FDA Briefing Document
Oncologic Drugs Advisory Committee Meeting
May 2, 2013

NDA 201848 – 001
Melblez Kit
Delcath Systems, Inc.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the Melblez Kit NDA with the Applicant's proposed indication " The Melblez Kit is a drug/device combination product containing melphalan hydrochloride and the Delcath Hepatic Delivery System, which is indicated for the treatment of patients with unresectable metastatic ocular melanoma in the liver" to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Executive Summary

The Division of Oncology Products 2 seeks the advice of the Oncologic Drugs Advisory Committee regarding the pending NDA for the Melblez Kit on the following points

1. Has Delcath provided substantial evidence demonstrating that Melblez kit treatment confers an improvement in the hepatic progression-free survival that is sufficient in magnitude to be considered direct clinical benefit for the requested indication?
2. For patients with hepatic-dominant metastatic ocular melanoma, do the benefits of Melblez Kit treatment outweigh its risks?
3. Discuss the design of an additional trial(s) to assess the risks and confirm retention of efficacy using the "to-be-marketed" version of the Melblez Kit device, which was not used in the clinical trials supporting this NDA.

The Melblez Kit is a combination product, as defined under 21 CFR 3.2 (e), and consists of a drug [melphalan (Melblez)] and device (Delcath Hepatic Delivery System) packaged together in a single package. Based on the primary mechanism of action, as determined by FDA's Office of Combination Products, this combination product will be approved under a New Drug Application (NDA) with the Center for Drug Evaluation and Research (CDER) as the lead Center responsible for review of the application. Therefore, Delcath will be required to provide substantial evidence of effectiveness in adequate and well-controlled clinical trials. The NDA will be reviewed under the provisions of 505(b)(2) since it relies on FDA's prior findings of safety and effectiveness for the reference listed product Alkeran (melphalan) for key non-clinical data and clinical safety data supporting the application. At FDA's request, the indication was narrowed to patients with metastatic melanoma arising in the eye because of the small number of patients with hepatic metastases arising from cutaneous melanoma (10 patients, 5 per arm) studies and the lack of comparison to effective alternative treatments for metastatic cutaneous melanoma that have demonstrated improved survival (ipilimumab) or very high response rates (vemurafenib). Therefore, all analyses of efficacy conducted by FDA were limited to patients with metastatic ocular melanoma.

The Melblez Kit contains drug and disposable supplies for a single treatment, specifically composed of 5 vials each containing 50 mg melphalan (Melblez) as a lyophilized powder and sterile, single-use device components (catheters, an extracorporeal circuit with hemofiltration cartridges) required for delivery of melphalan by percutaneous hepatic artery infusion and extraction of melphalan prior to venous return of the extracorporeally circulated blood. The recommended melphalan dose is 3 mg/kg ideal body weight with a maximum of 220 mg in a single administration, infused into the hepatic artery over 30 minutes, with subsequent treatment administered at 4 week intervals (with delay in treatment for a maximum of 8 weeks to allow for recovery of toxicity from the previous treatment). In the efficacy trial (Study 1), Melblez Kit treatment was conducted under general anesthesia requiring approximately 3 hours to complete the treatment and the median time to hospital discharge following the procedure was 4 days. The use of the Melblez Kit in clinical trials was permitted only after the successful completion of specialized training of the multidisciplinary team conducting the treatment as well as mandatory overnight monitoring in an intensive care unit or step-down unit. Despite these steps, substantial

morbidity and mortality was observed, resulting in numerous protocol amendments during the major efficacy trial. Because of these substantial risks, FDA informed Delcath that a Risk Evaluation and Mitigation Strategy (REMS) be included with the NDA re-submission. The REMS contains elements to assure safe use, restricting prescribing or using Melblez Kit to healthcare providers who have successfully completed educational training on the risks of severe hypotension with stroke and myocardial infarction; severe, prolonged, and fatal bone marrow suppression; severe and fatal hemorrhage; hepatic failure; and severe and fatal gastrointestinal ulceration and perforation and certification of both the healthcare providers prescribing or using Melblez Kit treatment and the hospitals where the treatment will be administered.

Efficacy is based on the results of Protocol DSI MEL 2005-001 (Study 1), an open-label, multicenter, randomized (1:1) trial that enrolled 93 efficacy-evaluable patients with unresectable, hepatic-dominant, metastastic cutaneous (n=10) or ocular melanoma (n=83). Randomization was stratified by melanoma prior site (ocular vs cutaneous). The primary efficacy analysis in Study 1 was comparison of hepatic progression-free survival (hPFS) of patients randomized to Melblez Kit treatment to those randomized to investigator-determined best alternative care (BAC). Patients randomized to BAC were allowed to receive Melblez Kit treatment at the time of documented hepatic disease progression, provided they continued to meet eligibility criteria for enrollment in Study 1.

For the reasons discussed above, FDA limited all efficacy analyses in Study 1 to the 83 patients with metastatic ocular melanoma, of whom 39 were randomized to Melblez Kit treatment and 44 to BAC. In the subgroup of patients with metastatic ocular melanoma, there was a statistically significant improvement in hPFS (hazard ratio (HR) 0.42) for patients randomized to Melblez treatment, with median hPFS times of 7.0 months in the Melblez Kit arm and 1.6 months in the BAC arm. There was less of an effect in terms of overall PFS, as the improvement in overall PFS was 3 months (median 4.7 vs. 1.6; HR = 0.40). There was no significant difference in overall survival between the two arms (HR 1.35) with median overall survival times of 9.8 months in the Melblez Kit arm and 10.0 months in the BAC arm. In patients randomized to Melblez Kit treatment, the hepatic response rate (hORR) was 36% with median duration of response of 7.3 months.

The assessment of safety included data obtained in 122 Melblez-Kit treated patients consisting of 70 patients randomized to Melblez Kit treatment (n=42) or who received Melblez Kit treatment following hepatic disease progression (n=28) in Study 1 and 52 patients with primary hepatic cancers or with hepatic metastases from a variety of primary cancers enrolled in an open-label, single center, parallel group, activity estimating trial (Study 2). Substantial and severe toxicity was identified in all three trials with a toxic death rate of 7%. FDA-identified toxic deaths consisted of hepatic failure (n=3), gastrointestinal hemorrhage (n=1), streptococcal sepsis in the setting of bone marrow failure (n=1), bone marrow failure (n=1), gastric perforation (n=1), and hemorrhagic brain lesions in the setting of bone marrow failure and neutropenic fever (n=1). The serious adverse reactions arising from Melblez Kit treatment were severe hypotension during treatment procedure (despite patients receiving vigorous pre-treatment hydration and aggressive vasopressor support during the procedure), prolonged and severe marrow suppression in ≥ 80% of patients, Grade 3-5 infections in 23%, Grade 3-5 hemorrhage in 6%, Grade 3-4 elevations in transaminases or bilirubin in ≥ 20%, gastrointestinal

perforation or ulceration due to reflux of melphalan into the gastrointestinal branches of the hepatic artery, and severe electrolyte abnormalities requiring close monitoring post-procedure.

During the clinical development program of the Melblez Kit, an increase in the risk of serious and fatal toxicities was identified following device modifications involving the hemoperfusion filter cartridge component. In exploratory safety analyses, the FDA medical officer identified clinically important differences in the adverse reaction profile in subgroups treated with the devices containing one of the two hemoperfusion filter cartridges in clinical trials. Based on additional exploratory analyses, there appear to be lot-by-lot differences in the risk of fatal adverse reactions. It is FDA's conclusion that differences in the clinical adverse reaction profile were not predicted by bench testing and that Delcath has not identified the critical quality attributes correlate with the changes in the incidence and severity of clinically important adverse reactions. Until the critical quality attributes are defined and validated, FDA will require clinical testing to support approval of modifications of the device for changes in the hemoperfusion filter cartridge component, to characterize the risks of such changes

Background

Indicated Population

Ocular melanoma is a diagnosed in ~2500 adults per year and is the most common primary intraocular malignant tumor in adults. Approximately 25-50% will develop metastatic disease within 2-5 years of the initial diagnosis. Metastases occur primarily to the liver. In the largest longitudinal series of patients with ocular melanoma, of the 770 patients with metastases, 89% had metastases to the liver and 43% had metastases only to the liver (Diener-West 2005). Historically, the expected survival from the diagnosis of metastatic disease was estimated to be from 2 to 9 months; however, a recent report of a Phase 3 trial conducted in patients with previously untreated metastatic ocular melanoma reported a median survival of approximately 14 months (Leyvraz 2012).

Ocular melanoma differs from cutaneous melanoma with regard to the molecular profile. Unlike cutaneous melanoma, mutations in BRAF or RAS do not occur in ocular melanoma. Mutations in GNA11 or GNAQ are found in 90% of ocular melanomas; however, these are not correlated with a poorer prognosis in terms of disease free or overall survival. (Van Raamsdonk 2010). Although loss of Chromosome 3 and gain of Chromosome 8 confer a poor prognosis and higher risk of metastastic disease in patients with early stage disease, it is not known whether these chromosomal abnormalities correlate with poorer survival in patients with metastatic ocular melanoma (Prescher 1992).

There are no FDA-approved drugs for the treatment of unresectable, hepatic-dominant, metastatic ocular melanoma. Current treatment options include surgical resection, liver-directed local ablative therapies (e.g., cryotherapy, radiofrequency ablation, ethanol ablation), liver-directed catheter-based antineoplastic therapy (e.g., transcatheter arterial chemotherapy embolization (TACE), drug-eluting beads, and radioembolization with yttrium-90 microspheres) and systemic therapy. The anti-tumor activity of local ablative therapeutic appears to correlate

with the number and size of the metastatic lesions in the liver and by anatomic considerations including the proximity of target lesions to vascular or biliary structures. These treatments produce modest response rates and no documented effect on survival.

At the 2012 Annual Meeting of the American Society of Clinical Oncology, a randomized trial in 171 patients with metastatic ocular melanoma comparing direct hepatic intra-arterial (HIA) infusion of fotemustine, an alkylating agent, with intravenous fotemustine failed to demonstrate a survival benefit (HR 1.09 CI [0.79, 1.50]; median months 14.6 vs. 13.0) despite improvements in overall response rates (14% vs. 2%) and improvements in PFS (median 5.4 months vs. 3.7 months) (Leyvraz 2012).

There are no FDA approved therapies for metastatic ocular melanoma. FDA-approved for the treatment of metastatic or unresectable melanoma include:

- vemurafenib (Zelboraf®) which is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF-V600E mutation as detected by an FDA-approved test. Approval was based on demonstration of improved survival and improved progression-free survival compared to an active control (dacarbazine). Trials supporting approval did not include patients with ocular melanoma. The use of Zelboraf is not indicated for tumors that do not have the BRAF V600E mutation due to the risks of secondary malignancies.
- ipilimumab (Yervoy®) which is indicated for the treatment of patients with unresectable or metastatic melanoma. The basis for approval was demonstration of improved overall survival against an inactive control (vaccine), supporting by improved survival in a second trial against compared to single agent dacarbazine. Trials demonstrating survival excluded patients with metastases arising from ocular melanoma.
- aldesleukin (Proleukin®), which is indicated for the treatment of patients with metastatic melanoma based on demonstration of durable objective responses (16% objective response rate with median duration of response of 9 months; 6% of patients achieved a complete response with median response duration of 59+ months).
- dacarbazine (DTIC-Dome), which is indicated for the treatment of melanoma based on demonstration of objective tumor responses. Based on published literature, the estimated response rate is approximately 10%.

Pre-Submission Regulatory History

Key milestones in the regulatory history of the Melblez Kit are summarized below

- October 26, 1989: IND 32617 for treatment of metastatic cancer limited to the liver with melphalan administered via percutaneous isolated hepatic perfusion allowed to proceed
- April 29, 2005: Fast Track designation granted for the treatment of hepatic tumors secondary to melanoma.
- April 26, 2005: End-of-Phase 2 meeting held
- June 2005-February 2006: FDA issued a series of communications providing comments on the request for Special Protocol Assessment for Protocol DSI MEL 2005-001.

- November 12, 2008: Orphan Drug designation granted for "treatment of patients with cutaneous melanoma" and for "treatment of patients with ocular (uveal) melanoma".
- March 10, 2010: pre-NDA meeting held

Regulatory history of the NDA

- April 30, 2010: first portion of "rolling review" NDA 201848 submitted
- December 22, 2010: final portion of NDA 201848 submitted
- February 18, 2011: FDA refusal to file letter issued. Major deficiencies were incomplete information on serious adverse reactions (hospitalizations, deaths on study) and incomplete quality information (Manufacturing and Controls)
- April 6, 2011: Type A meeting held to discuss RTF letter
- January 12, 2012: Meeting held to discuss planned approach to address deficiencies in the original NDA and plans for submission of an amendment to the NDA. FDA agreed with Delcath's plan for collection of missing safety information, proposed safety analyses, and proposed Risk Mitigation Strategy
- August 15, 2012: NDA 201848 resubmitted addressing items in the February 18, 2011 Refusal to File letter as agreed-upon during the January 12, 2012 meeting.

Design of the Major Efficacy Trial (Study 1)

Study 1 was a randomized (1:1), multicenter, open-label trial with the primary objective of comparing hepatic progression-free survival (hepatic PFS or hPFS) in patients with hepatic-dominant metastatic disease arising from cutaneous or ocular melanoma who were randomized to Melblez Kit treatment or to best alternative care (BAC).

Key Inclusion Criteria

- Unresectable hepatic metastases (measurable by CT or MRI) with limited, unresectable extrahepatic disease on baseline radiological studies, defined as
  - no more than four pulmonary nodules of < 1 cm each,
  - no more than ten skin/subcutaneous metastases of < 1 cm each, and
  - retroperitoneal lymph nodes < 3cm in diameter
- Confirmation of normal liver tissue by diagnostic laparoscopy (with liver biopsy as indicated) in patients with a CT or MRI demonstrating greater than 50% of the liver replaced with tumor
- ECOG performance status 0-2 at screening and 24 hours prior to Melblez Kit treatment
- Adequate organ function defined as
  - total serum bilirubin < 3.0 mg/dL
  - prothrombin time (PT) within 2 seconds of the upper limit of normal (ULN)
  - aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 10 times ULN.
  - platelet count > 75,000/μL,
  - hemoglobin ≥ 9 g/dL (correctable with transfusion),
  - absolute neutrophil count (ANC) ≥ 1,300/μL,
  - creatinine ≤ 1.5 mg/dL (unless measured creatinine clearance > 60 mL/min)

- No chemotherapy, radiotherapy, or biologic therapy in the month prior to treatment.

Key Exclusion Criteria

- Childs class B or C, cirrhosis, or evidence of portal hypertension by history, endoscopy, or radiologic studies
- History of congestive heart failure and left ventricular ejection fraction < 40%
- Significant chronic obstructive pulmonary disorder or other chronic pulmonary restrictive disease
- Requirement for immunosuppressive drugs or for ongoing, chronic anticoagulation
- History of bleeding disorder or evidence of intracranial abnormalities that put the patient at risk for bleeding with anticoagulation
- History of gastrinoma or Whipple procedure

Randomization

Patients were randomized 1:1 to receive Melblez Kit treatment or investigator-determined best alternative care (BAC). Randomization was stratified by melanoma site of origin (ocular versus cutaneous) and study institution.

Treatment

Arm 1 Melblez Kit treatment (melphalan 3.0 mg/kg, based upon ideal body weight, with a maximum dose of 220 mg for a single treatment) administered every 4 weeks with delays up to 4 additional weeks until resolution of toxicity to less than grade 2 for non-hepatic adverse reactions and to baseline values for hepatic toxicity. A maximum of 6 cycles of Melblez Kit treatment were to be administered to patients with an objective response and a maximum of 4 cycles of Melblez Kit treatment were to be administered to patients achieving stable disease as the best response.

Arm 2 Best Alternative Care (BAC) for each subject was chosen by the investigator prior to randomization, considering the following criteria:

- The site's standard of care
- Medical judgment of the treating physician (i.e., patient-specific criteria such as prior treatment history)
- The opinion of the referring physician
- The patient's preference

Patients with extrahepatic disease progression requiring systemic therapy discontinued protocol therapy. All reasonable attempts to follow these patients to assess the status of their hepatic melanoma were continued at the protocol specified time points until documentation of hepatic disease progression.

Patients randomized to BAC were allowed to cross over to receive Melblez Kit treatment at the time of hepatic disease progression provided that they still met study entry criteria.

Assessments
Patients in the Melblez Kit treatment arm were required to have treatment and follow-up for efficacy and safety at the investigational site while patients randomized to the BAC arm were able to receive BAC and follow-up care by a local oncologist and returned to the investigational site at tumor re-staging

CT or MRI of the chest, abdomen, and pelvis were to be performed at 6 weeks and 12 weeks following initiation of treatment then very 8 weeks for the remainder of the first year, once every 3 months for the second year, once every 4 months for the third year, once every 6 months for the fourth year.

Study Efficacy Endpoints
The primary efficacy endpoint was hepatic progression free survival (hPFS) as assessed by an independent review committee (IRC) (Bioclinica, Inc, Newtown, PA). Secondary efficacy endpoints were hepatic objective response rate (hOR) and overall survival (OS).

Modified Response Evaluation Criteria in Solid Tumors (RECIST) were used. In the IRC review, two board-certified radiologists performed blinded, independent assessments of individual patient radiographs. If a discrepancy in reviewer evaluations occurred in either date of progression, best overall hepatic response, or date of first confirmed response, a third board-certified radiologist independently assessed the discrepant case and determined which of the two primary radiologists' assessments was a more accurate representation of outcome.

Statistical Methods

The primary analysis for hPFS was an unstratified log-rank test comparing the randomized treatment arms. The median survival time was estimated for each arm with a 95% confidence interval. The hazard rate was also estimated and Kaplan-Meyer curves were presented. OS was analyzed in the same manner.

Protocol Amendments
The study was designed in collaboration with the NCI and was initiated as a single center study at the NCI under Protocol 06-C-0088; the first patient was enrolled on February 24, 2006. The protocol was subsequently amended (NCI Protocol amendment E) and approved by the IRB on May 31, 2007, to include additional investigational sites. The first patient was enrolled at a non-NCI site on June 10, 2008 and the last patient of Study 1 was enrolled on October 30, 2009. The additional investigational sites conducted the study under Delcath Protocol DSI MEL/MEL 2005-01 while the study continued at NCI under Protocol 06-C-0088 because of the institutional requirement for NCI to have its own protocol.

Table 1: Summary of Protocol Amendments

NCI Protocol Amendments	Summary of Changes
Amendment A May 16, 2006	• Added brain MRI to eligibility evaluation for Melblez Kit patients and excluded patients with evidence of intracranial abnormalities. • Required hormonal suppression during treatment for premenopausal women.
Amendment B	• Added that after the 4th treatment, only patients exhibiting response were to be offered a

July 6, 2006	5th and 6th treatment. • Added MRI of the brain to eligibility evaluation for BAC patients
Amendment C November 22, 2006	• Modified exclusion criteria to exclude patients with a history of bleeding disorders or evidence of intracranial abnormalities which would put them at risk for bleeding with anticoagulation • Reduced the melphalan dose to 2.5 mg/kg IBW because of safety concerns with the Delcath Gen 1 filters. The MTD was established at 3.0 mg/kg using the Asahi filters. • Revised reduced dose for patients experiencing a DLT from 2.5 mg/kg IBW to 2.0 mg/kg IBW (20% dose reduction). • Added requirement for diagnostic laparoscopy (with liver biopsy as indicated) for patients who have a diagnosis of melanoma with 50% of their liver replaced by tumor to further assess liver function
Amendment D March 22, 2007	• Modified melphalan dose to 3.0 mg/kg IBW after PK data analysis for patients who received melphalan 3 mg/kg using the Delcath Gen 1 filters showed post filtration melphalan levels to be within those previously obtained using the Asahi filters
Amendment E May 9, 2007	• Added enhanced guidelines for reversal of post procedure coagulopathy • Expanded trial to non-NCI sites
Amendment F September 18, 2007	• Inclusion of information on the administration of intra-arterial nitroglycerine for patients who experience arterial spasm.
Amendment J July 1, 2008	• Capped melphalan dose at 220 mg. Doses between 110-220 mg diluted in 500 mL saline. • Eliminated reporting of some grade 1 and 2 events and concomitant medications. Clarified that the only source for these grade 1 and 2 events and concomitant medications was the patient's source documentation (grade 1/2 occurring during hospitalization, grade 1/2 following discharge with the exception of grade 2 events that are related to study treatment (BAC or Melblez Kit); only those medications that the patient is taking at baseline on a routine basis, medications that are used to treat a reportable adverse event, or medications that cause an adverse event were to be captured
Amendment M January 8, 2009	• Clarified patient management during Melblez Kit for ACT as follows: An initial ACT of 300-350 seconds is desired prior to balloon inflation and initiation of veno-venous bypass
Amendment N March 3, 2009	• Revised serious adverse event reporting criteria for death due to disease progression as follows: all deaths with the exception of those due to progressive disease to be reported • Revised serious adverse event reporting to include all grade 3 and 4 adverse events that are not listed in the consent form that are possibly, probably or definitely related to research
Amendment O June 3, 2009	• Revised Statistical Analysis: Patients will have 2 PFSs. The first PFS is from the start of the BAC treatment (date of randomization) to time of hepatic progression in the control arm • PFS is defined as the time from randomization to the first observation of hepatic melanoma disease progression or death due to any cause.
Amendment Q August 3, 2009	• Information regarding sterilization was removed since filters will be supplied in a sterilized (see- thru) pouch, packed two per box. • Clarified that patients who crossed over from BAC to Melblez Kit will undergo evaluation at 8 and 16 weeks (+/- 5 days) following the second baseline scan.
Amendment R October 13, 2009	• Accrual ceiling increased to 100 patients to accommodate patients who had signed consent and were undergoing eligibility evaluation at the time of the enrollment of the 92nd patient.

Study 1 Population

Patient Demographics and Disease Characteristics

A total of 93 subjects were enrolled in Study 1. The majority of patients (46%) were enrolled at the National Cancer Institute, followed by John Wayne Cancer Institute (14%) and University of Pittsburgh Medical Center (13%). Of the total number enrolled, 83 patients (89%) had ocular melanoma as the primary tumor site. In response to FDA advice, Delcath narrowed the indication to patients with metastatic ocular melanoma. Therefore, all efficacy analyses are limited to the subset of patients with ocular melanoma.

Demographics of the intent-to-treat (ITT) study population are summarized in Tables 2 and 3 below Patient characteristics for this population and for the ocular melanoma subgroup are similar. In both the ITT and ocular melanoma populations, there were no clinically significant differences between treatment groups in age, gender, race or ethnic origin, and ECOG performance status. All patients were ECOG PS 0 or 1.

Table 2: Patient Demographics in the ITT Population In Study 1

Demographic Variable	Overall N=93	Randomized to Melblez Kit N=44	Randomized to BAC N=49
Age			
Median (yrs)	56.0	55.0	56.0
Range (yrs)	31-77	33 - 74	31 - 77
18 to <65 years ≥65 years	86% 14%	84% 16%	88% 12%
Gender			
Male Female	48% 52%	52% 48%	45% 55%

Prior cancer treatment is summarized in the table 3 below.

Table 3: Prior Cancer Treatment in the ITT Population in Study 1

Type of Therapy	Overall N=93	Randomized to Melblez Kit N=44	Randomized to BAC N=49
Therapeutic Surgery	59%	52%	65%
Radiation	54%	23%	27%
Chemotherapy	19%	18%	20%
Immunotherapy	17%	18%	16%
Image-Directed Local Therapy	12%	5%	6%
Unknown	1%	0	2%

Baseline disease characteristics are summarized in Table 4 below. The majority of study patients (~60%) had only hepatic metastases. Among patients with extra-hepatic metastases the lung was the most frequent site of disease. As previously indicated, a similar analysis excluding the 10 cutaneous melanoma patients produced nearly identical results.

Table 4: Baseline Disease Characteristics in the ITT Population in Study 1

Baseline Entry Characteristics	**Overall N=93**	**Randomized to Melblez Kit N=44**	**Randomized to BAC N=49**
Primary Tumor Site			
Ocular	89%	89%	90%
Cutaneous	11%	11%	10%
Median time from diagnosis to study entry	39 months	49 months	38 months
Median time from diagnosis to liver metastasis	37 months	46 months	30 months
Lesion presence (%)			
Hepatic lesions only	59%	61%	57%
Hepatic and extra-hepatic lesions	41%	39%	43%
Extra-hepatic lesions (%)			
0	59%	61%	57%
1	26%	23%	29%
2 or more	15%	16%	14%
Site of extra-hepatic lesions			
Lung	23%	18%	27%
Lymph node	7%	7%	6%
Bone	7%	7%	6%
Soft tissue	4%	2%	6%
Other	11%	14%	8%
Median LDH (UKAT/L) at Screening	328	342	275
Elevated LDH (above ULN)	55%	57%	53%

Liver status at baseline is summarized in Table 5 below. Most patients had 4 or more liver lesions with at least 25% liver replacement.

Table 5: Hepatic Tumor Burden at Baseline in the ITT Population in Study 1

Hepatic Tumor Burden Characteristics	Overall N=93	Randomized to Melblez Kit N=44	Randomized to BAC N=49
Number of liver lesions at baseline			
1	5%	7%	4%
2	2%	2%	2%
3	15%	11%	18%
4	24%	18%	29%
5 or more	51%	57%	45%
Median percentage of tumor burden in liver	25%	33%	25%
<25%	40%	39%	41%
25%-50%	40%	41%	39%
50%-75%	14%	14%	14%
>75%	7%	7%	6%

Study 1 Efficacy Analyses

Protocol- Specified Therapy and Treatment Exposure

Thirteen of the 49 patients randomized to BAC received their treatment outside of the study centers. In the remaining 36 patients, BAC was administered at the study investigative site. The majority of patients randomized to BAC received single agent chemotherapy, most frequently with temozolomide. Best alternative care received by patients randomized to the BAC arm is summarized in table 6 below.

Table 6: Best Alternative Care (BAC) Treatments Administered in the ITT Population in Study 1

Treatment Administered	Percentage of Patients in the Control Arm (N=49)
Systemic single agent chemotherapy	43%
Temozolomide	41%
DTIC	2%
Intrahepatic chemotherapy	22%
Supportive care	18%
Systemic combination chemotherapy	8%
Intrahepatic Y-90 chemoembolization	6%
Radiofrequency ablation	2%

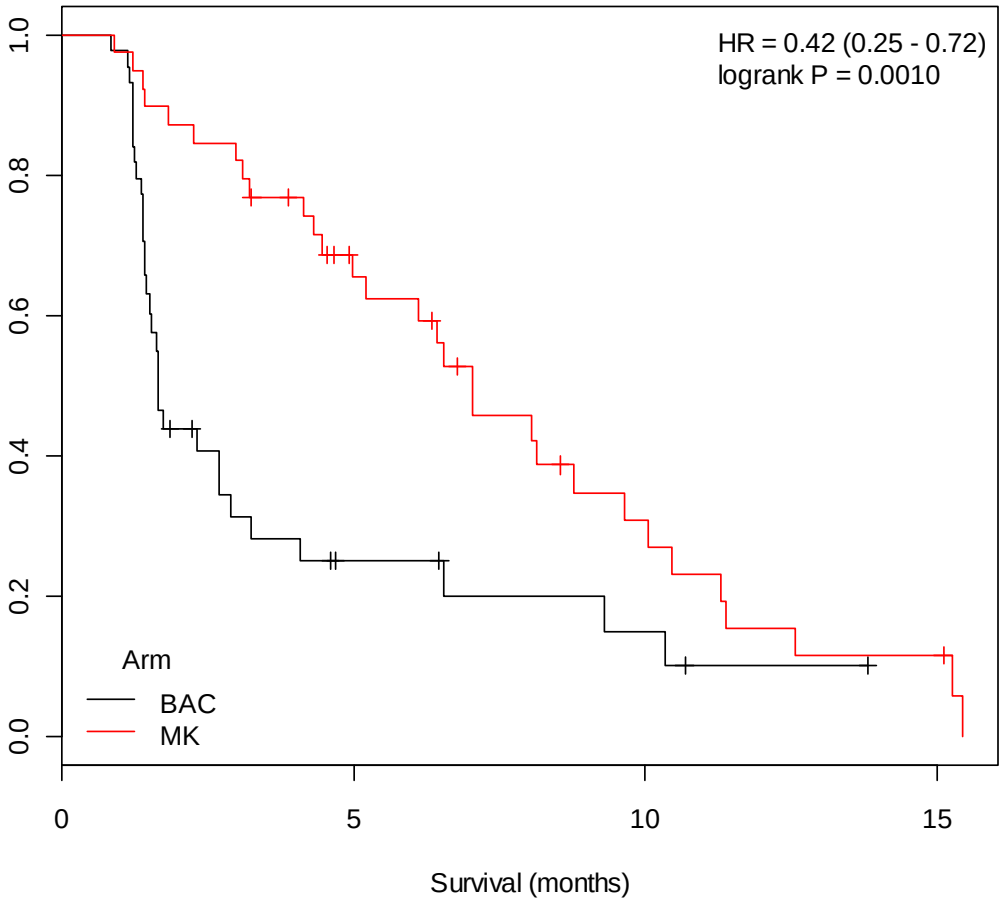
Efficacy Outcomes

Key efficacy outcomes for the 83 ocular melanoma patients are summarized in Table 7 below. Figures 1 and 2 are Kaplan-Meier plots for hPFS and OS, respectively.

Table 7: Efficacy Outcomes in the Subgroup of Patients with Ocular Melanoma in Study 1

Efficacy Outcome Measure	Melblez Kit (*N* = 39)	Best Alternative Care (*N* = 44)
Hepatic Progression-free Survival		
Patients with hepatic progression or death (%)	77%	73%
Median hPFS in months (95% CI)	7.03 (4.99, 9.66)	1.64 (1.41, 2.69)
Hazard Ratio 95% CI	0.42 (0.25, 0.72)	
p-value (Log-Rank Test)	0.001	
Overall Progression-free Survival		
Median PFS in months (95% CI)	4.67 (3.45, 7.03)	1.64 (1.41, 2.27)
Hazard Ratio 95% CI	0.40 (0.25, 0.63)	
p-value (Log-Rank Test)	<0.0001	
Overall Survival		
Patients who died (%)	100%	86%
Median survival (months) 95% CI	9.79 (6.70,13.60)	9.95 (4.50, 15.41)
Hazard Ratio 95% CI	1.35 (0.85, 2.15)	
p-value (Log-Rank Test)	0.20	

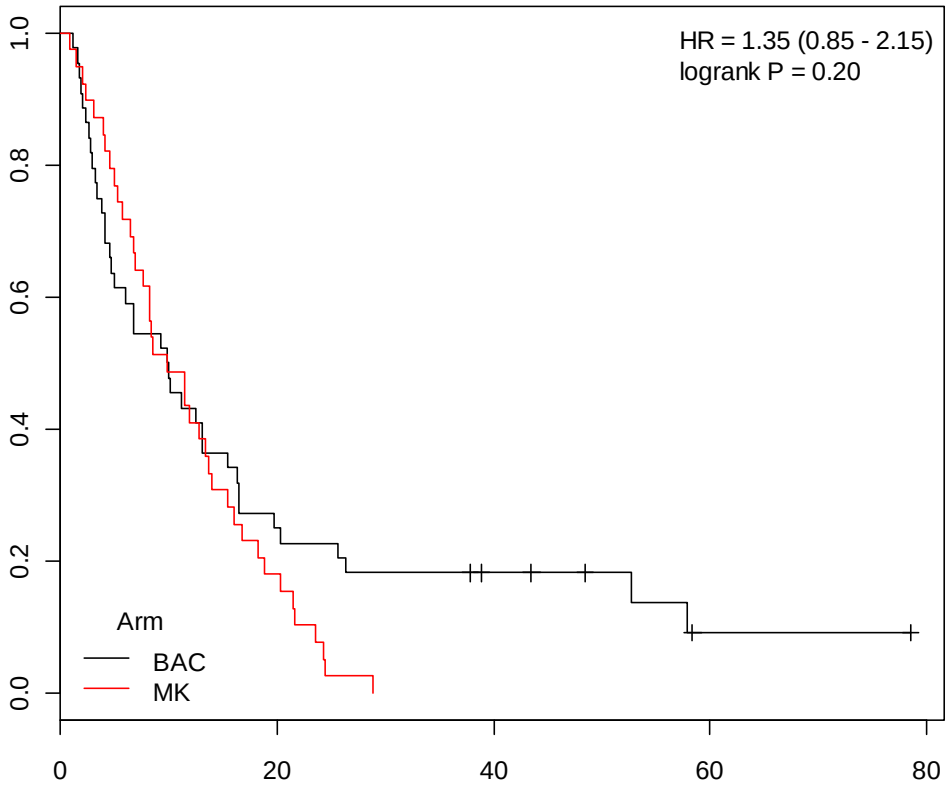
Figure 1: Hepatic Progression Free Survival in Study 1 in Patients with Ocular Melanoma



Number at risk				
BAC	44	6	3	0
MK	39	21	8	3

Note: MK=Melblez Kit.

Figure 2: Overall Survival in Study 1 in Patients with Ocular Melanoma



Number at risk					
BAC	44	11	6	1	0
MK	39	7	0	0	0

Note: MK=Melblez Kit.

In the ocular melanoma group, the hepatic objective tumor response rate (hORR), was 36% for the Melblez Kit arm and 2% for the BAC arm group. The median duration of the hOR was 7.3 months for the Melblez Kit group and indeterminate for the single BAC patient.

Based on the results of the randomized trial, there is no evidence that an improvement in hPFS correlated with an improvement in overall survival. FDA acknowledges that there was substantial cross-over from the control arm; the effect of such cross-over cannot be determined.

Safety Analyses

Safety Population – Source and Demographic Information

The integrated safety population consists of 122 patients in whom treatment with the Melblez Kit was attempted in two clinical trials: the major efficacy trial (Study 1) and Study 2. Key features of Study 2 are described below.

> **Study 2** (Protocol 04-C-0273) was an open-label, single-center, non-randomized, activity-estimating study designed to examine the anti-tumor activity of Melblez Kit treatment at a melphalan dose of 2.5-3.0 mg/kg IBW in patients with unresectable primary hepatic malignancies (i.e., hepatocellular cancer or intrahepatic cholangiocarcinoma) or unresectable metastatic hepatic malignancies from other tumor types (gastrointestinal adenocarcinoma, ocular or cutaneous melanoma and neuroendocrine tumors)

Across Study 1 and Study 2, of the 122 patients in whom Melblez Kit treatment was attempted, 117 patients completed at least one cycle of Melblez Kit treatment with a melphalan dose of ≥ 2.5 mg/kg IBW. Patient disposition for the integrated safety population is summarized in Table 8 below.

Table 8: Integrated Safety-Evaluable Population (Studies 1 and 2)

Study	Total Number of Patients in Cohort	Number of Patients Who Had Treatment Attempted	Number of Patients Who Completed at least 1 Cycle
Study 1 Randomized to Melblez Kit	44	42	40
Study 1 Randomized to BAC that Crossed-over to Melblez Kit post-hepatic progression	28	28	25
Study 2	56*	52	52
Total	128	122	117

*One patient was enrolled in Study 1, had progression of disease, waited several months and then enrolled on Study 2. This patient was analyzed as a separate patient in the pooled safety data analyses.

Exposure

Table 9 below provides information on the exposure to study treatment in the safety-evaluable population (those completing at least one cycle of protocol-specified treatment), by treatment assignment in Study 1.

Table 9: Exposure to Protocol-Assigned Treatment in the Safety-Evaluable Population in Study 1

	Melblez Kit	Best Alternative Care
Number of patients randomized	42	49
Number of patients exposed	40	49
Median exposure (days)	119.5	62

Table 10 below provides information on the exposure to melphalan in patients who were randomized to the Melblez Kit treatment arm and in patients who crossed over to receive Melblez Kit treatment upon disease progression. A dose reduction occurred in approximately 20% of the patients due to adverse reactions, with the majority of adverse reactions leading to dose reduction being related to bone marrow suppression. The median cycle duration exceeded the protocol specified 28 day cycle window; however, patients were allowed up to 8 weeks per cycle to recover from adverse reactions.

Table 10: Exposure to Melphalan in Patients with Ocular Melanama in Study 1

Exposure Parameter	**Randomized to Melblez Kit N=42**	**Crossover to Melblez Kit N=28**	**All Melblez Kit Treated Patients N=70**
Median number of completed cycles	3	2	3
Median dose of melphalan administered (mg)	519	408	513
Patients Requiring Dose reduction	26%	25%	26%
Adverse reaction	21%	14%	19%
Technical issue	5%	4%	4%
Other	7%	7%	7%
Percentage completing multiple treatment cycles			
1 or more	95%	89%	93%
2 or more	86%	64%	77%
3 or more	67%	11%	56%
4 or more	19%	5%	19%
5 or more	7%	1%	6%
6 or more	1%	1%	3%
Median cycle length (days)			
Cycle 1	39	42	41
Cycle 2	43	42	42
Cycle 3	42	42	42
Cycle 4	42	42	42
Cycle 5	42	54	48
Cycle 6	42	42	42

Forty-eight patients in the BAC arm experienced hepatic disease progression. Of these patients, 28 met original eligibility criteria and elected to receive Melblez Kit treatment; of these nine had received supportive care only as their BAC treatment. All 28 patients had Melblez Kit treatment attempted but only 25 patients completed at least 1 cycle of treatment and received melphalan.

The extent of liver disease for patients randomized to Melblez Kit treatment and for patients who crossed over after hepatic progression in the BAC arm is shown in table 11 below.

Table 11: Extent of Hepatic Tumor Burden in Melblez Kit-treated patients enrolled in Study 1 Immediately Prior to Melblez Kit Treatment

Median percentage of tumor burden in liver	Randomized to Melblez Kit (N=44)	Crossover to Melblez Kit (N=28)
<25%	39%	61%
25%-50%	41%	29%
50%-75%	14%	11%
>75%	7%	0

Deaths
In Study 1, there was no statistically significant difference in overall survival between the two treatment arms for the ITT population of 93 patients. The median overall survival time for patients randomized to Melblez Kit treatment was 9.8 months while the median overall survival time for patients randomized to BAC was 10.0 months.

Deaths Due To Treatment Related Adverse Reactions
Overall, 7% of the 122 patients in whom Melblez Kit treatment was attempted died as a result of treatment related adverse reactions.

In the 42 patients randomized to Melblez Kit treatment in Study 1, four patients (10%) died due to a treatment-related adverse reaction. There were no deaths due to adverse reactions on the BAC arm. Two deaths (7%) due to treatment-related adverse reaction occurred in the 28 patients who crossed over to receive Melblez Kit treatment, and in Study 2, two patients (4%) died due to adverse reactions.

FDA's attribution of death differs from that of Delcath's for three of these deaths. Two deaths, one in the Study 1 and one in Study 2, were recorded by the Delcath as deaths due to hepatic disease progression. The patient in Study 1 entered the trial with a large tumor burden (60%) but with normal bilirubin levels. Cycle 1 was complicated by Grade 4 vaginal hemorrhage, Grade 4 neutropenia, Grade 4 thrombocytopenia, and Grade 3 gastrointestinal hemorrhage, which was a sub-capsular hepatic hemorrhage at the site of the large tumor. The patient recovered from these adverse reactions and underwent cycle 2 of therapy. The patient experienced Grade 3 vaginal hemorrhage, Grade 4 neutropenia and thrombocytopenia, as well as hyperbilirubinemia which started immediately following the Melblez Kit procedure. The patient underwent MRI of the liver 11 days before her death which demonstrated a decrease in the size of the large tumor but increased hepatomegaly and ascites. As per comments by the investigator, progression was

determined by clinical parameters as opposed to radiographic findings. The patient died with Grade 3 hyperbilirubinemia and the cause of death was listed as hepatic disease progression even though the size of the tumor in the liver was decreasing. FDA review of these events could not exclude the possibility of fatal hepatic failure secondary to melphalan exposure.

The patient in Study 2 entered the trial with a Grade 2 hyperbilirubinemia (1.9 mg/dl) but by cycle 1 day 1 the total bilirubin level was 1.1. The extent of liver disease was not recorded. Following treatment with Melblez Kit, total and direct bilirubin climbed steadily and by day 4, total and direct bilirubin were 4.0 mg/dl and 2.5 mg/dl respectively. Bilirubin continued to rise and by day 19, total and direct bilirubin were 18.1 mg/dl and 12.6 mg/dl. The patient's death on day 48 was attributed by Delcath to hepatic disease progression; however, FDA review of these events could not exclude the possibility of fatal hepatic failure secondary to melphalan exposure as there were no imaging studies performed that assessed disease progression. The timing of the rise of bilirubin with the exposure to melphalan strongly suggests that drug exposure contributed to the death of this patient.

Delcath attributed one additional death in the Study 1 crossover patients to disease progression. This patient was found to have hemorrhagic lesions in the brain which occurred in the setting of high fever, Grade 4 neutropenia, Grade 4 thrombocytopenia, gram-negative bacteremia, and retinal hemorrhage. The patient had no CNS disease on screening MRI and had very limited (5%) liver involvement. FDA review of these events could not exclude the possibility of fatal bone marrow suppression and systemic infection secondary to Melblez kit treatment.

Deaths due to adverse reactions in all patients who had the Melblez Kit treatment attempted are summarized in table 12 below.

Table 12: Deaths Due to Treatment-Related Adverse Reactions across In Studies 1 and 2

Fatal Adverse Reactions	**Number of fatal adverse reactions N=122**
Hepatic Failure	3
Streptococcal Sepsis	1
Neutropenia and thrombocytopenia	1
Hemorrhagic Brain Lesions with Thrombocytopenia and Rential Hemorrhage	1
Gastric Perforation	1
Gastrointestinal Hemorrhage	1

Overall Adverse Reaction Profile

The proportion of patients experiencing any non-fatal Grade 3-4 adverse reaction or a serious adverse reaction was significantly higher on the Melblez Kit arm of Study 1 when compared to best alternative care. The results are summarized in Table 13. Adverse reactions related to bone marrow suppression, namely thrombocytopenia and neutropenia, and hepatotoxicity were the most common Grade 3-4 adverse reactions, serious adverse reactions, and adverse reactions leading to discontinuation in the Melblez Kit arm.

Table 13: Adverse Reaction Summary during the Randomized Treatment Period in Study 1

Adverse Reaction	**Melblez Kit N=42**	**Best Alternative Care N=49**
Grade 3-4 Adverse reaction	95%	41%
Serious Adverse reactions	79%	16%
Adverse reaction leading to discontinuation	41%	8%

Common, severe adverse reactions occurring at a frequency of ≥ 2% in the 122 patients in whom the Melblez kit treatment was attempted in Studies 1 and 2 are summarized in table 14 below.

Table 14: Selected Grade 3-5 Adverse Reactions in ≥ 2% Integrated Safety-Population

Selected Grade 3-5 Adverse Reactions	Per-Patient Incidence (N=122)
Blood and Lymphatic System Disorders	
Thrombocytopenia	91%
Neutropenia	88%
Anemia	80%
Hypotension and Sequelae	
Mean Arterial Pressure < 50 mmHg	45%
Cerebrovascular Ischemia[1]	3%
Troponin increased	6%
Creatinine increased	4%
Hepatic Investigations	
Aspartate aminotransferase increased	32%
Alanine aminotransferase increased	20%
Hyperbilirubinemia	21%
Blood alkaline phosphatase increased	14%
Infections and Infestations	
Febrile neutropenia	18%
Gastrointestinal Disorders	
Gastrointestinal ulceration and perforation[2]	6%
Hemorrhage	
Hemorrhagic adverse reactions[3]	6%
Coagulation	
Activated partial thromboplastin time prolonged	15%
International normalised ratio increased	11%
Electrolyte abnormalities	
Hypocalcemia	12%
Hypokalemia	7%
Hypoalbuminemia	38%

[1] Includes cerebral ischemia and hemorrhagic transformation stroke.
[2] Includes gastric ulcer, gastric perforation, duodenal ulcer, duodenal perforation, jejunal perforation.
[3] Includes hepatic hemorrhage, intra-abdominal hemorrhage, gastric hemorrhage, vaginal hemorrhage, pulmonary hemorrhage, intracranial hemorrhage, hematuria, retinal hemorrhage, and hematoma.

Significant Adverse Reactions

Hypotension with Cerebral Infarction, Myocardial Infarction, and Renal Insufficiency

Melblez kit treatment causes two discrete episodes of hypotension during the procedure. The first, a small decrease in blood pressure, occurs when the balloons are inflated and the second, which is a much larger decrease in blood pressure, occurs when the filters come online. Delcath postulates that the large decrease in blood pressure occurs due to adsorption of catecholamines to

the charcoal component of the filter. Table 15 summarizes the degree of hypotension experienced by the 70 patients treated with Melblez Kit in the Study 1. It is important to note that severe hypotension occurred despite pre-procedure hydration and aggressive use of vasopressors.

Table 15: Hemodynamic Profile in Melblez Kit-Treated Patients in Study 1

BP Parameter (n=70)*	Median Nadir Value (mmHg)	Nadir minimum (mmHg)	Median Change (mmHg)
Systolic Blood Pressure	63	35	-40
Diastolic Blood Pressure	40	0	-20
Mean Arterial Pressure	49	-	-

- Measurements available only for N=63 (systolic and diastolic pressures) and N=65 for MAP

The median nadir for mean arterial pressure (MAP) of 49 mmHg is concerning, as the lower threshold of cerebral autoregulation has traditionally been defined as approximately 50 mmHg (Lassen 1959, Jordan 2012). At MAPs lower than this value, key organs such as the brain, heart, and kidneys lose autoregulation and cannot maintain constant flow, introducing an imbalance between oxygen supply and demand. Therefore, this degree of hypotension is associated with a substantial risk of cerebral infarcts, myocardial infarction, and acute renal failure (Ono 2013, Landesberg 2009). These events are summarized in Table 16 below.

Table 16: Hypotension-Related End Organ Damage In Study 1 and in the Safety Evaluable Population

Toxicity	Study 1 N=70	Integrated Safety Population n=122
Mean Arterial Pressure < 50 mmHg	47%	45%
Cerebral Infarction	4%	4%
Myocardial Infarction*	3%	2%
Troponin Elevation**	10%	6%
Acute Renal Failure*	3%	2%
Grade 4 Creatinine	9%	5%

* As listed by investigator
** Troponins were not routinely monitored

The incidence of myocardial events in the integrated safety population may be underestimated due to a lack of adequate cardiac event monitoring, specifically post-procedural troponin evaluation. The 7 patients who had positive troponins included six patients from site 5 and one patient from site 7. These represented 100% of the patients who underwent the Melblez Kit procedure at these sites. The first patient receiving Melblez kit treatment at site 5 experienced a myocardial infarction as a result of the severe hypotension associated with the first cycle of treatment. Grade 3 troponins were measured and were accompanied by ST-T changes on ECG. The patient continued with Melblez kit treatment, but during cycle 4 of treatment, the patient experienced hypotension followed by an episode of ventricular tachycardia requiring immediate cardioversion by intravenous lidocaine. The patient's rhythm converted back to sinus rhythm with ST depressions. The patient recovered and was taken off study due to this event. This

discovery of myocardial infarction prompted this site to institute routine troponin measurements on all patients undergoing Melblez kit treatment. All subsequent patients at this site had Grade 3-4 troponin elevations, some of which were associated with adverse reactions of wall motion abnormalities, hypoxia, and pleural effusions.

Measurement of troponin levels at site 7 was prompted by evaluation of chest pain in the sole patient undergoing Melblez kit treatment at this site. The patient had a Grade 4 troponin elevation along with Grade 1 chest pain and Grade 1 dyspnea during cycle 2. The patient received cycle 3 of treatment and was taken off study due to hepatic disease progression.

No other site performed any evaluations of troponins.

Grade 4 troponin elevation is defined by CTCAE v 3.0 as levels consistent with myocardial infarction. During Melblez kit treatment, symptomatic events would not be detected as patients are anesthetized, and ECG changes are not a sensitive marker of clinically significant ischemic events in the perioperative setting (Landesberg 2009). Delcath did not institute routine troponin monitoring or post-procedural periodic evaluation of heart function. Thus, the true incidence of hypotension related troponin elevation and the long term effect on myocardial function is unknown.

Bone Marrow Suppression

The high rate and prolonged duration of bone marrow toxicity, pharmacodynamically similar to that associated with high dose melphalan (358 mg for a 70 kg male) used in conditioning regimens for autologous stem cell transplantation, suggests that unanticipated high systemic exposure to melphalan occurs as a result of Melblez kit treatment. According to the pharmacokinetic (PK) analysis conducted by Delcath, the filters demonstrated a filtration efficiency of 71% (% Filter efficiency = [(Prefilter AUClast) - (Postfilter AUClast)]/(Prefilter AUClast)) which would predict a toxicity profile closer to low dose (29 mg for a 70kg male) intravenous melphalan administration. Two possible mechanisms that may explain the apparent high systemic exposure are: 1) unaccounted leakage of melphalan bypassing the filter, leading to increased systemic exposure and 2) uptake of melphalan by the biliary system and storage until the balloons are deflated, after which melphalan is released systemically. This apparent prolonged exposure can not be verified because the PK sampling times that were performed in the clinical trials were inadequate. Sampling stopped when the filters were turned off and did not continue through the expected period of decay. Table 17 below provides a comparison of the incidence and duration of Grade 4 neutropenia and thrombocytopenia associated with varying doses of melphalan.

Table 17: Published Literature and Melblez Kit Safety Population Results for Adverse Reaction Profile as a Function of Melphalan Dose

Toxicity	Low Dose * 16 mg/m^2	Melblez Kit 3.0 mg/kg IBW	High Dose** 200 mg/m^2
Dose for 70 kg, 177 cm male	29 mg	Median dose administered via hepatic artery 210 mg Median systemic dose predicted by 71% filtration efficiency 63 mg	358 mg
Grade 4 Neutropenia	6%	71%	100%
Febrile Neutropenia	0	18%	Varies
Time to recover from Neutropenia	N/A	8 days	8 days with stem cell support
Grade 4 Thrombocytopenia	5%	78%	100%
Time to recover from thrombocytopenia	N/A	16 days	7 days with stem cell support

* Ponisch 2006
** Moreau 2002, Attal 2003

Hepatic Failure
Hepatotoxicity is a known consequence of liver-directed therapy. As described above, fatal hepatic toxicity occurred in 2% of patients in whom Melblez Kit treatment was attempted. Additionally, Grade 3 and 4 AST, ALT, and bilirubin elevations occurred in 32%, 20%, and 21% of the integrated safety population.

Hemorrhage
Hemorrhage occurs during the Melblez Kit procedure due to anticoagulation, thrombocytopenia and procedural related vascular injury and occurs after the procedure due to delayed thrombocytopenia. Grade 3-5 hemorrhagic adverse reactions of hepatic hemorrhage, intra-abdominal hemorrhage, gastric hemorrhage, vaginal hemorrhage, pulmonary hemorrhage, intracranial hemorrhage, hematuria, retinal hemorrhage, and hematoma occurred in 6% of patients treated with the Melblez Kit.

Gastrointestinal Perforation
Gastrointestinal perforation occurs due to reflux of melphalan into the gastrointestinal branches of the hepatic artery. Grade 3-5 adverse reactions of gastric ulcer, gastric perforation, duodenal ulcer, duodenal perforation, jejunal perforation, occurred in 6% of patients treated with the Melblez Kit.

Hospitalization
The median duration of initial hospitalization for Melblez Kit treatment was 4 days for the patients who were treated in Study 1. Prolonged hospitalization due to adverse reaction occurred in 34% of patients and 53% of patients required an additional hospitalization with a median duration of 5 days due to adverse reactions. Taking into account the initial hospitalization for the Melblez kit procedure and recovery, and the rehospitalization for treatment of delayed adverse reactions, the median duration of hospitalization during a cycle of Melblez kit treatment was 9 out of 42 days in Study 1.

Other Safety Concerns
Based on exploratory safety analyses of the intregrated safety population, the toxicity profile of Melblez kit treatment changed when the filter component of the Delcath Hepatic Delivery System was modified, with higher severity and fatal reactions observed with the device containing the Clark filter as compared to that observed with the device containing the Asahi filter. This increase in toxicity was not predicted by bench testing comparability studies or by pharmacokinetic comparability assessment of melphalan filtration efficiency in the clinical trials.

The hemofiltration filter is a key component of the Melblez kit because adsorption of melphalan to the filter is hypothesized to allow the dosing of melphalan to levels that far exceed systemic administration of the drug that is given in clinical practice. These hemoperfusion filters are known to adsorb and remove large numbers of components in blood, such as, cells, lipids, proteins, cytokines, as well as drugs.

During the course of the clinical development, the device filter was changed from the Asahi Hemosorba CH-350 Columns to the Clark Hemoperfusion Cartridge filter due to the lack of availability of the Asahi filter. The key physical differences between the 2 filters are summarized in table 18 below.

Table 18: Key Physical Differences Asahi Filter vs. Clark Filter

Component Characteristics	**Asahi Hemosorba CH-350**	**Clark Biocompatible**
Active Material		
Shape		
Particle Size		
Media Coating		
Coating Amount		

In 2006, the NCI investigators notified the NCI IRB that they had observed an increase in bleeding reactions with the use of Clark filters, including severe bleeding reactions in three patients treated with filters from the same lot. Melphalan dosing was reduced to 2.5 mg/kg IBW using Clark filters. After reviewing the bridging studies depicted in table 19 below, preliminary pharmacokinetic data, and safety data from six patients treated at a reduced dose, the NCI IRB permitted the completion of Studies 1 and 2 with the Clark filter at a melphalan dose of 3.0 mg/kg IBW.

Table 19: Bridging Studies for Asahi to Clark Transition

Study	Description
ANA-00-04	Melphalan Filtration Using the Delcath System: Measured the filter extraction of melphalan in Sorensen's Buffer using the Asahi Hemosorba CH-350 filter.
ANA-05-01	Melphalan in Sorensen's Buffer Filtration: Measured the filter extraction of melphalan in Sorensen's Buffer using Clark Biocompatible Hemoperfusion Cartridges
CBHCF-001	An In Vitro Experiment to Determine the Amount of Volume of Normal Saline Required to Produce Clear Effluent from the Clark Biocompatible Hemoperfusion Charcoal Filter.
CBHCF-006	An In Vitro Experiment to Determine the Amount of Particulates and Solubles Leached into the Effluent After Passing Through the Clark Biocompatible Hemoperfusion Charcoal Filter.
CBHCF-004	An In Vitro Experiment to Characterize the Efficiency of the Clark Biocompatible Hemoperfusion Charcoal Filter in Removing Melphalan in Normal Saline.
CBHCF-005	An In Vitro Experiment to Characterize the Binding Capacity of the Clark Biocompatible Hemoperfusion Charcoal Filter in Removing Melphalan in Normal Saline at Ten Times the Maximum Clinical Dose.

Analyses of the safety data from Melblez Kit-treated patients across the patients in Study 1, Study 2, and patients in a previously conducted Phase 1 trial who received a dose of melphlan of ≥ 2.5 mg/kg, reveal that the change in filter manufacturer led to dramatic differences in the safety profile of the Melblez Kit. A cross-study analysis of key safety parameters is depicted in Table 20. Despite the two filters having comparable filtration efficiencies and in vitro testing, the change in filters led to increases in fatal toxicities, increases in the incidence and severity of bone marrow suppression, increases in hemorrhagic reactions, increases in gastrointestinal ulceration and decreases in the nadir of mean arterial pressure during the procedure which are not attributable to differences in tumor types or doses of melphalan.

Table 20: Key Differences in Adverse Reaction Profile for Asahi Filter vs. Clark Filter

Type of Filter	**Phase 1 Study &Study 2 Asahi Hemosorba CH-350 Column**	**Study 2 Clark Biocompatible Hemoperfusion Cartridge**	**Study 1 Clark Biocompatible Hemoperfusion Cartridge**
Patient Population	Mixed Histology	Mixed Histology	Melanoma
Dose	2.5-3.5 mg/kg IBW	2.5-3.0 mg/kg IBW	2.5-3.0 mg/kg IBW
N	30	41	70
Filter Efficiency[1]	70%	73%	71%
General Parameters			
Median Nadir MAP[2]	60 mmHg	49 mmHg	49 mmHg
Treatment Related Death[3]	0%	5%	9%
Grade 3 or 4 adverse reaction	77%	98%	93%
Serious adverse reaction	47%	90%	74%
Toxicity resulting in discontinuation	7%	41%	41%
Organ-specific Parameters			
Febrile Neutropenia	7%	22%	17%
Grade 4 Neutropenia	60%	71%	74%
Grade 4 Thrombocytopenia	47%	78%	81%
Hemorrhagic adverse reactions	5%	13%	14%
Gastrointestinal Ulceration/Perforation	0	5%	7%
Thrombosis	0	5%	7%

[1] %Filter efficiency = [(Prefilter AUClast) - (Postfilter AUClast)]/(Prefilter AUClast)
[2] MAP = Mean Arterial Pressure
[3] Overall treatment related mortality = 7% in Studies 1 and 2

The substantial increase in the incidence and severity of the adverse reactions seen in patients treated with the Melblez kit using the Clark filter as compared to the Asahi filter was not predicted by the battery of in vitro tests or by the limited PK data collected in the clinical trials.

FDA concludes that other, unidentified factors caused the increase in toxicity observed in the change from Asahi to Clark filters. Therefore, any new filter introduced as a new component of the device (Delcath Hepatic Delivery System) for this combination product must be evaluated in a clinical trial in order to have confidence in the safety profile of that iteration of the Melblez Kit.

All eight deaths in clinical trials occurred in patients who received melphalan treatment with the Delcath Hepatic Delivery System containing the Clark filter in the cycle immediately preceeding death. These deaths were clustered in four of the 52 filter lots used in Studies 1 and 2. This pattern of clustering is summarized in table 21 below.

Table 21: Clustering of Fatal Adverse Reactions by Clark Filter Cartridge Lot

Patient	Lot Number	Cause of Death	Date of Death
A		Hepatic failure	
B		Hepatic failure	
C		Hepatic failure	
D		Gastric hemorrhage	
E		Gastric perforation	
F		Streprococcal sepsis	
G		Hemorrhagic brain lesions in the setting of bone marrow failure	
H		Neutropenia and thrombocytopenia	

In NDA 201848, Delcath has requested to market an iteration of the Delcath Hepatic Delivery System containing a new filter, referred to as the GEN 2 filter. No clinical trial data have been submitted to support the safety or efficacy of this device. A series of *in vitro* and *in vivo* animal bridging studies submitted in the application are summarized in table 22 below.

Table 22: Bridging Studies for Clark to GEN 2 Filter Transition

Study	Description
DV-A021R1	Clark Filter Efficiency in Bovine Blood
DV-B068R	GEN 2 Filter Efficiency in Bovine Blood
DV-A009	Clark Filter Particulate Analysis
DV-B069R	GEN 2 Particulate Analysis
DV-A015R	Clark Filter Integrity
DV-B070R	GEN 2 Filter Integrity
DV-C025R	Four Corners Filter Performance of Clark Filter at the Clinical Extremes of Melphalan Dose and Flow Rates
DV-C026R	Four Corners Filter Performance of GEN 2 Filter at the Clinical Extremes of Melphalan Dose and Flow Rates
DV-C034	non-GLP in vivo Porcine Study of Percutaneous Hepatic Perfusion with the GEN 2 filter versus the Clark Filter
DV-CO37	GLP in vivo Porcine Study of Percutaneous Hepatic Perfusion

Delcath argues that non-clinical studies are sufficient to support marketing of a device that includes a new filter; however, similar studies did not identify factors which caused the clinically important increase in toxicity seen in the Asahi-to-Clark transition. Therefore, these non-clinical studies are insufficient alone to safely bridge the marketing of a device containing a new filter, and clinical trial safety data are necessary to support an approval. In addition, the impact of a filter change on the efficacy of this drug-device combination product is unknown and its efficacy must be established in a randomized clinical trial.

Risk Evaluation and Mitigation Strategy

Background
The Food and Drug Administration Amendments Act (FDAAA) provides FDA authority to require risk evaluation and mitigation strategies (REMS) if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks [FDAAA Section 505-1(a)]. A REMS is a required risk management plan that uses risk minimization strategies beyond professional labeling.

REMS may include one or more of the following: A Medication Guide (MG) or patient package insert for patients, a communication plan (CP) for health care providers (HCPs), and elements to assure safe use (ETASU), which often involve some form of restricted distribution and or evidence of safe-use conditions.

A communication plan consists of FDA-approved materials used to aid a sponsor's implementation of the REMS and/or inform healthcare providers about serious risk(s) of an approved product. For example, "Dear Healthcare Professional" letters, collaboration with professional societies, brochures focusing on the important risk messages, and other educational materials have been required to alert prescribers to serious risks associated with the use of certain drugs and biologics.

ETASU can include one or more of the following requirements:

- HCPs who prescribe the drug have particular training or experience, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients only in certain health care settings;
- The drug is dispensed to patients with evidence or other documentation of safe use conditions
- Each patient using the drug is subject to certain monitoring
- Each patient using the drug is enrolled in a registry.

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling [FDAAA Section 505-1 f(1)(A)].

The statute [FDAAA Section 505-1(d)] also requires that all approved REMS for NDA and BLA products have a timetable for submission of assessments of the REMS. These assessments are prepared by the sponsor and reviewed by FDA.

Concerns
Even with appropriate patient selection, the risks of Melblez treatment as described in the safety section remain. Procedural risks, including hypotension, hemorrhage, hepatic failure, and

gastrointestinal ulceration are inherent to the use of Melblez Kit. Hypotension occurs in most patients despite the use of vasopressors to support blood pressure.

In clinical testing, the treatment team received training before being permitted to administer the product. The treatment teams consisted of an interventional radiologist (and IR staff), a perfusionist, an anesthesiologist, an oncologist, and a pharmacist. The training included a didactic component, and an experiential component. In the experiential component, the treatment team observed experienced HCPs performing the procedure, and then performed a procedure under the direct observation and with the assistance of experienced HCPs. Experienced HCPs were in contact via phone for an additional procedure. The procedure and training evolved through clinical testing as toxicities of Melblez Kit emerged. Despite the institution of additional measures to address the toxicities that emerged, patients treated with Melblez Kit in the clinical trials continued to experience serious adverse reactions.

Proposed REMS
At the request of FDA, Delcath has submitted a proposed REMS containing the basic required HCP training and certification and hospital certification that FDA believes is necessary for the safe use of this product. FDA believes the proposed REMS includes the appropriate elements; however Delcath's briefing document introduces new "patient management criteria" which were not included in the most recent REMS submission or in the proposed labeling, and have not been reviewed by FDA. These "patient management criteria" have not been evaluated in clinical studies and there is no evidence that the risks of the procedure will be mitigated by their inclusion. Delcath's proposed REMS program is still undergoing extensive review in the Agency.

The proposed REMS under review largely mimics the didactic and experiential training used in pre-marketing testing. It is anticipated that the risk of procedural toxicities in the post-marketing setting could be significantly worse without required training. However, at best, with the REMS-specified training and certification, the post-market safety profile of Melblez kit treatment might equal the safety profile observed in clinical testing. The REMS-specified training cannot be expected to improve the risk benefit profile beyond that observed in clinical trials.

Conclusion

Melblez Kit is an active treatment with anti-tumor activity; however active treatments are not equivalent to treatments that impart a clinical benefit. The improvements in hPFS and hORR demonstrated in Study 1 did not correlate into clinically important improvements in progression free survival or in overall survival. There is no statistical method that can be applied to demonstrate that crossover of patients to receive Melblez kit treatment is obscuring a survival benefit.

There are unavoidable, life-threatening risks of hypotension-associated stroke and myocardial infarction, bone marrow suppression, hemorrhage, hepatic failure, and gastrointestinal perforation associated with Melblez Kit treatment. Despite careful selection of patients and rigorous training of those who performed the procedure in the clinical trials, there was a high treatment related mortality rate that in the best-case scenario would be replicated in the post-marketing setting. Although the proposed REMS may assure that new treatment teams will be

taught the procedure and be properly certified, there is no basis for concluding that the outcomes will be superior to those observed in clinical trials, that is, that the adverse reaction profile will be better. The REMS program is designed to mitigate the severe risks of Melblez Kit treatment but cannot be expected to eliminate toxicities inherent to this treatment. In addition to the serious risks identified in the review of this application, it is important to include the number of days that the patient is expected to be hospitalized in determining the risk-benefit profile.

The proposed drug-device combination product is being reviewed as a NDA under CDER jurisdiction. Under NDA regulations, substantial evidence of effectiveness in adequate and well-controlled clinical trials utilizing the proposed drug-device combination product and a favorable benefit risk profile is required for approval.

Areas for Consideration by the Committee:

1. Has Delcath provided substantial evidence demonstrating that Melblez kit treatment confers an improvement in the hepatic progression-free survival that is sufficient in magnitude to be considered direct clinical benefit for the requested indication?

2. For patients with hepatic-dominant metastatic ocular melanoma, do the benefits of Melblez Kit treatment outweigh its risks?

3. Discuss the design of an additional trial(s) to assess the risks and confirm retention of efficacy using the "to-be-marketed" version of the Melblez Kit device, which was not used in the clinical trials supporting this NDA.

References:

Diener-West, M. "Development of Metastatic Disease After Enrollment in the COMS Trials for Treatment of Choroidal Melanoma: Collaborative Ocular Melanoma Study Group Report No. 26." *Archives of Ophthalmology* 123.12 (2005): 1639-643.

Jordan, D. "Cerebral Autoregulation and Acute Ischemic Stroke." *American Journal of Hypertension* 25.9 (2012): 946-50.

Landesberg, G. "Perioperative Myocardial Infarction." *Circulation* 119.22 (2009): 2936-944.

Lassen, N. "Cerebral Blood Flow and Oxygen Consumption in Man." *Physiological Reviews* 39.2 (1959): 183-238.

Leyvraz, S. "Randomized Phase III Trial of Intravenous (IV) versus Hepatic Intraarterial (HIA) Fotemustine in Patients with Liver Metastases from Uveal Melanoma: Final Results of the EORTC 18021 Study." *Jourrnal of Clinical Oncology* S (2012):

Moreau, P. "Comparison of 200 Mg/m2 Melphalan and 8 Gy Total Body Irradiation Plus140 Mg/m 2 Melphalan as Conditioning Regimens for Peripheral Blood Stem Cell Transplantation in Patients with Newly Diagnosed Multiple Myeloma: Final Analysis of the Intergroupe Francophone Du Myélome 9502 Randomized Trial." *Blood* 731st ser. 99.3 (2002): 731-35.

Ono, M. "Blood Pressure Excursions Below the Cerebral Autoregulation Threshold During Cardiac Surgery Are Associated With Acute Kidney Injury." *Critical Care Medicine* 41 (2013): 464-71.

Pönisch, W. "Treatment of Bendamustine and Prednisone in Patients with Newly Diagnosed Multiple Myeloma Results in Superior Complete Response Rate, Prolonged Time to Treatment Failure and Improved Quality of Life Compared to Treatment with Melphalan

and Prednisone—a Randomized Phase III Study of the East German Study Group of Hematology and Oncology (OSHO)." *Journal of Cancer Research and Clinical Oncology* 132.4 (2006): 205-12.

Prescher, G. "Chromosomal Aberrations Defining Uveal Melanoma of Poor Prognosis." *The Lancet* 339.8794 (1992): 691-92.

Van Raamsdonk, C. "Mutations in GNA11 in Uveal Melanoma." *New England Journal of Medicine* 363.23 (2010): 2191-199.