Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial

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Summary

Background All randomised phase 3 studies of selective internal radiation therapy for advanced hepatocellular carcinoma published to date have reported negative results. However, these studies did not use personalised dosimetry. We aimed to compare the efficacy of a personalised versus standard dosimetry approach of selective internal radiation therapy with yttrium-90-loaded glass microspheres in patients with hepatocellular carcinoma.

Methods DOSISPHERE-01 was a randomised, multicentre, open-label phase 2 trial done at four health-care centres in France. Patients were eligible if they were aged 18 years or older and had unresectable locally advanced hepatocellular carcinoma, at least one measurable lesion 7 cm or more in size, a hepatic reserve of at least 30% after selective internal radiation therapy, no extrahepatic spread (other than to the lymph nodes of the hilum, with a lesion <2 cm in size), and no contraindications to selective internal radiation therapy, as assessed by use of a technetium-99m macroaggregated albumin scan. Patients were randomly assigned (1:1) by use of a permutated block method, with block sizes of four and without stratification, to receive either standard dosimetry (120±20 Gy) targeted to the perfused lobe; standard dosimetry group) or personalised dosimetry (≥205 Gy targeted to the index lesion; personalised dosimetry group). Investigators, patients, and study staff were not masked to treatment. The primary endpoint was the investigator-assessed objective response rate in the index lesion, according to European Association for the Study of the Liver criteria, at 3 months after selective internal radiation therapy in the modified intention-to-treat population. Safety was assessed in all patients who received at least one selective internal radiation therapy injection, and analysed on the basis of the treatment actually received (defined by central dosimetry assessment). The trial is registered with ClinicalTrials.gov, NCT02582034, and has been completed.

Findings Between Dec 5, 2015, and Jan 4, 2018, 93 patients were assessed for eligibility. Of these patients, 60 were randomly assigned: 31 to the personalised dosimetry group and 29 to the standard dosimetry group (intention-to-treat population). 56 (93%) patients (28 in each group) were treated (modified intention-to-treat population). In the modified intention-to-treat population, 20 (71% [95% CI 51–87]) of 28 patients in the personalised dosimetry group and ten (36% [19–56]) of 28 patients in the standard dosimetry group had an objective response (p=0·0074). In the safety analysis population, a least one serious adverse event was reported in seven (20%) of the 35 patients who received personalised dosimetry, and in seven (33%) of the 21 patients who received standard dosimetry. The most frequent (ie, occurring in >5% of patients) grade 3 or higher adverse events were ascites (one [3%] patient who received personalised dosimetry *vs* two [10%] patients who received standard dosimetry), hepatic failure (two [6%] *vs* none), lymphopenia (12 [34%] *vs* nine [43%]), increased aspartate aminotransferase concentrations (three [9%] *vs* two [10%]), increased alanine aminotransferase concentrations (three [9%] *vs* none), anaemia (two [6%] *vs* one [5%]), gastrointestinal haemorrhage (none *vs* two [10%]), and icterus (none *vs* two [10%]). One treatment-related death occurred in each group.

Interpretation Compared with standard dosimetry, personalised dosimetry significantly improved the objective response rate in patients with locally advanced hepatocellular carcinoma. The results of this study suggest that personalised dosimetry is likely to improve outcomes in clinical practice and should be used in future trials of selective internal radiation therapy.

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed for articles published in English between Jan 1, 2000, and May 1, 2020, focusing on publications of randomised studies for hepatocellular carcinoma using the search terms "selective internal radiation therapy" or "radioembolisation", and "personalised dosimetry". We identified no randomised studies. Only two retrospective studies of personalised dosimetry were identified, and the results suggested that personalised dosimetry was associated with a significant improvement in objective response rate and a favourable overall survival compared with standard dosimetry.

We also searched PubMed for articles published in English between Jan 1, 2000, and May 1, 2020, focusing on publications of large randomised studies, using the search terms "selective internal radiation therapy" or "radioembolisation", and "sorafenib", with sorafenib being the standard of care for locally advanced hepatocellular carcinoma. We identified three studies. All studies found no increase in the overall survival of patients treated with selective internal radiation therapy, alone or in combination with sorafenib, when compared with sorafenib alone. Reported median overall survival was 8·0–12·1 months in the selective internal radiation therapy groups and 9·9–11·4 months in the selective internal radiation plus sorafenib group and sorafenib only group. Personalised dosimetry was not used in any of these studies.

The present randomised multicentre study was designed to assess the potential superiority of selective internal radiation therapy with personalised dosimetry over standard dosimetry in terms of the objective response rate in patients with hepatocellular carcinoma.

Added value of this study

To our knowledge, this is the first randomised study to compare personalised dosimetry and standard dosimetry in patients with hepatocellular carcinoma. In patients with locally advanced hepatocellular carcinoma, the objective response rate was significantly higher in the personalised dosimetry group compared with the standard dosimetry group, with no increase in the toxicity profile. A meaningful improvement in overall survival was also observed in the personalised dosimetry group compared with the standard dosimetry group.

Implications of all the available evidence

These results suggest that personalised dosimetry could become the definitive standard-of-care method of administering selective internal radiation therapy, and also challenge the conclusions of previous negative randomised phase 3 studies of selective internal radiation therapy, in which no personalised dosimetry was used. This study provides a strong rationale for new randomised studies to compare selective internal radiation therapy using personalised dosimetry (alone or in combination with standard of care) with standard of care alone in patients locally advanced hepatocellular carcinoma, to try to improve patient outcomes.

Introduction

Hepatocellular carcinoma is the most common primary liver cancer and the third leading cause of cancer-related death worldwide, with around 745 000 deaths reported annually.[1] Most often, patients are not operable because of the extent of disease or underlying liver cirrhosis, and treatment is challenging.[2]

Sorafenib became the standard of care for patients with advanced hepatocellular carcinoma in 2008, with a median overall survival of 10·7 months versus 7·9 months with best supportive care (hazard ratio [HR] 0·69 [95% CI 0·55–0·87]).[3] Only recently (2020) has a treatment been shown to significantly improve overall survival when compared with sorafenib, with the combination of bevacizumab with atezolizumab expected to become the new standard of care for patients with advanced hepatocellular carcinoma (median overall survival not yet reached with the immunotherapy combination versus 13·2 months with sorafenib, HR 0·58, 95% CI 0·42–0·79).[4]

For more than 20 years, selective internal radiation therapy for hepatocellular carcinoma has used yttrium-90 (^{90}Y)-loaded glass microspheres (TheraSphere, Boston Scientific, Marlborough, MA, USA) or resin microspheres (SIR-Sphere, Sirtex Medical, Australia).[5,6] The microspheres are injected directly into the hepatic artery. Microsphere injection is always preceded by a diagnostic liver angiography, including a liver perfusion scintigraphy with intra-arterial injection of technetium-99m (^{99m}Tc) macro-aggregated albumin (a macro-aggregated albumin scan). The main objective of these screening tools is to identify patients with absolute contraindication to selective internal radiation therapy, such as those with a high risk of lung shunt or gastrointestinal shunt.[7,8]

Several guidelines consider selective internal radiation therapy as an option for patients with hepatocellular carcinoma.[9,10] Selective internal radiation therapy has shown promising results in terms of response, safety, and overall survival in cohort studies and phase 2 studies.[11,12] However, three randomised phase 3 trials[13–15] failed to show any improvement in overall survival with selective internal radiation therapy compared with sorafenib. The absence of a personalised dosimetry approach could potentially explain these negative results.[16] Indeed, despite the fact that selective internal radiation therapy is a radiation oncology approach, personalised dosimetry, especially with regards to the tumour absorbed dose, is not addressed in the instructions for use of the products,[7,8] and was not used in these three randomised studies.[13–15] This absence of a personalised dosimetry approach is inaccurate according to radiobiological rules, in which a

threshold tumour absorbed radiation dose needs to be reached to achieve an effect.[17]

A macro-aggregated albumin scan can be done before selective internal radiation therapy to evaluate the tumour absorbed dose, and it provides an accurate predictive tool of response and overall survival.[5,18,19] The threshold tumour absorbed dose reported for glass microspheres is 205 Gy.[18,19] The concept of personalised dosimetry targeting more than 205 Gy to hepatocellular carcinomas has been described with favourable outcomes.[20,21]

The aim of this randomised multicentre study was to compare the efficacy of a standard versus personalised dosimetry approach of selective internal radiation therapy with ^{90}Y-loaded glass microspheres in patients with hepatocellular carcinoma.

Methods

Study design and participants

DOSISPHERE-01 was a randomised, multicentre, open-label phase 2 trial done at four health-care centres in France. According to the main prespecified inclusion criteria, eligible patients were aged 18 years or older and had histologically confirmed hepatocellular carcinoma that was not amenable to surgery or local ablative treatment; an Eastern Cooperative Oncology Group performance status of 0 or 1; a Child-Pugh liver function class A (or B7 if bilirubin concentrations were <35 µmol/L); a Barcelona Clinic Liver Cancer classification of A, B, or C; at least one measurable lesion 7 cm in size or larger; a hepatic reserve (ie, untreated liver fraction) of at least 30% after selective internal radiation therapy; and mainly unilateral involvement (minimal bilateral involvement allowed only with a hepatic reserve of ≥30% after bilateral selective internal radiation therapy). The following criteria for biological parameters had to be met: haemoglobin concentrations of 8·5 g/dL or greater; granulocyte counts of 1500 cells per µL or greater; platelet counts of 50 000 platelets per µL or greater; bilirubin <35 µmol/L; aspartate aminotransferase or alanine aminotransferase concentrations five or less times the upper limit of normal; and creatinine ≤1·5 times the upper limit of normal. Previous treatment with sorafenib was allowed if it had been stopped at least 4 weeks before the diagnostic angiography. The main prespecified exclusion criteria were: extrahepatic spread (other than to the lymph nodes of the hilum, with a lesion <2 cm in size); more than 70% of the liver having tumour involvement; a history of chemoembolisation of the principal lesion (except for a nodular residual lesion measuring at least 7 cm in size, or progression after an initial response); severe underlying biliary pathology (ie, a bile duct abnormality, including cirrhosis of biliary origin); having received treatment for another cancer less than 1 year previously; pulmonary shunting leading to pulmonary dosimetry of more than 30 Gy; a digestive shunt not correctable by embolisation; and poor targeting of the tumour or a main portal vein thrombosis on ^{99m}Tc macro-aggregated albumin scintigraphy. A complete list of inclusion and exclusion criteria are provided in the appendix (p 3). To ensure eligibility for selective internal radiation therapy, patients were included in the trial only after the ^{99m}Tc macro-aggregated albumin scan.

During the screening period, a diagnostic angiography was done for arterial mapping, selection of catheter position for treatment, embolisation of gastrointestinal arterial branches (if necessary), and ^{99m}Tc macro-aggregated albumin injection (over 20–30 s). Specific recommendations were followed to preserve blood flow, including the preferential use of a floppy catheter to avoid spasm.[22] For the macro-aggregated albumin scan, planar images were acquired for lung shunt evaluation. For tumour and portal vein thrombosis dosimetry evaluation, single-photon emission CT combined with CT (SPECT/CT) scans were acquired. Tumour and portal vein thrombosis targeting were evaluated visually on macro-aggregated albumin SPECT/CT images, with poor targeting defined as a lower macro-aggregated albumin uptake in the tumour or in the portal vein thrombosis than the uptake in healthy liver tissue. Indeed, macro-aggregated albumin is used as a ^{90}Y-loaded microsphere surrogate, and macro-aggregated albumin uptake quantifcation with SPECT/CT is used to calculate the absorbed dose of ^{90}Y assuming that the distributions of macro-aggregated albumin and ^{90}Y-loaded microspheres are the same. Patients were discharged and readmitted for selective internal radiation therapy 1 or 2 weeks later if eligibility was confirmed.

Patients provided written informed consent before undergoing study-specific procedures. The study was done in accordance with the Declaration of Helsinki and approved by the ethics committee of the University Hospital La Cavalle Blanche (Brest, France; IRB-ID: 2015-A00894–45). The trial protocol is available online.

For the **DOSISPHERE-01 trial protocol** see http://www.centre-eugene-marquis.fr/etude-clinique-dosisphere/

Randomisation and masking

Eligible patients were randomly assigned (1:1) to two parallel groups, in which patients received either personalised dosimetry or standard dosimetry. The randomisation list was computer-generated by the permutated block method with a block size of four and without stratification. Once eligibility was confirmed, physicians were informed of the randomised treatment allocated to the patient by the clinical project research assistant. The funder, investigators, patients, and research staff were masked to the randomisation list but were not masked to treatment.

Procedures

Selective internal radiation therapy was done during a therapeutic angiography, and a lobar approach was used in the trial. Dosimetry was evaluated by investigators using local software (Volumetric analysis [Syngo Workstation, Siemens, Malvern, PA, USA] and PLANET Dose [DOSIsoft, Paris, France]); the target dose was based on

macro-aggregated albumin-based dosimetry. The dosimetry target for patients in the standard dosimetry group was to deliver 120±20 Gy to the perfused lobe (the standard targeted perfused liver dose at time of study design),[7] while not exceeding 30 Gy to the lungs. The dosimetry targets for patients in the personalised dosimetry group were to deliver: (1) at least 205 Gy to the tumour (tumour dose), and more than 250 Gy, if possible; (2) a dose of 120 Gy or less to the healthy perfused liver tissue; and (3) a dose of 30 Gy or less to the lungs.[20,21]

The activity of ^{90}Y-loaded glass microspheres needed to meet the dosimetry target was calculated by use of the following formula:[17]

$$D_{VOI} = \frac{A_{VOI} \times 50}{W_{VOI}}$$

where D_{VOI} is the mean absorbed dose (measured in Gy) in the volume of interest (ie, the perfused liver, tumour, or healthy perfused liver tissue), A_{VOI} is the activity of ^{90}Y-loaded microspheres (measured in GBq) in the volume of interest, and W_{VOI} is the weight of the volume of interest (measured in kg), with the weight equal to the volume (measured in L) multiplied by 1·03.

Volume of interest was evaluated by use of macro-aggregated albumin SPECT/CT scan images in the personalised dosimetry group, and by use of standard diagnostic imaging (CT scan, MRI, or cone beam CT, when available) and the Couinaud classification in the standard dosimetry group.[18,20]

In patients who had two arteries that required treatment (ie, in those with an anatomical variant or a central lesion vascularised by two arteries), two macro-aggregated albumin evaluations in two separate angiography procedures were done at least 24 h apart, as macro-aggregated albumin quantification is technically only evaluable for one macro-aggregated albumin injection (one vessel).

In patients with bilobar disease, selective internal radiation therapy was first used to treat the liver lobe with the largest tumour load. The treatment of the lobe with the smaller tumour load was left at the discretion of investigators; selective internal radiation therapy was permitted providing that at least 30% of the liver volume was spared from radiation after both selective internal radiation therapies. If the two treatments were not done during the same session, they had to be separated by a prespecified time interval of 5–8 weeks.

Patients were followed up until disease progression. Visits, including those for clinical examination, laboratory tests (haematological, blood liver, and blood biochemistry), and abdominal imaging (CT or MRI), were scheduled 4–6 weeks after selective internal radiation therapy, and at 3, 6, and 12 months.

Outcomes

The primary endpoint was the objective response rate, defined as the proportion of patients who had a complete or partial response in the index lesion (ie, the largest treated lesion ≥7 cm in size), according to European Association for the Study of the Liver (EASL) criteria (appendix p 3), which was evaluated by one unmasked investigator at 3 months after selective internal radiation therapy.[23] Patients with stable disease, or progressive disease, or those who had started systemic cancer therapy (or local therapy targeting the index lesion) before 3 months, or had not had a radiological evaluation at 3 months, were considered not to have had an objective response.

Tumour response was evaluated with CT scan imaging by site investigators at week 6 and at 3, 6, and 12 months after selective internal radiation therapy. 6-week and 3-month CT scan response assessments were centrally reviewed by two masked central reviewers to confirm the primary endpoint results.

The overall response rate, defined as the proportion of patients who had a complete or partial response in the index lesion and other lesions, was evaluated according to EASL criteria in a post-hoc analysis. Patients with an extension of portal vein thrombosis at 3 months were considered as non-responders, regardless of the response in the other lesions.

Post-hoc analysis of objective response in the index lesion and overall response response, according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria, was done centrally by one masked study investigator.

Macro-aggregated albumin-based dosimetry was assessed centrally using Simplicit^{90}Y software (Mirada Medical, Oxford, UK) by one reviewer who was masked to treatment and response.

Secondary endpoints were dose-response evaluation, safety, and time-to-event measures of progression-free survival and overall survival. Progression-free survival was defined as the time from randomisation to progressive disease or death; patients were censored for progression-free survival if they were lost to follow-up, had initiated a systemic treatment or surgery, or had no progression before the end of the study follow-up period (at the 12-month visit). Overall survival was defined as the time from randomisation to death from any cause. Secondary endpoints of the dose-toxicity association and post-treatment ^{90}Y dosimetry will be reported elsewhere.

Vital status was updated until database lock (Aug 21, 2019), and follow-up was censored if the patient was still alive. Adverse events were recorded from the time of written informed consent to 30 days after selective internal radiation therapy. The adverse event data collection period was extended to 3 months for liver events, and the entire study period for selective internal radiation therapy-related liver serious adverse events. Adverse events were coded according to the Medical Dictionary for Regulatory Activities version 20.1,[24] and severity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse

Events version 4.03.[25] Radioembolisation-induced liver disease, as defined by Sangro and colleagues,[26] was analysed in a post-hoc analysis. Adverse event imputability to selective internal radiation therapy respected the following rule for liver adverse events: in patients with both a liver adverse event and no evidence of progression, the adverse event was attributed to selective internal radiation therapy; conversely, in patients with evidence of progressive disease on imaging, the adverse event was attributed to disease progression.

Statistical analysis

The study was designed to detect a 35% difference in objective response rate in the index lesion between the standard dosimetry and personalised dosimetry groups, with an expected objective response rate in the index lesion in the standard dosimetry group of 50%, a 5% two-sided type I error rate, and 80% power. An interim analysis was planned when 60 patients had been enrolled (allowing for 10% dropout after randomisation). If the estimated difference in objective response rate between standard dosimetry and personalised dosimetry groups was greater than 15% and the one-sided p value was less than 0·01348, the trial could be stopped and concluded as positive. Otherwise, the study could either be stopped early (with an estimated difference of <15% between the two groups) or the study could be continued in up to 254 patients.

All analyses were assessed in the modified intent-to-treat population, defined as all randomly assigned patients who received treatment. Sensitivity analyses were done in the intention-to-treat population, which included all randomly assigned patients. Safety was assessed in the safety analysis population, defined as all patients who received selective internal radiation therapy according to the treatment actually received, which was based on central dosimetry assessment. A patient in the standard dosimetry group was considered to have received personalised dosimetry if the perfused liver dose was more than 150 Gy (a perfused liver dose of >150 Gy represents a treatment intensification by definition),[20] and a patient in the personalised dosimetry group was considered to have received standard dosimetry if the index lesion dose was less than 205 Gy.

Statistical inferences were assessed at a two-sided 5% level of significance. Response rates with 95% CIs were presented by study group and compared by use of χ^2 or the Fisher's exact tests. Overall survival and progression-free survival were calculated with Kaplan-Meier estimators; product-limit estimates were presented by study group using median time, and 12-month, 18-month, and 24-month survival rates with the corresponding two-sided 95% CIs, which were derived using the log-log transformation of the survival function. Median follow-up and 95% CIs were calculated by use of the reverse Kaplan-Meier method.[27] Survival curves of the two study groups were compared by use of a log-rank test. The HR (95% CI) of the standard dosimetry group versus the personalised dosimetry group was computed by use of a univariable Cox regression approach. Pre-specified subgroup analyses were done to estimate HRs (personalised dosimetry *vs* standard dosimetry) in subpopulations defined by the following cofactors (using cutoff points frequently reported in the medical literature when applicable): sex, age (≤65 years *vs* >65 years), Child-Pugh score (A5 *vs* A6-B7), performance status (0 *vs* 1), cirrhosis (yes *vs* no), tumour distribution (unifocal *vs* multifocal), number of lobes affected (unilobar *vs* bilobar), portal vein thrombosis (yes *vs* no),

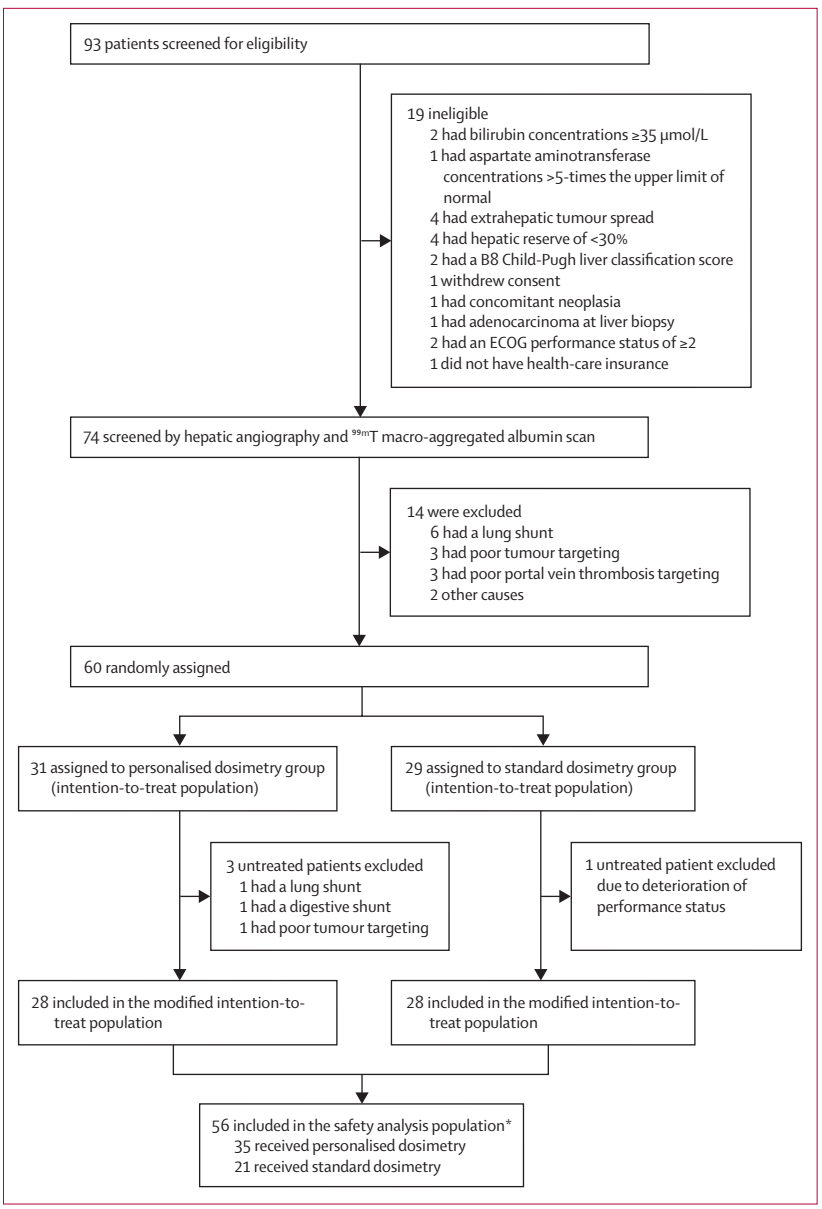

Figure 1: **Trial profile**
ECOG=Eastern Cooperative Oncology Group. ^{99m}Tc=technetium-99m. *Safety was measured according to treatment actually received, which was classified on the basis of central dosimetry review.

	Intention-to-treat population		Modified intention-to-treat population	
	Personalised dosimetry group (n=31)	Standard dosimetry group (n=29)	Personalised dosimetry group (n=28)	Standard dosimetry group (n=28)
Mean age, years	65·0 (10·1)	63·2 (13·4)	64·8 (10·1)	62·5 (13·1)
Sex				
Female	3 (10%)	2 (7%)	2 (7%)	2 (7%)
Male	28 (90%)	27 (93%)	26 (93%)	26 (93%)
Child-Pugh liver function classification				
A5	25 (81%)	23 (79%)	22 (79%)	22 (79%)
A6 or B7	6 (19%)	6 (21%)	6 (21%)	6 (21%)
ECOG performance status				
0	18 (58%)	14 (48%)	16 (57%)	13 (46%)
1	13 (42%)	15 (52%)	12 (43%)	15 (54%)
BCLC classification				
B	4 (13%)	3 (10%)	3 (11%)	2 (7%)
C	27 (87%)	26 (90%)	25 (89%)	26 (93%)
Portal vein invasion				
Absent	11 (36%)	8 (27%)	10 (36%)	7 (25%)
Present	20 (65%)	21 (72%)	18 (64%)	21 (75%)
Portal vein invasion location				
Segmental	10 (33%)	9 (31%)	8 (30%)	9 (32%)
Lobar or main	9 (30%)	12 (41%)	9 (33%)	12 (43%)
Unknown	1 (3%)	0	1 (4%)	0
Cause of cirrhosis				
Alcohol	9 (29%)	9 (31%)	9 (32%)	9 (32%)
Viral hepatitis	8 (26%)	9 (31%)	7 (25%)	9 (32%)
Haemochromatosis	1 (3%)	0	1 (4%)	0
Non-alcoholic steatohepatitis	3 (10%)	3 (10%)	3 (11%)	3 (11%)
Mixed (alcohol and other)	4 (13%)	3 (10%)	4 (14%)	3 (11%)
No cirrhosis	6 (19%)	5 (17%)	4 (14%)	4 (14%)
Treatment line				
First	21 (68%)	25 (86%)	20 (71%)	25 (89%)
Second and subsequent	8 (26%)	3 (10%)	8 (29%)	3 (11%)
Previous transarterial chemoembolisation	5 (16%)	0	5 (18%)	0
Unknown	2 (6%)	1 (3%)	0	0
Tumour distribution				
Unifocal	18 (58%)	12 (41%)	15 (54%)	12 (43%)
Multifocal	13 (42%)	17 (59%)	13 (46%)	16 (57%)
Lobes affected				
Unilobar disease	17 (55%)	12 (41%)	16 (57%)	12 (43%)
Bilobar disease	14 (45%)	17 (59%)	12 (43%)	16 (57%)
Number of lobes treated with selective internal radiation therapy				
One	25 (81%)	21 (72%)	25 (89%)	21 (75%)
Both	3 (10%)	7 (24%)	3 (11%)	7 (5%)
Neither	3 (10%)	1 (3%)	0	0
Tumoural involvement				
Mean	23·9% (14·4)	27·0% (15·8)	23·0% (13·9)	25·6% (14·1)
≥50%	3 (10%)	3 (10%)	2 (7%)	2 (7%)
<50%	27 (87%)	26 (90%)	26 (93%)	26 (93%)
Missing data	1 (3%)	0	0	0

(Table 1 continues on next page)

treatment line (first line *vs* subsequent line), largest diameter of the index lesion (<10 cm *vs* ≥10 cm), baseline α-fetoprotein concentrations (<200 µg/L *vs* ≥200 µg/L), and degree of tumour involvement (<50% *vs* ≥50%). Response and survival parameters were also estimated according to tumour dose (<205 Gy *vs* ≥205 Gy). Post-hoc subgroup analyses were also done to estimate HRs (personalised dosimetry *vs* standard dosimetry) in subpopulations defined by the location of portal vein thrombosis, the number of selective internal radiation therapy procedures done (unilobar or bilobar), and treatment centre.

Data were analysed using SAS software versions 9.4 and 7.1.

The trial is registered with ClinicalTrials.gov, NCT02582034, and has been completed.

Role of the funding source

The funder of the study validated the study design, but had no role in data collection, data analysis, or data interpretation. Editorial assistance for the report was funded by Boston Scientific. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Dec 5, 2015, and Jan 4, 2018, 93 patients were screened, of whom 60 patients were found to be eligible and were randomly assigned to either the personalised dosimetry group (n=31) or to the standard dosimetry group (n=29; figure 1). Three patients in the personalised dosimetry group did not receive treatment due to major protocol deviations (one patient had a digestive shunt, one patient had a high lung shunt, and one patient had no macro-aggregated albumin targeting of a main portal vein thrombosis) and one patient in the standard dosimetry group did not receive treatment due to deterioration of his general condition (performance status of 2). Therefore, the modified intention-to-treat population comprised 56 patients (28 in each group). Patient characteristics were not statistically different between the two groups (table 1). The cutoff date for the primary analysis was Aug 21, 2019.

In the personalised dosimetry group, treatment was unilobar in 25 (81%) of 28 patients and bilobar in three (11%) patients. In the standard dosimetry group, treatment was unilobar in 21 (72%) of 28 patients and bilobar in seven (24%) patients (appendix p 4). The bilobar treatments were not a result of progression. In patients with bilobar disease, details of treatment of the second lobe (with minimal tumour involvement) are presented in the appendix (p 4).

The median prescribed activity was 3·6 GBq (IQR 2·4–4·8) in the personalised dosimetry group compared with 2·6 GBq (2·2–3·0) in the standard dosimetry group (p=0·0049). All patients received less than 150 Gy to the whole liver (consistent with the

instructions for use of the product),[7] except in one patient in the personalised dosimetry group who received 150·6 Gy in one treatment, without any grade 3 or higher liver adverse events of interest.

Dosimetry was evaluated in the 56 treated patients; however, the index lesion dose and normal perfused liver dose was not evaluable for four patients in each group who received two macro-aggregated albumin administrations during the pretreatment angiography. According to the investigator assessment, a significant difference in all pretreatment macro-aggregated albumin dosimetry parameters was observed between the personalised dosimetry and standard dosimetry groups (table 2). These differences included the proportion of patients with an absorbed dose to the index lesion that met or surpassed the threshold dose of 205 Gy and the proportion of patients with an absorbed dose of greater than 150 Gy to the perfused liver (table 2). Centralised assessments confirmed these significant differences (table 2).

According to investigator assessment, the objective response rate in the index lesions in the modified intention-to-treat population at 3 months was significantly higher in the personalised dosimetry group than in the standard dosimetry group, with 20 (71% [95% CI 51–87]) of 28 patients in the personalised dosimetry group had an objective response compared with ten (36% [19–56]) of 28 patients in the standard dosimetry group (p=0·0074; table 3). These results met the prespecified stopping criteria and the study was interrupted for efficacy. Centralised assessment confirmed these results (table 3). The effect of personalised dosimetry on objective response rate was consistent across prespecified subgroups based on baseline characteristics (appendix p 7). The overall response rate according to EASL criteria in patients in the modified intention-to-treat population at 3 months was significantly higher in the personalised dosimetry group than in the standard dosimetry group, with 14 (50% [31–69]) patients in the personalised dosimetry group who had an overall response compared with five (14% [4–33]) patients in the standard dosimetry group (p=0·0042). The objective response rate in the index lesions and objective response rate as per RECIST version 1.1 criteria are presented in the appendix (p 4).

Resection with curative intent after selective internal radiation therapy was done in ten (36%) of 28 patients in the personalised dosimetry group and in one (4%) of 28 patients in the standard dosimetry group (p=0·029; appendix p 5). Of these 11 patients, ten (91%) underwent R0 (microscopic tumour-free margins) surgical resection, and one (9%) patient had a complete histological response. Among 39 patients with portal vein thrombosis, resection after selective internal radiation therapy was done in eight (44%) of 18 patients in the personalised dosimetry group and in no patients in the standard dosimetry group.

Patients were followed up for a median of 27·2 months (IQR 33·9–18·7). During the study, 37 (62%) of 60 patients in the intention-to-treat population had died, including 14 (45%) of 31 patients in the personalised dosimetry group and 23 (79%) of 29 patients in the standard dosimetry group. Median overall survival in the intention-to-treat population was 26·6 months (95% CI 11·7–not reached [NR]) in the personalised dosimetry group compared with 10·7 months (6·0–16·8) in the standard dosimetry group (HR 0·421 [95% CI 0·215–0·826], p=0·0096; figure 2A). Overall survival estimates in the intention-to-treat population were 66·5% (95% CI 46·6–80·4) in the personalised dosimetry group versus 44·8% (26·5–61·6) in the standard dosimetry group at 12 months, 62·6% (42·5–77·3) in the personalised dosimetry group versus 26·8% (12·3–43·7) in the standard dosimetry group at 18 months, and 53·3% (32·8–70·1) in the personalised dosimetry group versus 22·3% (9·0–39·3) in the standard dosimetry group at 24 months. The significant difference in median overall survival between the two groups was maintained after censoring at the date of surgery (post-hoc analysis; appendix p 8).

Median overall survival in the modified intention-to-treat population was 26·6 months (95% CI 11·7–NR) in the personalised dosimetry group versus 10·7 months (6·0–14·8) in the standard dosimetry group (HR 0·38 [95% CI 0·19–0·83], p=0·0063; appendix p 9). The effect of personalised dosimetry versus standard dosimetry was consistent across prespecified subgroups based on baseline characteristics (appendix p 10), including in

	Intention-to-treat population		Modified intention-to-treat population	
	Personalised dosimetry group (n=31)	Standard dosimetry group (n=29)	Personalised dosimetry group (n=28)	Standard dosimetry group (n=28)
(Continued from pervious page)				
Index tumour size, cm				
Mean	10·6 (2·8)	11·1 (2·8)	10·5 (2·4)	10·9 (2·57)
≥10	17 (55%)	18 (62%)	15 (54%)	17 (61%)
<10	14 (45%)	11 (38%)	13 (46%)	11 (39%)
α-fetoprotein concentration, kU/L				
Mean	8580·3 (27059·2)	12559·3 (25833·1)	4052·0 (9920·7)	13007·8 (26192·0)
≥200	13 (42%)	12 (41%)	11 (39%)	12 (43%)
<200	18 (58%)	17 (59%)	17 (61%)	16 (57%)
Bilirubin concentration, µmol/mL				
Mean	13·6 (6·1)	14·2 (6·3)	14·0 (6·0)	14·3 (6·4)
<35	31 (100%)	29 (100%)	28 (100%)	28 (100%)
Treatment site				
Site 1	10 (32%)	5 (17%)	10 (36%)	5 (18%)
Site 2	5 (16%)	7 (24%)	3 (11%)	6 (21%)
Site 3	5 (16%)	3 (10%)	4 (14%)	3 (11%)
Site 4	11 (36%)	14 (48%)	11 (39%)	14 (50%)

Data are n (%) or mean (SD). ECOG=Eastern Cooperative Oncology Group. BCLC=Barcelona Clinic Liver Cancer.

Table 1: **Demographic and baseline characteristics of patients in the intention-to-treat and modified intention-to treat populations**

patients with portal vein thrombosis, in whom median overall survival was 22·9 months (95% CI 9·1–NR) in the personalised dosimetry group versus 9·5 months (5·3–17·6) in the standard dosimetry group (HR 0·39 [95% CI 0·17–0·90], p=0·023).

According to investigator assessment, progression events occurred in 34 (57%) of 60 patients in the intention-to-treat analysis population (17 [55%] of 31 patients in the personalised dosimetry group and 17 [59%] of 29 patients in the standard dosimetry group). Median progression-free survival in this population was 6·0 months (95% CI 3·5–11·6) in the personalised dosimetry group compared with 3·4 months (2·9–8·5) in the standard dosimetry group (HR 0·71 [95% CI 0·39–1·30], p=0·26; figure 2B). In the 34 treated patients with confirmed recurrence, progression events occurred in untreated areas (in the opposite lobe or a distant metastatic lesion) in 24 (71%) patients, and in the treated area in ten (29%) patients (appendix p 5).

After selective internal radiation therapy, 28 (50%) of 56 patients in the modified intention-to-treat population received at least one second-line treatment (appendix p 5).

In the safety analysis, 35 patients were considered to have received personalised dosimetry treatment and 21 were considered to have received standard dosimetry treatment on the basis of centralised dosimetry assessment (table 2). One patient in the personalised dosimetry group received a tumour dose of less than 205 Gy and was considered to have received standard dosimetry. Eight patients in the standard dosimetry group received a dose of greater than 150 Gy to the lobe (ie, they had treatment intensification by definition).[20] Among the 56 patients, 50 (89%) had 241 adverse events, 37 (66%) had 67 grade 3 or worse adverse events, 27 (48%) had 35 grade 3 or worse treatment-related adverse events, 14 (25%) had 20 serious adverse events, and six (11%) had seven serious treatment-related adverse events (table 4). At least one adverse event was reported in 31 (89%) of 35 patients who received personalised dosimetry and in 19 (90%) of 21 patients who received standard dosimetry. A breakdown of type and grades of adverse events, including treatment-related adverse events and serious adverse events, is shown in table 4. One treatment-related death was reported in each group (table 4). Frequent adverse events (ie, those that occurred in ≥5% of patients) are presented in table 5. The most frequent (ie, occurring in ≥5% of patients) grade 3 or higher adverse events were ascites (one [3%] patient who received personalised dosimetry *vs* two [10%] patients who

	Personalised dosimetry group (n=28)	Standard dosimetry group (n=28)	p value
Investigator assessment			
Perfused liver dose, Gy			
Mean	178·4 (59·9)	120·3 (15·2)	0·0001
>150	19 (68%)	1 (4%)	<0·0001
Absorbed tumour dose, Gy*			
Mean	331·1 (131·5)	221·3 (139·4)	0·0007
≥205	21 (88%)	9 (38%)	0·0008
Normal perfused liver dose, Gy*	92·8 (30·1)	64·5 (36·6)	0·0069
Centralised assessment			
Perfused liver dose, Gy			
Mean	213·7 (70·2)	155·2 (97·4)	0·0002
>150	21 (75%)	8 (29%)	0·0011
Absorbed tumour dose, Gy*			
Mean	332·1 (94·8)	225·0 (126·2)	0·0010
≥205	23 (96%)	10 (42%)	<0·0001
Normal perfused liver dose, Gy*	119·7 (67·3)	79·2 (56·9)	0·029

Data are mean (SD) or n (%). ^{99m}Tc=technetium-99m. *Evaluated in 48 patients (24 in each group), as tumour dose and normal perfused liver dose was not evaluable for eight patients (four in each group) due to these patients receiving two ^{99m}Tc macro-aggregated albumin injections during the same pretreatment angiography.

Table 2: **Investigator and centralised ^{99m}Tc macro-aggregated albumin dosimetry results in patients who received selective internal radiation therapy**

	Investigator evaluation			Centralised evaluation		
	Personalised dosimetry group (n=28)	Standard dosimetry group (n=28)	p value	Personalised dosimetry group (n=28)	Standard dosimetry group (n=28)	p value
Objective response	20 (71%)	10 (36%)	..	22 (79%)	12 (43%)	..
Complete response	6 (21%)	3 (11%)	..	5 (18%)	6 (21%)	..
Partial response	14 (50%)	7 (25%)	..	17 (61%)	6 (21%)	..
No response	8 (29%)	18 (64%)	..	6 (21%)	16 (57%)	..
Stable disease	4 (14%)	14 (50%)	..	3 (11%)	11 (39%)	..
Progressive disease	1 (4%)	0	..	0	1 (4%)	..
Other	3 (11%)*	4 (14%)†	..	3 (11%)*	4 (14%)†	..
Objective response rate (95% CI)	71% (51–87)	36% (19–56)	0·0074	79% (59–92)	43% (24–63)	0·0062

Data are n (%), unless otherwise stated. *Two patients were evaluated at 3 months after the introduction of systemic treatment, and one patient was not evaluated at month 3. †One patient was evaluated at 3 months after the introduction of systemic treatment, and three patients were not evaluated at 3 months, including two patients who had died due to progressive disease.

Table 3: **Objective response evaluation of the index lesion at 3 months by investigator and centralised review in the modified intention-to-treat population**

received standard dosimetry), hepatic failure (two [6%] *vs* none), lymphopenia (12 [34%] *vs* nine [43%]), increased aspartate aminotransferase concentrations (three [9%] *vs* two [10%]), increased alanine aminotransferase concentrations (three [9%] *vs* none), anaemia (two [6%] *vs* one [5%]), gastrointestinal haemorrhage (none *vs* two [10%]), and icterus (none *vs* two [10%]; table 5). The number of grade 3 or higher liver events of interest did not differ between the two dosimetry treatments, and were reported in four (12%) patients who received personalised dosimetry treatment and in five (24%) patients who received standard dosimetry treatment (appendix p 6). Clinically relevant radioembolisation-induced liver disease, which is a post-selective internal radiation therapy liver-specific complication characterised by jaundice and ascites,[26] occurred in five (9%) of 56 patients in the safety analysis population (in three [9%] of 35 patients who received personalised dosimetry treatment and in two [10%] of 21 patients who received standard dosimetry treatment).

In 30 patients who received a tumour dose of 205 Gy or higher, 23 (77%) patients had an objective response in the index lesion compared with four (22%) of 18 patients who received less than 205 Gy (p=0·0002), as per investigator assessment of dose and response. The mean index lesion absorbed dose was 337·6 Gy (SD 145·4) in patients with an objective response compared with 210·3 Gy (118·2) in those without an objective response (p=0·0021).

Median overall survival in the modified intention-to-treat population was 26·6 months (95% CI 13·5–NR) in patients who received a tumour dose of 205 Gy or higher compared with 7·1 months (95% CI 4·6–14·8) in those who received a tumour dose of less than 205 Gy (HR 0·33 [95% CI 0·15–0·71], p=0·0029; figure 2C).

Discussion

The multicentre, randomised DOSISPHERE-01 trial compared personalised dosimetry with standard dosimetry treatment in patients with advanced hepatocellular carcinoma. The results showed that the objective response rate, according to EASL criteria, was significantly higher in the personalised dosimetry group than in the standard dosimetry group, with 20 (71% [95% CI 51–87]) of 28 patients in the personalised dosimetry group and ten (36% [19–56]) of 28 patients in the standard dosimetry group having had an objective response in the target lesion at the interim analysis (p=0·0074). These results met the prespecified hypothesis, with a significant difference (p<0·01348) in the objective response rate in the index lesion observed between the standard dosimetry and personalised dosimetry groups, and the study was interrupted for efficacy. The overall response rate according to EASL criteria was also significantly higher in the personalised dosimetry group than in the standard dosimetry group, with 14 (50% [95% CI 31–69]) of 28 patients in the personalised dosimetry group who had an overall response compared with five (14% [4–33]) of 28 patients in the standard dosimetry group (p=0·0042).

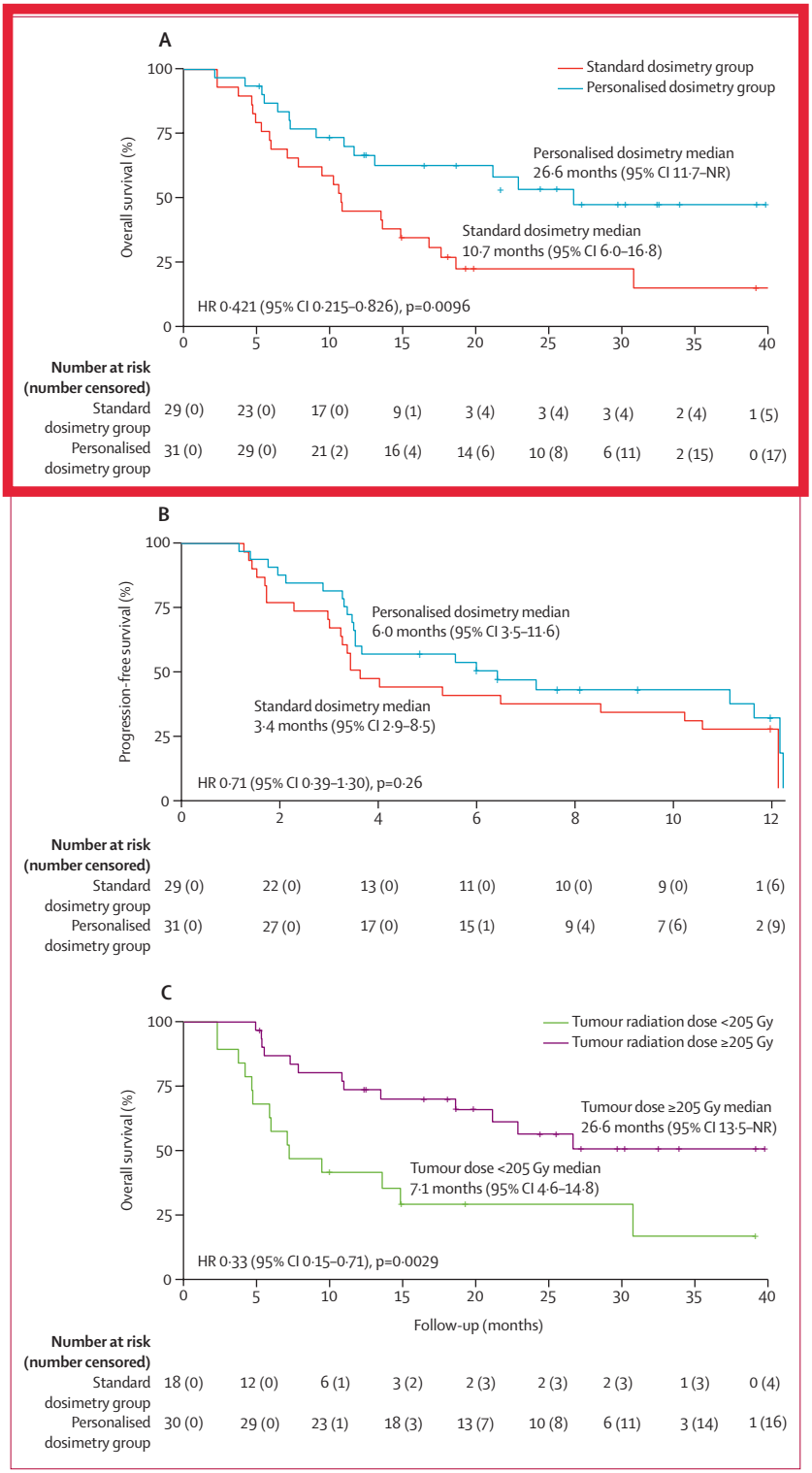

***Figure 2*: Kaplan-Meier survival curves**
Overall survival (A) and progression-free survival (B) in the intention-to-treat population. (C) Overall survival in the modified intention-to-treat population, according to tumour radiation dose (investigator assessment). Tumour radiation dose was not evaluable in eight patients (four in each group) because they received two technetium-99m macro-aggregated albumin injections during the same pretreatment angiography. NR=not reached. HR=hazard ratio.

	Personalised dosimetry treatment (n=35)		Standard dosimetry treatment (n=21)	
	Patients	Events	Patients	Events
Any adverse event	31 (89%)	158	19 (90%)	83
Grade 3	20 (57%)	30	14 (67%)	26
Grade ≥3	21 (60%)	36	16 (76%)	31
Grade 4	3 (9%)	3	2 (10%)	2
Grade 5	2 (6%)*	3	3 (14%)†	3
Any serious adverse event	7 (20%)	10	7 (33%)	10
Serious treatment-related adverse events				
Grade 3	14 (9%)	16	11 (67%)	16
Grade ≥3	16 (6%)	18	11 (52%)	17
Grade 4	1 (3%)	1	0	0
Grade 5	1 (3%)	1	1 (5%)	1
Serious treatment-related adverse events	3 (9%)	4	3 (14%)	3

Adverse events occurring in patients who reported one or more adverse event. 35 patients received personalised dosimetry treatment (>150 Gy to the perfused liver) and 21 patients received standard dosimetry treatment (<205 Gy to the index lesion). *One patient died due to hepatic failure (related to treatment) and the other patient died due to encephalopathy associated with deterioration of their general condition (unrelated to treatment; counted as two grade 5 events). †These patients died due to ascitis (related to treatment), spinal cord compression (unrelated to treatment), and cachexia (unrelated to treatment).

Table 4: **Adverse events in the safety analysis population**

The observed objective overall response rate in the personalised dosimetry group of 50% according to EASL criteria and 29% (eight of 28 patients) according to RECIST version 1.1 criteria is higher than that reported in previous studies of selective internal radiation therapy (36 [20%] of 190 according to RECIST criteria in the SARAH trial), and higher than that reported in studies of immunotherapy (108 [33%] of 325 according to modified RECIST criteria in the IMbrave150 study).[4,13] Tumour size is recognised as a strong prognostic indicator for response and overall survival after locoregional treatment.[19,28] Tumour size has also recently been suggested to have a strong negative impact on response to immunotherapy in different tumour types,[29,30] which could also be the case for hepatocellular carcinoma. Therefore, it is important to highlight the fact that the high objective response rate we observed was in selected patients who had at least one lesion larger than 7 cm in size, which was not an inclusion criterion in other previous studies, including the SARAH and IMbrave150 trials.[4,13,15]

Our study showed a meaningful effect of personalised dosimetry on overall survival, with a HR of death in the intention-to-treat population of 0·421 (95% CI 0·215–0·826, p=0·0096) when comparing personalised dosimetry with standard dosimetry. Of particular note, median overall survival was 26·6 months in patients in the personalised dosimetry group (intention-to-treat population), which is long considering that these patients had large lesions (ie, >7 cm in size) and that there was a high proportion of patients with portal vein thrombosis.

Our results compare favourably with the results of other randomised studies of selective internal radiation therapy. Median overall survival in the treated population was 9·9 months (95% CI 8·0–12·7) in the SARAH trial[13] and 11·3 months (9·2–13·6) in SIRveNIB trial.[14] It is important to observe that the median overall survival of 10·7 months (95% CI 6·0–16·8) observed in patients in the standard dosimetry group in the DOSISPHERE-01 trial is within the range of median overall survival observed in patients treated with selective internal radiation therapy in the SARAH[13] and SIRveNIB trials,[14] indicating that we did not select for patients with a better prognosis than in these previous studies.

Comparing the median overall survival observed in the DOSISPHERE-01 trial with studies of systemic drugs requires caution, as the study populations are not identical. Previous studies[2,3] of systemic drugs have included more patients with extrahepatic spread and therefore a poorer prognosis compared with the DOSISPHERE-01 trial, which only enrolled patients with large lesions and more patients with portal vein thrombosis. It should be noted that the prognosis of patients with portal vein thrombosis is not usually evaluated in studies of systemic therapy (in which patients with portal vein thrombosis and those with extrahepatic spread are evaluated together), except in the subgroup analysis of the SHARP study[31] of sorafenib, which showed that the prognosis of patients with portal vein thrombosis (median overall survival 4·9 months) was poorer than that of patients with extrahepatic spread (8·3 months) in the best supportive care group.[31] In the IMbrave150 study, median overall survival had not been reached at the time of the primary report, but is expected to be around 20 months in the atezolizumab plus bevacizumab group compared with 13·2 months in the sorafenib group (HR 0·58 [95% CI 0·42–0·79]).[4]

In our study, median overall survival in patients with portal vein thrombosis alone was longer in the personalised dosimetry group (22·9 months [95% CI 9·1–NR]) than in those in the standard dosimetry group (9·5 months [5·3–17·6]), and compares favourably with the overall survival of 8·1 months reported with sorafenib in the SHARP study.[31] The observation that eight (44%) of 18 patients with portal vein thrombosis in the personalised dosimetry group could undergo resection with curative intent after selective internal radiation therapy underscores the clinical benefit provided by personalised dosimetry, because surgery in patients with portal vein thrombosis is unusual after systemic therapy.

The effect of tumour dose on outcomes, as suggested in previous retrospective studies,[5,18–21] was prospectively confirmed in the DOSISPHERE-01 trial. Indeed, prospective dosimetry assessments done by investigators indicated that of the 30 patients who received a tumour dose of 205 Gy or higher, 23 (77%) patients had an objective response in the index lesion compared with four (22%) of 18 patients who received less than 205 Gy (p=0·0002), and median overall survival was 26·6 months (95% CI

	Personalised dosimetry treatment (n=35)				Standard dosimetry treatment (n=21)			
	Grade 1 or 2	Grade 3	Grade 4	Grade 5	Grade 1 or 2	Grade 3	Grade 4	Grade 5
Lymphopenia	4 (11%)	11 (31%)	1 (3%)	0	3 (14%)	9 (43%)	0	0
Asthenia	12 (34%)	1 (3%)	0	0	8 (38%)	1 (5%)	0	0
Ascites	3 (9%)	1 (3%)	0	0	6 (29%)	1 (5%)	0	1 (5%)
Increased blood bilirubin	5 (14%)	1 (3%)	0	0	5 (24%)	1 (5%)	0	0
Nausea	7 (20%)	0	0	0	3 (14%)	0	0	0
Abdominal pain	7 (20%)	0	0	0	2 (10%)	0	0	0
Increased aspartate aminotransferase	2 (6%)	3 (9%)	0	0	1 (5%)	1 (5%)	1 (5%)	0
Pyrexia	2 (6%)	0	0	0	2 (10%)	0	0	0
Anaemia	3 (9%)	2 (6%)	0	0	0	1 (5%)	0	0
Diarrhoea	5 (14%)	0	0	0	1 (5%)	0	0	0
Thrombocytopenia	5 (14%)	0	0	0	0	1 (5%)	0	0
Decreased weight	1 (3%)	0	0	0	2 (10%)	0	0	1 (5%)
Increased alanine aminotransferase increased	1 (3%)	3 (9%)	0	0	0	0	0	0
Constipation	4 (11%)	0	0	0	0	0	0	0
Increased blood alkaline phosphatase	1 (3%)	0	0	0	2 (10%)	0	0	0
Gastrointestinal haemorrhage	0	0	0	0	0	2 (10%)	0	0
Icterus	1 (3%)	0	0	0	0	2 (10%)	0	0
Cough	3 (9%)	0	0	0	0	0	0	0
Decreased appetite	3 (9%)	0	0	0	1 (5%)	0	0	0
Hepatic failure	1 (3%)	1 (3%)	0	1 (3%)	0	0	0	0
Vomiting	3 (9%)	0	0	0	1 (5%)	0	0	0
Acute kidney injury	2 (6%)	0	0	0	1 (5%)	0	0	0
Back pain	2 (6%)	0	0	0	0	0	0	0
Hypoalbuminaemia	2 (6%)	0	0	0	1 (5%)	0	0	0
Inflammation	2 (6%)	0	0	0	1 (5%)	0	0	0
Injection site haematoma	2 (6%)	0	0	0	0	0	0	0
Injection site pain	2 (6%)	0	0	0	0	0	0	0
Neutropenia	2 (6%)	0	0	0	0	0	0	0
Varices oesophageal	2 (6%)	0	0	0	0	0	0	0

One death related to treatment was reported in each group.

Table 5: **Adverse events occurring in 5% or more of patients**

13·5–NR) in those who received a tumour dose of more than 205 Gy compared with only 7·1 months (4·6–14·8) in those who received a tumour dose of less than 205 Gy (HR 0·33 [95% CI 0·15–0·71], p=0·0029). This point is of major interest and suggests that macro-aggregated albumin-based dosimetry can be used as standard practice in clinical sites to implement personalised dosimetry.

Progression-free survival did not differ significantly between the personalised dosimetry (6·0 months [95% CI 3·5–11·6]) and standard dosimetry groups (3·4 months [2·9–8·5]). However, due to the study design, progression-free survival had to be censored at the time of surgery because patients had to be withdrawn for resection. This censoring resulted in an important bias, as ten (35%) of 28 patients in the personalised dosimetry group had secondary resection compared with only one (4%) of 28 patients in the standard dosimetry group. With the low complete histological response, the importance of surgical resection in this population is highlighted. It seems that, given the high response rate in large lesions, selective internal radiation therapy with personalised dosimetry acts as a debulking agent for liver tumour load and has a positive effect on overall survival, even in patients with early recurrence. This debulking action of selective internal radiation therapy has already been described in a phase 2 study[32] done in patients with large non-operable intrahepatic cholangiocarcinoma, in which eight (30%) of 27 patients with unilobar disease underwent secondary resection.

Despite treatment intensification in 29 (83%) of 35 patients who received personalised dosimetry, safety was acceptable, with a similar proportion of liver adverse events of interest observed in the two groups in the safety analysis population. Clinically relevant radioembolisation-induced liver disease occurred in five (9%) of 56 treated patients, and occurred at a similar frequency in those who received personalised dosimetry (three [9%] of 35 patients) and standard dosimetry (two [10%] of 21 patients). These results are consistent with the 5–19% of patients with hepatocellular carcinoma who

developed radioembolisation-induced liver disease after selective internal radiation therapy in previous studies,[9,13] and is especially interesting for the patients who received personalised dosimetry in our study because they often underwent treatment intensification. This acceptable safety profile is probably the result of accurate patient selection, with the inclusion of patients with good liver function and a hepatic reserve of at least 30% after selective internal radiation therapy.

With regards to the design of the DOSISPHERE-01 trial, we used a multidisciplinary approach, with the input of oncologists, hepatologists, interventional radiologists, and nuclear medicine physicians, and personalised dosimetry to improve the efficacy of selective internal radiation therapy. Additionally, two other design elements were implemented. First, our study is the first to randomise patients only after determining whether they were able to receive selective internal radiation therapy (ie, by use of the macro-aggregated albumin scan to identify contra-indications, such as lung or digestive shunts). This reduces the number of patients who would otherwise have dropped out of the study after randomisation but before treatment. In the negative phase 3 trials, randomisation was done before the macro-aggregated albumin scan, [13,15] which led 22–28% of patients in the selective internal radiation therapy groups to not actually receive this treatment.[13,14] The second study design element relates to patient selection to preserve safety: patients were included only if they had good liver function and liver disease that had not spread too widely, with the possibility of sparing at least 30% of the liver from radiation. Furthermore, patients were excluded if they were poor candidates for selective internal radiation therapy due to poor targeting of the tumour or portal vein thrombosis.[20,21] All new selective internal radiation therapy trials should follow a similar design, in which the macro-aggregated albumin scan is used as a sort of biomarker for patient selection: randomisation after hepatic angiography and ^{99m}Tc macro-aggregated albumin scan simulation, personalised dosimetry, and more refined patient selection than has been used in previous studies, emphasising good tumour and main portal vein thrombosis targeting with macro-aggregated albumin.

Our study has some limitations. A small number of patients were included in the trial; however, this limitation resulted from the prespecified statistical criterion for stopping early for efficacy, and translated into a clinically meaningful benefit in overall survival. The use of macro-aggregated albumin as a surrogate for microspheres has been widely debated, and many confounding factors have been described.[17] However, this study showed that, at least in the case of hepatocellular carcinoma, and while taking care to limit the occurrence of spasm (which affects macro-aggregated albumin distribution), macro-aggregated albumin has sufficient accuracy for personalised dosimetry to be done with good clinical results. In addition, international recommendations from an expert group in the field supporting macro-aggregated albumin-based personalised dosimetry were published recently (2019).[33] Furthermore, we selected a specific population of patients for inclusion in the study. The generalisability of the results to patients with small lesions (ie, <7 cm) has yet to be evaluated. An improvement in the objective response rate and overall survival in these patients is expected, but the extent of this improvement compared with that observed in patients with large lesions would probably be lower, as the objective response rate in patients with small lesions treated with standard dosimetry is already higher than that observed in patients with large lesions. Even with the use of radiation segmentectomy,[34] the complete histological response rate is 66%, but might be improved with personalised dosimetry. The generalisability of DOSISPHERE-01 trial results to resin microspheres also needs to be evaluated. Theoretically, the concept of personalised dosimetry also applies to resin microspheres, but with a different hepatocellular carcinoma tumoricidal tumour dose of between 100 Gy and 120 Gy[5,35] compared with 205 Gy for glass microspheres. The effect of tumour dose on response and survival has already been described with resin microspheres; [5,34] however, the use of personalised dosimetry and its effects have not been analysed prospectively.

In summary, macro-aggregated albumin SPECT/CT-based personalised dosimetry is safe and leads to a meaningful improvement in the objective response rate and overall survival of patients with locally advanced hepatocellular carcinoma, with an acceptable toxicity profile and without increasing toxicity when compared with standard dosimetry. These results challenge the interpretation of the previously published negative phase 3 trials of selective internal radiation therapy, in which personalised dosimetry was not used. The promising results shown by the use of personalised dosimetry warrant further phase 3 randomised trials of selective internal radiation therapy with personalised dosimetry, either alone or in combination with newer agents.

Contributors

EG, BC-G, JE, and YR made substantial contributions to the conception and design of this study. All authors participated in acquiring the data, and EG, LT, BG, JC, JE, EA, YR, SL, and BC-G also contributed to data analysis and interpretation. EG, LT, BG, JC, JE, EA, YR, and BC-G wrote the manuscript. All authors contributed to the review and revision of the manuscript. All authors approved the final version of the manuscript and take responsibility for the accuracy and integrity of this work.

Declaration of interests

EG reports receiving a grant, personal fees, and non-financial support from Boston Scientific during the conduct of the study. LT reports personal fees from Boston Scientific, Sirtex, and GE Healthcare; grants from Terumo and the Bristol Myers Squibb Foundation; and non-financial support from GE Healthcare during the conduct of the study. BG reports personal fees from Boston Scientific during the conduct of the study. JE reports receiving a grant from Boston Scientific during the conduct of the study; personal fees from Boston Scientific, Bayer, Roche, Eisai, Merck Sharpe & Dohme, AstraZeneca, and Ipsen; grants and personal fees from Bristol Myers Squibb; and non-financial support from Amgen, outside the submitted work. TdB reports grants from Terumo; and personal fees from Guerbet and Terumo during the

conduct of the study. AH reports non-financial support from Servier, Incyte, and Lilly; and personal fees from Amgen, Eisai, and Gritstone Oncology, outside the submitted work. MK reports grants from DOSIsoft outside the submitted work. HR reports personal fees from Boston Scientific outside the submitted work. CR, XP, SLS, SL, BC-G, and YR report receiving a grant from Boston Scientific during the conduct of the study. All other authors declare no competing interests.

Data sharing

The study protocol, statistical analysis plan, and clinical study report can be obtained by contacting the corresponding author (EG). Individual participant data will not be made available.

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