

Delcath
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Delcath Systems, Inc.

STOCK ASSESSMENT

NASDAQ: DCTH

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Executive Summary: Understanding and Addressing Ocular Melanoma through Precision Targeting

Ocular Melanoma Overview

Ocular melanoma, primarily uveal melanoma, is a rare but aggressive cancer with an incidence of over 5,000 cases annually in the US and EU. Uveal melanoma, which originates from the uvea (choroid plexus, iris, or ciliary body), accounts for 85-90% of ocular melanoma cases. Despite early diagnosis and treatment, it often progresses to metastatic disease, particularly in the liver, resulting in a poor prognosis with a survival rate of only 10-25% in the first year.

Precision Targeting of Liver Metastasis

Given the limited efficacy of systemic treatments and the challenges in surgically addressing diffuse liver metastases, Delcath Systems developed the Percutaneous Hepatic Perfusion (PHP) system. This minimally invasive procedure delivers high-dose chemotherapy directly to the liver, minimizing systemic toxicity and side effects. PHP involves the use of catheters to isolate and filter blood in the liver, enhancing the effectiveness of chemotherapy with reduced systemic exposure.

Evolution and FDA Approval of PHP

Delcath's PHP system, initially designed in the 1990s, faced regulatory challenges but eventually received FDA approval in 2023 for treating metastatic uveal melanoma. The FOCUS Phase 3 trial demonstrated significant improvements in objective response rates and progression-free survival compared to standard treatments. Despite initial setbacks, including a refusal to file by the FDA in 2011, subsequent trials and adjustments led to the approval of the Hepzato Kit.

Comparative Analysis and Future Prospects

PHP shows better survival outcomes compared to other treatments like immune checkpoint inhibitors and Tebentafusp (KIMMTRAK). Emerging treatments such as Trisalus' SD-101 and combination therapies are being explored. PHP's recognition in NCCN guidelines and updated NICE guidance in the UK highlight its growing acceptance, although funding and broader application remain challenges.

Market Sentiment and Financial Outlook

Delcath Systems is gaining market attention, with increased insider and institutional ownership. The PHP therapy is projected to treat 240 patients annually in the US, generating significant revenue. The treatment's slow uptake compared to pill-based therapies suggests potential trading opportunities. Delcath's revenue growth is expected to accelerate, with profitability anticipated by Q4 2024 based on conservative assumptions and company guidance.

Conclusion

Delcath's PHP system offers a promising treatment for metastatic uveal melanoma, with potential for expansion into other liver cancers. While challenges remain in market adoption and reimbursement, the system's clinical efficacy and growing recognition position it as a valuable option in oncology.

Understanding Ocular Melanoma

Ocular melanoma is a relatively rare but devastating type of cancer with a poor prognosis. It is the second most common type of melanoma after cutaneous melanoma, accounting for less than 5% of all melanoma cases, with an incidence of over 5,000 cases per year in the US and EU combined. In the US alone, there are 3,490 new cases per year. Primary uveal melanoma is the most common ocular melanoma, accounting for 85 - 90% of ocular melanoma patients, which is approximately 2,500 cases. It originates from the choroid plexus, iris, or ciliary body, which form the uvea, the middle layer of the eye.

Uveal melanoma differs from cutaneous melanoma in terms of molecular characteristics and mutation profile, leading to differences in treatment approaches for these two cancers. Despite progress in understanding the biology of uveal melanoma, this knowledge has not yet translated into improved patient survival. Even with early diagnosis, appropriate treatment, and close follow-up, uveal melanoma remains an aggressive cancer type, with 50% of cases progressing to metastatic disease and a poor prognosis of only 10-25% survival within the first year.

High-risk uveal melanoma patients are routinely screened for metastasis, leading to a constant fear of potential cancer spread. This fear is compounded by the short life expectancy after metastasis is identified. Overall survival is heavily influenced by liver metastasis, which leads to liver failure in approximately 90% of patients at the time of death. Currently, there is no standard treatment to guide management.

Precision Targeting of Liver Metastasis

Fewer than 10% of patients qualify for surgical removal or thermal ablation of liver metastases because the disease is commonly diffused throughout the liver. Systemic treatments have shown low efficacy. Therefore, efforts have been made to develop treatments that target the liver selectively.

Delcath Systems has pioneered a unique system for treating disseminated metastases throughout the entire liver. Utilizing Percutaneous Hepatic Perfusion (PHP), a minimally invasive approach, the system is marketed as the Hepzato Kit in the US and as Chemosat in Europe. In contrast to conventional systemic chemotherapy, this system selectively administers chemotherapy to the liver. By doing so, patients can tolerate higher chemotherapy dosages than achievable through systemic administration via peripheral veins. This targeted delivery minimizes or significantly reduces systemic toxicity, thereby mitigating side effects.

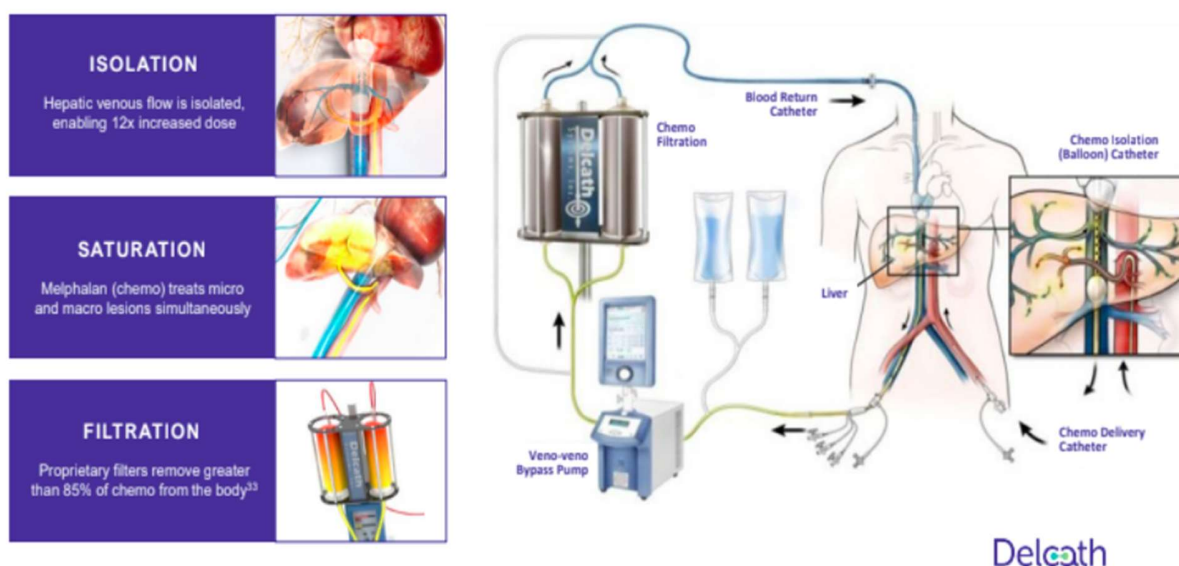
PHP capitalizes on the liver's distinct anatomy, allowing for vascular isolation. Given that the liver primarily receives blood from the hepatic artery, which is readily accessible, chemotherapy can be precisely directed to the liver. Previously conducted as an open procedure with a high mortality rate, this approach required a large incision in an operating room, rendering it non-repeatable. Delcath's innovative system now enables percutaneous, radiology-based administration of chemotherapy, offering a minimally invasive alternative.

Innovative Percutaneous Hepatic Perfusion Procedure

There are catheters required at three sites. One catheter is placed into the femoral artery, a second dual-balloon catheter is inserted into the femoral vein, and a third catheter returns blood back into the jugular vein. High doses

of chemotherapy (melphalan) are administered through the femoral artery all the way to the hepatic artery, which perfuses the entire liver. This is done under the guidance of angiogram imaging. The blood in the liver is then isolated with the dual-balloon catheter, with the balloons spaced apart to isolate hepatic venous outflow both above and below. The hepatic blood is drained out through holes in the lumen between these two balloons. The collected blood is drained through the femoral vein and passed through filters outside of the body, removing most of the chemotherapy. This blood is then returned to the body through the jugular vein in the neck (see Figure 1).

Figure 1.



Source: Delcath Corporate Presentation 2024

Patient's Journey through Percutaneous Hepatic Perfusion

Percutaneous hepatic perfusion requires a collaborative effort from a multidisciplinary team, including an interventional radiologist, an anesthetist, an oncologist, and a clinical perfusion scientist. Patients undergo a thorough assessment for procedure suitability, with ongoing monitoring provided by the

oncology team before, during, and after the intervention. Conducted under general anesthesia, the procedure lasts approximately 4-5 hours. Patients typically arrive at the hospital a day prior to the procedure and may stay for observation and recovery from general anesthesia, ranging from one to three days post-procedure. The most common side effects are well-known chemotherapy side effects (such as nausea, fatigue, and myelosuppression-associated side effects) and are routinely managed with standard care. There are also serious side effects such as hepatocellular injury, hemorrhagic, and thromboembolic events, but these are rare.

Delcath's Evolution: Navigating Challenges and Success

The PHP system, conceived by surgeons in the 1990s, originated from a personal tragedy, as one of the people joining Delcath as a CEO had a child die of Metastatic Ocular Melanoma, inspiring the system's development. Initially designed as a medical device, the focus was on meeting the requirements of the Center for Devices and Radiological Health (CDRH) rather than considering the Center for Drug Evaluation and Research (CDER) at the FDA. Despite completing a Phase III trial in 2009, the FDA issued a refusal to file in 2011, emphasizing the need to align the trial with CDER standards. Subsequent adjustments were made, and a refiled application was submitted. During drug development, modifications to the filter led to varying efficiencies, resulting in complications and unfortunate patient outcomes in the trial. However, the system received approval in Europe as a device (CE mark) in 2011, navigating a manufacturing-focused regulatory framework. Despite market entry in Europe, reimbursement proved challenging. The FDA issued a complete response letter, outlining necessary steps for approval. Following FDA guidance, the FOCUS trial was initiated in 2016, meeting enrollment completion in 2021 with a second generation of filters.

The FOCUS Phase 3 trial was a multi-center, open-label trial involving centers internationally across EU, UK, and US. Initially planned as a randomized two-arm study ((PHP vs. Best Alternative Care (BAC - transarterial chemoembolization, ipilimumab, pembrolizumab, or dacarbazine)), but it encountered patients' reluctance towards BAC. The issue arose because patients were informed about the outcomes of the initial Phase III trial and were unwilling to undergo BAC. Given the rarity of the disease and the well-informed patient population regarding treatments and research, individuals wanted to undergo PHP, and some were opting to travel to Europe for the procedure. In response, after discussions with the FDA, the trial was modified to a single-arm design. The study was conducted on patients with uveal melanoma and unresectable hepatic metastases. Limited extrahepatic disease was allowed, provided the life-threatening aspect was in the liver and the extrahepatic disease could be treated by resection or radiation. Exclusion criteria included metastases in $\geq 50\%$ of the liver, Child-Pugh Class B or C cirrhosis, or hepatitis B or C infection. Before the study was changed to a single arm trial, 91 patients received PHP and 32 received BAC. Patients receiving PHP had up to 6 cycles every 6-8 weeks apart, with an average of 4 cycles per patient. Results showed an objective response rate (ORR) of 36.3% (95% CI: 26.4, 47) compared to 12.5% (95% CI: 3.51 - 28.99) in BAC, as evaluated by an independent central review committee using RECIST v1.1. The progression-free survival (PFS) tripled in the PHP group; 9.03 months (95% CI: 6.34 - 11.56) in PHP vs 3.12 months (95% CI: 2.89 - 5.65) in the BAC. The median duration of response (DOR) was 14 months in PHP. This trial led to FDA approval on Aug 14, 2023, to HEPZATO KIT (melphalan for injection/hepatic delivery system), which includes melphalan (Hepzato, Delcath Systems, Inc.). The FDA approval only applies to the treatment of metastatic uveal melanoma. We remain confident there is a high probability Delcath's supply of melphalan hydrochloride will be uninterrupted. Delcath is required to place purchase orders for the Product at

least 210 days before the delivery date as per its License, Supply and Contract Manufacturing Agreement with Synerx Pharma and Mylan Teoranta (a recent amendment to the Agreement extends the Agreement term to December 31, 2028)

The HEPZATO KIT prescribing information includes a Boxed Warning regarding significant peri-procedural risks, such as hemorrhage, hepatocellular injury, and thromboembolic events. Additionally, there is a Boxed Warning for myelosuppression, which may lead to severe infection, bleeding, or symptomatic anemia.

Due to the heightened risk of severe peri-procedural complications access to the HEPZATO KIT is only available through a controlled program governed by a Risk Evaluation and Mitigation Strategy known as the HEPZATO KIT REMS. The REMS is a safety measure, ensuring vigilant monitoring and controlled access, thereby enhancing patient safety, and minimizing potential for adverse effects.

As of April 2024, Delcath has been assigned a permanent, product-specific J-code (J9248) by Centers for Medicare & Medicaid Services (CMS), making it easier to bill for this product when treating Medicare and Medicaid patients. It has also been granted a transitional pass-through payment status which could mean additional reimbursement for the product during a certain period.

Comparative Analysis with Other Treatments

Anti-PDI (Nivolumab or Pembrolizumab) and anti-CTLA4 (Ipilimumab) immune checkpoint inhibitors have been used individually or in combination for treating metastatic uveal melanoma. Initially designed for cutaneous melanoma, their response rate in uveal melanoma, particularly in the presence of metastasis, have been consistently low. Table 1. is a summary table which shows that

Hepzato has resulted in longer overall survival (OS) and progression free survival (PFS) compared to studies with checkpoint inhibitors.

Table 1.

Clinical Study/Publication	Study Type	Treatment	N	Median OS (months)	1 year OS	Median PFS (months)
FOCUS	Single-Arm	Hepzato	91 ^{AL}	20.53	80%	9.03
Khoja et al 2019 ³³	Meta-Analysis	systemic and liver-directed therapies	912	10.2	NA	3.3
Rantala et al 2019 ³⁴	Meta-Analysis	systemic and liver-directed therapies	2,494	12.84	NA	NA
Piulats et al 2021 ³⁵	Single-Arm	ipi plus nivo	52 ^{TN}	12.7	NA	3.0
Heppt et al 2019 ³⁶	Single-Arm	ipi plus (pembro or nivo)	64 ^{AL}	16.1	NA	3.0
Nathan et al 2021 ³⁷	Randomized	tebentafusp	252 ^{TN}	21.7	73%	3.3
		control	126 ^{TN}	16	59%	2.9

TN = Treatment Naïve, AL = Any Line
 *Studies from 2019 or later with >50 patients

Ipi = ipilimumab, nivo = nivolumab, pembro = pembrolizumab

Source: Delcath Corporate presentation 2024

The first ever FDA approved drug (Feb 2021) specifically for metastatic uveal melanoma was Tebentafusp (branded as KIMMTRAK) marketed by Immunocore. The overall survival is similar to that of Hepzato (table 1), however Tebentafusp is restricted to HLA-A*0201 positive patients (around 45 - 50 % of the Caucasians have this HLA type). Tebentafusp is currently being researched in the TebeMRD trial, a Phase II study set to yield results in 2025. This trial explores the early application of Tebentafusp in patients with molecularly relapsed disease who test positive for HLA-A*0201.

Several emerging treatments exhibit promise for metastatic uveal melanoma, albeit still in the very early stages of clinical trials. Trisalus has developed a SD-101 (a toll-like 9 agonist) delivered by Pressure-Enabled Drug Delivery (PEDD) system which has demonstrated encouraging outcomes in its study of metastatic uveal melanoma in PERIO-1 Phase 1 trial. The trial's primary completion date and the study completion date are estimated for 2024 and

2025, respectively. It's crucial to underscore that it is only the initial stage and further trials are imperative to assess its real efficacy and safety.

PHP Guidelines, Reimbursement and Emerging Trials

In the UK, the updated NICE guidance (2021) regarding the treatment of metastatic uveal melanoma has transitioned percutaneous hepatic perfusion from being solely a research practice to a recognized and safe treatment option. NICE acknowledges the benefits of this procedure for patients. It's noteworthy, however, that despite its recognition, the treatment is not presently funded under the NHS.

In the US, regional isolated perfusion of the liver (which includes PHP) is already in National Comprehensive Cancer Network (NCCN) guidelines for treating liver metastasis in uveal cancer. The inclusion of the procedure in NCCN guidelines holds significance for doctors when deciding on treatments for their patients. It serves as a recognized and authoritative endorsement, indicating that the procedure is considered a viable and recommended option based on current clinical evidence and expert consensus. Healthcare professionals are more likely to consider and choose the procedure for their patients when it aligns with the NCCN guidelines, providing a valuable reference for informed decision-making in cancer care.

In Europe, the PHP procedure has been used beyond metastatic uveal melanoma in other liver cancers, encompassing both primary and metastatic cases. These include metastatic breast and colorectal cancers and primary intrahepatic cholangiocarcinoma. Numerous publications have arisen from this showing its potential scope. Large multi-centre randomized trials are yet to be designed for these other indications. Regarding guidelines and reimbursement in Europe, reimbursement in Germany is subject to an annual hospital special request through the "ZE" process. The broader application is

pending the full publication of the FOCUS trial, pivotal for securing reimbursement support in Europe.

There is a potential for PHP to be used in combination with immune checkpoint inhibitors (such as Ipilimumab and Nivolumab). This is currently studied in an ongoing Chopin trial which is a Phase 1b/2 trial showing promising results. The trial is expected to be completed in 2024.

Advocating for PHP in Metastatic Uveal Melanoma

We currently view PHP as an option for treating metastatic uveal melanoma. While various treatments have been studied for this condition, there's no unanimous agreement on the optimal approach. We advocate for considering PHP as a viable treatment choice for eligible patients, supported by its favorable outcomes in a high-quality randomized control trial - an influential level of evidence.

In the medical field, physicians adapt their practices based on the best available evidence, and PHP, as demonstrated in clinical trials, holds substantial promise. Additionally, PHP presents an exciting opportunity for interventional radiologists to expand their professional scope. It's also crucial to acknowledge that, given the rarity of this disease, patients are often well-educated and actively seek information on the latest and most successful treatment options. Their awareness of advancements in uveal melanoma treatment underscores the importance of keeping abreast of cutting-edge therapies.

It's essential to note that, like with other cancers, the choice of treatment requires careful individual consideration on a case-by-case basis. A multidisciplinary team (MDT) approach is crucial for tailoring the treatment plan to the unique circumstances of each patient, ensuring the most effective and personalized care. Currently available in 3 cancer centers in the US, the

potential expansion of PHP to multiple centers signifies growing recognition and acceptance. Looking ahead, the future scope of PHP appears promising, especially considering its positive outcomes in studies involving other types of liver cancers.

Market Sentiment

Delcath Systems has not garnered a lot of attention, despite its promising PHP therapy, perhaps because the company has experienced a multitude of twists and turns over the years. A lover of euphemism might have put it as the company had been a destructor of shareholders capital historically. However, since Q1 2023 the insider and institutional ownership of Delcath Systems common stock has picked up. Indeed, Delcath stock has been on an inflection point in terms of market sentiment and we feel we are on the right side of the trade. Based on the total number of shares sold/bought by reporting hedge funds and insiders and adjusted for changes in the share count, our screening for key market sentiment metrics puts Delcath in the top 5% of the relevant subset of the stock universe.

Delcath's institutional ownership is standing at 28% of shares outstanding. Short interest measured as a percentage of float ranges between 3% and 4% while the days to cover ranges between 4 and 5. Based on 13D/G or 13F forms filled with the Securities Exchange Commission (SEC), Delcath has 58 institutional owners and shareholders out of which 11 are hedge funds. A significant part of those funds are activist positions and healthcare specialist funds. Vivo Capital LLC, Hirschman Orin, AIGH Capital Management LLC, Biotechnology Value Fund (Bvf), and Rosalind Advisors Inc are the largest shareholders as of the latest available filing. As per our analysis of daily prices and trading volumes evolution, institutions are in the process of stock ownership accumulation.

Overall, Delcath Systems falls into the category of the top 3% of stocks ranked by key insider metrics. Delcath has healthy insider ownership, currently standing at 15% of shares outstanding. Our stock universe screening puts Delcath on a shortlist of companies with the highest insider stock accumulation and the lowest relative insider selling for the same period.

Financial Model

Delcath: Capitalization and Financial Results (31/12/2023)									
Capitalization		Financial Results - Revenue and EV/Revenue							
			Q1'24E	Q2'24E	Q3'24E	Q4'24E	2025E	2026E	2027E
Share price (USD)	\$ 5.3								
Shares outstanding	28.6m	Revenue (m)							
Warrants	7.8m	Base case	\$1.9	\$5.0	\$8.4	\$14.0	\$89	\$126	\$147
Dilutive impact of options/RSUs	4.2m	Consensus case	\$1.9	\$5.2	\$9.6	\$17.3	\$99	\$141	\$174
Total (m)	40.6								
Fully diluted market cap (m)	215.2	EV/NTM Revenue	6.6 x						
Debt (m)	9.8	EV/Revenue ('25E)	2.2 x						
minus Cash (m)	32.5	EV/Revenue ('26E)	1.5 x						
Enterprise value (m)	192.5	EV/Revenue ('27E)	1.3 x						

Sources: Delcath Systems SEC filings, Quantinnova estimates and analysis

Model Description

There are two main questions in modeling the total revenue for Delcath: TAM and the speed of uptake. Let's start with the more important overall question.

Delcath management claims that 800 US patients are eligible for PHP treatment, which is a subset of the 2,000 Metastatic Uveal Melanoma patients diagnosed per year based on the metastasis profile of the liver. The CEO claims a target of 40% out of this 800 to be comparable to Immunocore's Tebentafusp ("Kimmtrak"), their only competitor, which captured this market share within the first 12 months post launch. We believe that 40% is an ambitious target and would rather assume a more conservative target of 25% for our base case, which we think is attainable as this is the only FDA-approved treatment for 55%

of the patients, adding a meaningful extension to their life expectancy. The treatment by Kimmtrak is restricted by the HLA genotype, all the while Kimmtrak can be combined with Hepzato. Given this, we assume 240 patients a year (30% of 800 patients).

When it comes to revenue estimate, Hepzato is priced at USD 182,500 per treatment, with a median treatment in the trial of 4.1 per case. It is possible and perhaps even likely the median will increase, yet we go with 4 per case. Putting it together, we have USD 730,000 per patient at 240 patients per year, totaling USD 175m per year.

Notably, Delcath has not stated any revenue sources outside of the US as of today but if this goes through, it will increase the TAM significantly. We find it interesting that the number of mUM cases in Europe is higher than what the population proportion suggests, making it even more interesting. Any other developed country market hasn't been spoken about yet, therefore, there can be further development in increasing the TAM.

The PHP uptake is expected to be much slower compared to a pill-based treatment. Therefore, it might not be straightforward for the market to price in the uptake correctly. We believe it might result in attractive trading opportunities in 2024 and perhaps also 2025.

When it comes to our modeling exercise of discounting the company's revenue guidance to our base case, so far, we have underestimated the revenue growth rate. Delcath management guided to have 10 sites opened by the end of Q2 2024 (up from 5 forecasted for Q1). In the beginning of April, 7 sites were confirmed, with 2 more sites already opened for patient sign-up. This gives good confidence for the treatment sites opening, and the treatment per site is only open for variability in the result.

At the moment, we can mostly rely on the company guidance, which is 1, 1.5, and 2 treatments run rate per month per site for Q2, Q3, and Q4 respectively, with the number of sites to be 10, 15, and 20, respectively. This gives a lot of space for additional assumptions, so the result per quarter will vary a lot. Nevertheless, the multiplicative effect of such guidance gives a huge jump to Q4 this year.

Finally, the revenue for Q3 can reach USD 10m with reasonable probability, making it a potential surprise for achieving profitability much sooner than expected. We estimate, based on our conservative assumptions, Delcath to achieve a significant profit in Q4 2024.

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Viktor Mikus
Portfolio Manager

QUANTINNOVA

Quantinova™ S.à r.l.
www.quantinova.com
info@quantinova.com