# Hepatic arterial infusion PUMP chemotherapy combined with systemic therapy versus systemic therapy alone as Induction Therapy for initially unresectable colorectal liver metastases: a randomised controlled trial

Published: 06-08-2024
Last updated: 27-12-2024

The main objective of this trial is to investigate whether HAIP with concomitant systemic therapy prolongs overall survival in chemo-naive patients with initially unresectable synchronous colorectal liver metastases as compared with systemic therapy...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Malignant and unspecified neoplasms gastrointestinal NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON56934

**Source**
ToetsingOnline

**Brief title**
PUMP-IT RCT

### Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Hepatobiliary neoplasms malignant and unspecified
- Gastrointestinal neoplasms malignant and unspecified

**Synonym**
'Colorectal liver metastases' 'colon cancer with liver metastases'

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Antoni van Leeuwenhoek Ziekenhuis
**Source(s) of monetary or material Support:** Cerona Therapeutics (in kind bijdrage),KWF,Tricumed Medizintechnik GmbH (in kind bijdrage)

## Intervention

**Keyword:** Colorectal Neoplasms, Infusion pumps, Infusions, intra-arterial, Liver Neoplasms / Surgery

## Outcome measures

### Primary outcome

overall survival (OS).

### Secondary outcome

progression-free survival (PFS), conversion-to-resection rate, R0/R1 resection

rate, hepatic progression-free survival (hPFS), radiological response,

pathological response, complication rates for pump placement, surgery for the

primary tumour and conversion surgery, toxicity of HAIP and systemic therapy,

quality of life and cost effectiveness.

# Study description

### Background summary

In patients with colorectal cancer metastases confined to the liver (CRLM), resection of the primary tumour and liver metastases may offer a chance of cure or long-term survival. The vast majority of these patients however presents with unresectable CRLM. Resection is a dominant contributor to long-term survival. Therefore, major efforts have focused on optimising induction treatment to convert unresectable CRLM to resectable CRLM.
Induction treatment with systemic therapy is the current treatment regime with reported conversion rates ranging from 22 to 57% due to heterogeneity of the

patient population and variation in resectability criteria. The recently published Dutch CAIRO5 study was designed to find the optimal induction regimen in chemotherapy-naive patients with initially unresectable CRLM based on predefined resectability criteria. Patients with right-sided and/or RAS/BRAFV600E mutated primary tumours were randomised to FOLFOX (5FU, leucovorin and oxaliplatin) or FOLFIRI (5FU, leucovorin and irinotecan) + bevacizumab (Bev) (arm A) and FOLFOXIRI (5FU, leucovorin, oxaliplatin and irinotecan) + Bev (arm B). Patients with left-sided and RAS/BRAFV600E wild-type tumours were randomised to FOLFOX/FOLFIRI (patient preference) plus either bevacizumab(arm C) or panitumumab (arm D). Besides a higher conversion rate after triplet therapy (arm B), no difference in progression free survival and overall survival was found. This could partially be explained by the high recurrence rates after conversion surgery. Early recurrence, defined as disease progression or death within 6 months after conversion, occurred in 43% of 240 patients who underwent conversion surgery. The majority (62%) had liver-only recurrence. Considering that the liver is the predominant site of recurrences, intensifying induction treatment might improve survival outcomes.
Hepatic arterial infusion pump (HAIP) chemotherapy is a promising method for optimising induction treatment. The HAIP is surgically placed and delivers chemotherapy continuously and directly to the liver via the hepatic artery. Floxuridine (FUDR) is the chemotherapeutic agent used in HAIP therapy. FUDR has a high first-pass liver extraction rate of 95% which results in limited systemic side effects and enables a 400-fold higher dose compared to systemic administration. In patients with unresectable CRLM, HAIP therapy is combined with systemic therapy (HAIP-SYST) to optimise conversion rates and control occult extrahepatic disease. The reported conversion rates after HAIP-SYST vary from 18-52%. In line with other studies describing induction therapy for unresectable CRLM, the wide range in conversion rates after HAIP-SYST could be explained by the heterogenity of both resectability criteria and the patient population.

In this diverse patient population, chemotherapy-naive patients appear to benefit most from HAIP-SYST as induction treatment. They show improved survival outcomes, in particular patients who convert to local treatment of the liver metastases. We analysed 58 consecutive chemo-naive patients with unresectable CRLM who were treated with HAIP-SYST at Memorial Sloan Kettering Cancer Center (MSKCC). Thirty-two patients (55%) converted to resectable CRLM and another two patients had a radiological complete response. After median follow-up of 116 months, median PFS was 16.7 months and median OS was 53.0 months for all patients. In converted patients or those with a radiological complete response versus patients who remained unresectable, the 3 year OS rate was 88% vs. 27%, and the 5 year OS rate was 72% vs. 0% ($P < 0.001$). Moreover, 19 converted patients (59%) had a complete or major pathological response.

These results of HAIP-SYST in chemo-naive patients are impressive, but until now just reported from a single centre. Most important barriers for implementing HAIP-SYST treatment worldwide include absence of marketing

authorization for FUDR in Europe, the technically challenging surgical procedure of pump placement and the need for stringent monitoring and specific management of patients undergoing HAIP-SYST which requires a highly skilled multidisciplinary treatment team.
To overcome these barriers we first conducted a phase II study in the Netherlands Cancer Institute and Erasmus MC to assess safety and feasibility of HAIP-SYST as induction treatment. The endpoint was feasibility, described as the percentage of patients completing 2 cycles of combined HAIP chemotherapy and systemic therapy. This endpoint was reached in 28 of 31 (90%) patients. Pump placement was combined with resection of the primary tumour in 22 of 30 patients. Anastomotic leakage and mortality were not observed. Clavien-Dindo grade >= 3 complications of the pump placement procedure (± resection of the primary tumour) were documented in 5 of 31 (16%) patients. Median time from surgery to first HAIP was 21 days (IQR 15-28). CTCAE toxicity grade 3 of more was seen in 10 of 29 (23%) patients during the first two courses of HAIP-SYST. After proven save and feasible, this multicentre randomised controlled trial is the subsequent step to provide insights on long-term outcomes of combined HAIP-SYST as induction treatment over systemic therapy alone for chemotherapy-naive patients with unresectable CRLM.

**Study objective**

The main objective of this trial is to investigate whether HAIP with concomitant systemic therapy prolongs overall survival in chemo-naive patients with initially unresectable synchronous colorectal liver metastases as compared with systemic therapy alone.

**Study design**

Multicentre, phase 3 randomised controlled trial

**Intervention**

Patients in the intervention arm will first undergo surgery for pump placement and resection of the primary tumour. Subsequently, these patients receive induction therapy with FUDR-HAIP combined with systemic therapy (FOLFOX or FOLFIRI). The control arm receives systemic therapy alone according to standard clinical practice (FOLFOX/FOLFIRI/CAPOX/FOLFOXIRI (+bevacizumab)).
A National Liver Panel consisting of radiologists and liver surgeons assess the CT-abdomen of all patients at baseline and during induction treatment. The panel evaluates resectability and treatment response. The duration of protocol treatment depends on toxicity, disease progression and treatment response. In case of conversion to resectable CRLM, the total duration of treatment is 6 months (i.e. 6 cycles) of active treatment: HAIP-SYST or SYST.
Patients in the intervention arm need an additional preoperative CT angiography to assess suitability for pump catheter placement and postoperative 99mTc-MAA

scintigraphy to exclude extrahepatic perfusion.
All patients will be asked to complete quality of life questionnaires at baseline and 3, 6, 9, 12 and 24 months after starting systemic therapy or after pump placement.

**Study burden and risks**

The anticipated benefit of HAIP-SYST induction therapy is longer overall survival, higher cure rate and better quality of life. Conversion to local treatment of CRLM with curative intent or a durable complete radiological response has been observed in 59% of chemo-naive patients who were treated with a combination of HAIP chemotherapy and first line systemic therapy. Irrespective of conversion, the combined therapy results in a median overall survival (OS) of 53 months and 5-year OS in 4% of patients. In case of conversion-to-surgery or complete radiological response, median OS was 141.7 months and 5-year OS was 72%. These data are impressive but retrospectively derived from single centre experience. Conversion rates and survival benefit have not yet been established elsewhere. We anticipate that a higher conversion rate will result in time without chemotherapy and therewith better quality of life. We anticipate that the cure rate, which is generally very low in this patient population, will be higher in the intervention arm because micrometastatic hepatic disease is eradicated in more patients.
In patients randomised to the intervention arm, HAIP will be combined with systemic therapy. To assess arterial anatomy, a CT scan with arterial phase has to be performed if not already available. The chemo pump will be implanted surgically and resection of the primary tumour will be performed during the same procedure. Surgical complications related to chemo pump implantation are uncommon (<10%) and include hepatic artery bleeding, dissection or thrombosis, HAIP pocket infection, and extrahepatic perfusion. Complications associated with surgery in general and colorectal surgery specifically may occur. These complications include bleeding, infection, or anastomotic leak. Due to the mandatory surgical procedure and recovery period, there is usually a short delay in start of chemotherapy. Surgical complications can lead to re-interventions and mortality. Severe complications may significantly postpone systemic treatment, or even keep the patient from treatment.
Prior to the first administration of HAIP chemotherapy, a technetium-99m-labeled macro-aggregated albumin nuclear medicine scan (99mTc-MAA scintigraphy) will be performed to confirm bilobar hepatic perfusion via the pump and to rule out extrahepatic perfusion. The effective radiation dose of the 99mTc-MAA scintigraphy is 3-4 mSv.
HAIP chemotherapy toxicities include ulcer disease and biliary sclerosis, which can both be largely avoided by imaging prior to treatment, monitoring of liver tests and dose adjustments (or cessation) or concurrent administration of dexamethasone via pump. Systemic side effects of HAIP chemotherapy are rare (<1%). Therefore this treatment is suitable for combined induction treatment.
The systemic therapy administered in this trial is well known standard treatment in metastatic colorectal cancer. Common toxicities include fatigue,

nausea, diarrhoea, neutropenia, palmar-plantar erythrodysesthesia (for 5-FU only), neuropathy (for oxaliplatin only) and alopecia (for irinotecan only).
When combined with FUDR-HAIP, the systemic chemotherapy dose is slightly reduced compared to the standard schemes. mFOLFOX6 is modified to a dose of 2000 mg/m2 fluorouracil without bolus of fluorouracil vs. 2400 mg/mg2 fluorouracil, respectively. FOLFIRI is modified by reducing the irinotecan dose is from 180 mg/m2 to 150 mg/m2 to reduce the risk of biliary toxicity.
Visits to the day care unit have a similar frequency for patients in the intervention arm and the control arm. Patients in both arms have planned visits every two weeks for systemic chemotherapy and patients in the intervention arm will additionally receive filling of the pump either with saline or FUDR.
Participating patients are asked to fill out Quality of Life questionnaires at baseline after inclusion, and 3, 6, 9, 12 and 24 months after the start of systemic therapy or after pump placement, in the control arm and intervention arm respectively.

## Contacts

**Public**
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066 CX
NL
**Scientific**
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066 CX
NL

## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**

Adults (18-64 years)
Elderly (65 years and older)

### Inclusion criteria

• Unresectable CRLM (as assessed by National Liver Panel)
• Resectable primary tumour without indication for neoadjuvant treatment
• No previous systemic therapy for colorectal cancer
• No extrahepatic metastases
• Suitable arterial anatomy for pump placement
• Written informed consent

### Exclusion criteria

• DPD-deficiency
• MMR-deficiency

## Study design

### Design

| | |
|---|---|
| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 22-11-2024 |
| Enrollment: | 306 |
| Type: | Actual |

### Medical products/devices used

| | |
|---|---|
| Generic name: | Tricumed IP2000V infusion pump |
| Registration: | No |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 06-08-2024 |
| Application type: | First submission |
| Review commission: | METC NedMec |

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

### In other registers

| Register | ID |
|---|---|
| Other | CTIS: 2023-506194-35-00 |
| CCMO | NL86326.041.24 |