

**Survival and Quality of Life after Isolated Hepatic Perfusion with Melphalan as a
Treatment for Uveal Melanoma Liver Metastases – Final Results from the Phase III
Randomized Controlled Trial SCANDIUM**

Original Report

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ABSTRACT

Objective: To investigate overall survival (OS) and health-related quality of life (HRQOL) of first-line isolated hepatic perfusion (IHP) compared to best alternative care (BAC) for patients with uveal melanoma liver metastases.

Summary Background Data: Approximately half of patients with uveal melanoma develop metastatic disease, most commonly in the liver and systemic treatment options are limited. Isolated hepatic perfusion (IHP) is a locoregional therapy with high response rates but with unclear effect on overall survival (OS).

Methods: In this phase III randomized controlled multicenter trial (the SCANDIUM trial) patients with previously untreated isolated uveal melanoma liver metastases were included between 2013-2021, with at least 24 months of follow-up. The planned accrual was 90 patients randomized 1:1 to receive a one-time treatment with IHP or BAC. Crossover to IHP was not allowed. The primary endpoint was the 24-month OS rate, with the hypothesis of a treatment effect leading to a 50% OS rate in the IHP group compared to 20% in the control group. HRQOL was measured by the EuroQol 5-domains 3-levels (EQ-5D-3L) questionnaire over 12 months.

Results: The intention-to-treat (ITT) population included 87 patients randomized to the IHP group (43 patients; 41 [89%] received IHP) or the control group (44 patients). The control

group received chemotherapy (49%), immunotherapy (39%), or localized interventions (9%). In the ITT population, the median PFS was 7.4 months in the IHP group compared with 3.3 months in the control group, with a hazard ratio of 0.21 (95% CI, 0.12-0.36). The 24-month OS rate was 46.5% in the IHP group vs 29.5% in the control group ($P=0.12$). The median OS was 21.7 months vs 17.6 months, with a hazard ratio of 0.64 (95% CI, 0.37-1.10). EQ-5D-3L showed a sustained high health status for the IHP group over 12 months, compared to a deteriorating trend in the control group.

Conclusions: For patients with liver metastases from uveal melanoma, IHP offers high response rates translating to a benefit in PFS including a trend of better HRQOL compared to the control group. However, the primary endpoint of OS at 24 months was not met.

Trial Registration:

ClinicalTrials number: NCT01785316 (Registered February 1, 2013)

EudraCT number: 2013-000564-29

INTRODUCTION

Uveal melanoma is a rare malignant disease, and despite effective management of the original tumor, approximately half of patients eventually develop metastatic disease. The liver is the most frequent site of metastases, affecting up to 90% of patients. Among this group of patients, median survival is about 12 months, and only a small number of patients survive beyond 5 years^{1,2}. Conventional chemotherapy has limited effectiveness in metastatic disease and does not improve survival rates. Immune checkpoint inhibition (ICI) has shown some benefits, but the combined use of ipilimumab and nivolumab has a poor overall response rate (10-18%) and uncertain effects on survival^{3,4}. Encouragingly, a phase III trial of tebentafusp, a bispecific fusion protein linking melanoma cells with T cells, in patients with the HLA-A*02:01 serotype showed significant improvements in overall survival (OS) compared to chemotherapy or ICI in monotherapy (16.0 vs 21.7 months)⁵. However, only approximately 45% of individuals in the United States and Europe are HLA-A*02:01-positive, making only a subset of patients potentially eligible for this treatment.

Isolated hepatic perfusion (IHP) with melphalan is a regional treatment method that isolates the liver from the systemic circulation, allowing for the administration of high concentrations of chemotherapy to the liver while minimizing systemic exposure⁶. As previously published, the SCANDIUM trial demonstrated a statistically superior response rate (40% vs 4.5%) and progression-free survival (PFS; 7.4 vs 3.3 months) compared to best alternative care in patients with liver metastases of uveal melanoma receiving first-line treatment with IHP⁷.

Here, we present results for the primary endpoint of OS rate at 24 months together with data on health-related quality of life (HRQOL), as well as updated data on safety, PFS and hepatic PFS (hPFS).

METHODS

Patients

Patients with histologically or cytologically confirmed liver metastases from uveal melanoma and Eastern Cooperative Oncology Group (ECOG) performance status 0-1 were eligible if they had measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, had received no previous systemic therapy for melanoma metastases (i.e., first-line therapy), and had no evidence of extrahepatic disease by Positron Emission Tomography-Computed Tomography (PET-CT). Patients were excluded if the metastases occupied $\geq 50\%$ of the liver volume as assessed by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI); if there was significant heart, lung, or renal dysfunction; or if the patient had a body mass index (BMI) above 35.

Study design and treatment

In this prospective, multicenter, phase III, randomized controlled trial, adult patients with previously untreated isolated liver metastases from uveal melanoma and ECOG performance status 0-1 were randomized in a 1:1 ratio between 2013 and 2021 to receive a one-time treatment with IHP or best alternative care (control group, investigator's choice of treatment). No crossover from the control group to the IHP group was allowed. Details of randomization and treatment have been published previously⁷.

Assessments

Radiological response was assessed at 3, 6, 12, 18, and 24 months by either CT or MRI of the liver using the same modality as at the baseline examination, with additional CT imaging of the thorax. Response was primarily assessed by a radiologist at the local institution followed

by a blinded independent central review according to RECIST version 1.1⁸. HRQOL was assessed at baseline and at 3, 6, 12, 18 and 24 months.

Endpoints

The primary endpoint was OS rate at 24 months. Secondary and exploratory endpoints reported here include PFS, hPFS and safety, as well as HRQOL, measured by the 3-level version of the EuroQol 5-domains questionnaire (EQ-5D-3L) and quality-adjusted life years (QALYs). The endpoints of response, PFS and hPFS have been reported earlier⁷, but is updated with longer follow-up in this manuscript. All efficacy endpoints were primarily assessed in the intention-to-treat (ITT) population, with all patients included in the treatment group to which they were randomly assigned. Safety, measured as severe adverse events (SAE) according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, was assessed in the per-protocol (PP) population, which was defined as all patients who underwent randomization and grouped according to the treatment that they eventually received. Overall survival was defined as the time from randomization to death from any cause. Progression-free survival was defined as the time from randomization to documented progression at any site or death from any cause, and hPFS from randomization to progression in the liver or death from any cause, both according to RECIST 1.1 criteria.

Statistical analysis

The sample size was based on assumptions of an estimated treatment effect with 50% survival in the study group and 20% survival in the control group after 24 months of follow-up. To reach a power of 80% with an alpha of 0.05, a treatment group ratio of 1:1, and using a two-sided Fisher's exact test, a sample size of 90 patients (45 patients per study arm) was required.

Based on an interim report from the data safety monitoring board, it was recommended to include an additional three patients to compensate for drop-out, i.e., a total of 93 patients.

Time-to-event analysis was performed including all participants in the ITT and per protocol populations using the Kaplan-Meier methodology and reported using medians together with 95% confidence intervals (CI) and estimated survival rates at 6, 12, and 24 months with 95% CI. Fisher's exact test was used to compare the overall response rate (ORR).

HRQOL outcomes were measured using EQ-5D-3L, which describes a participants' self-reported current health state in three levels of severity over five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) together with a visual analogue rating scale (VAS)⁹. Each health state can be mapped to a health utility value set, eliciting relative preferences for each state. The VAS uses a 100-point scale, in which a patient self-rates their health state with 0 being the worst health imaginable and 100 the best health imaginable. The results are presented using the mean (with 95% CIs) of each endpoint and visit in each trial arm up to 12 months. Differences in means between trial arms for each outcome and visit were tested by the Student's t-test for statistical significance (two-sided tests assuming equal variance). All outcomes were reported for each visit, without imputation of missing responses. At each visit/time point, the difference in accumulated QALYs between trial arms was adjusted for the mean baseline difference in health utility to account for any differences unrelated to the intervention. Accumulated QALYs were calculated by linear interpolation between each pair of observations, multiplying the average health utility index between each pair by the duration of time between observations. Deceased participants were assumed to have a patient health utility equal to 0 from the time of death until the end of the study (24 months). As the base case for all analyses, the UK value set was used¹⁰, while the

Swedish value set was used in a sensitivity analysis¹¹. All analyses were performed in STATA v16.

Study oversight

The original protocol and all amendments were approved by the Swedish Medical Product Agency (EudraCT number 2013-000564-29) and the Regional Ethical Review Board at the University of Gothenburg (Dnr 144-13). The study was registered at ClinicalTrials.gov: NCT01785316. The study was conducted in accordance with the protocol, Good Clinical Practice guidelines, and the provisions of the Declaration of Helsinki. All patients provided written informed consent before inclusion in the trial.

RESULTS

Patients

From July 2013 to March 2021, 147 patients were screened, and 93 patients were enrolled at six sites and randomly assigned to the IHP group (46 patients) or the control group (47 patients). In each arm three patients were excluded due to inappropriate enrollment or withdrawal of consent, and the final intention-to-treat cohort consisted of the IHP group (43 patients) and the control group (44 patients) (**Figure 1**); details have been published previously¹². The demographics and baseline disease characteristics of the patients are described in **Table 1**. The median age was 65 years (range 27-80) in the IHP group and 68 years (range 40-85) in the control group. Among patients in the IHP group, 41 (89%) were treated per protocol and two (4.5%) did not receive IHP due to the perioperative observation that >50% of the liver was occupied by metastases. These two patients are still included in the IHP arm in the main intention-to-treat analysis but are included in the control arm in the per protocol analysis. In the control group, the first-line treatment received was chemotherapy

in 21 (48%) patients, ICIs in 17 (39%) patients, and localized interventions in five (11%) patients. One (3%) patient did not receive any antitumor treatment due to clinical deterioration (**Table 2**). At the time of data cut-off (Feb 01, 2023) all surviving patients (n=33) had reached 24 months of follow-up.

Progression-free survival

Updated data on PFS and hPFS from the initial report showed minimal differences between the two arms. The estimated 6-month PFS rate was 58% in the IHP group compared with 8% in the control group. Median PFS was 7.4 months (95% CI, 5.2 to 11.6) in the IHP group compared with 3.3 months (95% CI, 2.9 to 3.7; log-rank test $p<0.0001$) in the control group, with a hazard ratio of 0.21 (95% CI, 0.12 to 0.36) (**Figure 2a**).

Hepatic progression-free survival

The estimated 6-month hPFS rate was 63% in the IHP group compared with 13% in the control group. Median hPFS was 9.1 months (95% CI, 5.6 to 13.4) in the IHP group compared with 3.3 months in the control group (95% CI, 2.9 to 4.0; log-rank test $p<0.0001$), with a hazard ratio of 0.21 (95% CI, 0.12 to 0.36) (**Figure 2b**).

Overall survival

In the ITT population, the primary endpoint defined as the OS rate at 24 months was 46.5% (95% CI, 31.2 to 60.4) in the IHP group compared with 29.5% (95% CI, 17.0 to 43.2) in the control group ($p=0.12$, Fisher's exact test). The median OS in the IHP group was 21.7 months (95% CI, 19.1 to NR) compared with 17.6 months (95% CI, 13.5 to 21.4) in the control group ($p=0.10$, log-rank test), with a hazard ratio of 0.64 (95% CI, 0.37 to 1.10) ~~in favor of the IHP group~~ (**Figure 2c**). In the pre-planned subgroup analysis, the only subgroups with a

significant statistical difference in OS, both favoring IHP, were patients aged <65 years with (HR 0.43; 95% CI, 0.19 to 0.97) and patients with M1a (largest metastases <3cm) according to the American Joint Committee on Cancer (AJCC) staging (HR 0.46; 95% CI, 0.22 to 0.95) (Supplemental Figure 1, Supplemental Digital Content 1, <http://links.lww.com/SLA/F33>).

Per protocol analysis

A per protocol analysis, dividing the control group into patients receiving ICI or chemotherapy, showed a significant difference between the treatment modalities, with a median PFS of 3.0 months (95% CI, 2.70 to 3.73) for chemotherapy, 3.3 months (95% CI, 2.60 to 3.57) for ICIs, and 7.5 months (95% CI, 5.57 to 11) for IHP ($p<0.0001$) (**Figure 3a**). Similarly, median hPFS was 3.0 months (95% CI, 2.7 to 4.3) for chemotherapy, 3.3 months (95% CI, 2.7 to 5.1) for ICIs compared with 11.6 months (95% CI, 5.7 to 14.0) for IHP ($p<0.0001$) (**Figure 3b**). Both IHP (22.6 months; 95% CI, 19.2 to NR) and ICI (22.7 months; 95% CI, 13.6 to NR) had a significantly longer median OS compared with patients receiving chemotherapy (13.3 months; 95% CI, 6.6 to 19.6, $p=0.003$) (**Figure 3c**).

Safety

During first-line treatment, SAEs were reported in eight (19.5%) patients in the IHP group and three (6.5%) in the control group (details have been published previously¹²). No additional SAEs were reported during the follow-up period.

Health-related quality of life

Throughout the 12-month follow-up period, the VAS scores remained stable in the IHP group but there was a decrease in the control group at 6 months (83 vs. 64, $p=0.002$) and 12 months (86 vs. 63), $p=0.002$) (**Figure 4a**). This difference was also significant when adjusting for

baseline VAS scores with a mean change from baseline at 6 months of -0.4 vs. -14.1 ($p=0.02$) and at 12 months 2.1 vs. -15.4 ($p=0.02$) favoring IHP. There were similar findings for health utility as measured by EQ-5D-3L, with a significant difference between IHP and controls at 6 months (0.87 vs. 0.70, $p=0.019$) and 12 months (0.88 vs. 0.66, $p=0.005$) (**Figure 4b**).

However, this difference was not significant when adjusting for baseline health utility scores with a mean change from baseline at 6 months of -0.02 vs. -0.10 ($p=0.36$) and at 12 months -0.02 vs. -0.08 ($p=0.49$). There was a nominally higher number of QALYs accumulated in the IHP group, but after adjusting for baseline differences in health utility, there were no statistically significant differences between the two groups (**Figure 4c**). HRQOL data are summarized in Supplementary Table 1, Supplemental Digital Content 1, <http://links.lww.com/SLA/F33>.

DISCUSSION

In the phase III RCT SCANDIUM of previously untreated patients with isolated uveal melanoma liver metastases, a single treatment with melphalan-based IHP resulted in significantly higher response rates and improved hPFS and PFS than the investigator's choice of available treatments. At 2 years, the proportion of patients alive was higher for those receiving IHP compared to the control group (46.5% vs 29.5%), but the difference was not statistically significant. This lack of significance could in part be attributed to the control group performing better than expected. The pre-defined analysis plan expected 50% of the patients to remain alive in the IHP group, which was very similar to the actual surviving proportion (46.5%). However, in the control group, a survival rate of 20% was expected based on historical Swedish data, but the actual survival rate was almost 10% higher (29.5%).

Notably, the per protocol analysis found no benefit in PFS or hPFS when comparing patients in the control group receiving chemotherapy with patients receiving immunotherapy, however, in the survival analysis, patients who received immunotherapy experienced a similar survival rate as those in the IHP group. Nevertheless, as these groups are small and did not have randomized allocation, caution is warranted regarding the interpretation of the per protocol analysis results.

Several phase II trials have reported ORRs ranging between 10-18% in patients with metastatic uveal melanoma treated with ipilimumab and nivolumab^{3,13,14}. Consistent with these reports, one of seven patients in the control arm of the current study that received ICI with ipilimumab and nivolumab in combination experienced a partial response (14% ORR). Of note, the recent approval of tebentafusp for the treatment of the HLA-A*02:01 uveal melanoma subtype is a major advance, however, no patients in the present trial received tebentafusp since it was not available during the inclusion phase.

While there was no significant benefit in OS, there were statistically significant differences between trial arms in terms of patients' self-rated health and health utility at 6- and 12-months post-baseline, where patients in the IHP group appeared to maintain their HRQOL whereas patients in the control group showed a decline. The differences between treatment arms were large enough to be considered clinically meaningful, where a difference of 7-12 points constitute a minimally important difference in VAS scores for patients with cancer¹⁵.

Nevertheless, these differences may be explained by small, albeit insignificant, differences at baseline. When controlling for differences in health utility at baseline, there was no difference between the trial arms in health utility or accumulated QALYs over the trial duration.

Conceptually, this finding is interesting since IHP is a one-time treatment, with adverse effects mainly in the immediate post-operative period, but few long-term consequences.

The outcomes for patients in the control group were similar to those reported in recent interventional studies corroborating that the control group is representative, and there was no cross-over allowing for IHP in the control arm. In the pivotal trial establishing tebentafusp as first-line treatment in a subset of patients with the HLA-A*02:01 serotype, the control group experienced an OS of 16.0 months⁵ compared to 17.6 months in our study. Interestingly, the median OS for patients receiving tebentafusp was 21.7 months, which was the same as those receiving IHP in SCANDIUM. The ORR in the control group of the present study was 4.5% and the median PFS was 3.3 months, similar to previously reported results in patients with metastatic uveal melanoma treated with chemotherapy or ICI with a CTLA-4 and/or a PD-1 inhibitor¹⁶.

A minimal-invasive version of IHP, percutaneous hepatic perfusion (PHP), combines conventional hepatic artery infusion with a dual-balloon vena cava catheter collecting the outflow from the liver. The venous outflow is then connected to an extracorporeal venous bypass circuit including a carbon filter to recover any of the drug that is not absorbed by the liver¹⁷⁻¹⁹. A recent phase III study, the FOCUS trial, compared PHP to the investigator's choice of transarterial chemoembolization, ipilimumab, pembrolizumab or dacarbazine in patients with metastatic uveal melanoma with hepatic-dominant disease²⁰. The response rate and PFS for PHP were very similar to IHP in the current trial, supporting that liver-directed therapies do improve response and PFS. Further support is provided by a recent meta-analysis, which did not identify any significant differences in hPFS (10.0 vs 9.5 months) or OS (17.1 vs 17.3 months) between IHP and PHP for patients with uveal melanoma liver

metastases. However, there was a higher complication rate (39.1% vs 23.8%) and a higher 30-day mortality (5.5% vs 1.8%) for IHP compared to PHP²¹, implicating that PHP might be the preferred future treatment option.

A promising development is the combination of IHP or PHP with systemic immunotherapy. We have previously shown a correlation between OS and a high infiltration of CD8⁺ T cells in metastases and an activated immune cell profile in the peripheral blood of patients treated with IHP²². Two ongoing studies are investigating the combination of CTLA-4 and PD-1 inhibitors with either PHP (CHOPIN trial ClinicalTrials.gov NCT04283890) or IHP (SCANDIUM-II trial ClinicalTrials.gov NCT04463368). The CHOPIN trial had a phase Ib lead-in including seven patients, which identified a safe dose of ipilimumab 1 mg/kg and nivolumab 3 mg/kg (i.e., ipi/nivo). Patients received four cycles of ipi/nivo every 3 weeks, and then two cycles of PHP 6 weeks apart. In a first report including seven patients, the results showed an ORR of 85.7% (5/7 patients), including one patient with a complete response. The combination therapy did not lead to unexpected or more severe adverse events as compared to treatment with either PHP or ipi/nivo alone. The CHOPIN trial is currently accruing the phase II part, aiming to include 76 patients with PFS as the primary endpoint²³. The SCANDIUM-II trial is also a phase Ib trial, combining IHP with ipilimumab 3 mg/kg and nivolumab 1 mg/kg. The study randomized 18 patients to either start the neoadjuvant approach (one cycle of ipi/nivo, followed by IHP, and then three additional cycles of ipi/nivo) or the adjuvant approach (IHP followed by four cycles of ipi/nivo). Both groups then received nivolumab 480 mg for up to 1 year. The first results were presented at ASCO 2023 and showed that 15/18 patients received at least IHP and one cycle ipi/nivo. The adjuvant approach had less immune-related adverse events than the neoadjuvant approach (CTCAE grade 3; 33% vs 89%) and also had a superior ORR (63% vs 29%)²⁴.

In conclusion, the SCANDIUM randomized controlled trial showed that a one-time treatment with IHP results in statistically superior anti-tumor responses and PFS compared to the investigator's choice of best alternative care, including chemotherapy or ICI, in systemic treatment-naïve patients with isolated liver metastases of uveal melanoma. In the ITT population, this translated to a 24-month OS rate of 46.5% in the IHP group compared with 29.5% in the control group; however, this difference was not statistically significant. Importantly, our results showed that patients' HRQOL was sustained in the IHP group over the study period, while the control group appeared to experience deteriorating health status. In summary, IHP offers very high response rates translating to a benefit in PFS and a trend of better HRQOL compared to the control group. However, the primary endpoint of OS at 24 months was not met.

CONFLICT OF INTEREST

ROB has received institutional research grants from Bristol-Myers Squibb (BMS) and SkyLineDx, speaker honoraria from Roche and Pfizer, and has served on advisory boards for Amgen, BD/BARD, Bristol-Myers Squibb (BMS), Merck Sharp & Dohme (MSD), Novartis, Roche and Sanofi Genzyme, and is a shareholder in SATMEG Ventures AB.

LN has received institutional research grants from Merck and Syndax Pharmaceuticals, speaker honoraria from BMS, Johnson&Johnson, Leo Pharma, MSD, Novartis, and Pfizer, has served on advisory boards for BMS, MSD, Novartis, Pierre Fabre, Sanofi Genzyme, and Zealth, and is a shareholder in SATMEG Ventures AB.

HH has received speaker honoraria from BMS, MSD, and Pierre Fabre and has served on advisory boards for MSD and Novartis.

ILJ has served on advisory boards for MSD and BMS.

JN is a shareholder in SATMEG Ventures AB.

GU has during the past two years received honoraria for teaching activities by BMS, MSD, Pierre Fabre, and Novartis and for consulting/advising by Incyte, BMS, Novartis, MSD, Alligator Bioscience, LIDDS, and SeqCure Immunology AB and is a stock owner in ESSITY and Oncopeptides.

PL has served on advisory boards for Pierre Fabre

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DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Figure 1. CONSORT flow diagram

IHP, isolated hepatic perfusion

* 3 patients were inappropriately enrolled in the IHP arm, 2 patients due to >50% of the liver being occupied with metastases and 1 patient due to the presence of systemic metastases. **

Liver metastases not verified by biopsy.

2 patients did not receive IHP since their tumor burden was estimated to be >50% after laparotomy and peri-operative evaluation, so these two patients then crossed over to the control group.

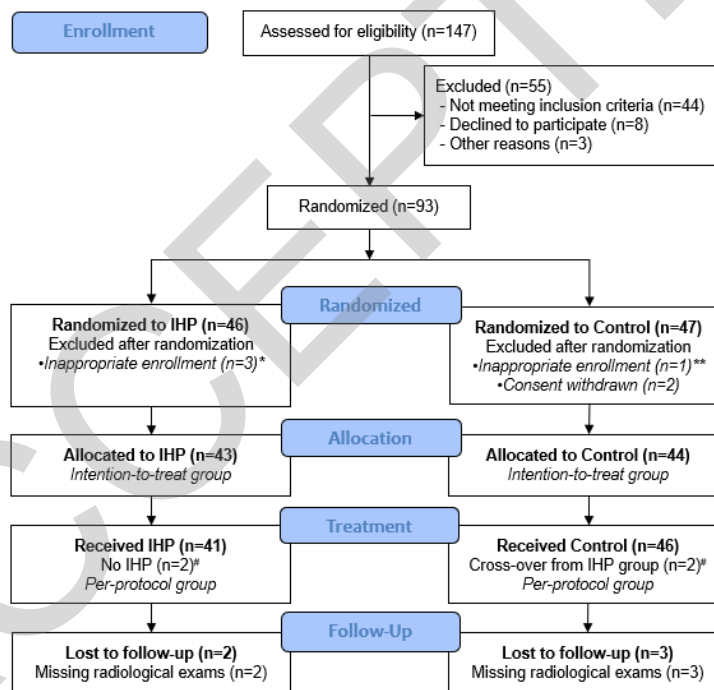


Figure 2. Kaplan-Meier estimates of progression free survival (a), hepatic progression free survival (b) and overall survival (c) for patients receiving isolated hepatic perfusion (IHP) compared to the control group.

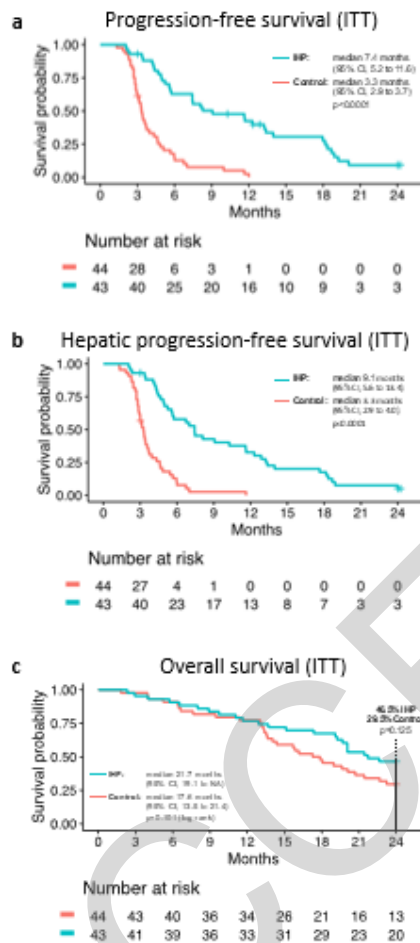


Figure 3. Kaplan-Meier estimates of progression free survival (a), hepatic progression free survival (b) and overall survival (c) for patients receiving isolated hepatic perfusion (IHP) compared to patients receiving immune checkpoint inhibitors or chemotherapy in the control group (per protocol analysis).

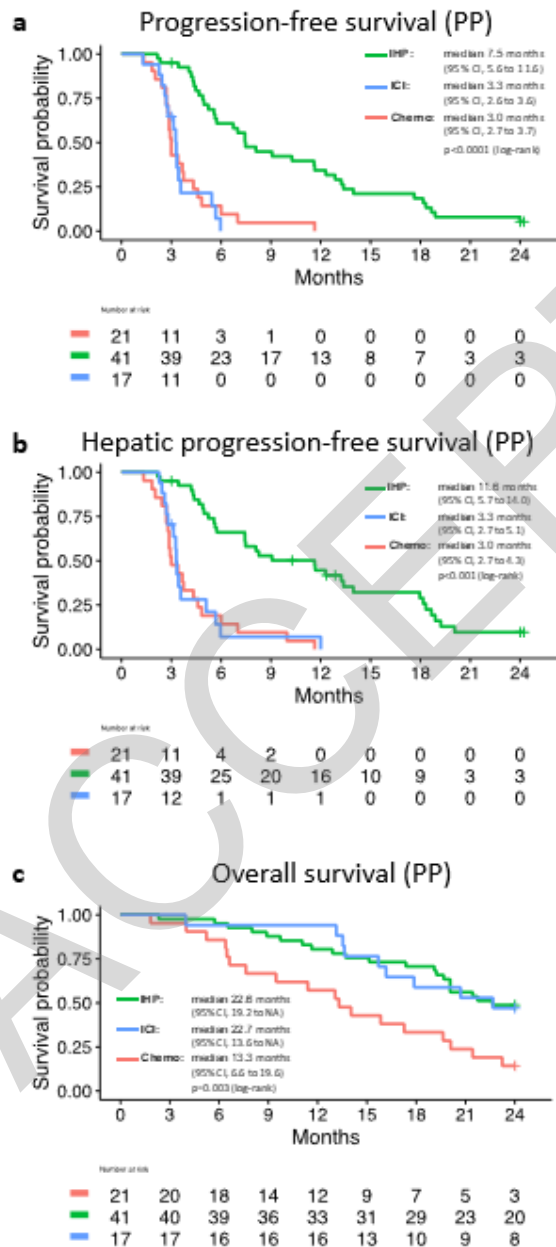


Figure 4. Patient-reported health status measured using the EQ-5D-3L questionnaire comparing patients receiving isolated hepatic perfusion (IHP) compared to control group over 12 months.

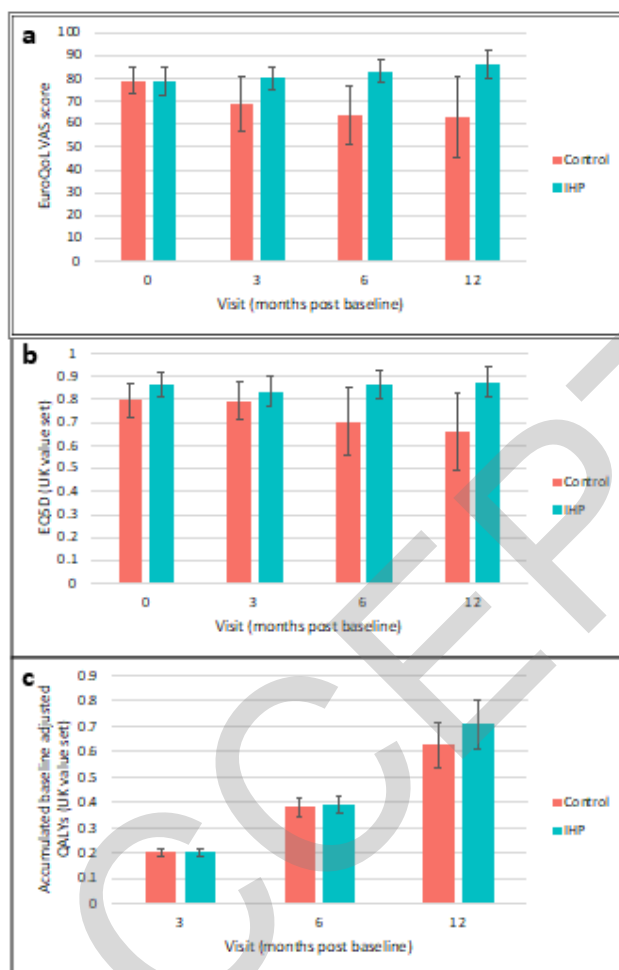


Table 1. Baseline patient characteristics

	IHP n=43	Control n=44
Median age (IQR), years	65 (58-71)	68 (59-73)
Sex		
<i>Female</i>	24 (56%)	16 (36%)
<i>Male</i>	19 (44%)	28 (64%)
Largest metastatic lesion		
$\leq 3.0cm$	31 (72%)	28 (64%)
<i>3.1-8.0cm</i>	10 (23%)	12 (27%)
$\geq 8.1cm$	2 (4.7%)	4 (9.1%)
Median time since primary diagnosis (IQR), years	1.72 (1.15-3.56)	2.48 (1.14-3.51)
Lactate dehydrogenase >ULN	16 (37%)	18 (41%)
Aspartate aminotransferase >ULN	2 (5%)	8 (18%)
Alanine transaminase >ULN	2 (5%)	3 (7%)
Alkaline phosphatase >ULN	1 (2%)	5 (11%)

IHP, intrahepatic perfusion; IQR, interquartile range; ULN, upper limit of normal.

Table 2. First-line treatments in the control group

Treatment	n (%)
<i>Chemotherapy</i>	
Dacarbazine or temozolomide	17 (39)
Platinum and dacarbazine	3 (7)
Platinum and taxane	1 (2)
<i>Immunotherapy</i>	
Ipilimumab and nivolumab	7 (16)
Pembrolizumab or nivolumab	3 (7)
Ipilimumab	4 (9)
Pembrolizumab and entinostat	3 (7)
<i>Other</i>	
Chemoembolization	1 (2)
Radiofrequency ablation	2 (5)
Selective internal radiation	2 (5)
Best supportive care	1 (2)