ENCODE
IDEAS

# Delcath Systems, Inc. (DCTH)
## INITIATION REPORT

**May 19, 2020**

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### FINANCIAL SUMMARY TABLE

| | |
|---|---|
| **Symbol** | DCTH |
| **Exchange** | NASDAQ |
| **Current Price** | $7.35* |
| **52 week High** | $24.25 |
| **52 week Low** | $0.0351 |
| **O/S** | ~6.5mm** |
| **Fully Diluted O/S** | ~10.5mm** |
| **Market Cap** | ~48mm* |
| **Cash** | ~$26.54mm** |

* as of 5/18/2020
** as of 3/31/2020 + May 20' Financing proceeds

### KEY CATALYST DATES

| | |
|---|---|
| **2H 2020** | Ph3 Results from FOCUS Trial |
| **2H 2020** | Ph3 ICC Protocol Amendment |
| **1H 2021** | NDA Submission to FDA |

### KEY DISCLOSURES

**One or more of the Encode Ideas partners own stock in the covered company; Encode Ideas, L.P. is currently engaged to provide research coverage and investor awareness to Delcath. Encode partners intend to continue transacting in the securities covered therein, and we may be long, short, or neutral thereafter.**

## HIGH CONVICTION INVESTMENT IDEA

*Encode Ideas is initiating coverage on Delcath Systems (Nasdaq: DCTH) as a high conviction investment idea. We believe Delcath's $50mm market cap today is a reflection of its colorful past, not its bright future.*

Delcath is an interventional oncology company developing a liver isolating technology, known as Hepatic Delivery System (HDS), that allows for high-dose chemotherapy, to be targeted towards tumors in the liver, while minimizing systemic exposure. HDS has been approved in Europe as a medical device, and is commercialized, as Chemosat, by Delcath's partner medac GmbH. In the United States, FDA considers HDS a drug/device combination, and therefore regulates it as a drug. Delcath is currently running an 80 patient Ph3 registrational study with HDS, called FOCUS, in patients with ocular melanoma metastatic to the liver (mOM). The study is completely enrolled and we are budgeting for top-line data late this year.

We are confident Delcath will report positive data for HDS on the primary endpoint of objective response rate (ORR), but also across other clinically meaningful secondary endpoints such as disease response rate (DCR) duration of response (DoR), and overall survival (OS). Assuming FOCUS delivers the efficacy and safety data we expect, Delcath will make an NDA (re)submission for HDS in early 2021, positioning it to become the first approved treatment of mOM in the United States later that year.

Delcath has a colorful history. Between 2010 and 2013 the company was one of the more topical micro/small-cap biotech stories on Nasdaq. Investors, enticed by HDS's platform potential to treat difficult tumors of the liver, propelled Delcath to a market cap of ~$600mm. However, after a series of ill-advised and ill-fated interactions with FDA, including a Refusal to File Letter, crushing Adcom outcome (16-0 vote to NOT approve), and eventual Complete Response Letter (CRL), Delcath had evaporated most of its value and investor goodwill. In the years that followed, Delcath began a new Ph3 study in mOM, but enrolment was sluggish and the company struggled to raise capital. In 2018 the company made a protocol amendment to the Ph3 study that helped facilitate enrolment, which was completed in early 2020. Today, Delcath is back on Nasdaq and fully financed through top-line data and NDA filing. In our opinion, the potential that propelled Delcath to $600mm in market cap many years ago remains very much intact today.

We believe Delcath's $50mm market cap today is a reflection of its colorful past, not its bright future. Since the Adcom and subsequent CRL, approximately 800 HDS treatments have been performed in Europe, and an abundance of peer-reviewed reports and studies have been published demonstrating the benefit and safety of HDS in mOM (and other tumor types). We believe the serious safety issues that derailed Delcath's earlier attempt at FDA approval, have been addressed. With Ph3 top-line data on the horizon, and an opportunity to become the first FDA-approved therapy for mOM, we believe Delcath, over the next 6-12 months, can meet and exceed its previous market cap highs.

Looking further into the horizon, we believe HDS will be deployed across multiple tumor types beyond mOM, and Delcath will become a growing and profitable, interventional oncology platform company. We see Delcath having parallels with Novocure (Nasdaq: NVCR), another company focused on treating rare aggressive

cancers. Novocure targeted a niche indication, recurrent glioblastoma (rGBM), for its first approval with its Tumor Treating Fields technology. It has subsequently expanded Tumor Treating Fields indications into first-line GBM and in 2019 malignant pleural mesothelioma (MPM), while also having a pipeline of studies exploring additional cancer indications. As Novocure has expanded its indications for Tumor Treating Fields from rGBM, through to first-line GBM, and recently MPM, its market cap has grown from ~$2b (2015 IPO) to today ~$7b, and its sales from $33mm (FY15) to $351mm (FY19). We believe 2022 Delcath could look very close to 2015 Novocure, and from there, follow a similar strategy for label expansion and growth.


(Novocure, NVCR Chart)

## The mOM Landscape

In simple terms, Delcath's HDS technology (sometimes also referred to as percutaneous hepatic perfusion or PHP) utilizes a system of catheters and balloons to isolate an organ or region, while bathing that area or region with an ultra-high dose of chemotherapy (melphalan), and then uses a filter to capture as much of the chemotherapy as possible, before the isolated blood is returned to systemic circulation. HDS is a minimally invasive procedure allowing for the delivery of an aggressive dose of chemotherapy to treat aggressive cancers. mOM is the first indication that Delcath is pursuing in the United States. The term 'unmet medical need' is thrown around rather casually by biotech companies and investors, but mOM, with an average survival of 6-months from diagnosis, is truly a disease that fits this description. There are currently no FDA-approved treatments for mOM.

Ocular melanoma is a rare cancer, making the incidence of mOM even rarer. It is estimated that there are approximately 1,000 patients per year in both the United States and Europe that develop mOM, making the addressable market (U.S. + EU) for HDS around 2,000 patients annually. Currently in Europe, HDS (marketed as Chemosat) is sold for US$25,000 per kit. HDS is registered as a medical device in Europe, so melphalan is not included in the Chemosat kits, and must be purchased separately. In the United States, regulated as a drug, the HDS kit would include melphalan. We think it is realistic to model $50,000 per kit in the United States. The HDS kits are single-use, so for every cycle a patient goes through, another kit is required. The number of cycles each patient goes through will vary, but based on the European experience, Delcath has been using 4 cycles per patient in their publicly disclosed modeling. Using these figures we arrive at a $200mm annual addressable market for mOM in the United States. Delcath has FDA orphan drug designation for melphalan in the treatment of mOM providing 7-years of market exclusivity, and a number of patents for HDS, including recently issued IP on the filtration system. We believe mOM is a beachhead indication, opening the U.S. market to HDS, after which Delcath will explore new indications, while physicians also experiment with off-label use.

## European Situation

Delcath received a CE Mark for HDS with the Gen-2 filter in Europe in 2012. We would caution investors from putting too much emphasis on the European approval. The regulatory bar for a medical device approval in Europe is far lower than a drug approval. We would also caution investors from putting too much emphasis on the lack of meaningful sales Chemosat has generated in Europe since its approval. The regulatory hurdle for a CE Mark may not be overly onerous, but achieving reimbursement, on a continent where socialized medicine prevails, is challenging. The ongoing Ph3 FOCUS study, if successful, should provide the data that open up broader reimbursement in Europe. Starting in 2019, Delcath's partner medac GmbH began marketing Chemosat throughout Europe. Specific economics of the deal have not been disclosed, but we know Delcath receives a transfer price per Chemosat kit and a royalty on sales. With 1,200 employees across Europe and a focus on oncology, medac appears to be an ideal partner for Delcath, and with broader reimbursement, should be able to generate meaningful commercial traction with Chemosat in the near future.

Europe may not have proven to be commercially lucrative for Delcath yet, but the real-world experience from the 800 treatments and the clinical data that is now being published, should prove invaluable for its U.S. endeavors. Over the last few years, there have been some excellent European retrospective data, and recently prospective data, published on HDS for mOM. We will dive into some of these data shortly, but suffice to say these studies have provided further evidence of HDS's efficacy in mOM, and allayed some of the safety concerns from the earlier generation HDS system. So even though Europe has proven commercially underwhelming thus far, the data coming out of Europe, alongside positive Ph3 FOCUS results, should be highly supportive towards Delcath achieving the real prize, FDA approval.

## Filtering Through the Data/History

The company's history, specifically the safety results from the previous Ph3 study and subsequent FDA interactions, have been fodder for Delcath bears, so we think it is important to address these historical issues. To be blunt, the safety data from the first HDS Ph3 study weren't good. These poor safety data are predominantly the result of the inefficiency of the Gen-1 Clark filter. The filter is an integral component of the HDS system, as it filters out the high-dose chemotherapy before returning the blood to a patients' systemic circulation. The data used to support the NDA in 2012 (all of the Ph3 data and some from Ph2), were predominantly generated using the Clark filter, which had suboptimal filtration efficiency, leading to serious systemic side effects and drug-related mortality. Delcath introduced the Gen-2 filter in 2012, it is the filter in the European Chemosat system and the filter in the HDS system for the ongoing Ph3 FOCUS study. Delcath has presented data showing a dramatic improvement in filtration efficiency with the Gen-2 filters over the Clark filters. Furthermore all the contemporary European clinical data being published demonstrate a vastly improved safety profile for the HDS system with the Gen-2 filter versus the earlier HDS data with the Clark filters. We are confident that the serious safety issues that derailed Delcath's earlier attempt at FDA approval, have been addressed with the Gen-2 filters.

The Clark filters may be the predominant cause of the most serious safety issues from the earlier Ph3 data, but candidly, the safety data are also a reflection of the nature of the intervention. No matter the efficiency of the filter, hematological side effects are common when using HDS. The improvements from the Clark filter to the Gen-2

filter are substantial, but when delivering the amount of chemotherapy necessary for this procedure to be effective, even with a highly efficient filter, a certain amount of drug will inevitably get into systemic circulation and lead to hematological side effects. What the Gen-2 filter has done, based on the contemporary European data, is dramatically cut down on the severity of the side effects and virtually eliminate drug-related mortality. In 2019 a 35 patient Ph2 prospective study on HDS in mOM was published, the investigators' conclusion was, "...hematologic toxicity after HDS 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." The same investigators gave an oral presentation at the 2019 European Conference on Interventional Oncology where they discussed HDS's efficacy from the study, including a profound and clinically meaningful impact on ORR and DCR, and a remarkable mean OS for HDS treated patients of 20.3 months. Recall that the life expectancy for an mOM patient is approximately 6-months from diagnosis. Other retrospective studies from Europe have also recently been published echoing similar safety and efficacy results. mOM is an aggressive cancer, HDS delivers an aggressive dose of chemotherapy which can cause real side effects, but also has profound benefits.

| Publication | CR | PR | ORR | SD | DCR | mOS (mos) | Safety |
|---|---|---|---|---|---|---|---|
| Hughes 2015 (n=44) (Gen 1 Filter) | 0.0% | 27.3% | 27.3% | 52.3% | 79.6% | 10.6 | Majority of adverse events were related to bone marrow suppression. Four deaths were attributed to PHP-Mel, three in the primary PHP-Mel group, and one post-crossover to PHP-Mel from BAC. |
| Karydis 2018 (n=51) (Gen 2 Filter) | 3.9% | 43.1% | 47.0% | 37.2% | 84.3% | 15.3 | 37.5% had Grade 3 or 4 non-hematologic toxicity<br>N=9 (17.6%) of PTS showed cardiovascular toxicity<br>31.3% PTS showed Grade 3 or 4 neutropenia vs 85.7% in prior P3 trial.<br>No TX related deaths. |
| Burgmans 2018* (n=35) (Gen 2 Filter) | 3.1% | 71.0% | 74.1% | 12.5% | 86.6% | 20.3 | Safety analysis showed 14 serious AEs, no deaths, no severe bleeding complications, myocardial or cerebral infarctions observed . |
| Artzner 2019 (n=15) (Gen 2 Filter) | 0.0% | 60.0% | 60.0% | 33.3% | 93.3% | 27.4 | Safety analysis showed Grade 3 SAEs observed in 14% of TX (anemia, leukopenia, thrombocytopenia).<br>Most SAEs were Grade 1/2, 5% of reported Grade 3/4 SAEs required intervention. |

(Delcath Jan 20' presentation, pg. 10
'Melphalan/HDS Response Comparison - Reason for Confidence'.)

In the 2013 CRL FDA stated that Delcath needed to perform a "...well controlled randomized trial(s) to establish the safety and efficacy of Melphalan / HDS using overall survival as the primary measure." Much has changed since 2013, both at Delcath and FDA. We have already discussed many of the changes at Delcath, including the improved filter for HDS, and the supportive efficacy and safety data that have emerged from Europe since the CRL. Delcath originally set out to enroll the study FDA suggested, and in 2016 entered into a Special Protocol Assessment (SPA) for a second randomized Ph3 study with survival as the primary endpoint. 10 years earlier, when the company started its first Ph3 study, patients were randomized to receive HDS or best alternative care (BAC). Patients randomized to BAC were allowed to crossover to the HDS treatment arm once their tumors progressed. The crossover allowed patients, already dealing with a devastating mOM diagnosis, and now having their tumors progress in the BAC arm, the humane option to receive the experimental therapy. In that study almost 60% of BAC patients crossed over to the HDS treatment arm. The problem was that the crossover patients confounded the survival data, because for the purposes of calculating the OS endpoint they were still

considered part of the BAC group, inflating survival for this arm. In order to avoid this confusion in the second Ph3, the crossover option was not included. It is also important to highlight that in the ten years between initiating the first and the second Ph3 studies, HDS was now commercially available in Europe, and mOM patients, with the financial means, could now fly to Europe to receive the treatment. So in 2016, Delcath began enrolling the study FDA wanted, where a patient with a recent mOM diagnosis, facing 6-months of survival, is offered to participate in a study with a 50% chance they get randomized to BAC with no hopes of crossing over to receive the experimental therapy once their tumors progress, while knowing the experimental therapy is available in Europe. Not surprisingly enrolment was lethargic, and in 2018, after interactions with FDA, Delcath revised the Ph3 protocol to single-arm study with ORR as the primary endpoint.

We think it is safe to say that the culture at FDA has changed over the past 3-5 years. In the 2013 CRL, FDA recommended Delcath perform a relatively standard Ph3 oncology study. The problem is that mOM isn't a standard oncology indication, it's ultra rare, with no approved therapies, and very poor prognosis. The 2018 change in the study design from randomized to single-arm, and primary endpoint from OS to ORR, in our opinion, better reflect the challenging nature of the disease. Delcath had regular interaction with FDA during the 2018 protocol change, and it appears from their disclosures that FDA was supportive (we do note the original SPA is no longer in effect). Over the past 5-6 years there has been a number of FDA-approvals for novel cancer medicines using ORR as their primary endpoint. Based on recent regulatory precedence in comparable situations (see chart below), we believe an ORR of 20-30% for HDS in mOM with supportive secondary endpoint data, should be approvable by FDA.

| | Approval | Endpoint | Trial Design/Results |
|---|---|---|---|
| Erivedge (vismodegib) | Standard (2012) | ORR | 1 single-arm trial; ORR 43%, duration 7.6 months; metastatic ORR 30%, duration 7.6 months |
| Istodax (romidepsin) | Standard (2009) | ORR | 2 single-arm trials; ORR 34% duration 454 days, ORR 35% duration 336 days |
| Libtayo (cemiplimab) | Standard (2018) | ORR | 2 single-arm trials; ORR 47% from pooled results |
| Darzalex (daratumumab) | Accelerated (2015) | ORR | Single-arm trial; ORR 29% |
| Kyprolis (carfilzomib) | Accelerated (2012) | ORR | Single-arm trial; ORR 23% duration 7.8 months |
| Velcade (bortezomib) | Accelerated (2003) | ORR | 2 Single-arm trials; ORR 29.6% |
| Darzalex with pomalidomide | Regular-sNDA (2017) | ORR | Single-arm trial; ORR 59.2% |
| Xpovio (selinexor) with dexamethasone | Accelerated (2019) | ORR | Single-arm trial; ORR 25.3% duration 3.8 months |
| Pemigatinib | Topline data released – NDA submission planned shortly | ORR | Single-arm trial; ORR 36% |

(Delcath Jan 20' presentation, pg. 11
'FDA Has Approved a Number of Treatments for Oncology Indications Based on Single-Arm Trials Measuing ORR'.)

## Beyond mOM - Platform Potential

Earlier, we referenced $200mm as the addressable mOM market for HDS in the United States. Some may be dismissive of a market this size, but HDS, as the only approved treatment for mOM, will be a high gross margin product (we estimate 90%), that requires a very small commercial footprint, given that the majority of treatments occur at a few select centres. We also think mOM is just the beginning for Delcath. HDS, as a liver-directed therapy, has the potential to be used across a

number of difficult to treat primary and metastatic tumors of the liver. The company had been enrolling (slowly) a global Ph3 study in intrahepatic cholangiocarcinoma (ICC), a very difficult to treat primary cancer of the liver. Delcath recently announced that it was pausing enrolment in order to discuss a protocol amendment with FDA. We anticipate an update on the company's FDA interactions in 2H20. ICC is also a rare cancer, but still estimated to have an addressable patient population 4-5x that of mOM. A recent 15 patient study was published on ICC patients treated with HDS in Europe, showing promising results.

In Europe, where HDS is regulated as a device, its label permits use across a broad range of primary and metastatic liver cancers. To date, Delcath has reported HDS has been used in 13 different tumor types since its launch in Europe. In the United States, HDS, regulated as a drug, would be approved specifically for mOM. In order to expand the HDS label beyond mOM, Delcath would need to complete late-stage clinical studies for each new indication. Although we expect Delcath to pursue label expansion into ICC and perhaps other cancers of the liver in the future, we also anticipate that data generated in Europe across a number of tumor types will drive off-label use for HDS in the United States.

Beyond the obvious platform potential for cancers of the liver, HDS does have potential to be used for other organs. Perhaps the most enticing future application for HDS though, would be delivering new medicines, such as immunotherapy. Upon success in mOM, we could foresee a collaboration between Delcath and a large cancer-focused BioPharma, exploring liver-directed immunotherapy therapy through HDS.

## Financial Considerations

After completing a $22mm financing earlier this month, we estimate Delcath has sufficient cash to complete the Ph3 FOCUS study, and prepare and submit its NDA. We anticipate all these milestones will be completed by 1H21. However between top-line data and the NDA filings, we foresee the company could look to raise additional capital, to finance itself comfortably through an FDA decision late in 2021. Alternatively, Delcath has approximately 4mm warrants struck at $10, which could be a source of capital.

Delcath's reported outstanding shares (O/S) as of their last 10-Q were 2.76mm. This number does not reflect their true O/S as there are just under 4mm additional common shares that will be issued upon conversion of legacy preferred shares from two 2019 PIPEs. These preferred shares no longer have any conversion preferences, so we expect the vast majority to be converted into commons by the time the company files its next 10-Q. For our purposes, we convert all the preferred shares to common and arrive at ~6.5mm for O/S, giving Delcath a market cap of ~$50mm.

Delcath has an eclectic shareholder base that consists of deep science funds, such as Rosalind Advisors and Altium, and faster money funds. On May 12th Rosalind's two founders, Dr. Steven Salamon and Dr. Gil Aharon, joined the Delcath board of directors. We take this as incrementally positive, as the largest shareholder (we estimate Rosalind owns 35-40%) is clearly taking a more active role in the company.

## Technical Summary

Primary liver cancer is the sixth most common cancer in the world. The liver is also the second most common site of metastases after the lymph nodes. In particular, the liver is the predominant site of metastases for patients with ocular melanoma, colorectal adenocarcinoma, and neuroendocrine tumors.

Delcath Systems, Inc. is a specialty pharmaceutical and medical device company focused on the treatment of primary and metastatic liver cancers. Delcath's proprietary product Melphalan Hydrochloride for Injection is used with the Delcath Hepatic Delivery System (Melphalan/HDS) to administer high dose chemotherapy to the liver.

The Melphalan/HDS System delivers chemosaturation with percutaneous hepatic perfusion and represents a minimally invasive and repeatable targeted liver therapy. The percutaneous hepatic perfusion process involves delivering Melphalan directly to the hepatic artery; venous blood from the liver is then recirculated through an extracorporeal filtration system, which removes the Melphalan before returning the blood to the systemic circulation. Utilizing this system, high doses of Melphalan can be directed to the liver while minimizing the toxic effects of systemic exposure.

In the United States, the Melphalan/HDS System is considered a combination drug/device product and is regulated as a drug by the Food and Drug Administration (FDA). Currently the Melphalan/HDS System is not approved for sale in the United States however, Delcath is currently seeking FDA approval for the treatment of patients with unresectable, metastatic ocular melanoma in the liver.

Delcath's initial clinical development program consisted of 3 clinical trials:

- Clinical trial 01-C-0215,
- Clinical trial 04-C-0273, and
- Clinical trial DSI MEL 2005-001

Clinical trial 01-C-0215, was a phase 1, open-label, dose-escalation study conducted at the National Cancer Institute (NCI) in patients with unresectable hepatic metastases from a variety of solid tumors. Clinical trial 04-C-0273 was a phase 2, open-label study conducted at the NCI in patients with unresectable primary or metastatic hepatic malignancies, including adenocarcinoma of the gastrointestinal tract, ocular or cutaneous melanoma, or neuroendocrine tumors. Clinical trial DSI MEL 2005-001 was a phase 3, randomized, controlled, multi-center study, conducted at 10 US centers in patients with confirmed cutaneous or ocular melanoma with metastases predominantly in the liver.

Initial efficacy of Melphalan/HDS for the treatment of unresectable, metastatic ocular melanoma in the liver was provided by clinical trial DSI MEL 2005-001, which compared the efficacy of Melphalan/HDS treatment to the best alternative care selected by the Investigator. In the trial patients in the best alternative care group were allowed to crossover to Melphalan/HDS treatment at the time of hepatic progression. The primary efficacy endpoint was hepatic progression free survival by Independent Review Committee assessment and secondary efficacy endpoints were hepatic progression free survival by Investigator assessment, the rate of hepatic objective response by Independent Review Committee and Investigator assessment and overall survival.

The key efficacy data from clinical trial DSI MEL 2005-001 have been summarized below:

- The primary efficacy endpoint of hepatic progression free survival by Independent Review Committee assessment was met in the overall patient population. Melphalan/HDS treatment of patients specifically with unresectable, metastatic ocular melanoma in the liver resulted in a statistically significant and clinically meaningful increase in hepatic progression free survival by Independent Review Committee assessment compared to best alternative care treatment with a median 5-month difference in favor of Melphalan/HDS treatment.
- Hepatic progression free survival results by Investigator assessment were similar to the Independent Review Committee.

- The robustness of the hepatic progression free survival benefit was evidenced by consistent results across pre-specified sensitivity analyses and all subgroup analyses, including patients with ocular melanoma.
- Statistically significant higher rates of hepatic objective response were observed by both the Independent Review Committee and Investigator assessment in the Melphalan/HDS group compared to the best alternative care group.
- Median survival was similar between the Melphalan/HDS and the best alternative care groups, but the survival data are confounded by the high percentage of best alternative care patients who experienced hepatic progression and crossed over to Melphalan/HDS treatment (57%).

The ocular melanoma subpopulation in Clinical trial 01-C-0215 (phase 1) and Clinical trial 04-C-0273 (phase 2) showed similar median hepatic progression free survival times and hepatic objective response rates as the phase 3 study.

In December 2010, Delcath filed a New Drug Application (NDA) with the FDA based on the results of the 3 clinical trials. In response the FDA issued a "Refusal to File" letter citing insufficient safety information that did not allow the FDA to adequately assess the benefit-risk profile. In response to the letter, a Type A meeting was held to discuss the items which needed to be included in a resubmission. Subsequently the NDA was resubmitted in August of 2012 and the Division of Oncology Products asked for the advice of the Oncologic Drugs Advisory Committee before making a decision. An advisory committee meeting was held in May of 2013. At that meeting the FDA raised both product efficacy and safety concerns. These concerns ultimately lead to the FDA issuing Delcath a Complete Response letter.

One of the FDA's major safety concerns was regarding a change in the hemofiltration system used during the clinical development program. The FDA argued that the change in filter manufacturer for the phase 3 study was associated with an increase in the incidence of toxic deaths as well as the incidence and severity of adverse reactions.

## Filter Adverse Reaction Profiles

| Filter Type | Asahi Hemosorba | Clark Cartridge (GEN 1) | Clark Cartridge (GEN 1) |
|---|---|---|---|
| Patient Population | Phase 1 and Phase 2<br>Mixed Histology | Phase 2<br>Mixed Histology | Phase 3<br>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 | 70% | 73% | 71% |
| Median Nadir MAP | 60 mmHg | 49 mmHg | 49 mmHg |
| Toxic Deaths | 0% | 5% | 9% |
| Grade 3 and 4 Adverse Reactions | 77% | 98% | 93% |
| Serious Adverse Reactions | 47% | 90% | 74% |
| Toxicity resulting in discontinuation | 7% | 41% | 41% |

Since increases in the incidence and severity of adverse reactions were not predicted by *in vitro* and pharmacokinetic testing, the FDA determined that any new combination drug/device product must undergo validation in adequate and well-controlled clinical trials demonstrating a favorable benefit-risk profile.

In 2012, Delcath introduced a second-generation detoxification cartridge (GEN 2 filter; Delcath Systems). A subsequent pharmacological study has shown that the mean extraction rate of the GEN 2 hemofiltration system was 86%, approximately 10% higher than that of first-generation filters. In addition, the results of a recent prospective study suggested that hematologic toxicity after Melphalan/HDS can be reduced by using the GEN 2 filter instead of a first generation filter.

After extensive discussions between Delcath and the FDA, a new pivotal phase 3 clinical trial (FOCUS) was designed and initiated using the GEN 2 hemofiltration system. FOCUS is a multi-center, single-arm, open-label study to evaluate the efficacy and safety of Melphalan/HDS in patients with hepatic dominant metastatic ocular melanoma. The study is being conducted at approximately 40 centers in the United States and Europe and is expected to be completed in late 2020.

In Europe, the Melphalan/HDS system is marketed as a device under the trade name Delcath Hepatic CHEMOSAT® Delivery System for Melphalan. CHEMOSAT has been commercially available in Europe since 2012 and has been used at major medical centers to treat a wide range of cancers of the liver, including ocular melanoma, intrahepatic cholangiocarcinoma, hepatocellular carcinoma, cutaneous melanoma, breast cancer, neuroendocrine tumors, anal mucosal melanoma, pancreatic cancer, colorectal cancer, sarcoma, gastric cancer, endometrium cancer and prostate cancer.

A systematic review of 186 patients in Europe who had received a total of 321 CHEMOSAT treatments was published in 2016. Most of the procedures were performed for patients with liver metastases from ocular melanoma. The majority of procedures were performed in Germany (75 procedures total in 11 hospitals), the United Kingdom (49 procedures total in four hospitals), and the Netherlands (33 procedures total in two hospitals). Melphalan/PHP was also performed in Italy (12 procedures total in two hospitals), France (nine procedures total in two hospitals), Spain (six procedures total in two hospitals), Ireland (one procedure total in one hospital), and Turkey (one procedure in one hospital).

A number of studies and case reports have been published on the use of CHEMOSAT in Europe.

## Summary of European Melphalan/HDS Studies

| Study Type | Number of Patients | Primary Tumor | Reference |
|---|---|---|---|
| Prospective Study | 35 | Ocular melanoma | Meijer et al, 2019 |
| Retrospective Study | 16 | Ocular melanoma | Artnzer et al, 2019 |
| Retrospective Study | 20 | Ocular melanoma | Hickson et al, 2015 |
| Retrospective Study | 30 | Ocular melanoma<br>Cutaneous melanoma<br>Unknown | Abbott et al, 2015 |
| Retrospective Study | 13 | Ocular melanoma<br>Cutaneous melanoma<br>Breast cancer<br>Cholangiocarcinoma | Vogl et al, 2014 |
| Retrospective Study | 11 | CRC<br>Ocular melanoma | Vahrmeijer et al, 2014 |
| Case Series | 7 | Ocular melanoma | Trennheuser et al, 2019 |

| | | | |
|---|---|---|---|
| Case Report | 1 | Solid pseudopapillary neoplasm of the pancreas | Hofman et al, 2014 |
| Case Report | 1 | Leiomyosarcoma | Deneve et al, 2012 |

The results indicate that percutaneous hepatic perfusion with Melphalan may be a therapeutic option for primary and secondary liver tumors, providing the rationale for ongoing and planned clinical trials across a spectrum of tumor histologies including ocular or cutaneous melanoma, colorectal cancer and cholangiocarcinoma.

In conclusion, Delcath is currently seeking FDA approval of its Melphalan/HDS System, using its GEN 2 hemofiltration system, for treatment of patients with unresectable, metastatic ocular melanoma in the liver. In addition, Decath is also looking to expand its use to other indications such as intrahepatic cholangiocarcinoma and hepatocellular carcinoma. Positive results have been obtained through Delcath's clinical development program and are supported by its extensive use in Europe.

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# 1 Introduction

## 1.1 Liver Cancer

The liver is frequently affected by cancer. Primary liver cancer is the sixth most common cancer in the world and the third leading cause of cancer-related death. It is estimated that 42,030 new cases of liver cancer (including intrahepatic bile duct cancers) will be diagnosed in the United States (US) in 2019 (American Cancer Society, 2019). The liver is also the second most common site of metastases after the lymph nodes and hepatic metastases are found in 30-70% of patients who die of cancer. (European Association for Study of the Liver, 2012; Jovanovic et al, 2013).

The liver is the predominant site of metastases for patients with ocular melanoma, colorectal adenocarcinoma, and neuroendocrine tumors (Table 1). In 2019, it is estimated that there will be over 145,600 new cases of colorectal cancer in the US (American Cancer Society, 2019) of which 20% to 40% will metastasize to the liver (Norstein et al, 1997). There are fewer patients with metastatic ocular melanoma (2,000 per year in the US; Krantz et al, 2017), however over 90% of cases will metastasize to the liver (Seregard et al, 1995). Neuroendocrine tumors (12,000 per year in the US; Dasari et al, 2017), although biologically more indolent in behavior, metastasize to the liver in 40 to 90% of patients (Chamberlain et al, 2000; Allen et al, 2005). More rarely, hepatic metastases arise in patients with soft tissue sarcomas, cutaneous melanoma, breast cancer, and renal cell cancer.

### Table 1 New Liver Cancer Cases in the US per Year

| Condition | US Cases Per Year | Metastasize to Liver |
|---|---|---|
| Primary Liver Cancer | 42,030* | N/A |
| Ocular Melanoma | 2,000** | >90% |
| Colorectal Adenocarcinoma | 145,600* | 20-40% |
| Neuroendocrine Tumors | 12,000# | 40-90% |
| N/A = Not Applicable; US = United States | | |

*American Cancer Society, 2019;** Krantz et al, 2017; #Dasari et al, 2017.

## 1.2 Regional Therapies

The current treatment armamentarium for cancers in the liver include:

- Surgery,
- Transplantation,
- Systemic chemotherapy,
- Focal and regional therapies, and
- Radiation therapy.

Each of these treatments have varying degrees of invasiveness, efficacy, and side effects (Agarwala et al, 2014). Hepatic resection remains the only potentially curative treatment for patients with liver metastases, however, most patients are not surgical candidates (Caralt et al, 2011; Pawlik et al 2006; Martel et al, 2015).

Unresectable metastases from solid organ malignancies isolated to the liver are a great clinical challenge. However, the unique anatomy of the liver allows vascular isolation permitting delivery of high doses of cytotoxic agents with minimal systemic toxicity. Treatment modalities such as hepatic artery chemoembolization, hepatic arterial infusion (HAI), isolated hepatic perfusion (IHP) and percutaneous hepatic perfusion (PHP) have the underlying advantage of limiting systemic toxicity and focusing treatment directly to the liver (Agarwala et al, 2014).

Chemosaturation with percutaneous hepatic perfusion represents a minimally invasive and repeatable targeted hepatic therapy. During this treatment Melphalan is directly delivered to the hepatic artery; venous blood from the liver is recirculated through an extracorporeal filtration system, which removes the Melphalan before returning the blood to the systemic circulation. By utilizing this method, high doses of Melphalan can be directed to the liver while minimizing systemic exposure (Vogl et al 2014; Vogl et al, 2017).

### 1.3 Delcath Systems Inc.

Delcath Systems, Inc. (Delcath) is a specialty pharmaceutical and medical device company focused on the treatment of primary and metastatic liver cancers. Delcath was founded in 1988 and began trading on the NASDAQ under the ticker symbol DCTH in October of 2001. The company is currently headquartered in New York City, New York.

Delcath's proprietary product Melphalan Hydrochloride for Injection is used with the Delcath Hepatic Delivery System (Melphalan/HDS) to administer high dose chemotherapy to the liver by PHP. In the US, the Melphalan/HDS System is considered a combination drug and device product, and is regulated as a drug by the Food and Drug Administration (FDA). Currently the Melphalan/HDS System is not approved for sale in the US. In Europe, the Melphalan/HDS system is marketed as a device under the trade name Delcath Hepatic CHEMOSAT® Delivery System for Melphalan (CHEMOSAT). This system has been commercially available in Europe since 2012 and has been used at major medical centers to treat a wide range of cancers of the liver.

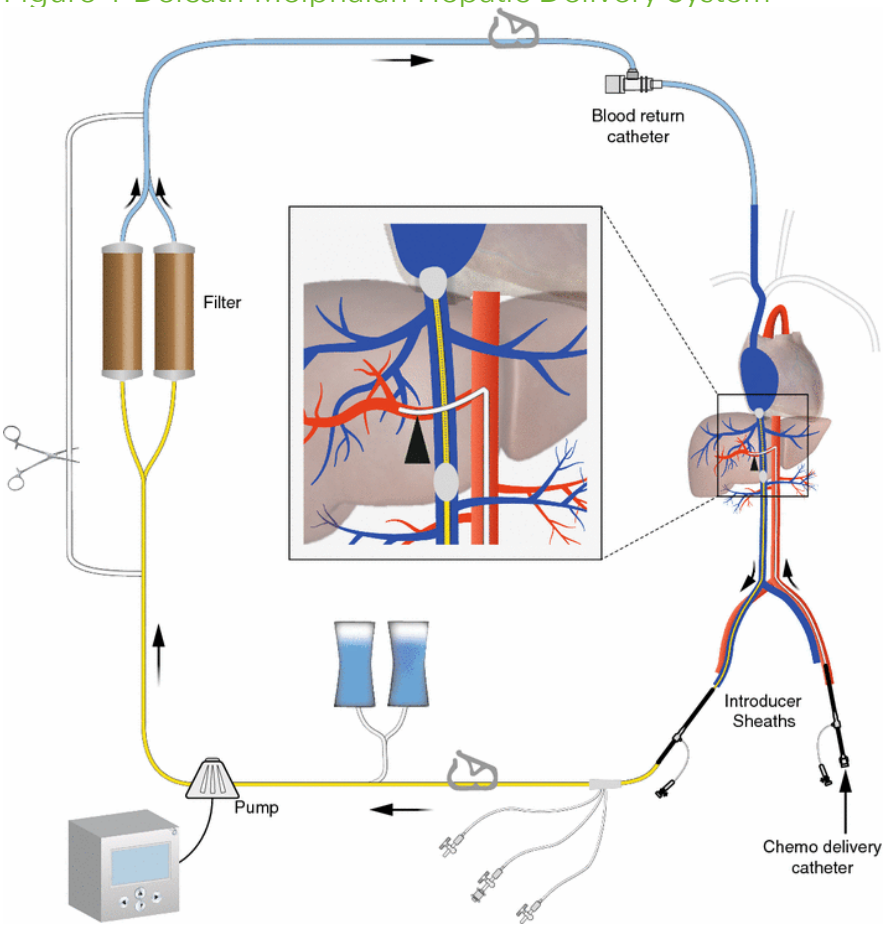
## 2 Discussion

### 2.1 Melphalan/HDS Technology

Delcath is an interventional oncology company focused on the treatment of primary and metastatic liver cancers. Delcath's investigational product – Melphalan Hydrochloride for Injection for use with the Delcath Hepatic Delivery System (Melphalan/HDS) – is a drug/device combination product that is composed of the chemotherapeutic agent Melphalan Hydrochloride and a number of sterile, single-use medical device components, including catheters and hemofiltration cartridges.
The device is used in a procedure known as percutaneous hepatic perfusion to deliver Melphalan directly to the liver via the hepatic artery using a catheter that is percutaneously inserted using standard interventional radiology techniques. The recommended dose of Melphalan is 3.0 mg/kg based on ideal body weight (IBW), infused over 30 minutes, with a maximum absolute dose of 220 mg per single treatment. Treatments are recommended to be administered every 6-8 weeks.

A schematic overview of the PHP procedure is provided in Figure 1. In the PHP procedure, Melphalan is delivered directly into the hepatic artery via a catheter in the proper hepatic artery. A double-balloon catheter is positioned in the retrohepatic inferior vena cava to isolate and collect hepatic venous outflow which is sent through an extracorporeal filtration system to lower the concentration of Melphalan in the blood before it is returned to the systemic circulation via an internal jugular vein sheath. Once the extracorporeal circuit is established, Melphalan is administered as a 30 minute infusion via the hepatic artery with simultaneous extracorporeal blood filtration. Extracorporeal filtration continues for an additional 30 minutes after infusion to filter any Melphalan that is released from the liver after completion of Melphalan infusion (Delcath Systems, 2013).

Figure 1 Delcath Melphalan Hepatic Delivery System




The PHP procedure requires a multi-disciplinary team with the knowledge and skills required to care for patients who undergo Melphalan/HDS treatment. Members of the procedural team and their role during Melphalan/HDS treatment are summarized in Table 2.

Table 2 Melphalan/HDS Procedure Team

| Team Member | Responsibility |
|---|---|
| Interventional radiologist | Leads procedural team during the procedure by communication and coordination with the entire procedural team |
| Surgical or medical oncologist | Complete management of patient |
| Anesthesiologist | Sedation, analgesia, and hemodynamic support |
| Perfusionist | Establishing, monitoring, and controlling the extracorporeal circuit |
| Certified healthcare provider for chemotherapy delivery | Melphalan administration |
| Interventional radiology staff | Assists in procedure and imaging |
| Pharmacist | Melphalan preparation |

Patients are typically hospitalized for 2-3 days for Melphalan/HDS treatment. The PHP procedure is conducted in an interventional radiology suite under general anesthesia and takes approximately 3 hours to complete. After completion of the procedure, the patient is observed in the intensive care unit (ICU), surgery recovery unit, or surgical ward by the interventional radiologist, anesthesiologist, and additional staff for 24 to 48 hours. The patients are monitored for evidence of systemic toxicity secondary to the perfusion procedure, for hemodynamic stability and to ensure that coagulation has returned to normal.

In order to avoid serious injury, illness, or deaths, patient selection criteria must be followed with respect to the following:

- Anatomical structure
- Extent of liver tumor burden and
- Propensity for adverse events (AEs) due to underlying disease conditions

Prior to the PHP procedure, there are laboratory assessments, imaging tests, and treatments (ie, gastroduodenal embolization if required) that must be performed to ensure patient eligibility for Melphalan/HDS treatment.

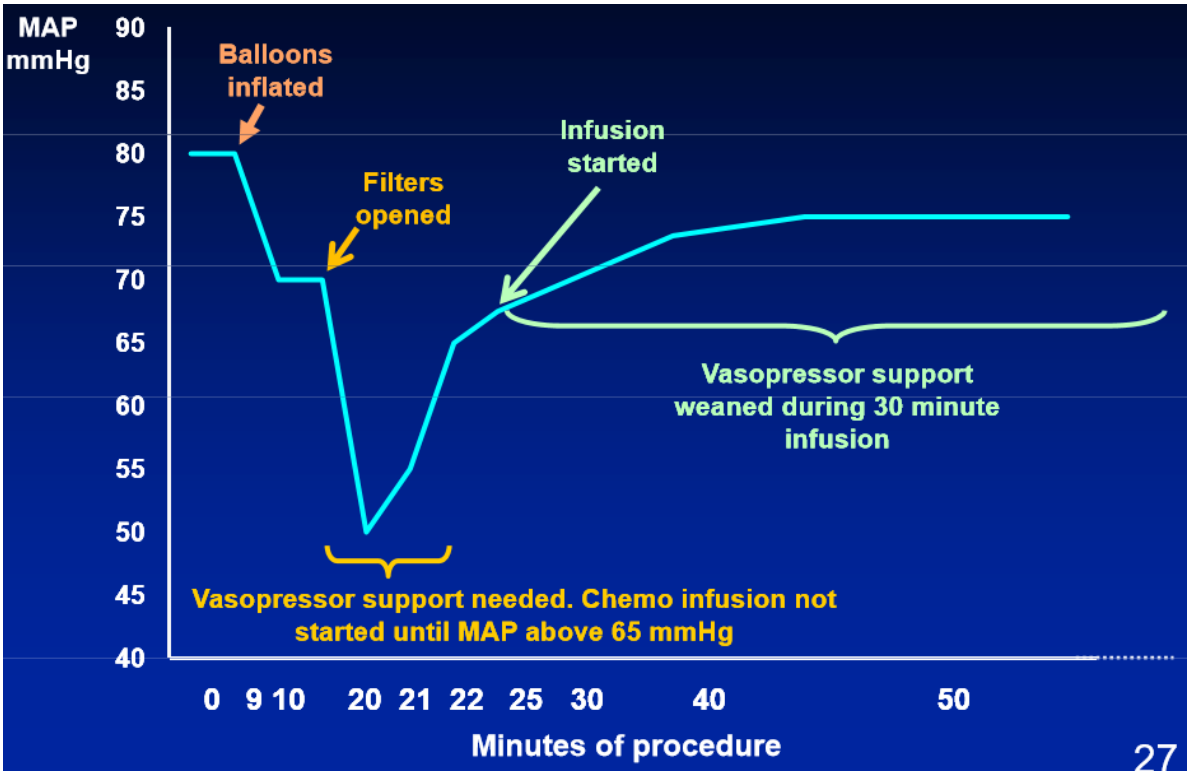
The patient is admitted to the hospital by the medical or surgical oncologist the night before for procedure preparation. Intravenous (IV) hydration is started to ensure an adequate fluid pre-load before the procedure. Proton pump inhibitors are administered to prevent gastritis which could occur as a result of regional Melphalan absorption during the procedure. Patients with a history of hepatobiliary surgery or ablative procedures are given antibiotics prophylactically to prevent infections.

Heparin is administered by the anesthesiologist to maintain the activated clotting time at therapeutic levels. Heparin is administered at the direction of the interventional radiologist before he/she isolates the liver and prior to the initiation of the extracorporeal circuit by the perfusionist. Vital signs are monitored continuously throughout the procedure by the anesthesiologist.

All patients experience hypotension (Figure 2) at two points during the procedure:

- When balloons are inflated within the inferior vena cava causing decreased cardiac return since blood flow from the lower body is temporarily obstructed
- When the extracorporeal circuit is connected to the body

Figure 2 Blood Pressure Changes during PHP




(Delcath, 2013)

The blood pressure drop is managed with pre-hydration and IV vasopressors until blood pressure normalizes. Vasopressors are administered by the anesthesiologist to maintain a mean arterial pressure >65 mmHg to prevent ischemic injury to the heart and brain. Patient responsiveness to the vasopressor is checked prior to balloon inflation. The Melphalan infusion is not started by the interventional radiologist until mean arterial pressure is >65 mmHg.

Vasopressor support is weaned during the 30 minute Melphalan infusion and is not required after conclusion of the procedure. Arterial patency is assessed by the interventional radiologist several times during the PHP procedure by injection of contrast media into the hepatic artery catheter to ensure that there is no vasospasm of the hepatic artery that could result in Melphalan reflux into proximal gastrointestinal (GI) branches. Nitroglycerin is administered by the interventional radiologist by intra-arterial injection if hepatic spasm is seen and the infusion of Melphalan is suspended until the spasm resolves. The procedure is terminated by the interventional radiologist if the spasm does not resolve with nitroglycerin administration.

Protamine, fresh frozen plasma and/or cryoprecipitate are administered immediately after the procedure to correct coagulopathy and to facilitate sheath removal. Platelets and red blood cells may be transfused by the interventional radiologist, as required, to correct thrombocytopenia and anemia that are a consequence of platelet and red blood cell sequestration by the filters. Some patients require electrolyte administration to correct electrolyte imbalances. One or two doses of furosemide may be necessary to counter edema as a result of IV hydration.

Total hospitalization for the PHP procedure is approximately 2-3 days, but may vary depending on the medical needs of the patient. The patient is discharged from the hospital once anticoagulation, liver function abnormalities, thrombocytopenia, and anemia are corrected.

The following are the recommendations for discharge:

- Prothrombin time (PT) within 2 seconds of upper limit of normal (ULN)
- Activated partial thromboplastin time (aPTT) within normal range
- Platelets >75,000/µL without platelet transfusion or >100,000/ µL with transfusion
- Hemoglobin >10 g/dL

Patients must be closely monitored on an outpatient basis after hospital discharge. When following-up on patients it is important for the oncologist to monitor for possible Melphalan and procedure-related toxicities, including bone marrow suppression. The interventional radiologist plays a unique leadership role in communicating the safe use conditions for Melphalan/HDS treatment and coordinating with oncologists and other key healthcare providers responsible for patient follow-up care and monitoring for post-procedure toxicities (Delcath Systems, 2013).

## 2.2 Indication

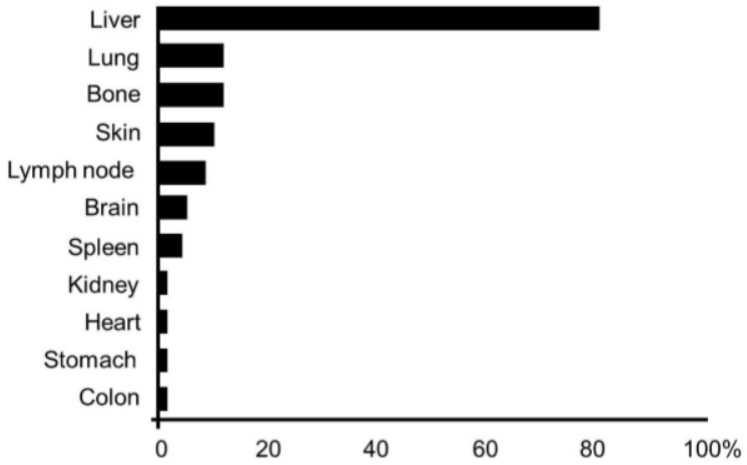
Delcath is seeking FDA approval of the Melphalan/HDS System for the treatment of patients with unresectable, metastatic ocular melanoma in the liver.

Ocular melanoma is the second most common type of melanoma after cutaneous and the most common primary intraocular malignant tumor in adults. The majority of ocular melanomas originate from uvea (~85%), while conjunctival melanomas (~5%) and other sites (~10%) are far less frequent (McLaughlin et al, 2005).

Uveal melanoma is considered a rare cancer, representing ~3%–5% of recorded melanoma cases in the US. Uveal melanoma incidence varies by sex, race, and country. Males have a 30% greater incidence than females (McLaughlin et al, 2005). In the US, the incidence is approximately five per million individuals, with a significantly higher incidence in non-Hispanic whites (6.02 per million) when compared with blacks and Asians (0.31 and 0.39 per million, respectively). Incidence in Hispanics is in the middle, at 1.67 per million (McLaughlin et al, 2005, Singh et al, 2011; Hu et al, 2005). In Europe, incidence increases with latitude, ranging from 2 per million in Spain and Italy, 4- 6 per million in Central Europe, and greater than 8 per million in Denmark and Norway (Virgili et al, 2007).

Ocular melanoma carries significant risk of metastatic spread, affecting approximately 35% of patients at 10 years with up to 50% lifetime risk (Diener-West et al, 2005). The liver is the most common site of metastatic spread and is responsible for 90% of metastatic disease (Spagnolo et al, 2012). Up to 80% of patients with ocular melanoma have liver metastasis as their only site of disease (Figure 3). Development of liver metastases is associated with a poor prognosis due to the lack of effective systemic treatment, with survival typically around 6 months (Pereira et al, 2013).

### Figure 3 Sites of Metastases in Patients with Ocular Melanoma




(Lillemoe et al, 2014)

Surgical resection of liver metastases from ocular melanoma can result in long term survival (Caralt et al, 2011; Pawlik et al 2006; Martel et al, 2015). However, less than 10% of ocular melanoma patients with liver metastases are suitable for surgical resection because of the multifocal and miliary distribution of their disease. Systemic chemotherapy has failed to show clinical efficacy against metastatic ocular melanoma. Various regional treatments (ie, transcatheter arterial chemoembolization (TACE)), immunoembolization) have been developed for the treatment of unresectable liver metastases, however, these treatments are limited to patients with isolated metastases and therefore are not an option for the majority of ocular melanoma patients. Therefore there is a critical unmet medical need for effective treatments for patients with hepatic metastases from ocular melanoma since there are no approved therapies.

## 2.3 Regulatory History

Melphalan/HDS is a combination product which consists of a drug (Melphalan) and device bundled in a single package. Based on the primary mechanism of action (MOA), the FDA determined that it needed to 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.

In June 2001, Delcath opened an Investigational New Drug Application (IND) for treatment of metastatic cancer limited to the liver with Melphalan administered via PHP. The key regulatory activities associated with the IND have been summarized in Table 3.

### Table 3 Summary of IND Associated Regulatory Activities

| Date | Regulatory Activity |
|---|---|
| June 2001 | IND 32617 for treatment of metastatic cancer limited to the liver with Melphalan administered via percutaneous isolated hepatic perfusion allowed to proceed |
| April 2005 | Fast Track designation granted for the treatment of hepatic tumors secondary to melanoma |
| April 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 2008 | Orphan Drug designation granted for "treatment of patients with cutaneous melanoma" and for "treatment of patients with ocular (uveal) melanoma" |
| March 2010 | Pre-NDA meeting held |
| FDA = Food and Drug Administration; IND = Investigational New Drug Application; NDA = New Drug Application | |

Subsequently, Delcath's filed an NDA as a 505(B)(2) application in December of 2010 with Melphalan Hydrochloride for Injection (approved in Europe and the USA in 1992) used as the reference listed drug (RLD). The NDA contained information on the following clinical studies:

- A Phase 1 study - 01-C-0215,
- A Phase 2 study - 04-C-0273 (NCT00096083), and
- A Phase 3 study (pivotal) - DSI MEL 2005-001 (NCT00324727)

The Phase 1 and Phase 2 studies were conducted at the National Cancer Institute (NCI) and the Phase 3 study was initiated at the NCI and expanded to 9 additional sites. A brief summary of the clinical results of these studies can be found in Section 3.3 below.

After the NDA was submitted, the FDA issued a Refusal to File (RTF) letter in February 2011, citing insufficient safety information that did not allow the FDA to adequately assess the benefit-risk profile. In response to the RTF, a Type A meeting was held with the FDA in April 2011 to discuss the items which needed to be included in an NDA resubmission to allow the FDA to complete its clinical review. The NDA was resubmitted in August of 2012. Subsequently the Division of Oncology Products asked for the advice of the Oncologic Drugs Advisory Committee and a meeting was held in May of 2013 (FDA, 2013; Delcath Systems, 2013; Oncologic Drugs Advisory Committee, 2013). Ultimately Delcath received a Complete Response letter (CRL).

The key regulatory activities associated with the NDA have been summarized in Table 4.

### Table 4 Summary of NDA 201848 Regulatory Activities

| Date | Regulatory Activities |
|---|---|
| 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 06, 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 RTF letter as agreed-upon during the January 12, 2012 meeting |
| May 02, 2013 | NDA 201848 resubmitted addressing items in the February 18, 2011 RTF letter as agreed-upon during the January 12, 2012 meeting |
| September, 2013 | Complete Response Letter |
| FDA = Food and Drug Administration; NDA = New Drug Application; RTF = Refusal to File | |

After extensive discussions between Delcath and the FDA, a new pivotal Phase III clinical trial was designed and initiated (NCT02678572). This clinical trial is currently in progress and is expected to be completed in mid/late-2020. A detailed description of this trial can be found in Section 3.5.1 below.

## 2.4 Delcath Clinical Trials - Completed

As part of Delcath's initial clinical development plan, 3 clinical trials were conducted and completed. A brief description of these trials is provided in Table 5 and a detailed summary of their results can be found in the Sections 3.4.1, 3.4.2, and 3.4.3 below.

### Table 5 Clinical Trials Submitted with Delcath's NDA 201848 in 2010

| Identifier | Description | Reference |
|---|---|---|
| 01-C-0215 | A Phase 1 study in 34 patients with unresectable hepatic metastases from solid tumors (ocular melanoma, 12 patients; cutaneous melanoma, 3 patients; other tumor types, 19 patients) that was conducted at the NCI | Pingpank et al, 2005<br><br>Delcath Systems, 2013 |

| | | |
|---|---|---|
| | A Phase 2 study in 56 patients with either unresectable primary hepatic tumors or unresectable hepatic metastases from solid tumors that was conducted at NCI | Delcath Systems, 2013 |
| | A pivotal Phase 3 study in 93 patients with unresectable hepatic metastases from either ocular (n=83) or cutaneous (n=10) melanoma that was conducted at NCI and 9 additional sites | Delcath Systems, 2013 |

### 2.4.1 Clinical Trial 01-C-0215

Clinical trial 01-C-0215, was a phase 1, open-label, dose-escalation study conducted at NCI in patients with unresectable hepatic metastases from a variety of solid tumors (ie, ocular melanoma, cutaneous melanoma, and other tumor types). Trial 01-C-0215 used Hemosorba (Asahi Medical Co, Tokyo, Japan) filters for hepatic venous hemofiltration during the PHP process (for more information on the filter see Section 3.4.5).

The objective of this study was to determine the dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) of Melphalan administered by PHP. Patients were hospitalized for treatment every 4 weeks, for up to 4 treatments. Prior to cycle 3, patients were required to have shown evidence of stable disease (SD) or better.

A total of 34 patients were enrolled in the study:
- 2.0 mg/kg cohort - 14
- 2.5 mg/kg cohort - 3
- 3.0 mg/kg cohort - 11
- 3.5 mg/kg cohort - 6

Twelve patients had ocular melanoma, 3 patients had cutaneous melanoma, and 19 patients had other solid tumor types.

Demographics and baseline disease characteristics were similar across the dose cohorts. The majority of the patients were white. More males (18 patients) than females (16 patients) were enrolled in the study and the median age was 50.0 years. The median time since diagnosis of the primary tumor was 33.2 months and the median time since diagnosis of hepatic metastasis at study entry was 9.2 months.

The median number of attempted treatment cycles was 2.0 and the majority of patients (69.7%) completed ≥ 2 cycles of treatment. Overall, 39.4% of patients completed ≥ 4 cycles of treatment.

The majority of patients in all cohorts had at least one adverse event (AE) and 79% of patients had at least one grade 3/4 AE. No deaths due to AEs occurred in the study. Overall, 42.4% of patients had at least one serious adverse event (SAE). Four patients prematurely discontinued the study due to an AE.

To determine which patients had significant Melphalan related toxicities and therefore DLTs, the Investigators reviewed each patient's AEs on a weekly basis and adjudicated the toxicities to determine the DLTs and to support dose escalation. In the DLT determination, the Investigators considered the protocol definition of a DLT and additional factors such as the time of event onset relative to Melphalan administration, other AEs that occurred within the same time frame, and the clinical consequences associated with the event (ie, medical interventions required to treat the event, could the patient continue PHP treatment without delay).

Three patients had DLTs as determined by the Investigators: 2 patients at 3.5 mg/kg and 1 patient at 3.0 mg/kg. Thus, 3.0 mg/kg was determined as the MTD of Melphalan delivered by PHP since only 1 patient had a DLT at this dose (Table 6). All of the DLTs were events related to bone marrow suppression, including neutropenia, febrile neutropenia, leukopenia, and thrombocytopenia.

### Table 6 Dose-limiting Toxicities and Maximum Tolerated Dose

| Clinical trial 01-C-0215 | Melphalan Dose | | | |
|---|---|---|---|---|
| | 2.0 mg/kg N=14 | 2.5 mg/kg N=3 | 3.0 mg/kg N=10 | 3.5 mg/kg N=6 |
| # of Patients with a DLT | 0 | 0 | 1 | 2 |
| Neutropenia | 0 | 0 | - | 2 |
| Leukopenia | 0 | 0 | 1 | 1 |
| Thrombocytopenia | 0 | 0 | 1 | 2 |
| Febrile Neutropenia | 0 | 0 | 1 | 1 |

Exploratory analyses of efficacy, including hepatic progression free survival (hPFS) and hepatic objective response (hOR) were performed in the study using Investigator assessments and the intent-to-treat (ITT) population (defined as all enrolled patients). Meaningful antitumor effects were seen in the liver of the ocular melanoma patients in the study. Four ocular melanoma patients had a hepatic objective response: 3 patients with a complete response (CR) and 1 patient with a partial response (PR). An additional 3 patients had stable disease (SD). Median hPFS for ocular melanoma patients was approximately 9 months (Table 7).

### Table 7 Antitumor Effects in Phase I Study 01-C-0215

| Objective Response | Ocular Melanoma N=12 | Cutaneous Melanoma N=3 | Other Tumor Types N=19 |
|---|---|---|---|
| Response | 4 | 0 | 0 |
| Complete Response | 3 | 0 | 0 |
| Partial Response | 1 | 0 | 0 |
| Stable Disease | 3 | 1 | 7 |
| hPFS (median, months) | 8.9 | 2.1 | 2.9 |
| hPFS = Hepatic Progression Free Survival | | | |

## 2.4.2 Clinical Trial 04-C-0273

Clinical trial 04-C-0273 (NCT00096083) was a phase 2 open-label study conducted at NCI, using either Asahi or Clark (GEN 1) filters for hemofiltration during the PHP procedure (for more information on the filters see Section 3.4.5).

The study population consisted of patients with unresectable primary (hepatocellular cancer or intrahepatic cholangiocarcinoma) or metastatic hepatic malignancies, including adenocarcinoma (ACC) of the GI, ocular or cutaneous melanoma, or neuroendocrine tumors (NET) (with the exception of gastrinoma) (Table 8). The study was originally designed to examine the efficacy of Melphalan/PHP treatment in several non-melanoma tumor types; however the protocol was amended during study to include a melanoma cohort who had received prior Melphalan treatment.

## Table 8 Overview of Clinical Trial 04-C-0273 (NCT00096083)

| Overview of Clinical Trial 04-C-0273 (NCT00096083 ClinicalTrials.gov) | |
|---|---|
| Title | Hepatic Arterial Infusion of Melphalan with Hepatic Perfusion in Treating Patients with Unresectable Liver Cancer |
| Condition | Cancer |
| Intervention | Drug: Isolated perfusion<br>Drug: Melphalan |
| Description | OBJECTIVES:<br>Primary<br>- Determine the response rate and duration of response in patients with unresectable primary or metastatic liver cancer treated with intrahepatic arterial infusion of Melphalan with venous filtration via PHP.<br>Secondary<br>- Determine the patterns of recurrence in patients treated with this regimen.<br>- Determine PFS and OS of patients treated with this regimen.<br>- Evaluate the safety and tolerability of this regimen in these patients.<br>- Assess the filter characteristics including Melphalan PK and filtration of cytokines and clotting factors during and after treatment.<br><br>OUTLINE: Patients are stratified according to primary tumor histology (neuroendocrine tumor vs primary hepatic malignancy vs adenocarcinoma of gastrointestinal or other origin).<br>Patients undergo PHP in which a catheter is placed via the groin into the hepatic artery and another into the hepatic vein. Patients then receive Melphalan as an intrahepatic arterial infusion over 15-30 minutes. Treatment repeats approximately every 3-8 weeks for up to 6 total infusions in the absence of disease progression or unacceptable toxicity.<br>Patients are followed every 3 months for 2 years, every 4 months for 1 year, and then periodically thereafter. |
| Phase | Phase 2 |
| Sponsor | Delcath Systems Inc. |
| Status | Completed |
| PFS = Progression Free Survival; PHP= Peripheral Hepatic Perfusion; PK = Pharmacokinetics; OS = Overall Survival | |

The primary objective of the study was to determine the response rate and duration of response for Melphalan/HDS treatment.

The secondary objectives were:
- To determine patterns of recurrence, hPFS, and overall survival (OS),
- To evaluate the safety and tolerability of Melphalan/HDS treatment, and
- To evaluate the filter efficiency/pharmacokinetics (PK).

A total of 56 patients were enrolled at the NCI:
- ACC - 20
- Primary hepatic malignancies - 8
- Ocular melanoma - 4
- NET - 24

Patients were treated with a Melphalan dose of 3.0 mg/kg IBW in 4 week cycles for a maximum of 4 cycles. Treatment could be delayed for up to an additional 4 weeks to allow for resolution or reduction of toxicity to ≤grade 2. A Melphalan dose reduction to 2.5 mg/kg IBW was also allowed during treatment for patients who experienced any of the following:

- Grade 4 neutropenia of >5 days duration with growth factor support or associated with neutropenic fever
- Grade 4 thrombocytopenia of >5 days duration or associated with a hemorrhage that required a transfusion
- Grade 4 hemoglobin level of >48 hours duration
- Grade 3 or 4 major non-hematologic organ toxicity not corrected within 24 hours of the procedure (excluding fever, nausea, and weight gain)
- Grade 4 bilirubin of any duration, and doubling of liver function test values above the baseline value

Melphalan/PHP treatment was to be permanently discontinued if patients had persistent toxicity that had not resolved to grade 2 or less by 8 weeks following treatment. Hepatic response was assessed by computerized tomography (CT) or magnetic resonance imaging (MRI) scans 4 weeks after cycles 2 and 4. Hepatic responses were categorized by the Investigator as complete response, partial response, stable disease, or progressive disease using RECIST version 1.0, with a modification to restrict target lesions to the liver and to allow up to 10 target liver lesions. Prior to starting cycle 3, patients must have shown evidence of SD or better and no abnormalities in a MRI scan of the brain.

The four primary tumor cohorts were generally similar with respect to demographic and baseline disease characteristics. Most of the patients were white with more males (32 patients) than females (24 patients) enrolled in the study. The median age was 53 years. The median time since diagnosis of the primary tumor ranged from 5.39 months in the primary hepatic tumor cohort to 71 months in the melanoma cohort.

Meaningful antitumor effects were seen in the liver of the ocular melanoma patients in this study. Three of the four ocular melanoma patients had a hOR (all PRs) with a median hPFS of approximately 9 months. Median survival for these patients was approximately 2 years (Table 9).

### Table 9 Antitumor Effects in Phase 2 Study 04-C-0273

| Response | MEL N=4 | ACC N=20 | HCC N=8 | NET N-24 |
|---|---|---|---|---|
| hOR | 3 (75%) | 0 | 1 (12.5%) | 10 (41.7%) |
| Complete Response | 0 | 0 | 0 | 0 |
| Partial Response | 3 (75%) | 0 | 1 (12.5%) | 10 (41.7%) |
| Stable Disease | 1 (25%) | 4 (20%) | 4 (50.0%) | 6 (25.0%) |
| hPFS (median, months) | 9.10 (3.1, 15.3) | 4.04 (1.2, 25.3) | 5.60 (2.7, 12.2) | 16.82 (2.1, 64.1) |
| OS (median, months) | 22.54 (5.7, 35.3) | 5.83 (1.7, 33.3) | 9.12 (3.4, 20.5) | 31.87 (2.4, 81.1) |
| ACC = Adenocarcinoma; HCC = Hepatocellular Carcinoma; hPFS = Hepatic Progression Free Survival; hOR = Hepatic Objective Response; MEL = Melanoma; NET = Neuroendocrine Tumor; OS = Overall Survival | | | | |

## 2.4.3 Clinical Trial DSI MEL 2005-001

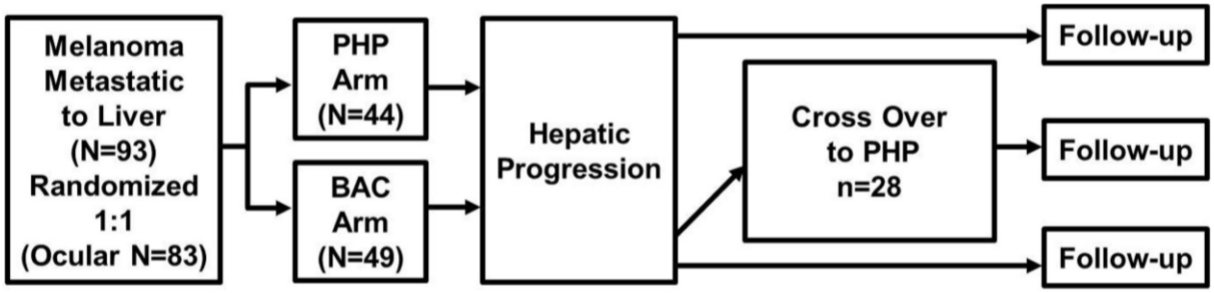
Clinical trial DSI MEL 2005-001 (NCT00324727) was a phase 3, randomized, controlled, multi-center study, conducted at 10 US centers in patients with histologically or cytologically confirmed cutaneous or ocular melanoma with metastases predominantly in the liver (Table 10). This clinical trial used Clark (GEN 1) filters for hemofiltration during the PHP procedure (for more information on the filter see Section 3.4.5).

## Table 10 Overview of Clinical Trial DSI MEL 2005-001 (NCT00324727)

| Overview of Clinical Trial DSL MEL 2005-001 (NCT00324727 ClinicalTrials.gov) | |
|---|---|
| Title | Hepatic Arterial Infusion with Melphalan Compared With Standard Therapy in Treating Patients with Unresectable Liver Metastases Due to Melanoma |
| Condition | Intraocular Melanoma<br>Melanoma (Skin)<br>Metastatic Cancer |
| Intervention | Drug: Melphalan<br>• Given through isolated hepatic artery infusion<br>Drug: regional chemotherapy<br>• Patients receive the best alternative therapy<br>Drug: systemic chemotherapy<br>• Patients receive the best alternative therapy<br>Procedure: hepatic artery embolization<br>• Patients receive the best alternative therapy |
| Description | OBJECTIVES:<br>Primary<br>- Compare the hPFS of patients with unresectable liver metastases secondary to ocular or cutaneous melanoma treated with PHP with Melphalan with subsequent venous hemofiltration vs the best alternative standard treatment.<br>Secondary<br>- Determine the response rate and duration of response in patients treated with Melphalan PHP.<br>- Determine the patterns of recurrence in patients treated with Melphalan PHP.<br>- Compare the overall survival of patients treated with these regimens.<br>- Compare the safety and tolerability of these regimens in these patients.<br>- Determine the pharmacokinetics of Melphalan after PHP.<br><br>OUTLINE: This is a multicenter study. Patients are stratified according to site of disease (ocular vs cutaneous). Patients are randomized to 1 of 2 treatment arms.<br>- Arm I: Patients undergo an isolated hepatic arterial infusion of Melphalan over 30 minutes on day 1. Treatment repeats every 4 weeks for 4 courses in the absence of disease progression or unacceptable toxicity. Patients with complete or partial response undergo 2 additional courses in the absence of ongoing or increasing toxicity.<br>- Arm II: Patients receive the best alternative therapy comprising supportive care, systemic or regional chemotherapy, hepatic artery (chemo)-embolization, or any other appropriate therapy at the NCI or therapy at the discretion of their physician. Patients may cross over to Arm I if they have evidence of disease progression.<br>Blood samples are collected periodically for PK analysis of Melphalan.<br>After completion of study treatment, patients are followed periodically for 4 years and then annually for survival.<br><br>PROJECTED ACCRUAL: A total of 92 patients will be accrued for this study. |
| Phase | Phase III |
| Sponsor | Delcath Systems Inc. |
| Status | Completed |
| hPFS = Hepatic Progression Free Survival; PHP = Peripheral Hepatic Perfusion; PK = Pharmacokinetics; NCI = National Cancer Institute | |

The objectives of the study were to evaluate and assess the efficacy, safety, and tolerability of Melphalan/HDS treatment versus best alternate care (BAC) selected by the Investigator (Figure 4)

## Figure 4 Experimental Design of Phase 3 Clinical Trial DSI MEL 2005-001




(Lillemoe et al, 2014)

A total of 93 patients were randomized:
- PHP group - 44
- BAC group - 49

Forty-eight patients in the BAC group experienced hepatic disease progression and were eligible to crossover to the PHP treatment. Twenty eight of these patients crossed over.

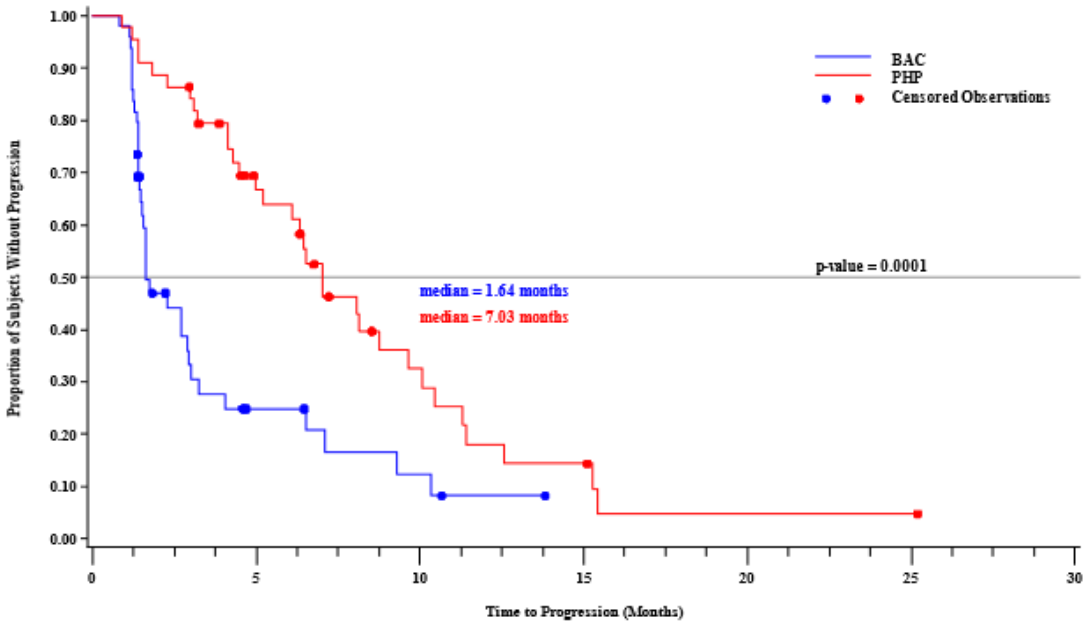
Study DSI MEL 2005-001, met its primary endpoint of hPFS by Independent Review Committee (IRC) assessment in both the overall patient population and the ocular melanoma subgroup (Table 11). The Investigators felt the magnitude of the hPFS improvement observed with Melphalan/HDS treatment was both statistically significant and clinically meaningful. The 5-month median advantage of Melphalan/HDS treatment in hPFS in melanoma patients was clinically meaningful given the short median time to hepatic progression or death in the comparator BAC arm (Melphalan/HDS, 7.03 months; BAC, 1.64 months).

## Table 11 Antitumor Effects of Phase 3 Study DSI MEL 2005-001

| DSI MEL 2005-001 | PHP (N=44) | BAC (N=49) |
|---|---|---|
| Patients with hepatic progression n (%) | 32 (72.7%) | 36 (73.5%) |
| Median (95% CI) time to hepatic progression (months) | 7.03 (5.22, 9.66) | 1.64 (1.48, 2.92) |
| Min, Max time to hepatic progression (months) | 0.9, 25.2+ | 0.8, 13.8+ |
| P-value from log-rank test | 0.0001 | |
| Hazard ratio (95% CI) | 0.39 (0.24, 0.64) | |
| BAC = Best Alternate Care; CI = Confidence Interval; Max = Maximum; Min = Minimum; PHP = Peripheral Hepatic Perfusion | | |

The Kaplan-Meier curves of event rates for hPFS show a clear, early separation of the curves that remain separate, with a 5-month difference at the median (Figure 5). Thus, the primary efficacy endpoint for the study was met.

## Figure 5 Kaplan Meier Curve of hPFS in the Overall Population in the Phase 3 Study




(Delcath, 2013)

The IRC and Investigator assessments of the hPFS results were consistent. The robustness of the hPFS benefit with Melphalan/HDS was observed across all sensitivity and subgroup analyses. Melphalan/HDS treatment also resulted in statistically significant and clinically meaningful improvements in the hOR rate compared to BAC.

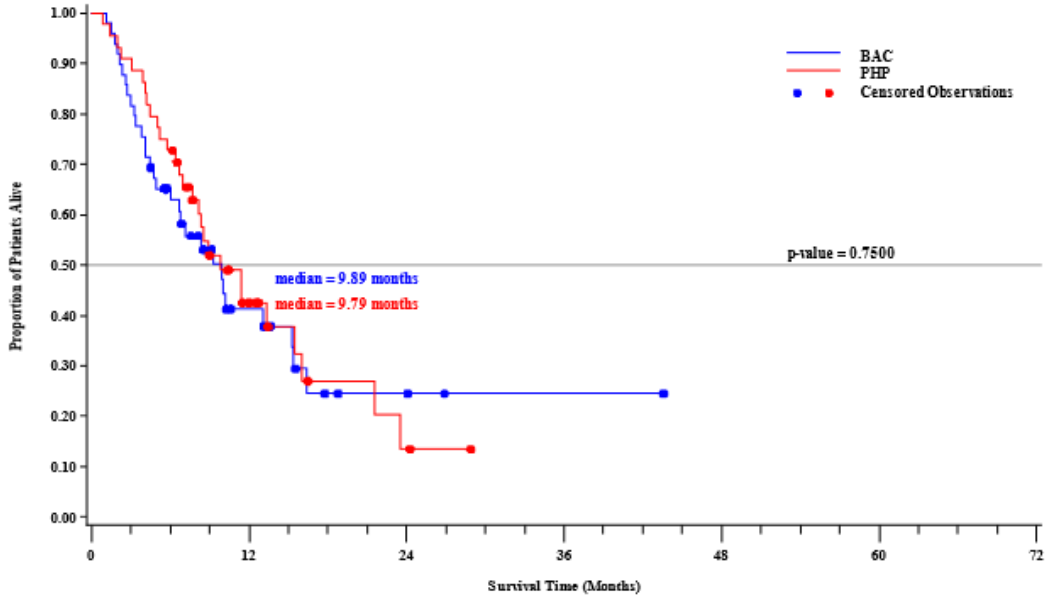
A treatment benefit for Melphalan/HDS treatment over BAC was not seen for OS. This was felt to likely be due to the high number of BAC patients who experienced hepatic progression and crossed over to PHP treatment (Table 12).

## Table 12 Overall Survival in the Phase 3 Study DSI MEL 2005-001

| DSI MEL 2005-001 | PHP (N=44) | BAC (N=49) |
|---|---|---|
| Patients who died, n (%) | 28 (63.6%) | 30 (61.2%) |
| Median (95% CI) time to death (months) | 9.79 (6.93, 15.44) | 9.89 (6.01, 15.28) |
| Min, Max time to death (months) | 0.9, 28.9+ | 1.1, 43.6+ |
| P-value from log-rank test | 0.7500 | |
| Hazard Ratio (95% CI) | 0.92 (0.55, 1.54) | |
| BAC = Best Alternate Care; CI = Confidence Interval; Max = Maximum; Min = Minimum; PHP = Peripheral Hepatic Perfusion | | |

Kaplan-Meier curves of OS in the PHP and BAC groups separated early in the study, but ultimately overlapped (Figure 6).

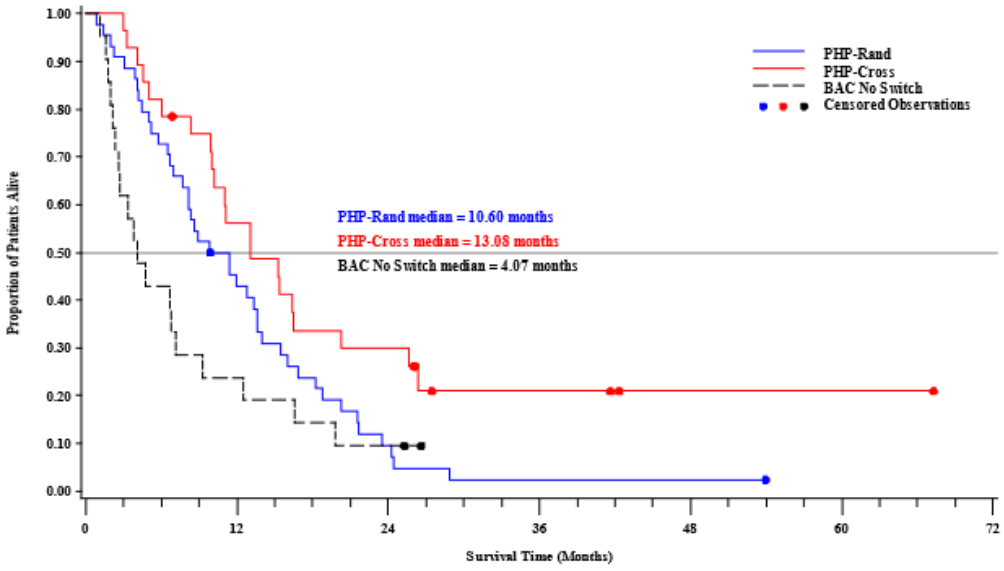
## Figure 6 Kaplan-Meier Curves of Overall Survival in the Overall Population in the Phase 3 Study




(Delcath, 2013)

An exploratory analysis was conducted to examine OS for patients who crossed over from BAC to Melphalan/PHP treatment upon hepatic progression versus non-crossovers. The Kaplan-Meier curve of OS in the crossover group was similar to that seen for the PHP group, suggesting that survival of the crossover group was like that observed in the PHP group; a heavier tail was observed for the curve of the crossover group versus the curve of the PHP group because of a number of survivors in the crossover group (Figure 7).

## Figure 7 Kaplan-Meier Curve of Overall Survival for Crossovers and Non-Crossovers in the Phase 3 Study




(Delcath, 2013)

### 2.4.4 Phase 2 and Phase 3 Clinical Trial Combined Safety Data

In the combined phase 2 and phase 3 clinical trial safety data set almost all patients in the PHP group had at least one AE. Most (80%) of these AEs were SAEs which included hospitalizations. In the studies there were 5 deaths that resulted from AEs:

- GI hemorrhage,
- Hepatic failure,
- Gastric perforation,
- Streptococcal sepsis, and
- Neutropenia.

Approximately 40% of patients had one or more AEs leading to treatment discontinuation.
Melphalan-related bone marrow suppression occurred in patients:

- Neutropenia (87%),
- Complicated neutropenia (21%),
- Thrombocytopenia (80%), and
- Anemia (59%)

There were two deaths from complicated neutropenia (streptococcal sepsis and neutropenia). Thrombocytopenia (22%), febrile neutropenia (15%), and neutropenia (15%) were the most frequent events resulting in rehospitalization. Thrombocytopenia (15.7%) and neutropenia (7.4%) were the most frequent AEs leading to treatment withdrawal. Most treatment withdrawals due to thrombocytopenia and neutropenia occurred after either the second or third Melphalan/HDS treatment.

There is a risk of cardiovascular events with Melphalan/HDS treatment because of intra-procedural hypotension. Cardiovascular events occurred in 24% of patients with 17% of patients with a Grade 3/4 cardiovascular event. Cardiovascular events included arrhythmias, cerebral ischemia/infarct, cardiac ischemia/infarct, thromboembolism, and cerebral hemorrhages; each of these events was reported in a small number of patients. No patients died from a cardiovascular event. Ten patients (8%) were withdrawn from treatment because of a cardiovascular event.

There was a risk of GI events because of perfusion of Melphalan into GI vessels either because vessels were not embolized or there was reflux of Melphalan into GI branches. GI events, including gastritis, ulceration, perforation, bleeding and gall bladder-related events occurred in 25% of patients with 11% of patients with a grade 3/4 GI event. There were two deaths from GI events (ruptured right hepatic artery and gastric perforation) in the clinical development program. Six patients (5%) were withdrawn from treatment because of a GI event.

There was a risk of bleeding events because of the anticoagulation required for performance of the procedure, hemofiltration-related thrombocytopenia, and Melphalan-related thrombocytopenia. Bleeding events occurred in 13% of patients with 7% of patients with a grade 3/4 bleeding event. One patient with brain metastases died from an intracranial hemorrhage. Four patients discontinued study treatment because of a bleeding event.

There was a risk of hepatic events as a consequence of underlying disease, liver-directed therapy, and Melphalan treatment. Hepatic events occurred in 44% of patients with all of these patients having grade 3/4 events. Hepatic events were predominantly laboratory changes in liver function tests that were reported as AEs, including elevated hepatic transaminases and hyperbilirubinemia. One patient died of hepatic failure related to underlying disease burden since his liver tissue was >90% tumor. Seven patients (5.8%) discontinued study treatment because of a hepatic event, including increased blood bilirubin, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, and hepatic failure.

### 2.4.5 Detoxification Filters

During the early stages of the Melphalan/HDS clinical development program two different filters were used for hepatic venous hemofiltration (Table 13).

## Table 13 Hemofiltration Filters Used in Early Clinical Development Clinical Trials

| Clinical Trial | Filter | Filter Efficiency (mean) |
|---|---|---|
| 01-C-0215 | Asahi Hemosorba | 2.0 mg/kg = 82.0%<br>2.5 mg/kg = 64.0%<br>3.0 mg/kg = 78.5%<br>3.5 mg/kg = 70.0% |
| 04-C-0273 (NCT00096083) | Asahi Hemosorba<br>or<br>Clark Biocompatible (GEN 1) | 3.0 mg/kg = 73.3% |
| DSI MEL 2005-001 (NCT00324727) | Clark Biocompatible (GEN 1) | 3.0 mg/kg = 71.2% |

FDA analyses of the combined safety data from the clinical trials revealed that changes in the filter manufacturer lead to dramatic differences in the safety profile of the Melphalan/HDS System (Table 14). This was despite the two filters having comparable filtration efficiencies and in vitro testing (FDA, 2013). The FDA believed that the change in the filter manufacturer 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 (FDA, 2013).

## Table 14 Differences in Filter Adverse Reactions

| | Study | Phase 1 and Phase 2 | Phase 2 | Phase 3 |
|---|---|---|---|---|
| | Filter | Asahi | Clark | Clark |
| | Population | Mixed Histology | Mixed Histology | Melanoma |
| | N | 30 | 41 | 70 |
| | Dose | 2.5-3.5 mg/kg IBW | 2.5-3.0 mg/kg IBW | 2.5-3.0 mg/kg IBW |
| | Filter Efficiency | 70% | 73% | 71% |
| General Parameters | Medium nadir MAP | 60 mmHg | 49 mmHg | 49 mmHg |
| | Treatment Related Death | 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% |
| IBW = Ideal Body Weight; MAP = Mean Arterial Pressure | | | | |

The FDA concluded that unidentified factors caused the increase in toxicity observed in the change from Asahi to Clark filters. Therefore, they determined that any new filter introduced as a new component of the Delcath Hepatic Delivery System must be evaluated in a clinical trial in order to have confidence in the safety profile.

Delcath introduced a second-generation detoxification cartridge (GEN 2 filter; Delcath Systems) in 2012. Changes were made to the filters activated carbon particles, including:

- Shape (granular to spherical),
- Density (0.600 - 0.560 to 0.195 - 0.185 g/mL),
- Size (1363 ± 457 to 720 ± 102 µm), and
- Volume per cartridge (500 to 550 mL).

A pharmacological study showed that the mean extraction rate of the GEN 2 hemofiltration system was 86%, which was approximately 10% higher than that of first-generation filters (de Leede et al, 2017).

Although initial data indicated that using the GEN 2 filter may reduce hematologic toxicity (Vogl et al, 2014; Kirstein et al, 2017) it had not been evaluated prospectively until recently.

The results of a recent prospective study suggests that hematologic toxicity after Melphalan/HDS can be reduced by using the GEN 2 filter instead of a first generation filter (Meijer et al, 2019). However, this study was limited by its small sample size, which is explained by the rarity of the disease. Other factors may play a role, such as insufficient sealing of the balloons or chemotherapeutics reaching the systemic circulation through venous collaterals.

## 2.5 Delcath Clinical Trials - Ongoing

Delcath is currently recruiting patients for 3 additional clinical trials. These clinical trial are listed in Table 15 and an overview of each is provided in the Sections 3.5.1, 3.5.2, and 3.5.3 below. All ongoing clinical trial utilize the GEN 2 filter.

### Table 15 Ongoing Delcath Clinical Trials in 2019

| Identifier | Title | Status | Filter |
|---|---|---|---|
| NCT02678572 | Percutaneous Hepatic Perfusion in Patients with Hepatic-dominant Ocular Melanoma | Recruiting | Gen2 |
| NCT03086993 | Percutaneous Hepatic Perfusion vs. Cisplatin/ Gemcitabine in Patients with Intrahepatic Cholangiocarcinoma | Recruiting | Gen2 |

| | | | |
|---|---|---|---|
| NCT03266042 | Collection of Safety, Efficacy and Resource Utilization Information in Patients Who Have Received Melphalan PHP with the Delcath Hepatic Delivery System for the Treatment of Unresectable Hepatic Malignancy | Recruiting | Gen2 |

### 2.5.1 Clinical Trial FOCUS (NCT02678572)

The FOCUS Trial (NCT02678572) is designed to evaluate patients who have melanoma that has spread from the eye to the liver. All patients in the study will be treated with Melphalan/HDS for up to 6 treatments. This study will evaluate the safety and effects of the treatment on how long patients live and how long it takes for the cancer to advance or respond to the treatment. An overview of the study can be found in Table 16.

### Table 16 Overview of Clinical Trial NCT02678572

| Overview of Clinical Trial FOCUS (NCT02678572 ClinicalTrials.gov) | |
|---|---|
| Title | Percutaneous Hepatic Perfusion in Patients with Hepatic-dominant Ocular Melanoma |
| Condition | Melanoma, Ocular |
| Intervention | Combination Product: Melphalan/HDS<br>Melphalan (3 mg/kg IBW) with HDS |
| Description | The study will consist of 3 phases: a screening phase, treatment phase, and follow-up phase.<br>Screening Phase: Screening assessments will be conducted within 28 days prior to the eligibility date to determine each patient's overall eligibility and baseline characteristics. These assessments will include medical history, physical examination, ECOG, PS, 12 lead ECG, ECHO, vital signs, full hematology and biochemistry, Quality of Life questionnaire, radiologic assessments of baseline disease status and concomitant medications.<br><br>For patients with a history of liver surgery or major vasculature surgery, an angiogram evaluation of their vasculature will be performed for compatibility for PHP prior to confirming eligibility.<br>Eligibility date: This is the date on which all screening assessments have been completed and the patient is determined to be eligible for the trial.<br><br>Treatment Phase: Eligible patients will be treated with Melphalan/HDS 3.0 mg/kg IBW and must begin treatment within 14 days being eligible. Melphalan/HDS treatment, patients will receive up to 6 treatments. Each treatment cycle consists of 6 weeks with an acceptable delay for another 2 weeks before the next planned treatment to allow for recovery of Melphalan-related toxicity, if needed. Tumor response will be assessed every 12 weeks (+ 2 weeks) until disease progression. If the patient receives only 1 treatment, the disease assessment scans will be conducted 12 weeks after the date of the first treatment. The assessment scans will be reviewed by an IRC, also referred to as Independent Central Review. At any time when PD is observed, the patient will be removed from further study treatment and followed until death. Melphalan/HDS treatment will also be discontinued in the event that recovery from treatment related toxicity requires more than 8 weeks from last treatment. An end-of-treatment visit will be conducted approximately 6 to 8 weeks following the final study treatment. Ongoing treatment related AEs at the end-of-treatment visit will be followed until the severity is within one of the following parameters: |

| | |
|---|---|
| | - Symptoms are resolved or return to baseline,<br>- CTCAE Grade < 1 or can be explained,<br>- Patient death.<br><br>The maximum possible duration of the study treatment for any patient will be 12 months.<br><br>NOTE: Active Melphalan/HDS patients (currently in treatment) on PHP-OCM-301 will continue treatment on PHP-OCM-301A following the re-consenting process.<br><br>NOTE: Patients on PHP-OCM-301 that have completed treatment and are entering or are already in the follow-up phase will be followed-up for survival and disease progression (as applicable) on PHP-OCM-301A following the re-consenting process.<br>Follow-up Phase: Once the patient has completed the EOT visit in accordance with the schedule of events they will enter the follow-up phase. If the disease has not progressed at the EOT, the patient will need to continue with disease assessment visits every 12 weeks (+ 2 weeks) until disease progression is documented. If the disease has progressed before or at the EOT their follow-up is to be by phone every 3 months for survival status until death.<br>Patients will be monitored, following the completion of study treatment, for the development of myelodysplasia and secondary leukemia. |
| Phase | Phase III |
| Sponsor | Delcath Systems Inc |
| Status | Recruiting |
| AEs = Adverse Events; ECG = Electrocardiogram; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; HDS = Hepatic Device System; IBW = Ideal Body Weight ; IRC = Independent Review Committee; PD = Progressive Disease; PHP = Percutaneous Hepatic Perfusion; PS = Performance Status | |

Delcath announced complete enrolment of 80 patients on January 13th, 2020 and anticipates top-line data mid/late-2020.

### 2.5.2 Clinical Trial NCT03086993

This study is designed to evaluate two groups of patients who have intrahepatic cholangiocarcinoma. Each group will receive induction treatment with Cisplatin and Gemcitabine per Standard of Care (SOC) for 4 treatment cycles. Following induction treatment patients will be randomize (1:1), to 2 arms of treatment. One group (50%) will receive high dose chemotherapy delivered specifically to the liver, while the other group (50%) will continue treatment with Cisplatin and Gemcitabine. Patients in each group will get repeating cycles of treatment until the cancer advances. All patients will be followed until death. This study will compare the OS in patients with intrahepatic cholangiocarcinoma. An overview of this study can be found in Table 17.

### Table 17 Overview of Clinical Trial NCT03086993

| Overview of Clinical Trial NCT03086993 (ClinicalTrials.gov) | |
|---|---|
| Title | Percutaneous Hepatic Perfusion vs. Cisplatin/Gemcitabine in Patients with Intrahepatic Cholangiocarcinoma |
| Condition | Bile Duct Cancer<br>Intrahepatic Cholangiocarcinoma |

| | |
|---|---|
| Intervention | Combination Product: Melphalan/HDS<br>Melphalan/HDS treatment for up to six cycles, followed by a re-induction of Cis/Gem.<br>Other Name: Melphalan/PHP<br>Drug: Cisplatin and Gemcitabine<br>continuous treatment with Cis/Gem until disease progression<br>Other Name: Cis/Gem |
| Description | The study will consist of 4 phases: a screening, an induction, randomization and follow-up phase.<br>Screening phase: Screening assessments will be conducted within 28 days prior to initiation of Induction Phase treatment to determine each patient's overall eligibility. These assessments will include medical history; physical examination;<br>ECOG, PS; 12 lead ECG; ECHO; vital signs; laboratory assessments; radiologic assessments of disease status; and an evaluation of the vasculature compatibility for PHP.<br><br>Induction phase: The initial 12 weeks of the study, all patients will receive 4 cycles of cisplatin/gemcitabine. Each cycle will be comprised of cisplatin dosed at 25 mg per square meter of BSA, followed by gemcitabine dosed at 1000 mg per square meter of BSA; dosing will occur on Days 1 and 8 of each cycle. At the completion of 3 cycles (week 8 (+1 week)) of Cis/Gem, an imaging scan is performed as per SOC to determine if the patient has progressed on treatment or should continue receiving the Cis/Gem induction therapy for one more cycle (4th cycle - prior to randomization). At the completion of 4 cycles (week 12 (+1 week)) of cisplatin/gemcitabine, patients will undergo whole-body imaging to determine the status of their disease. Patients with PD will be discontinued from study treatment, and will receive further treatment to be determined by the PI. They will continue to be followed until death or the end of the study. Patients who have at least SD at imaging after induction phase of 4 cycles of Cis/Gem (week 12 (+ 1 week)) will go on to the next phase of the study (Randomized Treatment Phase).<br><br>Randomization phase: Patients who have at least stable disease via imaging at the end of the Induction Phase will be randomized in a 1:1 ratio to Melphalan/HDS treatment or to continue cisplatin/gemcitabine in cycles previously described in the Induction Phase, until PD or unacceptable toxicity is observed. Patients who were randomized to treatment with Melphalan/HDS (dosed at 3.0 mg/kg IBW) must undergo their first treatment within 14 days following the whole body imaging performed at end of the Induction Phase. For Melphalan/HDS treatment, patients will receive up to 6 treatments. Each treatment cycle will consist of 6 weeks with an acceptable delay for up to another 2 weeks before the next planned treatment to allow for additional recovery, if needed. After the Melphalan/HDS treatment, in the absence of disease progression, the patient should undergo a re-induction of Cis/Gem. Tumor response will be assessed in both treatment arms every 8 weeks (+ 1 week) until PD.<br>The assessment scans will be reviewed by IRC. At any time when PD is observed, the patient will be removed from further study treatment; any further treatment will be at the discretion of the investigator. Melphalan/HDS treatment will also be discontinued in the event that recovery requires more than 8 weeks from last treatment. An EOT visit will be conducted approximately 6 to 8 weeks following the final dose of study treatment. Ongoing AEs at the EOT visit will be followed until the severity returns to common terminology CTCAE Grade < 1.<br><br>Follow-up phase: In the event that disease has not progressed at the EOT visit, disease assessment scans will continue every 8 weeks (+ 1 week) until PD is documented. Patients will be contacted by phone every 6 months for survival status for the first two years following the completion of study treatment, then yearly thereafter until death, withdrawal of informed consent or they become lost to follow-up, whichever occurs first. Patients will be monitored for two years following the completion of study treatment for the development of myelodysplasia and secondary leukemia. |

| | |
|---|---|
| Phase | Phase 2<br>Phase 3 |
| Sponsor | Delcath Systems Inc. |
| Status | Recruiting |
| AEs = Adverse Events; BSA = Body-surface Area; Cis/Gem = Cisplatin and Gemcitabine; CTCAE = Criteria for Adverse Events ECG = Electrocardiogram; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; HDS = Hepatic Device System; IBW = Ideal Body Weight ; IRC = Independent Review Committee; PD = Progressive Disease; PHP = Percutaneous Hepatic Perfusion; PI = Principal Investigator; PS = Performance Status; SD = Stable Disease; SOC = Standard of Care | |

The trial is expected to enroll 295 patients and was estimated to be completed in May 2023. Delcath announced in 2019, that it was pausing this study in order to discuss a protocol adjustment with FDA.

### 2.5.3 Clinical Trial NCT03266042

Clinical Trial NCT03266042 is a post marketing study to collect safety, efficacy and resource utilization information in patients who have received Melphalan/PHP with the Delcath Hepatic Delivery System for the treatment of unresectable hepatic malignancy in Europe. An overview of this study can be found in Table 18.

### Table 18 Overview of Clinical Trial NCT03266042

| Overview of Clinical Trial NCT03266042 (ClinicalTrials.gov) | |
|---|---|
| Title | Collection of Safety, Efficacy and Resource Utilization Information in Patients Who Have Received Melphalan PHP with the Delcath Hepatic Delivery System for the Treatment of Unresectable Hepatic Malignancy |
| Condition | Hepatic Malignant Neoplasm Primary Non-Resectable |
| Intervention | Not provided |
| Description | Post Marketing study:<br>The CHEMOSAT kit containing Gen 2 filters has been used to treat patients since April 2012. This registry study is designed to collect safety, resource utilization and treatment outcomes in patients who receive this treatment with CHEMOSAT by healthcare professionals. The safety and efficacy data from patients treated with CHEMOSAT is important in updating the safety profile and for collection of treatment information. The resource utilization information is essential in planning treatment strategy for patients.<br>This registry does not follow any pre-determined protocol with respect to diagnosis, treatment or follow-up of the patient. The data collected will be gathered exclusively from current medical practice at participating institutions.<br>Delcath holds a list of authorized customer hospitals to whom it supplies the CHEMOSAT System. To date these hospitals have treated over 300 patients with cancers of the liver.<br>The decision to treat with CHEMOSAT is clearly separated from the decision to collect data in the registry. No specific procedures or tests are required in this protocol. |
| Phase | Observational [Patient Registry] |
| Sponsor | Delcath Systems Inc. |
| Status | Recruiting |

This study is ongoing until the information from 200 patients is collected.

## 2.6 CHEMOSAT Clinical Data

In Europe, Delcath's Melphalan/HDS system is marketed as a device under the trade name Delcath Hepatic CHEMOSAT® Delivery System for Melphalan. This system has been commercially available in Europe since 2012 and used at major medical centers to treat a wide range of cancers of the liver, including: ocular melanoma, intrahepatic cholangiocarcinoma, hepatocellular carcinoma, cutaneous melanoma, breast cancer, neuroendocrine tumors, anal mucosal melanoma, pancreatic cancer, colorectal cancer, sarcoma, gastric cancer, endometrium cancer and prostate cancer.

A systematic review of 186 European patients who had received a total of 321 Melphalan/HDS treatments was carried out by Vogl et al in 2016. Most procedures were performed for patients with liver metastases from ocular melanoma. The majority of procedures were performed in Germany (75 procedures total in 11 hospitals), the United Kingdom (UK) (49 procedures total in four hospitals), and the Netherlands (33 procedures total in two hospitals). Melphalan/HDS was also performed in Italy (12 procedures total in two hospitals), France (nine procedures total in two hospitals), Spain (six procedures total in two hospitals), Ireland (one procedure total in one hospital), and Turkey (one procedure in one hospital) (Vogl et al, 2016).

In addition, a number of retrospective studies (Table 19) and case reports (Table 20) have been published on the use of CHEMOSAT in Europe.

### Table 19 European Studies of Delcath's CHEMOSTAT Product

| Reference | Number of Patients | Primary Tumor | Results |
|---|---|---|---|
| Meijer et al, 2019 | 35 | Ocular melanoma (35) | Objective response rate: 74%<br>1 CR<br>22 PR |
| Artnzer et al, 2019 | 16 | Ocular melanoma (16) | Objective response rate: 60%<br>9 PR |
| Hickson et al, 2015 | 20 | Ocular melanoma (20) | Objective response rate: 70%<br>2 CR<br>13 PR<br>2 SD<br>3 PD |
| Abbott et al, 2015 | 30 | Ocular melanoma (16)<br>Cutaneous melanoma (13)<br>Unknown (1) | hPFS<br>CS-PHP vs Y90 RR 0.08;<br>P < 0.001<br>PHP vs CE RR 0.13;<br>P = 0.008<br>CE vs Y90 RR 0.64;<br>P = 0.44<br><br>OS<br>CS-PHP vs Y90 RR 0.05;<br>P = 0.03<br>PHP vs CE RR 0.51;<br>P = 0.37<br>CE vs Y90 RR 0.09;<br>P = 0.06 |

| | | | |
|---|---|---|---|
| Vogl et al, 2014 | 13 | Ocular melanoma (8)<br>Cutaneous melanoma (3)<br>Breast cancer (1)<br>Cholangiocarcinoma (1) | Objective response rate: 58%<br>1 CR (CCA)<br>6 PR (3 ocular and 3 cutaneous)<br>5 SD (3 ocular, 1 breast, 1 gastric)<br>0 PD |
| Vahrmeijer et al, 2014 | 11 | CRC (6)<br>Ocular melanoma (5) | Objective response rate: 75%<br>6 PR (2 colorectal, 4 ocular)<br>2 PD |
| Hofman et al, 2014 | 1 | Solid pseudopapillary neoplasm of the pancreas (1) | 1 PR<br>0 PD |
| Deneve et al, 2012 | 1 | Leiomyosarcoma (1) | 1 SD<br>0 PD |

### Table 20 European Case Reports of Delcath's CHEMOSTAT Product

| Reference | Number of Patients | Primary Tumor |
|---|---|---|
| Trennheuser et al, 2019 | 7 | Ocular melanoma |
| Hofman et al, 2014 | 1 | Solid pseudopapillary neoplasm of the pancreas |
| Deneve et al, 2012 | 1 | Leiomyosarcoma |

The results from the European retrospective studies and case reports indicate that PHP with Melphalan appears to be a viable therapeutic option for primary and secondary liver tumors, providing the rationale for ongoing and planned clinical trials across a spectrum of tumor histologies including ocular or cutaneous melanoma, CRC and HCC.

## 2.7 Label Expansion

Delcath is initially seeking FDA approval of the Melphalan/HDS System for the treatment of patients with unresectable, metastatic ocular melanoma in the liver. However, a number of clinical trials are planned or are underway to further study liver directed high dose chemotherapy for treatment in cancers such as HCC, NET and CRC.

The CHEMOSAT system has been used to treat a large variety of liver cancers (Table 21) in Europe, therefore it also has the potential to be used off label in the US to treat patients with limited treatment options.

### Table 21 Number of CHEMOSAT Treatments in Europe by Tumor Type

| Tumor Type | Number of Treatment |
|---|---|
| Ocular melanoma | 213 |
| Cutaneous melanoma | 9 |
| Cholangiocarcinoma | 45 |
| Breast cancer | 5 |
| Hepatocellular carcinoma | 13 |
| Neuroendocrine tumors | 4 |

| | |
|---|---|
| Anal mucosal melanoma | 1 |
| Pancreatic cancer | 11 |
| Colorectal cancer | 20 |
| Sarcoma | 1 |
| Gastric cancer | 1 |
| Endometrium cancer | 1 |
| Prostate | 1 |

## 3 Conclusions

Delcath Systems, Inc. is an interventional oncology company focused on the treatment of primary and metastatic liver cancers. Delcath's proprietary product Melphalan Hydrochloride for Injection is used with the Delcath Hepatic Delivery System to administer high dose chemotherapy to the liver. In the US, the Melphalan/HDS system is considered a combination drug and device product and is regulated by the FDA as a drug. The Melphalan/HDS system is currently not approved for sale in the US however, in Europe the Melphalan/HDS system has been commercially available since 2012.

Delcath's initial clinical development program consisted of 3 clinical trials: Clinical trial 01-C-0215, Clinical trial 04-C-0273, and Clinical trial DSI MEL 2005-001. The initial efficacy of Melphalan/HDS for the treatment of unresectable, metastatic ocular melanoma in the liver was provided by clinical trial DSI MEL 2005-001, which compared the efficacy of Melphalan/HDS treatment to the BAC selected by the Investigator.

The key efficacy data from clinical trial DSI MEL 2005-001 has been summarized below:

- The primary efficacy endpoint of hPFS by IRC assessment was met in the overall patient population. Melphalan/HDS treatment of patients specifically with unresectable, metastatic ocular melanoma in the liver resulted in a statistically significant and clinically meaningful increase in hPFS by IRC assessment compared to best alternative care treatment with a median 5-month difference in favor of Melphalan/HDS treatment.
- Hepatic PFS results by Investigator assessment were similar to the IRC.
- The robustness of the hPSF benefit was evidenced by consistent results across pre-specified sensitivity analyses and all subgroup analyses, including patients with ocular melanoma.
- Statistically significant higher rates of hOR were observed by IRC and Investigator assessment in the Melphalan/HDS group compared to the BAC group.
- Median survival was similar between the Melphalan/HDS and the BAC groups, but the survival data are confounded by the high percentage of BAC patients who experienced hepatic progression and crossed over to Melphalan/HDS treatment (57%).

The ocular melanoma subpopulation in Clinical trial 01-C-0215 (phase 1) and Clinical trial 04-C-0273 (phase 2) showed similar median hepatic progression free survival times and hepatic objective response rates as the phase 3 study.

In 2012, Delcath introduced a second-generation detoxification cartridge (GEN 2 filter; Delcath Systems) and initiated a new pivotal phase 3 clinical trial (FOCUS). FOCUS is a multi-center, single-arm, open-label study to evaluate the efficacy and safety of Melphalan/HDS in patients with hepatic dominant metastatic ocular melanoma. The study is being conducted at approximately 40 centers in the United States and Europe and is expected to be completed in mid/late-2020.

In conclusion, Delcath is currently seeking FDA approval of its Melphalan/HDS system for the treatment of patients with unresectable, metastatic ocular melanoma in the liver. In addition, they are also looking to expand its use to other indications such as ICC and HCC. Encouraging results have been obtained from Delcath's clinical development program. These results are supported by its extensive clinical use in Europe.

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