Clinical trial results:
Phase II Trial for the Treatment of Advanced Classical Kaposis Sarcoma with the HIV Protease Inhibitor Indinavir in Combination with Chemotherapy

Summary

EudraCT number	2007-000567-26
Trial protocol	IT
Global end of trial date	09 June 2016

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	CKS/IND-CX/05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01067690
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Istituto Superiore di Sanità
Sponsor organisation address	Viale Regina Elena 299, Rome, Italy, 00161
Public contact	National HIV/AIDS Research Center, National HIV/AIDS Research Center, segr-cnaids@iss.it
Scientific contact	National HIV/AIDS Research Center, National HIV/AIDS Research Center, segr-cnaids@iss.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	06 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 October 2015
Global end of trial reached?	Yes
Global end of trial date	09 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical response in patients affected by advanced classical Kaposi's sarcoma (KS) (stage III/IV) treated with daily oral administration of Indinavir upon a debulking therapy based on cycles of systemic Vinblastine +/- Bleomycin, followed by a maintenance phase with Indinavir alone.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and in compliance with Good Clinical Practices (CPMP/ICH/135/95). The essential documents are archived as required by the applicable regulatory requirements.
The study and any amendment were reviewed by an Independent Ethics Committees or Institutional Review Boards.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 May 2008
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	Italy: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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)	7
From 65 to 84 years	17

85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Patients recruited within the cohort of patients followed by the Dermatologic Unit, Ospedale Maggiore Policlinico, Milan, Italy, and affected by advanced classical KS (stage III/IV), a rare tumor in Europe (incidence 1-9/100000, Orphanet).
First subject enrolled: June 3, 2008, last subject enrolled: June 13, 2014

Pre-assignment

Screening details:

28 subjects screened for inclusion.
Subjects with other tumors, severe bronchopneumopaties, nephropathies or nephrolitiasis, significant and persistent abnormal laboratory findings, therapy with immunomodulators or chemotherapy, were excluded.
A wash-out from other anti-KS therapies of at least 2 weeks was required before entering the study.

Period 1

Period 1 title	Induction phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Single arm

Arm description:

In order to assess tolerance, initially patients started Vinblastine i.v. weekly injection according to a dose escalation of 4 mg, 6 mg, and 8 mg, in association with Indinavir at the dose of 800 mg per os, 2 times/day (every 12 hours).
If well tolerated, after a 3 weeks stop, patients received Vinblastine 10 mg i.v. +/- Bleomycin 15 mg i.m., every 3 weeks, always in association with the daily Indinavir administration.
After the maximal response was obtained, patients received 2 additional cycles of Vinblastine +/- Bleomycin as consolidation and then stop chemotherapy, while continuing Indinavir.

Arm type	Experimental
Investigational medicinal product name	Indinavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

800 mg, twice a day

Investigational medicinal product name	Vinblastine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 mg every 3 weeks

Investigational medicinal product name	Bleomycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

15 mg i.m. every 3 weeks

Number of subjects in period 1	Single arm
Started	25
Completed	17
Not completed	8
Consent withdrawn by subject	3
Adverse event, non-fatal	4
Protocol deviation	1

Period 2

Period 2 title	Manteinance phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Single arm

Arm description:

12 months maintenance phase with Indinavir alone scaled up to 800 mg, 3 times/day, orally, to assess clinical response on the debulked tumor (after the induction phase).
If a patient dropped-out before phase completion, clinical response was censored at the time of the last disease assessment.

Arm type	Experimental
Investigational medicinal product name	Indinavir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

800 mg, 3 times a day

Number of subjects in period 2	Single arm
Started	17
Completed	12
Not completed	5
Physician decision	1
Disease progression	1
Adverse event, non-fatal	3

Period 3	
Period 3 title	Post-therapy follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Single arm

Arm description:

12 months post-therapy follow-up without any anti-KS treatment

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 3	Single arm
Started	12
Completed	11
Not completed	1
Disease progression	1

Baseline characteristics

Reporting groups	
Reporting group title	Induction phase

Reporting group description:

Patients underwent an induction phase where daily Indinavir (800 mg x 2/die, orally) was combined together with systemic Vinblastine (10 mg intravenously) +/- Bleomycin (15 mg intramuscularly) in cycles administered every 3 weeks. After the maximal response was obtained, patients received 2 additional cycles of Vinblastine +/-Bleomycin and then stopped chemotherapy, while continuing Indinavir

Reporting group values	Induction phase	Total	
Number of subjects	25	25	
Age categorical Units: Subjects			

Age continuous			
62.52 (8.24)			
Units: years arithmetic mean standard deviation	 62.52 ± 8.24	 -	
Gender categorical Units: Subjects			
Female	5	5	
Male	20	20	

End points

End points reporting groups

Reporting group title	Single arm

Reporting group description:

In order to assess tolerance, initially patients started Vinblastine i.v. weekly injection according to a dose escalation of 4 mg, 6 mg, and 8 mg, in association with Indinavir at the dose of 800 mg per os, 2 times/day (every 12 hours).
If well tolerated, after a 3 weeks stop, patients received Vinblastine 10 mg i.v. +/- Bleomycin 15 mg i.m., every 3 weeks, always in association with the daily Indinavir administration.
After the maximal response was obtained, patients received 2 additional cycles of Vinblastine +/- Bleomycin as consolidation and then stop chemotherapy, while continuing Indinavir.

Reporting group title	Single arm

Reporting group description:

12 months maintenance phase with Indinavir alone scaled up to 800 mg, 3 times/day, orally, to assess clinical response on the debulked tumor (after the induction phase).
If a patient dropped-out before phase completion, clinical response was censored at the time of the last disease assessment.

Reporting group title	Single arm

Reporting group description:

12 months post-therapy follow-up without any anti-KS treatment

Primary: Clinical response rate after the induction phase

End point title	Clinical response rate after the induction phase[1]

End point description:

Responders are defined as those patients that obtained a complete clinical response (CR), a partial response (PR), improved disease (ID) or a stabilized disease (SD) after the induction phase. If a patient dropped-out before induction completion, clinical response was censored at the time on last disease assessment.

End point type	Primary

End point timeframe:

Induction phase (Indinavir combined with Vinblastine +/- Bleomycin)

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: As this is a non-comparative study, which is not adequately powered for comparing groups, no formal statistical comparisons between treatment groups were done. Demographic and baseline laboratory results were summarized by group using descriptive statistics.
Demographic and baseline laboratory results were summarized by group using descriptive statistics.

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	22[2]			
Units: number of responders	22			

Notes:

[2] - 3 out of 25 pts that started induction were not evaluated for response because dropped-out too early

Statistical analyses

No statistical analyses for this end point

Primary: Clinical response rate after the maintenance phase

End point title	Clinical response rate after the maintenance phase[3]

End point description:

Responders are defined as those patients with complete clinical response (CR), partial response (PR), improved disease (ID) or a stabilized disease (SD) after the maintenance phase. If a patient dropped-out before maintenance completion, clinical response was censored at the time on last disease assessment.

End point type	Primary

End point timeframe:

12-months maintenance phase

Notes:

[3] - 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: As this is a non-comparative study, which is not adequately powered for comparing groups, no formal statistical comparisons between treatment groups were done. Demographic and baseline laboratory results were summarized by group using descriptive statistics.
Demographic and baseline laboratory results were summarized by group using descriptive statistics.

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	16[4]			
Units: number of responses	7			

Notes:

[4] - 1 of the 17 pts that completed induction dropped-out before starting maintenance for AE

Statistical analyses

No statistical analyses for this end point

Secondary: Response rate after the follow-up phase

End point title	Response rate after the follow-up phase

End point description:

Responders are those patients with a complete clinical response (CR), partial response (PR), improved disease (ID) or stable disease (SD) after the follow-up phase.
If a patient dropped-out before phase completion, clinical response was censored at the time of the last disease assessment

End point type	Secondary

End point timeframe:

12 months post-therapy follow-up

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: number of responders	6			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Whole treatment phase: induction phase plus maintenance phase

Adverse event reporting additional description:

Treatment safety was evalauted in all the 25 enrolled patients. AE occurrence was assessed at each study visit.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3

Reporting groups

Reporting group title	Treatment phase (Induction+maintenance)

Reporting group description:

All AE reported during the treatment phase (Induction+maintenance)

Serious adverse events	Treatment phase (Induction+maintenance)		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 25 (28.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer	Additional description: Colon adenocarcinoma diagnosed right after treatment start. Event graded as severe and unrelated to treatment. Patient dropped-out because enrolled in violation of the exclusion criteria		
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Hyposthenia of the left hemisoma	Additional description: The patient referred to the emergency room and thus the event was classified as SAE. Examinations did not reveal specific abnormalities. The event resolved in 24 h,was graded as mild and unrelated to study drug.		
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia and flu-like syndrome	Additional description: The patient referred to the emergency room and thus the event was classified as SAE. The event was graded as moderate; asthenia was considered as possibly related to study drug, while flu-like syndrome as unrelated.		

subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fever and cough	Additional description: The patient referred to the emergency room and thus the event was classified as SAE. Examinations did not reveal abnormalities. The event was graded as moderate and unlikely related to study drug.		
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Paralytic ileus	Additional description: The patient referred to the emergency room and thus the event was classified as SAE. Examinations did not reveal specific abnormalities. The event was graded as moderate and probably related to study drug.		
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain	Additional description: The patient referred to the emergency room and thus the event was classified as SAE; no specific abnormalities were found. The event was graded as moderate and unrelated to study drug		
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dorsal pain	Additional description: The patient referred to the emergency room and thus the event was classified as SAE. Examinations did not reveal specific abnormalities. The event was graded as moderate and possibly related to study drug.		
subjects affected / exposed	1 / 25 (4.00%)		
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	Treatment phase (Induction+maintenance)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 25 (96.00%)		
Investigations			
LDL cholesterol increased			
subjects affected / exposed	17 / 25 (68.00%)		
occurrences (all)	26		

Total cholesterol increased subjects affected / exposed occurrences (all)	16 / 25 (64.00%) 16		
Leukopenia subjects affected / exposed occurrences (all)	20 / 25 (80.00%) 37		
Haematocrit decreased subjects affected / exposed occurrences (all)	14 / 25 (56.00%) 25		
Red blood cell count decreased subjects affected / exposed occurrences (all)	13 / 25 (52.00%) 23		
Haemoglobin decreased subjects affected / exposed occurrences (all)	14 / 25 (56.00%) 23		
Cylindruria hyaline and/or hyaline-granular subjects affected / exposed occurrences (all)	16 / 25 (64.00%) 31		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	6 / 25 (24.00%) 9		
Pyrexia subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 8		
Gastrointestinal disorders Epigastric discomfort subjects affected / exposed occurrences (all)	7 / 25 (28.00%) 11		
Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 6		
Musculoskeletal and connective tissue disorders			

Musculosketal pain subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 6		

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