A Study of Oral Ixazomib Maintenance Therapy in Patients With Newly Diagnosed Multiple Myeloma Not Treated With Stem Cell Transplantation

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

Verified September 2016 by Takeda

Sponsor:
Millennium Pharmaceuticals, Inc.

Information provided by (Responsible Party):
Takeda (Millennium Pharmaceuticals, Inc.)

ClinicalTrials.gov Identifier:
NCT02312258

First received: December 5, 2014
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History of Changes

Purpose

The purpose of this study is to determine the effect of ixazomib maintenance therapy on progression free survival (PFS) compared with placebo, in participants with newly diagnosed multiple myeloma (NDMM) who have had a major response (complete response [CR], very good partial response [VGPR], or partial response [PR]) to initial therapy and who have not undergone stem-cell transplantation (SCT).

Condition	Intervention	Phase
Multiple Myeloma	Drug: Ixazomib Drug: Placebo	Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Primary Purpose: Treatment

Official Title: A Phase 3, Randomized, Placebo-Controlled, Double-Blind Study of Oral Ixazomib Maintenance Therapy After Initial Therapy in Patients With Newly Diagnosed Multiple Myeloma Not Treated With Stem Cell Transplantation

Resource links provided by NLM:

Genetics Home Reference related topics: multiple myeloma

MedlinePlus related topics: Multiple Myeloma

Drug Information available for: Ixazomib Ixazomib citrate

Genetic and Rare Diseases Information Center resources: Multiple Myeloma

U.S. FDA Resources

Further study details as provided by Takeda:

Primary Outcome Measures:

- Progression Free Survival (PFS) [Time Frame: Every 28 days up to 24 months and every 4 weeks during follow-up until progressive disease on next line therapy (Up to 88 months)] [Designated as safety issue: No]

  PFS is defined as the time from the date of randomization to the date of first documentation of disease progression, as evaluated by an independent review committee according to International Myeloma Working Group (IMWG) criteria, or death due to any cause, whichever occurs first.

Secondary Outcome Measures:

- Overall Survival (OS) [Time Frame: Every 28 days from the Randomization date to progressive disease on next line therapy and every 12 weeks during follow up afterwards (Up to 88 months)] [Designated as safety issue: No]

  OS will be measured as the time from the date of randomization to the date of death.

- Percentage of Participants who Achieve or Maintain Any Best Response Category during the Treatment Period [Time Frame: Up to 24 months] [Designated as safety issue: No]

  Response will be assessed according to IMWG criteria. Best response includes partial response (PR), very good partial response (VGPR) and complete response (CR).

- Time to Progression (TTP) [Time Frame: From the date randomization to the date of first documented progressive disease (Up to 88 months)] [Designated as safety issue: No]

  TTP is defined as the time from the date of randomization to the date of first documentation of progressive disease, using IMWG criteria.

- Second Progression-Free Survival (PFS2) [Time Frame: Every 12 weeks from the randomization to 2nd disease progression or death (Up to 88 months)] [Designated as safety issue: No]

  PFS2 is defined as the time from the date of randomization to objective disease progression on next-line treatment using IMWG criteria, or death due to any cause, whichever occurs first.

- Time to End of the Next Line of Therapy after Study Treatment [Time Frame: From the randomization to the date of last dose of the next line of therapy (Up to 88 months)] [Designated as safety issue: No]

  Time to end of the next line of therapy is defined as the time from the date of randomization to the date of last dose of the next line of antineoplastic therapy following study treatment or death due to any cause, whichever occurs first.

- Percentage of Participants Who Develop A New Primary Malignancy [Time Frame: From the randomization date till death or termination of the study (Up to 88 months)] [Designated as safety issue: No]
- Percentage of Participants with Conversion from Minimal Residual Disease (MRD) Positive to MRD Negative, or the Maintenance of MRD Negativity [Time Frame: Screening, Cycle 13 (± 2 cycles), and Cycle 26 (± 2 cycles)] [Designated as safety issue: No]

  Bone marrow aspirates and blood samples will be sent to a central laboratory and will be assessed for MRD using flow cytometry and a sequencing methodology. MRD negativity is defined as absence of MRD and MRD positivity is defined as presence of MRD.

- Overall (OS) Survival in a High-Risk Population [Time Frame: From randomization up to 88 months] [Designated as safety issue: No]

  High-risk population will include but not be limited to participants carrying deletion (del)17, t(4:14), t(14:16), amplification (ampl) 1q, del13, or del1p. OS will be measured as the time from the date of randomization to the date of death.

- Progression Free Survival (PFS) in a High-Risk Population [Time Frame: Screening, Day 1 of each cycle; End of Treatment and then every 4 weeks until disease progression (Up to 88 months)] [Designated as safety issue: No]

  High-risk population will include but not be limited to participants carrying deletion (del)17, t(4:14), t(14:16), amplification (ampl) 1q, del13, or del1p. PFS is defined as the time from the date of randomization to the date of first documentation of disease progression.

- Percentage of Participants with Serious Adverse Events and Adverse Events (AEs) [Time Frame: First dose of study drug through 30 days after last dose of study drug (Up to 25 months)] [Designated as safety issue: No]

  A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution that: results in death, is life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect or is medically significant. Adverse events are defined as any unfavorable and unintended sign, symptom or disease temporally associated with the use of a medicinal product reported from first dose of study drug through 30 days after the last dose of study drug.

- Change from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC) QLQ-C30 [Time Frame: Baseline and every 28 days (Up to 24 months)] [Designated as safety issue: No]

  The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC) QLQ-C30 is completed by the patient. The EORTC QLQ-30 contains 30 questions that incorporate 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The patient answers questions about their health during the past week. There are 28 questions answered on a 4-point scale where 1=Not at all (best) to 4=Very Much (worst) and 2 questions answered on a 7-point scale where 1=Very poor (worst) to 7= Excellent (best).

- Number of Participants with Any Markedly Abnormal Standard Safety Laboratory Values [Time Frame: From First dose date of study drug through 30 days after the last dose of study drug (Up to 25 months)] [Designated as safety issue: Yes]

  Clinical laboratory evaluations will be performed by a central laboratory. The number of participants with any markedly abnormal standard safety laboratory values collected throughout study.

- Correlation between Frailty Status and Progression Free Survival (PFS) and Overall Survival (OS) [Time Frame: Up to 88 months] [Designated as safety issue: No]

- Pharmacokinetic Parameter: Plasma Concentration of Ixazomib [Time Frame: Cycle 1 (1 and 4 hours post-dose Day 1, Days 8 and 15 pre-dose); Cycle 2 and 5 (Days 1 and 8 pre-dose) and Cycles 3,4,6-10 (Day 1 pre-dose)] [Designated as safety issue: No]

  Plasma concentrations of the complete hydrolysis product of ixazomib citrate (ixazomib) will be measured using a validated Liquid Chromatography-tandem Mass Spectrometry (LC/MS/MS) assay.

- Time to Resolution of Peripheral Neuropathy (PN) Events [Time Frame: From randomization date through 30 days after the last dose of drug (Up to 25 Months)] [Designated as safety issue: No]

  Peripheral neuropathy (PN) is defined as the treatment-emergent adverse event in the high-level term of peripheral neuropathies not elsewhere classified (NEC) according to the Medical Dictionary for Regulatory Activities (MedDRA). A PN event is considered as resolved if its final outcome is resolved with no subsequent PN event of the same preferred term occurring on the resolution date or the day before and after. Time to resolution is defined as the time from the initial onset date (inclusive) to the resolution date for resolved events.

- Time to Improvement of Peripheral Neuropathy (PN) Events [Time Frame: From randomization date through 30 days after the last dose of drug (Up to 25 Months)] [Designated as safety issue: No]

  Peripheral neuropathy (PN) is defined as the treatment-emergent adverse event in the high-level term of peripheral neuropathies not elsewhere classified (NEC) according to the Medical Dictionary for Regulatory Activities (MedDRA). A PN event is considered as resolved if its final outcome is resolved with no subsequent PN event of the same preferred term occurring on the improvement date or the day before and after. Time to improvement is defined as the time from the initial onset date (inclusive) to the improvement of event.

Estimated Enrollment:	761
Study Start Date:	April 2015
Estimated Study Completion Date:	July 2019
Estimated Primary Completion Date:	December 2018 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: Ixazomib Ixazomib 3 mg, capsule, orally, once, on Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 4. Ixazomib 3 or 4 mg, capsules, orally, once, on Days 1, 8 and 15 in a 28-day cycle for Cycles 5 through 26. Participants experiencing adverse events (AEs) attributed to study drug during any cycle may continue in the study but may have doses of study drug held or reduced by at least 1 dose level. Reduced doses are: 3 mg, 2.3 mg, 1.5 mg and discontinuation of study drug.	Drug: Ixazomib Ixazomib capsules
Placebo Comparator: Placebo Ixazomib placebo-matching 3 mg capsule, orally, once on Days 1, 8 and 15 in a 28-day cycle for Cycles 1 through 4. Ixazomib placebo-matching 3 or 4 mg capsules, orally, once on Days 1, 8 and 15 in a 28-day cycle for Cycles 5 through 26. Participants experiencing adverse events (AEs) attributed to study drug during any cycle may continue in the study, but may have doses of study drug held or reduced by at least 1 dose level. Reduced doses are: 3 mg, 2.3 mg, 1.5 mg and discontinuation of study drug.	Drug: Placebo Ixazomib placebo-matching capsules

Detailed Description:

The drug being tested in this study is called ixazomib citrate. Ixazomib citrate is being tested to slow disease progression and improve overall survival in people who have newly diagnosed multiple myeloma (NDMM) who have had a major positive response to initial therapy and have not undergone stem cell transplantation (SCT). This study will look at the effect of ixazomib citrate has on the length of time that participants are free of disease progression and their overall survival.

The study will enroll approximately 761 patients. Participants will be randomly assigned (by chance, like flipping a coin) to one of the two treatment groups—which will remain undisclosed to the patient and study doctor during the study (unless there is an urgent medical need):

- Ixazomib citrate 3 mg
- Placebo (dummy inactive pill) - this is a capsule that looks like the study drug but has no active ingredient

All participants will be asked to take one capsule on Days 1, 8 and 15 of each 28-day cycle, for up to 26 cycles.

This multi-center trial will be conducted worldwide. The overall time to participate in this study is up to 24 months. Participants will make 28 visits to the clinic during the treatment period and will continue to make follow-up visits every 4 weeks until the next line of therapy begins. Participants will also be contacted by telephone every 12 weeks after last treatment visit for a follow-up assessment.

Eligibility

Ages Eligible for Study:	18 Years and older (Adult, Senior)
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

1. Adult male or female participants 18 years or older with a confirmed diagnosis of symptomatic newly diagnosed multiple myeloma (NDMM) according to standard criteria.

2. Completed 6 to 12 months (± 2 weeks) of initial therapy, during which the participant was treated to best response, defined as the best response maintained for 2 cycles after the M-protein nadir is reached.
3. Documented major response [partial response (PR), very good partial response (VGPR), complete response (CR)] according to the International Myeloma Working Group (IMWG) uniform response criteria, version 2011, after this initial therapy.
4. Female participants who:
    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR
    - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 90 days after the last dose of study drug, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the participant. (Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

    Male participants, even if surgically sterilized (ie, status postvasectomy), who:
    - Agree to practice effective barrier contraception during the entire study Treatment period and through 90 days after the last dose of study drug, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the participant. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal are not acceptable methods of contraception.)
5. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the participant at any time without prejudice to future medical care.
6. Complete documentation of the details of the initial therapy before randomization including cytogenetics and International Staging System (ISS) is available.
7. Eastern Cooperative Oncology Group Performance Status of 0 to 2.
8. Suitable venous access for the study-required blood sampling and consent for the specific amounts that will be taken.
9. Is willing and able to adhere to the study visit schedule and other protocol requirements including blood sampling and bone marrow aspiration.
10. Must meet the following clinical laboratory criteria at study entry:
    - Absolute neutrophil count (ANC) ≥ 1,000/mm^3 without growth factor support and platelet count ≥ 75,000/mm^3. Platelet transfusions to help participants meet eligibility criteria are not allowed within 3 days before randomization.
    - Total bilirubin ≤ 1.5 x the upper limit of the normal range (ULN).
    - Alanine aminotransferase and aspartate aminotransferase ≤ 3 x ULN.
    - Calculated creatinine clearance ≥ 30 mL/min (using the Cockcroft-Gault equation).

Exclusion Criteria:

1. Multiple myeloma that has relapsed after, or was not responsive to, initial therapy.
2. Prior stem-cell transplantation (SCT).
3. Radiotherapy within 14 days before randomization.
4. Diagnosed or treated for another malignancy within 5 years before randomization or previous diagnosis with another malignancy. Participants with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
5. Female participants who are lactating and breastfeeding or have a positive serum pregnancy test during the Screening period.
6. Major surgery within 14 days before randomization.
7. Central nervous system involvement.
8. Infection requiring intravenous (IV) antibiotic therapy or other serious infection within 14 days before randomization.
9. Diagnosis of Waldenstrom's macroglobulinemia, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome, plasma cell leukemia, primary amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome.
10. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, uncontrolled congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.
11. Systemic treatment with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole), or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital) or use of Ginkgo biloba or St. John's wort within 14 days before randomization.
12. Ongoing or active infection, known human immunodeficiency virus positive, active hepatitis B or C infection.
13. Comorbid systemic illnesses or other severe concurrent disease that, in the judgment of the investigator, would make the participant inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens (eg, peripheral neuropathy (PN) that is Grade 1 with pain or Grade 2 or higher of any cause).
14. Psychiatric illness/social situation that would limit compliance with study requirements.
15. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.
16. Inability to swallow oral medication, inability or unwillingness to comply with the drug administration requirements, or gastrointestinal (GI) procedure that could interfere with the oral absorption or tolerance of treatment.
17. Treatment with any investigational products within 30 days before randomization.

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: NCT02312258

Contacts

Contact: Takeda Study Registration Call Center +1-877-825-3327 medicalinformation@tpna.com

Show 183 Study Locations

Sponsors and Collaborators

Millennium Pharmaceuticals, Inc.

Investigators

Study Director: Medical Director Clinical Science Millennium Pharmaceuticals, Inc.

More Information

Responsible Party:	Millennium Pharmaceuticals, Inc.
ClinicalTrials.gov Identifier:	NCT02312258 History of Changes
Other Study ID Numbers:	**C16021** U1111-1160-1702 2014-001394-13 REec-2015-1414 JapicCTI-152873 153300410A0048 1046003327 SNCTP000001745
Study First Received:	December 5, 2014
Last Updated:	September 30, 2016
Health Authority:	United States: Food and Drug Administration Argentina: Administración Nacional de Medicamentos, Alimentos y Tecnología Méica (ANMAT) Australia: Department of Health and Ageing Therapeutic Goods Administration Austria: Austria: Agency for Health and Food Safety Belgium: Federal Agency for Medicinal Products and Health Products Brazil: Agencia Nacional de Vigilancia Sanitaria (ANVISA) ANVISA Canada: Health Canada Chile: Instituto de Salud Pública de Chile China: Food and Drug Administration Colombia: INVIMA Instituto Nacional de Vigilancia de Medicamentos y Alimentos Croatia: Agency for Medicinal Products and Medical Devices Czech Republic: State Institute for Drug Control Denmark: Danish Health and Medicines Authority France: Agence Nationale de Sécurité du Médicament et des produits de santé Germany: Federal Institute for Drugs and Medical Devices; Paul-Ehrlich-Institut Greece: National Organization of Medicines Hungary: National Institute of Pharmacy Israel: Ministry of Health Italy: The Italian Medicines Agency Japan: Pharmaceuticals and Medical Devices Agency Korea: Food and Drug Administration Mexico: Comisión Federal para la Protección contra riesgos sanitarios, COFEPRIS Portugal: INFARMED, National Authority of Medicines and Health Products, IP Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products Russia: Ministry of Health of the Russian Federation Serbia: Medicines and Medical Devices Agency Singapore: Health Sciences Authority South Africa: South African Health Products Regulatory Authority (SAHPRA) Spain: Spanish Agency of Medicines and Health Products Sweden: Medical Products Agency Switzerland: Swissmedic Taiwan: Ministry of Health and Welfare Thailand: Food and Drug Administration Turkey: Ministry of Health United Kingdom: Medicines and Healthcare Products Regulatory Agency

Keywords provided by Takeda:
Ixazomib
Newly diagnosed

Additional relevant MeSH terms:

Multiple Myeloma	Immunoproliferative Disorders
Neoplasms, Plasma Cell	Immune System Diseases
Neoplasms by Histologic Type	Ixazomib

Neoplasms
Hemostatic Disorders
Vascular Diseases
Cardiovascular Diseases
Paraproteinemias
Blood Protein Disorders
Hematologic Diseases
Hemorrhagic Disorders
Lymphoproliferative Disorders

Glycine
Antineoplastic Agents
Protease Inhibitors
Enzyme Inhibitors
Molecular Mechanisms of Pharmacological Action
Glycine Agents
Neurotransmitter Agents
Physiological Effects of Drugs

ClinicalTrials.gov processed this record on November 22, 2016