

High Dose Conditioning With Ifosfamide, Carboplatin, and Etoposide With Autologous Stem Cell Transplantation for Patients With Recurrent Nasopharyngeal Carcinoma

NCT02137096

03/23/2017

HIGH DOSE CONDITIONING WITH IFOSFAMIDE, CARBOPLATIN AND ETOPOSIDE WITH AUTOLOGOUS STEM CELL TRANSPLANTATION FOR PATIENTS WITH RECURRENT NASOPHARYNGEAL CARCINOMA

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1. ABSTRACT / PURPOSE:

Nasopharyngeal carcinoma (NPC) is a rare disease in children and adolescents in the United States. There is no current standard treatment for recurrent disease. Treatment is individualized based on previous treatment (usually combined modality radiation and chemotherapy), sites of disease recurrence, and the patient's overall health status and anticipated tolerance of additional chemotherapy and radiotherapy. NPC is a highly chemosensitive disease, however, maintaining long-term remission is challenging. The role of consolidation with high dose chemotherapy has been investigated in number of pilot studies and shown to be tolerated. In this study, based on prior experience, the combination of high dose ifosfamide, carboplatin and etoposide followed by autologous stem cell rescue will be investigated as a consolidation therapy for locally advanced and metastatic NPC to increase disease remission rate and long term survival.

2. BACKGROUND:

Nasopharyngeal carcinoma (NPC) is a rare tumor in children accounting for approximately 1% of all childhood tumors, it also accounts for 20 – 50% of all primary nasopharyngeal tumors in this age group^{1,2}. It arises from the surface epithelial cells of the nasopharynx and has been associated with Epstein-Barr virus (EBV) infection². Most patients with childhood NPC have undifferentiated histology (WHO type III) and present with locoregionally advanced disease². Pediatric and adolescent patients are treated based on adult regimens with radiotherapy as the principal mode of treatment³. The addition of chemotherapy has been shown to improve survival in patients with locally advanced NPC⁴. Despite standard combined modality therapy, 20 – 30% of patients with NPC will present with recurrent or metastatic disease⁴. Most recurrences occur within the first two years of diagnosis and repeat radiation therapy is often not an option. Various combinations of chemotherapy have been tried in adults and in children with varying results, but overall response and survival have remained dismal.

The use of high dose chemotherapy followed by autologous peripheral blood stem cell (PBSC) transplantation in recurrent NPC has shown promise when compared with standard chemotherapy. Airoidi and colleagues⁵ reported long-term results of high dose chemotherapy as late intensification with autologous PBSC support in 6 patients. After conventional chemotherapy, there was 1 CR (16%), 3 PR (50%), and 2 NC (34%). After high dose chemotherapy, 4 patients achieved CR (66%), 1 PR (17%), and 1 MR (17%). Toxicity was manageable. After a median follow-up of 30 months (range, 14-50), two

patients were alive without disease (34%), one was alive with bone disease (16%), and three (50%) died of disease at 16, 18, and 24 months⁵.

Chen T-Y et al also reported that high dose chemotherapy followed by autologous stem cell transplantation is feasible with acceptable toxicity and can convert partial remission into complete remission⁶.

3. SPECIFIC AIMS:

3.1. To evaluate the response rates for patients undergoing high dose conditioning using Etoposide, Carboplatin and Ifsofamide followed by autologous stem cell transplantation for the treatment of recurrent NPC in children, adolescents, and young adults.

3.2. To evaluate the toxicities associated with undergoing high dose conditioning using Etoposide, Carboplatin and Ifsofamide followed by autologous stem cell transplantation for the treatment of recurrent NPC in children, adolescents, and young adults.

4. RESEARCH PLAN:

4.1. Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CRF50).

The study will be conducted in compliance with the protocol. The protocol, any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study.

All potential serious breaches must be reported to University of Florida IRB-01. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been evoked or where there has been scientific misconduct or fraud (eg. loss of medical licensure, debarment). Systems with procedures that ensure the quality of every aspect of the study will be implemented.

4.2. Institutional Review Board/Independent Ethics Committee

Investigators must ensure that subjects (or, in those situations where consent cannot be given by subjects, the legally acceptable representative) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given

written informed consent must be obtained from every subject (or, in those situations where consent cannot be given by subjects, the legally acceptable representative) before clinical study participation including informed consent for any screening procedures conducted to establish subject eligibility for the study.

The rights, safety, and well being of the study subjects are the most important considerations and should prevail over interests of science and society.

Subjects unable to give their written consent (eg. children less than 18 years of age, stroke patients, or those with severe dementia) may be enrolled in the study only with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subjects' understanding, and should they become capable, they must personally sign and date the consent form as soon as possible. The explicit wish of a subject unable to give his or her consent, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

5. INVESTIGATIONAL PLAN

5.1. Study Design

This is a Pilot study evaluating the role of high dose conditioning with Ifosfamide, Carboplatin, and Etoposide with autologous stem cell transplantation for children, adolescents and young adults with recurrent nasopharyngeal carcinoma.

5.2. Number of Patients Planned

A total of 10 patients are planned to be included in this study.

5.3. Duration of Treatment

The subjects will be on treatment for approximately 3 months which includes the pre-treatment evaluations, the conditioning treatment, and 6-8 weeks of post treatment supportive care.

5.4. Duration of Follow-Up

The subjects will begin follow-up care and the time of initial discharge after transplant and continue for up to 5 years from date of stem cell transplant or until death or patient withdrawal.

5.5. Study Population

5.5.1. Inclusion Criteria

- 5.5.1.1.** Pathologically confirmed nasopharyngeal carcinoma at original diagnosis.
- 5.5.1.2.** Imaging and/or tissue diagnosis of second or greater recurrent or progressive nasopharyngeal carcinoma
- 5.5.1.3.** Documentation of previous treatment including conventional chemotherapy and/or radiation therapy as clinically appropriate.
- 5.5.1.4.** Ages 2 to 30 years of age.
- 5.5.1.5.** Negative serum pregnancy test if applicable.
- 5.5.1.6.** Subjects must agree to use contraception if they are of childbearing age.

- 5.5.1.7.** Prior to initiation of high dose conditioning patient must have completed leukapheresis and stem cell preservation in accordance with institutional standards, with a minimum collection of $4 \times 10^6/\text{kg}$ CD34+ cells desired. Separate institutional informed consent forms will be used.
- 5.5.1.8.** Prior to initiation of high dose conditioning patients must have calculated creatinine clearance of greater than 60 mL/minute, serum creatinine of less than 120 mg/DL, total bilirubin less than 2 mg/dL and AST must be less than twice the upper limit of normal.
- 5.5.1.9.** Hematopoietic recovery prior to initiation of high dose conditioning would include ANC of greater than $1 \times 10^9/\text{L}$, and platelets greater than $100,000 \times 10^9/\text{L}$; or at the discretion of the attending physician based upon clinical situation.
- 5.5.1.10.** Patient and/or parent or legal guardian to sign informed consent form.

5.5.2. Exclusion Criteria

- 5.5.2.1.** Patient deemed unsuitable for autologous transplantation due to comorbidities or intractable psychosocial issues.
- 5.5.2.2.** Failure to give written informed consent.
- 5.5.2.3.** Pregnancy
- 5.5.2.4.** Breast-feeding women

5.5.3. Discontinuation of Subjects from Treatment

- 5.5.3.1.** Withdrawal of informed consent (subject's decision to withdraw for any reason)
- 5.5.3.2.** Progressive disease at any time
- 5.5.3.3.** Any clinical adverse event (AE), laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not the best interest of the subject.
- 5.5.3.4.** Pregnancy

5.5.4. Treatment Plan

5.5.4.1. Stem Cell collection and cryopreservation of peripheral blood stem cells

- 5.5.4.1.1.** The patient will undergo a collection of adequate numbers of hematopoietic stem cells. Stem cell harvesting may be done after priming with a cytokine (G-CSF, GM-CSF or other factors used singly or in combination according to institutional preference) or they may be collected following the salvage chemotherapy during the rebound phase with cytokine support. Chemotherapy in combination with growth factors is also allowed.
- 5.5.4.1.2.** Stem cells should be collected no longer than six weeks after completion of last cycle of salvage chemotherapy. The patient will undergo leukapheresis according to standard institutional procedures to collect a minimum of $4 \times 10^6/\text{kg}$ CD34+ cells desired. Separate institutional informed consent forms will be used.

5.5.4.1.3. The collected cells must be cryopreserved according to accepted methods using DMSO alone or DMSO/HES. The stem cells should not be purged or CD34 selected. The collected stem cells will be reinfused after conditioning chemotherapy.

5.5.4.1.4. Patients who fail to collect adequate CD34 cells will be excluded from the study.

5.5.4.1.5. Stem cells will be thawed and infused according to standard institutional practices on Day 0.

5.5.4.1.6. Patient may receive premedication with diphenhydramine, mannitol, hydrocortisone and acetaminophen per institutional protocol.

5.5.4.2. All patients transplanted per the PEDIATRIC BMT SERVICE will have chemotherapy dosed on actual body weight. If the patient's weight is more than 130% of their ideal body weight, then calculate the doses of chemotherapy according to the adjusted ideal body weight using the following formula:

Adjusted ideal body weight = ideal body weight + [(total body weight - ideal body weight) x 0.25].

5.5.4.2. Dose modifications may occur as clinically indicated, at the discretion of the treating physician.

5.5.4.3. Mesna shall be started prior to initiation of Ifosfamide administration per institutional standard. Other measures of uroprotection, such as hydration and furosemide shall be carried out per institutional standard and at the discretion of the treating physician.

5.5.4.4. Renal function shall be monitored as per institutional standard and Carboplatin dose adjusted if clinically indicated.

DAYS BEFORE TRANSPLANT						
Treatment	Day - 5	Day-4	Day-3	Day-2	Day - 1	Day 0
Ifosfamide (2.5 g/m ² /day) IV over 17 hours for four days	X	X	X	X		
Carboplatin (300 mg/m ² /day) IV over 3 hours for four days	X	X	X	X		
Etoposide (300mg/m ² /day) IV over 3 hours for four days	X	X	X	X		
Stem Cell Infusion (Minimum 48 of hours from last dose).						X

5.5.5. Supportive Care

- 5.5.5.1.** Prophylaxis with antiemetics for immediate and delayed nausea and vomiting shall be administered as per current supportive care guidelines.
- 5.5.5.2.** Subjects will have a multilumen indwelling venous catheter placed prior to initiation of therapy.
- 5.5.5.3.** Antibacterial, antiviral and antifungal prophylaxis/treatment will be administered in accordance with current supportive care guidelines.
- 5.5.5.4.** Blood component support will be administered in accordance with current supportive care guidelines.
- 5.5.5.5.** Growth factor support will be administered in accordance with the current supportive care guidelines.

5.5.6. Possible Risks

- 5.5.6.1.** Aggressive supportive care improves outcome. This study will follow the institutional supportive care guidelines for high-dose chemotherapy and stem cell transplant.
- 5.5.6.2.** The possible risks of this treatment include those associated with high-dose chemotherapy and autologous stem cell transplantation including:
 - 1. Pancytopenia requiring transfusion support
 - 2. Bacterial infection
 - 3. Fungal infection
 - 4. Nausea, vomiting
 - 5. Loss of appetite
 - 6. Mucositis
 - 7. Alopecia
 - 8. Allergic reactions to the chemotherapy agents or supportive care agents
 - 9. Liver damage
 - 10. Kidney damage
 - 11. Hemorrhagic cystitis
 - 12. Sinusoidal obstruction syndrome (SOS) of the liver
 - 13. Engraftment syndrome
 - 14. DMSO adverse effects during stem cell infusion

5.5.6.3. Drug specific risks are listed below:

Possible Side Effects of Carboplatin and Etoposide (Table Version Date: October 8, 2013)

COMMON, SOME MAY BE SERIOUS
In 100 people receiving Carboplatin, Etoposide, more than 20 and up to 100 may have:
<ul style="list-style-type: none">• Hair loss• Vomiting, nausea, diarrhea, loss of appetite• Infection, especially when white blood cell count is low

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Carboplatin, Etoposide, more than 20 and up to 100 may have:

- Anemia which may require blood transfusions
- Bruising, bleeding
- Belly pain
- Sores in mouth which may cause difficulty swallowing
- Tiredness
- Fever, chills

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Carboplatin, Etoposide, from 4 to 20 may have:

- Constipation
- Numbness and tingling in fingers and toes
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Heart failure or heart attack which may cause chest pain, shortness of breath, swelling of ankles, and tiredness
- Severe skin rash with blisters and peeling which can involve inside of mouth and other parts of the body
- Liver damage which may cause yellowing of eyes and skin, swelling

RARE, AND SERIOUS

In 100 people receiving Carboplatin, Etoposide, 3 or fewer may have:

- Changes in vision
- Changes in taste
- Damage to organs which may cause hearing and balance problems
- Cancer of bone marrow (leukemia) caused by chemotherapy

Possible Side Effects of Filgrastim (Table Version Date: October 24, 2013)**COMMON, SOME MAY BE SERIOUS**

In 100 people receiving Filgrastim, more than 20 and up to 100 may have:

- Nausea, vomiting
- Pain in bone

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Filgrastim, from 4 to 20 may have:

- Anemia which may cause tiredness, or may require transfusion
- Damage to the lungs which may cause shortness of breath
- Internal bleeding which may cause coughing up blood
- Swelling or tenderness of vessels

RARE, AND SERIOUS

In 100 people receiving Filgrastim, 3 or fewer may have:

RARE, AND SERIOUS
In 100 people receiving Filgrastim, 3 or fewer may have:
<ul style="list-style-type: none"> • Rupture of the spleen leading to bleeding in the belly

Possible Side Effects of Ifosfamide (Table Version Date: May 28, 2013)

COMMON, SOME MAY BE SERIOUS
In 100 people receiving Ifosfamide, more than 20 and up to 100 may have:
<ul style="list-style-type: none"> • Anemia which may require transfusion • Nausea, vomiting • Infection, especially when white blood cell count is low • Blood in urine • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving Ifosfamide, from 4 to 20 may have:
<ul style="list-style-type: none"> • Abnormal heartbeat • Bruising, bleeding • Kidney damage which may cause swelling, may require dialysis • Fluid around lungs • Confusion, sleepiness, disorientation • Sterility

RARE, AND SERIOUS
In 100 people receiving Ifosfamide, 3 or fewer may have:
<ul style="list-style-type: none"> • Damage to the heart or heart failure which may cause tiredness, shortness of breath, or swelling of ankles

Possible Side Effects of Mesna (Table Version Date: May 28, 2013)

COMMON, SOME MAY BE SERIOUS
In 100 people receiving Mesna, more than 20 and up to 100 may have:
<ul style="list-style-type: none"> • Nausea, vomiting • Tiredness, headache • Pain in arms, legs • Unpleasant taste

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving Mesna, from 4 to 20 may have:
<ul style="list-style-type: none"> • Low blood pressure which may cause feeling faint

RARE, AND SERIOUS
In 100 people receiving Mesna, 3 or fewer may have:
<ul style="list-style-type: none"> • None

Possible Side Effects related to blood stem cell harvest and infusion

COMMON, SOME MAY BE SERIOUS In 100 people receiving Ifosfamide, more than 20 and up to 100 may have:
<ul style="list-style-type: none">• Nausea and vomiting• Unpleasant taste and smell of agent used to preserve stem cells when frozen• Headache• Fever• Discolored urine• Tingling of the lips• Muscle cramping

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Ifosfamide, from 4 to 20 may have:
<ul style="list-style-type: none">• Seizures (rare)• Blood loss• Infection• Skin rash, hives• Flushing (redness and warmth of the skin)• Dizziness or fainting• Chills• Changes in heart rhythm (rare and easily treated)

RARE, AND SERIOUS In 100 people receiving Ifosfamide, 3 or fewer may have:
<ul style="list-style-type: none">• In rare cases, patients have allergic reactions (may be life threatening)• Increased bleeding or clotting (caused by a drug to prevent clotting of the blood during collection)

6. STORAGE, HANDLING, AND DISPENSING

6.1. All chemotherapy agents are commercially available and will be stored handled and dispensed per institutional protocols.

6.2. The use of Etoposide, Ifosfamide, and Carboplatin in this trial are approved use of FDA approved drugs. When a drug or combination of drugs are used in such a manner as part of a clinical trial, it is by rule, considered as an investigational treatment regimen. However, while these treatment regimens are not approved by the FDA, their use is exempt from the requirements for an IND to conduct this study as defined under Title 21, CFR 312.2(b) of the codified FDA regulations.

7. DOSE MODIFICATIONS

7.1. All toxicities should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

7.2. Dose modifications are based on dose level administered on the last treatment day. Dose adjustments of each agent may be made independently based on the specific toxicities observed.

7.3. Blinding/Unblinding is not applicable to this protocol.

8. STUDY ASSESSMENTS AND PROCEDURES

	Baseline	Day -5 to +14 or Discharge (Daily unless stated otherwise)	After Discharge: Weekly until stable	Day 30	Day 100	Every 3 – 6 months	1 Year	Yearly until 5 years from transplant
H&P with VSS	X	X	X	X	X	X	X	X
Performance Status	X	X	X	X	X	X	X	X
AE Assess		X	X	X	X	X		
ECG, ECHO, and/or MUGA Scan, and/or Cardiac MRI	X						X	yearly if abnormal
PFT's	X						X	yearly if abnormal
CBC & Diff	X	X	X	X	X	X	X	X
PT/PTT/INR	X							
BMP, Mg, Phos	X	X	X	X	X	X	X	X
LFT's, LDH	X	Weekly	X	X	X		X	X
TFT's (TSH, free T4)	X						X	X
IgG	X			X	X		X	
CD4, CD8				X	X		X	
CT or MRI Primary / Metastatic Site	X				X	X (at 6 months and 9 months)	X	X
PET Scan	X				X	X (at 6 and 9 months)	X	X

Audiogram	X						X	
Creatinine Clearance or GFR	X							
DEXA Scan							X	

9. SAFETY ASSESSMENTS

9.1. Subjects must undergo a history and physical examination by a licensed provider daily while in hospital and at each follow-up visit.

9.2. Laboratory testing should be completed as outlined in the study schedule. Additional laboratory testing may be done at the Investigator's discretion.

10. EFFICACY ASSESSMENTS

10.1. Tumor response will be assessed using MRI/CT/PET imaging of the primary site and known metastatic sites.

10.2. Measureable disease: the presence of at least one measurable lesion that can be accurately measure in at least one dimension (the longest diameter) and with a minimum size of 10 mm by CT or MRI scan.

10.3. Non-measurable lesions: all other lesions including leptomeningeal disease, pleural/pericardial effusion, and blastic bone lesions.

10.4. All measurements should be recorded in metric notation, using a ruler or calipers using the same method of assessment to characterize each identified and reported lesion at baseline and during follow-up.

10.5. All baseline evaluation should be performed as close as possible to the initiation of conditioning treatment and not more than 30 days before conditioning treatment begins.

10.6. Response Criteria include:

11. Response Criteria for Patients with Solid Tumors

This study will use a modified version of the Response Evaluation Criteria in Solid tumor (RECIST) from the NCI to evaluate disease response. The modifications will include volumetric measurement of the primary NPC and assessment of associated adenopathy. Measurable and non-measurable metastatic foci in the lungs, bones and liver will be evaluated as per RECIST.

12. ADVERSE EVENT REPORTING

12.1. An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding) symptom, or disease temporally associated with the use of the investigational product, whether or not considered related to the investigational product.

12.2. *Serious Adverse Events* – any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significantly disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event, defined as a medical event that may not be immediately life threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (eg. medical, surgical) to prevent one of the other serious outcomes listed above.
- All pregnancies, regardless of outcome must be reported including pregnancies that occur in the female partner of a male subject. All pregnancies must be followed to outcome.

12.3. *Non-serious Adverse Events* –all adverse events that are not classified as SAE's.

12.4. All adverse events, including those that are serious will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCICTCAE, Version 4.0).

12.5. The following categories and definitions of causal relationship to investigational product as determined by a physician should be used:

- 1 **Related** – there is a reasonable causal relationship to the investigational product administration and the adverse event.

- 2 **Not Related** – there is not a reasonable causal relationship to investigational product administration and the adverse event.

12.6 SAE Reporting: All grade 3 non-hematologic SAE's must be collected, including those thought to be associated with protocol-specified procedures. Collection of all SAEs must continue for 60 days after the last administration of the investigational products. All SAE's must be reported to UF-IRB-01 within 5 working days.

12.7 Laboratory Test Abnormalities – all laboratory test results captured as part of the study should be recorded following institutional procedures. In general, non-clinically significant laboratory deviations are not considered adverse events. Laboratory deviations which require treatment delay, modification or discontinuation or are otherwise clinically significant should be reported as adverse events.

13. DATA SAFETY MONITORING PLAN

This protocol will adhere to the policies of the UF Health Shands Cancer Center Data and Safety Monitoring Plan, in accordance with NCI regulations. The Data and Safety Monitoring Committee will review all serious adverse events and toxicity reports as well as annual reviews. The investigator will continuously monitor the progress of the study and the safety of the participants. All adverse events will be evaluated for causality and reported to the appropriate oversight committees as required.

14. DATA MANAGEMENT SYSTEM

To provide data collection we will utilize the ONCORE database for both accrual entry and trial data management. ONCORE is a Clinical Trials Management System designed with the capability for: study setup, activation, tracking, reporting, data monitoring and review and eligibility verification. It is housed on secured servers maintained at the University of Florida Health Science Center on the University of Florida campus. The e- CRFs on ONCORE are 21 CFR part 11 compliant, and all users are assigned password protected user accounts.

15. STATISTICAL CONSIDERATIONS

Statistical analyses will be conducted by the study biostatistician using SAS v9.1 (SAS Institute, Cary, NC).

Routine data listing or tabulation review during the study conduct will be performed to identify missing data, anomalies, outliers, etc. Missing data will generally not be imputed. Baseline is defined as the last non-missing measurement for a variable prior to the initial dose of any investigational product.

Descriptive statistics will be provided to summarize demographic and baseline characteristic parameters. Categorical data will be summarized as frequency and its corresponding percentage. For continuous data, frequency (n), mean, standard deviation, median (as appropriate), minimum, and maximum will be provided for each parameter.

15.1 Sample Size Determination

This is a pilot study and due to the limited number of potential patients who may present with this rare disease, a sample size of 10 patients was chosen based on availability.

15.2 Analysis of the Primary Endpoint

PFS is defined as the time from treatment start to the first of either (1) documented disease progression or (2) death as a result of any cause. Patients who did not progress nor die or are lost to follow-up will be censored at the day of their last objective tumor assessment. The Kaplan-Meier method will be used to estimate the median PFS time, together with a 95% confidence interval (CI). PFS will be determined by MRI imaging.

15.3 Analysis of Secondary Endpoints

The objective RR is equal to the proportion of patients achieving a best overall response of partial or complete response (CR + PR), according to imaging from the start of the treatment until disease progression/recurrence. Clinical benefit rate is equal to the objective RR plus the proportion of patients attaining stable disease (CR + PR + SD). Patients who do not have a tumor response assessment for any reason will be considered nonresponders and will be included in the denominator when calculating the response rate. The number of patients achieving a response will be divided by the total of patients treated to yield the proportion responding. Exact confidence bounds (95% CI) will be calculated.

Overall survival is defined as the time from the date of treatment start to the date of death from any cause. If the patient is alive at the end of the follow-up period or is lost to follow-up, OS will be censored on the last date the patient is known to be alive. OS will be evaluated by the Kaplan-Meier method and a 2-sided 95% CI will be provided for the median OS.

Time to progression (TTP) for responders only is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that the criteria for PD are met, or death. TTP will be

estimated with the Kaplan- Meier method; a 90% CI will be provided for the median TTP. Patients who do not relapse are censored at the day of their last objective tumor assessment. The freedom from metastasis rate is defined below and will be calculated based on an intention to treat principle. Determination of the anatomic site of first failure for patients with PD will be recorded and analyzed. Duration of response is also defined below.

15.4 Analysis of Safety Data

Safety analyses will be performed on all patients who receive any dose of study medication. Adverse events that occur more than 30 days after the administration of the last dose of treatment will not be included.

The safety and tolerability of study drug is determined by reported AEs, physical examinations, laboratory tests, and ECGs. All patients will be assessed regularly for potential occurrence of AEs from the time that treatment starts until 60 days after the last dose of study therapy. AEs will be summarized with the incidence and percentage of patients with at least one occurrence of a preferred term (according to the most severe NCI-CTCAE Version 4.0 grade) will be included. The number of AEs reported will also be summarized. Causality (relationship to study drug) will be summarized separately. Duration of AE will be determined and included in listings along with action taken and outcome. Laboratory AEs will be monitored from the time that treatment starts until 30 days after the last dose of study therapy. Laboratory results will be classified according to NCI-CTCAE, Version 4.0. Incidence of laboratory abnormalities will be summarized; laboratory results not corresponding to an NCI-CTCAE Version 4.0 term will not be graded. Laboratory toxicity shifts from baseline to worst grade will also be provided. The results from physical examination and vital sign measurement will be tabulated. Descriptive statistics will be provided as appropriate.

15.5 Duration of Response and other Endpoint Definitions

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started), or death.

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented, or death.

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Rate of freedom from metastasis (FFM) is defined as the proportion of patients with documentation of progression of disease, during study participation, in whom no new lesions appeared.

In rare situations where PD or other endpoints could not be clearly assessed, the PI will review the records with the treating physician and provide a clinical judgment for purposes of endpoint documentation.

16 ADMINISTRATIVE SECTION

16.1 Compliance with the Protocol

The study must be conducted as described in the final IRB/IEC-approved protocol. Documentation of approval, signed by the IRB/IEC chairperson or designee, will be sent to the BMS protocol manager.

All protocol amendments and revisions to the informed consent will be submitted to the BMS protocol manager and to the IRB/IEC. No protocol amendments will be implemented until written approval has been given by the IRB/IEC, except when necessary to eliminate an immediate hazard to study subjects. Administrative letters should also be sent to the BMS protocol manager and IRB/IEC; however, they do not require approval.

If a protocol amendment mandates a revision to the informed consent, the revised consent must be used to obtain consent from subjects currently enrolled in the study if it affects them (eg, if it contains new information regarding safety), and the revised consent must be used to obtain consent from new subjects before enrollment.

16.2 Records Retention

The investigator will retain, in a confidential manner, all data pertinent to the study for all treated subjects as well as those entered as control subjects. The investigator will retain source documents and accurate case histories that record all observations and other data pertinent to the investigation (eg, the medical record) for the maximum period required by applicable regulations and guidelines or following institutional procedures. If the investigator withdraws from the study (eg, relocation or retirement), the records will be transferred to a mutually agreed upon designee, such as another investigator or an IRB. Written documentation of such transfer will be provided to BMS.

17. GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or the sponsor to be related to the investigational product
Expedited Safety Report	Rapid notification to investigators of all SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the Investigator Brochure), or that could be associated with the study procedures.
SUSAR	Suspected, Unexpected, Serious Adverse Reaction as termed by the European Clinical Trial Directive (2001/20/EC).
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)

18. LIST OF ABBREVIATIONS

AE	Adverse event
ANC	Absolute Neutrophil Count
BID	Twice a Day
CAT (or CT scan)	Computed Axial Tomography
CBC	Complete Blood Count
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
EKG	Electrocardiogram
ESR	Expedited Safety Report
FDA	Food and Drug Administration

GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IST	Investigator-Sponsored Trial
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NSAE	Non-Serious Adverse Event
PD	Progressive Disease
PFS	Progression Free Survival
PO	By Mouth
PR	Partial Response
QD	Once Daily
RECIST	Response Evaluation Criteria In Solid Tumors

19. REFERENCES

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