Clinical trial results:
A Randomized, Double-Blind, Phase 2 Study of Ruxolitinib or Placebo in Combination With Capecitabine in Subjects With Advanced or Metastatic HER2-Negative Breast Cancer

Summary

EudraCT number	2014-002620-26
Trial protocol	IT GB PT ES
Global end of trial date	24 January 2017

Results information

Result version number	v1 (current)
This version publication date	06 January 2018
First version publication date	06 January 2018

Trial information

Trial identification

Sponsor protocol code	INCB18424-268

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02120417
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 Call Centre, Incyte Corporation, +44 (0)330 100 3677, globalmedinfo@incyte.com
Scientific contact	Incyte Corporation Call Centre, Incyte Corporation, +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	13 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 January 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This was a randomized, double-blind, placebo-controlled phase 2 clinical trial comparing the overall survival of women with advanced or metastatic HER2-negative breast cancer who received treatment with capecitabine in combination with ruxolitinib versus those who received treatment with capecitabine alone.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 May 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	Portugal: 2
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 137
Worldwide total number of subjects	149
EEA total number of subjects	12

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)	114
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 72 study centers (65 in the United States and 7 in the European Union [3 in the United Kingdom, 3 in Spain, and 1 in Portugal]).

Pre-assignment

Screening details:

Subjects received study treatment in continuous 21-day cycles until they met withdrawal criteria or until study termination.

Period 1

Period 1 title	Overall Period (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	Treatment A - Capecitabine and ruxolitinib

Arm description:

Capecitabine given as 1000 mg/m^2 twice a day (BID) on day 1 to day 14 of each 21-day cycle with the addition of Ruxolitinib 15 mg (three 5 mg tablets) BID to be administered by mouth on day 1 to day 21 of each 21-day cycle

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; Ruxolitinib 15 mg BID (starting dose).

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine 2000 mg/m^2 daily given as 1000 mg/m^2 twice a day (BID) (starting dose) Day 1-14 of each 21 day cycle.

Arm title	Treatment B - Capecitabine and placebo

Arm description:

Capecitabine given as 1000 mg/m^2 twice a day (BID) on day 1 to day 14 of each 21-day cycle with the addition of 15 mg (three 5 mg tablets) matching placebo BID to be administered by mouth on day 1 to day 21 of each 21-day cycle.

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	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine 2000 mg/m^2 daily given as 1000 mg/m^2 twice a day (BID) (starting dose) Day 1-14 of each 21 day cycle.

Number of subjects in period 1	Treatment A - Capecitabine and ruxolitinib	Treatment B - Capecitabine and placebo
Started	76	73
Completed	16	5
Not completed	60	68
Physician decision	2	3
Participant decision	4	4
Disease progression	41	45
Other unspecified	5	4
Adverse Event	3	9
Death	5	1
Noncompliance with study treatment	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Treatment A - Capecitabine and ruxolitinib
Reporting group description:	
Capecitabine given as 1000 mg/m^2 twice a day (BID) on day 1 to day 14 of each 21-day cycle with the addition of Ruxolitinib 15 mg (three 5 mg tablets) BID to be administered by mouth on day 1 to day 21 of each 21-day cycle	
Reporting group title	Treatment B - Capecitabine and placebo
Reporting group description:	
Capecitabine given as 1000 mg/m^2 twice a day (BID) on day 1 to day 14 of each 21-day cycle with the addition of 15 mg (three 5 mg tablets) matching placebo BID to be administered by mouth on day 1 to day 21 of each 21-day cycle.	

Reporting group values	Treatment A - Capecitabine and ruxolitinib	Treatment B - Capecitabine and placebo	Total
Number of subjects	76	73	149
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	61	53	114
From 65-84 years	15	20	35
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	54.3	55.0	
standard deviation	± 11.00	± 12.75	-
Gender categorical			
Units: Subjects			
Female	76	73	149
Male	0	0	0

End points

End points reporting groups

Reporting group title	Treatment A - Capecitabine and ruxolitinib

Reporting group description:

Capecitabine given as 1000 mg/m^2 twice a day (BID) on day 1 to day 14 of each 21-day cycle with the addition of Ruxolitinib 15 mg (three 5 mg tablets) BID to be administered by mouth on day 1 to day 21 of each 21-day cycle

Reporting group title	Treatment B - Capecitabine and placebo

Reporting group description:

Capecitabine given as 1000 mg/m^2 twice a day (BID) on day 1 to day 14 of each 21-day cycle with the addition of 15 mg (three 5 mg tablets) matching placebo BID to be administered by mouth on day 1 to day 21 of each 21-day cycle.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival is reported here as the number of days from randomization to death due to any cause until the data cutoff for the final analysis. The hazard ratio (80% CI) for ruxolitinib versus placebo was estimated using a Cox regression model stratified by hormone-receptor status.

End point type	Primary

End point timeframe:

Randomization until death due to any cause up to the data cutoff 08FEB2016.

End point values	Treatment A - Capecitabine and ruxolitinib	Treatment B - Capecitabine and placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76[1]	73[2]		
Units: participants				
number (not applicable)				
Death events	39	38		
Censored events	37	35		

Notes:

[1] - The Intent-to-Treat (ITT) population consisted of all participants randomized to the study.

[2] - The Intent-to-Treat (ITT) population consisted of all participants randomized to the study.

Statistical analyses

Statistical analysis title	Overall Survival (OS)
Comparison groups	Treatment B - Capecitabine and placebo v Treatment A - Capecitabine and ruxolitinib

Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.762 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.932
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.694
upper limit	1.252

Notes:

[3] - The P-value was analyzed by Log-Rank Test stratified by Hormone Receptor Status.

Primary: Median Survival

End point title	Median Survival[4]

End point description:

Survival was assessed by the time to death or censoring up until 08Feb2016. Participants with no observed death were treated as right-censored at their last date known to be alive. The median survival time was estimated by the Kaplan-Meier method.

End point type	Primary

End point timeframe:

Randomization until death due to any cause up to the data cutoff 08FEB2016.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analysis was planned or conducted for this primary endpoint.

End point values	Treatment A - Capecitabine and ruxolitinib	Treatment B - Capecitabine and placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76[5]	73[6]		
Units: months				
median (confidence interval 95%)	11.2 (7.5 to 12.7)	10.9 (6.0 to 13.1)		

Notes:

[5] - The Intent-to-Treat (ITT) population consisted of all participants randomized to the study.

[6] - The Intent-to-Treat (ITT) population consisted of all participants randomized to the study.

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of Participants Achieving Overall Survival

End point title	Proportion of Participants Achieving Overall Survival[7]

End point description:

Overall survival was assessed as the time to death or censoring up until 08Feb2016. Participants with no observed death were treated as right-censored at their last date known to be alive. The survival time was analyzed using the Kaplan-Meier method.

End point type	Primary

End point timeframe:

Randomization until death due to any cause at month 3, 6, 9, 12 and 15 or the data cutoff 08FEB2016.

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No formal statistical analysis was planned or conducted for this primary endpoint.

End point values	Treatment A - Capecitabine and ruxolitinib	Treatment B - Capecitabine and placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76[8]	73[9]		
Units: percentage of participants				
number (confidence interval 95%)				
Month 3 Survival Rate	0.855 (0.753 to 0.917)	0.750 (0.633 to 0.835)		
Month 6 Survival Rate	0.674 (0.554 to 0.769)	0.635 (0.511 to 0.735)		
Month 9 Survival Rate	0.537 (0.404 to 0.652)	0.546 (0.417 to 0.657)		
Month 12 Survival Rate	0.435 (0.289 to 0.573)	0.427 (0.286 to 0.561)		
Month 15 Survival Rate	0.319 (0.174 to 0.475)	0.294 (0.148 to 0.456)		

Notes:

[8] - The Intent-to-Treat (ITT) population consisted of all participants randomized to the study.

[9] - The Intent-to-Treat (ITT) population consisted of all participants randomized to the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

Progression-free survival was defined as the time from the randomization date to the earliest date of disease progression, as measured by investigator assessment of objective radiographic disease assessments per RECIST (v1.1), or death from any cause if earlier. Progression-free survival time distribution and median survival for each treatment group were analyzed using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

Randomization to disease progression, or death due to any cause if sooner up to the data cutoff 08FEB2016.

End point values	Treatment A - Capecitabine and ruxolitinib	Treatment B - Capecitabine and placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76[10]	73[11]		
Units: months				
median (confidence interval 95%)	4.5 (2.3 to 6.1)	2.5 (2.1 to 4.1)		

Notes:

[10] - The Intent-to-Treat (ITT) population consisted of all participants randomized to the study.

[11] - The Intent-to-Treat (ITT) population consisted of all participants randomized to the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Objective Response Rate

End point title	Percentage of Participants Achieving Objective Response Rate

End point description:

Objective response rate was determined by radiographic disease assessments per Response Evaluation Criteria in Solid Tumours (RECIST v1.1), by investigator assessment and was defined as the percentage of participants with Complete Response (CR) or Partial Response (PR) by RECIST at any post baseline visit. Per Response Evaluation Criteria In Solid Tumors 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 and no new lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions; Overall Response (OR) = CR + PR.

End point type	Secondary

End point timeframe:

Randomization through end of study up to the data cutoff 08FEB2016.

End point values	Treatment A - Capecitabine and ruxolitinib	Treatment B - Capecitabine and placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76[12]	73[13]		
Units: percentage of participants				
number (not applicable)				
Complete Response rate	0.0	0.0		
Partial Response rate	28.9	13.7		

Notes:

[12] - The Intent-to-Treat (ITT) population consisted of all participants randomized to the study.

[13] - The Intent-to-Treat (ITT) population consisted of all participants randomized to the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

The DOR was defined as the difference (in number of months) between the end of response and the start of response for participants who had at least 1 response measurement. The start of a response was the first visit where the participant achieved a partial response or better based on RECIST (v1.1) criteria. The end of response was the earlier of death or progressive disease based on RECIST (v1.1) criteria. The date of progressive disease was the date on which progression was first recorded. Per 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 and no new lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions; Overall Response (OR) = CR + PR.

End point type	Secondary

End point timeframe:

Randomization through end of study up to the data cutoff 08FEB2016.

End point values	Treatment A - Capecitabine and ruxolitinib	Treatment B - Capecitabine and placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76[14]	73[15]		
Units: months				
median (confidence interval 80%)	4.2 (3.5 to 4.6)	4.4 (3.8 to 6.4)		

Notes:

[14] - The Intent-to-Treat (ITT) population consisted of all participants randomized to the study.

[15] - The Intent-to-Treat (ITT) population consisted of all participants randomized to the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving Clinical Benefit Rate

End point title	Percentage of Participants Achieving Clinical Benefit Rate

End point description:

Clinical benefit rate was defined as a complete response, partial response, or stable disease, determined by investigator assessment of objective radiographic disease assessments per RECIST (v1.1) that lasted for ≥ 6 months. Per Response Evaluation Criteria In Solid Tumors 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), >=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

End point timeframe:

Randomization through end of study up to the data cutoff 08FEB2016.

End point values	Treatment A - Capecitabine and ruxolitinib	Treatment B - Capecitabine and placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76[16]	73[17]		
Units: percentage of participants				
number (not applicable)	13.2	6.8		

Notes:

[16] - The Intent-to-Treat (ITT) population consisted of all participants randomized to the study.

[17] - The Intent-to-Treat (ITT) population consisted of all participants randomized to the study.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Participants received study treatment in continuous 21-day cycles until they met withdrawal criteria up to the second data cutoff 13APR2016.

Adverse event reporting additional description:

The safety evaluable population consisted of all participants enrolled in the study who received at least 1 dose of any study treatment (ie, ruxolitinib, placebo, or capecitabine).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Treatment A - Capecitabine and Ruxolitinib

Reporting group description:

Capecitabine given as 1000 mg/m^2 twice a day (BID) on day 1 to day 14 of each 21-day cycle with the addition of Ruxolitinib 15 mg (three 5 mg tablets) BID to be administered by mouth on day 1 to day 21 of each 21-day cycle

Reporting group title	Treatment B - Capecitabine and Placebo

Reporting group description:

Capecitabine given as 1000 mg/m^2 twice a day (BID) on day 1 to day 14 of each 21-day cycle with the addition of 15 mg (three 5 mg tablets) matching placebo BID to be administered by mouth on day 1 to day 21 of each 21-day cycle

Serious adverse events	Treatment A - Capecitabine and Ruxolitinib	Treatment B - Capecitabine and Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 71 (39.44%)	29 / 71 (40.85%)	
number of deaths (all causes)	5	7	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	0 / 71 (0.00%)	3 / 71 (4.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 71 (1.41%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (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			
Non-cardiac chest pain			
subjects affected / exposed	2 / 71 (2.82%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 71 (2.82%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dyspnoea			
subjects affected / exposed	3 / 71 (4.23%)	4 / 71 (5.63%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 71 (2.82%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 71 (4.23%)	6 / 71 (8.45%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pleuritic pain			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 71 (1.41%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 71 (0.00%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Respiratory failure			
subjects affected / exposed	0 / 71 (0.00%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Psychiatric disorders			

Confusional state			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood creatinine increased			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	2 / 71 (2.82%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac arrest			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 71 (1.41%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Embolic stroke			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Encephalopathy			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 71 (0.00%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 71 (1.41%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 71 (1.41%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 71 (2.82%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	2 / 71 (2.82%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 71 (0.00%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 71 (1.41%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 71 (1.41%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 71 (2.82%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis haemorrhagic			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	5 / 71 (7.04%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	4 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	4 / 71 (5.63%)	4 / 71 (5.63%)	
occurrences causally related to treatment / all	2 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	2 / 71 (2.82%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (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 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	2 / 71 (2.82%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	3 / 71 (4.23%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	2 / 71 (2.82%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Urinary tract infection			
subjects affected / exposed	2 / 71 (2.82%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 71 (4.23%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 71 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 71 (1.41%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			

subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic disorder			
subjects affected / exposed	1 / 71 (1.41%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Treatment A - Capecitabine and Ruxolitinib	Treatment B - Capecitabine and Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 71 (100.00%)	69 / 71 (97.18%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 71 (8.45%)	4 / 71 (5.63%)	
occurrences (all)	6	4	
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 71 (14.08%)	5 / 71 (7.04%)	
occurrences (all)	12	8	
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 71 (7.04%)	4 / 71 (5.63%)	
occurrences (all)	5	4	
Blood creatinine increased			
subjects affected / exposed	4 / 71 (5.63%)	3 / 71 (4.23%)	
occurrences (all)	4	4	
Lymphocyte count decreased			
subjects affected / exposed	4 / 71 (5.63%)	2 / 71 (2.82%)	
occurrences (all)	7	3	
Neutrophil count decreased			
subjects affected / exposed	6 / 71 (8.45%)	2 / 71 (2.82%)	
occurrences (all)	14	3	
Platelet count decreased			

subjects affected / exposed	5 / 71 (7.04%)	0 / 71 (0.00%)	
occurrences (all)	5	0	
Weight decreased			
subjects affected / exposed	4 / 71 (5.63%)	5 / 71 (7.04%)	
occurrences (all)	4	5	
Weight increased			
subjects affected / exposed	6 / 71 (8.45%)	4 / 71 (5.63%)	
occurrences (all)	7	4	
White blood cell count decreased			
subjects affected / exposed	7 / 71 (9.86%)	1 / 71 (1.41%)	
occurrences (all)	16	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	6 / 71 (8.45%)	3 / 71 (4.23%)	
occurrences (all)	6	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	13 / 71 (18.31%)	13 / 71 (18.31%)	
occurrences (all)	17	13	
Dysgeusia			
subjects affected / exposed	1 / 71 (1.41%)	5 / 71 (7.04%)	
occurrences (all)	1	5	
Headache			
subjects affected / exposed	16 / 71 (22.54%)	9 / 71 (12.68%)	
occurrences (all)	20	9	
Hypoaesthesia			
subjects affected / exposed	4 / 71 (5.63%)	4 / 71 (5.63%)	
occurrences (all)	4	5	
Neuropathy peripheral			
subjects affected / exposed	3 / 71 (4.23%)	5 / 71 (7.04%)	
occurrences (all)	3	6	
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 71 (5.63%)	5 / 71 (7.04%)	
occurrences (all)	4	5	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	34 / 71 (47.89%)	18 / 71 (25.35%)	
occurrences (all)	50	18	
Neutropenia			
subjects affected / exposed	9 / 71 (12.68%)	5 / 71 (7.04%)	
occurrences (all)	11	7	
Thrombocytopenia			
subjects affected / exposed	6 / 71 (8.45%)	1 / 71 (1.41%)	
occurrences (all)	7	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	40 / 71 (56.34%)	31 / 71 (43.66%)	
occurrences (all)	45	35	
Oedema			
subjects affected / exposed	4 / 71 (5.63%)	3 / 71 (4.23%)	
occurrences (all)	4	3	
Oedema peripheral			
subjects affected / exposed	10 / 71 (14.08%)	14 / 71 (19.72%)	
occurrences (all)	12	14	
Pyrexia			
subjects affected / exposed	12 / 71 (16.90%)	10 / 71 (14.08%)	
occurrences (all)	12	11	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	5 / 71 (7.04%)	6 / 71 (8.45%)	
occurrences (all)	5	6	
Abdominal pain			
subjects affected / exposed	12 / 71 (16.90%)	6 / 71 (8.45%)	
occurrences (all)	14	6	
Constipation			
subjects affected / exposed	18 / 71 (25.35%)	17 / 71 (23.94%)	
occurrences (all)	20	20	
Diarrhoea			
subjects affected / exposed	32 / 71 (45.07%)	19 / 71 (26.76%)	
occurrences (all)	47	25	
Dyspepsia			

subjects affected / exposed	6 / 71 (8.45%)	4 / 71 (5.63%)	
occurrences (all)	7	4	
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 71 (5.63%)	4 / 71 (5.63%)	
occurrences (all)	4	4	
Nausea			
subjects affected / exposed	38 / 71 (53.52%)	34 / 71 (47.89%)	
occurrences (all)	47	37	
Stomatitis			
subjects affected / exposed	18 / 71 (25.35%)	12 / 71 (16.90%)	
occurrences (all)	20	15	
Vomiting			
subjects affected / exposed	27 / 71 (38.03%)	19 / 71 (26.76%)	
occurrences (all)	45	26	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 71 (19.72%)	9 / 71 (12.68%)	
occurrences (all)	15	9	
Dyspnoea			
subjects affected / exposed	21 / 71 (29.58%)	19 / 71 (26.76%)	
occurrences (all)	23	20	
Epistaxis			
subjects affected / exposed	5 / 71 (7.04%)	2 / 71 (2.82%)	
occurrences (all)	6	2	
Oropharyngeal pain			
subjects affected / exposed	4 / 71 (5.63%)	1 / 71 (1.41%)	
occurrences (all)	4	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	4 / 71 (5.63%)	0 / 71 (0.00%)	
occurrences (all)	4	0	
Dry skin			
subjects affected / exposed	3 / 71 (4.23%)	5 / 71 (7.04%)	
occurrences (all)	3	5	
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	33 / 71 (46.48%)	27 / 71 (38.03%)	
occurrences (all)	52	31	
Skin hyperpigmentation			
subjects affected / exposed	6 / 71 (8.45%)	2 / 71 (2.82%)	
occurrences (all)	6	2	
Hot flush			
subjects affected / exposed	5 / 71 (7.04%)	1 / 71 (1.41%)	
occurrences (all)	5	1	
Hypertension			
subjects affected / exposed	4 / 71 (5.63%)	2 / 71 (2.82%)	
occurrences (all)	6	2	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 71 (2.82%)	6 / 71 (8.45%)	
occurrences (all)	3	6	
Insomnia			
subjects affected / exposed	8 / 71 (11.27%)	9 / 71 (12.68%)	
occurrences (all)	8	9	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 71 (9.86%)	9 / 71 (12.68%)	
occurrences (all)	8	9	
Back pain			
subjects affected / exposed	11 / 71 (15.49%)	5 / 71 (7.04%)	
occurrences (all)	11	5	
Muscle spasms			
subjects affected / exposed	5 / 71 (7.04%)	3 / 71 (4.23%)	
occurrences (all)	5	3	
Muscular weakness			
subjects affected / exposed	5 / 71 (7.04%)	2 / 71 (2.82%)	
occurrences (all)	5	2	
Musculoskeletal chest pain			
subjects affected / exposed	4 / 71 (5.63%)	5 / 71 (7.04%)	
occurrences (all)	4	5	
Musculoskeletal pain			

subjects affected / exposed	4 / 71 (5.63%)	5 / 71 (7.04%)	
occurrences (all)	4	6	
Myalgia			
subjects affected / exposed	5 / 71 (7.04%)	2 / 71 (2.82%)	
occurrences (all)	5	2	
Neck pain			
subjects affected / exposed	4 / 71 (5.63%)	2 / 71 (2.82%)	
occurrences (all)	4	2	
Pain in extremity			
subjects affected / exposed	9 / 71 (12.68%)	5 / 71 (7.04%)	
occurrences (all)	10	5	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 71 (5.63%)	2 / 71 (2.82%)	
occurrences (all)	4	3	
Urinary tract infection			
subjects affected / exposed	6 / 71 (8.45%)	6 / 71 (8.45%)	
occurrences (all)	8	7	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	21 / 71 (29.58%)	19 / 71 (26.76%)	
occurrences (all)	22	21	
Dehydration			
subjects affected / exposed	11 / 71 (15.49%)	3 / 71 (4.23%)	
occurrences (all)	15	3	
Hypocalcaemia			
subjects affected / exposed	8 / 71 (11.27%)	0 / 71 (0.00%)	
occurrences (all)	9	0	
Hypokalaemia			
subjects affected / exposed	10 / 71 (14.08%)	4 / 71 (5.63%)	
occurrences (all)	11	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 July 2014	The primary purpose of the amendment was to add/clarify several items in the original protocol. • Clarified eligibility criteria • Clarified that the most recent available result prior to randomization would be used to determine subject eligibility. • Clarified that the total daily capecitabine dose (2000 mg/m^2) was to be administered in approximately equal doses BID, in the morning and evening, approximately 12 hours apart, and that the dose was to be calculated according to BSA. • Added that subjects would continue receiving study treatment until they met withdrawal criteria. • Added that subjects who required the use of a potent cytochrome P450 3A4 inhibitor should have their ruxolitinib dose reduced from BID to once daily with frequent complete blood count monitoring during the period of coadministration. • Clarified that informed consent was to be obtained before performing any study-specific procedures that were not considered standard of care for the treatment of breast cancer and that screening assessments performed per standard of care did not need to be repeated after the ICF was signed if performed within 28 days of the Cycle 1 Day 1 visit. • Changed the frequency of radiological assessments to every 9 weeks until subjects had received 12 months of treatment. Thereafter, the frequency of scans was reduced to every 12 weeks. Screening CT scan or MRI of the brain was only to be performed if brain metastases or CNS symptoms were present. Bone scans were to be done at screening or if clinically indicated. Nontarget bone lesions (per RECIST v1.1) were followed every 9 weeks by CT scan with bone window or MRI. • Clarified that subjects who discontinued treatment because of disease progression did not need to repeat radiographic assessments at the EOT visit. • Clarified that subjects should bring all study-related medications with them to each study visit to assess study drug compliance.
23 September 2014	The primary purpose of the amendment was to provide clarification regarding inclusion/exclusion criteria and acceptable forms of effective contraception. The clinically important changes included: • A new exclusion criterion was added to exclude pregnant and breastfeeding women. • Revised wording and updated the acceptable forms of effective contraception listed in the Protocol.
20 October 2014	The primary purpose of the amendment was to update information regarding contraceptive methods in the Protocol, to be consistent with contraception recommendations from the 15 SEP 2014 Clinical Trial Facilitation Group meeting in Rome. Only highly effective methods of birth control (ie, failure rate < 1% per year when used consistently and correctly) were considered acceptable.

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.

The study was terminated as other related studies of ruxolitinib did not provide sufficient efficacy to warrant continuation.

Notes: