

DELCATH SYSTEMS, INC.
Form 10-K
March 16, 2018

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-K

Annual report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 for the fiscal year ended
December 31, 2017

Transition report pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934 for the transition period from
_____ to _____

Commission file number: 001-16133

DELCATH SYSTEMS, INC.

Delaware
(State or other jurisdiction of
incorporation or organization)

06-1245881
(I.R.S. Employer
Identification No.)

1633 Broadway, Suite 22C New York, NY 10019
(Address of principal executive offices) (Zip Code)

212-489-2100

(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Common Stock, par value \$0.01 per share
Title of Each Class

OTCQB
Name of Exchange on Which
Registered

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Securities registered pursuant to Section 12(g) of the Act: None.

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes No

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days.

Yes No

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files).

Yes No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405) is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer or a smaller reporting company or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer", "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer

Accelerated filer

Non-accelerated filer (Do not check if smaller reporting company) Smaller reporting company

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 7(a)(2)(B) of the Securities Act .

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes No

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The aggregate market value of the voting common stock held by non-affiliates of the registrant, based on the closing sale price on The NASDAQ Capital Market of \$67.87 per share, was \$82,287,147 as of June 30, 2017.

At March 16, 2018, the registrant had outstanding 434,997,075 shares of common stock, par value \$0.01 per share.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement for its 2018 Annual Meeting of Stockholders are incorporated by reference into Part III (Items 10, 11, 12, 13 and 14) of this Annual Report on Form 10-K. The definitive Proxy Statement or an amendment to the Form 10-K containing all Part III information will be filed with the Securities and Exchange Commission within 120 days after the close of the fiscal year covered by this Annual Report on Form 10-K.

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Disclosure Regarding Forward-Looking Statements

This Annual Report on Form 10-K for the period ended December 31, 2017 contains certain “forward-looking statements” within the meaning of the “safe harbor” provisions of the Private Securities Litigation Reform Act of 1995 with respect to our business, financial condition, liquidity and results of operations. Words such as “anticipates,” “expects,” “intends,” “plans,” “predicts,” “believes,” “seeks,” “estimates,” “could,” “would,” “will,” “may,” “can,” “continue,” and the negative of these terms or other comparable terminology often identify forward-looking statements. Statements in this Annual Report on Form 10-K for the period ending December 31, 2017 that are not historical facts are hereby identified as “forward-looking statements” for the purpose of the safe harbor provided by Section 21E of the Securities Exchange Act of 1934, as amended (Exchange Act) and Section 27A of the Securities Act of 1933, as amended (Securities Act). These forward-looking statements are not guarantees of future performance and are subject to risks and uncertainties that could cause actual results to differ materially from the results contemplated by the forward-looking statements, including the risks discussed in this Annual Report on Form 10-K for the fiscal year ended December 31, 2017 in Item 1A under “Risk Factors” as well as in Item 7A “Quantitative and Qualitative Disclosures About Market Risk,” and the risks detailed from time to time in our future SEC reports. These forward-looking statements include, but are not limited to, statements about:

- our estimates regarding sufficiency of our cash resources, anticipated capital requirements and our need for additional financing;
- our ability to obtain shareholder approval in order to have sufficient authorized shares to meet current requirements for exercise of warrants and for future capital raises;
- the commencement of future clinical trials and the results and timing of those clinical trials;
- our ability to successfully commercialize CHEMOSAT/Melphalan/HDS, generate revenue and successfully obtain reimbursement for the procedure and system;
- the progress and results of our research and development programs;
- submission and timing of applications for regulatory approval and approval thereof;
- our ability to successfully source certain components of the system and enter into supplier contracts;
- our ability to successfully manufacture CHEMOSAT/Melphalan/HDS;
- our ability to successfully negotiate and enter into agreements with distribution, strategic and corporate partners; and
- our estimates of potential market opportunities and our ability to successfully realize these opportunities.

Many of the important factors that will determine these results are beyond our ability to control or predict. You are cautioned not to put undue reliance on any forward-looking statements, which speak only as of the date of this Annual Report on Form 10-K. Except as otherwise required by law, we do not assume any obligation to publicly update or release any revisions to these forward-looking statements to reflect events or circumstances after the date of this Annual Report on Form 10-K or to reflect the occurrence of unanticipated events.

Item 1. Business.

Unless the context otherwise requires, all references in this Annual Report on Form 10-K to the “Company”, “Delcath”, “Delcath Systems”, “we”, “our”, and “us” refers to Delcath Systems, Inc., a Delaware corporation, incorporated in August 1988, and all entities included in our consolidated financial statements. Our corporate offices are located at 1633 Broadway, Suite 22C, New York, New York 10019. Our telephone number is (212) 489-2100.

About Delcath

Delcath Systems, Inc. is an interventional oncology company focused on the treatment of primary and metastatic liver cancers. Our investigational product—Melphalan Hydrochloride for Injection for use with the Delcath Hepatic Delivery

System (Melphalan/HDS) —is designed to administer high-dose chemotherapy to the liver while controlling systemic exposure and associated side effects. In Europe, our system is commercially available under the trade name Delcath Hepatic CHEMOSAT[®] Delivery System for Melphalan (CHEMOSAT[®]), where it has been used at major medical centers to treat a wide range of cancers of the liver.

Our primary research focus is on ocular melanoma liver metastases (mOM) and intrahepatic cholangiocarcinoma (ICC), a type of primary liver cancer, and certain other cancers that are metastatic to the liver. We believe the disease states we are investigating represent a multi-billion dollar global market opportunity and a clear unmet medical need.

Our clinical development program for CHEMOSAT and Melphalan/HDS is comprised of The FOCUS Clinical Trial for Patients with Hepatic Dominant Ocular Melanoma (The FOCUS Trial), a Global Phase 3 clinical trial that is investigating overall survival in mOM, and a registration trial for intrahepatic cholangiocarcinoma (ICC) we plan to initiate in 2018. Our clinical development plan (CDP) also includes a commercial registry for CHEMOSAT non-clinical commercial cases performed in Europe and sponsorship of select investigator initiated trials (IITs) in colorectal cancer metastatic to the liver (mCRC) and pancreatic cancer metastatic to the liver.

The direction and focus of our CDP for CHEMOSAT and Melphalan/HDS is informed by prior clinical development conducted between 2004 and 2010, non-clinical, commercial CHEMOSAT cases performed on patients in Europe, and prior regulatory experience with the FDA. Experience gained from this research, development, early European commercial and United States regulatory activity has led to the implementation of several safety improvements to our product and the associated medical procedure.

In the United States, Melphalan/HDS is considered a combination drug and device product and is regulated as a drug by the FDA. The FDA has granted us six orphan drug designations, including three orphan designations for the use of the drug melphalan for the treatment of patients with mOM, HCC and ICC. Melphalan/HDS has not been approved for sale in the United States.

In Europe, the current version of our CHEMOSAT product is regulated as a Class IIb medical device and received its CE Mark in 2012. We are in an early phase of commercializing the CHEMOSAT system in select markets in the European Union (EU) where the prospect of securing reimbursement coverage for the procedure is strongest. In 2015 national reimbursement coverage for CHEMOSAT procedures was awarded in Germany. In 2016, coverage levels were negotiated between hospitals in Germany and regional sickness funds. Coverage levels determined via this process are expected to be renegotiated annually. In 2017, Dutch health authorities added CHEMOSAT to their treatment guidelines for patients with ocular melanoma metastatic to the liver, an important step toward eventual reimbursement in the Dutch market.

Currently there are few effective treatment options for certain cancers in the liver. Traditional treatment options include surgery, systemic chemotherapy, liver transplant, radiation therapy, interventional radiology techniques, and isolated hepatic perfusion. We believe that CHEMOSAT and Melphalan/HDS represent a potentially important advancement in regional therapy for primary liver cancer and certain other cancers metastatic to the liver and are uniquely positioned to treat the entire liver either as a standalone therapy or as a complement to other therapies.

Cancers in the Liver – A Significant Unmet Need

Cancers of the liver remain a major unmet medical need globally. According to the American Cancer Society's (ACS) Cancer Facts & Figures 2017 report, cancer is the second leading cause of death in the United States, with an estimated 600,920 deaths and 1,688,780 new cases expected to be diagnosed in 2017. Cancer is one of the leading causes of death worldwide, accounting for approximately 8.2 million deaths and 14.1 million new cases in 2012 according to GLOBOCAN. The financial burden of cancer is enormous for patients, their families and society. The Agency for Healthcare Quality and Research estimates that the direct medical costs (total of all healthcare expenditures) for cancer in the U.S. in 2014 was \$87.8 billion. The liver is often the life-limiting organ for cancer patients and one of the leading causes of cancer death. Patient prognosis is generally poor once cancer has spread to the liver.

Liver Cancers—Incidence and Mortality

There are two types of liver cancers: primary liver cancer and metastatic liver disease. Primary liver cancer (hepatocellular carcinoma or HCC, including intrahepatic bile duct cancers or ICC) originates in the liver or biliary tissue and is particularly prevalent in populations where the primary risk factors for the disease, such as hepatitis-B, hepatitis-C, high levels of alcohol consumption, aflatoxin, cigarette smoking and exposure to industrial pollutants, are

present. Metastatic liver disease, also called liver metastasis, or secondary liver cancer, is characterized by microscopic cancer cell clusters that detach from the primary site of disease and travel via the blood stream and lymphatic system into the liver, where they grow into new tumors. These metastases often continue to grow even after the primary cancer in another part of the body has been removed. Given the vital biological functions of the liver, including processing nutrients from food and filtering toxins from the blood, it is not uncommon for metastases to settle in the liver. In many cases patients die not as a result of their primary cancer, but from the tumors that metastasize to their liver. In the United States, metastatic liver disease is more prevalent than primary liver cancer.

Ocular Melanoma

Ocular melanoma is one of the cancer histologies with a high likelihood of metastasizing to the liver. Based on third party research we commissioned in 2016, we estimate that up to 4,700 cases of ocular melanoma are diagnosed in the United States and Europe annually, and that approximately 55% of these patients will develop metastatic disease. Of metastatic cases of ocular melanoma, we estimate that approximately 90% of patients will develop liver involvement. Once ocular melanoma has spread to the liver, current evidence suggests median overall survival for these patients is generally six to eight months. Currently there is no standard of care (SOC) for patients with ocular melanoma liver metastases. Based on the research conducted in 2016, we estimate that approximately 2,000 patients with ocular melanoma liver metastases in the United States and Europe may be eligible for treatment with the Melphalan/HDS.

Intrahepatic Cholangiocarcinoma

Hepatobiliary cancers include hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC), and are among the most prevalent and lethal forms of cancer. According to GLOBOCAN, an estimated 78,500 new cases of hepatobiliary cancers are diagnosed in the United States and Europe annually. According to the ACS, approximately 40,710 new cases of these cancers were expected to be diagnosed in the United States in 2017.

ICC is the second most common primary liver tumor and accounts for 3% of all gastrointestinal cancers and 15% of hepatobiliary cases diagnosed in the United States and Europe annually. We believe that 90% of ICC patients are not candidates for surgical resection, and that approximately 20-30% of these may be candidates for certain focal interventions. We estimate that approximately 9,300 ICC patients in the United States and Europe annually could be candidates for treatment with Melphalan/HDS, which we believe represents a significant market opportunity.

According to the ACS, the overall five-year survival rate for hepatobiliary cancers in the United States is approximately 18%. For patient diagnosed with a localized stage of disease, the ACS estimates 5-year survival at 31%. The ACS estimates that 5-year survival for all cancers is 68%.

About CHEMOSAT and Melphalan/HDS

CHEMOSAT and Melphalan/HDS administer concentrated regional chemotherapy to the liver. This “whole organ” therapy is performed by isolating the circulatory system of the liver, infusing the liver with chemotherapeutic agent, and then filtering the blood prior to returning it to the patient. During the procedure, known as percutaneous hepatic perfusion (PHP[®] therapy), three catheters are placed percutaneously through standard interventional radiology techniques. The catheters temporarily isolate the liver from the body’s circulatory system, allow administration of the chemotherapeutic agent melphalan hydrochloride directly to the liver, and collect blood exiting the liver for filtration by our proprietary filters. The filters absorb chemotherapeutic agent in the blood, thereby reducing systemic exposure to the drug and related toxic side effects, before the filtered blood is returned to the patient’s circulatory system.

PHP therapy is performed in an interventional radiology suite in approximately two to three hours. Patients remain in an intensive care or step-down unit overnight for observation following the procedure. Treatment with CHEMOSAT and Melphalan/HDS is repeatable, and a new disposable CHEMOSAT and Melphalan/HDS is used for each treatment. Patients treated in clinical settings are permitted up to six treatments. In non-clinical commercial settings patients have received up to eight treatments. In the United States, melphalan hydrochloride for injection will be included with the system. In Europe, the system is sold separately and used in conjunction with melphalan hydrochloride commercially available from a third party. In our clinical trials, melphalan hydrochloride for injection is provided to both European and United States clinical trial sites.

Risks associated with the CHEMOSAT and Melphalan/HDS Procedure

As with many cancer therapies, treatment with CHEMOSAT and Melphalan/HDS is associated with toxic side effects and certain risks, some of which are potentially life threatening. An integrated safety population comprised of patients treated during our prior clinical development using early versions of the Melphalan/HDS showed these risks to include grade 3 or 4 bone marrow suppression and febrile neutropenia, as well as risks of hepatic injury, severe hemorrhage, gastrointestinal perforation, stroke, and myocardial infarction in the setting of an incomplete cardiac risk assessment. Deaths due to certain adverse reactions within this integrated safety population were not observed to occur again during the clinical trials following the adoption of related protocol amendments.

Procedure and Product Refinements

The trials that comprised this integrated safety population used early versions of the device and procedure. As a consequence of these identified risks and experience gained in non-clinical, commercial usage in Europe, we have

continued to develop and refine both the CHEMOSAT and Melphalan/HDS and the PHP procedure. The procedure refinements have included modifications to the pre, peri and post procedure patient management and monitoring, as well as the use of the following: prophylactic administration of proton pump inhibitors, prophylactic platelet transfusions, prophylactic hydration at key pre-treatment intervals, use of vasopressor agents coupled with continuous monitoring for maintenance of blood pressure and prophylactic administration of growth factors to reduce risk of serious myelosuppression. In addition, in 2012 we introduced the Generation Two version of the CHEMOSAT system, which offered improved hemofiltration and other product enhancements.

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Reports from treating physicians in both Europe and the United States using the Generation Two CHEMOSAT and Melphalan/HDS in a non-clinical, commercial setting have suggested that these product improvements and procedure refinements have improved the safety profile. In 2017, physicians in Europe and the United States also presented the results of research that signaled an improved safety profile as well as efficacy in multiple tumor types at several major medical conferences.

Phase 3—Melanoma Metastases Trial

In February 2010, we concluded a randomized Phase 3 multi-center study for patients with unresectable metastatic ocular or cutaneous melanoma exclusively or predominantly in the liver. In the trial, patients were randomly assigned to receive PHP treatments with melphalan using the Melphalan/HDS, or to a control group providing best alternative care (BAC). Patients assigned to the PHP arm were eligible to receive up to six cycles of treatment at approximately four to eight week intervals. Patients randomized to the BAC arm were permitted to cross-over into the PHP arm at radiographic documentation of hepatic disease progression. A majority of the BAC patients did in fact cross over to the PHP arm. Secondary objectives of the study were to determine the response rate, safety, tolerability and overall survival.

On April 21, 2010, we announced that our randomized Phase 3 clinical trial of PHP with melphalan using Melphalan/HDS for patients with unresectable metastatic ocular and cutaneous melanoma in the liver had successfully achieved the study's primary endpoint of extended hepatic progression-free survival (hPFS). An updated summary of the results was presented at the European Multidisciplinary Cancer Congress organized by the European Cancer Organization and the European Society of Medical Oncology in September 2011. Data submitted in October 2012 to the FDA in Delcath's New Drug Application (NDA) comparing treatment with the PHP with melphalan (the treatment group) to BAC (the control group), showed that patients in the PHP arm had a statistically significant longer median hPFS of 7.0 months compared to 1.7 months in the BAC control group, according to the Independent Review Committee (IRC) assessment. This reflects a 4-fold increase of hPFS over that of the BAC arm, with 50% reduction in the risk of progression and/or death in the PHP treatment arm compared to the BAC control arm. Results of this study were published in *Annals of Surgical Oncology*, in December 2015.

Phase 2 Multi-Histology, Unresectable Hepatic Tumor Trial

Also, in 2010, we concluded a separate multi-arm Phase 2 clinical trial of PHP with melphalan using an early version of the Melphalan/HDS in patients with primary and metastatic liver cancers, stratified into four arms: neuroendocrine tumors (carcinoid and pancreatic islet cell tumors), ocular or cutaneous melanoma, metastatic colorectal adenocarcinoma (mCRC), and HCC. In the metastatic neuroendocrine (mNET) cohort (n=24), the objective tumor response rate was 42%, with 66% of patients achieving hepatic tumor shrinkage and durable disease stabilization. In the mCRC cohort, there was inconclusive efficacy possibly due to advanced disease status of the patients. Similar safety profiles were seen across all tumor types studied in the trial.

Phase 2 Multi-Histology Clinical Trial - HCC Cohort

In the HCC cohort (n=8) of our Phase 2 Multi-Histology trial, a positive signal in hepatic malignancies was observed in 5 patients. Among these patients, one patient received four treatments, achieved a partial response lasting 12.22 months, and survived 20.47 months. Three other patients with stable disease received 3-4 treatments, with hPFS ranging 3.45 to 8.15 months, and overall survival (OS) ranging 5.26 to 19.88 months. There was no evidence of extrahepatic disease progression. The observed duration of hPFS and OS in this limited number of patients exceeded that generally associated with this patient population.

Prior United States Regulatory Experience

Based on the results from our prior clinical development in August 2012, we submitted an NDA under Section 505(b)(2) of the Federal Food Drug Cosmetic Act (FFDCA) seeking an indication for the percutaneous intra-arterial administration of melphalan for use in the treatment of patients with metastatic melanoma in the liver, and subsequently amended the indication to ocular melanoma metastatic to the liver. Data submitted to the Food and Drug Administration (FDA) used the early clinical trial versions of the system along with early clinical procedure techniques. Our NDA was accepted for filing by the FDA on October 15, 2012 and was designated for standard review with an initial Prescription Drug User Fee Act (PDUFA) goal date of June 15, 2013. On April 3, 2013, the FDA extended its PDUFA goal date to September 13, 2013.

On May 2, 2013 we announced that an Oncologic Drug Advisory Committee (ODAC) panel convened by the FDA voted 16 to 0, with no abstentions, that the benefits of treatment with the early version of Melphalan/HDS did not outweigh the risks associated with the procedure. A significant portion of FDA's presentation to the ODAC panel was focused on the FDA's assessment of treatment related risks, including the analysis of treatment-related deaths that occurred during clinical trials. The FDA also expressed concerns about hypotension (low blood pressure) during the procedure, length of hospital stay, as well as risks of stroke, heart attack, renal failure, and bone marrow suppression. We believe that the protocol amendments and other procedure refinements instituted during clinical trials and subsequently in commercial, non-clinical usage in Europe, including changes to the way blood pressure is managed and monitored, may help address these procedure related risks. Collection of adequate safety data on all aspects of the procedure is a major focus of the clinical trials in our current CDP.

Briefing materials presented to the 2013 ODAC panel by both the FDA and Delcath are available on our website at <http://delcath.com/clinical-bibliography>.

2013 Complete Response Letter

In September 2013 the FDA issued a complete response letter (CRL) in response to our NDA. The FDA issues a CRL after the review of a file has been completed and questions remain that preclude approval of the NDA in its current form. The FDA comments included, but were not limited to, a statement that Delcath must perform another "well-controlled randomized trial(s) to establish the safety and efficacy of Melphalan/HDS using overall survival as the primary efficacy outcome measure," and which "demonstrates that the clinical benefits of Melphalan/HDS outweigh its risks." The FDA also required that the additional clinical trial(s) be conducted using the product the Company intends to market, and that certain clinical, clinical pharmacology, human factors and product quality elements of the CRL be addressed.

In January 2016, we announced the conclusion of a Special Protocol Assessment (SPA) with the FDA on the design of a new Phase 3 clinical trial of Melphalan/HDS to treat patients with hepatic dominant ocular melanoma. This SPA provides agreement that our new Phase 3 trial design adequately addresses objectives that, if met, would support the submission for regulatory approval of Melphalan/HDS. However, final determinations for marketing application approval are made by FDA after a complete review of a marketing application and are based on the entire data in the application. The SPA agreement also represents the satisfactory resolution of a substantial number of the FDA's CRL non-clinical trial related requirements in that without these successful resolutions, the SPA request would not have been permitted to be filed.

Current Clinical Development Program

The focus of our current CDP is to generate clinical data for the CHEMOSAT and Melphalan/HDS in various disease states and validate the safety profile of the current version of the product and treatment procedure. We believe that the improvements we have made to CHEMOSAT and Melphalan/HDS and to the PHP procedure have addressed the severe toxicity and procedure-related risks observed during the previous Phase 2 and 3 clinical trials. The CDP is also designed to support clinical adoption of and reimbursement for CHEMOSAT in Europe, and to support regulatory approvals in various jurisdictions, including the United States.

(the FOCUS Trial) - NCT02678572

In January 2016, we initiated a new pivotal Phase 3 clinical trial officially entitled A Randomized, Controlled, Phase 3 Study to Evaluate the Efficacy, Safety and Pharmacokinetics of Melphalan/HDS Treatment in Patients with Hepatic-Dominant Ocular Melanoma. Called the FOCUS Trial, this new global Phase 3 trial will evaluate the safety, efficacy and pharmacokinetic profile of Melphalan/HDS versus best alternative care in 240 patients with hepatic dominant OM. The primary endpoint is a comparison of overall survival between the two study arms. Secondary and exploratory endpoints include progression-free survival, overall response rate and Quality of Life (QoL) measures. In the FOCUS trial's treatment phase, patients randomized to the Melphalan/HDS arm will receive up to six treatments at intervals of six to eight weeks for up to 12 months. Tumor response will be assessed in both study arms every 12 weeks until evidence of hepatic disease progression. For patients progressing to the follow-up phase, disease assessment scans will continue every 12 weeks for up to two years.

The FOCUS Trial is being conducted at leading cancer centers in the United States and Europe. The Moffitt Cancer Center in Tampa, Florida was activated as a participating center in January 2016 with Jonathan Zager, M.D., FACS, Professor of Surgery in the Cutaneous Oncology and Sarcoma Departments and a Senior Member at Moffitt Cancer Center, serving as the trial's lead investigator. In October 2016 we announced the addition of several prestigious cancer centers in the United States and Europe. We intend to include approximately 40 leading cancer centers in the United States and Europe in the FOCUS Trial.

The FOCUS Trial is being conducted under a SPA we negotiated with the FDA in January 2016, and the first patient was enrolled in February 2016. In 2017, enrollment in this trial proceeded more slowly than anticipated, and cash constraints during the second half of the year limited our ability to take steps to accelerate enrollment. In January 2018 we announced a SPA modification agreement with the FDA to revise the patient eligibility criteria to permit a greater extent of extra-hepatic disease by removing the size restriction, number and location of extra-hepatic lesions, in conjunction with a treatment plan for the extra-hepatic metastases. We hope that once approved by the institutional review boards of our participating clinical trial sites, this modification will help accelerate enrollment in this registrational trial. Any impact on enrollment of the SPA modification is not expected to be immediate, and it is unlikely that enrollment for this trial will be completed in time to submit an NDA to FDA in 2019.

Under the terms of the SPA, the FOCUS Trial is the only Phase 3 trial required for submission of an NDA. However, final determinations for marketing application approval are made by FDA after a complete review of a marketing application and are based on the totality of data in the application.

There currently is no SOC for the treatment of hepatic dominant ocular melanoma. Melphalan hydrochloride has been granted orphan drug status by FDA for treatment of patients with ocular melanoma. Based on the strength of the efficacy data in this disease observed in our prior Phase 3 clinical trial and the reports of an improved safety profile observed in non-clinical trial experience in Europe, we are confident that this program can address the concerns raised by the FDA in its CRL. We believe that ocular melanoma liver metastases represent a significant unmet medical need, and that pursuit of an indication in this disease state represents the fastest path to potential marketing approval of the Melphalan/HDS in the United States.

Percutaneous Hepatic Perfusion (PHP) vs. Cisplatin/Gemcitabine in Patients with Intrahepatic Cholangiocarcinoma - NCT03086993

In March 2017 we announced another SPA agreement with the FDA for the design of a new pivotal trial of Melphalan/HDS to treat patients with intrahepatic cholangiocarcinoma (ICC) titled A Randomized, Controlled Study to Compare the Efficacy, Safety and Pharmacokinetics of Melphalan/HDS Treatment Given Sequentially Following Cisplatin/Gemcitabine versus Cisplatin/Gemcitabine (Standard of Care) in Patients with Intrahepatic Cholangiocarcinoma (Pivotal ICC Trial). Under the SPA, the Pivotal ICC Trial will enroll approximately 295 ICC patients at approximately 40 clinical sites in the U.S. and Europe. The primary endpoint is overall survival (OS) and secondary and exploratory endpoints include safety, progression-free survival (PFS), overall response rate (ORR) and quality-of-life measures. This Pivotal ICC Trial is designed to be cost effective and pursued in a financially prudent manner when financial resources permit. The SPA agreement for this trial indicates that the pivotal trial design adequately addresses objectives that, if met, would support regulatory requirements for approval of Melphalan/HDS in ICC. However, final determinations for marketing application approval are made by FDA after a complete review of a marketing application and are based on the totality of data in the application.

Phase 2 Hepatocellular Carcinoma (HCC) & Intrahepatic Cholangiocarcinoma (ICC) Program

In 2014 we initiated a Phase 2 clinical trial program in Europe and the United States, with the goal of obtaining an efficacy and safety signal for Melphalan/HDS in the treatment of HCC and ICC. Due to differences in treatment practice patterns between Europe and the United States, we established separate European and United States trial protocols for the HCC Phase 2 program with different inclusion and exclusion patient selection criteria:

Protocol 201 NCT02406508 – Conducted in the United States, this trial is intended to assess the safety and efficacy of Melphalan/HDS followed by sorafenib. The trial will evaluate overall response rate via modified Response Evaluation Criteria in Solid Tumors (mRECIST), progression free survival, characterize the systemic exposure of melphalan and assess patient quality of life. This trial is now closed to enrollment.

Protocol 202 NCT02415036 – Conducted in Europe, this trial is intended to assess the safety and efficacy of Melphalan/HDS without sorafenib. The trial will also evaluate overall response rate via mRECIST criteria, progression free survival, characterize the systemic exposure of melphalan and assess patient quality of life. This trial is now closed to enrollment.

ICC Cohort – In 2015 we expanded Protocol 202 to include a cohort of patients with ICC. The trial for this cohort is being conducted at the same centers participating in the Phase 2 HCC trial. This trial has completed enrollment and data collection for the ICC cohort is ongoing. We will announce results for this cohort once the data are fully mature.

ICC Retrospective Data Collection - The original goal to obtain an efficacy signal for the Phase 2 ICC cohort has been satisfied by the result of multicenter patient outcomes identified in the retrospective data collection of our commercial ICC cases conducted by our European investigators. These promising outcomes and observations were discussed with Key Opinion Leaders (KOL) at a Delcath-organized medical advisory panel meeting and led to the agreement that PHP® therapy does, indeed, "demonstrate an efficacy signal in ICC and is worthy of full clinical investigation." Data from this retrospective data collection provided important scientific support during our negotiations with the FDA for

our SPA for the Pivotal ICC Trial. Data for the retrospective data collection are being submitted for publication by the European investigators, and details of these findings will be announced when publicly available.

With the objectives of identifying an efficacy signal worthy of further clinical investigation now met, we have terminated enrollment in our Phase 2 program and will close the Phase 2 trials in order to focus available resources on the FOCUS Trial and the Pivotal ICC Trial.

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Clinical trials are long, expensive and highly uncertain processes and failure can unexpectedly occur at any stage of clinical development. The start or end of a clinical trial is often delayed or halted due to changing regulatory requirements, manufacturing challenges, required clinical trial administrative actions, slower than anticipated patient enrollment, changing standards of care, availability or prevalence of use of a comparator treatment or required prior therapy. A substantial portion of the Company's operating expenses consist of research and development expenses incurred in connection with its clinical trials. See the Company's Consolidated Financial included in Item 8 of this Annual Report on Form 10-K.

European Investigator Initiated Trials

In addition to the clinical trials in our CDP, we are supporting data generation in other areas. We are currently conducting one Investigator Initiated Trial (IIT) in colorectal carcinoma metastatic to the liver (mCRC) at Leiden University Medical Center in the Netherlands. We are planning two additional IITs – one for colorectal carcinoma metastatic to the liver at Heidelberg University in Heidelberg, Germany and one for pancreatic carcinoma metastatic to the liver at Spire Hospital in Southampton, England. We continue to evaluate other IITs as suitable opportunities present in Europe. We believe IITs will serve to build clinical experience at key cancer centers and will help support efforts to obtain full reimbursement in Europe.

European Clinical Data Generation

On April 2, 2015, we announced the activation of our prospective patient registry in Europe to collect uniform essential patient safety, efficacy, and QoL information using observational study methods. This registry will gather data in multiple tumor types from commercial cases performed by participating cancer centers in Europe. A prospective registry is an organized system that uses observational study methods to collect defined clinical data under normal conditions of use to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure. Registry data is non-randomized, and as such cannot be used for either registration approval, promotional or competitive claims. However, we believe the patient registry will provide a valuable supportive data repository from a commercial setting that can be used to identify further clinical development opportunities, support clinical adoption and reimbursement in Europe.

Recent Data Presentations

In January 2018, we announced the publication of a multi-center retrospective analysis of Delcath's PHP[®] Therapy published in the peer-reviewed Journal of Surgical Oncology. The study, "Percutaneous Hepatic Perfusion with Melphalan in Uveal Melanoma: A Safe and Effective Treatment Modality in an Orphan Disease", was conducted by researchers from Moffitt Cancer Center (Moffitt) in Tampa, FL and the University Hospital Southampton (UHS) in the United Kingdom. The retrospective analysis of outcomes in 51 patients with liver metastases from ocular melanoma represents the largest data set compilation on the use of PHP Therapy in this tumor type outside of a clinical trial setting.

Patients in the study were treated at the two centers between December 2008 and October 2016. Patients received up to four PHP treatments at UHS and up to six PHP treatments at Moffitt. All patients received at least one PHP treatment, the median number of treatments per patient was two, and a total of 134 PHP treatments had been administered. Results showed that of the 51 treated patients, 22 (43.1%) showed a partial response, 3 (5.9%) showed a complete response, and 17 (33.3%) had stable disease. The six-month overall and hepatic disease control rates were 64.7% and 70.6% respectively. Survival analysis showed median overall survival of 15.3 months at the time of data cut off. One year overall survival was 64.6%.

Safety analysis showed that 19 patients (37.5%) had Grade 3 or 4 non-hematologic toxicity. Cardiovascular toxicity was seen in 17.6% of patients, a rate comparable to the company's prior Phase 3 study. Further to implementation of the Gen 2 filter along with prophylactic use of growth factors, severe neutropenia was seen in 16 (31.3%) patients as

opposed to 60 (85.7%) patients in the prior Phase 3 trial. Most significantly, as compared to the prior Phase 3, there were no treatment related deaths. Researchers stated that PHP Therapy “can be safely employed in appropriately selected ocular melanoma patients in institutions with appropriate expertise.”

The study authors further concluded that “results clearly demonstrate that PHP Therapy appears to be an effective means of obtaining rapid intrahepatic disease control and is a sensible option in patients with predominant liver disease.” Researchers said their results support the use of PHP Therapy in an integrated approach to the management of metastatic ocular melanoma and looked to the company’s Phase 3 FOCUS Trial to further quantify the benefit and optimize treatment strategies for these patients.

In September 2017, we announced that results of a single institution study were presented at the Cardiology and Interventional Radiology of Europe (CIRSE) annual meeting, held in Copenhagen, Denmark on September 16-20, 2017.

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The study, Prospective Clinical and Pharmacological Evaluation of the Delcath System's Second Generation (GEN2) Hemofiltration System in Patients Undergoing Percutaneous Hepatic Perfusion (PHP) with Melphalan, was conducted by a team at the Leiden University Medical Center (LUMC) in Leiden, The Netherlands and presented by T.S. Meijer, MD. The study prospectively evaluated filtration efficiency and hematologic side effects in seven patients who received a total of ten PHP procedures with the GEN2 CHEMOSAT system. Pharmacokinetic sampling was conducted at several points during the PHP procedure, and filtration efficiency was calculated at several discrete points. Blood tests were conducted following each procedure to determine hematologic side effect Grade Levels until the blood values normalized.

Results of the study showed the GEN2 CHEMOSAT system had an overall efficiency of 86%, with efficiency highest at the time of highest concentration of melphalan in the blood and declining as melphalan blood concentration declined. Peak efficiency was 95.4% in samples taken after 10 minutes of filtration, 85.9% at the end of the drug infusion period, and 77.5% at the end of the saline washout period. Researchers noted these results were superior to and more consistent than prior experience published with the first generation CHEMOSAT system. Hematologic side effects were mainly Grade 1 and 2 with some Grade 3 and 4 side effects emerging post-procedure, including 40% of treatment cycles showing Grade 4 thrombocytopenia, 80% showing Grade 3 or 4 leucopenia, and 70% showing lymphocytopenia. All patients were asymptomatic and all lab results normalized in three weeks. Other adverse events were managed, and there was no mortality, no severe bleeding complications, and no hypotensive cardiac or cerebral events. Researchers concluded that the GEN2 CHEMOSAT system appears to have higher melphalan filter efficiency, more consistent performance, and appears safe but needs further validation.

In July 2017, the Journal of Cancer Research and Clinical Oncology published an analysis of clinical findings from 29 Hannover Medical School patients who were treated with percutaneous hepatic perfusion (PHP®) therapy with Melphalan/HDS as last-line therapy for primary and secondary liver tumors. Hannover Medical School physicians treated 29 patients with a total of 54 PHP procedures. Patients received as many as five treatments each, with an average of two per patient. Nineteen patients were diagnosed with unresectable liver metastases that arose from solid tumors, including 11 cases of ocular melanoma, and the remaining 10 patients had hepatocellular or cholangiocarcinoma.

Across all patients, the overall response rate (ORR) was 19.2 percent, with ocular melanoma patients experiencing the highest ORR (33.3 percent). As has been published previously, high tumor volumes negatively impact overall survival (OS). Median OS was 261 days for the entire patient group. Two patients with cholangiocarcinoma and one patient with ocular melanoma had the longest survival with 566, 465, and 477 days respectively. Overall, PHP with Melphalan/HDS was well tolerated. Complications including thrombocytopenia, cardiovascular events, ulcerous bleeding, and edema were reported. These results are summarized in the Journal of Cancer Research and Clinical Oncology article, "Safety and Efficacy of Chemosaturation in Patients with Primary and Secondary Liver Tumors."

In February 2017, we announced that the American Journal of Clinical Oncology published a single-center retrospective review, in which authors found that investigational PHP with Melphalan/HDS offers promising results with a doubling of overall survival and significantly longer progression-free survival (PFS) and hPFS than other targeted therapies. The review, "Hepatic Progression-free and Overall Survival After Regional Therapy to the Liver for Metastatic Melanoma," was written by a team from the Moffitt Cancer Center who analyzed clinical outcomes of three different non-randomized approaches used to treat 30 patients with liver metastases primarily resulting from ocular melanoma and skin melanoma. A third of the patients received PHP using melphalan delivered via the Delcath Hepatic Delivery System (Melphalan/HDS), 12 received chemoembolization (CE) and six received radioembolization with yttrium-90 (Y90). Two patients crossed over once their cancer progressed – one from PHP to Y90 and one from CE to PHP.

The paper's authors concluded that patients who received PHP with Melphalan/HDS had significantly longer median hPFS at 361 days compared to 54 days for Y90 and 80 days for CE, as well as a longer median PFS at 245 days compared to 54 days for Y90 and 52 days for CE. Median overall survival was also longest for PHP at 608 days compared to 295 days for Y90 and 265 days for CE. The authors noted that further studies, including a randomized controlled trial, would be needed to confirm whether clinically superior outcomes can be achieved with PHP compared to other liver-targeted treatments.

Side effects following all treatments were similar, with most complications recorded as anorexia, abdominal pain, fatigue and nausea. Laboratory irregularities, such as thrombocytopenia and abnormal liver function tests, were seen immediately after treatment in some patients, but returned to baseline within a few days.

Market Access and Commercial Clinical Adoption

Europe

Our market access and clinical adoptions efforts are focused on the key target markets of Germany, United Kingdom and the Netherlands, which represent a majority of the total potential liver cancer market (primary and metastatic) in the Europe and where progress in securing reimbursement for CHEMOSAT treatments offers the best near-term opportunities. We also continue to support clinical adoption of CHEMOSAT in Spain, France and Italy. We employ a combination of direct and indirect sales channels to market and sell CHEMOSAT in these markets. Our European Headquarters is in Galway, Ireland.

Since launching CHEMOSAT in Europe, over 500 treatments have been performed at over 25 leading European cancer centers. Physicians in Europe have used CHEMOSAT to treat patients with a variety of cancers in the liver, primarily ocular melanoma liver metastases, and other tumor types, including cutaneous melanoma, hepatocellular carcinoma, cholangiocarcinoma, and liver metastases from colorectal cancer, breast, pancreatic and neuroendocrine. In 2017, SPIRE Southampton Hospital in the U.K. and the Medical University of Hannover in Germany each surpassed 100 treatments with CHEMOSAT since initiating procedures. In 2017, we announced our first patient to receive eight CHEMOSAT treatments, and have seen the average number of repeat treatments performed on a per patient basis consistently increase.

European Reimbursement

A critical driver of utilization growth for CHEMOSAT in Europe is the expansion of reimbursement mechanisms for the procedure in our priority markets. In Europe, there is no centralized pan-European medical device reimbursement body. Reimbursement is administered on a regional and national basis. Medical devices are typically reimbursed under Diagnosis Related Groups (DRG) as part of a procedure. Prior to obtaining permanent DRG reimbursement codes, in certain jurisdictions, we are actively seeking interim reimbursement from existing mechanisms that include specific interim reimbursement schemes, new technology payment programs as well as existing DRG codes. In most EU countries, the government provides healthcare and controls reimbursement levels. Since the EU has no jurisdiction over patient reimbursement or pricing matters in its member states, the methodologies for determining reimbursement rates and the actual rates may vary by country.

Germany

In October 2015, we announced that the Institut für das Entgeltsystem im Krankenhaus (InEK), the German federal reimbursement agency, established a national Zusatzentgelt (ZE) reimbursement code for procedures performed with CHEMOSAT in Germany. The ZE diagnostic-related group (DRG) code is a national reimbursement code that augments existing DRG codes until a specific new DRG code can be created, and will replace the previous Neue Untersuchungs und Behandlungsmethoden (NUB) procedure that required patients in Germany to apply individually for reimbursement of their CHEMOSAT treatment. With the establishment of a ZE code for CHEMOSAT, the procedure is now permanently represented in the DRG catalog in Germany. Coverage levels under this process are negotiated between hospitals in Germany and regional sickness funds, with coverage levels renegotiated annually.

United Kingdom

In May 2014, NICE, a non-departmental public body that provides guidance and advice to improve health and social care in the UK, completed a clinical review of CHEMOSAT. The NICE review indicated that as the current body of evidence on the safety and efficacy of PHP with CHEMOSAT for primary or metastatic liver cancer is limited, the procedure should be performed within the context of research by clinicians with specific training in its use and techniques. Delcath expects to consult again with the Interventional Procedures Advisory Committee at the National Institute for Clinical Excellence (NICE) in England, to provide recent clinical evidence with a view to moving existing Interventional Procedural Guidance from research to specialist status. This would enable greater scope for commercialization because it would allow more use by NHS clinicians of the therapy. It might also pave the way for a full Medical Technology Assessment as a way towards longer term reimbursement with the NHS.

In the short term, public patients will continue to be treated in the UK through clinical trials. Private patients will continue to be treated through the established private treatment pathway such as private insurance coverage or self-pay.

Netherlands

In the Netherlands CHEMOSAT has been performed at the Netherlands Cancer Institute in 2013 and at Leiden University Medical Centre since 2014. In June 2017 the Medical Oncology National Treatment Guidelines for Uveal Melanoma were updated and now include recommendations to consider CHEMOSAT in the treatment of liver metastases. We are hopeful that inclusion in the national guidelines and the support of clinicians treating patients with CHEMOSAT will support an application for reimbursement in this market.

Spain

In April 2016, we announced that the General and Digestive Surgery team at HM Sanchinarro University Hospital had activated the hospital's CHEMOSAT program. The Sanchinarro team successfully performed three procedures with CHEMOSAT, using the procedure to treat patients with peripheral cholangiocarcinoma and neuroendocrine tumors liver metastases. HM Sanchinarro University Hospital is the second center in Spain to offer CHEMOSAT treatments.

Turkey

In April 2016 we announced the activation of the Hacettepe University Clinic in Ankara, Turkey as a CHEMOSAT treatment center. Hacettepe University Clinic successfully completed its first CHEMOSAT treatments in March 2016, and the center represents the first CHEMOSAT commercial location to be activated outside of the European Union. We believe that Hacettepe University can serve as an important hub for CHEMOSAT treatment to patients in Turkey and throughout the region.

Distribution Partners

As a result of the Company's strategy to prioritize resources on the key direct markets of Germany, the Netherlands and the United Kingdom, the Company expects that its distribution strategy will play a lesser role in its current commercial activities. In Spain, the Company has determined that there was no benefit to continuing with an indirect model and therefore terminated its relationship with its distributor in Spain and is now represented in Spain through a sales agency. The Company is represented in Turkey through a distribution partner.

Regulatory Status

Our products are subject to extensive and rigorous government regulation by foreign regulatory agencies and the FDA. Foreign regulatory agencies, the FDA and comparable regulatory agencies in state and local jurisdictions impose extensive requirements upon the clinical development, pre-market clearance and approval, manufacturing, labeling, marketing, advertising and promotion, pricing, storage and distribution of pharmaceutical and medical device products. Failure to comply with applicable foreign regulatory agency or FDA requirements may result in Warning Letters, fines, civil or criminal penalties, suspension or delays in clinical development, recall or seizure of products, partial or total suspension of production or withdrawal of a product from the market.

United States Regulatory Environment

In the United States, the FDA regulates drug and device products under the FDCA, and its implementing regulations. The Delcath Melphalan/HDS is subject to regulation as a combination product, which means it is composed of both a drug product and device product. If marketed individually, each component would therefore be subject to different regulatory pathways and reviewed by different centers within the FDA. A combination product, however, is assigned to a center that will have primary jurisdiction over its pre-market review and regulation based on a determination of its primary mode of action, which is the single mode of action that provides the most important therapeutic action. In the case of the Melphalan/HDS, the primary mode of action is attributable to the drug component of the product, which means that the Center for Drug Evaluation and Research, has primary jurisdiction over its pre-market development and review.

The process required by the FDA before drug product candidates may be marketed in the United States generally involves the following:

- submission to the FDA of an IND, which must become effective before human clinical trials may begin and must be updated annually;
- completion of extensive preclinical laboratory tests and preclinical animal studies, all performed in accordance with the FDA's Good Laboratory Practice, or GLP, regulations;
- performance of adequate and well-controlled human clinical trials to establish the safety and efficacy of the product candidate for each proposed indication;
- submission to the FDA of an NDA after completion of all pivotal clinical trials;
- a determination by the FDA within 60 days of its receipt of an NDA to file the NDA for review;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facilities at which the product is produced and tested to assess compliance with current good manufacturing practice, or cGMP, regulations; and
- FDA review and approval of an NDA prior to any commercial marketing or sale of the drug in the United States.

The development and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product will be granted on a timely basis, if at all.

The results of preclinical tests (which include laboratory evaluation as well as GLP studies to evaluate toxicity in animals) for a particular product candidate, together with related manufacturing information and analytical data, are submitted as part of an IND to the FDA. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises concerns or questions about the conduct of the proposed clinical trial, including concerns that human research subjects will be exposed to unreasonable health risks. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. IND submissions may not result in FDA authorization to commence a clinical trial. A separate submission to an existing IND must also be made for each successive clinical trial conducted during product development. Further, an independent institutional review board, or IRB, for each medical center proposing to conduct the clinical trial must review and approve the plan for any clinical trial before it commences at that center and it must monitor the study until completed. The FDA, the IRB or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk. Clinical testing also must satisfy extensive good clinical practice regulations and regulations for informed consent and privacy of individually identifiable information. Similar requirements to the United States IND are required in the European Economic Area (EEA) and other jurisdictions in which we may conduct clinical trials.

Clinical Trials

For purposes of NDA submission and approval, clinical trials are typically conducted in the following sequential phases, which may overlap:

Phase 1 Clinical Trials. Studies are initially conducted in a limited population to test the product candidate for safety, dose tolerance, absorption, distribution, metabolism and excretion, typically in healthy humans, but in some cases in patients.

Phase 2 Clinical Trials. Studies are generally conducted in a limited patient population to identify possible adverse effects and safety risks, explore the initial efficacy of the product for specific targeted indications and to determine dose range or pharmacodynamics. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more expensive Phase 3 clinical trials.

Phase 3 Clinical Trials. These are commonly referred to as pivotal studies. When Phase 2 evaluations demonstrate that a dose range of the product is effective and has an acceptable safety profile, Phase 3 clinical trials are undertaken in large patient populations to further evaluate dosage, provide substantial evidence of clinical efficacy and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial centers.

Phase 4 Clinical Trials. The FDA may approve an NDA for a product candidate, but require that the sponsor conduct additional clinical trials to further assess the drug after NDA approval under a post-approval commitment. In addition, a sponsor may decide to conduct additional clinical trials after the FDA has approved an NDA. Post-approval trials are typically referred to as Phase 4 clinical trials.

Sponsors of clinical trials may submit proposals for the design, execution, and analysis for their pivotal trials under a SPA. A SPA is an evaluation by the FDA of a protocol with the goal of reaching an agreement that the Phase 3 trial protocol design, clinical endpoints, and statistical analyses are acceptable to support regulatory approval of the drug product candidate with respect to effectiveness for the indication studied. Under a SPA, the FDA agrees to not later alter its position with respect to adequacy of the design, execution or analyses of the clinical trial intended to form the primary basis of an effectiveness claim in an NDA, without the sponsor's agreement, unless the FDA identifies a substantial scientific issue essential to determining the safety or efficacy of the drug after testing begins.

Prior to initiating our currently ongoing Phase 3 clinical trial(s), we submitted a proposal for the design, execution and analysis under a SPA.

New Drug Applications

The results of drug development, preclinical studies and clinical trials are submitted to the FDA as part of an NDA. NDAs also must contain extensive chemistry, manufacturing and control information. An NDA must be accompanied by a significant user fee, which may be waived in certain circumstances. Once the submission has been accepted for filing, the FDA's goal is to review applications within ten months of submission or, if the application relates to an unmet medical need in a serious or life-threatening indication, six months from submission. The review process is often significantly extended by FDA requests for additional information or clarification. The FDA may refer the application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. For new oncology products, the FDA will often solicit an opinion from an ODAC, a panel of expert authorities knowledgeable in the fields of general oncology, pediatric oncology, hematologic oncology, immunologic oncology, biostatistics, and other related professions. The ODAC panel reviews and evaluates data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of cancer, and makes appropriate recommendations to the Commissioner of Food and Drugs. The FDA is not bound by the recommendation of an advisory committee. The FDA may deny

approval of an NDA by issuing a Complete Response Letter (CRL) if the applicable regulatory criteria are not satisfied. A CRL may require additional clinical data and/or an additional pivotal Phase 3 clinical trial(s), and/or other significant, expensive and time-consuming requirements related to clinical trials, preclinical studies or manufacturing. Data from clinical trials are not always conclusive and the FDA may interpret data differently than we or our collaborators interpret data. Approval may be contingent on a Risk Evaluation and Mitigation Strategy (REMS) that limits the labeling, distribution or promotion of a drug product. Once issued, the FDA may withdraw product approval if ongoing regulatory requirements are not met or if safety problems occur after the product reaches the market. In addition, the FDA may require testing, including Phase IV clinical trials, and surveillance programs to monitor the safety effects of approved products which have been commercialized, and the FDA has the power to prevent or limit further marketing of a product based on the results of these post-marketing programs or other information.

There are three primary regulatory pathways for a New Drug Application under Section 505 of the FDCA: Section 505 (b)(1), Section 505 (b)(2) and Section 505(j). A Section 505 (b)(1) application is used for approval of a new drug (for clinical use) whose active ingredients have not been previously approved. A Section 505 (b)(2) application is used for a new drug that relies on data not developed by the applicant. Section 505(b)(2) of the FDCA was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act. This statutory provision permits the approval of an NDA where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. The Hatch-Waxman Act permits the applicant to rely in part upon the FDA's findings of safety and effectiveness for previously approved products. Section 505(j) application, also known as an abbreviated NDA, is used for a generic version of a drug that has already been approved.

Orphan Drug Exclusivity

Some jurisdictions, including the United States, may designate drugs for relatively small patient populations as orphan drugs. Pursuant to the Orphan Drug Act, the FDA grants orphan drug designation to drugs intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States. The orphan designation is granted for a combination of a drug entity and an indication and therefore it can be granted for an existing drug with a new (orphan) indication. Applications are made to the Office of Orphan Products Development at the FDA and a decision or request for more information is rendered in 60 days. NDAs for designated orphan drugs are exempt from user fees, obtain additional clinical protocol assistance, are eligible for tax credits up to 50% of research and development costs, and are granted a seven-year period of exclusivity upon approval. The FDA cannot approve the same drug for the same condition during this period of exclusivity, except in certain circumstances where a new product demonstrates superiority to the original treatment. Exclusivity begins on the date that the marketing application is approved by the FDA for the designated orphan drug, and an orphan designation does not limit the use of that drug in other applications outside the approved designation in either a commercial or investigational setting.

The FDA has granted Delcath six orphan drug designations. In November 2008, the FDA granted Delcath two orphan drug designations for the drug melphalan for the treatment of patients with cutaneous melanoma as well as patients with ocular melanoma. In May 2009, the FDA granted Delcath an additional orphan drug designation of the drug melphalan for the treatment of patients with neuroendocrine tumors. In August 2009, the FDA granted Delcath an orphan drug designation of the drug doxorubicin for the treatment of patients with primary liver cancer. In October 2013, the FDA granted Delcath an orphan drug designation of the drug melphalan for the treatment of HCC. In July 2015, the FDA granted Delcath an orphan drug designation of the drug melphalan for the treatment of cholangiocarcinoma, which includes ICC.

The granting of orphan drug designations does not mean that the FDA has approved a new drug. Companies must still pursue the rigorous development and approval process that requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product will be granted at all or on a timely basis.

Intellectual Property and Other Rights

Our success depends in part on our ability to obtain patents and trademarks, maintain trade secret and know-how protection, enforce our proprietary rights against infringers, and operate without infringing on the proprietary rights of third parties. Because of the length of time and expense associated with developing new products and bringing them through the regulatory approval process, the health care industry places considerable emphasis on obtaining patent protection and maintaining trade secret protection for new technologies, products, processes, know-how, and methods. The Company currently holds rights in eight U.S. utility patents, one U.S. design patent, five pending U.S. utility patent applications, six issued foreign counterpart utility patents (including the validation of a European patent directed to our filter apparatus in eight European countries, six issued foreign counterpart design patents, and eight pending foreign counterpart patent applications. In July 2017, a patent directed to our chemotherapy filtration system was issued by the U.S. Patent and Trademark Office.

When appropriate, the Company actively pursues protection of our proprietary products, technologies, processes, and methods by filing United States and international patent and trademark applications. We seek to pursue additional patent protection for technology invented through research and development, manufacturing, and clinical use of the CHEMOSAT and Melphalan/HDS that will enable us to expand our patent portfolio around advances to our current systems, technology, and methods for our current applications as well as beyond the treatment of cancers in the liver.

There can be no assurance that the pending patent applications will result in the issuance of patents, that patents issued to or licensed by us will not be challenged or circumvented by competitors, or that these patents will be found to be valid or sufficiently broad to protect our technology or provide us with a competitive advantage.

To maintain our proprietary position, we also rely on trade secrets and proprietary technological experience to protect proprietary manufacturing processes, technology, and know-how relating to our business. We rely, in part, on confidentiality agreements with our marketing partners, employees, advisors, vendors and consultants to protect our trade secrets and proprietary technological expertise. In addition, we also seek to maintain our trade secrets through maintenance of the physical security of the premises where our trade secrets are located. There can be no assurance that these agreements will not be breached, that we will have adequate remedies for any breach, that others will not independently develop equivalent proprietary information or that third parties will not otherwise gain access to our trade secrets and proprietary knowledge.

In certain circumstances, United States patent law allows for the extension of a patent's duration for a period of up to five years after FDA approval. The Company intends to seek extension for one of our patents after FDA approval if it has not expired prior to the date of approval. In addition to our proprietary protections, the FDA has granted Delcath five orphan drug designations that provide us a seven-year period of exclusive marketing beginning on the date that our NDA is approved by the FDA for the designated orphan drug. While the exclusivity only applies to the indication for which the drug has been approved, the Company believes that it will provide us with added protection once commercialization of an orphan drug designated product begins.

There has been and continues to be substantial litigation regarding patent and other intellectual property rights in the pharmaceutical and medical device areas. If a third party asserts a claim against Delcath, the Company may be forced to expend significant time and money defending such actions and an adverse determination in any patent litigation could subject us to significant liabilities to third parties, require us to redesign our product, require us to seek licenses from third parties, and, if licenses are not available, prevent us from manufacturing, selling or using our system. Additionally, Delcath plans to enforce its intellectual property rights vigorously and may find it necessary to initiate litigation to enforce our patent rights or to protect our trade secrets or know-how. Patent litigation can be costly and time consuming and there can be no assurance that the outcome will be favorable to us.

Patent No.	Title	Issuance Date	Owned or Licensed	Expiration Date
7,022,097	Method For Treating Glandular Diseases and Malignancies	4/4/2006	Owned	6/24/2023
9,707,331	Apparatus For Removing Chemotherapy Compounds from Blood	7/18/2017	Owned	9/17/2034
D708749	Dual Filter	7/8/2014	Owned	7/8/2028
9,314,561	Filter and Frame Apparatus and Method of Use	4/19/2016	Owned	2/7/2034
9,541,544	A Method of Selecting Chemotherapeutic Agents for an Isolated Organ or Regional Therapy	1/10/2017	Owned	8/28/2033
8,679,057	Recovery Catheter Assembly	3/25/2014	Licensed	3/4/2031
9,265,914	Recovery Catheter Assembly	2/23/2016	Licensed	4/5/2031

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9,108,029	Recovery Catheter Assembly and Method	8/18/2015	Licensed	2/9/2034
9,814,823	Recovery Catheter Assembly and Method	10/9/2017	Licensed	7/27/2032

Patent Applications in the United States

Application No.	Application Title	Filing Date	Owned or Licensed
15/651,141	Apparatus For Removing Chemotherapy Compounds from Blood	7/17/2017	Owned
15/071,896	Filter and Frame Apparatus and Method of Use	3/16/2016	Owned
15/346,239	A Method of Selecting Chemotherapeutic Agents for an Isolated Organ or Regional Therapy	11/8/2016	Owned
14/995,677	Recovery Catheter Assembly	1/14/2016	Licensed
14/797,108	Recovery Catheter Assembly and Method	7/11/2015	Licensed
15/728,296	Recovery Catheter Assembly and Method	10/9/2017	Licensed

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Foreign Patents

Patent No.	Title	Issuance Date	Owned or Licensed	Expiration Date
84.098	Dual Filter (Argentina)	6/29/2012	Owned	6/29/2027
343454	Dual Filter (Australia)	7/23/2012	Owned	6/25/2022
146201	Dual Filter (Canada)	5/15/2013	Owned	5/15/2023
ZL 201230277905.5	Dual Filter (China)	3/20/2013	Owned	6/22/2022
1333173	Dual Filter (Europe)	6/27/2012	Owned	6/25/2037
1456186	Dual Filter Cartridge for Fluid Filtration (Japan)	10/26/2012	Owned	10/26/2032
2797644	Filter and Frame Apparatus and Method of Use (Belgium)	4/12/2017	Owned	12/29/2032
2797644	Filter and Frame Apparatus and Method of Use (France)	4/12/2017	Owned	12/29/2032
602012031191.6	Filter and Frame Apparatus and Method of Use (Germany)	4/12/2017	Owned	12/29/2032
2797644	Filter and Frame Apparatus and Method of Use (Great Britain)	4/12/2017	Owned	12/29/2032
2797644	Filter and Frame Apparatus and Method of Use (Ireland)	4/12/2017	Owned	12/29/2032
2797644	Filter and Frame Apparatus and Method of Use (Italy)	4/12/2017	Owned	12/29/2032
2797644	Filter and Frame Apparatus and Method of Use (Luxembourg)			