Clinical trial results:
Phase II, randomised, placebo controlled, multicentre, feasibility study of low dose (metronomic) cyclophosphamide with or without nintedanib (BIBF 1120) in advanced ovarian cancer (METRO-BIBF)

Summary

EudraCT number	2011-005814-12
Trial protocol	GB
Global end of trial date	11 January 2018

Results information

Result version number	v1 (current)
This version publication date	23 January 2019
First version publication date	23 January 2019

Trial information

Trial identification

Sponsor protocol code	UCL10/0470

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01610869
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Gower Street, London, United Kingdom, WC1E 6BT
Public contact	Trial Co-ordinator, CR UK and UCL Cancer Trials Centre, +44 02076799237, ctc.metrobibf@ucl.ac.uk
Scientific contact	Trial Co-ordinator, CR UK and UCL Cancer Trials Centre, +44 02076799237, ctc.metrobibf@ucl.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	07 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 January 2018
Global end of trial reached?	Yes
Global end of trial date	11 January 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The trial objectives are to explore the efficacy and safety of an all oral combination of nintedanib (an inhibitor of angiogenic signalling) and metronomic cyclophosphamide in patients with multiply-relapsed advanced ovarian cancer, who have completed a minimum of two lines of previous chemotherapy and who for any reason are not suitable for further 'standard' intravenous chemotherapy treatments.

Protection of trial subjects:

The first 12 patients randomised were reviewed for toxicity every three weeks for the first 12 weeks, the data was reviewed by the Independent Data Monitoring Committee (IDMC) and the dosage was considered acceptable and patients were assessed 6 weekly thereafter. The IDMC further reviewed toxicity data and serious adverse events (SAEs) in July 2015, and this resulted in a decision to reduce the starting dose of nintedanib/matching placebo to 150mg b.d.. Patients randomised at this starting dose were reviewed at 3 and 6 weeks and thereafter every 6 weeks. Patients received oral nintedanib and cyclophosphamide or cyclophosphamide and matched placebo continuously until disease progression, death or unacceptable toxicity.

Patient safety was monitored using regular patient assessments, dose modification guidance, regular review of safety data by the IDMC and Trial Management Group (TMG) and through strict eligibility criteria.

Patient data was stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 1998 and the Data Protection Officer at UCL.

Background therapy:

Patients were given a supply of a suitable antiemetic as per local guidelines, to take as required for any nausea experienced with cyclophosphamide. Some patients required steroids as per local guidelines, for symptom control and this was permitted as was any other medication such as analgesia or laxatives for palliation of symptoms. All concomitant medication was recorded.

Evidence for comparator:

Cyclophosphamide has been used in the treatment of malignancies including breast and ovarian cancer for decades. All patients in the trial received cyclophosphamide +/- nintedanib.

In ovarian cancer, angiogenesis has been shown to have a central role in both disease progression and prognosis. A direct relationship has been demonstrated between the expression of biomarkers for angiogenesis such as VEGF, the degree of neovascularization and the behaviour of epithelial ovarian cancers. These data suggest that pharmacological inhibitors of angiogenesis may have the capacity to arrest tumour progression. Several phase II trials of different antiangiogenic drugs have demonstrated activity against relapsed ovarian cancer.

Nintedanib is a potent, orally available triple kinase inhibitor targeting VEGFRs, PDGFRs, and FGFRs. The specific and simultaneous abrogation of these pathways results in effective growth inhibition of both endothelial and, via PDGF- and FGF-receptors of perivascular cells, which may be more effective than inhibition of endothelial cell growth via the VEGF pathway alone. Furthermore, signalling by FGF-receptors has been identified as a possible escape mechanism for tumour angiogenesis when the VEGF pathway is disrupted. In addition preclinical models show that nintedanib may have a direct anti-tumour effect on those malignant cells which overexpress PDGFR and/or FGFR.

Previous studies have shown that nintedanib is generally well tolerated with mild to moderate adverse effects such as gastrointestinal symptoms (nausea, diarrhoea, vomiting, abdominal pain) and reversible elevations of liver enzymes. A randomised phase II maintenance trial in ovarian cancer in which the efficacy and safety of nine months of continuous twice daily doses of nintedanib following chemotherapy

was investigated, has identified the potential activity of nintedanib with a 36-week progression free survival (PFS) of 14.3 % compared to 5.0 % in the control group.

Actual start date of recruitment	26 August 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: 117
Worldwide total number of subjects	117
EEA total number of subjects	117

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)	62
From 65 to 84 years	55
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

117 patients were randomised from NHS hospitals across the UK between 26/08/2014 and 26/10/2016. 3 patients did not start the investigational drug and are excluded from this EudraCT submission.

The planned recruitment end date was 01/10/2017 (with 124 patients), but recruitment was suspended early following IDMC review due to lack of efficacy.

Pre-assignment

Screening details:

- Medical History (must have had >2 lines chemotherapy for ovarian cancer)
- Clinical examination - blood pressure, ECG, ECOG
- CT/MRI scan
- Liver function tests: AST and/or ALT, alkaline phosphatase, bilirubin and albumin
- Haematology, coagulation parameters and biochemistry
- Tumour marker (CA125)
- Urinalysis for proteinuria

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Use of a matched placebo.
The IWRS/IVRS system was used for randomised allocation, trial medication assignment, initial drug supply of nintedanib/placebo and resupply, discontinuation from study treatment, emergency code breaks (i.e. unblinding) and trial drug shipment confirmation. The IWRS/IVRS technology was managed and maintained by Almac Clinical Technologies. The system was accessible via the internet 24 hours a day, 7 days a week.

Arms

Are arms mutually exclusive?	Yes
Arm title	Control Arm

Arm description:

Placebo and cyclophosphamide

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

Dosage and administration details:

50mg tablets b.d. - daily dose of 100mg. Continuous daily dosing until withdrawal criteria are fulfilled e.g. progression of disease, death, or unacceptable toxicity. New bottles of medication will be dispensed on day 1 of the first two 21-day cycles and then every 42-day cycle.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

At randomisation the dose administered will be 150-200 mg twice daily of placebo (depending on the date the patient was randomised). Placebo will be provided in 150 mg and 100 mg capsules so,

depending on date of randomisation, patients will either take two 100 mg capsules in the morning and another two capsules approximately 12 hours later OR one x 150mg capsule in the morning and another one approximately 12 hours later. Continuous daily dosing until withdrawal criteria are fulfilled e.g. progression of disease, death, or unacceptable toxicity. New bottles of medication will be dispensed on day 1 of the first two 21-day cycles and then every 42-day cycle.

Arm title	Investigation arm
Arm description:	
Nintedanib and cyclophosphamide	
Arm type	Experimental
Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use
Dosage and administration details:	
50mg tablets b.d. - daily dose of 100mg. Continuous daily dosing until withdrawal criteria are fulfilled e.g. progression of disease, death, or unacceptable toxicity. New bottles of medication will be dispensed on day 1 of the first two 21-day cycles and then every 42-day cycle.	
Investigational medicinal product name	Nintedanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use
Dosage and administration details:	
At randomisation the dose administered will be 150-200 mg twice daily of nintedanib (depending on the date the patient was randomised). Nintedanib will be provided in 150 mg and 100 mg capsules so, depending on date of randomisation, patients will either take two 100 mg capsules in the morning and another two capsules approximately 12 hours later OR one x 150mg capsule in the morning and another one approximately 12 hours later. Continuous daily dosing until withdrawal criteria are fulfilled e.g. progression of disease, death, or unacceptable toxicity. New bottles of medication will be dispensed on day 1 of the first two 21-day cycles and then every 42-day cycle.	

Number of subjects in period 1[1]	Control Arm	Investigation arm
Started	55	59
Completed	55	59

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: As 3 patients did not start the study treatment, they have been excluded from the analysis.

Baseline characteristics

Reporting groups	
Reporting group title	Control Arm
Reporting group description:	
Placebo and cyclophosphamide	
Reporting group title	Investigation arm
Reporting group description:	
Nintedanib and cyclophosphamide	

Reporting group values	Control Arm	Investigation arm	Total
Number of subjects	55	59	114
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	65.7	62.4	
inter-quartile range (Q1-Q3)	56.4 to 69.8	54.7 to 70.2	-
Gender categorical			
Units: Subjects			
Female	55	59	114
Male	0	0	0

Subject analysis sets	
Subject analysis set title	Safety analysis
Subject analysis set type	Safety analysis
Subject analysis set description:	
These are the 114 patients who started the study drug	

Reporting group values	Safety analysis		
Number of subjects	114		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	63.9		
inter-quartile range (Q1-Q3)	55.4 to 69.9		
Gender categorical Units: Subjects			
Female	114		
Male	0		

End points

End points reporting groups	
Reporting group title	Control Arm
Reporting group description: Placebo and cyclophosphamide	
Reporting group title	Investigation arm
Reporting group description: Nintedanib and cyclophosphamide	
Subject analysis set title	Safety analysis
Subject analysis set type	Safety analysis
Subject analysis set description: These are the 114 patients who started the study drug	

Primary: Overall survival	
End point title	Overall survival
End point description:	
End point type	Primary
End point timeframe: Over the follow-up period	

End point values	Control Arm	Investigation arm	Safety analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	55	59	114	
Units: number of patients	55	59	114	

Statistical analyses

Statistical analysis title	Overall survival analysis
Comparison groups	Investigation arm v Control Arm v Safety analysis
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.57

Secondary: Progression free survival

End point title	Progression free survival
End point description:	
End point type	Secondary
End point timeframe:	
over the follow-up period	

End point values	Control Arm	Investigation arm	Safety analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	55	59	114	
Units: number of patients	55	59	114	

Statistical analyses

Statistical analysis title	Progression-free survival analysis
Comparison groups	Control Arm v Investigation arm v Safety analysis
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.32

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events:	
From informed consent to 30 days post last trial treatment administration.	
Adverse event reporting additional description:	
Clinical assessment and self-reported patient diary.	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.0

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Full reporting of adverse events will be done via the publication in a scientific journal

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2013	Filter Q2e amended in REC Application Form Change of PI at Mount Vernon Hospital
11 December 2013	Change of PI at St James's University Hospital and Royal United Hospital
07 April 2014	Updated protocol v2.0, updated IB for nintedanib, updated SmPC for cyclophosphamide, pregnancy monitoring PIS and CF: - Update to trial management group members - Updates to summary of trial design - Details of circulating tumour cell sub-study added (sponsored by East and North Herts NHS Trust). MRI sub-study removed - Information on incidence of ovarian cancer updated - PT removed as a coagulation parameter - Total (rather than indirect) and Direct Bilirubin required if bilirubin elevated - Total protein and calcium tests removed from screening assessments - Albumin added as a screening assessment - Clarification regarding treatment breaks added - Clarification that patient must be 18 years or older to be eligible - Clarification LMWH and warfarin treatment allowed (i.e. not an exclusion criteria), reference to in dwelling venous catheter removed. - Clarification regarding INR ranges in the presence/absence of therapeutic anticoagulants- - PT removed as a coagulation parameter. - Amended- patients on therapeutic anticoagulants with APTT greater than 2.5xULN not eligible (previously 1.5xULN). - Added extra information - poorly controlled diabetes mellitus or patient on sulphonylurea-type hypoglycaemics (e.g. glicazide) as main diabetic control (as contraindicated with cyclophosphamide) - Clarified VEGF within 4 weeks of study treatment (rather than study start) - Stratification factor – number of previous lines of chemotherapy corrected to ≤3 or >3 - Placebo added as IMP - Clarification that patients can have a maximum of three treatment breaks of less than 21 days, if more they need to contact the UCL CTC to discuss continued treatment - Clarification that re-screening must be performed for patients who have discontinued previous study treatment due to DLT or other adverse events for 21 to 30 days
07 November 2014	Change of PI at St James's University
14 July 2015	Urgent Safety Measure: trial recruitment halted following IDMC review requiring revision to protocol start dose for nintedanib

10 September 2015	Updated protocol v3 following urgent safety measure: - Update to trial management group members - Trial schema updated in line with new nintedanib start dose (150mg b.d.) and new week 3 safety visit - Introduction updated with information from IB version 14 (19Jan2015); the outcome of the July 2015 IDMC review; results from trials that have reported since last protocol update. - Clarification that there are no data available for patients with an inherited pre-disposition to bleeding or for patients receiving a full dose of anticoagulant treatment prior to starting treatment with nintedanib, therefore careful monitoring and caution is advised in this group of patients - Secondary end point added to confirm response according to RECIST 1.1 and GCIG will be assessed where data available (as mentioned in inclusion criteria) - Baseline MRI scan included as pre-randomisation evaluation if patient known to have stable brain metastases - Urinalysis for proteinuria included in screening investigation table - Clarification re-screening procedure in section 8.2 also needs to be followed if patient does not start treatment within 14 days of randomisation - Updated in line with new nintedanib start dose (150mg b.d.) and new week 3 safety visit for all patients randomised after July 2015 - Clarification on eligibility criteria and randomisation procedure - Further guidance added regarding dose modifications - Nintedanib with dietary soya products are known to cause allergic reactions including severe anaphylaxis in persons with soya allergy. Patients with known allergy to peanut protein carry an enhanced risk for severe reactions to soya preparations - Clarification to the emergency unblinding procedure - 3 weekly assessment table removed as safety cohort closed and trial patients no longer on 3 weekly visits - (6 weekly assessments) updated to include week 3 safety visit, check for germline BRCA mutation status (where information available) at baseline
27 October 2015	Updated investigator's brochure from Boehringer Ingelheim Ltd.
23 September 2016	Updated investigator's brochure from Boehringer Ingelheim Ltd.
08 November 2016	Recruitment suspension following IDMC recommendation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

14 July 2015	Following an IDMC review in July 2015 of adverse event data in this Phase II trial, a significant imbalance in the incidence of high grade (grade 3 and above) adverse events between the two arms of the study was noted, leading to the conclusion that there is a high probability that the combination of nintedanib and metronomic cyclophosphamide at the prescribed doses is not well tolerated in this population of patients. These events are spread over a number of different organ systems and are on the whole expected events for nintedanib and/or a consequence of having advanced and multiply relapsed ovarian cancer. Although these events occur at various time-points, a significant proportion occur within the first 6 weeks of treatment. Therefore, an Urgent Safety Measure (USM) was implemented on 14/07/2015 closing the trial to recruitment temporarily. The protocol amendment that was in the process of being drafted prior to the USM was updated to include safety measures to improve the tolerability of the regimen for patients already on the trial and for those to be recruited in future: the start dose of nintedanib was reduced to 150mg BD for new patients with mandatory 3 week visits for the first 6 weeks scheduled to enable general toxicity/symptom control review including repeat blood tests. However, it was noted that some patients did tolerate the higher 200mg dose nintedanib/placebo without any such adverse events and it was agreed patients who were still receiving 200mg BD nintedanib/placebo at the time of this review may continue on this dose at the discretion of the treating investigators. The trial reopened to recruitment in November 2015, after the protocol amendment (v3.0) was approved by by the competent authorities on 15/09/2015 (REC) and 19/10/2015 (MHRA). The first site was reopened to recruitment on 12/11/2015; all remaining sites were reactivated to recruitment by August 2016.	12 November 2015
26 October 2016	The IDMC reviewed the safety and efficacy of the trial in October 2016 following the previously reported Urgent Safety Measure which prompted a temporary recruitment suspension and protocol amendment to reduce the starting dose of nintedanib (200 mg BD to 150mg BD) and add a week 3 visit for all new patients randomised to the trial. The IDMC concluded that the safety profile was acceptable following the dose reduction in the nintedanib group, however the lack of superior efficacy in the combined regime resulted in an early suspension of recruitment on 26/10/2016. The total number of patients recruited to the trial is 117, slightly short of the 124 target. The TSC, IDMC and TMG agreed that patients who were still taking trial drug could continue trial treatment if the patient and clinician felt that this was appropriate. They considered there was no change in the overall safety assessment of the oral combination of nintedanib and cyclophosphamide.	-

Notes:

Limitations and caveats

None reported