Clinical trial results:
STOMP: Small cell lung cancer Trial of Olaparib (AZD2281) as Maintenance Programme: a randomised, double blind, multicentre phase II trial.

Summary

EudraCT number	2010-021165-76
Trial protocol	GB
Global end of trial date	11 December 2020

Results information

Result version number	v1 (current)
This version publication date	26 December 2021
First version publication date	26 December 2021
Summary attachment (see zip file)	Baseline Tables for (Non-) Target Lesions (Baseline Tables_(Non-)Target Lesion Data.pdf)

Trial information

Trial identification

Sponsor protocol code	LU2006 / STH15845

Additional study identifiers

ISRCTN number	ISRCTN73164486
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor Protocol Number: STH15845

Notes:

Sponsors

Sponsor organisation name	Sheffield Teaching Hospitals NHS Foundation Trust
Sponsor organisation address	Trust Headquarters, 8 Beech Hill Road, Sheffield, United Kingdom, S10 2SB
Public contact	Dr Dipak Patel, Sheffield Teaching Hospitals NHS Foundation Trust, sth.ResearchAdministration@nhs.net
Scientific contact	Dr Dipak Patel, Sheffield Teaching Hospitals NHS Foundation Trust, sth.ResearchAdministration@nhs.net

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	31 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2020
Global end of trial reached?	Yes
Global end of trial date	11 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the activity and safety of the PARP inhibitor olaparib as maintenance treatment for patients with chemoresponsive SCLC.

Protection of trial subjects:

This study was carried out in accordance with current guidelines for Good clinical Practice and the Declaration of Helsinki. The protocol gained ethical approval from the NRES Committee Yorkshire & The Humber - Leeds East. Before entering patients into the study, the Principal Investigator ensured that the protocol had approval from their local Research and Development (R&D) Office. Participants were provided with ethically approved comprehensive information about the trial and trial treatments, and given advice on who to contact with any questions or concerns at any time.

A participant's treatment response was determined by their treating physician who reviewed the patient every 4 weeks with: Physical examination, ECOG performance status, blood pressure, pulse and temperature measurements, haematological and biochemical tests, adverse event and concomitant medication reviews and alternate CT and X-ray scans.

Prohibited concomitant therapies were listed in the olaparib Investigators Brochure and trial protocol. All concomitant therapies were required to be recorded.

Any toxicity observed during the course of the trial was managed by dose interruption or permanent dose reduction if deemed appropriate by the treating physician and in accordance with the protocol.

Participants of child bearing potential were required to agree to use two highly effective forms of contraception throughout their participation in the trial and for 3 months after last dose of trial drug.

The independent monitoring committee (IDMC) met on a yearly basis during the trial recruitment phase. The IDMC could consider discontinuing the trial if the recruitment rate or data quality were found to be unacceptable or if any issues are identified which may compromise patient safety.

Background therapy:

Completed 3 cycles of first line chemotherapy or chemo-radiotherapy with:
(a) cisplatin in combination with etoposide or (b) carboplatin in combination with etoposide.

Evidence for comparator:

Olaparib (AZD2281, KU-0059436, KuDOS/AstraZeneca) is a PARP inhibitor in development for the treatment of patients who have cancers associated with genetic BRCA mutations and in patients with deficiency in DNA repair, specifically homologous recombination repair deficiency. Clinical study data to date in patients with advanced cancer have shown olaparib to have significant anti-tumour activity as a single agent in ovarian and breast cancer patients with known homologous recombination deficiency: BRCA1-/- or BRCA2-/-. Due to the molecular targeting of olaparib to specific subsets of tumours and sparing of normal cells, this has raised the opportunity for relatively less toxic cancer monotherapy using such a PARP 1 inhibitor compared with conventional treatments, such as chemotherapy.
Olaparib has been tested in a standard range of safety pharmacology studies e.g. dog cardiovascular and respiratory function tests, and the rat Irwin test. There were no noticeable effects on the cardiovascular or respiratory parameters in the anaesthetised dog or any behavioural, autonomic or motor effects in the rat at the doses studied. The toxicology studies indicate that the target organ of toxicity is the bone marrow. Further information can be found in the current version of the olaparib Investigator's Brochure.

More than 950 patients have now received olaparib either as monotherapy (11 studies) or in combination with other chemotherapy agents. Data from these studies indicate that olaparib is generally

well tolerated as monotherapy at doses up to 400 mg bd capsules in patients with solid tumours.

Actual start date of recruitment	21 November 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research, Efficacy
Long term follow-up duration	30 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 220
Worldwide total number of subjects	220
EEA total number of subjects	0

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)	115
From 65 to 84 years	103
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between 21 November 2013 and 11 December 2015 at multiple centres across the United Kingdom.

Pre-assignment

Screening details:

≥18 years, SCLC +ve (M0 or M1a/B, any T/N stage), complete/ partial response to ≥3 cycles of (chemo +/-)radiotherapy, ECOG 0-2. Without uncontrolled brain mets, interstitial lung disease, previous malignancies, history of malabsorption or major GI tract resection, treatment with PARP or CYP3A4 inhibitors, breast feeding women, poor medical risk.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Active and placebo tablets were matching in terms of size, colour and packaging to ensure blinding of the trial medication. Treatment allocation was by telephone to the central randomisation service. Treatment pack number was allocated to patients sequentially using a block randomisation scheme loaded onto the Cenduit Interactive Web Recognition System (IWRS) database and accessed by CRCTU on behalf of randomising sites.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

placebo 300mg BD and placebo 200mg TDS

Arm type	Placebo
Investigational medicinal product name	Matched placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Matched placebo 300mg po bd or 200mg po tds, taken continuously until death, disease progression, unacceptable toxicities or withdrawal of patient consent up to a maximum of 2 years.

Arm title	Olaparib BD

Arm description:

olaparib 300mg BD

Arm type	Experimental
Investigational medicinal product name	olaparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Olaparib 300mg po bd taken continuously until death, disease progression, unacceptable toxicities or withdrawal of patient consent up to a maximum of 2 years.

Arm title	Olaparib TDS

Arm description:	
olaparib 200mg TDS	
Arm type	Experimental
Investigational medicinal product name	olaparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

200mg tds taken continuously until death, disease progression, unacceptable toxicities or withdrawal of patient consent up to a maximum of 2 years.

Number of subjects in period 1	Placebo	Olaparib BD	Olaparib TDS
Started	74	73	73
Completed	74	73	73

Period 2

Period 2 title	Overall Trial - Intention to Treat
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Active and placebo tablets were matching in terms of size, colour and packaging to ensure blinding of the trial medication. Treatment allocation was by telephone to the central randomisation service. Treatment pack number was allocated to patients sequentially using a block randomisation scheme loaded onto the Cenduit Interactive Web Recognition System (IWRS) database and accessed by CRCTU on behalf of randomising sites.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo - ITT

Arm description:

placebo 300mg BD and placebo 200mg TDS

Arm type	Placebo
Investigational medicinal product name	Matched placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Matched placebo 300mg po bd or 200mg po tds, taken continuously until death, disease progression, unacceptable toxicities or withdrawal of patient consent up to a maximum of 2 years.

Arm title	Olaparib BD - ITT

Arm description:

olaparib 300mg BD

Arm type	Experimental
Investigational medicinal product name	olaparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

300mg po bd taken continuously until death, disease progression, unacceptable toxicities or withdrawal of patient consent up to a maximum of 2 years.

Arm title	Olaparib TDS - ITT

Arm description:

olaparib 200mg TDS

Arm type	Experimental
Investigational medicinal product name	olaparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

200mg tds taken continuously until death, disease progression, unacceptable toxicities or withdrawal of patient consent up to a maximum of 2 years.

Number of subjects in period 2	Placebo - ITT	Olaparib BD - ITT	Olaparib TDS - ITT
Started	74	73	73
Completed	74	73	73

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: placebo 300mg BD and placebo 200mg TDS	
Reporting group title	Olaparib BD
Reporting group description: olaparib 300mg BD	
Reporting group title	Olaparib TDS
Reporting group description: olaparib 200mg TDS	

Reporting group values	Placebo	Olaparib BD	Olaparib TDS
Number of subjects	74	73	73
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	42	35	38
From 65-84 years	31	37	35
85 years and over	1	1	0
Age continuous Units: years			
median	64	66	63
inter-quartile range (Q1-Q3)	58 to 68	58 to 70	55 to 69
Gender categorical Units: Subjects			
Female	40	37	42
Male	34	36	31
T-stage at diagnosis Units: Subjects			
TX	4	4	1
T0	0	1	2
T1	3	5	5
T1a	3	1	3
T1b	2	0	3
T2	4	2	3
T2a	4	3	4
T2b	0	5	1
T3	18	20	13
T4	36	32	38
N-stage at diagnosis			

Units: Subjects			
NX	2	0	0
N0	4	5	3
N1	9	6	4
N2	24	28	29
N3	35	34	37
M-stage at diagnosis			
Units: Subjects			
M0	21	22	23
M1a	6	6	5
M1b	47	45	45
Number of previous chemotherapy cycles			
Units: Subjects			
3 cycles	1	0	2
4 cycles	31	27	23
5 cycles	5	3	4
6 cycles	37	43	44
Prior chemotherapy type			
Units: Subjects			
Etoposide-Carboplatin	52	56	54
Etoposide-Cisplatin	18	16	13
Etoposide-Cisplatin-Carboplatin	4	1	6
Prior radiotherapy type			
Units: Subjects			
Thoracic & cranial	40	33	36
Thoracic only	2	5	5
Cranial only	25	25	24
None	7	10	8
Response to prior treatment at study baseline			
Units: Subjects			
Complete response	5	4	7
Partial response	69	64	66
Progression	0	5	0
Physical examination and assessment performed			
Units: Subjects			
No	0	1	1
Yes	74	72	72
ECOG Performance Status			
Units: Subjects			
Category 0	18	17	25
Category 1	48	51	44
Category 2	8	5	3
Not Known	0	0	1
Number of target lesions			
Units: Subjects			
1 Target lesion	25	31	18
2 Target lesion	11	14	18
3 Target lesion	6	5	6
4 Target lesion	1	1	0

5 Target lesion	1	0	1
No target lesions	30	22	30
Number of non-target lesions per patient Units: Subjects			
1 non-target lesion	23	28	19
2 non-target lesions	22	13	17
3 non-target lesions	4	9	12
4 non-target lesions	3	2	3
5 non-target lesions	0	0	2
6 non-target lesions	0	1	0
7 non-target lesions	0	1	1
0 non-target lesions	22	19	19
Liver metastases present at baseline Units: Subjects			
No	55	54	53
Yes	19	19	20
Time from diagnosis to randomisation Units: Weeks			
median	22	25	24
full range (min-max)	15 to 34	16 to 38	15 to 32
Time between last chemotherapy dose and trial entry Units: Weeks			
median	6.6	7.3	7.6
full range (min-max)	2.3 to 16.7	3.7 to 15.6	3.6 to 14.6
Chemotherapy duration Units: Weeks between first and last dose given			
median	14.6	15.0	15.0
full range (min-max)	9.0 to 20.7	7.1 to 20.0	6.0 to 21.0
Time between most recent radiotherapy dose and trial entry Units: Weeks			
median	1.7	2.1	2.1
inter-quartile range (Q1-Q3)	1.0 to 2.6	1.6 to 2.7	1.6 to 2.9
Blood pressure (systolic) Units: mmHg			
arithmetic mean	127	124	132
standard deviation	± 19	± 17	± 19
Blood pressure (diastolic) Units: mmHg			
arithmetic mean	76	75	78
standard deviation	± 13	± 11	± 10
Pulse Units: bpm			
arithmetic mean	84	84	83
standard deviation	± 13	± 13	± 14
Height Units: cm			
arithmetic mean	167	167	167
standard deviation	± 9	± 10	± 10
Weight			

Units: Kg			
arithmetic mean	74	75	74
standard deviation	± 15	± 18	± 20
Haemoglobin			
Units: g/L			
arithmetic mean	120.4	119.9	120.7
standard deviation	± 10.8	± 12.3	± 14.4
Absolute neutrophil count			
Units: x109/L			
arithmetic mean	4.7	4.3	4.6
standard deviation	± 2.4	± 1.8	± 2.3
White blood cells			
Units: x109/L			
arithmetic mean	6.7	6.1	6.5
standard deviation	± 2.7	± 2.0	± 2.4
Platelets			
Units: x109/L			
median	236.5	229.0	218.0
inter-quartile range (Q1-Q3)	190.0 to 300.0	181.0 to 276.0	175.0 to 280.0
Bilirubin			
Units: umol/L)			
arithmetic mean	7	7	7
standard deviation	± 3	± 4	± 3
Aspartate aminotransferase (AST)			
Units: units/L			
arithmetic mean	21	20	19
standard deviation	± 6	± 8	± 6
Alanine transaminase (ALT)			
Units: units/L			
arithmetic mean	18	22	23
standard deviation	± 8	± 10	± 19
Alkaline Phosphatase			
Units: units/L			
arithmetic mean	94	93	87
standard deviation	± 46	± 54	± 38
Total Serum Protein			
Units: g/L			
arithmetic mean	69	68	68
standard deviation	± 4	± 4	± 5
Urea			
Units: mmol/L			
arithmetic mean	5.3	5.4	5.1
standard deviation	± 2.0	± 1.9	± 1.9
Potassium			
Units: mmol/L			
arithmetic mean	4.1	4.2	4.3
standard deviation	± 0.3	± 0.3	± 0.4
Creatinine			
Units: umol/L			
arithmetic mean	75	72	72
standard deviation	± 18	± 15	± 18
Sodium			

Units: mmol/L			
arithmetic mean	139	138	138
standard deviation	± 3	± 4	± 4
Calcium			
Units: mmol/L			
arithmetic mean	2.38	2.37	2.38
standard deviation	± 0.11	± 0.12	± 0.11
Lesion diameter			
Units: mm			
arithmetic mean	29	25	23
standard deviation	± 17	± 14	± 10

Reporting group values	Total		
Number of subjects	220		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	115		
From 65-84 years	103		
85 years and over	2		
Age continuous			
Units: years			
median			
inter-quartile range (Q1-Q3)	-		
Gender categorical			
Units: Subjects			
Female	119		
Male	101		
T-stage at diagnosis			
Units: Subjects			
TX	9		
T0	3		
T1	13		
T1a	7		
T1b	5		
T2	9		
T2a	11		
T2b	6		
T3	51		
T4	106		
N-stage at diagnosis			
Units: Subjects			
NX	2		
N0	12		
N1	19		

N2	81		
N3	106		
M-stage at diagnosis Units: Subjects			
M0	66		
M1a	17		
M1b	137		
Number of previous chemotherapy cycles Units: Subjects			
3 cycles	3		
4 cycles	81		
5 cycles	12		
6 cycles	124		
Prior chemotherapy type Units: Subjects			
Etoposide-Carboplatin	162		
Etoposide-Cisplatin	47		
Etoposide-Cisplatin-Carboplatin	11		
Prior radiotherapy type Units: Subjects			
Thoracic & cranial	109		
Thoracic only	12		
Cranial only	74		
None	25		
Response to prior treatment at study baseline Units: Subjects			
Complete response	16		
Partial response	199		
Progression	5		
Physical examination and assessment performed Units: Subjects			
No	2		
Yes	218		
ECOG Performance Status Units: Subjects			
Category 0	60		
Category 1	143		
Category 2	16		
Not Known	1		
Number of target lesions Units: Subjects			
1 Target lesion	74		
2 Target lesion	43		
3 Target lesion	17		
4 Target lesion	2		
5 Target lesion	2		
No target lesions	82		
Number of non-target lesions per patient			

Units: Subjects			
1 non-target lesion	70		
2 non-target lesions	52		
3 non-target lesions	25		
4 non-target lesions	8		
5 non-target lesions	2		
6 non-target lesions	1		
7 non-target lesions	2		
0 non-target lesions	60		
Liver metastases present at baseline			
Units: Subjects			
No	162		
Yes	58		
Time from diagnosis to randomisation			
Units: Weeks			
median			
full range (min-max)	-		
Time between last chemotherapy dose and trial entry			
Units: Weeks			
median			
full range (min-max)	-		
Chemotherapy duration			
Units: Weeks between first and last dose given			
median			
full range (min-max)	-		
Time between most recent radiotherapy dose and trial entry			
Units: Weeks			
median			
inter-quartile range (Q1-Q3)	-		
Blood pressure (systolic)			
Units: mmHg			
arithmetic mean			
standard deviation	-		
Blood pressure (diastolic)			
Units: mmHg			
arithmetic mean			
standard deviation	-		
Pulse			
Units: bpm			
arithmetic mean			
standard deviation	-		
Height			
Units: cm			
arithmetic mean			
standard deviation	-		
Weight			
Units: Kg			
arithmetic mean			
standard deviation	-		
Haemoglobin			

Units: g/L arithmetic mean standard deviation	-		
Absolute neutrophil count Units: x109/L arithmetic mean standard deviation	-		
White blood cells Units: x109/L arithmetic mean standard deviation	-		
Platelets Units: x109/L median inter-quartile range (Q1-Q3)	-		
Bilirubin Units: umol/L) arithmetic mean standard deviation	-		
Aspartate aminotransferase (AST) Units: units/L arithmetic mean standard deviation	-		
Alanine transaminase (ALT) Units: units/L arithmetic mean standard deviation	-		
Alkaline Phosphatase Units: units/L arithmetic mean standard deviation	-		
Total Serum Protein Units: g/L arithmetic mean standard deviation	-		
Urea Units: mmol/L arithmetic mean standard deviation	-		
Potassium Units: mmol/L arithmetic mean standard deviation	-		
Creatinine Units: umol/L arithmetic mean standard deviation	-		
Sodium Units: mmol/L arithmetic mean standard deviation	-		
Calcium			

Units: mmol/L arithmetic mean standard deviation	-		
Lesion diameter Units: mm arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: placebo 300mg BD and placebo 200mg TDS	
Reporting group title	Olaparib BD
Reporting group description: olaparib 300mg BD	
Reporting group title	Olaparib TDS
Reporting group description: olaparib 200mg TDS	
Reporting group title	Placebo - ITT
Reporting group description: placebo 300mg BD and placebo 200mg TDS	
Reporting group title	Olaparib BD - ITT
Reporting group description: olaparib 300mg BD	
Reporting group title	Olaparib TDS - ITT
Reporting group description: olaparib 200mg TDS	
Subject analysis set title	Intention to Treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: Primary analysis	
Subject analysis set title	Per Protocol Analysis
Subject analysis set type	Per protocol
Subject analysis set description: Secondary analysis	
Subject analysis set title	Sensitivity analysis
Subject analysis set type	Sub-group analysis
Subject analysis set description: Olaparib BD vs placebo only	

Primary: Progression free survival time

End point title	Progression free survival time
End point description:	
End point type	Primary
End point timeframe: Months	

End point values	Placebo - ITT	Olaparib BD - ITT	Olaparib TDS - ITT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	73	73	
Units: Months				
median (confidence interval 90%)	2.50 (1.81 to 3.68)	3.65 (3.12 to 4.60)	3.58 (2.79 to 4.67)	

Statistical analyses

Statistical analysis title	PFS Olaparib BD vs Placebo
Statistical analysis description: Olaparib BD vs Placebo	
Comparison groups	Placebo - ITT v Olaparib BD - ITT
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1801
Method	Logrank

Statistical analysis title	PFS Olaparib TDS vs Placebo
Comparison groups	Placebo - ITT v Olaparib TDS - ITT
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1641
Method	Logrank

Statistical analysis title	PFS Olaparib BD vs Placebo
Comparison groups	Olaparib BD - ITT v Placebo - ITT
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.125
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.57
upper limit	1.02

Statistical analysis title	PFS Olaparib TDS vs Placebo
Comparison groups	Placebo - ITT v Olaparib TDS - ITT
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.402
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.64
upper limit	1.15

Secondary: Progression-free survival at 4 months from randomisation

End point title	Progression-free survival at 4 months from randomisation

End point description:

End point type	Secondary

End point timeframe:

4 months

End point values	Placebo	Olaparib BD	Olaparib TDS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	73	73	
Units: Percentage				
number (confidence interval 90%)	36 (27 to 45)	45 (35 to 54)	45 (35 to 54)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival time

End point title	Overall survival time

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Placebo - ITT	Olaparib BD - ITT	Olaparib TDS - ITT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	73	73	
Units: Months				
number (confidence interval 90%)	9.69 (7.13 to 12.19)	11.01 (7.85 to 12.94)	9.63 (6.80 to 11.76)	

Statistical analyses

Statistical analysis title	Overall Survival - Olaparib BD vs Placebo
Comparison groups	Placebo - ITT v Olaparib BD - ITT
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7094
Method	Logrank

Statistical analysis title	Overall Survival - Olaparib TDS vs Placebo
Comparison groups	Placebo - ITT v Olaparib TDS - ITT
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9904
Method	Logrank

Statistical analysis title	Overall Survival - Olaparib BD vs Placebo (HR)
Comparison groups	Placebo - ITT v Olaparib BD - ITT
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.376
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.63
upper limit	1.15

Statistical analysis title	Overall Survival - Olaparib TDS vs Placebo (HR)
Comparison groups	Placebo - ITT v Olaparib TDS - ITT
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.85
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.77
upper limit	1.39

Secondary: Overall survival at 6 months

End point title	Overall survival at 6 months

End point description:

End point type	Secondary

End point timeframe:

6 months

End point values	Placebo - ITT	Olaparib BD - ITT	Olaparib TDS - ITT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	73	73	
Units: percent				
number (confidence interval 90%)	66 (56 to 75)	69 (60 to 77)	66 (56 to 75)	

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in performance status

End point title	Changes in performance status

End point description:

ECOG Performance status at cycle 6.
Note: ECOG . category refers to patients where ECOG data is not available due to either patient death, trial withdrawal or that the data are missing.

End point type	Secondary

End point timeframe:
12 treatment cycles

End point values	Placebo - ITT	Olaparib BD - ITT	Olaparib TDS - ITT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	73	73	
Units: Performance status				
ECOG 0	2	6	3	
ECOG 1	15	13	9	
ECOG 2	1	0	0	
ECOG 3	0	1	0	
ECOG .	56	53	60	

Attachments (see zip file)	Table of ECOG scores cycle 7 to 12/Table of ECOG scores for Table of ECOG scores cycle 1 to 6/Table of ECOG scores for Plots of ECOG performance data/Plots of ECOG data on

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life (EQ-5D)

End point title	Quality of life (EQ-5D)

End point description:

End point type	Secondary

End point timeframe:
6 months

End point values	Placebo - ITT	Olaparib BD - ITT	Olaparib TDS - ITT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74	73	73	
Units: Quality of Life Adjusted Life months				
number (confidence interval 90%)				
Utility QALM	3.16 (2.80 to 3.52)	2.98 (2.65 to 3.31)	3.21 (2.87 to 3.56)	
Thermometer QALM	292.25 (259.21 to 325.30)	301.60 (273.38 to 329.82)	294.13 (264.37 to 323.89)	

Attachments (see zip file)	Table of EQ5D Thermometer Questionnaire Results BL_Cycle1- Table of EQ5D Utility Questionnaire Results BL_Cycle1-6.pdf Plots of QOL data.pdf Plots of QOL data 2.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events (experienced by >5% of population)

End point title	Adverse events (experienced by >5% of population)
End point description:	
End point type	Secondary
End point timeframe: 12 months	

End point values	Placebo - ITT	Olaparib BD - ITT	Olaparib TDS - ITT	Per Protocol Analysis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	74	73	73	217
Units: Number				
Anemia	15	37	41	93
Sinus tachycardia	4	0	1	5
Abdominal pain	6	6	8	20
Bloating	2	4	1	7
Constipation	19	16	14	49
Diarrhea	18	13	12	43
Dry mouth	3	1	7	11
Dyspepsia	13	11	6	30
Dysphagia	5	5	3	13
Mucositis oral	10	7	2	19
Nausea	44	47	51	142
Stomach pain	2	3	5	10
Vomiting	21	25	33	79
Fatigue	55	64	58	177
Non-cardiac chest pain	9	10	3	22
Pain	6	3	5	14
Lung infection	12	14	12	38
Mucosal infection	6	7	4	17
Upper respiratory infection	5	7	7	19

Urinary tract infection	3	3	6	12
Lymphocyte count decreased	0	8	9	17
Neutrophil count decreased	0	5	2	7
Platelet count decreased	2	4	5	11
Anorexia	30	34	28	92
Hyperglycemia	4	2	6	12
Hypoalbuminemia	4	4	7	15
Hypocalcemia	2	9	3	14
Hypokalemia	4	4	4	12
Hypomagnesemia	5	2	1	8
Hyponatremia	12	7	10	29
Arthralgia	17	6	9	32
Back pain	18	13	14	45
Bone pain	7	2	0	9
Joint effusion	2	5	4	11
Myalgia	4	2	3	9
Pain in extremity	2	13	5	20
Dizziness	14	16	15	45
Dysgeusia	12	12	12	36
Headache	18	19	17	54
Paresthesia	5	2	7	14
Peripheral sensory neuropathy	2	4	4	10
Anxiety	8	2	4	14
Confusion	3	1	5	9
Depression	7	7	6	20
Insomnia	10	8	5	23
Cough	26	22	25	73
Dyspnea	21	26	28	75
Productive cough	1	4	4	9
Wheezing	5	2	2	9
Alopecia	11	13	16	40
Dry skin	5	6	4	15
Pruritus	7	4	4	15
Rash maculo-papular	8	5	5	18
Hypertension	8	5	4	17
Hypotension	1	1	4	6
Thromboembolic event	3	3	6	12

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the date of consent until 28 days after the administration of the last dose of trial medication.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

placebo 300mg BD and placebo 200mg TDS. Per protocol population.

Reporting group title	Olaparib BD

Reporting group description:

olaparib 300mg BD. Per protocol population.

Reporting group title	Olaparib TDS

Reporting group description:

olaparib 200mg TDS. Per protocol population.

Serious adverse events	Placebo	Olaparib BD	Olaparib TDS
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 73 (31.51%)	21 / 71 (29.58%)	29 / 73 (39.73%)
number of deaths (all causes)	60	61	66
number of deaths resulting from adverse events	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Unspecified			
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (0.00%)	0 / 73 (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
New primary tumour			
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (0.00%)	0 / 73 (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
Vascular disorders			
Thromboembolic event			

subjects affected / exposed	1 / 73 (1.37%)	1 / 71 (1.41%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (0.00%)	0 / 73 (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			
Chills			
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (0.00%)	0 / 73 (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
Fatigue			
subjects affected / exposed	0 / 73 (0.00%)	2 / 71 (2.82%)	0 / 73 (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
Fever			
subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deteriorating condition			
subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	0 / 73 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 73 (5.48%)	1 / 71 (1.41%)	3 / 73 (4.11%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Acute exacerbation of COPD			
subjects affected / exposed	0 / 73 (0.00%)	0 / 71 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 71 (0.00%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 2
Psychiatric disorders			
Confusion			
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	0 / 73 (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
Neutrophil count decreased			
subjects affected / exposed	0 / 73 (0.00%)	0 / 71 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Splenic rupture			
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (0.00%)	0 / 73 (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
Cardiac disorders			
Left ventricular systolic dysfunction			
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (0.00%)	0 / 73 (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
Atrial fibrillation			

subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	0 / 73 (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			
Ischaemia cerebrovascular			
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Peripheral motor neuropathy			
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (0.00%)	0 / 73 (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
Seizure			
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (0.00%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Headache			
subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	0 / 73 (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
Intracranial hemorrhage			
subjects affected / exposed	0 / 73 (0.00%)	0 / 71 (0.00%)	1 / 73 (1.37%)
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			
Anemia			
subjects affected / exposed	0 / 73 (0.00%)	5 / 71 (7.04%)	5 / 73 (6.85%)
occurrences causally related to treatment / all	0 / 0	5 / 5	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	0 / 73 (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
Neutropenic sepsis			

subjects affected / exposed	0 / 73 (0.00%)	0 / 71 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Double vision			
subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	0 / 73 (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
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 73 (1.37%)	1 / 71 (1.41%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	3 / 73 (4.11%)	0 / 71 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 73 (0.00%)	0 / 71 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Diarrhoea			
subjects affected / exposed	0 / 73 (0.00%)	0 / 71 (0.00%)	2 / 73 (2.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucositis oral			
subjects affected / exposed	0 / 73 (0.00%)	0 / 71 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 73 (0.00%)	0 / 71 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Back pain			
subjects affected / exposed	1 / 73 (1.37%)	1 / 71 (1.41%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (0.00%)	0 / 73 (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
Generalized muscle weakness			
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (0.00%)	0 / 73 (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
Flank pain			
subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	0 / 73 (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
Muscle weakness lower limb			
subjects affected / exposed	0 / 73 (0.00%)	0 / 71 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle weakness right-sided			
subjects affected / exposed	0 / 73 (0.00%)	0 / 71 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lung infection			
subjects affected / exposed	4 / 73 (5.48%)	1 / 71 (1.41%)	5 / 73 (6.85%)
occurrences causally related to treatment / all	0 / 4	0 / 1	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Urinary tract infection			
subjects affected / exposed	1 / 73 (1.37%)	0 / 71 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Upper respiratory infection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	0 / 73 (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
Conjunctivitis infective			
subjects affected / exposed	0 / 73 (0.00%)	0 / 71 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	2 / 73 (2.74%)	0 / 71 (0.00%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Anorexia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 71 (1.41%)	0 / 73 (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
Dehydration			
subjects affected / exposed	0 / 73 (0.00%)	0 / 71 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	Placebo	Olaparib BD	Olaparib TDS
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 73 (98.63%)	70 / 71 (98.59%)	72 / 73 (98.63%)
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 73 (10.96%)	5 / 71 (7.04%)	4 / 73 (5.48%)
occurrences (all)	59	9	31
Hypotension			
subjects affected / exposed	1 / 73 (1.37%)	1 / 71 (1.41%)	4 / 73 (5.48%)
occurrences (all)	1	3	4
Thromboembolic event			
subjects affected / exposed	3 / 73 (4.11%)	3 / 71 (4.23%)	6 / 73 (8.22%)
occurrences (all)	16	14	10
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	55 / 73 (75.34%)	64 / 71 (90.14%)	58 / 73 (79.45%)
occurrences (all)	307	254	198
Non-cardiac chest pain			
subjects affected / exposed	9 / 73 (12.33%)	10 / 71 (14.08%)	3 / 73 (4.11%)
occurrences (all)	34	19	4
Pain			
subjects affected / exposed	6 / 73 (8.22%)	3 / 71 (4.23%)	5 / 73 (6.85%)
occurrences (all)	7	4	6
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	26 / 73 (35.62%)	22 / 71 (30.99%)	25 / 73 (34.25%)
occurrences (all)	103	81	67
Dyspnoea			
subjects affected / exposed	21 / 73 (28.77%)	26 / 71 (36.62%)	28 / 73 (38.36%)
occurrences (all)	87	102	70
Pneumonia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 71 (0.00%)	4 / 73 (5.48%)
occurrences (all)	0	0	5
Productive cough			
subjects affected / exposed	1 / 73 (1.37%)	4 / 71 (5.63%)	4 / 73 (5.48%)
occurrences (all)	2	5	6

Wheezing			
subjects affected / exposed	5 / 73 (6.85%)	2 / 71 (2.82%)	2 / 73 (2.74%)
occurrences (all)	17	4	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	8 / 73 (10.96%)	2 / 71 (2.82%)	4 / 73 (5.48%)
occurrences (all)	15	8	7
Confusion			
subjects affected / exposed	3 / 73 (4.11%)	1 / 71 (1.41%)	5 / 73 (6.85%)
occurrences (all)	5	1	5
Depression			
subjects affected / exposed	7 / 73 (9.59%)	7 / 71 (9.86%)	6 / 73 (8.22%)
occurrences (all)	29	19	15
Insomnia			
subjects affected / exposed	10 / 73 (13.70%)	8 / 71 (11.27%)	5 / 73 (6.85%)
occurrences (all)	18	20	9
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	0 / 73 (0.00%)	8 / 71 (11.27%)	9 / 73 (12.33%)
occurrences (all)	0	20	19
Neutrophil count decreased			
subjects affected / exposed	0 / 73 (0.00%)	5 / 71 (7.04%)	2 / 73 (2.74%)
occurrences (all)	0	10	4
Platelet count decreased			
subjects affected / exposed	2 / 73 (2.74%)	4 / 71 (5.63%)	5 / 73 (6.85%)
occurrences (all)	2	7	7
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	4 / 73 (5.48%)	0 / 71 (0.00%)	1 / 73 (1.37%)
occurrences (all)	12	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	14 / 73 (19.18%)	16 / 71 (22.54%)	15 / 73 (20.55%)
occurrences (all)	46	37	21
Dysgeusia			
subjects affected / exposed	12 / 73 (16.44%)	12 / 71 (16.90%)	12 / 73 (16.44%)
occurrences (all)	34	34	29

Headache			
subjects affected / exposed	18 / 73 (24.66%)	19 / 71 (26.76%)	17 / 73 (23.29%)
occurrences (all)	40	35	45
Paresthesia			
subjects affected / exposed	5 / 73 (6.85%)	2 / 71 (2.82%)	7 / 73 (9.59%)
occurrences (all)	18	6	26
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 73 (2.74%)	4 / 71 (5.63%)	4 / 73 (5.48%)
occurrences (all)	10	12	9
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	15 / 73 (20.55%)	37 / 71 (52.11%)	41 / 73 (56.16%)
occurrences (all)	49	242	221
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 73 (8.22%)	6 / 71 (8.45%)	8 / 73 (10.96%)
occurrences (all)	13	7	29
Bloating			
subjects affected / exposed	2 / 73 (2.74%)	4 / 71 (5.63%)	1 / 73 (1.37%)
occurrences (all)	5	7	1
Constipation			
subjects affected / exposed	19 / 73 (26.03%)	16 / 71 (22.54%)	14 / 73 (19.18%)
occurrences (all)	92	28	31
Diarrhoea			
subjects affected / exposed	18 / 73 (24.66%)	13 / 71 (18.31%)	12 / 73 (16.44%)
occurrences (all)	59	24	21
Dry mouth			
subjects affected / exposed	3 / 73 (4.11%)	1 / 71 (1.41%)	7 / 73 (9.59%)
occurrences (all)	9	1	25
Dyspepsia			
subjects affected / exposed	13 / 73 (17.81%)	11 / 71 (15.49%)	6 / 73 (8.22%)
occurrences (all)	49	20	20
Dysphagia			
subjects affected / exposed	5 / 73 (6.85%)	5 / 71 (7.04%)	3 / 73 (4.11%)
occurrences (all)	5	10	5
Mucositis oral			

subjects affected / exposed	10 / 73 (13.70%)	7 / 71 (9.86%)	2 / 73 (2.74%)
occurrences (all)	27	20	7
Nausea			
subjects affected / exposed	44 / 73 (60.27%)	47 / 71 (66.20%)	51 / 73 (69.86%)
occurrences (all)	119	134	133
Stomach pain			
subjects affected / exposed	2 / 73 (2.74%)	3 / 71 (4.23%)	5 / 73 (6.85%)
occurrences (all)	2	4	9
Vomiting			
subjects affected / exposed	21 / 73 (28.77%)	25 / 71 (35.21%)	33 / 73 (45.21%)
occurrences (all)	41	40	56
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	11 / 73 (15.07%)	13 / 71 (18.31%)	16 / 73 (21.92%)
occurrences (all)	60	33	46
Dry skin			
subjects affected / exposed	5 / 73 (6.85%)	6 / 71 (8.45%)	4 / 73 (5.48%)
occurrences (all)	37	22	9
Erythema			
subjects affected / exposed	4 / 73 (5.48%)	0 / 71 (0.00%)	2 / 73 (2.74%)
occurrences (all)	6	0	2
Pruritus			
subjects affected / exposed	7 / 73 (9.59%)	4 / 71 (5.63%)	4 / 73 (5.48%)
occurrences (all)	22	10	9
Rash maculo-papular			
subjects affected / exposed	8 / 73 (10.96%)	5 / 71 (7.04%)	5 / 73 (6.85%)
occurrences (all)	23	22	8
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 73 (23.29%)	6 / 71 (8.45%)	9 / 73 (12.33%)
occurrences (all)	68	8	63
Back pain			
subjects affected / exposed	18 / 73 (24.66%)	13 / 71 (18.31%)	14 / 73 (19.18%)
occurrences (all)	45	34	31
Bone pain			

subjects affected / exposed	7 / 73 (9.59%)	2 / 71 (2.82%)	0 / 73 (0.00%)
occurrences (all)	21	7	0
Cramp			
subjects affected / exposed	4 / 73 (5.48%)	2 / 71 (2.82%)	3 / 73 (4.11%)
occurrences (all)	5	12	15
Joint effusion			
subjects affected / exposed	2 / 73 (2.74%)	5 / 71 (7.04%)	4 / 73 (5.48%)
occurrences (all)	3	7	8
Myalgia			
subjects affected / exposed	4 / 73 (5.48%)	2 / 71 (2.82%)	3 / 73 (4.11%)
occurrences (all)	25	7	4
Pain in extremity			
subjects affected / exposed	2 / 73 (2.74%)	13 / 71 (18.31%)	5 / 73 (6.85%)
occurrences (all)	5	25	10
Infections and infestations			
Lung infection			
subjects affected / exposed	12 / 73 (16.44%)	14 / 71 (19.72%)	12 / 73 (16.44%)
occurrences (all)	28	37	21
Mucosal infection			
subjects affected / exposed	6 / 73 (8.22%)	7 / 71 (9.86%)	4 / 73 (5.48%)
occurrences (all)	8	14	5
Upper respiratory infection			
subjects affected / exposed	5 / 73 (6.85%)	7 / 71 (9.86%)	7 / 73 (9.59%)
occurrences (all)	8	17	15
Urinary tract infection			
subjects affected / exposed	3 / 73 (4.11%)	3 / 71 (4.23%)	6 / 73 (8.22%)
occurrences (all)	4	5	8
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	30 / 73 (41.10%)	34 / 71 (47.89%)	28 / 73 (38.36%)
occurrences (all)	71	88	62
Decreased protein			
subjects affected / exposed	0 / 73 (0.00%)	4 / 71 (5.63%)	1 / 73 (1.37%)
occurrences (all)	0	13	1
Hyperglycaemia			

subjects affected / exposed	4 / 73 (5.48%)	2 / 71 (2.82%)	6 / 73 (8.22%)
occurrences (all)	11	3	9
Hypoalbuminaemia			
subjects affected / exposed	4 / 73 (5.48%)	4 / 71 (5.63%)	7 / 73 (9.59%)
occurrences (all)	4	5	13
Hypocalcaemia			
subjects affected / exposed	2 / 73 (2.74%)	9 / 71 (12.68%)	3 / 73 (4.11%)
occurrences (all)	4	13	4
Hypokalaemia			
subjects affected / exposed	4 / 73 (5.48%)	4 / 71 (5.63%)	4 / 73 (5.48%)
occurrences (all)	14	6	6
Hypomagnesaemia			
subjects affected / exposed	5 / 73 (6.85%)	2 / 71 (2.82%)	1 / 73 (1.37%)
occurrences (all)	13	3	1
Hyponatraemia			
subjects affected / exposed	12 / 73 (16.44%)	7 / 71 (9.86%)	10 / 73 (13.70%)
occurrences (all)	21	23	17

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 May 2013	(1) The study design was amended to be a placebo controlled 3 arm study (2) Change of trial IMP from capsules to tablets (3) Increase in recruitment target (4) Change to the primary outcome measure
06 February 2014	(1) Change to eligibility criteria (2) Clarification of types of tumour sample
11 August 2014	(1) Change to definition of end of study (2) Clarification of indemnity arrangements (3) Clarification of treatment schedule assessments (4) Clarification of data reporting requirements (5) Change to SAE reporting period
18 February 2015	(1) Addition of AML as an SAE reporting requirement
21 June 2019	(1) Change to definition of end of study (2) Clarification to translational study details

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported