Clinical trial results:
A PHASE II, RANDOMIZED STUDY OF PACLITAXEL WITH GDC-0941 VERSUS PACLITAXEL WITH PLACEBO IN PATIENTS WITH LOCALLY RECURRENT OR METASTATIC BREAST CANCER

Summary

EudraCT number	2012-003262-41
Trial protocol	BE AT CZ GB ES
Global end of trial date	10 December 2015

Results information

Result version number	v1 (current)
This version publication date	07 December 2016
First version publication date	07 December 2016

Trial information

Trial identification

Sponsor protocol code	GO28509

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01740336
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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	10 December 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy (as measured by progression-free survival [PFS]) of paclitaxel + GDC-0941 versus paclitaxel + placebo in subjects with and without phosphatidylinositol-4,5-bisphosphate 3-kinase (PIK3CA) mutations and in all treated subjects

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 February 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United Kingdom: 37
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 26
Country: Number of subjects enrolled	Czech Republic: 18
Country: Number of subjects enrolled	Australia: 24
Country: Number of subjects enrolled	United States: 51
Country: Number of subjects enrolled	Korea, Republic of: 13
Worldwide total number of subjects	179
EEA total number of subjects	91

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)	139
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects with locally recurrent or metastatic HER2-negative,hormone receptor (HR) positive breast cancer previously untreated with chemotherapy in the metastatic setting (with the exception of capecitabine) were enrolled globally from 8 countries.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Paclitaxel

Arm description:

Subjects received matching placebo to GDC-0941 along with Paclitaxel weekly for 3 out of 4 weeks in every 28-day cycle.

Arm type	Active comparator
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received matching placebo to GDC-0941 260 once daily, orally beginning on cycle 1, Day 1 for 5 consecutive days followed by 2 consecutive days without treatment, repeated weekly in each 28-day cycle until progressive disease or intolerable toxicity.

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

Dosage and administration details:

Subjects received Paclitaxel intravenously (IV) at 90 milligram per metre square (mg/m^2) weekly for 3 of every 4 weeks (28-day cycle).

Arm title	Paclitaxel + GDC-0941

Arm description:

Subjects received GDC-0941 administered in repeated rounds of once daily dosing for 5 consecutive days followed by 2 consecutive days during which GDC-0941 is not administered (5/7-day schedule) along with Paclitaxel weekly for 3 out of 4 weeks in every 28-day cycle.

Arm type	Experimental

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

Dosage and administration details:

Subjects received Paclitaxel IV at 90 mg/m^2 weekly for 3 of every 4 weeks (28-day cycle).

Investigational medicinal product name	GDC-0941
Investigational medicinal product code	
Other name	Pictilisib
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received GDC-0941 260 mgs once daily beginning on cycle 1, Day 1 for 5 consecutive days followed by 2 consecutive days without GDC-0941 treatment and repeated weekly in each 28-day cycle until disease progression or intolerable toxicity.

Number of subjects in period 1	Placebo + Paclitaxel	Paclitaxel + GDC-0941
Started	92	87
Completed	0	0
Not completed	92	87
Death	31	32
Other	6	10
Study terminated by sponsor	44	39
Lost to follow-up	1	1
Withdrawal by subject	10	5

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + Paclitaxel
Reporting group description:	
Subjects received matching placebo to GDC-0941 along with Paclitaxel weekly for 3 out of 4 weeks in every 28-day cycle.	
Reporting group title	Paclitaxel + GDC-0941
Reporting group description:	
Subjects received GDC-0941 administered in repeated rounds of once daily dosing for 5 consecutive days followed by 2 consecutive days during which GDC-0941 is not administered (5/7-day schedule) along with Paclitaxel weekly for 3 out of 4 weeks in every 28-day cycle.	

Reporting group values	Placebo + Paclitaxel	Paclitaxel + GDC-0941	Total
Number of subjects	92	87	179
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 57.2 ± 10.1	 54.5 ± 11.3	 -
Gender categorical Units: Subjects			
Female	92	87	179
Male	0	0	0

End points

End points reporting groups

Reporting group title	Placebo + Paclitaxel

Reporting group description:

Subjects received matching placebo to GDC-0941 along with Paclitaxel weekly for 3 out of 4 weeks in every 28-day cycle.

Reporting group title	Paclitaxel + GDC-0941

Reporting group description:

Subjects received GDC-0941 administered in repeated rounds of once daily dosing for 5 consecutive days followed by 2 consecutive days during which GDC-0941 is not administered (5/7-day schedule) along with Paclitaxel weekly for 3 out of 4 weeks in every 28-day cycle.

Primary: Progression Free-Survival (PFS) Assessed by Investigator

End point title	Progression Free-Survival (PFS) Assessed by Investigator

End point description:

PFS is defined as time from randomisation to the first occurrence of disease progression as determined by investigator review of tumor assessments using modified Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or death on study from any cause (less than or equal to [<=] 30 days after the last dose of study treatment). As per modified RECIST v1.1 criteria, Progressive disease (PD) is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 millimetre (mm). The appearance of one or more new lesions is also considered progression. Results reported as cumulative data. Analysis population included all randomised subjects.

End point type	Primary

End point timeframe:

From the time of randomization to the progression of disease or death from any cause (<=30 days after the last dose of study treatment) at data cut-off date 12 September 2014 (planned efficacy analysis) in blinded period (Up to 19 months)

End point values	Placebo + Paclitaxel	Paclitaxel + GDC-0941		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	87		
Units: months				
median (confidence interval 95%)	7.3 (5.8 to 8.5)	8.2 (5.9 to 9.9)		

Statistical analyses

Statistical analysis title	PFS

Statistical analysis description:

Hazard ratios were estimated by Cox regression.

Comparison groups	Placebo + Paclitaxel v Paclitaxel + GDC-0941

Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.835
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.46

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR is defined as complete response (CR) or partial response (PR) using modified RECIST v1.1 criteria. CR is disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to less than (<) 10 mm; PR is at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. Results reported as cumulative data. Analysis population included all randomised subjects.

End point type	Secondary

End point timeframe:

From the time of randomization to the data cut-off date 12 September 2014 (planned efficacy analysis) in blinded period (Up to 19 months)

End point values	Placebo + Paclitaxel	Paclitaxel + GDC-0941		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	87		
Units: percentage of subjects				
number (confidence interval 95%)	20.7 (12.92 to 30.36)	23 (14.64 to 33.25)		

Statistical analyses

Statistical analysis title	ORR
Comparison groups	Placebo + Paclitaxel v Paclitaxel + GDC-0941
Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7051
Method	Chi-squared
Parameter estimate	Difference in Response Rates
Point estimate	2.34

Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.77
upper limit	14.44

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR is defined as the time interval between the date of the earliest qualifying response and the earliest date of PD or death from any cause (<=30 days after the last dose of study treatment). Results reported as cumulative data. Analysis population included all randomised subjects with qualifying response in blinded period. Here, 99999 indicates upper limit of confidence interval (CI) as it was not estimable.

End point type	Secondary

End point timeframe:

Date of the earliest qualifying response until the earliest date of PD or death from any cause (<=30 days after the last dose of study treatment) at data cut-off date 12 Sep 2014 in blinded period (Up to 19 months)

End point values	Placebo + Paclitaxel	Paclitaxel + GDC-0941		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19[1]	20[2]		
Units: months				
median (confidence interval 95%)	5.62 (4.86 to 99999)	6.8 (5.19 to 99999)		

Notes:

[1] - Number of subjects analysed for this endpoint.

[2] - Number of subjects analysed for this endpoint.

Statistical analyses

Statistical analysis title	DOR
Comparison groups	Placebo + Paclitaxel v Paclitaxel + GDC-0941
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9052
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	4.9

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

CBR is defined as the percentage of subjects with confirmed CR, PR, or stable disease as assessed according to modified RECIST v1.1. CR: disappearance of all target lesions with reduction in target/non-target pathological lymph nodes to < 10 mm. PR: ≥ 30% decrease in the sum of diameters of target lesions, compared to the baseline sum diameters. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, compared to the baseline sum diameters.

End point type	Secondary

End point timeframe:

Up to 38 months

End point values	Placebo + Paclitaxel	Paclitaxel + GDC-0941		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: percentage of subjects				
number (not applicable)				

Notes:

[3] - Data not analysed as per planned, hence not reported.

[4] - Data not analysed as per planned, hence not reported.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With any Adverse Event (AE)

End point title	Percentage of Subjects With any Adverse Event (AE)

End point description:

An AE was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The safety population included those subjects who had received any amount of study treatment. Safety data was collected for overall study period (blinded + open-label period).

End point type	Secondary

End point timeframe:

For overall study period (blinded + open-label period), Up to 38 months

End point values	Placebo + Paclitaxel	Paclitaxel + GDC-0941		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	87		
Units: percentage of subjects				
number (not applicable)	100	100		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For overall study period (blinded + open-label period)

Adverse event reporting additional description:

The safety population included those subjects who had received any amount of study treatment. Safety data was collected for overall study period (blinded + open-label period).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Placebo + Paclitaxel

Reporting group description:

Subjects received matching placebo to GDC-0941 along with Paclitaxel weekly for 3 out of 4 weeks in every 28-day cycle.

Reporting group title	Paclitaxel + GDC-0941

Reporting group description:

Subjects received GDC-0941 administered in repeated rounds of once daily dosing for 5 consecutive days followed by 2 consecutive days during which GDC-0941 is not administered (5/7-day schedule) along with Paclitaxel weekly for 3 out of 4 weeks in every 28-day cycle.

Serious adverse events	Placebo + Paclitaxel	Paclitaxel + GDC-0941	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 92 (33.70%)	34 / 87 (39.08%)	
number of deaths (all causes)	6	4	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	4 / 92 (4.35%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Breast cancer metastatic			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (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	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Central venous catheter removal			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
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			
Pyrexia			
subjects affected / exposed	5 / 92 (5.43%)	3 / 87 (3.45%)	
occurrences causally related to treatment / all	3 / 5	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 92 (1.09%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fatigue			
subjects affected / exposed	1 / 92 (1.09%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
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 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	3 / 92 (3.26%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 92 (3.26%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 92 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 92 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Asthma			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Electrocardiogram T wave inversion			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (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	2 / 92 (2.17%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	0 / 92 (0.00%)	2 / 87 (2.30%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microangiopathic haemolytic anaemia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 92 (2.17%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (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 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric volvulus			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastritis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic fibrosis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic haemorrhage			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Jaundice cholestatic			

subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 92 (0.00%)	3 / 87 (3.45%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 92 (2.17%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Joint swelling			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	2 / 92 (2.17%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 92 (0.00%)	3 / 87 (3.45%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 92 (1.09%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 92 (1.09%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 92 (2.17%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 92 (2.17%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	1 / 92 (1.09%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 92 (2.17%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
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 / 92 (1.09%)	0 / 87 (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	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	1 / 92 (1.09%)	0 / 87 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Tetany			
subjects affected / exposed	0 / 92 (0.00%)	1 / 87 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Paclitaxel	Paclitaxel + GDC-0941	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	92 / 92 (100.00%)	87 / 87 (100.00%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	12 / 92 (13.04%)	7 / 87 (8.05%)	
occurrences (all)	15	7	
Hypertension			
subjects affected / exposed	6 / 92 (6.52%)	9 / 87 (10.34%)	
occurrences (all)	11	13	
Lymphoedema			
subjects affected / exposed	7 / 92 (7.61%)	8 / 87 (9.20%)	
occurrences (all)	7	9	
Flushing			
subjects affected / exposed	8 / 92 (8.70%)	3 / 87 (3.45%)	
occurrences (all)	11	6	
Hypotension			
subjects affected / exposed	6 / 92 (6.52%)	3 / 87 (3.45%)	
occurrences (all)	9	6	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	53 / 92 (57.61%)	57 / 87 (65.52%)	
occurrences (all)	99	116	
Oedema peripheral			

subjects affected / exposed	17 / 92 (18.48%)	21 / 87 (24.14%)	
occurrences (all)	22	38	
Pyrexia			
subjects affected / exposed	9 / 92 (9.78%)	15 / 87 (17.24%)	
occurrences (all)	9	18	
Asthenia			
subjects affected / exposed	12 / 92 (13.04%)	9 / 87 (10.34%)	
occurrences (all)	20	20	
Pain			
subjects affected / exposed	4 / 92 (4.35%)	10 / 87 (11.49%)	
occurrences (all)	6	11	
Mucosal inflammation			
subjects affected / exposed	6 / 92 (6.52%)	5 / 87 (5.75%)	
occurrences (all)	7	5	
Chest pain			
subjects affected / exposed	5 / 92 (5.43%)	4 / 87 (4.60%)	
occurrences (all)	5	5	
Chills			
subjects affected / exposed	3 / 92 (3.26%)	5 / 87 (5.75%)	
occurrences (all)	3	7	
Face oedema			
subjects affected / exposed	1 / 92 (1.09%)	5 / 87 (5.75%)	
occurrences (all)	1	12	
Influenza like illness			
subjects affected / exposed	1 / 92 (1.09%)	5 / 87 (5.75%)	
occurrences (all)	1	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	23 / 92 (25.00%)	27 / 87 (31.03%)	
occurrences (all)	28	41	
Dyspnoea			
subjects affected / exposed	15 / 92 (16.30%)	28 / 87 (32.18%)	
occurrences (all)	27	41	
Epistaxis			

subjects affected / exposed	9 / 92 (9.78%)	10 / 87 (11.49%)	
occurrences (all)	12	12	
Oropharyngeal pain			
subjects affected / exposed	9 / 92 (9.78%)	10 / 87 (11.49%)	
occurrences (all)	10	14	
Dysphonia			
subjects affected / exposed	5 / 92 (5.43%)	0 / 87 (0.00%)	
occurrences (all)	5	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	19 / 92 (20.65%)	14 / 87 (16.09%)	
occurrences (all)	24	18	
Anxiety			
subjects affected / exposed	11 / 92 (11.96%)	9 / 87 (10.34%)	
occurrences (all)	11	9	
Depression			
subjects affected / exposed	11 / 92 (11.96%)	8 / 87 (9.20%)	
occurrences (all)	11	11	
Investigations			
Alanine Aminotransferase increased			
subjects affected / exposed	16 / 92 (17.39%)	8 / 87 (9.20%)	
occurrences (all)	33	14	
Neutrophil count decreased			
subjects affected / exposed	11 / 92 (11.96%)	9 / 87 (10.34%)	
occurrences (all)	22	38	
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 92 (14.13%)	6 / 87 (6.90%)	
occurrences (all)	32	9	
White blood cell count decreased			
subjects affected / exposed	8 / 92 (8.70%)	6 / 87 (6.90%)	
occurrences (all)	33	14	
Weight decreased			
subjects affected / exposed	4 / 92 (4.35%)	8 / 87 (9.20%)	
occurrences (all)	4	11	
Blood alkaline phosphatase increased			

subjects affected / exposed	6 / 92 (6.52%)	4 / 87 (4.60%)	
occurrences (all)	8	8	
Weight increased			
subjects affected / exposed	6 / 92 (6.52%)	0 / 87 (0.00%)	
occurrences (all)	6	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 92 (1.09%)	6 / 87 (6.90%)	
occurrences (all)	1	6	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	34 / 92 (36.96%)	26 / 87 (29.89%)	
occurrences (all)	66	52	
Dysgeusia			
subjects affected / exposed	28 / 92 (30.43%)	29 / 87 (33.33%)	
occurrences (all)	41	31	
Headache			
subjects affected / exposed	19 / 92 (20.65%)	27 / 87 (31.03%)	
occurrences (all)	26	44	
Peripheral sensory neuropathy			
subjects affected / exposed	22 / 92 (23.91%)	22 / 87 (25.29%)	
occurrences (all)	39	40	
Paraesthesia			
subjects affected / exposed	16 / 92 (17.39%)	14 / 87 (16.09%)	
occurrences (all)	30	21	
Dizziness			
subjects affected / exposed	12 / 92 (13.04%)	10 / 87 (11.49%)	
occurrences (all)	14	12	
Hypoaesthesia			
subjects affected / exposed	3 / 92 (3.26%)	8 / 87 (9.20%)	
occurrences (all)	3	14	
Lethargy			
subjects affected / exposed	6 / 92 (6.52%)	3 / 87 (3.45%)	
occurrences (all)	10	4	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	35 / 92 (38.04%)	13 / 87 (14.94%)	
occurrences (all)	72	39	
Neutropenia			
subjects affected / exposed	23 / 92 (25.00%)	23 / 87 (26.44%)	
occurrences (all)	45	71	
Leukopenia			
subjects affected / exposed	7 / 92 (7.61%)	8 / 87 (9.20%)	
occurrences (all)	25	30	
Thrombocytopenia			
subjects affected / exposed	2 / 92 (2.17%)	6 / 87 (6.90%)	
occurrences (all)	4	6	
Eye disorders			
Vision blurred			
subjects affected / exposed	8 / 92 (8.70%)	3 / 87 (3.45%)	
occurrences (all)	8	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	51 / 92 (55.43%)	47 / 87 (54.02%)	
occurrences (all)	93	93	
Diarrhoea			
subjects affected / exposed	39 / 92 (42.39%)	50 / 87 (57.47%)	
occurrences (all)	72	129	
Vomiting			
subjects affected / exposed	22 / 92 (23.91%)	32 / 87 (36.78%)	
occurrences (all)	58	56	
Constipation			
subjects affected / exposed	30 / 92 (32.61%)	23 / 87 (26.44%)	
occurrences (all)	39	27	
Dyspepsia			
subjects affected / exposed	18 / 92 (19.57%)	13 / 87 (14.94%)	
occurrences (all)	24	17	
Abdominal pain			
subjects affected / exposed	16 / 92 (17.39%)	12 / 87 (13.79%)	
occurrences (all)	21	14	
Stomatitis			

subjects affected / exposed	13 / 92 (14.13%)	15 / 87 (17.24%)	
occurrences (all)	17	20	
Dry mouth			
subjects affected / exposed	8 / 92 (8.70%)	9 / 87 (10.34%)	
occurrences (all)	8	9	
Abdominal pain upper			
subjects affected / exposed	8 / 92 (8.70%)	8 / 87 (9.20%)	
occurrences (all)	13	8	
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 92 (5.43%)	8 / 87 (9.20%)	
occurrences (all)	6	9	
Mouth ulceration			
subjects affected / exposed	4 / 92 (4.35%)	5 / 87 (5.75%)	
occurrences (all)	4	6	
Abdominal distension			
subjects affected / exposed	3 / 92 (3.26%)	5 / 87 (5.75%)	
occurrences (all)	3	5	
Oral pain			
subjects affected / exposed	5 / 92 (5.43%)	2 / 87 (2.30%)	
occurrences (all)	7	2	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	57 / 92 (61.96%)	50 / 87 (57.47%)	
occurrences (all)	69	63	
Rash			
subjects affected / exposed	26 / 92 (28.26%)	32 / 87 (36.78%)	
occurrences (all)	42	57	
Pruritus			
subjects affected / exposed	12 / 92 (13.04%)	13 / 87 (14.94%)	
occurrences (all)	18	14	
Rash maculo-papular			
subjects affected / exposed	5 / 92 (5.43%)	19 / 87 (21.84%)	
occurrences (all)	9	34	
Nail disorder			
subjects affected / exposed	10 / 92 (10.87%)	6 / 87 (6.90%)	
occurrences (all)	13	9	

Erythema			
subjects affected / exposed	11 / 92 (11.96%)	4 / 87 (4.60%)	
occurrences (all)	14	8	
Dry skin			
subjects affected / exposed	6 / 92 (6.52%)	7 / 87 (8.05%)	
occurrences (all)	6	14	
Nail discolouration			
subjects affected / exposed	6 / 92 (6.52%)	4 / 87 (4.60%)	
occurrences (all)	7	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	21 / 92 (22.83%)	16 / 87 (18.39%)	
occurrences (all)	31	23	
Back pain			
subjects affected / exposed	22 / 92 (23.91%)	14 / 87 (16.09%)	
occurrences (all)	31	16	
Pain in extremity			
subjects affected / exposed	18 / 92 (19.57%)	17 / 87 (19.54%)	
occurrences (all)	23	21	
Myalgia			
subjects affected / exposed	21 / 92 (22.83%)	13 / 87 (14.94%)	
occurrences (all)	30	21	
Bone pain			
subjects affected / exposed	6 / 92 (6.52%)	6 / 87 (6.90%)	
occurrences (all)	7	6	
Musculoskeletal chest pain			
subjects affected / exposed	8 / 92 (8.70%)	4 / 87 (4.60%)	
occurrences (all)	10	4	
Musculoskeletal pain			
subjects affected / exposed	8 / 92 (8.70%)	2 / 87 (2.30%)	
occurrences (all)	8	2	
Muscle spasms			
subjects affected / exposed	5 / 92 (5.43%)	3 / 87 (3.45%)	
occurrences (all)	5	3	
Infections and infestations			

Upper respiratory tract infection			
subjects affected / exposed	11 / 92 (11.96%)	12 / 87 (13.79%)	
occurrences (all)	15	13	
Nasopharyngitis			
subjects affected / exposed	14 / 92 (15.22%)	7 / 87 (8.05%)	
occurrences (all)	17	8	
Urinary tract infection			
subjects affected / exposed	6 / 92 (6.52%)	9 / 87 (10.34%)	
occurrences (all)	12	12	
Oral candidiasis			
subjects affected / exposed	3 / 92 (3.26%)	6 / 87 (6.90%)	
occurrences (all)	3	6	
Sinusitis			
subjects affected / exposed	6 / 92 (6.52%)	2 / 87 (2.30%)	
occurrences (all)	7	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 92 (17.39%)	26 / 87 (29.89%)	
occurrences (all)	29	37	
Hyperglycaemia			
subjects affected / exposed	11 / 92 (11.96%)	7 / 87 (8.05%)	
occurrences (all)	33	24	
Hypokalaemia			
subjects affected / exposed	5 / 92 (5.43%)	11 / 87 (12.64%)	
occurrences (all)	9	13	
Hypomagnesaemia			
subjects affected / exposed	8 / 92 (8.70%)	5 / 87 (5.75%)	
occurrences (all)	19	6	
Hypocalcaemia			
subjects affected / exposed	4 / 92 (4.35%)	7 / 87 (8.05%)	
occurrences (all)	6	7	
Dehydration			
subjects affected / exposed	5 / 92 (5.43%)	5 / 87 (5.75%)	
occurrences (all)	8	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2012	1. The eligibility criteria were modified to clarify that only women ³ 18 years of age would be eligible for enrollment 2. The following adverse events of special interest were added that would require immediate reporting to the Sponsor for real-time monitoring in order to enhance subject safety: cases of potential drug-induced liver injury including an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law. Suspected transmission of an infectious agent by the study drug 4. Abnormal Liver Function Tests was added to provide guidance for detecting and reporting liver function abnormalities 5. More detailed dose modification guidance for rash and hyperglycemia was added 6. "Rationale for the Collection of a Blood Sample for Analysis of Circulating Biomarkers" was added to clarify the rationale for collecting the baseline plasma biomarker sample 7. Typographical errors were corrected to improve clarity and consistency
19 October 2012	To clarify that participation in this study is limited to female subjects.
26 January 2013	1. Remove the requirement that steroid therapy must have been concluded greater than 2 weeks prior to Cycle 1 Day 1 2. Decrease the interval between the completion of radiotherapy and Cycle 1, Day 1 for the treatment of central nervous system disease
22 December 2014	1. The protocol-specified interim analysis for efficacy demonstrated that subjects receiving GDC-0941 with paclitaxel did not have a longer progression-free survival (primary endpoint) or an improved overall response rate (secondary endpoint) in both the all-comer population and the PIK3CA mutant population compared with subjects who received placebo with paclitaxel. Safety data from this study are consistent with data generated to date in other clinical trials involving GDC-0941 either as a single agent or in combination with paclitaxel. Based on the lack of clinical benefit, the Sponsor has recommended that investigators discontinue GDC0941 for subjects who are receiving GDC-0941 on the study; the decision to continue or discontinue treatment with GDC-0941 or paclitaxel is at the discretion of the investigator following consultation with the subject 2. This amendment to Protocol GO28509 will reduce the protocol-specified assessments for subjects who are either on active study treatment (GDC-0941 with paclitaxel or paclitaxel alone) or in the survival follow-up period.Subjects who are receiving study treatment will be allowed to continue treatment until disease progression, the onset of treatment-limiting toxicity, or when the treating physician decides to discontinue treatment, whichever occurs first. This protocol amendment will reduce the number and type of assessments required for the evaluation of study treatment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported