PROTOCOL

A Phase 2, Open-Label Study of Ixazomib+Daratumumab+Dexamethasone (IDd) in Relapsed and/or Refractory Multiple Myeloma (RRMM)

Sponsor:	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "Sponsor," or "Takeda".
Study Number:	C16047
Compound:	Ixazomib (NINLARO)
Date:	30 November 2017

7.0 STUDY POPULATION

7.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

- Adult patients (aged ≥18 years) who have been diagnosed with MM according to IMWG criteria [1-3].
- All patients must have measurable disease by at least 1 of the following measurements:
  - Serum M-protein ≥1 g/dL (≥10 g/L).
  - Urine M-protein ≥200 mg/24 hours.
- All patients must have documented evidence of PD on or after their last regimen as defined by IMWG criteria (see Appendix E) [1-3]. All patients must have received between 1 to 3 prior therapies for MM (a prior therapy is defined as 2 or more cycles of therapy given as a treatment plan for MM [eg, a single-agent or combination therapy or a sequence of planned treatments such as induction therapy followed by autologous SCT and then consolidation and/or maintenance therapy]).
- All patients must have achieved a response (PR or better) to at least 1 prior therapy.
- All patients must have an Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2.
- All patients must meet the following laboratory criteria:
  - Absolute neutrophil count (ANC) ≥1000/mm^3.
  - Platelet count ≥75,000/mm^3.
  - Total bilirubin ≤1.5 x the upper limit of the normal range (ULN) (except for Gilbert syndrome: direct bilirubin ≤2 x ULN).
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x ULN.
  - Calculated creatinine clearance ≥50 mL/min.
- Female patients 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 use effective contraceptive measures during and for 90 days following treatment. Advise women using hormonal contraceptives to also use a barrier method of contraception (see Appendix H for details).
- Male patients, even if surgically sterilized (ie, status postvasectomy), who:
  - Agree to use effective contraceptive measures during and for 90 days following treatment (see Appendix H for details).

- 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 patient at any time without prejudice to future medical care.
- Patient is willing and able to adhere to the study visit schedule and other protocol requirements.

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

- Patients have undergone prior allogenic bone marrow transplantation.
- Patients have received prior ixazomib at any time or daratumumab or other anti-CD38 therapies, except as part of initial therapy if this was stopped to move on to SCT and the patient did not progress on anti-CD38 treatment.
- Patients are refractory to bortezomib or carfilzomib at the last exposure before this study (defined as patient having PD while receiving bortezomib or carfilzomib therapy or within 60 days after ending bortezomib or carfilzomib therapy).
- Patients planning to undergo SCT prior to PD on this study (ie, these patients should not be enrolled in order to reduce disease burden prior to transplant).
- Patients receiving systemic treatment with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital, St. John's wort) within 14 days before randomization.
- Patient has received autologous SCT within 12 weeks before the date of study treatment.
- Patient has received an investigational drug (including investigational vaccines) within 4 weeks before study treatment (except for investigational antimyeloma agents, which cannot be taken within 2 weeks prior or 5 PK half-lives of the treatment, whichever is longer, before the date of study treatment). The only exception is emergency use of a short course of corticosteroids (equivalent of dexamethasone 40 mg/day for a maximum 4 days) before treatment.
- Patients with known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal. Note: FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 is <50% of predicted normal.
  - Patients with Grade 2 or higher residual toxicities from prior therapy (including Grade 2 or higher peripheral neuropathy or any grade neuropathy with pain; excluding alopecia). This includes recovery from any major surgery. Note: Subjects with planned surgical procedures to be conducted under local anesthesia may participate. Kyphoplasty or vertebroplasty are not considered major surgery.

- Patients with known allergy to any of the study medications, their analogues, their excipients, mAbs or human proteins or known sensitivity to mammalian-derived products.
- Patient has uncontrolled clinically significant cardiac disease, including myocardial infarction within 6 months before date of study entry or unstable or uncontrolled angina, congestive heart failure, New York Heart Association (NYHA) Class III-IV, uncontrolled cardiac arrhythmia (Grade 2 or higher).
- Patients with ongoing or active systemic infection requiring IV medical management, known HIV-RNA positive, known hepatitis B surface antigen seropositive, or known hepatitis C virus-RNA positive. Note: Patients who have positive hepatitis B core antibody can be enrolled but must have hepatitis B virus-DNA negative. Patients who have positive hepatitis C antibody can be enrolled but must have hepatitis C virus-RNA negative.
- Patient has any concurrent medical condition or disease that is likely to interfere with study procedures, results, or assessment of safety or toxicity or that in the opinion of the investigator would constitute a hazard for participating in this study.
- Patients diagnosed or treated for another malignancy within 2 years before randomization or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.