Radioembolization Plus Chemotherapy for First-line Treatment of Locally Advanced Intrahepatic Cholangiocarcinoma: A Phase 2 Clinical Trial

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Radioembolization plus chemotherapy as first-line treatment of locally-advanced intrahepatic cholangiocarcinoma.

The multi-center single-arm phase 2 MISPHEC study

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Short title: Phase 2 trial of SIRT and chemotherapy in BTC

Keyword: Radioembolization; SIRT; Yttrium-90; surgery; intrahepatic cholangiocarcinoma; biliary tract cancer; downstaging; chemotherapy

Electronic word count:

Number of Figures:

Number of Tables:

Conflict of interest statement: JE, EB, YR and EG acted as consultant for BTG. EB is currently employed by BTG.

Financial support statement: This study was partially funded by BTG and the Ligue Contre le Cancer.

Authors contribution: EB, BCG and EG conceived the study; all authors included patients in the trial; BCG conducted the statistical analysis; JE wrote the first draft of the article; all authors approved the final version of the article.

Key points:

Question: Does SIRT improve Response Rate in unresectable ICC?

Findings: In this multi-center phase 2 trial that included 41 patients, SIRT combined with chemotherapy was associated with increased response rate of 39%, and a high proportion of patients downstaged to surgery of 22%. Promising median PFS of 14 months, and median OS of 22 months were seen.

Meaning: SIRT should be considered a treatment option for downstaging of patients with unresectable ICC.

Structured Abstract:

Importance: Patients with unresectable intra-hepatic cholangiocarcinoma (ICC) have a poor prognosis. Selective Internal Radiation Therapy (SIRT) is a promising treatment option in hepatic tumors, but no prospective studies of combination of SIRT with chemotherapy have been published.

Objective: To determine the response rate (RR) following SIRT combined with chemotherapy.

Design: This phase II single-arm study (MISPHEC trial) included patients with unresectable ICC in 7 centers between November 2013 and June 2016.

Setting: Multicenter high volumes centers with experience for SIRT.

Participants: Patients with unresectable ICC, without previous chemotherapy or intra-arterial therapy.

Intervention: Patients received concomitant first-line chemotherapy with Cisplatin 25mg/m² and Gemcitabine 1000mg/m² (reduced to 300mg/m² the cycles just before and following SIRT) day 1 and 8 of a 21-days cycles for 8 cycles. SIRT was delivered during cycle 1 (one hemiliver disease), or cycles 1 and 3 (disease involving both hemiliver), using glass Yttrium-90 microspheres.

Main outcomes and measure: Primary objective was to measure response rate (RR) at 3 months according to RECIST 1.1. Secondary endpoints were toxicity, Progression-Free Survival (PFS), Overall Survival (OS), disease control rate (DCR) and RR according to Choi.

Results: 41 patients were included in the study. RR according to RECIST was 39% [90% CI: 26-53] at 3 months according to local review, and confirmed at 41% as best response by central

review, DCR was 98%. By Choi criteria, RR was 93%. After a median follow-up of 36 months, median PFS was 14 months [95%CI: 8-17], with 12- and 24-months PFS rates of 55% and 30%, respectively. Median OS was 22 months [95%CI: 14-52], with 12- and 24-months OS rates of 75% and 45%, respectively. 72% of patients had grade 3-4 toxicity. 9 patients (22%) could be downstaged to surgery, with 8 (20%) achieving R0 resection. After a median of 46 months following surgery, median relapse-free-survival was not reached in resected patients.

Conclusions and relevance: Combination of chemotherapy and SIRT achieved promising anti-tumor activity in first-line treatment of unresectable ICC, with a significant proportion of patients downstaged to surgery. A phase 3 trial is ongoing.

Trial registration: Clinicaltrials.gov (NCT01912053)

Introduction:

Intrahepatic cholangiocarcinoma (ICC) has a rising incidence in Western countries [1,2]. In advanced ICC, doublet chemotherapy with cisplatin and gemcitabine became the standard treatment after the results of the ABC-02 study, confirmed by a meta-analysis, with a median OS of 11.7 months [3–5]. However, results in the locally-advanced ICC population are less well described. Therapeutic improvements in BTC are necessary.

^{90}Y-microspheres radioembolization, also known as selective internal radiation therapy (SIRT), is applied as a loco-regional treatment for liver malignancies, both for primary tumors and hepatic metastases. Radiolabeled microspheres are administrated via the hepatic arteries, delivering radiation when reaching the tumor vasculature. Multiple single-center series reported results of SIRT in locally-advanced ICC [6–19], however the largest published to date included only 85 patients [18]. Results of these studies are heterogeneous, with median response rates (RR) ranging from to 5 to 36%, and median OS between 9 to 22 months, reflecting the heterogeneity of the population included. We previously suggested that in first-line treatment, concomitant chemotherapy and SIRT might provide additional benefit, with a median PFS of 21.7 months in case of concomitant chemotherapy vs 13.4 months when chemotherapy was performed before SIRT [8]. Based on this results, we designed a prospective multi-center single-arm phase II trial to assess the efficacy and safety of SIRT combined with chemotherapy in first-line treatment of unresectable, locally-advanced ICC.

Patients & methods:

Study design and population:

The Yttrium-90 MIcroSPHEres in Cholangiocarcinoma (MISPHEC) trial was designed as a first-line multicenter, open-label, single-arm phase II trial. The trial was conducted in 7 centers in France. Eligible patients were patients aged 18 or more, with unresectable ICC, with a measurable lesion (at least 2cm), with either non-cirrhotic liver or a cirrhosis with Child-Pugh score <B8, good ECOG performance status (0 or 1), with no or limited extra-hepatic disease (limited extra-hepatic disease was defined as hilar lymph node ≤3cm, less than 5 lung nodules, each ≤10mm), adequate hematological or kidney function, albumin ≥28g/L, bilirubin ≤3x upper limit of normal. Patient with previous resection and intra-hepatic unresectable recurrence could be included in the study. Unresectability was defined as inability to resect the cancer with negative margins leaving two adjacent segments of liver with intact portal venous and hepatic arterial inflow and intact biliary and hepatic venous outflow with the future liver remnant of sufficient volume to avoid post-operative liver insufficiency. Evaluation of unresectability was done locally by multidisciplinary team discussion involving hepatobiliary surgeons. Non-inclusion criteria were patients with extrahepatic cholangiocarcinoma, gallbladder cancer, pancreatic or ampullary cancer, portal vein thrombosis involving the trunk, patients with previous chemotherapy, intra-arterial or radiation treatment for ICC, or contra-indication to either gemcitabine or cisplatin. Patients were excluded if a contra-indication appeared during work-up angiography, such as lung shunting (lung dose >30Gy for a single treatment or >50Gy cumulative), or non-manageable extra-hepatic deposition of ^{99m}Tc macroaggregated albumin (MAA) on scintigraphy performed after planning angiography.

The trial was approved by an ethics committee and was conducted according to Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent before inclusion in the trial. This trial is registered on EudraCT (2012-001213-16) and Clinicaltrials.gov (NCT01912053).

Procedures:

After inclusion, patients started treatment with chemotherapy using the gemcitabine-cisplatin regimen. In case of one hemiliver involvement, the SIRT was performed during cycle 1, day 3 to day 21; in case of involvement of both hemiliver, a first SIRT was performed as described previously and a second SIRT procedure was done during cycle 3, day 3 to day 21, in order to cover both hemiliver. In case of anatomical variants of liver arteries, it was allowed to administer up to 3 SIRT sessions, at the discretion of the interventional radiologist. Chemotherapy was continued for a recommended number of 6 cycles, but prolongation of chemotherapy (GEMCIS or gemcitabine alone) was accepted when deemed necessary by the investigator. The gemcitabine-cisplatin regimen consisting in cisplatin 25 mg/m^2 on day 1 and 8 and gemcitabine 1000 mg/m^2 on day 1 and 8, cycles repeated every 3 weeks. For the cycle concomitant and the cycle following SIRT, the gemcitabine dose was decreased to 300 mg/m^2 due to concerns about potential toxicity of the combination with SIRT.

The SIRT procedure was performed as previously described [20]. Percentage of pulmonary shunting and absence of digestive uptake were assessed after ^{99m}Tc macroaggregated albumin was injected (185 MBq) during a first angiography. Planar and SPECT/CT acquisitions were performed. SIRT was performed 8 to 15 days later at a second angiography, using glass microspheres. Activity administered was calculated with the aim of administering a dose of

120 Gy +/- 20 Gy to the targeted liver volume (injected hemiliver) without exceeding a cumulative dose of 50 Gy to the lungs. Treatment personalization, with the aim to provide ≥205 Gy to the tumor using a treatment intensification (providing more than 150 Gy to the targeted liver), as previously described, was authorized [21]. Segmentation (targeted liver and tumor) was performed on SPECT/CT data, as previously described [22].

Follow-up consisted of clinical evaluation, radiological (CT-scan) and blood test (including hematological, liver and renal function tests, carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19.9 and alpha-fetoprotein (AFP)) were performed between week 12 and 15 then every 8 weeks thereafter. In case of secondary surgery, follow-up was planned every 12 weeks. Follow-up was planned for 2 years after inclusion.

Outcomes

The primary endpoint was response rate (RR) according to RECIST 1.1 at 3 months, according to the review by investigators. Secondary objectives were toxicity, progression-free survival (PFS), overall survival (OS), disease control rate (DCR, corresponding to patients with either stable disease or objective response at 3 months), quality of life and RR according to Choi criteria [23]. Choi evaluation of response is based on evaluation of both sum of maximal diameter and density as measured in Hounsfield units. A decrease in density ≥ 15% was accepted as a criterion of partial response according to Choi only if the absolute density change would account for at least 10 Hounsfield Units. A planned central review analysis of response evaluation according to RECIST 1.1 and Choi criteria was also performed, by a single radiologist (LB). Toxicity was assessed according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.

Statistical analysis

The unacceptable and expected RR thresholds were defined as respectively 22% (P0) and 45% (P1). Based on Simon's optimal two-step design, with type I and type II errors set at 5% and 10%, respectively, at least 41 patients were required to be included in the study. The Simon's plan allowed us to stop the study prematurely for futility (after inclusion of 17 patients) if fewer than 5 patients were considered responder. In addition, it was expected during trial design that up to 5 patients could not be treated because of the contraindication shown on the planning angiogram. The final analysis would include the 41 treated patients (excluding patients not treated due to contraindication).

Data were summarized by median, min and max, and frequency and percentage, for continuous and categorical data, respectively. In particular, with respect to the primary endpoint, response rates were presented with 90% bilateral confidence intervals, calculated using the exact Clopper-Pearson method.

OS, PFS and Relapse-Free Survival (RFS) curves were estimated by the Kaplan-Meier method. OS was defined as the time between inclusion and death, PFS as the time between inclusion and progression or death. In patients with secondary surgery, RFS was defined as the time between surgery and recurrence or death, and post-surgical OS was also presented as the time between surgery and death. The OS prognostic factors were also evaluated using a Cox proportional-hazard regression model. A stepwise algorithm in forward direction using Bayesian information criteria (BIC) was implemented to choose the final model. All the factors associated with OS at 0.1 p value level was introduced in the multivariable analysis. The model assumptions were evaluated with Martingale and Schoenfeld residuals. Median follow-up was estimated by the reverse Kaplan-Meier method. Tolerance and safety were reported as a frequency table of MedDRA 18.1 preferred terms occurred from the first

arteriography to the end of follow-up, and related or not to the experimental procedure. We also performed a post-hoc analysis of liver toxicity between cirrhotic and non-cirrhotic patients, as this parameter was likely to explain some of the toxicity observed.

Results:

Population

Between November 2013 and June 2016, 56 patients were screened, 45 respected inclusion and non-inclusion criteria before planning angiography, and 41 included and analysed in the ITT population, without contra-indication during this angiography (the 4 patients excluded had extrahepatic fixation on scintigraphy) (Figure 1).

The characteristics of the population are reported on Table 1.

Treatment received and safety

The median number of cycles of chemotherapy delivered was 6 (range: 1-15), with a relative dose intensity of gemcitabine of 81% and a relative dose intensity of cisplatin of 88%. Twenty-six patients (65%) had one SIRT session, 12 (30%) had 2 and 2 (5%) had 3 (due to hepatic arterial anatomy). The median dose delivered to targeted liver was 120Gy (range: 18-430), the median dose delivered to the tumor was 317Gy (range: 64-1673), the median dose delivered to the non-tumoral liver was 87Gy (range: 4-235Gy).

Number of the 41 patients of the ITT population with treatment-related adverse events are reported on Table 2. 29 (71%) of patients experienced grade 3 or 4 toxicities.

In patients with cirrhosis (12 patients), liver toxicity appeared higher than in non-cirrhotic patients, and as compared to what is usually seen in cirrhotic patients treated with SIRT without chemotherapy: 9/12 (75%) experienced some form of hepatic failure (all grade ascites or jaundice, in 5 cases non reversible) vs 5/29 (17%) in non-cirrhotic patients (all reversible) (p=0.0015). In all cases of non-reversible toxicities, patients had received whole-liver SIRT.

Efficacy

After a median follow-up of 36 months, 40 patients were evaluable for response (1 patient with early death deemed related to disease progression, and thus evaluated as Progressive Disease), 16 patients experienced a disease progression and 23 patients died. The primary endpoint, objective response as assessed by investigator according to RECIST 1.1 at 3 months was 39% (16/41) [90% CI: 26%-53%]. The disease control rate at 3 months was 98% (40/41). Results were confirmed by central review, with a best response rate according to RECIST 1.1 of 41% (17/41), and a Choi response rate of 93% (38/41). Results of central review of evolution of sum of maximal diameters and mean of density are shown on Figure 2.

Median progression-free survival was 14 months [95%CI: 8-17], with a 12-months PFS rate of 55% and 24-months PFS rate of 30% (Figure 3A). Median OS was 22 months [95% CI: 14-52], with a 12-months OS rate of 75% and 24-months OS rate of 45% (Figure 3B).

Downstaging to surgery

Following treatment, 9 patients (22%) could be downstaged to surgery. The initial reasons for non-resectability of these patients are reported on eTable 1. R0 surgery was performed in 8 patients (89%). In the 27 patients with tumor involving only one hemiliver, surgery could be performed in 8 (30%) of them. After a median follow-up of 46 months following surgery, 2 recurrences and 3 deaths (2 due to disease progression and 1 due to post-operative liver dysfunction) were observed. Post-surgical OS and Relapse-Free Survival curves are presented on Figures 3C and 3D, respectively; 12-months and 24-months were 67% and 67% for RFS, and 89% and 89% for post-surgical OS, respectively. Examples of patients downstaged to

surgery are shown in eFigure 1. Furthermore, 2 patients still unresectable after treatment, but with disease control, were offered liver transplantation. Both patients recurred at 16 and 17 months following transplantation, both with a single lung lesion, who were resected for 1 and planned to be treated with stereotactic radiotherapy for 1. Patients are alive at 19 and 18 months.

Prognostic model

We performed a Cox regression univariable and multivariable analysis of parameters potentially associated with OS (eTable 2). The parameters independently associated with worse OS were decreased albumin and elevated CEA.

Discussion

The MISPHEC trial is, to our knowledge, the first published prospective trial regarding the efficacy of SIRT in unresectable ICC. Furthermore, this is the first prospective trial evaluating the combination of chemotherapy and SIRT, and the first multicentre report. The results showed evidence of activity of the strategy, with an encouraging response rate by RECIST of 39% and a high disease control rate at 3 months of 98%. [3]. In addition, median OS and PFS of 22 months and 14 months are promising. Moreover, we confirmed the high proportion of patients that could be downstaged to surgery, and showed promising post-surgical outcomes for these patients. Finally, this strategy has an acceptable safety profile in non-cirrhotic patients.

Previous retrospective data of SIRT in ICC were very heterogeneous in terms of population of patients included (chemotherapy-naive or previously treated, presence or not of extra-hepatic disease), treatment delivered (glass- or resin-microspheres, use of chemotherapy or not). Consequently, results are difficult to interpret with heterogeneous median OS ranging from 9 to 22 months. A systematic review and meta-analysis found a 28% response rate and 15.5 months median OS, and concluded to the activity of the treatment but advocated for prospective trials [24]. Another systematic review suggested that first-line treatment and combination with chemotherapy might be the best design for such trial [25]. Another prospective trial in 25 patients with unresectable ICC was presented during the ASCO GI 2017 meeting, using glass-microsphere in first-line treatment, showing a response rate of 56%, a median PFS of 6 months and a median OS of 22 months [26]. Some guidelines already proposed SIRT in locally-advanced ICC, either in first-line [27], or in second-line [28]. The availability of prospective data will strengthen these recommendations, albeit we

acknowledge the need for randomized trials to demonstrate an improvement in OS. The SIRCCA phase III trial (clinicaltrials.gov identifier NCT02807181) is currently randomizing patients with unresectable ICC to either chemotherapy alone or resin-microspheres SIRT followed by chemotherapy.

We showed in this trial that a high proportion of patients (30% of patients with disease involving only one hemiliver) could be downstaged to surgery. Retrospective data not focusing on ICC suggested that surgery is safe following SIRT, in selected patients [30]. We previously published data on ICC patients resected following SIRT for ICC [31]. A retrospective analysis of patients treated with chemotherapy suggested that patients who could be resected following neoadjuvant chemotherapy and patients with upfront surgery had similar outcomes [32].

Furthermore, in this trial, surgical results are impressive. With a median follow-up of 46 months for the 9 resected patients, the cumulative RFS-rate was 67% at this time-point. These good outcomes post-surgery were achieved in a population initially unresectable, and are similar to those of recent adjuvant trials in more heterogeneous initially resectable BTC: the PRODIGE 12 trial, and the BILCAP trial [33,34]. This suggests that downstaging with SIRT, combined with secondary surgery, has a potential for curative treatment in patients otherwise considered for palliative treatment.

Other modalities of loco-regional therapies were also studied in ICC, including chemo-embolization, intra-arterial chemotherapy and external beam radiotherapy [36,37]. How these different modalities might compare with SIRT remain to be studied. A study is ongoing, comparing SIRT with chemo-embolization [29].

Toxicities shown in this trial were mainly consistent with chemotherapy-induced toxicity. Grade 3 or higher haematological toxicities were high. It is possible that SIRT somewhat increased this haematological toxicity, however the chemotherapy dose-intensity was high and not limited by this toxicity. By contrast, the hepatic toxicity was high in patients with cirrhosis. Based on these results, we recommend that the concomitant use of chemotherapy and SIRT should be avoided in cirrhotic patients. In non-cirrhotic patients, the liver toxicity was acceptable, and no irreversible liver toxicity was seen.

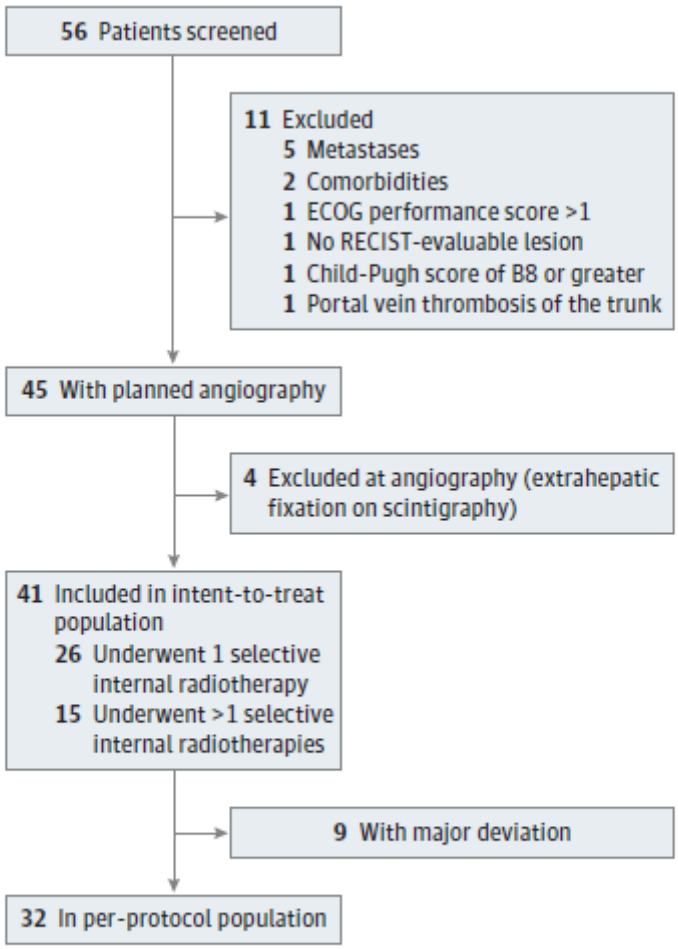
This study has some limitations. First, the single-arm nature of the study adds difficulty to the interpretation of results. The outcomes of patients with locally-advanced ICC might be better than these of all-comers locally-advanced or metastatic biliary tract cancers [38]. This study was performed in centres with experience with glass-microspheres. The SIRT doses recommended in this study were defined using label instruction, however accumulating evidence suggest that the definition of an appropriate dose delivered to the tumour, rather than a generic dose delivered to the targeted liver, might improve results [39,40]. Finally, we do not have data on the molecular alterations present, which might influence outcomes.

In conclusion, our study confirms activity of a combination of SIRT with chemotherapy as first-line treatment of ICC. The high disease control and downstaging rates suggest that this treatment is an important option in initially unresectable ICC. The promising post-surgical outcomes make a case for a potentially curative strategy with SIRT as downstaging treatment in patients otherwise considered for palliative-intent medical treatment. Safety profile was acceptable. These results should be confirmed by phase III randomized studies.

Acknowledgments:

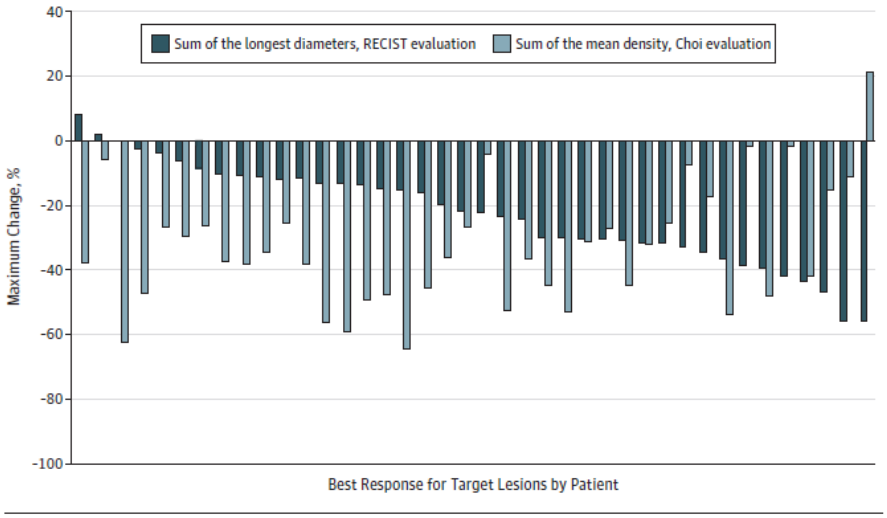
We would like to thank all the study personal involved in the conduct of the study, and all co-investigators participating in this study. We would like to thank the Ligue Nationale Contre le Cancer for their financial support. We would like to thanks the members of the IDMC: Dr Roger Faroux, CH de la Roche sur Yon, Pr Jean-pierre Pelage, CHU Caen and Karine Le Malicot, Universite de Bourgogne Dijon.

Figure Legends:



ECOG indicates Easter Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors.

Figure 1: CONSORT diagram of inclusion and analysis of patients



RECIST indicates Response Evaluation Criteria in Solid Tumors.

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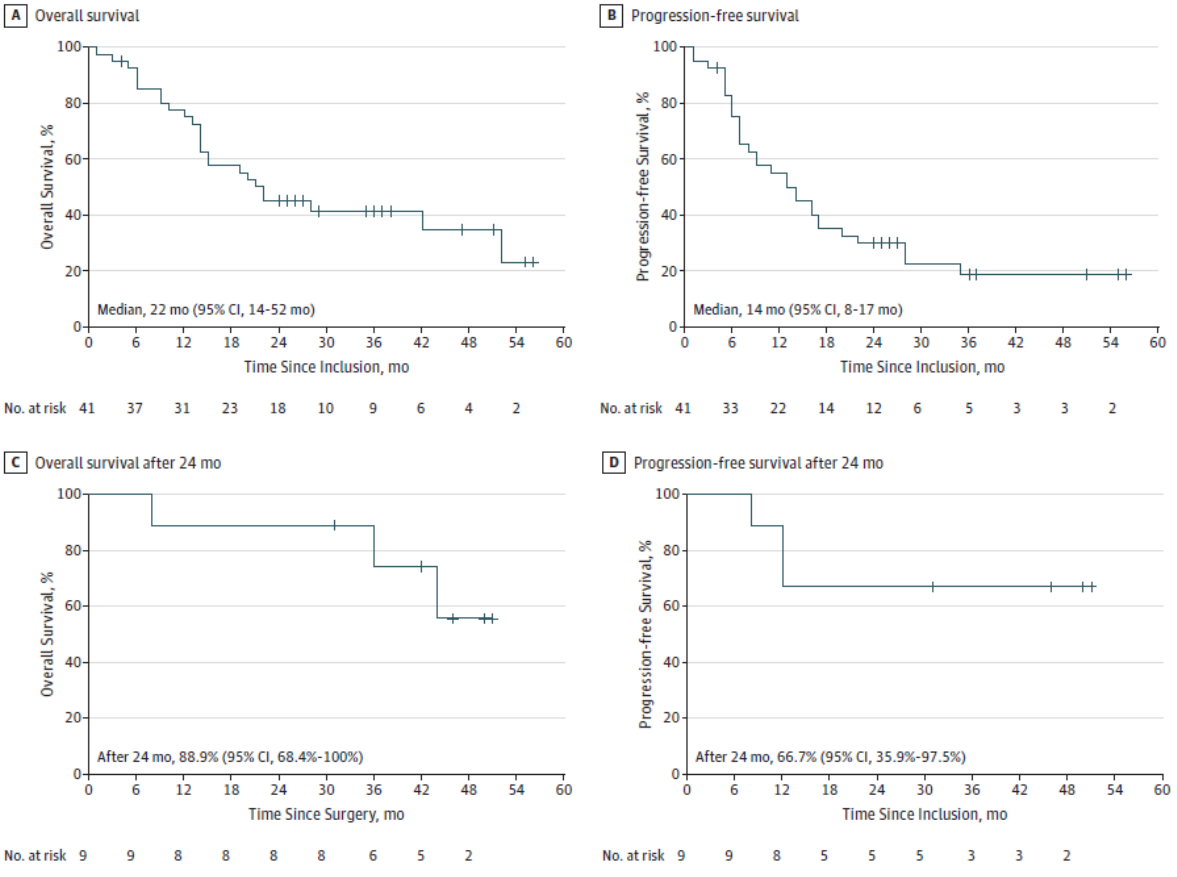
335 Figure 2: Best response for target lesions by patient, based on maximal change in percentage
336 of sum of the longest diameters (RECIST evaluation, in black) or of the mean density (Choi
337 evaluation, in grey) by central review.



A and B, Overall (A) and progression-free (B) survival in all patients in the intent-to-treat population. C and D, Overall (C) and relapse-free (D) survival among the 9 patients who underwent resection starting on the date of surgery.

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Figure 3: Overall (A) and progression-free (B) survival of the population in intent to treat population. Overall (C) and Relapse-Free (D) survival starting at the date of surgery for patients who were downstaged to surgery.

Tables

Table 1. Patient Characteristics

Characteristic	Population[a]	
	Intent to Treat (n = 41)	Downstaged (n = 9)
Age at inclusion	67.3 (36.7-82.2)	71.2 (46.5-74.9)
Male sex, No. (%)	26 (63)	4 (44)
Cirrhosis, No. (%)	12 (29)	2 (22)
Child-Pugh score at inclusion among patients with cirrhosis, No. (%)	(n = 12)	(n = 2)
A5	9 (75)	2 (100)
A6	2 (17)	0
B7	1 (8)	0
ECOG performance status of 0 at inclusion (n = 40), No. (%)	26 (65)	7 (78)
Albumin, g/L (n = 39)	40 (24-47)	41 (39-44)
Prothrombin time, % vs control	89 (32-117)	90 (73-117)
Total bilirubin level at inclusion, µmol/L	13.3 (4-38)	13.6 (4-20.1)
ALT level, U/L	28 (10-346)	20 (10-346)
AST level, U/L	36 (12-138)	27 (12-115)
Alkaline phosphatase level, U/L	111 (49-366)	106 (52-300)
γ-Glutamyltransferase level, U/L (n = 40)	136.5 (25-613)	166 (61-597)
Carbohydrate antigen 19.9 level, IU (n = 40)	52 (0.6-32099)	36.5 (1-499)
Carcinoembryonic antigen level, ng/mL (n = 40)	3.1 (0.4-51)	2.4 (1-5.1)
Previous resection, No. (%)	5 (12)	0 (0)
Time from diagnosis to inclusion, d	48 (13-728)	63 (14-77)
Unifocal tumor, No. (%)	14 (34)	7 (78)
Tumor confined to 1 hemiliver, No. (%)	27 (66)	8 (89)
Liver hilar lymph nodes ≤3 cm, No. (%)	12 (29)	2 (22)
Abdominal lymph nodes, No. (%)	14 (34)	2 (22)
Lung metastasis ≤1 cm, No. (%)	7 (17)	0 (0)
Patient with locally advanced disease only, including hilar nodules, without abdominal lymph nodes or lung metastasis, No. (%)	24 (58)	7 (78)

Abbrevations: ALT, alanine transferase; AST, aspartate transferase; ECOG, Eastern Cooperative Oncology Group.

SI conversion: To convert ALT, alkaline phosphatase, AST, and γ-glutamyltransferase levels to microkatals per liter, multiply by 0.0167; albumin level to grams per deciliter, divide by 10; bilirubin level to milligrams per deciliter, divide by 17.104.

[a] Data are presented as median (interquartile range) unless otherwise indicated.

Table 2. Treatment-Related Adverse Events

System Organ Class, Preferred Term[a]	Patients With Adverse Event, No. (%)	
	Grade 1 or 2	Grade ≥3
Skin and subcutaneous tissue disorders		
Rash	9 (22)	0
Alopecia	5 (12)	0
Palmar-plantar erythrodysaesthesia syndrome	3 (7)	0
Ear and labyrinth disorders: hypoacousia or hyperacousia	2 (5)	0
Renal and urinary tract disorders: renal failure	3 (7)	0
Nervous system disorders		
Peripheral sensorimotor neuropathy	11 (27)	0
Taste alteration	8 (20)	0
Gastrointestinal tract disorders		
Nausea	18 (44)	2 (5)
Abdominal pain	12 (29)	5 (12)
Vomiting	12 (29)	1 (2)
Diarrhea	10 (24)	2 (5)
Dysphagia	2 (5)	0
Constipation	7 (17)	0
Ascites	2 (5)	3 (7)
Blood and lymphatic system disorders		
Neutropenia	9 (22)	21 (51)
Febrile neutropenia	0	1 (2)
Anemia	19 (46)	8 (20)
Thrombocytopenia	16 (39)	10 (24)
Lymphopenia	4 (10)	3 (7)
Hepatobiliary disorders		
Abnormal liver function test	5 (12)	1 (2)
Acute hepatic failure	1 (2)	2 (5)
Cholecystitis acute	1 (2)	1 (2)
Cholangitis	0 (0)	1 (2)
Respiratory, thoracic, and mediastinal disorders: epistaxis	4 (10)	0
Vascular disorders: venous thrombosis	2 (5)	1 (2)
Infections and infestations: oral fungal infection	5 (12)	0
Metabolism and nutrition disorders		
Decreased appetite	21 (51)	3 (7)
Weight decreased	8 (20)	1 (2)
General disorders and administration site conditions		
Asthenia	32 (78)	9 (22)
Pain	7 (17)	0
Mucosal inflammation	5 (12)	0
Edema	6 (15)	0
Administration site reaction	6 (15)	0
General physical health deterioration	0	2 (5)

[a] According to Medical Dictionary for Regulatory Activities, version 18.1

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