HEADACHE			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	9 / 50 (18.00%)		
occurrences (all)	15		
LETHARGY			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
MEMORY IMPAIRMENT			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
NERVOUS SYSTEM DISORDERS - OTHER , SCIATICA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
NERVOUS SYSTEM DISORDERS, OTHER - PERIPHERAL NEUROPATHY			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	2		
PARESTHESIA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	2		
PERIPHERAL SENSORY NEUROPATHY			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	14 / 50 (28.00%)		
occurrences (all)	23		
SOMNOLENCE			
alternative dictionary used: AECTC 5.0			

<p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>1</p> <p>SYNCOPE</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>2 / 50 (4.00%)</p> <p>occurrences (all)</p> <p>2</p>			
<p>Blood and lymphatic system disorders</p> <p>ANEMIA</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>29 / 50 (58.00%)</p> <p>occurrences (all)</p> <p>144</p> <p>FEBRILE NEUTROPENIA</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>2 / 50 (4.00%)</p> <p>occurrences (all)</p> <p>2</p>			
<p>Ear and labyrinth disorders</p> <p>EAR AND LABYRINTH DISORDERS - OTHER, INTERMITTENT PRESSURE</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>1</p> <p>EAR PAIN</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>3 / 50 (6.00%)</p> <p>occurrences (all)</p> <p>4</p> <p>HEARING IMPAIRED</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>4 / 50 (8.00%)</p> <p>occurrences (all)</p> <p>8</p> <p>TINNITUS</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>9 / 50 (18.00%)</p> <p>occurrences (all)</p> <p>12</p>			
<p>Eye disorders</p>			

<p>DRY EYE</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 50 (2.00%)</p> <p>1</p>		
<p>EYE DISORDERS - OTHER, RED EYE</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 50 (2.00%)</p> <p>1</p>		
<p>EYE DISORDERS - OTHER, SUBCONJUNCTIVAL HAEMORRHAGE (LEFT)</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 50 (2.00%)</p> <p>1</p>		
<p>EYE DISORDERS, OTHER - SCRATCH TO THE LEFT EYE</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 50 (2.00%)</p> <p>1</p>		
<p>Gastrointestinal disorders</p> <p>ABDOMINAL DISTENSION</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 50 (2.00%)</p> <p>1</p>		
<p>GASTROINTESTINAL DISORDERS - OTHER, INDIGESTION</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 50 (2.00%)</p> <p>2</p>		
<p>GASTROINTESTINAL DISORDERS - OTHER, HYPER SALIVATION</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 50 (2.00%)</p> <p>1</p>		
<p>GASTROINTESTINAL DISORDERS - OTHER, MELENAS</p> <p>alternative dictionary used: AECTC 5.0</p>			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
GASTROINTESTINAL DISORDERS - OTHER, ODYNOPHAGIA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
GASTROINTESTINAL DISORDERS - OTHER, RECTAL MASS			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
GASTROINTESTINAL DISORDERS - OTHER, REDUCED APPETITE			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
GASTROINTESTINAL DISORDERS - OTHER, STEATORHEA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
GASTROINTESTINAL DISORDERS - OTHER, TENESMUS			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
GASTROINTESTINAL DISORDERS- OTHER, STOMATITIS			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	4		
GASTROINTESTINAL PAIN			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
HEMORRHOIDS			
alternative dictionary used: AECTC 5.0			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
MUCOSITIS ORAL			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	9		
NAUSEA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	27 / 50 (54.00%)		
occurrences (all)	42		
RECTAL PAIN			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
SMALL INTESTINAL OBSTRUCTION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
ABDOMINAL PAIN			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	18 / 50 (36.00%)		
occurrences (all)	29		
ASCITES			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	8		
BLOATING			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
COLONIC HEMORRHAGE			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		

CONSTIPATION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	22 / 50 (44.00%)		
occurrences (all)	32		
DIARRHEA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	14 / 50 (28.00%)		
occurrences (all)	23		
DRY MOUTH			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
DYSPEPSIA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
ESOPHAGEAL VARICES HEMORRHAGE			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
FLATULENCE			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	2		
GASTROESOPHAGEAL REFLUX DISEASE			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	6		
GASTROINTESTINAL DISORDERS - OTHER, ABDOMINAL DISTENTION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
GASTROINTESTINAL DISORDERS - OTHER, FRACTURED TOOTH			

alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
GASTROINTESTINAL DISORDERS - OTHER, MELAENA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
STOMACH PAIN			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	4		
TOOTHACHE			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
UPPER GASTROINTESTINAL HEMORRHAGE			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
VOMITING			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	15 / 50 (30.00%)		
occurrences (all)	21		
SMALL INTESTINAL PERFORATION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Hepatobiliary disorders			
HEPATOBIILIARY DISORDERS - OTHER, GRAM NEGATIVE INFECTION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
CHOLECYSTITIS			

<p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 50 (2.00%)</p> <p>2</p>		
<p>GALLBLADDER OBSTRUCTION</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 50 (2.00%)</p> <p>1</p>		
<p>GALLBLADDER PERFORATION</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 50 (2.00%)</p> <p>2</p>		
<p>HEPATOBIILIARY DISORDERS - OTHER, BILIARY OBSTRUCTION</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 50 (2.00%)</p> <p>1</p>		
<p>HEPATOBIILIARY DISORDERS - OTHER, CHOLESTASIS</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 50 (2.00%)</p> <p>4</p>		
<p>HEPATOBIILIARY DISORDERS - OTHER, HEPATIC ABSCESS</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 50 (2.00%)</p> <p>2</p>		
<p>HEPATOBIILIARY DISORDERS - OTHER, JAUNDICE</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 50 (2.00%)</p> <p>1</p>		
<p>Skin and subcutaneous tissue disorders</p> <p>ALOPECIA</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>BULLOUS DERMATITIS</p>	<p>10 / 50 (20.00%)</p> <p>12</p>		

alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
DRY SKIN			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
ERYTHEMA MULTIFORME			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
HYPERHIDROSIS			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
NAIL CHANGES			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
PRURITUS			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	8 / 50 (16.00%)		
occurrences (all)	12		
RASH ACNEIFORM			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
RASH MACULO-PAPULAR			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	3		
SCALP PAIN			
alternative dictionary used: AECTC 5.0			

<p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, ITCHING</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, ROSACEA</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, SKIN RASH</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>SKIN AND SUBCUTANEOUS TISSUE DISORDERS, OTHER</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>URTICARIA</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>2</p>			
<p>Renal and urinary disorders</p> <p>ACUTE KIDNEY INJURY</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>2 / 50 (4.00%)</p> <p>occurrences (all)</p> <p>3</p> <p>CHRONIC KIDNEY DISEASE</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>2</p> <p>CYSTITIS NONINFECTIVE</p> <p>alternative dictionary used: AECTC 5.0</p>			

<p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>1</p> <p>RENAL AND URINARY DISORDERS - OTHER, ACUTE RENAL FAILURE</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>1</p> <p>RENAL AND URINARY DISORDERS - OTHER, MALIGNANT CHOLESTASIS</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>1</p> <p>RENAL AND URINARY DISORDERS - OTHER, SPECIFY</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>1</p> <p>RENAL AND URINARY DISORDERS - OTHER, TUBULOINT. NEPHRITIS</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>1</p> <p>URINARY RETENTION</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>Endocrine disorders</p> <p>ADRENAL INSUFFICIENCY</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>1</p> <p>ENDOCRINE DISORDERS - OTHER, TSH DECREASED</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>1 / 50 (2.00%)</p> <p>occurrences (all)</p> <p>1</p> <p>HYPERTHYROIDISM</p> <p>alternative dictionary used: AECTC</p>			

5.0			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
HYPOTHYROIDISM			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	6		
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	6		
BACK PAIN			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	10		
BONE PAIN			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
FLANK PAIN			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
GENERALIZED MUSCLE WEAKNESS			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	2		
JOINT EFFUSION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
MUSCLE CRAMP			
alternative dictionary used: AECTC 5.0			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER,</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDER - OTHER, ACHE</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>MUSCULOSKELETAL CONNECTIVE TISSUE DISORDER- OTHER, HYPOTONIA</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>MYALGIA</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>NECK PAIN</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>PAIN IN EXTREMITY</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 50 (6.00%)</p> <p>3</p> <p>1 / 50 (2.00%)</p> <p>1</p> <p>1 / 50 (2.00%)</p> <p>1</p> <p>1 / 50 (2.00%)</p> <p>1</p> <p>2 / 50 (4.00%)</p> <p>2</p> <p>3 / 50 (6.00%)</p> <p>3</p> <p>1 / 50 (2.00%)</p> <p>1</p>		
<p>Infections and infestations</p> <p>BILIARY TRACT INFECTION</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>INFECTIONS AND INFESTATIONS -</p>	<p>2 / 50 (4.00%)</p> <p>4</p>		

OTHER, INFECTION OF UK SOURCE			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
INFECTIONS AND INFESTATIONS - OTHER, BACTERIAL PERITONITIS			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
INFECTIONS AND INFESTATIONS - OTHER, C.DIFFICILE INFECTION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	2		
INFECTIONS AND INFESTATIONS - OTHER, CHOLANGITIS			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
INFECTIONS AND INFESTATIONS - OTHER, ERYSIPEL			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
INFECTIONS AND INFESTATIONS - OTHER, INFECTION OF UK SOURCE			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
INFECTIONS AND INFESTATIONS - OTHER, NKNOWN SOURCE			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
INFECTIONS AND INFESTATIONS - OTHER, NON-NEUTROPENIC INF			
alternative dictionary used: AECTC 5.0			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
INFECTIONS AND INFESTATIONS - OTHER, NON-NEUTROPENIC INFECTION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
INFECTIONS AND INFESTATIONS - OTHER, SKIN INFECTION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
INFECTIONS AND INFESTATIONS - OTHER, VIRAL INFECTION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
INFECTIONS AND INFESTATIONS - OTHER, INFECTION UNKNOWN SOURCE			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
LUNG INFECTION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	9		
PARONYCHIA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
RHINITIS INFECTIVE			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
SEPSIS			
alternative dictionary used: AECTC 5.0			

subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	10		
SINUSITIS			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	2		
SKIN INFECTION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
THRUSH			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
TOOTH INFECTION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
UPPER RESPIRATORY INFECTION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	6		
UPPER RESPIRATORY INFECTION - OTHER, NOSE INFECTION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
URINARY TRACT INFECTION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	12		
Metabolism and nutrition disorders			
HYPOKALEMIA			
alternative dictionary used: AECTC 5.0			

subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
ANOREXIA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	11 / 50 (22.00%)		
occurrences (all)	14		
DEHYDRATION			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
HYPERCALCEMIA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	7		
HYPERGLYCEMIA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
HYPOALBUMINEMIA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
HYPOCALCEMIA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
HYPOMAGNESEMIA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	5		
HYPOPHOSPHATEMIA			
alternative dictionary used: AECTC 5.0			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		

<p>HYPONATREMIA</p> <p>alternative dictionary used: AECTC 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 50 (8.00%)</p> <p>12</p>		
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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 September 2019	<p>AMENDMENT 1</p> <ul style="list-style-type: none">-Patients selection criteria were modified to clearly specify that highly effective birth control measures according to the standard national guidelines should be used for patients (male or female) of childbearing / reproductive potential.-The request to renew/repeat pregnancy testing in women of childbearing potential up to 6 months after last dose of trial medication was added.-Appendix G for recommendation based on Clinical Trial Facilitation Group (CTFG) guidelines for sites and countries where applicable (e.g. Germany, Austria, ...) was added.-Systemic corticosteroids were allowed for supportive care and should use the lowest dose and duration feasible as per international and intuitional guidelines to align with MSD approach.-The guideline that pembrolizumab should be permanently discontinued in case of:<ul style="list-style-type: none">• recurrent colitis grade 3• liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT \geq 50% and lasts \geq 1 weekwas added.
17 July 2020	<p>AMENDMENT 2</p> <ul style="list-style-type: none">-Update of background section regarding pembrolizumab (pharmacokinetic, selected dosing, efficacy and safety data)-Guidance provided for administration of pembrolizumab, cisplatin and gemcitabine-Update safety guidance of pembrolizumab-Update about the drug-drug interactions for cisplatin and gemcitabine.
10 December 2020	<p>AMENDMENT 3</p> <ul style="list-style-type: none">-Eligibility: the C-reactive protein (CRP) has been removed from the eligibility. CRP is raised in advanced/metastatic setting of a cancer and therefore not relevant for the studied patient population.-Update of safety guidelines for gemcitabine and cisplatin-Update of concomitant treatments-Miscellaneous: clarifications implemented in the protocol in different sections.
24 June 2021	<p>AMENDMENT 4 -Following the update of reference documents for pembrolizumab (SmPC-Merck, dated 26 May 2021) and for cisplatin (SmPC-Hospira-dated 29/07/2020) a new addendum to the patient information sheet (PISIC) has been prepared for patients already enrolled.</p>
15 October 2021	<p>AMENDMENT 5 -Following the update of reference documents for pembrolizumab (SmPC-Merck, dated 15 September 2021), a new addendum to the patient information sheet (PISIC) has been prepared for patients already enrolled.</p>
13 January 2022	<p>AMENDMENT 6 -The Translational research has been now described in the protocol, for submission of the project to regulatory bodies.</p>
18 July 2022	<p>AMENDMENT 7 -Following the update of reference document for pembrolizumab (IB version 22, dated 13 May 2022), a new addendum to the patient information sheet (PISIC) has been prepared for patients already enrolled to update the safety language.</p>

16 December 2022	AMENDMENT 8 -Following the update of reference documents for pembrolizumab IB version 23, dated 26 October 2022 and the SmPC dated 17 November 2022, a new addendum to PISIC has been prepared to update the risk language. -The translational research section of the protocol has been revised to include the change with regards to the new lab that will perform the analyses of the collected samples.
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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.

<p>This study was not randomized. No internal control arm is available which limits the interpretation of these results. PFS is an endpoint which could be influenced by the prognosis of the enrolled study population.</p>
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Notes: