Aggressive Smoldering Curative Approach Evaluating Novel Therapies and Transplant

CLINICALTRIALS.GOV IDENTIFIER	RECRUITMENT STATUS	FIRST POSTED	LAST UPDATE POSTED
NCT03289299	RECRUITING	SEPTEMBER 20, 2017	AUGUST 12, 2020

STUDY DESCRIPTION

Brief Summary

This study evaluates the use of carfilzomib, lenalidomide, daratumumab, and dexamethasone in subjects with high-risk smoldering multiple myeloma (SMM). Subjects will receive treatment in 3 phases - induction (6 cycles), consolidation (6 cycles), and maintenance (12 cycles). Each cycle is 28 days.

Condition or Disease: Smoldering Multiple Myeloma

Intervention/treatment: Drug: Carfilzomib
Drug: Lenalidomide
Drug: Daratumumab
Drug: Dexamethasone

Phase: Phase 2

DETAILED DESCRIPTION

This study is a multi-center phase 2 study of carfilzomib, lenalidomide, daratumumab, and dexamethasone in subjects with high-risk smoldering multiple myeloma (SMM). Myeloma remains incurable with the current approaches. The typical natural history of myeloma is one of repeated relapses, accompanied by genetic evolution and development of new abnormalities, which are often responsible for drug resistance. The presence of a precursor phase of smoldering myeloma, and the ability to identify those at the highest risk of progression, sets the stage to examine the possibility that we can cure the disease through early intervention. In order to potentially achieve this, we need to develop a highly effective combination that includes the most active drugs from different classes. Carfilzomib in combination with lenalidomide and dexamethasone results in high response rates and deep responses in subjects with newly diagnosed myeloma. Daratumumab in combination with lenalidomide results in high response rates in relapsed refractory disease. All these drugs are well tolerated and subjects are able to stay on them long term as a maintenance treatment. The combination of the carfilzomib, lenalidomide, daratumumab and dexamethasone presents the potential to enhance the effectiveness of the regimens. We hypothesize that this combination will lead to deep response including a higher proportion of minimal residual disease (MRD) negative disease among those with high risk smoldering myeloma and may translate into cure or long term disease quiescence.

STUDY DESIGN

Study Type: Interventional

Estimated Enrollment : 83 participants

Intervention Model : Single Group Assignment

Masking: None (Open Label) ()

Primary Purpose: Treatment

Official Title: Aggressive Smoldering Curative Approach Evaluating Novel Therapies (ASCENT): A Phase 2 Trial of Induction, Consolidation, and Maintenance in Subjects With High Risk Smoldering Multiple Myeloma (SMM)

Actual Study Start Date: May 2018

Estimated Primary Completion Date: June 2022

Estimated Study Completion Date: June 2026

ARMS AND INTERVENTIONS

Arm	Intervention/treatment
Experimental: Arm A Non-high dose treatment in 3 phases Induction 6 cycles: carfilzomib, lenalidomide, daratumumab, dexamethasone Consolidation 6 cycles: carfilzomib, lenalidomide, daratumumab, dexamethasone Maintenance 12 cycles: lenalidomide, daratumumab	Drug: Carfilzomib 56 mg/m2 IV given on days 1, 8, and 15 of each cycle during induction and consolidation phases of the study. Drug: Lenalidomide 25 mg po given on days 1-21 of each cycle during the induction and consolidation phases. 10 mg po given on days 1-21 of each cycle during the maintenance phase. Drug: Daratumumab 16 mg/kg IV given on days 1, 8, 15, and 22 of cycles 1-2; days 1 and 15 of cycles 3-6; day 1 of cycle 7-12; Day 1 of odd cycles for cycles 13-24. Drug: Dexamethasone 40 mg oral given on days 1, 8, 15, and 22 of cycles 1-6 20 mg oral given on days 1, 8, 15, and 22 of cycles 7-12

OUTCOME MEASURES

Primary Outcome Measures:	1. Stringent complete response rate [Time Frame: During treatment] A confirmed sCR on 2 consecutive evaluations at any time during the course of treatment.
Secondary Outcome Measures:	1. MRD negativity after each treatment phase [Time Frame: 6 months, 12 months, and 2 years] MRD negativity after induction, consolidation, and maintenance 2. MRD negativity at 1 year post treatment [Time Frame: 1 year post treatment] Persistent MRD negativity rate will be evaluated at 1 year after completion of planned treatment consisting of induction, consolidation, and maintenance. 3. Overall Survival [Time Frame: up to 10 years post registration] time of registration to death due to any cause 4. Progression-free survival [Time Frame: up to 10 years post registration] the time from registration to the earliest date of documentation of disease progression or death due to any cause 5. Adverse events [Time Frame: 2 years] all eligible subjects that have initiated treatment will be considered evaluable for assessing adverse even rates. The maximum grade for each type of adverse event will be recorded. Relationship to trial treatment will be taken into consideration.

ELIGIBILITY CRITERIA

Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:
- Age 18 years and ≤ 80 years
- High risk smoldering myeloma, which is untreated, as defined by either of the two following criteria:
1. Presence of any two of the following: Serum M spike > 2 gm/dL OR an involved to uninvolved free light chain (FLC) ratio > 20 OR bone marrow PC% > 20%
2. Total score of 9 or above using the following scoring system:
FLC Ratio >10-25 = 2 >25-40 = 3 > 40 = 5
Serum M Protein (g/dL) >1.5-3 = 3 >3 = 4
BMPC% >15-20 = 2 >20-30 = 3 >30-40 = 5 >40 = 6
FISH abnormality (t(4,14), t(14,16), 1q gain, or del13q = 2
- The following laboratory values obtained 14 days prior to registration.
- Calculated creatinine clearance (using Cockcroft-Gault equation below)* ≥ 30 mL/min
- Absolute neutrophil count (ANC) ≥ 1000/mm3 (without the use of growth factors)
- Platelet count ≥ 75000/mm3
- Hemoglobin ≥8.0 g/dL
- Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
- alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x ULN
- left ventricular ejection fraction (LVEF) ≥ 40%
- LVEF ≥ 40%
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 (Appendix VII)
- Previously untreated.
- Provide informed written consent.
- Negative pregnancy test done ≤14 days prior to cycle 1 day 1, for women of childbearing potential only.
- All study participants must be registered into the mandatory Revlimid Risk Evaluation and Mitigation Strategy (REMS®) program and be willing and able to comply with the requirements of the REMS® program.
- Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.
- Willing to follow strict birth control measures as outlined in the protocol.
Female subjects: If they are of childbearing potential, agree to one of the following:
- Practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of trial drug, AND must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
- Agree to 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: even if surgically sterilized (i.e., status post-vasectomy), must agree to one of the following:
- Agree to practice effective barrier contraception during the entire trial treatment period and through 90 days after the last dose of trial drug, OR
- Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
- Agree to 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).
- Willing to return to enrolling institution for follow-up during the Active Treatment Phase of the trial.
- Male subjects must agree not to donate sperm for at least 90 days after the last dose of study treatment.
- Willing to provide samples for planned research
- Life expectancy > 6 months
- Able to take aspirin (325 mg) daily as prophylactic anticoagulation. Subjects intolerant to aspirin may use warfarin or low dose molecular weight heparin, novel oral anticoagulants, or low dose molecular weight heparin
Exclusion Criteria:
- monoclonal gammopathy of undetermined significance (MGUS), standard risk smoldering myeloma, active myeloma by current IMWG definition, light chain amyloidosis with organ involvement or patients with extramedullary disease.
- Diagnosed or treated for another malignancy ≤ 2 years before trial enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. NOTE: Subjects with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
- If any of the following exist at screening, subject will not be eligible for trial because this trial involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:
- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception (per protocol)
- Other co-morbidity which would interfere with subject's ability to participate in trial, e.g. uncontrolled infection, uncompensated heart or lung disease.
- Other concurrent chemotherapy, or any ancillary therapy considered investigational. NOTE: Bisphosphonates are considered to be supportive care rather than therapy, and are thus allowed while on protocol treatment.
- Peripheral neuropathy ≥ Grade 3 on clinical examination or grade 2 with pain within 30 days prior to C1D1.
- Major surgery ≤14 days prior to C1D1.
- Evidence of current uncontrolled cardiovascular conditions, including hypertension, cardiac arrhythmias, congestive heart failure, unstable angina, or myocardial infarction within the past 6 months. Note: Prior to trial entry, any ECG abnormality at screening must be documented by the investigator as not medically relevant.
- New York Heart Association (NYHA) II, III, IV heart failure
- Known human immunodeficiency virus (HIV) positive.
- Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie., subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are PCR positive will be excluded. EXCEPTION: subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.
- Known or suspected active hepatitis C infection.
- Any medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
- Prior radiation therapy for bony lesions or plasmacytomas
- Known allergies, hypersensitivity, or intolerance to corticosteroids, monoclonal antibodies or human proteins, or their excipients (refer to respective package inserts or Investigator's Brochure), or known sensitivity to mammalian-derived products. Known allergies, hypersensitivity, or intolerance to trial drugs.
- Inability to comply with protocol/procedures.

CONTACTS AND LOCATIONS

Contacts

Contact:
Contact:

Locations

United States, Florida	Moffitt Cancer Center	Tampa
United States, Illinois	University of Chicago Medical Center	Chicago
United States, Indiana	Indiana University Simon Cancer Center	Indianapolis
United States, Kansas	University of Kansas Cancer Center	Westwood
United States, Maryland	University of Maryland Medical Center	Baltimore
United States, Minnesota	Mayo Clinic	Rochester
United States, New York	Weill Cornell Medicine	New York
United States, North Carolina	Levine Cancer Institute	Charlotte
United States, Washington	Swedish Cancer Institute	Seattle
United States, Wisconsin	Medical College of Wisconsin	Milwaukee

Sponsors and Collaborators

International Myeloma Foundation

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Investigator

Principal Investigator :	Shaji Kumar, MD	Mayo Clinic
Principal Investigator :	Brian Durie, MD	International Myeloma Foundation

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MORE INFORMATION

Responsible Party :	International Myeloma Foundation
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Individual Participant Data (IPD) Sharing Statement:	
Plan to Share IPD:	Undecided
Studies a U.S. FDA-regulated Drug Product:	Yes
Studies a U.S. FDA-regulated Device Product:	No
Product Manufactured in and Exported from the U.S.:	Yes
Keywords provided by International Myeloma Foundation:	*myeloma* *MRD smoldering*
Additional relevant MeSH terms :	*Multiple Myeloma* *Smoldering Multiple Myeloma* *Neoplasms, Plasma Cell*