Clinical trial results:
A Randomized Phase 2, Double-blind, Placebo-controlled, Multi-center Study Comparing Pemetrexed in Combination with TH-302 vs. Pemetrexed in Combination with Placebo as Second-line Chemotherapy for Advanced Non-Squamous, Non-Small Cell Lung Cancer

Summary

EudraCT number	2013-004698-29
Trial protocol	HU IT DE CZ GR ES RO
Global end of trial date	15 April 2016

Results information

Result version number	v1 (current)
This version publication date	01 September 2017
First version publication date	01 September 2017

Trial information

Trial identification

Sponsor protocol code	TH-CR-415

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02093962
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 121080

Notes:

Sponsors

Sponsor organisation name	Threshold Pharmaceuticals, Inc.
Sponsor organisation address	170 Harbor Way Ste 300, South San Francisco, California, United States, 94080
Public contact	Kristen Quigley Vice President, Clinical Operations, Threshold Pharmaceuticals, Inc., +1 650 455-9622, kquigley@thresholdpharm.com
Scientific contact	Tillman Pearce, MD, Chief Medical Officer, Threshold Pharmaceuticals, Inc., +1 650 491-4956, tpearce@thresholdpharm.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 April 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Overall survival - To assess the efficacy of pemetrexed in combination with TH-302 as determined by overall survival in patients with advanced non-squamous NSCLC in the second-line chemotherapy setting compared with pemetrexed in combination with placebo

Protection of trial subjects:

HIPAA standards, skin care kits both prophylactically and during/after administration of evofosfamide, periodic data safety monitoring board meetings.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 June 2014
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	Poland: 19
Country: Number of subjects enrolled	Romania: 35
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	Germany: 31
Country: Number of subjects enrolled	Greece: 9
Country: Number of subjects enrolled	Hungary: 60
Country: Number of subjects enrolled	Italy: 27
Country: Number of subjects enrolled	Russian Federation: 33
Country: Number of subjects enrolled	United States: 34
Worldwide total number of subjects	265
EEA total number of subjects	198

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)	171
From 65 to 84 years	94
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment began June 2014 and ended December 2015.

Pre-assignment

Screening details:

All subjects eligible for screening signed the consent prior to the performance of any non-routine procedures. Before undertaking any study-related procedure, the investigators or their designees explained the nature and purpose of the study, participation and termination conditions, and risks and benefits to the subject.

Period 1

Period 1 title	Baseline period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

IXRS was used to ensure blinding was maintained.

Arms

Are arms mutually exclusive?	Yes
Arm title	TH-302 and Pemetrexed

Arm description:

TH-302 (evofosfamide) in combination with Pemetrexed

Arm type	Experimental
Investigational medicinal product name	Evofosfamide
Investigational medicinal product code	TH-302
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Each dose of TH-302 was prepared in 5% dextrose in water (D5W) or normal saline and administered intravenously via an infusion pump. If there were concerns for possible extravasation or phlebitis, TH-302 could have been administered through a central line.
TH-302 was administered at a dose of 400 mg/m^2 by IV infusion over 30-60 minutes on Days 1 and 8 of each 21-day cycle.

Investigational medicinal product name	PEMETREXED
Investigational medicinal product code	
Other name	Alimta
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed was administered at a dose of 500 mg/m^2 by IV infusion over 10 minutes on Day 1 of each 21-day cycle. Pemetrexed infusions started approximately 2 to 4 hours after the completion of TH-302 or placebo administration.

Arm title	Placebo and Pemetrexed

Arm description:

Control Arm

Arm type	Active comparator

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo was administered by IV infusion over 30-60 minutes on Days 1 and 8 of each 21-day cycle.

Investigational medicinal product name	PEMETREXED
Investigational medicinal product code	Alimta
Other name	
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pemetrexed was administered at a dose of 500 mg/m^2 by IV infusion over 10 minutes on Day 1 of each 21-day cycle. Pemetrexed infusions started approximately 2 to 4 hours after the completion of TH-302 or placebo administration.

Number of subjects in period 1	TH-302 and Pemetrexed	Placebo and Pemetrexed
Started	134	131
Completed	0	0
Not completed	134	131
Consent withdrawn by subject	4	2
Death	76	81
Lost to follow-up	1	1
Sponsor decision	53	47

Baseline characteristics

End points

End points reporting groups	
Reporting group title	TH-302 and Pemetrexed
Reporting group description:	
TH-302 (evofosfamide) in combination with Pemetrexed	
Reporting group title	Placebo and Pemetrexed
Reporting group description:	
Control Arm	

Primary: overall survival	
End point title	overall survival
End point description:	
End point type	Primary
End point timeframe:	
Overall survival was defined as the duration from date of randomization to date of death from any cause. For subjects who were alive or lost to follow-up, this time was censored at the date of last contact.	

End point values	TH-302 and Pemetrexed	Placebo and Pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	131		
Units: days				
median (confidence interval 95%)	279 (217 to 437)	272 (199 to 412)		

Statistical analyses

Statistical analysis title	OS - Primary analysis
Comparison groups	TH-302 and Pemetrexed v Placebo and Pemetrexed
Number of subjects included in analysis	265
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.9115
Method	Logrank
Confidence interval	
level	95 %

Secondary: Progression-free Survival	
End point title	Progression-free Survival

End point description:

End point type	Secondary

End point timeframe:

from randomization to disease progression or death)

End point values	TH-302 and Pemetrexed	Placebo and Pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	131		
Units: days				
median (confidence interval 95%)	137 (122 to 195)	87 (80 to 125)		

Statistical analyses

Statistical analysis title	PFS - Primary analysis
Comparison groups	TH-302 and Pemetrexed v Placebo and Pemetrexed
Number of subjects included in analysis	265
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.0137
Method	Logrank

Secondary: Response Rate (Partial Response or Better)

End point title	Response Rate (Partial Response or Better)

End point description:

End point type	Secondary

End point timeframe:

Best response recorded from the start of the study treatment including any post-treatment assessments.

End point values	TH-302 and Pemetrexed	Placebo and Pemetrexed		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	131		
Units: percentages	22	10		

Statistical analyses

Statistical analysis title	Partial Response or Better - Primary analysis
Comparison groups	TH-302 and Pemetrexed v Placebo and Pemetrexed
Number of subjects included in analysis	265
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.0217
Method	Mantel-Haenszel

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from the start of the first dose of study drug until 30 days after discontinuation of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19

Reporting groups

Reporting group title	TH-302 and Pemetrexed

Reporting group description:

TH-302 (evofosfamide) in combination with Pemetrexed

Reporting group title	Placebo and Pemetrexed

Reporting group description:

Control Arm

Serious adverse events	TH-302 and Pemetrexed	Placebo and Pemetrexed	
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 130 (40.00%)	72 / 130 (55.38%)	
number of deaths (all causes)	76	81	
number of deaths resulting from adverse events	11	8	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			

subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (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			
subjects affected / exposed	2 / 130 (1.54%)	2 / 130 (1.54%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (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			

Acute respiratory distress syndrome			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 130 (1.54%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 130 (1.54%)	3 / 130 (2.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pleural effusion			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	3 / 130 (2.31%)	5 / 130 (3.85%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	2 / 2	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory failure			
subjects affected / exposed	4 / 130 (3.08%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	3 / 3	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	4 / 130 (3.08%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Myocardial infarction			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			

subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Coma			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Convulsion			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Quadriplegia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis			

subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 130 (5.38%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	5 / 11	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 130 (2.31%)	2 / 130 (1.54%)	
occurrences causally related to treatment / all	3 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Foreign body sensation in eyes			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haematemesis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin necrosis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (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			
Renal failure			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Secondary adrenocortical insufficiency			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			

subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 130 (0.77%)	2 / 130 (1.54%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 130 (3.08%)	2 / 130 (1.54%)	
occurrences causally related to treatment / all	3 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			

subjects affected / exposed	4 / 130 (3.08%)	2 / 130 (1.54%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Sepsis			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	TH-302 and Pemetrexed	Placebo and Pemetrexed	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	130 / 130 (100.00%)	130 / 130 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour associated fever			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences (all)	3	1	
Tumour pain			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Circulatory collapse			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Deep vein thrombosis			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences (all)	1	1	
Haematoma			
subjects affected / exposed	2 / 130 (1.54%)	2 / 130 (1.54%)	
occurrences (all)	3	2	
Hypertension			
subjects affected / exposed	3 / 130 (2.31%)	3 / 130 (2.31%)	
occurrences (all)	3	8	
Hypotension			
subjects affected / exposed	3 / 130 (2.31%)	3 / 130 (2.31%)	
occurrences (all)	3	3	
Peripheral ischaemia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Phlebitis			

subjects affected / exposed	8 / 130 (6.15%)	0 / 130 (0.00%)	
occurrences (all)	10	0	
Subclavian vein thrombosis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Varicose vein			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Venous insufficiency			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Venous thrombosis limb			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	28 / 130 (21.54%)	19 / 130 (14.62%)	
occurrences (all)	48	30	
Catheter site pain			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	3 / 130 (2.31%)	4 / 130 (3.08%)	
occurrences (all)	3	4	
Chills			
subjects affected / exposed	2 / 130 (1.54%)	4 / 130 (3.08%)	
occurrences (all)	2	4	
Extravasation			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Face oedema			
subjects affected / exposed	0 / 130 (0.00%)	2 / 130 (1.54%)	
occurrences (all)	0	3	
Fatigue			

subjects affected / exposed	33 / 130 (25.38%)	25 / 130 (19.23%)	
occurrences (all)	44	33	
Feeling hot			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
General physical health deterioration			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Hyperthermia			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences (all)	2	1	
Influenza like illnes			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	2	0	
Infusion site erythema			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Infusion site extravasation			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences (all)	2	1	
Infusion site phlebitis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Infusion site reaction			
subjects affected / exposed	3 / 130 (2.31%)	0 / 130 (0.00%)	
occurrences (all)	3	0	
Infusion site vesicles			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences (all)	1	1	
Injection site erythema			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Injection site haematoma			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Injection site phlebitis			

subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Injection site reaction			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	2	0	
Injection site vesicles			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Local swelling			
subjects affected / exposed	1 / 130 (0.77%)	2 / 130 (1.54%)	
occurrences (all)	1	3	
Localised oedema			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	1 / 130 (0.77%)	2 / 130 (1.54%)	
occurrences (all)	1	2	
Medical device pain			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Mucosal dryness			
subjects affected / exposed	0 / 130 (0.00%)	2 / 130 (1.54%)	
occurrences (all)	0	2	
Mucosal inflammation			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	2	0	
Non-cardiac chest pain			
subjects affected / exposed	4 / 130 (3.08%)	6 / 130 (4.62%)	
occurrences (all)	5	6	
Oedema			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	10 / 130 (7.69%)	15 / 130 (11.54%)	
occurrences (all)	11	24	
Pain			

subjects affected / exposed	3 / 130 (2.31%)	2 / 130 (1.54%)	
occurrences (all)	3	2	
Pyrexia			
subjects affected / exposed	11 / 130 (8.46%)	12 / 130 (9.23%)	
occurrences (all)	15	17	
Sensation of foreign body			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Xerosis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Social circumstances			
Walking disability			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	3 / 130 (2.31%)	0 / 130 (0.00%)	
occurrences (all)	4	0	
Genital discomfort			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Genital erythema			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Genital rash			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Perineal erythema			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Pruritus genital			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Scrotal erythema			

subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences (all)	1	1	
Vaginal inflammation			
subjects affected / exposed	3 / 130 (2.31%)	1 / 130 (0.77%)	
occurrences (all)	3	2	
Vulvovaginal burning sensation			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Acquired diaphragmatic eventration			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Acute respiratory failure			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Bronchospasm			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	8 / 130 (6.15%)	15 / 130 (11.54%)	
occurrences (all)	8	22	
Dysphonia			
subjects affected / exposed	1 / 130 (0.77%)	3 / 130 (2.31%)	
occurrences (all)	1	3	
Dyspnoea			
subjects affected / exposed	19 / 130 (14.62%)	19 / 130 (14.62%)	
occurrences (all)	21	23	
Dyspnoea exertional			
subjects affected / exposed	1 / 130 (0.77%)	2 / 130 (1.54%)	
occurrences (all)	1	2	
Emphysema			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Epistaxis			

subjects affected / exposed	4 / 130 (3.08%)	5 / 130 (3.85%)	
occurrences (all)	5	5	
Haemoptysis			
subjects affected / exposed	1 / 130 (0.77%)	3 / 130 (2.31%)	
occurrences (all)	1	3	
Hiccups			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	2	0	
Nasal congestion			
subjects affected / exposed	2 / 130 (1.54%)	1 / 130 (0.77%)	
occurrences (all)	3	1	
Nasal dryness			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	6 / 130 (4.62%)	6 / 130 (4.62%)	
occurrences (all)	9	7	
Orthopnoea			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			
subjects affected / exposed	3 / 130 (2.31%)	2 / 130 (1.54%)	
occurrences (all)	3	2	
Pneumonitis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Productive cough			
subjects affected / exposed	3 / 130 (2.31%)	3 / 130 (2.31%)	
occurrences (all)	3	3	
Pulmonary embolism			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	2	0	
Rales			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Respiratory failure			

subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences (all)	1	1	
Rhinitis allergic			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	3 / 130 (2.31%)	3 / 130 (2.31%)	
occurrences (all)	3	3	
Sinus congestion			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Wheezing			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Anxiety			
subjects affected / exposed	2 / 130 (1.54%)	6 / 130 (4.62%)	
occurrences (all)	2	6	
Confusional state			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Delirium			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Depressed mood			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	2	

Insomnia			
subjects affected / exposed	5 / 130 (3.85%)	6 / 130 (4.62%)	
occurrences (all)	5	6	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	17 / 130 (13.08%)	16 / 130 (12.31%)	
occurrences (all)	26	27	
Amylase increased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 130 (6.15%)	11 / 130 (8.46%)	
occurrences (all)	11	14	
Bilirubin conjugated increased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Blood albumin decreased			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 130 (3.08%)	4 / 130 (3.08%)	
occurrences (all)	4	8	
Blood bilirubin increased			
subjects affected / exposed	2 / 130 (1.54%)	1 / 130 (0.77%)	
occurrences (all)	5	8	
Blood bilirubin unconjugated increased			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Blood chloride decreased			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Blood creatinine increased			
subjects affected / exposed	5 / 130 (3.85%)	7 / 130 (5.38%)	
occurrences (all)	7	12	
Blood glucose increased			

subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)		
occurrences (all)	0	1		
Blood lactate dehydrogenase increased				
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)		
occurrences (all)	2	1		
Blood pressure increased				
subjects affected / exposed	0 / 130 (0.00%)	2 / 130 (1.54%)		
occurrences (all)	0	2		
Blood urea increased				
subjects affected / exposed	2 / 130 (1.54%)	2 / 130 (1.54%)		
occurrences (all)	2	2		
Body temperature increased				
subjects affected / exposed	3 / 130 (2.31%)	0 / 130 (0.00%)		
occurrences (all)	3	0		
C-reactive protein increased				
subjects affected / exposed	2 / 130 (1.54%)	2 / 130 (1.54%)		
occurrences (all)	3	3		
Creatinine renal clearance decreased				
subjects affected / exposed	2 / 130 (1.54%)	2 / 130 (1.54%)		
occurrences (all)	2	2		
Electrocardiogram QT prolonged				
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)		
occurrences (all)	1	1		
Electrocardiogram T wave abnormal				
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)		
occurrences (all)	0	1		
Electrocardiogram abnormal				
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)		
occurrences (all)	0	1		
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)		
occurrences (all)	1	1		
Glomerular filtration rate decreased				

subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	5	0	
Glomerular filtration rate increased			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Heart rate increased			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Lymphocyte count decreased			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	4	0	
Neutrophil count decreased			
subjects affected / exposed	3 / 130 (2.31%)	2 / 130 (1.54%)	
occurrences (all)	7	2	
Pancreatic enzymes increased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Platelet count decreased			
subjects affected / exposed	5 / 130 (3.85%)	1 / 130 (0.77%)	
occurrences (all)	5	1	
Platelet count increased			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	2	0	
Protein total decreased			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Transaminases increased			
subjects affected / exposed	0 / 130 (0.00%)	3 / 130 (2.31%)	
occurrences (all)	0	3	
Troponin increased			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	13 / 130 (10.00%)	7 / 130 (5.38%)	
occurrences (all)	13	7	
White blood cell count decreased			

subjects affected / exposed	5 / 130 (3.85%)	1 / 130 (0.77%)	
occurrences (all)	7	1	
White blood cell count increased			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Excoriation			
subjects affected / exposed	2 / 130 (1.54%)	1 / 130 (0.77%)	
occurrences (all)	2	1	
Injury, poisoning and procedural complications			
Back injury			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences (all)	1	1	
Fall			
subjects affected / exposed	1 / 130 (0.77%)	3 / 130 (2.31%)	
occurrences (all)	1	3	
Foot fracture			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Infusion related reaction			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	2	
Laceration			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Radiation fibrosis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Skin wound			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Thermal burn			

subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Wrist fracture			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			
Pyloric stenosis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	2	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Arrhythmia			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences (all)	1	1	
Atrial fibrillation			
subjects affected / exposed	3 / 130 (2.31%)	3 / 130 (2.31%)	
occurrences (all)	3	3	
Atrial flutter			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Bradycardia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Cardiac failure			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences (all)	1	1	
Cardiomegaly			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Cardiovascular disorder			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Coronary artery disease			

subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Mitral valve incompetence			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Sinus tachycardia			
subjects affected / exposed	0 / 130 (0.00%)	2 / 130 (1.54%)	
occurrences (all)	0	3	
Tachycardia			
subjects affected / exposed	2 / 130 (1.54%)	1 / 130 (0.77%)	
occurrences (all)	2	1	
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Aphonia			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	2	0	
Ataxia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	3	
Cerebrovascular accident			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Depressed level of consciousness			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	2	0	
Dizziness			
subjects affected / exposed	8 / 130 (6.15%)	13 / 130 (10.00%)	
occurrences (all)	9	22	
Dysarthria			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	2 / 130 (1.54%)	4 / 130 (3.08%)	
occurrences (all)	2	4	

Headache			
subjects affected / exposed	11 / 130 (8.46%)	16 / 130 (12.31%)	
occurrences (all)	12	20	
Hemiparesis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Hypoaesthesia			
subjects affected / exposed	2 / 130 (1.54%)	1 / 130 (0.77%)	
occurrences (all)	2	1	
Intracranial pressure increased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Multiple sclerosis relapse			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Myoclonus			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Neuropathy peripheral			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	8 / 130 (6.15%)	7 / 130 (5.38%)	
occurrences (all)	13	16	
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 130 (3.08%)	3 / 130 (2.31%)	
occurrences (all)	4	7	
Polyneuropathy			
subjects affected / exposed	2 / 130 (1.54%)	3 / 130 (2.31%)	
occurrences (all)	2	3	
Sciatica			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Sinus headache			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	

Somnolence			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	4	0	
Syncope			
subjects affected / exposed	0 / 130 (0.00%)	3 / 130 (2.31%)	
occurrences (all)	0	3	
Tremor			
subjects affected / exposed	0 / 130 (0.00%)	2 / 130 (1.54%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	50 / 130 (38.46%)	40 / 130 (30.77%)	
occurrences (all)	80	56	
Leukocytosis			
subjects affected / exposed	3 / 130 (2.31%)	5 / 130 (3.85%)	
occurrences (all)	3	12	
Leukopenia			
subjects affected / exposed	13 / 130 (10.00%)	8 / 130 (6.15%)	
occurrences (all)	29	31	
Lymphadenopathy			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences (all)	1	1	
Lymphopenia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	30 / 130 (23.08%)	24 / 130 (18.46%)	
occurrences (all)	83	70	
Pancytopenia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Thrombocytopenia			
subjects affected / exposed	25 / 130 (19.23%)	10 / 130 (7.69%)	
occurrences (all)	47	19	
Thrombocytosis			

subjects affected / exposed	0 / 130 (0.00%)	2 / 130 (1.54%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	2	0	
Tinnitus			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Vertigo			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Dry eye			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	2	0	
Eye inflammation			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences (all)	1	1	
Eye irritation			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences (all)	2	1	
Eye pain			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Eye pruritus			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Eyelid oedema			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences (all)	1	1	
Foreign body sensation in eyes			

subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Lacrimation increased			
subjects affected / exposed	6 / 130 (4.62%)	3 / 130 (2.31%)	
occurrences (all)	7	5	
Macular fibrosis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Optic atrophy			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Periorbital oedema			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Retinal vein occlusion			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	1 / 130 (0.77%)	2 / 130 (1.54%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	3	0	
Abdominal hernia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	1 / 130 (0.77%)	2 / 130 (1.54%)	
occurrences (all)	1	2	
Abdominal pain lower			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	6 / 130 (4.62%)	7 / 130 (5.38%)	
occurrences (all)	6	8	

Abdominal tenderness			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Aerophagia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Anal fissure			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Anal inflammation			
subjects affected / exposed	4 / 130 (3.08%)	0 / 130 (0.00%)	
occurrences (all)	5	0	
Anal pruritus			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	2	0	
Anorectal discomfort			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Breath odour			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Cheilitis			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	2	0	
Constipation			
subjects affected / exposed	16 / 130 (12.31%)	7 / 130 (5.38%)	
occurrences (all)	22	7	
Defaecation urgency			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Dental caries			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	23 / 130 (17.69%)	16 / 130 (12.31%)	
occurrences (all)	43	24	

Diverticulum			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Dry mouth			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Duodenitis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	2 / 130 (1.54%)	3 / 130 (2.31%)	
occurrences (all)	2	3	
Dysphagia			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	2	0	
Faeces discoloured			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	3	0	
Gastritis erosive			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 130 (3.08%)	1 / 130 (0.77%)	
occurrences (all)	4	1	
Gingival bleeding			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Haematochezia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			
subjects affected / exposed	4 / 130 (3.08%)	0 / 130 (0.00%)	
occurrences (all)	4	0	

Inguinal hernia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Large intestinal haemorrhage			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Lip erosion			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	40 / 130 (30.77%)	37 / 130 (28.46%)	
occurrences (all)	76	79	
Odynophagia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Oesophagitis			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	2	0	
Oral dysaesthesia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Oral pain			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences (all)	1	1	
Perianal erythema			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Proctalgia			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	3	0	
Proctitis			
subjects affected / exposed	4 / 130 (3.08%)	0 / 130 (0.00%)	
occurrences (all)	4	0	
Rectal haemorrhage			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	

Saliva altered			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	24 / 130 (18.46%)	18 / 130 (13.85%)	
occurrences (all)	45	26	
Toothache			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	25 / 130 (19.23%)	17 / 130 (13.08%)	
occurrences (all)	34	20	
Hepatobiliary disorders			
Biliary dilatation			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Hepatic cyst			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Hepatic pain			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Hepatotoxicity			
subjects affected / exposed	3 / 130 (2.31%)	1 / 130 (0.77%)	
occurrences (all)	3	7	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 130 (0.00%)	4 / 130 (3.08%)	
occurrences (all)	0	23	
Liver injury			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Alopecia			

subjects affected / exposed	5 / 130 (3.85%)	0 / 130 (0.00%)	
occurrences (all)	5	0	
Blister			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Chloasma			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Dermatitis			
subjects affected / exposed	6 / 130 (4.62%)	2 / 130 (1.54%)	
occurrences (all)	6	2	
Dermatitis bullous			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	2	0	
Dermatitis contact			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	9 / 130 (6.92%)	4 / 130 (3.08%)	
occurrences (all)	9	4	
Ecchymosis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	2 / 130 (1.54%)	4 / 130 (3.08%)	
occurrences (all)	3	5	
Erythema multiforme			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Intertrigo			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Nail disorder			

subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Night sweats			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	2	
Onycholysis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	4 / 130 (3.08%)	4 / 130 (3.08%)	
occurrences (all)	4	4	
Purpura			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	10 / 130 (7.69%)	8 / 130 (6.15%)	
occurrences (all)	12	11	
Rash erythematous			
subjects affected / exposed	4 / 130 (3.08%)	3 / 130 (2.31%)	
occurrences (all)	9	3	
Rash macular			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	2	0	
Rash maculo-papular			
subjects affected / exposed	1 / 130 (0.77%)	3 / 130 (2.31%)	
occurrences (all)	1	7	
Rash papular			
subjects affected / exposed	0 / 130 (0.00%)	2 / 130 (1.54%)	
occurrences (all)	0	2	
Rash pruritic			
subjects affected / exposed	3 / 130 (2.31%)	2 / 130 (1.54%)	
occurrences (all)	3	2	

Rash vesicular			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Scar pain			
subjects affected / exposed	0 / 130 (0.00%)	2 / 130 (1.54%)	
occurrences (all)	0	2	
Skin discolouration			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	2	0	
Skin disorder			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	2	
Skin exfoliation			
subjects affected / exposed	1 / 130 (0.77%)	3 / 130 (2.31%)	
occurrences (all)	2	3	
Skin hyperpigmentation			
subjects affected / exposed	8 / 130 (6.15%)	2 / 130 (1.54%)	
occurrences (all)	10	2	
Skin irritation			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Skin reaction			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Skin toxicity			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Skin ulcer			
subjects affected / exposed	6 / 130 (4.62%)	0 / 130 (0.00%)	
occurrences (all)	6	0	
Stasis dermatitis			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	2	0	
Vasculitic rash			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	

Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Dysuria			
subjects affected / exposed	5 / 130 (3.85%)	0 / 130 (0.00%)	
occurrences (all)	5	0	
Haematuria			
subjects affected / exposed	0 / 130 (0.00%)	2 / 130 (1.54%)	
occurrences (all)	0	2	
Nephrolithiasis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Nephropathy			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Proteinuria			
subjects affected / exposed	0 / 130 (0.00%)	2 / 130 (1.54%)	
occurrences (all)	0	2	
Renal cyst			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Renal failure			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Renal failure acute			
subjects affected / exposed	0 / 130 (0.00%)	2 / 130 (1.54%)	
occurrences (all)	0	2	
Renal impairment			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Urethral discharge			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	3 / 130 (2.31%)	7 / 130 (5.38%)	
occurrences (all)	3	7	
Arthritis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	6 / 130 (4.62%)	16 / 130 (12.31%)	
occurrences (all)	8	16	
Bone pain			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Coccydynia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Groin pain			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	2	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Mobility decreased			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	1 / 130 (0.77%)	2 / 130 (1.54%)	
occurrences (all)	1	2	
Muscular weakness			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences (all)	1	2	
Musculoskeletal chest pain			
subjects affected / exposed	4 / 130 (3.08%)	2 / 130 (1.54%)	
occurrences (all)	4	2	
Musculoskeletal pain			
subjects affected / exposed	0 / 130 (0.00%)	5 / 130 (3.85%)	
occurrences (all)	0	6	

Musculoskeletal stiffness			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	7 / 130 (5.38%)	3 / 130 (2.31%)	
occurrences (all)	13	3	
Neck pain			
subjects affected / exposed	2 / 130 (1.54%)	4 / 130 (3.08%)	
occurrences (all)	2	5	
Osteoarthritis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Osteochondrosis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	8 / 130 (6.15%)	3 / 130 (2.31%)	
occurrences (all)	15	3	
Sacroiliitis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Spinal pain			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 130 (3.08%)	5 / 130 (3.85%)	
occurrences (all)	4	7	
Bronchopneumonia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Cellulitis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	3	
Conjunctivitis			

subjects affected / exposed	4 / 130 (3.08%)	2 / 130 (1.54%)		
occurrences (all)	5	2		
Cystitis				
subjects affected / exposed	2 / 130 (1.54%)	1 / 130 (0.77%)		
occurrences (all)	2	1		
Ear infection				
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)		
occurrences (all)	2	0		
Erysipelas				
subjects affected / exposed	1 / 130 (0.77%)	2 / 130 (1.54%)		
occurrences (all)	1	3		
Folliculitis				
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)		
occurrences (all)	0	1		
Furuncle				
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)		
occurrences (all)	2	0		
Gastric infection				
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)		
occurrences (all)	0	1		
Nasopharyngitis				
subjects affected / exposed	1 / 130 (0.77%)	3 / 130 (2.31%)		
occurrences (all)	1	3		
Oral candidiasis				
subjects affected / exposed	2 / 130 (1.54%)	2 / 130 (1.54%)		
occurrences (all)	2	2		
Oral herpes				
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)		
occurrences (all)	1	0		
Pharyngitis				
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)		
occurrences (all)	1	0		
Pneumonia				
subjects affected / exposed	4 / 130 (3.08%)	2 / 130 (1.54%)		
occurrences (all)	4	2		
Pyoderma				

subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Rash pustular			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Skin infection			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Soft tissue infection			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Subcutaneous abscess			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 130 (0.77%)	2 / 130 (1.54%)	
occurrences (all)	1	2	
Urethritis			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	4 / 130 (3.08%)	4 / 130 (3.08%)	
occurrences (all)	4	4	
Vaginal infection			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Viral infection			

subjects affected / exposed	2 / 130 (1.54%)	2 / 130 (1.54%)	
occurrences (all)	2	3	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Vulvitis			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	4	0	
Vulvovaginitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 130 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	17 / 130 (13.08%)	20 / 130 (15.38%)	
occurrences (all)	27	27	
Dehydration			
subjects affected / exposed	2 / 130 (1.54%)	3 / 130 (2.31%)	
occurrences (all)	2	3	
Diabetes mellitus			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences (all)	1	1	
Gout			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	4 / 130 (3.08%)	11 / 130 (8.46%)	
occurrences (all)	7	20	
Hyperkalaemia			
subjects affected / exposed	1 / 130 (0.77%)	1 / 130 (0.77%)	
occurrences (all)	1	1	
Hypoalbuminaemia			
subjects affected / exposed	3 / 130 (2.31%)	5 / 130 (3.85%)	
occurrences (all)	3	5	
Hypocalcaemia			
subjects affected / exposed	2 / 130 (1.54%)	2 / 130 (1.54%)	
occurrences (all)	3	2	

Hypokalaemia			
subjects affected / exposed	1 / 130 (0.77%)	6 / 130 (4.62%)	
occurrences (all)	1	9	
Hypomagnesaemia			
subjects affected / exposed	3 / 130 (2.31%)	5 / 130 (3.85%)	
occurrences (all)	3	7	
Hyponatraemia			
subjects affected / exposed	2 / 130 (1.54%)	7 / 130 (5.38%)	
occurrences (all)	2	8	
Hypophosphataemia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 130 (0.77%)	
occurrences (all)	0	1	
Hypoproteinaemia			
subjects affected / exposed	2 / 130 (1.54%)	0 / 130 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 September 2014	The primary purposes of Protocol Amendment 1 were to: 1. Add an inclusion criterion requiring testing for EGFR-activating mutations and ALK rearrangement and, if positive, to require appropriate tyrosine kinase inhibitor therapy prior to enrollment 2. Amend the inclusion criterion for adequate hematologic function as measured by hemoglobin from 10 g/dL to 8 g/dL 3. Amend the contraception inclusion criterion to allow implementation of institutional standards for contraception 4. Correct the recommendations regarding use of concomitant anti-inflammatory drugs to accurately reflect pemetrexed labelling 5. Correct the stratification factor regarding extent of disease from M1a vs. M1b to M0/M1a vs M1b 6. Addition of Exclusion Criterion #19 (Section 4.2 Exclusion Criteria) to exclude patients who are concurrently participating in another clinical trial or study 7. To amend the exclusion criterion regarding eligibility of patients with prior additional cancers

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

TH-CR-415 study enrolment ended prematurely in December 2015 due to a futility analysis which determined efficacy threshold would likely not be met. The last study visit occurred on 15April2016, and the database locked in May, 2016.

Notes: