



Clinical trial results:

A Randomized, Double-Blind Phase 2 Study of Ruxolitinib or Placebo in Combination With Pemetrexed/Cisplatin and Pemetrexed Maintenance for Initial Treatment of Subjects With Nonsquamous Non-Small Cell Lung Cancer That Is Stage IIIB, Stage IV, or Recurrent

Summary

EudraCT number	2014-001436-10
Trial protocol	IT DK ES NL PT
Global end of trial date	21 June 2016

Results information

Result version number	v1
This version publication date	10 August 2017
First version publication date	10 August 2017

Trial information

Trial identification

Sponsor protocol code	INCB 18424-266
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02119650
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Incyte Corporation
Sponsor organisation address	1801 Augustine Cut-Off, Wilmington, DE, United States, 19803
Public contact	Incyte Corporation, Incyte Corporation Call Centre, +44 (0)330 100 3677, globalmedinfo@incyte.com
Scientific contact	Incyte Corporation, Incyte Corporation Call Centre, +44 (0)330 100 3677, globalmedinfo@incyte.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	21 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2016
Global end of trial reached?	Yes
Global end of trial date	21 June 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

- Part 1: To evaluate the safety and tolerability of ruxolitinib in combination with pemetrexed/cisplatin and select a dose for further evaluation
- Part 2: To evaluate and compare the OS of subjects with nonsquamous NSCLC that is Stage IIIB, Stage IV, or recurrent when treated with ruxolitinib or placebo in combination with pemetrexed/cisplatin and subsequently pemetrexed maintenance

Protection of trial subjects:

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Conference on Harmonisation Guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 February 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	Netherlands: 2
Country: Number of subjects enrolled	Portugal: 4
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Denmark: 6
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	United States: 31
Worldwide total number of subjects	76
EEA total number of subjects	45

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)	49
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 42 study centers (25 in the United States, 4 in Spain, 3 in France, 3 in Portugal, 2 in Denmark, 2 in Germany, 2 in Italy, 1 in the Netherlands).

Pre-assignment

Screening details:

Randomized, Double-Blind Portion:

Anticipated duration of treatment for an individual subject was approximately 8 months: up to 28 days for screening and baseline.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind Treatment: Ruxolitinib plus Pemetrexed/Cisplatin

Arm description:

Ruxolitinib was self-administered as a 15 mg twice daily (BID) oral treatment during the randomized, double-blind treatment, without regard to food. Pemetrexed 500 mg/m² was administered as an intravenous infusion over 10 minutes, and 75 mg/m² Cisplatin was infused over 2 hours beginning 30 ± 5 minutes after the end of the pemetrexed infusion on Day 1 of each 21-day cycle (Treatment Cycles).

Arm type	Experimental
Investigational medicinal product name	Ruxolitinib
Investigational medicinal product code	
Other name	Jakafi®, Jakavi®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg tablets to be administered by mouth at dose selected from safety run-in phase (Ruxolitinib 15 mg twice daily (BID)).

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	Alimta®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

500 mg/m² administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle.

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

Dosage and administration details:

75 mg/m² infused over 2 hours beginning 30 ± 5 minutes after the end of the pemetrexed infusion.

Arm title	Double-Blind Treatment: Placebo Plus Pemetrexed/Cisplatin
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Arm description:

Matching placebo was self-administered as a 15 mg BID oral treatment during the randomized, double-blind treatment, without regard to food. Pemetrexed 500 mg/m² was administered as an intravenous infusion over 10 minutes, and 75 mg/m² Cisplatin was infused over 2 hours beginning 30 ± 5 minutes after the end of the pemetrexed infusion on Day 1 of each 21-day cycle (Treatment Cycles).

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg matching placebo tablets to be administered by mouth.

Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	Alimta®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

500 mg/m² administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle.

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

Dosage and administration details:

75 mg/m² infused over 2 hours beginning 30 ± 5 minutes after the end of the pemetrexed infusion.

Number of subjects in period 1	Double-Blind Treatment: Ruxolitinib plus Pemetrexed/Cisplatin	Double-Blind Treatment: Placebo Plus Pemetrexed/Cisplatin
Started	39	37
Completed	14	11
Not completed	25	26
Multiple reasons for termination	2	1
Physician decision	-	2
Disease progression	11	14
Adverse event, non-fatal	3	4
Subject decision	2	3
Death	5	1
Noncompliance with study treatment	1	1
Study terminated by the sponsor	1	-

Baseline characteristics

Reporting groups

Reporting group title	Double-Blind Treatment: Ruxolitinib plus Pemetrexed/Cisplatin
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Reporting group description:

Ruxolitinib was self-administered as a 15 mg twice daily (BID) oral treatment during the randomized, double-blind treatment, without regard to food. Pemetrexed 500 mg/m² was administered as an intravenous infusion over 10 minutes, and 75 mg/m² Cisplatin was infused over 2 hours beginning 30 ± 5 minutes after the end of the pemetrexed infusion on Day 1 of each 21-day cycle (Treatment Cycles).

Reporting group title	Double-Blind Treatment: Placebo Plus Pemetrexed/Cisplatin
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Reporting group description:

Matching placebo was self-administered as a 15 mg BID oral treatment during the randomized, double-blind treatment, without regard to food. Pemetrexed 500 mg/m² was administered as an intravenous infusion over 10 minutes, and 75 mg/m² Cisplatin was infused over 2 hours beginning 30 ± 5 minutes after the end of the pemetrexed infusion on Day 1 of each 21-day cycle (Treatment Cycles).

Reporting group values	Double-Blind Treatment: Ruxolitinib plus Pemetrexed/Cisplatin n	Double-Blind Treatment: Placebo Plus Pemetrexed/Cisplatin n	Total
Number of subjects	39	37	76
Age categorical Units: Subjects			
Adults (18-64 years)	26	23	49
From 65-84 years	13	14	27
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	61.6	62	
standard deviation	± 8.85	± 8.55	-
Gender categorical Units: Subjects			
Female	15	14	29
Male	24	23	47
Body Mass Index (BMI) Units: kg/m ²			
arithmetic mean	27.67	27.65	
standard deviation	± 6.402	± 7.26	-

End points

End points reporting groups

Reporting group title	Double-Blind Treatment: Ruxolitinib plus Pemetrexed/Cisplatin
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Reporting group description:

Ruxolitinib was self-administered as a 15 mg twice daily (BID) oral treatment during the randomized, double-blind treatment, without regard to food. Pemetrexed 500 mg/m² was administered as an intravenous infusion over 10 minutes, and 75 mg/m² Cisplatin was infused over 2 hours beginning 30 ± 5 minutes after the end of the pemetrexed infusion on Day 1 of each 21-day cycle (Treatment Cycles).

Reporting group title	Double-Blind Treatment: Placebo Plus Pemetrexed/Cisplatin
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Reporting group description:

Matching placebo was self-administered as a 15 mg BID oral treatment during the randomized, double-blind treatment, without regard to food. Pemetrexed 500 mg/m² was administered as an intravenous infusion over 10 minutes, and 75 mg/m² Cisplatin was infused over 2 hours beginning 30 ± 5 minutes after the end of the pemetrexed infusion on Day 1 of each 21-day cycle (Treatment Cycles).

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

Overall survival is defined as the time from randomization to death due to any cause. Participants without death observed at the time of the analysis were censored at last date known to be alive. The median overall survival time was estimated using the Kaplan-Meier method. Overall survival was compared between treatment groups using log-rank test.

End point type	Primary
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End point timeframe:

Randomization until death due to any cause; up to 16 months or data cutoff 11FEB2016.

End point values	Double-Blind Treatment: Ruxolitinib plus Pemetrexed/Cisplatin	Double-Blind Treatment: Placebo Plus Pemetrexed/Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39 ^[1]	37 ^[2]		
Units: months				
median (confidence interval 80%)	7.5 (5.7 to 999.99)	5.9 (4 to 999.99)		

Notes:

[1] - (ITT) population.

999.99= Not evaluable due to insufficient number of participants with events.

[2] - (ITT) population.

999.99= Not evaluable due to insufficient number of participants with events.

Statistical analyses

Statistical analysis title	Overall Survival
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Comparison groups	Double-Blind Treatment: Placebo Plus Pemetrexed/Cisplatin v
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	Double-Blind Treatment: Ruxolitinib plus Pemetrexed/Cisplatin
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7562 ^[3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.877
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.509
upper limit	1.51

Notes:

[3] - The 2-sided p-value was calculated based on the log-rank test and stratified by modified Glasgow Prognostic Score (mGPS).

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)
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End point description:

PFS is defined as the time from randomization until the earliest date of disease progression determined by investigator assessment of objective radiographic disease assessments per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or death due to any cause if sooner. Progressive Disease (PD) is defined using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as at least a 20% increase in the sum of the Longest Diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions, unequivocal progression of non-target lesions or increase in disease burden for subjects with only nonmeasurable disease.

End point type	Secondary
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End point timeframe:

Randomization to disease progression, or death due to any cause if sooner; up to 16 months or to the data cutoff 11FEB2016.

End point values	Double-Blind Treatment: Ruxolitinib plus Pemetrexed/Cisplatin	Double-Blind Treatment: Placebo Plus Pemetrexed/Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39 ^[4]	37 ^[5]		
Units: months				
number (not applicable)	0	0		

Notes:

[4] - PFS was not conducted due to early termination and insufficient number of participants with events.

[5] - PFS was not conducted due to early termination and insufficient number of participants with events.

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)
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End point description:

Objective response rate determined by radiographic disease assessments per RECIST (v1.1), by investigator assessment and was defined as the percentage of participants with Complete Response (CR) or Partial Response (PR) by Response Evaluation Criteria in Solid Tumours (RECIST) at any post baseline visit. Per Response Evaluation Criteria In Solid Tumours Criteria (RECIST) for target lesions and assessed by computed tomography (CT) and/or magnetic resonance imaging (MRI) : Complete Response (CR), Disappearance of all target and non-target lesions; Partial Response (PR), $\geq 30\%$ decrease in the sum of the longest diameter of target lesions with no worsening of non-target lesions and no new lesions; Overall Response (OR) = CR + PR.

End point type	Secondary
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End point timeframe:

Baseline through end of study; up to 16 months or to the data cutoff 11FEB2016.

End point values	Double-Blind Treatment: Ruxolitinib plus Pemetrexed/Cisplatin	Double-Blind Treatment: Placebo Plus Pemetrexed/Cisplatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39 ^[6]	37 ^[7]		
Units: participants				
number (not applicable)				
Overall Response	12	13		
Complete Response	0	0		
Partial Response	12	13		
Stable Disease	4	5		
Progressive Disease	6	4		
Unable to Evaluate	2	3		
Not Assessed	15	12		

Notes:

[6] - The intent-to-treat (ITT) population consisted of participants that were randomized in the study.

[7] - The intent-to-treat (ITT) population consisted of participants that were randomized in the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response
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End point description:

For objective responders, the duration of response is defined as the difference of the end of response and the start of response for subjects who have at least 1 response measurement. The start of a response was the first visit where the subject achieves PR or better based on RECIST v1.1 criteria. The end of response was the first visit after PD based on RECIST v1.1 criteria.

End point type	Secondary
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End point timeframe:

From the start of response to the end of response; up to 16 months or to the data cutoff 11FEB2016.

End point values	Double-Blind Treatment: Ruxolitinib plus Pemetrexed/Ci splatin	Double-Blind Treatment: Placebo Plus Pemetrexed/Ci splatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12 ^[8]	13 ^[9]		
Units: weeks				
median (confidence interval 80%)	20.14 (18 to 30.71)	12.14 (6 to 24)		

Notes:

[8] - The intent-to-treat (ITT) population consisted of participants that were randomized in the study.

[9] - The intent-to-treat (ITT) population consisted of participants that were randomized in the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Participants With Treatment-emergent Adverse Events (TEAEs)

End point title	Participants With Treatment-emergent Adverse Events (TEAEs)
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End point description:

A treatment-emergent AE was defined as an event occurring after exposure to at least 1 dose of study drug (ruxolitinib or placebo). A treatment-related AE was defined as an event with a definite, probable, or possible causality to study medication. A serious AE is an event resulting in death, hospitalization, persistent or significant disability/incapacity, or is life threatening, a congenital anomaly/birth defect or requires medical or surgical intervention to prevent 1 of the outcomes above. The intensity of an AE was graded according to the National Cancer Institute common terminology criteria for adverse events (NCI-CTCAE) version 4.03: Grade 1 (Mild); Grade 2 (Moderate); Grade 3 (Severe); Grade 4 (life-threatening).

End point type	Secondary
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End point timeframe:

Baseline through approximately 30 days post treatment discontinuation; up to 16 months or to the data cutoff 11FEB2016.

End point values	Double-Blind Treatment: Ruxolitinib plus Pemetrexed/Ci splatin	Double-Blind Treatment: Placebo Plus Pemetrexed/Ci splatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39 ^[10]	37 ^[11]		
Units: participants				
number (not applicable)				
Participants who had any TEAEs	39	36		
Participants who had treatment-related TEAEs	16	28		
Participants with any serious TEAE	19	16		

Participants who had Grade 3 or higher TEAEs	25	22		
Participants with a fatal TEAE	4	4		
TEAEs related to reference therapy	30	35		
Participants who were hospitalized due to TEAEs	16	15		
Participants who discontinued drug due to TEAEs	2	4		
Participants who interrupted drug due to TEAEs	11	15		
Discontinued reference therapy due to TEAEs	4	7		
Interrupted reference therapy due to TEAEs	8	7		
Participants given concomitant meds due to TEAEs	36	32		
Procedure/nondrug therapy due to TEAEs	17	12		

Notes:

[10] - Safety evaluable population consisted of all participants exposed to at least 1 dose of study drug.

[11] - Safety evaluable population consisted of all participants exposed to at least 1 dose of study drug.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study medication through approximately 30 days post treatment discontinuation; up to 16 months or to the data cutoff 11FEB2016.

Adverse event reporting additional description:

The safety evaluable population consisted of all participants exposed to at least 1 dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Double-Blind Treatment: Ruxolitinib + Pemetrexed/Cisplatin
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Reporting group description:

Ruxolitinib was self-administered as a 15 mg BID oral treatment during the randomized, double-blind treatment, without regard to food. Pemetrexed 500 mg/m² was administered as an intravenous infusion over 10 minutes, and 75 mg/m² Cisplatin was infused over 2 hours beginning 30 ± 5 minutes after the end of the pemetrexed infusion on Day 1 of each 21-day cycle (Treatment Cycles).

Reporting group title	Double-Blind Treatment: Placebo Plus Pemetrexed/Cisplatin
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Reporting group description:

Matching placebo was self-administered as a 15 mg BID oral treatment during the randomized, double-blind treatment, without regard to food. Pemetrexed 500 mg/m² was administered as an intravenous infusion over 10 minutes, and 75 mg/m² Cisplatin was infused over 2 hours beginning 30 ± 5 minutes after the end of the pemetrexed infusion on Day 1 of each 21-day cycle (Treatment Cycles).

Serious adverse events	Double-Blind Treatment: Ruxolitinib + Pemetrexed/Cisplatin	Double-Blind Treatment: Placebo Plus Pemetrexed/Cisplatin	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 39 (48.72%)	16 / 37 (43.24%)	
number of deaths (all causes)	4	4	
number of deaths resulting from adverse events	4	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic pain			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 39 (0.00%)	2 / 37 (5.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 39 (2.56%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Acute respiratory failure			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 39 (7.69%)	2 / 37 (5.41%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	1 / 1	1 / 1	
Pulmonary embolism			
subjects affected / exposed	2 / 39 (5.13%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 39 (0.00%)	2 / 37 (5.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pleuritic pain			
subjects affected / exposed	0 / 39 (0.00%)	2 / 37 (5.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary toxicity			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 39 (2.56%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Amylase increased			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood potassium decreased			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Chemical peritonitis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 39 (0.00%)	2 / 37 (5.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			

subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIth nerve disorder			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (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	3 / 39 (7.69%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 39 (5.13%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			

subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 39 (0.00%)	2 / 37 (5.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 39 (2.56%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 39 (5.13%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pancreatitis acute			

subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (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			
Back pain			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 39 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 39 (2.56%)	0 / 37 (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 Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 39 (7.69%) 1 / 3 0 / 0	3 / 37 (8.11%) 0 / 3 0 / 0	
Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 39 (2.56%) 0 / 1 0 / 0	1 / 37 (2.70%) 1 / 1 1 / 1	
Septic shock subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 39 (5.13%) 1 / 2 0 / 0	0 / 37 (0.00%) 0 / 0 0 / 0	
Post procedural infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 39 (0.00%) 0 / 0 0 / 0	1 / 37 (2.70%) 0 / 1 0 / 0	
Respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 39 (2.56%) 0 / 1 0 / 0	0 / 37 (0.00%) 0 / 0 0 / 0	
Urinary tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 39 (2.56%) 0 / 1 0 / 0	1 / 37 (2.70%) 0 / 1 0 / 0	
Wound infection staphylococcal subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 39 (0.00%) 0 / 0 0 / 0	1 / 37 (2.70%) 0 / 1 0 / 0	
Metabolism and nutrition disorders Failure to thrive subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 39 (2.56%) 0 / 1 1 / 1	0 / 37 (0.00%) 0 / 0 0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Double-Blind Treatment: Ruxolitinib + Pemetrexed/Cisplatin	Double-Blind Treatment: Placebo Plus Pemetrexed/Cisplatin	
Total subjects affected by non-serious adverse events subjects affected / exposed	37 / 39 (94.87%)	36 / 37 (97.30%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 39 (5.13%)	0 / 37 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 39 (7.69%)	2 / 37 (5.41%)	
occurrences (all)	3	2	
Fatigue			
subjects affected / exposed	13 / 39 (33.33%)	14 / 37 (37.84%)	
occurrences (all)	13	14	
Oedema peripheral			
subjects affected / exposed	8 / 39 (20.51%)	5 / 37 (13.51%)	
occurrences (all)	8	5	
Pyrexia			
subjects affected / exposed	7 / 39 (17.95%)	4 / 37 (10.81%)	
occurrences (all)	7	4	
Asthenia			
subjects affected / exposed	7 / 39 (17.95%)	12 / 37 (32.43%)	
occurrences (all)	7	12	
Malaise			
subjects affected / exposed	0 / 39 (0.00%)	2 / 37 (5.41%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			

Acute respiratory failure subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	2 / 37 (5.41%) 2	
Cough subjects affected / exposed occurrences (all)	6 / 39 (15.38%) 6	9 / 37 (24.32%) 9	
Dyspnoea subjects affected / exposed occurrences (all)	7 / 39 (17.95%) 7	9 / 37 (24.32%) 9	
Dyspnoea exertional subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3	1 / 37 (2.70%) 1	
Nasal congestion subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	2 / 37 (5.41%) 2	
Epistaxis subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	2 / 37 (5.41%) 2	
Haemoptysis subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	3 / 37 (8.11%) 3	
Productive cough subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	2 / 37 (5.41%) 2	
Wheezing subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	2 / 37 (5.41%) 2	
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	2 / 37 (5.41%) 2	
Depression subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	2 / 37 (5.41%) 2	
Insomnia			

subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	3 / 37 (8.11%) 3	
Investigations			
Blood calcium decreased subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	2 / 37 (5.41%) 2	
Blood creatinine increased subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 4	2 / 37 (5.41%) 2	
Weight decreased subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 4	3 / 37 (8.11%) 3	
C-reactive protein increased subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	3 / 37 (8.11%) 3	
Platelet count decreased subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	3 / 37 (8.11%) 3	
Cardiac disorders			
Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	2 / 37 (5.41%) 2	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	6 / 37 (16.22%) 6	
Dysgeusia subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2	6 / 37 (16.22%) 6	
Headache subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3	2 / 37 (5.41%) 2	
Neuropathy peripheral subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3	0 / 37 (0.00%) 0	
Peripheral sensory neuropathy			

subjects affected / exposed	1 / 39 (2.56%)	3 / 37 (8.11%)	
occurrences (all)	1	3	
Syncope			
subjects affected / exposed	0 / 39 (0.00%)	2 / 37 (5.41%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	15 / 39 (38.46%)	12 / 37 (32.43%)	
occurrences (all)	15	12	
Neutropenia			
subjects affected / exposed	8 / 39 (20.51%)	4 / 37 (10.81%)	
occurrences (all)	8	4	
Thrombocytopenia			
subjects affected / exposed	3 / 39 (7.69%)	0 / 37 (0.00%)	
occurrences (all)	3	0	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 39 (2.56%)	4 / 37 (10.81%)	
occurrences (all)	1	4	
Ototoxicity			
subjects affected / exposed	1 / 39 (2.56%)	4 / 37 (10.81%)	
occurrences (all)	1	4	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 39 (5.13%)	2 / 37 (5.41%)	
occurrences (all)	2	2	
Constipation			
subjects affected / exposed	13 / 39 (33.33%)	13 / 37 (35.14%)	
occurrences (all)	13	13	
Diarrhoea			
subjects affected / exposed	9 / 39 (23.08%)	10 / 37 (27.03%)	
occurrences (all)	9	10	
Dyspepsia			
subjects affected / exposed	0 / 39 (0.00%)	4 / 37 (10.81%)	
occurrences (all)	0	4	
Dysphagia			

subjects affected / exposed	2 / 39 (5.13%)	2 / 37 (5.41%)	
occurrences (all)	2	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 39 (5.13%)	0 / 37 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	20 / 39 (51.28%)	32 / 37 (86.49%)	
occurrences (all)	20	32	
Stomatitis			
subjects affected / exposed	10 / 39 (25.64%)	7 / 37 (18.92%)	
occurrences (all)	10	7	
Vomiting			
subjects affected / exposed	7 / 39 (17.95%)	12 / 37 (32.43%)	
occurrences (all)	7	12	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 39 (5.13%)	1 / 37 (2.70%)	
occurrences (all)	2	1	
Rash			
subjects affected / exposed	1 / 39 (2.56%)	4 / 37 (10.81%)	
occurrences (all)	1	4	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	2 / 39 (5.13%)	1 / 37 (2.70%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 39 (7.69%)	0 / 37 (0.00%)	
occurrences (all)	3	0	
Back pain			
subjects affected / exposed	4 / 39 (10.26%)	4 / 37 (10.81%)	
occurrences (all)	4	4	
Muscular weakness			
subjects affected / exposed	0 / 39 (0.00%)	2 / 37 (5.41%)	
occurrences (all)	0	2	
Musculoskeletal chest pain			

subjects affected / exposed	2 / 39 (5.13%)	1 / 37 (2.70%)	
occurrences (all)	2	1	
Musculoskeletal pain			
subjects affected / exposed	2 / 39 (5.13%)	0 / 37 (0.00%)	
occurrences (all)	2	0	
Myalgia			
subjects affected / exposed	2 / 39 (5.13%)	1 / 37 (2.70%)	
occurrences (all)	2	1	
Neck pain			
subjects affected / exposed	0 / 39 (0.00%)	3 / 37 (8.11%)	
occurrences (all)	0	3	
Pain in extremity			
subjects affected / exposed	3 / 39 (7.69%)	0 / 37 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Candida infection			
subjects affected / exposed	2 / 39 (5.13%)	0 / 37 (0.00%)	
occurrences (all)	2	0	
Pneumonia			
subjects affected / exposed	1 / 39 (2.56%)	2 / 37 (5.41%)	
occurrences (all)	1	2	
Rhinitis			
subjects affected / exposed	1 / 39 (2.56%)	2 / 37 (5.41%)	
occurrences (all)	1	2	
Urinary tract infection			
subjects affected / exposed	3 / 39 (7.69%)	1 / 37 (2.70%)	
occurrences (all)	3	1	
Bronchitis			
subjects affected / exposed	0 / 39 (0.00%)	2 / 37 (5.41%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	1 / 39 (2.56%)	3 / 37 (8.11%)	
occurrences (all)	1	3	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	5 / 39 (12.82%)	14 / 37 (37.84%)
occurrences (all)	5	14
Dehydration		
subjects affected / exposed	4 / 39 (10.26%)	2 / 37 (5.41%)
occurrences (all)	4	2
Hypokalaemia		
subjects affected / exposed	3 / 39 (7.69%)	7 / 37 (18.92%)
occurrences (all)	3	7
Hyponatraemia		
subjects affected / exposed	2 / 39 (5.13%)	3 / 37 (8.11%)
occurrences (all)	2	3
Hyperglycaemia		
subjects affected / exposed	0 / 39 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	2
Hyperkalaemia		
subjects affected / exposed	2 / 39 (5.13%)	0 / 37 (0.00%)
occurrences (all)	2	0
Hypomagnesaemia		
subjects affected / exposed	2 / 39 (5.13%)	6 / 37 (16.22%)
occurrences (all)	2	6
Hypophosphataemia		
subjects affected / exposed	1 / 39 (2.56%)	2 / 37 (5.41%)
occurrences (all)	1	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 January 2014	The primary purpose of the amendment was to clarify the designation of study visits: Cycles where both pemetrexed and cisplatin were given were designated TCycles. Cycles where maintenance pemetrexed was given were designated MCycles. Ruxolitinib or placebo were given during both TCycles and MCycles
01 July 2014	The primary purpose of the amendment was to revise requirements regarding prior treatments and to clarify language referring to pleural/pericardial effusion. The clinically important changes included: • Revision of the requirement for wash-out for prior treatments of central nervous system metastases • Removal of language referring to pleural/pericardial effusion as a descriptor for Stage IIIB NCSLC.
10 September 2014	The primary purpose of the amendment was to add or clarify several items. The clinically important changes included: • Addition of an additional exclusion criteria of prior JAK inhibitor use • Addition of a risks summary for granulocyte colony-stimulating factor (GCSF) • Addition of additional information on the DMC • Update to information regarding contraceptive use • Addition of a listing of inducers of CYP 3A4.
02 February 2015	The primary purpose of the amendment was to add or clarify several items. The clinically important changes included: • Addition of a brief summary of Part 1 and to designate the dose for Part 2 as 15 mg BID ruxolitinib/matching placebo, without prophylactic GCSF in a randomized, double-blind comparison • Removal of language describing prophylactic GCSF use and the possibility for open label study for clarity • Addition of a prescreening C-reactive protein measurement and an optional tissue biopsy for consenting subjects • Update to contraceptive language • Addition of options for administration of vitamin B12 • Addition of options for use of dexamethasone as both an anti-inflammatory and anti emetic prophylaxis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
11 February 2016	The study was terminated as other related studies of ruxolitinib did not provide sufficient efficacy to warrant continuation.	-

Notes:

Limitations and caveats

None reported