National Institute for Health and Care Excellence

IP 1062/2 / Melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic liver cancer

IPAC date: 8th October 2020 – First round of public consultation

	There were 2 consultations for this guidance. The first ended in July 2020 and the second ran from 19 November 2020 to 17 December 2020.			
	Consultation 1			
Com. no.	**Consultee name and organisation**	**Sec. no.**	**Comments**	**Response** Please respond to all comments
1	Consultee 1 NHS Professional	**General**	This procedure offers hope to many cancer sufferers and a life line to extend their lives a little bit longer. my friend who has had this procedure had a good quality of life while on the treatment and never felt really unwell and continued to work as a radiographer right up to almost the end of her life as it was a job she loved and gave her purpose the beauty of this treatment is the patient has little or no side effects which helps them feel positive about their illness	Thank you for your comment. The committee very much welcomes hearing from patients or friends of patients who have undergone this procedure and considered your experience and views in their deliberations.
2	Consultee 1 NHS Professional	**General**	As a radiographer taking part in delcath procedures i see the patients 4 times over their treatments and it is a privilege to take part in such a procedure that might help them	Thank you for your comment.

3	Consultee 2 NHS Professional	**3.1**	Much of the evidence that has been considered for chemosaturation is historic both in terms of efficacy and safety.	Thank you for your comment. The committee added a new comment in section 3.6: ‘’*The technology has changed over time, and the newest filter may be associated with less haematological toxicity*.’’
4	Consultee 2 NHS Professional	**Title and Section 1**	There are two facets that I would like to draw to the panel's attention: 1. The evidence for efficacy is solely to be considered for metastatic uveal melanoma. The title makes reference to primary and metastatic cancer in general. This is incorrect. I would request the panel consider approving treatment only for 'metastases for uveal melanoma that is not surgically resectable'. There is no other suitable treatment for this very small group of patients.	Thank you for your comment. The committee have changed their recommendations for metastatic uveal melanoma to special arrangements. Section 1.1 now reads: 1.1 Evidence on the safety of melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein

				isolation for cancer or metastases in the liver shows there are serious but well-recognised complications: • For patients with metastases in the liver from ocular melanoma, there is some evidence of short-term tumour response. For these patients, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. Find out what special arrangements mean on the NICE interventional procedures guidance page. • For patients with primary liver cancer or metastases in the liver that are not from ocular melanoma, evidence of efficacy is inadequate in

				quality and quantity. For these patients, this procedure should only be used in the context of research. Find out what only in research means on the NICE interventional procedures guidance page.
5	Consultee 2 NHS Professional	**1.1 and 1.2**	2. I have personally either supervised or carried out over 260 treatments in over 95 patients worldwide, 89 of which have been treated in Southampton. This compares to a total European experience of around 1050. The side effects or complications that have been reported from previous publications are now uncommon, in part because of the generation 2 filter, but also because the technique has since been radically modified. Any side effects that have occurred have been easy to manage and been well tolerated by patients. The risks are mitigated by the procedure being restricted to experienced sites only (my suggestion is > 6 per year) and a robust training programme for new sites or personnel conducting the treatment.	Thank you for your comment and for sharing your clinical experience with this procedure The committee added a new comment in section 3.6: ‘’*The technology has changed over time, and the newest filter may be associated with less haematological toxicity*.’’

				Section 1.4 of the guidance also says: ‘’ *The procedure should only be done in specialist centres by a multidisciplinary team that includes an interventional radiologist, an anaesthetist and a clinical perfusion scientist trained and experienced in the procedure*. ‘’
6	Consultee 2 NHS Professional	**3.1**	The two major complications that I have encountered have been non-treatment related and were unpredictable. They include a cardiac arrest due to protamine allergy and a patient with heparin induced thrombocytopenia causing post-op haemorrhage. Both patients made a full recovery.	Thank you for your comment and for sharing your clinical experience with this procedure.
7	Consultee 2 NHS Professional	**2.4**	Our current process involves a four hour procedure followed by a 2 hour observation in recovery. From recovery they are immediately transferred to a general ward and are ready for discharge the following day. In other less experienced centres, patients are still managed in ICU as a precaution.	Thank you for your comment and for sharing your clinical experience with this procedure.
8	Consultee 2 NHS Professional	**1.1**	Therefore, in summary, I would request the panel to consider approval of this treatment but restricted to experienced centres with the sole indication of metastatic uveal melanoma.	Thank you for your comment.

				The committee have changed their recommendations for metastatic uveal melanoma to special arrangements. Section 1.1 now reads: 1.1 Evidence on the safety of melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for cancer or metastases in the liver shows there are serious but well-recognised complications: • For patients with metastases in the liver from ocular melanoma, there is some evidence of short-term tumour response. For these patients, this procedure should only be used with special arrangements for

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9	Consultee 3 NHS Professional	**1.1**	While this document is an excellent effort to summarise the available information on Melphalan Chemosaturation in general, it is clear that the quality of evidence for indications other uveal melanoma is lacking.	Thank you for your comment.

			When the data for uveal melanoma patients in particular is taken into account the picture is clearer, with disease control achieved for more than 6 months in >50% of cases in studies focusing on this patient population. Notably uveal melanoma stands apart from other cancer types - including cutaneous melanoma - as having a unique propensity for liver spread : in almost 50% of cases it is the solitary site of metastatic disease in such patients and is the proximal cause of death in the majority of involved patients. Effective systemic treatment options for uveal melanoma are sorely lacking - even combination immunotherapy offers response rates below 20% and single agent anti PD-1 and anti CTLA-4 below 10% unlike cutaneous melanoma, and cytotoxic chemotherapy offers no survival benefit. Moreover long term outcomes in this patient population are poor – historical data point to median survival in the 6 month range which is consistent to the outcomes seen in the quoted studies for uveal melanoma patients who fail to respond to chemosaturation.. In view of this I feel that the value of melaphalan chemosaturation for uveal melanoma patients – and in particular those with liver predominant disease - needs to be evaluated separately from other indications where its utility may be diluted by the different natural history of disease and availability of alternative treatment modalities.	The committee have changed their recommendations for metastatic uveal melanoma to special arrangements. Section 1.1 now reads: 1.1 Evidence on the safety of melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for cancer or metastases in the liver shows there are serious but well-recognised complications: • For patients with metastases in the liver from ocular melanoma, there is some evidence of short-term tumour response. For these patients, this procedure should only be used with special arrangements for

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10	Consultee 4 Carer	**3.1**	Since the publication of this document results of a further trial have been published 'Chemosaturation with percutaneous hepatic perfusion is effective in patients with ocular melanoma and cholangiocarcinoma' Schonfeld et al. J.Cancer Research and Clinical Oncology (20 June 2020)	Thank you for your comment and for pointing out a new

			The trial included 60 patients, 30 of whom had metastatic ocular melanoma (OM).Overall Responce Rate (ORR) for the OM patients was 42.3% and for cholangiocarcinoma(CCA) 30.8% during 27 months follow-up. Other livers tumours fared less well. Median overall survival was 12 months for OM patients, 8 months for CCA. The treatment can be repeated and has recently started to be used in combination with tumour resection This study is an extension of the authors previous trial with an enlarged cohort and longer treatment and follow-up period (KIrstein et all 2017, See No 3 of your refs). They conclude that patients with OM represent particularly eligible candidated for Chemostat percutaneous hepatic perfusion (CS-PHP) as these patients develop exclusively hepatic metastases which are highly sensitive to melphalan.Moreover there are no established alternative therapies for patients with metastatic OM.Patients with CCA also responded well . Haematological toxicities were significant but transient and manageable in this study, which is the largest real-life study on CS-PHP in patients with liver tumours. Since 2018 this procedure has been included in the German Guidelines Programme for Oncology in the S3 Guidelines, with Evidence level 1B (indicating the second highest level of evidence) for liver metastases from melanomas. (Source Delcath Systems Inc)	study and German guidelines. The Schönfeld et al. (2020) study has been retrieved by our post-consultation update literature search and has been included in the key evidence table in the overview. This is a case studies of 60 patients with a median follow-up of 27 months. The guidelines from the German Guidelines Programme for Oncology are not all translated in English and the guidelines referring to this procedure were not found in English language so they were not included in the overview.
11	Consultee 5 Private sector professional	**General**	I have been coordinator chemosaturations treatments, the chemosat team and patient pathway for the last 4 years. The treatment has proved very successful and despite it not being a cure patients have a good extended quality of life. Some patients go on to have a considerably longer period	Thank you for your comment and for sharing your

			between treatments and also an extended period off treatment. They are able to continue with the things they enjoy without the horrible side effects of conventional chemotherapy. It would appear the sooner the patients are referred and treated the better their long-term result.	experience with this procedure.
12	Consultee 6 NHS Professional	**2.1 and 2.2**	Comment on 2.1 (the condition) and 2.2 (current treatments). PHP has the strongest evidence in the treatment of uveal melanoma. While it has been assessed in a range of other cancers with liver metastases, there is considerably less evidence and in my view PHP should only be considered for liver metastatic uveal melanoma (with other conditions remaining research only). Whereas the other conditions listed have other standards options available, there remains no standard of care for metastatic uveal melanoma. Checkpoint inhibitors are routinely used but have reported response rates of 3-8% and ~10-15% for single agent and combination therapy; responses are also not durable. Only small proportion (10-15%) of patients have resectable mets (point 3.6), and even then recurrence is inevitable. In patients on regular surveillance scanning, overall survival from diagnosis of metastases is reported to be in the region of 12 months. This is significantly lower in patients presenting with symptoms. While there are other liver directed therapies for metastatic uveal melanoma, these all have significantly less evidence.	Thank you for your comment. The committee have changed their recommendations for metastatic uveal melanoma to special arrangements. Section 1.1 now reads: 1.1 Evidence on the safety of melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for cancer or metastases in the liver shows there are serious but well-recognised complications: • For patients with metastases in the liver from ocular melanoma, there is some evidence of

				short-term tumour response. For these patients, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. Find out what special arrangements mean on the NICE interventional procedures guidance page. • For patients with primary liver cancer or metastases in the liver that are not from ocular melanoma, evidence of efficacy is inadequate in quality and quantity. For these patients, this procedure should only be used in the context of research. Find out what only in research means on the NICE interventional

				procedures guidance page. Section 2.2 currently states**:** *‘’Treatment for primary or metastatic cancer in the liver depends on the location and stage of the cancer and how much liver function is preserved. Treatment options include surgical resection, thermal ablation, systemic chemotherapy, transarterial chemoembolisation , isolated hepatic perfusion and selective internal radiation therapy. In patients with primary liver cancer, surgical removal with curative intent and liver transplantation may be possible. For most patients with liver metastases,*

				treatment with curative intent is not possible.''
13	Consultee 6 NHS Professional	**1.1**	1.1- draft recommendations (toxicity) The safety of the current generation of filter is excellent, and there have been no fatalities with the current version (which has been in use for many years now). There are significant immediate effects of treatment which require mitigation through treatment in the appropriate setting as detailed in point 1.2. However following the treatment and immediate aftercare, patients have relatively limited toxicity. This is in keeping with the agent, melphalan's, mechanism of action and is in fact lower than with most systemic chemotherapy. Management of these side effects is straightforward and uses standard protocols that are widely available.	Thank you for your comment. The committee have changed their recommendations for metastatic uveal melanoma to special arrangements. Section 1.1 now reads: 1.1 *Evidence on the safety of melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for cancer or metastases in the liver shows there are serious but well-recognised complications:* • *For patients with metastases in the liver from ocular melanoma, there is*

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				procedures guidance page.'' The committee also added a new comment in section 3.6: ''*The technology has changed over time, and the newest filter may be associated with less haematological toxicity*.''
14	Consultee 6 NHS Professional	**1.1 and 3.2**	point 1.1 (efficacy) and 3.2. It is true that there is only one randomised trial published. This showed statistically significant improvement in PFS but not OS, partly no doubt due to the design which allowed cross over. As stated there have been a number of case series, and there is an ongoing clinical trial (which will be predominantly single arm). In the largest clinical series in uveal melanoma, Karydis et al reported an overall response rate of ~50%; this is supported by other case series. This response rate is in stark contrast to that achieved with other therapies in uveal melanoma (which are mostly less than 10%). Median overall survival was ~15 months which also compares favourably to other studies. See for example the PUMMA meta-analysis (**https://doi.org/10.1093/annonc/mdz176**), where median OS was 10.2 months. While there are obviously confounding factors such as rigorous patient selection, the high response rate along with an overall PFS of 8.1 months suggests a significant clinical benefit for patients with this rare disease for which there are no other licensed effective agents.	Thank you for your comment. The Karydis et al. (2018) study is included in the key evidence table. The PUMMA study (Khoja et al. 2019) is a meta-analysis carried out to determine progression-free and overall survival benchmarks in metastatic uveal melanoma.

				The committee have changed their recommendations for metastatic uveal melanoma to special arrangements. Section 1.1 now reads: 1.1 *Evidence on the safety of melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for cancer or metastases in the liver shows there are serious but well-recognised complications:* • *For patients with metastases in the liver from ocular melanoma, there is some evidence of short-term tumour response. For these patients, this procedure should only be used with special arrangements for*

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15	Consultees 7 and 8 Professional expert	**1.1**	Dr [redacted] & Dr [redacted] [redacted]	Thank you for your comment and for sharing your clinical

	NHS Professional		[redacted] [redacted] [redacted] [redacted] NICE Interventional Procedures Advisory Committee (IPAC) To whom it may concern, Re: Melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer in the liver IP1062/2 We are grateful to the IPAC committee for evaluating this procedure and wanted to give some insight into our personal experience, including the evolution of the technique over the last 9 years. As an interventional oncology centre with a specific interest in ocular melanoma and liver directed cancer therapies, we have been involved in development of the procedure in the U.K from the outset. We currently have the largest worldwide experience for treating patients with chemosaturation and have a dedicated and engaged multi-modality team focussed on patient safety and continual refinement of the technique.	experience with this procedure. The committee have changed their recommendations for metastatic uveal melanoma to special arrangements. Section 1.1 now reads: 1.1 *Evidence on the safety of melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for cancer or metastases in the liver shows there are serious but well-recognised complications:* • *For patients with metastases in the liver from ocular melanoma, there is some evidence of short-term tumour response. For these patients, this procedure should*

			Our initial experience with our first cohort of patients in 2012-2014 was of a procedure that whilst safe, resulted in overnight ITU admissions and a median 5 day inpatient stay. Procedure length had a median time of 3.5hours. Patients were consented for the usual complications as well as a mortality rate of 10%. Refinement of the procedure has included changes to anaesthetic /perfusion protocols and interventional radiology technique, which have led to significant safety and efficiency improvements. Currently our experience is of patients recovering in a normal surgical ward with no requirement of intensive/high care (Level 1 or 2 care) post a 2 hour procedure. Patients are now almost always discharged on day 2 and return to baseline activities of daily living or work rapidly. Follow up has been reduced and now simply comprises of includes weekly FBC test for 3 weeks. Given our experience, we now quote patients a procedural mortality of 0.5%. The [redacted] experience to date encompasses 260 chemosaturation treatments in 90 different patients, all with biopsy confirmed ocular melanoma. We have had 0/260 procedural/ inpatient mortality and have 0/260 30 day mortality. We have both been involved in proctoring other sites in the U.K and Europe. We feel this technique would now be applicable and reproducible in other interventional oncology centres with experience of liver directed treatments provided they have on site perfusion and anaesthetic expertise. Personally, as two operators we provide a wide range of liver directed interventional oncology procedures including SIRT, TACE and TAE. We both have more confidence in the procedure safety profile and the speed of recovery of this technique compared to other liver directed therapies and see none of the post embolic symptoms and side effects which impact on recovery from other liver directed interventions. We both feel the safety profile of the current technique is not reflected in the current assessment which highlights procedure related mortality from historic cohorts (we are unaware of any procedure or 30 day mortality in the last 5 years in Europe) and the haematological effects, which are easily managed with minimum morbidity in experienced hands (high rates of haematological grade3/4 complications are probably a marker of poor procedural technique as they involve the chemotherapy entering the systemic circulation). We feel the case for the safety of the technique in experienced centres with engaged teams has	*only be used with special arrangements for clinical governance, consent, and audit or research. Find out what special arrangements mean on the NICE interventional procedures guidance page.* • *For patients with primary liver cancer or metastases in the liver that are not from ocular melanoma, evidence of efficacy is inadequate in quality and quantity. For these patients, this procedure should only be used in the context of research. Find out what only in research means on the NICE interventional procedures guidance page*.''

			been made and would hope the current guidance would acknowledge this change. Our team and MDT feel this treatment offers the best prospect of disease control and improved survival for a cohort of patients with ocular melanoma liver metastatic disease – a condition which confounds all other conventional treatment approaches. Yours sincerely, Dr [redacted] Dr [redacted] Consultant Interventional Radiologists [redacted]	
16	Consultee 9 NHS Professional and Patient organisation OcuMel UK	**1.1**	Dear Sir, I wish to express my strong support for chemosaturation (percutaneous hepatic perfusion with melphalan chemotherapy) as a treatment for metastatic ocular melanoma within the liver. I am writing principally in my capacity as [redacted] of the charity OcuMel UK which works to support patients with ocular melanoma and their families. Previously I was a consultant liver surgeon treating patients with primary liver cancers and liver metastases from a range of tumours including ocular melanoma. It was my experience seeing the hopeless plight of patients with metastatic ocular melanoma which led to my involvement with this charity. This is an incredibly rare malignancy in which approximately 50% of patients go on to develop metastatic disease, which is extremely hard to treat and rapidly fatal. The majority of patients who develop metastases do so in the liver, typically without any other organs affected. A tiny proportion (<5%) are suitable for surgery, the majority have a more diffuse pattern of disease which quickly progresses to overwhelm the patient and for which there is no effective systemic treatment. Although expensive immunotherapy treatments used for cutaneous melanoma, such as	Thank you for your comment and for sharing your clinical experience with this procedure. The committee have changed their recommendations for metastatic uveal melanoma to special arrangements. Section 1.1 now reads:

			Pembrolizumab are licenced in this condition, response rates are low (10% or less) for ocular melanoma. I have met more than 20 patients from the UK and Ireland who have had this treatment, either in my role as a surgeon or more commonly through meeting them at the charities patient conferences. There is no question from my experience of talking with these patients and their families that this treatment can be extremely effective, changing the course of this disease within the liver and changing lives. Considering the magnitude of the treatment it is also relatively well tolerated by the majority of patients. Indeed I remember well the first patient treated in the UK, who had a partial response to his treatment and got married on a beach in the Caribbean within three weeks of his first treatment. I have many more stories that I could tell of patients who have been bought quality time by this innovative treatment. The published data of the largest combined case series from Southampton University and Moffat University is compelling. In particular the waterfall plots demonstrating response rates show that over 70% of patients respond to treatment, with a high proportion showing not just stable disease, but partial response and even a small number of complete responses within the liver. This correlates to their survival data. We are now seeing five year survivors following this treatment. This was unheard of for this disease a decade ago and we only see this in patients who have either surgery or chemo saturation. It is highly unusual to ever see randomised controlled trial data for treatments in patients with extremely rare and rapidly lethal diseases such as metastatic ocular melanoma. So it is to be applauded that there is already one RCT published, although it's crossover design was flawed, it was a positive trial for its primary end points of treatment response rates and hepatic progression free survival. There is another ongoing RCT, which is near to being closed, it is my understanding that the best alternative care treatment arm within this trial has been closed to recruitment early because of difficulty recruitment to an arm of the trial which does not offer an effective treatment. Patients were dropping out early and clinicians felt it was becoming ethically and morally unacceptable to recruit to the best alternative care arm when they could see the high response rates in the chemo saturation treatment arm. It is likely to be a year or more before this study reports outcome data. The Southampton experience of this trial suggests that around 50% of patients with ocular melanoma liver metastases are suitable for treatment.	1.1 *Evidence on the safety of melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for cancer or metastases in the liver shows there are serious but well-recognised complications:* • *For patients with metastases in the liver from ocular melanoma, there is some evidence of short-term tumour response. For these patients, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. Find out what special arrangements mean on the NICE interventional procedures guidance page.*

				• *For patients with primary liver cancer or metastases in the liver that are not from ocular melanoma, evidence of efficacy is inadequate in quality and quantity. For these patients, this procedure should only be used in the context of research. Find out what only in research means on the NICE interventional procedures guidance page*.'' The consultee refers to the Karydis et al. (2018) study that is included in the key evidence table in the overview.

				IPAC is pleased to hear that more research is on the way.
17	Consultee 9 NHS Professional and Patient organisation OcuMel UK	**1.1**	More recently my roles within the NHS have been as associate medical director for safety in University Hospital Southampton and currently reviewing mortality as lead medical examiner for Southampton. I am happy to report that there have been no serious adverse safety events or any deaths reported following chemosaturation, despite over 200 treatments here in Southampton. I believe that I have expert knowledge of the management of metastatic ocular melanoma within the liver and outcomes following chemo saturation treatment, both as a professional and as an advocate for patients and families living with this terrible and extremely rare disease. I have no hesitation in saying that this treatment is the single most effective therapy available for this condition and I would strongly recommend that you reconsider your NICE / IPAC review of this therapy and make it acceptable as a treatment specifically for ocular melanoma metastatic to the liver. Yours sincerely, [redacted] [redacted] OcuMel UK (and Lead Medical Examiner for Southampton)	Thank you for your comment and for sharing your clinical experience with this procedure. The committee have changed their recommendations for metastatic uveal melanoma to special arrangements. Section 1.1 now reads: 1.1 *Evidence on the safety of melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for cancer or metastases in the liver shows there are serious but well-recognised complications:* • *For patients with metastases in the liver from ocular*

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				interventional procedures guidance page.''
18	Consultee 10 Patient organisation OcuMel UK	**General**	[redacted] attended as an observer the NICE meeting regarding the Chemosat review with regards to it being used for Uveal Melanoma (UM) metastases that have spread to the liver. OcuMel UK learnt of this review ahead of the review meeting in February and [redacted] attended as an observer where the discussions were strictly directed at Chemosat as a treatment for Uveal Melanoma metastases. We were surprised to learn the draft consultation document includes primary or metastatic cancer in the liver. To our knowledge there is limited data on its efficacy in treating other cancers as most of the data we have seen supports the use in Uveal Melanoma metastasis. The viewpoint shared in this submission is therefore intended to reflect the viewpoints of Ocular Melanoma patients, although we understand there could be benefits for other cancers such as cholangiocarcinoma.	Thank you for your comment. The title of the procedure under review is: IP 1062/2 Melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic liver cancer. The committee have split their main recommendations between metastatic uveal melanoma and other cancers with primary liver cancer or metastases in the liver. Section 1.1 now reads:

				1.1 *Evidence on the safety of melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for cancer or metastases in the liver shows there are serious but well-recognised complications:* • *For patients with metastases in the liver from ocular melanoma, there is some evidence of short-term tumour response. For these patients, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. Find out what special arrangements mean on the NICE interventional procedures guidance page.*

				• *For patients with primary liver cancer or metastases in the liver that are not from ocular melanoma, evidence of efficacy is inadequate in quality and quantity. For these patients, this procedure should only be used in the context of research. Find out what only in research means on the NICE interventional procedures guidance page*.''
19	Consultee 10 Patient organisation OcuMel UK	**1.1**	In response to the draft recommendations within the consultation document, OcuMel UK would like the following comments to be noted: 1.1: the recommendation suggests that there are 'serious but well recognised complications' but these could be historical complications. And we would expect these to have reduced over the years as specialist centres become more experienced. 1:1 connects both primary and metastases in the same context and also we would like to point out that in absence of any other treatment most patients would accept side effects over palliative care and death.	Thank you for your comment. The committee changed their main recommendations for uveal melanoma but decided to keep the wording about safety.

				Section 1.1 now reads: 1.1 *Evidence on the safety of melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for cancer or metastases in the liver shows there are serious but well-recognised complications:* • *For patients with metastases in the liver from ocular melanoma, there is some evidence of short-term tumour response. For these patients, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. Find out what special arrangements mean on the NICE interventional*

				procedures guidance page. • *For patients with primary liver cancer or metastases in the liver that are not from ocular melanoma, evidence of efficacy is inadequate in quality and quantity. For these patients, this procedure should only be used in the context of research. Find out what only in research means on the NICE interventional procedures guidance page*.''
20	Consultee 10 Patient organisation OcuMel UK	**1.1**	1:1 also states that there is some evidence for quality of life being 'inadequate.' We are saddened to hear this could be an influencing factor as patients should not be penalised for their views being unheard (see 3:4). 1:1 states that 'the procedure 'should only be used in the context of research.' To our knowledge, all research of this cancer has concluded with statements such as: CS-PHP is a safe and efficacious treatment modality for liver-dominant metastatic uveal melanoma." A copy of the paper containing this statement can be found here. Another recent paper can be found here. In a disease where patients are dying of liver failure, more research without access would be a tragedy.	Thank you for your comment. Section 1.1 has been changed as follows: 1.1 *Evidence on the safety of melphalan chemosaturation with percutaneous*

				hepatic artery perfusion and hepatic vein isolation for cancer or metastases in the liver shows there are serious but well-recognised complications: • *For patients with metastases in the liver from ocular melanoma, there is some evidence of short-term tumour response. For these patients, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. Find out what special arrangements mean on the NICE interventional procedures guidance page.* • *For patients with primary liver cancer or metastases in the liver that are not from ocular*

				melanoma, evidence of efficacy is inadequate in quality and quantity. For these patients, this procedure should only be used in the context of research. Find out what only in research means on the NICE interventional procedures guidance page.''
				We have now received the patient organisation submission from OcuMel UK and section 3.4 has been changed to:
				'' *NICE received 1 submission from a patient organisation*. ''
				The consultee refers to the study from Artzner et al. (2019) which is included in the key evidence table in the overview. The other recent paper

				the consultee refers to is the Schonfeld et al. (2020) study which has been retrieved by our post-consultation update literature search and has been included in the key evidence table in the overview. This is a case studies of 60 patients with a median follow-up of 27 months.
21	Consultee 10 Patient organisation OcuMel UK	**1.3**	Further research in the form of randomised controlled trials as mentioned in 1:3 must surely put patients lives at risk? There are well documented drawbacks of randomised controlled trials, especially for small populations. Uveal Melanoma is a rare cancer (affecting 7 per million people) and to put them on a best alternative care in the absence of any statistically significant treatment may result in a dangerous situation for the patients. A suggestion for further research (1:3) would allow all suitable patients to be given access to the treatment if their clinicians felt it could be a beneficial treatment and quality of life and efficacy should be documented, so treatment options for patients could also increase outside the UK.	Thank you for your comment. The committee considered you comment but decided not to change section 1.5 of the guidance.
22	Consultee 10 Patient organisation OcuMel UK	**3.4**	3:4 clearly states that patient commentary was sought but none was received. OcuMel UK did not receive an invitation to comment but we would like to share the findings of a survey we had previously conducted: Introduction: The intention of this survey was to enquire how patients felt about Chemosat being a trial only drug and whether it should be authorised by NICE. 30 participants replied to the survey.	Thank you for your comment and for sharing the findings of your survey. We are sorry that you did not receive the email from the Patient Involvement

			Findings: The participants fell into 4 groups: Family members of patients who have received the treatment (10) Family members of patients who have NOT received the treatment (1) Patients who have received the treatment (8) Patients who have NOT received the treatment (11) 20 participants felt that the drug is 'safe' with one family member giving a low safety score (2) and one patient who chose not to take advantage of the trial also giving a score of 4. Including the two less than positive comments the mean average is 8/10 confidence in its overall safety. The remaining 9 patients did not have the treatment and did not give a score and were not counted in the mean average. The same 20 participants felt that the treatment was beneficial insofar as offering improvement to life. One 'family member' participant, although not stating that the treatment had no benefits, it was the side effects that caused them to give such a low score (2). Another patient participant who did not take up the trial felt that the treatment was an 'old approach' offering only 'temporary' benefits whereas there are 'safer and equally effective … treatments that do not rely on chemotherapy …'. Despite such criticisms, both participants felt that the treatment should be authorised by NICE. The other 16 participants gave more positive comments and the mean average score was 8.6 /10 that the treatment was beneficial. The participants were aware that treatments can be measured in clinical trials differently to how a patient or family member would view the success of the treatment. Overall the participants felt that the treatment should be authorised by NICE because as part of a treatment plan it can extend life (and more importantly the quality of life) by years. One participant noted that it gave the patient an extra 3 ½ years of life and the opportunity to 'meet [their] two grandchildren' and gives the chance to 'create memories'. When asked if they thought that NICE should authorised Chemosat, the overwhelming majority	Programme inviting you to send a submission. The committee very much welcomes hearing from patients who have undergone this procedure and considers their experience and views in their deliberations. NICE has now received the patient organisation submission from OcuMel UK and section 3.4 of the guidance has been amended as follows: '' *NICE received 1 submission from a patient organisation.''*

			said ‘absolutely yes’ comments such as ‘definitely yes’ and even those who lower quality of life due to the side effects still said that the treatment should be authorised. One noted: ‘I feel very strongly that this treatment should be available to all patients that could benefit from it.’ Further comments supporting the treatment and suggesting NICE authorise Chemosat are below: Participants described the treatment as having ‘minimal impact after the surgery and [the patient] was able to enjoy every day activities at a time when quality of life was important.’ This particular patient ‘gained more time’ and ‘(m)entally it was good to have a treatment that [the patient] felt would make a difference. Another patient noted that because the side effects were ‘minimal’ they ‘quickly felt well between treatments, so quality of life is excellent.’ The patient continued saying: ‘My scans after treatment 2 showed some reduction and some disappearance in multiple small tumours. So I live in hope.’ Another noted that ‘My original consultant had basically written me off. A year on from this after having 3 treatments I’m feeling fit and well and enjoying a full life with my family.’ For some the tumours reduce. ‘Smaller tumours have disappeared and at last scan largest tumours are less than half size.’ And for some the quality of life remained high: ‘excellent quality of life’; ‘I found I was quite well following the procedure. Physically, it didn’t impact on my life as much as I’d envisaged.’ ‘ ...it can allow me to continue to have a good quality of life’ and it is ‘very tolerable.’ Note. One participant did not answer any of the questions other than they would NOT like to receive the newsletter. Conclusion: With regard to approving Chemosat and the use of Melphalan which has already received the CE mark for safety, the members of OcuMel UK who answered our survey voted overwhelmingly for NICE to approve the drug. The survey scored a mean average of 8 out of 10 for patient confidence in its overall safety and 8.6/10 that the treatment is beneficial. Here it should be noted that, and to use a quote from the MPNE website: ‘only a patient knows what it is like to be a patient’ the survey	

			is about patients speaking on behalf of patients.	
23	Consultee 10 Patient organisation OcuMel UK	**3.1**	However, given that most of the evidence published is around how Chemosat tackles UM metastases on the liver, papers also indicate that there is some effectiveness regarding other secondary cancers spreading to the liver and therefore it could help people with other types of metastasising primary tumours. The issue would then be that the wording, should NICE approve Chemosat for all metastasising cancers, ensure that Chemosat is primarily approved for UM metastases.	Thank you for your comment. The committee have split their main recommendations between metastatic uveal melanoma and other cancers with primary liver cancer or metastases in the liver. Section 1.1 now reads: 1.1 *Evidence on the safety of melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for cancer or metastases in the liver shows there are serious but well-recognised complications:* • *For patients with metastases in*

				the liver from ocular melanoma, there is some evidence of short-term tumour response. For these patients, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. Find out what special arrangements mean on the NICE interventional procedures guidance page. • *For patients with primary liver cancer or metastases in the liver that are not from ocular melanoma, evidence of efficacy is inadequate in quality and quantity. For these patients, this procedure should only be used in the context of research. Find out what only in research means*

				on the NICE interventional procedures guidance page.''
24	Consultee 10 Patient organisation OcuMel UK	**3.6**	In 3:6 it states' the committee was informed the procedure is used for patients with unresectable liver cancer'. We feel the scope of this review needs to be clarified so that uveal melanoma patients are not unduly affected by the lack of evidence in other disease areas.	Thank you for your comment. The committee have changed their recommendations and split these between metastatic uveal melanoma and other cancers with primary liver cancer or metastases in the liver. Please refer to comment 23.
25	Consultee 10 Patient organisation OcuMel UK	**3.8**	In 3:8 it states 'there are other emerging therapies for treating liver cancer and metastasis' We are unaware of any treatments giving as good results as this treatment for uveal melanoma patients. There are other clinical trials but data has not been published and patients need to fulfil inclusion & exclusion criteria to access them.	Thank you for your comment. This section of the guidance was changed after the second consultation.
26	Consultee 10 Patient organisation OcuMel UK	**3.9**	In 3:9 it discusses toxicity of and the removal of melphalan. It should be noted that patients have limited options available to them if the tumours cannot be surgically removed.	Thank you for your comment. This section of the guidance was changed after the

				second consultation.
27	Consultee 10 Patient organisation OcuMel UK	**3.1**	All in all, we have patients who are losing their lives in the UK at the moment who could be treated. We sincerely hope this submission offers you a separate viewpoint to consider and you can implement changes for our patients.	Thank you for your comment. The main recommendations for uveal melanoma have been changed to special arrangements. Please refer to comment 23.
28	Consultee 11 Private Sector Professional	**General**	Since 2015 I have provided general anaesthetic for more than 20 Chemosaturation with PHP. All the patient had metastatic liver disease mostly from ocular melanoma. The procedure was well tolerated in all cases and all patient were extubated at the end of the procedure. At the end of the procedure all patient were haemodynamically stable and only one required a minimal dose of Noradrenaline for less than 24 hours. The post operative course was smooth and side effects were similar to those observed with different chemotherapy regimens	Thank you for your comment and for sharing your clinical experience with this procedure.
29	Consultee 12 Company Medac Pharma	**Title**	I wanted just to raise an issue with you that is causing us some concern regarding the above IPAC review. This is a matter about which I wrote to [redacted] on January 6th 2020. I wrote then: *"I note that this title encompasses a wide range of liver involved diseases. However, Chemosat is a treatment that focuses on liver metastases only. Therefore we would like to propose to narrow the title to better reflect the respective patient population."* [redacted] responded to say: *"As we have existing guidance in this area (IPG488), the process to consider an update to this guidance will take the same title.* *When we come to update the existing guidance the IP committee (IPAC) can consider whether to change the title and or specific indication depending on what is found in the updated literature*	Thank you for your comment. The committee have split their main recommendations between metastatic uveal melanoma

			searches. The searches will cover the same population as per the original guidance, but IPAC can consider the issues you raise below in more detail." My notes and my memory from the IPAC meeting held on the 13th February say that the Committee was left with the understanding that this was a very specific treatment for ocular melanoma (metastases) and these patients had few other options. This is, to our way of thinking, a correct analysis of the situation. I was surprised, therefore, to find that the title had not changed and that the weighting of the consultation document was much broader that we feel is warranted by the evidence or the way that the intervention is currently used. We are not seeking for this intervention to be used in a wider patient population at this point. Would it be possible to ask again that the title of the review is narrowed and to confirm with you that the focus of the Committee is only on this much more restricted use of the intervention? Kind regards [redacted]	and other cancers with primary liver cancer or metastases in the liver. Section 1.1 now reads: 1.1 *Evidence on the safety of melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for cancer or metastases in the liver shows there are serious but well-recognised complications:* • *For patients with metastases in the liver from ocular melanoma, there is some evidence of short-term tumour response. For these patients, this procedure should only be used with special arrangements for clinical governance, consent, and audit*

				or research. Find out what special arrangements mean on the NICE interventional procedures guidance page. • *For patients with primary liver cancer or metastases in the liver that are not from ocular melanoma, evidence of efficacy is inadequate in quality and quantity. For these patients, this procedure should only be used in the context of research. Find out what only in research means on the NICE interventional procedures guidance page*.''
30	Consultee 12 Company Medac Pharma	**2.1**	**medac response to NICE Interventional procedure review:** **IP1062/2 Melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic car in the liver**	Thank you for your comment. The committee have split their main recommendations

			Who are medac and Delcath? medac Pharma LLP (Stirling, UK), as a subsidiary of medac GmbH (Wedel, DE), is a pharmaceutical company with experience in diagnosis and treatment of oncological diseases. We have a focus in rare diseases and have products to help with allogenic stem cell transplants and high-grade gliomas as well as supplying a range of generic chemotherapy agents. medac would like strongly to emphasize that chemosaturation with melphalan is intended as a treatment for patients suffering from liver metastases of ocular melanoma (OM) which is an orphan disease (classified by Orphanet: ORPHA:39044). Therefore, this treatment is for the benefit of a narrow well-defined group of patients. Delcath Systems Inc. (Queensbury, New York, USA) had worked with specialist clinical teams in the US, Europe and the UK (Southampton) to develop the chemosaturation procedure. medac entered into an agreement with the manufacturer Delcath in December 2018 to distribute CHEMOSAT® in Europe. Our understanding has always been that CHEMOSAT® is the device kit that enables chemosaturation of the liver along with the clinical expertise of the centres. The expertise of the treatment team is a crucial part of the procedure. All centres providing chemosaturation have to undergo intense training by a proctor team.	between metastatic uveal melanoma and other cancers with primary liver cancer or metastases in the liver. Section 1.1 now reads: 1.1 *Evidence on the safety of melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for cancer or metastases in the liver shows there are serious but well-recognised complications:* • *For patients with metastases in the liver from ocular melanoma, there is some evidence of short-term tumour response. For these patients, this procedure should only be used with special arrangements for*

				clinical governance, consent, and audit or research. Find out what special arrangements mean on the NICE interventional procedures guidance page. • *For patients with primary liver cancer or metastases in the liver that are not from ocular melanoma, evidence of efficacy is inadequate in quality and quantity. For these patients, this procedure should only be used in the context of research. Find out what only in research means on the NICE interventional procedures guidance page*.'' Section 1.4 of the guidance says: ‘’*The procedure should only be*

				done in specialist centres by a multidisciplinary team that includes an interventional radiologist, an anaesthetist and a clinical perfusion scientist trained and experienced in the procedure.''
31	Consultee 12 Company Medac Pharma	**3.6 and 3.7**	**What is the procedure for?** Referring to Committee comments 3.6 and 3.7, chemosaturation of the liver is mainly for miliary metastatic disease. These tumours are small, possibly microscopic, and spread out. This means that resection of the liver metastases is not possible. It is not intended to treat primary liver cancer or localised metastatic tumours that can be resected in the liver. We have always been aware that this is a treatment for relatively few patients. In the case of ocular melanoma, there are around 600 new cases per year and around 50% will develop metastatic disease, most of which is in the liver. We estimate that around 50-75 patients per year will be suitable for this treatment, after factors such as patient health, tumour burden, cardiovascular risk are taken into consideration. Any other patient treated by this procedure will have liver dominant miliary tumours that are untreatable with systemic drugs, local radiotherapy or surgery.	Thank you for your comment. The committee have changed their recommendations. Please refer to comment 31. Section 3.7 of the guidance says*:* *''The procedure is used for unresectable liver cancer.''*
32	Consultee 12 Company Medac Pharma	**Title**	**What is our reaction to the consultation document?** With regards to Committee comment 3.6, we would like to remind the Committee that medac requested that the title of the procedure be changed in January 2020 (before the IPAC meeting) to one that did not include primary liver cancer. A narrower description of metastatic liver cancer would also have been preferred. At the meeting itself there was good discussion around ocular melanoma. These patients do not have other treatment options and it appeared to be understood that these	Thank you for your comment. The committee have changed their recommendations.

			patients have an appalling outlook. We assumed that it was mutually agreed by the Committee that chemosaturation is a specific treatment for liver metastases of ocular melanoma (OM), since this was reflected in the summary of the Chair. We were very surprised that the consultation document did not reflect the role of this treatment for OM patients and presented it in the context of wider liver cancer therapies.	Please refer to comment 31.
33	Consultee 12 Company Medac Pharma	**1.1**	**What do we (medac) want to happen?** We would like the Committee to reconsider the title of this procedure and review chemosaturation in the light of the benefit that the small group of difficult metastatic OM patients can receive with what has been proven to be a relatively safe procedure. medac therefore asks IPAC if it will reassess whether chemosaturation can gain specialised status recommendation.	Thank you for your comment. The committee have decided to split their main recommendations between metastatic uveal melanoma and other cancers with primary liver cancer or metastases in the liver. Please refer to comment 31.
34	Consultee 12 Company Medac Pharma	**Title**	**Comments on the draft consultation document** 1. The scope of the guidance is too wide as it encompasses all liver cancers, many of which can be treated effectively by other means.	Thank you for your comment. The committee have decided to split their main recommendations between metastatic uveal melanoma and other cancers with primary liver cancer or

				metastases in the liver. Please refer to comment 31.
35	Consultee 12 Company Medac Pharma	**1.1**	2. The relatively small group of OM metastatic cancer in the liver patients cannot be treated by other means and therefore there is an unmet clinical need due to lack of treatment options. This group, although mentioned, is not emphasized in the consultation document.	Thank you for your comment. The committee have decided to split their main recommendations between metastatic uveal melanoma and other cancers with primary liver cancer or metastases in the liver. Please refer to comment 31.
36	Consultee 12 Company Medac Pharma	**General**	3. Data was submitted in September 2019 by medac in the SIR. This response highlighted OM several times.	Thank you for your comment and for answering the Standard Information Request. This was considered by the IP team during the preparation of the overview. This guidance is an update of an existing guidance (IPG488) for which the procedure indication is

				primary or metastatic liver cancer.
37	Consultee 12 Company Medac Pharma	**1.1**	4. Chemosaturation provides a controlled risk procedure potentially to treat these difficult tumours in this specific group of patients. Evidence as to why the Committee regards this as a high-risk procedure was not offered – in fact the treatment has resulted in no procedure related deaths with second generation filter (GEN2 filter). GEN2 filter has been commercially available since early 2012. First generation filter (GEN1 filter) was only ever used in early clinical trials.	Thank you for your comment. The committee have decided to split their main recommendations between metastatic uveal melanoma and other cancers with primary liver cancer or metastases in the liver. Please refer to comment 31.
38	Consultee 12 Company Medac Pharma	**1.2**	5. Chemosaturation is a specialised procedure that needs a skilled multidisciplinary team to deliver the treatment. The manufacturer and the distributors recognised this need and will only supply CHEMOSAT® to sites that have been appropriately trained and accredited.	Thank you for your comment. Section 1.4 of the guidance says: ‘’*The procedure should only be done in specialist centres by a multidisciplinary team that includes an interventional radiologist, an anaesthetist and a clinical perfusion scientist trained*

				and experienced in the procedure.''
39	Consultee 12 Company Medac Pharma	**1.1**	6. Given that this is an orphan disease (small enough in patient numbers and administered in sufficiently few centres, likely to qualify for NICE's HST assessment process). The fact that there is one RCT is actually noteworthy. The data that is available demonstrates a benefit by way of extension to life but this has not been acknowledged by the Committee.	Thank you for your comment. The committee have decided to split their main recommendations between metastatic uveal melanoma and other cancers with primary liver cancer or metastases in the liver. Please refer to comment 31.
40	Consultee 12 Company Medac Pharma	**General**	7. The verbal briefing given to the Committee during the meeting in February 2020 did not reflect what we as distributor, and many others with knowledge of this area, know about the procedure. We understand that maybe not all stakeholders received notification to comment (clinical experts and patients groups) before the Committee meeting. Therefore we do wonder whether the Committee has received all the briefing it needs to be fully apprised of the facts here.	Thank you for your comment and for answering the Standard Information Request. This was considered by the IP team during the preparation of the overview. The consultation period only starts after the draft recommendations have been developed by the committee and is

				opened to all for comments. Before the first committee meeting, the following professional societies have been contacted to nominate professional experts to answer a questionnaire providing advice to the committee: • British Society of Interventional Radiology • Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland • British Association of Surgical Oncology • Royal College of Radiologists – Faculty of Clinical Oncology • British Society of Gastroenterology

				• British Association for the Study of the Liver At the same time, the following patient organisations were contacted by the patient involvement programme to provide submissions: • Macmillan Cancer Support • Cancer Research UK • Marie Curie Cancer Care • Pelican Cancer Foundation • British liver Trust • Liver4Life • Cancer52 • OcuMel UK
41	Consultee 12 Company Medac Pharma	**Title**	8. medac has requested that the title be changed before the IPAC meeting in February 2020 and again at the beginning of this consultation.	Thank you for your comment. This guidance is an update of an existing guidance

				(IPG488) for which the procedure indication is primary or metastatic liver cancer so the title could not be changed before the first IPAC meeting. After the first round of consultation the committee has decided to keep the original title and to split their main recommendations between metastatic uveal melanoma and other cancers with primary liver cancer or metastases in the liver. Please refer to comment 31.
42	Consultee 12 Company Medac Pharma	**Title**	**Scope of the review** **<u>Title:</u>** Current title: Melphalan chemosaturation with percutaneous perfusion and hepatic vein isolation *for primary or metastatic cancer in the liver.*	Thank you for your comment. The committee considered your comment but decided not to change the title.

			The description of the procedure in the title is accurate. However, the indication is misleading. It suggests chemosaturation could be used for primary liver cancer and for all metastatic cancer in the liver. This chemosaturation procedure was developed for metastatic cancer of the liver that could not be treated by other means. Therefore, a more accurate title would be: Melphalan chemosaturation with percutaneous perfusion and hepatic vein isolation *for unresectable metastatic cancer in the liver primarily from ocular melanoma.*	Section 3.6 of the guidance says: *'' The procedure is used for unresectable liver cancer. ''*
43	Consultee 12 Company Medac Pharma	**2.1**	**Description of indication:** **Uveal or Ocular Melanoma (OM)** In our view the scope of this review is well described in "Clinical Commissioning Policy: Chemosaturation for liver metastases from ocular melanomas" NHS England 16014/P This is taken from section 4: Epidemiology and needs assessment. *It is estimated that between 500 - 600 people are diagnosed with uveal melanoma in the United Kingdom each year, representing approximately 420 - 500 people across England alone (Macmillan Cancer Support, 2014). As conjunctival melanoma, estimated at below 80 new patients in England each year, is typically associated with a different pattern of disease rarely metastasising to the liver only and thus chemosaturation is not an optimal therapy. Therefore this policy concerns the use of chemosaturation for liver metastases from uveal melanoma only. Of the 420 - 500 uveal melanoma patients in England each year, between 30-50% of patients (approximately 210 - 250 people) will suffer a recurrence of their cancer within 5-10 years of initial diagnosis, typically associated with metastatic liver disease (Agarwala S. et al., 2014). Of these patients, 90% will have liver involvement of their melanoma, however 70% (approximately 150 - 175 people) are likely to have metastasis isolated purely to the liver (Ocular Melanoma Foundation, 2015). Of this patient cohort, clinicians have estimated that between five and seven patients may be suitable for surgical resection, one or two patients suitable for thermal ablative therapy and another one or two patients suitable for chemoembolisation. The patient cohort for whom chemosaturation could be considered is those who are reasonably fit and have a disease burden less than 60% (i.e. metastases are involving less than 60% of the liver) without significant liver failure. Exclusion criteria include significant cardiac or*	Thank you for your comment. The clinical commissioning policy on chemosaturation for liver metastases from ocular melanomas published by the NHS England Specialised Commissioning Team in 2016 is included in the overview.

			respiratory disease and any anticoagulant pathologies that increase the risk of bleeding. In addition, metastases to the brain and abnormal liver anatomy would also exclude a patient from chemosaturation suitability. On this basis, clinicians estimate that 50-75 patients per year could be suitable for chemosaturation. Although classified as a melanoma, ocular or uveal melanoma it is significantly different to cutaneous melanoma and the two cancers have different responses to the available therapies. PD-L1 expression in tumour metastases is different for uveal melanoma and cutaneous melanoma (see figure 1) (Javed et al., 2017). It has been shown in several clinical trials that immune checkpoint inhibitors are not very effective in metastatic OM. (Wessely et al., 2020). Figure 1: Expression of PD-L1 in metastatic melanoma [taken from Javed et al. 2017] [Figure removed for copyright reasons].	
44	Consultee 12 Company Medac Pharma	**3.1**	**Comparison of different treatment strategies for liver metastasis of ocular melanoma from Dutch Registry** The following graphic shows 175 metastatic OM patients from 2012-2018 with all treatment options (local treatment, systemic treatment, and not treated patients). One year survival for patients in the local treatment group showed best overall survival (Jochems et al., 2019). Figure 2: Comparison of different treatment strategies for liver metastasis of ocular melanoma from Dutch Registry [Figure removed for copyright reasons].	Thank you for your comment. The Jochems et al. (2019) study is a registry study of 175 patients with metastatic uveal melanoma with a 1-year follow-up. This study was not included in the overview because the group of people receiving local treatment included people having surgical resection

<table>
<tr><td></td><td></td><td></td><td></td><td>of metastases, isolated hepatic perfusion with melphalan, radiotherapy, radiofrequency ablation or radio-embolisation.</td></tr>
<tr><td>45</td><td>Consultee 12 Company Medac Pharma</td><td>3.1</td><td><u>Chemosaturation - evidence in published literature:</u>

Chemosaturation targets the whole liver and delivers a high concentration of melphalan enabling the treatment of small dispersed tumours that might not be reached with TACE (Transcatheter Arterial ChemoEmbolism) and SIRT (Selective Internal Radiation Therapy).

Main publications on chemosaturation with GEN2 filter
<table>
<tr><th>Author</th><th>Karydis et al</th><th>Artzner et al</th><th>Meijer et al</th><th>Kirstein et al</th><th>Schönfeld et al</th></tr>
<tr><td>Journal</td><td>Journal of Surgical Oncology</td><td>Cancer Imaging</td><td>CardioVascular and Interventional Radiology (safety gen 2 filter)</td><td>Journal of Cancer Research and Clinical Oncology</td><td>Journal of Cancer Research and Clinical Oncology</td></tr>
<tr><td>Publication year</td><td>2018</td><td>2019</td><td>2019/ 2020</td><td>2017</td><td>2020</td></tr>
<tr><td>Number of patients (pts)</td><td>51 (retrospective analysis)</td><td>16</td><td>35 (21 pts no prior therapy)</td><td>29 (solid tumours, last-line patients)</td><td>60 pts (30 OM)</td></tr>
<tr><td>ORR</td><td>47%</td><td>not available</td><td>not available</td><td>19.2% (OM 33.3%)</td><td>33.3% (OM 42.3%)</td></tr>
</table></td><td>Thank you for your comment and for listing the publications related to this procedure.

All the studies listed in the table are included in the overview including the Meijer et al. (2020) study that has been published recently and that has been included after the first round of consultation.</td></tr>
</table>

mPFS in months	8.1	11.1 (after 1st PHP)	not available	3.9	4 (OM pts 6 months)
mhPFS	9.1	not available	not available	4.5	5 (OM pts 6 months
OS in months	15.3	27.4 (after first CS-PHP)	19.1 (Meijer/Burgmans, Ann Surg Oncol, 2020)	8.7	mOS 9 (OM pts 12.6)

Table 1: Main publications on chemosaturation with GEN2 filter

This summarizing table 1 shows the number of patients and the corresponding key efficacy outcomes of OM liver metastasis patients treated with chemosaturation. In total this reflects the treatment of around 200 patients with an estimated average treatment number of 2.5. Based on this overview it can be shown that there is increasing evidence in the published literature that documents chemosaturation efficacy in the treatment of OM liver metastasis.

We estimate that around 50-75 patients (UK) per year would be eligible for treatment with chemosaturation based on the NHS Commissioning Policy: Chemosaturation for liver metastases from ocular melanoma.

The RCT, published in 2016 (Hughes et al.) was conducted between 2006 and 2009. Since 2012 over 1050 chemosaturation procedures have taken place in Europe in both clinical trials and private treatments (Communication from Delcath Systems Inc).

In 8 years there has been one reported death related to the procedure. This patient had a blood clotting anomaly (Milan 2012) that was not diagnosed prior to the procedure and was not related to the procedure itself.

The number of treatments undertaken to date equates to what would be expected to be undertaken in the UK over a similar period.

The Hughes et al. (2016) RCT and the Vogl et al.

<table>
<tr><td></td><td></td><td></td><td></td><td>(2014) case series are included in the main extraction table in the overview.</td></tr>
<tr><td>46</td><td>Consultee 12 Company Medac Pharma</td><td>3.1</td><td>Summary of patients treated from published data in Europe (based on table 1)
<table><tr><th>Patient profile</th><th>Number of patients</th></tr><tr><td>Patients with OM liver metastases treated with chemosaturation</td><td>132 patients</td></tr><tr><td>Patients with liver metastases from other primary cancers treated with chemosaturation</td><td>10 patients (2x CRC, 2x pancreatic cancer, 2x periampuliar cancer, 2x neuroendocrine tumours, 1x breast cancer, 1x endometrial cancer)</td></tr><tr><td>Primary liver cancer treated with chemosaturation</td><td>20 patients (14x CCA, 6x HCC)</td></tr></table>Table 2: Summary of patients treated from published data in Europe

The majority with 81% of the patients treated in clinical trials have been patients with OM liver metastases.

Total number of chemosaturation PHP treatments in this patient population = 370</td><td>Thank you for your comment and for analysing the data from patients who had this procedure in Europe.</td></tr>
</table>

47	Consultee 12 Company Medac Pharma	**3.1**	**<u>UK chemosaturation experience:</u>** The team at University Hospital Southampton has been involved with developing chemosaturation since the early days. They have now performed a combined (private + clinical trial) >220 treatments with zero treatment related deaths. The team published in 2017 a report on 51 patients (Karydis et al., 2017). 45 patients have been treated in the private sector (Spire Hospital, Southampton). Full report attached (appendix 1). • 141 treatments over 6 years. • 0 treatment related deaths • All 45 patients had at least 2 procedures • 14 patients had 4 treatment procedures • 2 patients had 7 treatment procedures • Average hospital stay was 3.36 days for first treatment dropping to 2 days for the 7th treatment cycle Other sites with clinical experience of using chemosaturation in UK: • Aintree Hospital, Liverpool. Clinical trial • Harley Street Clinic, London. Private patients only • The Christie Clinic, Manchester. Private patients All involved personnel in all sites receive extensive training in the procedure. This takes the form of presentations and practical training. Delcath has set up a training programme with a team of proctors where trainees can visit experienced sites and experienced people (proctors) will travel to new or inexperienced sites to supervise for the first 3 treatments. CHEMOSAT® kits will only be supplied when the centre has been certified.	Thank you for your comment. The Karydis et al. (2017) study is included in the main extraction table in the overview.

48	Consultee 12 Company Medac Pharma	**1.1**	**We believe that we have presented solid evidence as to the clinical efficacy of this intervention in the narrower metastasized OM population. We have also provided data showing how safe the treatment is. In addition to the complete absence of deaths, the treatment is tolerated as well or better than many other oncological interventions.** **In conclusion, therefore, we would ask the IPAC Committee to reconsider the current draft recommendations from June 2020 in consideration of this letter.**	Thank you for your comment. The committee have decided to split their main recommendations between metastatic uveal melanoma and other cancers with primary liver cancer or metastases in the liver. Please refer to comment 31.
49	Consultee 12 Company Medac Pharma	**3.1**	**References** Artzner, Christoph; Mossakowski, Oliver; Hefferman, Gerald; Grosse, Ulrich; Hoffmann, Rüdiger; Forschner, Andrea et al. (2019): Chemosaturation with percutaneous hepatic perfusion of melphalan for liver-dominant metastatic uveal melanoma: a single center experience. In: *Cancer imaging: the official publication of the International Cancer Imaging* Society 19 (1), S. 31. DOI: 10.1186/s40644-019-0218-4. Hughes; Marybeth S, Zager; Jonathan, Faries; Mark, Alexander; H. Richard, Royal; Richard E, Wood; Bradford, Choi; Junsung, McCluskey; Kevin, Whitman; Eric, Agarwala; Sanjiv, Siskin; Gary, Nutting; Charles, Toomey; Mary Ann, Webb; Carole, Beresnev; Tatiana & Pingpank; James F. (2016) Results of a randomized controlled multicenter phase III trial of percutaneous hepatic perfusion compared with best available care for patients with melanoma liver metastases. In: *Annals of Surgical Oncology* 2016; 23(4):1309-19 DOI: 10.1245/s10434-015-4968-3. Javed; A, Arguello; D, Johnstone; C, Gatalica; Z, Terai; M, Weight; RM, Orloff; M, Mastranglelo; MJ & Sato; T. (2017) PD-L1 expression in tumour metastases is different between uveal melanoma and cutaneous melanoma. Immunotherapy 9(16), 1323-1330.	Thank you for your comment. The Artzner et al. (2019) study, the Hughes et al. (2016) RCT, the Karydis et al. (2017) study, the Kirstein et al. (2017) study and the Meijer et al. (2019) study are all included in the main extraction table in the overview. The Javed et al. (2017) study is not a clinical study.

			Jochems A; van der Kooij MK; Fiocco M; Schouwenburg MG; Aarts MJ; van Akkooi AC; et al. Metastatic Uveal Melanoma: Treatment Strategies and Survival Results from the Dutch Melanoma Treatment Registry. Cancers (Basel) 2019; 11(7). Karydis, Ioannis; Gangi, Alexandra; Wheater, Matthew J.; Choi, Junsung; Wilson, Iain; Thomas, Kerry et al. (2018): Percutaneous hepatic perfusion with melphalan in uveal melanoma: A safe and effective treatment modality in an orphan disease. In: *Journal of surgical oncology* 117 (6), S. 1170–1178. DOI: 10.1002/jso.24956. Kirstein, Martha M.; Marquardt, Steffen; Jedicke, Nils; Marhenke, Silke; Koppert, Wolfgang; Manns, Michael P. et al. (2017): Safety and efficacy of chemosaturation in patients with primary and secondary liver tumors. In: *J Cancer Res Clin Oncol* 143 (10), S. 2113–2121. DOI: 10.1007/s00432-017-2461-z. Meijer, T.S.; Burgmans, M.C.; Fiocco, Marta; Geus-Oei, Lioe-Fee de; Kapiteijn, Ellen; Leede, Eleonora M. de et al. (2019): Safety of Percutaneous Hepatic Perfusion with Melphalan in Patients with Unresectable Liver Metastases from Ocular Melanoma Using the Delcath Systems' Second-Generation Hemofiltration System: A Prospective Non-randomized Phase II Trial. In: *Cardiovascular and interventional radiology*. DOI: 10.1007/s00270-019-02177-x. Meijer, T.S.; Burgmans, M.C. (2020): ASO Author Reflections: Percutaneous Hepatic Perfusion with Melphalan in Patients with Unresectable Hepatic Metastases from Ocular Melanoma. In: *Ann Surg Oncol*. DOI: 10.1245/s10434-020-08806-x Schönfeld, Leon; Hinrichs, Jan B.; Marquardt, Steffen; Voigtländer, Torsten; Dewald, Cornelia; Koppert, Wolfgang et al. (2020): Chemosaturation with percutaneous hepatic perfusion is effective in patients with ocular melanoma and cholangiocarcinoma. In: *J Cancer Res Clin Oncol*. DOI: 10.1007/s00432-020-03289-5. Wessely, Anja; Steeb, Theresa; Erdmann, Michael; Heinzerling, Lucie; Vera, Julio; Schlaak, Max et al. (2020): The Role of Immune Checkpoint Blockade in Uveal Melanoma. In: *International journal of molecular sciences* 21 (3). DOI: 10.3390/ijms21030879. Appendix	Therefore, it has not been included in the overview. The Jochems et al. (2019) study is a registry study. This study was not included in the overview because the group of people receiving local treatment included people having surgical resection of metastases, isolated hepatic perfusion with melphalan, radiotherapy, radiofrequency ablation or radio-embolisation. The Meijer et al. (2020) study and the Schönfeld et al. (2020) study have been published recently and have been included in the main extraction table after the first round of consultation. The Wessely et al. (2020) study is not

			1: Data analysis report of 45 patients treated at Spire Hospital Southampton **[pdf removed]**	about the efficacy or safety of this procedure. Therefore it has not been included in the overview. The data analysis report of 45 patients treated at Spire Hospital Southampton is not a peer-reviewed study. The NICE IP programme manual highlights that efficacy outcomes from non peer-reviewed or unpublished studies are not normally presented to the committee, unless they contain important safety data.
50	Consultee 13 Company Delcath	**Title**	**Interventional Procedures Consultation Document: Chemosaturation with percutaneous artery perfusion and hepatic vein isolation for primary or metastatic cancer in the liver** Delcath Systems Inc, the manufacturer (The Company), thanks the Committee for their time and consideration of the procedure “chemosaturation with percutaneous artery perfusion and hepatic vein isolation for primary or metastatic cancer in the liver.”	Thank you for your comment. The committee have decided to split their main

<table>
<tr><td></td><td></td><td></td><td>The Committee is reminded that during the IPAC meeting conducted on 13 February 2020, it was stated that the guidance regarding this interventional procedure would be considered only in the context of liver metastases from ocular melanoma. This was reiterated by the Chair at the closing of this meeting of the IPAC Committee.</td><td>recommendations between metastatic uveal melanoma and other cancers with primary liver cancer or metastases in the liver. Please refer to comment 31.</td></tr>
<tr><td>51</td><td>Consultee 13 Company Delcath</td><td>1.1</td><td>Comments on Draft Guidance
1.1 Evidence on the safety of melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for cancer or metastases in the liver shows there are serious but well-recognised complications. There is some evidence of short-term tumour response but evidence on quality of life and survival is inadequate in quality and quantity. Therefore, this procedure should only be used in the context of research.

Efficacy results are summarised in the tables below.
<table>
<tr><th>Publication</th><th>CR</th><th>PR</th><th>SD</th><th>DCR</th></tr>
<tr><td>Meijer 2020† (n=32)</td><td>3.1%</td><td>68.7%</td><td>12.5%</td><td>71.9%</td></tr>
<tr><td>(1) Hughes 2016 (n=44*)</td><td>0.0%</td><td>27.3%</td><td>52.3%</td><td>79.6%</td></tr>
<tr><td>(2) Karydis 2018 (n=51)</td><td>3.9%</td><td>43.1%</td><td>37.2%</td><td>84.3%</td></tr>
<tr><td>(3) Kirstein 2017 (n=29)</td><td>0.0%</td><td>19.2%</td><td>55.2%</td><td>74.4%</td></tr>
<tr><td>(4) Abbott 2017 (n=10*)</td><td>not reported</td><td>not reported</td><td>not reported</td><td>not reported</td></tr>
<tr><td>(5) Vogl 2017 (n=18)</td><td>0.0%</td><td>44.4%</td><td>38.9%</td><td>83.3%</td></tr>
<tr><td>(6) Artzner 2019 (n=16)</td><td>0.0%</td><td>60.0%</td><td>33.3%</td><td>93.3%</td></tr>
<tr><td>(7) Marquardt 2019 (n=15)</td><td>[ICC patients]</td><td>[ICC patients]</td><td>[ICC patients]</td><td>[ICC patients]</td></tr>
<tr><td>(8) Meijer 2019 (n=35)</td><td>not reported</td><td>not reported</td><td>not reported</td><td>not reported</td></tr>
<tr><td>(9) Vogl 2014** (n=12)</td><td>8.3%</td><td>50.0%</td><td>41.7%</td><td>100.0%</td></tr>
</table>
Please note that the patient populations noted in this table reflect the number of patients who were evaluable for a tumour response.</td><td>Thank you for your comment and for summarising the efficacy results of the studies included in the overview.

The Meijer et al. (2020) study has been published recently and has been included in the main extraction table after the first round of consultation.

The Mignard et al. (2018) et the Algazi (2016) studies are not reporting on the efficacy or safety of the procedure under consideration.</td></tr>
</table>

Publication	hPFS (median)	PFS (median)	OS (median)
Meijer 2020† (n=35)	11.2 months	7.6 months	19.1 months
(1) Hughes 2016 (n=44*)	7.0 months	5.4 months	10.6 months
(2) Karydis 2018 (n=51)	9.1 months	8.1 months	15.3 months
(3) Kirstein 2017 (n=29)	4.4 months	3.8 months	8.6 months
(4) Abbott 2017 (n=10*)	11.5 months	9.0 months	19.9 months
(5) Vogl 2017 (n=18)	not reported	12.4 months	9.6 months
(6) Artzner 2019 (n=16)	not reported	11.1 months	27.4 months
(7) Marquardt 2019 (n=15)	[ICC patients]	[ICC patients]	[ICC patients]
(8) Meijer 2019 (n=35)	not reported	not reported	not reported
(9) Vogl 2014** (n=13)	not reported	not reported	not reported

*Chemosaturation with PHP cohort only
**Multi-histological study
†Manuscript attached as additional evidence
Additionally, the Company has included Quality of Life data as presented in an article manuscript which is currently pending publication; detailed data from this manuscript is provided below.
Currently, there is no standard of care for treatment of liver metastases from ocular melanoma. Immunotherapy, which was approved for treatment of metastatic melanoma, is commonly used to treat liver metastases from ocular melanoma despite a lack of inclusion of ocular melanoma patients in the trials used to obtain approval for metastatic melanoma and despite data showing that it has limited efficacy in this setting.
According to Karydis et al, “Immunotherapy of UM to date has been extremely disappointing with response rates of <10%, much lower than those seen in CM. This is especially true in the context of progressive liver disease, which is common in metastatic UM as the liver is involved in >85% of cases of metastatic spread.”
According to Abbott et al, “there is evidence that systemic immunotherapies are not very effective in treating metastatic ocular melanoma to the liver.”
This has recently been discussed in greater detail in the following articles (among other publications):

Mignard Cet al. Efficacy of Immunotherapy in Patients with Metastatic Mucosal or Uveal Melanoma. *J Oncol*. 2018 Dec 2;2018:1908065. doi: 10.1155/2018/1908065. eCollection 2018.

Therefore, they have not been included in the overview.

The IP programme does not assess the efficacy and safety of comparator interventions.

			Algazi AP et al. Clinical outcomes in metastatic uveal melanoma treated with PD-1 and PD-L1 antibodies. *Cancer*. 2016;122: 3344-3353. doi:10.1002/cncr.30258 The Committee is encouraged to consider the efficacy data presented in literature regarding immunotherapy for liver metastases from ocular melanoma when making a determination regarding the use of chemosaturation with PHP for this disease.	
52	Consultee 13 Company Delcath	**1.2**	**1.2 The procedure should only be done in specialist centres by a multidisciplinary team that includes an interventional radiologist, an anaesthetist and a clinical perfusion scientist trained and experienced in the procedure.** The Company affirms that the procedure should only be performed in a handful of specialist centres in the UK, where the multidisciplinary teams have undergone the required training programme provided by the Company and are certified by the Company to perform the procedure.	Thank you for your comment. The consultee agrees with section 1.4 of the guidance.
53	Consultee 13 Company Delcath	**1.3**	**1.3 Further research should be in the form of randomised controlled trials against current best practice. It should report details of patient selection, concurrent therapies, technique and adverse events, including those related to chemotherapy.** The Company reiterates that there is currently no established best practice for the treatment of liver metastases from ocular melanoma. There is considerable difficulty in performing an RCT in an orphan disease, thus the scarcity of results from RCTs in orphan diseases. Of the treatments presently used in the clinical setting for liver metastases from ocular melanoma, none (apart from chemosaturation with PHP) was investigated in an RCT of patients with liver metastases from ocular melanoma. The Company notes that the only RCT performed for patients with liver metastases from ocular melanoma has been reviewed and addressed by the Committee in the Overview document (Hughes et al) and this trial met its primary endpoint of progression free survival.	Thank you for your comment. The committee considered your comment but decided not to change section 1.5 of the guidance.
54	Consultee 13 Company Delcath	**2.1**	**2.1 The most common types of primary liver cancer are hepatocellular carcinoma (also known as hepatoma) and cholangiocarcinoma. However, cancer in the liver is often metastases from other sites such as the lung, colon, stomach and eye (particularly ocular melanoma).** The Company reiterates that the Committee is requested to consider this procedure for the treatment of liver metastases from ocular melanoma.	Thank you for your comment. The committee have decided to split their main recommendations between metastatic uveal melanoma and other cancers

				with primary liver cancer or metastases in the liver. Please refer to comment 31.
55	Consultee 13 Company Delcath	**2.2**	**2.2 Treatment for primary or metastatic cancer in the liver depends on the location and stage of the cancer and how much liver function is preserved. Treatment options include surgical resection, thermal ablation, systemic chemotherapy, transarterial chemoembolisation, isolated hepatic perfusion and selective internal radiation therapy. In patients with primary liver cancer, surgical removal with curative intent and liver transplantation may be possible. For most patients with liver metastases, treatment with curative intent is not possible.** The Company reiterates its request that the procedure be considered for patients with liver metastases from ocular melanoma. As the Committee has noted in section 3.6 of the draft guidance, liver metastases from ocular melanoma often present in a miliary disease pattern which is often unresectable. Chemosaturation with PHP has the benefit of treating the entire liver, including miliary disease which may not be visible on imaging. Transarterial chemoembolizaion and selective internal radiation therapy are not suitable treatment modalities for patients with micrometastases or miliary disease that cannot be visualised on imaging. As stated in an article reviewed by the Committee (Vogl et al, 2017) “TACE is a liver-directed regional therapy to only visible metastases. In contrast, PIHP has an effect on the entire metastasized tissue with effects also on non-visible metastases.”	Thank you for your comment. The committee considered your comment but decided not to change section 2.2 of the guidance. The committee have decided to split their main recommendations between metastatic uveal melanoma and other cancers with primary liver cancer or metastases in the liver. Please refer to comment 31..
56	Consultee 13 Company Delcath	**2.5**	**2.5 The procedure causes significant changes in the patient’s haemodynamic status, which must be managed by the anaesthetic team with support from a clinical perfusion scientist.** The Company acknowledges that there are significant changes in the patient’s haemodynamic status, but notes that this is well-recognised as occurring during certain timepoints during the	Thank you for your comment. The consultee agrees with section 2.5 of the guidance.

			procedure, and is well-manageable. Detailed guidance on when these haemodynamic changes occur and management of these changes is included in the CHEMOSAT Instructions for Use (IFU).	
57	Consultee 13 Company Delcath	**3.1**	**3.1 NICE did a rapid review of the published literature on the efficacy and safety of this procedure. This comprised a comprehensive literature search and detailed review of the evidence from 9 sources, which was discussed by the committee. The evidence included 1 randomised controlled trial, 1 non-randomised comparative study and 7 case series. It is presented in table 2 of the interventional procedures overview. Other relevant literature is in the appendix of the overview.** The Company has included an additional manuscript (which is due to be published shortly) for the Committee to consider as additional evidence. This prospective Phase 2 manuscript is provided below.	Thank you for your comment. The Meijer et al. (2020) study has now been published and has been included in the main extraction table after the first round of consultation.
58	Consultee 13 Company Delcath	**3.4**	**3.4 Patient commentary was sought but none was received.** A representative of OcuMel UK (a patient advocacy group) was present at the meeting conducted on 13 Feb 2020 and was prepared to make a statement; however, this representative was not called to speak.	Thank you for your comment. A patient organisation submission from OcuMel Uk has been received by NICE and was discussed during the IPAC meeting following the first round of consultation. OcuMel UK also responded to the public consultation on the draft guidance and their comments were discussed. The

<table>
<tr><td></td><td></td><td></td><td></td><td>NICE Interventional Procedures programme gathers the views of the patients through questionnaires sent to patients or patients organisations. It also has 2 lay members in the committee.</td></tr>
<tr><td>59</td><td>Consultee 13 Company Delcath</td><td>3.1</td><td>Additional relevant evidence for consideration
The Company invites the Committee to consider the attached manuscript titled "Percutaneous hepatic perfusion with melphalan in patients with unresectable ocular melanoma metastases confined to the liver: a prospective phase II study." The authors have kindly provided this manuscript, which has been accepted for publication in Annals of Surgical Oncology, for the Committee's consideration. This article is expected to be published shortly.
As the Committee has indicated, Meijer et al 2019 (one of the studies included in the literature review performed by the Committee) reports safety data from a prospective Phase II study, with efficacy results being published separately. The attached manuscript contains these efficacy results. This prospective Phase II study also gathered quality of life data, which is also reported in this manuscript.
The Company feels that the efficacy and quality of life data reported in this manuscript are highly relevant additional evidence for the Committee to consider.
For ease of reference, this data is also summarised in the below tables.
<table>
<tr><td>Study type</td><td>Prospective Phase II Trial</td></tr>
<tr><td>Country</td><td>Netherlands</td></tr>
<tr><td>Recruitment period</td><td>February 2014 - June 2017</td></tr>
<tr><td>Study population and number</td><td>n=35
Patients with ocular melanoma liver metastases</td></tr>
<tr><td>Age and sex</td><td>Median 59 years
46% (16/35) male</td></tr>
<tr><td>Patient selection criteria</td><td>Inclusion criteria: histologically proven, unresectable ocular melanoma metastases confined to the liver

Exclusion criteria:
• aPTT >1.5 × ULN</td></tr>
</table></td><td>Thank you for your comment.

The Meijer et al. (2020) study has now been published and has been included in the main extraction table after the first round of consultation.</td></tr>
</table>

				• PT > 1.5 × ULN • Leukocytes < 3.0 × 10^9/L • Thrombocytes <100 × 10^9/L • Creatinine clearance < 40 ml/min • AST > 2.5 × ULN • ALT > 2.5 × ULN • Serum bilirubin > 1.5 × ULN • ALP > 2.5 × ULN • LDH >2 × ULN • Age < 18 or > 75 years • Extrahepatic disease (on CECT or FDG-PET/CT) • WHO performance status ≥2 • Severe comorbidity precluding general anesthesia • Diabetes with nephropathy • Active infections • < 40% healthy liver tissue • Other liver disease • Vascular anatomy impeding M-PHP • Intracranial lesions with propensity to bleed (on CT/MRI) • Pregnancy
			Technique	Treatment consisted of two M-PHP procedures with hepatic artery infusion of melphalan 3 mg/kg (maximum dose 220 mg) at 6-8 weeks interval. Patients demonstrating progressive disease (PD) or unacceptable adverse events after the first M-PHP received only one procedure. If grade 3/4 hematologic toxicity occurred after the first procedure, melphalan dose was reduced by 20-25%. Patients routinely received a subcutaneous injection of granulocyte-colony stimulating factor (pegfilgrastim 6 mg) within 72h after each M-PHP.	
			Follow up	Median follow-up of 19.1 months	
			Conflict of interest/source of funding	The Leiden University Medical Center received financial support (no grant number applies) and in kind contributions from Delcath Systems Inc, New York, NY, for conducting this study. The authors declare that Delcath Systems Inc. had no involvement in any part of the study.	
			Key efficacy and quality of life findings		
			Efficacy		

Response Analysis
32 patients were included in the response analysis.

- In two patients, a therapeutic melphalan dose could not be administered due to peri-procedural complications and therefore no treatment effect could be evaluated.
- In one patient, target lesions were absent (all lesions with maximal diameter <1cm).

Best Overall Response

	All evaluable pts		pts with 2 M-PHPs	
	n	%	n	%
CR	1	3	1	4
PR	22	69	19	70
SD	4	13	3	11
PD	5	16	4	15
Total	32	100	27	100

Best Hepatic Response

	All evaluable pts		pts with 2 M-PHPs	
	n	%	n	%
CR	1	3	1	4
PR	25	78	22	82
SD	6	19	4	15
PD	0	0	0	0
Total	32	100	27	100

Survival Analysis
There was no loss to follow up.

At median follow up (19.1 months), 17% (6/35) patients were still alive.

1-yr OS: 77% (27/35)
2-yr OS: 43% (15/35)

Median OS: 19.1 months (all included patients, n=35)

Median OS by Best Overall Response:

- CR/PR: 27.5 months (95% CI: 23.7-31.3)
- SD: 14.2 months (95% CI: 11.4-17.0)

			• PD: 9.1 months (95% CI: 5.5-12.8) This was a significant difference (p<0.001) Median OS by Best Hepatic Response: • CR/PR: 26.3 months (95% CI: 15.3-36.8) • SD: 11.9 months (95% CI: 7.3-16.5) This was a significant difference (p=0.001) Median PFS: 7.6 months (95% CI: 4.9-10.3) 1-yr PFS: 26.5% Median PFS by Best Hepatic Response: • CR/PR: 9.3 months (95% CI: 8.6-10.0) • SD: 5.6 months (95% CI: 2.7-8.5) This was a significant difference (p=0.001) Median hPFS: 11.2 months (95% CI: 9.0-13.4) 1-yr hPFS: 35.3% Median OS by relative hPFS (≥median hPFS vs <median hPFS): • Relatively long hPFS (≥median): 29.9 months (95% CI: 11.1-48.7) • Relatively short hPFS (<median): 14.2 months (95% CI: 10.1-18.3) This was a significant difference (p<0.001)	
			Quality of life At baseline, 18 out of 35 (51%) patients completed the EORTC QLQ-C30 v3.0 form. Return rates of the questionnaire at 6 weeks after the first M-PHP procedure, 6 weeks after the second M-PHP procedure, and 6 months after the first M-PHP procedure were 74% (26/35), 59% (17/29), and 49% (17/35), respectively. Questionnaire scores after treatment did not significantly differ from scores prior to treatment, except for physical functioning which was significantly impaired 6 weeks after the second M-PHP (p = 0.011). The level of physical functioning was restored to normal 3 months later (Table 5). (*continued on next page*) [Table 5 taken from the journal article]	

			In this prospective Phase II study of 35 patients with ocular melanoma liver metastases confined to the liver, efficacy results were favourable and included an overall response rate of 72% (complete response of 3% and partial response of 69%) and a median overall survival of 19.1 months. One-year OS was 77% and two-year OS was 43%. The hepatic response rate was 81% (hepatic complete response of 3% and hepatic partial response of 78%). Median PFS was 7.6 months, and one-year PFS was 26.5%. Median hPFS was 11.2 months, and one-year hPFS was 35.3%. This prospective Phase II study also gathered Quality of Life (QoL) data at four timepoints: prior to treatment, 6 weeks after the first procedure, 6 weeks after the second procedure, and 6 months after the first procedure. Patients completed the EORTC QLQ-30 v3.0 questionnaire, which asks patients to rate how well they are functioning, their symptoms, and their overall health status. This study found that QoL scores after treatment did not significantly differ from QoL scores prior to treatment, with the sole exception of "physical functioning" which was noted to be impaired 6 weeks after the second treatment, but which resolved to normal 3 months later. Median overall health status was 83 (on a scale of 0-100) prior to treatment, and remained consistent 6 weeks after the first procedure, 6 weeks after the second procedure, and 6 months after the first procedure at 83 for all three timepoints. These findings indicate that chemosaturation with PHP is well-tolerated and only mildly affects Quality of Life.		
60	Consultee 13 Company Delcath	**3.1**	**Comments on Overview** The Company would additionally call the Committee's attention to the following excerpts from the "Safety Summary" section of the Overview (Interventional Procedures Consultation Document). These excerpts appear with a box around them. In each case, the Company has made comments to provide additional context which the Company considers to be integral when analysing the excerpted data. In some cases, the Company has made a comment to provide information about a factual inaccuracy.		Thank you for your comment.

61	Consultee 13 Company Delcath	**3.1**	**Death** Adverse events that caused death were reported in 4% (4/93) of patients in the RCT of 93 patients. 2 deaths happened because of bone marrow suppression (1 from complication of neutropenia and 1 from streptococcal sepsis). 1 patient died because of progressive hepatic failure and 1 patient from the crossover population died because of gastric perforation.[1] Regarding the four deaths that occurred during the RCT, a number of protocol amendments and procedural improvements were put in place subsequent to each of these deaths during the course of the trial. Subsequently, there were no reoccurrences of those events which lead to patient death. Details of the amendments and procedural improvements for each event that led to death are provided below. **1. Hepatic failure** The death due to hepatic failure occurred in a 56-year old male patient during the first cycle of chemosaturation with PHP. Following treatment, this patient experienced fluid overload, myelosuppression, and hepatorenal syndrome. An autopsy revealed that this patient's death was related to underlying disease burden as the tumor burden in his liver was >90%. **2. Gastric perforation** The death due to gastric perforation occurred in a 62-year old male patient who crossed over to chemosaturation with PHP after hepatic progression on Best Alternative Care. After his second cycle of chemosaturation with PHP, the patient had evidence of gastrointestinal bleeding. During an endoscopy to investigate the gastrointestinal bleed, a gastric ulcer was perforated. An exploratory laparotomy was performed and a gastric perforation was repaired. However, during the laparotomy, the patient went into cardiopulmonary arrest and died. An autopsy revealed two gastric ulcers which likely resulted from the infusion of melphalan during a hepatic artery spasm with consequent misperfusion into the gastrointestinal vasculature. Protocol amendments were put in place during the clinical development programme, including restricting the liver tumour burden to 50% or less; and recommending the administration of nitroglycerin if hepatic artery spasm was seen during chemosaturation with PHP, to not infuse melphalan until the spasm resolved, and to terminate the procedure if the spasm did not resolve with nitroglycerin administration. These amendments have been incorporated into the patient selection criteria and training programme for use of CHEMOSAT. The above treatment requirements are in place for current treatments occurring in Europe. Since these requirements were put in place, no further deaths have occurred. Two patients died as a result of complications of neutropenia during their second cycle of treatment: **3. Streptococcal sepsis** A 54-year old female patient died of streptococcal sepsis. This patient experienced myelosuppression at cycle 1, but her melphalan dose was not reduced for cycle 2. The patient was readmitted to hospital on Day 11 of	Thank you for your comment.

			cycle 2 with hypoxia, pancytopenia, and sepsis and started on a multi-antibiotic regimen. The patient died of sepsis on Day 13. **4. Neutrophil count decreased** A 66-year old male patient died of neutropenic complications in cycle 2. This patient experienced myelosuppression in cycle 1 and had his melphalan dose reduced for cycle 2. The patient was hospitalised from day 13 to day 23 of cycle 2 with pneumonia and neutropenia and was readmitted on day 33 of cycle 2 with grade 4 pancytopenia, a necrotic herpes simplex infection of the mouth, and pulmonary oedema. The patient died on Day 40 of cycle 2. Prophylactic administration of colony-stimulating factors was not mandated during this trial and only a small percentage of patients received prophylactic growth factors during either the first (5%) or subsequent treatment cycles (12%). After the above events, prophylactic administration of colony-stimulating factors was stipulated in the protocol and training programme and has since been incorporated into the instructions for use of CHEMOSAT. Since these above safety measures have been incorporated into the procedure, no further procedure-related deaths have occurred due to the above causes in over 1050 procedures which have taken place in Europe since this trial. 1 patient died at 46 days after having the first cycle of PHP treatment in the case series of 15 patients. The cause of death was sepsis and liver failure.[7] Kindly recall that the patients in this case series were treated with PHP as a last-line therapy. We note that 93% of included patients had received previous treatment with chemotherapy. Corresponding with this, the eligibility criteria for this case series allowed for patients with a relatively worse hepatic function in comparison with the eligibility criteria in the RCT. For example, in this case series the maximum allowable total serum bilirubin was 3 times the upper limit of normal, and did not include AST or ALT elevations as a factor in determining eligibility. The authors have stated the following regarding this patient's death: "The patient with the highest tumour load (40% of liver volume) and impaired liver function in our cohort experienced severe hepatic complications with a prolonged hospital stay, and died due to liver and kidney failure 46 days after the procedure." 1 patient died in the case series of 14 patients. The patient died 30 hours after chemosaturation with PHP, after developing a giant retroperitoneal haematoma.[9] The authors have stated that:	

			"The remaining patient, who had a large fast-growing liver metastasis from ocular melanoma, died of a retroperitoneal giant hematoma 30 hours after chemosaturation-PHP. A post-mortem necropsy revealed multisite vascular bleeding with no damage to the inner surface of the abdominal veins and arteries." This finding is indicative of a bleeding disorder in this patient, which was not found prior to the patient beginning treatment. Indeed, the authors go on to state: "This unusual complication was most likely related to heparin which was needed for extracorporeal circulation." The potential risks of anticoagulation are well known. The CHEMOSAT Instructions for Use (IFU) stipulate that coagulation studies be performed pre-procedure as well as during and after the procedure, and also provides detailed guidance regarding management of anticoagulation during the procedure. This is the only procedure-related death that has occurred in over 1050 procedures in Europe since 2012.	
62	Consultee 13 Company Delcath	**3.1**	**Haematological toxicity** In the RCT of 93 patients, grade 3 or 4 anaemia was reported in 60% (42/70) of patients during the periprocedural period and 63% (44/70) of patients during the postprocedural period. Thrombocytopenia of grade 3 or 4 was reported in 74% (52/70) of patients in the periprocedural period and 80% (56/70) of patients in the postprocedural period. Neutropenia (grade 3 or 4) was reported in 4% (3/70) of patients during the periprocedural period and 86% (60/70) of patients in the postprocedural period. Increased international normalised ratio (INR) happened in 20% (14/70) of patients but only 1 patient had an increased INR during the postprocedural period. Prolonged activated partial thromboplastin time was reported in 26% (18/70) of patients during the periprocedural period.[1] In the "Discussion" section, the authors have summarised the observed haematological toxicities as follows: "Toxicity associated with therapy was significant but not resistant to effective management in the majority of patients." The authors go on to state, "Subsequent trials and treatment guidelines were developed with planned mitigation and treatment of these expected marrow-related toxicities in mind, including the use of prophylactic bone marrow growth factors in all patients, and the close monitoring of laboratories between treatments." Support with granulocyte colony-stimulating factors (G-CSF) has become a typical method of managing expected toxicities from bone marrow suppression, with administration of G-CSF typically occurring 24 hours post-procedure to 72 hours post-procedure.	Thank you for your comment. The overview (p9) has been amended as follows: *In the case series of 18 patients, anaemia was reported in 3% (1/35), leukopenia in 31% (11/35) of procedures and thrombocytopenia in 23% (8/35) of procedures.*[5] *p 10: In the case series of 14 patients, who had a total of 18*

			Grade 3 or 4 anaemia was reported in 41% (12/29) of patients in the case series of 29 patients. The study also reported grade 3 or 4 thrombocytopenia in 90% (26/29) of patients and grade 3 or 4 leukopenia in 35% (10/29) of patients.[3] Please recall that all patients were treated with chemosaturation with PHP as a last-line therapy. Correspondingly, the eligibility criteria for this retrospective case series allowed for the inclusion of patients with leukocyte count of >2,000/μL (i.e. patients with grade 2 or better leukopenia at baseline), and platelet count >50,000/μL (i.e. patients with grade 2 or better thrombocytopenia at baseline). The authors have summarised the observed haematological events as follows: "There was a significant deterioration of hematologic function as assessed by platelet, leukocyte count and hemoglobin, but myelosuppression was transient and recovered within 21 days of the procedure." This recovery trend is presented in Figures 4a and 4b of the publication. Platelet and leukocyte "Day 0" values are presented in the first column of Figures 4a and 4b, respectively, which are excerpted below: [Figures 4a and 4b have been removed for copyright reasons].	*PHP treatments, anaemia was reported in 72% (13/18) of procedures. Thrombocytopenia was reported in 56% (10/18) and leukocytopenia was reported in 56% (10/18).*[10] The main extraction table has also been amended. For study 10 (Vogl 2014), it is acknowledged in the overview that only 13 patients received PHP but 14 patients were initially recruited so this study is named ''the case series of 14 patients''.

The figures regarding haematological events in this publication were reported per procedure, rather than per patient. Therefore, kindly note that anaemia was reported in 3% (1/35), leukopenia in 31% (11/35) and thrombocytopenia in 23% (8/35) of procedures. This data is also presented in Table 3 of the publication, which has been excerpted below:

[Table 3 has been removed for copyright reasons].

> In the case series of 16 patients, who had 28 procedures in total, anaemia was reported in 96% (27/28) of the procedures done. Similarly, leukopenia was reported in 96% (27/28) and thrombocytopenia was reported in 75% (21/28) of the total procedures done.[6]

The figures given in this paragraph are for events of all grades. The authors state that most events were grade 1 or 2, and a complete breakdown of observed events and their grades are presented in Table 2 of the publication. This table is excerpted below:
[Table 2 has been removed for copyright reasons.]

> In the case series of 18 patients, anaemia was reported in 6% (1/18), leukopenia in 61% (11/18) of patients and thrombocytopenia in 44% (8/18) of patients.[5]

Additionally, in the "Discussion" section the authors have summarised the observed haematological toxicities as follows:
"The most common … SAEs were anemia, leukopenia, and thrombocytopenia. Fortunately, grade three and grade four SAEs, which by definition necessitate the need for additional treatment, were observed only in a small number of patients."

> In the case series of 15 patients who had 26 procedures in total, anaemia that needed a transfusion was reported in 27% (7/26) of the total procedures done. Thrombocytopenia that needed a platelet transfusion was reported in 23% (6/26) of procedures done. Leukopenia that needed treatment with a granulocyte-colony stimulating factor was reported in 15% (4/26) of the total procedures done.[7]

In the "Discussion" section the authors have summarised the observed haematological toxicities as follows:
"In the present study we observed a significant haematological toxicity expressed by anaemia and thrombocytopenia the day after the PHP procedure, both improving after 5–7 days….However, the

			haematological toxicities in our study are in line with those reported in the ABC-02 trial, the landmark trial for systemic chemotherapy for CCA." Additionally, kindly recall that these patients were treated in the last-line setting as previously discussed. Accordingly, patients with platelets >50,000/µL (i.e. patients with Grade 2 or better thrombocytopenia at baseline) were eligible for inclusion in this case series. In a case series of 35 patients who had PHP with melphalan for unresectable liver metastases from ocular melanoma, anaemia was reported in 18% (6/33) of patients. Thrombocytopenia was reported in 55% (18/33) of patients, leukopenia was reported in 75% (25/33), neutropenia was reported in 67% (22/33) and lymphocytopenia was reported in 85% (28/33). All of these were classified as grade 3 or 4.[8] In the "Discussion" section of this publication the authors have summarised the observed haematological toxicities as follows: "The results of this study show that grade 3/4 hematologic events are common after M-PHP, even with the GEN 2 filter. All events, however, were well manageable or self-limiting. Hematologic and hepatic toxicity percentages are significantly lower compared to studies using first-generation filters. …In a RCT by Hughes et al., 65 patients with ocular or cutaneous melanoma were treated with at least one M-PHP (median of three procedures) using the first-generation filter [1]. Similar to the current study, hematologic complications were categorized as early (days 0–3) or late (days 4–30) events enabling a direct comparison of toxicity in M-PHP with the GEN 2 and first-generation filter. We reported lower percentages of early grade 3/4 anemia (3.0% vs. 60.0%) and thrombocytopenia (12.1% vs. 74.3%). This indicates that the GEN 2 filter causes less damage to blood cells than first-generation filters. In addition, the lower rates of late grade 3/4 anemia (15.2% vs. 91.4%), thrombocytopenia (51.5% vs. 80.0%) and neutropenia (66.7% vs. 85.7%) in the current study strongly suggest that there is less bone marrow suppression due to a higher mean filter efficiency in the GEN 2 filter. Our patients even received a higher total dose of melphalan as a dose of 3 mg/kg actual body weight was used compared to 3 mg/kg ideal body weight in the RCT (in our population, median actual and ideal body weight was 77 kg and 66 kg, respectively). In addition, the current study protocol differed from Hughes' protocol in that G-CSF was used as preventive drug in virtually all patients, whereas Hughes et al. only administered G-CSF when indicated. This may have contributed to the differences in observed neutropenia." In the case series of 14 patients, a total of 16 PHP treatments, anaemia was reported in 81% (13/16) of the procedures. Thrombocytopenia was reported in 63% (10/16) and leukocytopenia was reported in 63% (10/16).[9]	

			Kindly note that in this case series, 13 patients received a total of 18 PHP treatments. The remaining patient developed vaginal bleeding after systemic heparinization and treatment was stopped before melphalan was administered. Additionally, in the "Discussion" section the authors have summarised the observed haematological toxicities as follows: "Mild to moderate filter-related toxicity, i.e. thrombocytopenia and anemia resulting from the removal of platelets and RBC by the hemofiltration system, was observed immediately after the procedure. Only patients treated with the first-generation filter needed platelet and RBC transfusions. Persistent and more severe melphalan-related pancytopenia tended to emerge later. Although these events were generally grade 3/4 in severity, they were predictable and were managed effectively in all patients with supportive measures."	
63	Consultee 13 Company Delcath	**3.1**	**Liver Toxicity** In the RCT of 93 patients, 20% (14/70) of patients had increased aspartate transaminase (AST) enzyme, 10% (7/70) had increased bilirubin and 37% (26/70) had decreased albumin during the preprocedural period. During the postprocedural period, the proportion of patients who had an increased AST rate was 10% (7/70), those who had increased bilirubin was 14% (10/70) and those with decreased albumin was 6% (4/70).[1] Kindly note that the figures reported in the first sentence occurred during the **peri**-procedural period, not the pre-procedural period. In the case series of 51 patients, transaminitis was reported in 29% (15/51) of patients, and was classified as grade 3 or 4 in 6% (3/51).[2] The authors have characterised the observed transaminitis as follows: Transaminitis was seen in 29.4% of patients but was typically mild and resolved rapidly (within 1-2 weeks) after the procedure in almost all the cases. Only 5.9% of patients experienced grade 3-4 events. In the case series of 29 patients, increased AST enzyme (grade 3 or 4) was reported in 41% (12/29) of patients. An increased level of alanine aminotransferase (grade 3 or 4) was reported in 17% (5/29) of patients and increased serum bilirubin was reported in 17% (5/29) of patients.[3] Kindly note that the observed cases of increased serum bilirubin were grade 3. The increase in bilirubin and subsequent recovery is presented in Figure 4 of the publication, which is excerpted below:	Thank you for your comment. p10 of the overview has been changed as follows: *In the RCT of 93 patients, 20% (14/70) of patients had increased aspartate transaminase (AST) enzyme, 10% (7/70) had increased bilirubin and 37% (26/70) had decreased albumin during the peri-procedural period.* The Kirstein study has been replaced

			[Figure removed for copyright reasons]. Similarly, the authors have also presented figures showing the increase and subsequent recovery of AST and ALT in Figure 4 of the publication which is excerpted below: [Figures removed for copyright reasons.] Please note that all cases of liver toxicity in this case series were reported as Grade 1. Transaminitis was reported in 13% (2/16) of the total procedures done in the case series of 14 patients.[9] Kindly note that in this case series, 13 patients received a total of 18 PHP treatments. The authors state that the cases of transaminitis were Grade 1/2, and that "all values returned to baseline levels within 1 week." In the case series of 16 patients who had 28 procedures in total, liver toxicity was reported in 46% (13/28) of the total procedures done.[6]	by the Schönfeld (2020) study in the key evidence table in the overview. The Kirstein (2017) study has been included in the Appendix. p 10 of the overview has been changed as follows: *Transaminitis was reported in 11% (2/18) of the total procedures done in the case series of 14 patients.[10]* It is acknowledged in the overview that only 13 patients received PHP but 14 patients were initially recruited so this study is named ''the case series of 14 patients''.
64	Consultee 13 Company Delcath	**3.1**	**Cardiovascular Events** Cardiac toxicity was reported in 17% (12/70) of patients during the periprocedural period in the RCT of 93 patients. This included raised troponin in 6 patients and sinus tachycardia in 2 patients. 1 patient had myocardial infarction, 1 had atrial fibrillation, 1 had pericardial effusion and 1 had ventricular tachycardia. Hepatic artery spasm was reported in 67% of patients. Cerebral ischaemia was reported in 1 patient and facial paresis was reported in 1 patient.[1]	Thank you for your comment. p11 of the overview has been amended as follows:

			Please note that cardiac toxicities were reported only in the periprocedural period. Cardiac complications (ST elevation) happened in 1 patient in the case series of 29 patients. Other cardiovascular complications reported in the study were atrioventricular block (1 patient), dissection of the hepatic artery (1 patient), pseudoaneurysm at the puncture site (1 patient) and hemiparesis (1 patient).[3] Kindly note that the authors note that the case of ST-segment elevation occurred in a patient "with coronary heart disease," and that the case "was completely normalized after the procedure." The authors discuss the case of hemiparesis in detail, and state: "Lysis was not performed in view of the mild symptoms, which improved spontaneously within hours. Subsequently, the patient received physiotherapy and logopedics and all symptoms have completely resolved." In the case series of 18 patients, periprocedural hypotension was reported in 11% (2/18) of patients, tachycardia in 6% (1/18) of patients, ventricular fibrillation in 6% (1/18), asystole in 6% (1/18), coagulopathy in 6% (1/18), aneurysma spurium in 6% (1/18) and crisis of hypertension in 6% (1/18).[5] The figures regarding safety events in this publication were reported per procedure, rather than per patient. Therefore, kindly note that periprocedural hypotension was reported in 6% (2/35), tachycardia in 3% (1/35), ventricular fibrillation in 3% (1/35), asystole in 3% (1/35), coagulopathy in 3% (1/35), aneurysma spurium in 3% (1/35) and crisis of hypertension in 3% (1/35) of procedures. This data is also presented in Table 3 of the publication, which was previously excerpted. Additionally, kindly note that the cases of asystole, aneurysma spurium, and crisis of hypertension occurred post-procedurally (whereas the remaining aforementioned events occurred during the procedure). Hypotension and tachycardia were reported during the periprocedural period in the case series of 15 patients (values not reported). Temporary stroke was reported in 1 patient in the study.[7] The authors have characterised the observed hypotension and tachycardia as follows: "Hypotension and tachycardia were common during the time of haemofiltration but could be adequately treated by use of volume replacement and catecholamine administration, and were self-limiting at the end of the procedure." Additionally, the authors state that the temporary stroke "resolved spontaneously without any neurological deficits over a time period of 2 months."	*"In the case series of 18 patients, periprocedural hypotension was reported in 6% (2/35) of procedures, and tachycardia, coagulopathy and ventricular fibrillation were each reported during 1 procedure. Asystole, aneurysma spurium, and hypertensive crisis were each reported once up to 30 days after the procedure.[5]"*

65	Consultee 13 Company Delcath	**3.1**	**Febrile neutropenia and infection** Infection was reported in 11% (2/18) of patients in the case series of 18 patients.[5] The figures regarding safety events in this publication were reported per procedure, rather than per patient. Therefore, kindly note that infection was reported in 6% (2/35) of procedures. This data is also presented in Table 3 of the publication, which was previously excerpted. Infection or inflammation was reported in 18% (5/28) of the total procedures done in the case series of 16 patients.[6] Please note that all cases of infection or inflammation were reported as Grade 1. Pneumonia was reported in 1 patient and otitis was reported in 1 patient in the case series of 15 patients.[7] Kindly note that pneumonia was reported in 4 patients. The authors stated that these cases were treated with antibiotics. Febrile neutropenia was reported in 2 patients in the case series of 14 patients.[9] Kindly note that in this case series, 13 patients received a total of 18 PHP treatments. The remaining patient developed vaginal bleeding after systemic heparinization and treatment was stopped before melphalan was administered.	Thank you for your comment. p 11 of the overview has been changed to: ‘’*Infection was reported in 6% (2/35) of procedures in the case series of 18 patients*.[5]’’ ‘’*Pneumonia was reported in 4 patients and otitis was reported in 1 patient in the case series of 15 patients. The pneumonias were treated with antibiotics.* [7]’’ For study 10 (Vogl 2014), it is acknowledged in the overview that only 13 patients received PHP but 14 patients were initially recruited so this study is named

				the ''case series of 14 patients''.
66	Consultee 13 Company Delcath	**3.1**	**Haemorrhage** Haemorrhagic events were reported in 20% (10/51) of patients in the case series of 51 patients, 2 cases of which were classified as grade 3 or 4. Haemorrhagic events included 1 patient with disseminated intravascular coagulation, 1 patient with intraabdominal bleeding and 1 patient with intracerebral haemorrhage.[2] The authors have characterised the observed bleeding events as follows: "Bleeding events were common peri-operatively and seen in 19.6% of patients, but most were minor. There was 1 case each of DIC requiring prolonged clotting factor support, intra-abdominal bleeding, and intracerebral haemorrhage—not tumor related—all resolved with no long term sequelae." Haematemesis and epistaxis were reported in 1 patient each in the case series of 18 patients.[5] The figures regarding safety events in this publication were reported per procedure, rather than per patient. This data is also presented in Table 3 of the publication, which was previously excerpted. In the case series of 35 patients, procedural haemorrhage was reported in 31% (11/35) of patients and vaginal haemorrhage with grade 2 anaemia was reported in 3% (1/35) of patients.[8] Please note that the case of vaginal haemorrhage is included in the reported cases of procedural haemorrhage. Vaginal bleeding was reported in 1 patient in the case series of 14 patients. Retroperitoneal haematoma was reported in 1 patient in the study, who died 30 hours after the treatment (described previously).[9] Kindly note that in this case series, 13 patients received a total of 18 PHP treatments. The remaining patient developed vaginal bleeding after systemic heparinization and treatment was stopped before melphalan was administered.	Thank you for your comment. p12 of the overview has been changed to: '' *Haematemesis and epistaxis were reported in 1 procedure each in the case series of 18 patients.*[5]'' p 12 of the overview has been changed to: '' *In the case series of 35 patients, post-procedural haemorrhage was reported in 31% (11/35) of patients including vaginal*

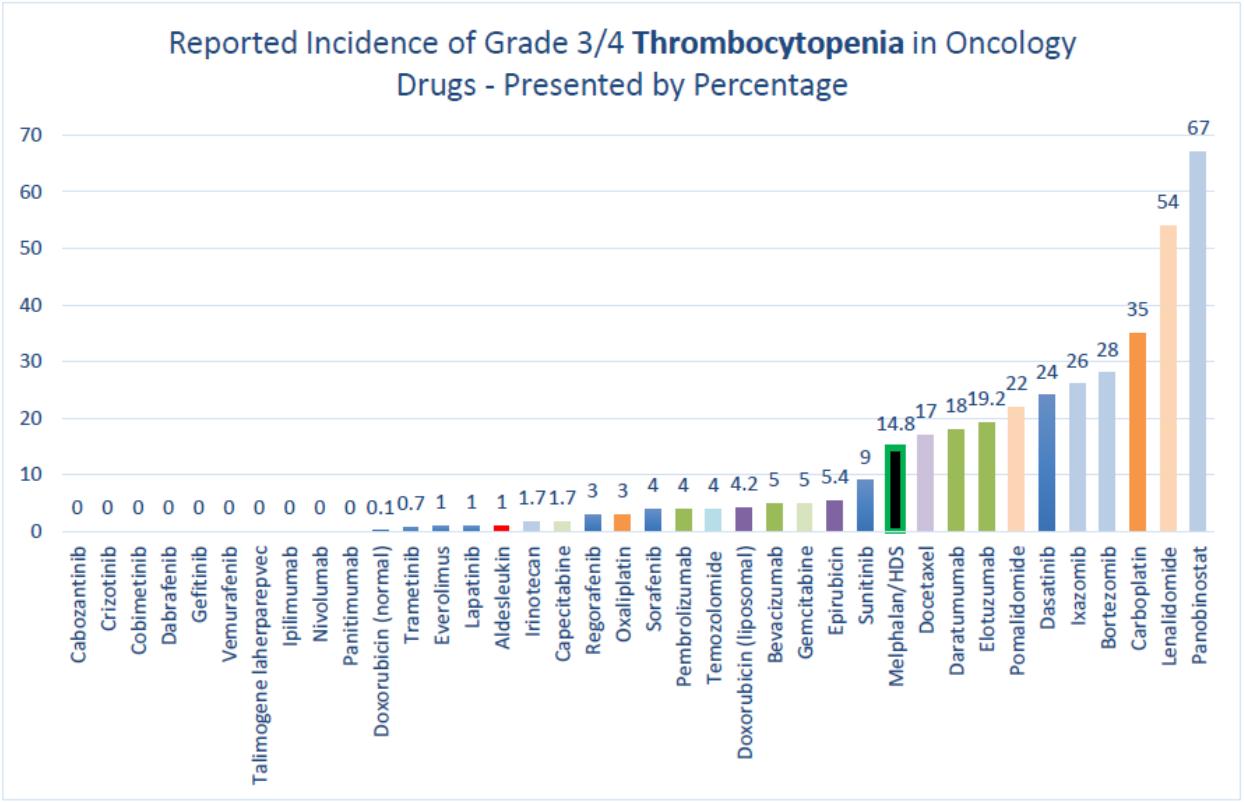
			This patient subsequently underwent a gynecological exam, which showed that the vaginal bleeding was "most likely caused by heparin-induced bleeding of the endometrium." The patient recovered without sequelae. This patient did not go on to receive chemosaturation with PHP.	*haemorrhage with grade 2 anaemia in 1 patient.*[8] ‘’ ‘’*Vaginal bleeding was reported in 1 patient in the case series of 14 patients. This was probably induced by heparin. The patient did not receive chemosaturation with PHP and recovered without sequelae*.’’ For study 10 (Vogl 2014), it is acknowledged in the overview that only 13 patients received PHP but 14 patients were initially recruited so this study is named the ‘’case series of 14 patients’’.
67	Consultee 13 Company Delcath	**3.1**	**Thromboembolic events** Inferior vena cava thrombosis occurred in 1 patient and liver vein thrombosis were reported in 1 patient in the case series of 18 patients.[5]	Thank you for your comment.

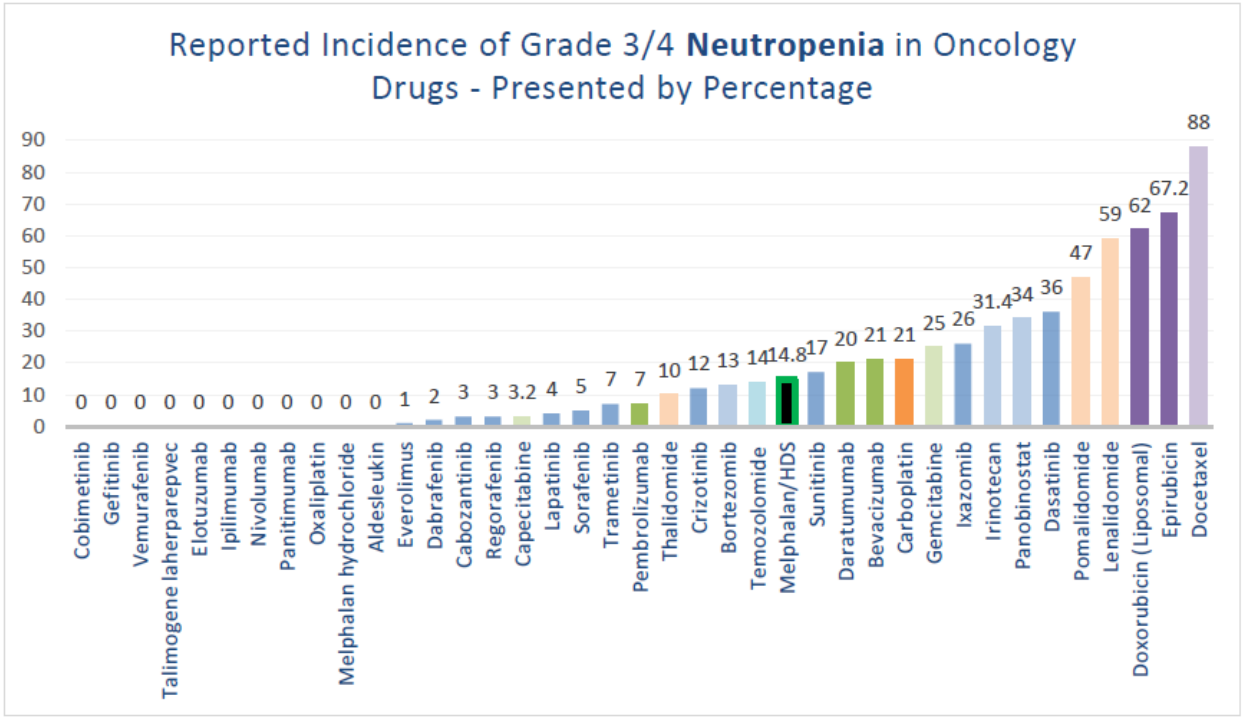
			The figures regarding safety events in this publication were reported per procedure, rather than per patient. This data is also presented in Table 3 of the publication, which was previously excerpted.	p 12 of the overview has been changed to: '' *Inferior vena cava thrombosis and liver vein thrombosis were reported in 1 procedure each in the case series of 18 patients*.[5]''
68	Consultee 13 Company Delcath	**3.1**	**Other adverse events** Increased serum calcium was reported in 23% (16/93) of patients in the RCT of 93 patients, all of which happened in the periprocedural period. End organ toxicity that was caused by the procedure-related hypotension was also reported in the study (no values reported).[1] Kindly note that the authors reported decreased serum calcium, not increased serum calcium. The non-randomised comparative study of 30 patients reported complications of PHP treatment in 60% (6/10) of patients. The complications included thrombocytopenia, liver function test abnormalities, anorexia, abdominal pain, fatigue, nausea or emesis (no values reported).[4] This comparative study does not distinguish which complications were observed in each of the treatment modalities analysed in the study (PHP, Y90, and chemoembolisation). The authors noted that liver function test abnormalities "came back to baseline within a few days after treatment." In the case series of 18 patients, 1 patient had balloon rupture and 2 patients had hypotension during the periprocedural period. In the postprocedural period, oedema was reported in 2 patients. Ascites, hypoxia, right leg compartment syndrome, pleural effusion and vertigo were all reported in 1 patient each in the postprocedural period.[5] The figures regarding safety events in this publication were reported per procedure, rather than per patient. Additionally, please recall that the cases of hypotension were previously included in the section regarding	Thank you for your comment. On p12-13 of the overview, the following changes have been made: ''*Decreased serum calcium was reported in 23% (16/93) of patients in the RCT of 93 patients, all of which happened in the periprocedural period. End organ toxicity that was caused by the procedure-related hypotension was also reported in the study (no values reported)*.''[1]

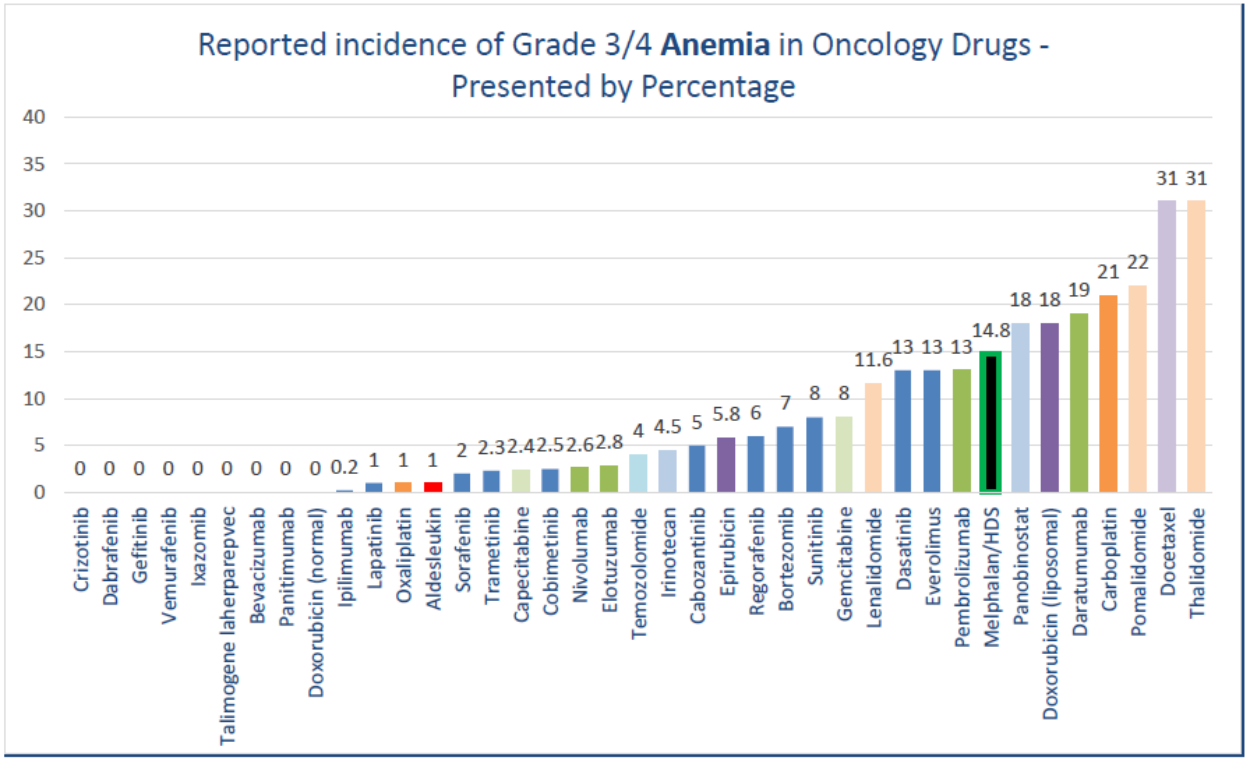
			cardiovascular toxicities. This data is also presented in Table 3 of the publication, which was previously excerpted. The authors noted, in the case of the balloon which ruptured during placement, that the balloon was able to be replaced successfully.	'' *The non-randomised comparative study of 30 patients reported complications of PHP treatment in 60% (6/10) of patients (no details provided).*''[4] p13 of the overview has been amended as follows: '' *In the case series of 18 patients, 1 balloon rupture was reported during the periprocedural period. In the postprocedural period, oedema was reported after 2 procedures. Ascites, hypoxia, right leg compartment syndrome, pleural effusion and vertigo were all reported after 1 procedure each.* [5]''

69	Consultee 13 Company Delcath	**3.1**	**Validity and generalisability of the studies** • Most of the studies are retrospective case series with small sample size. Only 1 RCT is included which had 93 patients. One prospective study is also included but only safety data were reported. The Committee is requested to additionally consider the data in the attached manuscript, which details efficacy and quality of life results as observed in a prospective phase II study. This is the same prospective study for which safety data were reported and previously discussed.	Thank you for your comment. The Meijer et al. (2020) study has now been published and has been included in the main extraction table after consultation.
70	Consultee 13 Company Delcath	**1.1**	**Conclusions** The Company acknowledges that there are serious adverse events observed in the literature on chemosaturation with PHP. The Company considers that these adverse events are not only well-known but also well-manageable. Indeed, eight of the nine articles considered by the Committee characterise the tolerability of the procedure as follows: Hughes et al: "Toxicity associated with therapy was significant but not resistant to effective management in the majority of patients." Karydis et al: "M-PHP was well tolerated in this study population." Kirstein et al: "Toxicity associated with therapy was significant but manageable and transient in our study." Vogl et al (2017): "PIHP was well tolerated by the majority of patients." The authors also stated there are "few, well treatable side-effects." Artzner et al: "SAEs were frequent, with most limited to grades one and two and not requiring additional intervention." Marquardt et al: "Side effects…seem to be tolerable and comparable to other systemic or local treatment strategies [for the treatment of ICC]." Meijer et al: "This study suggests that hematologic toxicity after M-PHP can be reduced by using the GEN 2 filter instead of a first generation filter. Although grade 3/4 hematologic events were still observed in the majority of patients, they were all well manageable or self-limiting." Vogl et al (2014): "Haematological events, which are the predominant toxicities associated with chemosaturation-PHP, are predictable and manageable with appropriate supportive care." The additional article considered by the Committee (Abbott et al) compared results of treatment with PHP (n=10), chemoembolisation (n=12) and Y90 (n=6). Complications were reported in 60% (6/10) of patients treated with PHP, in 83% (10/12) of patients treated with chemoembolisation and in 100% (6/6) of patients treated with Y90.	Thank you for your comment. The committee have decided to split their main recommendations between metastatic uveal melanoma and other cancers with primary liver cancer or metastases in the liver. Please refer to comment 31.

			As indicated by the Committee in section 3.3 of the draft recommendations, procedure-related complications, haematological toxicities, and death are key safety parameters. The Company is in agreement regarding the importance of these safety outcomes. The Company has implemented a comprehensive and mandatory training programme for the multidisciplinary teams at specialist centres that would perform the procedure. Learnings from the RCT (Hughes et al) have been incorporated into the training programme, along with learnings from the over 1050 procedures conducted in Europe since 2012. The training programme includes observation of a procedure (as performed by an experienced multidisciplinary team at a specialist centre), as well as required proctoring of the initial procedures performed by the initiate multidisciplinary team. After successful and satisfactory completion of this training programme, the multidisciplinary team is then certified by the Company to perform the procedure. With regards to procedure-related complications (including bleeding, thrombosis, and cardiovascular events), as seen in the reviewed publications there were no significant or long-term events related to chemosaturation with PHP. The potential complications of the procedure are discussed in detail in the CHEMOSAT instructions for use (IFU) and are reviewed as part of the mandatory didactic training programme. Haematological toxicities should be monitored in patients undergoing chemosaturation with PHP. Among centres in Europe that perform chemosaturation with PHP, post-procedure administration of G-CSF has become a standard practice in order to manage haematological toxicity. Of note, the investigators in the prospective study (Meijer et al) utilised a multivariate generalised mixed model to investigate the impact of potential risk factors on late haematological toxicity. Analysed variables were previous therapy, patient characteristics (age, gender, and BMI), and procedure-related variables (total melphalan dose, melphalan dose per kg of patient body weight, melphalan dose per ml liver volume, size of double-balloon catheter [50mm or 62mm], and total filtration time). The investigators reported: "The only variable that was found to be a predictor of late grade 3/4 neutropenia was prior therapy for liver metastases (systemic and/or local therapy) with an odds ratio of 5.5 (95% CI 1.4–21.7)." In accordance with this research, patients undergoing chemosaturation with PHP who have received prior therapy should particularly be monitored for haematological toxicities. The Company performed an analysis of the rates of grades 3/4 thrombocytopenia, neutropenia, and anaemia, as reported in US prescribing information, in drugs used to treat liver cancer. The rates of grade 3/4 thrombocytopenia, neutropenia, and anemia as observed in clinical trial data of chemosaturation with PHP were added for comparison. Kindly note that in this report, chemosaturation with PHP is referred to as "Melphalan via the Hepatic Delivery System" or "Melphalan/HDS." The results of this analysis are excerpted below.	







Based on this analysis, the percentages of grades 3/4 thrombocytopenia, neutropenia, and anaemia for chemosaturation with PHP from clinical trials is comparable to those of other approved drugs.
This analysis report is included with this submission for the Committee's reference.
The Company has provided commentary above on the deaths that occurred, and reiterates that subsequent to the changes made (including guidance critieria for patient selection, guidance regarding the management of hematological toxicity, and guidance on management of anticoagulation therapy), there has only been one procedure-related death (due to an unrecognised clotting disorder, Vogl et al 2014) in the 1050 procedures which have taken place in Europe since 2012.

The Company kindly requests that the Committee consider the data provided in this document in your assessment of this treatment. The Company requests that the Committee consider a specialist recommendation for chemosaturation with PHP in patients with liver metastases from ocular melanoma.

Consultation 2				
Com. no.	**Consultee name and organisation**	**Sec. no.**	**Comments**	**Response** Please respond to all comments
71	Consultee 3 Patient	**1.1**	"I think we need to recognise the difference between the advances in the procedure over the years. When we say 'serious but well recognised complications' is this referring to earlier studies or later studies. We need to distinguish between the earlier and later advances in this treatment. Data from earlier trials/ individual studies should be used to recognise efficacy of the procedure and to adverse reactions however analysis of this data should be used with caution. Delivery of this procedure has moved on and although there may be less data to support the fact there are less adverse reactions it is imperative that more recent data for the new procedure should be given more weighting.	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.
72	Consultee 5 Patient	**1.1, 3.6, 3.7**	My understanding is that the procedural risks mentioned predominantly date back to the early stages of trials (mainly in the US) and were due to technical machinery malfunction. With the cause of the problem recognised however, the technology used during the procedure has improved. Further, experience has taught practitioners the symptoms to look out for after the procedure and they are closely monitored. This means that the risk is greatly diminished. Indeed I would argue that any statistics that incorporate data from the early trials disproportionally "skews" the results. The Committee seem to acknowledge the technological advancement point at paras 3.6 and 3.7 when they note that: 'the toxicity of the procedure is principally related to how efficiently the melphalanis removed and prevented from entering the systemic circulation.... The technology has changed over time, and the newest filter may be associated with less haematological toxicity.'	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.

			Indeed, I have been told that my treatment centre has carried out circa 300 procedures to date, without any loss of life.	
73	Consultee 6 Patient	**1.1**	"GID-IPG10177 1.1 Having received this treatment on two occasions I question the word ""serious but well recognised complications"" what are these related too? as I personally have not experienced any side effects from my treatments what so ever, in fact i do not know of any other person that i have met during my treatment that have had side effects. i returned home after four days, I only spent approximately 3/4 hours in ICU on both treatment occasions as i did not require this due to me feeling so well. This continues to be the case. Following my treatment I was able and still carry on my everyday chores and excercise without any difficulty. i would like to know what studies have been done in relation to side effects of the treatment over what period of time since this procedure was first introduced and would like the most up to date version of this. my feelings are that these side effects are based on early studies some years back.	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.
74	Consultee 13 Mother of patient	**1.1**	"This comment states that 'there are serious but well-recognised complications'.This is true but does not take into account that these are short-term, that the Southampton team and centres of excellence in other countries have been refining their techniques in the light of experince and most patients have no or very short-term complications., and none have long-term complications. This comment also needs to be into the context of 'What other options are available for non-resectable metastatic UM ?' At the present time there is no other option which is as effective as PHE with melphalan, and this factor weighs heavily with patients when deciding to undergo an invasive procedure.	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.
75	Consultee 22 NHS clinician on behalf of BSIR	**1.1**	Comments from [redacted] on behalf of BSIR: On assessing the evidence submitted my comments are the following Evidence	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.

			Evidence supports the use of chemosaturation in cases of metastatic disease from primary ocular melanoma with statistically significant median progression free survival demonstrated in the form of a RCT(Hughes et al) in comparison with best alternative care. Overall survival is difficult to assess due to cross over. There are a number of further case studies demonstrating treatment response post treatment in cases of ocular melanoma metastatic disease e.g Karydis L et al overall hepatic response of 43.1%. Safety First generation filters did cause a significant drop in blood pressure once the patient was on bypass which may have contributed to the complication profile however, the second generation filters have significantly improved this. Safety profile also considered in literature presented to the committee.	
76	Consultee 23 NHS clinician on behalf of BSIR	**General**	Comments from [redacted] on behalf of BSIR Chemosaturation is intended as a treatment for patients who have diffuse/miliary metastases that are liver dominant, and for whom other treatment options are innefective. The majority of data available to date for Chemosaturation, is from patients who have ocular melanoma that has metastasised to the liver. Ocular melanoma is inexorably and rapidly progressive when metastasised to the liver. These patients have a prognosis of 4-6 months of life with no other effective treatment options. In this subset there evidence that chemosaturation is effective, either in maintaining stability, or reducing burden. Whilst an RCT shows no significant overall survival benefit, it should be recognised that this is almost certainly due to crossover into the chemosaturation arm in a group of patients for whom supportive care is the other option.	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.

			Other findings within this study are positive with respect to tumour response, and that is mirrored in other non-RCTs. It is a procedure with very specific and recognised toxicities and recognised complications. These include, but are not limited to: Bleeding complications due to the high doses of heparin during the procedure, and marrow suppression due to systemic 'leak' of melphalan. Physiological and cardiovascular complications due to periprocedural fluid requirements to support cardiovascular stability. Many of these historical toxicities have been reduced with an evolution of the technique, and an evolution of equipment. In particular, new generation filters significantly reduce systemic melphalan leak. This reduces marrow suppression and delayed bleeding risk. Periprocedural bleeding risk can be reduced by novel use of radial access (one femoral complication required surgery in the data subset) The technique is now delivered with deliberate fluid restriction, with a less labile post procedural course and less ICU/HDU bed stay and less patient morbidity. It is a labour intensive technique and requires high end anaesthetic support and experienced dialysis clinicians. Thus, it will not be within the remit of many hospitals to provide this and given the incidence of ocular melanoma, I would imagine that a small number of expert centres should provide this, to maintain competency and safety requirements. In summary, I believe it to be an effective tool for treatment of ocular melanoma, as there is a recognised paucity of alternative or effective treatment for liver dominant disease. Liver dominant disease in this subset is rapidly progressive with morbididty and mortality due to hepatic dysfunction. There is some, but limited evidence of efficacy in other tumour types, (cholangioca, breast, NET, CRC) and that would need to be considered on a more individual level.	

77	Consultee 10 Patient	**1.2**	1.2 As with all medical procedures, the clinicians need to outline the risks. The Delcath procedure has gained a reputation and has increased efficacy both in stabilising and eradicating metastatic liver tumours and thereby prolonging lives. Recent improvements to the filters have increased the safety and reduced toxicity. As with all procedures, patients need to be assessed for eligibility and then monitored during treatment. Numerous people I know with my condition (Ocular Melanoma) are keen to have the treatment as it is basically the best hope there is of living. In addition, having a systemic treatment (such as immunotherapy or another trial) after Delcath can be to the patient's advantage.	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.
78	Consultee 10 Patient	**1.1**	"1.1 From personal experience of having the procedure via the FOCUS trial (6 treatments all 6 - 8 weeks apart) during 2020, I would contest the 'serious but well recognised complications'. I personally had no such complications and the other people on my trial didn't either. In the short-term, the 3-day stay for each treatment was intense and tiring, but I had no great pain or discomfort and was able to resume normal life a few days after returning home. My quality of life between treatments was good and the scans I had after treatments 2, 4 and 6, show marked improvement and stability with some tumours having disappeared and others shrunk. Basically, my only alternative treatment was ipi/nivo immunotherapy which has a 14% success rate at stabilising tumours and often drastic side effects such as colitis requiring long hospitalisation, development of Type 1 diabetes and thyroid problems. I felt the Delcath procedure was my only chance at prolonging my life, enabling me to have a quality existence in terms of continuing to work and spending time with family and loved ones.	Thank you for your comment. The Committee welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations.
79	Consultee 15 Patient	**1.1**	"RE: point 1.1 For those who have Ocular Melanoma that then develops as metastasis to the liver (stats show that approximately half of all OM patients will develop liver mets at some point), time is of the essence with regards to receiving the appropriate life-saving treatment options as liver mets has a tendency to develop very quickly and will	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.

			undoubtedly debilitate and subsequently kill a person in a considerably short timeframe, as we have seen with numerous OM patients . In terms of side effects, most Ocular Melanoma patients we are used to having unpleasant side-effects as a result from treatment, however that is a small price to pay for something that will save our lives. Any side effects are likely to be much more bearable than dying a painful death, and are most likely to be short-lived, therefore, it can be seen as being much more dangerous and risky to prolong any treatment and even worse to not treat the mets with Chemosat at all. "	
80	Consultee 21 OcuMel UK	**1.1**	"Draft Document 1.1 Evidence on the safety of melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for cancer or metastases in the liver shows there are serious but well recognised complications: Response The statement within 1.1 does not adequately reflect the efficacy of this procedure and states that 'there are serious but well recognised complications' we feel it should be noted that while some patients experienced some serious side effects, they were well managed and short term. Our research notes that one man took a plane trip to a rock concert immediately after he was discharged and a woman was able to clean the outside of her windows four days after her treatment. Nonetheless, it would be beneficial if this difference was noted as the effects described in the chemosat studies are short term and well managed by the patient's team. Conversely, one participant although not stating that the treatment had no benefits, it was the side effects that caused them to give a low score.	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.

			It is important to take risk in context: for a patient with no suitable alternative, the level of risk is higher given that without treatment, death is inevitable and from that there is no recovery. We are in support of data being gathered with each treatment. The majority of recent patients we hear from have not experienced what is described in the publications relied on in the NICE document. Instead patients and researchers could benefit from 'real world data. This is particularly noteworthy as our communities are online and people voluntarily disclose information, a situation in which we know that negative experiences are reported more commonly than positive ones. We therefore believe it is critical to distinguish between complications that are due to the procedure itself and those related to the management that will improve with teams gaining experience. "	
81	Consultee 24 Company Delcath Systems, Inc.	**General**	**Conclusions** The Company welcomes the Committee's determination regarding the use of CHEMOSAT with PHP for patients with liver metastases from ocular melanoma, a rare and aggressive disease for which patients have few options. There is currently no standard of care for treatment of liver metastases from ocular melanoma, and while immunotherapy is commonly used to treat liver metastases from ocular melanoma, data shows that it has limited efficacy in this patient population. The Company will continue its implementation of the comprehensive and mandatory training programme for the multidisciplinary teams at specialist centres that will perform the procedure. The Company additionally looks forward to any new insights that are gained from experience at these specialist centres, as recommended in the Committee's guidelines. The Company is of the opinion that the designation of chemosaturation with PHP as a specialist treatment for patients with liver metastases with ocular melanoma will have a meaningful positive impact in the lives of these patients and their loved ones.	Thank you for your comments. Consultee agrees with draft recommendation on ocular melanoma.

82	Consultee 5 Patient	**1.1**	"'NICE interventional procedures consultation document November 2020' 8. I note at paragraph 1.1 of the above mentioned document that the recommendation for my condition is 'special arrangements'. My understanding is that this will be an upgrade from the existing position of 'research only' (as set out at line B89 – IPG488 of 'Published IP Guidance Nov 16' and at para 1.1 of 'Interventional Procedures Guidance document IPG488 – 27 May 2014'). 9. I support the proposal to stop this treatment being classified as 'research only'. My view is that all sufferers of this condition should have access to chemosaturation. 10. The consultation document captures at paragraphs 3.3 and 3.4 the rationale for the recommendation. In case it assists, I now set out below my experience on the points listed:"	Thank you for your comment. Consultee agrees with draft recommendations for ocular melanoma.
83	Consultee 17 Company medac Pharma LLP	**1.1**	"Melphalan chemosaturation with percutaneous hepatic artery perfusion hepatic vein isolation for primary or metastatic cancer in the liver Response to the consultation document issued on November 20th 2020. Medac Pharma LLP is pleased to note that recent publications, comments from healthcare professionals and from relevant patient groups have been taken into consideration following the public consultation around the June 2020 draft. We note that the guidelines have been amended accordingly and appropriately and we welcome the current guidance. 1.1 We also acknowledge that the procedure should only be used with special arrangements for patients with liver metastases from ocular melanoma primary cancer. The draft guidance also states that the use of the procedure for primary liver cancer and other liver metastases requires further data and should be used in the context of research. We note that further	Thank you for your comment. Consultee agrees with draft recommendations.

			clinical trials are planned in intracholangiocarcinoma (ICC) (ALIGN trial : NCT03086993) in the near future.	
84	Consultee 24 Company Delcath Systems, Inc.	**1.1**	Delcath Systems Inc, the manufacturer (The Company), thanks the Committee for their time and consideration of the procedure "chemosaturation with percutaneous artery perfusion and hepatic vein isolation for primary or metastatic cancer in the liver." Our comments on the Draft Guidance and Overview are provided below. **Comments on Draft Guidance** **1.1: Evidence on the safety of melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for cancer or metastases in the liver shows there are serious but well-recognised complications:** • **• For patients with metastases in the liver from ocular melanoma, there is some evidence of short-term tumour response. For these patients, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. Find out what special arrangements mean on the NICE interventional procedures guidance page.** • **• For patients with primary liver cancer or metastases in the liver that are not from ocular melanoma, evidence of efficacy is inadequate in quality and quantity. For these patients, this procedure should only be used in the context of research. Find out what only in research means on the NICE interventional procedures guidance page.** The Company thanks the Committee for their consideration of chemosaturation with PHP in the specialist setting for patients with liver metastases from ocular melanoma. The Company affirms the use of chemosaturation with PHP in the context of research for patients with primary liver cancer or liver metastases that are not from ocular melanoma. The Company would call the Committee's attention to the following excerpts from the Overview (Interventional Procedures Consultation Document). These excerpts appear with a box around them.	Thank you for your comment. Consultee agrees with draft recommendation on primary liver cancer or metastases in the liver that are not from ocular melanoma.

			In each case, the Company has made comments to provide additional context which the Company considers to be integral when analysing the excerpted data. In some cases, the Company has made a comment to provide information about a factual inaccuracy.	
85	Consultee 13 Mother of patient	**1.1**	2 - Also in section 1.1 there is a reference to 'ocular' melanoma.This condition is more accurately known as uveal melanoma	Thank you for your comment. The procedure description will be changed to state that the condition is also known as ‘uveal’ melanoma.
86	Consultee 13 Mother of patient	**1.1**	3 - 'evidence on quality of life and survival is inadequate in quality and quantity' However it is the first line recommendation by all oncologists explerienced in treating non-resectable MUM. ! There has been so much work published on it since 2014 that Germany are now recommending it as a standard treatment for MUM. Also in the USA patients have had the procedure repeated when the metastases returned after some years, which again provided several years of PFS	Thank you for your comment. Section 1.1 states that ‘For patients with metastases in the liver from ocular melanoma, there is some evidence of short-term tumour response.’
87	Consultee 21 OcuMel UK	**1.1**	"Draft Document For patients with metastases in the liver from ocular melanoma, there is some evidence of short-term tumour response. For these patients, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research. Response We feel it is important to note that there are systemic treatments being developed but these are not available to patients until the data has been published. These treatments can only benefit our stage IV patients should they survive the next two years. We also feel it is so important that patients have timely access to this kind of treatment. "	Thank you for your comment. Section 1.5 has been changed to: ‘Further research should be in the form of randomised controlled trials against current best practice, **including other liver-directed and systemic therapies**.’
88	Consultee 21 OcuMel UK	**1.1**	"Draft Document For patients with primary liver cancer or metastases in the liver that are not from ocular melanoma, evidence of efficacy is inadequate in quality and quantity. For these patients, this procedure should only be used in the context of research. Find out what only in research means on the NICE interventional procedures guidance page.	Thank you for your comment.

			Response We have no experience of the above in settings other than Ocular Melanoma. "	
89	Consultee 13 Mother of patient	**1.2**	1.2 - Absolutely agree , this procedure should only be done in specialist centres by a multi-disciplinary team.	Thank you for your comment. Consultee agrees with section 1.2.
90	Consultee 17 Company medac Pharma LLP	**1.2**	1.2 With respect to the use of the procedure in patients with liver metastases from ocular melanoma primary cancer, this has to date been carried out only in two NHS hospitals (University Hospital of Southampton and University Hospital of Liverpool). Three additional sites in the private sector have used the procedure. No new NHS sites are planned. We should like to reassure IPAC that, in all sites: • There is a highly specialised team of healthcare professionals to carry out the procedure • All HCPs involved must be trained and accredited by experienced practitioners • All sites are checked by the manufacturer (Delcath Systems Inc) for equipment and facilities compliance in accordance with a detailed written manual. • Clinical Governance leads are aware of the procedure • Patients are provided with detailed information which is explained to them in an accessible way. New patient information is in development to improve on this further. • All patients go through a detailed multidisciplinary team review before they can be accepted for treatment. • Data has been collected for clinical trial purposes according to protocols. • All patients treated in the private sector have been recorded. • A detailed audit of patients is in the process of being developed by medac	Thank you for your comment. NICE's interventional procedure outcomes audit tool will be available on the NICE website when the guidance is published.

			• It is the company's intention that there shall be a treatment centre forum to share good practice and insights. Please note that NICE's interventional procedure outcomes audit tool has not been available for this procedure. However, the company is in discussions with an experienced provider to set up such a tool. All other points are acceptable without comment."	
91	Consultee 3 Patient	**1.4**	I think this is an extremely important point. I think the experience of the teams is vital to the continued successful delivery of this treatment. Highly skilled teams should be carrying out this procedure. As I understand, the treatment has seen to be most successful in ocular melanoma patients. This cancer effects 6 in a million people with 50% going on to develop liver metastases. With this in mind, I think it is very important that treatment is only available at specialised centres as I think this will ensure better patient care, better data gathering and above all, better patient outcomes. Outstanding patient care and effective data gathering will be vital to the continuous delivery of this treatment.	Thank you for your comment. Section 1.4 of the draft guidance states that 'The procedure should only be done in specialist centres by a multidisciplinary team that includes an interventional radiologist, an anaesthetist, an oncologist and a clinical perfusion scientist trained and experienced in the procedure.'
92	Consultee 21 OcuMel UK	**1.4**	"Draft Document 1.4 The procedure should only be done in specialist centres by a multidisciplinary team that includes an interventional radiologist, an anaesthetist and a clinical perfusion scientist trained and experienced in the procedure. Response We strongly support the above statement. We would further like to see a systematic integration with medical oncology as patients will also be seen by their cancer-specific team and the procedure should be seen as a part of an overall and consistent treatment strategy. "	Thank you for your comment. Section 1.4 has been changed to include an oncologist in the multidisciplinary team.
93	Consultee 22 NHS clinician on behalf of BSIR	**1.4**	Procedure The procedure should only be considered in centres with appropriate anaesthetic support with cardiovascular experience. Further access and experience with a perfusionist team is essential. The	Thank you for your comment. Section 1.4 of the draft guidance states that the

			interventional radiology team should be appropriately trained under a proctoring programme. Further access/cover from hepatic surgeons should be in place to ensure appropriate cover for potential complications. The patient will require ITU admission post procedure and therefore appropriate facilities are required on-site. • Chemosaturation is intended as a treatment for patients who have difficulty to treat miliary metastases that are dominant in the liver, not primary liver cancer. • The majority of data available to date for Chemosaturation, is from patients who have ocular melanoma that has metastasised to the liver. Without Chemosaturation, these patients have a prognosis of 4-6 months of life with no treatment options.	procedure should only be done in specialist centres by a multidisciplinary team trained and experienced in the procedure.
94	Consultee 21 OcuMel UK	**1.2**	"Draft Document 1.2 Clinicians wishing to do melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for patients with metastases in the liver from ocular melanoma should:.... Response We would also like to see added to this list: Clinicians must be made aware of the time frame that the patients' treatment should begin, starting from the 'decision to treat.' Clarification of whether the clinical governance lead be responsible for sourcing funding and how this may impact treatment times."	Thank you for your comment. Funding is not within the remit of the Interventional Procedures programme. It is not within the remit of the guidance to determine diagnosis to treatment targets for the NHS.
95	Consultee 21 OcuMel UK	**1.3**	"Draft Document 1.3 Healthcare organisations should:... Response We would like to see measures in place that patients are not penalised when healthcare organisations fail to adhere to timelines.	Thank you for your comment. This is the responsibility of the commissioner and falls outside the scope of the guidance.

			"	
96	Consultee 6 Patient	**1.5**	1.5 Reference to further research of a randomised controlled trial I personally would not want to take part in this type of trial as it would be unfair for half the people to have the chance to live who will receive the chemosaturation treatment That would be choosing who will live and who will die. Are there not other ways in which the data you require available to allow a fair chance for everyone needing this treatment to stay alive	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.
97	Consultee 3 Patient	**1.5**	I agree further research is vital, especially for rare cancers where treatment and research is limited. However, I do not agree with 'randomised controlled trials against current best practice' For me, there was no alternative. So current best practice is no treatment. I am aware there are some other immunotherapy drugs however with extremely limited effectiveness and these are also clinical trials.	Thank you for your comment. Section 1.5 has been changed to: 'Further research should be in the form of randomised controlled trials against current best practice, **including other liver-directed and systemic therapies**.'
98	Consultee 10 Patient	**1.5**	1.5 I don't believe randomised trials would attract enough patients who would stay on the trial long enough to collect feasible data. Additionally, liver metastases can develop quickly, so trial patients would also die during the course of the trial.	Thank you for your comment. Section 1.5 has been changed to: 'Further research should be in the form of randomised controlled trials against current best practice, **including other liver-directed and systemic therapies**.'
99	Consultee 13 Mother of patient	**1.5**	1.3 - Recommends the use of randomised control trials against current best practice. As there is no effective current best practice for MUM, patients are not prepared to be on control arm and this is therefore impossible to carry out. Trials have had to change to single-arm trials. On 20/9/2020 Delcath published early safety data for a FOCUS trial which showed a vastly improved safety profile for Chemostat with the latest techniques.	Thank you for your comment. Section 1.5 has been changed to: 'Further research should be in the form of randomised controlled trials against current best practice, **including other**

				liver-directed and systemic therapies.'
100	Consultee 21 OcuMel UK	**1.5**	"Draft Document 1.5 Further research should be in the form of randomised controlled trials against current best practice. It should report details of patient selection, concurrent therapies and techniques, and adverse events, including those related to chemotherapy Response We support further research but consider randomised controlled trials against best practice as unethical for this condition as 1) metastatic Ocular Melanoma is without effective standard of care; randomisation against the current standard thereby would mean sending people to their certain deaths and 2) the differences in management, as well as the expertise required, for the procedure itself are unlikely to generate Randomised Controlled Trial data that truly reflects the situation that our patients encounter in the real world. Ocular Melanoma is a rare cancer and because there is no clear treatment pathway for metastases we see differences in the way it is currently treated. We would therefore like to see an introductory scheme that a) standardizes the treatment pathways for all ocular patients b) systematically captures the data from every patient, including risk factors and outcomes and c) that allows to measure and control for the quality of the performance of the procedure at local sites. "	Thank you for your comment. The committee discussed this comment and did not feel such a trial would be unethical. It noted that current best practice could include systemic therapies as well as liver directed therapies that are effective. The guidance has been changed to make this clear.
101	Consultee 15 Patient	**1.5**	"RE: 1.5 Why is there a suggestion for the requirement of ""further research"" for this treatment option when it was already given the green light earlier in the year, and decided that Chemosaturation/Chemosat would be a viable and suitable option for treating Ocular Melanoma patients who have gone on to develop liver mets?	Thank you for your comment. The draft recommendation for the first consultation was that the procedure should only be used in the context of research. In response to comments from consultees, the recommendation was subsequently changed for

			In delaying this treatment from getting implemented as a matter of urgency, essentially, you're playing with people's lives. There are already patients who are currently with liver mets who are in limbo over the Christmas period waiting to see if this treatment will get the go-ahead, as promised, or whether they will have to start finalising their personal affairs and saying their goodbyes to loved ones (because this is the stark reality); people ARE dying without treatment! Every day that goes by that these patients are not receiving treatment is like a ticking time-bomb that is waiting to go off. In other countries, there are proven cases that this treatment IS effective in treating liver mets in OM patients, so surely this data counts for something, especially for such a rare form of cancer?! Any more waiting is adding to the anxiety and frustration to the patients and their families and it is, potentially, signing peoples' death warrants. How would you feel if it were your family member going through this? I know first-hand what it is like to lose a family member to cancer and it was heartbreaking! Throughout the first two years of my personal Cancer journey with Ocular Melanoma, I nursed my mum through terminal cancer right up until her death which was was six months after my 2nd diagnosis and subsequent cancer treatment, I have seen the pain of losing someone to cancer, and just how harrowing it is for the patient. I would not wish this upon anyone. Knowing that there IS an effective treatment available that was approved months ago yet is being delayed for no apparent reason is frightening for all of us who have Ocular Melanoma and even more upsetting for those who are bankrupting themselves in an attempt to fund treatment. We all know that anxiety and stress lower the immune system and any chances of recovery, so why make an. already difficult situation worse?"	ocular melanoma to say that the procedure should only be used with special arrangements for clinical governance, consent, and audit or research. The committee considered that there was still a need for further research before the procedure could be recommended for use with standard arrangements for clinical governance, consent and audit.
102	Consultee 21 OcuMel UK	**2.1**	"Draft Document 2.1 The most common types of primary liver cancer are hepatocellular carcinoma (also known as hepatoma) and cholangiocarcinoma. However, cancer in the liver often metastases from other sites such as the lung, colon, stomach and eye (particularly ocular melanoma).	Thank you for your comment. The cited study showed small, apparently dormant micrometastasis in the liver of

			Response We agree with the above statement but note that hepatic metastases occur in up to 95% of patients with metastatic uveal melanoma, and result in death in almost all cases. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4472306/) "	10 patients with uveal melanoma.
103	Consultee 21 OcuMel UK	**2.2**	"Draft Document 2.2 Treatment for primary or metastatic cancer in the liver depends on the location and stage of the cancer and how much liver function is preserved. Treatment options include surgical resection, thermal ablation, systemic chemotherapy, transarterial chemoembolisation, isolated hepatic perfusion and selective internal radiation therapy. In patients with primary liver cancer, surgical removal with curative intent and liver transplantation may be possible. For most patients with liver metastases, treatment with curative intent is not possible. Response We would like to see the importance of effective local control in the combination with systemic treatment previously mentioned. Metastases to the liver are known to be particularly hard to treat with systemic treatments, and patients die because of liver failure but with well-controlled disease outside the liver. The addition of an effective liver-directed therapy therefore promises to compensate for a weakness of systemic therapies."	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.
104	Consultee 21 OcuMel UK	**2.5**	"Draft Document 2.5 The procedure causes significant changes in the patient's haemodynamic status, which must be managed by the anaesthetic team with support from a clinical perfusion scientist. Response We are in support of the above and would like to highlight the need for training and expertise in the centres performing these procedures to ensure patient safety."	Thank you for your comment. Section 1.4 of the draft guidance states that the procedure should only be done in specialist centres by a multidisciplinary team trained and experienced in the procedure.

105	Consultee 3 Patient	**3.3**	For me, I was told this is my only option. I am aware there are emerging therapies for treating liver cancer. However for ocular melanoma patients with liver mets there are limited successful therapies. The only other options are also in clinical trials (e.g. immunotherapy) but are significantly less effective than chemostauration and also have significant side effects that are much more long lasting and chronic. We were informed that the side effects of immunotherapy are highly likely to result in multiple hospital visits, hospital admission and that the side effect from this would outweigh the effectiveness of this treatment.	Thank you for your comment. The Committee considered this comment but decided not to change the guidance.
106	Consultee 6 Patient	**3.9**	3.9 How does this help us now when we need this treatment so urgently. Does this mean that there are any other treatments available before April 2021. I would be grateful for clarification of this.	Thank you for your comment. The committee accepted this comment was unhelpful in isolation. Discussion on other emerging therapies was outside the remit of this guidance which is specifically on Melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic liver cancer. Therefore section 3.9 of the draft guidance has been deleted.
107	Consultee 10 Patient	**3.9**	3.9 NICE claims 'There are other emerging therapies for treating liver cancer and metastases'. This needs to be expanded to give more information in terms of the treatments and when they will be available. It isn't tangible enough for those with liver metastases who have a short life expectancy without treatment. "	Thank you for your comment. The committee accepted this comment was unhelpful in isolation. Discussion on other emerging therapies was outside the remit of this guidance which is specifically on Melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic

				vein isolation for primary or metastatic liver cancer. Therefore section 3.9 of the draft guidance has been deleted.
108	Consultee 13 Mother of patient	**3.8**	3.8 The committee was informed that 'There are other emerging therapies for treating liver cancer and metastases'. Who by? What specialist knowledge did they have ? This may be true for some cancers but for MUM there is no emerging therapy which has anywhere near the success rate of mephalan chemosaturation. TILS may be regarded as an emerging therapy but is vastly more expensive, has more severe and longer lasting side effects and is still in the experimental stage. It is no help to patients who have MUM at the present time	Thank you for your comment. The committee accepted this comment was unhelpful in isolation. Discussion on other emerging therapies was outside the remit of this guidance which is specifically on Melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic liver cancer. Therefore section 3.9 of the draft guidance has been deleted.
109	Consultee 15 Patient	**3.9**	"RE: 3.9 What other effective and proven ""emerging therapies for treating liver cancer and metastases"" are there currently on offer? Please could you provide examples and their effectivness. Re: ""Emerging"" , this implies that these alleged therapies you have mentioned in section 3.9 are not currently available on the market, and there is no indicator as to the timeframes of when, exactly, they are likely to be available, so this is not helpful to anyone who has developed liver metastasis as this also suggests yet more delays in treatment and more waiting for an indefinite solution, thus, again, playing Russian roulette with people's lives. Why are there even delays in pushing chemosat through when it has already been	Thank you for your comment. The committee accepted this comment was unhelpful in isolation. Discussion on other emerging therapies was outside the remit of this guidance which is specifically on Melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic liver cancer. Therefore section 3.9 of the

			approved? Other countries in Europe such as Germany, have already proven its effectiveness so why the delay in the UK? Time is of the essence, why wait for months and waste precious time? Please can you push Chemosat through quickly, before January, and give it special approval so that precious lives may be saved. Another thing to note is the psychological impact of delaying Chemosat is quite a heavy one that will impact not just the OM patients but their families, friends and communities. Not just that, there is also a heavy financial impact for pretty much every single person who is having to pay privately to even get this lifesaving treatment. Living with a rare form of cancer plus liver mets is stressful enough without facing the possibility of being forced to sell one's own home and place of safety . Most people cannot afford to spend £40,000 every six weeks to fund treatment, and those who are having to do so, at present, are facing financial ruin. How is a person supposed to recover or even live out what could potentially be their last days whilst living in fear of becoming homeless and bankrupt whilst knowing that the one treatment that can save them is being delayed despite having been approved months ago?"	draft guidance has been deleted. Interventional procedures guidance does not consider how much the procedures would cost the NHS, or whether the NHS should allocate funding for them. These decisions are made at a local NHS level and usually on a case-by-case basis.
110	Consultee 21 OcuMel UK	**3.9**	"Draft Document 3.9 There are other emerging therapies for treating liver cancer and metastases. Response This statement would benefit from context. Alternatively this statement can be removed as it does not provide any clear information. If additional comments can be made in this section, it would help to: highlight that ocular melanoma is typically an aggressive cancer treatment should start swiftly as a lower tumour burden increases its effectiveness. "	Thank you for your comment. The committee accepted this comment was unhelpful in isolation. Discussion on other emerging therapies was outside the remit of this guidance which is specifically on Melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic liver cancer. Therefore section 3.9 of the draft guidance has been deleted.

111	Consultee 1 Family Member	**General**	My mother has self funded three rounds of Melphalen chemosaturation 'Delcath' at [redacted] in [redacted]. She has found the three procedures tolerable. She was first diagnosed with 30 Liver Metastases as a result of Uveal Melanoma, in November 2019. The 30 liver metastases were diffused across her liver and we were given no treatment options via the NHS. She was given an approximate life expectancy of 6 months. I found the option of Delcath via my own research and my mother has undergone three mephalen chemosaturations. After the first treatment in December 2019 a scan 6 weeks later showed her tumors had remained stable and the two larger tumors had experienced 2mm shrinkage. After her second mephalen chemosaturation in Feburary 2020 there was furthur shrinkage on the largest tumors and the rest had remained stable. She then, due to Covid did not have another scan until August 2020 making it 6 months and once again, the tumors had not only remained stable but there was further shrinkage. She underwent her third treatment in October 2020 and we are waiting to do another scan until the Covid wave declines. If we did not have access to personal funds to do the Melphalen Chemosaturation I have no doubt that my mothers tumors would have spread and she would no longer be with us today. I have known Melphalen Chemosaturation patients who have had to crowd fun or sell their homes at 70 years old in order to pay for their treatment. My mother will continue to pay for the procedures as they are clearly extending her life and there is no other available treatment option for liver metastases secondary to Uveal Melanoma.	Thank you for your comment. The Committee welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations.
112	Consultee 2 Mother to Uveal Melanoma patient	**General**	"My daughter is 25 years old with Uveal Melanoma and metastasis to the liver. She has received two types of immunotherapy with no success. As a family we are racing £240,000 to give her this life extending treatment (whilst we wait for something else to come along). She has had two treatments with no side effects. She has recovered well each time. The scans are showing no progression and the large tumours are reducing.	Thank you for your comment. The draft recommendations for ocular melanoma were changed because of comments received during the first consultation. This meant that there needed to be another consultation on the revised

			The pressure of trying to save our daughter as well as having to raise an ENORMOUS amount of money is massive. Please please give the people that need this treatment to stay alive the chance to have this paid for so that they do not need to worry. Our daughter is doing amazingly since starting this treatment. But April 2021 is a long way away. Please bring the date back to January. Thank you. [redacted]"	recommendation, which has delayed publication of the final guidance. Interventional procedures guidance does not consider how much the procedures would cost the NHS, or whether the NHS should allocate funding for them. These decisions are made at a local NHS level and usually on a case-by-case basis.
113	Consultee 3 Patient	**General**	From personal experience I have had two procedures (10 weeks apart) at [redacted] I was enrolled on the FOCUS clinical trial in [redacted] and I had been made aware of all of the potential side effects from this treatment. I was also reassured that although these adverse reactions had happened in the past when using the older filter, with the newer filter we were seeing less and less incidences of these adverse reactions. As there is no other effective treatment I was prepared to take the risk. My trial was cancelled due to the COVID pandemic. After the trial was cancelled, I was put under 'surveillance only.' There was no other option for me. I then went on to privately fund 2 treatments at the [redacted]. Although unfortunately my data cannot be used as part of the trial, I feel strongly that my experience should be recognised and taken into consideration. I would like to share my experience after my first and second procedure: Comments from [redacted] MEDICAL TEAM Effectiveness after first two treatments: "She underwent repeat imaging during the admission to assess response to her first treatment. Pleasingly this shows an excellent response with a reduction in size and number of her liver metastases,	Thank you for your comment. The Committee welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations.

			no new disease and no metastases outside the liver. This is clearly extremely reassuring” Side effects: “made an excellent recovery from her treatment” “she also developed some fatigue post procedure but again this has now resolved, and she has been able to return to work” “she underwent her second procedure on the 5th October which again went uneventfully and she made an excellent recovery in the immediate post procedure phase”	
114	Consultee 3 Patient	**General**	"My own personal comments: For my first and second procedure I was admitted to hospital for 5 and 4 days respectively. During the first admission I spent the first night on ICU because I went down to theatre late in the afternoon. For the second treatment I went to theatre first thing in the morning and I did not go to ICU and was discharged after three nights. My sides effects both times were fatigue and nausea. The nausea subsided by the time I left hospital. The fatigue lasted up to 2 weeks following the first procedure and just a few days following the second. Following both procedures I returned to work to work as a Child Psychologist after three weeks. From the second week post procedure I was able to resume light exercise on my exercise bike and do my usual 5 days per week! I am not aware of any longer-term side effects and haven’t experienced any. I was extremely pleased to know the treatment had reduced the number and size of my liver lesions. I had no other treatment option available to me, so to hear this kind of result has been fantastic for me and my family. Throughout the treatment I have remained physically well and after each procedure I have returned to my pre-procedure fitness levels three to four weeks after the treatment. This amounts to an hour of cardio exercise a day, five days a week. With no other options I would take the risk of the ‘serious but well recognised’ complications. I have been told by the medical team that I tolerate this treatment really well and the weekly blood tests that are	Thank you for your comment. The Committee welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations.

			taken every week for the first four week following treatment have all been normal and I have not required any further intervention."	
115	Consultee 3 Patient	**General**	Will the chemosaturation treatment be defined into the ocular melanoma treatment guidelines/pathway for ocular melanoma patients that meet the criteria to have this treatment. We would need to agree timelines for patients that meet the criteria to have this treatment. By not defining treatment guidelines and timelines, patients could have to wait to have the treatment and this could significantly reduce the effectiveness of the treatment and may require more chemosaturaton. Ocular melanoma patients with liver mets typically have no other options and waiting for treatment would pose a significant negative effect on their mental and physical health. I have experienced significant trauma after initially being on the FOCUS clinical trial in March (cancelled due to covid pandemic) and had to wait until July when I could access the treatment privately. By this point by tumours had grown 50%. I am curious to know how effective my treatment would have been if I could have accessed it at the start of the pandemic as originally planned.	Thank you for your comment. The Interventional Procedures programme at NICE assesses the safety and efficacy of new interventional procedures. The Committee makes recommendations on conditions for the safe use of a procedure including training standards, consent, audit and clinical governance. It does not have a remit to determine the placement of a procedure in the pathway of care for a disease or condition.
116	Consultee 4 Patient	**General**	I was recently diagnosed with liver mets after getting a rare ocular melanoma 4 years ago. I have done all I Can to prevent the Mets, living a healthy lifestyle, organic veg food. But finally I got them. My oncologist told me I would have to self fund for this chemo saturation. If I don't get the treatment I only have a year to live. Devastating to hear I got the mets and the added stress of finding money to fund the treatment. Which costs 40 thousand pounds a go. I've had to beg and borrow money for the first treatment making my life throughly depressing. I will need more than one treatment. I know others in the same situation having to sell their homes. Please help.	Thank you for your comment.
117	Consultee 5 Patient	**General**	"Introduction 1. I am [redacted], a patient. I am 64 years old and reside in England. In Spring 2020 I presented with blurred vision, was diagnosed with Ocular Melanoma, and had my right eye removed. In August 2020, I was diagnosed with Stage 4 metastatic cancer of the	Thank you for your comment. The Committee welcomes hearing from patients who have undergone this procedure and

			liver. Given the limited options available and their prospects of success, I am self-funding chemosaturation treatment. 2. I understand that interventional procedural consultation for Melphalan chemosaturation with percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic cancer in the liver, closes on 17th December 2020. This is my patient submission under that process. 3. This submission first comments generally on the content of 'NICE interventional procedures consultation document November 2020'. It then, by way of further supporting submission, provides my patient experience using the guidelines set out in 'Contribution to Nice interventional procedure guidance – a guide to patients and carers'. I have not contributed to date given that diagnoses only occurred earlier this year. 4. By way of overview, as a patient who has experience of the procedure, my answer to the question: 'in the light of your experience would you, with hindsight, have chosen to undergo the procedure and/or recommend it to other patients?' My answer is wholeheartedly 'yes', on both accounts."	considered your experience and views in their deliberations.
118	Consultee 5 Patient	**General**	"Background 5. I chose not to receive immunotherapy treatment (available via the NHS) as the prospects of some negligible, or actual, positive response to treatment was reported as only circa 10%. Further, having discussed my options with other patients, I was informed that the side effects of immunotherapy severely impact on quality of life and in some cases, even resulted in abandonment of treatment altogether.	Thank you for your comment. The Committee welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations.

			6. Unfortunately, Chemosaturation was initially unavailable to me given that all trials had been suspended due to Covid-19. I therefore sold my family house (together with all possessions of value), moved in with my sister (together with my husband), borrowed savings from my elderly parents and started fundraising, all in order to privately purchase chemosaturation treatment. I chose this treatment as it has a 50% prospect of reducing the size of the tumours. An acceptable alternative is that it has a 30% chance of preventing the tumours from growing. Either option increases longevity of life. 7. At the time of writing, I have received two courses of chemosaturation treatment. The percentage of cancer within my liver was circa 15% prior to administration of the first round. My family and I were ecstatic to hear the results of the initial treatment; that all tumours had responded well and shrunk and/or disappeared. There was also no evidence of cancer having spread outside the liver. I await the results of the second round of treatment."	
119	Consultee 5 Patient	**General**	"'NICE interventional procedures consultation document November 2020' (cont) 10.1 'Overall Survival/Progression Free Survival/Downstaging of Cancer' Prior to treatment, my liver was peppered all over with lesions (the largest measuring 4cm) with overall coverage circa 15%. After just one course of treatment, all lesions had either been reduced in size or even, in some cases, removed altogether. There was a 50% prospect of this being the case. This is why I chose (and sold so much) to purchase this treatment. Having become friends with others who are going through this same process, I am aware that many of them are also responding positively to treatment. I do not know anyone that has been in the unlucky 20% where the treatment has had no effect. I do know one patient who has received 6 courses of treatment and, whilst the tumours did not reduce in size, they did not grow either.	Thank you for your comment. The Committee welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations.

			There was a 30% chance that this would be the case. The treatment has at least bought that person more time to live and they have enjoyed their quality of life. Conversely, I met a few people who could not afford to fund chemosaturation. They were left with immunotherapy as their only option. Unfortunately those people have all died already, either because the treatment was unsuccessful (there is only circa 10% chance of some success), or the side effects were so bad that they chose to stop treatment. 10.2 'Quality of life' As just mentioned, some acquaintances who chose immunotherapy (the available NHS treatment), found that the side effects impacted so heavily upon their quality of life, that they prematurely terminated treatment. This is due in part, as I understand it, because the prospects of success are so low that a combination therapy ("double dose") is often administered, despite there being negligible benefit. Chemosaturation on the other hand has minimal side effects and has provided me with an excellent quality of life. I suffer some minor impact for a few days after treatment (nausea and shortness of breath after exercise) but they are tolerable. Then the five to seven weeks after that (before the next treatment) have a negligible reduction in quality of life, despite treatment. I feel and look well, I am not prohibited in what I can do. In fact, the only detriment has been the significant impact on our mental wellbeing because we have to spend the time that we have bought, fundraising to pay for the next treatment (as the NHS do not provide it and trials have ceased due to Covid-19).	

			10.3 'Procedure-related complications (including bleeding, thrombosis and cardiovascular events), bone marrow or haematological toxicity, and death' None of the above applies to me personally to date. "	
120	Consultee 5 Patient	**General**	"'Contribution to Nice interventional procedure guidance – a guide to patients and carers' 11. Moving now from the consultation document to general patient comments, I note the statement at page 6 of the above mentioned document, 'Patients and carers can help those responsible for developing interventional procedure guidance understand what it is like to have had a particular procedure, and the key issues from a patient's perspective'. I therefore address each applicable listed item mentioned below: 11.1 'The practical, physical and emotional aspects of undergoing – or caring for someone who has undergone – a particular interventional procedure' The three consultants and lead nurse held a consultation with me to discuss my initial scans. My liver was peppered all over with lesions (the largest measuring 4cm) and overall coverage was circa 15%. Resection was not an option. We then discussed in detail my treatment choice; chemosaturation. They spent considerable time explaining the details of the procedure and all its implications and risks. I asked them how many times they had performed this procedure (circa 300) and how many people had died (zero). I also asked about prospects of success. This consultation allayed all my fears and confirmed this was the correct treatment for me. They made it clear this was life extending treatment but not a cure.	Thank you for your comment. The Committee welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations.

			When I was admitted to hospital for the first treatment I had a high level of anxiety. This was quickly allayed as the three consultants and lead nurse visited me to run through the procedure again and gave me the chance to ask questions. I had the treatment the following morning and 3-4 hours later woke in the high dependency unit where I was monitored continuously with a very high level of care. By later in the afternoon I was able to return to my room but was still monitored continuously. The following day I was well enough to wash, dress and walk with only a low level of nausea and tiredness. I returned home after three days with clear instructions on next steps and leaflets. The lead nurse phoned every week to monitor my progress and give results of weekly blood tests. This will always be emotional as I am trying to deal with my own mortality but having this treatment gives me hope that I can prolong my life and maintain a good quality of life. "	
121	Consultee 5 Patient	**General**	"'Contribution to Nice interventional procedure guidance – a guide to patients and carers' (cont) 11.2 'The views of patients and carers on: − 11.2.1 'What results or outcomes patients want from the procedure' I want to: prolong my life as long as possible; and, have as good a quality of life as possible. 11.2.2 'How well the procedure works from a patient point of view – for instance, the tolerability and acceptability of the procedure, its side effects and benefits ' The procedure went exceptionally well with minimal side effects. Having witnessed firsthand my Husband having chemotherapy	Thank you for your comment. The Committee welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations.

			treatment I am very aware of the side effects that systemic chemotherapy has on patients. My side effects are miniscule by comparison. Whilst the chemosaturation trials were regimented with the trial parameters requiring six courses of treatments administered six weeks apart, clinicians have found that without these constraints they can prolong life by: extending the space between treatments to eight weeks; and, reducing the number of initial treatments from six to three or four (if there is good evidence of tumour shrinking), thereby reserving further treatments until necessary. Life expectancy can now be measured in years rather than months. There are currently patients living who are three to four years on from their first chemosaturation treatment. The procedure works well. The issue for me however, is the lack of accessibility. After a life time of never needing the NHS I thought that in the event of a serious illness good treatment would be available to me. My mental health has suffered significantly from having to deal with my diagnosis, sell my home, sell my possessions, borrow my parents' lifelong savings and learn how to navigate the complexities of fundraising. I did not expect a magic, cure all treatment from the NHS, but I did expect a reasonable treatment with a reasonable prospects of success (e.g. chemosaturation). 11.2.3 'The safety of the procedure and its risks – in the short and long term − the preferences of patients (for example, preferences for a procedure compared with a direct alternative, if available, or compared with choosing not to have a procedure at all)' I have now received two treatments of chemosaturation. I have also spoken to recipients of both this treatment and Immunotherapy. I am in no doubt that my choice of treatment was the correct one."	

122	Consultee 5 Patient	**General**	"Conclusion 12. I have read, and fully support, the content of the written consultation submission by OcuMel UK. I hope that the final decision on this consultation can be expedited and not delayed until April (if the process allows it). 13. I repeat here the answer to the question, 'in the light of your experience would you, with hindsight, have chosen to undergo the procedure and/or recommend it to other patients?' My answer is wholeheartedly 'yes', on both accounts. 14. Finally, I note at paragraph 7 of the Guide the statement that: 'NICE interventional procedures programme looks at whether particular procedures used for diagnosing an illness or treating a patient are safe enough and work well enough for wider use in the NHS'. My experience, for what it is worth, is that people without the money to pay for this treatment are dying whilst they wait for the NHS to approve its use. The alternative (immunotherapy) is, to be frank, no real alternative at all. Evidence for chemosaturation is plentiful, worldwide, and other EU countries (e.g. Netherlands, Germany) have already, as I understand it, approved its use as the first line of treatment for Ocular Melanoma. Thank you for taking the time to read this submission"	Thank you for your comment. The draft recommendations for ocular melanoma were changed because of comments received during the first consultation. This meant that there needed to be another consultation on the revised recommendation, which has delayed publication of the final guidance.
123	Consultee 6 Patient	**General**	If this treatment is working so well for people and giving positive results, quality of life, using chemotherapy which is able to be delivered in such a way that other organs are not damaged as in the conventional way of treatment why would you not want to fast forward this treatment for us the patient. the mother, the grandmother and wife	Thank you for your comment. The draft recommendations for ocular melanoma were

			and others who should have an equal chance to live. Bringing this treatment forward will help save our lives, by delaying further consultation to the 28th April 2021 By denying people the chance to get this treatment it will potentially loose lives. Time is not on our side. My results so far following two treatments over a period of 18 weeks my first treatment results two lesions have actually disappeared and 4 have significantly shrunk. My second treatment further shrinkage and two lesions have stayed stable. . 1.2 By delaying the review until the 28th April 2021 for us as a patient could cost us a further 120,000 pounds. I have already self funded my first two treatments via cashing in all my pensions at the age of 57years. With the added fear of having to sell our family home to fund further treatments could I ask for you to seriously consider bringing this time frame forward. I have paid into the system all my life and have worked endlessly to support my family. I have never been in a position where I have had to ask for help from others however I have now been forced to do so just to try and save my life.	changed because of comments received during the first consultation. This meant that there needed to be another consultation on the revised recommendation, which has delayed publication of the final guidance.
124	Consultee 6 Patient	**3.1**	3.1 NICE have included the most recent papers can I ask why this is relevant? treatments should be available to us now as it is impossible to raise the amounts of money required for each treatment. Prior to Covid 19 in March 2020 I was assessed and advised that I would be a prime candidate for this treatment as I am a fit and healthy 57 year old who has taken care to look after myself. I am now £80,000 spent already this has been via my private pensions and fund raising which has been so very hard and there is only a certain amount of times you can ask people to support you. I I I now need help to get this treatment approved from NICE ASAP	Thank you for your comment. Section 3.1 describes the evidence that was discussed by the committee when the draft recommendations were made. Interventional procedures guidance does not consider how much the procedures would cost the NHS, or whether the NHS should allocate funding for them. These decisions are made at a

				local NHS level and usually on a case-by-case basis.
125	Consultee 7 Patient	**General**	I had ocular melanoma and am at high risk of Mets in liver. It is so important to my mental and physical well-being that this melphalan chemo saturation of the liver be available to me should I need it in the future. It needs to be available quickly. I know you have to follow procedures but there should be a time limit between diagnosis and treatment. If this specific treatment is provided quickly on the NHS it would make me feel more positive about my survival times. A positive mindset alone will give me a better future and prognosis.. I know there are risks but there are no alternatives. This treatment shouldn't be delayed to April 21. It should be available in January.. liver mets kill you rapidly. We can't wait months for funding! Also I definitely wouldn't want to be put on another random clinic trial. I would want Chemosaturation. [redacted]	Thank you for your comment. The draft recommendations for ocular melanoma were changed because of comments received during the first consultation. This meant that there needed to be another consultation on the revised recommendation, which has delayed publication of the final guidance. Interventional procedures guidance does not consider how much the procedures would cost the NHS, or whether the NHS should allocate funding for them. These decisions are made at a local NHS level and usually on a case-by-case basis.
126	Consultee 7 Patient	**General**	This is an additional comment of mine. Please make this treatment available on the NHS without delay. My next scan is due in January. I am High risk of mets. I would not be able to travel abroad for treatment or pay for treatment. I have severe anxiety and cannot travel.	Thank you for your comment.
127	Consultee 8 Patient Husband	**General**	Melphalan chemosaturation has been an extremely effective course of treatment for my wife. The procedures were uncomfortable but she tolerated them well, recovered quickly each time and is able to enjoy a good quality of life. This is the best treatment option available for her but we have had to spend our life savings in order to extend her life. My wife has so far had three Melphalan chemosaturation procedures (Delcath), this has been a very successful procedure for her but incredibly expensive and it seems unfair that for people with	Thank you for your comment.

			liver mets due to uveal melanoma their only effective treatment is self funded and for us has caused financial worries on top of the mental stress of a stage 4 cancer diagnosis.	
128	Consultee 9 Patient	**General**	"This is a subject close to my heart and one that i feel very passionate about. Having worked as a clinician in the NHS for 42 years and fairly recently retired, it was devastating to learn that two years after an occular melanoma diagnosis I had liver metastases affecting 30% of my liver. My daughter spent a huge amount of time researching treatment options and that was how I found myself under the amazing mephalen chemo saturation team at Southampton. Sadly for me the clinical trial was full at the time and my only option was to self fund. I have currently had three Delcath treatments ,although dreading it at first and fairly terrified, I found the experience pretty comfortable,very efficient and have recovered quickly after each procedure and able to get back to normal life ,walking ,gardening and enjoying everyday things .Due to Covid I had an eight month gap between treatments two and three but scans following treatment three are positive ,the tumours are not progressing, I feel well and am able to enjoy a very good quality of life. We are now in the position of worrying where the next £40.000 for treatment four will come ,this will have to be my last one -no more money in the pot for another. The mental stress involved in scrabbling around to find the money from our not very large life savings compounds the misery of the situation we are in -added to this I have not been able to get the required MRI scan the doctors at [redacted] need to monitor my tumours between treatments via the NHS and have been paying privately for those also. Please look with favour on this amazing treatment ,I was given four months to live and now more than a year later am able to enjoy life with my husband and grandchildren and have hope for a longer future . Thankyou	Thank you for your comment. The Committee welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations. Interventional procedures guidance does not consider how much the procedures would cost the NHS, or whether the NHS should allocate funding for them. These decisions are made at a local NHS level and usually on a case-by-case basis.

129	Consultee 11 Family member of patient	**General**	I am writing based on the experience my mother-in-law has had with Melphalan chemosaturation. She was diagnosed with with uveal melanoma three years ago and had her eye removed just after the diagnosis. Over a year ago, she was diagnosed with liver metastases and given. Without treatment, her prognosis wasn't promising -- roughly around six months. We learned about Melphalan chemosaturation and sought treatment, but were unable to secure a space in a trial. Fortunately, my mother-in-law has been able to self-fund three treatments privately over the past year and the results have been quite positive. The tumors on her liver haven't grown at all and some have even shrunk in size. The procedure has given my wife, myself and our three children invaluable quality time with my mother-in-law, --time we probably wouldn't have had if she had not been able to receive treatment in the timely manner she did or if she had not been able to afford the high cost for the treatment. Every day we are thankful for this extra time, but we realize there are other patients who are not so lucky, patients who may have to forego this life-saving treatment because it's either unavailable or financially out of reach. For all these reasons, please consider bringing the review date back to January, rather than April. It will make a huge difference in many people's lives, my mother-in-law's included.	Thank you for your comment. The Committee welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations. The draft recommendations for ocular melanoma were changed because of comments received during the first consultation. This meant that there needed to be another consultation on the revised recommendation, which has delayed publication of the final guidance.
130	Consultee 12 Patient	**General**	"I am perturbed that this is the second consultation document for this particular procedure. I am even more worried that the consultation is now having to wait until 28th April 2021 for the results. I am a 66 year old woman who has Ocular Melanoma. At the moment it is at stage 1 but, according to various reports and papers, it is 50/50 as to whether it metastasises to my liver, and if it does then I will certainly die an early death. In the next village to me is a gentleman who unfortunately has Stage IV Ocular Melanoma and cannot afford the private hospital fees for the chemosaturation operation. He is on a treatment (I believe it is called IpiNivo) and at his last MRI the prognosis was not good. If the chemosaturation was available on the NHS then he would have a much better prognosis and I would not have to watch him knowing that this could be my future too.	Thank you for your comment. The draft recommendations for ocular melanoma were changed because of comments received during the first consultation. This meant that there needed to be another consultation on the revised recommendation, which has delayed publication of the final guidance.

			The issue is that the treatment has already been proposed and yet Ocular Melanoma patients (such as me) need to wait for another 4 or 5 months for you to confirm the decision. I am sure you do not realise the amount of stress your lack of urgency is causing. I have to have an MRI every every 6 months and the stress is phenomenal, this is made worse knowing that there is the chance of a cure, one that you have been reviewing for what seems like forever. What happens in the meantime if I develop a tumour? I can't afford private medicine and am very upset that you blithely feel that it is an automatic assumption that all stage IV patients are capable of paying for private medicine or even that we have the luxury of waiting! You have read the reports and papers, you are aware that without any treatment I have a very short time to live, and most treatments on offer only have a very low chance of reducing the tumours. Please, I urge you to stand by your proposed decision and grant immediate approval instead of making us wait until April.	Interventional procedures guidance does not consider how much the procedures would cost the NHS, or whether the NHS should allocate funding for them. These decisions are made at a local NHS level and usually on a case-by-case basis.
131	Consultee 14 Patient	**General**	Having read the document I understand that the results for metastatic Ocular Melanoma are mixed and that there is no guarantee that the treatment would work but as an OM patient I also know that there is no alternative treatment available for me should my cancer spread. The cost of Chemosaturation from a private provider is prohibitive for me and so the approval of this procedure would be my only chance of survival. I understand that value for money must be a consideration but there are currently no alternative treatments, aside from clinical trials, and I ask that you give weight to this fact in your decision.	Thank you for your comment. The Interventional Procedures programme at NICE assesses the safety and efficacy of new interventional procedures. Cost-effectiveness is not part of the remit.
132	Consultee 16 Patient	**General**	"I`m 56 years old and still have plenty to do with my life. Unfortunately, 2018 I was diagnosed with uveal melanoma ad my left eye was removed. April 2020 the cancer had spread to my liver. The only available treatment on the nhs is immunotherapy. Its not even treatment for my cancer, its for skin melanoma. Its classed as palliative care, no cure. My life expectancy is 2 to 3 years - I wont make 60.	Thank you for your comment. The draft recommendations for ocular melanoma were changed because of comments received during the first consultation. This meant that

			I then hear that a trail was available called chemosaturation which is for my cancer and has given approximately a 60% increase on life expectancy - this is wonderful news. Then covid-19 put a stop to the trail and left me back at square one. I have read through the guidance and it is really promising and exciting, but the decision is 5 months away. Bringing the date forward could save my life - it sounds very dramatic I know but it really could. Today I am an ideal candidate - who knows if that will be the case come the end of April 2021. As I understand chemosaturation only works while the cancer is contained in the liver, so every day is crucial for this treatment to be available now not in a few months. The constant worry is 24/7 is it spreading, is it too late for any help, We know from the findings from the trail of this it gives me and other patients with liver metastasis from uveal melanoma the best chance of survival. Also to be able to have this treatment I need to be healthy, cancer patients can only control so much, the stress and anxiety of living with cancer is terrible and a downward spiral, mental strength can only last so long and 6 months could see this diminish rapidly. I'm on immunotherapy at the moment and the twice weekly visits every four weeks, with the side effects is so stressful. My last scan showed some lesion's had grown, so we don't even know if its working. I have just started crowdfunding to raise enough for 3 treatments - £120,000,more stress but I have to do something to try and prolong my life. making a decision and getting the treatment available to us now, I wouldn't need to do this and could concentrate on keeping as well as I can. Please please bring the review date forward and make it available to sooner. [redacted]"	there needed to be another consultation on the revised recommendation, which has delayed publication of the final guidance. Interventional procedures guidance does not consider how much the procedures would cost the NHS, or whether the NHS should allocate funding for them. These decisions are made at a local NHS level and usually on a case-by-case basis.
133	Consultee 18	**General**	"I wish to comment from a patient's prospective.	Thank you for your comment.

	Patient		I was diagnosed with uveal melanoma in October 17 and was found to have developed metastasis in March 19. Immunotherapy did not work for me due to severe side effects, and I was left with no treatment options. After considerable stress and anxiety I became aware of the above treatment. Fortunately my husband's health insurance partially covered the cost of the treatments as we would never have been able to raise the funds ourselves. I have had three treatments, the last was March 2020. The treatment reduced the size and amount of tumours significantly. My most recent scans show my liver to be stable. I have had no side effects from the treatments apart from initially some tiredness. These treatments, while I realise that they will not cure me, have given me a good quality of life that I would not have had. I have had time to live as normal as possible, with stage 4 cancer. I have been able to enjoy my life with my family etc. I feel very strongly that this treatment should be available for those that would benefit from it, not only those that have deep pockets or wealthy friends. When a person is dealing with stage 4 cancer it should not be necessary for them to have to search for money to pay for treatment. We only want the same as other cancer patients, access to effective treatment ."	The Committee welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations. Interventional procedures guidance does not consider how much the procedures would cost the NHS, or whether the NHS should allocate funding for them. These decisions are made at a local NHS level and usually on a case-by-case basis.
134	Consultee 19 Patient	**General**	"This is the only recommended treatment with proven increased survival times for metastatic ocular melanoma. Patients are having to self fund at a cost of £40000 per treatment. Up to 6 are needed. People who cannot raise the money are likely to live months possibly weeks They can not wait 4 months for NICE to sort this. Many people have had success with this treatment with few side effects but it needs to be given the go ahead now. "	Thank you for your comment. Interventional procedures guidance does not consider how much the procedures would cost the NHS, or whether the NHS should allocate funding for them. These decisions are made at a local NHS level and usually on a case-by-case basis.
135	Consultee 20 Patient	**General**	I am a patient diagnosed with Stage 1 Ocular Melanoma. I was diagnosed in March last year and have had radioactive plaque treatment. After much deliberation I decided to have a biopsy taken to	Thank you for your comment.

			understand what my health may be in the future and the likelihood of me developing metastases. Every six months, like all Ocular Melanoma patients, I go through the worrying process of scans to see if I have developed metastases in my Liver or nearby organs. Each time I have these scans done, I just have to hope that I am not in the 50% of patients who do go on to develop fatal spread of this horrible disease. Currently many patients are having to wait longer than the recommended 6 months for scans because of the influence of Covid on routine scans. The biggest part of the worry is knowing that there a very few treatment options should Liver metastases develop, the most effective option, Chemosat, is now only available through private health insurance or at a personal cost of a minimum of £120,000 or £40,000 per treatment. I have watched friends of mine desperately try to fund raise for Chemosat treatment, even selling their family home to have the hope of a future. This obviously worries me greatly and I think it is completely unacceptable to have a good treatment option, the Only good treatment option apart from surgery, not available on the NHS. I would like to see NICE approve Chemosat as a treatment for Ocular Melanoma and the period of time for it to become available to patients shortened from the proposed four and a half month wait to April 2022. In the consultation document there is data to support patient access to this treatment by a specialist team. We have those teams already in place, please allow access to the drug as soon as possible without this prolonged delay. I know of ten families currently paying for their own treatment and some individuals who just cannot raise the money required. Please give these people a chance to live a longer life and a hope for the future for those of us still at stage 1 Ocular Melanoma."	The Committee welcomes hearing from patients who have undergone this procedure and considered your experience and views in their deliberations. Interventional procedures guidance does not consider how much the procedures would cost the NHS, or whether the NHS should allocate funding for them. These decisions are made at a local NHS level and usually on a case-by-case basis.
136	Consultee 24 Company Delcath Systems, Inc.	**Overview**	**Overview** **Overall survival**	Thank you for your comment.

			In the case series of 60 patients, median overall survival from the first diagnosis of the metastatic disease was 56 months and, from the first treatment, was 9 months.3 The authors additionally stated that, among the cohort of ocular melanoma patients (n=30), median overall survival from first treatment was 12 months. **Progression-free survival** The authors additionally stated that, among the cohort of ocular melanoma patients (n=30), median hepatic progression-free survival was 6 months and median progression-free survival was 6 months. Kindly note that the standard deviation for progression-free survival was 515.5 days, not 515.5 years.	A statement on overall survival and progression-free survival of patients with ocular melanoma will be added to the overview. 'Years' will be changed to 'days' in the last sentence in the paragraph on 'progression-free survival'.
137	Consultee 24 Company Delcath Systems, Inc.	**Overview**	**Study 11 Brüning R (2020)** Although this data is shown in Table 1 "Baseline Data," it reflects disease status after the first treatment of chemosaturation with PHP, rather than at baseline.	Thank you for your comment. The last sentence of 'Study population issues' will be deleted in Study 11.

"Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees."