1. Inclusion Criteria

To be eligible for the clinical trial, a subject must meet all of the following criteria:

1.1. General

- Age ≥ 18 years.
- Pancreatic or breast cancer, as described below.
- Stage IV (based on AJCC staging guidelines) at the time of enrollment.
    - Note that potential subjects with stage IV cancer that have had a complete response from prior chemotherapy are still potentially eligible.
- Expected survival time ≥ 6 months, as determined by the investigator.
- Life expectancy not severely limited by diseases other than malignancy, as determined by the investigator.
- Karnofsky score ≥ 60%.
- No chemotherapy within 2 weeks of enrollment.
- Prior surgical resection or ablation of the primary tumor is allowed but not required.
- If post-surgical, the subject must be at least 28 days post-op with the surgical wounds healed and significant complications resolved.
- Potential subjects who have received previous chemotherapy and/or PARP inhibitors may be enrolled.
- Measurable or non-measurable disease by the revised response evaluation criteria in solid tumors (RECIST) v.1.1.

1.2. Germline Mutation

- Must have an inherited BRCA1, BRCA2, or PALB2 mutation.
- If the mutation is a BRCA1 or BRCA2 mutation, it must be confirmed by Myriad's BRACAnalysis CDx test.
- If the mutation is a BRCA1 or BRCA2 mutation, it must be known to be deleterious or suspected to cause functional impairment as reported in the BRACAnalysis CDx test. For the sake of clarity, the Table 7-1 and Table 7-2 immediately below provide the criteria used by the BRACAnalysis CDx test.

- If the mutation is a PALB2 mutation, it must be known to be deleterious or suspected to cause functional impairment according to the variant classification criteria described in the study protocol.

1.3. Criteria Specific to Patients With Pancreatic Cancer

- Pancreatic ductal adenocarcinoma or pancreatic acinar cell carcinoma.
- If the potential subject has had surgical resection of the primary tumor, then there must be no evidence of disease progression between the time of surgical resection of the primary tumor and screening for enrollment if the patient is seeking enrollment in the immediate post-surgery period.

1.4. Criteria Specific to Patients With Breast Cancer

- Adenocarcinoma of the breast.
- HER2-negative cancer as per American Society of Clinical Oncology/College of American Pathologists human epidermal growth factor receptor 2 (HER2) testing in breast cancer guidelines.
- Male or female sex.

1.5. Histological or Cytological Confirmation

- Histological or cytological confirmation of the primary cancer diagnosis is required.
- Metastatic disease must be histologically or cytologically confirmed unless in the clinical judgment of the investigator a biopsy is not needed for diagnostic purposes.

1.6. Reproductive

- Female subjects:
    - A female of childbearing potential is any sexually mature female that has not (A) had a hysterectomy or bilateral oophorectomy (the surgical removal of both ovaries) or (B) been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months). Amenorrhea following cancer therapy does not rule out childbearing potential.
    - Female subjects of childbearing potential must agree to do one of the following from the time of signing of the informed consent through 6 months after the last dose of melphalan:
        - Simultaneously practice two effective barrier methods of contraception. Oral and injectable contraceptives are not allowed. Barrier methods of birth control (e.g., diaphragm and spermicide, or condom and spermicide) are required due to the

markedly increased risk of sinusoidal obstruction syndrome associated with progesterone/estrogen exposure after stem cell transplantation.

- Practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, and withdrawal) are not acceptable methods of contraception.

- Male subjects:
  - Unless the male is in a monogamous relationship with a female that does not have child-bearing potential, male subjects (even if surgically sterilized) must agree to do one of the following from the time of signing of the informed consent through 6 months after the last dose of melphalan:
    - Practice effective barrier contraception, plus a second method of effective contraception.
    - Practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, and withdrawal) are not acceptable methods of contraception.

2. Exclusion Criteria

A subject who meets any of the following criteria is ineligible for the clinical trial:

2.1. Cancer-Related

- Biliary tract obstruction.
- Current cholangitis. A biliary stent in situ does not otherwise exclude protocol participation.
- A history of only one episode of cholangitis and fewer than 30 days have passed since discontinuation of antibiotic treatment.
- A history of multiple episodes of cholangitis and after discussion between the site study team and sponsor medical monitor and careful evaluation for suitability the patient is deemed to be unsuitable for the trial due to risk of recurring cholangitis.
- Portal hypertension.
- Sinistral portal hypertension.
- Clinically significant malignant ascites or malignant pleural effusion, as determined by the investigator.
- Metastatic lesion to the heart or eye.

- Chemotherapy for an indication other than treatment of the current cancer within the past 1 year with a more than 30% risk of recurrence as determined by the investigator.

2.2. Brain/CNS Metastatic Lesions

- Known or suspected metastatic involvement of the central nervous system.

2.3. Cardiac

- Left ventricular ejection fraction less than 45% by Multigated Acquisition Scan or echocardiogram (or significantly below the lower limit of normal for the specific test).
- Clinically significant structural heart disease or vascular disease.
- Myocardial infarction within 6 months prior to enrollment; New York Heart Association (NYHA) Class III or IV heart failure; angina; uncontrolled ventricular arrhythmias; or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.
- Clinically significant prolongation of QTc (Bazett formula) on EKG, defined as > 0.45 s in males and > 0.47 s in females.
- Severe hypertension, which is defined as the presence of any of the following:
    - History of hypertensive crisis, hypertensive emergency, or malignant hypertension within the last year.
    - Sustained or persistent systolic BP > 165 mm Hg or diastolic > 110 mm Hg.
- Other clinically significant cardiovascular disease.

Note that:

- A past history of severe hypertension that is well-controlled with therapy or that was addressed by removal of the cause (e.g., removal of a medicine that caused the severe hypertension) is *not* an exclusion criterion.
- The presence of a pacemaker is *not* a contraindication and is *not* considered an exclusion criterion.

2.4. Pulmonary

- History or evidence of interstitial lung disease (e.g., pneumonitis or pulmonary fibrosis).
- If a smoker, refusal to stop smoking for the duration of the trial.
- FEV1 or DLCO (adjusted for hemoglobin) < 50% of predicted.

2.5. Liver

- Total bilirubin > 2x upper normal limit, except that potential subjects with Gilbert's Disease are permitted to exceed 2x upper normal limit.
- ALT or AST > 2.5x upper normal limit.
- Alkaline phosphatase > 2.5x upper normal limit, in conjunction with elevated GGT.
- Albumin < 3.0 g/dl.
- Clinical evidence of sinusoidal obstruction syndrome.

2.6. Renal

- Corrected creatinine clearance consistently < 50 ml/min/1.73 m^2.
- Clinically significant renal disease.

2.7. Hematologic

- Hemolytic anemia.
- Catalase deficiency.
- Evidence of bone marrow insufficiency or failure, in the judgment of the investigator.
- A hemoglobin < 9 g/dL.
- G6PD deficiency as measured by quantitative enzyme levels below the normal reference range in blood.

2.8. Coagulation-Related

- Pre-existing bleeding diathesis or coagulopathy.

2.9. Reproductive

- Potential subject is pregnant.
- Breast feeding and unwilling to stop.

2.10. Disorders of Iron or Copper Metabolism

- Wilson's disease.
- Primary or secondary hemochromatosis.

2.11. Metabolic

- Hgb A1c > 9%.
- Hyperuricemia that is not responsive to therapy.
- Plasma oxalate greater than 10 μM, which is not responsive to measures to reduce the level below 10 μM.

2.12. Hepatitis

- Prior or current hepatitis B or C.

2.13. Infectious Disease

- HIV infection or seropositivity for HIV.
- Active, clinically significant bacterial, viral, or fungal infection.
- History of colonization with a multidrug-resistant "superbug" that poses a high risk of an *untreatable* infection in the setting of neutropenia.

2.14. Neurologic

- Uncontrolled seizure disorder.

2.15. Radiation Exposure

- If a potential subject has received radiation, then any of the following:
  - A volume ≥ 700 ml of normal liver received a dose ≥ 4 Gy.
  - The mean dose to normal liver (i.e., liver minus gross tumor volume) was ≥ 4 Gy.
  - The mean dose to normal lung (i.e., lung minus gross tumor volume) was ≥ 4 Gy.

2.16. Contraindications to Clinical Trial Drugs

- History of significant allergy or other contraindication to BCNU, melphalan, vitamin B12b, vitamin C, pegfilgrastim, or Neupogen, or to any excipient in those drugs.

2.17. Drug-Related

- Use of any of the following cytochrome P450 2b6 (CYP2b6) inducers within 21 days of the planned date of BCNU treatment: phenobarbital, carbamazepam, rifampicin, phenytoin, sulfinpyrazone, or verapamil.
- Disulfiram (Antabuse) use within 30 days of the planned ethanol administration.

- Current chronic use of immunosuppressive agents (e.g., methotrexate, cyclosporine, corticosteroids).

2.18. Prior Treatments

- Prior bone marrow stem cell transplant.
- Except for adjuvant therapy for breast cancer or pancreatic cancer, prior radiation therapy to the brain, kidneys, pelvis, or GI tract or treatment with yttrium-90.
- Prior treatment with bleomycin or BCNU.
- Subject has not fully recovered (i.e., there remain toxicities > Grade 1) from the reversible effects of prior chemotherapy, with the exception of chemotherapy-induced alopecia and grade 2 peripheral neuropathy, unless in the opinion of the investigator the effects are not of clinical significance.

2.19. Concurrent Treatments

- Any concurrent anticancer treatment.

2.20. Serious Underlying Conditions

- Serious underlying medical or psychiatric illness or another condition that in the clinical judgment of the investigator is likely to interfere with the potential subject completing participation in the trial, based on safety concerns or otherwise.

2.21. Other

- Inability or unwillingness to adhere to the study protocol.
- Unwillingness to receive ethanol.
- Participation in other interventional clinical trials within 30 days of enrollment.