OPEN

# 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*

*Roger Olofsson Bagge, MD, PhD,*†‡✉ Axel Nelson, MD, PhD,§*
*Amir Shafazand, MD,‡‖ Charlotta All-Eriksson, MD, PhD,¶*
*Christian Cahlin, MD, PhD,# Nils Elander, MD, PhD,***
*Anders Gustavsson, MD, PhD,††‡‡ Hildur Helgadottir, MD, PhD,§§*
*Jens Folke Kiilgaard, MD, PhD,‖‖ Sara Kinhult, MD, PhD,¶¶*
*Ingrid Ljuslinder, MD, PhD,## Jan Mattsson, MD, PhD,† Magnus Rizell, MD, PhD,#*
*Malin Sternby Eilard, MD, PhD,# Gustav J. Ullenhag, MD, PhD,***†††*
*Jonas A. Nilsson, PhD,*‡‡‡ Lars Ny, MD, PhD,§ and Per Lindnér, MD, PhD#*

**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 for patients with uveal melanoma liver metastases.

**Background:** Approximately half of the patients with uveal melanoma develop metastatic disease, most commonly in the liver, and systemic treatment options are limited. IHP is a locoregional therapy with high response rates but with an unclear effect on 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 and 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 best alternative care. 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 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 intention-to-treat population, the median progression-free survival 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 versus 29.5% in the control group ($P = 0.12$). The median OS was 21.7 months versus 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.

From the *Department of Surgery, Sahlgrenska Center for Cancer Research, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; †Department of Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden; ‡Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg, Gothenburg, Sweden; §Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden; ‖Department of Radiology, Alingsås Hospital, Alingsås, Sweden; ¶Department of Ophthalmology, Mölndal Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden; #Transplant Institute, Institute of Clinical Sciences, Sahlgrenska Academy at University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden; **Department of Oncology and Department of Clinical and Biomedical Sciences, Linköping University, Linköping, Sweden; ††Department of Neurobiology, Division of Neurogeriatrics, Care Sciences and Society, Karolinska Institute, Solna, Sweden; ‡‡Quantify Research, Stockholm, Sweden; §§Department of Oncology, Karolinska University Hospital, Stockholm, Sweden; ‖‖Department of Ophthalmology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; ¶¶Department of Oncology, Skåne University Hospital, Lund, Sweden; ##Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden; ***Department of Immunology, Genetics and Pathology (IGP), Science for Life Laboratories, Uppsala University, Uppsala, Sweden; †††Department of Oncology, Uppsala University Hospital, Uppsala, Sweden; and ‡‡‡Harry Perkins Institute of Medical Research, University of Western Australia, Perth, WA, Australia.

✉roger.olofsson.bagge@gu.se.

This study was presented at ASCO 2023, Chicago, LBA9512.

This study was supported by grants from the Signe and Olof Wallenius Foundation, The Göteborg Medical Society, Assar Gabrielsson Foundation, Knut and Alice Wallenberg Foundation, Wilhelm and Martina Lundgren's Foundation, The Sjöberg Foundation, The Swedish Cancer Society, the Swedish Research Council, and donations made in memoriam of Karin Lindholm.

R.O.B. 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. L.N. 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. H.H. has received speaker honoraria from BMS, MSD, and Pierre Fabre and has served on advisory boards for MSD and Novartis. I.L.J. has served on advisory boards for MSD and BMS. J. N. is a shareholder in SATMEG Ventures AB. G.U. has during the past 2 years received honoraria for teaching activities by BMS, MSD, Pierre Fabre, and Novartis and consulting/advising by Incyte, BMS, Novartis, MSD, Alligator Bioscience, LIDDS, and SeqCure Immunology AB and is a stock owner in ESSITY and Oncopeptides. P.L. has served on advisory boards for Pierre Fabre. The remaining authors report no conflicts of interest.

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.annalsofsurgery.com.



DOI: 10.1097/SLA.0000000000006255

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

**Key words:** isolated hepatic perfusion, liver metastases, locoregional treatment, melphalan, uveal melanoma

(*Ann Surg* 2025;282:100–107)

Uveal melanoma is a rare malignant disease, and despite effective management of the original tumor, approximately half of the 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 (ORR) (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 ~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 exposure.[6] 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 the best alternative care (BAC) in patients with liver metastases of uveal melanoma receiving first-line treatment with IHP.[7] 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 (ie, first-line therapy), and had no evidence of extrahepatic disease by positron emission tomography-computed tomography (CT). Patients were excluded if the metastases occupied $\geq 50\%$ of the liver volume as assessed by CT or magnetic resonance imaging; if there was significant heart, lung, or renal dysfunction; or if the patient had a body mass index 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 BAC (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 previously.[7]

### Assessments

The radiological response was assessed at 3, 6, 12, 18, and 24 months by either CT or magnetic resonance imaging of the liver using the same modality as at the baseline examination, with additional CT imaging of the thorax. The response was primarily assessed by a radiologist at the local institution followed by a blinded independent central review according to RECIST version 1.1.[8] HRQOL was assessed at baseline and 3, 6, 12, 18, and 24 months.

### Endpoints

The primary endpoint was the 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 earlier,[7] but are 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 (SAEs) 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. OS was defined as the time from randomization to death from any cause. PFS 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 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 3 patients to compensate for drop-out, that is, a total of 93 patients.

Time-to-event analysis was performed including all participants in the ITT and PP populations using the Kaplan-Meier methodology and reported using medians together with 95% CIs and estimated survival rates at 6, 12, and 24 months with 95% CI. Fisher exact test was used to compare the ORR.

HRQOL outcomes were measured using EQ-5D-3L, which describes a participant's self-reported current health state in 3 levels of severity over 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) together with a visual analog 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 *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 used,[10] while the Swedish value set was used in a sensitivity analysis.[11] 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 6 sites and randomly assigned to the IHP group (46 patients) or the control group (47 patients). In each arm, 3 patients were excluded due to inappropriate enrollment or withdrawal of consent, and the final ITT cohort consisted of the IHP group (43 patients) and the control group (44 patients) (Fig. 1); details have been published previously.[12] 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 2 (4.5%) did not receive IHP due to the perioperative observation that > 50% of the liver was occupied by metastases. These 2 patients are still included in the IHP arm in the main ITT analysis but are included in the control arm in the PP 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 5 (11%) patients. One (3%) patient did not receive any antitumor treatment due to clinical deterioration (Table 2). At the time of data cutoff (February 1, 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 2 arms. The estimated 6-month PFS rate was 58% in the IHP group compared with 8% in the control group. The median PFS was 7.4 months (95% CI,

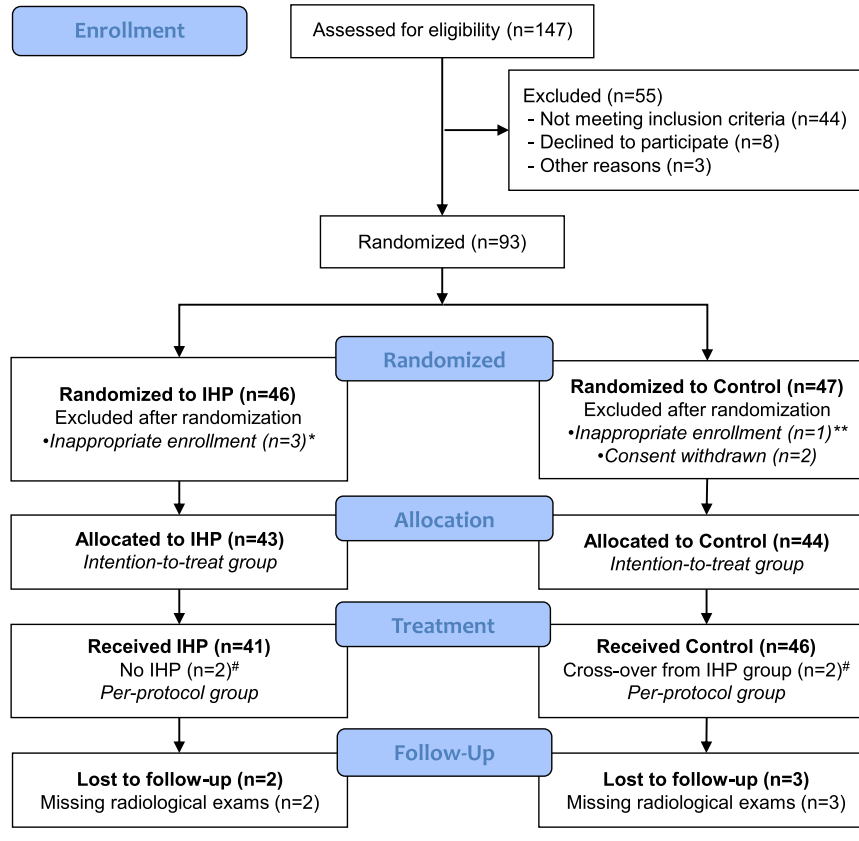


**FIGURE 1.** CONSORT flow diagram. *Three patients were inappropriately enrolled in the IHP arm, 2 patients due to > 50% of the liver being occupied with metastases and 1 patient due to the presence of systemic metastases. **Liver metastases not verified by biopsy. #Two patients did not receive IHP since their tumor burden was estimated to be > 50% after laparotomy and perioperative evaluation, so these 2 patients then crossed over to the control group.

**TABLE 1.** Baseline Patient Characteristics

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

IQR, interquartile range; ULN, upper limit of normal.

5.2–11.6) in the IHP group compared with 3.3 months (95% CI, 2.9–3.7; log-rank test $P < 0.0001$) in the control group, with a hazard ratio of 0.21 (95% CI, 0.12–0.36) (Fig. 2A).

## Hepatic PFS

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

## Overall Survival

In the ITT population, the primary endpoint defined as the OS rate at 24 months was 46.5% (95% CI, 31.2–60.4) in the IHP group compared with 29.5% (95% CI, 17.0–43.2) in the control group ($P = 0.12$, Fisher exact test). The median OS in the IHP group was 21.7 months (95% CI, 19.1–NR) compared with 17.6 months (95% CI, 13.5–21.4) in the control group ($P = 0.10$, log-rank test), with a hazard ratio of 0.64 (95% CI, 0.37–1.10) (Fig. 2C). In the preplanned 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, 0.19–0.97) and patients with M1a (largest metastases <3 cm) according to the American Joint Committee on Cancer (AJCC) staging (HR, 0.46; 95% CI, 0.22–0.95) (Supplemental Figure 1, Supplemental Digital Content 1, http://links.lww.com/SLA/F33).

**TABLE 2.** First-line Treatments in the Control Group

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

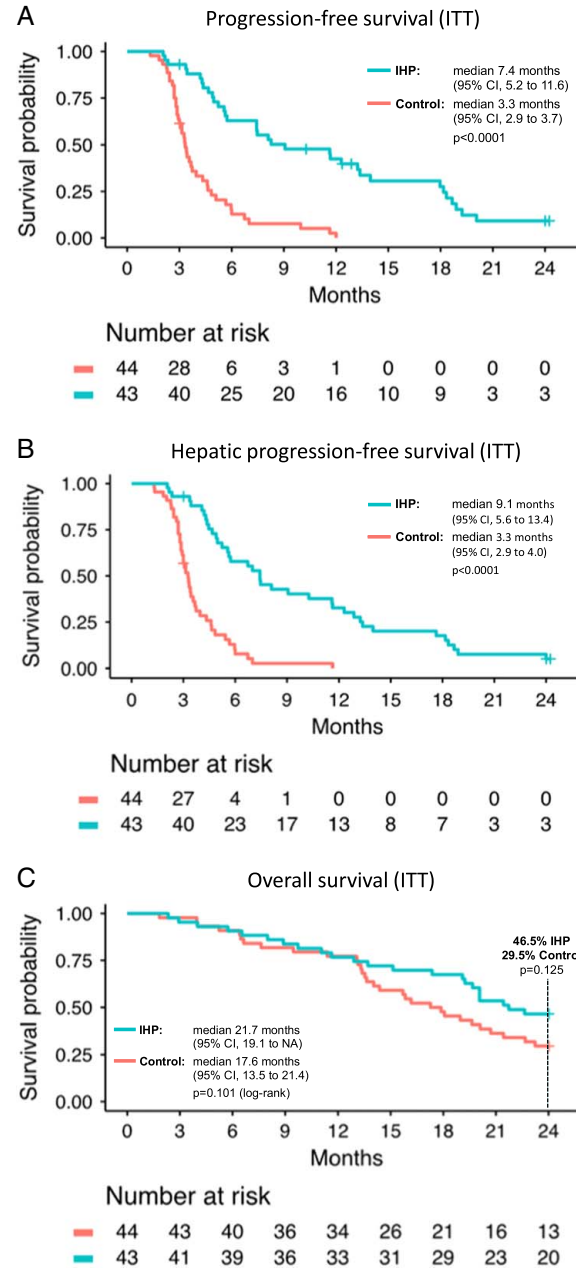


**FIGURE 2.** Kaplan-Meier estimates of progression-free survival (A), hepatic progression-free survival (B), and overall survival (C) for patients receiving isolated hepatic perfusion (IHP) compared to the control group.

## PP Analysis

A PP 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, 2.70–3.73) for chemotherapy, 3.3 months (95% CI, 2.60–3.57) for ICIs, and 7.5 months (95% CI, 5.57–11) for IHP ($P < 0.0001$) (Fig. 3A). Similarly, the median hPFS was

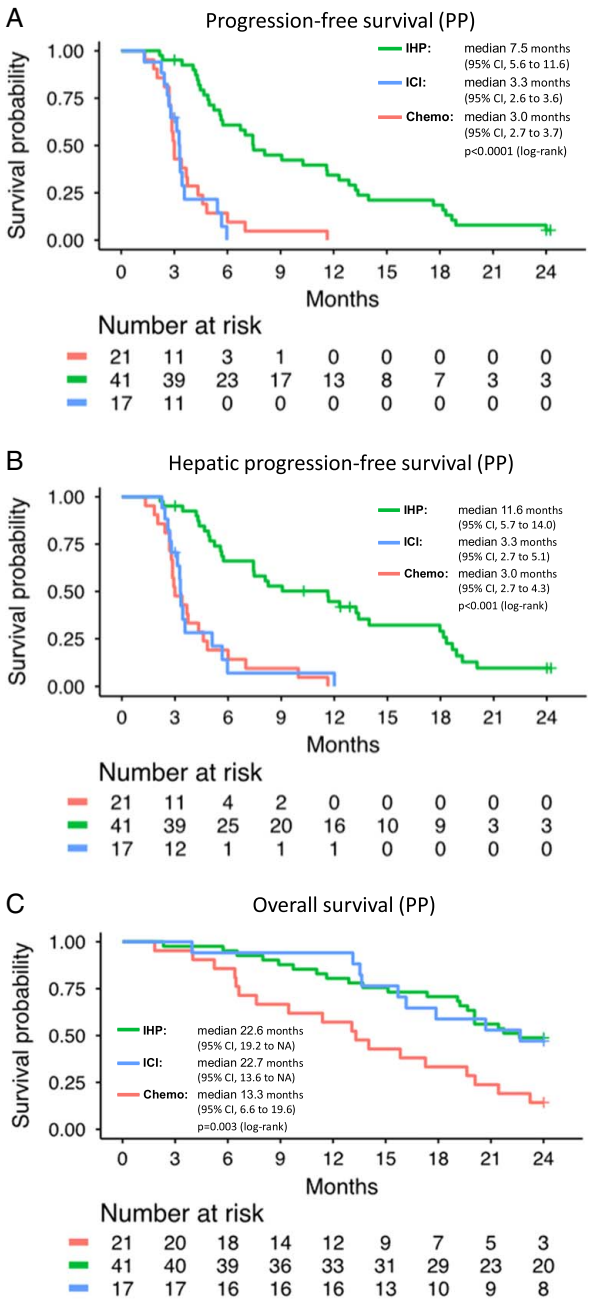


**FIGURE 3.** Kaplan-Meier estimates of progression-free survival (A), hepatic progression-free survival (B), and overall survival (C) for patients receiving isolated hepatic perfusion (IHP) compared to patients receiving immune checkpoint inhibitors or chemotherapy in the control group (per-protocol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

3.0 months (95% CI, 2.7–4.3) for chemotherapy, 3.3 months (95% CI, 2.7–5.1) for ICIs compared with 11.6 months (95% CI, 5.7–14.0) for IHP ($P < 0.0001$) (Fig. 3B). Both IHP (22.6 months; 95% CI, 19.2–NR) and ICI (22.7 months; 95% CI, 13.6–NR) had a significantly longer median OS compared with patients receiving chemotherapy (13.3 months; 95% CI, 6.6–19.6, $P = 0.003$) (Fig. 3C).

## Safety

During first-line treatment, SAEs were reported in 8 (19.5%) patients in the IHP group and 3 (6.5%) in the control group (details have been published previously[12]). 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), $P = 0.002$) (Fig. 4A). This difference was also significant when adjusting for baseline VAS scores with a mean change from baseline at 6 months of −0.4 versus −14.1 ($P = 0.02$) and at 12 months 2.1 versus −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, $P = 0.005$) (Fig. 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 versus −0.10 ($P = 0.36$) and at 12 months −0.02 versus −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 2 groups (Fig. 4C). HRQOL data are summarized in Supplemental 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 predefined 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 PP 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 PP analysis results.

Several phase II trials have reported ORRs ranging between 10% and 18% in patients with metastatic uveal melanoma treated with ipilimumab and nivolumab.[3,4,13] Consistent with these reports, 1 of 7 patients in the control arm of the current study who 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.

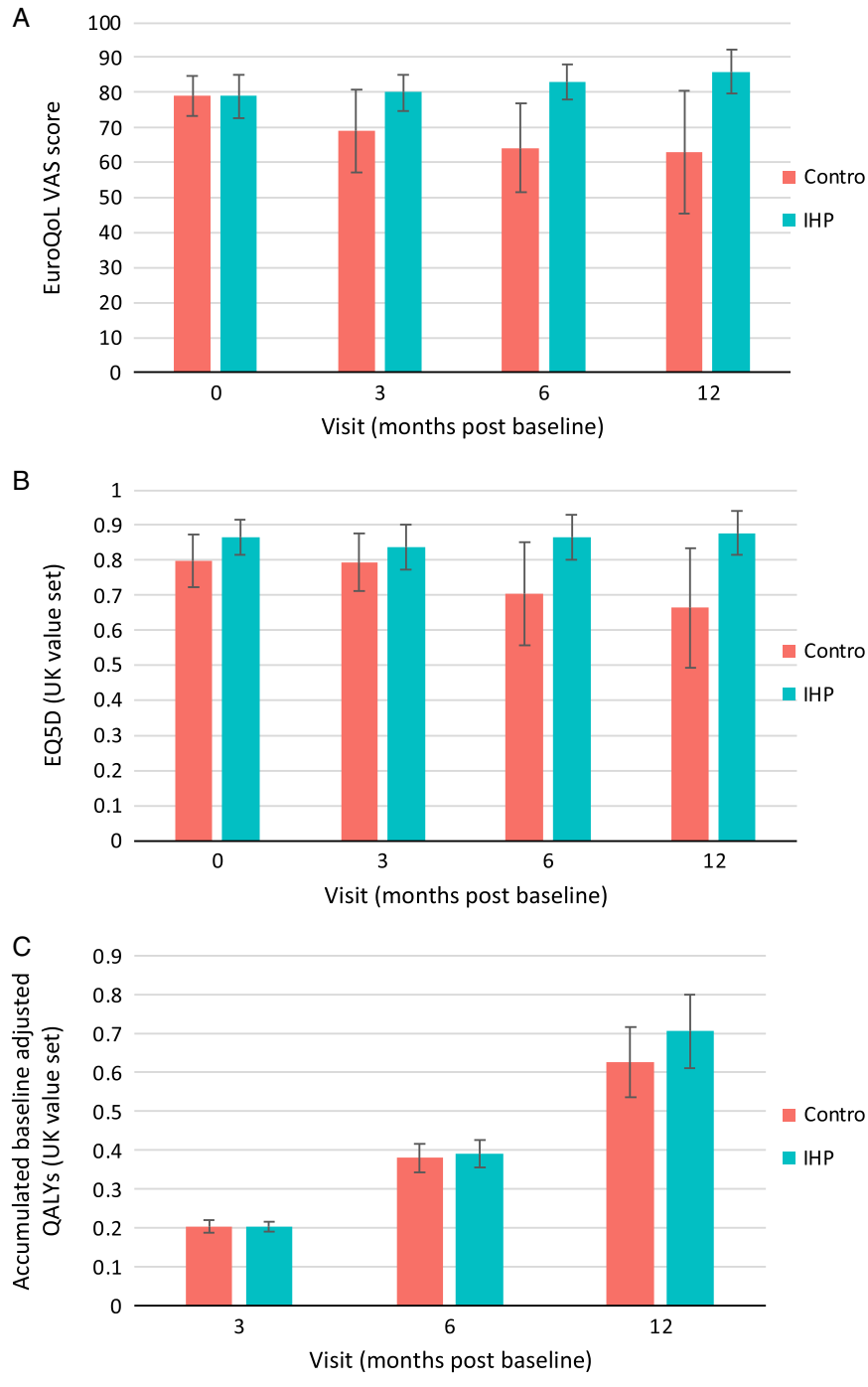


**FIGURE 4.** Patient-reported health status measured using the EQ-5D-3L questionnaire comparing patients receiving isolated hepatic perfusion (IHP) compared to the control group over 12 months. (A) EuroQoL VAS score (B) EQ5D using the UK value set and (C) accumulated QALYs using the UK value set adjusted for baseline levels.

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 constitutes a minimally important difference in VAS scores for patients with cancer.[14] 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 crossover 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 months[5] 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 inhibitor.[15]

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 liver.[16–18] 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 disease.[19] 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 PHP,[20] 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 IHP.[21] 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 7 patients, which identified a safe dose of ipilimumab 1 mg/kg and nivolumab 3 mg/kg (ie, ipi/nivo). Patients received 4 cycles of ipi/nivo every 3 weeks, and then 2 cycles of PHP 6 weeks apart. In a first report including 7 patients, the results showed an ORR of 85.7% (5/7 patients), including 1 patient with a complete response. The combination therapy did not lead to unexpected or more SAEs 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 endpoint.[22] 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 (1 cycle of ipi/nivo, followed by IHP, and then 3 additional cycles of ipi/nivo) or the adjuvant approach (IHP followed by 4 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 1 cycle of ipi/nivo. The adjuvant approach had fewer immune-related adverse events than the neoadjuvant approach (CTCAE grade 3; 33% vs. 89%) and also had a superior ORR (63% vs. 29%).[23]

In conclusion, the SCANDIUM randomized controlled trial showed that a one-time treatment with IHP results in statistically superior antitumor responses and PFS compared to the investigator's choice of BAC, 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.

## ACKNOWLEDGMENTS

*Statistical analysis was performed by John Pavia at Statistikkonsulterna Väst AB, and the health status statistical analysis was performed by Anders Gustavsson at Quantify. The authors are grateful for the editing support provided by Nesrin Vurgun, PhD, at the Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg. The authors sincerely thank the patients and their families participating in this trial. The authors' thoughts are with you when they present these data; they have met you all in person, they have shared your tears, and they will continue to work for a better future. The authors also acknowledge everyone who has been involved and supported this trial: research nurses, oncologists, surgeons, radiologists, and statisticians, among others.*

## REFERENCES

1. Diener-West M, Earle JD, Fine SL, et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma, III: initial mortality findings. COMS Report No. 18. *Arch Ophthalmol*. 2001;119:969–982.
2. Rantala ES, Kivela TT, Hernberg MM. Impact of staging on survival outcomes: a nationwide real-world cohort study of metastatic uveal melanoma. *Melanoma Res*. 2021;31:224–231.
3. Pelster MS, Gruschkus SK, Bassett R, et al. Nivolumab and ipilimumab in metastatic uveal melanoma: results from a single-arm phase II study. *J Clin Oncol*. 2021;39:599–607.
4. Piulats JM, Espinosa E, de la Cruz Merino L, et al. Nivolumab plus ipilimumab for treatment-naive metastatic uveal melanoma: an open-label, multicenter, phase II trial by the Spanish Multidisciplinary Melanoma Group (GEM-1402). *J Clin Oncol*. 2021;39:586–598.
5. Nathan P, Hassel JC, Rutkowski P, et al. Overall survival benefit with tebentafusp in metastatic uveal melanoma. *N Engl J Med*. 2021;385:1196–1206.
6. Ausman RK, Aust JB. Isolated perfusion of the liver with HN2. *Surg Forum*. 1960;10:77–79.
7. Olofsson Bagge R, Nelson A, Shafazand A, et al. Isolated hepatic perfusion with melphalan for patients with isolated uveal melanoma liver metastases: a multicenter, randomized, open-label, phase III trial (the SCANDIUM trial). *J Clin Oncol*. 2023;41:3042–3050.
8. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228–247.
9. Brooks R. EuroQol: the current state of play. *Health Pol*. 1996;37:53–72.
10. Dolan P. Modeling valuations for EuroQol health states. *Med Care*. 1997;35:1095–108,.
11. Burstrom K, Sun S, Gerdtham UG, et al. Swedish experience-based value sets for EQ-5D health states. *Qual Life Res*. 2014;23:431–42.
12. Olofsson Bagge R, Nelson A, Shafazand A, et al. Isolated hepatic perfusion as a treatment for uveal melanoma liver metastases, first results from a phase III randomized controlled multicenter trial (the SCANDIUM trial). *J Clin Oncol*. 2022;40:LBA9509.
13. Heppt MV, Amaral T, Kahler KC, et al. Combined immune checkpoint blockade for metastatic uveal melanoma: a retrospective, multi-center study. *J Immunother Cancer*. 2019;7:299.
14. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes*. 2007;5:70.

15. Khoja L, Atenafu EG, Suciu S, et al. Meta-analysis in metastatic uveal melanoma to determine progression free and overall survival benchmarks: an international rare cancers initiative (IRCI) ocular melanoma study. *Ann Oncol*. 2019;30:1370–1380.
16. Ku Y, Saitoh M, Nishiyama H, et al. [Extracorporeal adriamycin-removal following hepatic artery infusion: use of direct hemoperfusion combined with veno-venous bypass]. *Nihon Geka Gakkai Zasshi*. 1989;90:1758–1764.
17. Curley SA, Newman RA, Dougherty TB, et al. Complete hepatic venous isolation and extracorporeal chemofiltration as treatment for human hepatocellular carcinoma: a phase I study. *Ann Surg Oncol*. 1994;1:389–99.
18. Beheshti MV, Denny DF Jr, Glickman MG, et al. Percutaneous isolated liver perfusion for treatment of hepatic malignancy: preliminary report. *J Vasc Interv Radiol*. 1992;3:453–458.
19. Zager JS, Orloff MM, Ferrucci PF, et al. FOCUS phase 3 trial results: percutaneous hepatic perfusion (PHP) with melphalan for patients with ocular melanoma liver metastases (PHP-OCM-301/301A). *J Clin Oncol*. 2022;40:9510–9510.
20. Bethlehem MS, Katsarelias D, Olofsson Bagge R. Meta-analysis of isolated hepatic perfusion and percutaneous hepatic perfusion as a treatment for uveal melanoma liver metastases. *Cancers (Basel)*. 2021; 13:4726.
21. Johansson J, Siarov J, Kiffin R, et al. Presence of tumor-infiltrating CD8 (+) T cells and macrophages correlates to longer overall survival in patients undergoing isolated hepatic perfusion for uveal melanoma liver metastasis. *Oncoimmunology*. 2020;9:1854519.
22. Tong TML, Burgmans MC, Speetjens FM, et al. Combining melphalan percutaneous hepatic perfusion with ipilimumab plus nivolumab in advanced uveal melanoma: first safety and efficacy data from the phase Ib part of the Chopin trial. *Cardiovasc Intervent Radiol*. 2023;46:350–359.
23. Nelson A, Shafazand A, Cahlin C, et al. A phase I, randomized, controlled, multicentre trial of isolated hepatic perfusion in combination with ipilimumab and nivolumab in patients with uveal melanoma metastases (the SCANDIUM 2 trial). *J Clin Oncol*. 2023;41:9533.

 