Doxorubicin-loaded nanoparticles for patients with advanced hepatocellular carcinoma after sorafenib treatment failure (RELIVE): a phase 3 randomised controlled trial

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Summary

Background Cytotoxic chemotherapy is generally ineffective in patients with hepatocellular carcinoma. We assessed the intravenous perfusion of doxorubicin-loaded nanoparticles in patients with hepatocellular carcinoma in whom previous sorafenib therapy had failed.

Methods We did a multicentre, open-label, randomised, controlled phase 3 trial at 70 sites in 11 countries. Patients with hepatocellular carcinoma with one or more previous systemic therapies, including sorafenib, were randomly assigned to receive 30 mg/m² doxorubicin-loaded nanoparticles (30 mg/m² group), 20 mg/m² doxorubicin-loaded nanoparticles (20 mg/m² group), or standard care using a computer-generated randomisation list prepared by the funder and stratified by geographic region. Patients in the experimental groups received perfusion of the drug every 4 weeks and those in the control group received any systemic anticancer therapy (except sorafenib) as per investigator decision. The primary endpoint was overall survival in the intention-to-treat population. Safety was assessed in the population of patients who received at least one dose of their assigned treatment. This trial is registered with ClinicalTrials.gov, number NCT01655693.

Findings Between June 15, 2012, and Jan 27, 2017, 541 patients were screened, of whom 144 were excluded and 397 were randomly assigned to one of the groups (133 to the 30 mg/m² group; 130 to the 20 mg/m² group; and 134 to the control group). Median follow-up was 22·7 months (IQR 11·2–34·9). After pooling the doxorubicin groups for the efficacy analysis, median overall survival was 9·1 months (95% CI 8·1–10·4) in the pooled doxorubicin-loaded nanoparticles group and 9·0 months (7·1–11·8) in the control group (HR 1·00 [95% CI 0·78–1·28], two-sided p=0·99). 227 (94%) of 242 patients who received doxorubicin-loaded nanoparticles and 100 (75%) of 134 patients in the control group had at least one treatment-emergent adverse event. The most common drug-related grade 3 or 4 treatment-emergent adverse events were neutropenia (25 [10%] of 242 treated with doxorubicin-loaded nanoparticles and eight [6%] of 134 in the control group), asthenia (six [2%] and four [3%]), and thrombocytopenia (three [1%] and ten [7%]). Six (2%) patients treated with doxorubicin-loaded nanoparticles and one (1%) of those in the control group were deemed by investigators to have had a drug-related death. Serious adverse events occurred in 74 (31%) patients who received doxorubicin-loaded nanoparticles and 48 (36%) in the control group.

Interpretation Doxorubicin-loaded nanoparticles did not improve overall survival for patients with hepatocellular carcinoma in whom previous sorafenib treatment had failed.

Funding Onxeo.

Introduction

The treatment of hepatocellular carcinoma follows guidelines based on the Barcelona Clinic Liver Cancer (BCLC) staging system.[1] Surgical resection, transplantation, and thermoablation are potential curative therapies for patients with early-stage hepatocellular carcinoma, whereas chemoembolisation is recommended as a palliative option for intermediate-stage hepatocellular carcinoma. For patients with advanced hepatocellular carcinoma, or with intermediate stage disease that is no longer a candidate for chemoembolisation, systemic strategies based on oral tyrosine kinase inhibitors such as sorafenib as first-line treatment[2,3] and regorafenib as second-line treatment[4] provide a clinically significant improvement in overall survival. Lenvatinib is non-inferior to sorafenib as first-line treatment[5] and cabozantinib is efficacious as second-line or third-line treatment.[6] Ramucirumab, a monoclonal antibody targeting vascular endothelial growth factor receptor 2, has shown efficacy in the subgroup of patients with hepatocellular carcinoma who have concentrations of alpha-fetoprotein of at least 400 ng/mL after sorafenib

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See Online for appendix

For the **study protocol** see http://www.onxeo.com/site/wp-content/uploads/2019/03/20170727_BA003_Protocol_Relive_v7.pdf

Research in context

Evidence before this study

We searched PubMed for phase 3 randomised controlled studies of advanced inoperable hepatocellular carcinoma, published between Jan 1, 2000, and Feb 4, 2018, and in English. We used the search terms "hepatocellular carcinoma" AND "randomized trial" AND "chemotherapy" OR "doxorubicin". Our search showed that no cytotoxic chemotherapy has improved survival in a previous randomised controlled phase 3 trial in patients with advanced hepatocellular carcinoma, except the small study published by Lai and colleagues in 1988. However, although free doxorubicin was shown to be effective in terms of overall survival, this drug has never become the standard of care for advanced hepatocellular carcinoma because of the weak evidence (small sample size) and the high toxicity in patients with cirrhosis (sepsis, mucositis, and cardiotoxicity).

Added value of this study

The results of RELIVE show that treatment with doxorubicin-loaded nanoparticles, which overrides multiple mechanisms of drug resistance-related chemoresistance, did not result in a significant improvement in overall survival compared with best standard of care in patients with disease progression on sorafenib alone or with other subsequent systemic treatment lines. The secondary endpoints of progression-free survival, time to progression, disease control, and overall tumour response also showed no improvement.

Implications of all the available evidence

This phase 3 trial of doxorubicin-loaded nanoparticles demonstrates the absence of a benefit in overall survival for patients with advanced hepatocellular carcinoma in whom sorafenib treatment had failed. These findings are in contrast with preclinical and phase 1 or 2 clinical studies that had positive results with this treatment for hepatocellular carcinoma. The absence of more effective therapies is an unmet clinical need, but so far, chemotherapy has been clearly demonstrated to be ineffective and toxic in these patients.

treatment failure,[7] whereas ramucirumab did not show any significant benefit in non-selected patients with hepatocellular carcinoma.[8] All other systemic drugs in phase 3 trials showed no efficacy in this population.[9–16] Further, radioembolisation with yttrium-90 has not shown superiority to sorafenib in a randomised phase 3 study in patients with advanced hepatocellular carcinoma or in those with intermediate hepatocellular carcinoma in whom chemoembolisation has failed.[17,18] The best observed overall survival in a systemic setting was for sorafenib followed by regorafenib (median 26·0 months [95% CI 22·6–28·1]).[19] More effective systemic therapies are needed to increase overall survival of patients with advanced hepatocellular carcinoma.

To date, no phase 3 trials of cytotoxic chemotherapy for hepatocellular carcinoma have shown signs of efficacy. Doxorubicin was a potential candidate, but the administration of free doxorubicin is associated with high morbidity in cirrhosis;[20] it also did not show any additive or synergistic effects when added to sorafenib.[21] Doxorubicin-loaded nanoparticles in the liver overwhelm the efflux pumps encoded by multiple drug resistance genes.[22,23] A phase 1–2 trial suggested a potential benefit of doxorubicin-loaded nanoparticles on overall survival of patients with hepatocellular carcinoma, although the trial was prematurely stopped because of lung toxicity associated with doxorubicin-loaded nanoparticles injected by the hepatic arterial route.[24] Preclinical data from Wistar rats showed that this lung toxicity was reduced when doxorubicin-loaded nanoparticles were infused over 2 h.[24] Thus, here, we assessed the efficiency of doxorubicin-loaded nanoparticles administered by a 6 h intravenous infusion in patients with hepatocellular carcinoma after failure of sorafenib therapy.

Methods

Study design

This multicentre, open-label, randomised, controlled phase 3 trial was done at 70 sites in 11 countries in Europe, the USA, the Middle East, and North Africa. The trial was approved by each centre's ethics committee or institutional review board and complied with Good Clinical Practice guidelines, the Declaration of Helsinki, and applicable local laws. The protocol is available online.

Patients

Eligibility criteria were age of at least 18 years; hepatocellular carcinoma confirmed by pathological or non-invasive assessment according to the American Association for the Study of Liver Diseases or European Association for the Study of the Liver as per protocol criteria;[1] at least one measurable lesion by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; BCLC stage B (intermediate) or C (advanced) ineligible for surgical resection, liver transplantation, local ablation, or chemoembolisation;[1] receipt of one or several previous systemic lines of treatment, including sorafenib if stopped at least 2 weeks before randomisation; Child–Pugh score of A5 to B7; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; normal laboratory results (platelets ≥50 000 cells per µL, neutrophils ≥1000 cells per µL, haemoglobin ≥10 g/dL, serum aminotransferases less than five times upper limit of normal [ULN], alkaline phosphatase less than five times ULN, and serum bilirubin <35 µmol/L), and adequate cardiac (normal left ventricular ejection fraction) and pulmonary functions (oxygen saturation ≥95%). Exclusion criteria were untreated hepatitis B; previous malignancy without complete remission in the

past 5 years; HIV infection; hepatocellular carcinoma on transplanted liver; risk of variceal bleeding; previous cumulative dose of more than 300 mg/m² doxorubicin; ongoing immunosuppressive treatment; unstable medical or surgical conditions, particularly uncontrolled diabetes, that might disrupt study participation; uncontrolled systemic infection; life expectancy less than 2 months; receipt of an experimental drug in another clinical trial in the past 30 days; and unwillingness or inability to use two forms of contraception for 6 months after final study drug administration. All patients provided written informed consent.

Randomisation and masking

Patients were randomly assigned to receive either 30 mg/m² doxorubicin-loaded nanoparticles (30 mg/m² group) or 20 mg/m² doxorubicin-loaded nanoparticles (20 mg/m² group) or standard care (1:1:1) using a computer-generated randomisation list prepared by the funder. This list was stratified by geographic region (Europe, USA, or Middle East and North Africa) using blocks (size 6). Investigators, patients, and the funder were unmasked to treatment assignment in this open-label trial. However, independent central review as per RECIST, version 1.1, and data review by the data review committee before database lock were performed blindly. The assignment of number and code for patient identification ensured patient anonymity.

Procedures

In both experimental groups, doxorubicin-loaded nanoparticles were delivered by intravenous perfusion every 4 weeks with a maximum allowed cumulative dose of doxorubicin of 550 mg/m². Patients assigned to the

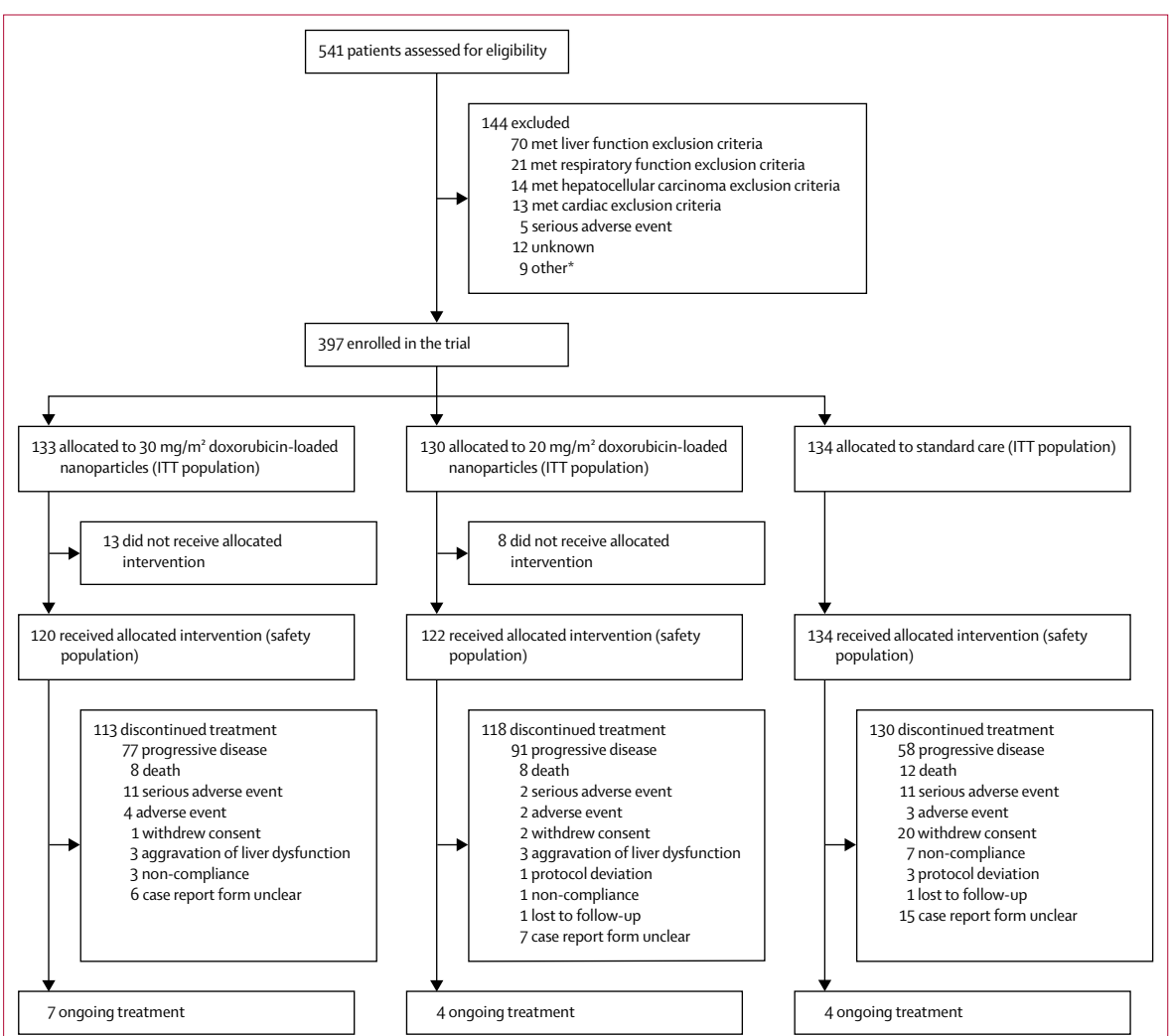

Figure 1: **Trial profile**
Data cutoff was May 28, 2017. ITT=intention to treat. *Includes one concomitant cancer, four non-compliance, two patient withdrawal, one previous other cancer, and one previous cumulative dose of doxorubicin.

	Pooled experimental group (n=263)	Control group (n=134)
Sex		
Men	224 (85%)	117 (87%)
Women	39 (15%)	17 (13%)
Age, years	67 (60–73)	66 (61–72)
Geographical region		
Europe	237 (90%)	119 (89%)
USA	5 (2%)	3 (2%)
Middle East or North Africa	21 (8%)	12 (9%)
Race		
White	242 (92%)	125 (93%)
Black	5 (2%)	3 (2%)
Asian	5 (2%)	3 (2%)
Other	11 (4%)	3 (2%)
ECOG performance status		
0	150 (57%)	70 (52%)
1	108 (41%)	63 (47%)
2	5 (2%)	1 (1%)
Macrovascular invasion	92 (35%)	46 (34%)
Extrahepatic disease	152 (58%)	83 (62%)
Alpha-fetoprotein of at least 400 ng/mL	108 (41%)	63 (47%)
Child–Pugh class*		
A5	118 (45%)	60 (45%)
A6	105 (40%)	54 (40%)
B7	29 (11%)	17 (13%)
Greater than B7	11 (4%)	3 (2%)
Barcelona Clinic Liver Cancer stage		
A (early)	0%	0%
B (intermediate)	71 (27%)	34 (25%)
C (advanced)	192 (73%)	100 (75%)
Liver cirrhosis (investigator assessed)	192 (73%)	103 (77%)
Cause of hepatocellular carcinoma†		
Alcohol use	124 (47%)	68 (51%)
Hepatitis C	79 (30%)	38 (28%)
Unknown	39 (15%)	16 (12%)
Non-alcoholic steatohepatitis	34 (13%)	23 (17%)
Hepatitis B	24 (9%)	13 (10%)
Other	26 (10%)	7 (5%)
Number of previous systemic therapies (including sorafenib)		
One (only sorafenib)	205 (78%)	99 (74%)
Two	47 (18%)	26 (19%)
Three or more	11 (4%)	9 (7%)
Reason for sorafenib interruption		
Tumour progression	174 (66%)	96 (72%)
Intolerance to sorafenib	79 (30%)	35 (26%)
Other	10 (4%)	3 (2%)
Duration of sorafenib treatment, months	4·1 (2·4–9·3)	4·9 (2·6–8·7)
Daily sorafenib dose, months	722 (458–800)	800 (600–800)
Previous locoregional treatments before sorafenib‡		
Surgical resection	89 (34%)	40 (30%)
Percutaneous ablations	50 (19%)	24 (18%)
Transarterial chemoembolisation	150 (57%)	78 (58%)
External beam radiotherapy	29 (11%)	9 (7%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. *The Child–Pugh system describes liver disease severity: patients are divided into classes A–C. †Patients may have more than one cause. ‡Patient can be counted more than once in case of multiple treatments.

Table 1: **Baseline characteristics**

standard care control group received any systemic anticancer therapy (except sorafenib) according to the centre's practice and the decision of the principal investigator at that centre, being aware that any type of these systemic therapies had not shown efficacy in phase 3 trials at the time of randomisation. In all groups, patients received best supportive care. Treatment continued until disease progression as defined by RECIST, version 1.1, or clinical progression, death, unacceptable toxicity, withdrawal of consent by the patient, or decision by the principal investigator. Patients were followed up for tumour assessments every 8 weeks. Treatment could be continued beyond progression at the decision of the principal investigator. To prevent the occurrence of acute respiratory adverse events that we observed in our phase 1–2 trial,[24] perfusion of doxorubicin-loaded nanoparticles was done over 6 h intravenously with safety measures (premedication with methylprednisolone 32 mg orally and one antihistamine drug given 24 h and 1 h before perfusion and 24 h after perfusion). Respiratory symptoms and oxygen saturation were continuously monitored during the 6 h of perfusion: in case of dyspnoea or oxygen saturation decrease from 95% or more to 93% or less, the infusion rate was reduced by half (to a 12 h infusion) without changing the total dose; in case of persistence of dyspnoea beyond 1 h or oxygen saturation decrease to 90% or less, perfusion was immediately and definitively stopped. Safety was monitored continuously throughout the study and patients had safety assessments every 4-week treatment cycle. Blood tests were assessed every 2 weeks. Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Outcomes

The primary endpoint was overall survival, defined as the time from randomisation to death from any cause.

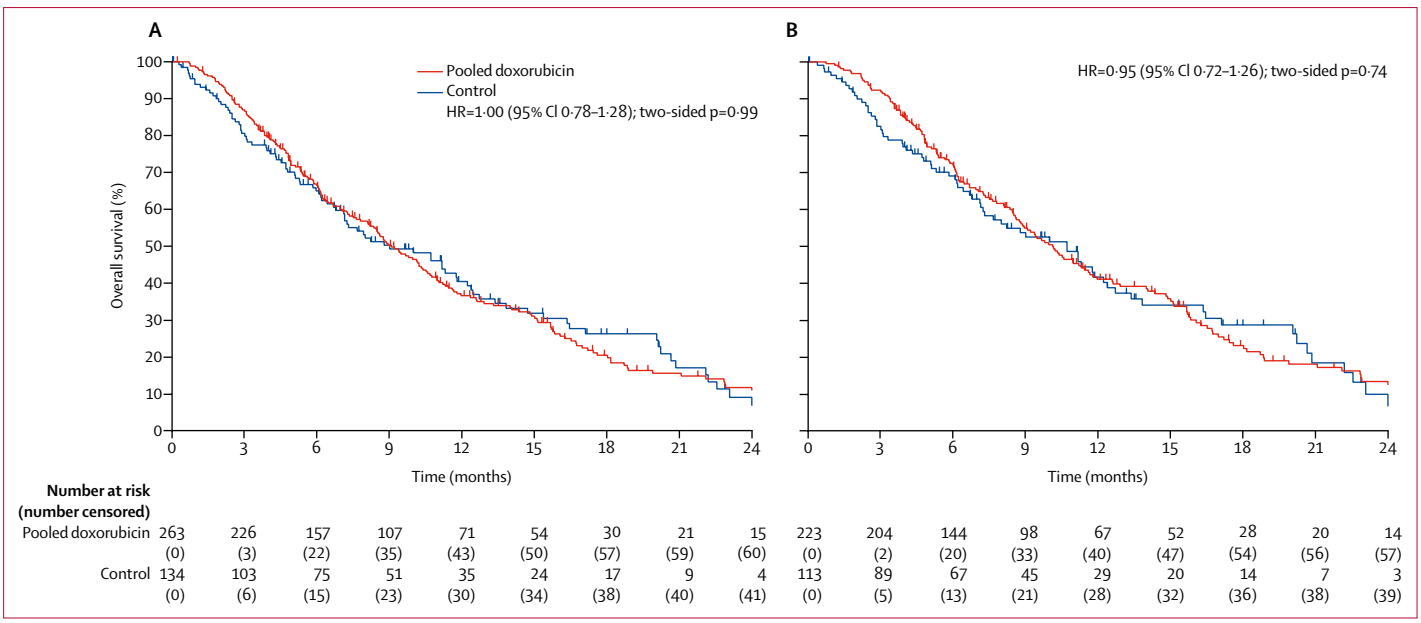

Figure 2: **Kaplan–Meier analysis of overall survival**
(A) Intention-to-treat population. (B) Child–Pugh A subpopulation. HR=hazard ratio.

Secondary endpoints were safety, and overall survival for patients with Child–Pugh score A, progression-free survival (defined as time from randomisation to radiological or clinical disease progression or death), the proportion of patients achieving an objective response (defined as a complete or partial response), and the proportion of patients achieving disease control (defined as complete response, partial response, or stable disease maintained for ≥8 weeks). Responses to treatment were assessed using RECIST (version 1.1), with independent central review. Safety was assessed by adverse events, laboratory abnormalities, vital signs, chest x-ray, and left ventricular ejection fraction by cardiac echography and electrocardiography.

Exploratory endpoints were progression-free survival and objective response as assessed by investigators and time to progression (time from randomisation to radiological or clinical disease progression) assessed by independent central review per RECIST version 1.1.

Statistical analysis

At study initiation in 2011, the initial sample size calculation was done on the basis of an estimated median survival of 6·6 months in the control group and 10·9 months in the experimental groups (hazard ratio [HR] 0·60); an accrual period of 36 months; and a one-sided α level of 2·5%. The required sample size to achieve a 90% power was 130 patients per group (for the two tests of the two doses at a 5% level).

In 2016, Bruix and colleagues[4] published the results of a phase 3 trial of regorafenib, with a median overall survival of 7·8 months (95% CI 6·3–8·8) in the placebo group. The revised power of the estimated required sample size for our study in view of these new results and according to our accrual period of 54 months would be decreased from 90% to 58%.

Considering these results, study feasibility, and the need for results in this serious, life-threatening disease, the statistical analysis plan was amended after validation by the US Food and Drug Administration (July 24, 2017) and signed off by the scientific committee (Aug 25, 2017) before database lock (Aug 28, 2017). The revised statistical analysis plan pooled the two doxorubicin-loaded nanoparticle groups; assuming a median overall survival in the control group of 8 months, and aiming for a hazard ratio of 0·69, the required total sample size to achieve 85% power to compare the experimental groups with control (two-sided α of 5%) was 348 patients (116 patients in the control group and 232 patients in the pooled experimental group). We expected recruitment to take 55 months, with 6 months of follow-up after the last inclusion (total follow-up 61 months), and around 10% of patients to be lost to follow-up. Thus the recalculated total sample size was 390 patients. The analysis was planned for when 285 events (deaths) occurred. For the primary efficacy endpoint of overall survival and the secondary endpoint of progression-free survival, the groups were compared using a non-stratified log-rank test. The HR for overall survival and its 95% CI were calculated using the stratified Cox model.

The primary analysis was done in the intention-to-treat (ITT) population, defined as all patients who had been randomly assigned to a group; safety analyses included all patients who received at least one dose of the study drug. The study was overseen by an independent data safety monitoring committee. To

	Pooled doxorubicin group (n/N)	Control group (n/N)	Median (months)		Hazard ratio (95% CI)	p value
			Pooled doxorubicin group	Control group		
Age, years						
<65	77/112	34/57	8·1	11·2	1·09 (0·73–1·63)	0·682
≥65	119/151	58/77	10·0	8·8	0·96 (0·70–1·31)	0·796
Sex						
Women	29/39	9/18	9·4	11·8	1·18 (0·55–2·51)	0·670
Men	167/224	83/116	9·0	8·2	0·96 (0·74–1·25)	0·778
Geographical region						
Europe or USA	182/242	88/122	9·7	8·8	0·95 (0·74–1·23)	0·706
North Africa and Middle East	14/21	4/12	5·8	NE	2·14 (0·70–6·55)	0·182
Race						
White	183/239	86/125	9·1	9·0	1·03 (0·79–1·33)	0·845
Asian	1/4	2/2	NE	18·2	0·24 (0·02–2·77)	0·254
Other	11/18	3/6	10·2	NE	0·66 (0·18–2·40)	0·524
ECOG performance status						
0	100/150	45/69	11·0	13·4	1·12 (0·78–1·59)	0·540
>0	96/113	47/65	5·9	5·1	0·90 (0·64–1·28)	0·563
Child–Pugh						
A	159/223	73/113	10·1	10·7	0·95 (0·72–1·26)	0·724
B	36/39	19/21	3·8	5·3	1·35 (0·77–2·38)	0·299
Macroscopic vascular invasion						
No	124/170	58/89	10·6	11·3	0·97 (0·71–1·33)	0·872
Yes	73/93	34/45	7·0	6·0	0·97 (0·64–1·46)	0·876
Extrahepatic spread						
Yes	114/152	57/83	8·6	8·2	0·90 (0·65–1·23)	0·507
Intrahepatic spread						
Yes	77/103	31/45	10·0	11·2	1·27 (0·84–1·94)	0·258
Alpha-fetoprotein concentration, ng/mL						
≥400	86/109	49/63	6·0	5·3	0·90 (0·63–1·28)	0·566
<400	110/154	42/70	11·7	13·8	1·18 (0·83–1·69)	0·352
Number of previous treatments						
1	150/204	70/99	9·2	9·0	1·00 (0·75–1·33)	0·984
>1	46/59	22/35	8·8	8·8	0·94 (0·57–1·57)	0·820
Anticancer therapy						
Yes	177/242	58/79	9·5	8·2	0·96 (0·71–1·29)	0·775
Last reason for sorafenib discontinuation						
Progression	130/174	65/97	8·4	10·0	1·13 (0·84–1·52)	0·422
Intolerance	58/78	26/35	12·4	7·1	0·70 (0·44–1·11)	0·132
Previous sorafenib within 10 weeks*						
Yes	95/126	45/63	8·8	7·7	0·97 (0·68–1·38)	0·851
Alcohol use						
Yes	94/124	48/68	8·8	8·0	1·12 (0·79–1·59)	0·531
Hepatitis C virus						
Yes	58/80	22/38	8·6	10·0	0·91 (0·55–1·49)	0·703
Non-alcoholic steatohepatitis						
Yes	29/35	18/23	10·1	9·0	1·11 (0·61–2·00)	0·738
Hepatitis B virus						
Yes	15/23	10/14	11·3	8·0	0·69 (0·30–1·56)	0·372
Treatment group						
Doxorubicin 20 mg/m²	97/130	92/134	10·1	9·0	0·99 (0·74–1·32)	0·947
Doxorubicin 30 mg/m²	99/133	92/134	8·9	9·0	1·00 (0·75–1·33)	0·984

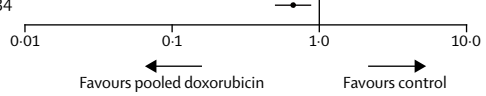

***Figure 3*: Forest plot of overall survival in predefined subgroups**

*Exposure for at least 20 days at a concentration of at least 400 mg and discontinuation less than 10 weeks before randomisation. ECOG=Eastern Cooperative Oncology Group. n=events. N=group size. NE=not estimable.

assess the primary endpoint of overall survival in the ITT population and the secondary endpoints of overall survival in the subpopulation of patients with Child–Pugh score A and progression-free survival and objective response in the whole population and Child–Pugh score A subpopulation, we used a hierarchical sequential closed-test procedure to control the overall type I error rate of 5%, with the following sequence: overall survival in the ITT population, overall survival in the Child–Pugh A subpopulation, progression-free survival in the Child–Pugh A subpopulation, and objective response in the Child–Pugh A subpopulation. If the closed-test procedure fails, all other analyses will be presented as exploratory.

We did a sensitivity analysis using a Cox model adjusting for predefined selected prognostic factors. We first analysed these prognostic factors in separate univariate analyses and then in multivariate analysis. More specifically, we tested each potential predictor in a Cox model in which the considered predictor was the only covariate included (treatment was not included in the model). We selected potential predictors with a p value

less than 0·10 for the multivariate analysis. We then included the selected predictors in a multivariate Cox model (treatment not included in the model) and further selected them with a backward selection procedure eliminating covariates with a p value above 0·10 in presence of the other covariates. We then introduced treatment and well known predictors (macroscopic vascular invasion, extrahepatic spread, Child–Pugh, hepatitis B virus infection, and alpha-fetoprotein) as an additional covariate in the reduced model obtained at the end of the backward selection procedure. We tested the covariate by treatment interactions by adding in a separate model all interactions corresponding to the finally retained covariates. We compared overall survival using a naive test based on the comparison of Kaplan–Meier estimates of survival. We compared proportions of patients achieving responses and disease control in the two groups using Fisher's exact test.

We did statistical analyses with the SAS software, version 9.4. This trial is registered with ClinicalTrials.gov, number NCT01655693.

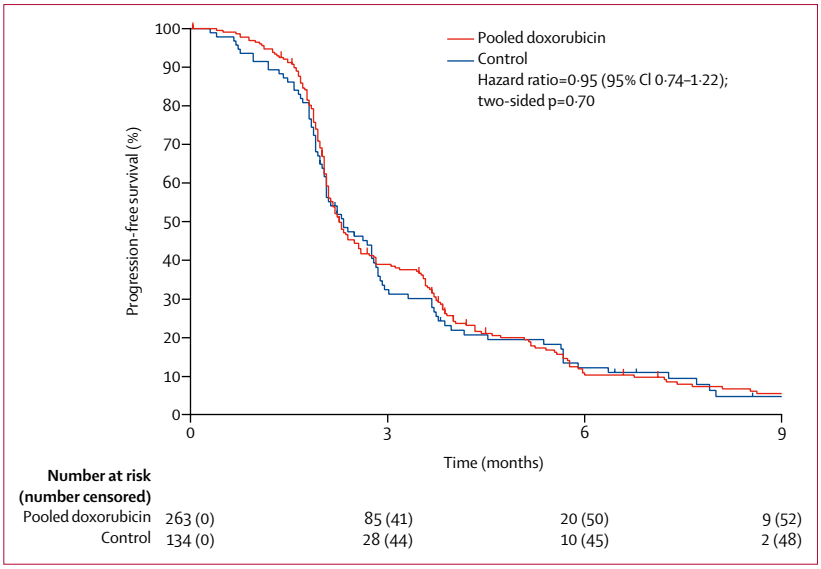

Figure 4: **Kaplan–Meier analysis of progression-free survival in the intention-to-treat population**

Role of the funding source

The funder was involved in study design, data collection, analysis, and interpretation, and writing of the report. Data management was done by Lincoln Pharmaceuticals and Aixial and statistical analyses were done by Chiltern International, both supervised by eXYSTAT. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

541 patients were screened between June 15, 2012, and Jan 27, 2017, and 144 were excluded because they did not meet eligibility criteria. 397 patients were randomly assigned to either the 30 mg/m² group (n=133), the 20 mg/m² group (n=130), or the control group (n=134) and included in ITT analysis (figure 1). 376 (95%) patients started treatment (120 in the 30 mg/m² group, 122 in the 20 mg/m² group, and 134 in the control group) and comprised the safety population. Of the patients who started treatment, 113 (94%) of 120 receiving 30 mg/m² doxorubicin-loaded nanoparticles, 118 (97%) of 122 receiving 20 mg/m² doxorubicin-loaded nanoparticles, and 130 (97%) of 134 patients in the control group discontinued study treatment. The most common reason for discontinuation was radiological progression (77 [68%] of 113 in the 30 mg/m² group, 91 [77%] of 118 in the 20 mg/m² group, and 58 [45%] of 130 in the control). The mean treatment duration was 3·7 months (SD 3·9) in the 30 mg/m² group, 3·4 months (3·9) in the 20 mg/m² group, and 3·0 months (2·6) in the control group. In both experimental groups, the mean number of cycles was 4·6 (SD 4·0); 64 (26%) of 244 patients who received their allocated intervention delayed at least one treatment cycle, and 17 (7%) patients had at least one dose reduction; the mean dose-intensity of doxorubicin-loaded nanoparticles was 99% (SD 7). In the control group, 55 (41%) of 134 patients received only best supportive care whereas 79 (59%) were administered a systemic anticancer therapy considered as the best standard of care by the investigator, the most common of which was oxaliplatin plus gemcitabine in 37 (28%) patients (appendix p 12).

At the cutoff date for the final analysis (May 28, 2017), median follow-up was 22·7 months (IQR 11·2–34·9) and 288 (73%) of the 397 randomised patients had died (99 [74%] of 133 in the 30 mg/m² group; 97 [75%] of 130 in the 20 mg/m² group; and 92 [69%] of 134 in the control group). Baseline demographics were similar between the pooled experimental groups and the control group (table 1). Median previous time on sorafenib was 4·1 months (IQR 2·4–9·3) in the pooled doxorubicin group and 4·9 months (2·6–8·7) in the control group. About a quarter of patients received additional systemic treatment lines after sorafenib and before RELIVE inclusion. Treatments received after withdrawal from RELIVE are shown in the appendix (p 11).

There was no significant difference in overall survival between the groups in the ITT population; median overall survival was 9·1 months (95% CI 8·1–10·4) in the pooled doxorubicin-loaded nanoparticle group and 9·0 months (7·1–11·8) in the control group (HR 1·00 [95% CI 0·78–1·28], two-sided p=0·99; figure 2A). In exploratory analyses, overall survival since start of sorafenib was also not significantly different between the groups, (HR 1·04 [95% CI 0·81–1·32], p=0·77). Overall survival in the Child–Pugh A subpopulation was also similar between groups: median overall survival was 10·1 months (95% CI 8·8–11·6) in the pooled experimental group and 10·7 months (7·2–12·4) in the control group (HR 0·95 [95% CI 0·72–1·26], p=0·74;

	Pooled doxorubicin group (n/N)	Control group (n/N)	Median (months)		Hazard ratio (95% CI)	p value
			Pooled doxorubicin group	Control group		
Age, years						
<65	91/112	34/57	2·2	2·1	0·97 (0·65–1·44)	0·866
≥65	115/151	77/51	2·3	2·8	0·93 (0·67–1·29)	0·647
Sex						
Women	30/39	8/18	2·2	2·8	0·71 (0·32–1·56)	0·389
Men	176/224	77/116	2·3	2·3	0·97 (0·74–1·27)	0·812
Geographical region						
Europe or USA	192/242	79/122	2·3	2·3	0·94 (0·72–1·22)	0·626
North Africa and Middle East	14/21	6/12	2·0	2·2	1·26 (0·45–3·53)	0·654
Race						
White	190/239	79/125	2·3	2·4	1·00 (0·77–1·30)	0·994
Asian	3/4	1/2	1·9	1·6	<0·01 (<0·01–NE)	0·997
Other	12/18	4/6	2·5	1·3	0·28 (0·09–0·91)	0·034
ECOG performance status						
0	120/150	45/69	2·5	2·8	1·08 (0·76–1·52)	0·674
>0	86/113	40/65	2·1	2·1	0·83 (0·57–1·21)	0·326
Child–Pugh						
A	173/223	73/113	2·4	2·4	0·91 (0·69–1·19)	0·482
B	32/39	12/21	2·0	2·0	1·16 (0·60–2·26)	0·663
Macroscopic vascular invasion						
No	135/170	54/89	2·4	2·6	1·08 (0·76–1·52)	0·626
Yes	71/93	31/45	2·1	2·0	0·72 (0·47–1·09)	0·121
Extrahepatic spread						
Yes	123/152	50/83	2·1	2·4	1·18 (0·85–1·64)	0·319
Intrahepatic spread						
Yes	76/103	30/45	2·8	2·2	0·64 (0·42–0·99)	0·044
Alpha-fetoprotein concentration, ng/mL						
≥400	86/109	45/63	2·2	1·9	0·81 (0·56–1·16)	0·255
<400	120/154	39/70	2·5	2·8	1·15 (0·80–1·65)	0·458
Number of previous treatments						
1	156/204	61/99	2·3	2·3	0·86 (0·64–1·16)	0·333
>1	50/59	24/35	2·2	2·8	1·32 (0·80–2·17)	0·275
Anticancer therapy						
Yes	196/242	56/79	2·3	2·7	0·97 (0·72–1·31)	0·848
Last reason for sorafenib discontinuation						
Progression	144/174	63/97	2·2	2·2	1·02 (0·76–1·37)	0·888
Intolerance	52/78	20/35	2·8	2·8	0·79 (0·47–1·34)	0·387
Previous sorafenib within 10 weeks*						
Yes	99/126	39/63	2·2	2·4	0·76 (0·52–1·10)	0·141
Alcohol use						
Yes	94/124	43/68	2·3	2·4	0·95 (0·66–1·36)	0·776
Hepatitis C virus						
Yes	58/80	24/38	2·1	2·1	0·81 (0·50–1·30)	0·373
Non-alcoholic steatohepatitis						
Yes	27/35	15/23	2·5	2·1	0·95 (0·50–1·80)	0·875
Hepatitis B virus						
Yes	19/23	9/14	2·2	2·1	0·93 (0·41–2·14)	0·869
Treatment group						
Doxorubicin 20 mg/m²	100/130	85/134	2·3	2·3	0·94 (0·70–1·25)	0·668
Doxorubicin 30 mg/m²	106/133	85/134	2·3	2·3	0·96 (0·72–1·27)	0·758

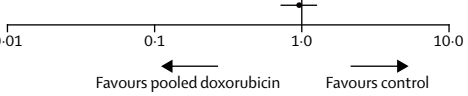

Figure 5: **Forest plot of progression-free survival in predefined subgroups**

*Exposure for at least 20 days at a concentration of at least 400 mg and discontinuation less than 10 weeks before randomisation. ECOG=Eastern Cooperative Oncology Group. n=events. N=group size. NE=not estimable.

figure 2B). No differences in overall survival were noted in any of the predefined subgroups (figure 3).

Median progression-free survival was 2·3 months (95% CI 2·1–2·6) in the pooled experimental group and 2·3 months (2·1–2·8) in the control group (HR 0·95 [95% CI 0·74–1·22], two-sided p=0·70; figure 4). Progression-free survival in the Child–Pugh A subpopulation was also similar between groups (median 2·4 months [95% CI 2·2–2·8] in the pooled doxorubicin group and 2·4 months [2·1–2·8] in the control group). No differences in progression-free survival were noted in any of the predefined subgroups (figure 5). Results were similar for progression-free survival per investigator assessment (appendix p 9).

In other exploratory analyses, time to progression by independent central review showed similar results, with an HR of 0·96 (95% CI 0·74–1·23; two-sided p=0·74; appendix p 10) and a median time to progression of 2·3 months (95% CI 2·1–2·6) in the pooled group and 2·3 months (2·1–2·8) in the control group.

Independent imaging central review was possible in 276 (70%) of the 397 randomised patients (204 [78%] of

263 patients in the pooled doxorubicin-loaded nanoparticles group and 72 [54%] of 134 in the control group; table 2). Review was not possible for 121 patients because of absence of imaging data (n=29), poor quality imaging or identification issues (n=11), and presence of baseline imaging but no follow-up imaging (n=81). Among those with available data, the proportion of patients achieving an objective response or disease control was similar in both groups, by both independent and investigator review (table 2). In the Child–Pugh A subpopulation, response were also similar between the groups (no patients achieved a complete response in either group, partial response in two [1%] of 179 in the pooled doxorubicin group *vs* one [2%] of 64 in the control group, stable disease in 72 [40%] *vs* 28 [44%], and progressive disease in 105 [59%] *vs* 35 [55%]).

227 (94%) of 242 patients in the pooled doxorubicin-loaded nanoparticles group and 100 (75%) of 134 patients in the control group had at least one treatment-emergent adverse event (table 3). These were deemed related to the study drug in 177 (73%) patients in the pooled doxorubicin group and 58 (43%) of the patients in the control group. Serious adverse events occurred in 74 (31%) patients receiving doxorubicin-loaded nanoparticles and 48 (36%) in the control group, and were attributed to the study drug in 31 (13%) cases in the doxorubicin group and 13 (10%) in the control group. The most common grade 3 or 4 drug-related treatment-emergent adverse events were asthenia (six [3%] of 242 patients) and neutropenia (25 [10%]) in the pooled doxorubicin group and asthenia (four [3%] of 134), neutropenia (eight [6%]), and thrombocytopenia (ten [7%]) in the control group. Neutropenia was more frequent in those treated with doxorubicin-loaded nanoparticles than in those in the control group; by contrast, thrombocytopenia was less common in those treated with doxorubicin-loaded nanoparticles than in those in the control group (table 3).

Cardiorespiratory toxicity was rare and not severe for most patients treated with doxorubicin-loaded nanoparticles. Asymptomatic decreases of left ventricular ejection fraction below 50% occurred in five (2%) of 242 patients; respiratory symptoms in 11 (5%); and oxygen desaturation in 31 (13%), which led to interruption or reduction of the speed of perfusion in 13 (5%) patients.

Few drug-related treatment-emergent adverse events led to dose reduction (six [2%] of 242 patients treated with doxorubicin-loaded nanoparticles *vs* 22 [16%] of 134 in the control group), dose delay (45 [19%] *vs* 24 [18%]), study withdrawal (24 [10%] *vs* 12 [9%]), or death (six [2%] *vs* one [1%]; appendix pp 13, 15). No difference in the median time to deterioration of Child–Pugh score from baseline was noted between those treated with doxorubicin-loaded nanoparticles (8·1 months [IQR 2·6–not reached]) and those in the control group (6·4 months [2·4–not reached]). More patients given 30 mg/m² doxorubicin-treated nanoparticles had drug-related treatment-emergent adverse events (98 [82%]) than those given than 20 mg/m² (79 [65%]; p=0·003) but it did not affect the continuity of the trial in terms of treatment-emergent adverse events leading to study withdrawal or death (appendix pp 14, 15).

	Indpendent central review		Investigator review	
	Pooled experimental group (n=204)	Control group (n=72)	Pooled experimental group (n=219)	Control group (n=78)
Best overall response				
Complete response	0	0	0	0
Partial response	2 (1%)	1 (1%)	6 (3%)	4 (5%)
Stable disease	80 (39%)	31 (43%)	112 (51%)	41 (53%)
Progressive disease	121 (59%)	40 (56%)	101 (46%)	33 (42%)
Objective response	2 (1%)	1 (1%)	6 (3%)	4 (5%)
Disease control	82 (40%)	32 (44%)	118 (54%)	45 (58%)

Table 2: **Objective responses in evaluable patients by independent central review and per investigator review**

Discussion

The absence of more effective therapies for hepatocellular carcinoma is an unmet clinical need; however, chemotherapy has been clearly shown to be ineffective and toxic in patients with advanced disease. In this phase 3 trial assessing doxorubicin-loaded nanoparticles as subsequent-line treatment for patients in whom sorafenib has failed, no difference was detected between doxorubicin-loaded nanoparticles and control in terms of overall survival.

Survival in patients with hepatocellular carcinoma is influenced by many factors related not only to tumour burden but also to underlying liver conditions, and minor imbalances in prognostic factors can have a meaningful effect on overall survival. Nonetheless, baseline characteristics were similar between the groups and thus are not a possible explanation for these results. One explanation could be insufficient power, because patients with a better prognosis than in previous trials were enrolled.[9,13] Indeed, median overall survival in the control group was unexpectedly high in the whole population (9·0 months [95% CI 7·1–11·8]) as well as in the subpopulation of patients with Child–Pugh score A (10·7 months [7·2–12·4]). By contrast, median overall survival results in the Child–Pugh A populations of other phase 3 trials such as SHARP[2] (sorafenib) and RESORCE[4] (regorafenib) were lower: median overall survival was 7·9 months in the control group of both studies, and was 8·0 months in the cabozantinib trial.[6] Equivalent data were observed for overall survival in the control groups of other phase 3 trials of drugs being tested after failure of sorafenib: in the brivanib trial it was 8·2 months,[13] 7·3 months in the trial of everolimus,[14] and 7·6 months in the REACH trial of ramucirumab;[8] overall survival in the control group in a phase 3 study of tivantinib was 9·1 months.[9] In the RELIVE trial, only three-quarters of patients had previously received only sorafenib as systemic treatment whereas a quarter had received at least two lines of treatment (sorafenib plus one or more additional lines). Thus, the RELIVE trial might have selected patients with

	Treatment-emergent adverse events							Drug-related treatment-emergent adverse events						
	Pooled experimental group (n=242)				Control group (n=134)				Pooled experimental group (n=242)				Control group (n=134)			
	Any grade	Grade 3	Grade 4	Leading to death	Any grade	Grade 3	Grade 4	Leading to death	Any grade	Grade 3	Grade 4	Leading to death	Any grade	Grade 3	Grade 4	Leading to death
Asthenia	99 (4%)	12 (5%)	1 (<1%)	0	41 (31%)	9 (7%)	1 (1%)	0	73 (30%)	5 (2%)	1 (<1%)	0	24 (18%)	4 (3%)	0	0
Nausea	59 (24%)	3 (1%)	0	0	24 (18%)	0	0	0	43 (18%)	1 (<1%)	0	0	18 (13%)	0	0	0
Diarrhoea	44 (18%)	2 (1%)	0	0	20 (15%)	4 (3%)	0	0	28 (12%)	2 (1%)	0	0	15 (11%)	2 (1%)	0	0
Peripheral oedema	35 (14%)	1 (<1%)	0	0	24 (18%)	1 (1%)	0	0	5 (2%)	0	0	0	2 (1%)	0	0	0
Ascites	29 (12%)	5 (2%)	0	0	27 (20%)	12 (9%)	2 (1%)	1 (1%)	7 (3%)	0	0	0	2 (1%)	0	0	0
Anorexia	35 (14%)	3 (<1%)	1 (<1%)	0	21 (16%)	3 (2%)	0	0	17 (7%)	0	0	0	12 (9%)	0	0	0
Vomiting	37 (15%)	6 (2%)	0	0	10 (7%)	1 (1%)	0	0	23 (10%)	2 (1%)	0	0	7 (5%)	0	0	0
Constipation	33 (1%)	0	0	0	12 (9%)	1 (1%)	0	0	0	0	0	0	0	0	0	0
Abdominal pain	30 (12%)	7 (3%)	1 (<1%)	1 (<1%)	13 (10%)	4 (3%)	0	0	0	0	0	0	0	0	0	0
Fever	33 (1%)	2 (1%)	0	0	10 (7%)	0	0	0	0	0	0	0	0	0	0	0
Back pain	28 (1%)	5 (2%)	0	1 (<1%)	6 (4%)	0	0	0	0	0	0	0	0	0	0	0
Headache	27 (11%)	1 (<1%)	0	0	6 (4%)	0	0	0	16 (7%)	0	0	0	1 (1%)	0	0	0
Dyspnoea	25 (10%)	4 (2%)	0	0	9 (7%)	0	0	0	0	0	0	0	0	0	0	0
Cough	22 (9%)	0	0	0	10 (7%)	0	0	0	0	0	0	0	0	0	0	0
Paraesthesia	3 (1%)	0	0	0	18 (13%)	3 (2%)	0	0	3 (1%)	0	0	0	18 (13%)	1 (1%)	0	0
Anaemia	39 (16%)	6 (2%)	0	0	24 (18%)	8 (6%)	1 (1%)	0	22 (9%)	3 (1%)	0	0	9 (7%)	1 (1%)	0	
Neutropenia	23 (10%)	17 (7%)	8 (3%)	0	8 (6%)	6 (4%)	4 (3%)	0	23 (10%)	17 (7%)	8 (3%)	0	7 (5%)	4 (3%)	4 (3%)	0
Thrombocytopenia	16 (7%)	3 (1%)	0	0	25 (19%)	9 (7%)	2 (1%)	0	14 (6%)	3 (1%)	0	0	22 (16%)	8 (6%)	2 (1%)	0

Data are n (%).

Table 3: **Treatment-emergent adverse events and drug-related treatment-emergent adverse events of any grade occurring in at least 10% of patients in either treatment group (safety population)**

the most indolent hepatocellular carcinomas, with good ECOG performance statuses (0–1) and acceptable liver functions (Child–Pugh A5–B7), and a tumour burden small enough to keep the patients alive after several lines of systemic treatment before randomisation in RELIVE. Indeed, the patients with the most aggressive forms of hepatocellular carcinoma might have either died during the previous systemic lines or did not meet the eligibility criteria to enter RELIVE because of end-stage liver disease.

Another possible explanation for the failure to detect a treatment difference in the RELIVE study is based on the fact that all the phase 3 trials used a placebo as the control group, whereas the control group in our trial was standard treatment, at the decision of each principal investigator. In our control group, although 55 (41%) of 134 patients received only best supportive care, 79 (59%) received a systemic anticancer therapy, of whom 37 (47%) were given gemcitabine plus oxaliplatin (GEMOX). It is possible that GEMOX might be of benefit for patients with hepatocellular carcinoma, thus concealing the potential benefit of doxorubicin-loaded nanoparticles. Data from phase 3 randomised controlled trials using GEMOX in advanced hepatocellular carcinoma are still needed. In a prospective cohort study by Taïeb and colleagues,[25] overall survival with GEMOX was 12 months and in a phase 2 single-arm study of 32 patients by Louafi and colleagues,[26] it was 11·5 months. In addition, in a large multicentre retrospective study of 204 patients, overall survival with GEMOX was 11 months.[27] By contrast, overall survival with free doxorubicin was only 4·9 months in a phase 2 randomised controlled trial in Asia.[28]

Furthermore, the antitumour activity of doxorubicin-loaded nanoparticles might not be strong enough to extend survival. This idea is supported by the negative findings of the secondary and exploratory endpoints such as progression-free survival, objective response, and time to progression, as well as subgroup analyses, which all clearly show no difference between the 20 mg/m² and the 30 mg/m² groups. Furthermore, the 30 mg/m² group had more patients with drug-related treatment-emergent adverse events than the 20 mg/m² group, thus demonstrating a dose-dependent toxicity of doxorubicin.

Consistent with previously published data, clinically significant (observed in at least 10% of patients) drug-related treatment-emergent adverse events of any grade attributable to doxorubicin were mostly asthenia, nausea, vomiting, and neutropenia, whereas thrombocytopenia (probably due to gemcitabine) and paraesthesia (probably due to oxaliplatin) were observed in the control group. Although acute respiratory distress syndrome occurred in some patients due to intrahepatic arterial injection of doxorubicin-loaded nanoparticles in the phase 1–2 trial,[24] no clinically significant pulmonary treatment-emergent adverse events were observed after 6 h of intravenous perfusion in RELIVE. Headache was more prevalent in the patients who received the nanoparticle-loaded

doxorubicin, which might be specific to the nanoformulation, since this is not commonly reported with free doxorubicin, but is reported with other forms of nanoformulation of doxorubicin such as liposomal doxorubicin.[29] Causes of three deaths (in the pooled experimental group) considered by investigators and the data safety monitoring board to be treatment related were not unusual for this patient population (interstitial lung disease, lung infection, and peritoneal haemorrhage). Of note, only about a tenth of patients in the pooled doxorubicin-loaded nanoparticle group withdrew from the trial prematurely because of drug toxicity.

In conclusion, this first phase 3 study of doxorubicin-loaded nanoparticles in patients with advanced hepatocellular carcinoma who have already been treated with sorafenib did increase overall survival. The results of our trial could inform the design of future studies in this patient population.

Contributors

PM, PA, and BV conceived and designed the study. Principal investigators at each site enrolled patients. PM and JLeB collected the data. PM, BV, and JLeB analysed and interpreted the data. All authors participated in the drafting, review, and approval of the manuscript and the decision to submit for publication.

Declaration of interests

PM has received consultancy and advisory fees from Onxeo, Bayer, Lilly, Ipsen, Bristol-Myers Squibb (BMS), and Merck Sharp & Dohme (MSD). J-FB has received consultancy and advisory fees from Onxeo, Bayer, Lilly, Ipsen, and BMS. J-PB has received consultancy and advisory fees from Onxeo and Bayer. GP has received consultancy and advisory fees from Bayer, AbbVie, Novartis, and Gilead. AA has received consultancy and advisory fees from AbbVie, MSD, and Gilead. IW has received consultancy and advisory fees from Janssen, AbbVie, MSD, Marcyrl, Pharco, and Gilead. NSY reports grants from Penn State Cancer Institute, Halozyme, Boston Biomedical, Caris Life Sciences, Foundation Medicine, Pharmacyclics, EMD Serono, Onxeo, Regeneron, Momenta, Merck, Daiichi Sankyo, Eli Lilly, Novartis, Taiho, Bayer, Celgene, Lexicon, Incyte, Pfizer, and BMS. PA is an Onxeo shareholder and an author of a patent for nanoparticles loaded with chemotherapeutic antitumoral drug (US Patent and Trademark Office 9763874). All other authors declare no competing interests.

Data sharing

Data collected for this study (including individual participant data and a data dictionary defining each field in the set) will be made available to others after approval by the corresponding author. Additional, related documents will be also available (case report forms, statistical analysis plan, and informed consent forms) on request by the corresponding author and sponsor's approval. These data will be available after publication.

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