THE ORPHAN ONCOLOGY INNOVATOR

CLINICAL TRIAL PROTOCOL

NCT Number: 01655693

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

Compound Name:	Doxorubicin Transdrug™
EudraCT Number:	[redacted]
IND:	[redacted]
Protocol Number:	BA2011/03/04
Phase:	Phase III
Version and Date:	Version 7.0, July 27th, 2017 Replaces 6.0, April 29th, 2016
Sponsor:	ONXEO (formerly known as BioAlliance Pharma) [redacted]

STUDY CONTACT LIST

INTERNATIONAL COORDINATING INVESTIGATOR

Name [redacted]
Address [redacted]

SPONSOR:

Clinical Development Director
Company ONXEO (formerly known as BioAlliance Pharma)
Name [redacted]
Contact [redacted]

Head Drug Safety
Company ONXEO (formerly known as BioAlliance Pharma)
Name [redacted]
Contact [redacted]

Clinical Project Managers
Company ONXEO (formerly known as BioAlliance Pharma)
Name [redacted]
Contact [redacted]

Name [redacted]
Contact [redacted]

RESEARCH FACILITIES

Monitoring Europe and Turkey
Company CHILTERN INTERNATIONAL SARL
Address [redacted]

Monitoring US
Company CHILTERN INTERNATIONAL SARL
Address [redacted]

Monitoring MENA (Middle East and North Africa)
Company MCT
Address [redacted]

Drug packaging
Company AMATSI
Address [redacted]

Pharmacokinetics Analyses
Company Bertin Pharma at CEA/LEMM
Address [redacted]

Data Management
Company LINCOLN
Address [redacted]

Biostatistics (Safety data for DSMB meetings)
Company Effi-Stat
Address [redacted]

Biostatistics (Final analysis)
Company CHILTERN INTERNATIONAL SARL
Address [redacted]

ACCEPTANCE OF THE PROTOCOL BY THE SPONSOR AND THE INVESTIGATOR

TITLE OF THE PROTOCOL:

Multicentre, randomised, controlled, open-label study comparing the efficacy and safety of slow repeated IV infusions of 2 doses of Doxorubicin-Transdrug™ (DT) (20mg/m² or 30mg/m²) to those of Best Standard of Care (BSC) in patients with advanced Hepatocellular Carcinoma (HCC) after failure or intolerance to Sorafenib.

ReLive study

Name	Position	Date	Signature
The Sponsor:			
[redacted]	Clinical Development Director		
Principal Investigator:			

The signature constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local and regulatory requirements and applicable US federal regulations, European regulations, other local regulations and ICH E6 Guidance for Good Clinical Practice.

SYNOPSIS

NAME OF COMPANY: **Onxeo** (formerly known as BioAlliance Pharma)	**NAME OF FINISHED PRODUCT: Doxorubicin Transdrug™ 10 mg**	**NAME OF ACTIVE INGREDIENT: Doxorubicin**

Study Title: Multicentre, randomised, controlled, open-label study comparing the efficacy and safety of slow repeated IV infusions of 2 doses of Doxorubicin Transdrug™ (DT) (20mg/m^2 or 30mg/m^2) to those of Best Standard of Care (BSC) in patients with advanced Hepatocellular Carcinoma (HCC) after failure or intolerance to Sorafenib. The ReLive Study

Study Code Number: BA2011/03/04

Objectives:

Primary objective :

- To compare the overall survival (OS) of repeated slow IV infusions of 20 mg/m² or 30 mg/m² DT to the Best Standard of Care (BSC) in patients with advanced HCC after failure or intolerance to Sorafenib.

Secondary objectives :

- To compare additional efficacy parameters as progression free-survival (PFS) and objective response rate;
- To determine the optimal dose of DT infusions;
- To evaluate the safety of DT;
- To assess PK parameters of DT at the doses of 20 and 30 mg/m^2;
- To evaluate pharmacodynamics parameters and predictive factors of safety and efficacy: relationship between efficacy and safety (clinical, biological…) parameters, concentrations of doxorubicin and blood biomarkers.
- To measure QoL using a generic health-related questionnaire

Methodology/Study Design:

Multicentre, open label, randomised, with 3 parallel groups study comparing DT 20 mg/m^2, DT 30 mg/m^2 to BSC

Phase: III

Number of Subjects: 130 patients per group for a total of 390 patients

Number of centres: around 100 centres

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria:

1. Male or non-pregnant, non-breast feeding female;
2. Aged ≥ 18 years;
3. Patients with
   - advanced HCC (BCLC-C according to BCLC staging classification) having progressed under Sorafenib therapy or intolerant to Sorafenib, or
   - intermediate HCC (BCLC-B) non eligible or non responders to transarterial chemoembolization (TACE), and having progressed under or intolerant to Sorafenib therapy;
4. Patients with porta hepatis lymph nodes, extrahepatic metastases, or portal/suprahepatic vein thrombosis without extension in inferior/superior vena cava, are eligible;
5. HCC diagnosed according to the AASLD and/or EASL criteria:

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- Radiological Criteria applicable in cirrhotic liver:
  - Nodule ≥ 10 mm: one imaging technique among MRI and CT-scan showing typical appearances for HCC defined as arterial enhancement and rapid washout in portal venous or delayed phase;
  - If appearance not typical for HCC on initial imaging: second contrast enhanced study (CT or MRI) showing typical appearances for HCC defined as arterial enhancement and rapid wash-out in portal venous or delayed phase;
- And/Or cyto-histology criteria (e.g. in case of atypical lesions for HCC at imaging, absence of cirrhosis);

6. Without cirrhosis or with a non decompensated cirrhosis (Child-Pugh score from A5 to B7 included);
7. ECOG Performance Status 0 or 1;
8. Adequate laboratory tests, in particular with:
   - Platelets ≥ 50,000 /mm^3
   - Neutrophil count ≥ 1000 /mm^3
   - Hemoglobin ≥ 10g/dL
   - Serum transaminases < 5 ULN (NCI/CTC grades 0, 1, or 2)
   - Alkaline phosphatases < 5 ULN (NCI/CTC grades 0, 1, or 2)
   - Serum bilirubin < 35 µM/L (or 2.0 mg/dL);
9. Signed and dated written informed consent form.

Exclusion criteria: Patients with any of the following criteria must not be included

1. Cirrhosis with a Child-Pugh score B8-C15;
2. Untreated chronic hepatitis B (in case of chronic hepatitis B, an efficacious antiviral treatment should have been started before randomisation to be included in the study);
3. Patients eligible for curative treatments (transplantation, surgical resection, percutaneous treatment);
4. Patients eligible for palliative treatments with demonstrated efficacy: TACE, sorafenib; Patients who failed to sorafenib treatment or intolerant to sorafenib are eligible and can be included if sorafenib has been stopped at least 2 weeks before randomisation;
5. Other prior malignancy without complete remission in the last five years, with the exception of adequately treated basal cell carcinoma or in situ cervical cancer; in case of other prior malignancy, the diagnosis of HCC has to be histologically proven;
6. HCC developed on transplanted liver;
7. Known HIV infection;
8. Risk of variceal bleeding - i.e. patients with stage 2-3 varices with fragility signs (patients at risk for variceal bleeding may be included after a preventive treatment (oesophageal varices ligation, beta blockers) has been administered); DT will not be administered in case of digestive bleeding in the 4 previous weeks;
9. SaO2 < 95%;
10. Presence of a significant acute or chronic respiratory disease defined as NCI /CTCAE > grade 2;
11. Presence of recent (< 6 months) or current cardiac failure (class II, III or IV NYHA classification), baseline LVEF < LLN by either cardiac ultrasound or cardiac scintigraphy; recent (< 6 months) acute coronary syndrome, clinically significant ECG abnormalities or recent (less than 6 months) acute vascular diseases (stroke, MI…);
12. Prior cumulative dose of 300 mg/m² of doxorubicin or equivalent;
13. Patients currently treated with immunosuppressive agents that cannot be stopped;
14. Patients whose medical or surgical conditions are unstable and may not allow the study completion or compliance, and especially patients with uncontrolled diabetes;
15. Uncontrolled systemic infection;
16. Patients with a life expectancy of less than 2 months;

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17. Patients who have received an experimental drug in another clinical trial in the last 30 days prior to randomisation in the present clinical trial;
18. Women of child-bearing age who are unwilling or unable to use an effective contraception method (oral contraception or intra-uterine device for woman) during the study treatment period and for 6 months after the last administration of study drug, and their male partner(s) refusing to use a condom (if applicable),
    Men who are unwilling or unable to use a condom during the study treatment period and for 6 months after the last administration of study drug, and their female partner(s) refusing to use one of the appropriate effective contraception methods (if applicable);
19. Patients unwilling or unable to comply with protocol requirements and scheduled visits.

Randomisation : Randomisation will be performed using IWRS with stratification per region

Drug Being Tested, Dose, Method of Administration :

Product name:	Doxorubicin Transdrug™ 10 mg (DT)
Unit dose:	Two dose levels: 20 mg/m^2 and 30 mg/m^2
Regimen:	Once every 4 weeks
Mode/route:	Slow IV Infusion over 6 hours

Study treatment period:

1. The patients randomised in Doxorubicin Transdrug™ groups will be hospitalized or will have an outpatient visit on D0 to check eligibility criteria for continuing treatment and to ensure that the premedication will be taken. Patient will receive DT infusion on D1 and will be hospitalized until D2. Patient could be discharged on D2 or on D3 in the absence of toxicity. Study treatment will be repetead every 4 weeks until unequivocal progression (assessed by the investigator) or unacceptable toxicity. Study visits will be performed at the beginning of each cycle, at day 14 of each cycle and one month after the last study drug administration (end of study visit).
2. The patients randomised in control group will receive the Best Standard of Care per local practice. Study visits in the control group will be performed at the same schedule than in the DT arms on each cycle initiation, day 14 and one month after the last study drug administration (end of study visit).

Duration of Treatment:
In all groups, until disease progression or unacceptable toxicity. For patient randomised in Doxorubicin Transdrug™ group, the total dose of Doxorubicin or equivalent will not exceed 550 mg/m^2 (this takes into account prior anthracyclins cumulative dose and DT cumulative dose).

Follow-up period:

Follow-up survival status of all patients (including patients who prematurely withdraw) will be maintained every 3 months until death. The follow-up period is defined as “until 2 years after the Last Patient In”.

Criteria for Evaluation:

Primary endpoint: Overall survival (OS)

Secondary efficacy endpoints:

- Progression-free survival (PFS) by the Independent Radiological Review according to RECIST 1.1;

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- Objective Response Rate (ORR) by the Independent Radiological Review according to RECIST 1.1

Exploratory efficacy endpoints*:

- Progression-free survival by the investigator's evaluation according to RECIST 1.1;
- Objective Response Rate by the investigator's evaluation according to RECIST 1.1;
- Time To Progression (TTP), Best Overall Response and Disease Control Rate;
- Time to Objective Response and Duration of Response;
- Evolution in serum α-fœtoprotein levels (AFP).

*PFS and ORR will be analyzed by the investigator evaluation according to RECIST 1.1 and according to modified RECIST for HCC (if possible), and by the Independent Radiological Review according to the modified RECIST for HCC (if possible). TTP, Best Overall Response, Disease Control Rate, time to objective response and duration of response will be analyzed by the Investigator Evaluation and by the Independent Radiological Review, according to RECIST 1.1 and according to modified RECIST for HCC (if possible).

Safety endpoints:

Respiratory:
- Incidence and duration of reduction of SaO2 during DT infusion (in DT arms);
- Incidence and severity of respiratory events;

Cardiac
- Incidence and severity of cardiovascular events (including BP and HR);
- ECG and LVEF change;

Overall
- Incidence and severity of all TEAEs and SAEs according to NCI-CTCAE v4.0 scale;
- Biological (haematology and biochemistry analyses, and particularly AST/ALT, WBC).

Pharmacokinetic endpoints (in selected sites for PK):

- Pharmacokinetic profile of Doxorubicin and its metabolites;
- Relationship between efficacy and safety (e.g., clinical, biological) parameters, concentrations of total and free doxorubicin and doxorubicinol and blood biomarkers

Quality of Life:
- EuroQoL EQ-5D questionnaire to be completed by patients during the study treatment period: at baseline, then every 2 cycles and finally, at progression or at the latest, if treatment is stopped for other-than-progression reasons (e.g., end of study visit)

Statistical methods: **Sample size calculation and main efficacy analyses**

The study primarily aims at demonstrating the efficacy of a 6-hour slow DT infusion in patients with advanced HCC after failure or intolerance to Sorafenib.

Sample Size Calculation:

Overall population:

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Under the assumptions of a median survival of the control group of 8 months and a hazard ratio of 0.69, the required total sample size to achieve a 85% power to compare the experimental group (pooled DT 20mg/m^2 and DT 30mg/m^2 groups) versus BSC with a significance level of 2.5% one sided is 348 patients in the ITT population (116 patients in the BSC group and 232 patients in DT groups). It is expected that 10% of patients will be lost to follow-up; this leads to a calculated total sample size of 390 randomised patients.

Child Pugh A population (85% of the patient population):

Under the assumptions of a median survival of the control group of 9 months and a hazard ratio of 0.68, the required total sample size to achieve a 80% power to compare experimental group (pooled DT 20mg/m^2 and DT 30mg/m^2 groups) versus BSC with a significance level of 2.5% one sided is 291 patients in the ITT Child Pugh A population (97 patients in the BSC group and 194 patients in DT groups). It is expected that 10% of patients will be lost to follow-up; this requires for a calculated total sample size of 324 ITT Child Pugh A randomised patients.

Main efficacy analyses:

Results will be presented by treatment group and with all treatment groups pooled.

The primary endpoint is overall survival in the ITT population (all randomized patients). The 95% confidence intervals for hazard ratios and median times will be constructed and the Kaplan-Meier method will be used and plotted as curves by treatment group (pooled DT 20mg/m^2 and DT 30mg/m^2 groups) versus BSC group. The comparison between experimental group and BSC group will be made using the unstratified LogRank test. The analysis will be performed when 285 events have been observed.

The hierarchical sequential closed test procedure will be used to control the overall type I error rate of 5% to evaluate first the OS primary endpoint in the ITT overall population, then if statistically significant, the OS primary endpoint in ITT Child Pugh A population and then if statistically significant, the two main secondary endpoints (PFS and OOR) in the ITT Child Pugh A population.

To determine the optimal dose of DT between 20mg/m^2 or 30 mg/m^2, all statistical analyses (efficacy and safety) will be repeated as exploratory in the DT 20mg/m^2 group alone versus BSC and DT 30mg/m^2 group alone versus BSC. The dose of DT which presents the best benefit/risk ratio will be selected.

For secondary and exploratory endpoints, all time to event endpoints will be estimated using the Kaplan-Meier method and plotted as curves by treatment groups. The comparisons between DT groups and BSC will be made using LogRank tests. Proportion of subjects with objective response, disease control… will be compared between DT groups and BSC by the chi-square test. Estimates and 95% confidence intervals for the difference in proportions between DT groups and BSC will be provided. Estimate and confidence intervals for the odds-ratio will also be provided.

Data and Safety Monitoring Board (DSMB):

An independent DSMB will be organized to regularly evaluate the safety of DT during the study. The DSMB will be regularly provided with safety data. Safety data will be provided by patient and by treatment group with relevant information every 75 patients (around 25 patients/group) or at least twice a year. The DSMB will remain blinded for its evaluation but may ask for unblinding if required. The DSMB will receive every serious adverse

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events within 24 hours and will recommend to continue or halt the recruitment in case of serious and related adverse events in the respective cohort.

Following their risk evaluation, the DSMB reserves the possibility of alerting the Sponsor in the event of observation of highly unexpected events. The DSMB may request a futility analysis on the primary criterion of overall survival. This futility analysis serves one objective: to recommend the potential discontinuation when it is unlikely, based on the interim results, to achieve statistically significant results at the end of the study. This futility analysis will be realized under the responsibility of the DSMB statistician. The results of this futility analysis will be disclosed only to DSMB members. No one in the Sponsor representatives has access to such information. No information about these results will be communicated to investigators and the International Coordinating Investigator.

Study Timelines:
Study Duration (FPI to final primary endpoint analysis) : 5 years
Start date (FPI): Quarter 2 2012
End of recruitment date (LPI): anticipated End 2016/Q1 2017
Final primary endpoint analysis): anticipated 2017
End of Study: End of overall survival follow-up period defined as 2 years after LPI; anticipated Q1 2019

Safety measures:

For patients randomised in the DT groups:

Premedication will be administered during three consecutive days starting one day before DT administration. It will consist of methylprednisolone 32 mg (or equivalent) + cetirizine 20 mg (or equivalent) per day.

SaO_2 will be monitored during 24 hours as follows:

- During the 6-hour DT infusion
  - Continuous monitoring of SaO_2:
    - If $SaO_2 < 93\%$ → reduction of DT infusion rate by half. No changes in dose;
    - If $SaO_2 \leq 90\%$ → immediate and definitive infusion stop;
  - Monitoring of respiratory symptoms:
    - In case of a respiratory symptom (dyspnoea, increase in respiratory rate by 5 beats/min and RR > 20/min) → reduction of DT infusion rate by half. No changes in dose;
    - In case of persistence of symptoms within 1 hour → immediate and definitive infusion stop.
- After the end of DT infusion.
  - In case of marked decrease in SaO2 or occurrence of respiratory symptoms, the patient should be transferred to intensive care unit for monitoring and treatment up to recovery.

In case of SaO_2 decrease ($\leq 90\%$) during or after DT infusion, SaO_2 will be closely monitored and collected every hour until resolution to $SaO_2 \geq 93\%$.

Patients with a respiratory adverse event during a previous DT infusion who remain eligible to continue DT treatment will have reinforced respiratory safety measures for each additional DT infusions and SaO_2 collected every hour during infusion and within the 6 hours after the end of infusion.

The recommended treatment of drug-induced pneumonitis is based on systemic corticosteroids with methylprednisolone 1 g/day for 3 days in patients with respiratory failure or lower doses of corticosteroids (i.e

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methylprednisolone 60 mg every 6 hours) in less severe cases. Before initiating corticosteroid therapy, an infectious etiology must be excluded. Supportive care, bronchodilators, IV fluid, vasopressors, and mechanical ventilation could be indicated in patients with severe hypersensitivity reactions and circulatory collapse.

In case of ARDS and/or any related life-threatening respiratory serious adverse event, DT study therapy will be definitively stopped (i.e. patient will not receive any additional DT infusion).

Before each additional DT infusions, the following criteria must be met:

- Adequate liver function :
  - Child-Pugh score from A5 to B7 included (if cirrhosis)
  - Serum bilirubin < 35 µM/L (or 2.0 mg/dL)
- Adequate respiratory function defined as $SaO_2 \geq 95\%$;
- Absence of ongoing infection
- Adequate haematologic tests :
  - Neutrophil count ≥ 1000 /mm^3
  - Platelets count $\geq 50{,}000$ /mm^3
  - Haemoglobin ≥ 10 g/dL
- No clinical evidence of upper gastrointestinal bleeding
- No other limiting toxicity > grade 2

In case of grade 3-4 AE, infusion should be delayed up to 4 weeks until resolution or recovery to CTC grade ≤ 2.

For patients randomised in the BSC group

For patients enrolled in the BSC group, safety measure will be done according to the specificity of the Standard of Care and the local practice.

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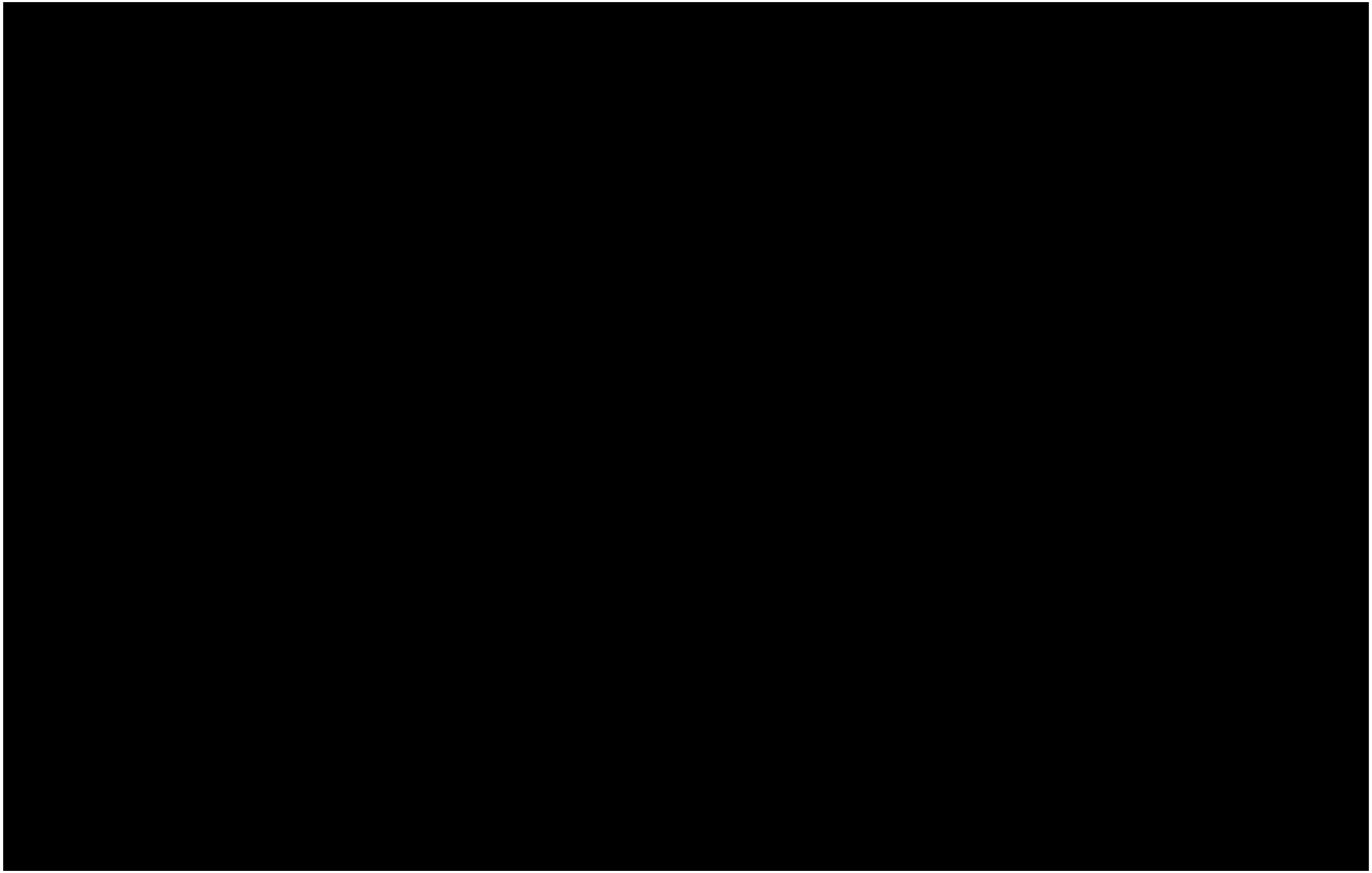

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AASLD	American Association for Study of Liver Diseases
AE	Adverse Event
AFP	Alpha foetoprotein
ALD	Alcoholic Liver Diseases
ALP	Alkaline Phosphatase
ALT	SGPT or GPT, Alanine Transaminase
AML	Acute Myeloide Leukemia
ARDS	Acute Respiratory Distress Syndrom
AST	SGOT or GOT, Aspartate Transaminase
AUC	Area Under the Curve
BCLC	Barcelona Clinic Liver Cancer
BP	Blood Pressure
BSA	Body Surface Area
BSC	Best Standard of Care
BW	Body Weight
°C	Celsius degree
CBC	Complete Blood Counts
CHF	Congestive Heart Failure
CI	Confidence Interval
Cl	Clearance
CLD	Chronic Liver Disease
CLIP	Cancer of the Liver Italian Program
CK	Creatinin Protein Kinase
CR	Complete Response
CRA	Clinical Research Assistant
e-CRF	Electronic Case Report Form
CRP	C-Reactive Protein
CT	Computed Tomography
CTC	Common Toxicity Criteria
CT scan	Computed tomography Scanner
CV	Coefficient of Variation
D	Day
DCR	Disease Control Rate
DLCO	Carbon Monoxide Diffusing Capacity
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board

DT	Doxorubicin-Transdrug™ 10mg
EASL	European Association for the Study of the Liver
EC	Ethic Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic acid
FEV_1	Forced Expiratory Volume in one second
GCP	Good Clinical practice
GGT	Gamma Glutamyl Transferase
H	Hours
Hb	Hemoglobin
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
β-HCG	Human Chorionic Gonadotropin
Hct	Hematocrit
HCV	Hepatite C virus
HIA	Hepatic intra-Arterial
HIV	Human immunodeficiency virus
HR	Heart Rate
IA	Intra Arterial
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IC50	Half maximal Inhibitory Concentration
IEC	Independent Ethic Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
ITT	Intent To Treat
IV	Intra-venous
IWRS	Interactive Web Response System
LDH	Lactate Deshydrogenase
LVEF	Left Ventricular Ejection Fraction
MDR	Multidrug Resistance
MedDRA	Medical Dictionary for Regulatory Affairs
MELD	Model for End-stage Liver Disease
MI	Myocardial infarction
µg	Microgram
MRI	Magnetic Resonance Imaging
MRP	Multidrug Resistance associated Protein
MTD	Maximale Tolerate Dose

NASH	Non Alcoholic Steato-Hepatitis
NCI/CTC	National Cancer Institute/Common Toxicity Criteria
NE	Not Evaluable
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall Survival
PCT	Percutaneous Treatment
PD	Progressive Disease
PFS	Progression Free Survival
Pgp	P-glycoprotein
[redacted]	[redacted]
PK	Pharmacokinetics
p.o.	Per Os
PP	Per Protocol
PR	Partial Response
PS	Performance Status
RECIST	Response Evaluation Criteria In Solid Tumour
RF	RadioFrequency
RFA	Radio Frequency Ablation
RR	Respiratory Rate
SAE	Serious Adverse Event
SaO_2	Oxygen saturation
SAP	Statistic Analysis Plan
SD	Stable Disease
SmPC	Summary of Product Characteristics
TACE	Trans Arterial ChemoEmbolisation
TEAE	Treatment Emergent Adverse Event
TNM staging system	Tumor lymph Node Metastasis staging system
TTP	Time To Progression
ULN	Upper Limit Normal
VS	Versus
WBC	White Blood Cells
WHO	World Health Organization

Table of Contents

1 INTRODUCTION

1.1 Background

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1.2 Rationale

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2 TRIAL OBJECTIVES

2.1 Primary objective

To compare the efficacy of repeated slow IV infusions of DT at doses of 20 mg/m² or 30 mg/m² to Best Standard of Care (BSC) in patients with advanced HCC after failure or intolerance to Sorafenib on overall survival (OS).

2.2 Secondary objectives

- To compare DT and BSC in additional efficacy parameters as progression free-survival (PFS) and objective response rate,
- To determine the optimal dose of DT infusions;
- To evaluate the safety of DT;
- To assess PK parameters of DT at the doses of 20 and 30 mg/m^2;
- To evaluate pharmacodynamics parameters and predictive factors of safety and efficacy.
- To measure QoL using a generic health-related questionnaire

3 TRIAL DESIGN

This is a multicentre, open-label, randomised, comparative, 3 arms (DT 20 mg/m², DT 30 mg/m², Best Standard of Care) study in patients suffering from hepatocellular carcinoma.

The study will be carried out at multiple hepatology or oncology centres that manage patients with HCC with or without cirrhosis. Approximately 100 centres will be involved in the trial.

Based on the survival data obtained in the phase II clinical trial, it has been calculated that 390 patients have to be included to adequately compare the efficacy of DT 20 mg/m² and DT 30 mg/m² to that of BSC.

A safety evaluation will be carried out on a regular basis at least twice a year by the Data Safety Monitoring Board (DSMB) and every 75 patients (around 25 patients/group) whichever comes first.

Patients who meet the inclusion/exclusion criteria will be randomised according to a 1:1:1 ratio to receive either DT 20 mg/m², DT 30 mg/m², or BSC. Only those patients whose survival expectations is longer than 2 months and could receive more than 1 DT infusion will be enrolled.

The study duration for each patient includes a screening period of 28 +/- 2 days maximum before baseline visit (D0 Cycle 1). The patient will then be randomised to receive either DT 20 mg/m² or DT 30 mg/m² as protracted IV infusion over 6 hours once every 4 weeks or BSC.

Patients will receive study therapy until unequivocal tumour progression (assessed by the investigator) or occurrence of unacceptable toxicity.

All patients will be evaluated by CT scan or MRI every 2 months for tumour assessements.

After study therapy discontinuation, an end of study visit will be performed 1 month +/- 7 days after the last DT infusion or last BSC treatment.

Then, a follow up of all patients (including those who withdrew prematurely from the study) will be maintained every 3 months until death. The following information will be recorded:

- Survival (patient alive or deceased)
- Date of progression (in the case of withdrawal for other reason than progression during the study treatment period)
- Administration of any other anti-cancer treatment.

The follow-up period is defined as “until 2 years after Last Patient In”.

4 SUBJECT SELECTION

The study will be carried out in patients suffering from advanced hepatocellular carcinoma (HCC), who meet all the inclusion and exclusion criteria presented in sections 4.1 and 4.2.

4.1 Inclusion Criteria

All patients included in the study will have to meet the following criteria for inclusion in the study:

1. Male or non-pregnant, non-breast feeding female;
2. Aged ≥ 18 years;
3. Patients with:
   - advanced HCC (BCLC-C according to BCLC staging classification) having progressed under Sorafenib therapy or intolerant to Sorafenib, or;
   - intermediate HCC (BCLC-B) non eligible or non responders to transarterial chemoembolization (TACE), and having progressed under or intolerant to Sorafenib therapy;
4. Patients with porta hepatis lymph nodes, extrahepatic metastases, or portal/suprahepatic vein thrombosis without extension in inferior/superior vena cava, are eligible;
5. HCC diagnosed according to the AASLD and/or EASL criteria:
   - Radiological Criteria applicable in cirrhotic liver:
     - Nodule ≥ 10 mm: one imaging technique among MRI and CT scan showing typical appearances for HCC defined as arterial enhancement and rapid washout in portal venous or delayed phase;
     - If appearance not typical for HCC on initial imaging: second contrast enhanced study (CT or MRI) showing typical appearances for HCC defined as arterial enhancement and rapid wash-out in portal venous or delayed phase;
   - And/Or cyto-histology criteria (e.g. in case of atypical lesions for HCC at imaging, absence of cirrhosis);
6. Without cirrhosis or with a non decompensated cirrhosis (Child-Pugh score from A5 to B7 included (appendix II));
7. ECOG Performance Status 0 or 1 (appendix IV);
8. Adequate laboratory tests, in particular with:
   - Platelets ≥ 50,000/mm^3
   - Neutrophil count ≥ 1000/mm^3
   - Haemoglobin ≥ 10g/dL
   - Serum transaminases < 5 ULN (NCI/CTC grades 0, 1, or 2)
   - Alkaline phosphatases < 5 ULN (NCI/CTC grades 0, 1, or 2)
   - Serum bilirubin < 35 µM/L (or 2.0 mg/dL)
9. Having given a written informed consent.

4.2 Exclusion Criteria

Exclusion criteria are as follows:

1. Cirrhosis with a Child Pugh score B8-C15;
2. Untreated chronic hepatitis B (in case of chronic hepatitis B, an efficacious antiviral treatment should be prescribed before randomisation to be included in the study);
3. Patients eligible for curative treatments (transplantation, surgical resection, percutaneous treatment);
4. Patients eligible for other efficacious treatments: TACE, Sorafenib. Patients who failed to Sorafenib treatment or intolerant to Sorafenib are eligible and can be included if Sorafenib has been stopped at least 2 weeks before randomisation;
5. Other prior malignancy without complete remission in the last five years with the exception of adequately treated basal cell carcinoma or in situ cervical cancer. In case of other prior malignancy, the diagnosis of HCC has to be histologically proven;
6. HCC developed on transplanted liver;
7. Known HIV infection;
8. Risk of variceal bleeding - i.e. patients with stage 2-3 varices with fragility signs (patients at risk for variceal bleeding) may be included after a preventive treatment (oesophageal varices ligation, beta blockers) has been administered; DT will not be administered in case of digestive bleeding in the 4 previous weeks;
9. SaO2 < 95%;
10. Presence of a significant acute or chronic respiratory disease defined as NCI /CTCAE > grade 2;
11. Presence of recent (< 6 months) or current cardiac failure (class II, III or IV NYHA classification), baseline LVEF < LLN by either cardiac ultrasound or cardiac scintigraphy, recent (< 6 months) acute coronary syndrome, clinically significant ECG abnormalities or recent (less than 6 months) acute vascular diseases (stroke, MI…);
12. Previous cumulative dose of > 300 mg/m² of doxorubicin (or equivalent);
13. Patients currently treated with immunosuppressive agents that cannot be stopped;
14. Patient whose medical or surgical conditions are unstable and may not allow the study completion or compliance, and specially patients with uncontrolled diabetes;
15. Uncontrolled systemic infection;
16. Patient with a life expectancy of less than 2 months;
17. Patients who have received an experimental drug in another clinical trial in the last 30 days prior to randomisation in the present clinical trial;
18. (a) Women of child-bearing age who are unwilling or unable to use an effective contraception method (oral contraception or intra-uterine device for woman) during the study treatment period and for 6 months after the last administration of study drug, and their male partner(s) refusing to use a condom (if applicable),

    (b) Men who are unwilling or unable to use a condom during the study treatment period and for 6 months after the last administration of study drug, and their female partner(s) refusing to use one of the appropriate effective contraception method (if applicable);
19. Patients unwilling or unable to comply with protocol requirements and scheduled visits.

4.3 Patient Registration

Enrollment will occur after informed consent has been obtained and all screening assessments have been performed.

The assignment of number and code for patient's identification will ensure patient's anonymity. Patients will be assigned a sequential patient number in each center and will be identified by:

- The identification center number (a 3-digit number)
- The patient number (a 4-digit number); these four numbers being allocated according to the sequence of presentation for trial participation in each centre.

As soon as a potential patient is screened by an investigational centre, the investigator will have to complete the eCRF. If needed, he may contact Onxeo (formerly known as BioAlliance Pharma) or its representative in order to review the inclusion criteria.

ONXEO
(formerly known as BioAlliance Pharma)

[redacted]

If eligibility criteria are met, patients will be included, randomised in one of the three groups :

- Doxorubicin Transdrug™ at 20mg/ m²
- Or Doxorubicin Transdrug™ at 30 mg/m².
- or Best Standard of Care.

Randomisation will be performed using IWRS with stratification on region (Europe versus United States versus other countries (Turkey, Egypt, Lebanon, Saudi Arabia)).

4.4 Subject Premature Withdrawal

In accordance with the Declaration of Helsinki as amended from time to time, subjects are free to withdraw from the study at any time if they wish so, for any reason specified or unspecified.

The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient should be discontinued from the study and Onxeo (formerly known as BioAlliance Pharma) or its designee must be contacted. An exception may be granted in rare circumstances where there is a compelling ethical reason to allow the patient to continue taking study drug. In these rare cases, the investigator must obtain documented approval from the Onxeo (formerly known as BioAlliance Pharma) medical monitor to allow the patient to continue in the study.

In addition, a patient's participation may also be discontinued at any time at the discretion of the investigator or Sponsor. The following are some of the potential reasons that could lead the investigator or sponsor to remove a patient from the study drug or the study, or both:

- The investigator believes that a change of therapy would be in the best interest of the patient (e.g. the patient needs to be treated, for any reason, with another anti cancer therapy);
- The patient experiences an intolerable AE. An intolerable AE is an event that, even with optimal treatment, causes such discomfort or disability that the patient is unable or unwilling to continue further study participation
- The patient is non compliant with study requirements
- The patient becomes pregnant during the study or fails to use adequate birth control (for those patients who are able to conceive)
- The patient requires a medication prohibited by the study protocol
- The Sponsor decides to terminate the trial

The reason for withdrawal will have to be recorded in the e-CRF for all withdrawn subjects.

The e-CRF has to be completed until the time of drop out. All drop outs after the first intake of investigational product should be given a post-study assessment as appropriate.The premature termination form in the e-CRF must be completed for all drop outs. The survival status of all patients (including patients prematurely withdrawn) will be collected every 3 months until death with the follow-up contact

5 ENDPOINTS and ASSESSMENTS

5.1 Primary endpoint

[redacted]

5.2 Secondary efficacy endpoints

[redacted]

5.3 Exploratory efficacy endpoints

[redacted]

[redacted]

5.4 Safety endpoints

[redacted]

5.5 Pharmacokinetic endpoints

[redacted]

5.6 Quality of life

[redacted]

6 TRIAL TREATMENTS

6.1 Allocation to Treatment

Patients will be assigned identification numbers as described in section 4.3.

6.2 Drug Supplies

Doxorubicin Trandrug (DT) will be supplied by the Sponsor as an investigational medicinal product (IMP). The IMP will be packaged, labeled and released according to current good manufacturing practice (GMP) guidelines, GCP guidelines and national legal requirements (as applicable).

In the control group, patients will receive the usual standard of care as decided by the investigator. The standard of care treatment will be handled, used and stored according to local's practice.

DT Formulation and Packaging

[redacted] for suspension for injection that is to be reconstituted with 25 mL of glucose 2,5% for injection and filtered. See Appendix VII for details on study drug preparation procedures:

Name	Doxorubicin Transdrug™ 10 mg
INN	Doxorubicin
Excipients	[redacted]
Pharmaceutical Form	powder for suspension for injection
Route of Administration	Intravenous
Method of Administration	Slow IV infusion of 6 hours
Dosage Strength and Form	10 mg/vial
Name of Manufacturing Laboratory	[redacted]
Packaging	[redacted]
Distribution	[redacted]
Storage	5°C ± 3°C

DT Dispensing

The investigational products will be sent from [redacted] to the pharmacy of each investigational centre, which will ensure storage, dispensation and the reconstitution for each Cycle.

6.3 DT Administration

In DT groups, based on DSMB recommendation after their careful review of the safety profile reported in the first 75 patients, a shorter period of hospitalization could be recommended since

version 5.0, June 10th, 2014 as compared to the previous protocol version. The premedication will be unchanged as compared to the previous protocol version and administered to the patient according to each centre's usual practice. On D0, one day before each DT administration, patient will be hospitalized or will have an outpatient visit to check eligibility criteria for continuing treatment and to ensure that the premedication is taken. Patient will receive DT infusion on D1 and will be hospitalized until D2. Patient could be discharged on D2 or on D3 in the absence of toxicity. Hospitalization until D3 is optional.

Hospitalization or outpatient visit on D0 and prolonged hospitalization until D3 will be adapted according to hospital practice and/or patient preference.

Day 0 defined as one day before the treatment with DT

- Premedication with methylprednisolone 32 mg p.o. (or equivalent) and cetirizine 20 mg p.o.(or equivalent);

Day 1 : Day of therapy with DT

- H-1: premedication with methylprednisolone 32 mg p.o. (or equivalent) and cetirizine 20 mg p.o.(or equivalent);
- Fasting is not needed;
- **H0:** 20 mg/m² or 30 mg/m² of DT will be prepared and infused over 6 hours through intravenous route (Appendix VII).
- Patient will have a continuous SaO_2 monitoring during infusion and the 24 hours after the infusion start.

Any modification in the infusion rate must be recorded in the e-CRF (see section 7.6: safety measures).

Day 2 : The day after the DT therapy:

- Premedication with methylprednisolone 32 mg p.o. (or equivalent) and cetirizine 20 mg p.o.(or equivalent);

D0 = D28

Each Cycle will be repeated every 28 days up to progression or toxicity.

6.4 Best Standard of Care administration

The patient in BSC group will be treated and monitored according to the centre's usual practice. Patients will receive BSC as judged by their treating physician. Those therapies considered acceptable include, but are not limited to, anticancer therapy and/or supportive care (e.g. antibiotics, analgesics, antiemetics, ascitis drainage, blood transfusions, and/or nutritional support (enteral or parenteral)). If it is unclear whether a therapy would be regarded as BSC, Onxeo (formerly known as BioAlliance Pharma) should be consulted.

6.5 Compliance

Patients in the DT arm need to be hospitalised at the investigational site to receive the study therapy. Patients in the control arm may not be hospitalized if the local pratice doesn't require hospitalisation for the study therapy administration. However, per protocol, they should comply with the planned visits on days 1 and 14 of each cycle.

For the DT groups : the drug accountability will be assessed by recording the dispensation of treatment. The investigator and/or the hospital pharmacist must keep an up-to-date drug dispensing log containing the following information:

- Identification of the patient to whom the medication was dispensed
- Dates of the study drug administered to the patient
- The total dose administered to the patient

The investigator or the hospital pharmacist must only use DT for patients participating in the study.

For BSC group: The patient will be treated according to the centre's usual practice and no drug accountability is required. Any treatment administered to the patient (usual supportive care and/or anticancer treatment) will be recorded in the e-CRF.

6.6 Dose adjustment, dose delay and infusion duration

6.6.1 Dose Adjustment: DT Arms

Dose adjustement will be based upon haematologic and non haematologic toxicities observed after the previous dose administration.

All dose reductions for patients randomised to receive either treatment A (DT 20 mg/m^2) or B (DT 30 mg/m^2) will be calculated based upon the following dose level reduction guidelines.

Dose level reduction guidelines:

Arm A (DT 20 mg/m^2)

Initial Dose Level	20 mg/m^2
Dose Level -1	15 mg/m^2

Arm B (DT 30 mg/m^2)

Initial Dose Level	30 mg/m^2
Dose Level -1	20 mg/m^2
Dose Level -2	15 mg/m^2

Haematologic criteria for dose modifications:

- In case of grade 3 (500 – 1000/mm^3) or grade 4 (< 500/mm^3) neutropenia whatever the duration of neutropenia and/or in case of grade 3 (25 000 – 50 000/mm^3) or grade 4 (< 25 000/mm^3) thrombocytopenia, DT will be interrupted until resolution to a grade ≤ 2.

A new cycle of DT could be administered only if neutrophil count ≥ grade 2 (≥ 1000 /mm^3) and platelets count ≥ grade 2 (≥ 50,000 /mm^3).

- In case of grade 4 neutropenia (< 500/mm^3) lasting > 7 days, grade 4 febrile neutropenia of any duration and grade 4 thrombocytopenia (< 25,000/mm^3), the dose to be administered will be the minus 1 dose level (refer to the table below).
- If the haematologic toxicity has not returned to grade ≤ 2, the cycle will be delayed to a maximum of 4 weeks. In case of persistent (more than 4 weeks) haematologic toxicity > grade 2, the treatment should be definitively stopped (i.e. patient will not receive any additional DT infusion.
- Any patient who requires a dose reduction will be treated with a reduced dose for any subsequent doses.
- Arm A patients requiring dose reductions below dose level -1 must discontinue. Arm B patients requiring dose reduction below dose level -2 must discontinue.

DT dose level decrease in case of haematologic toxicity recovering to grade ≤ 2

Drug Related Toxicity	DT dose level
Grade 4 neutropenia (< 500/mm^3) lasting > 7 days	Decrease 1 level
Grade 4 Febrile neutropenia of any duration	Decrease 1 level
Grade 4 thrombocytopenia (< 25,000/mm^3)	Decrease 1 level

Non haematologic criteria for dose modifications:

- In case of ARDS, the patient will be definitively stopped from the DT therapy (i.e. patient will not receive any additional DT infusion).
- In case of life-threatening serious and non haematologic AE related to DT, the treatment will be definitively stopped (i.e. patient will not receive any additional DT infusion).
- In case of grade 3 or grade 4 non haematologic toxicity related to DT (e.g. nausea/vomiting, stomatitis, asthenia… despite adequate/maximal medical intervention and/or prophylaxis), a resolution to a grade ≤ 2 has to be observed to initiate a new cycle. The dose to be administered will be the minus 1 dose level. If the non haematologic toxicity has not returned to grade ≤ 2, the cycle will be delayed to a maximum of 4 weeks. In case of persistent (more than 4 weeks) non haematologic toxicity > Grade 2, the treatment should be definitively stopped (i.e. patient will not receive any additional DT infusion.

Any patient who requires a dose reduction will be treated with a reduced dose for any subsequent doses.

Arm A patients requiring dose reductions below dose level -1 must discontinue. Arm B patients requiring dose reduction below dose level -2 must discontinue.

6.6.2 Dose Delay: DT arms

To initiate a new DT infusion, the patient needs to meet the following continuing treatment criteria:

- Adequate liver function:
  - Child-Pugh score from A5 to B7 included (if cirrhosis)
  - Serum bilirubin < 35 µM/L (or 2.0 mg/dL)
- Adequate respiratory function defined as $SaO_2 \geq 95\%$;
- Absence of ongoing infection
- Adequate haematologic tests :
  - Neutrophil count ≥ 1000 /mm^3
  - Platelets count $\geq 50{,}000$ /mm^3
  - Haemoglobin ≥ 10 g/dL
- No clinical evidence of upper gastrointestinal bleeding
- No other limiting toxicity > grade 2

If one of these criteria is not met, the next infusion should be delayed for a maximum of four weeks. In case one of these criteria is not met after the 4 weeks delay, the patient will be withdrawn from the study treatment period and the end of therapy notification form will be completed.

6.6.3 DT Infusion duration

DT will be administered as a protracted i.v infusion during 6 consecutive hours. That infusion duration will be prolonged up to 12 consecutive hours if any of the condition described in section 7.6 occurs. In case of accidental infusion acceleration, i.e accidental infusion duration ≤ 2 hours, urgent safety precautions should be rapidly available at the patient bedside. Those measures include, but are not limited to, mechanical respirator and supplemental oxygen, i.v corticosteroids, i.v antibiotics if infection is suspected.

The maximum allowed cumulative dose of doxorubicin (or equivalent) is < or equal to 550 mg/m² (this takes into account prior anthracyclins cumulative dose and DT cumulative dose).

6.6.4 Best Standard of Care Arm

Throughout the study, dose adjustement or delay in the BSC arm will be based upon the specific standard of care and according to local pratice.

6.7 Drug Storage and Drug Accountability

The investigational product (DT) will be stored in a secure limited access area at 5°C± 3°C. The pharmacist at the trial centre will be responsible for the correct storage, handling of the study products and for all the documentation on drug supplies.

A drug movement form of all investigationals products dispensed during the study will be maintained.

All investigational materials (medication and packaging) unused in the study will be returned to [redacted] (or its designee) before, or at the termination of the study, together with an accountability form.

All DT administered units will be destroyed on site, according to routine hospital practice and current national guidelines/regulations.

6.8 Concomitant Medication(s)

As doxorubicin is metabolized by the liver and is a subtrate of CYP3A4, CYP2D6 and P-gp, the concurrent use of inhibitors or inducers of CYP3A4, CYP2D6 and P-gp should be used with caution and based on the benefit/risk for the patient. A list of the most commun CYP3A4, CYP2D6, P-gp inhibitors or inducers is provided in appendix XII. All treatments administered and date of administration must be recorded in the e-CRF. Use of any concomitant medication will be recorded in the e-CRF with the following information:

- reason for treatment;
- name of the drug, type of formulation, and unit strength;
- dose administered;
- duration of treatment.

6.9 Prohibited Medications during the study therapy

The following treatments are not allowed at inclusion and during treatment period :

- For all patients :
  - Other investigational drugs;
  - Sorafenib;

- Only for patients randomised in the Doxorobucin Transdrug™ groups:
  - TACE;
  - Loco-regional treatment (Percutaneous ethanol...);
  - Cytotoxic drugs;
  - Interferon;
  - Recently introduced statins (less than 1 month);
  - Hormone therapy.

6.10 Post study therapy

No cross over to DT is allowed for the patients enrolled in the control arm. After disease progression, patients in both arms will be allowed to receive any anti cancer therapy as deemed appropriate by the investigator including Sorafenib. Post anticancer therapy will be recorded in the eCRF.

7 TRIAL PROCEDURES

7.1 Screening (Day-28 to Day-1)

Within 28 days (± 2 days) before baseline visit (D0 Cycle 1), all patients (DT groups and control group) will have the following investigations performed after collection of signed and dated Informed Consent form (ICF).

- Medical history and demographic data: including HCC history with staging information (Child-Pugh (appendix II), CLIP (appendix III), MELD (appendix III) and BCLC (appendix I)), prior treatments;
- Concomitant diseases and medications will be recorded;
- Physical examination: a full physical examination will be performed: height, body weight (BW) and ECOG performance status (appendix IV) will be recorded;
- Vitals signs: subject's vital signs will be recorded after a rest of at least 5 minutes: Blood pressure (BP), Heart rate (HR), Respiratory rate (RR), Oxygen saturation (SaO_2), body temperature in °C;
- ECG recording: print-outs for each ECG will include: date, time, initials of the investigator or its deputy, at least 2 complexes for each lead and V_5 for monitoring HR and cardiac conduct changes. The corresponding source data will consist on the cardiograph paper print-outs;

- Left ventricular ejection fraction (LVEF) evaluation using cardiac ultrasound or cardiac scintigraphy; the same technique for the same patient is recommended throughout the study;
- Respiratory Function Tests: vital capacity (VC), total lung capacity, carbon monoxide diffusing capacity (DLCO), Forced Expiratory Volume in one second (FEV_1);
- Clinical laboratory tests:
    - Haematology: complete blood counts (CBC), platelets count;
    - Biochemistry: AST, ALT, GGT, ALP, total bilirubin, albumin, protein electrophoresis, ferritin, CRP, LDH, CPK;
    - Na^+, Cl^-, K^+, $HCO3^-$, urea and creatinine;
    - Coagulation: INR/Prothrombin, Factor V;
    - Calcium and phosphorus;
    - Metabolism : Total cholesterol, triglycerides, glycaemia;
    - α-foetoprotein (AFP);
    - Serum β-HCG for women of childbearing potential.

  Factor V and protein electrophoresis (at screnning, baseline and throughout the study) are not mandatory if sites cannot perform these tests at their routine local lab. For Egyptian sites, a central lab may be used.
- Imaging:
    - Chest X-ray;
    - Abdominal and pelvic including hepatic spiral CT scan or MRI;
    - Thoracic CT scan.

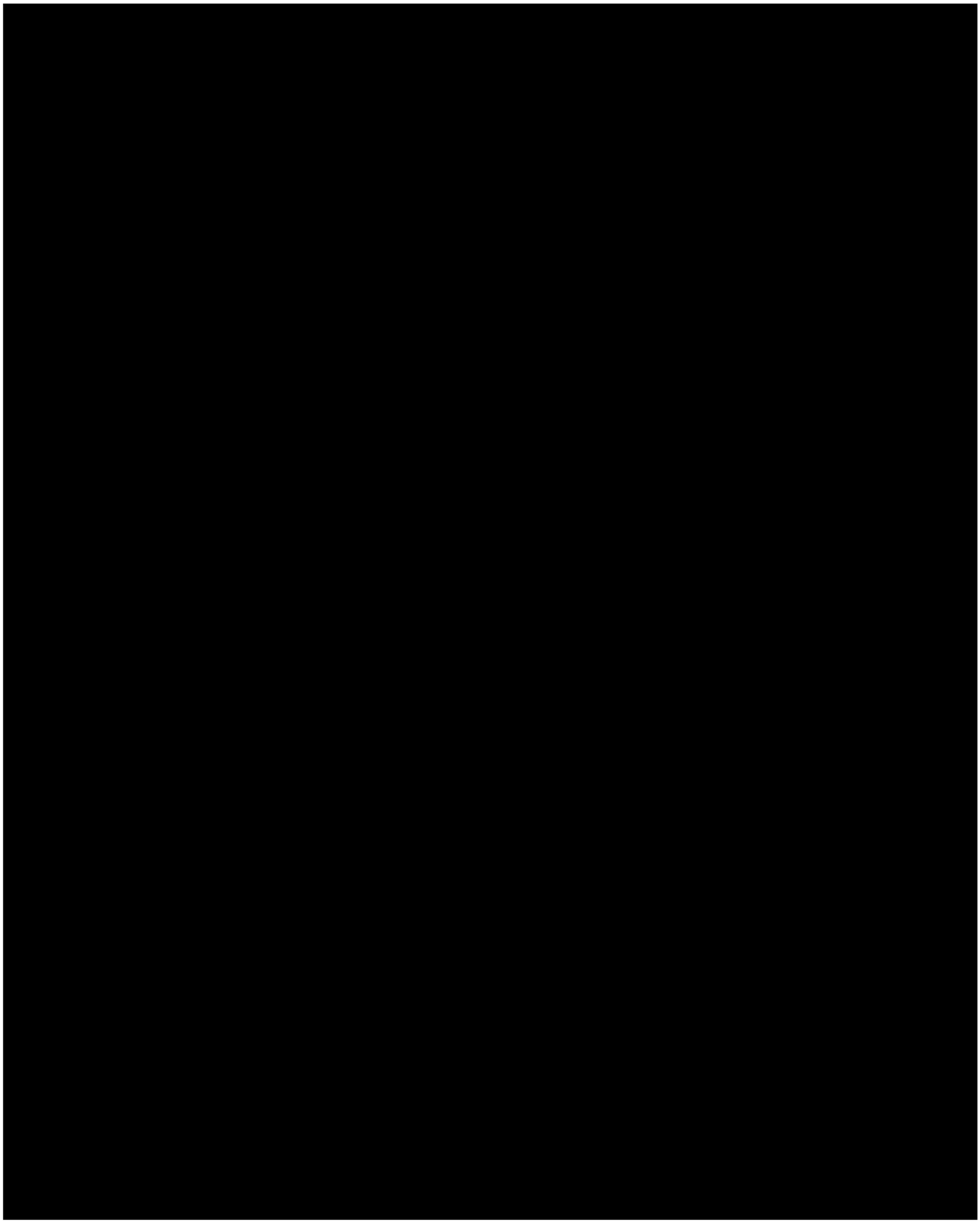
  If one of these imaging have been realized as part as routine pratice before screnning (i.e. before ICF signed), these radiologic exams can be considered as sufficient for the screnning period if realized within 28 days before baseline.

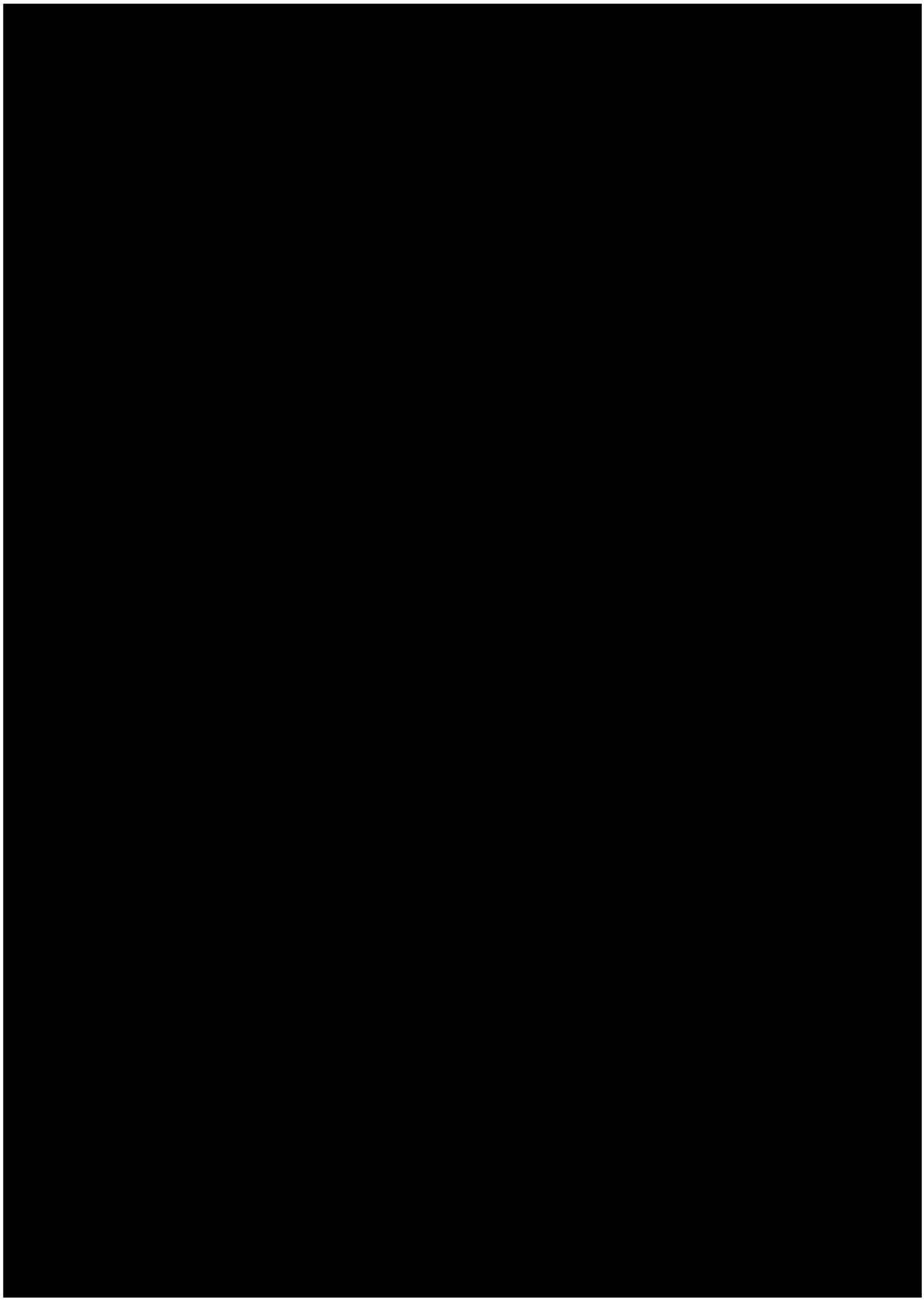
7.2 Trial Period

7.2.1. Design of each Cycle of treatment during treatment period

[redacted]

7.2.1.1 On Day 0 (24h before study treatment)





[redacted]

7.2.1.2 On Day 1 – Treatment visit

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

7.2.1.3 On Day 2 and Day 3 (optional) after study treatment

[redacted]

[redacted]

[redacted]

[redacted]

7.2.1.4 On Day 14 after study treament

[redacted]

[redacted]

[redacted]

7.2.2 Additional Cycles.

[redacted]

7.2.3 End of treatment Notification

[redacted]

7.2.4 End of Study treatment visit: 1 month after last infusion

[redacted]

[redacted]

[redacted]

7.2.5 Follow-up period

[redacted]

7.3 Biobank and biological material taken during the study

During the study, biological material consisting of blood samples will be taken and stored. The biological material will be kept in a biobank, initially stored in trial centres and later on sent to Onxeo (formerly known as BioAlliance Pharma) and to Pharmacokinetics department – Bertin Pharma at CEA/LEMM (France). All biological material will be anonymised and the sponsor will not be aware of the participants' identities. All samples will be kept in the biobank for 15 years maximum after the end of the study, and will then be destroyed. The biological material can only be used in a new research project after acceptance from legal authorities.

7.3.1. Pharmacokinetic study

The pharmacokinetic study of DT will be performed only in selected centers that can meet the requirements of blood sampling.

The primary aim of pharmacokinetic evaluation will be to determine the population pharmacokinetic parameters. The secondary objective will be to analyse the pharmacokinetic/pharmacodynamic correlation with DT efficacy and toxicity, and to evaluate inter-cycles AUC stability. For this purpose, blood sampling will be performed at the first and third treatment cycles. For patients still on treatment after Cycle 3, an optional and limited sampling at cycle 4, cycle 6 and beyond (e.g. every 2 cycles until the end of study treatment) will also be performed.

The bioanalytic method will be described in separate bioanalytical study plans and analysis of the study samples will be centrally performed at [redacted] Blood samples collected and stored in the biobank are aimed at measuring total doxorubicin, free doxorubicin and doxorubicinol plasma concentrations. Each sequence of analysis will be performed according to current quality standards, especially in term of quality control samples, calibration curve and acceptance criteria.

Pharmacokinetic data analysis will be performed under the responsibility of the Sponsor. A formal Statistical Analysis Plan (SAP) for PK analysis will provide further details of the statistical analyses and will be finalized before database lock. The section below is an overview of the PK statistical analyses planned for this study.

Total doxorubicin, free doxorubicin and doxorubicinol concentration data will be analysed using a 3 compartment model. This will allow for determination of both the steady-state and the elimination pharmacokinetic parameters of free doxorubicin, total doxorubicin and its major metabolite doxorubicinol.

The following pharmacokinetic parameters will be derived for total doxorubicin, free doxorubicin and doxorubicinol:

Cmax, Tmax, AUC (last, and inf), Half-life, Clearance

The study protocol is planned to present pharmacokinetic parameters as mean, standard deviation (SD), coefficient of variation (CV%), median, minimum and maximum values (and geometric mean when appropriate).

The influence of covariates such as demographics and liver impairment will be investigated.

<u>Amount of blood samples taken for the pharmacokinetic study (see appendix VIII)</u>

A maximum of thirty-six (36) blood samples will be taken for PK during the study within the first 3 months. The amount of blood taken each time will be less than 10 ml each: fourteen (14) times during treatment period Day 0 to Day 3, during the 1st and the 3rd Cycle of treatment to measure the study drug concentration in the blood and, if possible, one additional blood sample at Day 4, Day 8, Day 14 and Day 28 of the 1st and the 3rd Cycle.

In patients still on study treatment after Cycle 3, an optional and limited blood sampling will be drawn on each Day 1 (4 times: at T0, 4h, 6h, 8h), Day 14 (once) and Day 28 (once) of Cycle 4, Cycle 6, and beyond (e.g. every 2 cycles until the end of study treatment).

Thus, total amount of blood to be drawn during the study period will not exceed 360 ml throughout the first 3 months (a blood donor usually donates about 500 ml at once). The amount of each additional and optional limited sampling after 3 months for the ongoing patients will not exceed 60 ml every 2 months.

7.3.2. Pharmacogenetic study

The pharmacogenetic study will be realized in all patients who have accepted and signed an appropriate genetic informed consent form.

A blood sample bank will be constituted to evaluate any other potential biomarkers which will be identified as possibly relevant predictive / prognostic factors.

One additional blood sample will be taken for the pharmacogenetic study. The amount of blood is around 10 ml. Measurement of plasma concentrations of biomarkers will be realized before treatment (at baseline).

Analysis will be centrally performed under the responsibility of sponsor (see Annex VIII).

7.4 Supporting board: Independent Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be organized to regularly evaluate the safety of DT during the study. The complete role and responsibilities of DSMB is described in the DSMB charter. The DSMB will be provided with blinded safety data by patient and treatment group every 75 patients (around 25 patients/group) and will review the data at least twice a year. The DSMB will remain blinded for its evaluation, but may ask for unblinding if required.

At the end of each meeting, the DSMB will have to make recommendations to the Sponsor as follows:

- To continue the trial without modification;
- To continue the trial and amend the protocol, as specified;
- To suspend the trial pending further information or evaluations;
- To terminate the trial prematurely.

The DSMB will receive every SAE within 24 hours of the knowledge of the occurrence or at the latest, on the following working day.

In case of suspected pulmonary SAEs, DSMB will recommend whether to continue, suspend or definitively stop the recruitment and infusions in the respective cohort and make recommendations to the sponsor.

If deemed necessary, the DSMB may elect to postpone the recommendation, pending external consultation(s) with required specialists and/or receipt of additional data and a subsequent closed DSMB meeting session.

The DSMB members will be appointed by the Sponsor. DSMB is an independent expert group consisting of specialists in hepatology, liver oncology disease, lung diseases and statistics, well experienced in the management of patients with HCC and adverse lung reactions. DSMB will elect the chairman. Appropriate Onxeo (formerly known as BioAlliance Pharma) employees (including Pharmacovigilance and Clinical Departments) will participate to the DSMB meetings but will not have any voting rights.

DSMB will have the responsibility for providing the following:

- Assurance of patient safety,
- Trial integrity,
- Discussion with the Sponsor and required specialists,
- Recommendations and commitment in the study.

Following their risk evaluation, the DSMB reserves the possibility of alerting the Sponsor in the event of observation of highly unexpected events. The DSMB may request a futility analysis on the primary criterion of overall survival. This futility analysis serves one objective: to recommend the potential discontinuation when it is unlikely, based on the interim results, to achieve statistically significant results at the end of the study. This futility analysis will be realized under the responsibility of the DSMB statistician. The results of this futility analysis will be disclosed only to DSMB members. No one in the Sponsor representatives has access to

such information. No information about these results will be communicated to investigators and the International Coordinating Investigator.

Copies of correspondence between the sponsor and DSMB members will be distributed to all DSMB members.

National Authorities as applicable and all investigational centres will be informed of the DSMB recommendations.

7.5 Possible risks or discomforts

Like with any other medicines in cancer treatment, side-effects may occur during the treatment period.

The following side-effects were reported in previous studies: leukopenia, neutropenia, lymphopenia, abdominal pain, thrombopenia, elevated liver enzymes, nausea, anaemia, headache, moderate fever, asthenia, hypotension, cough, diarrhoea, O_2 desaturation, tachycardia, pain, minor dyspnoea, alopecia, vomiting, moderate dorsal, lumbar or chest pains.

The progression of all of these side-effects was favourable more or less rapidly, either spontaneously or after symptomatic treatment. The complete list of TEAE is given in the Investigator's Brochure.

Some serious respiratory disorders have also occurred consisting mainly of decrease in SaO_2, pleural effusion and for the worst cases pulmonary oedema, acute respiratory distress syndrome (ARDS), and death.

Pulmonary adverse events will be collected on a specific adverse event form in the e-CRF.

7.6 Safety measures

In case of unexpected life-threatening AE that may or may not be related to the investigational product, all clinical measures considered as mandatory should be taken and symptomatic treatments administered.

Dose adjustement and dose delay are described in section 6.6. Dose adjustement will be based upon haematologic and non haematologic toxicities observed after the previous dose administration. Any patient who requires a dose reduction will be treated with a reduced dose for any subsequent doses. Arm A patients requiring dose reductions below dose level -1 must discontinue and arm B patients requiring dose reductions below dose level -2 must discontinue.

7.6.1 Pulmonary toxicity

In previous studies where DT was injected through the hepatic intra arterial route in 15-30 minutes, 5 cases of ARDS were reported in 5 patients, resulting in death in two of them. Preclinical experiments showed that respiratory events were prevented by reduction of the DT infusion rate. A careful review of human safety data confirmed that dose and infusion rates were parameters driving the DT toxicity and led to recommend to infuse DT through the IV route over 6 hours. In order to prevent the occurrence of ARDS, respiratory safety measures have been implemented, including premedication with methylprednisolone 32 mg p.o (or equivalent) + non sedating antihistamine H_1 at double dose (e.g. cetirizine 20 mg p.o or equivalent) administered the day and 1 hour before infusion, then the day after infusion, and close monitoring following each infusion:

SaO_2 monitoring during the 6-hour infusion:

- Continuous monitoring of SaO_2:
  - In case of SaO_2 decrease to < 93%, the DT infusion rate will be reduced by half (12-hour infusion). The total dose will not be changed;
  - In case of SaO_2 decrease to ≤ 90%, DT infusion will be **immediately and definitively** stopped;
- Monitoring of respiratory symptoms:
  - In case of a respiratory symptom (dyspnoea, increase in respiratory rate by 5 beats/min and RR > 20/min), the DT infusion rate will be reduced by half (12-hour infusion); the total dose will not be changed;
  - In case of persistence of symptoms in the following hour, DT infusion will be **immediately and definitively** stopped.

SaO_2 monitoring after the end of DT infusion :

A SaO2 monitoring during 24 hours after infusion start is mandatory.

In case of a marked decrease in SaO_2 or occurrence of respiratory symptoms, the patient will be transferred to intensive care unit for monitoring and treatment until recovery.

In case of SaO2 decrease (≤ 90%) during or after DT infusion, SaO2 will be closely monitored and collected every hour until resolution to SaO2 ≥ 93%.

Patient with a respiratory adverse event during a DT infusion who remain eligible to continue DT treatment will have reinforced respiratory safety measures for each additional DT infusions and SaO2 collected every hour during infusion and within the 6 hours after the end of infusion.

The recommended treatment of drug-induced pneumonitis is based on systemic corticosteroids with methylprednisolone 1 g/day for 3 days in patients with respiratory failure or lower doses of corticosteroids (i.e methylprednisolone 60 mg every 6 hours) in less severe cases. Before initiating corticosteroid therapy, an infectious etiology must be excluded. Supportive care, bronchodilators, IV fluid, vasopressors, and mechanical ventilation could be indicated in patients with severe hypersensitivity reactions and circulatory collapse (Vahid B., 2008[49]).

In case of ARDS and/or any related life-threatening respiratory serious adverse event, DT will be definitively stopped and the patient will not receive any additional DT infusion.

In case of grade 3 or grade 4 AE, infusion should be delayed up to 4 weeks, when AE decreases to grade ≤ 2. Further DT infusions should be performed only if adequate respiratory function defined as SaO2 ≥ 95% is obtained (see section 6.6).

A decrease of SaO2 below 90%, regardless of any respiratory symptoms or signs, will be considered as SAE and reported to Onxeo (formerly known as BioAlliance Pharma) within 24 hours.
In any case, the total DT dose administered will be carefully recorded in the source document and e-CRF.

7.6.2 Haematological toxicity

Asymptomatic neutropenia and thrombopenia are frequent in patients with cirrhosis and related to hypersplenism and portal hypertension. The risk of neutropenia, anemia and thrombopenia will be carefully monitored before each study treatment administration, then every day for 3 days, at day 14 and day 28 during each cycle.

- In case of febrile neutropenia or any suspicion of infection, the patient should be hospitalized without delay for monitoring and treatment up to recovery;
- In case of neutropenia or anemia, patient will be treated according to the centre's usual practices; haematopoietic growth factors (G-CSF) and/or erythropoietin (EPO) could be administered according their respective SmPC in patients with documented anemia or cytopenia;

In case of febrile neutropenia, any grade 3 or grade 4 thrombopenia or neutropenia, DT will be interrupted and infusion should be delayed up to 4 weeks until resolution to a grade ≤ 2.
Further DT infusions should be performed only if haematologic tests fulfil the following criteria: neutrophil count ≥ 1000 / mm^3 (grade ≤ 2) , platelets count ≥ 50,000 /mm^3 (grade ≤ 2) and haemoglobin ≥ 10 g/dL (grade < 2).
Dose reduction is authorized in case of grade 4 related heamatological adverse events as described in section 6.6.1. The dose to be administered will be reduced (minus 1 dose level) in case of febrile neutropenia of any duration, grade 4 neutropenia lasting > 7 days and grade 4 thrombocytopenia.

7.6.3 Liver toxicity

Cirrhosis may decompensate and liver function may deteriorate in cirrhotic patients. Clinical signs and symptoms and liver function tests will be closely monitored thoughout the study, before each study treatment administration, then every day for 3 days, at days 14 and 28 during each cycle.
In case of aggravation of liver function tests, the investigator may prolong the hospitalisation, take all appropriate measures and administer symptomatic treatments as required. **If hospitalisation is prolonged (> Day 3), investigator should inform Onxeo (formerly known as BioAlliance Pharma), fill in and fax a SAE form.**

Further DT infusions should be performed only if liver function tests returned to baseline values with a Child-Pugh score from A5 to B7 included (if cirrhosis) and serum bilirubin < 35 µM/L (or 2.0 mg/dL) (see section 6.6).

Infusion could be delayed by up to 4 weeks. Dose reduction is authorized as described in section 6.6.1.

7.6.4 Cardiac toxicity

Cardiac toxicity has been reported with doxorubicin. Congestive heart failure (CHF) is among the most serious toxicities of doxorubicin, increases with the cumulative dose of doxorubicin, and is estimated to be 5 % at a cumulative dose of 400 mg/m^2, 16 % at 500 mg/m^2 and 26 % at 550 mg/m^2. To date, no cardiac events have been reported in patients suffering from HCC and treated with DT.

According to the potential cardiac risk, LVEF will be monitored every other month and ECG every month before each infusion.

In case of ECG modifications or any symptoms associated to a decreased LVEF and/or LVEF below the lower limit of normal values, additional DT infusions will not be authorized until a cardiologist is consulted for aetiologic work-up. The investigator will decide whether further DT infusions should be performed or definitively stopped, taking into account the benefit/risk ratio.

Infusion could be delayed by up to 4 weeks. In case of grade 3 or 4 related adverse events, dose reduction is authorized as described in section 6.6.1.

The maximum authorized cumulative dose of doxorubicin is 550 mg/m^2 (or its equivalent for other anthracyclins).

7.6.5 Any other adverse events

In case of any other grade 3-4 toxicity at the time of next infusion, the infusion should be delayed by up to 4 weeks until AE decreases to grade ≤ 2. In case of persisting grade 3-4 AE, the study treatment will be definitively stopped.

In case of life-threatening serious AE related to DT, the treatment will be stopped and the patient will not be re-administered DT.

8 SAFETY CRITERIA

The investigator is responsible for monitoring the safety of subjects who have been enrolled in the study. All adverse events occurring during the conduct of the study will be captured on the eCRF. All serious adverse events (related or not related) must be reported to Onxeo (formerly known as BioAlliance Pharma) Pharmacovigilance Department (Cf. section 8.7).

- **Any study drug-related AE (Cf. definition section 8.1) or any related or not related SAE (Cf. definition section 8.3) is to be followed until resolution or until mutually agreed by the investigator and an Onxeo (formerly known as BioAlliance Pharma) physician to discontinue reporting;**
- **All AEs and SAEs will be reported until 30 days after the last infusion of study-drug;**
- **Any respiratory SAE either related or not related to the study or to the study drug must be reported to Onxeo (formerly known as BioAlliance Pharma) Pharmacovigilance Department within 24 hours of the knowledge of the occurrence.**

Periodic review of the safety data will be conducted by an independent data safety monitoring board.

Subjects must be carefully monitored for AE. AEs should be assessed in terms of their seriousness, severity, and relationship to the study drug.

8.1 Adverse Events

The term AE is defined as any unfavorable and unintended sign, symptom, or disease (including an abnormal laboratory finding) temporally associated with the use of a medicinal investigational product, whether or not considered related to the investigational medicinal product.

AEs associated with the use of a drug in humans, whether or not considered drug related, include the following:

- An AE occurring in the Cycle of the use of a drug product in professional practice
- An AE occurring from an overdose whether accidental or intentional
- An AE occurring from drug abuse
- An AE occurring from drug withdrawal
- An AE where there is a reasonable possibility that the event occurred purely as a result of the patient's participation in the study must also be reported as an AE even if it is not related to the investigational product.

The clinical manifestation of any failure of expected pharmacological action will not be recorded as an AE if it is already reported as efficacy criteria in the e-CRF. If, however, the event fulfils any of the criteria for a SAE, it must be recorded and reported as such.

Underlying conditions (existing prior to the trial) which become aggravated or recur after resolution during a clinical trial must be reported as an AE. An AE may be deemed serious if it meets any of the seriousness criteria given in Section 8.3.

8.2 Unexpected Adverse Event Definition

An unexpected AE is any event, the nature, specificity or severity of which is not consistent with the current Investigator's Brochure. Also, reports which add significant information on specificity or severity of a known, already documented AE constitute unexpected AEs. For example, an event more specific or more severe than described in the investigator's Brochure would be considered unexpected. Specific examples would be as follows: (a) acute renal failure as a labeled AE with a subsequent new report of interstitial nephritis, and (b) hepatitis with a first report of fulminant hepatitis.

8.3 Serious Adverse Events

An AE is classed as being "serious" during a clinical trial if it:

- Results in death
- Is life-threatening
- Results in persistent or significant disability or incapacity
- Requires in-patient hospitalisation or prolongation of existing hospitalization
- Is a congenital anomaly, or birth defect
- Is a suspected transmission of an infectious agent
- Is an important medical event (requires medical intervention to prevent outcomes listed above).

Life-threatening: The term "life-threatening" in the definition of "serious" refers to an event in which the patient or the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.

Hospitalisation: Any event leading to hospitalisation or prolongation of hospitalisation will be considered as serious, unless at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours
- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study)
- The admission is not associated with an AE (e.g., social hospitalisation for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalisation may fulfill the criteria of medically important and, as such, may be reportable as a SAE depending on clinical investigator's judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability: A substantial disruption of a person's ability to conduct normal life functions.

Important Medical Event: Any AE may be considered serious because it may jeopardize the patient and may require intervention to prevent another serious condition. As guidance for determination of important medical events, refer to the WHO Adverse Reaction Terminology "Critical Terms List", these terms either refer to or might be indicative of a serious disease state. Such reported events warrant special attention because of their possible association with a serious disease state and may lead to more decisive action.

Note: **previous studies have identified acute respiratory distress syndrome (ARDS) as SAE. In order to prevent the occurrence of ARDS, a decrease of SaO_2 below 90% will be considered as SAE.**

Pregnancy :

Any pregnancy that occurs from date of informed consent to six (6) months after end of therapy must be reported to Onxeo (formerly known as BioAlliance Pharma) immediately and followed up until after delivery on the Pregnancy report form. Pregnant patients will be withdrawn from the trial and will be advised to present at a center specialized in human genetics for genetics councelling. In case of still birth, spontaneous abortion/miscarriage, or congenital malformation/abnormality, a Pregnancy report form must be provided as well.

8.4 Severity Assessment

The NCI CTC AE v4.0 classification should be used to determine and to grade the severity of AEs.

For AEs not specified and detailed in the NCI CTC, severity will be categorized as mild corresponding to grade 1, moderate corresponding to grade 2, severe corresponding to grade 3 or life-threatening corresponding to grade 4, according to the following NCI CTC definitions:

Mild is defined as usually transient in nature and generally not interfering with normal activities. No medical intervention/therapy required.

Moderate is defined as sufficiently discomforting to interfere with normal activities. No or minimal medical intervention/therapy required.

Severe or medically significant is defined as prevents normal activities. Some assistance is usually required, medical intervention/therapy required, hospitalization possible.

8.5 Causality Assessment

The assessment of the relationship of an AE to the administration of study drug is a clinical decision based on all available information at the time of the completion of the e-CRF.

Related adverse events are those that are judged unlikely, possibly, probably or definitely related to the study or to the study drug by the investigator.

Unrelated adverse events are those that are judged to be not related to the study or to the study drug by the investigator.

An assessment of "No relation to study drug" would include:

- The existence of a clear alternative explanation (i.e., mechanical bleeding at surgical site) **or**
- Non plausibility (e.g., the patient is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event, cancer developing a few days after the first drug administration).

An assessment of "Yes, related to study drug" indicates that there is a reasonable suspicion that the AE is associated with the use of the investigational drug.

Factors to be considered in assessing the relationship of the AE to study drug include the following:

- The temporal sequence of the event related to the time of drug administration. The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery from the event on discontinuation (dechallenge), recurrence on reintroduction of the drug (rechallenge) should be evaluated. Patient's response after drug discontinuation (dechallenge) or patients response after drug reintroduction (rechallenge) should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, concurrent diseases. Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication or treatment. The other drugs the patient is taking or the treatment the patient received should be examined to determine whether any of them may be suspected in the cause of the event in question.
- The pharmacology and pharmacokinetics of the test drug: The pharmacokinetic properties (absorption, distribution, metabolism, and excretion) of the test drug(s), coupled with the individual patient's pharmacodynamics, should be considered.

8.6 Withdrawal Due to Adverse Events

(See Subject Premature Withdrawal, section 4.4 and End of treatment Notification, section 7.2.3).

8.7 Reporting Requirements

8.7.1 Non-Serious Adverse Event Reporting Requirements

All AEs occurring after the patient has signed the informed consent must be fully recorded in the patient's e-CRF. Documentation must be supported by an entry in the patient's file. A laboratory test abnormality considered clinically relevant (e.g., causing the patient to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator) should be reported as an AE. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

For all adverse events, the investigator has to pursue and obtain adequate information to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as non serious or SAE requiring immediate notification to the Sponsor (see below). Follow-up of the AE, even after the date of therapy discontinuation, is required if the AE or its after-effects persist.

Follow-up is required until the event or its after-effects are resolved or stabilized at a level acceptable to the investigator and the Sponsor. For subjects withdrawn from the study and subjects experiencing AE at the end of the study and within 30 days following the last treatment day, the investigator will arrange for appropriate follow up (if required until the AEs are resolved or attributed to a cause other than the study drug).

8.7.2 Serious Adverse Event Reporting Requirements

SAEs must be documented on the designated SAE form in accordance with the instructions for reporting SAEs occurring in clinical trials. This form must be completed and supplied to Onxeo (formerly known as BioAlliance Pharma) within 24 hours of the knowledge of the occurence, or at the latest, on the following working day.

Any respiratory SAE either related or not related to the study or to the study drug must be reported to Onxeo (formerly known as BioAlliance Pharma) Pharmacovigilance Department within 24 hours of the knowledge of the occurrence.

In addition and as possible, clinical department of Onxeo (formerly known as BioAlliance Pharma) should be informed by telephone or by email at the same time, as soon as possible after the occurrence of a SAE or other clinically notable AE.

The Sponsor will ensure that all legal reporting requirements are met.

The initial report must be as complete as possible, including details of the current illness and (serious) AE, and an assessment of the causal relationship between the event and the study medication.

Information not available at the time of the initial report (e.g., an end date for the AE or laboratory values received after the report) must be documented on a follow-up SAE form and handled within the same time frame.

Any SAE occurring during the trial and within 30 days following the last treatment day must be reported in as short a time as possible and, at the latest, within 24 hours, to the drug monitoring team at Onxeo (formerly known as BioAlliance Pharma), even if the investigator considers that its occurrence is not related to the study drug.

Procedure and contact details for SAE reporting to Onxeo (formerly known as BioAlliance Pharma) are the following:

SAE reporting to

ONXEO Drug Safety Dpt:

[redacted]

An inquiry will then be conducted by Drug Safety Department of Onxeo (formerly known as BioAlliance Pharma) in order to determine whether the event was caused by the treatment and to make the necessary statutory declarations. In any case, the causal relationship assessed by the investigator will never be downgraded.

The head of the Drug Safety Department will inform the Health Authorities in writing in accordance with current regulations and the Clinical Department will take care of the Ethics Committees information.

8.7.3 Progression of underlying malignancy

Progression of underlying malignancy is not reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST or mRECIST criteria or based on clinical progression assessed by the investigator.

Death or hospitalization due solely to the progression of underlying malignancy should NOT be reported as a SAE.

Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as being exclusively due to progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Progression could be evident in the patient's clinical symptoms, and the investigator may elect not to perform further disease assessments. In such cases, the progression is based on symptomatic deterioration and considered as a clinical progression. As far as possible, these evaluations should be a rare exception and every effort should be made to document the progression.

If there is any uncertainty about an AE or SAE being due ONLY to the progression of the underlying malignancy, it should be reported as an AE or SAE.

9 DATA ANALYSIS/STATISTICAL METHODS

9.1 Statistical considerations

9.1.1 Statistical Analysis Plan (SAP)

Statistical analysis will be performed by [redacted] under responsibility of the sponsor.

The material of this section is the basis for the statistical analysis plan for the study. This plan may be revised during the study to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution and data that affect planned analysis.
A separate SAP will provide further details of the statistical analyses and handling of missing data, as well as specifications for the data tables, figures, and listings. The final SAP will be finalized before database lock.

9.1.2 Sample Size Determination

The primary aim of the study is to demonstrate the superiority of DT infused through the IV route in 6 hours at the dose of 20mg/m^2 or 30mg/m^2 in comparison with Best Standard of Care (BSC) in the treatment of advanced HCC in patients with non decompensated cirrhosis or without cirrhosis, according to overall survival.

Statistical Hypothesis for the Sample-Size Estimation

The explicit intention of the trial is to perform one comparison (two-sided unstratified log-rank test) on the overall survival considered as time-to-event data between the experimental group (pooled DT 20mg/m^2 and DT 30mg/m^2 groups) versus BSC group.

The null hypothesis (H0) corresponds to the absence of difference between treatment groups (hazard ratio=1.00) and the alternative hypothesis (H1) retained is a hazard ratio of 0.69.

Hypothesis	Chosen Scenario
Type of Test	Two-sided log-rank test
Hazard ratio under H0	1.00
Hazard ratio under H1	0.69
Type I Error (α)	5% two sided
Type II Error (β)	15%

Summary of Clinical and Statistical Assumptions

Sample-Size Estimation

In the Phase II DOTAHCC1 clinical trial comparing 3 HIA injections of DT to Best Standard of Care, the median survival time was 449 days (95% CI: [239, 564]) for the control group (n=11) and 979 days (95%CI: [245, NE]) for the DT group (n=17). The treatment effect was significant for the logrank test (p=0.0494).

The treatment effect is not significant (p=0.0570) for the Wald test in the Cox model (assuming proportional hazards) as reflected by the corresponding 95%CI of the hazard ratio [0.15, 1.03] which includes 1.00, the hazard ratio estimate being 0.39. Assuming an exponential distribution

of the survival time within each treatment group leads to predictions of the 2-year survival rate of 24.2% for Control and of 51.4% for Doxorubicin, respectively and to predictions of median survival times of 356.7 days and 760.4 days, respectively.

Actually the population expected in the ReLive study will be markedly different from the population observed in the DOTAHCC1 study. Patients are expected to be more severe and consequently the median survival time of the control group should be markedly lower. A Korean study conducted on a population closer to the one expected for ReLive study has reported a median survival time of 187 days (Woo H.Y., 2011[50]). Under an exponential distribution, a median survival time of 187 days would correspond to a 1-year survival rate of 25.8% (2-year survival rate of 6.7%). A French cohort study conducted on 1287 naive patients with HCC reported that only 187 patients were eligible for Sorafenib treatment and 103 received Sorafenib in whom a 1-year survival of 16% was reported (Rosa L., 2011[27]). Under an exponential distribution, a 1-year survival rate of 16% would correspond to a median survival time of 138 days and to a 2-year survival rate of 2.6%.

Following the publication of the positive RESORCE regorafenib phase 3 study in Child Pugh A patients tolerant and progressing under sorafenib, the SAP was revised in order to handle the potential risk of lack of power. Analysis of efficacy and safety of the pooled DT groups versus BSC group was chosen as primary analysis and a more realistic OS in the control group of 8 months instead of 6.6 months (200 days) and an HR of 0.69 instead of 0.60 were considered. Following the recent data of prospective non interventional studies showing that the Child Pugh status is a strong prognostic factor for OS in patients treated by sorafenib (median OS of 13 months in Child Pugh A patients versus 5 months in Child Pugh B), analysis of efficacy and safety in this homogeneous population of Child Pugh A patients from whom the clinical benefit is expected to be higher has been added. An OS in the control group of 9 months and an HR of 0.68 were considered in this population.

The hierarchical sequential closed test procedure will be used to control the overall type I error rate of 5% to evaluate first the primary endpoint OS in the ITT population, then if statistically significant the primary endpoint OS in the ITT Child Pugh A population and then if statistically significant the main secondary endpoints (PFS and OOR) in the ITT Child Pugh A population.

The following sequence will be followed:

- OS in the overall ITT population
- OS in the ITT Child Pugh A population
- PFS in the ITT Child Pugh A population
- ORR in the ITT Child Pugh A population

Overall population:

Under the assumptions of a median survival of the control group of 8 months and a hazard ratio of 0.69, the required total sample size to achieve a 85% power to compare the experimental groups (pooled DT 20mg/m2 and DT 30mg/m2) versus BSC and performed at a significance level of 2.5% one sided is 348 patients in the ITT population (116 patients in the BSC group

and 232 patients in the DT group). It is expected 10% of patients will be lost to follow-up; this leads to a calculated total sample size of 390 randomised patients.

Child Pugh A population (85% of the patient population):

Under the assumptions of a median survival of the control group of 9 months and a hazard ratio of 0.68, the required total sample size to achieve a 80% power to compare the experimental group (pooled DT 20mg/m^2 and DT 30mg/m^2 groups) versus BSC with a significance level of 2.5% one sided is 291 patients in the ITT Child Pugh A population (97 patients in the BSC group and 194 patients in DT groups). It is expected that 10% of patients will be lost to follow-up; this leads to a calculated total sample size of 324 ITT Child Pugh A randomised patients.

Thus the study will be completed once a total of 390 patients will have been randomized. The analysis will be performed when 285 events have occurred (corresponding to 230 events in the ITT Child Pugh A population).

9.1.3 General conventions

Descriptive statistics for parameters of interest will be provided by treatment group (pooled DT groups, DT 20 mg/m2 alone, DT 30 mg/m2 alone and BSC control group) and overall.
The baseline value will be defined as the last available value prior to first DT infusion for patients in tested dose groups or prior to first BSC administration for patients in BSC.
The type I (α) error will to be 5% (two-sided) for all analyses.
From a statistical point of view, this study will not be comparative between the two doses of DT. So comparison of confidence intervals between each DT group versus BSC will be exploratory in order to define the benefit-risk ratio for each dose (see 9.6).

9.1.4 Disposition of patients

The number of screened, included, randomised and treated patients will be given overall and according to the group which they belong to (if appropriate).

Eligibility criteria of treated patients will be checked. The number of treated patients who will complete or discontinue the study will be provided. Reasons for study discontinuation will be provided with detailed patient information.

9.1.5 Protocol deviations

Protocol deviations will be examined relative to criteria of inclusion and exclusion, and to compliance with the protocol with regard to administration of treatment and prohibited medications.

Major deviations will be defined, listed and summarized in the final statistical analysis plan issued prior to database lock.

9.2 Population to be analyzed

The Safety Population is defined as all included subjects receiving at least one DT infusion or at least one anti-cancer therapy or supportive care as BSC. For safety analyses, patients will be affected to the group of treatment they actually received.

The following populations are planned for the efficacy analyses:

- The Intent To Treat (ITT) Population : all randomized patients. In this population, patients will be analysed in their randomisation group whatever the treatment they received.
- The Per Protocol (PP) population includes all the patients of the ITT population without any major protocol deviation. Patients terminating the study prematurely will be included in the PP population provided that there is no protocol deviation. Before locking the database, the precise reasons for excluding patients from the PP dataset will be fully defined and documented by the Blind Review Committee.

9.3 Subjects characteristics

Subjects' characteristics will be evaluated according to demographic characteristics, physical examination, medical history and previous and concomitant treatments.

Demographic data will be summarized with usual descriptive statistics. Previous and concomitant treatments will be organised according to the WHO Drug dictionary. Parameters that cannot be easily organised by class will be listed individually.

9.4 Efficacy endpoints

9.4.1 Primary endpoint

The primary endpoint is overall survival (OS), defined as the time from the date of randomisation to the date of death from any cause. Patients without death at the time of the statistical analysis will be censored at the date they were last known to be alive.

The primary endpoint will be analyzed in ITT population (primary analysis), with an additional analysis in PP population.

Definition of date of death or censoring will refer to FDA guidelines for OS (definition including documented death only).

OS will be estimated using the Kaplan-Meier method and plotted as curves by treatment group.

The comparison between groups (pooled DT groups versus BSC) will be made using the unstratified LogRank test. The analysis will be performed when 285 events have been observed. The hierarchical sequential closed test procedure for a comparison of pooled DT groups with

BSC in the ITT Child Pugh A population will be used to control the overall type I error rate of 5%.

In addition to the analysis not adjusted for baseline characteristics considered above, a sensitivity analysis will be conducted using a Cox model adjusting for geographical region and pre-defined selected prognostic factors as recently described in this population such as ECOG score, BCLC stage, macroscopic vascular invasion, extrahepatic spread and hepatic impairment (Child Pugh score, prothrombine time) (Marrero J.A., 2013[54], Reig M., 2013[55], Iavarone M., 2015[56]). HR, median and mean survival and OS rates every 3 months will be given with the corresponding 95% confidence intervals.

9.4.2 Secondary endpoints

A sequential (closed) testing procedure will be used to control the overall type I error rate. Formal testing of the first secondary endpoint will be undertaken only if a statistically significant result is achieved on the primary endpoint of OS in the Child Pugh A population and formal testing of the second secondary endpoint will be undertaken only if a statistically significant result is achieved on the first secondary endpoint.

1. Progression Free Survival (PFS):

PFS is defined as the time from the date of randomisation to the date of the first documented progression or death from any cause. The assessment of progression will be done by an independent radiological review according to RECIST 1.1. Patients without progression or death at the end of study treatment period will be censored at the date of their last tumour assessment.

PFS will be analyzed in the ITT Child Pugh A population with an additional analysis in ITT and PP populations.

Definition of date of progression or censoring will refer to FDA guidelines for PFS.

PFS will be estimated using the Kaplan-Meier method and plotted as curves by treatment group. The comparison between groups (pooled DT 20mg/m^2 and 30mg/m^2 versus BSC) will be made using LogRank test.

HR, median and mean survival and PFS rates every 2 months will be given with the corresponding 95% confidence intervals.

If the primary endpoint of OS is statistically significant for the pooled DT 20 mg/m^2 and 30mg/m^2 groups versus BSC in the Child Pugh A population, PFS will be formally tested at significance level of 5% for the pooled DT 20 mg/m^2 and 30mg/m^2 group versus BSC in the Child Pugh A population. The analysis of the other comparison will be considered as exploratory.

In addition to the analysis not adjusted for baseline characteristics considered above, a sensitivity analysis will be conducted using a model adjusting for geographical region and pre-defined selected prognostic factors as recently described in this population such as ECOG score, BCLC stage and macroscopic vascular invasion, extrahepatic spread and hepatic impairment

(Child Pugh score, prothrombine time) (Marrero J.A., 2013[54], Reig M., 2013[55], Iavarone M., 2015[56]).

2. Objective Response Rate (ORR):

ORR is defined as the proportion of patients whose best overall response is complete or partial response during the study treatment period. The assessment of tumour response will be done by an Independent Radiological Review according to RECIST 1.1.

ORR will be analyzed in the ITT Child Pugh A population with an additional analysis in ITT and PP populations.

The comparisons between groups (pooled DT 20mg/m^2 and 30mg/m^2 versus BSC) will be made using chi-square test.

If the PFS is statistically significant for the pooled DT 20mg/m^2 and 30mg/m^2 group versus BSC in the Child Pugh A population, ORR will be formally tested at significance level of 5% for the pooled DT 20mg/m^2 and 30mg/m^2 group in the Child Pugh A population. The analysis of the other comparison will be considered as exploratory.

In addition to the analysis not adjusted for baseline characteristics considered above, a sensitivity analysis will be conducted using a model adjusting for geographical region and pre-defined selected prognostic factors as recently described in this population such as ECOG score, BCLC stage and macroscopic vascular invasion, extrahepatic spread and hepatic impairment (Child Pugh score, prothrombine time) (Marrero J.A., 2013[54], Reig M., 2013[55], Iavarone M., 2015[56]).

9.4.3 Exploratory endpoints

No adjustment for multiple testing will be performed in the analysis of exploratory endpoints and p-values will be interpreted as exploratory.

All exploratory analyses will be conducted in ITT and ITT Child Pugh A population.

1. PFS by the Independent Radiological Review according to mRECIST is defined as the time from the date of randomisation to the date of the first documented progression or death from any cause. Patients without documented progression or death at the end of study treatment period will be censored at the date of their last tumour assessment.

PFS will be estimated by the Kaplan-Meier method and plotted as curves by treatment group. The comparison between groups (pooled DT 20mg/m^2 and 30mg/m^2 versus BSC) will be made using LogRank test.

2. PFS by the investigator according to RECIST 1.1 (and mRECIST if possible) is defined as the time from the date of randomisation to the date of the first progression (documented or clinical) or death from any cause. Patients without progression or death at the end of study treatment period will be censored at the date of their last tumour assessment.

PFS will be estimated by the Kaplan-Meier method and plotted as curves by treatment group. The comparison between groups (pooled DT 20mg/m^2 and 30mg/m^2 versus BSC) will be made using LogRank test.

3. ORR by the independent radiological review according to mRECIST is defined as the proportion of patients whose best overall response is complete or partial response during the study treatment period.

The comparison between groups (pooled DT 20mg/m^2 and 30mg/m^2 versus BSC) will be made using chi-square test .

4. ORR by the investigator according to RECIST 1.1 (and mRECIST if possible) is defined as the proportion of patients whose best overall response is complete or partial response during the study treatment period.

The comparison between groups (pooled DT 20mg/m^2 and 30mg/m^2 versus BSC) will be made using chi-square test.

5. Time To Progression (TTP):

TTP is defined as the time from the date of randomisation to the date of the 1st documented progression or death related to tumour progression. The assessment of progression will be done by the independent radiological review according to RECIST 1.1 and mRECIST (if possible) and by the investigator according to RECIST 1.1 and mRECIST (if possible). Patients without progression at the end of study treatment period will be censored at the date of their last tumour assessment.

Definition of date of progression or censoring will refer to FDA guidelines for TTP.

TTP will be estimated by the Kaplan-Meier method and plotted as curves by treatment group. The comparison between groups (pooled DT 20mg/m^2 and 30mg/m^2 versus BSC) will be made using LogRank test.

6. Best Overall Response and Disease Control Rate:

The assessment of tumour response will be done by the Independent Radiological Review according to RECIST 1.1 and mRECIST (if possible) and by the investigator according to RECIST 1.1 and mRECIST (if possible).
Best Overall Response is defined as the best response observed during the study treatment period (no requirement for confirmation).
Disease Control Rate is defined as the proportion of patients whose Best Overall Response is complete response, partial response or stable disease during the study treatment period.
The comparison between groups (pooled DT 20mg/m^2 and 30mg/m^2 versus BSC) will be made using chi-square test.

7. Time to Objective Response:

Time to Objective Response will be calculated from randomisation to the date to first documented objective response (CR or PR). Patients without documented response (CR or PR) at the end of study treatment period will be censored at the date of their last tumour assessment.
The assessment of tumour response will be done by the Independent Radiological Review according to RECIST 1.1 and mRECIST (if possible) and by the investigator according to RECIST 1.1 and mRECIST (if possible).

8. Duration of Response:

Duration of response will be calculated in the subpopulation of patients experiencing a response (CR or PR) from the time when objective response (CR or PR) is first met to the date of first documented progression. The assessment of tumour response and progression will be done by the Independent Radiological Review according to RECIST 1.1 and mRECIST (if possible) and by the investigator according to RECIST 1.1 and mRECIST (if possible). Patients without documented progression at the end of study treatment period will be censored at the date of their last tumour assessment.

Duration of Response will be estimated only for patients achieving an objective response using the Kaplan-Meier method and plotted as curves by treatment group.

9. Evolution in serum α-fœtoprotein levels (AFP):

Serum AFP levels will be summarized by visit and by dose. Differences between AFP levels every other month and at baseline will be summarized as well. Comparisons between groups will also be made using non parametric tests. The number of patients with a decrease in AFP from baseline will be shown overall and by dose of DT.

9.5 Safety endpoints

Safety analyses will be descriptive and conducted in the safety population.
Descriptive data will be provided for adverse events, laboratory values (biochemistry and hematology), vital signs (weight, blood pressure), clinical exams (normal/abnormal), and concomitant treatments.
Patients with at least one AE, SAE, severe AE, AE leading to discontinuation, AE leading to dose reduction, and AEs of interest will be summarized. Adverse events will be coded using MedDRA.

Respiratory:

- Incidence and duration of reduction of SaO2 during DT infusion (in DT arms);
- Incidence and severity of respiratory events;

Cardiac:

- Incidence and severity of cardiovascular events (including BP and HR);
- ECG and LVEF change ;

Overall:

- Incidence and severity of all TEAEs and SAEs according to NCI-CTC v4.0 scale;
- Biological (haematology and biochemistry analyses and particularly AST/ALT, WBC);
- Child Pugh Score deterioration.

Safety endpoints will be individually described per subject number, presenting: emergence, description, body system, preferred term, date and time of onset, date and time of last study

drug administration before AE, time from onset since last study drug administration, frequency, severity and seriousness, relationship to study drug, action taken (corrective treatment, hospitalisation…) required and outcome if any.

The treatment emergent AEs (TEAEs), defined as those events that occurred or worsened after the first drug administration, will be summarized by body system and preferred term. The number of emergent AEs and the number of subjects reporting these emergent AEs will be presented by treatment group and overall.

The same table presentation will be used for serious TEAEs, drug related TEAEs and drug related serious TEAEs.

9.6 Determination of the optimal dose of DT

The statistical analyses comparing the experimental group (pooled DT 20mg/m^2 and 30mg/m^2 groups) versus BSC will also be conducted in the DT 20mg/m^2 group alone vs BSC and DT 30mg/m^2 group alone vs BSC in the ITT population.
Baseline demographic characteristics, exposure, efficacy, safety and adjustment for covariates (as described in Sections 9.3, 9.4 and 9.5 of the protocol) will be compared for each DT group versus BSC (as exploratory analysis).
The selection of the optimal DT dose will be based on the benefit/risk ratio of each dose of DT, taking into account:

- **Benefit/Efficacy**: The optimal dose of DT in term of efficacy will be the one which is associated with the best survival in comparison with the BSC group.

This will be assessed through the measure of OS and tested by the unstratified log-rank test.
The optimal dose for efficacy will be identified if one out of the 2 exploratory unstratified log-rank tests between the DT 30 mg/m^2 versus BSC or DT 20 mg/m^2 group versus BSC is statistically significant or if a clinically relevant difference is observed in favour of one DT group versus BSC (i.e. unstratified log-rank tests between the DT 30 mg/m^2 versus BSC or DT 20 mg/m^2 group versus BSC less than 15%).
If there is no difference between the DT 30mg/m^2 versus BSC and DT 20mg/m^2 group versus BSC (i.e. unstratified log-rank tests between the DT 30 mg/m^2 versus BSC or DT 20 mg/m^2 group versus BSC more than 15%), it will be concluded that DT 20 mg/m^2 and DT 30 mg/m^2 are similar in term of efficacy.

- **Risk/Safety:** The optimal dose of DT in term of safety will be the one which is associated with the lowest incidence of treatment discontinuations due to adverse drug reactions and the lowest incidence of deaths due to adverse drug reactions.

Difference between the two doses of DT (DT 30 mg/m^2 versus DT 20 mg/m^2) will be explored via two-sided Fisher exact tests on the incidence of treatment discontinuations and on the incidence of death due to adverse drug reactions.
If at least one exploratory Fisher test leads to conclude to a statistically significant difference between the DT 30 mg/m^2 group and the DT 20 mg/m^2 group, or if a clinically

relevant difference is observed between groups (absolute difference of more than 5%), the optimal dose of DT for safety will be the one which is associated with the lowest incidence of study treatment interruptions or deaths due to adverse drug reactions. If there is no difference between the dose groups for these safety criteria, it will be concluded that DT 20 mg/m^2 and DT 30 mg/m^2 are similar in term of safety.

In summary, the optimal DT dose will be the dose of DT associated with the best OS (if any). If OS is similar between the 2 doses of DT, the optimal DT dose will be the one associated with the best tolerance. If OS and safety are found to be comparable between doses, then the lowest dose (20mg/m^2) will be selected.

9.7 Interim Efficacy Analysis

No interim efficacy statistical analysis is planned.

If futility analysis is performed by the independant DSMB, this analysis will not be considered as interim because of the absence of impact on the Type 1 error.

9.8 Risk estimation of any event according to drug exposure

Safety data will be carefully and regularly reviewed by the DSMB every 75 patients, corresponding to the collection of data in around 25 patients per treatment group. Estimates of the risk of serious respiratory effects (or any other serious events) are given in the following table.

The 95% and 90% (exact binomial) confidence intervals are presented for different sample sizes:

Sample size	0 respiratory SAE (ARDS)	1 respiratory SAE (ARDS)
25	0/25 (0.00%) 90%CI [0.00%, 11.29%] 95%CI [0.00%, 13.72%]	1/25 (4.00%) 90%CI [0.20%, 17.61%] 95%CI [0.10%, 20.35%]
50	0/50 (0.00%) 90%CI [0.00%, 5.82%] 95%CI [0.00%, 7.11%]	1/50 (2.00%) 90%CI [0.10%, 9.14%] 95%CI [0.05%, 10.65%]
75	0/75 (0.00%) 90%CI [0.00%, 3.92%] 95%CI [0.00%, 4.80%]	1/75 (1.33%) 90%CI [0.07%, 6.17%] 95%CI [0.03%, 7.21%]
100	0/100 (0.00%) 90%CI [0.00%, 2.95%] 95%CI [0.00%, 3.62%]	1/100 (1.00%) 90%CI [0.05%, 4.66%] 95%CI [0.03%, 5.45%]

A first approach assumes that the 'experimental unit' is the patient and that the risk considered is the risk to see a serious respiratory AE (i.e. ARDS) in a patient receiving a series of injections. In this first approach, the table above is interpreted as follows:

- seeing 0 serious respiratory AE in a series of 25 patients leaves a risk of 5% that the true incidence could be above 11.29% and a risk of 2.5% that the true incidence could be above 13.72%.
- seeing 1 serious respiratory AE in a series of 25 patients leaves a risk of 5% that the true incidence could be above 17.61% and a risk of 2.5% that the true incidence could be above 20.35%.

A second approach is to consider that the 'experimental unit' is the injection and that the risk considered is the risk to see a serious respiratory AE after an injection. In this situation, the risk remains the same at each injection and is not influenced by the injection being repeated in the same patient or being applied to a new patient. In this second approach, the table above is interpreted as follows:

- seeing 0 serious respiratory AE in a series of 100 injections (e.g. 25 patients having had 4 injections on average) leaves a risk of 5% that the true incidence could be above 2.95% and a risk of 2.5% that the true incidence could be above 3.62%.
- seeing 1 serious respiratory AE in a series of 100 injections leaves a risk of 5% that the true incidence could be above 4.66% and a risk of 2.5% that the true incidence could be above 5.45%.

Based on these assumptions, the probability to see 1 serious respiratory AE or more is presented for different sample sizes and possible true serious respiratory AE incidences:

Sample size	ARDS: 0.1%	ARDS: 1%	ARDS: 5%	ARDS: 10%
25	0.0247	0.2222	0.7226	0.9282
50	0.0488	0.3950	0.9231	0.9948
75	0.0723	0.5294	0.9787	0.9996
100	0.0952	0.6340	0.9941	1.0000

This table shows that in a series of 25 patients, if the true serious respiratory AE incidence is 0.1%, there is a probability of 2.47% to see 1 serious respiratory AE or more (and a probability of 97.53% to see 0 ARDS). If the incidence is 10%, there is a probability of 92.82% to see 1 serious respiratory AE or more (and a probability of 7.18% to see 0 ARDS). Sample size may apply to patients (either all patients treated with DT or patients belonging to one treatment group) or injections.

On the basis of these assumptions, safety analyses will be performed when a total of 75 patients have been included.

10 DATA QUALITY ASSURANCE

10.1 Data Collection

The Investigator/coordinator at each site must enter the information required by the protocol into the electronic Case Report Form (eCRF) provided by Onxeo (formerly known as BioAlliance Pharma). These will be forwarded to the sponsor, Onxeo (formerly known as BioAlliance Pharma), and their representatives. All additions to the eCRF during the study and SAE forms must be forwarded to the sponsor. Details on responses need to be accurately documented in the patient's hospital records.

10.2 Study Monitoring

Before study initiation at a site initiation visit, an Onxeo (formerly known as BioAlliance Pharma) representative will review the protocol and eCRF with the investigators and their staff.

A Clinical Research Associate (CRA) will be appointed by the sponsor to monitor this study and periodically contact the study centre, including the conduct of site visits.

Monitoring visits at the investigational site will be made regularly to ensure that all aspects of the protocol, Good Clinical Practice (GCP), and national and local requirements are observed.

Source documents will be verified for consistency with the data on the eCRF. The investigator guarantees direct access to source documents by the sponsor. Source data verification is performed in accordance with data protection regulations and guidelines and all information reviewed will be kept confidential.

The investigator is responsible for completing the eCRFs within five days of the patient's visit and the Onxeo (formerly known as BioAlliance Pharma) monitor/representative is responsible for reviewing them in order to clarify and resolve any data queries. The completed and monitored eCRFs for completed visits will be locked by the monitor appointed by Onxeo (formerly known as BioAlliance Pharma) and data will be processed by the sponsor Data Management. At the end of the study, a copy of the completed eCRFs will be provided to the respective sites for retention with other study documents, such as the protocol, the investigator's brochure and any protocol amendments, in a secure place.

10.3 Data Management

Data Management will be performed under the responsibility of the Sponsor.

Data from the eCRFs are entered into the study database using EDC (Electronic Data Capture).

Subsequently, the information entered into the database is systematically checked

- On line with automatic checks
- Off line by Data Management staff

Using error messages from validation programs or database listings.

Error message will be entered on Data Clarification Forms and entered into the database by the investigator using EDC. Investigator will sign the final eCRF with electronic signature. This

process is followed until the lock of the database. Quality control audits of all key safety and efficacy data in the database will be made by the data-manager before locking the data-base.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List which employs the Anatomical Therapeutic Chemical classification system. Coexistent diseases and adverse events will be coded using MedDRA.

When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement between the Clinical Operations Manager and the Responsible of Biometry appointed by Onxeo (formerly known as BioAlliance Pharma).

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Training of Investigators

Training of Investigators will be performed during the Study Initiation Visit. During this visit, study protocol, study procedures, administrative and regulatory procedures, reporting of Serious Adverse Events and Good Clinical Practices Guidelines will be reviewed.

11.2 Training of Monitors – Clinical Research Associates (CRA)

Monitors will be trained on study protocol, study procedures, administrative and regulatory procedures, monitoring guidelines (including handling of Adverse Events), Operating Procedures related to their activities and Good Clinical Practices Guidelines.

11.3 Standard Operating Procedures

The study will be conducted according to Sponsor's Standard Operating Procedures, or after Sponsor approval, according to CRO's Standard Operating Procedures.

11.4 Monitoring

Regular monitoring visits by CRAs at the Investigator's site, prior to the start, during and at the end of the study will be done in order to assure compliance with the protocol, accuracy of the data collected and to follow the progress of the study.

As source data verification is important for monitoring, the investigator and the institution allow access to source data (medical records, patient chart, CRF, pharmacy file, drug accountability log, etc.) in connection with the study.

11.5 Auditing the Trial by the Sponsor

The Sponsor's Quality Assurance will implement a specific audit plan/program for the study. This audit plan will detail all Quality Assurance activities related to the study. Audit plan will cover all critical aspects of the trial.

Audits of selected clinical sites will be conducted in accordance with Sponsor's written procedures, by appointed qualified auditors who will be independent of the clinical trial.

In this respect, Investigator and institution will allow access to duly appointed representatives of the Sponsor, to all documentation and source data (medical records, patient chart, CRF, pharmacy file, drug accountability log, etc.) in connection with the study.

11.6 Auditing the Trial by Regulatory Authorities

Regulatory Authorities may request to audit the trial at any time during and after the completion of the study.

In this respect, Investigator and institution will allow access to duly appointed Regulatory Authorities Auditors to all documentation and source data (medical records, patient chart, CRF, pharmacy file, drug accountability log, etc.) in connection with the study.

12 DATA HANDLING AND RECORD KEEPING

12.1 Case report form and Source Data

In accordance with legislation concerning the protection of data relating directly or indirectly to named individuals, any data collected during a clinical trial will be treated confidentially in order to guarantee the rights of the subject.

The investigator must agree to place source documents relating to the subject(s) at the disposal of the CRA during his monitoring visits. The CRA will verify the data recorded in the e-CRFs against the source documents wherever necessary.

The clinical study may also be inspected by the appropriate regulatory authorities to verify that the study was conducted in accordance with protocol requirements as well as the applicable regulations and guidelines.

Regulatory authorities, the IEC, and an auditor authorized by the Sponsor may request access to all source documents, e-CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that subject names are obliterated on the copies to ensure confidentiality.

12.2 Monitoring Plan (visits)

The clinical research assistant (CRA) will remain in regular contact with the investigator to assess if the data are recorded correctly in the e-CRF.

It is the responsibility of the CRA to regularly check that the protocol is being adhered to and that the e-CRFs are being filled in correctly through comparison with the source data.

The investigator agrees to cooperate with the CRA in order to resolve any problems identified by the latter following the outcome of each monitoring visit.

The CRA will monitor the study progress at the following times:

- Before the initiation of the study to visit the site and determine the site's ability to conform with the requirements of the protocol (as applicable);
- At the initiation visit, the investigator may only enroll his first subject after the CRA has completed this visit;
- During the study the number of monitoring visits will be adapted to suit recruitment at each centre;
- A closing visit will be conducted at the end of the trial.

12.3 Archiving Clinical Trial Files

The investigator shall maintain the essential clinical study documents (including e-CRFs, source documents, clinical drug-disposition records, signed subject ICFs, AE reports, and other

regulatory documents) as required by the applicable regulatory requirements. The investigator should take adequate measures to prevent accidental or premature destruction of these documents. In the event of accidental destruction, the investigator must notify Onxeo (formerly known as BioAlliance Pharma) immediately. The following essential clinical study documents must be maintained:

- Signed informed consent documents for all subjects
- Screening log and enrollment log
- Record of all communication between the investigator and IEC
- Composition of the IEC or other applicable statement
- Record of all communications between the investigator and Sponsor/CRO
- List of sub investigators and other appropriately qualified persons to whom the Principal Investigator has delegated significant trial-related duties, together with their roles in the study and their signatures
- Copies of e-CRFs and of documentation of corrections for all subjects
- Drug-accountability records
- Record of any body fluids or tissues retained
- All other source documents (i.e., subject records, hospital records, laboratory records, etc.)
- All other documents as listed in Section 8 of the consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial)

Essential clinical study documents shall be retained for at least 15 years following the date a marketing application is approved for the drug with the indication for which it is being investigated, or, if no application is to be submitted or if the application is not approved for such indication, until 2 years after the investigation is discontinued and the appropriate regulatory authorities are notified.

These documents shall be retained for a longer period, however, if required by additional applicable regulatory requirements or by an agreement with Onxeo (formerly known as BioAlliance Pharma). The investigator must, therefore, obtain approval in writing from the Sponsor prior to destruction of any records.

The investigator shall notify Onxeo (formerly known as BioAlliance Pharma) prior to any change in the location or status of any essential, clinical-study documents. Onxeo (formerly known as BioAlliance Pharma) shall be responsible for informing the investigator when these documents no longer need to be retained.

13 ETHICS, REGULATORY & LEGAL CONSIDERATION

The study will be conducted in accordance with the Good Clinical Practice (GCP) and local country requirements, the recommendations of the Declaration of Helsinki, as amended from time to time and the rules of International Conference on Harmonisation (ICH).

13.1 Ethical aspects

Research is designed to benefit society and Public Health by gaining new knowledge.

There is no guarantee, though, that the individual participant will personally benefit from study participation. The study treatment may result in an improvement of the disease or there may be no improvement at all. This is clearly described in the participant information.

Overall it is considered that the study does not cause undue constrain to the participants.
On this basis it is considered that the potential usefulness of the study exceeds the inconvenience and risks, and is reasonable to implement the study.

13.2 Independent Ethics Committees (IEC)

Documented approval from the appropriate IEC will be obtained for the participating centre prior to study initiation, according to GCP, local laws, regulations, and organizations. When necessary, an extension, amendment, or renewal of the IEC approval must be obtained and also forwarded to the Sponsor. The IEC must supply to the Sponsor, upon request, a list of the IEC members involved in the vote and a statement to confirm that the IEC is organized and operates according to GCP and applicable laws and regulations.

13.3 Ethical Conduct of the Study

The procedures described in this protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor and investigator abide by GCP Guidelines and operate under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an inspection by the Sponsor representatives and/or regulatory authority representatives at any time. The investigator must agree to the inspection of study-related records by the regulatory authority/Sponsor representatives, and must allow direct access to source documents by the regulatory authority/Sponsor representatives.

Modifications to the study protocol will not be implemented by either the Sponsor or the investigator without agreement by both parties. However, the investigator may implement a deviation form or a change of the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/Sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol

amendment should be submitted to the IEC/Sponsor. Any deviations from the protocol must be fully explained and documented by the investigator.

13.4 Regulatory Authority Approvals/Authorizations

Regulatory Authority approvals/authorizations/notifications, where required, must be in place and fully documented prior to study start.

13.5 Subject Information and Consent

A core information and Informed Consent Form (ICF) will be reviewed with each subject. Prior to the beginning of the study, the investigator must have the IEC written approval of the written ICF and any other written information to be provided to patients. The informed consent should be in accordance with the current revision of the Declaration of Helsinki, current ICH and GCP guidelines, and Onxeo (formerly known as BioAlliance Pharma) policy. The written approval of the IEC together with the approved (signed and dated) patient information/ICFs must be filed in the study file.

The principal investigator, or co-investigators licensed to do so, will provide the oral information and simultaneously will go through the written participant information and ICF. The conversation will be conducted in a quiet and undisturbed environment at the hospital. Appropriate time for reflection (ideally at least 24 hours) will be given. If needed or requested, the patient could have a second meeting or seek for another opinion before signing the inform consent form.

Written ICF must be obtained from each subject before any study-specific procedures take place. Participation in the study and the date of informed consent given by the subject should be documented appropriately in the subject's file. The ICF should be written in a language in which the subject is fluent.

The investigator must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the trial and any discomfort it may entail. Subjects will be informed that they are free to not participate in the trial and that they may withdraw consent to participate at any time. They will be told that refusal to participate in the study will not prejudice future treatment. They will also be told that their records may be examined by competent authorities and authorized persons but that personal information will be treated as strictly confidential and will not be publicly available. Subjects must be given the opportunity to ask questions. After this explanation and before entry into the trial, consent should be appropriately recorded by means of the subject's dated signature. This document should be prepared in duplicate, one for the subject and the other for the investigator. The investigator must retain his copy in his archives for a period of 15 years in accordance with current legislation. The subject should receive a signed and dated copy of the ICF. The original signed ICF should be retained in the study files. The investigator shall maintain a log of all subjects who sign the ICF and indicate if the subject was enrolled into the study or the reason for failure to enroll.

13.6 Amendment to the protocol

Modifications to the clinical study protocol will be made as an amendment and must be approved by Onxeo (formerly known as BioAlliance Pharma) and the IEC prior to being implemented, unless an amendment is to eliminate an immediate hazard to the clinical study subjects.

Neither the investigator nor Onxeo (formerly known as BioAlliance Pharma) may modify the protocol without the agreement of the other. Once the study has started, amendments may only be made in exceptional cases. The IEC will be notified of such amendments. Modifications must be made in writing and signed by all parties concerned. The modifications will become an integral part of the protocol. Onxeo (formerly known as BioAlliance Pharma) or their designee shall be responsible for notifying the regulatory authorities of any amendments to the protocol.

14 CONFIDENTIALITY

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Subject names will not be supplied to the Sponsor. Only the subject number will be recorded in the e-CRF, and if the subject name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that representatives of the Sponsor, IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.
The investigator will maintain a list to enable subject's records to be identified for Health Authority inspections.

15 DOCUMENTATION AND SOURCE DOCUMENTS

Study Documents

The investigator is responsible for providing and maintaining essential study documents. Essential study documents are those documents that individually and collectively permit the evaluation of the conduct of the study and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator and Onxeo (formerly known as BioAlliance Pharma) with the standards of GCP and with all applicable regulatory requirements.

Essential study documents include regulatory documents as well as source documents which are original documents, data records of clinical findings, observations, and other activities in a clinical study necessary for the reconstruction and evaluation of the study.

Source Data corresponds to all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for

the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source data is documented in source documents.The following list gives examples of source documents where source data may be located:

- medical records
- laboratory reports
- subject diaries
- nurses' notes
- dispensing logs
- electrocardiogram (ECG) print-outs
- case report forms (CRF)
- X-ray images
- radiological reports, etc.

As the location of source data could vary from one investigator site to another depending on the organisation of the site and/or the investigator, some source data may be recorded directly in the Case Report Form (CRF). This corresponds, for example, to specific data requested by the study protocol and/or in case of data usually not fully described and/or collected in routine practice (e.g. ethnic origine, classification of AE / pain / other according to specific scale, body mass index, body surface aera, calculated creatinin clairance, disease staging..). These data collected and validated in the CRF are considered as source document.
In addition, all efforts have to be made to maintain the anonymity and confidentiality of medical records during this study as per local country regulation.

Technical Documentation

All information relating to the investigational drug, and to the strategy of Onxeo (formerly known as BioAlliance Pharma), such as the clinical indication of the drug, the method of preparation, and the scientific data supplied by Onxeo (formerly known as BioAlliance Pharma) and as yet unpublished, is confidential and remains the property of Onxeo (formerly known as BioAlliance Pharma). The investigator agrees to use this information only for conducting this study and not for any other purposes, except with the prior written agreement of the Sponsor.

The e-CRFs completed in the context of the study remain the property of Onxeo (formerly known as BioAlliance Pharma). The investigator has to retain the documents pertaining to the study, the written ICFs, the list identifying the participants, and a copy of the e-CRFs for a period of 15 years. The medical records and source documents for the e-CRFs shall be kept for the maximum period allowed by the investigator's centre. The Sponsor should be notified in writing before any files are destroyed at the centre.
An in-house statistical and clinical report shall be prepared and signed jointly by the Principal Investigator and Onxeo (formerly known as BioAlliance Pharma).

The results of the study are the property of Onxeo (formerly known as BioAlliance Pharma).

16 PUBLICATION OF TRIAL RESULTS

Data from the study will be published in an international peer-reviewed journal. Order of the authors will be agreed based on the contribution of each author in the definition, executing and writing stages.

17 FINANCIAL CONDITIONS

This study is initiated by Onxeo (formerly known as BioAlliance Pharma).

The study drug will be provided to participants at no cost. Patient will not be reimbursed for participation in this study. Actual reasonable travel reimbursement assistance may be available if needed after agreement of the sponsor.

This research is funded by Onxeo (formerly known as BioAlliance Pharma). The researchers do not, however, hold a direct financial interest in the sponsor or in the outcome of the study.

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19 LIST OF APPENDICES

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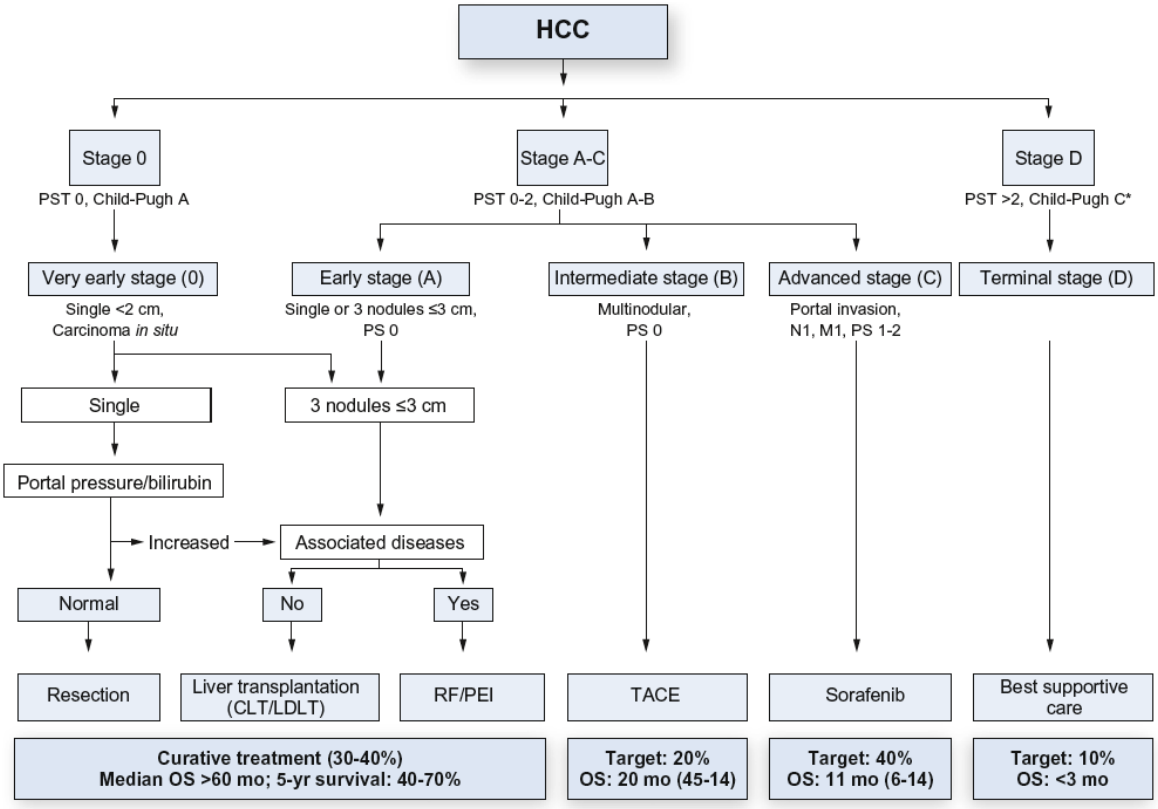
I. BCLC proposal for HCC staging



Barcelona Clinic Liver Cancer (BCLC) classification in HCC (adapted from EASL-EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma, J. Hepatol 2012)

II. Child-Pugh score

	1 point	2 points	3 points
Encephalopathy	Absent	Asterixis	Confusion
Ascites	Absent	Mild/Moderate	Severe/Refractory
Albumin	> 35g/L	35-28g/L	< 28g/L
Total bilirubin	< 35µM/L ≤ 2mg/dl	35-50µM/L 2-3 mg/dl	> 50µM/L >3 mg/dl
Prothrombin time rate (INR)	> 50% (< 1.7)	40-50% (1.7-2.3)	< 40% (> 2.3)

Class A: 5-6 points
Class B: 7-9 points
Class C: 10-15 points

III. CLIP Score and MELD score

CLIP Score

	0 point	1 point	2 points
Child-Pugh	A	B	C
Tumour morphology	Uninodular extension ≤ 50%	Multinodular extension ≤ 50%	Massive or extension > 50%
AFP	< 400	≥ 400	
Portal vein thrombosis	No	Yes	

Clip Score = 0
Clip Score = 1
Clip Score = 2
Clip Score = 3
Clip Score = 4 to 6

MELD Score

MELD (Model for End-stage Liver Disease) score is calculated according to the formula below:

MELD = 9.57*Log creatinine (mg/dl) + 3.78*Log bilirubin (mg/dl) + 11.2*Log INR+ 6.43

IV. ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, (eg, light house work, office work)
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

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V. Stages of Heart Failure – NYHA Classification

The New York Heart Association (NYHA) functional classification system relates symptoms to everyday activities and the patient's quality of life:

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnoea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

VI. Doxorubicin Transdrug™ protocol of reconstitution

**DOXORUBICIN TRANSDRUG™ 10 mg - POWDER FOR SUSPENSION FOR INJECTION
PROTOCOL OF RECONSTITUTION AND ADMINISTRATION PROCEDURE**

1. DOSAGE FORM

Doxorubicin Transdrug™ 10 mg (DT) is a powder for suspension for injection which contains doxorubicin, an antineoplastic agent as active drug. DT is a [redacted] for suspension for intravenous injection, presented in glass vials with a rubber cap and a flip-off seal. Each vial contains 10 mg equivalent doxorubicin and [redacted]

2. RECOMMENDATION FOR SAFE HANDLING

The following information is intended for medical and healthcare professionals only. Caution should be exercised in the handling and preparation of DT. The reconstitution must be carried out under a laminar flow, by a suitably trained staff. The vials must never be opened before reconstitution. DT must be injected by strict intravenous route. If any signs or symptoms of extravasation have occurred, the infusion should be immediately stopped and restarted in another vein. The waste disposal must be performed with respect to each centre procedure for genotoxic and cytotoxic compounds.

3. STORAGE

Store in the refrigerator (2°C-8°C).

After reconstitution:

Chemical and physical in-use stability has been demonstrated for 24h following initial reconstitution when stored at refrigerated conditions (2°C-8°C).

All precaution should be taken during the reconstitution in order to avoid any microbiological contamination. In-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C to 8°C.

Do not store partially used vials for future patient use.

4. MATERIAL FOR RECONSTITUTION

- Vent needles dispensing pin
- 5 µm filters (green colour code)
- 1.2 µm filters (blue colour code)
- 30 ml Luer Lock Syringes
- Needles 21G x 1 ½ " (0.8 x 38 mm)
- 250 ml sterile bag for injectable solution
- 2.5% sterile glucose solution for injection

5. RECONSTITUTION AND FILTRATION *(Hospital Pharmacy, under laminar flow)*

It is important to read the entire content of this section prior to the preparation of this medicinal product.

Aseptic technique must be strictly observed throughout handling of DT since no preservative is present.

Caution should be exercised in the handling and preparation of DT. The use of gloves is required.

The preparation for intravenous infusion of DT is performed according to two main steps (reconstitution and filtration) as described hereafter.

Step 1 – Reconstitution of DT powder

- Calculate the dose of DT and determine the number of vials needed, based upon the recommended dose and the patient's body surface area (BSA), according to the tables below.
- Get the vials for reconstitution out of the refrigerator.
- Keep the vials for reconstitution at room temperature for at least 30 min before reconstitution.
- Reconstitute each vial containing HCl Doxorubicin 10 mg with 25 mL of 2.5% glucose as follows :
    - Remove the flip-off seal of each vial.
    - Insert a vent needle through the rubber cap.
    - Open the vent needle protective cap.
    - Add 25 ml of sterile glucose 2.5% for injection using a 30 ml syringe to each DT vial, to yield a suspension containing 0.4 mg/ml of doxorubicin HCl. The addition of glucose may induce the formation of a foam;
    - Close the vent needle and shake each vial for a minimum of 10 seconds to completely disperse the DT. Visually inspect the vial for particulate matter and continue shaking until complete dispersion is obtained. Once reconstituted the resulted nanoparticle suspension for infusion of DT is a red-orange homogeneous suspension.

Step 2 - Double filtration of the DT suspension through 5 µm filter and 1.2 µm filter into a sterile bag

Each individual vial has to be filtered using one unique set of 5 µm and 1.2 µm filters and 30 mL syringe.

- Carefully open the protective cap of the vent needle.
- Withdraw the suspension of DT into a sterile 30 mL syringe. During the collection of reconstitued suspensions, pay attention to avoid the aspiration of the foam in the syringe
- Remove the 30mL syringe with the suspension of DT.
- Adapt on each 30 mL syringe containing the suspension of DT and in series according the following sequence :
    - one 5 µm filter provided (green colour code),
    - one 1.2 µm filter provided (blue colour code) and then,

- the sterile bag provided.

- Instill the suspension of each syringe into the sterile bag.
- Operate as above to reconstitute other vials intended for the preparation in order to obtain in the sterile bag the appropriate volume of DT 0.4 mg/mL as determined previously.
- The total suspension of DT corresponding to the appropriate volume for the patient will be administered to the patient without any futher dilution.
- Stick the label onto the bag and store it in a refrigerator at 2°C to 8°C.
- If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be more than 24 hours following preparation and should be stored at 2°C to 8°C.
- Discard any unused portion of suspension of DT.
- Do not futher dilute the reconstituted suspension of DT.

6. ADMINISTRATION TO THE PATIENT

1. Day 0 – Oral premedication the Day before study treatment administration

- The day before DT injection, patient will receive a premedication with methylprednisolone 32 mg p.o. (or equivalent) + cetirizine 20 mg p.o (or equivalent)

2. Day 1 – Study treatment administration

- Get the suspension bag out of the refrigerator and leave it at room temperature for at least 30 min;
- One hour before DT administration (H-1), patient will receive premedication with methylprednisolone 32 mg p.o. (or equivalent) and cetirizine 20 mg p.o (or equivalent);
- Then, the suspension of DT will be infused over 6 hours through intravenous route using an infusion pump or a syringe-pump in order to insure a constant flow;
- Patient will have a continuous SaO_2 monitoring during infusion and then 24 hours after the infusion starts;
- The duration of infusion must be increased (flow reduced by half) in case of occurrence of pulmonary toxicity (cf section 7.6: Urgent Safety Measures). Any modification in the infusion rate must be recorded in the e-CRF;
- Fasting is not needed.

3. Day 2 – Oral premedication the Day after study treatment administration

- The Day after DT administration (D2), patient will receive a premedication with methylprednisolone 32 mg p.o. (or equivalent) and cetirizine 20 mg p.o (or equivalent);

DT dosing table and volume to be administered at a dose of 20 mg/m² according to patient's body surface area

DOXORUBICIN TRANSDRUG™ - DOSE = 20 mg/m²									
Body surface area*	**1.5 m²**	**1.6 m²**	**1.7 m²**	**1.8 m²**	**1.9 m²**	**2.0 m²**	**2.1 m²**	**2.2 m²**	**2.3 m²**
Total dose per patient	30 mg	32 mg	34 mg	36 mg	38 mg	40 mg	42 mg	44 mg	46 mg
Number of vials (10 mg/vial) to reconstitute**	3	4	4	4	4	4	5	5	5
Final volume of suspension obtained to be administered (0.4 mg/mL)	**75 ml**	**80 ml**	**85 ml**	**90 ml**	**95 ml**	**100 ml**	**105 ml**	**110 ml**	**115 ml**

DT dosing table and volume to be administered at a dose of 30 mg/m² according to patient's body surface area

DOXORUBICIN TRANSDRUG™ - DOSE = 30 mg/m²									
Body surface area*	**1.5 m²**	**1.6 m²**	**1.7 m²**	**1.8 m²**	**1.9 m²**	**2.0 m²**	**2.1 m²**	**2.2 m²**	**2.3 m²**
Total dose per patient	45 mg	48 mg	51 mg	54 mg	57 mg	60 mg	63 mg	66 mg	69 mg
Number of vials (10 mg/vial) to reconstitute**	5	5	6	6	6	6	7	7	7
Final volume suspension obtained to be administered (0.4 mg/mL)	**112.5 ml**	**120 ml**	**127.5 ml**	**135 ml**	**142.5 ml**	**150 ml**	**157.5 ml**	**165 ml**	**172.5 ml**

DT dosing table and volume to be administered at a dose of 15 mg/m² according to patient's body surface area

DOXORUBICIN TRANSDRUG™ - DOSE = 15 mg/m²									
Body surface area*	**1.5 m²**	**1.6 m²**	**1.7 m²**	**1.8 m²**	**1.9 m²**	**2.0 m²**	**2.1 m²**	**2.2 m²**	**2.3 m²**
Total dose per patient	22.5 mg	24 mg	25.5 mg	27 mg	28.5 mg	30 mg	31.5 mg	33 mg	34.5 mg
Number of vials (10 mg/vial) to reconstitute**	3	3	3	3	3	4	4	4	4
Final volume suspension obtained to be administered (0.4 mg/mL)	**56.5ml**	**60 ml**	**64 ml**	**67.5 ml**	**71.5 ml**	**75 ml**	**79 ml**	**82.5 ml**	**86.5 ml**

* Round off the Body surface area in the following way:
From 1.50 to 1.54 m², round down to 1.5 m²
From 1.55 to 1.59 m², round up to 1.6 m²

**The number of vials to reconstitute could be over if the volume of suspension collected is not sufficient.

VII. Pharmacokinetic protocol

During the previous HCC studies, preliminary pharmacokinetic parameters were evaluated and individual pharmacokinetic profiles have been determined. The data obtained pointed out a wide inter-individual variability, which require evaluation of the pharmacokinetic profile in patients with HCC.

In this study, patients will be treated with doses at 20 or 30 mg/m² of Doxorubicin Transdrug™, repeated every 4 weeks until progression of the disease or unacceptable toxicity.

The aim of pharmacokinetic evaluation is first, to determine the population pharmacokinetic parameters. Secondly, the objective is to analyse the pharmacokinetic / pharmacodynamic correlation with DT efficacy and toxicity, and to evaluate inter-Cycles AUC stability.

Due to its specific formulation ([redacted]), late exposure (>48 hours after DT infusion) has to be evaluated in order to be able to characterize the pharmacokinetic profile of doxorubicin and doxorubicinol.

For this purpose, blood sampling will be performed at the first and third treatment Cycles. For patients still on study treatement after Cycle 3, an optional and limited pharmacokinetic blood sampling will be done at Cycle 4, Cycle 6 (e.g. every 2 cycles until the end of study treatment). Blood collection (10mL/sample) will have to be taken from a peripheral vein. DT will be infused at D1 of each cycle over 6 hours through intravenous route.

<u>At Cycle 1 and Cycle 3:</u>

Blood samples will be collected at the following times on D1, D2, D3, D4, D8, D14 and D28 during the 1st and the 3rd Cycle of DT treatment, to perform total and free doxorubicin and doxorubicinol assays.

D1 (D1= DT administration) (in patient)											D2 (in patient)	
T0	T30min	T60min	T2h	T4h	T6h	T6h30	T7h	T7h30	T8h	T12h ± 2h	T24h ± 2h	T33h ± 2h
Before infusion	30min after start of infusion	60min after start of infusion	2h after start of infusion	4h after start of infusion	3 to 5 min before the end of infusion	30min after end of infusion	1h after end of infusion	1h30 after end of infusion	2h after end of infusion	6h± 2 hours after end of infusion	24h± 2 hours after start of infusion	33h± 2 hours after start of infusion

- D1: T_0: before the beginning of treatment injection,
- D1: T_{30min}, T_{60min}, T_{2h}, T_{4h} after start of the infusion, T_{6h} (3-5 min before the end of infusion), then $T_{6h30min}$ (30 min after the end of infusion), T_{7h} (1 hour after the end of infusion), T_{7h30} (1 hour 30 after the end of infusion), T_{8h} (2 hours after the end of infusion) and $T_{12h \pm 2h}$ (6 ± 2 hours after the end of infusion)
- D2: T_{24h} and T_{33h} (24 ± 2 hours and 33 ± 2 hours after start of infusion); The time H_{33h} has been taken in order to avoid blood sampling during night

- Then D3: T_{48h} (48 ± 2 hours after start of infusion), D4: T_{72h} (72 ± 2 hours after start of infusion), D8, D14 and D28 after DT administration.

D3 (in or outpatient)	D4 (in or outpatient)	D8 (outpatient)	D14 (outpatient)	D28 (in or outpatient)
T48h ± 2h	T72h ± 2h	T7days	T13days	T27days
48h± 2 hours after start of infusion	72h± 2 hours after start of infusion	7 days after infusion (morning or afternoon)	13 days after infusion (morning or afternoon)	27 days after infusion (morning or afternoon)

At Cycle 4, Cycle 6, then every 2 cycles until the end of study treatment (optional):

D1 (D1= DT administration) (in patient)				D14 (outpatient)	D28 (in or outpatient)
T0	T4h	T6h	T8h	T13days	T27days
Before infusion	4h after start of infusion	3 to 5 min before the end of infusion	2h after end of infusion	13 days after infusion (morning or afternoon)	27 days after infusion (morning or afternoon)

Blood Sampling procedures:

The blood will be taken in 10 ml EDTA tubes. Blood samples will be immediately put into a glass of ice + water after sampling. Then,**centrifugation will be performed immediately at 3000 rpm, at +4°C ± 2°C for 20 min, to separate out the plasma**.

The plasma will then **be divided into 2 polypropylene cryotubes, each of which must contain at least 1.5ml of plasma, and then immediately frozen at -80°C; Plasma can be alternatively kept at -20°C if -80°C is not feasible**.

The samples may be centrifuged **individually**, after the sample is collected.

Each sample shall be identified as follows, using a label that is resistant to the storage temperature of -80°C:

- the protocol number BA2011/03/04,
- the centre number,
- the identification number of the patient,
- the theoretical sampling time,
- the date of sampling.

A check-list will be kept, including the exact identification of each sample and the real sampling times.

Onxeo (formerly known as BioAlliance Pharma) will ensure dispatching of samples to third parties in charge of doxorubicin and its metabolite dosage. Study samples will be transferred

periodically to the laboratory in charge of these dosages using a container filled with enough dry ice to ensure that samples will be kept deep frozen at about -80°C.

VIII. Biomarkers protocol

The blood will be taken in a 10 ml K2EDTA tube. Immediately gently invert the tube 10 times, and store it at room temperature until centrifugation.

Aliquoting and freezing should be completed within 60 min of specimen collection.

1. **Set the centrifuge at 6°C**. Plasma is obtained by centrifugating the blood sample in a swing **centrifuge at the speed =1300 g for 10 min** under refrigerated conditions (2-6°C).
    a. NOTE: Ensure rotor is balanced.

2. Using a pipette the resultant plasma is transferred (but not the white cells in the buffy coat) to a **15 ml conical** bottom Falcon® tube.

    - **Centrifuge the second plasma tube at 2400 g or rpm for 15 min** under **refrigerated conditions (2-6° C)** to remove all potentially remaining cellular material.

    - Save the "buffy coat" containing white cells and the red blood cells (RBC), separately as a source of DNA. Using a pipette, transfer buffy coat aliquots and red blood cell aliquots into **labelled 1.8 ml cryovials and freeze them at -70°C to -80°C.**

3. Transfer the resultant plasma after second centrifugation, into a new **15 mL conical bottom Falcon® tube,** using a pipette. Pipette to approximately 10% from the bottom of the tube to ensure no cellular material is collected.

    The purpose of double spinning the plasma is to remove all cellular contaminants so that the plasma is suitable for plasma DNA analysis. It is extremely important, therefore, not to disturb the buffy coat after the first spin, and any pellet after the second spin.

4. Gently mix the plasma and transfer 800-1000 µl aliquots into labeled **1.8 ml cryovials**, without delay. Freeze the cryovials **at -70°C to -80°C**.

IX. RECIST1.1 and mRECIST Criteria (Lencioni and Llovet 2010[53])

Tumour response and progression will be assessed by CT scan or MRI according to Response Evaluation Criteria In Solid Tumors (RECIST) guideline version 1.1 and modified RECIST Critera for HCC (Eisenhauer 2009[54]).

RECIST 1.1 Criteria

Target lesions: the number of lesions to select as target lesions is a maximum of 2 lesions per organ and 5 lesions in total. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements.

At baseline, the sum of the diameters: longuest diameters (LD) for extra nodal target lesions and short axis diameters (SAD) for nodal lesions will be calculated and reported as the baseline sum LD. This baseline sum LD will be used as the reference by which to characterize the objective tumour response.

Non target lesions: all other lesions should be identified as non-target lesions and should be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout the study.

RECIST 1.1 response criteria used to determine the response on target lesions:

Evaluation of target lesions

Complete Response (CR):	Disappearance of all targets extra nodal lesions and the regression of all nodal lesions to < 10 mm SAD.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is considered progression.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumour marker level. All lymph nodes must be non pathological in size (< 10 mm short axis)

Non-CR/Non-PD::	Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits
Progressive Disease (PD):	*Unequivocal progression* of existing non-target lesions and/or appearance of one or more new lesions *

**Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).*

Evaluation of overall response (RECIST 1.1)

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Modified RECIST:

Modified RECIST (mRECIST) criteria are considered as the best criteria to evaluate the efficacy of treatment of HCC. mRECIST criteria are endorsed by EASL and AASLD societies and recently by the FDA (Lencioni and Llovet, 2010). The definitions used in the mRECIST are described below:

Target lesions: the lesion should be located in the LIVER:

- Be classified as a RECIST measurable lesion (in at least one dimension as 1 cm or more);
- Be suitable for repeat measurement;
- Show intratumoural arterial enhancement on contrast-enhanced CT or MRI.

mRECIST response criteria used to determine the response on target lesions:

- **Complete response (CR)** = Disappearance of any intratumoural arterial enhancement in all target lesions;

- **Partial response (PR)** = At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions taking as reference the baseline sum of the diameters of target lesions;
- **Progressive Disease (PD)** = An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started;
- **Stable Disease (SD)** = Any cases that do not qualify for either partial response or progressive disease.

Note: Infiltrative–type HCC should be defined as non target lesion when the mass shows ill-defined, not suitable for repeat measurements. The same applies for HCC lesions previously treated with local or systemic treatments. They may or not be considered as target lesions according to delineation and suitability for repeat measurements.

mRECIST response criteria used to determine the response on non target lesions are the same as RECIST 1.1 response criteria. However, as for target lesions, tumour necrosis should be taken into account when assessing the response to nontarget lesions. The disappearance of any intratumoural arterial enhancement in nontarget lesions should be considered equivalent to the disapperance of nontarget lesions. Likewise, the persistence of intratumoural arterial enhancement in one or more nontarget lesions should be considered equivalent to the persistence of one or more nontarget lesions and therefore declared incomplete response/stable disease.

Special recommendations can be made:

- Portal vein thrombosis should be considered a non measurable lesion due to the difficulty in performing consistent measurements of the malignant thrombus during the course of the treatment;
- Porta hepatis lymph node can be considered as malignant if the lymph node axis is at least 20 mm;
- Pleural effusion or ascites: cytopathologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumour has met criteria for response or stable disease (peritoneal carcinomatosis is a rare event in HCC).

<u>New lesions are:</u>

- A newly detected hepatic nodule is classified as HCC when its longest diameter is at least 1 cm and the nodule shows the typical vascular pattern of HCC on dynamic imaging (hypervascularisation in the arterial phase with washout in the venous or late venous phase);
- Liver lesions larger than 1 cm without typical vascular pattern with evidence of at least 1 cm interval growth in subsequent scans;

- Individual radiological event will be adjudicated in retrospect as progression at the time it was 1st detected by imaging techniques even if strict criteria were fulfilled only on subsequent radiological testings.

Overall tumoural response takes into account all possible combinations of tumoural responses on target and non target lesions. The guidelines for the evaluation of overall response are similar using RECIST 1.1 or mRECIST for HCC and as shown in table below.

Evaluation of overall response (mRECIST for HCC)

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

X. NCI CTC classification

The NCI Commun Terminology Criteria for Adverse Events version 4.0 is located on the internet at the following URL:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

XI. List of inhibitors and inducers of CYP3A4, CYP2D6 or P-gp

Non exhaustive list adapted from FDA recommendations on Drug development and Drug Interactions: table of substrates, inhibitors and inducers:

http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Enzyme	**Inhibitor**		**Inducer**	
CYP3A4	**Class**	**DCI**	**Class**	**DCI**
	Antifungal drugs	ketoconazole itraconazole posaconazole voriconazole fluconazole	**Antibiotics**	rifampin nafcillin
	Antibiotics	clarithromycin telithromycin erythromycin ciprofloxacin isoniazid	**Antiepileptic drugs**	carbamazepine phenytoin rufinamide
	Antiviral drugs	boceprevir telaprevir ritonavir saquinavir indinavir lopinavir/ritonavir ritonavir nelfinavir amprenavir atazanavir darunavir/ritonavir fosamprenavir tipranavir/ritonavir	**Antiviral drugs**	efavirenz etravirine amprenavir
			Others	modafinil armodafinil prednisone bosentant aprepitant pioglitazone echinacea
	Calcium channel blockers	mibefradil diltaziem verapamil amlodipine		
	Antiarrytmics	amiodarone ranozaline		
	Antidepressant/Anxiolytic	nefazodone alprozolam fluoxetine fluvoxamine		
	Others	cimetidine ranitidine		

		aprepitant cyclosporine bicalutamide imatinib grapefruit juice goldenseal	atorvastatin oral contraceptives cilostazol nilotinib ginkgo		
Enzyme	**Inhibitor**			**Inducer**	
CYP2D6	**Antiarrytmics**	quinidine propafenone	amiodarone	*none known*	
	Calcium channel blockers	diltaziem	verapamil		
	Antidepressant	fluoxetine paroxetine desvenlafaxine sertraline	bupropion duloxetine escitalopram		
	Antifungal drugs	terbinafine			
	Antibiotics	telithromycin			
	Antiviral drugs	ritonavir			
	Others	methadone cimetidine oral contraceptives cinacalcet hydroxychloroquine gefitinib hydralazine	diphenhydramine ranitidine febuxostat celecoxib imatinib echinacea		
P-gp	**Antifungal drugs**	itraconazole	ketoconazole	**Antibiotics**	rifampin
	Antibiotics	azithromycin erythromycin	clarithromycin	**Antiepileptic drugs**	carbamazepine phenytoin
	Antiviral drugs	lopinavir	ritonavir	**Antiviral drugs**	tipranavir/ritonavir

	Antiarrytmics	amiodarone carvedilol	dronedarone quinidine		
	Calcium channel blockers	diltaziem verapamil	felodipine		
	Others	captopril cyclosporine quercetin	ranolazine conivaptan		

XII. EQ- 5D™ Questionnaire

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

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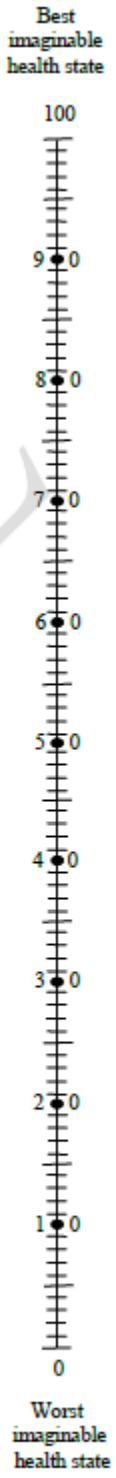
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



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