Clinical trial results:
REACTION: A phase II study of etoposide and cis/carboplatin with or without pembrolizumab in untreated extensive small cell lung cancer

Summary

EudraCT number	2014-003090-42
Trial protocol	GB IT
Global end of trial date	22 June 2022

Results information

Result version number	v1 (current)
This version publication date	17 July 2024
First version publication date	17 July 2024

Trial information

Trial identification

Sponsor protocol code	1417-LCG

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02580994
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	European Organisation for Research and Treatment of Cancer
Sponsor organisation address	Avenue Emmanuel Mounier 83/11, Brussels, Belgium, 1200
Public contact	Clinical Operations Department, European Organisation for Research and Treatment of Cancer (EORTC), +32 2 774 15 11, regulatory@eortc.be
Scientific contact	Clinical Operations Department, European Organisation for Research and Treatment of Cancer (EORTC), +32 2 774 15 11, regulatory@eortc.be

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 April 2020
Global end of trial reached?	Yes
Global end of trial date	22 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main aim of this study is to evaluate the activity measured by progression free survival (PFS) of pembrolizumab in combination with etoposide and cis/carboplatin followed by pembrolizumab alone (continuation maintenance) versus etoposide and cis/carboplatin alone in chemo-sensitive patients with ED-SCLC.

Protection of trial subjects:

The responsible investigator will ensure that this study is 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 has been written, and the study will be 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 must be approved by the competent ethics committee(s) as required by the applicable

Background therapy:

Combination chemotherapies are the current standard of care for ED-SCLC. The chemotherapy agents commonly available for the treatment of SCLC include cyclophosphamide, doxorubicin, methotrexate, etoposide, vincristine, cisplatin and carboplatin. In this trial, the control arm will involve treatment with a combination of etoposide and carboplatin or cisplatin

Evidence for comparator:

Cisplatin and carboplatin as combination partners for etoposide display a similar efficacy profile in terms of OS, PFS, or ORR (median OS: 9.6 versus 9.4 months; median PFS: 5.5 versus 5.3 months; and ORR: 67 versus 66%, respectively) for patient with Extensive-disease SLCL (Rossi A, Di Maio M, Chiodini P et al. J Clin Oncol 2012).

Actual start date of recruitment	07 February 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	France: 93
Country: Number of subjects enrolled	Italy: 23
Worldwide total number of subjects	125
EEA total number of subjects	116

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)	64
From 65 to 84 years	61
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 07/02/2018 and 31/10/2019, 125 patients with ED-SCLC, unselected for PD-L1, having an objective response after 2 cycles of platinum-etoposide, with PS 0/1 and controlled brain metastases at the time of tumor evaluation were randomized in 3 countries
(France, Italy, United Kingdom).

Pre-assignment

Screening details:

Patients' enrollment followed a two-step process. Upon signing the informed consent, patients were registered and a sample of the tumor, if available, was sent for PD-L1 expression assessment (registration step). After two cycles of chemotherapy, the patient was reassessed to verify eligibility for the randomization (randomization step).

Pre-assignment period milestones

Number of subjects started	169[1]
Number of subjects completed	125

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 3
Reason: Number of subjects	Physician decision: 1
Reason: Number of subjects	No response after induction chemotherapy: 19
Reason: Number of subjects	Patients died before randomization: 9
Reason: Number of subjects	Clinical progression without radiological evidence: 2
Reason: Number of subjects	Patient ineligible for another reason: 10

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Patients who entered the pre-assignment period and are not randomized are screen failures. Reasons for screening failures were provided.

Period 1

Period 1 title	From randomization
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:

4 cycles of cisplatin/carboplatin and etoposide (after the 2 cycles before randomization)

A maximum of 4 cycles of chemotherapy (after randomization) will be administered (6 cycles overall) unless there is tumor progression, unacceptable toxicity, consent withdrawal, or withdrawal from the study at the discretion of the investigator or his/her designated associate(s).

Cross-over at the time of progressive disease according to RECIST 1.1 is allowed for the standard arm.

Arm type	Active comparator

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

Dosage and administration details:

Cisplatin 80 mg/m2 on day 1 (3-weekly cycles for 4 cycles)

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

Dosage and administration details:

Carboplatin AUC 5 IV infusion on day 1 [the dose of carboplatin will be determined for each cycle using the Calvert's formula (carboplatin dose (mg) = target AUC 5 x estimated glomerular filtration rate (eGFR, mL/min) + 25)] (3-weekly cycles for 4 cycles)

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

Dosage and administration details:

Etoposide 100 mg/m2 IV infusion on day 1, 2 and 3 (3-weekly cycles for 4 cycles)

Arm title	Experimental arm

Arm description:

Pembrolizumab (MK-3475) in combination with cisplatin/carboplatin and etoposide for 4 cycles (after the 2 cycles before randomization) and pembrolizumab (MK-3475) to be continued alone as maintenance until a total of 35 cycles, progressive disease (PD) or death.

Dosing cycles of pembrolizumab will continue until administration of a total of 35 cycles, tumor progression, unacceptable toxicity, consent withdrawal, or withdrawal from the study at the discretion of the investigator or his/her designated associate(s) occurs.
If at the time of disease progression, the patient still has a major clinical benefit, the patient is allowed to continue receiving the treatment if the investigator thinks this is in the best interest of the patient up to a total of 35 cycles of pembrolizumab.

Rechallenge with pembrolizumab alone is allowed with a maximum of 17 cycles of pembrolizumab after disease progression.

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

Dosage and administration details:

Cisplatin 80 mg/m2 on day 1 (3-weekly cycles for 4 cycles)

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

Dosage and administration details:

Carboplatin AUC 5 IV infusion on day 1 [the dose of carboplatin will be determined for each cycle using the Calvert's formula (carboplatin dose (mg) = target AUC 5 x estimated glomerular filtration rate (eGFR, mL/min) + 25)] (3-weekly cycles for 4 cycles)

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

Dosage and administration details:

Etoposide 100 mg/m2 IV infusion on day 1, 2 and 3 (3-weekly cycles for 4 cycles)

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

Dosage and administration details:

Pembrolizumab (MK-3475) will be administered via IV infusion at the dose of 200 mg on day 1 (30 minutes: -5/+10 min) every three weeks

Number of subjects in period 1	Standard arm	Experimental arm
Started	64	61
Completed	56	44
Not completed	8	17
Adverse event, serious fatal	1	1
On treatment or end of treatment form not received	1	8
Adverse event, non-fatal	4	8
Death not due to malignant disease or AE	1	-
Missing reason	1	-

Period 2

Period 2 title	Cross-over to pembrolizumab
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Standard arm

Arm description:

Cross-over at the time of progressive disease according to RECIST 1.1 is allowed for the standard arm.

Patients assigned to the standard arm who experience disease progression at least 3 months after the last dose of chemotherapy treatment and meet all crossover criteria, will have the opportunity to crossover to cisplatin/carboplatin and etoposide and pembrolizumab every three weeks for a maximum of 6 cycles followed by pembrolizumab alone every three weeks until 35 cycles are administered or disease progression.

Arm type	Active comparator

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

Dosage and administration details:

Cisplatin 80 mg/m2 on day 1 (3-weekly cycles for 4 cycles)

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

Dosage and administration details:

Carboplatin AUC 5 IV infusion on day 1 [the dose of carboplatin will be determined for each cycle using the Calvert's formula (carboplatin dose (mg) = target AUC 5 x estimated glomerular filtration rate (eGFR, mL/min) + 25)] (3-weekly cycles for 4 cycles)

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

Dosage and administration details:

Etoposide 100 mg/m2 IV infusion on day 1, 2 and 3 (3-weekly cycles for 4 cycles)

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

Dosage and administration details:

Pembrolizumab (MK-3475) will be administered via IV infusion at the dose of 200 mg on day 1 (30 minutes: -5/+10 min) every three weeks

Number of subjects in period 2[2]	Standard arm
Started	19
Completed	14
Not completed	5
Adverse event, serious fatal	1
On treatment or treatment form not received	3
Adverse event, non-fatal	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Cross-over was allowed at the time of progressive disease according to RECIST 1.1 in the standard arm. Cross-over was therefore only applicable to the standard arm and to patients experiencing progressive disease.

Baseline characteristics

Reporting groups

Reporting group title	Standard arm

Reporting group description:

4 cycles of cisplatin/carboplatin and etoposide (after the 2 cycles before randomization)

A maximum of 4 cycles of chemotherapy (after randomization) will be administered (6 cycles overall) unless there is tumor progression, unacceptable toxicity, consent withdrawal, or withdrawal from the study at the discretion of the investigator or his/her designated associate(s).

Cross-over at the time of progressive disease according to RECIST 1.1 is allowed for the standard arm.

Reporting group title	Experimental arm

Reporting group description:

Pembrolizumab (MK-3475) in combination with cisplatin/carboplatin and etoposide for 4 cycles (after the 2 cycles before randomization) and pembrolizumab (MK-3475) to be continued alone as maintenance until a total of 35 cycles, progressive disease (PD) or death.

Dosing cycles of pembrolizumab will continue until administration of a total of 35 cycles, tumor progression, unacceptable toxicity, consent withdrawal, or withdrawal from the study at the discretion of the investigator or his/her designated associate(s) occurs.
If at the time of disease progression, the patient still has a major clinical benefit, the patient is allowed to continue receiving the treatment if the investigator thinks this is in the best interest of the patient up to a total of 35 cycles of pembrolizumab.

Rechallenge with pembrolizumab alone is allowed with a maximum of 17 cycles of pembrolizumab after disease progression.

Reporting group values	Standard arm	Experimental arm	Total
Number of subjects	64	61	125
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	63.5	65	
inter-quartile range (Q1-Q3)	58 to 68.5	60 to 69	-
Gender categorical Units: Subjects			
Female	28	17	45
Male	36	44	80

ECOG performance status Units: Subjects			
ECOG 0	24	18	42
ECOG 1	37	41	78
ECOG 2	2	2	4
ECOG 3	1	0	1
Cigarette usage Units: Subjects			
Never	3	0	3
Current	21	22	43
Former	40	39	79
Known CNS metastases (before induction chemotherapy) Units: Subjects			
No	57	56	113
Yes, stable	7	5	12
Induction chemotherapy Units: Subjects			
Cisplatin/etoposide	19	18	37
Carboplatin/etoposide	45	43	88
Response to induction Units: Subjects			
Complete response (CR)	1	1	2
Partial response (PR)	63	60	123

End points

End points reporting groups

Reporting group title	Standard arm

Reporting group description:

4 cycles of cisplatin/carboplatin and etoposide (after the 2 cycles before randomization)

A maximum of 4 cycles of chemotherapy (after randomization) will be administered (6 cycles overall) unless there is tumor progression, unacceptable toxicity, consent withdrawal, or withdrawal from the study at the discretion of the investigator or his/her designated associate(s).

Cross-over at the time of progressive disease according to RECIST 1.1 is allowed for the standard arm.

Reporting group title	Experimental arm

Reporting group description:

Pembrolizumab (MK-3475) in combination with cisplatin/carboplatin and etoposide for 4 cycles (after the 2 cycles before randomization) and pembrolizumab (MK-3475) to be continued alone as maintenance until a total of 35 cycles, progressive disease (PD) or death.

Dosing cycles of pembrolizumab will continue until administration of a total of 35 cycles, tumor progression, unacceptable toxicity, consent withdrawal, or withdrawal from the study at the discretion of the investigator or his/her designated associate(s) occurs.
If at the time of disease progression, the patient still has a major clinical benefit, the patient is allowed to continue receiving the treatment if the investigator thinks this is in the best interest of the patient up to a total of 35 cycles of pembrolizumab.

Rechallenge with pembrolizumab alone is allowed with a maximum of 17 cycles of pembrolizumab after disease progression.

Reporting group title	Standard arm

Reporting group description:

Cross-over at the time of progressive disease according to RECIST 1.1 is allowed for the standard arm.

Patients assigned to the standard arm who experience disease progression at least 3 months after the last dose of chemotherapy treatment and meet all crossover criteria, will have the opportunity to crossover to cisplatin/carboplatin and etoposide and pembrolizumab every three weeks for a maximum of 6 cycles followed by pembrolizumab alone every three weeks until 35 cycles are administered or disease progression.

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

Subject analysis set description:

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

Note: The primary analyses of the primary and secondary endpoints will be performed on the per-protocol population. A sensitivity analysis of efficacy based on intent to treat (ITT) population was conducted for PFS and OS in addition to the primary analysis based on per protocol population.

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

Subject analysis set description:

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

Note: The primary analyses of the primary and secondary endpoints will be performed on the per-protocol population. A sensitivity analysis of efficacy based on intent to treat (ITT) population was conducted for PFS and OS in addition to the primary analysis based on per protocol population.

Subject analysis set title	Per protocol population - cross-over
Subject analysis set type	Per protocol

Subject analysis set description:

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

Primary: Progression free survival according to RECIST 1.1

End point title	Progression free survival according to RECIST 1.1

End point description:

Progression Free Survival (PFS) is defined as the time interval between the date of randomization and the date of disease progression according to RECIST 1.1 or death, whichever comes first. If neither event has been observed, then the patient is censored at the date of the last follow up examination.

End point type	Primary

End point timeframe:

Disease evaluation will be performed every six weeks during treatment period and every 3 months during follow up until PD/death 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	64	61	61	58
Units: Months				
median (confidence interval 95%)	5.4 (4.7 to 5.5)	4.6 (4.2 to 5.5)	5.4 (4.7 to 5.6)	4.7 (4.2 to 5.6)

Attachments (see zip file)	Progression free survival - per protocol/PFS_per_protocol.pdf

Statistical analyses

Statistical analysis title	Primary analysis adjusted (per protocol)

Statistical analysis description:

The primary analysis of PFS was performed on the per protocol population. Cox regression (Wald Test) was used to compare the experimental versus the control arms adjusted by the stratification factors in randomization (except for centers) at 1-sided 10% significant level.

Comparison groups	Per protocol population - standard arm v Per protocol population - experimental arm
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1941 [1]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.65
upper limit	1.09

Notes:

[1] - The one-sided p-value for the primary test of a difference in PFS in favor of the experimental arm is 0.1941, not significant at 1-sided 10% significant level.

Statistical analysis title	Sensitivity analysis adjusted (ITT)

Statistical analysis description:

A sensitivity analysis of PFS based on the intent to treat (ITT) population will be conducted in addition to the primary analysis based on the per protocol population.

Comparison groups	Standard arm v Experimental arm
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2304 [2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.68
upper limit	1.11

Notes:

[2] - The one-sided p-value for the primary test of a difference in PFS in favor of the experimental arm is 0.2304, not significant at 1-sided 10% significant level.

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall Survival (OS) is defined as the time interval between the date of randomization and the date of death from any cause. If no event has been observed, then the patient is censored at the last date known to be alive.

End point type	Secondary

End point timeframe:

After the end of treatment, patients will be followed for survival (all arms). Follow-up visits to the hospital and frequency of tumor evaluation will be performed every three months.

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	64	61	61	58
Units: Months				
median (confidence interval 95%)	11.1 (8.3 to 14.4)	12.3 (8.9 to 14.8)	10.4 (8.2 to 12.2)	12.3 (8.9 to 14.8)

Attachments (see zip file)	Overall survival - per protocol/OS_per_protocol.pdf

Statistical analyses

Statistical analysis title	Primary analysis adjusted (per protocol)

Statistical analysis description:

The primary analysis of OS was performed on the per protocol population. Cox regression (Wald Test) was used to compare the experimental versus the control arms adjusted by the stratification factors in

randomization (except for centers) at 1-sided 10% significant level.

Comparison groups	Per protocol population - standard arm v Per protocol population - experimental arm
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0971 [3]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.54
upper limit	1

Notes:

[3] - The one-sided p-value for the test of a difference in OS in favor of the experimental arm is 0.0971.

Statistical analysis title	Sensitivity analysis adjusted (ITT)

Statistical analysis description:

A sensitivity analysis of OS based on the intent to treat (ITT) population will be conducted in addition to the primary analysis based on the per protocol population.

Comparison groups	Standard arm v Experimental arm
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1958 [4]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.61
upper limit	1.1

Notes:

[4] - The one-sided p-value for the test of a difference in OS in favor of the experimental arm is 0.1958.

Secondary: Response according to RECIST 1.1

End point title	Response according to RECIST 1.1

End point description:

All patients will have their BEST OVERALL RESPONSE (BOR) evaluated according to the RECIST 1.1 criteria from the start of treatment until the end of treatment and classified as complete response (CR) or partial response (PR) or stable disease (SD) or progressive disease (PD) or not evaluable or early death according to RECIST 1.1 criteria. Response is CR or PR.

End point type	Secondary

End point timeframe:

Disease evaluation will be performed every six weeks during the treatment period.

End point values	Per protocol population - standard arm	Per protocol population - experimental arm	Per protocol population - cross-over	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	61	58	17	
Units: Subject				
Complete response (CR)	2	3	1	
Partial response (PR)	32	36	6	
Stable disease (SD)	22	15	6	
Progressive disease (PD)	3	3	4	
Inevaluable	1	1	0	
Early death	1	0	0	

Statistical analyses

Statistical analysis title	Primary analysis - comparative

Statistical analysis description:

The analysis of response rate according to RECIST 1.1 will be performed on the per-protocol population.

Comparison groups	Per protocol population - standard arm v Per protocol population - experimental arm
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.1977
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	0.115
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0585
upper limit	0.2886

Notes:

[5] - The response rates in each arm and their 95% confidence intervals will be provided. In addition, response rates in the 2 arms will be compared using a two-sample test at 5% 2-sided level.

Statistical analysis title	Descriptive analysis - standard arm

Statistical analysis description:

The response rates in each arm and their two-sided 95% confidence intervals will be provided.

Comparison groups	Per protocol population - standard arm v Per protocol population - experimental arm v Per protocol population - cross-over
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Proportion
Point estimate	55.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	42.4
upper limit	68.5

Notes:

[6] - This is not a formal comparative analysis between the two arms but a descriptive analysis in each arm and in the standard arm for the cross-over treatment.

Statistical analysis title	Descriptive analysis - experimental arm

Statistical analysis description:

The response rates in each arm and their two-sided 95% confidence intervals will be provided.

Comparison groups	Per protocol population - experimental arm v Per protocol population - standard arm v Per protocol population - cross-over
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	other[7]
Parameter estimate	Proportion
Point estimate	67.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	53.7
upper limit	79

Notes:

[7] - This is not a formal comparative analysis between the two arms but a descriptive analysis in each arm and in the standard arm for the cross-over treatment.

Statistical analysis title	Descriptive analysis - cross-over

Statistical analysis description:

The response rates to the cross-over treatment and their 95% confidence intervals will be provided.

Comparison groups	Per protocol population - cross-over v Per protocol population - standard arm v Per protocol population - experimental arm
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	other[8]
Parameter estimate	Proportion
Point estimate	41.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.4
upper limit	67.1

Notes:

[8] - This is not a formal comparative analysis between the two arms but a descriptive analysis in each arm and in the standard arm for the cross-over treatment.

Secondary: Disease control according to RECIST 1.1

End point title	Disease control according to RECIST 1.1

End point description:

All patients will have their BEST OVERALL RESPONSE (BOR) evaluated according to the RECIST 1.1 criteria from the start of treatment until the end of treatment. Disease control is achieved when BOR is complete response (CR) or partial response (PR) or stable disease (SD).

End point type	Secondary

End point timeframe:

Disease evaluation will be performed every six weeks during the treatment period.

End point values	Per protocol population - standard arm	Per protocol population - experimental arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	58		
Units: Subject				
Yes	56	54		
No	5	4		

Statistical analyses

Statistical analysis title	Descriptive analysis - standard arm

Statistical analysis description:

The disease control rates in each arm and their two-sided 95% confidence intervals will be provided.

Comparison groups	Per protocol population - standard arm v Per protocol population - experimental arm
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other[9]
Parameter estimate	Proportion
Point estimate	91.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	81.9
upper limit	97.3

Notes:

[9] - This is not a formal comparative analysis between the two arms but a descriptive analysis in each arm.

Statistical analysis title	Descriptive analysis - experimental arm

Statistical analysis description:

The disease control rates in each arm and their two-sided 95% confidence intervals will be provided.

Comparison groups	Per protocol population - experimental arm v Per protocol population - standard arm
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other[10]
Parameter estimate	Proportion
Point estimate	93.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	83.3
upper limit	98.1

Notes:

[10] - This is not a formal comparative analysis between the two arms but a descriptive analysis in each arm.

Secondary: Progression free survival according to RECIST 1.1 after cross-over

End point title	Progression free survival according to RECIST 1.1 after cross-over

End point description:

Progression free survival (PFS) after cross-over is defined as the time interval between the start of the cross-over treatment and the date of disease progression according to RECIST 1.1 or death, whichever comes first. If neither event has been observed, then the patient is censored at the date of the last follow up examination.

End point type	Secondary

End point timeframe:

Disease evaluation will be performed every six weeks during cross-over treatment period and every 3 months during follow up until PD/death whichever occurs first.

End point values	Per protocol population - cross-over			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: Months				
median (confidence interval 95%)	6.7 (3.1 to 9.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival at second progression (PFS-2)

End point title	Progression free survival at second progression (PFS-2)

End point description:

PFS-2 is calculated as the time between randomization and the PD or death, not of the current treatment
but the PD after the subsequent treatment thus taking into account the influence of the treatment under investigation on the following treatment line. Details on the events for PFS-2 are given Table 1 (see uploaded attachment).

End point type	Secondary

End point timeframe:

Disease evaluation will be performed every six weeks during treatment period and every 3 months during follow up until PD/death whichever occurs first.

End point values	Per protocol population - standard arm	Per protocol population - experimental arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	61	58		
Units: Months				
median (confidence interval 95%)	9.0 (7.9 to 10.3)	10.3 (7.8 to 13.7)		

Attachments (see zip file)	Table 1. Events for PFS-2/Table 1. Events for PFS-2.pdf PFS-2 per protocol/PFS-2_per_protocol.pdf

Statistical analyses

Statistical analysis title	Primary analysis adjusted (per protocol)

Statistical analysis description:

The primary analysis of PFS-2 was performed on the per protocol population. Cox regression (Wald Test) was used to compare the experimental versus the control arms adjusted by the stratification factors in randomization (except for centers) at 1-sided 10% significant level.

Comparison groups	Per protocol population - standard arm v Per protocol population - experimental arm
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0124 [11]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.44
upper limit	0.8

Notes:

[11] - The one-sided p-value for the primary test of a difference in PFS in favor of the experimental arm is 0.0124, significant at 1-sided 10% significant level.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported from the randomization till the end of treatment (within 30 days after treatment discontinuation).

Adverse event reporting additional description:

CRF for AEs contains pre-specified items + additional boxes for all "other" AEs.
AEs are evaluated using CTC grading, SAEs using MedDra. Non-SAEs have not been collected specifically, all AEs will be reported in non-SAE section.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Experimental arm

Reporting group description:

Pembrolizumab (MK-3475) in combination with cisplatin/carboplatin and etoposide for 4 cycles (after the 2 cycles before randomization) and pembrolizumab (MK-3475) to be continued alone as maintenance until a total of 35 cycles, progressive disease (PD) or death.

Dosing cycles of pembrolizumab will continue until administration of a total of 35 cycles, tumor progression, unacceptable toxicity, consent withdrawal, or withdrawal from the study at the discretion of the investigator or his/her designated associate(s) occurs.
If at the time of disease progression, the patient still has a major clinical benefit, the patient is allowed to continue receiving the treatment if the investigator thinks this is in the best interest of the patient up to a total of 35 cycles of pembrolizumab.

Rechallenge with pembrolizumab alone is allowed with a maximum of 17 cycles of pembrolizumab after disease progression.

Reporting group title	Standard arm

Reporting group description:

4 cycles of cisplatin/carboplatin and etoposide (after the 2 cycles before randomization)

A maximum of 4 cycles of chemotherapy (after randomization) will be administered (6 cycles overall) unless there is tumor progression, unacceptable toxicity, consent withdrawal, or withdrawal from the study at the discretion of the investigator or his/her designated associate(s).

Cross-over at the time of progressive disease according to RECIST 1.1 is allowed for the standard arm.

Serious adverse events	Experimental arm	Standard arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 60 (35.00%)	20 / 64 (31.25%)	
number of deaths (all causes)	27	23	
number of deaths resulting from adverse events	0	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEOPLASM PROGRESSION			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARANEOPLASTIC SYNDROME			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
VENOUS THROMBOSIS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 60 (1.67%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
PYREXIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	3 / 60 (5.00%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
alternative dictionary used:			

MedDRA 24.1			
subjects affected / exposed	1 / 60 (1.67%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY OEDEMA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
INTERSTITIAL LUNG DISEASE			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
CONFUSIONAL STATE			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPHIL COUNT DECREASED			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
FALL			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ATRIAL FLUTTER			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
ATRIAL FIBRILLATION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 60 (0.00%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
CARDIAC FAILURE			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL INFARCTION			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
MYOCARDITIS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CEREBROVASCULAR ACCIDENT			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEPRESSED LEVEL OF CONSCIOUSNESS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GUILLAIN-BARRE SYNDROME			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
SYNCOPE			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
FEBRILE NEUTROPENIA			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
HAEMOLYTIC ANAEMIA				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
ANAEMIA				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	2 / 60 (3.33%)	0 / 64 (0.00%)		
occurrences causally related to treatment / all	1 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
NEUTROPENIA				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	2 / 60 (3.33%)	0 / 64 (0.00%)		
occurrences causally related to treatment / all	1 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
THROMBOCYTOPENIA				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	2 / 60 (3.33%)	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 2	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gastrointestinal disorders				
ABDOMINAL PAIN				
alternative dictionary used: MedDRA 24.1				
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (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 24.1				

subjects affected / exposed	1 / 60 (1.67%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPHAGIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
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 24.1			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ULCER			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
RENAL FAILURE			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 60 (3.33%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL TUBULAR NECROSIS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
HYPOTHYROIDISM			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ADRENAL INSUFFICIENCY			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 60 (1.67%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
LOWER RESPIRATORY TRACT INFECTION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 60 (3.33%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 60 (1.67%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA BACTERIAL			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
UPPER RESPIRATORY TRACT INFECTION			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPTIC SHOCK			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Metabolism and nutrition disorders			
HYPONATRAEMIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 60 (0.00%)	2 / 64 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOMAGNESAEMIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOCALCAEMIA			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	1 / 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	59 / 60 (98.33%)	60 / 64 (93.75%)	
Vascular disorders			
HEMATOMA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
HYPERTENSION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	9 / 64 (14.06%)	
occurrences (all)	1	14	
PHLEBITIS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
SUPERFICIAL THROMBOPHLEBITIS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
THROMBOEMBOLIC EVENT			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	8 / 60 (13.33%)	1 / 64 (1.56%)	
occurrences (all)	9	1	
General disorders and administration site conditions			
ALOPECIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
FEVER			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	8 / 60 (13.33%)	1 / 64 (1.56%)	
occurrences (all)	9	1	
FATIGUE			
alternative dictionary used: CTC 4.0			

subjects affected / exposed	23 / 60 (38.33%)	23 / 64 (35.94%)	
occurrences (all)	36	39	
EDEMA LIMBS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
EDEMA FACE			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
CHILLS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
ALTERATION OF GENERAL CONDITION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
HEADACHE			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
GENERAL DISORDERS ANDADMINISTRATION SITE CONDITIONS -OTHER, DETERIORATION OF THE GENERAL CONDITION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - OTHER, DETERIORATION OF HEALTH STATUS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
GENERAL DISORDERS AND			

ADMINISTRATION SITE CONDITIONS - OTHER, ALTERATION OF GENERAL CONDITION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
GAIT DISTURBANCE			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
MALAISE			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
FLU LIKE SYMPTOMS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
NON-CARDIAC CHEST PAIN			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 60 (5.00%)	1 / 64 (1.56%)	
occurrences (all)	3	1	
OTHER			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	5 / 60 (8.33%)	3 / 64 (4.69%)	
occurrences (all)	5	3	
PAIN			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	4 / 60 (6.67%)	1 / 64 (1.56%)	
occurrences (all)	4	1	
Immune system disorders			
ALLERGIC REACTION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	3 / 64 (4.69%)	
occurrences (all)	0	4	
Reproductive system and breast disorders			

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - OTHER, PENIS INFLAMMATION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - OTHER, BLEEDING FROM FORESKIN			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
DYSPNEA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	13 / 60 (21.67%)	14 / 64 (21.88%)	
occurrences (all)	16	14	
COUGH			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	8 / 60 (13.33%)	5 / 64 (7.81%)	
occurrences (all)	10	5	
BRONCHIAL OBSTRUCTION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
ALLERGIC RHINITIS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
PULMONARY EDEMA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
PNEUMONITIS			
alternative dictionary used: CTC 4.0			

subjects affected / exposed	2 / 60 (3.33%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
OTHER			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 60 (5.00%)	0 / 64 (0.00%)	
occurrences (all)	3	0	
NASAL CONGESTION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
LARYNGEAL HEMORRHAGE			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
HOARSENESS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	3	0	
EPISTAXIS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
PULMONARY FIBROSIS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
RESPIRATORY OTHER			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
RESPIRATORY FAILURE			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	

WORSENING OF RESPIRATORY FAILURE			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
VOICE ALTERATION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
SORE THROAT			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDER - OTHER, LUNG BOOP SYNDROM			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
INSOMNIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
CONFUSION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
ANXIETY			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
OTHER			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Investigations			

ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	2 / 64 (3.13%)	
occurrences (all)	8	2	
CD4 LYMPHOCYTES DECREASED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	1 / 64 (1.56%)	
occurrences (all)	7	1	
LYMPHOCYTE COUNT DECREASED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
INVESTIGATIONS - OTHER, LACTATE DEHYDROGENASE INCREASED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
GGT INCREASED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	7 / 60 (11.67%)	5 / 64 (7.81%)	
occurrences (all)	12	7	
ELECTROCARDIOGRAM QT CORRECTED INTERVAL PROLONGED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
CREATININE INCREASED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	7 / 60 (11.67%)	2 / 64 (3.13%)	
occurrences (all)	13	2	
ALKALINE PHOSPHATASE			

INCREASED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 60 (5.00%)	2 / 64 (3.13%)	
occurrences (all)	4	2	
NEUTROPHIL COUNT DECREASED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	11 / 60 (18.33%)	13 / 64 (20.31%)	
occurrences (all)	22	20	
WHITE BLOOD CELL DECREASED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	1 / 64 (1.56%)	
occurrences (all)	4	1	
WHITE BLOOD CELL DECREASE			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
WEIGHT LOSS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	5 / 60 (8.33%)	3 / 64 (4.69%)	
occurrences (all)	5	3	
WEIGHT GAIN			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
PLATELET COUNT DECREASED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	17 / 60 (28.33%)	18 / 64 (28.13%)	
occurrences (all)	22	38	
OTHER			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			

FALL			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Cardiac disorders			
CARDIAC ARREST			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
CHEST PAIN - CARDIAC			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
HEART FAILURE			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
ATRIAL FLUTTER			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
ATRIAL FIBRILLATION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
OTHER			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	2 / 64 (3.13%)	
occurrences (all)	2	2	
MYOCARDITIS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
MYOCARDIAL INFARCTION			
alternative dictionary used: CTC 4.0			

subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
PALPITATIONS alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
SUPRAVENTRICULAR TACHYCARDIA alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
SINUS TACHYCARDIA alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 60 (5.00%)	3 / 64 (4.69%)	
occurrences (all)	3	3	
SINUS BRADYCARDIA alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
THROMBOEMBOLIC EVENT alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	3	0	
VENTRICULAR ARRHYTHMIA alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Nervous system disorders			
ACOUSTIC NERVE DISORDER alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
ATAXIA alternative dictionary used: CTC 4.0			

subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
DEPRESSED LEVEL OF CONSCIOUSNESS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
DIZZINESS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 60 (5.00%)	1 / 64 (1.56%)	
occurrences (all)	3	1	
DYSGEUSIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	4 / 60 (6.67%)	2 / 64 (3.13%)	
occurrences (all)	5	2	
HEADACHE			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 60 (5.00%)	1 / 64 (1.56%)	
occurrences (all)	3	1	
MYELITIS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
OTHER			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	3 / 64 (4.69%)	
occurrences (all)	2	7	
PARESTHESIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 60 (5.00%)	5 / 64 (7.81%)	
occurrences (all)	4	6	
PERIPHERAL MOTOR NEUROPATHY			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	

PERIPHERAL SENSORY NEUROPATHY alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	2 / 64 (3.13%)	
occurrences (all)	1	2	
SEIZURE alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
TREMOR alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
TRANSIENT ISCHEMIC ATTACKS alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
SYNCOPE alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
STROKE alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders ANEMIA alternative dictionary used: CTC 4.0			
subjects affected / exposed	30 / 60 (50.00%)	24 / 64 (37.50%)	
occurrences (all)	76	48	
FEBRILE NEUTROPENIA alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
Ear and labyrinth disorders			

HEARING IMPAIRED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	4 / 64 (6.25%)	
occurrences (all)	1	5	
VERTIGO			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
TINNITUS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	2 / 64 (3.13%)	
occurrences (all)	2	2	
Eye disorders			
PHOTOPHOBIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
OTHER			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
DRY EYE			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
CONJUNCTIVITIS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
BLURRED VISION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
RETINAL DETACHMENT			
alternative dictionary used: CTC 4.0			

subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
DYSPEPSIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	3 / 64 (4.69%)	
occurrences (all)	1	3	
DRY MOUTH			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
DIARRHEA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	10 / 60 (16.67%)	4 / 64 (6.25%)	
occurrences (all)	14	7	
CONSTIPATION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	9 / 60 (15.00%)	7 / 64 (10.94%)	
occurrences (all)	9	8	
COLITIS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
ABDOMINAL PAIN			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
DYSPHAGIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	2 / 64 (3.13%)	
occurrences (all)	4	3	
TOOTHACHE			
alternative dictionary used: CTC 4.0			

subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
NAUSEA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	17 / 60 (28.33%)	13 / 64 (20.31%)	
occurrences (all)	27	26	
MUCOSITIS ORAL			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 60 (5.00%)	2 / 64 (3.13%)	
occurrences (all)	4	2	
HEMORRHOIDS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
GASTROESOPHAGEAL REFLUX DISEASE			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	3 / 64 (4.69%)	
occurrences (all)	1	3	
ESOPHAGEAL PAIN			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
VOMITING			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	4 / 60 (6.67%)	2 / 64 (3.13%)	
occurrences (all)	5	3	
Hepatobiliary disorders			
BILE DUCT STENOSIS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
HEPATIC FAILURE			
alternative dictionary used: CTC 4.0			

subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
ALOPECIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	6 / 64 (9.38%)	
occurrences (all)	2	6	
RASH MACULO-PAPULAR			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, FOLLICULITIS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - OTHER, GENITAL CUTANEOUS LESIONS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
RASH ACNEIFORM			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	5 / 60 (8.33%)	1 / 64 (1.56%)	
occurrences (all)	6	1	
PRURITUS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	7 / 60 (11.67%)	2 / 64 (3.13%)	
occurrences (all)	7	3	
OTHER			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
ERYTHRODERMA			
alternative dictionary used: CTC 4.0			

subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
DRY SKIN			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	5 / 60 (8.33%)	4 / 64 (6.25%)	
occurrences (all)	5	4	
Renal and urinary disorders			
RENAL AND URINARY DISORDERS - OTHER, ACUTE TUBULAR NECROSIS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
RENAL AND URINARY DISORDERS - OTHER, POLYURO-POLYDIPSIC SYNDROME			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
OTHER			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
CYSTITIS NONINFECTIVE			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
CREATININE INCREASED			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
ACUTE KIDNEY INJURY			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
URINARY TRACT PAIN			
alternative dictionary used: CTC 4.0			

subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Endocrine disorders			
ADRENAL INSUFFICIENCY			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
HYPERTHYROIDISM			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	8 / 60 (13.33%)	3 / 64 (4.69%)	
occurrences (all)	8	5	
OTHER			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
HYPOTHYROIDISM			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	4 / 60 (6.67%)	1 / 64 (1.56%)	
occurrences (all)	6	1	
Musculoskeletal and connective tissue disorders			
BONE PAIN			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	2 / 64 (3.13%)	
occurrences (all)	2	2	
BACK PAIN			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	3 / 64 (4.69%)	
occurrences (all)	1	4	
ARTHRALGIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	0 / 64 (0.00%)	
occurrences (all)	3	0	
NECK PAIN			
alternative dictionary used: CTC 4.0			

subjects affected / exposed	1 / 60 (1.67%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
PAIN IN EXTREMITY			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
MYALGIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 60 (5.00%)	2 / 64 (3.13%)	
occurrences (all)	4	2	
MUSCLE WEAKNESS UPPER LIMB			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
Infections and infestations			
BLADDER INFECTION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	1 / 64 (1.56%)	
occurrences (all)	1	1	
BRONCHIAL INFECTION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
PHARYNGITIS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
PAPULOPUSTULAR RASH			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
OTHER			
alternative dictionary used: CTC 4.0			

subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
NAIL INFECTION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
LUNG INFECTION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 60 (5.00%)	3 / 64 (4.69%)	
occurrences (all)	4	4	
KIDNEY INFECTION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
ESOPHAGEAL INFECTION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
PYELONEPHRITIS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
VULVAL INFECTION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
URINARY TRACT INFECTION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
UPPER RESPIRATORY INFECTION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	3 / 64 (4.69%)	
occurrences (all)	2	3	

TOOTH INFECTION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
SKIN INFECTION			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
SEPSIS			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	2 / 64 (3.13%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
ANOREXIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	9 / 60 (15.00%)	7 / 64 (10.94%)	
occurrences (all)	9	9	
HYPERKALEMIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	4 / 60 (6.67%)	0 / 64 (0.00%)	
occurrences (all)	7	0	
HYPERGLYCEMIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	3 / 60 (5.00%)	3 / 64 (4.69%)	
occurrences (all)	3	6	
HYPERCALCEMIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
HYPERURICEMIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	2 / 60 (3.33%)	0 / 64 (0.00%)	
occurrences (all)	5	0	
HYPONATREMIA			
alternative dictionary used: CTC 4.0			

subjects affected / exposed	3 / 60 (5.00%)	2 / 64 (3.13%)	
occurrences (all)	3	6	
HYPOMAGNESEMIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	4 / 60 (6.67%)	2 / 64 (3.13%)	
occurrences (all)	5	3	
HYPOKALEMIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	4 / 64 (6.25%)	
occurrences (all)	1	6	
HYPOGLYCEMIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
HYPOCALCEMIA			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	4 / 60 (6.67%)	3 / 64 (4.69%)	
occurrences (all)	6	3	
OTHER			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
METABOLISM AND NUTRITION DISORDERS - OTHER: VITAMIN B9 DEFICIENCY			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	0 / 60 (0.00%)	1 / 64 (1.56%)	
occurrences (all)	0	1	
METABOLISM AND NUTRITION DISORDERS - OTHER, DIABETIC NEPHROPATHY			
alternative dictionary used: CTC 4.0			
subjects affected / exposed	1 / 60 (1.67%)	0 / 64 (0.00%)	
occurrences (all)	1	0	
HYPOPHOSPHATEMIA			
alternative dictionary used: CTC 4.0			

subjects affected / exposed occurrences (all)	0 / 60 (0.00%) 0	1 / 64 (1.56%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2016	SCIENTIFIC AMENDMENT 1 1) In order to clarify the language and align with Merck standard language some eligibility criteria have been rephrased. 2) According to the last version of the IB for Pembrolizumab (v12) the safety language has been updated. 3) After review with Study Coordinators and Statistician, activity of pembrolizumab in combination with carboplatin and etoposide in case of cross over in the control arm and Activity of pembrolizumab alone in case of re-challenge in the experimental arm have been moved from Exploratory to Secondary objectives. 4) To be consistent with other sections some eligibility criteria has been moved from section on Eligibility check to section on Randomization check 7) The protocol has been updated with the correct type and amount of samples for TR projects. The laboratories in charge of the storage and analysis have been added.
30 March 2017	SCIENTIFIC AMENDMENT 2 Following the routine update of the safety language for Pembrolizumab (IBv13) the protocol and PISIC have been amended and some other clarifications have been added about the Translational research.
18 December 2017	SCIENTIFIC AMENDMENT 3 -Treatment duration with pembrolizumab alone has been changed to 2 years in order to be consistent with the current protocol. -Risk language was updated according to the IB v14 and v15. -Addition of wording to cover the transfer of data to the US (i.e. MediData).
23 May 2018	SCIENTIFIC AMENDMENT 4 Following the requirements from the UK MHRA, the protocol was amendment: - Adequate methods of birth control were added; - Cross-over and re-challenge criteria were added; - The three days window and +/- 10% deviation from reference laboratory values were removed; - Temperature was added to the list of vital signs.

14 December 2018	SCIENTIFIC AMENDMENT 5 Based on the evidence of a discrepancy in the definition of crossover, the following changes were implemented to the protocol: - Crossover will be allowed for patients randomized in arm B who completed the chemotherapy treatment and progress at least 3 months after the completion of chemotherapy. - A close safety monitoring has been added to be performed on the first 5 patients and then 10 patients in arm B who crossover. In case of safety concern, the study will be presented to the IDMC. - The protocol has been adapted in order to provide information on the examination to be performed as follow-up for those patients who completed treatment and are waiting for crossover or rechallenge and also to provide information on the examination to be performed before re-challenge or crossover and during the re-challenge or crossover treatment period. - The end of treatment has been better defined. Additional changes include: - Primary objective and primary and secondary endpoints have been updated in order to refer to RECIST criteria v1.1 - “Assessment of adequate tissue availability for PD-L1 immunohistochemistry testing” has been removed from the eligibility criteria, as tumor tissue collection is not mandatory for enrolment. - Contraception period required has been adapted in order to be consistent with the SmPCs of chemotherapy drugs and the pregnancy reporting has been adapted accordingly. - For evaluation of eGFR, Cockroft-Gault Formula has been replaced by MDRD formula in the eligibility criteria. - The split of cisplatin administration in 2 days has been added as allowed. - In the withdrawal criteria has been added: “Disease progression according RECIST v1" (Exception: patients who are qualified for re-challenge and crossover)”. -The collection of creatinine clearance during the study treatment has been added. -Recommendation for the pregnancy test has been added. The PISIC has been updated accordingly.
05 July 2019	SCIENTIFIC AMENDMENT 6 Based on Italian competent authory (AIFA) comment, the following change is added to the protocol: Recurrent G3 colitis has been added as a reason of treatment discontinuation.
13 May 2020	SCIENTIFIC AMENDMENT 7 A new appendix to protocol and an addendum to patient information sheet have been prepared to include recommendations related to treatment and evaluations only applicable during the COVID-19 pandemic.
16 December 2020	SCIENTIFIC AMENDMENT 8 There was a change in the central laboratory which will analyze the tissue samples for TR purpose. Centre Léon Bérard (France) was replaced by the Targos (Kassel, Germany). In addition to the above, the following changes/clarifications have been added: - Appendix was added to provide guidance on protocol procedures during the COVID-19 crisis (COVID-19 appendix and PISIC addendum already released on 13/May/2020) - PISIC has been updated to include the change in the central lab and to include the updated safety language for permbolizumab.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported