Clinical trial results:
A phase II, open label, non-randomized study of second or third line treatment with the combination of sorafenib and everolimus in patients affected by relapsed and non-resectable high-grade osteosarcoma.

Summary

EudraCT number	2011-000561-12
Trial protocol	IT
Global end of trial date	19 June 2015

Results information

Result version number	v1 (current)
This version publication date	26 June 2022
First version publication date	26 June 2022
Summary attachment (see zip file)	2015 - Lancet Oncol - SERIO (2015 - Lancet Oncol - SERIO.pdf)

Trial information

Trial identification

Sponsor protocol code	S.E.R.I.O.

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01804374
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	ISG Italian Sarcoma Group
Sponsor organisation address	Via Farini 31, Bologna, Italy, 40124
Public contact	D.O. Oncologia Medica a Dir.Univ., Fondazione del Piemonte per l'Oncologia IRCC Candiolo, 0039 0119933278, clinicaltrials@italiansarcomagroup.org
Scientific contact	D.O. Oncologia Medica a Dir.Univ., Fondazione del Piemonte per l'Oncologia IRCC Candiolo, 0039 0119933278, giovanni.grignani@ircc.it

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	18 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 June 2014
Global end of trial reached?	Yes
Global end of trial date	19 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective of the study will be to assess the antitumor activity of sorafenib 400 mg twice a day in combination with everolimus 5mg/die as second or third line treatment of relapsed unresectable/metastatic high-grade osteosarcoma

Protection of trial subjects:

Any sign of tumor-related pain improvement was evaluated by Pain and Analgesic Score (PAS) and the Brief Pain Inventory short form score (BPI).
Patients were carefully monitored for adverse events during the whole trial.

Background therapy: -

Evidence for comparator:

This is an open-label, single arm trial.

Actual start date of recruitment	30 April 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 38
Worldwide total number of subjects	38
EEA total number of subjects	38

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)	38

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From June 16, 2011, to June 4, 2013, 38 patients were enrolled in Italy only.

Pre-assignment

Screening details:

Histologically-documented not amenable to surgery, locally advanced/metastatic high grade osteosarcoma progressing after standard treatments. Eligibility criteria: progressive and measurable disease according to RECIST 1.1 (bone lesions allowed), 18 years or older, ECOG PS <1, life expectancy ≥3 months, adequate organs and bone marrow function

Period 1

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

Arms

Arm title	Sorafenib+Everolimus
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 400mg BID	
Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 5mg QD	

Number of subjects in period 1	Sorafenib+Everolimus
Started	38
Completed	38

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	38	38	
Age categorical Units: Subjects			
Adults (18-64 years)	38	38	
Age continuous Units: years			
median	31		
full range (min-max)	18 to 64	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	23	23	
ECOG PS Units: Subjects			
ECOG 0	16	16	
ECOG 1	20	20	
ECOG 2	2	2	
metastatic at diagnosis Units: Subjects			
yes	9	9	
no	29	29	
osteosarcoma histotypes Units: Subjects			
osteoblastic	27	27	
chondroblastic	8	8	
fibroblastic	2	2	
teleangectatic	1	1	
lines of chemotherapy after MAP/I Units: Subjects			
=1	2	2	
>1	36	36	
sites of metastases Units: Subjects			
lung only	12	12	
lung + bone or viscera	22	22	
bone only	4	4	
previous surgery Units: number			
median	2		
full range (min-max)	0 to 7	-	

End points

End points reporting groups

Reporting group title	Sorafenib+Everolimus
Reporting group description: -	
Subject analysis set title	Overall trial
Subject analysis set type	Intention-to-treat
Subject analysis set description: Intention-to-treat	

Primary: Progression-free survival rate at 6-month

End point title	Progression-free survival rate at 6-month
End point description:	
End point type	Primary
End point timeframe: Progression Free Survival (PFS) refers to the time from registration into the study to the date of progressive disease or death. In the absence of progression time will be censored at the date of last tumor assessment or follow-up. The primary endpoint is	

End point values	Sorafenib+Everolimus	Overall trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	17	21		
Units: subjects	9	8		

Statistical analyses

Statistical analysis title	Final Statistical Analysis
Comparison groups	Sorafenib+Everolimus v Overall trial
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Rate
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	0.61

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

End point type	Secondary

End point timeframe:

PFS was calculated from trial entry until progression, unacceptable toxicity, or death—whichever came first.

End point values	Sorafenib+Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: months				
median (confidence interval 95%)	5 (2 to 7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Secondary

End point timeframe:

OS was calculated from trial entry until death. In the absence of an event or loss to follow-up, all survival endpoints were censored on the last date the patient was free from the event

End point values	Sorafenib+Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: months				
median (confidence interval 95%)	11 (8 to 15)			

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:

DOR was calculated from first non-progression assessment until either progression or death. In the absence of an event or loss to follow-up, all survival endpoints were censored on the last date the patient was free from the event

End point values	Sorafenib+Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: months				
median (confidence interval 95%)	5 (4 to 6)			

Statistical analyses

No statistical analyses for this end point

Secondary: overall response rate

End point title	overall response rate

End point description:

End point type	Secondary

End point timeframe:

From treatment start to trial end

End point values	Sorafenib+Everolimus			
Subject group type	Reporting group			
Number of subjects analysed	38			
Units: subjects				
CR	0			
PR	2			
MR	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From treatment start to end of safety follow up	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4

Reporting groups	
Reporting group title	All trial patients

Reporting group description: -

Serious adverse events	All trial patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 38 (2.63%)		
number of deaths (all causes)	36		
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Pneumothorax	Additional description: grade 3 sec CTCAE v 4.03		
subjects affected / exposed	1 / 38 (2.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All trial patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 38 (100.00%)		
Cardiac disorders			
Hypertension			
subjects affected / exposed	6 / 38 (15.79%)		
occurrences (all)	6		
Ejection fraction decrease			
subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Nervous system disorders			

Headache				
subjects affected / exposed	2 / 38 (5.26%)			
occurrences (all)	2			
Blood and lymphatic system disorders				
Thrombocytopenia				
subjects affected / exposed	22 / 38 (57.89%)			
occurrences (all)	22			
Anaemia				
subjects affected / exposed	19 / 38 (50.00%)			
occurrences (all)	19			
Lymphopenia				
subjects affected / exposed	14 / 38 (36.84%)			
occurrences (all)	14			
Leucopenia				
subjects affected / exposed	12 / 38 (31.58%)			
occurrences (all)	12			
Neutropenia				
subjects affected / exposed	10 / 38 (26.32%)			
occurrences (all)	10			
Febrile neutropenia				
subjects affected / exposed	1 / 38 (2.63%)			
occurrences (all)	1			
Hypophosphataemia				
subjects affected / exposed	18 / 38 (47.37%)			
occurrences (all)	18			
Hypercholesterolaemia				
subjects affected / exposed	15 / 38 (39.47%)			
occurrences (all)	15			
Hypokalaemia				
subjects affected / exposed	14 / 38 (36.84%)			
occurrences (all)	14			
Hypertriglyceridaemia				
subjects affected / exposed	14 / 38 (36.84%)			
occurrences (all)	14			
Aminotransferase increase				

subjects affected / exposed	12 / 38 (31.58%)		
occurrences (all)	12		
Hyperglycaemia			
subjects affected / exposed	11 / 38 (28.95%)		
occurrences (all)	11		
CK increase			
subjects affected / exposed	10 / 38 (26.32%)		
occurrences (all)	10		
Hypomagnesaemia			
subjects affected / exposed	9 / 38 (23.68%)		
occurrences (all)	9		
GGT increase			
subjects affected / exposed	8 / 38 (21.05%)		
occurrences (all)	8		
Bilirubin increase			
subjects affected / exposed	5 / 38 (13.16%)		
occurrences (all)	5		
Amylase or lipase increase			
subjects affected / exposed	4 / 38 (10.53%)		
occurrences (all)	4		
Creatinine increase			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	16 / 38 (42.11%)		
occurrences (all)	16		
Weight loss			
subjects affected / exposed	13 / 38 (34.21%)		
occurrences (all)	13		
Cough			
subjects affected / exposed	3 / 38 (7.89%)		
occurrences (all)	3		
Bleeding			

subjects affected / exposed	2 / 38 (5.26%)		
occurrences (all)	2		
Gastrointestinal disorders			
Oral mucositis			
subjects affected / exposed	20 / 38 (52.63%)		
occurrences (all)	20		
Diarrhoea			
subjects affected / exposed	18 / 38 (47.37%)		
occurrences (all)	18		
Nausea			
subjects affected / exposed	14 / 38 (36.84%)		
occurrences (all)	14		
Abdominal cramps			
subjects affected / exposed	11 / 38 (28.95%)		
occurrences (all)	11		
Vomiting			
subjects affected / exposed	8 / 38 (21.05%)		
occurrences (all)	8		
Constipation			
subjects affected / exposed	8 / 38 (21.05%)		
occurrences (all)	8		
Dysphagia			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 38 (2.63%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Hand–foot skin reaction			
subjects affected / exposed	27 / 38 (71.05%)		
occurrences (all)	27		
Rash			
subjects affected / exposed	24 / 38 (63.16%)		
occurrences (all)	24		
Acneiform eruption			

subjects affected / exposed occurrences (all) Xerosis subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	16 / 38 (42.11%) 16 11 / 38 (28.95%) 11 5 / 38 (13.16%) 5		
Musculoskeletal and connective tissue disorders Myalgia/arthralgia subjects affected / exposed occurrences (all)	6 / 38 (15.79%) 6		
Infections and infestations Infection subjects affected / exposed occurrences (all)	9 / 38 (23.68%) 9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/25498219