Clinical trial results:
A Randomized, Controlled, Open-Label, Multicenter Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, Ibrutinib, versus Temsirolimus in Subjects with Relapsed or Refractory Mantle Cell Lymphoma Who Have Received at Least One Prior Therapy

Summary

EudraCT number	2012-000601-74
Trial protocol	SE BE DE GB IE HU PT CZ NL ES IT
Global end of trial date	15 December 2016

Results information

Result version number	v1 (current)
This version publication date	31 December 2017
First version publication date	31 December 2017

Trial information

Trial identification

Sponsor protocol code	PCI-32765MCL3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01646021
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International NV
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, B-2340
Public contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen-Cilag International NV, ClinicalTrialsEU@its.jnj.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 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate whether treatment with ibrutinib compared with temsirolimus would result in prolongation of progression-free survival (PFS) in subjects with relapsed or refractory mantle cell lymphoma (MCL) who have received at least 1 prior rituximab-containing chemotherapy regimen.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Safety evaluations included monitoring of adverse events, clinical laboratory tests, physical examinations, Eastern Cooperative Oncology Group (ECOG) criteria for performance status, and concomitant medication usage.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 December 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	Brazil: 15
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Colombia: 7
Country: Number of subjects enrolled	Czech Republic: 14
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Korea, Republic of: 14
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Netherlands: 2

Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Russian Federation: 29
Country: Number of subjects enrolled	Sweden: 18
Country: Number of subjects enrolled	Taiwan: 6
Country: Number of subjects enrolled	Ukraine: 10
Worldwide total number of subjects	280
EEA total number of subjects	188

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)	107
From 65 to 84 years	170
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 280 subjects were enrolled in this study. 139 subjects were randomized and treated in the ibrutinib arm. 141 subjects were randomized to the temsirolimus arm and 139 were treated, 2 subjects were randomized but did not receive treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Arm A: Ibrutinib

Arm description:

Subjects received 560 milligram (mg) ibrutinib (4*140-mg capsules) by mouth once daily continuous (without interruption) self-administered home treatment during the 21 day cycle.

Arm type	Experimental
Investigational medicinal product name	Ibrutinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received 560 mg ibrutinib (4*140 mg capsules) once daily continuously during the 21-day cycle.

Arm title	Treatment Arm B: Temsirolimus

Arm description:

Subjects received temsirolimus intravenous (IV) infusion 175 mg on Days 1, 8, 15 of the first cycle followed by 75 mg on Days 1, 8, 15 of each subsequent 21-day cycle. Each temsirolimus dose is infused over a 30 to 60 minute period.

Arm type	Active comparator
Investigational medicinal product name	Temsirolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received temsirolimus intravenous infusion 175 mg on Days 1, 8, 15 of the first cycle followed by 75 mg on Days 1, 8, 15 of each subsequent 21-day cycle.

Number of subjects in period 1	Treatment Arm A: Ibrutinib	Treatment Arm B: Temsirolimus
Started	139	141
Treated	139	139
Completed	0	0
Not completed	139	141
Consent withdrawn by subject	10	15
Death	77	83
Study terminated by sponsor	50	41
Lost to follow-up	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Treatment Arm A: Ibrutinib
Reporting group description:	
Subjects received 560 milligram (mg) ibrutinib (4*140-mg capsules) by mouth once daily continuous (without interruption) self-administered home treatment during the 21 day cycle.	
Reporting group title	Treatment Arm B: Temsirolimus
Reporting group description:	
Subjects received temsirolimus intravenous (IV) infusion 175 mg on Days 1, 8, 15 of the first cycle followed by 75 mg on Days 1, 8, 15 of each subsequent 21-day cycle. Each temsirolimus dose is infused over a 30 to 60 minute period.	

Reporting group values	Treatment Arm A: Ibrutinib	Treatment Arm B: Temsirolimus	Total
Number of subjects	139	141	280
Title for AgeCategorical Units: subjects			
Adults (18-64 years)	53	54	107
From 65 to 84 years	86	84	170
85 years and over	0	3	3
Title for AgeContinuous Units: years			
arithmetic mean	66.7	67.1	
standard deviation	± 8.68	± 9.83	-
Title for Gender Units: subjects			
Female	39	33	72
Male	100	108	208

End points

End points reporting groups

Reporting group title	Treatment Arm A: Ibrutinib
Reporting group description:	
Subjects received 560 milligram (mg) ibrutinib (4*140-mg capsules) by mouth once daily continuous (without interruption) self-administered home treatment during the 21 day cycle.	
Reporting group title	Treatment Arm B: Temsirolimus
Reporting group description:	
Subjects received temsirolimus intravenous (IV) infusion 175 mg on Days 1, 8, 15 of the first cycle followed by 75 mg on Days 1, 8, 15 of each subsequent 21-day cycle. Each temsirolimus dose is infused over a 30 to 60 minute period.	

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description:	
PFS is defined as the duration in months from the date of randomization to the date of progression disease (PD) or relapse from complete response (CR) or death whichever was reported first and was assessed based on the investigator assessment. Revised Response Criteria for Malignant Lymphoma categorizes the response of the treatment of a patient's tumour to CR (the disappearance of all evidence of disease), Relapsed Disease or PD (Any new lesion or increase by greater than or equal to [>=] 50 percent [%] of previously involved sites from nadir). The Intent-to-Treat (ITT) population included all subjects randomized into the study regardless of treatment actually received.	
End point type	Primary
End point timeframe:	
Time from the date of randomization until the date of first documented evidence of progressive disease (or relapse for subjects who experience CR during the study) or death, whichever occurred first (approximately 48 months)	

End point values	Treatment Arm A: Ibrutinib	Treatment Arm B: Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	141		
Units: Months				
median (confidence interval 95%)	15.6 (10.6 to 25.1)	6.2 (4.2 to 7.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Treatment Arm A: Ibrutinib v Treatment Arm B: Temsirolimus

Number of subjects included in analysis	280
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.6

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

ORR is defined as the percentage of participants who achieved either CR or PR as best overall response based on the investigator assessment where CR is defined as disappearance of all target lesions, PR is defined as greater than or equal to 30 % decrease in the sum of the longest diameter of target lesions and Overall Response (OR) is the sum of CR and PR. The ITT population included all subjects randomized into the study regardless of treatment actually received.

End point type	Secondary

End point timeframe:

Approximately 48 months

End point values	Treatment Arm A: Ibrutinib	Treatment Arm B: Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	141		
Units: Percentage of Subjects				
number (not applicable)	77.0	46.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

Duration of response was defined as the interval between the date of initial documentation of a response and the date of the first documented evidence of progressive disease or death, whichever event occurred first. The analysis was based on the investigator assessment. The ITT population included all subjects randomized into the study regardless of treatment actually received. Here 'N' signifies number of subjects analysed for this endpoint.

End point type	Secondary

End point timeframe:

Approximately 48 months

End point values	Treatment Arm A: Ibrutinib	Treatment Arm B: Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	66		
Units: Months				
median (confidence interval 95%)	23.1 (16.2 to 28.1)	6.3 (4.7 to 8.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Next Treatment (TTNT)

End point title	Time to Next Treatment (TTNT)

End point description:

Time to next treatment was measured from the date of randomization to the start date of any anti-neoplastic treatment subsequent to study treatment. Here, for Upper 95% CI '99999' indicates median TTNT that was not estimable at primary analysis due to in less than 50% patients event had occurred. The ITT population included all subjects randomized into the study regardless of treatment actually received.

End point type	Secondary

End point timeframe:

Approximately 48 months

End point values	Treatment Arm A: Ibrutinib	Treatment Arm B: Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	141		
Units: Months				
median (confidence interval 95%)	31.8 (23.3 to 99999)	11.6 (8.0 to 13.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival (OS) was defined as the interval between the date of randomization and the date of death from any cause. The ITT population included all subjects randomized into the study regardless of treatment actually received.

End point type	Secondary

End point timeframe:

Approximately 48 months

End point values	Treatment Arm A: Ibrutinib	Treatment Arm B: Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	141		
Units: Months				
median (confidence interval 95%)	30.3 (19.1 to 42.1)	23.5 (13.0 to 30.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Treatment Arm A: Ibrutinib v Treatment Arm B: Temsirolimus
Number of subjects included in analysis	280
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0621
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.02

Secondary: Progression-Free Survival 2

End point title	Progression-Free Survival 2

End point description:

Progression-free survival 2 defined as the time interval between the date of randomization and date of event, defined as progressive disease as assessed by investigator that started after the next line of subsequent antineoplastic therapy (including cross-over to ibrutinib), death from any cause, or the start of the second subsequent antineoplastic therapy if no progressive disease was recorded after the first subsequent antineoplastic therapy. The ITT population included all subjects randomized into the study regardless of treatment actually received.

End point type	Secondary

End point timeframe:

Approximately 48 months

End point values	Treatment Arm A: Ibrutinib	Treatment Arm B: Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	141		
Units: Months				
median (confidence interval 95%)	26.2 (17.2 to 32.4)	15.4 (10.2 to 21.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Worsening in the Lymphoma Subscale of the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym)

End point title	Time to Worsening in the Lymphoma Subscale of the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym)

End point description:

Time to worsening in the Lym subscale of the FACT-Lym, defined as the interval from the date of randomization to the start date of worsening. Worsening was defined by a 5-point decrease from baseline. The FACT-Lym PRO questionnaires were administered to assess functional status and well-being and lymphoma symptoms over time. FACT-Lym Lymphoma subscale contains 15 questions, scores from 0 to 4 for each question (higher the worse). Lymphoma subscale score is the total of reverse scores, range 0 to 60. Here, 99999 indicates median and upper limit of CI of FACT-Lym that was not estimable at final analysis due to less than 50% patients had events occurred. The ITT population included all subjects randomized into the study regardless of treatment actually received.

End point type	Secondary

End point timeframe:

Approximately up to 48 months

End point values	Treatment Arm A: Ibrutinib	Treatment Arm B: Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	141		
Units: Weeks				
median (confidence interval 95%)	99999 (81.4 to 99999)	10.6 (6.6 to 15.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Affected With Treatment-emergent Adverse Events

End point title	Number of Subjects Affected With Treatment-emergent Adverse Events

End point description:

An AE is any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An serious adverse event (SAE) is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Safety population included all randomized subjects who received at least 1 dose of the study drug.

End point type	Secondary

End point timeframe:

Time from first dose of study drug until the last dose date + 30 days or the start of a subsequent anti-neoplastic therapy, whichever occur earlier

End point values	Treatment Arm A: Ibrutinib	Treatment Arm B: Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	139		
Units: Subjects	139	138		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to Response

End point title	Time to Response

End point description:

Time to response for subjects with CR/PR, defined as the interval between the date of randomization and date of initial documentation of response. The Intent -to -Treat population included all subjects randomized into the study. The 'N' signifies the number of subjects responded for this outcome measure.

End point type	Other pre-specified

End point timeframe:

Approximately 2.8 years

End point values	Treatment Arm A: Ibrutinib	Treatment Arm B: Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	57		
Units: Months				
median (full range (min-max))	2.15 (0.5 to 10.4)	2.14 (0.9 to 12.0)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Extent of Exposure of Time

End point title	Extent of Exposure of Time

End point description:

Extent of exposure is defined as the duration of the treatment administered during the study. Duration of exposure is calculated as the number of months between the start and end of treatment. Safety Analysis Set (SAS) population includes all the randomized subjects who received at least 1 dose of study agent (ibrutinib or temsirolimus) during the treatment phase.

End point type	Other pre-specified

End point timeframe:

Approximately up to 46.8 months

End point values	Treatment Arm A: Ibrutinib	Treatment Arm B: Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	139		
Units: Months				
median (full range (min-max))	14.39 (0.0 to 46.8)	3.02 (0.0 to 31.4)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Area Under the Plasma Concentration of Ibrutinib during Steady State (AUC-ss)

End point title	Area Under the Plasma Concentration of Ibrutinib during Steady State (AUC-ss)[1]

End point description:

The AUC-ss is the area under the plasma concentration time curve observed during steady state. The pharmacokinetics population was included in the study.

End point type	Other pre-specified

End point timeframe:

Cycle 1 and 2 (Day 1): Predose, 1, 2, 4 hr postdose; Cycle 3 (day 1): Predose

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Endpoint was planned to be reported for the specified arms only.

End point values	Treatment Arm A: Ibrutinib			
Subject group type	Reporting group			
Number of subjects analysed	139			
Units: nanogram*hour per milliliter (ng*h/mL)				
arithmetic mean (standard deviation)	561.6 (± 448)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Bio markers That Alter B-cell Receptor (BCR) signaling or Activate Alternative Signaling Pathways and to Explore Their Association With Response or Resistance to Ibrutinib

End point title	Number of Subjects With Bio markers That Alter B-cell Receptor (BCR) signaling or Activate Alternative Signaling Pathways and to Explore Their Association With Response or Resistance to Ibrutinib

End point description:

Next-generation sequencing at baseline identifies possible primary resistance mutations and those found only at progression are acquired mutations on therapy.

End point type	Other pre-specified

End point timeframe:

Approximately up to 28.2 months

End point values	Treatment Arm A: Ibrutinib	Treatment Arm B: Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	141		
Units: Subjects				
number (not applicable)	61	53		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Hospitalizations Reported Related Medical Resource Utilization Information (MRUI)

End point title	Number of Hospitalizations Reported Related Medical Resource Utilization Information (MRUI)

End point description:

Medical resource utilization data associated with medical encounters related to disease was reported for all subjects throughout the study. The Intent--to -Treat population included subjects randomized into the study. The 'N' signifies the number of subjects responded for this outcome measure.

End point type	Other pre-specified

End point timeframe:

Approximately up to 28.2 months

End point values	Treatment Arm A: Ibrutinib	Treatment Arm B: Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	91		
Units: Hospitalizations				
arithmetic mean (standard deviation)	3.1 (± 4.6)	2.8 (± 4.3)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Emergency Room Visits Reported Related Medical Resource Utilization Information (MRUI)

End point title	Number of Emergency Room Visits Reported Related Medical Resource Utilization Information (MRUI)

End point description:

Medical resource utilization data associated with medical encounters related to disease was reported for all subjects throughout the study. The Intent-to--Treat population included subjects randomized into the study. The 'N' signifies the number of subjects responded for this outcome measure.

End point type	Other pre-specified

End point timeframe:

Approximately up to 28.2 months

End point values	Treatment Arm A: Ibrutinib	Treatment Arm B: Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: Emergency room visits				
arithmetic mean (standard deviation)	1.2 (± 0.4)	1.2 (± 0.4)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Days of Hospitalization and Emergency Room Visits Reported Related Medical Resource Utilization Information (MRUI)

End point title	Days of Hospitalization and Emergency Room Visits Reported Related Medical Resource Utilization Information (MRUI)

End point description:

Medical resource utilization data associated with medical encounters related to disease was reported for all subjects throughout the study. The Intent--to--Treat population included subjects randomized into

the study. The 'n' signifies the number of subjects analyzed at this time point.

End point type	Other pre-specified

End point timeframe:

Approximately up to 28.2 months

End point values	Treatment Arm A: Ibrutinib	Treatment Arm B: Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	141		
Units: Days				
arithmetic mean (standard deviation)				
Mean days of hospitalization (n=83, 91)	19.7 (± 20.5)	20.3 (± 22.4)		
Mean days of emergency room visits (n=5, 5)	1.8 (± 1.3)	1.6 (± 1.3)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: The Mean Change From Baseline in the EuroQol-5 Dimension 5-Level Instrument (EQ-5D-5L) Scores for Each Post Baseline Assessment

End point title	The Mean Change From Baseline in the EuroQol-5 Dimension 5-Level Instrument (EQ-5D-5L) Scores for Each Post Baseline Assessment

End point description:

The EQ-5D is a subject rated questionnaire to assess health-related quality of life in terms of a single utility score. Health State Profile component assesses level of current health for 5 domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression, using 5 levels (1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, and 5=extreme problems). Scoring formula developed by EuroQol Group assigns a utility value for each domain in the profile. Score is transformed and possible total score range -0.594 to 1; higher score indicates a better health state. Here, number of subjects analyzed 'N' signifies number of subjects evaluable for this endpoint. 'n' signifies the number of subjects analyzed at specified time point. The ITT population included all subjects randomized into the study regardless of treatment actually received.

End point type	Other pre-specified

End point timeframe:

Baseline, Cycle 2, 3, 4, 5, 6, 7, 8, 11, 14, 17, 20, 28, 36 and End of treatment (approximately 23 months)

End point values	Treatment Arm A: Ibrutinib	Treatment Arm B: Temsirolimus		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	130		
Units: Unit on a Scale				
arithmetic mean (standard deviation)				
Baseline (n= 130, 120)	0.7 (± 0.2)	0.7 (± 0.2)		

Change at Cycle 2 (n= 113, 95)	0.0 (± 0.2)	0.0 (± 0.2)		
Change at Cycle 3 (n=115, 85)	0.1 (± 0.2)	-0.1 (± 0.2)		
Change at Cycle 4 (n=103, 70)	0.0 (± 0.2)	0.0 (± 0.3)		
Change at Cycle 5 (n=102, 57)	0.0 (± 0.2)	0.0 (± 0.2)		
Change at Cycle 6 (n=99, 49)	0.1 (± 0.2)	0.0 (± 0.2)		
Change at Cycle 7 (n=98, 39)	0.0 (± 0.2)	0.0 (± 0.2)		
Change at Cycle 8 (n=90, 37)	0.0 (± 0.2)	0.0 (± 0.2)		
Change at Cycle 11 (n=88, 33)	0.0 (± 0.2)	0.0 (± 0.2)		
Change at Cycle 14 (n=72, 26)	0.0 (± 0.2)	0.0 (± 0.1)		
Change at Cycle 17 (n=69, 19)	0.0 (± 0.2)	0.0 (± 0.2)		
Change at Cycle 20 (n=64, 16)	0.0 (± 0.2)	0.0 (± 0.2)		
Change at Cycle 28 (n=22, 6)	-0.1 (± 0.2)	0.1 (± 0.2)		
Change at Cycle 36 (n=10, 4)	0.0 (± 0.3)	-0.1 (± 0.2)		
End of treatment (n= 23, 65)	0.0 (± 0.2)	-0.1 (± 0.3)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately up to 48 months

Adverse event reporting additional description:

Safety population included all randomized subjects who received at least 1 dose of study agent (ibrutinib or temsirolimus) during the treatment phase.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Temsirolimus

Reporting group description:

Subjects in Treatment Arm B received temsirolimus intravenous (IV) infusion 175 mg on Days 1, 8, 15 of the first cycle followed by 75 mg on Days 1, 8, 15 of each subsequent 21-day cycle. Each temsirolimus dose is infused over a 30 to 60 minute period.

Reporting group title	Ibrutinib

Reporting group description:

Subjects in Treatment Arm A received 560 milligram (mg) oral ibrutinib (4*140-mg capsules) once daily continuously (self-administration at home) during the 21-day cycle.

Serious adverse events	Temsirolimus	Ibrutinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	83 / 139 (59.71%)	79 / 139 (56.83%)	
number of deaths (all causes)	82	77	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma Gastric			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal Cell Carcinoma			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder Transitional Cell Carcinoma			

subjects affected / exposed	0 / 139 (0.00%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal Cancer Metastatic			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary Gland Cancer			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous Cell Carcinoma			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thymoma			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional Cell Carcinoma			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			

subjects affected / exposed	0 / 139 (0.00%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic Hypotension			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
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			
Fatigue			
subjects affected / exposed	3 / 139 (2.16%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	3 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General Physical Health Deterioration			
subjects affected / exposed	5 / 139 (3.60%)	3 / 139 (2.16%)	
occurrences causally related to treatment / all	1 / 6	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 0	
Malaise			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal Inflammation			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-Organ Failure			
subjects affected / exposed	0 / 139 (0.00%)	4 / 139 (2.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 2	
Oedema			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	7 / 139 (5.04%)	3 / 139 (2.16%)	
occurrences causally related to treatment / all	5 / 11	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic Pain			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (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			
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 139 (0.00%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	5 / 139 (3.60%)	6 / 139 (4.32%)	
occurrences causally related to treatment / all	3 / 6	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	2 / 139 (1.44%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial Lung Disease			
subjects affected / exposed	2 / 139 (1.44%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Disorder			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infiltration			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	0 / 139 (0.00%)	6 / 139 (4.32%)	
occurrences causally related to treatment / all	0 / 0	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	3 / 139 (2.16%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	0 / 139 (0.00%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	1 / 139 (0.72%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary Oedema			
subjects affected / exposed	1 / 139 (0.72%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory Failure			
subjects affected / exposed	1 / 139 (0.72%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Psychiatric disorders			
Confusional State			
subjects affected / exposed	2 / 139 (1.44%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental Disorder			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood Creatinine Increased			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin Decreased			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil Count Decreased			

subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet Count Decreased			
subjects affected / exposed	0 / 139 (0.00%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula Fracture			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign Body			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar Vertebral Fracture			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Procedural Haemorrhage			
subjects affected / exposed	1 / 139 (0.72%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Procedural Swelling			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib Fracture			

subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic Rupture			
subjects affected / exposed	1 / 139 (0.72%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Subdural Haematoma			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Toxicity to Various Agents			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Pectoris			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina Unstable			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis Coronary Artery			

subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	2 / 139 (1.44%)	7 / 139 (5.04%)	
occurrences causally related to treatment / all	1 / 3	8 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac Failure Acute			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac Failure Chronic			
subjects affected / exposed	1 / 139 (0.72%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure Congestive			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (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	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary Artery Insufficiency			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary Artery Stenosis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Ischaemia			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Ischaemia			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			

subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive Disorder			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 139 (0.00%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial Paresis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic Stroke			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Memory Impairment			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonus			

subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	2 / 139 (1.44%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 139 (3.60%)	4 / 139 (2.88%)	
occurrences causally related to treatment / all	6 / 6	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune Haemolytic Anaemia			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	1 / 139 (0.72%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			

subjects affected / exposed	0 / 139 (0.00%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocytosis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 139 (0.72%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic Infarction			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	3 / 139 (2.16%)	5 / 139 (3.60%)	
occurrences causally related to treatment / all	2 / 3	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Retinopathy			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous Haemorrhage			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal Hernia			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain			
subjects affected / exposed	1 / 139 (0.72%)	5 / 139 (3.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 139 (2.88%)	3 / 139 (2.16%)	
occurrences causally related to treatment / all	6 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Stenosis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Ulcer			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis Haemorrhagic			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Haemorrhage			

subjects affected / exposed	1 / 139 (0.72%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhoids			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal Haemorrhage			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	3 / 139 (2.16%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis Toxic			

subjects affected / exposed	1 / 139 (0.72%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Guttate Psoriasis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panniculitis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Ulcer			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 139 (0.72%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis Haemorrhagic			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic Syndrome			

subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	4 / 139 (2.88%)	3 / 139 (2.16%)	
occurrences causally related to treatment / all	1 / 4	1 / 5	
deaths causally related to treatment / all	0 / 1	0 / 2	
Renal Impairment			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 139 (0.72%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Pain			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis Pyrophosphate			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral Disc Compression			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			

subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
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 / 139 (0.72%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess Limb			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical Pneumonia			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary Aspergillosis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Difficile Colitis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			

subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device Related Infection			
subjects affected / exposed	2 / 139 (1.44%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 139 (1.44%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 139 (1.44%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious Colitis			

subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis Fungal			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Abscess			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
subjects affected / exposed	1 / 139 (0.72%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	2 / 2	9 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infection			
subjects affected / exposed	2 / 139 (1.44%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Sepsis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral Candidiasis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			

subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis Jirovecii Infection			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis Jirovecii Pneumonia			
subjects affected / exposed	1 / 139 (0.72%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	12 / 139 (8.63%)	16 / 139 (11.51%)	
occurrences causally related to treatment / all	9 / 15	15 / 21	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumonia Escherichia			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Tuberculosis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	5 / 139 (3.60%)	6 / 139 (4.32%)	
occurrences causally related to treatment / all	6 / 8	3 / 10	
deaths causally related to treatment / all	1 / 1	1 / 4	
Septic Shock			
subjects affected / exposed	1 / 139 (0.72%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Sinusitis			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis Aspergillus			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin Infection			
subjects affected / exposed	1 / 139 (0.72%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft Tissue Infection			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth Infection			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			

subjects affected / exposed	2 / 139 (1.44%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	3 / 139 (2.16%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	2 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection Bacterial			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased Appetite			
subjects affected / exposed	2 / 139 (1.44%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 139 (0.72%)	2 / 139 (1.44%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes Mellitus			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic Ketoacidosis			
subjects affected / exposed	0 / 139 (0.00%)	1 / 139 (0.72%)	
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 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 139 (0.72%)	0 / 139 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour Lysis Syndrome			
subjects affected / exposed	3 / 139 (2.16%)	1 / 139 (0.72%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Temsirolimus	Ibrutinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	137 / 139 (98.56%)	130 / 139 (93.53%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	3 / 139 (2.16%)	11 / 139 (7.91%)	
occurrences (all)	4	18	
Hypertension			
subjects affected / exposed	5 / 139 (3.60%)	16 / 139 (11.51%)	
occurrences (all)	5	22	
Hypotension			
subjects affected / exposed	3 / 139 (2.16%)	7 / 139 (5.04%)	
occurrences (all)	3	10	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	26 / 139 (18.71%)	12 / 139 (8.63%)	
occurrences (all)	48	15	
Fatigue			
subjects affected / exposed	40 / 139 (28.78%)	31 / 139 (22.30%)	
occurrences (all)	71	57	
Mucosal Inflammation			

subjects affected / exposed	21 / 139 (15.11%)	2 / 139 (1.44%)	
occurrences (all)	44	3	
Oedema Peripheral			
subjects affected / exposed	33 / 139 (23.74%)	19 / 139 (13.67%)	
occurrences (all)	60	22	
Pyrexia			
subjects affected / exposed	26 / 139 (18.71%)	24 / 139 (17.27%)	
occurrences (all)	32	46	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	31 / 139 (22.30%)	31 / 139 (22.30%)	
occurrences (all)	55	50	
Dyspnoea			
subjects affected / exposed	13 / 139 (9.35%)	12 / 139 (8.63%)	
occurrences (all)	13	18	
Epistaxis			
subjects affected / exposed	31 / 139 (22.30%)	13 / 139 (9.35%)	
occurrences (all)	42	23	
Oropharyngeal Pain			
subjects affected / exposed	8 / 139 (5.76%)	8 / 139 (5.76%)	
occurrences (all)	11	10	
Pleural Effusion			
subjects affected / exposed	5 / 139 (3.60%)	10 / 139 (7.19%)	
occurrences (all)	5	12	
Pneumonitis			
subjects affected / exposed	7 / 139 (5.04%)	0 / 139 (0.00%)	
occurrences (all)	16	0	
Productive Cough			
subjects affected / exposed	5 / 139 (3.60%)	7 / 139 (5.04%)	
occurrences (all)	5	8	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	15 / 139 (10.79%)	7 / 139 (5.04%)	
occurrences (all)	18	11	
Investigations			

Alanine Aminotransferase Increased			
subjects affected / exposed	9 / 139 (6.47%)	4 / 139 (2.88%)	
occurrences (all)	15	4	
Aspartate Aminotransferase Increased			
subjects affected / exposed	10 / 139 (7.19%)	5 / 139 (3.60%)	
occurrences (all)	25	6	
Blood Alkaline Phosphatase Increased			
subjects affected / exposed	9 / 139 (6.47%)	4 / 139 (2.88%)	
occurrences (all)	30	5	
Blood Creatinine Increased			
subjects affected / exposed	18 / 139 (12.95%)	16 / 139 (11.51%)	
occurrences (all)	32	36	
Blood Lactate Dehydrogenase Increased			
subjects affected / exposed	7 / 139 (5.04%)	2 / 139 (1.44%)	
occurrences (all)	9	2	
Neutrophil Count Decreased			
subjects affected / exposed	10 / 139 (7.19%)	7 / 139 (5.04%)	
occurrences (all)	40	20	
Platelet Count Decreased			
subjects affected / exposed	23 / 139 (16.55%)	11 / 139 (7.91%)	
occurrences (all)	165	18	
Weight Decreased			
subjects affected / exposed	18 / 139 (12.95%)	9 / 139 (6.47%)	
occurrences (all)	24	10	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 139 (2.16%)	10 / 139 (7.19%)	
occurrences (all)	3	13	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	1 / 139 (0.72%)	8 / 139 (5.76%)	
occurrences (all)	1	10	
Nervous system disorders			

Dysgeusia			
subjects affected / exposed	7 / 139 (5.04%)	1 / 139 (0.72%)	
occurrences (all)	9	1	
Headache			
subjects affected / exposed	17 / 139 (12.23%)	13 / 139 (9.35%)	
occurrences (all)	20	20	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	57 / 139 (41.01%)	27 / 139 (19.42%)	
occurrences (all)	196	70	
Neutropenia			
subjects affected / exposed	36 / 139 (25.90%)	21 / 139 (15.11%)	
occurrences (all)	94	47	
Thrombocytopenia			
subjects affected / exposed	77 / 139 (55.40%)	25 / 139 (17.99%)	
occurrences (all)	323	83	
Eye disorders			
Cataract			
subjects affected / exposed	7 / 139 (5.04%)	2 / 139 (1.44%)	
occurrences (all)	9	2	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	11 / 139 (7.91%)	8 / 139 (5.76%)	
occurrences (all)	14	16	
Abdominal Pain Upper			
subjects affected / exposed	3 / 139 (2.16%)	8 / 139 (5.76%)	
occurrences (all)	4	27	
Constipation			
subjects affected / exposed	21 / 139 (15.11%)	13 / 139 (9.35%)	
occurrences (all)	25	15	
Diarrhoea			
subjects affected / exposed	42 / 139 (30.22%)	45 / 139 (32.37%)	
occurrences (all)	94	113	
Dyspepsia			
subjects affected / exposed	1 / 139 (0.72%)	9 / 139 (6.47%)	
occurrences (all)	1	14	
Mouth Ulceration			

subjects affected / exposed	8 / 139 (5.76%)	0 / 139 (0.00%)	
occurrences (all)	10	0	
Nausea			
subjects affected / exposed	30 / 139 (21.58%)	20 / 139 (14.39%)	
occurrences (all)	37	22	
Oral Pain			
subjects affected / exposed	9 / 139 (6.47%)	1 / 139 (0.72%)	
occurrences (all)	16	1	
Stomatitis			
subjects affected / exposed	28 / 139 (20.14%)	4 / 139 (2.88%)	
occurrences (all)	43	5	
Vomiting			
subjects affected / exposed	9 / 139 (6.47%)	17 / 139 (12.23%)	
occurrences (all)	18	17	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	18 / 139 (12.95%)	12 / 139 (8.63%)	
occurrences (all)	28	13	
Rash			
subjects affected / exposed	25 / 139 (17.99%)	18 / 139 (12.95%)	
occurrences (all)	37	25	
Rash Generalised			
subjects affected / exposed	7 / 139 (5.04%)	1 / 139 (0.72%)	
occurrences (all)	10	1	
Rash Maculo-Papular			
subjects affected / exposed	7 / 139 (5.04%)	5 / 139 (3.60%)	
occurrences (all)	11	7	
Skin Lesion			
subjects affected / exposed	8 / 139 (5.76%)	6 / 139 (4.32%)	
occurrences (all)	13	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 139 (6.47%)	10 / 139 (7.19%)	
occurrences (all)	15	16	
Back Pain			

subjects affected / exposed	14 / 139 (10.07%)	15 / 139 (10.79%)	
occurrences (all)	15	23	
Muscle Spasms			
subjects affected / exposed	4 / 139 (2.88%)	26 / 139 (18.71%)	
occurrences (all)	5	36	
Pain in Extremity			
subjects affected / exposed	12 / 139 (8.63%)	5 / 139 (3.60%)	
occurrences (all)	14	5	
Infections and infestations			
Bronchitis			
subjects affected / exposed	8 / 139 (5.76%)	8 / 139 (5.76%)	
occurrences (all)	8	8	
Conjunctivitis			
subjects affected / exposed	9 / 139 (6.47%)	17 / 139 (12.23%)	
occurrences (all)	12	21	
Herpes Zoster			
subjects affected / exposed	5 / 139 (3.60%)	10 / 139 (7.19%)	
occurrences (all)	5	10	
Nasopharyngitis			
subjects affected / exposed	16 / 139 (11.51%)	16 / 139 (11.51%)	
occurrences (all)	25	25	
Oral Herpes			
subjects affected / exposed	15 / 139 (10.79%)	4 / 139 (2.88%)	
occurrences (all)	18	9	
Paronychia			
subjects affected / exposed	5 / 139 (3.60%)	9 / 139 (6.47%)	
occurrences (all)	10	12	
Pneumonia			
subjects affected / exposed	14 / 139 (10.07%)	6 / 139 (4.32%)	
occurrences (all)	18	8	
Respiratory Tract Infection			
subjects affected / exposed	14 / 139 (10.07%)	9 / 139 (6.47%)	
occurrences (all)	31	13	
Rhinitis			
subjects affected / exposed	5 / 139 (3.60%)	8 / 139 (5.76%)	
occurrences (all)	7	11	

Sinusitis			
subjects affected / exposed	6 / 139 (4.32%)	11 / 139 (7.91%)	
occurrences (all)	9	12	
Upper Respiratory Tract Infection			
subjects affected / exposed	15 / 139 (10.79%)	28 / 139 (20.14%)	
occurrences (all)	25	45	
Urinary Tract Infection			
subjects affected / exposed	7 / 139 (5.04%)	10 / 139 (7.19%)	
occurrences (all)	10	12	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	25 / 139 (17.99%)	26 / 139 (18.71%)	
occurrences (all)	43	30	
Diabetes Mellitus			
subjects affected / exposed	7 / 139 (5.04%)	1 / 139 (0.72%)	
occurrences (all)	61	3	
Hypercholesterolaemia			
subjects affected / exposed	18 / 139 (12.95%)	2 / 139 (1.44%)	
occurrences (all)	46	2	
Hyperglycaemia			
subjects affected / exposed	26 / 139 (18.71%)	4 / 139 (2.88%)	
occurrences (all)	93	17	
Hyperkalaemia			
subjects affected / exposed	3 / 139 (2.16%)	9 / 139 (6.47%)	
occurrences (all)	3	25	
Hypertriglyceridaemia			
subjects affected / exposed	25 / 139 (17.99%)	1 / 139 (0.72%)	
occurrences (all)	77	1	
Hypokalaemia			
subjects affected / exposed	24 / 139 (17.27%)	12 / 139 (8.63%)	
occurrences (all)	52	23	
Hypomagnesaemia			
subjects affected / exposed	4 / 139 (2.88%)	9 / 139 (6.47%)	
occurrences (all)	5	22	
Hyponatraemia			

subjects affected / exposed occurrences (all)	7 / 139 (5.04%) 14	1 / 139 (0.72%) 23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2012	This amendment was implemented to clarify management of ibrutinib with CYP3A4/5 inhibitors/inducers and anticoagulants, including warfarin, and to clarify perioperative management of study medication.
30 July 2014	This amendment was implemented to introduce crossover treatment for subjects randomized to temsirolimus who have IRC-confirmed disease progression; and to update the protocol with new safety-related information and safety instructions, minor revisions to operational aspects of the study, provide updates based on new information, and perform minor modifications and formatting changes.
04 August 2015	This amendment was implemented to include the information on the conduct of the study after the clinical cutoff for the primary analysis occurs, and to include the new safety-related information and safety instructions.

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.

Within this context, there were no notable study limitations identified by the Sponsor.

Notes: