Clinical trial results:
A randomized, double-blind, placebo controlled, multicenter Phase II study to assess the efficacy and safety of Sorafenib added to standard treatment with Topotecan in patients with platinum-resistant recurrent ovarian cancer

Summary

EudraCT number	2009-011922-33
Trial protocol	DE
Global end of trial date	10 February 2015

Results information

Result version number	v1 (current)
This version publication date	09 September 2022
First version publication date	09 September 2022

Trial information

Trial identification

Sponsor protocol code	TRIAS2009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01047891
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité – Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Dr Radoslav Chekerov, Department of Gynecology, Augustenburger Platz 1, 13353 Berlin, +49 030450 664399, radoslav.chekerov@charite.de
Scientific contact	Dr Radoslav Chekerov, Department of Gynecology, Augustenburger Platz 1, 13353 Berlin, +49 030450 664399, radoslav.chekerov@charite.de

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	27 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 February 2015
Global end of trial reached?	Yes
Global end of trial date	10 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determination of the progression-free survival (PFS) of patients treated with topotecan + sorafenib versus topotecan + placebo

Protection of trial subjects:

The study was conducted in accordance with the 1996 Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice (GCP) recommendations, and provisions of the German Medicines Act and the GCP Ordinance of August 2000.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 January 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 172
Worldwide total number of subjects	172
EEA total number of subjects	172

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)	86
From 65 to 84 years	86
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 18 January 2010, and 19 September 2013, 185 patients were enrolled from 20 sites in Germany; Two patients in the sorafenib group had serious adverse events before treatment and were excluded from analyses

Pre-assignment

Screening details:

assessed for eligibility: 185
excluded: 11
randomised: 174

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sorafenib+topotecan Group

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

400mg on days 6-15 every 21 days for six cycles followed by daily maintance sorafenib for up to 1 year in patients without progression

Investigational medicinal product name	Topotecan
Investigational medicinal product code	
Other name	Hycamtin
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.25 mg/m² on days 1-5

Arm title	Placebo+topotecan Group

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Topotecan
Investigational medicinal product code	
Other name	Hycamtin
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.25 mg/m² on days 1-5

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

Dosage and administration details:

400mg placebo twice daily on days 6-15, repeated every 21 days for up to six cycles.

Number of subjects in period 1	Sorafenib+topotecan Group	Placebo+topotecan Group
Started	83	89
Completed	47	47
Not completed	36	42
Adverse event, serious fatal	4	-
Consent withdrawn by subject	11	6
N/A	6	3
Adverse event, non-fatal	6	6
Lost to follow-up	1	-
disease progression	8	27

Period 2

Period 2 title	Maintenance phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Sorafenib+topotecan group

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

400mg on days 6-15 every 21 days for six cycles followed by daily maintance sorafenib for up to 1 year in patients without progression

Arm title	Placebo+topotecan Group

Arm description: -

Arm type	Placebo

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

Dosage and administration details:

400mg placebo twice daily on days 6-15, repeated every 21 days for up to six cycles.

Number of subjects in period 2	Sorafenib+topotecan group	Placebo+topotecan Group
Started	47	47
Completed	1	0
Not completed	46	47
Adverse event, serious fatal	-	1
Consent withdrawn by subject	6	-
N/A	2	2
Adverse event, non-fatal	1	2
Lost to follow-up	1	-
disease progression	24	29
Protocol deviation	12	13

Baseline characteristics

Reporting groups	
Reporting group title	Sorafenib+topotecan Group
Reporting group description: -	
Reporting group title	Placebo+topotecan Group
Reporting group description: -	

Reporting group values	Sorafenib+topotecan Group	Placebo+topotecan Group	Total
Number of subjects	83	89	172
Age categorical Units: Subjects			
Age continuous Units: years			
median	59	58	
full range (min-max)	31 to 78	25 to 79	-
Gender categorical Units: Subjects			
No gender specifications	83	89	172
FIGO stage			
FIGO=International Federation of Gynecology and Obstetrics			
Units: Subjects			
Stage I	0	4	4
Stage II	7	3	10
Stage III	49	54	103
Stage IV	18	20	38
Unknown	9	8	17
Histology Units: Subjects			
Serous	69	67	136
Other	14	22	36
Grade Units: Subjects			
Grade 1	3	2	5
Grade 2	22	25	47
Grade 3	49	58	107
Unknown	9	4	13
Ascites Units: Subjects			
Yes	30	33	63
No	48	54	102
unknown	5	2	7
ECOG performance			
ECOG=Eastern Cooperative Oncology Group			
Units: Subjects			
Status 0	45	47	92
Status 1	33	38	71

Status 2	3	1	4
Unknown	2	3	5
Residual disease after primary debulking Units: Subjects			
No surgery	11	12	23
Microscopic	25	26	51
<1 cm	16	17	33
≥1 cm	13	15	28
Missing/unknown	18	19	37

End points

End points reporting groups

Reporting group title	Sorafenib+topotecan Group
Reporting group description: -	
Reporting group title	Placebo+topotecan Group
Reporting group description: -	
Reporting group title	Sorafenib+topotecan group
Reporting group description: -	
Reporting group title	Placebo+topotecan Group
Reporting group description: -	

Primary: Progression-free survival

End point title	Progression-free survival

End point description:

The primary endpoint was investigator-assessed PFS, defined as the interval between first treatment cycle and disease progression or death from any cause.

End point type	Primary

End point timeframe:

36 months

End point values	Sorafenib+topotecan Group	Placebo+topotecan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	89		
Units: Months				
median (confidence interval 95%)	6.7 (5.8 to 7.6)	4.4 (3.7 to 5.0)		

Statistical analyses

Statistical analysis title	Change of the PFS
Comparison groups	Sorafenib+topotecan Group v Placebo+topotecan Group
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Secondary: objective response rate by RECIST

End point title	objective response rate by RECIST

End point description:

End point type	Secondary

End point timeframe:

60 months

End point values	Sorafenib+topotecan Group	Placebo+topotecan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	50		
Units: percent				
number (not applicable)	31	12		

Statistical analyses

No statistical analyses for this end point

Secondary: duration of response

End point title	duration of response

End point description:

End point type	Secondary

End point timeframe:

60 months

End point values	Sorafenib+topotecan Group	Placebo+topotecan Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	89		
Units: Month				
median (confidence interval 95%)	21.0 (17.3 to 24.7)	14.0 (8.2 to 19.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

60 months

Adverse event reporting additional description:

for more AE/SAE details see table 2 https://linkinghub.elsevier.com/retrieve/pii/S1470-2045(18)30372-3 "open manuscript"

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Topotecan/sorafenib

Reporting group description:

Grad 3/4/5 were put together as sAE

Reporting group title	Topotecan/placebo

Reporting group description: -

Serious adverse events	Topotecan/sorafenib	Topotecan/placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	80 / 83 (96.39%)	82 / 89 (92.13%)	
number of deaths (all causes)	2	5	
number of deaths resulting from adverse events	0		
Investigations			
Hypokalaemia			
subjects affected / exposed	4 / 83 (4.82%)	5 / 89 (5.62%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	4 / 83 (4.82%)	4 / 89 (4.49%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
ALT			
subjects affected / exposed	2 / 83 (2.41%)	4 / 89 (4.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leucopenia			

subjects affected / exposed	58 / 83 (69.88%)	47 / 89 (52.81%)	
occurrences causally related to treatment / all	0 / 58	0 / 47	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutropenia			
subjects affected / exposed	46 / 83 (55.42%)	48 / 89 (53.93%)	
occurrences causally related to treatment / all	0 / 46	0 / 48	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	23 / 83 (27.71%)	20 / 89 (22.47%)	
occurrences causally related to treatment / all	0 / 23	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anamia			
subjects affected / exposed	12 / 83 (14.46%)	17 / 89 (19.10%)	
occurrences causally related to treatment / all	0 / 12	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 83 (12.05%)	4 / 89 (4.49%)	
occurrences causally related to treatment / all	0 / 10	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	4 / 83 (4.82%)	8 / 89 (8.99%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death	Additional description: Not associated with CTCAE term		
subjects affected / exposed	1 / 83 (1.20%)	4 / 89 (4.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Non-malignant ascites			
subjects affected / exposed	4 / 83 (4.82%)	6 / 89 (6.74%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	4 / 83 (4.82%)	4 / 89 (4.49%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	5 / 83 (6.02%)	5 / 89 (5.62%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	7 / 83 (8.43%)	5 / 89 (5.62%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Hand-foot skin reaction			
subjects affected / exposed	11 / 83 (13.25%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 11	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other dermatological symptoms			
subjects affected / exposed	11 / 83 (13.25%)	0 / 89 (0.00%)	
occurrences causally related to treatment / all	0 / 11	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Febrile neutropenia			
subjects affected / exposed	6 / 83 (7.23%)	5 / 89 (5.62%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other infection			
subjects affected / exposed	6 / 83 (7.23%)	9 / 89 (10.11%)	
occurrences causally related to treatment / all	0 / 6	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Topotecan/sorafenib	Topotecan/placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 83 (65.06%)	62 / 89 (69.66%)	
Investigations			
ALT			
subjects affected / exposed	18 / 83 (21.69%)	15 / 89 (16.85%)	
occurrences (all)	18	15	
AST			
subjects affected / exposed	21 / 83 (25.30%)	15 / 89 (16.85%)	
occurrences (all)	21	15	
Creatine			
subjects affected / exposed	7 / 83 (8.43%)	10 / 89 (11.24%)	
occurrences (all)	7	10	
GGT			
subjects affected / exposed	3 / 83 (3.61%)	7 / 89 (7.87%)	
occurrences (all)	3	7	
Hypokalaemia			
subjects affected / exposed	5 / 83 (6.02%)	6 / 89 (6.74%)	
occurrences (all)	5	6	
Hyponatraemia			
subjects affected / exposed	7 / 83 (8.43%)	3 / 89 (3.37%)	
occurrences (all)	7	3	
Vascular disorders			
Haemorrhage/bleeding			
subjects affected / exposed	6 / 83 (7.23%)	5 / 89 (5.62%)	
occurrences (all)	6	5	
Nervous system disorders			
Neuropathy			
subjects affected / exposed	18 / 83 (21.69%)	23 / 89 (25.84%)	
occurrences (all)	18	23	
Blood and lymphatic system disorders			
Leucopenia			
subjects affected / exposed	15 / 83 (18.07%)	23 / 89 (25.84%)	
occurrences (all)	15	23	
Neutropenia			
subjects affected / exposed	6 / 83 (7.23%)	8 / 89 (8.99%)	
occurrences (all)	6	8	

Thrombocytopenia			
subjects affected / exposed	39 / 83 (46.99%)	27 / 89 (30.34%)	
occurrences (all)	39	27	
Anaemia			
subjects affected / exposed	54 / 83 (65.06%)	62 / 89 (69.66%)	
occurrences (all)	54	62	
Lymphopenia			
subjects affected / exposed	8 / 83 (9.64%)	2 / 89 (2.25%)	
occurrences (all)	8	2	
Oedema			
subjects affected / exposed	6 / 83 (7.23%)	14 / 89 (15.73%)	
occurrences (all)	6	14	
General disorders and administration site conditions			
Coagulation			
subjects affected / exposed	6 / 83 (7.23%)	5 / 89 (5.62%)	
occurrences (all)	6	5	
Fatigue			
subjects affected / exposed	33 / 83 (39.76%)	50 / 89 (56.18%)	
occurrences (all)	33	50	
Weight loss			
subjects affected / exposed	9 / 83 (10.84%)	2 / 89 (2.25%)	
occurrences (all)	9	2	
Diarrhoea			
subjects affected / exposed	29 / 83 (34.94%)	22 / 89 (24.72%)	
occurrences (all)	29	22	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	29 / 83 (34.94%)	25 / 89 (28.09%)	
occurrences (all)	29	25	
Nausea			
subjects affected / exposed	48 / 83 (57.83%)	41 / 89 (46.07%)	
occurrences (all)	48	41	
Vomiting			
subjects affected / exposed	31 / 83 (37.35%)	31 / 89 (34.83%)	
occurrences (all)	31	31	
Abdominal pain			

subjects affected / exposed	25 / 83 (30.12%)	26 / 89 (29.21%)	
occurrences (all)	25	26	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	15 / 83 (18.07%)	12 / 89 (13.48%)	
occurrences (all)	15	12	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	46 / 83 (55.42%)	47 / 89 (52.81%)	
occurrences (all)	46	47	
Hand-foot skin reaction			
subjects affected / exposed	25 / 83 (30.12%)	3 / 89 (3.37%)	
occurrences (all)	25	3	
Other dermatological symptoms			
subjects affected / exposed	39 / 83 (46.99%)	20 / 89 (22.47%)	
occurrences (all)	39	20	
Renal and urinary disorders			
Renal/genitourinary			
subjects affected / exposed	4 / 83 (4.82%)	10 / 89 (11.24%)	
occurrences (all)	4	10	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	4 / 83 (4.82%)	2 / 89 (2.25%)	
occurrences (all)	4	2	
Other infection			
subjects affected / exposed	15 / 83 (18.07%)	12 / 89 (13.48%)	
occurrences (all)	15	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 June 2010	expanded to two prior therapies for relapsed disease in Protocol
04 May 2011	eligibility of patients treated with bevacizumab or vascular endothelial growth factor receptor tyrosine kinase inhibitors and increasement of the recruitment period

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.

-maintenance treatment only 12 months
-completion of the QoL not mandatory

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30100379