



Clinical trial results:

Multicentre, randomised, controlled, open-label, study comparing the efficacy and safety of slow repeated intravenous infusions of 2 doses of Doxorubicin Transdrug™ (DT) (20 mg/m² or 30 mg/m²) to those of best standard of care (BSC) in patients with advanced hepatocellular carcinoma (HCC) after failure or intolerance to Sorafenib - ReLive Study Summary

EudraCT number	2011-002843-92
Trial protocol	BE IT ES HU AT DE
Global end of trial date	25 February 2019

Results information

Result version number	v1 (current)
This version publication date	03 April 2020
First version publication date	03 April 2020

Trial information

Trial identification

Sponsor protocol code	BA2011/03/04
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01655693
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Onxeo S.A.
Sponsor organisation address	49 bd du Général Martial Valin, Paris, France, 75015
Public contact	Clinical Director, Onxeo S.A., 33 145587600, clinicaltrials@onxeo.com
Scientific contact	Clinical Director, Onxeo S.A., 33 145587600, clinicaltrials@onxeo.com

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	26 June 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of repeated slow intravenous infusions of DT at doses of 20 or 30 mg/m² to best standard of care (BSC) in patients with advanced hepatocellular carcinoma (HCC) after failure or intolerance to sorafenib on overall survival (OS).

Protection of trial subjects:

This investigation was carried out in accordance with the basic ethical principles put forth in the Declaration of Helsinki of the World Medical Assembly and its revisions, as well as the rules of GCP and local regulatory requirements in each country where the study was conducted.

It was the responsibility of the investigator to obtain written informed consent from each patient participating in this study. The consent was obtained in accordance with ICH-GCP requirements (ICH-E6). Every effort was made to maintain anonymity and confidentiality of medical records during this investigation. However, because of the experimental nature of this treatment, periodic monitoring of the medical records by representatives of Onxeo or FDA was allowed.

Each patient signed the informed consent form (ICF) after receiving oral and written information describing the nature and duration of the study. No patient was screened or treated until an ICF, written in a language in which the patient was fluent, had been obtained. The signed ICF was retained with the study records at the study site. Each patient was given a copy of his or her signed ICF.

Background therapy:

Prior medications were to be recorded at screening.

The study enrolled patients with advanced or intermediate HCC who had progressed on or were intolerant to sorafenib.

Evidence for comparator: -

Actual start date of recruitment	15 June 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	45 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	France: 238
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Hungary: 30

Country: Number of subjects enrolled	Italy: 29
Country: Number of subjects enrolled	Egypt: 28
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Turkey: 4
Country: Number of subjects enrolled	Lebanon: 1
Worldwide total number of subjects	397
EEA total number of subjects	357

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)	169
From 65 to 84 years	226
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

A total of 541 patients were screened, and 397 patients were randomized at 69 sites in 11 countries worldwide.

Pre-assignment

Screening details:

The most common reason for screen failure was meeting liver function exclusion criteria.

Prior medications were to be recorded at screening. Any therapy or medication (except protocol-prescribed) administered from screening until the end of the study was to be considered a concomitant therapy or medication.

Period 1

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

Blinding implementation details:

This was an open-label study with respect to treatment assignments and administration. Central review of imaging to assess cancer progression occurred in a blinded fashion, and data review committee assessments were also blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Doxorubicin Transdrug (DT) at 20mg/m2

Arm description:

DT was infused over 6 hours through the intravenous (IV) route at dose of 20 mg/m2 on Day 1 and then repeated every 4 weeks until disease progression or unacceptable toxicity.

Arm type	Experimental
Investigational medicinal product name	Doxorubicin Transdrug™ (DT) 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

DT 10 mg; 20 mg/m2: Slow intravenous infusion over 6 hours of suspension reconstituted with 25 mL glucose 2.5% for injection, given once every 4 weeks.

Arm title	Doxorubicin Transdrug (DT) at 30mg/m2
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Arm description:

DT was infused over 6 hours through the IV route at dose of 30 mg/m2 on Day 1 and then repeated every 4 weeks until disease progression or unacceptable toxicity

Arm type	Experimental
Investigational medicinal product name	Doxorubicin Transdrug™ (DT) 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

DT 10 mg; 30 mg/m2: Slow intravenous infusion over 6 hours of suspension reconstituted with 25 mL glucose 2.5% for injection, given once every 4 weeks.

Arm title	Best Standard of Care
Arm description:	
Patients randomized in the control group were treated and monitored according to the usual practice (BSC) at the center and according to their physician's judgment, until disease progression or unacceptable toxicity.	
Acceptable therapies could include, but were not limited to, anticancer therapy and supportive care (eg, antibiotics, analgesics, antiemetics, ascites drainage, blood transfusions, and/or nutritional support).	
Arm type	Active comparator
Investigational medicinal product name	Best Standard of Care (BSC)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

BSC (commercial supplies), as prescribed.

The route of administration and pharmaceutical form included do not reflect the whole range of BSC used, as it depends on prescription of each principal investigator.

Number of subjects in period 1	Doxorubicin Transdrug (DT) at 20mg/m ²	Doxorubicin Transdrug (DT) at 30mg/m ²	Best Standard of Care
Started	130	133	134
Completed	0	0	0
Not completed	130	133	134
Non Compliance	-	-	8
Aggravation of liver dysfunction	5	4	-
No respect of criteria	1	3	-
Serious Adverse Event	4	15	11
Consent withdrawn by subject	3	3	20
Screening failure	1	-	-
Adverse event, non-fatal	4	11	3
Death	8	9	12
Other	9	6	16
Progressive Disease	93	81	58
Progressive Disease - Other	-	-	1
Lost to follow-up	1	-	1
Progression disease-AE-Aggravation liver dysfunct.	-	-	1
Protocol deviation	1	-	3
Progression disease-Aggravation liver dysfunction	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	397	397	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	169	169	
From 65-84 years	226	226	
85 years and over	2	2	
Age continuous			
Units: years			
median	67		
full range (min-max)	19.0 to 89.2	-	
Gender categorical			
Units: Subjects			
Female	56	56	
Male	341	341	

End points

End points reporting groups

Reporting group title	Doxorubicin Transdrug (DT) at 20mg/m2
Reporting group description: DT was infused over 6 hours through the intravenous (IV) route at dose of 20 mg/m2 on Day 1 and then repeated every 4 weeks until disease progression or unacceptable toxicity.	
Reporting group title	Doxorubicin Transdrug (DT) at 30mg/m2
Reporting group description: DT was infused over 6 hours through the IV route at dose of 30 mg/m2 on Day 1 and then repeated every 4 weeks until disease progression or unacceptable toxicity	
Reporting group title	Best Standard of Care
Reporting group description: Patients randomized in the control group were treated and monitored according to the usual practice (BSC) at the center and according to their physician's judgment, until disease progression or unacceptable toxicity. Acceptable therapies could include, but were not limited to, anticancer therapy and supportive care (eg, antibiotics, analgesics, antiemetics, ascites drainage, blood transfusions, and/or nutritional support).	
Subject analysis set title	Doxorubicin Transdrug (Livatag) pooled
Subject analysis set type	Intention-to-treat
Subject analysis set description: The pooling of the 2 DT arms into the DT pooled group was added to the plan for the analysis of Overall Survival (OS) compared with BSC.	

Primary: Overall Survival

End point title	Overall Survival ^[1]
End point description: The primary endpoint of Overall Survival (OS) was defined as the time from the date of randomization to the date of death from any cause. Data for patients without death at the time of the statistical analysis were censored at the date last known alive (or date of randomization if no post baseline assessments were available). Overall survival was estimated using the Kaplan-Meier method and plotted as curves by treatment group, and the primary comparison of treatment groups (pooled DT groups versus BSC arm) was performed using a nonstratified log-rank test as the primary analysis.	
End point type	Primary
End point timeframe: From the date of randomization to the date of death from any cause (maximum follow-up until month 45)	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The DT groups have been pooled for the primary comparison of treatment groups.

End point values	Best Standard of Care	Doxorubicin Transdrug (Livatag) pooled		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	134	264		
Units: Months				
median (confidence interval 95%)				
Overall Survival	9.0 (7.2 to 11.8)	8.9 (8.1 to 10.3)		

Statistical analyses

Statistical analysis title	Primary comparison of treatment groups
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Statistical analysis description:

Primary comparison of treatment groups (pooled DT groups versus BSC arm) was performed using a nonstratified log-rank test as the primary analysis.

Comparison groups	Best Standard of Care v Doxorubicin Transdrug (Livatag) pooled
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.796
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During treatment, and an end-of-study visit was performed approximately 1 month after the last DT infusion or BSC treatment, after which follow-up was conducted every 3 months until death.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Doxorubicin Transdrug (DT) at 20mg/m2
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Reporting group description:

DT will be infused over 6 hours through the intravenous (IV) route at dose of 20 mg/m2 on Day 1 and will be repeated every 4 weeks until disease progression or unacceptable toxicity

Reporting group title	Doxorubicin Transdrug (DT) at 30mg/m2
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Reporting group description:

DT will be infused over 6 hours through the IV route at dose of 30 mg/m2 on Day 1 and will be repeated every 4 weeks until disease progression or unacceptable toxicity

Reporting group title	Best Standard of Care
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Reporting group description:

Patients randomized in the control group will receive treatment according to the investigator's choice, until disease progression or unacceptable toxicity.

Serious adverse events	Doxorubicin Transdrug (DT) at 20mg/m2	Doxorubicin Transdrug (DT) at 30mg/m2	Best Standard of Care
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 122 (33.61%)	42 / 120 (35.00%)	52 / 134 (38.81%)
number of deaths (all causes)	113	112	101
number of deaths resulting from adverse events	6	5	1
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	3 / 122 (2.46%)	2 / 120 (1.67%)	8 / 134 (5.97%)
occurrences causally related to treatment / all	0 / 3	1 / 2	1 / 8
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 4
Fatigue			
subjects affected / exposed	0 / 122 (0.00%)	3 / 120 (2.50%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anemia			

subjects affected / exposed	1 / 122 (0.82%)	1 / 120 (0.83%)	4 / 134 (2.99%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Esophageal varices hemorrhage			
subjects affected / exposed	1 / 122 (0.82%)	3 / 120 (2.50%)	7 / 134 (5.22%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 3
Ascites			
subjects affected / exposed	3 / 122 (2.46%)	1 / 120 (0.83%)	3 / 134 (2.24%)
occurrences causally related to treatment / all	2 / 3	1 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Abdominal pain			
subjects affected / exposed	3 / 122 (2.46%)	0 / 120 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	1 / 4	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	3 / 122 (2.46%)	0 / 120 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic encephalopathy			
subjects affected / exposed	1 / 122 (0.82%)	5 / 120 (4.17%)	7 / 134 (5.22%)
occurrences causally related to treatment / all	1 / 1	3 / 6	1 / 9
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	3 / 134 (2.24%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Infections and infestations			
Catheter site infection			

subjects affected / exposed	3 / 122 (2.46%)	0 / 120 (0.00%)	2 / 134 (1.49%)
occurrences causally related to treatment / all	2 / 3	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis with spontaneous bacterial peritonitis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 120 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Doxorubicin Transdrug (DT) at 20mg/m ²	Doxorubicin Transdrug (DT) at 30mg/m ²	Best Standard of Care
Total subjects affected by non-serious adverse events			
subjects affected / exposed	113 / 122 (92.62%)	114 / 120 (95.00%)	100 / 134 (74.63%)
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 122 (6.56%)	5 / 120 (4.17%)	3 / 134 (2.24%)
occurrences (all)	10	5	5
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	42 / 122 (34.43%)	57 / 120 (47.50%)	42 / 134 (31.34%)
occurrences (all)	66	83	51
Edema peripheral			
subjects affected / exposed	9 / 122 (7.38%)	26 / 120 (21.67%)	24 / 134 (17.91%)
occurrences (all)	10	29	26
Pyrexia			
subjects affected / exposed	10 / 122 (8.20%)	23 / 120 (19.17%)	10 / 134 (7.46%)
occurrences (all)	15	32	10
Fatigue			

subjects affected / exposed occurrences (all)	9 / 122 (7.38%) 11	16 / 120 (13.33%) 21	15 / 134 (11.19%) 16
General physical health deterioration subjects affected / exposed occurrences (all)	5 / 122 (4.10%) 5	4 / 120 (3.33%) 4	12 / 134 (8.96%) 13
Mucosal inflammation subjects affected / exposed occurrences (all)	2 / 122 (1.64%) 2	6 / 120 (5.00%) 7	5 / 134 (3.73%) 5
Respiratory, thoracic and mediastinal disorders			
Dyspnea subjects affected / exposed occurrences (all)	12 / 122 (9.84%) 22	13 / 120 (10.83%) 17	9 / 134 (6.72%) 9
Cough subjects affected / exposed occurrences (all)	13 / 122 (10.66%) 19	9 / 120 (7.50%) 10	10 / 134 (7.46%) 12
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	3 / 122 (2.46%) 3	8 / 120 (6.67%) 8	5 / 134 (3.73%) 5
Investigations			
Weight decreased subjects affected / exposed occurrences (all)	5 / 122 (4.10%) 5	13 / 120 (10.83%) 13	7 / 134 (5.22%) 8
Blood bilirubin increased subjects affected / exposed occurrences (all)	8 / 122 (6.56%) 9	2 / 120 (1.67%) 3	7 / 134 (5.22%) 12
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	3 / 122 (2.46%) 3	6 / 120 (5.00%) 6	3 / 134 (2.24%) 5
Oxygen saturation decreased subjects affected / exposed occurrences (all)	2 / 122 (1.64%) 3	7 / 120 (5.83%) 7	2 / 134 (1.49%) 4
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	11 / 122 (9.02%) 12	16 / 120 (13.33%) 23	6 / 134 (4.48%) 8

Paraesthesia			
subjects affected / exposed	4 / 122 (3.28%)	2 / 120 (1.67%)	20 / 134 (14.93%)
occurrences (all)	5	2	35
Dizziness			
subjects affected / exposed	7 / 122 (5.74%)	1 / 120 (0.83%)	1 / 134 (0.75%)
occurrences (all)	8	2	1
Neuropathy peripheral			
subjects affected / exposed	0 / 122 (0.00%)	0 / 120 (0.00%)	9 / 134 (6.72%)
occurrences (all)	0	0	9
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	17 / 122 (13.93%)	23 / 120 (19.17%)	24 / 134 (17.91%)
occurrences (all)	27	31	32
Thrombocytopenia			
subjects affected / exposed	2 / 122 (1.64%)	14 / 120 (11.67%)	25 / 134 (18.66%)
occurrences (all)	2	26	41
Neutropenia			
subjects affected / exposed	4 / 122 (3.28%)	19 / 120 (15.83%)	6 / 134 (4.48%)
occurrences (all)	16	43	10
Leukopenia			
subjects affected / exposed	1 / 122 (0.82%)	11 / 120 (9.17%)	3 / 134 (2.24%)
occurrences (all)	6	25	3
Lymphopenia			
subjects affected / exposed	5 / 122 (4.10%)	7 / 120 (5.83%)	3 / 134 (2.24%)
occurrences (all)	6	16	4
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	26 / 122 (21.31%)	33 / 120 (27.50%)	24 / 134 (17.91%)
occurrences (all)	44	62	28
Diarrhoea			
subjects affected / exposed	22 / 122 (18.03%)	23 / 120 (19.17%)	20 / 134 (14.93%)
occurrences (all)	40	31	26
Vomiting			
subjects affected / exposed	16 / 122 (13.11%)	21 / 120 (17.50%)	10 / 134 (7.46%)
occurrences (all)	20	29	13
Constipation			

subjects affected / exposed	18 / 122 (14.75%)	15 / 120 (12.50%)	12 / 134 (8.96%)
occurrences (all)	22	18	14
Abdominal pain			
subjects affected / exposed	15 / 122 (12.30%)	15 / 120 (12.50%)	13 / 134 (9.70%)
occurrences (all)	19	18	18
Ascites			
subjects affected / exposed	15 / 122 (12.30%)	14 / 120 (11.67%)	27 / 134 (20.15%)
occurrences (all)	19	14	42
Abdominal pain upper			
subjects affected / exposed	11 / 122 (9.02%)	15 / 120 (12.50%)	5 / 134 (3.73%)
occurrences (all)	14	16	5
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 122 (0.82%)	3 / 120 (2.50%)	7 / 134 (5.22%)
occurrences (all)	1	3	7
Hepatobiliary disorders			
Hepatic encephalopathy			
subjects affected / exposed	3 / 122 (2.46%)	7 / 120 (5.83%)	9 / 134 (6.72%)
occurrences (all)	4	9	12
Hyperbilirubinaemia			
subjects affected / exposed	2 / 122 (1.64%)	7 / 120 (5.83%)	3 / 134 (2.24%)
occurrences (all)	2	17	3
Jaundice			
subjects affected / exposed	2 / 122 (1.64%)	9 / 120 (7.50%)	1 / 134 (0.75%)
occurrences (all)	2	10	1
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	7 / 122 (5.74%)	9 / 120 (7.50%)	7 / 134 (5.22%)
occurrences (all)	10	10	7
Dry skin			
subjects affected / exposed	3 / 122 (2.46%)	7 / 120 (5.83%)	3 / 134 (2.24%)
occurrences (all)	3	7	3
Alopecia			
subjects affected / exposed	3 / 122 (2.46%)	8 / 120 (6.67%)	2 / 134 (1.49%)
occurrences (all)	3	8	2
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed occurrences (all)	0 / 122 (0.00%) 0	1 / 120 (0.83%) 1	7 / 134 (5.22%) 11
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	11 / 122 (9.02%) 13	17 / 120 (14.17%) 25	6 / 134 (4.48%) 6
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	7 / 122 (5.74%) 10	7 / 120 (5.83%) 7	4 / 134 (2.99%) 4
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hypoalbuminaemia subjects affected / exposed occurrences (all)	16 / 122 (13.11%) 16 4 / 122 (3.28%) 5 3 / 122 (2.46%) 9	19 / 120 (15.83%) 20 11 / 120 (9.17%) 15 6 / 120 (5.00%) 13	21 / 134 (15.67%) 23 6 / 134 (4.48%) 7 6 / 134 (4.48%) 11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 June 2014	Protocol Version 5.0: The protocol was amended to shorten the hospitalization period and to modify the PK substudy according to FDA and PK expert recommendations; this version applied to all participating countries.
23 October 2014	Protocol Version 5.1: The protocol was amended to reflect the change of the Sponsor's name following the merger of BioAlliance Pharma with Topotarget. The global content is the same as the Protocol Amendment Version 5.0, only the name "BioAlliance Pharma" has been replaced by "Onxeo" (formerly known as BioAlliance Pharma).
29 April 2016	Protocol Version 6.0: This protocol version applied to all participating countries and implemented the following changes: – For sites that participated in the PK study: Limited and optional blood sampling for PK dosage adjustments were added for participating patients; the PK section was simplified (the analysis plan is provided separately from the protocol); and 1 optional ECG was added at the end of DT infusion; the PK appendix was updated accordingly. – The statistical analysis descriptions, including the definition of the ITT population, were clarified. – The background and references sections were updated with results of recent studies and to add prognostic factors in HCC survival. – The EQ-5D questionnaire was added for a subgroup of patients for pharmacoeconomic assessments; it was also added to the appendix.
27 July 2017	Protocol Version 7.0: This protocol version applied to all participating countries and implemented the following changes: – The pooling of the 2 DT arms into the DT pooled group was added to the plan for the analysis of OS compared with BSC. – The Child-Pugh A subpopulation was defined for analysis because this population was most likely to benefit from DT treatment. In addition, this subpopulation analysis would allow for greater comparability with results generated for other drugs (which were assessed in this population).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported