Clinical trial results:
The Scandinavian Randomized Controlled Trial of Isolated Hepatic Perfusion for Uveal Melanoma Liver Metastases

Summary

EudraCT number	2013-000564-29
Trial protocol	SE
Global end of trial date	11 March 2023

Results information

Result version number	v1 (current)
This version publication date	28 March 2024
First version publication date	28 March 2024
Summary attachment (see zip file)	Study protocol (https:www.ncbi.nlm.nih.gov:pmc:articles:PMC4138407:pdf:13 Results response (Isolated Hepatic Perfusion With Melphalan for Patients With Isolated Uveal Melanoma Liver Metastases: A Multicenter, Randomized, Open-Label, Phase III Trial (the SCANDIUM Trial) | Journal of Clinical Oncology.pdf) Final results SCANDIUM (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 Annals of Surgery 2024-02.pdf)

Trial information

Trial identification

Sponsor protocol code	SUGBG-013001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01785316
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Transplant Institute, Sahlgrenska University Hospital
Sponsor organisation address	Bruna straket 5, Gothenburg, Sweden, 413 45
Public contact	Transplant institute, Sahlgrenska University Hospital, per.lindner@surgery.gu.se
Scientific contact	Transplant institute, Sahlgrenska University Hospital, 46 705548400, per.lindner@surgery.gu.se

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 January 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 March 2023
Global end of trial reached?	Yes
Global end of trial date	11 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate if IHP increases the Overall survival compared to BAC.

Protection of trial subjects:

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 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.

Background therapy:

Isolated hepatic perfusion (IHP) with melphalan is a regional treatment where the liver is completely isolated from the systemic circulation, to allow hepatic perfusion with high concentrations of chemotherapy, with minimal systemic exposure. IHP has been evaluated in several studies, mainly for liver metastases derived from colorectal cancer, melanoma, neuroendocrine tumours and primary hepatic malignancies. A retrospective study comparing patients with uveal melanoma metastases treated with IHP with the longest surviving patients in Sweden during the same time period showed a 14-month increase in survival (26 vs. 12 months) in the IHP group.

Evidence for comparator:

Among patients with liver metastases from ocular melanoma, the median survival is approximately 10-12 months and only few patients survive more than five years. These disappointing outcomes reflect generally poor responses to systemic chemotherapy, which shows minimal efficacy and delivers no detectable survival benefit.

In contrast to cutaneous melanoma, immune checkpoint inhibition (ICI) has been of only limited benefit in uveal melanoma patients, with combined ipilimumab and nivolumab showing an overall response rate of 10-18% and an uncertain impact on survival.

As no therapy currently is established for metastasized ocular melanoma , best alternative care (BAC) was chosen as the comparator.

Actual start date of recruitment	01 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 93
Worldwide total number of subjects	93
EEA total number of subjects	93

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	46
From 65 to 84 years	47
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with histologically or cytologically confirmed liver metastases from uveal melanoma were recruited to the study if they fulfilled the inclusion criteria. Recruitment was performed via the oncology clinics at the swedish university hospitals.

Pre-assignment

Screening details:

From July 2013 to March 2021, 147 patients were screened, and 93 patients were enrolled at six sites.

Pre-assignment period milestones

Number of subjects started	93
Number of subjects completed	93

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Study was by its nature not blinded for either patient or investigator.

Arms

Are arms mutually exclusive?	Yes
Arm title	Isolated Hepatic Perfusion (IHP)

Arm description:

Isolated Hepatic Perfusion means that the liver blood circulation is isolated from the rest of the body. Perfusion is performed with a target flow rate of 500-1200 ml/min with a target liver temperature of 40°C. When the perfusion circuit is established, melphalan at a dose of 1 mg/kg body weight is added to the perfusion system divided into two doses. Perfusion is continued for 60 minutes, after which the perfusion is discontinued and the liver irrigated and the normal blood flow is re-established.

Arm type	Experimental
Investigational medicinal product name	melphalan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Other use

Dosage and administration details:

1 mg/kg was injected into the liver perfusion circuit, divided in 2 portions given with a 30 minutes interval.

Arm title	Control

Arm description:

Patients randomized to the control group received the investigator’s choice of treatment according to the discretion of the treating physician at each study site. All available treatments including surgery and other experimental treatments were accepted; however, no crossover to IHP was allowed.

Arm type	Best alternative care according to patient's physi

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Isolated Hepatic Perfusion (IHP)	Control
Started	46	47
Completed	43	44
Not completed	3	3
Consent withdrawn by subject	-	2
Protocol deviation	3	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	93	93	
Age categorical			
Adults			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	46	46	
From 65-84 years	47	47	
85 years and over	0	0	
Gender categorical			
Male/female			
Units: Subjects			
Female	42	42	
Male	51	51	

Subject analysis sets

Subject analysis set title	Overall survival at 24 months
Subject analysis set type	Intention-to-treat

Subject analysis set description:

43 patients allocated to IHP, 44 patients allocated to control
Additionally 3 patients were randomized to IHP-arm but excluded due to to much tuner burden or systemic metastases. In the control group 2 patients were excluded as they withdrew consent and 1 patient did not have verified metastases-

Reporting group values	Overall survival at 24 months		
Number of subjects	87		
Age categorical			
Adults			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		

Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	41		
From 65-84 years	46		
85 years and over	0		
Gender categorical			
Male/female			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Isolated Hepatic Perfusion (IHP)

Reporting group description:

Isolated Hepatic Perfusion means that the liver blood circulation is isolated from the rest of the body. Perfusion is performed with a target flow rate of 500-1200 ml/min with a target liver temperature of 40°C. When the perfusion circuit is established, melphalan at a dose of 1 mg/kg body weight is added to the perfusion system divided into two doses. Perfusion is continued for 60 minutes, after which the perfusion is discontinued and the liver irrigated and the normal blood flow is re-established.

Reporting group title	Control

Reporting group description:

Patients randomized to the control group received the investigator’s choice of treatment according to the discretion of the treating physician at each study site. All available treatments including surgery and other experimental treatments were accepted; however, no crossover to IHP was allowed.

Subject analysis set title	Overall survival at 24 months
Subject analysis set type	Intention-to-treat

Subject analysis set description:

43 patients allocated to IHP, 44 patients allocated to control
Additionally 3 patients were randomized to IHP-arm but excluded due to to much tuner burden or systemic metastases. In the control group 2 patients were excluded as they withdrew consent and 1 patient did not have verified metastases-

Primary: Overall survival at 24 months

End point title	Overall survival at 24 months

End point description:

Subjects alive 24 months after randomization

End point type	Primary

End point timeframe:

24 months after randomization

End point values	Isolated Hepatic Perfusion (IHP)	Control	Overall survival at 24 months	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	43	44	87	
Units: Alive				
Alive	20	13	33	
Dead	23	31	54	

Statistical analyses

Statistical analysis title	Primary endpoint analysis ITT

Statistical analysis description:

Two-sided Fisher's exact test

Comparison groups	Isolated Hepatic Perfusion (IHP) v Control

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12 [1]
Method	Fisher exact

Notes:

[1] - There was no significant difference between the groups.

Secondary: Overall response rate

End point title	Overall response rate

End point description:

ORR was defined as the proportion of patients who had a partial or complete response to therapy. ORR was defined as the percentage of patients with a best overall response of complete response (CR) or partial response (PR) according to RECIST. Efficacy was assessed in the intention-to-treat population, with all patients included in the treatment group to which they were randomly assigned.

End point type	Secondary

End point timeframe:

Radiological response within 24 months

End point values	Isolated Hepatic Perfusion (IHP)	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43[2]	44[3]		
Units: Radiological response				
Overall response (CR or PR)	17	2		
No response (SD or PD)	26	42		

Notes:

[2] - 3 excluded after randomization due to inappropriate enrollment

[3] - 2 withdrawn due to inappropriate enrollment, 1 due to withdrawn consent

Statistical analyses

Statistical analysis title	Comparison of overall response rate

Statistical analysis description:

Fisher’s exact test was used to compare ORR

Comparison groups	Isolated Hepatic Perfusion (IHP) v Control
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Fisher exact

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Serious adverse events were collected during first-line therapy during the whole study period. Adverse events were not collected.

Adverse event reporting additional description:

SAEs occurring after secondary line treatment were not reported.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTC for AE
Dictionary version	4.0

Reporting groups

Reporting group title	Isolated hepatic perfusion(IHP)

Reporting group description:

Experimental group

Reporting group title	Control

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: In this study we collected all Serious Adverse Events were collected, but Adverse Events were not collected.

Serious adverse events	Isolated hepatic perfusion(IHP)	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 41 (19.51%)	3 / 46 (6.52%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Vascular disorders			
Arterial repair			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver artery dissection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nervous system disorders			
Headache			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
thromboembolic event			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver artery thrombosis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic infection			

subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Wound infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypophysitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Wound dehiscence			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			

subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Isolated hepatic perfusion(IHP)	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 41 (0.00%)	0 / 46 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/36940407

http://www.ncbi.nlm.nih.gov/pubmed/25106493

http://www.ncbi.nlm.nih.gov/pubmed/38420778