Percutaneous Hepatic Perfusion vs Best Alternative Care in Patients With Hepatic-dominant Ocular Melanoma (FOCUS)

This study is currently recruiting participants. (see Contacts and Locations)

Verified February 2016 by Delcath Systems Inc.

Sponsor:
Delcath Systems Inc.

Collaborator:
United BioSource Corporation

Information provided by (Responsible Party):
Delcath Systems Inc.

ClinicalTrials.gov Identifier:
NCT02678572

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History of Changes

Purpose

This study will evaluate two groups of patients who have melanoma that has spread from the eye to the liver: one group (50%) will get high-dose chemotherapy delivered specifically to the liver, while the other group (50%) will get one of 4 standard best alternative care treatments. Patients in each group will get repeating cycles of treatment until the cancer in the liver advances and will be followed until death. This study will evaluate the effect of the treatments on how long patients live and how long it takes for the cancer to advance or respond to the treatment.

Condition	Intervention	Phase
Melanoma, Ocular	Procedure: Melphalan Procedure: TACE Drug: Dacarbazine Drug: Ipilimumab Drug: Pembrolizumab	Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: A Randomized, Controlled, Phase 3 Study to Evaluate the Efficacy, Safety and Pharmacokinetics of Melphalan/HDS Treatment in Patients With Hepatic-Dominant Ocular Melanoma

Resource links provided by NLM:

MedlinePlus related topics: Melanoma

Drug Information available for: Melphalan Melphalan hydrochloride Dacarbazine Ipilimumab Pembrolizumab

Genetic and Rare Diseases Information Center resources: Carcinoid Tumor Neuroepithelioma Ocular Melanoma

U.S. FDA Resources

Further study details as provided by Delcath Systems Inc.:

Primary Outcome Measures:

- Overall Survival (OS) [Time Frame: Patients will be assessed for their survival status from randomization through end of treatment and contacted every 6 months for the first 2 years and yearly thereafter until death.] [Designated as safety issue: No]

  Patients will be followed until death

Secondary Outcome Measures:

- Progression Free Survival (PFS) as determined by Investigator [Time Frame: PFS will be assessed every 10-14 weeks following the start of 1st treatment until there is evidence of disease progression of the tumor.] [Designated as safety issue: No]

Period of time from 1st treatment until the patient's tumor progresses

- Objective Response Rate (ORR) as determined by Investigator [Time Frame: ORR will be assessed every 10-14 weeks from the start of 1st treatment and continues until the earlier of either when there is evidence of disease progression or 1 year from 1st treatment.]
  [Designated as safety issue: No]

  The ratio of patients with either a complete or partial response over the total of all patients in a given group.

Other Outcome Measures:

- Progression Free Survival (PFS) as determined by Imaging Core Lab [Time Frame: PFS will be assessed every 10-14 weeks following the start of 1st treatment until there is evidence of disease progression of the tumor.] [Designated as safety issue: No]

  Period of time from treatment until the patient's tumor progresses

- Objective Response Rate (ORR) as determined by Imaging Core Lab [Time Frame: ORR will be assessed every 10-14 weeks from the start of 1st treatment and continues until the earlier of when there is evidence of disease progression or 1 year from 1st treatment.]
  [Designated as safety issue: No]

  The ratio of patients with either a complete or partial response over the total of all patients in a given group

- Hepatic Progression Free Survival (hPFS) as determined by Imaging Core Lab [Time Frame: PFS will be assessed every 10-14 weeks following the start of 1st treatment until there is evidence of disease progression of the tumor in the liver.] [Designated as safety issue: No]

  Period of time from treatment until the patient's tumor in the liver progresses

- Hepatic Objective Response Rate (hORR) as determined by Imaging Core Lab [Time Frame: ORR will be assessed every 10-14 weeks from the start of 1st treatment and continues until the earlier of when there is evidence of disease progression in the liver or 1 year from 1st treatment.] [Designated as safety issue: No]

  The ratio of patients with either a complete or partial response in the liver over the total of all patients in a given group

- Quality of Life [Time Frame: Quality of life will be assessed at screening (up to 28 days before randomization) and at week 6 (or last week of each cycle) and at end of treatment, which is the earlier of either disease progression or 6-8 weeks after the last treatment.]
  [Designated as safety issue: No]

  Using a questionnaire, patients will self-assess how they feel after the treatment.

- Clinical Labs (Chemistry and Hematology) [Time Frame: Clinical labs will be collected up to 14 days before randomization, and for each cycle at day 1, week 2: days 1,4; weeks 3 and 4: day 1, week 6: day 7, and at end of treatment.] [Designated as safety issue: Yes]

  Clinical labs will be monitored to look for evidence of adverse events resulting from study treatment and evaluated for clinical significance.

- Vital Signs (blood pressure, heart rate, breathing rate, and temperature) [Time Frame: Vital signs will be taken up to 14 days before randomization, and for each cycle at day 1 (throughout the procedure), weeks 2 and 3: day 1; and at end of treatment.]
  [Designated as safety issue: Yes]

  Vital signs will be monitored to look for evidence of adverse events resulting from study treatment and evaluated for clinical significance.

- ECG and ECHOs (electrocardiograms and echocardiograms) [Time Frame: ECGs and ECHOs will be taken up to 14 days before randomization, and for each cycle at day 1; and at end of treatment.] [Designated as safety issue: Yes]

  ECGs and ECHOs will be monitored to look for evidence of adverse cardiac events resulting from study treatment and evaluated for clinical significance.

- Evidence of Secondary Disease (Leukemia or Myelodysplastic Syndrome) [Time Frame: Secondary disease will be assessed from time of randomization, at each visit, and during the follow-up period via phone calls every 6 months for the 1st two years and then yearly thereafter until death.] [Designated as safety issue: Yes]

  These secondary diseases are used to determine if patients develop later disease that can occur in cancer patients and to evaluate if treatment has an effect on when or if it develops.

- Peak Plasma Concentration (Cmax) [Time Frame: Blood concentrations will be assessed in the Melphalan/PHP group at each cycle at 10, 20, 30 minutes during the infusion, at 10, 20, 30 minutes during the washout, at 5-10 minutes, 10-60 minutes, 1-3 hours, and 3-6 hours during the post-washout period.] [Designated as safety issue: No]

  Patients in the Melphalan/PHP group will have blood drawn at specific time points throughout the procedure and after the procedure to generate composite data to determine the peak concentration of melphalan in the blood.

- Area Under the Plasma Concentration vs Time Curve (AUC) [Time Frame: Blood concentrations will be assessed in the Melphalan/PHP group at each cycle at 10, 20, 30 minutes during the infusion, at 10, 20, 30 minutes during the washout, at 5-10 minutes, 10-60 minutes, 1-3 hours, and 3-6 hours during the post-washout period.] [Designated as safety issue: No]

  Patients in the Melphalan/PHP group will have blood drawn at specific time points throughout the procedure and after the procedure to generate composite data to determine the exposure of melphalan in the blood over time.

Estimated Enrollment:	240
Study Start Date:	January 2015

Estimated Study Completion Date: June 2019
Estimated Primary Completion Date: June 2019 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: Melphalan/PHP 3 mg/kg ideal body weight of melphalan for infusion administered directly to the liver via percutaneous hepatic perfusion (PHP) over 30 minutes followed by a 30 minute washout. Treatment cycles are to be repeated every 6-8 weeks until disease progression.	Procedure: Melphalan Melphalan (3 mg/kg IBW) with PHP Other Name: Alkeran
Active Comparator: BAC - TACE 1 of 4 options under BAC: TACE (transarterial chemoembolization)	Procedure: TACE Transarterial chemoembolization is a procedure in which the blood supply to a tumor is blocked (embolized) and chemotherapy is administered directly into the tumor. Other Name: Transarterial Chemoembolization
Active Comparator: BAC - Dacarbazine 1 of 4 options under BAC: Systemic Dacarbazine.	Drug: Dacarbazine Dacarbazine is to be administered at 250 mg/m2 of body surface area/day given IV for 5 days, with treatment repeated every 3 weeks. Other Name: DTIC-Dome, DTIC, DIC, Imidazole Carboxamide
Active Comparator: BAC - Ipilimumab 1 of 4 options under BAC: Systemic Ipilimumab	Drug: Ipilimumab Ipilimumab is to administered at 3 mg/kg IV over 90 minutes every 3 weeks for a total of 4 treatments. Other Name: Yervoy
Active Comparator: BAC - Pembrolizumab 1 of 4 options under BAC: Systemic Pembrolizumab	Drug: Pembrolizumab Pembrolizumab is to be administered at 2 mg/kg as an IV infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity. Other Name: Keytruda

Detailed Description:

The study will consist of 3 phases: a screening phase, treatment phase, and follow-up phase.

Screening Phase: Screening assessments will be conducted within 28 days prior to randomization to determine each patient's overall eligibility. These assessments will include medical history, physical examination, Eastern Cooperative Oncology Group (ECOG) performance status (PS), 12 lead electrocardiogram (ECG), echocardiogram (ECHO), vital signs, full hematology and biochemistry, radiologic assessments of disease status, and an evaluation of the vasculature compatibility for Percutaneous Hepatic Perfusion (PHP).

Treatment Phase: Eligible patients will be randomized to treatment with Melphalan/HDS 3.0 mg/kg Ideal Body Weight (IBW) or Best Alternative Care (BAC) and must begin treatment within 14 days following randomization. BAC treatment will be: dacarbazine (DTIC); transarterial chemoembolization (TACE); ipilimumab; or pembrolizumab, based on each institution's rank order of their BAC treatments based on their standard of care (SOC). For Melphalan/HDS treatment, patients will receive up to 6 treatments. Each treatment cycle consists of 6 weeks with an acceptable delay for another 2 weeks before the next planned treatment to allow for recovery of melphalan-related toxicity, if needed. Tumor response will be assessed in both cohorts every 12 weeks (+ 2 weeks) until hepatic disease progression. If the patient receives only 1 treatment, the disease assessment scans will be conducted 12 weeks after the date of the first treatment. The assessment scans will be reviewed by an Independent Review Committee (IRC), also referred to as Independent Central Review. At any time when hepatic progressive disease (PD) is observed, the patient will be removed from further study treatment. Melphalan/HDS treatment will also be discontinued in the event that recovery from treatment related toxicity requires more than 8 weeks from last treatment. An end-of-treatment visit will be conducted approximately 6 to 8 weeks following the final dose of study treatment. Ongoing adverse events (AEs) at the end-of-treatment visit will be followed until the severity returns to baseline of CTCAE Grade < 1. The maximum possible duration of the study treatment for any patient will be 12 months.

Follow-up Phase: In the event that disease has not progressed at the end-of-treatment visit, disease assessment scans will continue every 12 weeks (+ 2 weeks) until disease progression is documented. Patients will be contacted by phone every 6 months for survival status for the first two years following the completion of study treatment, then yearly thereafter, until death, withdrawal of informed consent or they become lost to follow-up, whichever occurs first. Patients will be monitored for two years, following the completion of study treatment, for the development of myelodysplasia and secondary leukemia.

Eligibility

Ages Eligible for Study: 18 Years to 90 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

1. Male or female patients ≥ 18 years of age.
2. Patients must weigh ≥ 35 kg (due to possible size limitations with respect to percutaneous catheterization of the femoral artery and vein using the Delcath Hepatic Delivery System).
3. 50% or less histologically or cytologically-proven ocular melanoma metastases in the parenchyma of the liver.
4. Disease in the liver must be measurable by computed tomography (CT) and/or magnetic resonance imaging (MRI).

5. Evidence of limited extrahepatic disease on preoperative radiological studies is acceptable if the life threatening component of PD is in the liver. Limited extrahepatic disease is defined in this protocol as follows: metastasis in up to one other organ (bone, subcutaneous, or pulmonary), limited to up to 2 nodules and amenable to resection or radiation. The extrahepatic lesions should be no larger than 2 cm in diameter each. The rationale for permitting this limited extrahepatic disease is that these types of lesions are amenable to surgical resection or radiation.
6. Scans used to determine eligibility (CT scan of the chest/abdomen/pelvis and MRI of the liver) must be performed within 28 days prior to randomization. An MRI of the liver is required at screening to validate that CT accurately reflects the extent of disease in the liver.
7. Patients must have had no chemotherapy or radiotherapy for their malignancy in the month prior to treatment and must have recovered from all side effects of therapeutic and diagnostic interventions except those listed in Appendix B of the study protocol. Patients receiving anti programmed cell death protein 1 (PD-1) immunotherapy such as pembrolizumab or nivolumab, or human cytotoxic T-lymphocyte antigen 4 blocking antibody such as ipilimumab should wait 8 weeks before Melphalan/HDS treatment.
8. Patients must have an ECOG PS of 0-1 at screening and on the day prior to treatment.
9. Patients must have adequate hepatic function as evidenced by total serum bilirubin ≤ 1.5 x the upper limit of normal (ULN) and a prothrombin time (PT) within 2 seconds of the upper normal limit. Aspartate aminotransferase/alanine aminotransferase (AST/ALT) must be ≤ 2.5 x ULN.
10. Patients must have a platelet count > 100,000/μL, hemoglobin ≥ 10.0 gm/dL, white blood cell count (WBC) > 2,000/uL, absolute neutrophil count (ANC) ≥ 1.5 x 109/L, and a serum creatinine ≤ 1.5 mg/dL unless the measured creatinine clearance is > 40 mL/min/1.73 m2.
11. Provided signed informed consent.

Exclusion Criteria:

1. Patients with Child-Pugh Class B or C cirrhosis or with evidence of portal hypertension by history, endoscopy, or radiologic studies.
2. Those with New York Heart Association functional classification II, III or IV active cardiac conditions, including unstable coronary syndromes (unstable or severe angina, recent myocardial infarction), worsening or new-onset congestive heart failure, significant arrhythmias and severe valvular disease must be evaluated for risks of undergoing general anesthesia.
3. History or evidence of clinically significant pulmonary disease that precludes the use of general anesthesia.
4. For female patients of childbearing potential (i.e., have had a menstrual period within the past 12 months): unwilling or unable to undergo hormonal suppression to avoid menstruation during treatment.
5. For female patients of childbearing potential (i.e. have had a menstrual period within the past 12 months): a positive serum pregnancy test (β-human chorionic gonadotropin) within 7 days prior to enrollment.
6. Sexually active females of childbearing potential and sexually active males with partners of reproductive potential: unwilling or unable to use appropriate contraception from screening until at least 4 months after last administration of study treatment.
7. Lactating women are excluded from study participation.
8. Patients taking immunosuppressive drugs or who are unable to be temporarily removed from chronic anti-coagulation therapy.
9. Patients with active bacterial infections with systemic manifestations (malaise, fever, leucocytosis) are not eligible until completion of appropriate therapy.
10. Patients with severe allergic reaction to iodine contrast, which cannot be controlled by premedication with antihistamines and steroids (because a hepatic angiogram is needed for the Delcath system procedure).
11. Patients with a history of or known hypersensitivity to melphalan or the components of the Melphalan/HDS system.
12. Patients previously treated with any intra-arterial regional hepatic therapy.
13. Patients with latex allergy.
14. Patients with a history of hypersensitivity to heparin or the presence of heparin-induced thrombocytopenia.
15. Patients with a history of bleeding disorders or evidence of intracranial abnormalities which would put them at risk for bleeding with anti-coagulation (e.g., strokes, active metastases).
16. Patients with a history of gastrinoma, hepatic vasculature incompatible with perfusion, hepatofugal flow in the portal vein or known unresolved venous shunting.
17. Known varices at risk of bleeding, including medium or large esophageal or gastric varices, or active peptic ulcer.
18. Patients with prior Whipple's procedure.
19. Patients with brain metastases or presence of other intracranial lesions at risk for bleeding by history or baseline radiologic imaging. Active infection, including Hepatitis B and Hepatitis C infection. Patients with anti-hepatitis B core antibody (HBc) positive, or hepatitis B surface antigen (HBsAg) but DNA negative are exception(s).
20. Uncontrolled endocrine disorders including diabetes mellitus, hypothyroidism, or hyperthyroidism.
21. Received any investigational agent for any indication within 30 days prior to first treatment.
22. Not recovered from side effects of prior therapy to ≤ Grade 1 (according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v. 4.03). Certain side effects that are unlikely to develop into serious or life-threatening events (e.g. alopecia) are allowed at > Grade 1.

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT02678572

Contacts

Contact: Johnny John, MD 212-489-2100 ext 244 jjohn@delcath.com

Contact: John S Shea, MS 212-489-2100 ext 249 jshea@delcath.com

Locations

United States, California

City of Hope — **Not yet recruiting**
Duarte, California, United States, 91010
Contact: Houri Yeghiayan

John Wayne Cancer Institute — **Not yet recruiting**
Santa Monica, California, United States, 90404
Contact: Lisa Van Kreuningen

United States, Connecticut

Yale University — **Not yet recruiting**
New Haven, Connecticut, United States, 06520
Contact: Matthew Madura

United States, Florida

Moffitt Cancer Center — **Recruiting**
Tampa, Florida, United States, 33612
Contact: Adam Karpisek, BS 813-745-4798 adam.karpisek@moffitt.org

United States, Georgia

Emory University — **Not yet recruiting**
Atlanta, Georgia, United States, 30322
Contact: Susan Maio

United States, Illinois

University of Chicago — **Not yet recruiting**
Chicago, Illinois, United States, 60637
Contact: Rukiat Dosunmu

United States, Maryland

University of Maryland Cancer Center — **Not yet recruiting**
Baltimore, Maryland, United States, 21201
Contact: Tamara Khashab, MD

Johns Hopkins Hospital — **Not yet recruiting**
Baltimore, Maryland, United States, 21287
Contact: Dene Palazzi-Khan

United States, North Carolina

Duke University Medical Center — **Not yet recruiting**
Durham, North Carolina, United States, 27710
Contact: Kristen Linney

United States, Ohio

The Ohio State University Wexner Medical Center — **Not yet recruiting**
Columbus, Ohio, United States, 43210
Contact: Heather Heise

United States, Pennsylvania

Thomas Jefferson University — **Not yet recruiting**
Philadelphia, Pennsylvania, United States, 19107
Contact: Tracey Newhall

United States, Texas

MD Anderson Cancer Center — **Not yet recruiting**
Houston, Texas, United States, 77030
Contact: David Welch

France

Centre Leon Berard — **Not yet recruiting**
Lyon, France, 69373

Germany

Charité Comprehensive Cancer Center — **Not yet recruiting**
Berlin, Germany, 10117

Universitaetsklinikum Knappschaftskrankenhaus — **Not yet recruiting**
Bochum, Germany, 44892

Universitaetsklinikum Mainz — **Not yet recruiting**
Mainz, Germany, 55131

Universitaetsklinikum Giessen und Marburg — **Not yet recruiting**
Marburg, Germany, 35043

Italy

Instituto Scientifico Romagnolo per lo studio de la cura dei tumori — **Not yet recruiting**

Meldola, Italy, 47014

Instituto Europeo di Oncologia — **Not yet recruiting**
Milano, Italy, 20141

United Kingdom

St. George's University Hospital of London — **Not yet recruiting**
London, England, United Kingdom, SW17 ORE
Contact: M Dunne

University Hospital Southampton NHS Trust — **Not yet recruiting**
Southampton, Hampshire, United Kingdom, SO16 6YD
Contact: Julie Gilt

Sheffield Teaching Hospitals NHS Trust — **Not yet recruiting**
Sheffield, Yorkshire, United Kingdom, S10 2SJ

Sponsors and Collaborators

Delcath Systems Inc.

United BioSource Corporation

Investigators

Principal Investigator: Jonathan Zager, MD Moffitt Cancer Center

More Information

No publications provided

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Keywords provided by Delcath Systems Inc.:
uveal liver PHP hepatic perfusion chemosaturation Delcath

Additional relevant MeSH terms:

Melanoma
Neoplasms
Neoplasms by Histologic Type
Neoplasms, Germ Cell and Embryonal
Neoplasms, Nerve Tissue
Neuroectodermal Tumors
Neuroendocrine Tumors
Nevi and Melanomas
Melphalan
Alkylating Agents
Antineoplastic Agents
Antineoplastic Agents, Alkylating
Immunologic Factors
Immunosuppressive Agents
Molecular Mechanisms of Pharmacological Action
Myeloablative Agonists
Pharmacologic Actions
Physiological Effects of Drugs
Therapeutic Uses

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