A phase I/II study of twice-weekly ixazomib plus pomalidomide and dexamethasone in relapsed and refractory multiple myeloma

Omar Nadeem,[1] Robert A. Redd,[2] Peter M. Barth,[3] Trevor J. Bayliss,[4] Jacob P. Laubach,[1] Giada Bianchi,[1] Clifton C. Mo,[1] John L. Reagan,[3] Shonali Midha,[1] Adam S. Sperling,[1] Yuxin Liu,[1] Monique A. Hartley-Brown,[1] Madison P. Chuma,[1] Taylor Nicholson,[1] Emily J. Benjamin,[1] Alexandra Distaso,[1] Eileen Regan,[1] Ann Marie Van Hof,[1] Adam J. Dahill,[1] Rachel Goldbaum,[1] Keemia Mohammadi,[1] Audrey Lewis,[1] Raja Poda,[1] Nikhil C. Munshi,[1] Kenneth C. Anderson,[1] Irene M. Ghobrial[1] and Paul G. Richardson[1]

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [2]Department of Data Science, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [3]Department of Medicine, Alpert Medical School of Brown University, Providence, RI and [4]Berkshire Health Services, Pittsfield, MA, USA

Correspondence: O. Nadeem
omar_nadeem@dfci.harvard.edu

Received: March 13, 2026.
Accepted: May 15, 2026.
Early view: May 28, 2026.

https://doi.org/10.3324/haematol.2026.300897

©2026 Ferrata Storti Foundation
Published under a CC BY-NC license

Supplementary Information

Supplementary Methods

Additional eligibility criteria

Patients required adequate hematologic (absolute neutrophil count ≥1 x 10^9/L; platelets ≥75 x 10^9/L, without transfusion requirement within 14 days prior to therapy; hemoglobin ≥8.0 g/dL), hepatic (total bilirubin ≤1.5 x upper limit of normal [ULN], or <3.0 x ULN if patient had Gilbert Syndrome; alanine aminotransferase and aspartate aminotransferase ≤1.5 x ULN), and renal (calculated creatinine clearance ≥45 mL/min) function and an Eastern Cooperative Oncology Group performance status of 0–2. Patients had to have been registered into and in compliance with the mandatory POMALYST REMS® program.

Patients were excluded if they: had prior ixazomib exposure; were pomalidomide-refractory; or had received IMiDs or PIs within 14 days, cytotoxic therapies for MM within 21 days, other investigational therapies and/or mAbs within 4 weeks, live vaccines within 30 days, prior peripheral stem cell transplant (SCT) within 12 weeks, or prior allogeneic SCT with active graft-versus-host disease prior to first dose of study treatment. Additional exclusion criteria included: known gastrointestinal disease or procedure that could interfere with oral absorption/tolerance of treatment; known central nervous system involvement; systemic treatment with strong CYP3A inhibitors or inducers or strong CYP1A2 inhibitors within 14 days; major surgery or radiotherapy within 14 days; any active or uncontrolled cardiovascular conditions; concurrent systemic amyloidosis or plasma cell leukemia, or POEMS syndrome; any serious infection within 14 days; or known seropositivity for HIV, hepatitis B, or hepatitis C.

Definition of dose-limiting toxicity (DLT)

DLTs were defined as: grade ≥3 non-hematologic toxicity not related to disease progression; thrombocytopenia of grade 4 (>1 occurrence, not attributable to underlying disease), grade 3 or ≥2 with bleeding; grade 4 neutropenia for >5 days and/or febrile neutropenia; any grade 5 events unless due to progressive disease (PD); inability to receive treatment on day 1 of cycle 2 due to possibly treatment-related toxicity.

Concomitant medications

Patients were required to receive prophylactic anti-thrombotic therapy. Additionally prophylactic anti-emetics prior to ixazomib, antimicrobial and antiviral (pneumocystis carinii pneumonia) prophylaxis, and prophylactic acyclovir or valacyclovir were recommended.

Objectives and Assessments

Secondary objectives were to assess duration of response (DOR), time to progression (TTP), PFS, and OS, and to determine the minimal residual disease (MRD)-negative response rate in patients achieving a complete response (CR).

Disease response and progression was assessed using the 2011/2016 IMWG criteria[1,2] on day 1 of each treatment cycle and at follow-up visits prior to PD. Bone marrow aspiration and biopsy was done at screening for cytogenetics assessment and subsequently as required to confirm CR and assess MRD status. MRD was to be evaluated using the clonoSEQ Assay (Adaptive Biotechnologies, Inc., Seattle, WA, USA) employing multiplex polymerase chain reaction and next-generation sequencing. MRD status was determined based on a sensitivity threshold of 10^{-5}. Extramedullary plasmacytomas were assessed at screening, as clinically indicated, and to confirm response or progression using a consistent method (computerized tomography, magnetic resonance imaging, or positron emission tomography).

AEs were assessed throughout treatment and until 30 days after last dose of study drug; serious AEs (SAEs) and possibly treatment-related AEs were followed until resolution or stabilization. If required due to AEs, protocol-specified ixazomib dose reductions were from 4.0 to 3.0 to 2.3 mg, twice-weekly, and then to 2.3 mg once-weekly, pomalidomide dose reductions were from 4 to 3 to 2 to 1 mg, and dexamethasone dose reductions were from 12 to 8 to 4 mg for patients aged <75 years and from 8 to 4 mg and then to 4 mg on the day of ixazomib dosing only.

Toxicity and accrual data were monitored and reviewed up to four times a year by the Dana-Farber/Harvard Cancer Center Data and Safety Monitoring Committee.

Statistical analysis

The safety analysis set comprised all patients who received at least one dose of any study drug and was used for evaluation of exposure, outcomes, and safety. The DLT analysis set comprised all patients in phase I who completed cycle 1 or discontinued during cycle 1 due to a DLT. The efficacy analysis set for the evaluation of the primary efficacy endpoint, ORR, comprised all patients who receive at least one cycle, had a baseline disease assessment, and had at least 1 post-baseline disease assessment (≥28 days after first dose). Response rates are reported as proportions with 95% exact binomial confidence intervals (CIs).

DOR (time from response to disease progression or death), TTP (time from first dose to disease progression), PFS (time from first dose to disease progression or death, and OS

(time from first dose to death) were estimated using Kaplan–Meier methodology, with patients who had not progressed or died censored at the date last known to be progression-free or alive (according to endpoint); 95% CIs for medians and landmark rates were calculated using Greenwood's method to estimate variance. Median follow-up was calculated using the reverse Kaplan–Meier method. Statistical analyses were performed using R version 4.4.2 (October 31, 2024).

Supplementary references

1. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117(18):4691-4695.
2. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016;17(8):e328-e346.