Safety and Efficacy of Combination Maintenance Therapy with Ixazomib and Lenalidomide in Patients with Posttransplant Myeloma

Krina K. Patel[1], Jatin J. Shah[2], Lei Feng[1], Hans C. Lee[1], Elisabet M. Manasanch[1], Jasper Olsem[1], Ashley Morphey[1], Xiao Jiao Huo[1], Sheeba K. Thomas[1], Qaiser Bashir[3], Muzaffar H. Qazilbash[3], Donna M. Weber[1], and Robert Z. Orlowski[1,4]

ABSTRACT

Purpose: In this study, the addition of ixazomib to lenalidomide maintenance post-autologous stem cell transplant (ASCT) in 64 patients with newly diagnosed multiple myeloma was evaluated on the basis of the observed benefit of lenalidomide-only maintenance in prior studies.

Patients and Methods: Patients were started on maintenance therapy with lenalidomide and ixazomib within 60–180 days of stem cell infusion.

Results: Response rates deepened over time from baseline post-ASCT for 39 patients. The complete response (CR)/stringent CR rate was 43% and median overall survival was not reached with a median follow-up of 62 months (range, 25–82 months). Median PFS (mPFS) for all patients was 73 months and has not been reached for those with International Staging System (ISS) stage 1 disease. mPFS in 9 patients who had ISS stage 3 disease and 14 patients who had high-risk cytogenetics was 34 and 25 months, respectively. Twenty-two patients had progressive disease, while 19 patients continue to receive dual maintenance. The most common grade 3/4 adverse events included neutropenia, leukopenia, thrombocytopenia, lung infections, diarrhea, and maculopapular rash. Second primary malignancies occurred in 9 patients. Toxicity led to dose reductions in ixazomib and lenalidomide in 20 and 31 patients, respectively. Discontinuation of ixazomib due to toxicity occurred in 4 patients. Grade 1/2 neuropathy occurred in 22 patients and led to reduction or discontinuation of ixazomib in 2 patients.

Conclusions: The addition of ixazomib to lenalidomide maintenance demonstrated a better than expected PFS compared with historical data using lenalidomide alone and was safe and tolerable.

Introduction

Multiple myeloma is a hematologic malignancy characterized by the accumulation of plasma cells in the bone marrow, which may be further complicated by organ dysfunction, including hypercalcemia, renal insufficiency, anemia, and bone destruction (1). An estimated 34,920 new cases and 12,410 deaths are projected for 2021 (2). Currently, induction treatment with a triplet regimen such as lenalidomide-bortezomib-dexamethasone, followed by autologous stem cell transplant (ASCT) and maintenance therapy is recommended for newly diagnosed multiple myeloma (NDMM) and offers improved progression-free survival (PFS) and quality of life (3, 4). While this treatment regimen is non-curative for most patients, response rates and survival have increased remarkably in the past decade with this approach. Induction followed by maintenance therapy is also recommended for transplant-ineligible patients with multiple myeloma (4, 5).

Maintenance therapy after ASCT has improved patient outcomes because many patients progress within 2–3 years after a single ASCT without maintenance. Lenalidomide, an immunomodulatory agent, is the preferred and currently recommended maintenance therapy for patients with myeloma who have undergone ASCT and for those who are transplant ineligible (4). Patients with NDMM who were transplant-ineligible demonstrated improved PFS with lenalidomide maintenance after induction with melphalan-prednisone-lenalidomide, with the greatest benefit observed in patients between 65 and 75 years of age (6). Lenalidomide maintenance therapy has also demonstrated improved PFS when compared with observation in transplant-eligible patients after induction and ASCT, in transplant-ineligible patients and patients with high-risk cytogenetic factors (7–11). Lenalidomide maintenance therapy is associated with toxicities including febrile neutropenia, thrombocytopenia, pancytopenia, and diarrhea; the incidence of second primary malignancies (SPM) was relatively increased in the lenalidomide maintenance cohorts (7, 9, 11, 12). Nonetheless, the significant clinical benefit with improved PFS and, in some studies, overall survival (OS) has established lenalidomide as the frontrunner in maintenance therapy. For patients who are not eligible for lenalidomide maintenance therapy, other recommended therapies are available (4).

Proteasome inhibition has been evaluated in multiple myeloma, and bortezomib is recommended as maintenance therapy in posttransplant and transplant-ineligible patients. Bortezomib, when used as part of the induction regimen, followed by ASCT and maintenance with bortezomib, demonstrated improved PFS and OS with increased

[1]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston Texas. [2]Karyopharm Therapeutics, Newton, Massachusetts. [3]Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston Texas. [4]Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston Texas.

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Corresponding Author: Krina K. Patel, Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston TX 77030. Phone: 713-792-6662; Fax: 713-792-1897; E-mail: kpatel1@mdanderson.org

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Translational Relevance

The current recommended treatment for newly diagnosed multiple myeloma involves induction treatment with a triplet or quadruplet regimen such as lenalidomide-bortezomib-dexamethasone, followed by autologous stem cell transplant (ASCT) and maintenance therapy. While this approach offers improved progression-free survival (PFS) and quality of life, it is noncurative for most patients. Currently, maintenance therapy with lenalidomide post ASCT is recommended, as this has been observed to improve outcomes after ASCT. In this study, we evaluated the combination of lenalidomide and ixazomib as an all oral maintenance therapy to determine whether it would further improve clinical response in patients with myeloma after ASCT, without significantly increasing toxicity. Our results demonstrate a better than expected PFS and suggest that patients with myeloma may benefit further with combination maintenance therapy.

complete response (CR) rates when compared with induction or maintenance regimens without bortezomib (13). In addition, bortezomib maintenance therapy following induction with bortezomib-containing regimens in transplant-ineligible patients resulted in good outcomes (14). At the time the current study began enrolling patients, preclinical studies had demonstrated activity of ixazomib in cell culture and xenograft models, and several clinical trials were in the process of evaluating ixazomib in multiple myeloma (15, 16). Subsequently, ixazomib was evaluated as maintenance therapy after ASCT and demonstrated a decrease in the risk of disease progression without increasing the incidence of second malignancies (17). Ixazomib also demonstrated favorable outcomes when used as part of induction and maintenance regimens in transplant-ineligible patients with myeloma (18). A study comparing lenalidomide versus bortezomib as maintenance therapies post-ASCT supports using lenalidomide as a preferred maintenance regimen, with bortezomib being an alternative maintenance regimen (19).

The combination of proteasome inhibitors and immunomodulatory agents as part of the induction regimen in the treatment of patients with myeloma has produced strong clinical responses. Current recommendations include using this combination for frontline therapy in multiple myeloma (4). We hypothesized that a maintenance regimen comprised of lenalidomide and ixazomib was likely to provide additional clinical benefit in patients with myeloma post-ASCT without any new safety signals based on the observed clinical benefit of lenalidomide-only maintenance therapy and preclinical studies of ixazomib (7, 11, 15, 16). Subsequently, other studies demonstrated that the combination of lenalidomide and ixazomib as part of an induction regimen (20) and each of these agents administered individually as maintenance therapy post-ASCT were beneficial in multiple myeloma (8–10, 17). The addition of ixazomib to lenalidomide and dexamethasone demonstrated an improved PFS in patients with refractory and/or relapsed myeloma when compared with lenalidomide and dexamethasone plus placebo (21). A significant advantage that the combination of lenalidomide and ixazomib offers is that both agents are oral therapies, which are more conveniently administered and are preferred by many patients (22). New treatment strategies, including maintenance therapy, provide an important opportunity to improve survival in patients with myeloma.

Patients and Methods

The goal of this study was to establish the safety and efficacy of lenalidomide and ixazomib in the maintenance setting after ASCT with PFS as the primary endpoint. Secondary objectives included evaluation of best response rates, time to progression, time to next therapy, tolerability and toxicity, and incidence of SPMs.

Patients

Patients were eligible to enroll in this study if they were newly diagnosed with multiple myeloma, had undergone ASCT with melphalan as a preparative regimen, and had not relapsed since ASCT. Patients were enrolled between 60–180 days after stem cell infusion. Eligibility criteria included Eastern Cooperative Oncology Group (ECOG) score 0–2, absolute neutrophil count >1,000/mm^3, platelets >100,000/mm^3, and creatinine <2.5 mg/dL. Patients whose primary therapy was changed because of suboptimal response or toxicity were eligible for this study; however, no more than two regimens should have been used before ASCT. Patients with the following conditions were excluded from the study: grade 2 or higher peripheral neuropathy; major surgery or radiotherapy within 14 days of starting on the study; central nervous system involvement; treatment with modulators of CYP1A2 and CYP3A enzyme activity; and cardiovascular complications or ongoing systemic infections. The study protocol was approved by the Institutional Review Board at The University of Texas MD Anderson Cancer Center (Houston, TX), and all study participants provided written informed consent before enrollment. The study was conducted in accordance with ethical principles defined by the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. This clinical trial is registered at ClinicalTrials.gov, registration ID: NCT01718743.

Study design and treatment

Each cycle was defined as 28 days with lenalidomide starting at 10 mg/day orally for 28 days with the option to increase the dose to 15 mg after three cycles based on the treating physician's discretion. Ixazomib was provided at 3 mg ($n = 48$ patients) or 4 mg ($n = 16$ patients) orally on days 1, 8, and 15 of each 28-day cycle. Further treatment was delayed if any observed toxicities considered to be associated with the study drugs did not resolve to a level that was acceptable based on the protocol criteria or the physician's discretion. Delays greater than 4 weeks resulted in dose reductions, whereas delays of 6 weeks or greater warranted withdrawal from the study.

Assessments

Response assessments were performed as per IMWG criteria every 1–3 cycles (23). Before each cycle, patients were evaluated for toxicity based on physical examination, ECOG performance status, clinical laboratory values, and the occurrence of any adverse events (AE). AEs were assessed for intensity or severity based on the NCI Common Terminology Criteria for Adverse Events, version 4.0. Bone marrow biopsies were performed at multiple timepoints for patients. For minimal residual disease (MRD) assessment, bone marrow biopsies were performed and evaluated using multi-color flow cytometry with 10^{-5} level of detection 4–6 years after maintenance therapy for patients who remained on the trial at the time, when this technology became available.

Statistical analysis

This was a single-arm, open-label, phase II trial where the primary endpoint of PFS was defined as the time from ASCT to the time of

clinical disease progression or death, whichever occurred first, and patients without disease progression or death were censored at the date of last contact. OS was calculated from ASCT date to the date of death or last contacted date if death did not occur. The duration of response was calculated from the date of best response after maintenance treatment to date of progression of disease or death, whichever occurred first, and patients with no disease progression or death were censored as of the last contact date. It was hypothesized that the combination would prolong the median PFS time by 12 months from 40 months for the current standard regimen. PFS was monitored using the method of Thall and colleagues (24), where we assumed that PFS time follows an exponential distribution. PFS was monitored every 6 months, and the study would have been terminated early if there was little evidence (< 3.5%) based on the available data that the median PFS time of the patients treated with the combination is 12 months or more than that of the standard regimen. The operating characteristics of this monitoring rule were obtained using the one-arm TTE software developed at the Department of Biostatistics at MDACC (Houston, TX). The monitoring was carried out via the Clinical Trial Conduct (CTC) website, housed on a secure server at MDACC (Houston, TX), and maintained by the MDACC Department of Biostatistics. Training on the use of the CTC was provided by the biostatistical collaborator of the study, with emphasis on the importance of timely updating of follow-up times and recoding of events.

Toxicity (defined as treatment-related unmanageable toxicities including grade 3 non-hematologic effects or grade 4 hematologic effects that required delay or termination of the treatment during cycle 1) was monitored by a cohort size of 4 using the Bayesian stopping boundaries calculated on the basis of beta-binomial distribution. Assuming the prior probability of toxicity followed a beta-binomial distribution (0.3, 0.7), the trial would have been stopped for toxicity if the posterior probability of the toxicity rate being greater than 30% was greater than 95%. The stopping boundaries were provided in the protocol (25).

Descriptive statistics, including mean, SD, median, and range for continuous variables such as age and frequency counts and percentages for categorical variables such as stage and response status are provided. Response rates were estimated with 95% confidence intervals (CI). Kaplan–Meier method was used to estimate the time-to-event endpoints, including PFS, OS, and duration of response, and log-rank test was performed to test the difference in time-to-event distributions between patient groups. Statistical software SAS 9.4 (SAS) and S-Plus 8.2 (TIBCO Software Inc.) were used for all the analyses.

Data availability statement

Deidentified patient data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Patients and treatments

A total of 64 patients were enrolled in this study between December 4, 2012, and May 13, 2015. Of these patients, 41 (64.06%) were 60 years of age or older and 42 (65.63%) were male. Fourteen patients had high-risk cytogenetic features [1q gain, Del17p, t(14:16), t(4:14)], 50 patients had standard cytogenetic risk features [t(11:14), t(6:14), hyperdiploidy, normal], and 9 patients had International Staging System (ISS) stage 3 disease. Patient demographics are summarized in **Table 1**. Induction regimens used before ASCT are summarized in Supplementary Table S1. Patients received a median of 37 cycles of maintenance therapy with a mean of 39 cycles.

Table 1. Patient demographics.

Age	Number	Percentage
<60 years	23	35.9%
≥60	41	64.1%
Sex	Number	Percentage
Female	22	34.4%
Male	42	65.6%
Response at baseline	Number	Percentage
CR	3	4.7%
VGPR	39	60.9%
PR	18	28.1%
SD	2	3.1%
PD	1	1.6%
Unknown	1	1.6%
Cytogenetic FISH risk	Number	Percentage
Standard	50	78.1%
High	14	21.9%
ISS stage at diagnosis	Number	Percentage
I	33	51.6%
II	13	20.3%
III	9	14.1%
Unknown	9	14.1%
R-ISS stage		
I	17	26.6%
II	20	31.3%
III	3	4.7%
Unknown	24	37.5%
Myeloma diagnosis	Number	Percentage
IgG Kappa	31	48.44%
IgG Lambda	12	18.75%
IgA Kappa	5	7.81%
IgA Lambda	7	10.94%
Kappa LC	7	10.94%
Lambda LC	2	3.13%

Abbreviations: CR, complete response; FISH, fluorescence in situ hybridization; Ig, immunoglobulin; ISS, International Staging System; LC, light chain; PD, progressive disease; PR, partial response; R-ISS, revised International Staging System; SD, stable disease; VGPR, very good partial response.

Response rates

Baseline responses post-ASCT in the 64 patients enrolled were CR ($N = 3$), very good partial response (VGPR; $N = 39$), partial response (PR; $N = 19$), stable disease (SD; $N = 2$), and unknown ($N = 1$). Of these 64 patients, 33 patients (51.6%) retained their baseline response from ASCT after maintenance. Thirty-one patients (48.4%) had improvement from their baseline response after maintenance therapy: 6 patients improved from PR to VGPR; 7 from PR to stringent CR (sCR)/CR; 16 from VGPR to sCR/CR; 1 from SD to CR; and 1 patient improved from SD to VGPR. The median time to response in the 31 patients with improved response to maintenance therapy was 10.9 months (range, 0.9–51.3 months). At baseline, the rate of VGPR or higher was 65.6%, with a CR rate of 4.6%. After maintenance therapy, the rate of VGPR or higher was 89.1%, with an sCR/CR rate of 42.2% (**Fig. 1**). MRD was evaluated in 21 patients by bone marrow biopsy and 8 patients were MRD positive.

PFS, OS, and duration of response

The median PFS for all patients was 73.3 months [95% CI, 59.9 months–not reached (NR)], with a 5-year PFS rate of 61.4% (95% CI, 49.9–75.5; **Fig. 2A**). The median PFS in patients with standard-risk cytogenetic features was NR, and the 5-year PFS rate was 69% (95% CI, 57–85), which was significantly greater

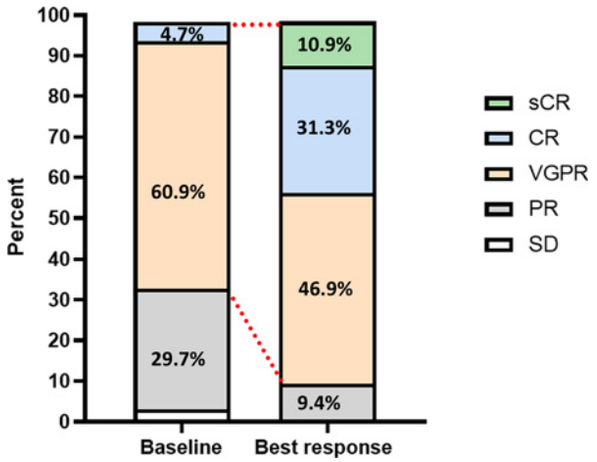

Figure 1.
Distribution of responses at baseline (after ASCT) and after maintenance therapy. Thirty three patients retained their response and 31 patients had improved response after maintenance therapy. Six patients improved from PR to VGPR; 7 patients improved from PR to sCR/CR; 16 patients improved from VGPR to sCR/CR; 1 patient improved from SD to CR; and 1 patient improved from SD to VGPR.

when compared with patients with high-risk cytogenetic features who demonstrated a median PFS of 25.41 months (95% CI, 13.5 months–NR) and a 5-year PFS rate of 34% (95% CI, 16–72; $P = 0.0068$; **Fig. 2B**). Subgroup analysis of PFS based on ISS stage at diagnosis and revised-ISS stage did not demonstrate statistically significant differences between groups (Supplementary Fig. S1).

There were 10 patient deaths as of the cut-off date for this study (October 1, 2020). With a median follow-up time of 62.04 months (range, 25.43–83.13 months), median OS had not been reached, and the 5-year OS rate was 88.4% (95% CI, 80.6–96.9; **Fig. 2C**).

The median duration of response for all patients was 58.5 months (95% CI, 48.6 months–NR), with a statistically significant increase in the duration of response in patients with standard-risk cytogenetic features (60.84 months; 95% CI, 56.44 months–NR) when compared with patients with high-risk cytogenetic features (26.38 months; 95% CI, 9.63 months–NR; $P = 0.043$; **Fig. 2D** and **E**). A statistically significant difference in the median duration of response was also seen based on the ISS stage at diagnosis (**Fig. 2F**).

Of the 64 patients enrolled in this study, 45 were taken off the study and 19 remained on the study. The 45 patients taken off the study were withdrawn for the following reasons: progressive disease (PD; $N = 22$), consent withdrawal ($N = 14$), PI withdrawal ($N = 7$), toxicity ($N = 1$), and second malignancy ($N = 1$). The median number of cycles for patients who withdrew from the study was 20, with a mean of 25.02 cycles (range, 1–74 cycles). Of the 45 patients who were taken off the study, 27 received salvage therapy, 6 received lenalidomide only, 6 were observed with no other therapy, 3 patients withdrew consent, 2 died, and 1 developed a secondary malignancy (leukemia).

AEs and dose reductions

The most frequent hematologic AEs of any grade were neutropenia (89.1%), leukopenia (78.1%), thrombocytopenia (76.6%), and anemia (68.8%), whereas the most frequent non-hematologic events of any grade were diarrhea (82.8%), fatigue (78.1%), nausea (75%), constipation (67.2%), upper respiratory infection (65.6%), vomiting (64.1%), and hyperglycemia (60.9%). The most frequent hematologic AEs of grade 3 or higher included neutropenia (46.9%), leukopenia (20.3%), thrombocytopenia (15.6%), and anemia (3.1%). The most frequent non-hematologic AEs of grade 3 or higher included lung infections (26.6%), diarrhea (12.5%), maculopapular rash (12.5%), fatigue (10.9%), peripheral sensory neuropathy (10.9%), upper respiratory infection (7.8%), nausea (6.7%), constipation (6.7%), elevated aspartate aminotransferase levels (6.3%), and other infections (6.3%; see **Table 2**). Serious AEs (SAE) included lung infections ($N = 12$ patients), treatment-related secondary malignancy ($N = 9$), respiratory disorders including respiratory failure ($N = 8$), and other infections ($N = 5$). A list of SAEs is provided in **Table 3**.

Lenalidomide dose reductions occurred in 52% of patients. In 1 patient, the dose was increased to 15 mg/day × 28 days after three cycles, but the dose was then reduced to 10 mg/day × 28 days. In 2 patients, the dose was decreased to 10 mg/day × 21 days; 7 of these patients further reduced the dose to 5 mg/day × 21 days. Eleven patients had a dose reduction to 5 mg/day × 28 days; 4 of these patients had a further dose reduction to 5 mg/day × 21 days. Reasons for lenalidomide dose reduction included neutropenia, rash, fatigue, thrombocytopenia, and diarrhea.

Of the 64 patients enrolled, the first 16 patients started ixazomib at the approved dose of 4 mg on days 1, 8, and 15. However, the dose of ixazomib was reduced to 3 mg for all subsequent patients ($n = 48$) based on the increased incidence of cytopenias seen with the 4 mg dose in phase III trials with ixazomib (26). Ixazomib dose reduction to 2.4 mg occurred in 20 patients. Reasons for ixazomib reduction included neuropathy ($N = 12$), neutropenia ($N = 3$), hearing loss ($N = 2$), thrombocytopenia ($N = 1$), and rash ($N = 1$). Six patients had a further dose reduction to 1.5 mg due to neuropathy ($N = 4$), neutropenia ($N = 1$), and thrombocytopenia ($N = 1$). Four patients eventually discontinued ixazomib due to neuropathy ($N = 2$), neutropenia ($N = 1$), and thrombocytopenia ($N = 1$).

SPMs

In this study, 9 patients developed treatment-related SPMs. These malignancies included squamous cell carcinoma, basal cell carcinoma, hepatocellular carcinoma, melanoma, and leukemia (**Table 4**). In all cases except for the patient with leukemia, the lesions were removed by surgery, and the patients continued with treatment on the study. No patients died because of secondary malignancies.

Discussion

The goal of this study was to determine whether maintenance therapy with lenalidomide and ixazomib was safe and effective when compared with results from prior studies where lenalidomide-only maintenance therapy was evaluated in multiple myeloma patients who have undergone ASCT. While maintenance therapy with only lenalidomide after ASCT has demonstrated improved PFS in patients with multiple myeloma as compared with observation alone (7–11), we hypothesized that the addition of ixazomib to lenalidomide as maintenance therapy would further improve PFS because this combination has demonstrated favorable outcomes when used as induction therapy and ixazomib alone as maintenance therapy has clinical benefit (17, 20). Overall, no new safety signals were observed with combination maintenance therapy. The additional advantage of this combination is that both drugs are given orally, enabling more convenient administration and is preferred by many patients (22).

A limitation of our study is that it was a single-arm study of ixazomib-lenalidomide maintenance; however, our results show a better than expected median PFS time of 73.3 months with

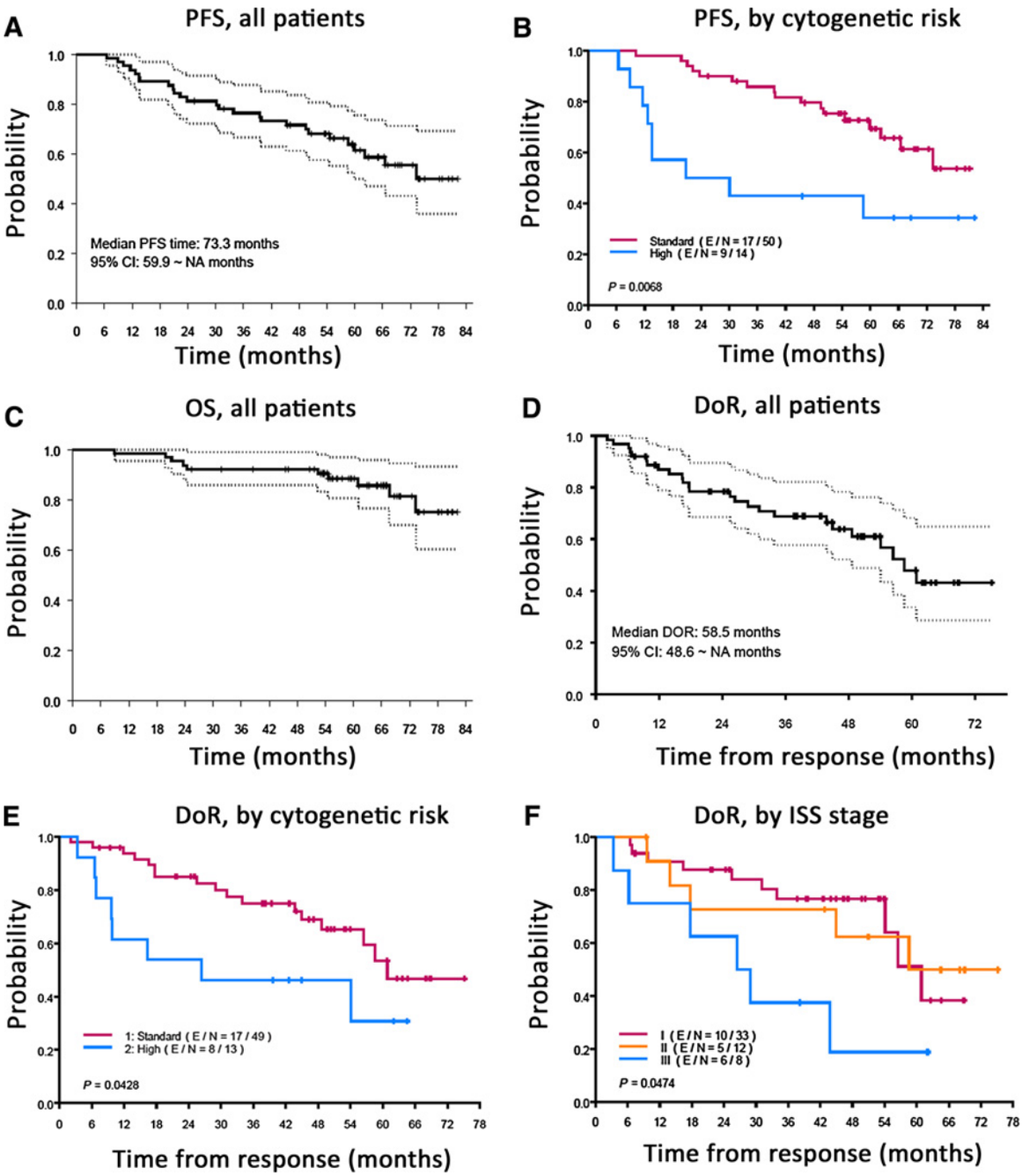

Figure 2.

Response rates and duration of response after maintenance therapy. **A,** PFS in all patients. **B,** PFS by cytogenetic risk. **C,** OS in all patients. **D,** Duration of response in all patients. **E,** Duration of response by cytogenetic risk. **F,** Duration of response by ISS stage. E/N, events/number of patients.

lenalidomide and ixazomib combination maintenance therapy when compared with lenalidomide-only maintenance therapy seen in previous studies (median PFS range, 41–52.8 months; refs. 7, 9–11). We also observed a 3-year OS rate of 92.2% (95% CI, 85.8–99), which is greater than the 3-year OS rate observed in studies with lenalidomide-only maintenance (range, 80–88; refs. 7, 9, 11). A recent communication from Takeda Oncology regarding the use of ixazomib in the maintenance setting in multiple myeloma indicates that there may not be a significant survival benefit with ixazomib maintenance compared with placebo based on interim analysis of data from an ongoing phase III randomized clinical trial; the PFS endpoint in the study was met. It remains to be determined whether the lack of OS benefit persists in the final analysis of the study. A study of carfilzomib plus lenalidomide maintenance therapy versus lenalidomide-only maintenance therapy

Table 2A. Hematologic AEs seen in >20% of patients (all grades) and >5% of patients (grade 3 or higher).

Hematologic AE	Any grade	Grade 3 or higher
Neutropenia	89.1%	46.88%
Leukopenia	78.1%	20.31%
Thrombocytopenia	76.6%	15.63%
Anemia	68.8%	3.13%

Table 2B. Non-hematologic AEs of any grade, seen in >50% of patients.

Non-hematologic AE	Any grade
Diarrhea	82.8%
Fatigue	78.1%
Nausea	75.0%
Constipation	67.2%
Upper respiratory infection	65.6%
Vomiting (emesis)	64.1%
Hyperglycemia	60.9%
Dyspnea	59.4%
Dizziness	54.7%
Aspartate aminotransferase increased	53.1%
Fever	53.1%
Hypomagnesemia	53.1%

Table 2C. Non-hematologic AEs of grade 3 or higher, seen in >5% of patients.

Non-hematologic AE	Grade 3 or higher
Lung infections	26.6%
Diarrhea	12.5%
Rash (Maculopapular)	12.5%
Fatigue	10.9%
Peripheral sensory neuropathy	10.9%
Upper respiratory infection	7.8%
Nausea	6.3%
Constipation	6.3%
Aspartate aminotransferase increased	6.3%
Infections	6.3%

Table 3. SAEs.

Serious adverse event	Number of patients
Lung infection	12
Respiratory, thoracic, and mediastinal disorders, including respiratory failure	8
Infections and infestations	5
Treatment-related secondary malignancy	5
Sepsis	3
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	3
Upper respiratory infection	2
Acute kidney injury	1
Dehydration	1
Vomiting	1
Fracture	1
Pancreatitis	1
Pleural effusion	1
Urinary tract infection	1
Urinary retention	1
Fever	1
Diarrhea	1
Thromboembolic event	1
Nervous system disorders	1
Non-cardiac chest pain	1
Syncope	1

following induction with carfilzomib, lenalidomide, and dexamethasone and ASCT in patients with NDMM demonstrated an improved PFS and increased MRD-negativity conversion rate with combination maintenance (27). A study of daratumumab maintenance versus observation alone after induction with a daratumumab-containing regimen and ASCT demonstrated improved PFS with daratumumab maintenance, but the rate of conversion to MRD-negativity was not significantly different with daratumumab maintenance (28). While cross-trial comparisons are difficult to make, it is likely that proteasome inhibitors in the maintenance setting in NDMM may be beneficial, even when used in induction previously.

Our results also demonstrate a statistically significant difference in response to maintenance therapy with lenalidomide and ixazomib in patients with myeloma with standard-risk cytogenetic features compared with patients with high-risk cytogenetic features. Frontline therapy of patients with newly diagnosed myeloma with carfilzomib, lenalidomide, and dexamethasone demonstrated a clinical response that was not significantly different between different cytogenetic risk groups (29). Frontline induction with lenalidomide, bortezomib, and dexamethasone in patients with newly diagnosed myeloma demonstrated a median PFS time of 40.3 months and median OS time of 78.2 months in high-risk patients (3). In addition, lenalidomide maintenance therapy in patients with high-risk multiple myeloma has demonstrated an improved 3-year OS of 74.9% compared with observation alone (63.7%; ref. 8). An improved PFS was also seen across all cytogenetic risk groups treated with lenalidomide maintenance compared with observation alone (8). While these latter two studies demonstrate poorer outcomes in patients with high-risk multiple myeloma compared with standard-risk patients, the combination of immunomodulatory agents and proteasome inhibitors and the use of maintenance therapy demonstrate clinical benefit in high-risk patients. Another study has demonstrated the benefit of combination maintenance/consolidation therapy with lenalidomide, bortezomib, and dexamethasone in patients with high-risk myeloma post ASCT, with an observed mPFS of 32 months and 3-year OS of 93%, which was an improvement when compared with single-agent maintenance or no maintenance therapy (30). The addition of carfilzomib to lenalidomide maintenance also demonstrated benefit in patients with high-risk NDMM (27). On the basis of the results of previous studies, high-risk patients are likely to receive maximum benefit when treated with doublet or triplet maintenance regimens (27, 29, 30). While additional studies with a larger number of patients are warranted to determine the impact of ixazomib and lenalidomide maintenance therapy in high-risk patients, our results and those of previous studies suggest that maintenance therapy may be beneficial across all cytogenetic risk groups.

The most common AEs and SAEs of any grade observed in this study were similar to those reported in previous studies with lenalidomide-only maintenance therapy (7–11). Nine patients (14.1%)

Table 4. SPMs.

Malignancy	Number of patients	Treatment cycle at SPM occurrence	Action taken
Squamous cell carcinoma	4	30–67	Lesion removed by surgery
Squamous cell carcinoma and basal cell carcinoma	1	61	Lesion removed by surgery
Basal cell carcinoma	1	76	Lesion removed by surgery
Melanoma	1	47	Lesion removed by surgery
Hepatocellular carcinoma	1	57	Lesion removed by surgery
Acute lymphocytic leukemia	1	56	Patient was taken off study

developed SPMs, which is slightly increased compared with the 8% rate of SPMs reported by McCarthy and colleagues (11). In a meta-analysis of three studies that evaluated lenalidomide maintenance therapy in patients with NDMM after ASCT, the frequencies of hematologic and solid tumor SPMs before and after PD in the lenalidomide group were 6.1% and 7.3%, respectively, with an increased incidence of SPMs in the lenalidomide maintenance group compared with placebo/observation (10). The risk of developing PD was higher than the risk of developing an invasive SPM in both lenalidomide maintenance and observation groups, the cumulative incidence rates of PD were higher than incidence rates of SPMs, and there was an increase in the time to death as a result of multiple myeloma in the lenalidomide maintenance group (10). Although the incidence of SPM in our study was slightly higher than that observed in previous studies, most patients who developed SPMs had the lesion removed and continued maintenance treatment; only 1 patient was taken off the study due to SPM. It is possible that the incidence of SPMs was higher in our study due to the longer duration of maintenance therapy, with a median time to SPM from the start of maintenance therapy of 58 months (range, 29–75 months). While further study with more patients is needed to more extensively evaluate the risk of SPM with the combination of lenalidomide and ixazomib maintenance therapy, the benefit of maintenance therapy likely outweighs the risk of SPM.

While we observed significant clinical benefit with combination maintenance therapy, some questions remain concerning specific patient groups and the length of therapy. For patients who achieve MRD-negative status, the timing of stopping maintenance therapy with one or both drugs needs to be addressed. Some studies have sought to address whether maintenance therapy in multiple myeloma should be used for a fixed time or until disease progression (31). There is evidence that reduced duration of lenalidomide maintenance results in reduced PFS and OS benefit; however, prolonged use of lenalidomide increases the risk of SPMs and other toxicities. The results of the IFM 2009 clinical trial suggest that induction and ASCT followed by maintenance provide improvement in quality of life for patients with NDMM (32). Therefore, it is important to weigh the benefit of prolonged maintenance therapy against the cost of therapy, risk of toxicity, and adverse effects. Disease heterogeneity may be an additional consideration in treatment decision-making (31). In our study, the benefit of continued maintenance therapy remains to be evaluated in patients who did not achieve CR or MRD-negative disease. The depth of response to maintenance therapy may depend on the initial response to ASCT; however, due to the limited number of patients in our study, this correlation has not been evaluated. Further studies with larger cohorts could address this question and determine whether there are specific patients in whom lenalidomide plus ixazomib maintenance therapy is recommended. Several combinations of lenalidomide with other agents are being evaluated as maintenance therapies in patients with multiple myeloma in the post-ASCT setting, including mAbs, histone deacetylase inhibitors, and tumor vaccines (31). As these combination approaches are further evaluated in specific multiple myeloma patient subgroups, optimal therapy for patients based on the depth of their initial response, type of myeloma, and cytogenetic risk factors is likely to emerge. In conclusion, our study demonstrates that the combination of lenalidomide and ixazomib as maintenance therapy in the post-ASCT setting is safe and clinically effective, with no additional safety signals and a better than expected PFS when compared with lenalidomide maintenance alone in historical controls. This combination will likely provide an additional benefit in deepening the response to ASCT in patients with multiple myeloma.

Authors' Disclosures

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Authors' Contributions

K.K. Patel: Data curation, formal analysis, supervision, investigation, methodology, project administration, writing–review and editing. **J.J. Shah:** Conceptualization, funding acquisition, investigation, methodology. **L. Feng:** Software, formal analysis. **H.C. Lee:** Supervision, writing–review and editing, enrollment and evaluation of patients. **E.M. Manasanch:** Supervision, writing–review and editing, enrollment of patients and evaluation/treatment. **J. Olsem:** Data curation, supervision, project administration, writing–review and editing. **A. Morphey:** Data curation, supervision, investigation, writing–review and editing. **X.J. Huo:** Data curation, writing–review and editing. **S.K. Thomas:** Investigation, writing–review and editing, patient enrollment and care. **Q. Bashir:** Writing-review and editing, patient care, stem cell transplant. **M.H. Qazilbash:** Conceptualization, investigation, writing–review and editing, patient care, stem cell transplant. **D.M. Weber:** Investigation, visualization, writing–review and editing, patient enrollment and care. **R.Z. Orlowski:** Conceptualization, resources, supervision, investigation, project administration, writing–review and editing, patient enrollment and care.

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