

Hepatic Arterial Infusion Pump Chemotherapy in Patients With Unresectable Intrahepatic Cholangiocarcinoma—PUMP-2 Trial

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ABSTRACT

PURPOSE The 3-year overall survival (OS) for advanced intrahepatic cholangiocarcinoma (iCCA) confined to the liver after systemic chemotherapy with gemcitabine-cisplatin (gem-cis) is only 3%. Hepatic arterial infusion pump (HAIP) chemotherapy with floxuridine aims to control the liver disease and improve survival. The aim of this study was to assess the effectiveness of HAIP chemotherapy with floxuridine and concurrent systemic gem-cis in patients with unresectable liver-confined iCCA in the Netherlands.

METHODS We performed a nonrandomized multicenter phase II trial. Treatment-naïve patients and patients previously treated with systemic therapy were eligible. Up to six cycles of HAIP floxuridine and eight cycles of concurrent systemic gem-cis were administered. The primary endpoint was 1-year OS compared with a historical cohort.

RESULTS From January 2020 to September 2022, 50 patients had a pump placed. Two patients (4%) did not start HAIP floxuridine; one patient died due to COVID-19, and one patient had a hepatic arterial dissection. The remaining 48 patients (96%) started HAIP chemotherapy, combined with systemic gem-cis in the 37 patients (74%) who had not received gem-cis previously. Twenty-two patients (44%) achieved a partial response and 42 patients (84%) disease control at 6 months. Five patients (10%) converted to resection, of whom one had a complete pathologic response. The median OS was 22.3 months (95% CI, 19.7 to 35.9 months). The 1-year OS of 80.0% (95% CI, 69.6% to 91.9%) was superior to the historical control of 47% ($P < .001$). The 3-year OS was 31.5% (95% CI, 20.4% to 48.6%).

CONCLUSION Combining HAIP chemotherapy with floxuridine and systemic gem-cis in patients with unresectable liver-confined iCCA had a 1- and 3-year OS superior to gem-cis alone in historical cohorts.

ACCOMPANYING CONTENT

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INTRODUCTION

Intrahepatic cholangiocarcinoma (iCCA) is the second most common primary liver cancer after hepatocellular carcinoma, and its incidence is increasing worldwide.^{1,2} It arises from the epithelium of the intrahepatic bile ducts.^{3,4} Most patients with iCCA have no known risk factors.⁵

Complete resection is performed in about 15% of patients with a 5-year overall survival (OS) of 43% and a 10% chance of cure.^{6,7} All other patients present with advanced iCCA, of whom 50% have disease confined to the liver.^{8,9} Gemcitabine with cisplatin (gem-cis) has been the standard of care for

patients with advanced biliary tract cancer, until the recent addition of immunotherapy.¹⁰⁻¹² A post hoc analysis of 34 ABC-trial patients with unresectable liver-confined iCCA treated with gem-cis showed a response rate of 21% and a 3-year OS of 3%.¹³ A large cohort study of MD Anderson found that 72% of patients with advanced iCCA died of disease progression in the liver.¹⁴ Therefore, locoregional treatments are promising to improve survival for patients with iCCA.¹⁵

Hepatic arterial infusion pump (HAIP) chemotherapy is such a locoregional treatment involving continuous chemotherapy with floxuridine directly into the hepatic artery using a subcutaneous pump. The biological rationale for intra-

CONTEXT

Key Objective

Does hepatic arterial infusion pump chemotherapy with floxuridine combined with systemic gemcitabine and cisplatin (gem-cis) improve overall survival (OS) in patients with advanced liver-confined intrahepatic cholangiocarcinoma (iCCA), compared with systemic therapy alone?

Knowledge Generated

The 1-year OS rate was superior compared with our historical cohort (80% v 47%). The 3-year OS rate was superior to similar patients in the ABC trials who received gem-cis (32% v 3%). No other locoregional or systemic treatment has shown a consistent 3-year OS rate of 1 in 3 for advanced iCCA.

Relevance (A.H. Ko)

While further prospective studies will be required to validate this strategy, PUMP-2 offers compelling evidence to support the benefit of hepatic artery infusion pump therapy in iCCA. Careful selection of patients, coupled with institutional expertise and experience, are absolutely necessary when considering this therapeutic approach.*

*Relevance section written by JCO Associate Editor Andrew H. Ko, MD, FASCO.

arterial chemotherapy is that floxuridine (a pyrimidine analog that is metabolized to fluorouracil) has a 95% first-pass effect allowing for a 200-fold higher dose in the tumor without systemic side effects.¹⁶

Three nonrandomized prospective phase II trials investigated HAIP chemotherapy combined with gemcitabine and oxaliplatin for unresectable liver-confined iCCA. All three trials were performed at Memorial Sloan Kettering Cancer Center (MSKCC) and found a consistent response rate of about 50% and a 3-year OS of about 35%.^{17–19} These results compare favorably with the results of the ABC trials.¹³ However, experts have raised concerns about safety and feasibility of HAIP chemotherapy. The main criticism has been that the effectiveness has not been investigated in a clinical trial outside MSKCC. Moreover, floxuridine has not been combined with the standard chemotherapy gem-cis. The primary aim of this study was to assess the effectiveness of HAIP chemotherapy with floxuridine and concurrent gem-cis in patients with unresectable liver-confined iCCA.

METHODS

Study Design

We performed a multicenter phase II trial (ICTRP: NL8234) in the Netherlands in patients with histologically confirmed advanced (ie, unresectable) liver-confined iCCA (National Trial Register, NL8234). Unresectability was confirmed by hepatobiliary surgeons at multidisciplinary review considering an inability to achieve an R0 resection owing to extensive vascular and/or biliary involvement, multifocal liver disease, poor performance status, or a combination of these factors. Intrahepatic disease progression on prior systemic therapy and metastatic disease to locoregional lymph nodes

(porta hepatis, porto-caval, or common hepatic artery) were permitted. All patients underwent a computed tomographic angiogram before inclusion to evaluate hepatic arterial blood supply. Aberrant hepatic arterial anatomy was allowed, but patients were ineligible if the gastroduodenal artery was not connected to a proper hepatic artery feeding at least one segment of the liver. Patients with dihydropyrimidine dehydrogenase deficiency (cutoff: minimal activity score 1.0) were excluded (protocol).

The study was approved by the institutional review boards at Erasmus MC Cancer Institute, Amsterdam UMC, and UMC Utrecht (ICTRP: NL8234). Written informed consent was obtained from all participants.

Study Intervention

Guidelines for pump implantation have been previously reported.^{21,22} Briefly, a catheter was placed robot-assisted or with a laparotomy in the gastroduodenal artery with the tip at the hepatic artery. The catheter was connected to a subcutaneous pump. A cholecystectomy was performed at the time of pump implantation to avoid chemical cholecystitis. The HAIP chemotherapy with floxuridine was initiated 2 weeks after pump implantation on a 4-week cycle. On day 1, the pump reservoir was filled with floxuridine (0.12 mg/kg/day). If the actual body weight was more than 25% above the ideal weight, the dose of floxuridine was calculated as the average of the actual and ideal weight. Floxuridine was administered in a solution of 35,000 IE heparin and 25 mg dexamethasone in NaCl 0.9% with a total volume of 35 mL. On day 15, the pump was emptied and refilled with a heparin and saline solution (35,000 IE heparin in NaCl 0.9% with a total volume of 35 mL) for 2 weeks. Six cycles of HAIP floxuridine were administered. Patients

received systemic cisplatin (25 mg/m²), followed by gemcitabine (800 mg/m²) during each subsequent pump access, which occurred once every 2 weeks. Eight cycles of concurrent systemic chemotherapy with gemcitabine (800 mg/m²) and cisplatin (25 mg/m²) were administered on day 1 and 15 of treatment to a total of 16 doses, if not administered previously. Dose reductions for floxuridine were performed as needed based on laboratory values (protocol). HAIP floxuridine was discontinued in the event of severe biliary toxicity. A prophylactic dose of 20 mg of a proton pump inhibitor was administered daily during HAIP chemotherapy.

HAIP chemotherapy was discontinued after completing all six scheduled cycles. Postprotocol HAIP chemotherapy was allowed in patients with intrahepatic tumor progression during follow-up at the discretion of the treating physicians.

Sample Size Calculation

In a historical cohort of consecutive patients with unresectable iCCA treated with gem-cis in two of the three participating centers (Amsterdam UMC and Erasmus MC), the 1-year OS of 76 patients was 47%. Therefore, the power analysis assumed a 1-year OS of 50% with gem-cis alone. The hypothesis of this study was that the combination of HAIP chemotherapy with floxuridine and systemic gem-cis could increase the 1-year OS to at least 72%, based on previous phase II trials.¹⁷⁻¹⁹ A single-arm phase II trial with two-sided significance level $\alpha = .05$ and 80% power required a total of 38 patients.²³ To account for drop-out, two patients were added. An expansion cohort of 10 patients was added before data analyses and after approval by the ethics committee; hence, the total sample size was 50. Patients who were ineligible for pump placement after signing informed consent were replaced.

Statistical Analysis

The primary outcome was 1-year survival, defined as the interval between the date of surgery (pump implantation) until the date of death or last follow-up. One-year OS was reported as a proportion and compared with 1-year OS of 50% of our historical cohort, using a t-test. In three sensitivity analyses, OS was analyzed including patients who had peritoneal disease at surgical exploration, excluding patients who never received HAIP chemotherapy, and with OS defined from the time of diagnosis. Post hoc subgroup analyses investigated patients who received HAIP chemotherapy as first-line treatment together with systemic gem-cis, patients with a single liver lesion (v multifocal), and patients with node-positive disease.

Postoperative mortality and major complications (Clavien-Dindo classification, grade 3 or higher) within 90 days after pump placement were presented as proportions with 95% CI. Chemotherapy-related adverse events (chemotherapy related according to Common Terminology Criteria for Adverse

Events, grade 3 or higher) were reported as proportions with 95% CI. Response rate was measured according to the RECIST 1.1 criteria.²⁴ Response rate was defined as a complete response, a partial response, stable disease, or progressive disease. Progression-free survival (PFS) and hepatic PFS were defined as the interval between surgery (pump implantation) and the earliest occurrence of disease progression. Survival was measured until the time of data cutoff on March 16, 2025.

Ethical Approval

This study was reviewed and approved by the ethics committee of the Erasmus MC Cancer Institute on November 27, 2019 (MEC-2019-0499). All human participants gave written informed consent.

RESULTS

Patient Characteristics

From January 2020 until September 2022, 261 patients presented with a suspicion of iCCA in the three participating centers. Of these 261 patients, 43 patients underwent a surgical resection, 106 patients had extrahepatic disease, and 54 patients were ineligible for other reasons, such as poor performance status, cirrhosis with portal hypertension on imaging, and main portal vein thrombosis (Fig 1). All 58 eligible patients with histologically proven iCCA without distant metastases gave written informed consent. One patient died due to COVID-19 infection before pump implantation. Seven patients were excluded for pump placement during surgery; in six patients, occult peritoneal metastases were found during surgical exploration, and in one patient, it was impossible to insert the catheter in the gastroduodenal artery because of a frozen liver hilum. The remaining 50 patients underwent pump implantation.

Patients were classified as having advanced disease by the multidisciplinary team because of one or more factors; multifocal liver disease in 33 patients (66%), locally advanced disease not allowing for an R0 resection in 15 patients (30%), and two patients (4%) were unfit to undergo a major hepatectomy (Table 1). Six patients (12%) presented with biliary obstruction and required biliary drainage before pump implantation. Thirteen patients (26%) received systemic therapy before inclusion. Genomic alterations were analyzed in 32 patients (64%).

Study Treatment

The median time from diagnosis to pump implantation was 57 days (range, 26-157) for patients who were treated with first-line treatment HAIP chemotherapy, and 251 days (range, 182-434) for patients who were treated with second-line HAIP chemotherapy. The median time from pump implantation to start of HAIP floxuridine was 15 days (range, 10-78). In 22 patients (44%), the pump was placed robot-

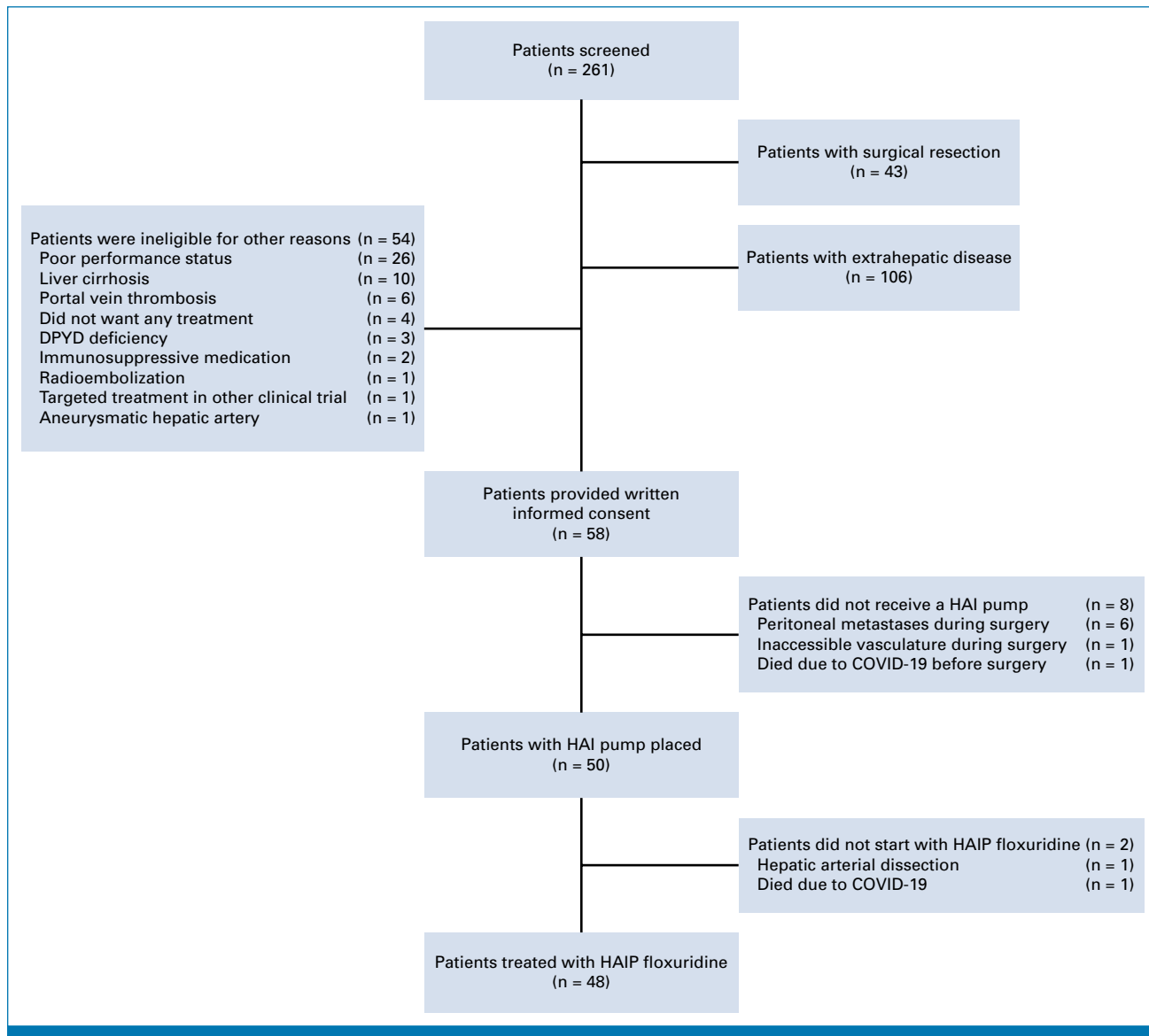


FIG 1. Patient screening and enrollment flowchart. DPYD, dihydropyrimidine dehydrogenase deficiency; HAIP, hepatic arterial infusion pump.

assisted.²⁵ The median length of hospital stay was 4 days (IQR, 3–6). Two patients (4%) did not start HAIP floxuridine; one patient died 19 days after pump implantation due to COVID-19, and one patient had a hepatic arterial dissection precluding intra-arterial chemotherapy. The median cumulative total dose delivered for the patients treated with HAIP floxuridine was 617 mg (IQR, 470–1,054). The median number of HAIP cycles was 6 (IQR, 5–6). Thirty-three patients (66%) completed all planned six cycles of HAIP chemotherapy. Forty-seven patients (94%) received at least two cycles of HAIP chemotherapy.

HAIP chemotherapy was combined with gem-cis as first-line treatment in 35 patients (70%) and administered as second-line treatment with gem-cis in two patients (4%), because of previous systemic therapy other than gem-cis.

HAIP chemotherapy was administered without systemic chemotherapy in 11 patients (22%) because of previous systemic chemotherapy with gem-cis (Fig 1). The median number of gem-cis cycles as first-line treatment was 6 (IQR, 5–7). Forty-seven patients (94%) still had a functioning pump after the last cycle of floxuridine, 39 patients (78%) at 1 year after implantation, 23 patients (46%) at 2 years, and 10 patients (20%) at 3 years.

Survival

No patients were lost to follow-up and all patients had at least 1 year of follow-up. Thirty-three patients (66%) died during follow-up, and the median follow-up of patients alive at last follow-up was 43.1 months (95% CI, 32.6 to 58.1 months). One-year OS was 80.0% (95% CI, 69.6% to 91.9%)

TABLE 1. Baseline Patient Characteristics

Characteristic	N = 50, No. (%) / Median (IQR)
Female	36 (72)
Age, years	65 (56-72)
BMI (kg/m ²)	25 (23-28)
WHO performance status	
0	30 (60)
1	20 (40)
ASA score	
2	24 (48)
3	26 (52)
Histologic grade, differentiated	
Well	0 (0)
Moderately	9 (18)
Poorly	7 (14)
Not specified	34 (68)
Genomic alterations—Analyzed in 32 patients	
IDH	6 (19)
FGFR	4 (13)
HER2	2 (6)
Largest tumor diameter, cm	9.2 (6.8-11.0)
Multifocal liver disease	33 (66)
2 or 3 lesions	10 (20)
4 or more lesions	23 (46)
Lymph node disease	
pNx: No nodes dissected	8 (16)
pN0: 1-3 nodes dissected	17 (34)
pN0: 4-5 nodes dissected	6 (12)
pN0: 6 or more nodes dissected	2 (4)
pN1	17 (34)
Prior biliary drainage	6 (12)
Prior systemic therapy	13 (26)
Gemcitabine + cisplatin	11 (22)
Paclitaxel + carboplatin	1 (2)
Pemigatinib	1 (2)

Abbreviations: ASA, American Society of Anesthesiologists; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; IDH, isocitrate dehydrogenase.

compared with the 47% 1-year OS of the historical cohort of systemic chemotherapy with gem-cis alone ($P < .001$). The median OS was 22.3 months (95% CI, 19.7 to 35.9 months, Fig 2A, blue curve). The 3-year OS was 31.5% (95% CI, 20.4% to 48.6%). The median PFS was 11.4 months (95% CI, 9.0 to 12.4 months), and the median hepatic PFS was 12.1 months (95% CI, 11.1 to 17.1 months).

In a sensitivity analysis, including also the eight patients who did not get a pump implanted (Fig 2A, red curve), the median OS was 21.5 months (95% CI, 17.7 to 30.2 months) and the 3-year OS was 27.2% (95% CI, 17.4% to 42.4%). When excluding the two patients who never received HAIP

chemotherapy, the median OS was 23.9 months (95% CI, 21.3 to 41.6 months), and the 3-year OS 32.8% (95% CI, 21.4% to 50.1%). With OS measured from the time of diagnosis rather than pump placement, the median OS was 28.6 months (95% CI, 23.2 to 40.0 months) and the 3-year OS was 37.6% (95% CI, 26.2 to 53.9).

The median OS was similar for HAIP chemotherapy as initial treatment (25.3 months [95% CI, 19.4 to 43.4 months] v 22.1 months [95% CI, 18.5 months to not reached]) for HAIP chemotherapy after previous systemic treatment ($P = .645$, Fig 2B). Patients with multifocal liver disease had a median OS of 21.3 months (95% CI, 15.7 to 30.2 months) versus 35.9 months (95% CI, 26.0 months to not reached) in patients with a solitary liver lesion ($P = .034$, Fig 2C). Patients with node-positive disease had a median OS of 16.2 months (95% CI, 12.4 months to not reached) versus 22.5 months (95% CI, 21.3 to 41.6 months) without nodal disease ($P = .373$, Fig 2D).

Treatment Response and Disease Control

Twenty-two patients (44%) demonstrated a partial response (Fig 3). Disease control at 6 months was achieved in 42 patients (84%). In the subgroup of 37 patients who received HAIP as initial treatment, a partial response was observed in 22 patients (59%). At last follow-up, 42 of the 50 patients (84%) had disease progression. Twenty-two patients (44%) had initial disease progression only in the liver, 17 patients (34%) outside the liver, and three patients (6%) both. Initial extrahepatic progression concerned the lungs in 10 patients (20%), peritoneum in nine patients (18%), and bone in one patient (2%). Initial progression in the liver concerned the primary (target) lesion in nine patients (18%) and nontarget liver lesions in 16 patients (32%). Eight patients (16%) developed biliary obstruction and ultimately liver failure after a median period of 11 months.

Subsequent Treatment

After completing protocol treatment, 42 patients (84%) were still alive without disease progression. Thirteen patients (26%) had HAIP chemotherapy restarted (post-protocol treatment) after a median treatment-free interval of 7.1 months (IQR, 6.9–7.4 months). They received a median of five additional cycles (IQR, 3–8). Fifteen patients (30%) restarted systemic treatment with gem-cis after a treatment-free interval.

Second-line systemic infusional fluorouracil, leucovorin, and oxaliplatin was administered in six patients (12%). Second-line targeted therapy was administered in three patients (6%) with FGFR2 fusions, in two patients (4%) with IDH1 mutations, and in one patient (2%) with a human epidermal growth factor receptor 2 amplification. Selective internal radiation therapy was performed in four patients (8%). Five patients (10%) underwent a resection of whom one had a complete pathologic response.

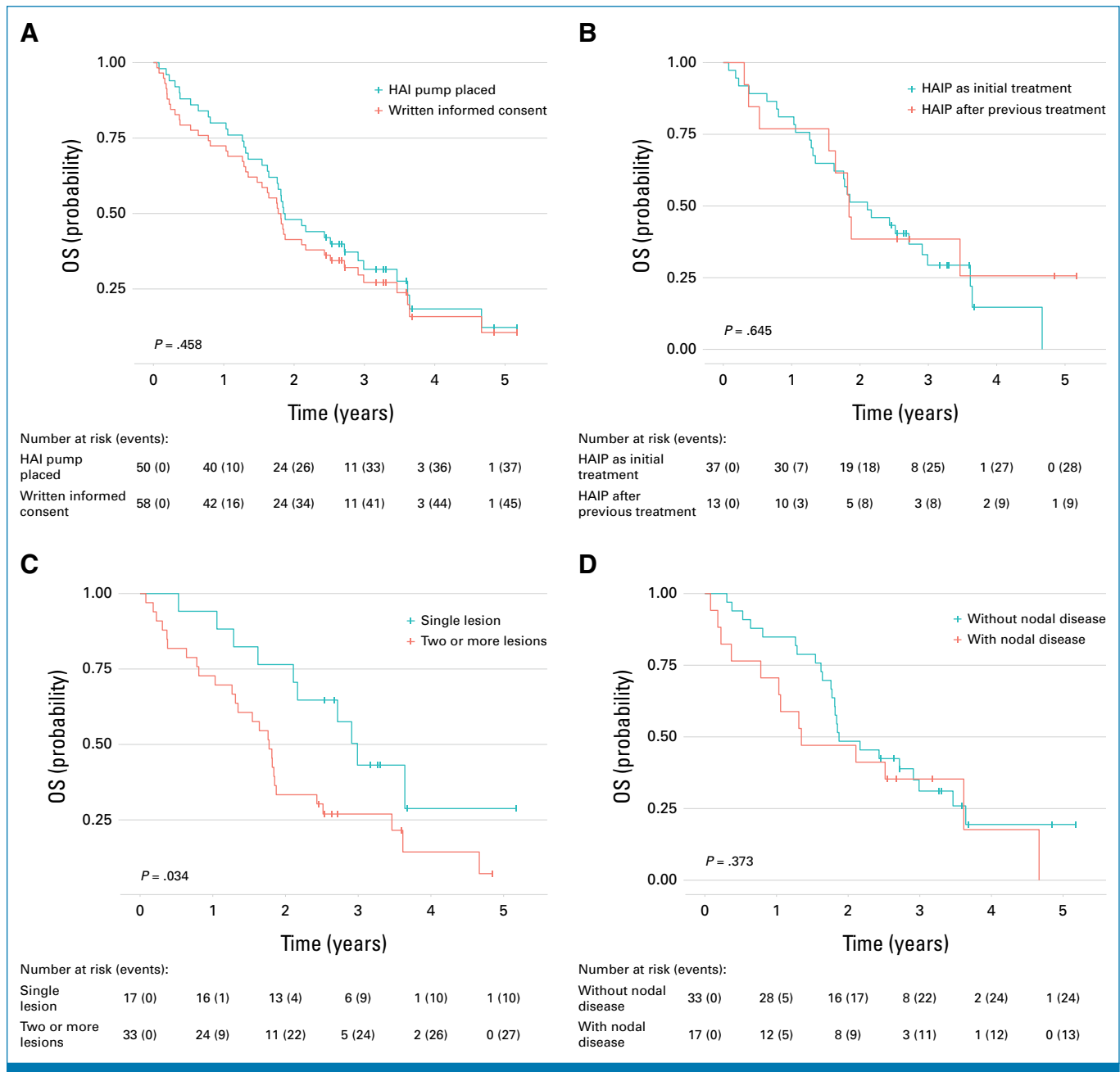


FIG 2. Kaplan-Meier curves of OS. Sensitivity analysis (A) and post hoc subgroup analyses (B-D). HAIP, hepatic arterial infusion pump; OS, overall survival.

Surgical Complications and Adverse Events

One patient died within 90-day after surgery due to COVID-19 on postoperative day 19. Initial recovery after surgery of this patient was uneventful. Thirteen patients (26%) had postoperative major complications after pump implantation. All but one major complications were resolved with a reintervention allowing for subsequent HAIP chemotherapy. Three patients (6%) developed ascites, which was resolved with a percutaneous drain. These patients had a primary tumor larger than 10 cm. Two patients (4%) developed an intra-abdominal abscess treated with

percutaneous drainage and antibiotics. Two patients (4%) underwent a relaparotomy; one had a small bowel perforation that was closed, and one had a hepatic arterial dissection that could not be resolved. One patient (2%) had a bile leak of the extrahepatic bile duct, which was resolved with an endoscopic covered stent. Six patients (12%) had a HAI-specific complication. One patient developed a hepatic artery thrombosis, and therefore, HAIP chemotherapy was discontinued after two cycles. Five patients (10%) required a reoperation for the subcutaneous pump; two had a dysfunctioning pump that was replaced, two had a flipped pump that was fixed again to the fascia, and one

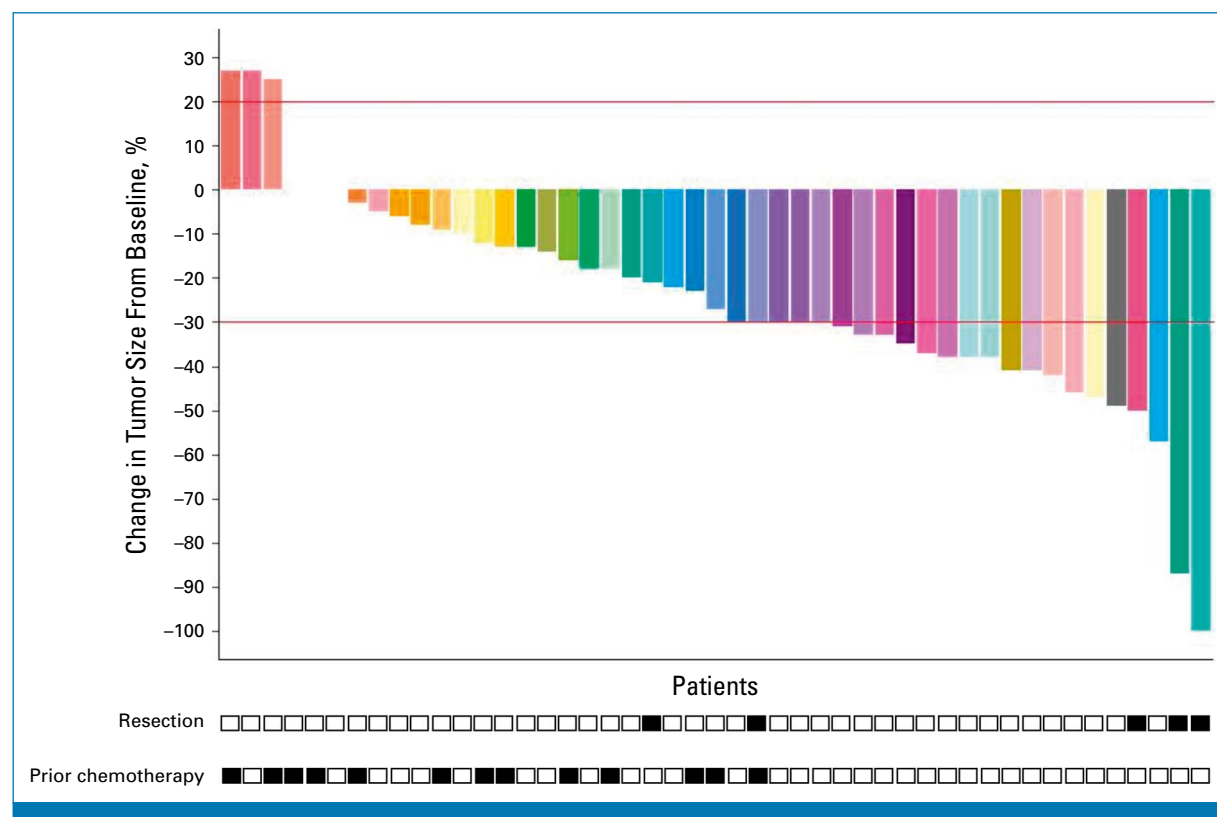


FIG 3. Waterfall plot for % change in tumor size from baseline.

had a pump pocket infection that was resolved by placing a new pump in the contralateral abdominal wall and connected to the same catheter.

Toxic Effects

Grade 3 and 4 adverse events because of floxuridine were observed in seven patients (14%). One patient (2%) required biliary stents for floxuridine-induced biliary sclerosis. Thirty-two patients (64%) received the scheduled six cycles of floxuridine, of whom 20 patients (63%) had a dose reduction. Reasons for treatment discontinuation included toxicity (ie, elevated liver function tests, grade 3) in nine patients (18%), disease progression in two patients (4%),

arterial thrombosis in one patient (2%), and biliary sepsis in one patient (2%).

DISCUSSION

In this phase II trial, 50 patients with unresectable liver-confined iCCA had a pump placed for HAIP chemotherapy using floxuridine with prior or concurrent systemic chemotherapy with gem-cis. The study met its primary end point with a clinically relevant improved 1-year OS of 80% compared with 47% in the historical cohort with systemic chemotherapy with gem-cis alone. The response rate was 44%, and the disease control rate at 6 months was 84%. The 3-year OS rate was 32% and clearly superior to the 3-year OS

TABLE 2. Phase II Trials Hepatic Arterial Infusion Pump Chemotherapy for Liver-Confined iCCA Versus Gemcitabine and Cisplatin

Variable	Jarnagin ¹⁸	Kemeny ¹⁹	Cercek ¹⁷	Franssen (this study)	Lamarca/ABC trials ¹³
Year	2009	2011	2020	2025	2020
N	26	18	42	50	32
Response rate, %	54	39	58	44	21
Median OS (months)	30	31	25	22	17
1-year OS, %	88	90	90	80	63
2-year OS, %	67	65	50	50	25
3-year OS, %	29	31	43	32	3

Abbreviation: OS, overall survival.

TABLE 3. Overview Clinical Trials Investigating Targeted and Immune Checkpoint Blockade Treatments for BTC/iCCA

Author	Year	Journal	Study Design	Patient Population	Drug Class	Drug	Setting	Treatment Group (n)	Median OS (months)	95% Confidence Interval (CI)	1-year OS (%)	3-year OS (%)
Oh (TOPAZ-1) ²⁸	2024	Lancet Gastroenterol Hepatol	RCT	BTC	PD-L1 inhibitor	Durvalumab v placebo	1st line	341 v 344	12.9 v 11.3	11.6 to 14.1	54 v 47	17
Kelley (KEY-NOTE-966) ¹²	2023	Lancet	RCT	BTC	PD-L1 inhibitor	Pembrolizumab v placebo	1st line	533 v 536	12.7 v 10.9	11.5 to 13.6	52 v 44	NR
Abou-Alfa ²⁹	2020	Lancet Oncol	Single arm	BTC	FGFR2 inhibitor	Pemigatinib	2nd line	146	21.1	14.8 to not reached	68	NR
Goyal ³⁰	2023	N Eng J Med	Single arm	iCCA	FGFR2 inhibitor	Futibatinib	2nd line	103	21.7	14.5 to not reached	72	NR
Javle ³¹	2021	Lancet Gastroenterol Hepatol	Single arm	BTC	FGFR2 inhibitor	Infigratinib	2nd line	108	12.2	10.7 to 14.9	50	25
Zhu ³²	2021	JAMA Oncol	RCT with cross-over	BTC	IDH1 inhibitor	Ivosidenib	2nd line	126 v 63	10.3	7.8 to 12.4	43	NR
Harding ³³	2023	Lancet Oncol	Single arm	BTC	HER2 targeted antibodies	Zanidatamab	2nd line	87	NR	NR	NR	NR
Nakamura ³⁴	2023	J Clin Oncol	Single arm	BTC	HER2 targeted antibodies	Tucatinib + trastuzumab	2nd line	30	15.5	6.5 to 16.7 (90% CI)	54	NR
Franssen (this study)	2025		Single arm	iCCA	Chemo-therapy	Floxuridine	1st/2nd line	50	22.3	19.7 to 35.9	80	32

Abbreviations: BTC, biliary tract cancer; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; IDH, isocitrate dehydrogenase; NR, not reported; OS, overall survival; RCT, randomized controlled trial.

rate of 3% when compared with the historic ABC cohort with systemic chemotherapy alone.^{13,26}

To our knowledge, this is the first clinical trial of HAIP chemotherapy in unresectable liver-confined iCCA outside of the United States. The results of the present phase II trial were remarkably consistent with the three prior phase II trials from MSKCC (Table 2).^{17–19} The response rate of 39%–58% across the four trials is clearly superior to 21% with gem-cis alone in the ABC trials. The 3-year OS ranging from 29% to 43% compared favorably with 3% for similar patients receiving gem-cis alone in the ABC trials (Table 2).¹³ A SEER population-based cohort study of 5,616 patients with advanced iCCA also reported a 3-year OS rate of 3% with only systemic chemotherapy.²⁷ The nationwide registry of the Netherlands included 1,747 patients with liver-confined iCCA found a 3-year OS rate of 5% with only systemic chemotherapy.²⁶

After accrual of the PUMP-2 trial, two randomized controlled trials (RCTs) investigating immunotherapy in advanced biliary cancer were published (Table 3). The TOPAZ-1 and Keynote-966 trials both found superior median OS when adding immune checkpoint inhibitors to gem-cis.^{11,12} The TOPAZ-1 recently published a mature 3-year OS of 17%.²⁸

Future studies should investigate whether the combination of HAIP chemotherapy with immunotherapy can further improve OS.

Several trials have shown promising results of targeted treatments for patients with advanced iCCA (Table 3). In the present trial, six patients (12%) received second-line targeted treatments after HAIP and systemic chemotherapy. During the PUMP-2 trial, targeted treatments were available in the Netherlands only in clinical trials or compassionate use programs. HAIP chemotherapy avoids or postpones disease progression in the liver, allowing for targeted treatments in second or third line.

Liver-directed therapies are increasingly used and recommended by international guidelines for advanced liver-confined iCCA.^{15,35} The main rationale is that most patients

die from progressive disease in the liver with biliary obstruction and liver failure.¹⁴ SIRT appears to be the most promising percutaneous approach.^{36–38} A phase II trial investigated the combination of first-line SIRT and systemic gem-cis in patients with locally advanced iCCA (n = 41) with a median OS of 22 months (95% CI, 14 to 52 months).³⁹ A phase III trial investigating first-line SIRT in patients with liver-confined iCCA was prematurely closed and has not been published (ClinicalTrials.gov identifier: [NCT02807181](https://clinicaltrials.gov/ct2/show/study?term=NCT02807181)). The currently available evidence for locoregional treatment of iCCA is strongest for HAIP chemotherapy with four consistent phase II trials.

This study has some limitations. First, the favorable OS after HAIP chemotherapy compared with historical and other cohorts could be partly attributable to selection bias. However, the flowchart (Fig 1) demonstrates that almost all eligible patients were included in this study. Moreover, in a sensitivity analysis including also six patients with occult peritoneal disease at surgery, the 3-year OS was still 27%, far superior to the 3%–5% in our historical cohort, ABC trials, and SEER database. Second, the multidisciplinary team decided whether a patient with iCCA had unresectable disease for which no universal criteria exist. Guidelines recommend against resection for patients with multifocal disease, which was present in two thirds of patients in the present trial.⁴⁰ Most of the remaining patients had a very large tumor for whom a complete margin-negative resection was either infeasible or associated with a very high surgical mortality. A recent meta-analysis found that the average 90-day mortality for a major liver resection for iCCA was 11.4%.⁴¹

In conclusion, HAIP chemotherapy with floxuridine is safe, feasible, and effective in patients with unresectable liver-confined iCCA. The 1-year OS rate was superior compared with our national historical cohort (80% v 47%). The 3-year OS rate was superior to similar patients in the ABC trials who received gem-cis (32% v 3%). No other locoregional or systemic treatment has shown a consistent 3-year OS rate of one in three for iCCA patients with advanced disease. HAIP chemotherapy should be considered in addition to systemic treatment for patients with advanced iCCA confined to the liver.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Hepatic Arterial Infusion Pump Chemotherapy in Patients With Unresectable Intrahepatic Cholangiocarcinoma—PUMP-2 Trial

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