



Clinical trial results:

Phase II randomized trial of the Polo-like kinase 1 inhibitor BI 6727 monotherapy versus investigator's choice chemotherapy in ovarian cancer

patients resistant or refractory to platinum-based cytotoxic therapy

Summary

EudraCT number	2009-015770-35
Trial protocol	FR ES BE SE SK
Global end of trial date	03 June 2014

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	01 August 2015

Trial information

Trial identification

Sponsor protocol code	1230.18
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01121406
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim Pharma GmbH & Co. KG, +1 800 2430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim Pharma GmbH & Co. KG, +1 800 2430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 April 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 October 2011
Global end of trial reached?	Yes
Global end of trial date	03 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy and safety of intravenous infusion of volasertib (BI 6727) monotherapy given once every 3 weeks compared to investigator's choice chemotherapy in platinum-refractory or -resistant ovarian cancer patients

Protection of trial subjects:

Written informed consent was obtained from all the patients before the enrollment and the study was approved by the Ethic Committee and Competent Authority (EC/CA) before start and were conducted in accordance with Declaration of Helsinki, International Conference on Harmonisation (ICH) , Good Clinical Practise (GCP) and Boehringer Ingelheim (BI) Standard operating Procedures (SOP).

Background therapy: -

Evidence for comparator:

Investigator's choice chemotherapy

Actual start date of recruitment	23 April 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	France: 68
Country: Number of subjects enrolled	Slovakia: 7
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	Sweden: 10
Worldwide total number of subjects	122
EEA total number of subjects	122

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)	76
From 65 to 84 years	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The "Not completed" category in the Subject Disposition table represents "Treatment permanently discontinued" and "The reasons for non-completion" in the table represent "Reason for treatment discontinuation".

24 patients switched to Volasertib (BI 6727) due to disease progression or occurrence of toxicity.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial.

Period 1

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

Blinding implementation details:

Open-label design was used

Arms

Are arms mutually exclusive?	No
Arm title	Volasertib (BI 6727)

Arm description:

Volasertib (BI 6727 300 mg) was administered as intravenous infusion over 2 hours at Day 1 of each 21-day treatment course.

Treatment was to be administered until disease progression or occurrence of toxicity leading to treatment discontinuation. Patients withdrawn from volasertib treatment could receive a treatment according to investigator's choice. The patients were to be followed for survival status.

One patient was randomised to the Volasertib (BI 6727) arm, however this patient was not treated. Consequently, number of subject that started is 55 but only 54 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

Arm type	Experimental
Investigational medicinal product name	Volasertib
Investigational medicinal product code	BI 6727
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Infusion over 2 hours at Day 1 of each treatment course

Arm title	Cytotoxic
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Arm description:

Patients received a non-platinum cytotoxic single agent.

The investigator chose the most appropriate drug according to patient status (previous chemotherapy effects, cumulative toxic effects, performance status, and nutritional status), the product Summary of Product Characteristics (SPC), and the local standard of care. The following non-platinum regimens were recommended because they are regarded efficacious and safe in patients with resistant ovarian cancer:

- Pegylated liposomal doxorubicin (PLD): 40 mg/m² at Day 1 (1 course = 28 days)
- Topotecan: 1.25 mg/m² from Days 1 to 5 (1 course = 21 days), or 4 mg/m² at Days 1, 8, and 15 (1 course = 28 days)
- Paclitaxel: 80 mg/m² at Days 1, 8, 15, and 21 (1 course = 28 days)
- Gemcitabine: 1000 mg/m² at Days 1 and 8 (1 course = 21 days)

Arm type	Investigator's choice chemotherapy
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Investigational medicinal product name	Pegylated liposomal doxorubicin (PLD)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 40 mg/m ² at Day 1 (1 course = 28 days)	
Investigational medicinal product name	Topotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 1.25 mg/m ² from Days 1 to 5 (1 course = 21 days), or 4 mg/m ² at Days 1, 8, and 15 (1 course = 28 days)	
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 80 mg/m ² at Days 1, 8, 15, and 21 (1 course = 28 days)	
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 1000 mg/m ² at Days 1 and 8 (1 course = 21 days)	

Number of subjects in period 1	Volasertib (BI 6727)	Cytotoxic
Started	54	55
Completed	0	0
Not completed	54	55
Refused continuation of study med.	1	2
Wors. or AE of underlying cancer disease	4	6
Adverse event, non-fatal	3	10
Other reason	2	6
Progressive disease (PD) RECIST	44	28
Non-compliant with protocol	-	2
Lost to follow-up	-	1

Baseline characteristics

Reporting groups^[1]

Reporting group title	Volasertib (BI 6727)
Reporting group description:	
Volasertib (BI 6727 300 mg) was administered as intravenous infusion over 2 hours at Day 1 of each 21-day treatment course.	
Treatment was to be administered until disease progression or occurrence of toxicity leading to treatment discontinuation. Patients withdrawn from volasertib treatment could receive a treatment according to investigator's choice. The patients were to be followed for survival status.	
One patient was randomised to the Volasertib (BI 6727) arm, however this patient was not treated. Consequently, number of subject that started is 55 but only 54 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.	

Reporting group title	Cytotoxic
Reporting group description:	
Patients received a non-platinum cytotoxic single agent.	
The investigator chose the most appropriate drug according to patient status (previous chemotherapy effects, cumulative toxic effects, performance status, and nutritional status), the product Summary of Product Characteristics (SPC), and the local standard of care. The following non-platinum regimens were recommended because they are regarded efficacious and safe in patients with resistant ovarian cancer:	
- Pegylated liposomal doxorubicin (PLD): 40 mg/m ² at Day 1 (1 course = 28 days)	
- Topotecan: 1.25 mg/m ² from Days 1 to 5 (1 course = 21 days), or 4 mg/m ² at Days 1, 8, and 15 (1 course = 28 days)	
- Paclitaxel: 80 mg/m ² at Days 1, 8, 15, and 21 (1 course = 28 days)	
- Gemcitabine: 1000 mg/m ² at Days 1 and 8 (1 course = 21 days)	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one of the trial medication.

Reporting group values	Volasertib (BI 6727)	Cytotoxic	Total
Number of subjects	54	55	109
Age categorical			
Units: Subjects			

Age Continuous			
Treated set (TS) consisted of all patients who received at least one administration of the trial drug and is the population used for Baseline characteristics.			
Units: years			
arithmetic mean	61.3	60.9	
standard deviation	± 9.88	± 9.26	-
Gender, Male/Female			
Treated set (TS) consisted of all patients who received at least one administration of the trial drug and is the population used for Baseline characteristics.			
Units: participants			
Female	54	55	109
Male	0	0	0

End points

End points reporting groups

Reporting group title	Volasertib (BI 6727)
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Reporting group description:

Volasertib (BI 6727 300 mg) was administered as intravenous infusion over 2 hours at Day 1 of each 21-day treatment course.

Treatment was to be administered until disease progression or occurrence of toxicity leading to treatment discontinuation. Patients withdrawn from volasertib treatment could receive a treatment according to investigator's choice. The patients were to be followed for survival status.

One patient was randomised to the Volasertib (BI 6727) arm, however this patient was not treated.

Consequently, number of subject that started is 55 but only 54 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

Reporting group title	Cytotoxic
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Reporting group description:

Patients received a non-platinum cytotoxic single agent.

The investigator chose the most appropriate drug according to patient status (previous chemotherapy effects, cumulative toxic effects, performance status, and nutritional status), the product Summary of Product Characteristics (SPC), and the local standard of care. The following non-platinum regimens were recommended because they are regarded efficacious and safe in patients with resistant ovarian cancer:

- Pegylated liposomal doxorubicin (PLD): 40 mg/m² at Day 1 (1 course = 28 days)

- Topotecan: 1.25 mg/m² from Days 1 to 5 (1 course = 21 days), or 4 mg/m² at Days 1, 8, and 15 (1 course = 28 days)

- Paclitaxel: 80 mg/m² at Days 1, 8, 15, and 21 (1 course = 28 days)

- Gemcitabine: 1000 mg/m² at Days 1 and 8 (1 course = 21 days)

Subject analysis set title	Cytotoxic to volasertib switch
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Subject analysis set type	Full analysis
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Subject analysis set description:

Patients of the cytotoxic arm who switched to treatment with Volasertib (BI 6727).

Primary: Disease Control Rate (DCR) at week 24 according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1

End point title	Disease Control Rate (DCR) at week 24 according to Response Evaluation Criteria In Solid Tumours (RECIST) version 1.1
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End point description:

DCR was defined as the proportion of patients who had an overall response of complete response (CR), partial response (PR), or stable disease (SD).

End point type	Primary
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End point timeframe:

Week 24

End point values	Volasertib (BI 6727)	Cytotoxic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[1]	55 ^[2]		
Units: percentage of participants				
number (confidence interval 95%)	30.6 (18 to 43.2)	43.1 (29.5 to 56.7)		

Notes:

[1] - TS

[2] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Kaplan Meier estimates and confidence intervals (CI) were calculated using Greenwood's variance estimate within each treatment arm and the asymptotic CI for the difference in the rates found. The time was censored in those cases where there was no death or progression until the last trial visit. 95% CI using Greenwood's variance estimate.

Volasertib (BI 6727) minus Cytotoxic.

Comparison groups	Volasertib (BI 6727) v Cytotoxic
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	other ^[3]
Parameter estimate	Difference in Kaplan–Meier DC rates
Point estimate	-12.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.1
upper limit	6

Notes:

[3] - Exploratory

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)
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End point description:

Progression-free survival of a patient was based on the investigator's assessment; it was defined as the number of days from the date of randomisation until the date of either disease progression or death from any cause, whichever occurred first.

Definition of disease progression according to RECIST version 1.1;

Patients with measurable tumour lesions at baseline,

Target-lesions: at least a 20% increase in the sum of diameters of target lesions, the sum of diameters must also demonstrate an absolute increase of at least 5 mm, taking as reference the smallest sum on study, or appearance of 1 or more new lesions.

Non-target lesions: unequivocal progression of existing non-target lesions or appearance of 1 or more new lesions

Patients with non-measurable tumour lesions at baseline,

Non-target lesions: requires unequivocal progression of existing non-target lesions or appearance of 1 or more new lesions

End point type	Secondary
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End point timeframe:

From randomization until disease progression, death or study discontinuation; Up to 213 weeks

End point values	Volasertib (BI 6727)	Cytotoxic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[4]	55 ^[5]		
Units: weeks				
median (inter-quartile range (Q1-Q3))	13.1 (6.6 to 30.1)	20.6 (11.6 to 30.7)		

Notes:

[4] - TS

[5] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Cox proportional-hazards regression model, stratified by disease status at baseline (measurable vs. non measurable disease) and platinum resistant vs platinum refractory disease at baseline. HR calculated as Volasertib (BI 6727) /Cytotoxic.	
Comparison groups	Volasertib (BI 6727) v Cytotoxic
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.53

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	
OS is defined as time from randomisation to death irrespective of the cause of the death.	
End point type	Secondary
End point timeframe:	
From randomization until death or study discontinuation; Up to 213 weeks	

End point values	Volasertib (BI 6727)	Cytotoxic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[6]	55 ^[7]		
Units: weeks				
median (inter-quartile range (Q1-Q3))	60.1 (31.3 to 95.4)	68.6 (28.7 to 119.4)		

Notes:

[6] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Cox proportional–hazards regression model, stratified by disease status at baseline (measurable vs. non measurable disease) and platinum resistant vs platinum refractory disease at baseline. HR calculated as Volasertib (BI 6727)/ Cytotoxic	
Comparison groups	Volasertib (BI 6727) v Cytotoxic
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.42

Secondary: Best Overall Response

End point title	Best Overall Response
End point description: Best overall response (BOR) is defined as the best response recorded at any time from the date of randomisation until the end of treatment. Missing categories signify that no tumour imaging has been performed post baseline, and therefore the response status could not be assessed.	
End point type	Secondary
End point timeframe: Time from the date of randomisation until study completion/discontinuation; Up to 213 weeks	

End point values	Volasertib (BI 6727)	Cytotoxic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[8]	55 ^[9]		
Units: participants				
number (not applicable)				
CR- Measurable disease	0	0		
PR- Measurable disease	7	8		
SD- Measurable disease	24	24		
PD- Measurable disease	14	10		

Missing- Measurable disease	0	2		
CR- Non-measurable disease	0	1		
Non-CR/Non-PD- Non-measurable disease	6	9		
PD- Non-measurable disease	3	0		
Missing- Non-measurable disease	0	1		

Notes:

[8] - TS

[9] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Biological progression-free survival based on serum cancer antigen 125 (CA-125) according to the Gynaecologic Cancer Intergroup (GCIG) criteria

End point title	Biological progression-free survival based on serum cancer antigen 125 (CA-125) according to the Gynaecologic Cancer Intergroup (GCIG) criteria
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End point description:

Biological PFS including assessment of CA-125 levels was defined as the time from randomisation until the first occurrence of progressive disease according to CA-125, progressive disease according to radiological evidence, or death.

Also according to the below criterias,

- In patients with radiological measurable disease, disease progression during study treatment could not be declared on the basis of CA-125 alone.
- Patients with elevated CA-125 pre-treatment and normalization of CA-125 had to show evidence of CA-125 \geq to two times the upper normal limit on two occasions at least one week apart or
- Patients with elevated CA-125 pre-treatment, which never normalized, had to show evidence of CA-125 \geq to two times the nadir value on two occasions at least one week apart or
- Patients with CA-125 in the normal range pre-treatment had to show evidence of CA-125 \geq to two times the upper normal limit on two occasions at least one week apart.

End point type	Secondary
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End point timeframe:

At screening and every 6 weeks thereafter (Up to 213 weeks)

End point values	Volasertib (BI 6727)	Cytotoxic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[10]	55 ^[11]		
Units: weeks				
median (inter-quartile range (Q1-Q3))	13.1 (6.6 to 25.6)	20.6 (11.6 to 30)		

Notes:

[10] - TS

[11] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Cox proportional-hazards regression model, stratified by disease status at baseline (measurable vs. non measurable disease) and platinum resistant vs platinum refractory disease at baseline.
HR calculated as Volasertib (BI 6727)/ Cytotoxic

Comparison groups	Volasertib (BI 6727) v Cytotoxic
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.7

Secondary: Time to deterioration in global health status/Quality of life (QOL)

End point title	Time to deterioration in global health status/Quality of life (QOL)
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End point description:

Time to deterioration in global health status/Quality of life (QOL) and symptom control assessed by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, QLQ-OV28, and individual symptom questionnaires.

The time to deterioration was defined as the time from randomisation to a score increased (i.e. worsened) by at least 10 points from baseline (0-100 point scale). If score is missing, and patient died within 28 days after scheduled time for completion, the patient was considered deteriorated. In this case, time to deterioration is time to death.

99999 is the "Missing value"; Missing median or percentiles signify that a sufficient number of events have not yet occurred to produce these estimates.

End point type	Secondary
End point timeframe:	
Every 6 weeks (Up to 213 weeks)	

End point values	Volasertib (BI 6727)	Cytotoxic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[12]	55 ^[13]		
Units: weeks				
median (inter-quartile range (Q1-Q3))	99999 (12.3 to 99999)	39.6 (13.1 to 47.2)		

Notes:

[12] - TS

[13] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Cox proportional-hazards regression model, stratified by disease status at baseline (measurable vs. non measurable disease) and platinum resistant vs platinum refractory disease at baseline.

HR calculated as Volasertib (BI 6727)/ Cytotoxic.

Comparison groups	Volasertib (BI 6727) v Cytotoxic
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Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.61

Secondary: Time to deterioration in fatigue/Quality of life (QOL)

End point title	Time to deterioration in fatigue/Quality of life (QOL)
End point description:	
Time to deterioration in fatigue/Quality of life (QOL) and symptom control assessed by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, QLQ-OV28, and individual symptom questionnaires.	
The time to deterioration was defined as the time from randomisation to a score increased (i.e. worsened) by at least 10 points from baseline (0-100 point scale). If score is missing, and patient died within 28 days after scheduled time for completion, the patient was considered deteriorated. In this case, time to deterioration is time to death.	
99999 is the "Missing value"; Missing median or percentiles signify that a sufficient number of events have not yet occurred to produce these estimates.	
End point type	Secondary
End point timeframe:	
Every 6 weeks (Up to 213 weeks)	

End point values	Volasertib (BI 6727)	Cytotoxic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[14]	55 ^[15]		
Units: weeks				
median (inter-quartile range (Q1-Q3))	99999 (18.3 to 99999)	67.1 (12.4 to 99999)		

Notes:

[14] - TS

[15] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Cox proportional-hazards regression model, stratified by disease status at baseline (measurable vs. non measurable disease) and platinum resistant vs platinum refractory disease at baseline.	
HR calculated as Volasertib (BI 6727)/ Cytotoxic	
Comparison groups	Volasertib (BI 6727) v Cytotoxic

Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	1.65

Secondary: Time to deterioration in pain/ Quality of life (QOL)

End point title	Time to deterioration in pain/ Quality of life (QOL)
End point description:	
Time to deterioration in pain/ Quality of life (QOL) and symptom control assessed by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, QLQ-OV28, and individual symptom questionnaires.	
The time to deterioration was defined as the time from randomisation to a score increased (i.e. worsened) by at least 10 points from baseline (0-100 point scale). If score is missing, and patient died within 28 days after scheduled time for completion, the patient was considered deteriorated. In this case, time to deterioration is time to death.	
99999 is the "Missing value"; Missing median or percentiles signify that a sufficient number of events have not yet occurred to produce these estimates.	
End point type	Secondary
End point timeframe:	
Every 6 weeks (Up to 213 weeks)	

End point values	Volasertib (BI 6727)	Cytotoxic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[16]	55 ^[17]		
Units: weeks				
median (inter-quartile range (Q1-Q3))	99999 (16.6 to 99999)	54.1 (25 to 99999)		

Notes:

[16] - TS

[17] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Cox proportional-hazards regression model, stratified by disease status at baseline (measurable vs. non measurable disease) and platinum resistant vs platinum refractory disease at baseline.	
HR calculated as Volasertib (BI 6727)/ Cytotoxic	
Comparison groups	Volasertib (BI 6727) v Cytotoxic

Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.93

Secondary: Time to deterioration in abdominal bloating/ Quality of life (QOL)

End point title	Time to deterioration in abdominal bloating/ Quality of life (QOL)
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End point description:

time to deterioration in abdominal bloating/ Quality of life (QOL) and symptom control assessed by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, QLQ-OV28, and individual symptom questionnaires.

The time to deterioration was defined as the time from randomisation to a score increased (i.e. worsened) by at least 10 points from baseline (0-100 point scale). If score is missing, and patient died within 28 days after scheduled time for completion, the patient was considered deteriorated. In this case, time to deterioration is time to death.

99999 is the "Missing value"; Missing median or percentiles signify that a sufficient number of events have not yet occurred to produce these estimates.

End point type	Secondary
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End point timeframe:

Every 6 weeks (Up to 213 weeks)

End point values	Volasertib (BI 6727)	Cytotoxic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[18]	55 ^[19]		
Units: weeks				
median (inter-quartile range (Q1-Q3))	99999 (12.9 to 99999)	47.2 (17.3 to 67.1)		

Notes:

[18] - TS

[19] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

Cox proportional-hazards regression model, stratified by disease status at baseline (measurable vs. non measurable disease) and platinum resistant vs platinum refractory disease at baseline.

HR calculated as Volasertib (BI 6727)/ Cytotoxic

Comparison groups	Volasertib (BI 6727) v Cytotoxic
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Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	1.47

Secondary: Time to deterioration in the three most troublesome disease specific symptoms/ Quality of life (QOL)

End point title	Time to deterioration in the three most troublesome disease specific symptoms/ Quality of life (QOL)
End point description:	
<p>Three most troublesome disease specific symptoms, defined by the patient at baseline. Patients that have defined more than 3 most troublesome symptoms have not been taken into account in the analysis.</p> <p>Quality of life (QOL) and symptom control assessed by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, QLQ-OV28, and individual symptom questionnaires. The time to deterioration was defined as the time from randomisation to a score increased (i.e. worsened) by at least 10 points from baseline (0-100 point scale). If score is missing, and patient died within 28 days after scheduled time for completion, the patient was considered deteriorated. In this case, time to deterioration is time to death.</p> <p>99999 is the "Missing value"; Missing median or percentiles signify that a sufficient number of events have not yet occurred to produce these estimates.</p>	
End point type	Secondary
End point timeframe:	
Every 6 weeks (Up to 213 weeks)	

End point values	Volasertib (BI 6727)	Cytotoxic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[20]	55 ^[21]		
Units: weeks				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	18.9 (6.3 to 99999)		

Notes:

[20] - TS

[21] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
<p>Cox proportional-hazards regression model, stratified by disease status at baseline (measurable vs. non measurable disease) and platinum resistant vs platinum refractory disease at baseline.</p> <p>HR calculated as Volasertib (BI 6727)/ Cytotoxic</p>	
Comparison groups	Volasertib (BI 6727) v Cytotoxic

Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	0.77

Secondary: Clinically relevant changes in laboratory and ECG data

End point title	Clinically relevant changes in laboratory and ECG data
End point description:	Clinically relevant changes in laboratory and ECG data
End point type	Secondary
End point timeframe:	From first treatment administration to 21 days after the last drug administration (Up to 1403 days)

End point values	Volasertib (BI 6727)	Cytotoxic	Cytotoxic to volasertib switch	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	54 ^[22]	55 ^[23]	24 ^[24]	
Units: percentage of participants				
number (not applicable)				
Blood alkaline phosphatase increased	3.7	12.7	8.3	
Blood creatinine increased	9.3	3.6	0	
Platelet count decreased	9.3	0	8.3	
Alanine aminotransferase increased	1.9	9.1	4.2	
Aspartate aminotransferase increased	3.7	5.5	4.2	
Blood uric acid increased	1.9	5.5	0	
Gamma–glutamyltransferase increased	3.7	5.5	4.2	
Alanine aminotransferase abnormal	0	0	4.2	
Electrocardiogram QT prolonged	0	0	4.2	
Haemoglobin decreased	3.7	3.6	4.2	
Neutrophil count decreased	1.9	0	4.2	
Troponin I increased	0	0	4.2	
Blood lactate dehydrogenase increased	3.7	0	0	
Blood magnesium decreased	3.7	0	0	
White blood cell count decreased	3.7	0	0	
Blood urea increased	1.9	3.6	0	
Alanine aminotransferase decreased	1.9	0	0	
Blood bilirubin increased	1.9	0	0	
Blood creatine phosphokinase decreased	1.9	0	0	
Blood potassium decreased	1.9	0	0	
Hepatic enzyme increased	1.9	0	0	

Aspartate aminotransferase abnormal	0	1.8	0	
Transaminases increased	0	1.8	0	

Notes:

[22] - TS

[23] - TS

[24] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: AUC (0-24); area under the concentration-time curve in plasma over the time interval from 0 to 24 hours for CD 10899 BS

End point title	AUC (0-24); area under the concentration-time curve in plasma over the time interval from 0 to 24 hours for CD 10899 BS ^[25]
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End point description:

AUC (0-24); area under the concentration-time curve in plasma over the time interval from 0 to 24 hours for CD 10899 BS (metabolite of Volasertib BI 6727)

Pharmacokinetic set (PKS): All evaluable patients were to be included in the pharmacokinetic analysis. A patient was considered not evaluable if they had an important protocol violation relevant to the evaluation of pharmacokinetics or had insufficient data.

End point type	Secondary
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End point timeframe:

-0.083 hours (h), 2h, 4h, 6h, 24h, 168h and 336 h after first drug administration

Notes:

[25] - 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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Volasertib (BI 6727)			
Subject group type	Reporting group			
Number of subjects analysed	51 ^[26]			
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	204 (\pm 65.3)			

Notes:

[26] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: AUC (0-24); area under the concentration-time curve in plasma over the time interval from 0 to 24 hours for BI 6727 BS

End point title	AUC (0-24); area under the concentration-time curve in plasma over the time interval from 0 to 24 hours for BI 6727 BS ^[27]
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End point description:

AUC (0-24); area under the concentration-time curve in plasma over the time interval from 0 to 24 hours for BI 6727 BS.

End point type	Secondary
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End point timeframe:

-0.083 hours (h), 2h, 4h, 6h, 24h, 168h and 336 h after first drug administration

Notes:

[27] - 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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Volasertib (BI 6727)			
Subject group type	Reporting group			
Number of subjects analysed	51 ^[28]			
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	2140 (\pm 25.5)			

Notes:

[28] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: AUC (0-inf); area under the concentration-time curve in plasma over the time interval from 0 extrapolated to infinity for BI 6727 BS

End point title	AUC (0-inf); area under the concentration-time curve in plasma over the time interval from 0 extrapolated to infinity for BI 6727 BS ^[29]
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End point description:

AUC (0-inf); area under the concentration-time curve in plasma over the time interval from 0 extrapolated to infinity for BI 6727 BS

End point type	Secondary
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End point timeframe:

-0.083 hours (h), 2h, 4h, 6h, 24h, 168h and 336 h after first drug administration

Notes:

[29] - 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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Volasertib (BI 6727)			
Subject group type	Reporting group			
Number of subjects analysed	49 ^[30]			
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	6240 (\pm 29.8)			

Notes:

[30] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: AUC (0-inf); area under the concentration-time curve in plasma over the time interval from 0 extrapolated to infinity for CD 10899 BS

End point title	AUC (0-inf); area under the concentration-time curve in plasma over the time interval from 0 extrapolated to infinity for CD 10899 BS ^[31]
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End point description:

AUC (0-inf); area under the concentration-time curve in plasma over the time interval from 0 extrapolated to infinity for CD 10899 BS (metabolite of Volasertib BI 6727)

End point type	Secondary
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End point timeframe:

-0.083 hours (h), 2h, 4h, 6h, 24h, 168h and 336 h after first drug administration

Notes:

[31] - 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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Volasertib (BI 6727)			
Subject group type	Reporting group			
Number of subjects analysed	51 ^[32]			
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)	1400 (\pm 35.8)			

Notes:

[32] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax; maximum measured concentration of BI 6727 BS in plasma

End point title	Cmax; maximum measured concentration of BI 6727 BS in plasma ^[33]
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End point description:

Cmax; maximum measured concentration of BI 6727 BS in plasma

End point type	Secondary
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End point timeframe:

-0.083 hours (h), 2h, 4h, 6h, 24h, 168h and 336 h after first drug administration

Notes:

[33] - 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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Volasertib (BI 6727)			
Subject group type	Reporting group			
Number of subjects analysed	51 ^[34]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	341 (\pm 42.2)			

Notes:

[34] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax; maximum measured concentration of CD 10899 BS in plasma

End point title	Cmax; maximum measured concentration of CD 10899 BS in plasma ^[35]
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End point description:

Cmax; maximum measured concentration of CD 10899 BS (metabolite of Volasertib BI 6727) in plasma

End point type	Secondary
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End point timeframe:

-0.083 hours (h), 2h, 4h, 6h, 24h, 168h and 336 h after first drug administration

Notes:

[35] - 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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Volasertib (BI 6727)			
Subject group type	Reporting group			
Number of subjects analysed	51 ^[36]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	10.8 (± 63.4)			

Notes:

[36] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: tmax; time from dosing to maximum measured concentration of BI 6727 BS in plasma

End point title	tmax; time from dosing to maximum measured concentration of BI 6727 BS in plasma ^[37]
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End point description:

tmax; time from dosing to maximum measured concentration of BI 6727 BS in plasma

End point type	Secondary
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End point timeframe:

-0.083 hours (h), 2h, 4h, 6h, 24h, 168h and 336 h after first drug administration

Notes:

[37] - 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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Volasertib (BI 6727)			
Subject group type	Reporting group			
Number of subjects analysed	51 ^[38]			
Units: hours				
median (full range (min-max))	2 (1.83 to 3)			

Notes:

[38] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: tmax; time from dosing to maximum measured concentration of CD 10899 BS in plasma

End point title	tmax; time from dosing to maximum measured concentration of CD 10899 BS in plasma ^[39]
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End point description:

tmax; time from dosing to maximum measured concentration of CD 10899 BS (metabolite of Volasertib BI 6727) in plasma

End point type	Secondary
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End point timeframe:

-0.083 hours (h), 2h, 4h, 6h, 24h, 168h and 336 h after first drug administration

Notes:

[39] - 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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Volasertib (BI 6727)			
Subject group type	Reporting group			
Number of subjects analysed	51 ^[40]			
Units: hours				
median (full range (min-max))	6.07 (3.83 to 24.3)			

Notes:

[40] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: t1/2; Terminal half-life of BI 6727 BS in plasma

End point title	t1/2; Terminal half-life of BI 6727 BS in plasma ^[41]
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End point description:

t1/2; Terminal half-life of BI 6727 BS in plasma

End point type	Secondary
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End point timeframe:

-0.083 hours (h), 2h, 4h, 6h, 24h, 168h and 336 h after first drug administration

Notes:

[41] - 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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Volasertib (BI 6727)			
Subject group type	Reporting group			
Number of subjects analysed	51 ^[42]			
Units: hours				
geometric mean (geometric coefficient of variation)	143 (\pm 21.3)			

Notes:

[42] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: CL; total clearance of BI 6727 BS in plasma after intravenous administration

End point title	CL; total clearance of BI 6727 BS in plasma after intravenous administration ^[43]
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End point description:

CL; total clearance of BI 6727 BS in plasma after intravenous administration

End point type	Secondary
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End point timeframe:

-0.083 hours (h), 2h, 4h, 6h, 24h, 168h and 336 h after first drug administration

Notes:

[43] - 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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Volasertib (BI 6727)			
Subject group type	Reporting group			
Number of subjects analysed	49 ^[44]			
Units: mL/min				
geometric mean (geometric coefficient of variation)	801 (\pm 29.8)			

Notes:

[44] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: MRT; Mean residence time of BI 6727 BS in the body

End point title	MRT; Mean residence time of BI 6727 BS in the body ^[45]
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End point description:

MRT; Mean residence time of BI 6727 BS in the body

End point type	Secondary
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End point timeframe:

-0.083 hours (h), 2h, 4h, 6h, 24h, 168h and 336 h after first drug administration

Notes:

[45] - 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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Volasertib (BI 6727)			
Subject group type	Reporting group			
Number of subjects analysed	49 ^[46]			
Units: hours				
geometric mean (geometric coefficient of variation)	118 (\pm 31.2)			

Notes:

[46] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Vss;apparent volume of distribution at steady state following intravenous administration for BI 6727 BS

End point title	Vss;apparent volume of distribution at steady state following intravenous administration for BI 6727 BS ^[47]
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End point description:

Vss;apparent volume of distribution at steady state following intravenous administration for BI 6727 BS

End point type	Secondary
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End point timeframe:

-0.083 hours (h), 2h, 4h, 6h, 24h, 168h and 336 h after first drug administration

Notes:

[47] - 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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Volasertib (BI 6727)			
Subject group type	Reporting group			
Number of subjects analysed	49 ^[48]			
Units: Litres				
geometric mean (geometric coefficient of variation)	5690 (\pm 25.8)			

Notes:

[48] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: t_{1/2}; Terminal half-life of CD 10899 BS in plasma

End point title	t1/2; Terminal half-life of CD 10899 BS in plasma ^[49]
End point description:	t1/2; Terminal half-life of CD 10899 (metabolite of Volasertib BI 6727) BS in plasma
End point type	Secondary
End point timeframe:	-0.083 hours (h), 2h, 4h, 6h, 24h, 168h and 336 h after first drug administration

Notes:

[49] - 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: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

End point values	Volasertib (BI 6727)			
Subject group type	Reporting group			
Number of subjects analysed	53 ^[50]			
Units: hours				
geometric mean (geometric coefficient of variation)	146 (\pm 21.5)			

Notes:

[50] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Biomarkers and Pharmacogenetics Analysis (Optional)

End point title	Biomarkers and Pharmacogenetics Analysis (Optional)
End point description:	This endpoint has not been statistically analysed in the study report
End point type	Secondary
End point timeframe:	6 months

End point values	Volasertib (BI 6727)	Cytotoxic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[51]	0 ^[52]		
Units: NA				
number (not applicable)				

Notes:

[51] - Endpoint has not been statistically analysed in the study report

[52] - Endpoint has not been statistically analysed in the study report

Statistical analyses

No statistical analyses for this end point

Secondary: Biological tumour response based on serum cancer antigen 125 (CA-125) according to the Gynaecologic Cancer Intergroup (GCIG) criteria

End point title	Biological tumour response based on serum cancer antigen 125 (CA-125) according to the Gynaecologic Cancer Intergroup (GCIG) criteria
End point description:	
<p>Patients were to have a pre-treatment CA-125 of at least twice the upper limit of normal to be considered for CA-125 response. Patients were not evaluable by CA-125 if they had received mouse antibodies or if they had undergone medical and/or surgical interference with their peritoneum or pleura during the previous 28 days. In eligible patients, a CA-125 response was defined as the moment the CA-25 was reduced by 50%, with this being confirmed with a consecutive CA-125 assessment not earlier than 28 days after the previous one.</p> <p>Biological response rate based on serum CA-125 levels was assessed according to the guidelines by the Gynaecologic Cancer Intergroup. Monitoring of blood levels of the tumour marker CA-125 was performed at screening and every 6 weeks thereafter.</p>	
End point type	Secondary
End point timeframe:	
At screening and every 6 weeks thereafter (Up to 213 weeks)	

End point values	Volasertib (BI 6727)	Cytotoxic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54 ^[53]	55 ^[54]		
Units: participants				
number (not applicable)				
Yes	10	12		
No	33	23		
Not evaluable	4	11		
Missing	7	9		

Notes:

[53] - TS

[54] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence and intensity of adverse events according to the United States National Cancer Institute (US NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0

End point title	Incidence and intensity of adverse events according to the United States National Cancer Institute (US NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0
End point description:	
Incidence and intensity of adverse events according to the United States National Cancer Institute (US NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0	
End point type	Secondary
End point timeframe:	
From first treatment administration to 21 days after the last drug administration (Up to 1403 days)	

End point values	Volasertib (BI 6727)	Cytotoxic	Cytotoxic to volasertib switch	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	54 ^[55]	55 ^[56]	24 ^[57]	
Units: participants				
number (not applicable)				
Grade 1	4	3	1	
Grade 2	6	19	3	
Grade 3	16	25	9	
Grade 4	25	5	6	
Grade 5	3	3	3	

Notes:

[55] - TS

[56] - TS

[57] - TS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first treatment administration to 21 days after the last drug administration (Up to 1403 days)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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Reporting groups

Reporting group title	Volasertib (BI 6727)
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Reporting group description:

Volasertib (BI 6727 300 mg) was administered as intravenous infusion over 2 hours at Day 1 of each 21-day treatment course. Treatment was to be administered until disease progression or occurrence of toxicity leading to treatment discontinuation. Patients withdrawn from volasertib treatment could receive a treatment according to investigator's choice. The patients were to be followed for survival status.

Reporting group title	Cytotoxic to Volasertib Switch
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Reporting group description:

Patients of the cytotoxic arm who switched to treatment with Volasertib (BI 6727).

Reporting group title	Cytotoxic
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Reporting group description:

Patients received a non-platinum cytotoxic single agent. The investigator chose the most appropriate drug according to patient status previous chemotherapy effects, cumulative toxic effects, performance status, and nutritional status), the product Summary of Product

Characteristics (SPC), and the local standard of care. The following non-platinum regimens were recommended because they are regarded efficacious and safe in patients with resistant ovarian cancer:

Pegylated liposomal doxorubicin (PLD): 40 mg/m² at Day 1 (1 course = 28 days)

Topotecan: 1.25 mg/m² from Days 1 to 5 (1 course = 21 days), or 4 mg/m² at Days 1, 8, and 15 (1 course = 28 days)

Paclitaxel: 80 mg/m² at Days 1, 8, 15, and 21 (1 course = 28 days)

Gemcitabine: 1000 mg/m² at Days 1 and 8 (1 course = 21 days)

Serious adverse events	Volasertib (BI 6727)	Cytotoxic to Volasertib Switch	Cytotoxic
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 54 (44.44%)	12 / 24 (50.00%)	19 / 55 (34.55%)
number of deaths (all causes)	46	20	49
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 54 (0.00%)	1 / 24 (4.17%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to heart			

subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm progression			
subjects affected / exposed	0 / 54 (0.00%)	1 / 24 (4.17%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tumour invasion			
subjects affected / exposed	0 / 54 (0.00%)	1 / 24 (4.17%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Poor venous access			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Condition aggravated			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 54 (0.00%)	0 / 24 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Euthanasia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 24 (4.17%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 54 (0.00%)	0 / 24 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Multi-organ failure			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction			
subjects affected / exposed	2 / 54 (3.70%)	0 / 24 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 54 (3.70%)	0 / 24 (0.00%)	2 / 55 (3.64%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 54 (0.00%)	0 / 24 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	4 / 54 (7.41%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pleural effusion			
subjects affected / exposed	0 / 54 (0.00%)	1 / 24 (4.17%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 54 (3.70%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 54 (0.00%)	0 / 24 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic reaction			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Neutrophil count decreased			
subjects affected / exposed	0 / 54 (0.00%)	1 / 24 (4.17%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 54 (0.00%)	1 / 24 (4.17%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 54 (0.00%)	0 / 24 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 54 (0.00%)	2 / 24 (8.33%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	2 / 54 (3.70%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			

subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	4 / 54 (7.41%)	2 / 24 (8.33%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	2 / 54 (3.70%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 54 (0.00%)	0 / 24 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 54 (0.00%)	0 / 24 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 54 (0.00%)	1 / 24 (4.17%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastrointestinal obstruction			
subjects affected / exposed	0 / 54 (0.00%)	0 / 24 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileal perforation			

subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	2 / 54 (3.70%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	2 / 55 (3.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 54 (1.85%)	1 / 24 (4.17%)	3 / 55 (5.45%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 54 (0.00%)	0 / 24 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 54 (0.00%)	0 / 24 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	3 / 54 (5.56%)	0 / 24 (0.00%)	2 / 55 (3.64%)
occurrences causally related to treatment / all	1 / 3	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 24 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Pyelocaliectasis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 24 (4.17%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Device related sepsis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 24 (4.17%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 24 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 24 (4.17%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Pyelonephritis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 24 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 54 (0.00%)	1 / 24 (4.17%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 54 (0.00%)	0 / 24 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 54 (1.85%)	1 / 24 (4.17%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Volasertib (BI 6727)	Cytotoxic to Volasertib Switch	Cytotoxic
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 54 (98.15%)	21 / 24 (87.50%)	53 / 55 (96.36%)
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 54 (3.70%)	1 / 24 (4.17%)	3 / 55 (5.45%)
occurrences (all)	3	1	4
Alanine aminotransferase increased			
subjects affected / exposed	1 / 54 (1.85%)	1 / 24 (4.17%)	5 / 55 (9.09%)
occurrences (all)	1	1	7
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 54 (1.85%)	2 / 24 (8.33%)	7 / 55 (12.73%)
occurrences (all)	5	2	8
Blood creatinine increased			
subjects affected / exposed	4 / 54 (7.41%)	0 / 24 (0.00%)	2 / 55 (3.64%)
occurrences (all)	6	0	2
Blood uric acid increased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	3 / 55 (5.45%)
occurrences (all)	2	0	3
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 54 (1.85%)	1 / 24 (4.17%)	3 / 55 (5.45%)
occurrences (all)	1	1	3
Platelet count decreased			

subjects affected / exposed	5 / 54 (9.26%)	2 / 24 (8.33%)	0 / 55 (0.00%)
occurrences (all)	10	2	0
Weight decreased			
subjects affected / exposed	4 / 54 (7.41%)	0 / 24 (0.00%)	2 / 55 (3.64%)
occurrences (all)	4	0	2
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	4 / 55 (7.27%)
occurrences (all)	1	0	4
Headache			
subjects affected / exposed	8 / 54 (14.81%)	0 / 24 (0.00%)	4 / 55 (7.27%)
occurrences (all)	10	0	4
Neuropathy peripheral			
subjects affected / exposed	2 / 54 (3.70%)	0 / 24 (0.00%)	8 / 55 (14.55%)
occurrences (all)	2	0	9
Paraesthesia			
subjects affected / exposed	3 / 54 (5.56%)	0 / 24 (0.00%)	4 / 55 (7.27%)
occurrences (all)	3	0	4
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	3 / 55 (5.45%)
occurrences (all)	1	0	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	29 / 54 (53.70%)	5 / 24 (20.83%)	20 / 55 (36.36%)
occurrences (all)	50	5	30
Neutropenia			
subjects affected / exposed	34 / 54 (62.96%)	7 / 24 (29.17%)	17 / 55 (30.91%)
occurrences (all)	138	15	36
Leukopenia			
subjects affected / exposed	15 / 54 (27.78%)	2 / 24 (8.33%)	8 / 55 (14.55%)
occurrences (all)	43	3	19
Lymphopenia			
subjects affected / exposed	7 / 54 (12.96%)	0 / 24 (0.00%)	8 / 55 (14.55%)
occurrences (all)	14	0	16
Thrombocytopenia			

subjects affected / exposed occurrences (all)	26 / 54 (48.15%) 63	4 / 24 (16.67%) 9	4 / 55 (7.27%) 5
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	18 / 54 (33.33%)	4 / 24 (16.67%)	26 / 55 (47.27%)
occurrences (all)	28	4	45
Mucosal inflammation			
subjects affected / exposed	4 / 54 (7.41%)	1 / 24 (4.17%)	7 / 55 (12.73%)
occurrences (all)	7	1	12
Fatigue			
subjects affected / exposed	4 / 54 (7.41%)	4 / 24 (16.67%)	12 / 55 (21.82%)
occurrences (all)	4	5	21
Chest pain			
subjects affected / exposed	4 / 54 (7.41%)	1 / 24 (4.17%)	2 / 55 (3.64%)
occurrences (all)	4	1	2
Oedema peripheral			
subjects affected / exposed	8 / 54 (14.81%)	3 / 24 (12.50%)	5 / 55 (9.09%)
occurrences (all)	9	4	5
Pyrexia			
subjects affected / exposed	5 / 54 (9.26%)	4 / 24 (16.67%)	4 / 55 (7.27%)
occurrences (all)	6	5	4
Pain			
subjects affected / exposed	2 / 54 (3.70%)	1 / 24 (4.17%)	4 / 55 (7.27%)
occurrences (all)	2	1	6
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	2 / 54 (3.70%)	2 / 24 (8.33%)	0 / 55 (0.00%)
occurrences (all)	2	2	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	6 / 54 (11.11%)	3 / 24 (12.50%)	7 / 55 (12.73%)
occurrences (all)	6	4	8
Abdominal pain			
subjects affected / exposed	13 / 54 (24.07%)	5 / 24 (20.83%)	20 / 55 (36.36%)
occurrences (all)	16	5	33
Abdominal distension			

subjects affected / exposed	3 / 54 (5.56%)	0 / 24 (0.00%)	2 / 55 (3.64%)
occurrences (all)	5	0	2
Ascites			
subjects affected / exposed	1 / 54 (1.85%)	2 / 24 (8.33%)	3 / 55 (5.45%)
occurrences (all)	1	2	3
Intestinal obstruction			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	3 / 55 (5.45%)
occurrences (all)	1	0	4
Dyspepsia			
subjects affected / exposed	6 / 54 (11.11%)	0 / 24 (0.00%)	2 / 55 (3.64%)
occurrences (all)	7	0	2
Diarrhoea			
subjects affected / exposed	15 / 54 (27.78%)	2 / 24 (8.33%)	12 / 55 (21.82%)
occurrences (all)	26	3	16
Constipation			
subjects affected / exposed	16 / 54 (29.63%)	5 / 24 (20.83%)	13 / 55 (23.64%)
occurrences (all)	23	6	14
Vomiting			
subjects affected / exposed	15 / 54 (27.78%)	2 / 24 (8.33%)	18 / 55 (32.73%)
occurrences (all)	26	7	32
Stomatitis			
subjects affected / exposed	3 / 54 (5.56%)	0 / 24 (0.00%)	3 / 55 (5.45%)
occurrences (all)	3	0	3
Rectal haemorrhage			
subjects affected / exposed	3 / 54 (5.56%)	1 / 24 (4.17%)	1 / 55 (1.82%)
occurrences (all)	3	1	1
Nausea			
subjects affected / exposed	19 / 54 (35.19%)	5 / 24 (20.83%)	25 / 55 (45.45%)
occurrences (all)	35	7	36
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 54 (14.81%)	1 / 24 (4.17%)	4 / 55 (7.27%)
occurrences (all)	13	1	4
Dyspnoea			

subjects affected / exposed	2 / 54 (3.70%)	0 / 24 (0.00%)	5 / 55 (9.09%)
occurrences (all)	5	0	6
Epistaxis			
subjects affected / exposed	4 / 54 (7.41%)	1 / 24 (4.17%)	5 / 55 (9.09%)
occurrences (all)	4	4	6
Oropharyngeal pain			
subjects affected / exposed	0 / 54 (0.00%)	0 / 24 (0.00%)	3 / 55 (5.45%)
occurrences (all)	0	0	3
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	16 / 54 (29.63%)	4 / 24 (16.67%)	12 / 55 (21.82%)
occurrences (all)	16	4	12
Erythema			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	4 / 55 (7.27%)
occurrences (all)	1	0	4
Hair colour changes			
subjects affected / exposed	1 / 54 (1.85%)	2 / 24 (8.33%)	0 / 55 (0.00%)
occurrences (all)	1	2	0
Nail toxicity			
subjects affected / exposed	0 / 54 (0.00%)	0 / 24 (0.00%)	4 / 55 (7.27%)
occurrences (all)	0	0	4
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 54 (3.70%)	0 / 24 (0.00%)	4 / 55 (7.27%)
occurrences (all)	2	0	5
Rash			
subjects affected / exposed	2 / 54 (3.70%)	0 / 24 (0.00%)	6 / 55 (10.91%)
occurrences (all)	2	0	7
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 54 (0.00%)	1 / 24 (4.17%)	3 / 55 (5.45%)
occurrences (all)	0	1	3
Anxiety			
subjects affected / exposed	1 / 54 (1.85%)	1 / 24 (4.17%)	4 / 55 (7.27%)
occurrences (all)	2	1	4
Insomnia			

subjects affected / exposed occurrences (all)	4 / 54 (7.41%) 6	2 / 24 (8.33%) 2	4 / 55 (7.27%) 8
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 54 (7.41%)	2 / 24 (8.33%)	4 / 55 (7.27%)
occurrences (all)	5	2	6
Back pain			
subjects affected / exposed	7 / 54 (12.96%)	2 / 24 (8.33%)	7 / 55 (12.73%)
occurrences (all)	11	3	7
Myalgia			
subjects affected / exposed	4 / 54 (7.41%)	1 / 24 (4.17%)	5 / 55 (9.09%)
occurrences (all)	9	1	5
Muscle spasms			
subjects affected / exposed	4 / 54 (7.41%)	2 / 24 (8.33%)	2 / 55 (3.64%)
occurrences (all)	4	2	2
Pain in extremity			
subjects affected / exposed	3 / 54 (5.56%)	3 / 24 (12.50%)	3 / 55 (5.45%)
occurrences (all)	5	4	3
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 54 (7.41%)	1 / 24 (4.17%)	2 / 55 (3.64%)
occurrences (all)	4	1	2
Urinary tract infection			
subjects affected / exposed	2 / 54 (3.70%)	0 / 24 (0.00%)	5 / 55 (9.09%)
occurrences (all)	3	0	7
Rhinitis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 24 (0.00%)	3 / 55 (5.45%)
occurrences (all)	0	0	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	11 / 54 (20.37%)	1 / 24 (4.17%)	14 / 55 (25.45%)
occurrences (all)	15	1	18
Hyperglycaemia			
subjects affected / exposed	4 / 54 (7.41%)	0 / 24 (0.00%)	5 / 55 (9.09%)
occurrences (all)	9	0	7
Hyperkalaemia			

subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	4 / 55 (7.27%)
occurrences (all)	1	0	8
Hyperuricaemia			
subjects affected / exposed	3 / 54 (5.56%)	0 / 24 (0.00%)	1 / 55 (1.82%)
occurrences (all)	3	0	1
Hypoalbuminaemia			
subjects affected / exposed	2 / 54 (3.70%)	0 / 24 (0.00%)	3 / 55 (5.45%)
occurrences (all)	3	0	3
Hypocalcaemia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 24 (0.00%)	4 / 55 (7.27%)
occurrences (all)	1	0	5
Hypokalaemia			
subjects affected / exposed	7 / 54 (12.96%)	1 / 24 (4.17%)	2 / 55 (3.64%)
occurrences (all)	9	1	4
Hypomagnesaemia			
subjects affected / exposed	3 / 54 (5.56%)	1 / 24 (4.17%)	4 / 55 (7.27%)
occurrences (all)	4	1	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 March 2010	Amendment 1 introduced accurate recommendations for the management of QTcF interval prolongation and ventricular tachyarrhythmia.
27 September 2010	<ul style="list-style-type: none">- Amendment 2 added drug-related QTcF prolongation >60 ms from baseline or drug-related prolongation of absolute QTcF >500 ms as a further unacceptable volasertib toxicity.- Amendment 2 detailed in the ECG investigations section that supervision of the patient had to be performed by an intensive care unit physician.- Amendment 2 corrected footnote 9 in the flow chart for screening and the first treatment course: safety laboratory had to be performed within 7 days prior to the start of the study treatment.- Amendment 2 corrected the time interval given in inclusion criterion 3: patients with disease progression occurring up to 4 weeks after the last administration of platinum-based therapy were considered as platinum refractory- Amendment 2 specified the conditions for patient cross-over from Arm B to volasertib treatment and described the procedures and recommendations for these patients.- Amendment 2 clarified that the interim analysis of safety was conducted by a data safety management board that was independent from the sponsor.- Amendment 2 added the collection of information on the type of progression before the patient was entered into the trial to the section on demographics and history.
13 December 2010	Amendment 3 further specified the conditions for patient cross-over from Arm B to volasertib treatment and clarified the procedures for ECG monitoring in these patients.
29 March 2011	Amendment 4 was implemented to facilitate the procedures for dispensing the commercial cytotoxic agents in the comparator arm and allowed the drugs to be dispensed by the pharmacy service of the site as marketed in each country with the approved local label and appropriate documentation.
20 February 2012	<ul style="list-style-type: none">- Amendment 5 prolonged the duration of the trial until September 2012 due to some non-progressing patients still being on treatment.- Amendment 5 updated details on specified optional tumour biopsy biomarker testing on samples collected during the study.- Amendment 5 included guidance and procedures to complement AE reporting of DILI.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported