



Clinical trial results:

Adjuvant immunotherapy in patients with resected gastric cancer following preoperative chemotherapy with high risk for recurrence (N+ and/or R1): an open label randomized controlled phase-2-study (VESTIGE)

Summary

EudraCT number	2018-000406-36
Trial protocol	GB DE PL NO ES IT
Global end of trial date	11 August 2023

Results information

Result version number	v1 (current)
This version publication date	08 September 2024
First version publication date	08 September 2024

Trial information

Trial identification

Sponsor protocol code	EORTC-1707-GITCG
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03443856
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	European Organisation for the Research and Treatment of Cancer
Sponsor organisation address	Avenue Emmanuel Mounier 83/11, Brussels, Belgium, 1200
Public contact	Clinical Operations Department, European Organisation for the Research and Treatment of Cancer, 0032 27741334, murielle.mauer@gmail.com
Scientific contact	Clinical Operations Department, European Organisation for the Research and Treatment of Cancer, 0471693363 27741334, 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	12 March 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 August 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to investigate if nivolumab plus ipilimumab given as adjuvant treatment improve disease free survival (DFS) in patients with stage Ib-IVa gastric and esophagogastric junction (EGJ) adenocarcinoma and high risk of recurrence (defined by ypN1-3 and/or R1 status) following neoadjuvant chemotherapy and resection.

Protection of trial subjects:

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-clinical-practice_en.pdf).

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

Background therapy:

Adjuvant chemotherapy based on the latest ESMO guidelines.

Perioperative chemotherapy consisted of FLOT (docetaxel 50 mg/m² given as a 1 hour infusion, followed by oxaliplatin 85 mg/m² given as a 2 hour infusion, leucovorin 200 mg/m² over 2 hours and 5-FU 2600 mg/m² given as a 24 hour infusion) or an established non-FLOT perioperative chemotherapy regimen according to the study protocol (ECX, FOLFOX). The duration of preoperative chemotherapy was a minimum of 6 weeks and a maximum of 12 weeks.

Evidence for comparator:

The standard treatment is adjuvant chemotherapy as specified by the ESMO guidelines.

Actual start date of recruitment	09 August 2019
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	Israel: 19
Country: Number of subjects enrolled	Norway: 12
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Czechia: 9
Country: Number of subjects enrolled	France: 27

Country: Number of subjects enrolled	Germany: 48
Country: Number of subjects enrolled	Italy: 22
Worldwide total number of subjects	195
EEA total number of subjects	156

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)	123
From 65 to 84 years	72
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 09/08/2019 and 14/06/2022, 195 patients with resected gastro-oesophageal adenocarcinoma following preoperative chemotherapy with high risk for recurrence (ypN+ and/or R1) were randomized at 26 medical centres in 9 countries (Czech Republic, France, Germany, Israel, Italy, Norway, Poland, Spain, and UK).

Pre-assignment

Screening details:

Upon signing the informed consent and after verification of eligibility, patients were centrally randomized between the two arms in a 1:1 ratio. Treatment allocation was open-label and stratified for location (gastric vs. OGJ), histology (intestinal vs. non-intestinal), R0 vs. R1 status, preoperative chemotherapy (FLOT vs. non-FLOT).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard arm

Arm description:

Adjuvant chemotherapy based on the latest ESMO guidelines.

Perioperative treatment consisted of FLOT or an established non-FLOT perioperative chemotherapy regimen according to the study protocol (ECX, FOLFOX). The duration of preoperative chemotherapy was a minimum of 6 weeks and a maximum of 12 weeks.

Arm type	Active comparator
Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

-Epirubicin + cisplatin + capecitabine (ECX):

Epirubicin 50 mg/m² intravenously day 1, cisplatin 60 mg/m² intravenously day 1, and capecitabine 625 mg/m² twice daily on days 1–21. Cycled every 21 days for 3 cycles preop and 3 cycles postop.

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

Dosage and administration details:

-Epirubicin + cisplatin + capecitabine (ECX):

Epirubicin 50 mg/m² intravenously day 1, cisplatin 60 mg/m² intravenously day 1, and capecitabine 625 mg/m² twice daily on days 1–21. Cycled every 21 days for 3 cycles preop and 3 cycles postop.

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

-Epirubicin + cisplatin + capecitabine (ECX):

Epirubicin 50 mg/m² intravenously day 1, cisplatin 60 mg/m² intravenously day 1, and capecitabine 625 mg/m² twice daily on days 1–21. Cycled every 21 days for 3 cycles preop and 3 cycles postop.

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

Dosage and administration details:

-Fluorouracil + leucovorin + oxaliplatin (FOLFOX):

day 1: oxaliplatin 85 mg/m² IV infusion, 400 mg/m² leucovorin IV infusion, followed by 5-FU 400 mg/m² IV push then 5-FU 1200 mg/m²

IV infusion for 22 hours; day 2: 5-FU 1200 mg/m² IV infusion for 24 hours daily on Days 1 and 2.

Cycled every 14 days for 4 cycles.

-Fluorouracil + leucovorin + oxaliplatin + docetaxel (FLOT):

FLOT is administered in cycles of 2 weeks for 4 cycles (= 8 weeks) on day 1, 15, 29 and 43 pre- and postoperatively. Docetaxel 50 mg/m²

is given as 1 hour infusion, followed by oxaliplatin 85 mg/m² as a 2 hour infusion, leucovorin 200 mg/m² over 2 hours, and 5-FU 2600 mg/m² as a 24 hour-infusion, with oral dexamethasone for prevention of fluid retention and allergic reactions.

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

Dosage and administration details:

-Fluorouracil + leucovorin + oxaliplatin (FOLFOX):

day 1: oxaliplatin 85 mg/m² IV infusion, 400 mg/m² leucovorin IV infusion, followed by 5-FU 400 mg/m² IV push then 5-FU 1200 mg/m²

IV infusion for 22 hours; day 2: 5-FU 1200 mg/m² IV infusion for 24 hours daily on Days 1 and 2.

Cycled every 14 days for 4 cycles.

-Fluorouracil + leucovorin + oxaliplatin + docetaxel (FLOT):

FLOT is administered in cycles of 2 weeks for 4 cycles (= 8 weeks) on day 1, 15, 29 and 43 pre- and postoperatively. Docetaxel 50 mg/m²

is given as 1 hour infusion, followed by oxaliplatin 85 mg/m² as a 2 hour infusion, leucovorin 200 mg/m² over 2 hours, and 5-FU 2600 mg/m² as a 24 hour-infusion, with oral dexamethasone for prevention of fluid retention and allergic reactions.

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

Dosage and administration details:

-Fluorouracil + leucovorin + oxaliplatin (FOLFOX):

day 1: oxaliplatin 85 mg/m² IV infusion, 400 mg/m² leucovorin IV infusion, followed by 5-FU 400 mg/m² IV push then 5-FU 1200 mg/m²

IV infusion for 22 hours; day 2: 5-FU 1200 mg/m² IV infusion for 24 hours daily on Days 1 and 2.

Cycled every 14 days for 4 cycles.

-Fluorouracil + leucovorin + oxaliplatin + docetaxel (FLOT):

FLOT is administered in cycles of 2 weeks for 4 cycles (= 8 weeks) on day 1, 15, 29 and 43 pre- and postoperatively. Docetaxel 50 mg/m²

is given as 1 hour infusion, followed by oxaliplatin 85 mg/m² as a 2 hour infusion, leucovorin 200 mg/m² over 2 hours, and 5-FU 2600 mg/m² as a 24 hour-infusion, with oral dexamethasone for prevention of fluid retention and allergic reactions.

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

Dosage and administration details:

-Fluorouracil + leucovorin + oxaliplatin + docetaxel (FLOT):

FLOT is administered in cycles of 2 weeks for 4 cycles (= 8 weeks) on day 1, 15, 29 and 43 pre- and postoperatively. Docetaxel 50 mg/m²

is given as 1 hour infusion, followed by oxaliplatin 85 mg/m² as a 2 hour infusion, leucovorin 200 mg/m² over 2 hours, and 5-FU 2600 mg/m² as a 24 hour-infusion, with oral dexamethasone for prevention of fluid retention and allergic reactions.

Arm title	Experimental arm
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Arm description:

- Nivolumab 3 mg/kg intravenously every 2 weeks on day 1 of each 14 day cycle for one year

- Ipilimumab 1 mg/kg intravenously every 6 weeks on day 1 of each 42 day cycle for one year

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

Dosage and administration details:

Nivolumab 3 mg/kg intravenously every 2 weeks on day 1 of each 14 day cycle for one year.

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

Dosage and administration details:

Ipilimumab 1 mg/kg intravenously every 6 weeks on day 1 of each 42 day cycle for one year.

Number of subjects in period 1	Standard arm	Experimental arm
Started	97	98
Completed	71	20
Not completed	26	78
Adverse event, serious fatal	-	1
Adverse event, non-fatal	9	30
Patient's decision not to start treatment	10	1
Treatment not started due to patient ineligibility	2	-
Progression of disease	-	33
Patient's decision to stop treatment	4	13
Treatment not started due to other malignancy	1	-

Baseline characteristics

Reporting groups

Reporting group title	Standard arm
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Reporting group description:

Adjuvant chemotherapy based on the latest ESMO guidelines.

Perioperative treatment consisted of FLOT or an established non-FLOT perioperative chemotherapy regimen according to the study protocol (ECX, FOLFOX). The duration of preoperative chemotherapy was a minimum of 6 weeks and a maximum of 12 weeks.

Reporting group title	Experimental arm
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Reporting group description:

- Nivolumab 3 mg/kg intravenously every 2 weeks on day 1 of each 14 day cycle for one year
- Ipilimumab 1 mg/kg intravenously every 6 weeks on day 1 of each 42 day cycle for one year

Reporting group values	Standard arm	Experimental arm	Total
Number of subjects	97	98	195
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	60	61	
inter-quartile range (Q1-Q3)	26 to 82	35 to 80	-
Gender categorical			
Units: Subjects			
Female	37	29	66
Male	60	69	129
WHO performance status			
Units: Subjects			
PS 0	51	55	106
PS 1	46	43	89
Histologically proven gastric, lower oesophageal or OGJ adenocarcinoma (Siewert I-III)			
Units: Subjects			
Gastric adenocarcinoma	57	58	115
Lower oesophageal adenocarcinoma	8	11	19
OGJ adenocarcinoma	32	29	61
Histological subtype			
Units: Subjects			

Intestinal	49	52	101
Non-intestinal	48	46	94
Total or distal gastrectomy with D2 lymphadenectomy or oesophagectomy with two-field lymphadenectomy			
done according to the ESMO guidelines			
Units: Subjects			
Yes	97	98	195
Resection status of primary tumor			
according to TNM version 8			
Units: Subjects			
R0	81	84	165
R1	16	14	30
ypN stage			
according to TNM version 8			
Units: Subjects			
ypN0	4	2	6
ypN1	31	24	55
ypN2	25	22	47
ypN3	37	50	87
Pre-operative chemotherapy regimen			
Units: Subjects			
non-FLOT	7	8	15
FLOT	90	90	180
Neoadjuvant chemotherapy duration			
Units: weeks			
median	8	8	
inter-quartile range (Q1-Q3)	6 to 8	6 to 8	-

End points

End points reporting groups

Reporting group title	Standard arm
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Reporting group description:

Adjuvant chemotherapy based on the latest ESMO guidelines.

Perioperative treatment consisted of FLOT or an established non-FLOT perioperative chemotherapy regimen according to the study protocol (ECX, FOLFOX). The duration of preoperative chemotherapy was a minimum of 6 weeks and a maximum of 12 weeks.

Reporting group title	Experimental arm
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Reporting group description:

- Nivolumab 3 mg/kg intravenously every 2 weeks on day 1 of each 14 day cycle for one year
- Ipilimumab 1 mg/kg intravenously every 6 weeks on day 1 of each 42 day cycle for one year

Subject analysis set title	Per protocol population - standard arm
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Subject analysis set type	Per protocol
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Subject analysis set description:

All patients who are eligible and have started their allocated treatment (at least one dose of the study drugs).

Subject analysis set title	Per protocol population - experimental arm
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Subject analysis set type	Per protocol
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Subject analysis set description:

All patients who are eligible and have started their allocated treatment (at least one dose of the study drugs).

Primary: Disease free survival

End point title	Disease free survival
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End point description:

Disease free survival is defined as the time interval between randomization and the date of disease recurrence or death from any cause, whichever comes first. Patients alive with no disease recurrence are censored at the date of the last follow-up examination.

End point type	Primary
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End point timeframe:

Disease evaluation was to be performed every 3 months during the treatment period for 2 years after randomization and every 6 months during follow up for consecutive 3 years until PD/death/lost to follow-up whichever occurs first.

End point values	Standard arm	Experimental arm	Per protocol population - standard arm	Per protocol population - experimental arm
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	97 ^[1]	98 ^[2]	79 ^[3]	93 ^[4]
Units: Months				
median (confidence interval 95%)	20.8 (15.0 to 29.9)	11.4 (8.4 to 16.8)	20.8 (15.0 to 29.9)	11.7 (8.5 to 17.3)

Notes:

[1] - The primary analysis of DFS was conducted in the Intention-to-treat population.

[2] - The primary analysis of DFS was conducted in the Intention-to-treat population.

[3] - A sensitivity analysis was performed in the per protocol population.

[4] - A sensitivity analysis was performed in the per protocol population.

Attachments (see zip file)	Disease free survival - ITT population/DFS_ITT.pdf Disease free survival - per protocol population/DFS_per
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Statistical analyses

Statistical analysis title	Primary analysis (ITT)
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Statistical analysis description:

The primary test for the primary endpoint DFS was conducted in the Intention-to-treat population according to the intent to treat principle. The superiority of the experimental arm against the control arm was tested for DFS at a 1-sided level of significance of 0.1 using an unstratified log-rank test. A Cox regression model with treatment as covariate was used to provide an estimate of the treatment effect (hazard ratio) together its 1-sided 90% confidence interval.

Comparison groups	Standard arm v Experimental arm
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9902 ^[5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.55
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	1.22
upper limit	1.98

Notes:

[5] - The one-sided p-value from the one-tailed unstratified log-rank test (primary analysis) is 0.99 and therefore not below the level of significance of 0.1. The primary endpoint, prolonged DFS in the experimental arm, was not met.

Statistical analysis title	Sensitivity analysis (per protocol)
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Statistical analysis description:

A sensitivity analysis consisted in repeating the primary analysis in the per protocol population.

Comparison groups	Per protocol population - standard arm v Per protocol population - experimental arm
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9803 ^[6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.49
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	1.16
upper limit	1.92

Notes:

[6] - The one-sided p-value from the one-tailed unstratified log-rank test (primary analysis) is 0.98 and therefore not below the level of significance of 0.1.

Secondary: Overall survival

End point title	Overall survival
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End point description:

Overall survival is defined as the time interval between the date of randomization and the date of death from any cause. Patients who are still alive when last traced are censored at the date of last follow up.

End point type	Secondary
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End point timeframe:

After the end of treatment, patients were to be followed up for survival. Each patient was to be followed until death or for approximately 5 years following randomization in order to document the long-term outcomes.

End point values	Standard arm	Experimental arm	Per protocol population - standard arm	Per protocol population - experimental arm
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	97 ^[7]	98 ^[8]	79 ^[9]	93 ^[10]
Units: Months				
median (confidence interval 95%)	38.0 (25.8 to 999)	27.6 (25.4 to 999)	38.0 (25.8 to 999)	27.6 (25.4 to 999)

Notes:

[7] - The primary analysis of OS was conducted in the Intention-to-treat population.

999=Not reached

[8] - The primary analysis of OS was conducted in the Intention-to-treat population.

999=Not reached

[9] - A sensitivity analysis was performed in the per protocol population.

999=Not reached

[10] - A sensitivity analysis was performed in the per protocol population.

999=Not reached

Attachments (see zip file)	Overall survival - ITT population/OS_ITT.pdf
	Overall survival - per protocol population/OS_per protocol.pdf

Statistical analyses

Statistical analysis title	Primary analysis (ITT)
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Statistical analysis description:

The primary analysis of the secondary endpoint OS was conducted in the Intention-to-treat population according to the intent to treat principle. A Cox regression model with treatment as covariate was used to provide an estimate of the treatment effect (hazard ratio) together its two-sided 95% confidence interval.

Comparison groups	Standard arm v Experimental arm
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other ^[11]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.32

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	2.1

Notes:

[11] - descriptive analysis

Statistical analysis title	Sensitivity analysis (per protocol)
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Statistical analysis description:

A sensitivity analysis consisted in repeating the primary analysis in the per protocol population.

Comparison groups	Per protocol population - experimental arm v Per protocol population - standard arm
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	other ^[12]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.29

Confidence interval

level	95 %
sides	2-sided
lower limit	0.8
upper limit	2.1

Notes:

[12] - descriptive analysis

Secondary: 12-month disease-free survival rate

End point title	12-month disease-free survival rate
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End point description:

DFS rates at 12 months and its two-sided 95% confidence interval were estimated in both treatment arms using the log-log transformation of the Kaplan-Meier estimates and the standard deviation of the Kaplan Meier estimate based on the Greenwood formula.

End point type	Secondary
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End point timeframe:

Disease evaluation was to be performed every 3 months during the treatment period for 2 years after randomization.

End point values	Standard arm	Experimental arm	Per protocol population - standard arm	Per protocol population - experimental arm
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	97 ^[13]	98 ^[14]	79 ^[15]	93 ^[16]
Units: Percentage				
number (confidence interval 95%)	64.0 (52.7 to 73.2)	47.1 (36.8 to 56.8)	64.5 (52.7 to 74.1)	48.1 (37.5 to 57.9)

Notes:

[13] - The primary analysis was conducted in the Intention-to-treat population.

[14] - The primary analysis was conducted in the Intention-to-treat population.

[15] - A sensitivity analysis was performed in the per protocol population.

[16] - A sensitivity analysis was performed in the per protocol population.

Statistical analyses

No statistical analyses for this end point

Secondary: Pattern and rate of relapse

End point title	Pattern and rate of relapse
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End point description:

-Loco-regional failure:

Local recurrence is defined as evidence of tumor in the anastomotic area. Regional recurrence is defined as evidence of tumor in the locoregional lymph nodes or other surrounding structures apart from the anastomotic site.

-Distant failure:

Distant recurrence is defined as recurrence not considered as local or regional.

End point type	Secondary
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End point timeframe:

Disease evaluation was to be performed every 3 months during the treatment period for 2 years after randomization and every 6 months during follow up for consecutive 3 years until PD/death/lost to follow-up whichever occurs first.

End point values	Standard arm	Experimental arm	Per protocol population - standard arm	Per protocol population - experimental arm
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	97 ^[17]	98 ^[18]	79 ^[19]	93 ^[20]
Units: Patients				
Loco-regional recurrence	12	19	12	18
Distant recurrence	30	39	27	37
Both	4	6	4	6
Death	2	2	2	2
No DFS event	49	32	34	30

Notes:

[17] - The primary analysis was conducted in the Intention-to-treat population.

[18] - The primary analysis was conducted in the Intention-to-treat population.

[19] - A sensitivity analysis was performed in the per protocol population.

[20] - A sensitivity analysis was performed in the per protocol population.

Statistical analyses

No statistical analyses for this end point

Secondary: 12-month loco-regional failure rate

End point title	12-month loco-regional failure rate
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End point description:

Time to loco-regional failure is defined as the time interval between randomization and the date of loco-regional recurrence.

Distant failure as first recurrence or death in absence of loco-regional failure is considered as a competing risk in the estimation of the cumulative incidence of loco-regional failures. Patients alive with no disease recurrence are censored at the date of the last follow-up examination. The 1-year cumulative incidence rates together with their two-sided 95% confidence intervals are estimated in each arm using the competing risk methodology by means of a Fine-and-Gray model.

End point type	Secondary
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End point timeframe:

Disease evaluation was to be performed every 3 months during the treatment period for 2 years after randomization and every 6 months during follow up for consecutive 3 years until PD/death/lost to follow-up whichever occurs first.

End point values	Standard arm	Experimental arm	Per protocol population - standard arm	Per protocol population - experimental arm
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	97 ^[21]	98 ^[22]	79 ^[23]	93 ^[24]
Units: Percent				
number (confidence interval 95%)	10.8 (5.3 to 18.6)	20.2 (12.8 to 28.9)	11.8 (5.8 to 20.2)	20.0 (12.4 to 28.9)

Notes:

[21] - The primary analysis was conducted in the Intention-to-treat population.

[22] - The primary analysis was conducted in the Intention-to-treat population.

[23] - A sensitivity analysis was performed in the per protocol population.

[24] - A sensitivity analysis was performed in the per protocol population.

Statistical analyses

Statistical analysis title	Primary analysis (ITT)
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Statistical analysis description:

The primary analysis of this secondary endpoint was conducted in the Intention-to-treat population according to the intent to treat principle. Locoregional failure was analyzed using the competing risk methodology by means of a Fine-and-Gray model. Competing risk hazard ratios with their two-sided 95% confidence intervals will be provided.

Comparison groups	Standard arm v Experimental arm
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other ^[25]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	2.76

Notes:

[25] - descriptive analysis

Statistical analysis title	Sensitivity analysis (per protocol)
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Statistical analysis description:

A sensitivity analysis consisted in repeating the primary analysis in the per protocol population.

Comparison groups	Per protocol population - standard arm v Per protocol population - experimental arm
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	other ^[26]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	2.52

Notes:

[26] - descriptive analysis

Secondary: 12 months distant failure rate

End point title	12 months distant failure rate
End point description:	
Time to distant failure is defined as the time interval between randomization and the date of distant recurrence.	
Loco-regional failure as first recurrence or death in absence of distant failure is considered as a competing risk in the estimation of the cumulative incidence of distant failures. Patients alive with no disease recurrence are censored at the date of the last follow-up examination. The 1-year cumulative incidence rates together with their two-sided 95% confidence intervals are estimated in each arm using the competing risk methodology by means of a Fine-and-Gray model.	
End point type	Secondary
End point timeframe:	
Disease evaluation was to be performed every 3 months during the treatment period for 2 years after randomization and every 6 months during follow up for consecutive 3 years until PD/death/lost to follow-up whichever occurs first.	

End point values	Standard arm	Experimental arm	Per protocol population - standard arm	Per protocol population - experimental arm
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	97 ^[27]	98 ^[28]	79 ^[29]	93 ^[30]
Units: Percent				
number (confidence interval 95%)	26.4 (17.4 to 36.3)	35.8 (26.2 to 45.5)	25.0 (15.8 to 35.1)	35.2 (25.5 to 45.1)

Notes:

[27] - The primary analysis was conducted in the Intention-to-treat population.

[28] - The primary analysis was conducted in the Intention-to-treat population.

[29] - A sensitivity analysis was performed in the per protocol population.

[30] - A sensitivity analysis was performed in the per protocol population.

Statistical analyses

Statistical analysis title	Primary analysis (ITT)
Statistical analysis description:	
The primary analysis of this secondary endpoint was conducted in the Intention-to-treat population according to the intent to treat principle. Distant failure was analyzed using the competing risk methodology by means of a Fine-and-Gray model. Competing risk hazard ratios with their two-sided 95% confidence intervals are provided.	
Comparison groups	Standard arm v Experimental arm
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other ^[31]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	2.08
Notes:	
[31] - descriptive analysis	

Statistical analysis title	Sensitivity analysis (per protocol)
Statistical analysis description:	
A sensitivity analysis consisted in repeating the primary analysis in the per protocol population.	
Comparison groups	Per protocol population - standard arm v Per protocol population - experimental arm
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	other ^[32]
Parameter estimate	Hazard ratio (HR)
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	2.11
Notes:	
[32] - descriptive analysis	

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected on a CRF to be submitted at pre-specified timepoint : Adverse events are reported from day 1 of study treatment (after the "Baseline" period) till the 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. 1 SAE with SOC Product issues and PT Device dislocation occurred in the experimental arm and is not reported as no matching EudraCT ID for the MedDra coding was identified.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	27

Reporting groups

Reporting group title	Experimental arm
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Reporting group description:

- Nivolumab 3 mg/kg intravenously every 2 weeks on day 1 of each 14 day cycle for one year
- Ipilimumab 1 mg/kg intravenously every 6 weeks on day 1 of each 42 day cycle for one year

Reporting group title	Standard arm
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Reporting group description:

Adjuvant chemotherapy based on the latest ESMO guidelines.

Perioperative treatment consisted of FLOT or an established non-FLOT perioperative chemotherapy regimen according to the study protocol (ECX, FOLFOX). The duration of preoperative chemotherapy was a minimum of 6 weeks and a maximum of 12 weeks.

Serious adverse events	Experimental arm	Standard arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 97 (42.27%)	19 / 84 (22.62%)	
number of deaths (all causes)	41	30	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
ORTHOSTATIC HYPOTENSION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PHLEBITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
PYREXIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	2 / 97 (2.06%)	2 / 84 (2.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASTHENIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUCOSAL INFLAMMATION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DISEASE PROGRESSION			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHILLS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
DRUG HYPERSENSITIVITY			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 97 (0.00%)	2 / 84 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
IMMUNE-MEDIATED LUNG DISEASE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS ASPIRATION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
NEUTROPHIL COUNT DECREASED			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
ANIMAL BITE			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HUMERUS FRACTURE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
PERICARDIAL EFFUSION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC TAMPONADE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 97 (0.00%)	2 / 84 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
PERIPHERAL SENSORY NEUROPATHY			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUROPATHY PERIPHERAL			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIC CEREBRAL INFARCTION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL INFARCTION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	0 / 97 (0.00%)	2 / 84 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
GASTROINTESTINAL DISORDER			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUMPING SYNDROME			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	5 / 97 (5.15%)	2 / 84 (2.38%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	5 / 97 (5.15%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
GASTROINTESTINAL TOXICITY				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
IMMUNE-MEDIATED ENTEROCOLITIS				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	3 / 97 (3.09%)	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 3	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
ILEUS				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
HAEMORRHOIDAL HAEMORRHAGE				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
GASTROESOPHAGEAL REFLUX DISEASE				
alternative dictionary used: MedDRA 25				
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
INTESTINAL OBSTRUCTION				
alternative dictionary used: MedDRA 25				

subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINAL OBSTRUCTION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 97 (0.00%)	2 / 84 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL STENOSIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS ACUTE			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	2 / 84 (2.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 97 (0.00%)	2 / 84 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
AUTOIMMUNE HEPATITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTRANSAMINASAEMIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMMUNE-MEDIATED HEPATITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
DERMATITIS ALLERGIC			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
URINARY RETENTION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC KIDNEY DISEASE			

alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE KIDNEY INJURY			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
HYPOPHYSITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTHYROIDISM			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOPITUITARISM			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHRITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CERVICAL SPINAL STENOSIS			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ABSCCESS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERIAL INFECTION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTERITIS INFECTIOUS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL INFECTION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN INFECTION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTION			
alternative dictionary used: MedDRA 25			

subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DIABETIC METABOLIC DECOMPENSATION			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETIC KETOACIDOSIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACIDOSIS			
alternative dictionary used: MedDRA 25			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Experimental arm	Standard arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	95 / 97 (97.94%)	81 / 84 (96.43%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
MALIGNANT FRACTURE			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
CYST IN LEG			
alternative dictionary used: CTCAE 5.0			

subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
PERITONEAL CARCINOMATOSIS			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
TUMOR PAIN			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
SUSPECTED BONE METASTASES			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
VASCULITIS			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
HOT FLASHES			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)	
occurrences (all)	2	0	
HYPERTENSION			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	6 / 97 (6.19%)	0 / 84 (0.00%)	
occurrences (all)	9	0	
HYPOTENSION			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	3 / 84 (3.57%)	
occurrences (all)	1	3	
PHLEBITIS			
alternative dictionary used: CTCAE 5.0			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>SUPERFICIAL THROMBOPHLEBITIS</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>THROMBOEMBOLIC EVENT</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 97 (0.00%)</p> <p>0</p> <p>1 / 97 (1.03%)</p> <p>1</p> <p>2 / 97 (2.06%)</p> <p>3</p>	<p>1 / 84 (1.19%)</p> <p>1</p> <p>0 / 84 (0.00%)</p> <p>0</p> <p>1 / 84 (1.19%)</p> <p>1</p>	
<p>Surgical and medical procedures</p> <p>WOUND HEALING DEFICIT</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 97 (1.03%)</p> <p>1</p>	<p>0 / 84 (0.00%)</p> <p>0</p>	
<p>General disorders and administration site conditions</p> <p>EXERCISE INTOLERANCE</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>EDEMA LIMBS</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>EDEMA FACE</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>DETERIORATION OF GENERAL CONDITION</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>COLD INTOLERANCE</p> <p>alternative dictionary used: CTCAE 5.0</p>	<p>1 / 97 (1.03%)</p> <p>1</p> <p>4 / 97 (4.12%)</p> <p>4</p> <p>1 / 97 (1.03%)</p> <p>1</p> <p>1 / 97 (1.03%)</p> <p>1</p>	<p>0 / 84 (0.00%)</p> <p>0</p> <p>3 / 84 (3.57%)</p> <p>4</p> <p>0 / 84 (0.00%)</p> <p>0</p> <p>0 / 84 (0.00%)</p> <p>0</p>	

subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	1
CLINICAL PROGRESSIVE DISEASE		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	2	0
CHILLS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	3 / 97 (3.09%)	1 / 84 (1.19%)
occurrences (all)	4	1
FACIAL PAIN		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	2
WORSENING OF GENERAL CONDITION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
PAIN		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	2 / 97 (2.06%)	1 / 84 (1.19%)
occurrences (all)	2	1
NON-CARDIAC CHEST PAIN		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	2 / 97 (2.06%)	1 / 84 (1.19%)
occurrences (all)	2	1
MUCOSITIS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	1
INFUSION RELATED REACTION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0

<p>HEADACHE</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 97 (1.03%)</p> <p>1</p>	<p>0 / 84 (0.00%)</p> <p>0</p>	
<p>FLU LIKE SYMPTOMS</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 97 (0.00%)</p> <p>0</p>	<p>2 / 84 (2.38%)</p> <p>2</p>	
<p>FEVER</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>15 / 97 (15.46%)</p> <p>18</p>	<p>5 / 84 (5.95%)</p> <p>7</p>	
<p>FATIGUE</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>48 / 97 (49.48%)</p> <p>66</p>	<p>37 / 84 (44.05%)</p> <p>54</p>	
<p>Immune system disorders</p> <p>SARCOIDOSIS</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 97 (1.03%)</p> <p>1</p>	<p>0 / 84 (0.00%)</p> <p>0</p>	
<p>ALLERGIC REACTION</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 97 (0.00%)</p> <p>0</p>	<p>4 / 84 (4.76%)</p> <p>4</p>	
<p>Reproductive system and breast disorders</p> <p>ERECTILE DYSFUNCTION</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 97 (0.00%)</p> <p>0</p>	<p>1 / 84 (1.19%)</p> <p>1</p>	
<p>Respiratory, thoracic and mediastinal disorders</p> <p>SORE THROAT</p> <p>alternative dictionary used: CTCAE 5.0</p>			

subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
ALLERGIC RHINITIS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
COMMON COLD		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)
occurrences (all)	2	0
COMMON COLD SYMTOMS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
COUGH		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	9 / 97 (9.28%)	2 / 84 (2.38%)
occurrences (all)	11	2
DYSPNEA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	3 / 97 (3.09%)	2 / 84 (2.38%)
occurrences (all)	4	3
EPISTAXIS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	5 / 84 (5.95%)
occurrences (all)	3	6
HICCUPS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	1
HOARSENESS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	1

INFLAMED MUCOUS MEMBRANE IN THE NOSE			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
PLEURAL EFFUSION			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	1 / 84 (1.19%)	
occurrences (all)	1	2	
PNEUMONITIS			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	10 / 97 (10.31%)	0 / 84 (0.00%)	
occurrences (all)	15	0	
POSTNASAL DRIP			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
PRODUCTIVE COUGH			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
RHINITIS - NON INFECTIVE			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
RHINORRHEA			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	1 / 84 (1.19%)	
occurrences (all)	1	1	
SARCOIDOSIS			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			

<p>CONFUSION</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>DEPRESSION</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>INSOMNIA</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>LOW MOOD</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ANXIETY</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>			
	1 / 97 (1.03%)	0 / 84 (0.00%)	
	2	0	
	2 / 97 (2.06%)	0 / 84 (0.00%)	
	2	0	
	8 / 97 (8.25%)	2 / 84 (2.38%)	
	8	3	
	0 / 97 (0.00%)	1 / 84 (1.19%)	
	0	1	
	1 / 97 (1.03%)	1 / 84 (1.19%)	
	1	1	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	10 / 97 (10.31%)	0 / 84 (0.00%)	
occurrences (all)	27	0	
ALKALINE PHOSPHATASE INCREASED			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	3 / 97 (3.09%)	2 / 84 (2.38%)	
occurrences (all)	4	2	
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	10 / 97 (10.31%)	0 / 84 (0.00%)	
occurrences (all)	21	0	
BLOOD BILIRUBIN INCREASED			

alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
BLOOD CORTICOTROPHIN DECREASED			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
BLOOD LACTATE DEHYDROGENASE INCREASED			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
CPK INCREASED			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
CREATININE INCREASED			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	3 / 97 (3.09%)	0 / 84 (0.00%)	
occurrences (all)	3	0	
CRP INCREASED			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
ELECTROLYTE IMBALANCE			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
FOLINAT ACID DECREASE			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
GGT INCREASED			
alternative dictionary used: CTCAE 5.0			

subjects affected / exposed	2 / 97 (2.06%)	1 / 84 (1.19%)
occurrences (all)	4	1
GRANULOCYTOPENIA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	3
HYPERTRANSAMINASEMIA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)
occurrences (all)	10	0
HYPERTRANSAMINEMIA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
INTERMITTENT LEUKOCYTOSIS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
LIPASE INCREASED		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	2	0
NEUTROPHIL COUNT DECREASED		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	5 / 97 (5.15%)	33 / 84 (39.29%)
occurrences (all)	8	57
PLATELET COUNT DECREASED		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	3 / 97 (3.09%)	6 / 84 (7.14%)
occurrences (all)	8	9
SERUM AMYLASE INCREASED		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0

THYROID STIMULATING HORMONE INCREASED			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
TRANSAMINASE INCREASE			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
TRANSAMINASE INCREASED			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
TSH DECREASED			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	3	0	
WEIGHT GAIN			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
WEIGHT LOSS			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	6 / 97 (6.19%)	7 / 84 (8.33%)	
occurrences (all)	8	11	
WHITE BLOOD CELL DECREASED			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	10 / 84 (11.90%)	
occurrences (all)	4	19	
LYMPHOCYTE COUNT DECREASED			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			

PEJ LEAKAGE		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	2	0
INFUSION RELATED REACTION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	1 / 84 (1.19%)
occurrences (all)	1	1
FRACTURE		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
ESOPHAGEAL ANASTOMOTIC LEAK		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
BURN		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
BRUISING		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	2 / 84 (2.38%)
occurrences (all)	0	2
A BITE WOUND INFLICTED BY A DOG		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
PAIN AT THE SURGICAL SUTURE		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
PULLING OUT PEJ AFTER FALL		
alternative dictionary used: CTCAE 5.0		

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>SEROMA</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>WOUND INCISED CONTUSED</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 97 (1.03%)</p> <p>1</p> <p>1 / 97 (1.03%)</p> <p>1</p> <p>1 / 97 (1.03%)</p> <p>1</p>	<p>0 / 84 (0.00%)</p> <p>0</p> <p>0 / 84 (0.00%)</p> <p>0</p> <p>0 / 84 (0.00%)</p> <p>0</p>	
<p>Cardiac disorders</p> <p>CORONARY ARTERY DISEASE</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>TACHYCARDIA</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ATRIAL FIBRILLATION</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>HEART FAILURE</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>PALPITATIONS</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>PERICARDIAL EFFUSION</p> <p>alternative dictionary used: CTCAE 5.0</p>	<p>0 / 97 (0.00%)</p> <p>0</p> <p>1 / 97 (1.03%)</p> <p>1</p> <p>1 / 97 (1.03%)</p> <p>1</p> <p>0 / 97 (0.00%)</p> <p>0</p> <p>0 / 97 (0.00%)</p> <p>0</p>	<p>1 / 84 (1.19%)</p> <p>1</p> <p>0 / 84 (0.00%)</p> <p>0</p> <p>2 / 84 (2.38%)</p> <p>2</p> <p>1 / 84 (1.19%)</p> <p>1</p> <p>1 / 84 (1.19%)</p> <p>1</p>	

subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
PERICARDIAL TAMPONADE			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
RIGHT BUNDLE BRANCH BLOCK			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
SINUS BRADYCARDIA			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
SINUS TACHYCARDIA			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
CARDIOMYOPATHY			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
VENTRICULAR ARRHYTHMIA			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
STROKE			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	3	0	
COGNITIVE DISTURBANCE			
alternative dictionary used: CTCAE 5.0			

subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
DIZZINESS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	3 / 97 (3.09%)	3 / 84 (3.57%)
occurrences (all)	3	4
DYSARTHRIA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	1
DYSESTHESIA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
DYSGEUSIA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	4 / 84 (4.76%)
occurrences (all)	1	4
DYSPHAGIA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	1
HEADACHE		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	10 / 97 (10.31%)	4 / 84 (4.76%)
occurrences (all)	11	4
HYPOESTHESIA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	2 / 84 (2.38%)
occurrences (all)	0	2
LOSS OF CONTACT		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	2

NEURALGIA alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	1 / 97 (1.03%)	0 / 84 (0.00%)	
	1	0	
PARESTHESIA alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	7 / 97 (7.22%)	9 / 84 (10.71%)	
	7	12	
PERIPHERAL MOTOR NEUROPATHY alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	1 / 97 (1.03%)	1 / 84 (1.19%)	
	1	1	
PERIPHERAL SENSORY NEUROPATHY alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	8 / 97 (8.25%)	24 / 84 (28.57%)	
	11	39	
PRESYNCOPE alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	0 / 97 (0.00%)	1 / 84 (1.19%)	
	0	1	
TREMOR alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	1 / 97 (1.03%)	0 / 84 (0.00%)	
	1	0	
Blood and lymphatic system disorders			
LEUKOCYTOSIS alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	1 / 97 (1.03%)	1 / 84 (1.19%)	
	1	1	
IRON DEFICIENCY ANEMIA alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	1 / 97 (1.03%)	0 / 84 (0.00%)	
	1	0	
FEBRILE NEUTROPENIA alternative dictionary used: CTCAE 5.0			

subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	2 / 84 (2.38%) 2	
EOSINOPHILIA alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	2 / 97 (2.06%) 3	0 / 84 (0.00%) 0	
ANEMIA alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	9 / 97 (9.28%) 12	11 / 84 (13.10%) 12	
Ear and labyrinth disorders VERTIGO alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	2 / 97 (2.06%) 3	0 / 84 (0.00%) 0	
TINNITUS alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	2 / 97 (2.06%) 2	0 / 84 (0.00%) 0	
MUFFLED HEARING alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	0 / 97 (0.00%) 0	1 / 84 (1.19%) 1	
HEARING IMPAIRED alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	0 / 84 (0.00%) 0	
EAR PAIN alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	1 / 97 (1.03%) 1	0 / 84 (0.00%) 0	
Eye disorders DRY EYE alternative dictionary used: CTCAE 5.0			

subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)	
occurrences (all)	2	0	
DOUBLE VISION			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
BLURRED VISION			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	3 / 97 (3.09%)	1 / 84 (1.19%)	
occurrences (all)	3	1	
EYE PAIN			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	1 / 84 (1.19%)	
occurrences (all)	1	1	
VISION DECREASED			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	1 / 84 (1.19%)	
occurrences (all)	1	1	
WATERING EYES			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
XEROPHTHALMIA			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
STY			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
DYSPEPSIA			
alternative dictionary used: CTCAE 5.0			

subjects affected / exposed	3 / 97 (3.09%)	0 / 84 (0.00%)
occurrences (all)	3	0
ABDOMINAL PAIN		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	23 / 97 (23.71%)	10 / 84 (11.90%)
occurrences (all)	35	15
ANAL FISSURE		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
ASCITES		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	1
BLOATING		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	2 / 97 (2.06%)	2 / 84 (2.38%)
occurrences (all)	2	2
CHOLANGITIS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
DUMPING SYNDROME		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	2 / 97 (2.06%)	1 / 84 (1.19%)
occurrences (all)	2	1
DRY MOUTH		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	4 / 97 (4.12%)	0 / 84 (0.00%)
occurrences (all)	4	0
DIARRHEA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	43 / 97 (44.33%)	53 / 84 (63.10%)
occurrences (all)	81	86

COPROSTASIS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	2	0
CONSTIPATION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	7 / 97 (7.22%)	4 / 84 (4.76%)
occurrences (all)	11	6
COLONIC OBSTRUCTION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)
occurrences (all)	2	0
COLITIS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	11 / 97 (11.34%)	0 / 84 (0.00%)
occurrences (all)	23	0
ILEAL OBSTRUCTION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	2 / 84 (2.38%)
occurrences (all)	0	2
ILEUS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	3	0
DYSPHAGIA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	3 / 97 (3.09%)	6 / 84 (7.14%)
occurrences (all)	3	7
ENTEROCOLITIS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
EPIGASTRIC INTERMITTENT FEELING OF PRESSURE		
alternative dictionary used: CTCAE 5.0		

subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	2
ESOPHAGEAL PAIN		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	1
ESOPHAGEAL STENOSIS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)
occurrences (all)	9	0
FAT STOOLS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
FATTY STOOLS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
FLATULENCE		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	2 / 84 (2.38%)
occurrences (all)	2	3
GASTRITIS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)
occurrences (all)	2	0
GASTROESOPHAGEAL REFLUX DISEASE		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	10 / 97 (10.31%)	7 / 84 (8.33%)
occurrences (all)	12	7
GASTROINTESTINAL TOXICITY		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	2

HEARTBURN		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	1
HEMORRHOIDAL HEMORRHAGE		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	2
HEMORRHOIDS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	2 / 84 (2.38%)
occurrences (all)	1	3
SMALL INTESTINAL OBSTRUCTION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	2 / 97 (2.06%)	1 / 84 (1.19%)
occurrences (all)	4	1
TOOTHACHE		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)
occurrences (all)	2	0
RECTAL TENESMUS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
RECTAL PAIN		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
PANCREATITIS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	3 / 97 (3.09%)	0 / 84 (0.00%)
occurrences (all)	3	0
NAUSEA		
alternative dictionary used: CTCAE 5.0		

subjects affected / exposed	21 / 97 (21.65%)	34 / 84 (40.48%)
occurrences (all)	30	53
MUCOSITIS ORAL		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	2 / 97 (2.06%)	7 / 84 (8.33%)
occurrences (all)	2	10
MUCOSITIS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	1
MOUTH SORE		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
INTESTINAL VOLVULUS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
SOFT STOOL		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
STEATORRHEA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	1 / 84 (1.19%)
occurrences (all)	1	2
STEATORRHOEA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
STOMACH PAIN		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	2	0

<p>SIALORRHEA</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 97 (2.06%)</p> <p>2</p>	<p>0 / 84 (0.00%)</p> <p>0</p>	
<p>WOUND IN THE LIPS</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 97 (1.03%)</p> <p>1</p>	<p>0 / 84 (0.00%)</p> <p>0</p>	
<p>VOMITING</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>10 / 97 (10.31%)</p> <p>13</p>	<p>10 / 84 (11.90%)</p> <p>14</p>	
<p>TRANSVERSE TOOTH FRACTURE</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 97 (1.03%)</p> <p>1</p>	<p>0 / 84 (0.00%)</p> <p>0</p>	
<p>Hepatobiliary disorders</p> <p>CHOLESTASIS</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 97 (2.06%)</p> <p>2</p>	<p>0 / 84 (0.00%)</p> <p>0</p>	
<p>HEPATITIS</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 97 (4.12%)</p> <p>9</p>	<p>0 / 84 (0.00%)</p> <p>0</p>	
<p>IMMUNE RELATED HEPATITIS</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 97 (2.06%)</p> <p>2</p>	<p>0 / 84 (0.00%)</p> <p>0</p>	
<p>IMMUNE-MEDIATED HEPATITIS</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 97 (1.03%)</p> <p>1</p>	<p>0 / 84 (0.00%)</p> <p>0</p>	
<p>TRANSAMINASES INCREASED</p> <p>alternative dictionary used: CTCAE 5.0</p>			

subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
TRANSAMINITIS			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	2	0	
HEPATIC CYTOLYSIS			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
ALOPECIA			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	6 / 84 (7.14%)	
occurrences (all)	2	6	
RASH ACNEIFORM			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	4 / 97 (4.12%)	1 / 84 (1.19%)	
occurrences (all)	4	1	
CONTACT DERMATITIS, BOTH HANDS			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
DRY SKIN			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	2 / 97 (2.06%)	4 / 84 (4.76%)	
occurrences (all)	3	4	
ECZEMA			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	2 / 97 (2.06%)	1 / 84 (1.19%)	
occurrences (all)	2	1	
ERYTHEMA MULTIFORME			
alternative dictionary used: CTCAE 5.0			

subjects affected / exposed	3 / 97 (3.09%)	0 / 84 (0.00%)
occurrences (all)	3	0
ERYTHEMA, LEFT ARM AROUND PICC LINE		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
ERYTHRODERMA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	1
EXCORIATION OF THE RIGHT CLAVICLE		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
HYPERKERATOTIC RHAGADIFORM HAND ECZEMA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
IMMUNE-INDUCED SKIN PATHOLOGY		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
NAIL CHANGES		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	1 / 84 (1.19%)
occurrences (all)	1	1
NAIL RIDGING		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	1 / 84 (1.19%)
occurrences (all)	1	1
PALMAR-PLANTAR ERYTHRODYSESTHESIA SYNDROME		
alternative dictionary used: CTCAE 5.0		

subjects affected / exposed	0 / 97 (0.00%)	3 / 84 (3.57%)
occurrences (all)	0	4
PRURITUS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	24 / 97 (24.74%)	1 / 84 (1.19%)
occurrences (all)	34	1
PSORIASIS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)
occurrences (all)	2	0
RASH		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
RASH (NOS)		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
BULLOUS DERMATITIS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
RASH MACULO-PAPULAR		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	14 / 97 (14.43%)	1 / 84 (1.19%)
occurrences (all)	20	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, RASH		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
SKIN RASH		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0

<p>SUBCUTANEOUS ABSCESS</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>URTICARIA</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>VITILIGO</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</p> <p>alternative dictionary used: CTCAE 5.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>			
	1 / 97 (1.03%)	0 / 84 (0.00%)	
	1	0	
	1 / 97 (1.03%)	0 / 84 (0.00%)	
	1	0	
	1 / 97 (1.03%)	0 / 84 (0.00%)	
	1	0	
	1 / 97 (1.03%)	0 / 84 (0.00%)	
	1	0	
Renal and urinary disorders			
URINARY STONES			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
ACUTE KIDNEY FAILURE			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
ACUTE KIDNEY INJURY			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
CHRONIC KIDNEY DISEASE			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)	
occurrences (all)	4	0	
CYSTITIS NONINFECTIVE			
alternative dictionary used: CTCAE			

5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
DYSURIA			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
HEMATURIA			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
NEPHRITIS			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)	
occurrences (all)	2	0	
PROTEINURIA			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
RENAL INSUFFICIENCY			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
URINARY FREQUENCY			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
URINARY INCONTINENCE			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
URINARY RETENTION			
alternative dictionary used: CTCAE 5.0			

subjects affected / exposed	1 / 97 (1.03%)	1 / 84 (1.19%)	
occurrences (all)	1	1	
URINARY TRACT OBSTRUCTION			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)	
occurrences (all)	2	0	
Endocrine disorders			
ADRENALITIS			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
ADRENAL INSUFFICIENCY			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	5 / 97 (5.15%)	0 / 84 (0.00%)	
occurrences (all)	6	0	
HYPERTHYROIDISM			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	20 / 97 (20.62%)	2 / 84 (2.38%)	
occurrences (all)	22	2	
THYROIDITIS			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
HYPOTHYROIDISM			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	20 / 97 (20.62%)	1 / 84 (1.19%)	
occurrences (all)	28	1	
HYPOPITUITARISM			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	3 / 97 (3.09%)	0 / 84 (0.00%)	
occurrences (all)	4	0	
HYPOPHYSITIS			
alternative dictionary used: CTCAE 5.0			

subjects affected / exposed	8 / 97 (8.25%)	0 / 84 (0.00%)	
occurrences (all)	11	0	
Musculoskeletal and connective tissue disorders			
BONE PAIN			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
ALGIC SYNDROME			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
ARTHRALGIA			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	9 / 97 (9.28%)	0 / 84 (0.00%)	
occurrences (all)	10	0	
ARTHRITIS			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	5 / 97 (5.15%)	0 / 84 (0.00%)	
occurrences (all)	7	0	
ARTHROMYALGIA			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
BACK PAIN			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	9 / 97 (9.28%)	3 / 84 (3.57%)	
occurrences (all)	10	3	
BURSITIS IN THE RIGHT FOREARM			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
CHEST WALL PAIN			
alternative dictionary used: CTCAE 5.0			

subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
COLD TOE		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	1
CRITICAL-ILLNESS-MYOPATHIE		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
GENERALIZED MUSCLE WEAKNESS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	2 / 97 (2.06%)	2 / 84 (2.38%)
occurrences (all)	2	2
GOUT ATTACK		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
GOUT ATTACK LEFT KNEE		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
MUSCLE WEAKNESS UPPER LIMB		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	3	0
MYALGIA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	5 / 97 (5.15%)	1 / 84 (1.19%)
occurrences (all)	5	1
NECK PAIN		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0

PAIN IN EXTREMITY alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	6 / 97 (6.19%)	1 / 84 (1.19%)	
	7	1	
PULLED GROIN MUSCLE alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	0 / 97 (0.00%)	1 / 84 (1.19%)	
	0	1	
RIGHT ILIAC FOSSA PAIN alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	1 / 97 (1.03%)	0 / 84 (0.00%)	
	1	0	
SPINE PAIN alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	1 / 97 (1.03%)	0 / 84 (0.00%)	
	1	0	
TENDONITIS alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	1 / 97 (1.03%)	0 / 84 (0.00%)	
	1	0	
CERVICAL SPINAL STENOSIS C5-6 AND C6-7 alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all)	1 / 97 (1.03%)	0 / 84 (0.00%)	
	1	0	
Infections and infestations COVID-19 alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all) COVID INFECTION alternative dictionary used: CTCAE 5.0 subjects affected / exposed occurrences (all) COVID 19 INFECTION alternative dictionary used: CTCAE			
	1 / 97 (1.03%)	0 / 84 (0.00%)	
	1	0	
	1 / 97 (1.03%)	0 / 84 (0.00%)	
	1	0	

5.0		
subjects affected / exposed	3 / 97 (3.09%)	0 / 84 (0.00%)
occurrences (all)	3	0
COLD SYMPTOMS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
CATHETER RELATED INFECTION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)
occurrences (all)	2	0
BRONCHIAL INFECTION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	2 / 84 (2.38%)
occurrences (all)	1	2
APPENDICITIS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
ABSCESS RIGHT THORACIC		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
COVID-19 INFECTION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	4 / 97 (4.12%)	2 / 84 (2.38%)
occurrences (all)	4	2
COVID-19 VIRUS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	1
PYELONEFRITIS-CYSTITIS		
alternative dictionary used: CTCAE 5.0		

subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
POSITIVE ANTIGENURIA FOR PNEUMOCOCCUS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	1
PARONYCHIA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	1 / 84 (1.19%)
occurrences (all)	1	1
OTITIS MEDIA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	2	0
OTITIS EXTERNA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
LUNG INFECTION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	5 / 97 (5.15%)	2 / 84 (2.38%)
occurrences (all)	7	3
LOWER RESPIRATORY TRACT INFECTION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	3	0
KIDNEY INFECTION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
INFLAMMATORY NIDUS CHEST RIGHT SITE		
alternative dictionary used: CTCAE 5.0		

subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
INFECTION WITHOUT FOCUS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
INFECTION OF UNCLEAR ORIGIN		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
INFECTION JEJUNAL TUBE		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	1
HERPES SIMPLEX REACTIVATION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	1 / 84 (1.19%)
occurrences (all)	1	1
GASTROENTERITIS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	1
GALLBLADDER INFECTION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
CYSTITIS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
RASH PUSTULAR		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0

WOUND INFECTION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	2	0
VIRAL INFECTION (FLU)		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	1
URINARY TRACT INFECTION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	4 / 97 (4.12%)	1 / 84 (1.19%)
occurrences (all)	7	2
UPPER RESPIRATORY INFECTION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	2 / 84 (2.38%)
occurrences (all)	1	2
UNSPECIFIED BACTERIAL INFECTION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0
SKIN INFECTION		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	1 / 84 (1.19%)
occurrences (all)	1	1
SHINGLES		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)
occurrences (all)	3	0
SEPSIS		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)
occurrences (all)	2	0
SARS COVID-19 INFECTION		
alternative dictionary used: CTCAE 5.0		

subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
HYPERGLYCEMIA DECOMPENSATION OF DIABETES			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
ACIDOSIS			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)	
occurrences (all)	3	0	
ANOREXIA			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	17 / 97 (17.53%)	7 / 84 (8.33%)	
occurrences (all)	20	9	
DEHYDRATION			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
DIABETIC KETOACIDOSIS			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
HYPERGLYCEMIA			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	2 / 84 (2.38%)	
occurrences (all)	1	5	
HYPERKALEMIA			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)	
occurrences (all)	3	0	
HYPERPHOSPHATEMIA			
alternative dictionary used: CTCAE 5.0			

subjects affected / exposed	2 / 97 (2.06%)	0 / 84 (0.00%)
occurrences (all)	2	0
HYPOALBUMINEMIA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	1 / 84 (1.19%)
occurrences (all)	1	1
HYPOCALCEMIA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	3	0
HYPOGLYCEMIA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	2	0
HYPOKALEMIA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	7 / 97 (7.22%)	2 / 84 (2.38%)
occurrences (all)	11	3
HYPOMAGNESEMIA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)
occurrences (all)	0	1
HYPONATREMIA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	4	0
HYPOPHOSPHATEMIA		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	3 / 97 (3.09%)	0 / 84 (0.00%)
occurrences (all)	3	0
IRON DEFICIENCY		
alternative dictionary used: CTCAE 5.0		
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)
occurrences (all)	1	0

POSTPRANDIAL SYNDROME			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
STORAGE IRON DEFICIENCY			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	1 / 97 (1.03%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
HYPERLIPIDEMIA			
alternative dictionary used: CTCAE 5.0			
subjects affected / exposed	0 / 97 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2018	<p>SCIENTIFIC AMENDMENT 1</p> <ul style="list-style-type: none"> -Amendment of PISIC following new GDPR Regulation in May 2018. -Amendment of dosing of immunotherapy in the experimental arm (Protocol and PISIC) based on DMC recommendation to close the Nivolumab 1 mg/kg + ipilimumab 3 mg/kg of the CHECKMATE 649 study. Dosing is changed back to IB recommendations: Nivolumab 3 mg/kg + ipilimumab 1 mg/kg. -Clarification of the assessment schedule.
06 April 2020	<p>SCIENTIFIC AMENDMENT 2</p> <ul style="list-style-type: none"> -Added text discussing the balance between benefit versus life-threatening and fatal SARs listed for nivo+ipi in SmpC (requested by NL and and Norway competent authorities) -Added possible men contraception methods (requested by regulatory bodies) -Pregnancy testing for 6 months after EOT added as per IB/SMPC -Positive testing to HIV according to local practice (requested by German regulatory bodies) -Clarification of timelines and time windows for evaluation -Safety updated according to new nivolumab IB -Capecitabine dosage corrected - now aligned with ESMO guidelines
15 October 2020	<ul style="list-style-type: none"> -COVID-19 addendum -Safety guidelines clarified based on safety guidance of the Investigator's brochures (IBs) -Risks and side effects related to nivolumab and ipilimumab updated based on CTFG recommendations (v1.1) -Clarification of timeline of FU assessments by our DM following feedback from sites
03 March 2021	<p>SCIENTIFIC AMENDMENT 4</p> <ul style="list-style-type: none"> -Eligibility criteria: inclusion of patients with prior malignancies provided they have no impact on patient's prognosis -Removal of BP monitoring post immunotherapy infusion except for cycle 1 -Authorization of off-site lab assessments for Biochemistry, hematology, pregnancy, thyroid function, except for Screening assessment -Update of toxicity management algorithms to CTCAE V5 as per ipi IB addendum 01 & 02 -COVID addendum to PISIC: to inform patients about potential measures specific to the COVID health crisis -Update of PIS/IC: mention of Pelvic imaging during treatment and follow for consistency with protocol and database
25 October 2021	<p>SCIENTIFIC AMENDMENT 5</p> <ul style="list-style-type: none"> -Eligibility criteria: inclusion of patients with partial DPD deficiency and clarification of surgery timelines. -Update of toxicity management algorithms as per ipilimumab and nivolumab IBs v24 and v20. -Statistical analysis: Given the low frequencies of patients with R1 resection (17.5%) and receiving other regimen than FLOT (8.3%) and the phase of the study (phase II with no intent for regulatory submission), an unstratified log-rank test will be used for the primary analysis. -Update of pregnancy reporting: Within 12 months (for a female subject) or 9 months (for a female partner of a male subject); possibility to report by e-mail in addition to fax. -Update of PIS/IC: New safety information for nivolumab and ipilimumab; update of duration of contraception.

29 April 2022	SCIENTIFIC AMENDMENT 6 -Clarification of inclusion of partially deficient patients based on SoC testing (genetic or uracil levels) as per request of French CA
05 October 2022	SCIENTIFIC AMENDMENT 7 -Update of PISIC: The investigator brochures of both nivolumab and ipilimumab were updated, leading to Nivo IB v 21.0 and ipilimumab IB v 25.0. The safety language of the study PISIC was updated accordingly. Clarification of duration of pregnancy testing during treatment and after end of treatment depending on treatment arm.
27 January 2023	ADMINISTRATIVE AMENDMENT 8 -To specify TR laboratory -To clarify TR lab responsibilities

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported