Clinical trial results:
Efficacy of Olaratumab and Rechallenge with Doxorubicin in anthracycline pretreated, advanced soft tissue sarcoma patients. An exploratory phase-II study - The OlaReDo Phase II Trial

Summary

EudraCT number	2018-001124-20
Trial protocol	DE
Global end of trial date	25 June 2020

Results information

Result version number	v1 (current)
This version publication date	04 November 2021
First version publication date	04 November 2021

Trial information

Trial identification

Sponsor protocol code	GISG-17

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03698227
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest
Sponsor organisation address	Steinbacher Hohl 2-26, Frankfurt, Germany, 60488
Public contact	IKF, Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, 0049 6976014420, olaredo@ikf-khnw.de
Scientific contact	IKF, Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, 0049 6976014420, olaredo@ikf-khnw.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	17 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 June 2020
Global end of trial reached?	Yes
Global end of trial date	25 June 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The present study aimed to evaluate efficacy and safety of olaratumab and doxorubicin combined with the cardioprotective prophylaxis with dexrazoxane in anthracycline pretreated patients. Efficacy was adressed by the progression-free survival rate after 3 months (PFSR3), assessed by applying RECIST 1.1, as primary endpoint and PFS, objective resposne rate, disease control rate and overall survival as secondary endpoints.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and the trial was approved by an Independent Ethics Committee. The eligibility of a new patient was determined by the local investigator during regular clinical visits. The examinations for the study and the inclusion of the patient were done after detailed written and oral education by use of the informed consent forms and after given written consent of the patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 November 2018
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	Germany: 2
Worldwide total number of subjects	2
EEA total number of subjects	2

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)	2

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Based on the negative results (lack of efficacy) on olaratumab in the ANNOUNCE study (press release dated January 18th, 2019), recruitment of the OlaReDo study was stopped immediately and the so far two enrolled patients were informed by the investigators accordingly.

Pre-assignment

Screening details:

Study was prematurely stopped after enrollment of 2 patients

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Arm A

Arm description:

patients received 8 cycles (q3w) of olaratumab administered IV (20 mg/kg on day 1 and day 8 of cycle 1 and 15 mg/kg on day 1 and day 8 of cycle 2 to 8) combined with doxorubicin administered IV (75 mg/m2 on day 1 of each cycle for 8 cycles) and dexrazoxane administered IV (at a dose equal to 10 times the doxorubicin dose [mg/m2] on day 1 of each cycle for 8 cycles). According to the study protocol, beginning with cycle 9 Olaratumab maintenance monotherapy should have been performed at 15 mg/kg administered IV on day 1 and day 8 of each subsequent 21 day cycle until documented progressive disease (PD), unacceptable toxicity, or other discontinuation criteria are met. However, due to negative results (lack of efficacy) on olaratumab in the ANNOUNCE study, treatment in the maintenance phase was not performed.

Arm type	Experimental
Investigational medicinal product name	Olaratumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Infusion , Injection

Dosage and administration details:

olaratumab was administered IV; 20 mg/kg on day 1 and day 8 of cycle 1 and 15 mg/kg on day 1 and day 8 of cycle 2 to 8

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

doxorubicin was administered IV; 75 mg/m2 on day 1 of each cycle for 8 cycles

Investigational medicinal product name	Dexrazoxane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

dexrazoxane was administered IV at a dose equal to 10 times the doxorubicin dose [mg/m2] on day 1 of each cycle for 8 cycles

Number of subjects in period 1	Arm A
Started	2
Completed	2

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	2	2	
Age categorical Units: Subjects			
Adults (18-64 years)	2	2	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	1	1	
Male	1	1	
type of tumor Units: Subjects			
Chondrosarcoma, upper extremity	1	1	
Synovial sarcoma, trunk	1	1	
ECOG Performance Status Units: Subjects			
ECOG 0	1	1	
ECOG 1	1	1	
TNM stage and histopathological grade Units: Subjects			
unknown	1	1	
T/N - not documented; M0; G3	1	1	
AJCC stage at study entry Units: Subjects			
IV	1	1	
unknown	1	1	

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

patients received 8 cycles (q3w) of olaratumab administered IV (20 mg/kg on day 1 and day 8 of cycle 1 and 15 mg/kg on day 1 and day 8 of cycle 2 to 8) combined with doxorubicin administered IV (75 mg/m2 on day 1 of each cycle for 8 cycles) and dexrazoxane administered IV (at a dose equal to 10 times the doxorubicin dose [mg/m2] on day 1 of each cycle for 8 cycles). According to the study protocol, beginning with cycle 9 Olaratumab maintenance monotherapy should have been performed at 15 mg/kg administered IV on day 1 and day 8 of each subsequent 21 day cycle until documented progressive disease (PD), unacceptable toxicity, or other discontinuation criteria are met. However, due to negative results (lack of efficacy) on olaratumab in the ANNOUNCE study, treatment in the maintenance phase was not performed.

Primary: Progression Free survival after 3 months PFSR3

End point title	Progression Free survival after 3 months PFSR3[1]

End point description:

Due to the small sample size of only two patients, it was not possible to perform statistical analyses with aggregated data. Thus, only data listings by individual patient have been provided. Out of two enrolled patients, both patients showed progressive-free survival after 3 months of study treatment

End point type	Primary

End point timeframe:

tumor response was determined radiologically prior every second combination treatment cycle (approx. every 6 weeks ± 7 days), during follow up tumor assessment was performed every 3 months ± 3 weeks

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: Due to sample size of only 2 patients no statistical analyses were possible

End point values	Arm A			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Subjects				
YES	2			
NO	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression-free survival (PFS) was defined as the time from the first dosing date of any study medication to the date of the first objectively documented tumor progression, or death due to any cause

End point type	Secondary

End point timeframe:

eventual signs of progressive disease and death events were to be assessed and recorded during trial participation (i.e. study drug medication) and the follow-up period which was 6 months

End point values	Arm A			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Subjects				
No Progression	1			
Progression	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival (OS) was defined as the time from date of the first dosing date of any study medication to the date of death (due to any cause). Subjects who are alive were censored at the last known alive dates

End point type	Secondary

End point timeframe:

eventual signs of progressive disease and death events were to be assessed and recorded during trial participation (i.e. study drug medication) and the follow-up period which was 6 months

End point values	Arm A			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Subjects				
No Death	2			
Death	0			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Best overall response

End point title	Best overall response

End point description:

both patients revealed detectable tumor lesions and valid restaging data for applying RECIST 1.1 criteria. Out of these, 1 patient showed stable disease (SD) until end of study (EOS), the other patient

showed stable disease (SD) until the cycle 8 and revealed progressive disease (PD) thereafter

End point type	Other pre-specified

End point timeframe:

tumor response was determined radiologically prior every second combination treatment cycle (approx. every 6 weeks ± 7 days). During follow up (until disease progressin of EOS) tumor assessment was performed every 3 months ± 3 weeks

End point values	Arm A			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Subjects				
Stable disease	1			
progressive disease	1			
complete response	0			
partial response	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were assessed continuously during the study (signature of the informed consent form - up to 30 days after last administration IMP). Thereafter, only SAEs at least possibly related to study treatment were reported

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Arm A

Reporting group description:

patients received 8 cycles (q3w) of olaratumab administered IV (20 mg/kg on day 1 and day 8 of cycle 1 and 15 mg/kg on day 1 and day 8 of cycle 2 to 8) combined with doxorubicin administered IV (75 mg/m2 on day 1 of each cycle for 8 cycles) and dexrazoxane administered IV (at a dose equal to 10 times the doxorubicin dose [mg/m2] on day 1 of each cycle for 8 cycles). According to the study protocol, beginning with cycle 9 Olaratumab maintenance monotherapy should have been performed at 15 mg/kg administered IV on day 1 and day 8 of each subsequent 21 day cycle until documented progressive disease (PD), unacceptable toxicity, or other discontinuation criteria are met. However, due to negative results (lack of efficacy) on olaratumab in the ANNOUNCE study, treatment in the maintenance phase was not performed.

Serious adverse events	Arm A		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 2 (50.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 2 (50.00%)		
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	Arm A		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
Investigations			
Neutrophil count decreased			

subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	5		
Platelet count decreased			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	10		
White blood cell count decreased			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	14		
Cardiac disorders			
Cardiac disorder - anthracycline induced cardiomyopathy			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	6		
Chills			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	3		
Edema limbs			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 2 (50.00%)		
occurrences (all)	1		
Constipation			

subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Mucositis oral subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1 1 / 2 (50.00%) 1 1 / 2 (50.00%) 2 2 / 2 (100.00%) 4 1 / 2 (50.00%) 1		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	1 / 2 (50.00%) 1		

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? Yes

Date	Interruption	Restart date
18 January 2019	Based on the negative results (lack of efficacy) on olaratumab in the ANNOUNCE study (press release dated January 18th, 2019), recruitment of the OlaReDo study was stopped immediately and the two enrolled patients were informed by the investigators accordingly. A halt of the OlaReDo study was notified by the Sponsor to the Competent Authority and Ethics Committee on January 22nd, 2019. Acknowledgement of receipt PEI: 28-Jan-2019; acknowledgement of receipt IRB: 25-Jan-2019	-

Notes:

Limitations and caveats

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

The OlaReDo study was stopped prematurely with only 2 patients treated according the study protocol. Due to the small sample size of only two patients, statistical analyses were not possible

Notes: