# 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 |

**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 | Safety, Efficacy, 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 |

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/m2 | Doxorubicin Transdrug (DT) at 30mg/m2 | 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<br>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<br>Units: years | | | |
| median | 67 | | |
| full range (min-max) | 19.0 to 89.2 | - | |
| Gender categorical<br>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 |
|---|---|

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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Doxorubicin Transdrug (DT) at 20mg/m2 |

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 |

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 |

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/m2 | Doxorubicin Transdrug (DT) at 30mg/m2 | 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 | 9 / 122 (7.38%) | 16 / 120 (13.33%) | 15 / 134 (11.19%) |
| occurrences (all) | 11 | 21 | 16 |
| General physical health deterioration | | | |
| subjects affected / exposed | 5 / 122 (4.10%) | 4 / 120 (3.33%) | 12 / 134 (8.96%) |
| occurrences (all) | 5 | 4 | 13 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 2 / 122 (1.64%) | 6 / 120 (5.00%) | 5 / 134 (3.73%) |
| occurrences (all) | 2 | 7 | 5 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnea | | | |
| subjects affected / exposed | 12 / 122 (9.84%) | 13 / 120 (10.83%) | 9 / 134 (6.72%) |
| occurrences (all) | 22 | 17 | 9 |
| Cough | | | |
| subjects affected / exposed | 13 / 122 (10.66%) | 9 / 120 (7.50%) | 10 / 134 (7.46%) |
| occurrences (all) | 19 | 10 | 12 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 3 / 122 (2.46%) | 8 / 120 (6.67%) | 5 / 134 (3.73%) |
| occurrences (all) | 3 | 8 | 5 |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 5 / 122 (4.10%) | 13 / 120 (10.83%) | 7 / 134 (5.22%) |
| occurrences (all) | 5 | 13 | 8 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 8 / 122 (6.56%) | 2 / 120 (1.67%) | 7 / 134 (5.22%) |
| occurrences (all) | 9 | 3 | 12 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 3 / 122 (2.46%) | 6 / 120 (5.00%) | 3 / 134 (2.24%) |
| occurrences (all) | 3 | 6 | 5 |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 2 / 122 (1.64%) | 7 / 120 (5.83%) | 2 / 134 (1.49%) |
| occurrences (all) | 3 | 7 | 4 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 11 / 122 (9.02%) | 16 / 120 (13.33%) | 6 / 134 (4.48%) |
| occurrences (all) | 12 | 23 | 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 | 0 / 122 (0.00%) | 1 / 120 (0.83%) | 7 / 134 (5.22%) |
| occurrences (all) | 0 | 1 | 11 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 11 / 122 (9.02%) | 17 / 120 (14.17%) | 6 / 134 (4.48%) |
| occurrences (all) | 13 | 25 | 6 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 7 / 122 (5.74%) | 7 / 120 (5.83%) | 4 / 134 (2.99%) |
| occurrences (all) | 10 | 7 | 4 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 16 / 122 (13.11%) | 19 / 120 (15.83%) | 21 / 134 (15.67%) |
| occurrences (all) | 16 | 20 | 23 |
| Hypokalaemia | | | |
| subjects affected / exposed | 4 / 122 (3.28%) | 11 / 120 (9.17%) | 6 / 134 (4.48%) |
| occurrences (all) | 5 | 15 | 7 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 3 / 122 (2.46%) | 6 / 120 (5.00%) | 6 / 134 (4.48%) |
| occurrences (all) | 9 | 13 | 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:<br>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:<br>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:<br>− 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.<br>− The statistical analysis descriptions, including the definition of the ITT population, were clarified.<br>− The background and references sections were updated with results of recent studies and to add prognostic factors in HCC survival.<br>− The EQ-5D questionnaire was added for a subgroup of patients for pharmaco-economic 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:<br>− 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.<br>− 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