



Clinical trial results:

CiPHER - Phase II multicentre study assessing the efficacy of Cabazitaxel in Patients with HER2-negative metastatic breast cancer and having unresectable brain metastases.

Summary

EudraCT number	2012-000542-35
Trial protocol	GB
Global end of trial date	25 July 2018

Results information

Result version number	v1 (current)
This version publication date	04 August 2019
First version publication date	04 August 2019

Trial information

Trial identification

Sponsor protocol code	RDD490
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	The Clatterbridge Cancer Centre NHS Foundation Trust
Sponsor organisation address	Clatterbridge Road, Bebington, Wirral, United Kingdom, CH63 4JY
Public contact	Charlotte Rawcliffe, CRUK Liverpool Cancer Trials Unit, +44 01517948167, clr001@liverpool.ac.uk
Scientific contact	Charlotte Rawcliffe, CRUK Liverpool Cancer Trials Unit, +44 01517948167, clr001@liverpool.ac.uk

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	28 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 July 2018
Global end of trial reached?	Yes
Global end of trial date	25 July 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary aim of this study is to assess the efficacy of Cabazitaxel in patients with HER2-negative metastatic breast cancer and brain metastases. This study is designed to assess the feasibility of Cabazitaxel use in breast cancer with brain metastases.

Primary outcome: Overall survival from randomisation.

Protection of trial subjects:

Consent was obtained prior to each patient participating in the trial, after a full explanation had been given of the treatment options, including the conventional and generally accepted methods of treatment. All risks and potential benefits were explained to the patients, and all patients were provided with Patient Information Sheets prior to consent. Patients were given the right to refuse their consent to participate in the trial, and to withdraw at any time.

Haematology/biochemistry tests and physical examinations will be performed regularly throughout each patient's participation and follow-up. Patients were checked and asked about any adverse events they may have experienced regularly while on treatment, and during follow-up. Treatment was delayed or withdrawn for any patient unfit to receive Cabazitaxel. Patients were also given emergency contact details for the research team.

Patients were exposed to ionising radiation via CT/MRI scans (MRI/CT scans of the brain were performed 6 weekly following randomisation until cycle 6, then 8 weekly until end of treatment. CT scans of the chest, abdomen and pelvis were performed 12 weeks after randomisation, and then 6 weekly until cycle 6, then 12 weekly until end of treatment. Scans were only performed in follow-up if they were carried out as standard care. This imaging schedule was chosen to ensure that significant disease progression was detected, and also to prevent unnecessary imaging.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	15
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

CiPHER was opened to recruitment on 10/10/2014 and the first patient was recruited on 06/01/2015. A total of 19 were randomised (13 to receive Cabazitaxel, 6 to receive standard care. The trial was closed to recruitment on recommendation of the TSC in November 2017. The last patient was randomised on 27/10/2017. The end of study date is 25/07/2018.

Pre-assignment

Screening details:

19 of the 97 patients screened for the CiPHER trial were recruited. Patients with HER2-negative breast cancer and brain metastases provided consent and were screened to determine eligibility. Patients who met all the eligibility criteria were randomised to either Cabazitaxel or standard care (physician's choice/radiotherapy).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cabazitaxel

Arm description:

Patients received 25mg/m² Cabazitaxel on Day 1 of each treatment cycle (every 21 days) as a 1 hour IV infusion until disease progression, unacceptable toxicity or withdrawal of consent.

Arm type	Experimental
Investigational medicinal product name	Cabazitaxel
Investigational medicinal product code	L01CD
Other name	Jevtana
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

25mg/m² Cabazitaxel was administered as a 1 hour IV infusion on day 1 of each cycle, every 21 days until disease progression (according to RECIST V1.1), unacceptable toxicity or withdrawal of consent (patient request).

Arm title	Standard care
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Arm description:

This is the control arm. Patients on this arm received either physician's choice of chemotherapy until disease progression or radiotherapy (patients who had previously received whole brain radiotherapy were given physician's choice, patients who had not previously received whole brain radiotherapy were given radiotherapy).

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Cabazitaxel	Standard care
Started	13	6
Completed	13	6

Baseline characteristics

Reporting groups

Reporting group title	Cabazitaxel
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Reporting group description:

Patients received 25mg² Cabazitaxel on Day 1 of each treatment cycle (every 21 days) as a 1 hour IV infuson until disease progression, unacceptable toxicity or withdrawal of consent.

Reporting group title	Standard care
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Reporting group description:

This is the control arm. Patients on this arm received either physician's choice of chemotherapy until disease progression or radiotherapy (patients who had previously received whole brain radiotherapy were given physician's choice, patients who had not previously received whole brain radiotherapy were given radiotherapy).

Reporting group values	Cabazitaxel	Standard care	Total
Number of subjects	13	6	19
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)	10	5	15
From 65-84 years	3	1	4
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	13	6	19
Male	0	0	0
ECOG Performance Status			
Units: Subjects			
ECOG 0	5	2	7
ECOG 1	8	4	12
ECOG 2	0	0	0
ECOG 3	0	0	0
ECOG 4	0	0	0
Presence of visceral disease			
Units: Subjects			
Yes	10	4	14
No	3	2	5
Presentation with brain metastases de novo			
Units: Subjects			
Yes	4	3	7
No	9	3	12
ACE 27 Comorbidity score			

Units: Subjects			
None	6	4	10
Mild	3	0	3
Moderate	2	0	2
Severe	2	1	3
Unknown	0	1	1
Previous Primary Treatment, neoadjuvant/adjuvant chemotherapy: anthracyclines			
Units: Subjects			
Yes	9	2	11
No	4	4	8
Previous Primary Treatment, neoadjuvant/adjuvant chemotherapy: anthracyclines + Taxane			
Units: Subjects			
Yes	8	5	13
No	5	1	6
Previous Primary Treatment, neoadjuvant/adjuvant chemotherapy: Adjuvant Endocrine			
Units: Subjects			
Yes	7	3	10
No	6	3	9
Previous Primary Treatment, neoadjuvant/adjuvant chemotherapy: other			
Units: Subjects			
Yes	9	2	11
No	4	4	8
Previous Treatment for Brain Metastases - Chemotherapy agent			
Units: Subjects			
Yes	0	0	0
No	13	6	19
Previous Treatment for Brain Metastases: Endocrine			
Units: Subjects			
Yes	3	1	4
No	10	5	15
Previous Treatment for Brain Metastases: Previous Cranial Radiotherapy			
Units: Subjects			
Yes	7	3	10
No	6	3	9
Previous Treatment for Brain Metastases: Previous Cranial Neurosurgery			
Units: Subjects			
Yes	4	4	8
No	9	2	11
Baseline FACT-Br - physical			
Units: Score			
arithmetic mean	20	23.2	

standard deviation	± 5.29	± 2.59	-
Baseline FACT-Br - Social/Family Units: Score			
arithmetic mean	22.8	23.8	
standard deviation	± 3.48	± 3.19	-
Baseline FACT-Br - Emotional Units: Score			
arithmetic mean	15.9	14.2	
standard deviation	± 4.09	± 8.84	-
Baseline FACT-Br - Functional Units: Score			
arithmetic mean	14.5	13.8	
standard deviation	± 5.68	± 4.38	-
Baseline FACT-Br - Additional concerns Units: Score			
arithmetic mean	44.2	48.2	
standard deviation	± 9.24	± 6.34	-
Baseline Fact-Br - Trial Outcome index Units: Score			
arithmetic mean	78.7	85.2	
standard deviation	± 16.61	± 10.47	-
Total FACT-Br Units: Score			
arithmetic mean	117	123	
standard deviation	± 20.64	± 17.09	-
Time from diagnosis to cranial metastases Units: days			
arithmetic mean	1961	2037	
standard deviation	± 1338	± 1974	-
Time from diagnosis to other metastases Units: days			
arithmetic mean	1443	1775	
standard deviation	± 1051	± 1893	-
Physical findings - Height Units: cm			
arithmetic mean	165	164	
standard deviation	± 7.98	± 5.59	-
Physical Findings - Weight Units: kg			
arithmetic mean	73.3	7.06	
standard deviation	± 18.26	± 8.80	-
Physical Findings - Blood pressure: Systolic Blood Pressure Units: mm/Hg			
arithmetic mean	127	122	
standard deviation	± 19.10	± 19.51	-
Physical Findings - Blood pressure: Diastolic Blood Pressure Units: mmHg			
arithmetic mean	76.7	78.2	
standard deviation	± 12.70	± 10.83	-

Physical Findings - Temperature Units: degrees celcius arithmetic mean standard deviation	36.5 ± 0.44	36.7 ± 0.78	-
Biochemistry results - Serum Creatinine Units: µmol/L arithmetic mean standard deviation	64.2 ± 17.36	64.3 ± 13.98	-
Biochemistry results - Creatinine clearance Units: ml/min arithmetic mean standard deviation	139 ± 198.8	322 ± 351.7	-
Biochemistry results - Sodium Units: mmol/L arithmetic mean standard deviation	139 ± 2.11	138 ± 3.45	-
Biochemistry results - Potassium Units: mmol/L arithmetic mean standard deviation	4.2 ± 0.32	4.1 ± 0.41	-
Biochemistry results - Calcium Units: mmol/L arithmetic mean standard deviation	2.4 ± 0.14	2.4 ± 0.15	-
Biochemistry results - Urea Units: mmol/L arithmetic mean standard deviation	6.7 ± 2.33	6.2 ± 1.24	-
Biochemistry results - Bilirubin Units: µmol/L arithmetic mean standard deviation	5.3 ± 2.75	8.0 ± 3.41	-
Biochemistry results - Albumin Units: g/L arithmetic mean standard deviation	39.2 ± 6.19	41.7 ± 5.89	-
Biochemistry results - GGT Units: IU/L arithmetic mean standard deviation	229 ± 673.3	45.5 ± 38.32	-
Biochemistry results - ALP Units: IU/L arithmetic mean standard deviation	112 ± 142.6	66.8 ± 19.35	-
Biochemistry results - ALT Units: IU/L arithmetic mean standard deviation	38.1 ± 74.02	26.3 ± 15.54	-
Biochemistry results - AST Units: IU/L arithmetic mean	17.0	15.0	

standard deviation	± 6.60	± 1.41	-
Haematology results - Haemoglobin Units: g/L			
arithmetic mean	127	94.6	
standard deviation	± 9.70	± 65.71	-
Haematology results - WBC Units: 10 ⁹ /L			
arithmetic mean	9.7	10.9	
standard deviation	± 5.54	± 4.58	-
Haematology results - Absolute neutrophil count Units: 10 ⁹ /L			
arithmetic mean	7.4	8.9	
standard deviation	± 5.24	± 3.99	-
Haematology - Lymphocytes Units: 10 ⁹ /L			
arithmetic mean	1.6	1.2	
standard deviation	± 0.57	± 0.65	-
Haematology results - Platelets Units: 10 ⁹ /L			
arithmetic mean	315	246	
standard deviation	± 111.7	± 56.00	-

End points

End points reporting groups

Reporting group title	Cabazitaxel
Reporting group description: Patients received 25mg ² Cabazitaxel on Day 1 of each treatment cycle (every 21 days) as a 1 hour IV infusion until disease progression, unacceptable toxicity or withdrawal of consent.	
Reporting group title	Standard care
Reporting group description: This is the control arm. Patients on this arm received either physician's choice of chemotherapy until disease progression or radiotherapy (patients who had previously received whole brain radiotherapy were given physician's choice, patients who had not previously received whole brain radiotherapy were given radiotherapy).	
Subject analysis set title	Full Analysis set
Subject analysis set type	Full analysis
Subject analysis set description: In order to follow the Intention to Treat (ITT) principle this consists of all randomised patients excepting for a) patients withdrawing consent between randomisation and starting therapy b) patients withdrawn from the study after randomisation because of irregularities with the consent process and c) patients whose information determining ineligibility existed before randomisation but was not read until after randomisation.	
Subject analysis set title	Per Protocol (PP) set
Subject analysis set type	Per protocol
Subject analysis set description: This consists of those patients in the Full Analysis set without any major protocol deviations.	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description: All patients who received any trial treatment	

Primary: Overall survival

End point title	Overall survival
End point description: Overall survival from randomisation, defined for each participant as the time from randomisation to the earlier of death or censoring.	
Outcome variable: overall length of survival from randomisation Efficacy parameter: Hazard ratio (relative to Arm 1)	
Supported by Median overall survival time and 12 month survival Method: Stratified Cox proportional hazards (PH) model	
Median survival - Standard care arm - upper limit = N/A (9999 entered to satisfy system validations)	
End point type	Primary
End point timeframe: Measured (as months) from randomisation, defined for each participant as the time from randomisation to the earlier of death or censoring.	

End point values	Cabazitaxel	Standard care	Full Analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	13	6	19	
Units: months				
number (confidence interval 90%)				
Median Survival in Months	4.80 (2.07 to 20.36)	8.16 (1.74 to 9999)	8.16 (2.07 to 20.36)	

Attachments (see zip file)	Figure 3.PNG
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Statistical analyses

Statistical analysis title	Overall Survival Analysis (Hazard Ratio)
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.582
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.45
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.48
upper limit	4.45

Primary: Overall survival (countable endpoint data)

End point title	Overall survival (countable endpoint data) ^[1]
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End point description:

End point type	Primary
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End point timeframe:

From randomisation to the earlier of death or censoring.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis provided separately under 'overall survival'

End point values	Cabazitaxel	Standard care	Full Analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	13	6	19	
Units: Percent				
Number of deaths	69	50	63	
12 month survival rate	48	44	48	

Statistical analyses

No statistical analyses for this end point

Primary: Results for Sensitivity Analyses for Overall Survival

End point title	Results for Sensitivity Analyses for Overall Survival
End point description:	
Where value is N/A '00' has been entered.	
End point type	Primary
End point timeframe:	
From randomisation	

End point values	Cabazitaxel	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: subjects				
number (confidence interval 90%)	00 (00 to 00)	00 (00 to 00)		

Statistical analyses

Statistical analysis title	Treatment by centre interaction
Comparison groups	Standard care v Cabazitaxel
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Hazard ratio (HR)
Point estimate	3.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.52
upper limit	29.03

Statistical analysis title	Pre-protocol analysis
Comparison groups	Cabazitaxel v Standard care

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.39
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.38
upper limit	5.14

Statistical analysis title	Covariate (Visceral disease)
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.28
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.41
upper limit	3.98

Secondary: Time to CNS Progression

End point title	Time to CNS Progression
End point description:	
Time to CNS progression (TTP) - defined as time from randomisation to earlier of disease progression or death from CNS disease or censoring.	
Where value is N/A '00' or '9999' has been entered.	
End point type	Secondary
End point timeframe:	
Measured (as months) from randomisation to CNS progression or death from CNS disease	

End point values	Cabazitaxel	Standard care	Full Analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	13	6	19	
Units: months				
number (confidence interval 90%)				
Median Survival in Months	2.76 (1.38 to 4.80)	6.46 (00 to 9999)	3.55 (1.74 to 8.16)	

Attachments (see zip file)	Figure 4.PNG
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Statistical analyses

Statistical analysis title	Time to CNS Progression
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.145
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	2.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	7.47

Secondary: Best overall response (extracranial visceral metastases)

End point title	Best overall response (extracranial visceral metastases)
End point description:	
Overall response for overall extracranial visceral metastases. Response is defined as occurrence of PR or CR at any point to death or end of study. Efficacy parameter = difference in proportion with objective response.	
End point type	Secondary
End point timeframe:	
From randomisation to death or end of study	

End point values	Cabazitaxel	Standard care	Full Analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	13	6	19	
Units: Number of patients				
Progressive disease/death	0	0	0	
Stable disease	3	1	4	
Partial Response	3	1	4	
Complete Response	0	0	0	
Missing	7	4	11	
Response to treatment	3	1	4	

Statistical analyses

Statistical analysis title	Best overall visceral response
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.751
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.123
upper limit	18.358

Statistical analysis title	Best overall visceral response by centre
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.76
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	30.8

Statistical analysis title	Best overall visceral response by centre*treatment
Comparison groups	Cabazitaxel v Standard care

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.757
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	24.99

Secondary: Best overall response (cranial metastases)

End point title	Best overall response (cranial metastases)
End point description:	
Overall response for overall cranial metastases. Response is defined as occurrence of PR or CR at any point to death or end of study. Efficacy parameter = difference in proportion with objective response.	
End point type	Secondary
End point timeframe:	
From randomisation to death or end of study	

End point values	Cabazitaxel	Standard care	Full Analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	13	6	19	
Units: Number of patients				
Progressive disease/death	1	0	1	
Stable disease	7	1	8	
Partial response	2	1	3	
Complete response	0	1	1	
Missing	3	3	6	
Response to treatment	2	2	4	

Statistical analyses

Statistical analysis title	Best overall cranial response
Comparison groups	Cabazitaxel v Standard care

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.382
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.038
upper limit	3.518

Statistical analysis title	Best overall response (Cranial) by Centre
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.309
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	6.03

Statistical analysis title	Best overall cranial response by Centre*Treatment
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.29
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	6.67

Secondary: Quality of Life - Physical Wellbeing

End point title	Quality of Life - Physical Wellbeing
End point description: Where value is N/A '00' has been entered.	
End point type	Secondary
End point timeframe: From baseline to end of study	

End point values	Cabazitaxel	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: score				
arithmetic mean (standard deviation)				
Baseline/Cycle 1	20 (± 5.29)	23.2 (± 2.59)		
Cycle 2	20 (± 5.69)	25.0 (± 1.41)		
Cycle 3	20.5 (± 6.41)	25.5 (± 0.71)		
Cycle 4	21.6 (± 2.61)	25.5 (± 0.71)		
Cycle 5	20.8 (± 2.99)	25.5 (± 0.71)		
Cycle 6	18.3 (± 8.14)	25.0 (± 1.41)		
Cycle 7	13.5 (± 7.78)	00 (± 00)		
Cycle 8	15.0 (± 00)	00 (± 00)		
Cycle 9	24.0 (± 00)	00 (± 00)		
Cycle 10	19.0 (± 00)	00 (± 00)		
Cycle 11	19.0 (± 00)	00 (± 00)		
Cycle 12	19.0 (± 00)	00 (± 00)		
Cycle 13	21.0 (± 00)	00 (± 00)		
Cycle 14	21.0 (± 00)	00 (± 00)		
Cycle 15	22.0 (± 00)	00 (± 00)		
Cycle 16	19.0 (± 00)	00 (± 00)		
Cycle 17	15.0 (± 00)	00 (± 00)		
Cycle 18	19.0 (± 00)	00 (± 00)		
Cycle 19	21.0 (± 00)	00 (± 00)		
Cycle 20	20.0 (± 00)	00 (± 00)		
Cycle 21	23.0 (± 00)	00 (± 00)		
Cycle 22	21.0 (± 00)	00 (± 00)		
Follow-up 1	26.0 (± 1.41)	24.0 (± 1.73)		
Follow-up 2	25.5 (± 3.54)	18.0 (± 00)		
Follow-up 3	24.0 (± 5.66)	22.0 (± 00)		
Follow-up 4	24.5 (± 4.95)	24.0 (± 00)		
Follow-up 5	25.5 (± 3.54)	24.0 (± 00)		
Follow-up 6	21.0 (± 00)	22.0 (± 00)		
Follow-up 7	22.0 (± 00)	00 (± 00)		
Follow-up 8	11.0 (± 00)	00 (± 00)		

Statistical analyses

Statistical analysis title	Cycle 2 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.55
Method	ANCOVA

Statistical analysis title	Cycle 3 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.632
Method	ANCOVA

Statistical analysis title	cycle 4 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.727
Method	ANCOVA

Statistical analysis title	Cycle 5 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.597
Method	ANCOVA

Statistical analysis title	Cycle 6 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.098
Method	ANCOVA

Statistical analysis title	Follow-up 1 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.873
Method	ANCOVA

Statistical analysis title	Follow-up 2 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.565
Method	ANCOVA

Statistical analysis title	Follow-up 3 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.958
Method	ANCOVA

Statistical analysis title	Follow-up 4 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.714
Method	ANCOVA

Statistical analysis title	Follow-up 5 P-value
Comparison groups	Cabazitaxel v Standard care

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.714
Method	ANCOVA

Secondary: Time to CNS Progression (countable endpoint data)

End point title	Time to CNS Progression (countable endpoint data)
End point description:	
End point type	Secondary
End point timeframe:	
From randomisation to CNS progression or death from CNS disease	

End point values	Cabazitaxel	Standard care	Full Analysis set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	13	6	19	
Units: percent				
Number of deaths	92	67	84	
12-month survival rate	21	33	24	

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life - Functional Well-Being

End point title	Quality of Life - Functional Well-Being
End point description:	
Where value is N/A '00' has been entered.	
End point type	Secondary
End point timeframe:	
From baseline to end of study	

End point values	Cabazitaxel	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: score				
arithmetic mean (standard deviation)				
Baseline/Cycle 1	14.5 (± 5.68)	13.8 (± 4.38)		
Cycle 2	15.5 (± 5.13)	18.0 (± 2.83)		

Cycle 3	17.9 (± 5.64)	16.5 (± 2.12)		
Cycle 4	15.8 (± 5.78)	17.0 (± 4.24)		
Cycle 5	14.7 (± 2.68)	19.5 (± 3.54)		
Cycle 6	14.3 (± 0.58)	22.0 (± 2.83)		
Cycle 7	11.5 (± 0.71)	00 (± 00)		
Cycle 8	14.0 (± 00)	00 (± 00)		
Cycle 9	17.0 (± 00)	00 (± 00)		
Cycle 10	13.0 (± 00)	00 (± 00)		
Cycle 11	14.0 (± 00)	00 (± 00)		
Cycle 12	18.0 (± 00)	00 (± 00)		
Cycle 13	17.0 (± 00)	00 (± 00)		
Cycle 14	17.0 (± 00)	00 (± 00)		
Cycle 15	17.0 (± 00)	00 (± 00)		
Cycle 16	15.0 (± 00)	00 (± 00)		
Cycle 17	15.0 (± 00)	00 (± 00)		
Cycle 18	15.0 (± 00)	00 (± 00)		
Cycle 19	18.0 (± 00)	00 (± 00)		
Cycle 20	17.5 (± 00)	00 (± 00)		
Cycle 21	16.0 (± 00)	00 (± 00)		
Cycle 22	20.0 (± 00)	00 (± 00)		
Follow-up 1	23.5 (± 6.36)	20.2 (± 15.9)		
Follow-up 2	24.0 (± 5.66)	10.0 (± 00)		
Follow-up 3	22.5 (± 6.36)	17.0 (± 00)		
Follow-up 4	23.0 (± 4.24)	17.0 (± 00)		
Follow-up 5	24.0 (± 5.66)	16.0 (± 00)		
Follow-up 6	18.0 (± 00)	14.0 (± 00)		
Follow-up 7	14.0 (± 00)	00 (± 00)		
Follow-up 8	7.0 (± 00)	00 (± 00)		

Statistical analyses

Statistical analysis title	Cycle 2 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.418
Method	ANCOVA

Statistical analysis title	Cycle 3 P-value
Comparison groups	Cabazitaxel v Standard care

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.948
Method	ANCOVA

Statistical analysis title	Cycle 4 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.234
Method	ANCOVA

Statistical analysis title	Cycle 5 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.106
Method	ANCOVA

Statistical analysis title	Cycle 6 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.257
Method	ANCOVA

Statistical analysis title	Follow-up 1 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.888
Method	ANCOVA

Statistical analysis title	Follow-up 2 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.129
Method	ANCOVA

Statistical analysis title	Follow-up 3 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.807
Method	ANCOVA

Statistical analysis title	Follow-up 4 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.936
Method	ANCOVA

Statistical analysis title	Follow-up 5 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.568
Method	ANCOVA

Secondary: Quality of Life - Additional Concerns

End point title	Quality of Life - Additional Concerns
End point description:	Where value is N/A '00' has been entered.
End point type	Secondary
End point timeframe:	From randomisation until end of study

End point values	Cabazitaxel	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: score				
arithmetic mean (standard deviation)				
Baseline/Cycle 1	44.2 (± 9.24)	48.2 (± 6.34)		
Cycle 2	50.2 (± 6.74)	58.4 (± 6.48)		
Cycle 3	53.5 (± 9.50)	64.7 (± 1.89)		
Cycle 4	48.5 (± 5.89)	64.8 (± 3.93)		
Cycle 5	45.7 (± 3.09)	64.1 (± 2.63)		
Cycle 6	54.3 (± 2.38)	64.7 (± 1.02)		
Cycle 7	49.0 (± 2.83)	00 (± 00)		
Cycle 8	53.0 (± 00)	00 (± 00)		
Cycle 9	51.0 (± 00)	00 (± 00)		
Cycle 10	53.0 (± 00)	00 (± 00)		
Cycle 11	49.0 (± 00)	00 (± 00)		
Cycle 12	55.0 (± 00)	00 (± 00)		
Cycle 13	54.0 (± 00)	00 (± 00)		
Cycle 14	50.0 (± 00)	00 (± 00)		
Cycle 15	52.0 (± 00)	00 (± 00)		
Cycle 16	49.0 (± 00)	00 (± 00)		
Cycle 17	56.0 (± 00)	00 (± 00)		
Cycle 18	51.0 (± 00)	00 (± 00)		
Cycle 19	55.9 (± 00)	00 (± 00)		
Cycle 20	48.0 (± 00)	00 (± 00)		
Cycle 21	50.0 (± 00)	00 (± 00)		
Cycle 22	52.0 (± 00)	00 (± 00)		
Follow-up 1	53.0 (± 7.07)	51.1 (± 12.20)		
Follow-up 2	63.0 (± 7.07)	38.0 (± 00)		
Follow-up 3	60.5 (± 3.54)	51.0 (± 00)		
Follow-up 4	51.5 (± 4.95)	51.0 (± 00)		
Follow-up 5	62.5 (± 4.95)	55.0 (± 00)		
Follow-up 6	52.0 (± 00)	41.0 (± 00)		
Follow-up 7	51.0 (± 00)	00 (± 00)		
Follow-up 8	35.6 (± 00)	00 (± 00)		

Statistical analyses

Statistical analysis title	Cycle 2 P-value
Comparison groups	Cabazitaxel v Standard care

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.925
Method	ANCOVA

Statistical analysis title	Cycle 3 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.836
Method	ANCOVA

Statistical analysis title	Cycle 4 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.677
Method	ANCOVA

Statistical analysis title	Cycle 5 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.245
Method	ANCOVA

Statistical analysis title	Cycle 6 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.895
Method	ANCOVA

Statistical analysis title	Follow-up 1 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.061
Method	ANCOVA

Statistical analysis title	Follow-up 2 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.253
Method	ANCOVA

Statistical analysis title	Follow-up 3 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.373
Method	ANCOVA

Statistical analysis title	Follow-up 4 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.015
Method	ANCOVA

Statistical analysis title	Follow-up 5 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.316
Method	ANCOVA

Secondary: Quality of Life - Overall TOI Score

End point title	Quality of Life - Overall TOI Score
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End point description:

Where value is N/A '00' has been entered

End point type	Secondary
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End point timeframe:

From randomisation until end of study

End point values	Cabazitaxel	Standard care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	6		
Units: score				
arithmetic mean (standard deviation)				
Baseline/Cycle 1	78.7 (± 16.61)	85.2 (± 10.47)		
Cycle 2	85.7 (± 13.66)	101.4 (± 10.72)		
Cycle 3	91.9 (± 18.03)	106.7 (± 4.71)		
Cycle 4	85.8 (± 10.90)	107.3 (± 0.39)		
Cycle 5	81.2 (± 3.82)	109.1 (± 6.87)		
Cycle 6	86.9 (± 8.67)	111.7 (± 2.44)		
Cycle 7	74.0 (± 9.90)	00 (± 00)		
Cycle 8	82.0 (± 00)	00 (± 00)		
Cycle 9	92.0 (± 00)	00 (± 00)		
Cycle 10	85.0 (± 00)	00 (± 00)		
Cycle 11	82.0 (± 00)	00 (± 00)		
Cycle 12	92.0 (± 00)	00 (± 00)		
Cycle 13	92.0 (± 00)	00 (± 00)		
Cycle 14	88.0 (± 00)	00 (± 00)		
Cycle 15	91.0 (± 00)	00 (± 00)		
Cycle 16	83.0 (± 00)	00 (± 00)		
Cycle 17	86.0 (± 00)	00 (± 00)		
Cycle 18	85.0 (± 00)	00 (± 00)		
Cycle 19	94.9 (± 00)	00 (± 00)		
Cycle 20	85.5 (± 00)	00 (± 00)		
Cycle 21	89.0 (± 00)	00 (± 00)		
Cycle 22	93.0 (± 00)	00 (± 00)		
Follow-up 1	102.5 (± 0.71)	95.3 (± 14.97)		
Follow-up 2	112.5 (± 16.3)	66.0 (± 00)		
Follow-up 3	107.0 (± 15.6)	90.0 (± 00)		
Follow-up 4	99.0 (± 4.24)	92.0 (± 00)		
Follow-up 5	112.0 (± 14.1)	95.0 (± 00)		
Follow-up 6	91.0 (± 00)	77.0 (± 00)		
Follow-up 7	87.0 (± 00)	00 (± 00)		
Follow-up 8	53.6 (± 00)	00 (± 00)		

Attachments (see zip file)	Figure A1.PNG Figure A2.PNG Figure A3.PNG Figure A4.PNG
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Statistical analyses

Statistical analysis title	Cycle 2 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.546
Method	ANCOVA

Statistical analysis title	Cycle 3 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.725
Method	ANCOVA

Statistical analysis title	Cycle 4 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.415
Method	ANCOVA

Statistical analysis title	Cycle 5 P-value
Comparison groups	Cabazitaxel v Standard care

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.158
Method	ANCOVA

Statistical analysis title	Cycle 6 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.252
Method	ANCOVA

Statistical analysis title	Follow-up 1 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.283
Method	ANCOVA

Statistical analysis title	Follow-up 2 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.159
Method	ANCOVA

Statistical analysis title	Follow-up 3 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.732
Method	ANCOVA

Statistical analysis title	Follow-up 4 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.167
Method	ANCOVA

Statistical analysis title	Follow-up 5 P-value
Comparison groups	Cabazitaxel v Standard care
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.688
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start date of trial treatment until 28 days following the last dose of trial treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.03
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Reporting groups

Reporting group title	Cabazitaxel
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Reporting group description:

Patients received 25mg² Cabazitaxel on Day 1 of each treatment cycle (every 21 days) as a 1 hour IV infusion until disease progression, unacceptable toxicity or withdrawal of consent.

Reporting group title	Standard care
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Reporting group description:

This is the control arm. Patients on this arm received either physician's choice of chemotherapy until disease progression or radiotherapy (patients who had previously received whole brain radiotherapy were given physician's choice, patients who had not previously received whole brain radiotherapy were given radiotherapy).

Serious adverse events	Cabazitaxel	Standard care	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 13 (61.54%)	4 / 6 (66.67%)	
number of deaths (all causes)	9	3	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Worsening of condition (study disease)			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			

subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphasia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Probable meningeal disease			
subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Bone marrow hypcellular			
subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Raised intracranial pressure			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			

subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective myositis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cabazitaxel	Standard care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 13 (69.23%)	4 / 6 (66.67%)	
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed occurrences (all)	5 / 13 (38.46%) 5	0 / 6 (0.00%) 0	
Gait disturbance subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 6 (0.00%) 0	
Pain subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 6 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 6 (16.67%) 1	
Dyspnoea subjects affected / exposed occurrences (all)	3 / 13 (23.08%) 3	0 / 6 (0.00%) 0	
Cough subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 6 (0.00%) 0	
Sore throat subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 6 (0.00%) 0	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 6 (0.00%) 0	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 4	2 / 6 (33.33%) 4	
Lymphocyte count decreased subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 6 (16.67%) 9	
Neutrophil count decreased subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 6 (16.67%) 8	
Platelet count decreased			

subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	4	
White blood cell count decreased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	13	
Alkaline phosphatase increased			
subjects affected / exposed	3 / 13 (23.08%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Blood bilirubin increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Haemoglobin increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Lethargy			
subjects affected / exposed	1 / 13 (7.69%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Dizziness			
subjects affected / exposed	0 / 13 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	2 / 13 (15.38%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Dysgeusia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Seizure			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 13 (23.08%)	1 / 6 (16.67%)	
occurrences (all)	10	6	
Eye disorders			

Photophobia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 6 (16.67%) 1	
Gastrointestinal disorders			
Mucositis oral subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 6 (16.67%) 1	
Nausea subjects affected / exposed occurrences (all)	3 / 13 (23.08%) 5	3 / 6 (50.00%) 3	
Abdominal distension subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 6 (16.67%) 1	
Oral dysaesthesia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 6 (16.67%) 1	
Abdominal pain subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2	0 / 6 (0.00%) 0	
Constipation subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2	0 / 6 (0.00%) 0	
Diarrhoea subjects affected / exposed occurrences (all)	4 / 13 (30.77%) 4	0 / 6 (0.00%) 0	
Dyspepsia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 6 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 6 (0.00%) 0	
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 6 (16.67%) 1	
Rash papular			

subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 6 (0.00%) 0	
Renal and urinary disorders Cystitis noninfective subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 6 (0.00%) 0	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Muscle weakness left-sided subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0 1 / 13 (7.69%) 1	1 / 6 (16.67%) 1 0 / 6 (0.00%) 0	
Infections and infestations Soft tissue infection subjects affected / exposed occurrences (all) Otitis externa subjects affected / exposed occurrences (all) Mucosal infection subjects affected / exposed occurrences (all) Otitis media subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Infections and infestations other, specify - left big toe subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1	1 / 6 (16.67%) 1 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0	
Metabolism and nutrition disorders Hypercalcaemia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 6 (16.67%) 2	

Hypoalbuminaemia			
subjects affected / exposed	3 / 13 (23.08%)	2 / 6 (33.33%)	
occurrences (all)	6	3	
Hyperkalaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	2 / 13 (15.38%)	1 / 6 (16.67%)	
occurrences (all)	2	3	
Hypocalcaemia			
subjects affected / exposed	2 / 13 (15.38%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Hyponatraemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Anorexia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 6 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 October 2013	Protocol Version 2 - Standard care arm added in addition to treatment arm Study duration extended to incorporate increase in sample size as a result of the additional treatment arm Primary outcome changed as patients may continue to receive treatment beyond cycle 6 CTCAE v4.03 to be used instead of v4.0 Acute toxicity measured until end of treatment instead of 18 weeks Time to radiotherapy removed Time to neurological deterioration removed as this will be captured in the QoL FACT-Br form QoL FACT-Br form added Treatments allocated 2:1 Cabazitaxel:standard treatment Blood sample at end of treatment removed as deemed unnecessary
29 April 2014	Protocol Version 3 - Cabazitaxel will not be distributed directly from Sanofi to NHS sites - details added regarding this. Cabazitaxel crosses the blood brain barrier and should be particularly effective against CNS disease. Progression-free survival (PFS) includes all causes of death and combines them with progressive CNS disease. Time to progression (TTP) only combines CNS disease progression and death due to CNS disease and should therefore be an outcome more sensitive to the advantage of Cabazitaxel. References to SmPC replaced with IB
21 November 2014	Protocol Version 4 - Inclusion criteria updated to make clear that "previously treated brain metastases with or without surgery +/- radiotherapy does not exclude the patient from this trial". References to sample collection made consistent throughout. Baseline CT and MRI scans and screening assessments to be performed within 28 days prior to randomisation. Anti-emetics table updated
09 September 2015	Protocol Version 5 - Bone scan - amended to clarify that bone scan should be performed at baseline and only repeated if clinically indicated. Extra cranial imaging scan updated from 8 weekly to 12 weekly to bring in line with standard practices at sites. Full blood count - previously stated that full blood count should be done within 24 hours of day 1 of each cycle, updated to 'taken according to local practice'
14 March 2016	Protocol Version 6 - ACE-21 form added to baseline procedures Schedule of assessments added for radiotherapy Drug ordering - initial order changed from 18 to 6 vials Inclusion criteria - hormone therapy removed as it is covered in exclusion criteria as 'anti-cancer treatment' Exclusion criteria - GFR updated to state that creatinine clearance can be calculated using CKD-EPI Information added on which events do not need to be reported as SAEs

17 October 2016	Protocol Version 7 - Inclusion criteria updated so that patients with resectable brain metastases are eligible for the trial. Inclusion criteria updated so that measurable target lesion needs to be 5mm or above (previously 10mm). Exclusion criteria updated so that patients would still be eligible for the trial if they have had up to 2 lines of chemotherapy for extracranial disease since diagnosis of brain metastases. Exclusion criteria updated to allow patients to be on steroids to control CNS symptoms, PI discretion to be used to assess eligibility. Exclusion criteria relating to liver function tests updated in line with the summary of product characteristics. Information regarding dose reduction for patients with hepatic impairment updated. Secondary objective updated to specify which objectives are to be evaluated for RECIST-evaluable patients only (due to change in target lesion size for eligibility). Sentence added to statistical methods section to state that sample size calculation is based on 12 sites.
07 March 2017	Protocol Version 8 - Reference Safety Information section added to the protocol to explain which RSI is used for the trial and where it is taken from. List of expected adverse events for patients receiving brain radiotherapy added. Contact details of trial coordinator updated.
18 October 2017	Protocol Version 9 - Information added to dose modifications for clarity regarding patients with hepatic impairment. All references to 'pegfilgrastim' changed to 'neulasta' for consistency (these are the same drug). Pharmacovigilance section updated to reflect that SAE reporting was done with paper SAE forms (rather than an online LCTU pharmacovigilance system).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the low recruitment rate, the study did not have the statistical power to identify significant differences between the treatment arms. However, treatment was well tolerated in the investigational arm with acceptable toxicity profile.

Notes: