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ORIGINAL ARTICLE

# Preliminary results of the Phase 1 Lip-Re I clinical trial: biodistribution and dosimetry assessments in hepatocellular carcinoma patients treated with $^{188}$Re-SSS Lipiodol radioembolization

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## Abstract

**Purpose** This study sought to provide preliminary results on the biodistribution and dosimetry following intra-arterial liver injection of $^{188}$Re-SSS Lipiodol on hepatocellular carcinoma patients included in the Phase I Lip-Re 1 study.

**Methods** Results of the first six patients included are reported. Analysis of the $^{188}$Re-SSS Lipiodol biodistribution was based on planar scintigraphic and tomoscintigraphic (SPECT) studies performed at 1, 6, 24, 48, and 72 h post-administration. Quantification in blood, urine, and stool samples was performed. Determination of the tumour to non-tumour uptake ratio (T/NT) was calculated. Absorbed doses to target organs and tumours were evaluated using the MIRD formalism.

**Results** The mean injected activity of $^{188}$Re-SSS Lipiodol was 1645 ± 361 MBq. Uptakes were seen in the liver (tumour and healthy liver) and the lungs only. All these uptakes were stable over time. A mean 1.4 ± 0.7% of $^{188}$Re-SSS Lipiodol administered was detected in serum samples at 6 h, declining rapidly thereafter. On average, 1.5 ± 1.6% of administered activity was eliminated in urine and feces over 72 h. Overall, 90.7 ± 1.6% of detected activity on SPECT studies was found in the liver (74.9 ± 1.8% in tumours and 19.1 ± 1.7% in the healthy liver) and 9.3 ± 1.6% in the lungs (5.7 ± 1.1% in right and 3.7 ± 0.5% in left lungs). Mean doses absorbed were 7.9 ± 3.7Gy to the whole liver, 42.7 ± 34.0Gy to the tumours, 10.2 ± 3.7Gy to the healthy liver, and 1.5 ± 1.2Gy to the lungs. Four patients had stable disease on CT scans at 2 months. The first patient with rapidly progressive disease died at 1 month, most probably of massive tumour progression. Due to this early death and using a conservative approach, the trial independent evaluation committee decided to consider this event as a treatment-related toxicity.

**Conclusion** $^{188}$Re-SSS Lipiodol has a favorable biodistribution profile concerning radioembolization, with the highest in-vivo stability among all radiolabeled Lipiodol compounds reported to date. These preliminary results must be further confirmed while completing this Phase I Lip Re1 study.

**Keywords** $^{188}$Re · Lipiodol · Hepatocellular carcinoma · Liver · Oncology

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## Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide and the second most common cause of cancer-related death [1–5]. In spite of using sorafenib and $^{90}$Y-loaded microsphere radioembolization, the treatment of advanced Barcelona Clinic Liver Cancer (BCLC) classification B patients and those with portal vein thrombosis (PVT) is still highly challenging. In this setting, overall survival is only 10.7 months under sorafenib [2]. In addition, the two recently published randomized studies comparing $^{90}$Y-loaded resin microsphere therapy versus sorafenib did not demonstrate any increase in overall survival when using radioembolization [3–5].

$^{131}$I-Lipiodol has, meanwhile, been applied for many years since a randomized study demonstrated a superior overall survival in HCC patients with PVT treated with this novel therapeutic modality in comparison with best supportive care [6]. However, $^{131}$I-Lipiodol marketing was discontinued in 2010 by the manufacturer for several reasons, including sorafenib approval, $^{90}$Y-loaded microsphere development, and radioprotection constraints, as well as lung toxicities in several cases. Furthermore, $^{131}$I has long half-life (8 days) and an abundant high-energy photon emission (364 keV, 81.7%) resulting in major radioprotection constraints. These observations highlight the necessity of developing new therapeutic agents for managing advanced HCC.

With this objective in mind, Lipiodol labeling with a new radiolabeled stable complex of rhenium 188 ($^{188}$Re) has been developed over the last years, namely $^{188}$Re-SSS Lipiodol [7–14]. $^{188}$Re exhibits a short half-life (17 h), with only a small amount of lower-energy gamma radiation compared to $^{131}$I-Lipiodol (155 keV, abundance 14%), resulting in more favorable radioprotection constraints. Using $^{188}$Re-SSS Lipiodol in HCC patients is presently being evaluated in the Phase I Lip-Re 1 study that is still ongoing (ClinicalTrials.gov, number NCT01126463 [15]). The main objective of this report is to provide preliminary results on $^{188}$Re-SSS Lipiodol biodistribution and dosimetry assessments in humans, from the first six patients treated in this Phase 1 trial.

## Methods

### Patients

Patients with unresectable HCC were enrolled in this prospective, interventional, mono-center Phase I Lip Re 1 activity-escalation study of intra-arterial $^{188}$Re-SSS Lipiodol. A classical 3 ± 3 patients scheme was used: three patients included by activity step, plus 3 patients if a limiting toxicity occurred in the first three patients, the higher activity step allowed only if ≤ 1 limiting toxicity occurred in the evaluated step. The maximal tolerated dose (MTD) is defined by the highest activity level producing no more than one limiting toxicity. A maximum of four steps was a priori defined (1850, 3700, 5550, and 7400 MBq).

For study inclusion, patients had to comply with the following inclusion criteria: age ≥ 18 years; WHO performance status score 0–2; histologically- or cytologically-proven HCC, or liver tumour associated with chronic hepatopathy and alpha-fetoprotein (aFP) > 400 ng/ml, or tumorous hepatic formation considered as hypervascularized by at least two imaging methods in cirrhotic patients considered non-operable, non-resecable, non-transplantable, non-accessible to percutaneous treatment tumour; measurable tumour, either uninodular or multinodular, taking up less than 50% of hepatic volume, Stage A to C of BCLC classification (or Stage 0 to 4 of CLIP) with intolerance causing sorafenib treatment discontinuation, contraindication to sorafenib, or therapeutic escape to sorafenib. Patients with Stage ≥ 3 toxicity of the CTCAE Version 4.03, Stage D of BCLC classification, acute hepatic functions impairment (Child–Pugh B9 or C), Grade III HCC of Okuda classification, encephalopathy with even moderate cognitive impairment, advanced chronic respiratory insufficiency, creatinine clearance < 55 ml/min, polynuclear neutrophils < 1500 G/l, platelets < 50 G/l, prothrombin < 40% (INR > 2.3), contraindication to intra-arterial administration, patients unable to undergo follow-up for psychological or geographical reasons, patients dependent on another person for daily care, urinary incontinence, progressive cancer, pregnant or breastfeeding women, as well as women not employing effective contraception were excluded from participating to the study.

All patients provided written informed consent before enrolment. Ethical approval for this study was obtained from the institutional review board. This study was registered on ClinicalTrials.gov, number NCT01126463 [15].

### Synthesis of $^{188}$Re-SSS lipiodol

$^{188}$Re-super six sulfur Lipiodol ($^{188}$Re-(PhCS2)(PhCS3)2, abbreviated as $^{188}$Re-SSS Lipiodol) was prepared, as previously described [9, 11, 12]. $^{188}$Re as carrier-free Na[$^{188}$ReO4] in physiological solution was obtained by saline elution and concentration of $^{188}$W/$^{188}$Re generator (Institut des RadioEléments, Fleurus, Belgium). Automation of Lipiodol radiolabeling was conducted on a remotely controlled TADDEO module (COMECER, Italy). Radiochemical purity (RCP) of $^{188}$Re compounds was assessed using an HPLC system (Dionex U3000).

A lyophilized reducing kit (Vial A) was reconstituted with Na[$^{188}$ReO4] in 0.5–1 ml saline. After 5 min at room temperature, vial B containing the dithiobenzoate ligand was reconstituted in 0.5–1 ml EtOH and 0.5 ml Lipiodol. This solution was then transferred into reaction vessel R. The

content of vial A was subsequently transferred into reaction vessel R, which was then heated at 100° C. After 15 min of heating, reaction vessel R was cooled down by an air flux for 7 min. Next, the reactor's content was purified on a Sep-Pak column (C8), with the $^{188}$Re-SSS complex washed with 10 ml of water followed by 2 ml of a water:EtOH (1:1) mixture, and finally eluted with 2.5 ml EtOH into empty sterile vial C, using a sterile 0.2 mm filter. After EtOH evaporation, the residue was resuspended with 2–3 ml Lipiodol (Lipiodol ultra-fluide, Guerbet, France).

## Treatment

Intra-arterial injection of $^{188}$Re-SSS Lipiodol into the hepatic artery was performed under local anesthesia using the classical Seldinger technique. The activity targeted in this first step of the trial was 1850 MBq.

## Biodistribution analysis

Following $^{188}$Re-SSS Lipiodol administration, patients were hospitalized in a dedicated radionuclide therapy room for 3 days for biodistribution analysis.

## Images acquisition

Whole body planar scintigraphic studies (256 × 1054 matrix), thoraco-abdominal planar scintigraphic studies (256 × 256 matrix), and thoraco-abdominal single-photon emission computed tomography (SPECT) studies (ordered-subset expectation maximization, 32 projections, 180°, 128 × 128 matrix, five iterations, eight subsets with a Gauss filter, 4.8 mm/pixel) were acquired for each patient at 1, 6, 24, 48, and 72 h post-administration, using a double-headed gamma camera (Symbia T2, Siemens Healthcare) equipped with high-energy parallel-hole collimators (due to the emission in low abundance of high-energy gamma rays, i.e., 633 keV and higher energies). The imaging window was set at 155 keV (20%). All SPECT/CT images were reconstructed using corrections for attenuation (low-dose CT-based attenuation), dead time, and scatter (dual-energy-window-based scatter correction [16]). No correction for partial volume effect was performed, due to the large-sized lesions.

## Quantitative analysis

For quantitative purposes, the geometric mean of anterior and posterior measurements on planar scintigraphic studies was computed.

On each geometric mean image, in whole-body planar scintigraphic studies, regions of interest (ROIs) were drawn around the liver (including tumour), tumour, lungs, and a background region in order to calculate the total amount of activity in these areas. Area and activity in the healthy liver were calculated by subtraction of the liver and tumour parameters. Tumour to non-tumour (T/NT) uptake ratio was likewise calculated on planar scintigraphic studies (using a 1 cm$^2$ ROI positioned on the higher-uptake area of the tumour and surrounding healthy liver). The lung shunt fraction (%) was calculated as the ratio of lung activity to total activity detected on a geometric mean planar scintigraphy.

On each SPECT study, volume of interests (VOIs) were drawn around the liver (including tumour), tumour, lungs, and a background region in order to calculate the total activity amount in these volumes. Volume and activity in the healthy liver were calculated by subtraction of the liver and tumour parameters. T/NT uptake ratio was likewise calculated on abdominal SPECT studies (using a 3 cm$^3$ VOI positioned on the higher-uptake area of the tumour and on the surrounding healthy liver).

Full organ segmentation on planar and SPECT studies was performed by a single experienced nuclear physician (syngo Volumetric Analysis®, Siemens®). All these segmentations were reproduced as faithfully as possible at each analysis timepoint.

## Dosimetric studies

Dosimetric steps were schematically as follows: 1) identify all source organs, 2) calculate time-integrated activity in each source organ, 3) calculate personalized S factor for each source organ, and 4) sum all source organ contributions to target organ irradiation.

## MIRD formalism

From the distribution percentages determined on scintigraphic studies (planar scintigraphy and SPECT), the absorbed doses (in Gray [Gy]) to the various organs that concentrate $^{188}$Re-SSS Lipiodol were calculated according to the medical internal radiation dose (MIRD) formalism [17, 18] and based on Zanzonico [19], while adjusting for the personalized S factors. The personalized S factor was calculated by adjusting for the difference in mass between the patient and reference-man organ from the MIRD abaq [17–19] (Table 1). Patient's organ volume was defined manually on CT scans (in cm$^3$, Simplicit90Y, BTG). The volume of the healthy liver was calculated by subtraction of the whole liver and tumour volume. Time-integrated activities in source organ (in h) were calculated according to Zanzonico [19], with the biological elimination considered negligible (effective half-life and physical half-life were identical, equal to 60,840 s) and calculated from the SPECT images as a percent of injected activity corrected for biological elimination (urines and feces). The absorbed dose to the red marrow was calculated as well, employing the Sgouros methods [20].

**Table 1** S factors (in Gy/MBq.s) from MIRD abaq [17–19]

| | Source organ $r_h$ | | | | |
|---|---|---|---|---|---|
| Target organ $r_k$ | Liver | Lungs | Healthy liver | RM | HCC tumour |
| Liver | 7.13213E-08 | 6.83183E-11 | – | – | – |
| Healthy liver | – | – | 1.33634E-09 | – | – |
| Lungs | 7.05706E-11 | 1.27628E-07 | – | – | – |
| RM | 2.7027E-11 | 3.37838E-11 | – | 5.63063E-08 | – |
| HCC tumour | – | – | – | – | 2.44E-07 |

HCC: hepatocellular carcinoma

### Blood, urine, and feces collecting

Total urine and feces emissions were collected during hospitalization. Blood was sampled at 1, 6, 12, 24, 48, and 72 h post-treatment for $^{188}$Re content measurements. The total activity (in % of administrated activity, % AI) was then extrapolated by considering a blood volume of 6 l and a hematocrit of 40%. Samples were analyzed using a gamma counter calibrated for $^{188}$Re (Packard Bioscience Cobra II model 5002).

### Exposure analysis

The patient's dose rate was regularly measured at 1 m, 50 cm, 30 cm distance and in contact with the liver region with an ionizing chamber (Babyline, Eurisys Mesures) at 1, 6, 12, 24, 48, and 72 h post-treatment.

### Follow up

Follow-up consisted of physical examinations, clinical chemistry assessments (including electrolytes, renal and liver function tests, and alpha-fetoprotein [aFP]) hematological tests at 24, 48, 72 h post administration, which were performed every month for 4 months, with a triphasic contrast-enhanced abdominal CT carried out at 4, 8, 16 weeks post-treatment.

### Toxicity assessment and limiting toxicity definition

Any clinical or laboratory adverse event was scored according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. For each parameter, the highest CTCAE grade was recorded upon follow-up. Imputability of treatment for the suspected toxicity was defined according to ICH E2B (R3), meaning that for patients with both liver toxicity and evidence of largely progressive disease, toxicity was attributed to disease progression (rather than to the treatment). A limiting toxicity was defined as a permanent Grade $\geq 3$ toxicity not compatible with a retreatment at the same activity occurring within the 2 months after the treatment and still present at 2 months with regard to liver toxicity.

### Response evaluation

Tumour response assessment on triphasic contrast-enhanced abdominal CT was evaluated at 2 months according to the response evaluation criteria in Solid Tumours Version 1.1. The aFP reduction was measured as well. Concerning αFP, patients were classified into: 1) partial biochemical responders when αFP reduction was > 50%, 2) stable disease when αFP change was between −50% and + 50%, and 3) progression when αFP increase was > 50%.

### Statistical analysis

Quantitative values were expressed as means ± standard deviation. Statistical analyses were performed using R software (R Foundation for Statistical Computing, version 3.2.4, Vienna, Austria).

## Results

### Patients

Between May 19, 2010 and September 1, 2017, six patients (five males and one female) were administered 1645 ± 361 MBq of $^{188}$Re-SSS Lipiodol (Table 2). All six had multifocal disease, and three PVT.

### Visual analysis

Uptakes were seen in only two organs on whole-body and abdominal scintigraphic studies and SPECT studies, namely the liver (tumour and healthy liver) and lungs (Fig. 1). No gastro-intestinal, bladder, or thyroid activity was observed on whole-body scintigraphic studies and abdominal SPECT. These uptakes were stable over time.

### Biodistribution and relative quantification assessment

The hepatic uptake on planar scintigraphic studies (geometric mean) proved to be high (Fig. 2a): 79.9 ± 0.3% detected

**Table 2** Patient characteristics

| Characteristics | Step 1 ($N = 6$) |
|---|---|
| Age (years) | |
| Mean | 71.1 |
| DS | 3.9 |
| Gender | |
| Male | 5 |
| Female | 1 |
| Cirrhosis | |
| Child–Pugh A5 | 3 |
| Child–Pugh A6 | 1 |
| Child–Pugh B7 | 2 |
| Etiology | |
| Alcohol | 2 |
| NASH | 3 |
| Mixed (alcohol + NASH) | 1 |
| PVT | 3 |
| Tumour type | |
| Unifocal | 0 |
| Multifocal | 6 |
| Alpha fetoprotein | |
| Mean | 7769.1 |
| SD | 18,750.5 |
| Whole-liver volume ($cm^3$) | |
| Mean | 2535.0 |
| SD | 2034.6 |
| Tumoral volume (cm3) | |
| Mean | 884.5 |
| SD | 1289.6 |
| Administered activity (MBq) | |
| Mean | 1645 |
| SD | 361 |
| max | 2290 |
| min | 1300 |

NASH: non-alcoholic steatohepatitis; SD: standard deviation

activity was quantified in the whole liver; 59.1 ± 1.5% of detected activity in the tumour, 20.8 ± 5.2% of detected activity in the healthy liver, and 9.7 ± 0.6% of detected activity in the lungs, with 11.3 ± 0.3% and 8.3 ± 0.3% in the right and left lungs respectively.

The hepatic uptake on SPECT studies was likewise high (Fig. 2b): 90.7 ± 1.6% of activity was detected in the liver, with 74.9 ± 1.8% of detected activity in the tumour. On SPECT studies, 19.1 ± 1.7% of detected activity was in the healthy liver and 9.3 ± 1.6% in the lungs, with 5.7 ± 1.1% in the right lung and 3.7 ± 0.5% in the left lung.

Average T/NT uptake ratio was high, measured at 5.4 ± 0.4 on planar scintigraphic studies and at 42.7 ± 7.8 on SPECT studies. These T/NT uptake ratios were stable over time (Fig. 3).

## Blood samples, and urinary and feces excretion

The average amount of $^{188}$Re-SSS Lipiodol excreted in blood samples was 1.4 ± 0.7% (min: 0.6%; max: 2.1%) of administrated activity at 6 h post-administration, declining rapidly thereafter. The activity was insignificant at 72 h post-administration, 0.2% ± 0.2% of administered activity (min: 0.1%; max: 0.7%).

A mean 1.4 ± 1.6% (min: 0.3%; max: 4.5%) of administered activity was excreted in urine within 72 h post-administration. The largest fraction was excreted within the first 24 h (mean: 0.9 ± 1.1%; min: 0.1%; max 2.9%), declining rapidly thereafter. The total activity excreted in feces was very low, assessed at 564 ± 767 kBq at 96 h post-administration. On average, 1.5 ± 1.6% (min: 0.3%; max: 4.5%) of administered activity was biologically eliminated in urine and feces. Consequently, biological elimination was considered negligible.

## Dosimetric assessment

Absorbed doses to whole liver, tumour, healthy liver, and lungs were calculated based on planar scintigraphic studies and SPECT studies, individually for each patient (Table 3). Based on planar scintigraphic biodistribution studies, the mean absorbed doses were as follows: 7.0 ± 3.3Gy to whole liver, 42.4 ± 37.0Gy to tumour, 9.1 ± 3.5Gy to healthy liver, and 3.2 ± 1.5Gy to lungs. Based on SPECT studies, mean absorbed doses were as follows: 7.9 ± 3.7Gy to whole liver, 42.7 ± 34.0Gy to tumour, 10.2 ± 3.7Gy to healthy liver, and 1.5 ± 1.2Gy to lungs. Based on blood activities, the mean absorbed dose to red marrow was 7.0 ± 4.7 mGy.

## Dose rate

The average dose rate at 1 m was 11.9 ± 6.0 μSv/h (0.007 ± 0.002 μSv/h/MBq injected) at 1 h post-administration. At 72 h, dose rate at 1 m was 2.0 ± 1.8 μSv/h (0.001 ± 0.001 μSv/h/MBq injected) (Fig. 4). At 50 cm distance, the average dose rate was 38.5 ± 12.3 μSv/h (0.02± 0.01 μSv/h/MBq injected) at 1 h and 3.4 ± 2.3 μSv/h (0.0± 0.0 μSv/h/MBq injected) at 72 h. At 30 cm distance, the average dose rate was 68.5± 44.5 μSv/h (0.04± 0.00 μSv/h/MBq injected) at 1 h and 5.2 ± 3.0 μSv/h (0.0± 0.0 μSv/h/MBq injected) at 72 h. In contact with the liver region, the average dose rate was 275.0± 85.8 μSv/h (0.15± 0.03 μSv/h/MBq injected) at 1 h and 26.7 ± 13.3 μSv/h (0.01± 0.01 μSv/h/MBq injected) at 72 h.

## Toxicity

All events attributable to $^{188}$Re-SSS Lipiodol were Grade 1 or 2, transitory, asymptomatic, and non-limiting. No Grade 3 or 4 events definitely attributable to $^{188}$Re-SSS Lipiodol were observed. However, the first patient with a large (12 cm) and

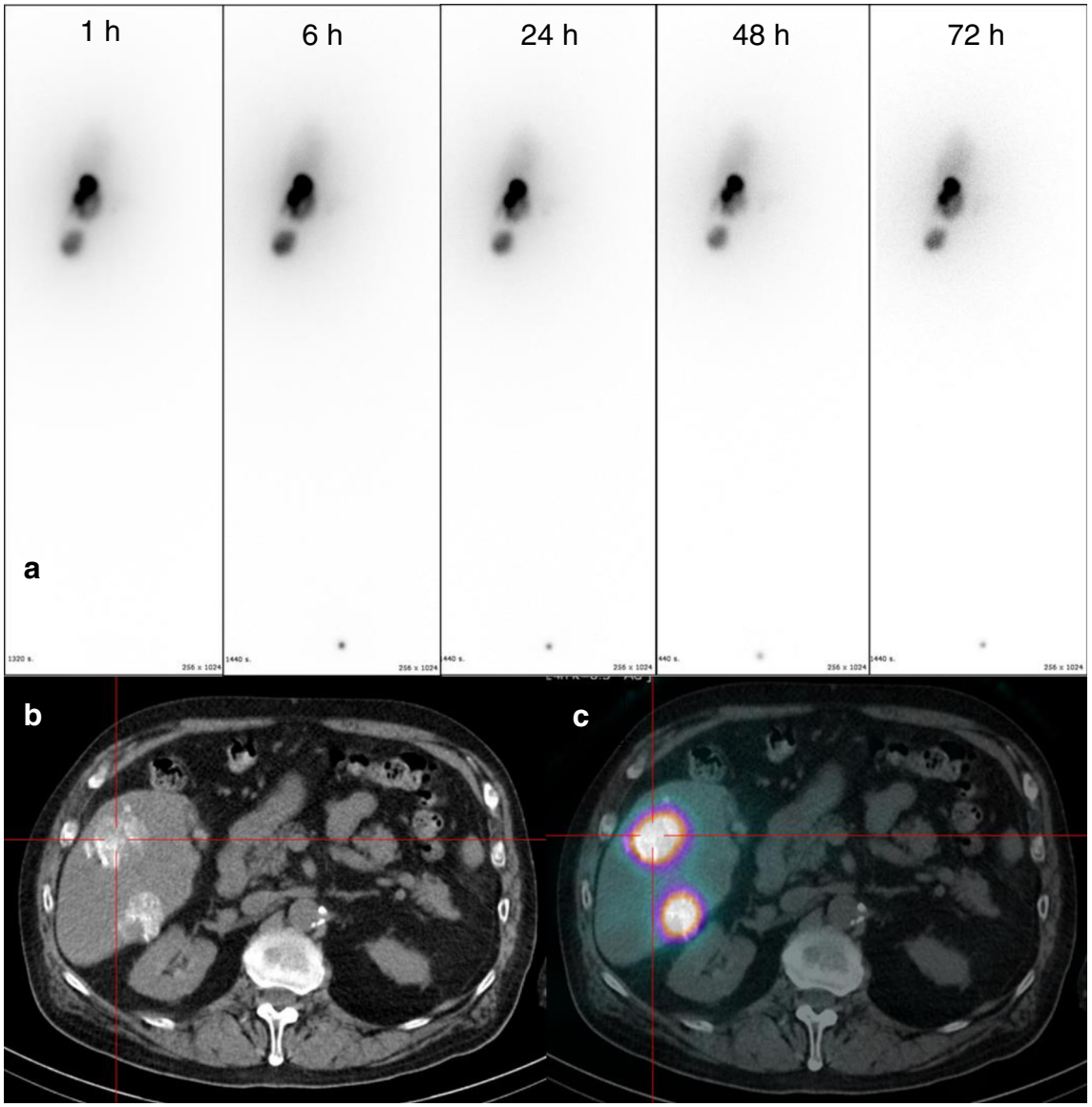


**Fig. 1** Examples of sequential planar whole-body scintigraphic studies (mean geometric) of patient #2 at each time (**a**), SPECT-CT studies (**b**: CT; **c**: fused SPECT CT) at 24 h post-administration of $^{188}$Re-SSS Lipiodol (**b** and **c**)

rapidly progressive HCC with portal vein thrombosis died of liver decompensation at 1 month post-treatment, most probably in relation with a massive tumour progression (progression of aFP from 46,046 UI at baseline to 298,594 UI at week 3). The trial independent evaluation committee agreed with the fact that tumour progression was the most probable cause of death but, due to this early death (occurring before the time point of toxicity evaluation of 2 months) and also considering that it was not possible to formally exclude a treatment-related toxicity, decided to use a conservative approach and considered this death as a treatment-related toxicity.

The most remarkable biologic event was lymphopenia (83%, in five patients). Increases in bilirubin, ASAT, and gamma GT levels were recorded as well, although these increases were only transitory.

## Response

Response on CT-scan was as follows: during the first month post-treatment, four patients experienced stable disease, and two patients progressive disease. The time to progression was 152 ± 123 days (min: 1; max: 297). The survival was 236 ± 155 days (min: 27; max: 424).

## Discussion

In general, anti-tumour radiopharmaceuticals (RP) must display the following characteristics: (1) a high T/NT uptake ratio, rapid, intense, and selective tumour biodistribution, (2) long intratumor retention in order to maximize the tumoricidal

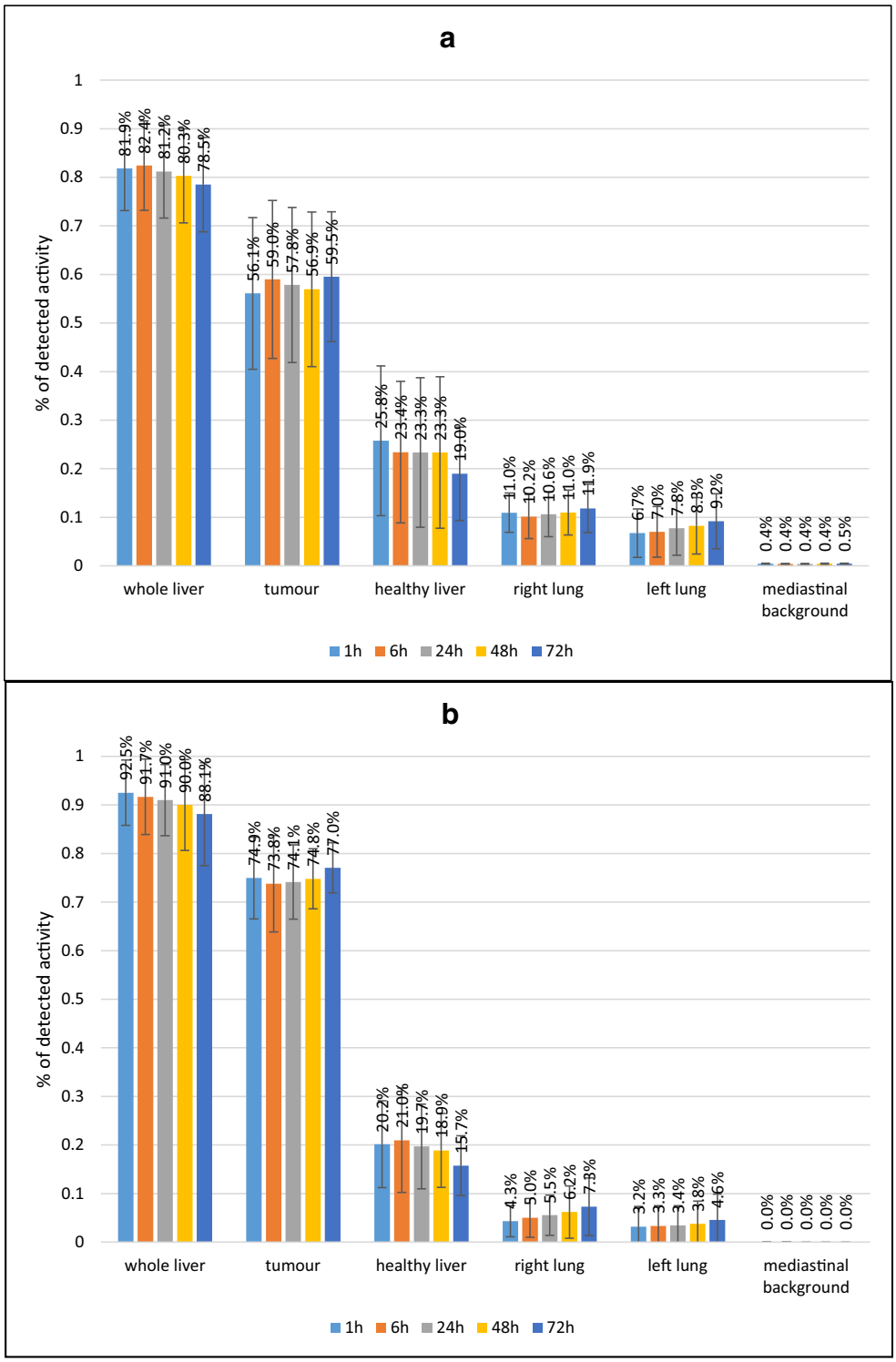


**Fig. 2** Average biodistribution profile of six patients treated with $^{188}$Re-SSS Lipiodol. **a** Planar scintigraphic studies. **b** SPECT studies

effect, and (3) extratumor retention as reasonable as possible so as to limit toxicity, evaluated by residence time. In-vivo stability and pharmacokinetics are determinants of RP efficacy. The RP must be stable post-administration, while the tumour retention (measured by the residence time) should be high enough to ensure selective irradiation of the tumour compartment. In contrast, RP exposure to non-target tissues should be minimal.

Our preliminary results have clearly shown that $^{188}$Re-SSS Lipiodol displays remarkable biodistribution characteristics and in-vivo stability, as well as tumour targeting and retention, in addition to favorable dosimetric features in humans. The results of biodistribution and in-vivo stability revealed in this study are perfectly in line with our previously described findings in animals [9, 11].

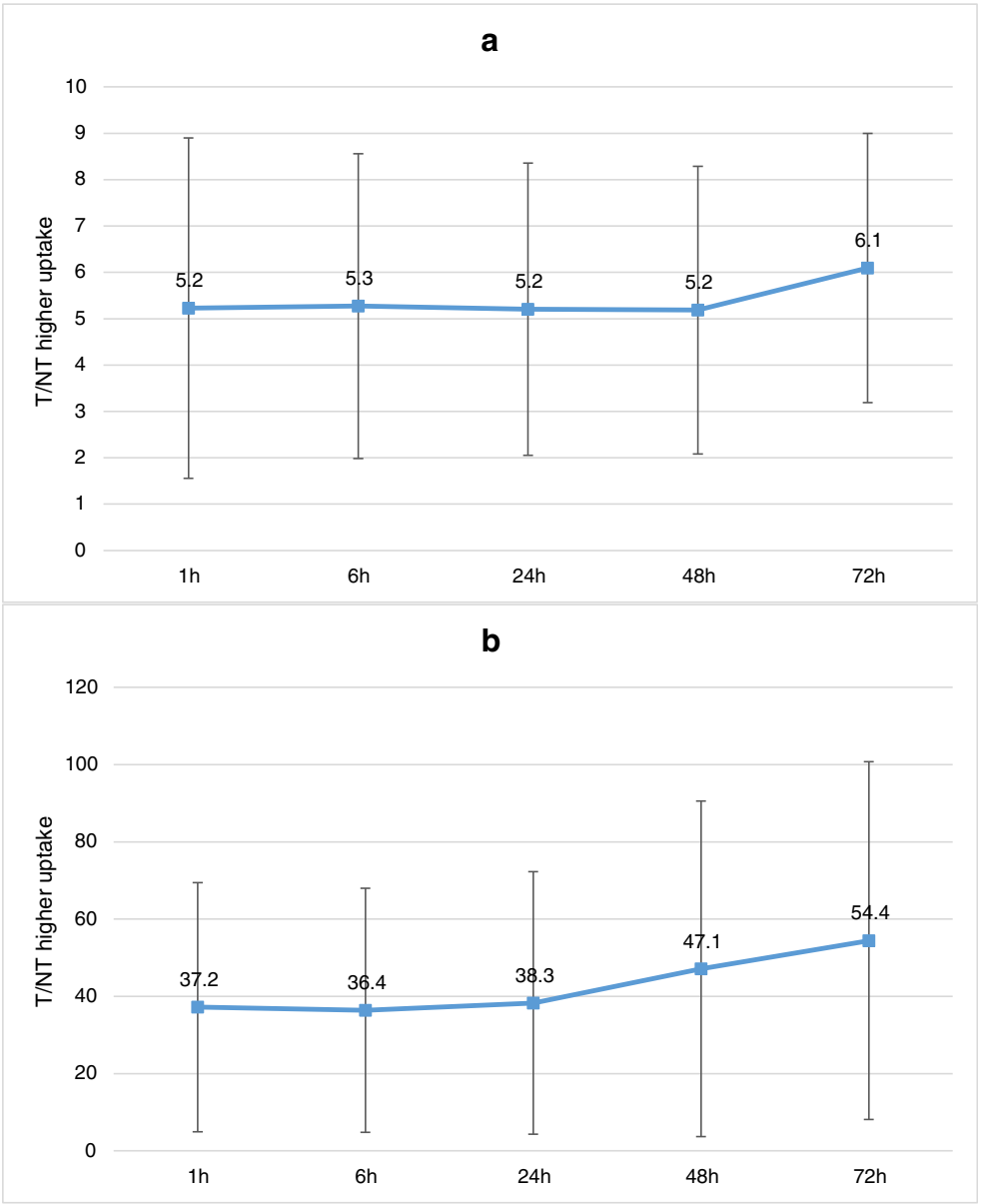


**Fig. 3** Average T/NT uptake of six patients treated with $^{188}$Re-SSS/Lipiodol. **a** Planar scintigraphic studies. **b** Tomoscintigraphic studies

Only three different $^{188}$Re Lipiodol radiolabeled complexes have been tested in humans to date, namely $^{188}$Re-SSS Lipiodol, $^{188}$Re-HDD Lipiodol, and $^{188}$ReN-DEDC Lipiodol (Table 4).

$^{188}$Re-HDD Lipiodol is the most extensively studied compound and is still in use only in Asia. The complex displays, in fact, major disadvantages: its in-vivo stability does prove to be not optimal, and the RP shows high urinary excretion. Based on clinical trial results with $^{188}$Re-HDD Lipiodol [21, 22], 36.2% ± 5.7% [22] to 44.1 ± 11.7% [21] of injected activity was excreted in urine within 52 to 76 h post-injection. In comparison, with $^{188}$Re-SSS Lipiodol only 1.4 ± 1.6% (min: 0.3%; max: 4.5%) of administered activity was excreted in urine within 72 h post-administration.

Consequently, dosimetric assessments obtained with $^{188}$Re-HDD Lipiodol proved to be less favorable than those acquired with $^{188}$Re-SSS Lipiodol. When employing $^{188}$Re-SSS Lipiodol, we have achieved an absorbed dose to the whole liver (based on planar scintigraphic biodistribution studies) of 7.0Gy for 1.645 GBq injected, resulting in an absorbed dose of 4.2Gy/GBq injected versus only 1.3 to 2.3Gy/GBq injected with $^{188}$Re-HDD Lipiodol [21–24]. For tumours, we have achieved a mean dose of 25.8 Gy/GBq injected with $^{188}$Re-SSS Lipiodol. Only one single study conducted by Bernal et al. assessed dose to tumour. For $^{188}$Re-HDD Lipiodol, with 3.9GBq injected in this study, the authors achieved a mean 63.4Gy to tumour, with an absorbed dose of 15.9Gy/GBq administered [25, 26]. Nevertheless, no dose to critical

**Table 3** Dosimetric assessments of $^{188}$Re SSS Lipiodol in each patient based on scintigraphic biodistribution studies

| | | Dose (in Gy) to | | | |
|---|---|---|---|---|---|
| | Based on | Whole-liver | Tumour | Healthy liver | Lungs |
| Patient 1 | planar | 4.8 | 10.2 | 7.4 | 2.6 |
| Patient 2 | planar | 8.0 | 26.5 | 11.7 | 3.2 |
| Patient 3 | planar | 5.4 | 94.7 | 5.6 | 5.6 |
| Patient 4 | planar | 2.5 | 4.0 | 5.3 | 2.3 |
| Patient 5 | planar | 11.4 | 74.6 | 13.7 | 4.1 |
| Patient 6 | planar | 9.8 | 48.0 | 10.7 | 1.4 |
| Mean | | 7.0 | 43.0 | 9.1 | 3.2 |
| SD | | 3.3 | 36.2 | 3.5 | 1.5 |
| | | Whole-liver | Tumour | Healthy liver | Lungs |
| Patient 1 | SPECT | 5.6 | 12.7 | 8.7 | 0.8 |
| Patient 2 | SPECT | 8.9 | 22.8 | 13.0 | 1.7 |
| Patient 3 | SPECT | 6.5 | 57.3 | 6.8 | .38 |
| Patient 4 | SPECT | 2.8 | 4.3 | 5.8 | 0.8 |
| Patient 5 | SPECT | 12.8 | 73.2 | 15.4 | 1.6 |
| Patient 6 | SPECT | 10.8 | 86.0 | 11.7 | 0.4 |
| Mean | | 7.9 | 42.7 | 10.2 | 1.5 |
| SD | | 3.7 | 34.0 | 3.7 | 1.2 |

organs was evaluated by Bernal et al., with no dose to tumour assessed by Lambert et al. Therefore, due to their unavailability, these data could not be employed for comparison with our results [21–23].

The absorbed doses to the lungs were likewise shown to be lower with $^{188}$Re-SSS Lipiodol. In our study, we have achieved a mean absorbed dose (based on SPECT biodistribution studies) of 1.5Gy for 1.645GBq administered, resulting in an absorbed dose of 0.9Gy/GBq administered, as compared to 1.1 [23] to 1.3 [23–25] Gy/GBq administered with $^{188}$Re-HDD Lipiodol.

In these trials, dosimetric assessments were quite approximated with regard to several points. In the Lambert et al. publication, only whole-body images but no tomoscintigraphic studies were performed. In the Bernal et al. paper, dosimetric assessments were carried out using a scout dose of $^{188}$Re-HDD Lipiodol, with whole-body scintigraphic studies conducted. In all cases, dose to target organs or critic organs were calculated considering that there was no biological elimination, as recommended by Zanzonico [19]. This approximation, however, is not accurate. Overall, $^{188}$Re-HDD Lipiodol displays elevated urinary excretion (36.2% to 44.1% within 52 to 76 h [21, 22]), and in these studies, doses to the whole liver or to tumour are therefore overestimated. In our study, we have calculated the dose to both target and critic organs, integrating biological elimination in both urine and feces.

Another complex, the $^{188}$ReN-DEDC Lipiodol, has been tested in both animals and humans [27], though no dosimetric measurements were conducted. The authors only assessed biodistribution in animals and humans, and concluded that when applying $^{188}$ReN-DEDC Lipiodol, there was no significant release of this complex after in-vivo administration, with excellent retention in tumour. It should be noted that biodistribution was not quantified, particularly in the human studies.

This superior in-vivo stability of $^{188}$Re-SSS Lipiodol compared to other radiolabeling complexes, such as $^{188}$Re-HDD Lipiodol and $^{188}$ReN-DEDC Lipiodol, is probably due to the lower oxidation degree of the rhenium complex, with an oxidation degree + III for $^{188}$Re-SSS complex versus an oxidation degree + V for the others. Overall, + III is an oxidation level that is chemically more stable than the + V level [8, 14]. Consequently, $^{188}$Re-HDD Lipiodol exhibits an increased risk of re-oxidation, and thus of $^{188}$Re release in serum than $^{188}$Re-SSS Lipiodol. Owing to its superior in-vivo stability, the dosimetric profile and tolerance profile obtained with $^{188}$Re-SSS Lipiodol appear more favorable than those acquired with $^{188}$Re-HDD Lipiodol and $^{188}$ReN-DEDC Lipiodol.

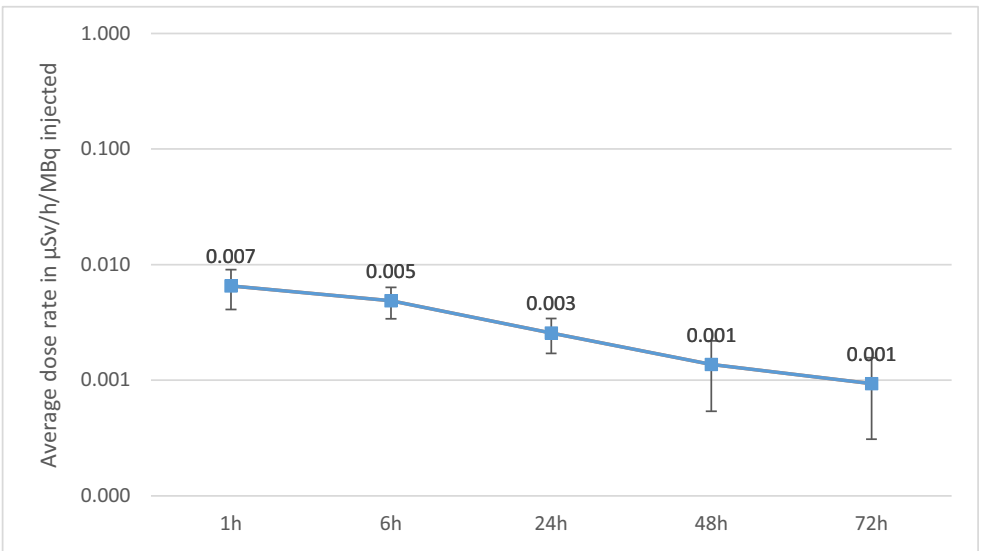


**Fig. 4** Average dose (± SD) rate at 1 m of six patients treated with $^{188}$Re-SSS Lipiodol

**Table 4** Different complexes of $^{188}$Re Lipiodol radiolabeled injected in humans (RCP: radiochemistry purity; NE: not evaluated)

| Radiopharmaceutical | $^{188}$Re-HDD Lipiodol [23–27, 30, 31] | $^{188}$Re-SSS Lipiodol [10, 12, 16] | $^{188}$ReN-DEDC Lipiodol [28] |
|---|---|---|---|
| Chemical characteristics | | | |
| RCP | > 97% | 93% | 97 ± 2% |
| Total radiochemical yield | 50–60% | 98.6 ± 1.2% | 96 ± 3% |
| In-vitro stability | NE | 96–97% at 48 h | NE |
| Pharmacokinetic characteristics / biodistribution | | | |
| Organs | Liver – lungs – digestive tract – urinary tract – thyroid | Liver – lungs | Liver – lungs – digestive tract – urinary tract |
| T/NT uptake ratio | 6.25 ± 4.5 to 11.7 ± 10.7 | 5.4 ± 0.4 | NE |
| Quantification of elimination | Urine (43.5% at 72 h) | Urine and digestive (< 1.4% at 72 h) | NE |
| In-vivo stability | 56.5% at 72 h | > 98% | Lower activity: 93.8% at 48 h<br>Higher activity: 50.2% at 24 h |
| Clinical trials | | | |
| Phase 1 | 3 trials ($n$ = 110 patients) | 1 trial ($n$ = 12 patients) | 1 trial ($n$ = 12 patients) |
| Phase 2 | 1 trial ($n$ = 185 patients) | No one | No one |
| Phase 3 | No one | No one | No one |
| Administered activity | 3.6 to 7.0GBq | 1.5 and 3.7GBq | 2.5 to 6.0GBq |
| Dosimetric assessments (Gy/GBq injected | Based on planar scintigraphic studies — no biological elimination corrected | Based on planar (P) and SPECT scintigraphic studies — biological elimination corrected | NE |
| Whole liver | 1.6 to 2.3 | 4.2 (P) to 4.8 (SPECT) | NE |
| Healthy liver | NE | 5.5 (P) to 6.2 (SPECT) | NE |
| Tumour | 15.85 | 25.8 (P) to 26.0 (SPECT) | NE |
| Lungs | 1.1 to 1.3 | 1.9 (P) to 0.9 (SPECT) | NE |

One clinical interest of dosimetric analysis is the potential ability to demonstrate a dose/response correlation (and an eventual impact of tumour dose on survival). Even if the two patients with progressive disease in our preliminary results received a quite low tumour dose (patients 2 and 4, TD of respectively 12,7 and 4,3 Gy based on SPECT studies) such dose/response correlation is not evaluable in tis study due to the patients selected (end-stage patients with huge lesions refractory to any previous therapy) and the small number of cases required in a phase 1 study. This interesting point will have to be evaluated further in a phase 2 study, including more and better selected patients.

At present, the most common compounds used for radioembolization are $^{90}$Y-labeled resin or glass microspheres. However, $^{90}$Y-labeled microspheres display several disadvantages. Their high costs (around €12,000 per treatment) limit their accessibility in many countries, especially in developing countries. $^{188}$Re is an interesting candidate for nuclear therapy, emitting $\beta^-$ particles of 2.12 MeV (80%) and 1.96 MeV (18%). As comparison $\beta^-$ particle energy is of 2.28 Mev (99.9%) for $^{90}$Y and only 0.606 MeV (89%) and 0.303 MeV (7%) for $^{131}$I. Furthermore, $^{188}$Re is generator-produced. The $^{188}$W/$^{188}$Re generator has a long useful shelf-life of several months and is of reasonable cost, resulting in a quite low cost for one therapetic vial of $^{188}$Re [28, 29].

Moreover, Lipiodol, currently used for chemoembolization, is a vector that completely differs from microspheres for liver therapies. Lipiodol has the ability to penetrate peritumoral sinusoidal capillaries, the interstitium, and tumour cells themselves [30, 31], which does not apply to microspheres. Therefore, as a vector, Lipiodol may prove to be more suitable than microspheres. This point underlines the specific usefulness of radiolabeled Lipiodol for radioembolization of liver tumours. Lastly, two recently performed Phase III studies failed to demonstrate any increase in overall survival in comparison with sorafenib in advanced HCC patients [3–5].

One limitation of our study is the absence of absolute $^{188}$Re quantification for dosimetric analysis. This must be accounted for by the fact that quantification of $^{188}$Re is not very easy, with no one single absolute quantification method clearly described to date. That is the reason why in this study, we have applied relative quantification on planar and SPECT studies (in % of detected activity) with attenuation, scatter, and dead-time correction. As an example, there are no generalized recommendations for tomographic reconstruction with correct scatter correction for $^{188}$Re available. $^{188}$Re emits many gamma rays: a 155 keV gamma ray (15%), 478 and 633 keV high gamma rays (2.3%), and bremsstrahlung gamma rays (generated by the interaction of beta particles with tissues) which result in contaminated images and $^{188}$Re activity overestimations in organs. Several methods have

meanwhile been proposed for quantitative purposes. Zanzonico recommended DEW scatter correction [19] whereas several studies based on phantom experiments recommended triple-energy-window (TEW) scatter correction [32, 33]. Moreover, to acquire truly absolute quantitative results, corrections for scatter, dead time, and attenuation should be recommended. As a result, absolute quantification appears very difficult to perform, requiring further development.

Guidelines for calculating dose to tumour and to critical organs likewise proved to be contradictory. Zanzonico did not integrate biological elimination when calculating dose to tumour or to critical organs [19], while for $^{188}$Re-HDD Lipiodol, approximately half of the administered activity is eliminated in urine. Though biological elimination of $^{188}$Re-SSS Lipiodol proved to be rather low in our study, we have integrated biological elimination in our dose calculations. Consequently, our dose measurements appear to be more rigorous.

## Conclusion

$^{188}$Re-SSS Lipiodol displays favorable biodistribution features for radioembolization, exhibiting the highest in-vivo stability of any radiolabeled Lipiodol compound described to date. These preliminary results must be further confirmed while completing this phase I Lip Re1 study.

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## Compliance with ethical standards

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Conflict of interest** Yan Rolland, Julien Edeline, and Etienne Garin are consultants for BTG UK Ltd.



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