Supplementary table 1:

Primary endpoint(s) of the trial

Study part A: To compare the plasma $AUC_{(0-t)}$ for IDA and IDAol between the two doses of 10 or 15 mg of idarubicin.

Study part B: To compare the plasma C(t) for IDA and IDAol between the two doses of 10 or 15 mg of idarubicin.

Secondary end-points

Study part A

- To evaluate tumour-uptake of lipiodol with computer tomography (CT).
- To evaluate the anti-tumour effect defined as changes in tumour volume (evaluated with mRECIST), and the amount of necrosis using PET and MRI.
- To evaluate the effect of the IDA-lipiodol-emulsion on the regulation of the lipidome and proteome (metabolomics) of HCC and non-tumour cells with multi-omics analytical techniques in liver biopsies from tumour and non-tumour tissues as well as liquid biopsies from blood/serum/plasma.
- To explore changes in RNA-isolation, protein extraction, and metabolomics/lipidomics assays in primary tumour material grown from liver biopsies cultured in 3D hydrogels in comparison with baseline.
- To detect lipiodol in lymph ducts during TACE.
- To evaluate cardiotoxicity, hematologic and liver safety, and other adverse events.

Study part B

- Pharmacokinetics (PK) endpoints:
- Differences in plasma population C(t) for IDA and IDAol between the two doses of 10 or 15 mg.

Imaging endpoints:

- To quantify and localize Lipiodol deposition in the liver, reflecting the uptake of IDA, on CT after all TACE treatments.
- To assess tumour volume with mRECIST and viability before and after the first TACE on CT.
- To investigate whether any differences between HCCs within and between patients identified in study part A on pre-TACE MRI are correlated to overall treatment response (evaluated with mRECIST), PFS (progression-free survival), OS (overall survival), and the occurrence and severity of adverse events.
- To detect lipiodol in lymph vessels at fluoroscopy during TACE.

Biochemistry and cell biology endpoints:

- To compare the plasma concentrations of α-fetoprotein before and after TACE.
- To detect circulating tumour cells in systemic blood circulation
- To compare the anti-tumour effect (amount of necrosis) achieved in vivo and in vitro in the same tumours and whether there is a correlation to any differences between HCCs within patients identified in study part A

Safety endpoints:

- To evaluate cardiotoxicity with plasma and blood serum concentrations of troponin I and N-terminal pro-brain natriuretic peptide (NT-proBNP), respectively.
- To evaluate hematologic toxicity and liver safety with neutropenia and thrombocytopenia before and after treatment.

- To evaluate liver safety with serum/plasma bilirubin and serum aminotransferase before and after treatment.
- To evaluate the clinical tolerability of the treatment.
- To estimate the quality of life

Overall endpoints:

- To investigate whether the differences between HCCs detected with histopathology correlate with those detected with PET/MRI and/or any of the multi-omics techniques.
- To evaluate the ability of single or combined imaging and multi-omics biomarkers to predict treatment response.
- To evaluate progression-free and overall survival.