



Clinical trial results:

A phase Ib/II trial evaluating the efficacy of MK-3475 and trastuzumab in patients with trastuzumab-resistant, HER2-positive metastatic breast cancers.

Summary

EudraCT number	2013-004770-10
Trial protocol	BE IT AT
Global end of trial date	04 August 2017

Results information

Result version number	v1 (current)
This version publication date	07 February 2020
First version publication date	07 February 2020
Summary attachment (see zip file)	Publication_Loi et al._Lancet Oncol 2019 Mar;20(3):316-318. doi: 10.1016/S1470-2045(19)30068-3. Epub 2019 Feb 11. (371_Loi_PANACEA_Lancet Oncol_2019_Editorial.pdf)

Trial information

Trial identification

Sponsor protocol code	IBCSG_45-13/BIG_4-13
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02129556
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IBCSG
Sponsor organisation address	Effingerstrasse 40, Bern, Switzerland, 3008
Public contact	IBCSG Coordinating Center, International Breast Cancer Study Group (IBCSG), +41 313899391, regulatoryoffice@ibcs.org
Scientific contact	IBCSG Coordinating Center, International Breast Cancer Study Group (IBCSG), +41 313899391, regulatoryoffice@ibcs.org

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 August 2017
Global end of trial reached?	Yes
Global end of trial date	04 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this phase Ib/II study are to determine the recommended dose of the anti-PD-1 mAb, MK-3475, in combination with standard dose trastuzumab, and to evaluate the efficacy and safety profile of the drug combination in patients with PD-L1 expressing, HER2-positive, unresectable loco-regional or metastatic breast cancer who have experienced progression during prior trastuzumab based therapy.

Protection of trial subjects:

The PANACEA Trial (IBCSG 45-13 / BIG 4-13) was conducted in accordance with the principles of the Declaration of Helsinki, national laws and regulations, and in compliance with the principles outlined in the ICH Tripartite Guideline/Guideline for Good Clinical Practice (January 1997). The trial protocol was reviewed by the IBCSG Ethics Committee and the Ethics Committees and Competent Authorities of the participating centers and countries. The PANACEA Data Safety Monitoring Committee (DSMC) provided semi-annual review of study procedures and safety data, in addition to special review of the interim safety data from the Phase II trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 February 2015
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	Australia: 21
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Italy: 7
Worldwide total number of subjects	58
EEA total number of subjects	37

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)	51
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All patients will have central review of the biopsy to assess HER2-positivity and PD-L1 status. For the primary objectives, only patients with central confirmation of HER2-positivity and presence of PD-L1 expression on metastatic biopsy (or biopsy from unresectable locoregional disease) after registration for screening will be eligible to enroll.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Phase Ib
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Arm description:

The phase Ib portion was designed to determine the recommended phase II dose (RP2D) of MK-3475 (pembrolizumab) based on three possible dose levels: 2 mg/kg, 10mg/kg, or a fall-back dose of 1 mg/kg.

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

Dosage and administration details:

MK-3475 at dose of 2 mg/kg or 10 mg/kg (i.v.), or a fall-back dose of 1 mg/kg, together with trastuzumab 6mg/kg by (i.v.) once every 3 weeks.

Arm title	Phase II PD-L1+
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Arm description:

HER2-positive, PD-L1 expressing, unresectable loco-regional or metastatic breast carcinoma that progressed on prior trastuzumab-based therapy. The Phase II portion of the trial used a flat dose of 200 mg of MK-3475 based on emerging data from the sponsor.

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

Dosage and administration details:

MK-3475 at a flat dose of 200mg (i.v.) together with trastuzumab 6mg/kg (i.v.) once every 3 weeks until progression, lack of tolerability, or 24 months of treatment. A dose of 8mg/kg trastuzumab will be used in cycle 1 if prior treatment with trastuzumab was stopped more than 3 months before.

Arm title	Phase II PD-L1-
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Arm description:

HER2-positive, PD-L1 negative, unresectable loco-regional or metastatic breast carcinoma that progressed on prior trastuzumab-based therapy. The Phase II portion of the trial used a flat dose of 200 mg of MK-3475 based on emerging data from the sponsor.

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

Dosage and administration details:

MK-3475 at a flat dose of 200mg (i.v.) together with trastuzumab 6mg/kg (i.v.) once every 3 weeks until progression, lack of tolerability, or 24 months of treatment. A dose of 8mg/kg trastuzumab will be used in cycle 1 if prior treatment with trastuzumab was stopped more than 3 months before.

Number of subjects in period 1	Phase Ib	Phase II PD-L1+	Phase II PD-L1-
Started	6	40	12
Completed	6	37	12
Not completed	0	3	0
Protocol deviation	-	3	-

Baseline characteristics

Reporting groups

Reporting group title	Phase Ib
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Reporting group description:

The phase Ib portion was designed to determine the recommended phase II dose (RP2D) of MK-3475 (pembrolizumab) based on three possible dose levels: 2 mg/kg, 10mg/kg, or a fall-back dose of 1 mg/kg.

Reporting group title	Phase II PD-L1+
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Reporting group description:

HER2-positive, PD-L1 expressing, unresectable loco-regional or metastatic breast carcinoma that progressed on prior trastuzumab-based therapy. The Phase II portion of the trial used a flat dose of 200 mg of MK-3475 based on emerging data from the sponsor.

Reporting group title	Phase II PD-L1-
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Reporting group description:

HER2-positive, PD-L1 negative, unresectable loco-regional or metastatic breast carcinoma that progressed on prior trastuzumab-based therapy. The Phase II portion of the trial used a flat dose of 200 mg of MK-3475 based on emerging data from the sponsor.

Reporting group values	Phase Ib	Phase II PD-L1+	Phase II PD-L1-
Number of subjects	6	40	12
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	48	51.2	54.5
standard deviation	± 9.5	± 10.4	± 5.2
Gender categorical Units: Subjects			
Female	6	40	12
Male	0	0	0
Race/Ethnicity Units: Subjects			
Caucasian	4	30	8
Asian	0	2	1
Other	0	1	0
Missing	2	7	3

Reporting group values	Total		
Number of subjects	58		

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 arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	58		
Male	0		
Race/Ethnicity Units: Subjects			
Caucasian	42		
Asian	3		
Other	1		
Missing	12		

End points

End points reporting groups

Reporting group title	Phase Ib
Reporting group description: The phase Ib portion was designed to determine the recommended phase II dose (RP2D) of MK-3475 (pembrolizumab) based on three possible dose levels: 2 mg/kg, 10mg/kg, or a fall-back dose of 1 mg/kg.	
Reporting group title	Phase II PD-L1+
Reporting group description: HER2-positive, PD-L1 expressing, unresectable loco-regional or metastatic breast carcinoma that progressed on prior trastuzumab-based therapy. The Phase II portion of the trial used a flat dose of 200 mg of MK-3475 based on emerging data from the sponsor.	
Reporting group title	Phase II PD-L1-
Reporting group description: HER2-positive, PD-L1 negative, unresectable loco-regional or metastatic breast carcinoma that progressed on prior trastuzumab-based therapy. The Phase II portion of the trial used a flat dose of 200 mg of MK-3475 based on emerging data from the sponsor.	

Primary: Dose-Limiting Toxicity (DLT) of MK-3475 in Combination With Trastuzumab

End point title	Dose-Limiting Toxicity (DLT) of MK-3475 in Combination With Trastuzumab ^{[1][2]}
End point description: Determination of dose-limiting toxicity (DLT) which is defined as an adverse event or abnormal laboratory value assessed as suspected to be trial treatment related (possible, probable or definite) and unrelated to disease or disease progression. Toxicities and lab values will be graded according to the NCI CTCAE (v4.0). Any grade-3 or greater non-hematological adverse event lasting at least one week; Any grade-4 hematological toxicity; or, Any adverse event resulting in a delay starting cycle 2 of more than 14 days.	
End point type	Primary
End point timeframe: Within the first 21 days.	

Notes:

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

Justification: Dose escalation occurred using a standard '3+3' dose escalation approach. The RP2D is defined as the highest dose level at which <33% (0 of three patients, or 0 or 1 of six patients) has experienced a DLT in cycle 1. Once dose escalation for MK-3475 reaches a dose of 10 mg/kg, no further escalation will occur.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This end point is only applied to the Phase Ib (dose finding).

End point values	Phase Ib			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Participants	0			

Statistical analyses

No statistical analyses for this end point

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)
End point description: Confirmed CR or PR as best overall response. At the time of each restaging, patients will be classified as achieving complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or non-evaluable for response according to RECIST (Version 1.1) criteria.	
End point type	Primary
End point timeframe: Clinical and radiological tumor assessment will be performed by CT scan or MRI at baseline, at weeks 12, 18 and 24, then every 12 weeks until progression, or 24 weeks after stop of treatment if before progression.	

End point values	Phase Ib	Phase II PD-L1+	Phase II PD-L1-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	40	12	
Units: Proportion of participants				
number (confidence interval 90%)	0.17 (0.01 to 0.58)	0.15 (0.07 to 0.29)	0.00 (0.00 to 0.18)	

Statistical analyses

Statistical analysis title	Statistical analysis primary endpoint
Statistical analysis description: A Simon optimal two-stage design was used in the phase II portion to assess the primary outcome of objective response. The null hypothesis of a true objective response rate of 7% was tested against a one-sided alternative response rate of 22%.	
Comparison groups	Phase II PD-L1+ v Phase II PD-L1- v Phase Ib
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other ^[3]
Parameter estimate	response rate
Point estimate	0.15
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.07
upper limit	0.29

Notes:

[3] - This single-arm study conducted an estimation-only, non-comparative analysis

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)
End point description: Duration of response (DoR) is defined among patients with objective response (confirmed CR or PR as best overall response) as the interval between dates of first documentation of objective response and	

first documentation of progressive disease. In the absence of documented progressive disease, follow-up will be censored at date of last disease assessment.

End point type	Secondary
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End point timeframe:

From date of first documentation of objective response until first documentation of progressive disease, up to 24 weeks after stop of treatment (=30 months).

End point values	Phase Ib	Phase II PD-L1+	Phase II PD-L1-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	6	0 ^[4]	
Units: Months				
median (confidence interval 90%)	23.1 (23.1 to 23.1)	3.5 (2.7 to 999999)	(to)	

Notes:

[4] - Objective Response Rate in this arm was 0. Therefore, Duration of Response not measurable

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)
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End point description:

Time to progression (TTP) defined as the interval between the dates of the start of trial treatment and first documentation of progressive disease. In the absence of documented progressive disease, follow-up will be censored at date of last disease assessment.

End point type	Secondary
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End point timeframe:

From the first trial treatment until first documentation of progressive disease up to 24 weeks after stop of treatment (=30 months).

End point values	Phase Ib	Phase II PD-L1+	Phase II PD-L1-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	40	12	
Units: Months				
median (confidence interval 90%)	2.5 (1.1 to 2.7)	2.7 (2.6 to 4.9)	2.5 (1.4 to 999999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)
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End point description:

The proportion of patients with best confirmed RECIST response of CR, PR, or duration of SD of at least 24 weeks (measured from first dose of trial treatment).

End point type Secondary

End point timeframe:

From the start of trial treatment until confirmed CR, PR, or SD lasting for 24 weeks or longer.

End point values	Phase Ib	Phase II PD-L1+	Phase II PD-L1-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	40	12	
Units: Proportion of participants				
number (confidence interval 90%)	0.17 (0.01 to 0.58)	0.25 (0.14 to 0.39)	0.00 (0.00 to 0.18)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title Progression-Free Survival (PFS)

End point description:

The interval between the dates of the first dose of trial treatment until first documentation of disease progression or death, whichever occurs first. Patients with new non-breast cancer malignancy must continue to be followed for progression of the original breast cancer. For patients without progression, follow-up is censored at the date of last disease assessment without progression, unless death occurs within 12 weeks following the date last known progression-free, in which case the death will be counted as a PFS event.

End point type Secondary

End point timeframe:

From the date of first treatment dose until documented disease progression or death from any cause, whichever occur first, assessed up to 30 months.

End point values	Phase Ib	Phase II PD-L1+	Phase II PD-L1-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	40	12	
Units: Months				
median (confidence interval 90%)	2.5 (1.1 to 2.7)	2.7 (2.6 to 4.0)	2.5 (1.4 to 2.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) at 12 Months

End point title	Overall Survival (OS) at 12 Months
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End point description:

OS is defined as the time from the first dose of trial treatment to death from any cause. For patients who are lost to follow-up or who have no documentation of death at the time of final analysis, follow-up is censored at the date of last assessment of vital status. OS at 12 months by Kaplan-Meier estimates.

End point type	Secondary
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End point timeframe:

Time from start of trial treatment to death from any cause, assessed up to 30 months.

End point values	Phase Ib	Phase II PD-L1+	Phase II PD-L1-	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	40	12	
Units: Proportion of participants				
number (confidence interval 90%)	0.67 (0.27 to 0.88)	0.65 (0.50 to 0.76)	0.12 (0.01 to 0.36)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were to be reported at the end of every treatment cycle, at the End-of-Treatment visit, and up to 30 days after cessation of trial treatment. Serious adverse event and pregnancy data were to be collected for 90 days following the end of treatment.

Adverse event reporting additional description:

Any grade of any observed AE was to be reported on the AE form. There were no specifications of targeted AEs. Symptoms of the targeted cancer were not to be reported as AEs.

Assessment type	Systematic
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Dictionary used

Dictionary name	NCI CTCAE
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Dictionary version	V4.
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Reporting groups

Reporting group title	Phase II
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Reporting group description:

(PD-L1+ and PD-L1-)

Reporting group title	Phase Ib
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Reporting group description: -

Serious adverse events	Phase II	Phase Ib	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 52 (48.08%)	4 / 6 (66.67%)	
number of deaths (all causes)	25	4	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Glioblastoma multiforme			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Intracranial hypertension			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (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			
Death			

subjects affected / exposed	9 / 52 (17.31%)	2 / 6 (33.33%)	
occurrences causally related to treatment / all	1 / 9	0 / 2	
deaths causally related to treatment / all	1 / 9	0 / 2	
Immune system disorders			
Lambert-Eaton syndrome			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Autoimmune hepatitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Disease progression			
subjects affected / exposed	6 / 52 (11.54%)	2 / 6 (33.33%)	
occurrences causally related to treatment / all	1 / 6	0 / 2	
deaths causally related to treatment / all	0 / 6	0 / 2	
Breast infection			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Upper respiratory infection			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnea			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Cognitive disturbance			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
GGT increased			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Takotsubo cardiomyopathy			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CNS metastases			

subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paresthesia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological paresis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (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			
Anemia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal vein occlusion			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastroenteritis			

subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct dilatation			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic haemorrhage			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute renal impairment			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (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			
Shoulder pain			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Catheter-related infection			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (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	Phase II	Phase Ib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 52 (96.15%)	6 / 6 (100.00%)	
Vascular disorders			
Hot flashes			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	6 / 52 (11.54%)	0 / 6 (0.00%)	
occurrences (all)	12	0	
Hypotension			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Intracranial hypertension			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Lymphedema			

subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Lymphedema right leg			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Thromboembolic event			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Anemia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Asthenia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Diaphoresis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Edema limbs			
subjects affected / exposed	4 / 52 (7.69%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Edema trunk			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	16 / 52 (30.77%)	3 / 6 (50.00%)	
occurrences (all)	23	4	
Fever			
subjects affected / exposed	3 / 52 (5.77%)	1 / 6 (16.67%)	
occurrences (all)	5	1	
Flu-like symptoms			
subjects affected / exposed	5 / 52 (9.62%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Hoarseness			

subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Infusion related reaction			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Left breast tumour bleeding			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Localized edema			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Pain			
subjects affected / exposed	6 / 52 (11.54%)	0 / 6 (0.00%)	
occurrences (all)	10	0	
Immune system disorders			
Autoimmune disorder			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Bronchopulmonary hemorrhage			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	9 / 52 (17.31%)	1 / 6 (16.67%)	
occurrences (all)	12	1	
Dyspnea			

subjects affected / exposed	11 / 52 (21.15%)	3 / 6 (50.00%)
occurrences (all)	18	4
Epistaxis		
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)
occurrences (all)	1	0
Epistaxis: seasonal		
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)
occurrences (all)	1	0
Laryngeal inflammation		
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)
occurrences (all)	1	0
Nasal congestion		
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	1
Pleural effusion		
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)
occurrences (all)	3	0
Pneumonia		
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	2
Pneumonitis		
subjects affected / exposed	4 / 52 (7.69%)	0 / 6 (0.00%)
occurrences (all)	4	0
Pneumothorax		
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)
occurrences (all)	1	0
Productive cough		
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)
occurrences (all)	2	0
Respiratory distress		
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)
occurrences (all)	1	0
Shortness of breath		
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)
occurrences (all)	1	0
Sinus disorder		

subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Sore throat subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 4	1 / 6 (16.67%) 1	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2	1 / 6 (16.67%) 1	
Insomnia subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	2 / 6 (33.33%) 2	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	4 / 52 (7.69%) 4	1 / 6 (16.67%) 1	
Alkaline phosphatase increased subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 4	0 / 6 (0.00%) 0	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 4	0 / 6 (0.00%) 0	
Blood bilirubin increased subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 3	0 / 6 (0.00%) 0	
Drug induced liver injury subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Ggt increased			

subjects affected / exposed occurrences (all)	5 / 52 (9.62%) 11	0 / 6 (0.00%) 0	
Hypercalcaemia subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Leucocyte count decreased subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Lipase increased subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 6	0 / 6 (0.00%) 0	
Lymphocyte count decreased subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	1 / 6 (16.67%) 1	
Neutrophil count decreased subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2	0 / 6 (0.00%) 0	
Serum amylase increased subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 3	0 / 6 (0.00%) 0	
Weight loss subjects affected / exposed occurrences (all)	4 / 52 (7.69%) 4	0 / 6 (0.00%) 0	
White blood cell decreased subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Cardiac disorders			
Pericardial effusion subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Sinus tachycardia subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Takotsubo cardiomyopathy subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	1 / 6 (16.67%) 2	

Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Aphonia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Ataxia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Balance disorder			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Cognitive disturbance			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Dysesthesia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Dysgeusia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Dysphasia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	8 / 52 (15.38%)	2 / 6 (33.33%)	
occurrences (all)	15	3	
Loss of hand motor traction			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Memory impairment			

subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	1 / 6 (16.67%) 1	
Paresthesia subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Static cerebellar syndrom subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Tremor subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Vasovagal reaction subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Blood and lymphatic system disorders			
Anemia subjects affected / exposed occurrences (all)	8 / 52 (15.38%) 8	4 / 6 (66.67%) 6	
Fever subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Lymph node pain subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Reactive thrombocytosis subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Ear and labyrinth disorders			
Ear pain subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Hearing impaired subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	1 / 6 (16.67%) 1	
Vertigo			

subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 3	1 / 6 (16.67%) 3	
Eye disorders			
Dry eye			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Retinal vascular disorder			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Visual field defect left lower quadrants			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Abdominal pain, intermittent			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Colitis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	5 / 52 (9.62%)	0 / 6 (0.00%)	
occurrences (all)	6	0	
Diarrhea			
subjects affected / exposed	9 / 52 (17.31%)	2 / 6 (33.33%)	
occurrences (all)	11	5	
Dry mouth			
subjects affected / exposed	2 / 52 (3.85%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Gastritis			
subjects affected / exposed	1 / 52 (1.92%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Gastroenteritis			

subjects affected / exposed	1 / 52 (1.92%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Gastroesophageal reflux disease			
subjects affected / exposed	2 / 52 (3.85%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal pain			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Mucositis oral			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Nausea			
subjects affected / exposed	11 / 52 (21.15%)	1 / 6 (16.67%)	
occurrences (all)	14	2	
Nausea with weight loss			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Tongue mycosis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	3 / 52 (5.77%)	2 / 6 (33.33%)	
occurrences (all)	4	2	
Hepatobiliary disorders			
Bile duct dilatation			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Cutaneous rash			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	7	0	
Cutaneous toxicity on legs and arms			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Dry skin			

subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Erysipelas			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Hyperhidrosis			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Photosensitivity			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	5 / 52 (9.62%)	0 / 6 (0.00%)	
occurrences (all)	6	0	
Rash - face			
subjects affected / exposed	0 / 52 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Rash acneiform			
subjects affected / exposed	2 / 52 (3.85%)	1 / 6 (16.67%)	
occurrences (all)	3	2	
Rash maculo-papular			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Redness ankle and feet			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Shingles			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute renal impairment			

subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Chronic kidney disease subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
UTI subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	1 / 6 (16.67%) 1	
Hypothyroidism subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2	1 / 6 (16.67%) 1	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	6 / 52 (11.54%) 6	2 / 6 (33.33%) 3	
Back pain subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 5	0 / 6 (0.00%) 0	
Bone pain subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2	0 / 6 (0.00%) 0	
Buttock pain subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 2	0 / 6 (0.00%) 0	
Shoulder pain subjects affected / exposed occurrences (all)	0 / 52 (0.00%) 0	2 / 6 (33.33%) 2	
Myalgia subjects affected / exposed occurrences (all)	4 / 52 (7.69%) 4	2 / 6 (33.33%) 2	
Neck pain			

subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Pain subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Pain in extremity subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Stiffness subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Infections and infestations			
Bronchial infection subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 3	0 / 6 (0.00%) 0	
Catheter-related infection subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	1 / 6 (16.67%) 1	
Dental subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Esophageal infection subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Laryngitis subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	
Pharyngitis subjects affected / exposed occurrences (all)	2 / 52 (3.85%) 4	0 / 6 (0.00%) 0	
Rhinitis infective subjects affected / exposed occurrences (all)	3 / 52 (5.77%) 4	0 / 6 (0.00%) 0	
Sepsis subjects affected / exposed occurrences (all)	1 / 52 (1.92%) 1	0 / 6 (0.00%) 0	

Sinusitis			
subjects affected / exposed	1 / 52 (1.92%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Skin infection			
subjects affected / exposed	1 / 52 (1.92%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Upper respiratory infection			
subjects affected / exposed	2 / 52 (3.85%)	2 / 6 (33.33%)	
occurrences (all)	3	4	
Urinary tract infection			
subjects affected / exposed	2 / 52 (3.85%)	2 / 6 (33.33%)	
occurrences (all)	3	4	
Yeasts in the stool			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	4 / 52 (7.69%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Hypercalcemia			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Hyperglycemia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hyperkalemia			
subjects affected / exposed	3 / 52 (5.77%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Hyperuricemia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hypoalbuminemia			
subjects affected / exposed	2 / 52 (3.85%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Hypocalcemia			

subjects affected / exposed	1 / 52 (1.92%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Hypokalemia			
subjects affected / exposed	1 / 52 (1.92%)	0 / 6 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2016	<p>-Study the efficacy and tolerability of the combination of pembrolizumab with trastuzumab also in an additional cohort of 15 PD-L1 negative patients in this trial.</p> <p>-When the phase II part of the trial was opened, the dose of pembrolizumab was fixed at a flat dose of 200mg; the amendment now contains the rationale for the choice of this dose.</p> <p>-The availability of trastuzumab emtansine (T-DM1) as monotherapy or in combination with pertuzumab and taxanes for the treatment for the targeted population has been taken into account to reformulate the definition of trastuzumab resistance.</p> <p>-The protocol is now open to any line of treatment for metastatic or unresectable loco-regional disease. Patients having recurred while on adjuvant trastuzumab or within 12 months of completing adjuvant trastuzumab, and for whom the treatment with the first-line combination of trastuzumab, pertuzumab and taxanes is not an option (e.g., due to refusal or contraindication) can be considered for enrollment into the trial, as well.</p> <p>-In line with recommendations for other immunotherapies, the protocol now allows continuation of trial treatment beyond confirmed progression if the investigator feels that the patient can tolerate treatment and may potentially benefit from it</p> <p>-The amendment also contains an update on safety of the IMP based on the version 10 of the Investigator's Brochure. Merck's "Events of clinical interest guidance document" has been integrated into the body of the protocol as it is no longer available as a separate document. •Participating centers will submit a final update on subsequent therapy and survival status of all enrolled patients.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported