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# Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma

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abstract

**PURPOSE** Observation is the current standard of care for smoldering multiple myeloma. We hypothesized that early intervention with lenalidomide could delay progression to symptomatic multiple myeloma.

**METHODS** We conducted a randomized trial that assessed the efficacy of single-agent lenalidomide compared with observation in patients with intermediate- or high-risk smoldering multiple myeloma. Lenalidomide was administered orally at a dose of 25 mg on days 1 to 21 of a 28-day cycle. The primary end point was progression-free survival, with disease progression requiring the development of end-organ damage attributable to multiple myeloma and biochemical progression.

**RESULTS** One hundred eighty-two patients were randomly assigned—92 patients to the lenalidomide arm and 90 to the observation arm. Median follow-up is 35 months. Response to therapy was observed in 50% (95% CI, 39% to 61%) of patients in the lenalidomide arm, with no responses in the observation arm. Progression-free survival was significantly longer with lenalidomide compared with observation (hazard ratio, 0.28; 95% CI, 0.12 to 0.62; $P = .002$). One-, 2-, and 3-year progression-free survival was 98%, 93%, and 91% for the lenalidomide arm versus 89%, 76%, and 66% for the observation arm, respectively. Only six deaths have been reported, two in the lenalidomide arm versus four in the observation arm (hazard ratio for death, 0.46; 95% CI, 0.08 to 2.53). Grade 3 or 4 nonhematologic adverse events occurred in 25 patients (28%) on lenalidomide.

**CONCLUSION** Early intervention with lenalidomide in smoldering multiple myeloma significantly delays progression to symptomatic multiple myeloma and the development of end-organ damage.

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ASSOCIATED CONTENT

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See accompanying Oncographic at doi: 10.1200/JCO.19.02273

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Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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## INTRODUCTION

Smoldering multiple myeloma (SMM) is an asymptomatic precursor stage of multiple myeloma (MM).[1,2] It is associated with a risk of progression to symptomatic MM of 10% per year,[3] although patients with certain adverse prognostic factors may have a higher risk of progression of approximately 25% per year.[4-6]

Observation has been the current standard of care for SMM until the emergence of end-organ dysfunction meeting the criteria for clinical MM.[7,8] Data from randomized trials that show the efficacy of therapy to prevent such end-organ dysfunction or improve outcome are limited. Types of early therapy can take two different approaches. First, one can take a prevention approach with low-intensity therapy directed at clonal control or, second, one can take a more intensive treatment approach for which the goal is the eradication of the malignant clone. The Spanish myeloma group assessed the combination of lenalidomide plus dexamethasone versus observation in patients with high-risk SMM.[7] Although the study demonstrated improved progression-free survival (PFS) and overall survival with early intervention, it was not adopted as the standard of care for three main reasons. First, a combination regimen was used and the specific added value of lenalidomide could not be clearly isolated. Second, the study did not use modern imaging at randomization as the trial was designed before the use of magnetic resonance imaging or positron emission tomography scans were introduced as standard, more sensitive measures,[9,10] leading to concerns about the possible enrollment of patients with symptomatic myeloma in this trial. Third, multiparametric flow cytometry criteria that were used to define high-risk SMM for this trial was

not readily available outside of the centers that conducted the trial, which limited the generalizability of results.

To our knowledge, we conducted the largest randomized trial in SMM wherein patients received either single-agent lenalidomide or observation, which included modern imaging at the time of study entry, and used laboratory criteria that are widely available to risk classify patients. We hypothesized that the immune-modulatory effects of lenalidomide alone could prevent end-organ dysfunction without the need for corticosteroids. We also conducted quality-of-life analysis over the course of therapy in an effort to better identify the impact of early intervention in this SMM setting.

## METHODS

### Trial Design, Oversight, and Treatment

In this randomized, open-label, multicenter phase III trial, patients were randomly assigned with equal allocation to receive oral lenalidomide 25 mg on days 1 to 21 of every 28-day cycle or to observation. Therapy or observation was continued until disease progression, toxicity, or withdrawal for other reasons. Patients were encouraged to mobilize stem cells after four to six cycles of therapy. Patients who were assigned to lenalidomide were required to take thrombosis prophylaxis, with a minimum recommendation of aspirin at a suggested dose of 325 mg per day. Patients were stratified at randomization by

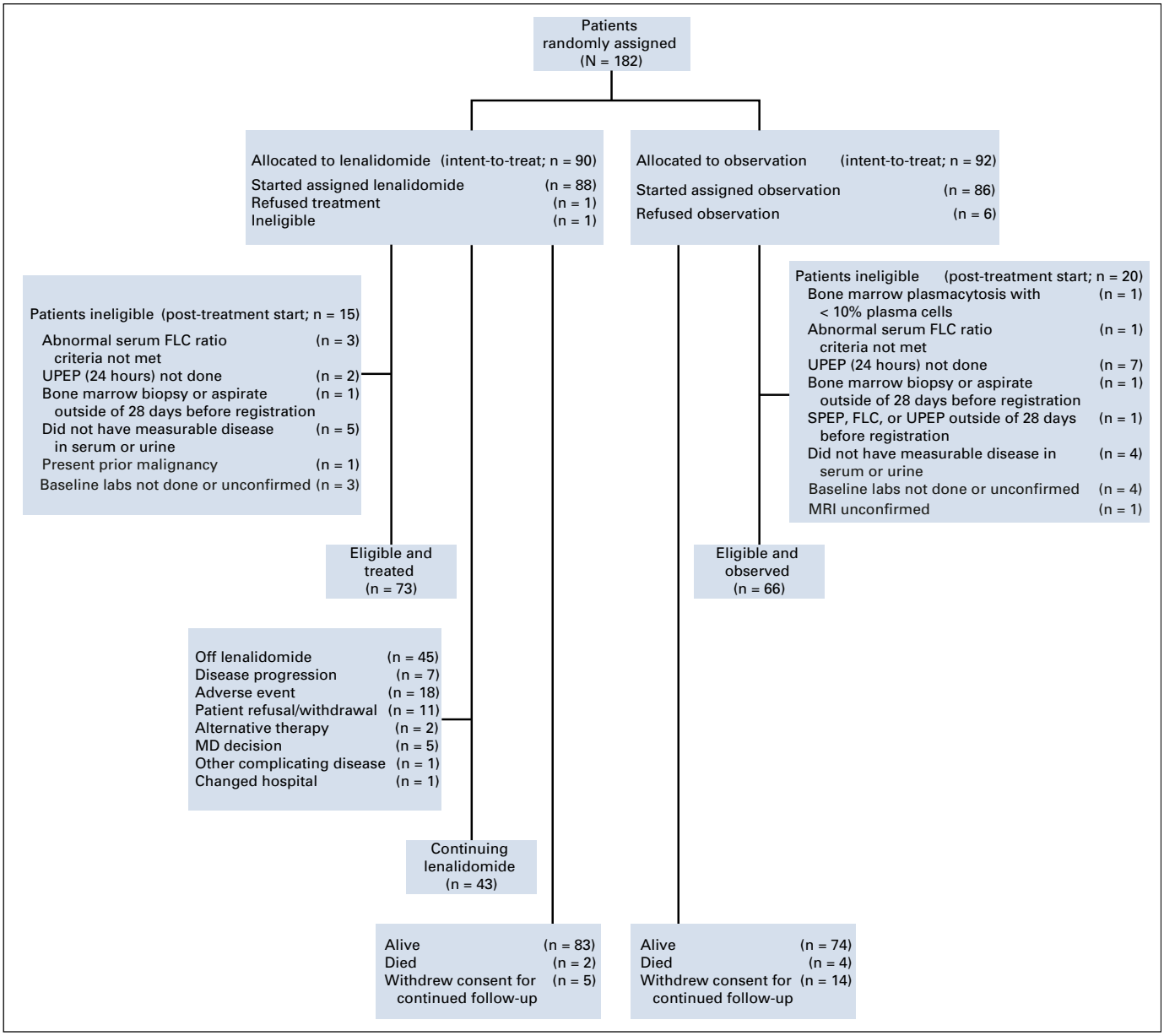


**FIG 1.** CONSORT diagram for phase III. FLC, free light chain; SPEP, serum protein electropheresis; UPEP, urine protein electropheresis.

**TABLE 1.** Baseline Patient Characteristics

| | Phase II Run In | Phase III Randomized Trial | | |
|---|---|---|---|---|
| **Characteristic** | **Lenalidomide (n = 44)** | **Lenalidomide (n = 90)** | **Observation (n = 92)** | **Total (N = 182)** |
| Median age, years (range) | 62 (36-83) | 63 (31-82) | 64 (33-96) | 64 (31-86) |
| Sex, No. (%) | | | | |
| Male | 20 (45.5) | 42 (46.7) | 46 (50.0) | 88 (48.4) |
| Female | 24 (54.5) | 48 (53.3) | 46 (50.0) | 94 (51.6) |
| Race, No. (%) | | | | |
| White | 37 (86.0) | 72 (84.7) | 68 (77.3) | 140 (80.9) |
| Black | 6 (14.0) | 12 (14.1) | 19 (21.6) | 31 (17.9) |
| Other | 0 (0.0) | 1 (1.2) | 1 (1.1) | 2 (1.2) |
| Missing/unknown | 1 | 5 | 4 | 9 |
| Ethnicity, No. (%) | | | | |
| Non-Hispanic or Latino | 43 (100.0) | 81 (97.6) | 81 (97.6) | 162 (96.4) |
| Hispanic or Latino | 0 (0.0) | 2 (2.4) | 4 (4.7) | 6 (3.6) |
| Missing | 1 | 7 | 7 | 14 |
| ECOG PS | | | | |
| 0 | 40 (90.9) | 66 (73.3) | 68 (73.9) | 134 (73.6) |
| > 0 | 4 (9.1) | 24 (27.0) | 24 (26.1) | 48 (26.4) |
| Missing | 0 | 0 | 0 | 0 |
| Time since SMM diagnosis, years, No. (%)* | | | | |
| ≤ 1 | 33 (82.5) | 68 (77.3) | 68 (76.4) | 136 (76.8) |
| > 1 | 7 (17.5) | 20 (22.7) | 21 (23.6) | 41 (23.2) |
| Missing | 4 | 2 | 3 | 5 |
| Median time since SMM diagnosis, months (range) | 1.5 (0-78) | 2.6 (0-78) | 3.4 (0-174) | 2.8 (0-174) |
| Time since high-risk SMM diagnosis, years, No. (%) | | | | |
| ≤ 1 | 43 (100.0) | 84 (93.3) | 82 (89.1) | 166 (91.2) |
| > 1 | 0 (0.0) | 6 (6.7) | 10 (10.9) | 16 (8.8) |
| Missing | 1 | 0 | 0 | 0 |
| Median time, months (range) | 0.8 (0-11) | 1.3 (0-56) | 0.9 (0-54) | 1.1 (0-56) |
| Percent BMPC, No. (%) | | | | |
| < 10 | 1 (2.3) | 2 (2.2) | 4 (4.4) | 6 (3.3) |
| ≥ 10† | 43 (97.7) | 88 (97.8) | 88 (95.6) | 176 (96.7) |
| > 20‡ | 27 (61.4) | 31 (34.4) | 41 (44.6 | 72 (39.6) |
| ≥ 60 | 2 (4.6) | 3 (3.3) | 3 (3.3) | 6 (3.3) |
| FLC ratio, No. (%) | | | | |
| < 0.125 or > 8.0† | 41 (93.2) | 65 (72.2) | 67 (72.8) | 132 (72.5) |
| Normal | 3 (6.8) | 25 (27.8) | 25 (27.2) | 50 (27.5) |
| < 0.26 or > 1.65 | 43 (97.7) | 87 (96.7) | 89 (96.7) | 176 (96.7) |
| > 20‡ | 15 (34.1) | 26 (28.9) | 22 (23.9) | 48 (26.4) |
| > 100 (involved > 10 mg/dL) | 6 (13.6) | 6 (6.7) | 9 (9.8) | 15 (8.2) |
| Serum M protein, g/dL, No. (%) | | | | |
| < 3 | 30 (68.2) | 74 (82.2) | 75 (81.5) | 149 (81.9) |
| ≥ 3† | 14 (31.8) | 16 (17.8) | 17 (18.5) | 33 (18.1) |
| > 2‡ | 26 (59.1) | 37 (41.1) | 41 (44.6) | 78 (42.9) |
| < 1 | 2 (4.6) | 9 (10.0) | 8 (8.7) | 17 (9.3) |

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**TABLE 1.** Baseline Patient Characteristics (continued)

| | Phase II Run In | Phase III Randomized Trial | | |
|---|---|---|---|---|
| **Characteristic** | **Lenalidomide (n = 44)** | **Lenalidomide (n = 90)** | **Observation (n = 92)** | **Total (N = 182)** |
| Median IgA, mg/dL (range) | 55 (7-3,139) | 76 (10-4,384) | 81 (5-4,470) | 77 (5-4,470) |
| MRI abnormality, No. (%) | | | | |
| Absent | 26 (61.9) | 48 (53.9) | 47 (51.7) | 95 (52.8) |
| Present | 16 (38.1) | 41 (46.1) | 44 (48.4) | 85 (47.2) |
| Missing | 2 | 1 | 1 | 2 |
| FISH risk stratification, No. (%)§ | | | | |
| Low | 7 (38.9) | 26 (60.5) | 22 (59.5) | 48 (60.0) |
| Intermediate | 7 (38.9) | 13 (30.2) | 12 (32.4) | 25 (31.3) |
| High | 4 (22.2) | 4 (9.3) | 3 (8.1) | 7 (8.8) |
| Missing | 26 | 47 | 55 | 102 |
| Mayo 2008 risk stratification, No. (%)† | | | | |
| Low (zero to one risk factor) | 3 (6.8) | 24 (26.7) | 25 (27.2) | 49 (26.9) |
| Intermediate (two risk factors) | 28 (63.6) | 52 (57.8) | 52 (56.5) | 104 (57.1) |
| High (three risk factors) | 13 (29.6) | 14 (15.6) | 15 (16.3) | 29 (15.9) |
| Mayo 2018 risk stratification, No. (%)‡ | | | | |
| Low (zero risk factors) | 7 (15.9) | 31 (34.4) | 27 (29.4) | 58 (31.9) |
| Intermediate (one risk factor) | 12 (27.3) | 34 (37.8) | 34 (37.0) | 68 (37.4) |
| High (two to three risk factors) | 25 (56.8) | 25 (27.8) | 31 (33.7) | 56 (30.8) |

Abbreviations: BMPC, bone marrow plasma cell; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; FLC, free light chain; IgA, immunoglobulin A; M, monoclonal; MRI, magnetic resonance imaging; SMM, smoldering multiple myeloma.

*Stratification at randomization defined as time since initial SMM diagnosis.

†Mayo 2008 risk stratification factors: BMPCs ≥ 10%, serum M protein ≥ 3 g/dL, and serum FLC ratio < 0.125 or > 8.

‡Mayo 2018 risk stratification factors: BMPCs > 20%, serum M protein > 2 g/dL, and involved/uninvolved serum FLC ratio > 20.

§FISH classification: high-risk: presence of t(4;14) or del 17; intermediate risk: presence of trisomies in the absence of immunoglobulin heavy chain translocations; low risk: all others, including normal or insufficient plasma cells for analysis.

time since diagnosis of SMM (≤ 1 year *v* > 1 year). The study protocol with the statistical analysis plan was approved by the institutional review boards of all participating institutions. Celgene provided lenalidomide but had no role in the design of the protocol, data collection, data analysis, or preparation of the manuscript.

## Patients

Eligible patients had a diagnosis of asymptomatic intermediate or high-risk SMM made within the past 60 months as confirmed by both of the following within 28 days before registration: bone marrow plasmacytosis with 10% or more plasma cells—or sheets of plasma cells—and an abnormal serum free light chain (FLC) ratio (< 0.26 or > 1.65) by serum FLC assay. Original eligibility criteria, time since high-risk SMM diagnosis within 1 year, and abnormal FLC ratio of less than 0.125 or greater than 8 were revised early on in the phase III study—addendum activated in December 2013 when 21 patients had enrolled—to enhance the accrual rate. Patients who met the most recent myeloma-defining event definition of symptomatic myeloma were excluded from the trial.

## End Points and Assessments

The primary end point was PFS defined as the time since randomization to the development of symptomatic MM as outlined in the American Society of Hematology/US Food and Drug Administration panel consensus.[11] Accordingly, progression to symptomatic MM required the presence of biochemical disease progression as defined by the International Myeloma Working Group (IMWG) criteria for MM[12] and evidence of end-organ damage felt related to the underlying clonal plasma cell proliferative disorder on the basis of the presence of one or more of the following: hypercalcemia (> 11 mg/dL), renal insufficiency (rise in serum creatinine ≥ 2 mg/dL), anemia (decrease of hemoglobin of ≥ 2 g/dL), or bone disease (development of myeloma bone lesions or soft-tissue plasmacytoma; Appendix Tables A1 and A2, online only). Response was assessed according to IMWG criteria. In patients who received lenalidomide, relative dose intensity was calculated as a percentage of full dose per protocol.

## Statistical Analysis

The Kaplan-Meier method was used to characterize event-time distributions and the corresponding treatment hazard

ratio (HR; lenalidomide/observation) was estimated using a stratified Cox regression model. PFS was compared between treatment groups using a stratified log-rank test in an intent-to-treat analysis including all randomized patients. Cumulative incidence (CI) estimates of second primary cancers (SPC) and progression considered death as a competing risk. Response, toxicity, SPC, and health-related quality of life (HRQoL) were evaluated in all patients starting assigned treatment. HRQoL was measured with the Physical (P) and Functional (F) domains of the Functional Assessment of Cancer Therapy-Global (FACT-G: P+F; 14 items, scored 0-56) and the FACT-Multiple Myeloma (FACT-MM;14 items scored 0-56) at registration, on treatment every 6 cycles up to 4 years and at early treatment discontinuation. Higher scores indicate better HRQoL. The mean difference in scores between arms was calculated with 95% confidence intervals with the change in FACT-G: P+F from baseline to cycle 24 the primary HRQoL endpoint. A minimally important difference (MID) of 4-6 points for between treatment group differences was pre-specified.[13]

The study was monitored by the ECOG-ACRIN data safety monitoring committee (DSMC). Data cutoff for this report was January 25, 2019. Additional details on the methods are provided in the Appendix (online only).

## RESULTS

### Patients and Treatment

Between January 2011 and January 2013, 44 patients were enrolled in the phase II safety run in portion of the study and were treated with lenalidomide as a single agent (Appendix Fig A1, online only). Between February 2013 and July 2017, 182 patients were randomly assigned between the two treatment arms, with 90 in the lenalidomide arm and 92 in the observation arm (Fig 1).

Baseline patient and disease characteristics are listed in Table 1 for both phases of the study. Patient characteristics were well balanced between randomized arms, including classification by proposed risk models and related underlying parameters.[14,15,16] Treatment duration, reason for going off treatment, and treatment exposure are listed in Appendix Tables A3, A4, and A5 (online only). Of patients who started treatment, 80% (phase II) and 51% (phase III) are off lenalidomide. Overall median treatment duration was 33.5 cycles and 23 cycles for the phase II and III studies, respectively, with patients off treatment contributing much less time. Going off treatment was primarily a result of patient withdrawal or adverse events. Among the 69% of phase III patients on treatment by cycle 12, relative dose intensity was 55% with 80% of treated patients on a reduced dose.

**TABLE 2.** Best Response Among Lenalidomide-Treated Patients

| | Phase II Run In | Phase III Randomized Trial |
|---|---|---|
| **Variable** | **Lenalidomide (n = 44)** | **Lenalidomide (n = 88)** |
| Complete response, No. | 1 | 0 |
| VGPR, No. | 3 | 4 |
| PR, No. | 17 | 40 |
| Stable disease, No. | 21 | 40 |
| Unevaluable, No. | 2 | 4 |
| VGPR rate, % | 9.1 | 4.5 |
| 95% CI | 2.5 to 21.7 | 1.2 to 11.2 |
| PR rate, % | 47.7 | 50.0 |
| 95% CI | 32.5 to 63.3 | 39.1 to 60.8 |
| Eligible and treated | (n = 34) | (n = 73) |
| VGPR rate, % | 11.8 | 5.5 |
| 95% CI | 3.3 to 27.5 | 1.5 to 13.4 |
| PR rate, % | 52.9 | 49.3 |
| 95% CI | 35.1 to 70.3 | 37.4 to 61.3 |

Abbreviations: PR, partial response; VGPR, very good partial response.

### Efficacy

In the phase II run in, median overall survival follow-up was 82 months (95% CI, 72 months to 84 months) and the 5-year PFS was 78% (95% CI, 65% to 93%). Seven deaths have occurred, resulting in a 5-year overall survival rate of 88% (95% CI, 78% to 98%; Appendix Fig A2, online only). Three-year cumulative incidence of progression was 10.4% (Appendix Fig A2).

At the second planned interim analysis of PFS (July 2018 data extraction with 38% of full information available), the prespecified criteria for significance was met (one-sided stratified log-rank test $P = .00025$ compared with the nominal significance level of .0005) for the randomized trial. The independent DSMC recommended the release of the data. Median overall survival follow-up at the time of analysis was 35 months (95% CI, 30 months to 37 months). Response to therapy is shown in Table 2 with partial response or better rate equal to 50% (95% CI, 39% to 61%) for the lenalidomide arm. Time to response was a median of 5 months (range, 1 month to 23 months). There were no responses in the observation arm. PFS was significantly longer for lenalidomide compared with observation (treatment HR, 0.28; 95% CI, 0.12 to 0.62; $P = .002$). One-, 2-, and 3-year PFS was 98%, 93%, and 91% for the lenalidomide arm versus 89%, 76%, and 66% for the observation arm, respectively (Fig 2A). The basis of progression is shown in Appendix Table A6 (online only), with bone progression being the most common cause in the observation group, despite monthly follow-up for both arms. Cumulative incidence of progression at 3 years was 7.3% in the lenalidomide arm and 31.6% in the observation arm (Fig 2B). Six deaths have been reported—two in the lenalidomide arm versus four in the observation

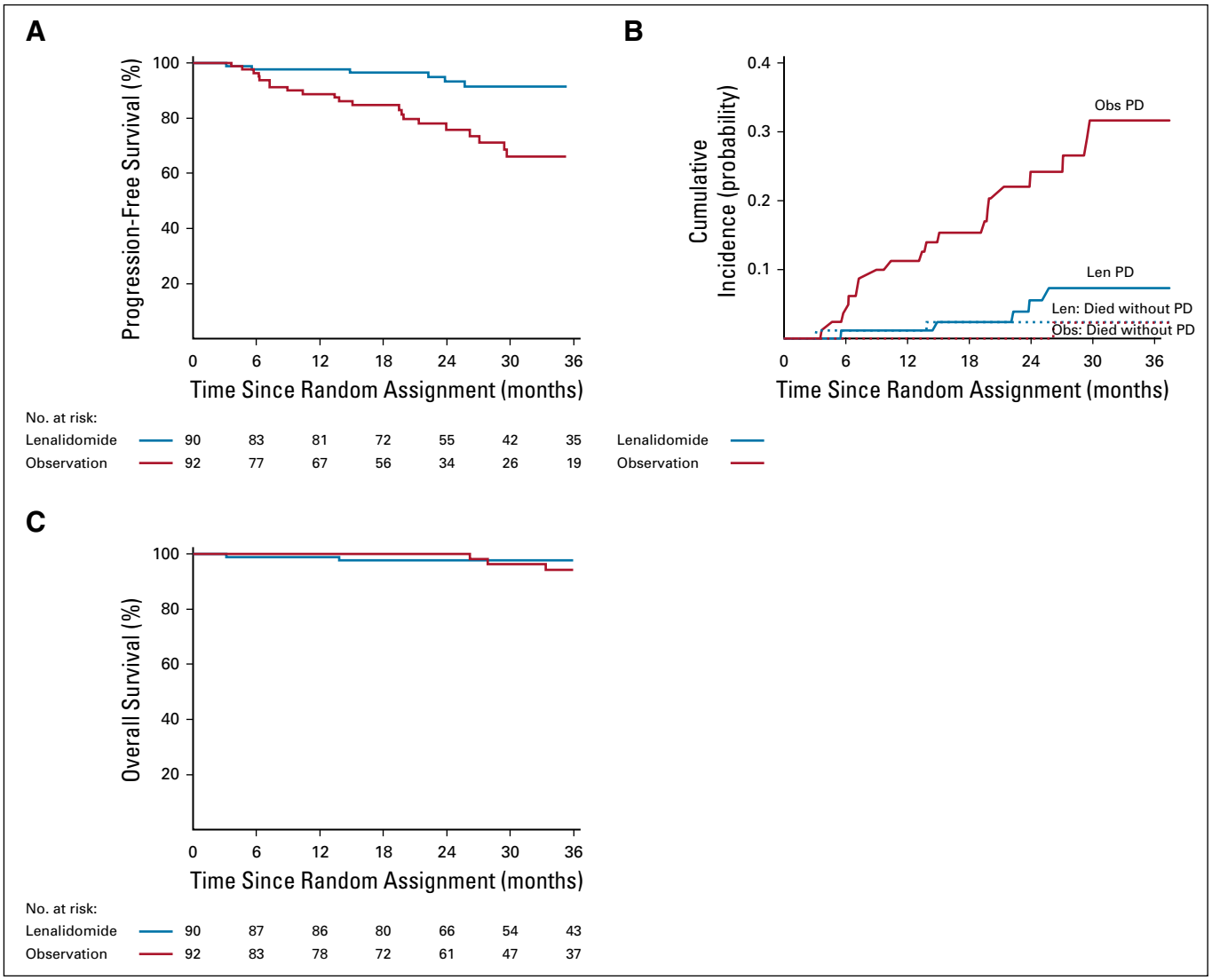


**FIG 2.** Time to event estimates by treatment arm in phase III: (A) progression-free survival, (B) cumulative incidence of progression, and (C) overall survival in patients with smoldering multiple myeloma. Len, lenalidomide; Obs, observation.

arm, with an HR for death of 0.46 (95% CI, 0.08 to 2.53; Fig 2C).

The benefit of lenalidomide was observed in most subgroups, although many subsets are relatively small. Of note, patients in all risk groups listed in Table 1 of Mayo 2008 risk stratification[16] and Mayo 2018 risk stratification[15] seemed to have an HR that favored early treatment (Figs 3, 4, and 5 and Appendix Fig A3, online only), but this was most pronounced in the Mayo 2018 high-risk category.

### Safety

Adverse events are listed in Tables 3 and 4. In the phase II run in, 44 patients were evaluable for adverse events. Grade 3 or 4 hematologic and nonhematolgic treatment-related adverse events occurred in 20 patients (45%), with nonhematolgic adverse events occurring in 15 patients (34%). Among the phase II patients who were off treatment (n = 35), 34% (n = 12) came off therapy as a result of adverse events. One death from pulmonary embolism occurred during the study and was determined to be therapy related.

In the randomized trial, among the lenalidomide-treated patients, grade 3 or 4 hematologic and nonhematologic adverse events occurred in 36 patients (41%), with nonhematologic adverse events occurring in 25 patients (28%). Among the phase III patients who were off treatment (n = 45), 40% (n = 18) came off therapy as a result of adverse events. Patients off treatment as a result of adverse events did not seem to have shortened PFS follow-up as evidenced by PFS follow-up extending well beyond the duration of delivered therapy (Appendix Fig A4, online only).

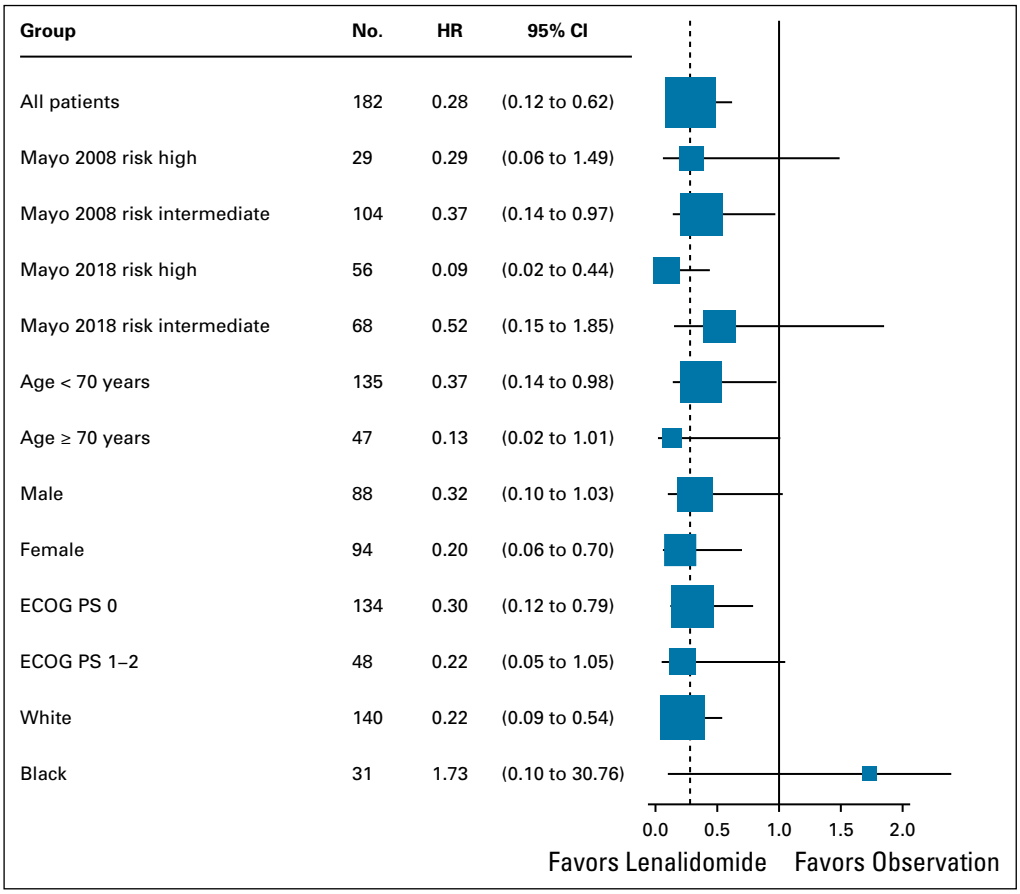


**FIG 3.** Treatment hazard ratio (HR) for progression-free survival in subgroups in phase III. ECOG PS, Eastern Cooperative Oncology Group performance status.

The cumulative incidence of invasive second primary cancers at 4 years was 4.9% in the phase II run in. In the randomized trial, the 3-year CI of invasive second primary cancers was 5.2% in the lenalidomide arm and 3.5% in the observation arm (Appendix Table A7, online only).

### Prognostic Factors and Quality-of-Life Analysis

Prognosis of patients in the trial on the basis of baseline risk factors is shown in Appendix Table A8 (online only). There were too few patients with high-risk SMM by fluorescence in situ hybridization to determine the impact of high-risk cytogenetics on prognosis (Appendix Fig A5, online only). Among patients who started the assigned treatment, 97% of lenalidomide-treated patients and 98% of observation patients had baseline health-related quality-of-life data; the difference in mean change score at 24 cycles was −0.1 (95% CI, −4.2 to 4.0; Appendix Table A9, online only; Appendix Fig A6, online only).

## DISCUSSION

Kyle and Greipp[16] described SMM in 1980 as intermediate disease state between the premalignant monoclonal gammopathy of undetermined significance (MGUS) and symptomatic MM. Patients with SMM are at much higher risk of progression to MM or a related disorder (10% per year)[3] compared with patients who have MGUS (1% per year).[17] However, the paucity of effective drugs, lack of biomarkers that can identify patients who are at high risk of progression, and the absence of randomized controlled trial data that demonstrate clinical benefit justified observation alone as the standard of care.[4] Early attempts to intervene in SMM to prevent end-organ damage were unsuccessful as the drugs used had high toxicity without significant benefit.[18-21] In 2014, in an attempt to help patients who were at the highest risk of progression, the IMWG revised the diagnostic criteria for MM, incorporating three biomarkers that identify patients with SMM who faced an 80% risk of progression within 2 years.[1] However this change affects only a small proportion of patients with SMM, and patients who fit this new definition of myeloma were not included in the current trial.

In this randomized trial, we demonstrate a significant prolongation of the time to symptomatic MM (PFS) with single-agent lenalidomide in a patient population that was well classified at baseline using modern imaging and widely available prognostic factors. Whereas we did include patients who would not be considered high risk by the current definition, we do not currently recommend that they be

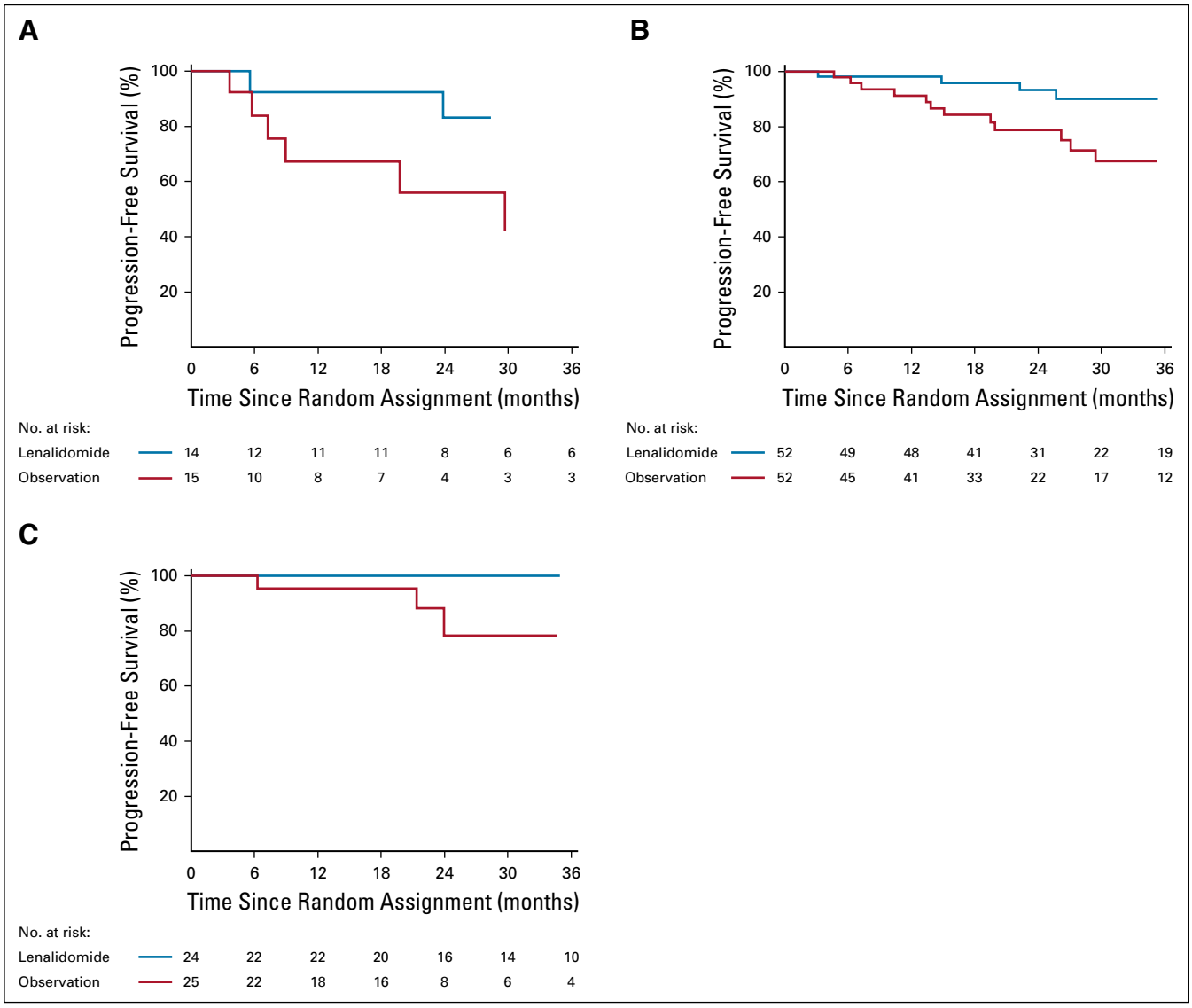


**FIG 4.** Kaplan-Meier estimates of progression-free survival by treatment arm within Mayo 2008 risk subgroups in phase III: (A) high risk, (B) intermediate risk, and (C) low risk.

started on early therapy pending confirmation data. Our results mirror those previously published by the Spanish group in effect size (similar HR for early treatment *v* observation), which confirms the benefit of early therapy for the high-risk group.[22] Too few deaths have occurred in our study to determine the impact on overall survival in our trial; however, with a similar magnitude of benefit in PFS, a survival benefit has already been demonstrated in the Spanish trial. Prevention of serious symptomatic end-organ damage—osteolytic bone lesions, acute renal failure, etc—is by itself an important goal given the longevity of patients with myeloma with modern therapy and should be recognized as an important goal of therapy in the smoldering population. Bone progression was the most common reason for progression in the trial overall but occurred far more frequently in the observation arm compared with the treatment arm (11 *v* three; Appendix Table A6). Hence, we believe that our results support the use of early intervention in patients with high-risk SMM—as defined by the 20/2/20 criteria where our magnitude of benefit was the greatest—rather than continued observation.

The concept of interception, or prevention of progression, for a premalignant condition has emerged as an important concept in human cancer.[23] There is a distinction between myeloma therapy—standard induction; consolidation, including stem-cell transplantation; and maintenance—versus prevention, which can take a less-intensive approach. This is especially important given data that suggest that immune control of the malignant clone may be a powerful and important regulator of progression from smoldering to symptomatic myeloma.[24] Before the current study, only one trial had demonstrated benefit with a control

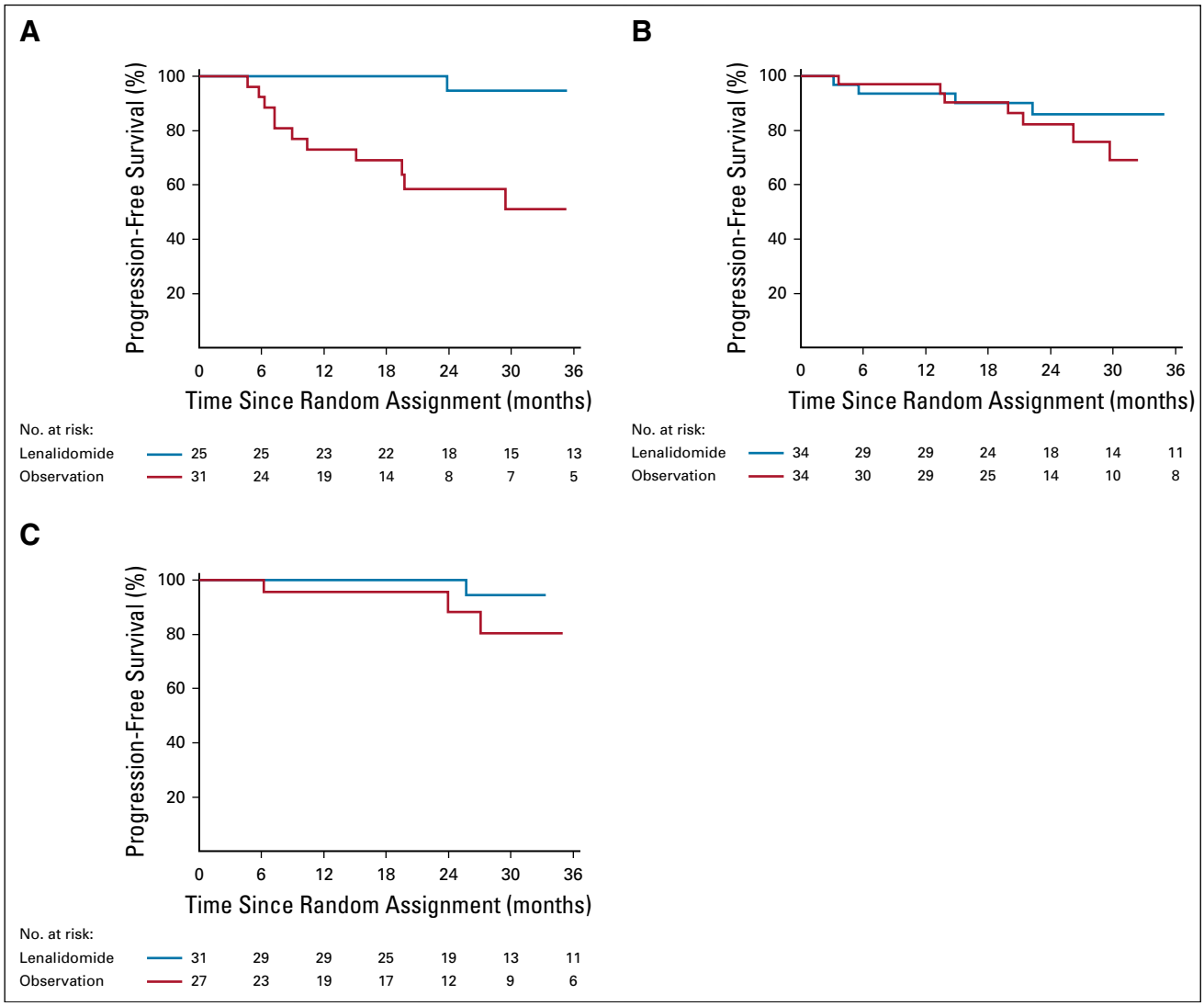


**FIG 5.** Kaplan-Meier estimates of progression-free survival by treatment arm within Mayo 2018 risk subgroup: (A) high risk, (B) intermediate risk, and (C) low risk.

arm—the Spanish trial—and whereas it did prove the principle that early therapy can affect outcomes without causing harm, sufficient design issues precluded widespread adoption as a standard. The current trial builds on the knowledge from that trial and here again has demonstrated benefit with lenalidomide alone in preventing the development of myeloma with associated organ damage. As such, this trial represents a paradigm shift in hematologic malignancies. We have demonstrated that early intervention with prevention does prevent the development of organ damage and symptoms, with a 72% risk reduction in more than 2 years compared with the control arm, and among the Mayo 2018 high-risk category, an HR of 0.09 that favored early intervention. Three-year PFS for the lenalidomide arm in the phase III trial is comparable to that which has been demonstrated in other smaller, phase II trials of more intensive therapy. Five-year PFS for the phase II portion of the study (78%) is also on par with that of other smaller, phase II studies that used more aggressive treatment approaches despite a short duration of therapy. Whereas other approaches using traditional myeloma therapy may ultimately be proven to be superior in the long term, they have not been tested or validated in phase III randomized trials as we currently report here. Given the data on immune regulation of progression, these therapies may be worse in the long run. This is an important distinction as we seek to answer the question of which approach—prevention or treatment—is optimal for these patients with SMM. It is also possible that, although a small fraction of patients may be cured with more aggressive therapy early, an operational cure with prevention using less intensive therapy may net similar end points without the toxicity of standard therapy. Use of surrogate end points, such as minimal residual disease negativity at early timepoints, remains unclear, and our trial suggests that control can be achieved without major responses.

  

**TABLE 3.** Grade 3 or Higher (≥ 5%) Adverse Events Among Lenalidomide-Treated Patients

| | Phase II Run In | | Phase III Randomized Trial | |
|---|---|---|---|---|
| | Lenalidomide (n = 44) | | Lenalidomide (n = 88) | |
| Adverse Event | Grade 3* | Grade 4 | Grade 3* | Grade 4 |
| Neutrophil count decreased | 5 (11.4) | 2 (4.5) | 8 (9.1) | 4 (4.5) |
| ALT increased | 4 (9.1) | — | — | — |
| Infection | 4 (9.1) | 2 (4.5) | 9 (10.2) | — |
| Dehydration | 3 (6.8) | — | — | — |
| Dermatology/skin | 2 (4.5) | — | 5 (5.7) | — |
| Dyspnea | — | — | 5 (5.7) | — |
| Fatigue | 5 (11.4) | — | 6 (6.8) | — |
| Hypertension | 3 (6.8) | — | 8 (9.1) | — |
| Hypokalemia | 4 (9.1) | — | 3 (3.4) | — |
| Surgical and medical | 3 (6.8) | — | — | — |

NOTE. Data are presented as No. (%) unless otherwise noted.
*Grade 3 hematologic events did not require reporting.

Therapy with single-agent lenalidomide in our study did not have a negative impact on health-related quality of life and the toxicity profile was consistent with previous descriptions of lenalidomide-related adverse events and, in most cases, could be managed with dose modifications. Given data from the Spanish trial with limited duration therapy and our median duration of therapy of 23 months in the phase III trial, we would recommend 2 years of therapy for the highest-risk patients to limit long-term adverse events. Although only a few patients achieved deep responses—very good partial response or complete response—the effect of even limited duration of lenalidomide still offered benefit of much longer PFS. This suggests that prolonged stability is feasible in the absence of a major reduction in clonal burden. Data from a Southwest Oncology Group trial suggest that preexisting antitumor immunity is an independent predictor of the risk of progression of SMM to symptomatic MM.[24] If this is correct, using such treatments as lenalidomide which enhance immune function and long-term immunologic memory can result in prolonged disease stability. Early intervention to achieve durable immunologic control is also supported by recent studies that show enrichment of stem-like memory cells in MGUS, which undergo attrition in MM.[25] Conversely, it is possible that more aggressive therapy as that currently used to treat clinical MM may provide greater benefit; however, this has not yet been tested in a randomized trial. A current

**TABLE 4.** Global Adverse Event Rates Among Patients Starting Assigned Therapy

| | Adverse Events: Treatment Related | | Adverse Events: Any Attribution | |
|---|---|---|---|---|
| Arm and Grade | Hematologic and Nonhematologic* | Nonhematologic | Hematologic and Nonhematologic* | Nonhematologic |
| Phase II Run In | | | | |
| Lenalidomide (n = 44) | | | | |
| Grade 3 | 15 (34.1) | 12 (27.3) | 23 (52.3) | 23 (52.3) |
| Grade 4 | 5 (11.4) | 3 (6.8) | 5 (11.4) | 3 (6.8) |
| Grade 5 | 2 (4.5) | 2 (4.5) | 2 (4.5) | 2 (4.5) |
| Total | 22 (50.0) | 17 (38.6) | 30 (68.2) | 28 (63.6) |
| Grades 3-5 95% CI, % | 34.6 to 65.4 | 24.4 to 54.5 | 52.4 to 81.4 | 47.8 to 77.6 |
| Phase III Randomized Trial | | | | |
| Lenalidomide (n = 88) | | | | |
| Grade 3 | 31 (35.2) | 25 (28.4) | 46 (52.3) | 44 (50.0) |
| Grade 4 | 5 (5.7) | 0 (0.0) | 6 (6.8) | 0 (0.0) |
| Grade 5 | 0 (0.0) | 0 (0.0) | 1 (1.1) | 1 (1.1) |
| Total | 36 (40.9) | 25 (28.4) | 53 (60.2) | 45 (51.1) |
| Grades 3-5 95% CI, % | 30.5 to 51.9 | 19.3 to 39.0 | 49.2 to 70.5 | 38.4 to 63.8 |
| Observation (n = 86) | | | | |
| Grade 3 | 3 (3.5) | 3 (3.5) | 25 (29.1) | 25 (29.1) |
| Grade 4 | 1 (1.2) | 1 (1.2) | 4 (4.7) | 3 (3.5) |
| Grade 5 | 0 (0.0) | 0 (0.0) | 1 (1.2) | 1 (1.2) |
| Total | 4 (4.7) | 4 (4.7) | 30 (34.9) | 29 (33.7) |
| Grades 3-5 95% CI, % | 1.3 to 11.5 | 1.3 to 11.5 | 24.5 to 46.5 | 23.9 to 44.7 |

*Grade 3 hematologic events did not require reporting.

randomized trial by ECOG-ACRIN (ClinicalTrials.gov identifier: NCT03937635) is comparing daratumumab, lenalidomide, and dexamethasone—treatment strategy using an approved MM triplet regimen—versus lenalidomide plus dexamethasone—preventive strategy—and will provide clarity on this issue.

In summary, our data, together with the results of the Spanish trial,[7] support early therapy as the new standard of care in high-risk SMM on the basis of clear clinical benefit in the prevention of end-organ damage demonstrated in two independent randomized trials. Patients defined as having high-risk SMM by Mayo 2018 criteria,[15] which has recently been validated by the IMWG,[28] gain the greatest benefit from early therapy and are the only group for whom we recommend early intervention using lenalidomide/lenalidomide plus dexamethasone. Additional trials seeking to increase the intensity of treatment in these patients should use this less intensive approach as a comparator.


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**Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma**

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APPENDIX

## Trial Design, Oversight, and Treatment

Randomization was conducted centrally using permuted blocks within stratification levels while allowing for institutional balancing. This trial also incorporated a safety Phase 2 run in prior to the start of the randomized portion of the trial. The study was coordinated by the ECOG-ACRIN Cancer Research Group.

## Patients

Patients needed to have measurable levels of monoclonal protein (M-protein) at baseline defined as ≥ 1g/dL in the serum and/or ≥ 200 mg/24 hours in the urine. Baseline skeletal survey and magnetic resonance imaging of the spine and pelvis were required to exclude myeloma bone lesions or plasmacytomas. Patients were required to have ECOG performance status of 0-2, and adequate organ function. All patients were required to provide written informed consent.

## Endpoints and Assessments

Disease assessments were performed at the same times for both treatment and observation arms (every cycle on treatment and in long-term follow-up) from study entry. Adverse events as described are based on the NCI Common Terminology Criteria for Adverse Events v4.0 (v5.0 since 4-1-2018). Grade 3 hematologic AEs were not required reporting. All new cases of second primary cancers (SPC; second or secondary malignancies) were required to be reported within 30 days of diagnosis throughout the entire follow-up period of 10 years. Fluorescent in situ hybridization was used to identify key SMM cytogenetic risk factors.[14]

## Statistical Analysis

With 180 patients accrued over 45 months and an additional 9 months of follow-up to achieve full information (n=76 events), there was 96% power to detect a hazard ratio of 0.40 at a one-sided 2.5% significance level. This corresponded to a 150% improvement in median progression-free survival from 24.8 months on the observation arm to 62 months on the lenalidomide arm given exponential distribution of failure. There also was adequate power (81%) to detect a 60% reduction in the risk of death at a one-sided 2.5% significance level assuming full event information (47 deaths) at 7.5 years from activation.

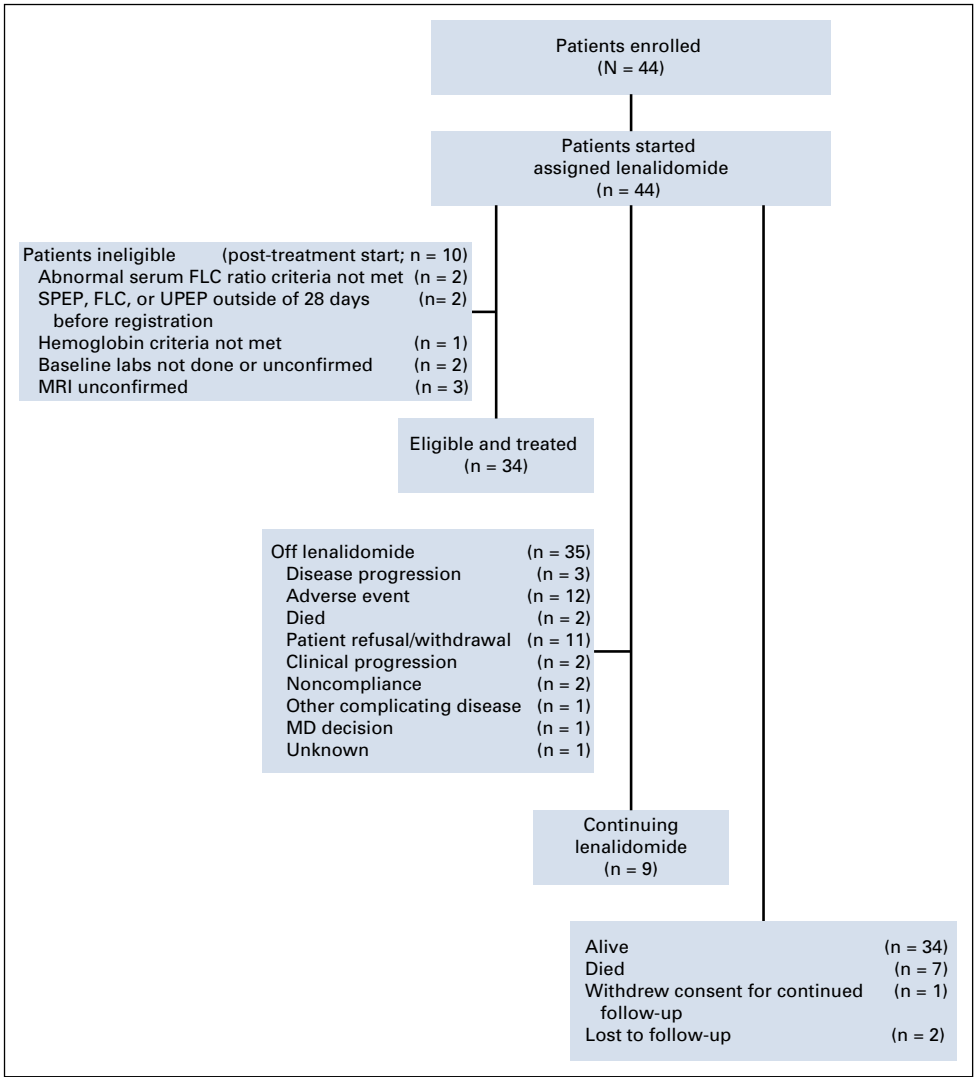


**FIG A1.** CONSORT diagram for phase II. FLC, free light chain; SPEP, serum protein electropheresis; UPEP, urine protein electropheresis.

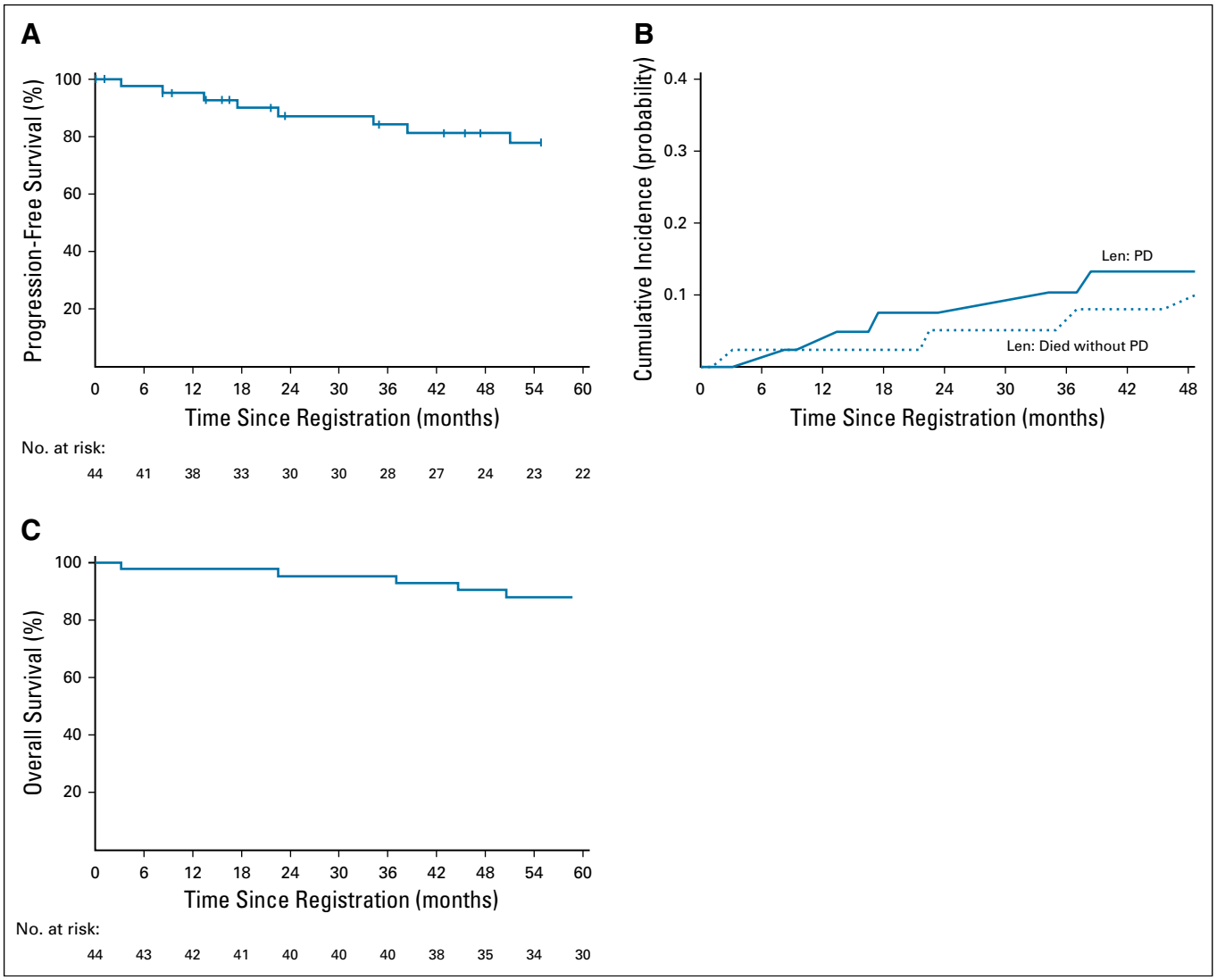


**FIG A2.** Time to event estimates in phase II: (A) progression-free survival, (B) cumulative incidence of progression, and (C) overall survival in patients with smoldering multiple myeloma. Len, lenalidomide.

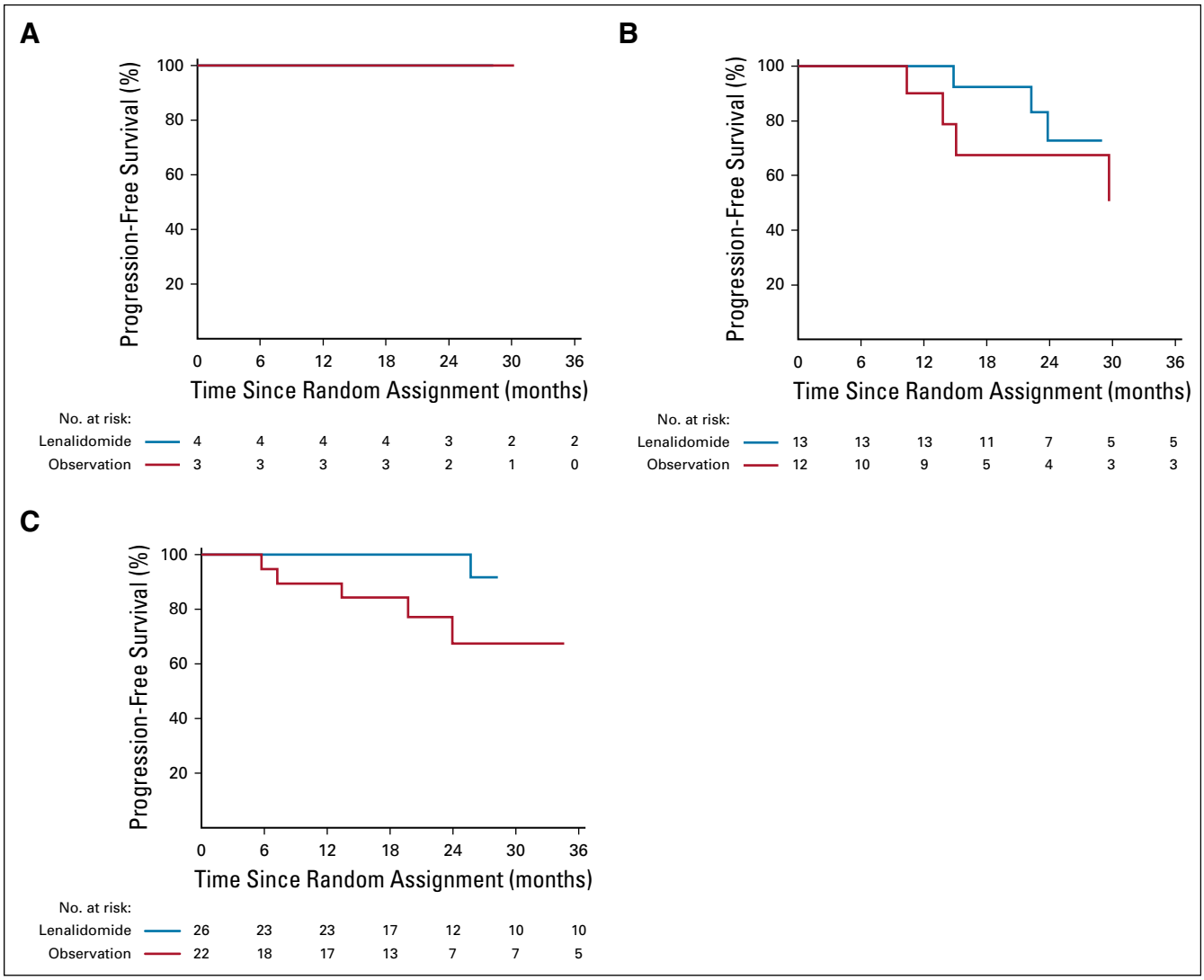


**FIG A3.** Kaplan-Meier estimates of progression-free survival by treatment arm within fluorescence in situ hybridization risk subgroups in phase III: (A) high risk, (B) intermediate risk, and (C) low risk.

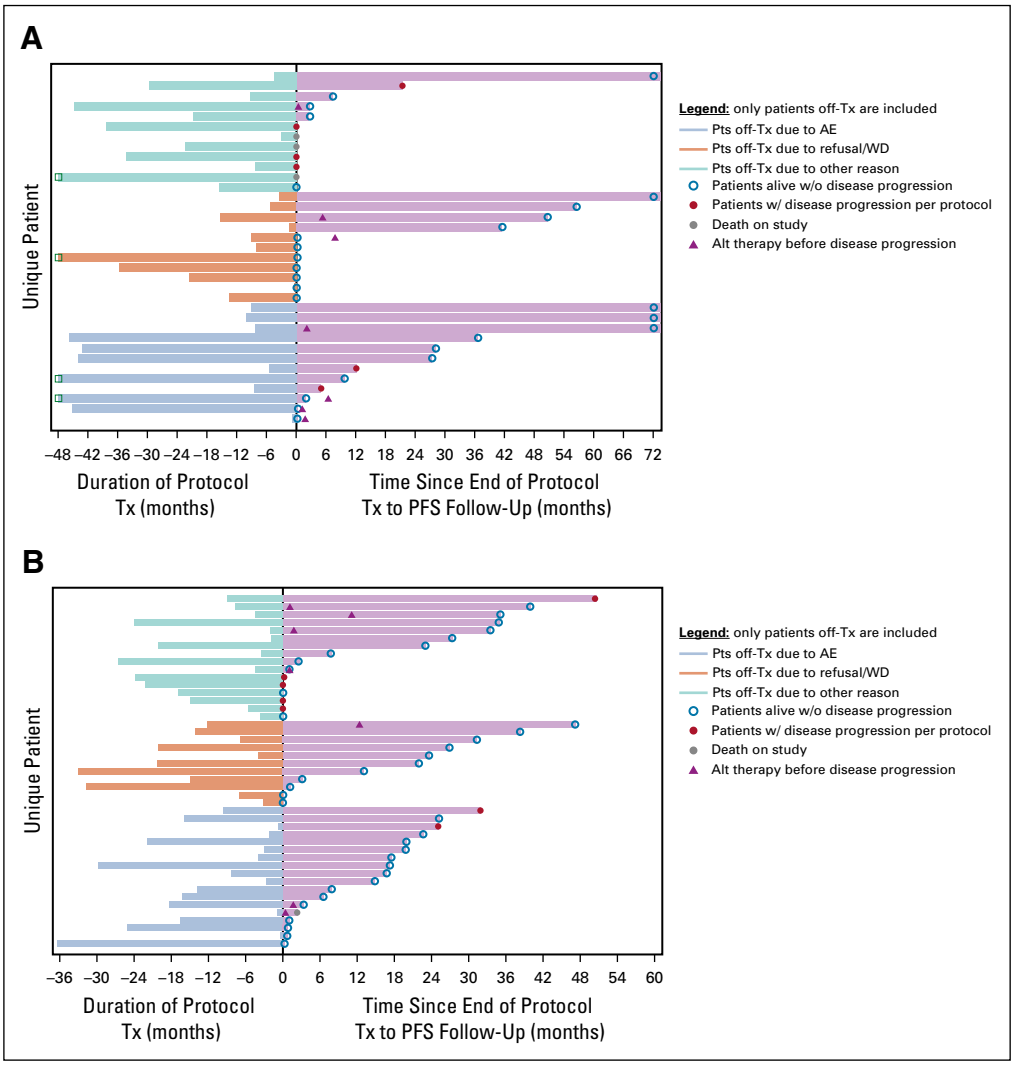


**FIG A4.** Swimmer's plot patterns of treatment duration and follow-up by reason off-treatment (Tx): (A) Patients off-treatment phase II. (B) Patients off treatment phase III. AE, adverse event; PFS, progression-free survival; WD, withdrawal.

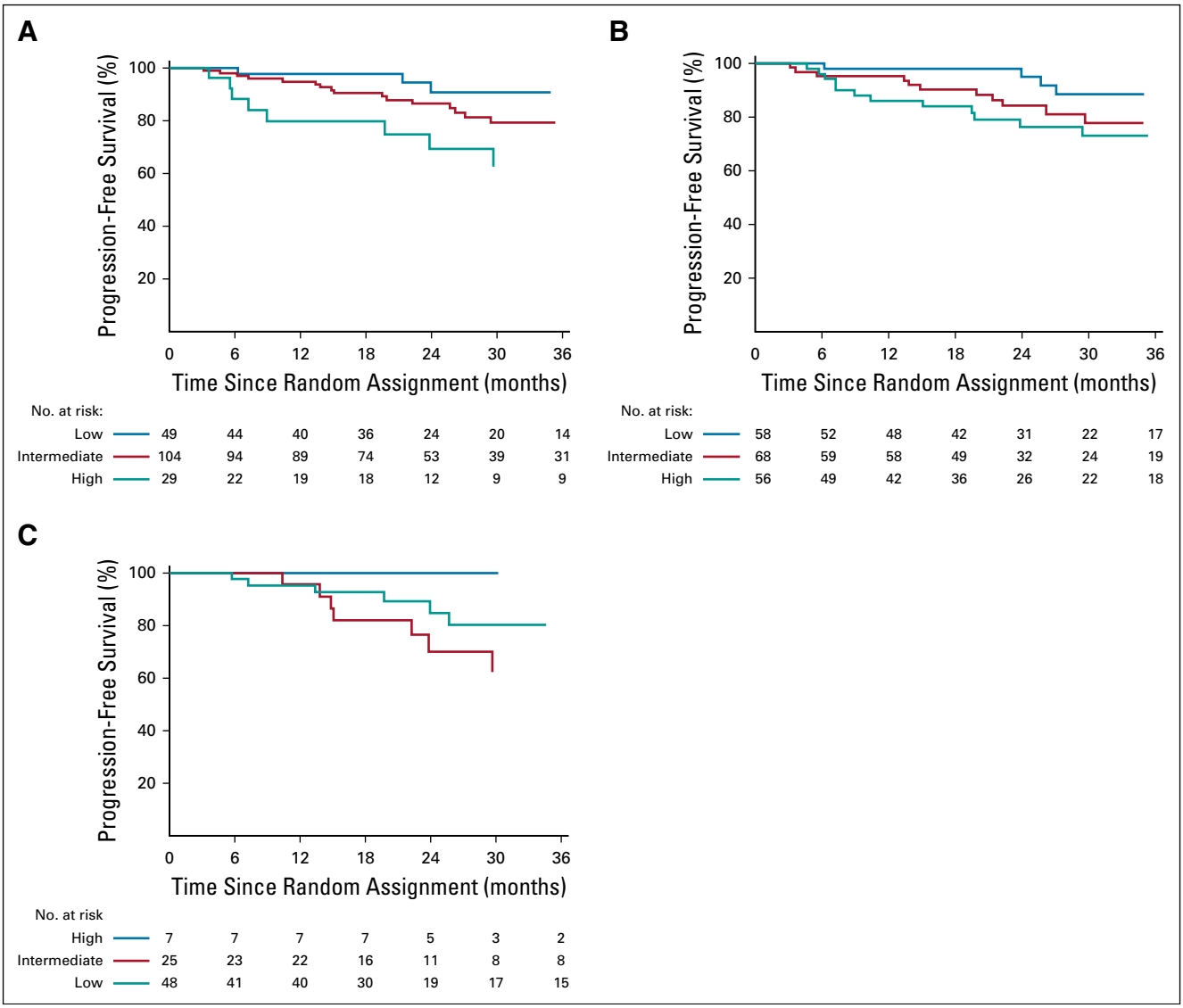


**FIG A5.** Kaplan-Meier estimates of progression-free survival within prognostic subgroups in phase III: (A) Mayo 2008 risk stratification, (B) Mayo 2018 risk stratification, and (C) fluorescence in situ hybridization risk stratification.

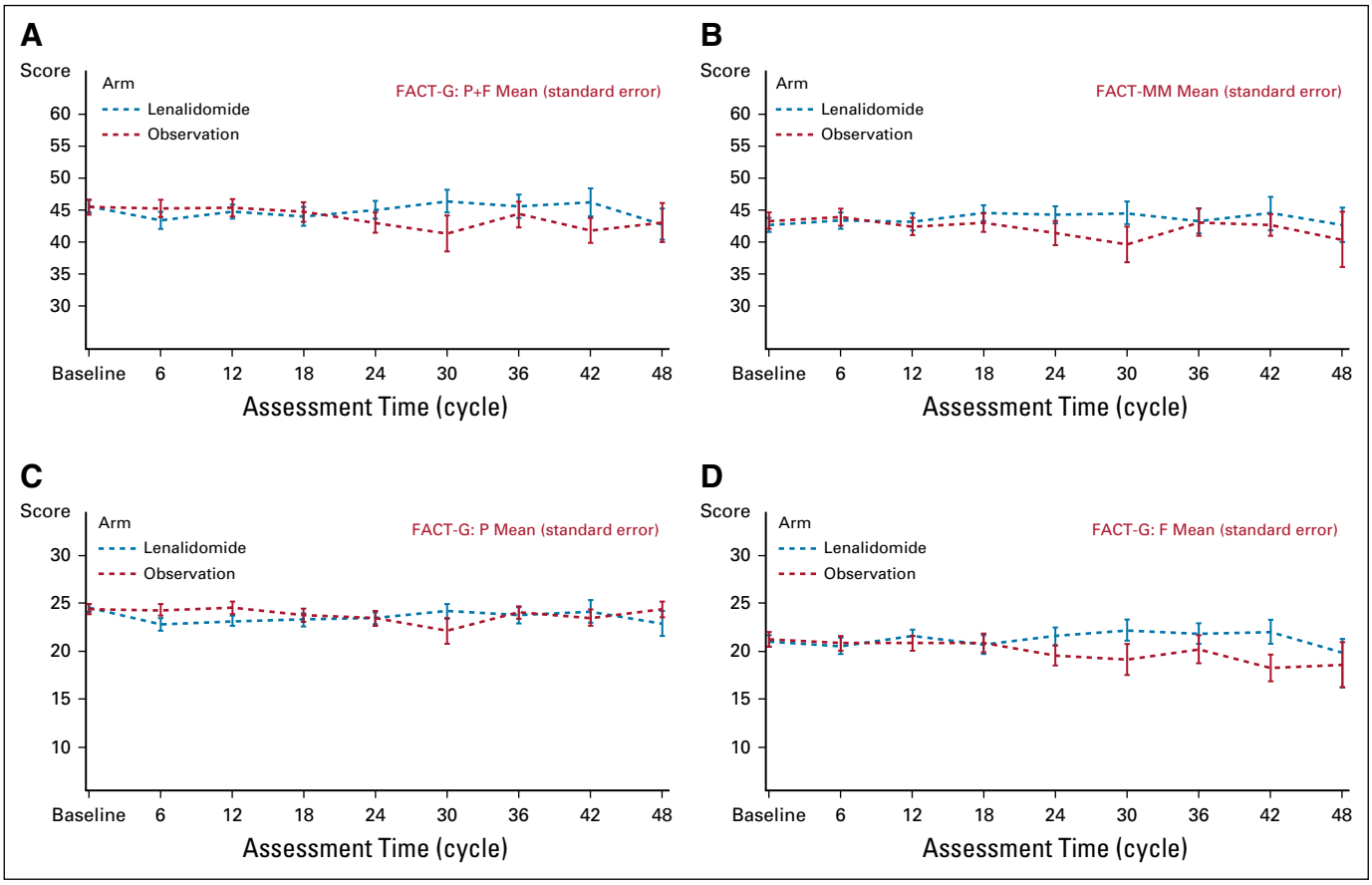


**FIG A6.** Health-related quality of life scores over time in phase III by Functional Assessment of Cancer Therapy-General (FACT-G): (A) FACT-G: Physical plus functional (P+F) well-being score (range, 0-56). (B) FACT-multiple myeloma (MM) score (range, 0-56). (C) FACT-G: Physical (P) well-being score (range, 0-28). (D) FACT-G: Functional (F) well-being score (range, 0-28).

**TABLE A1.** International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma[12]

| Category*† | Multiple Myeloma Response Criteria |
|---|---|
| Stringent complete response | Negative immunofixation on the serum and urine and |
| | Disappearance of any soft tissue plasmacytomas and |
| | ≤ 5% plasma cells in bone marrow and |
| | Normal serum free light-chain (FLC) ratio and |
| | Absence of clonal cells in bone marrow |
| Complete response | Negative immunofixation on the serum and urine and |
| | Disappearance of any soft tissue plasmacytomas and |
| | ≤ 5% plasma cells in bone marrow |
| Very good partial response | Serum and urine M-protein detectable by immunofixation but not on electrophoresis or |
| | ≥ 90% reduction in serum M-protein with urine M-protein < 100 mg per 24 hours |
| Partial response | ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours |
| | If followed by FLC only, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels |
| | If unmeasurable disease by serum M-protein, urine M-protein, and serum FLC at baseline, a ≥ 50% reduction in plasma cells provided baseline bone marrow percentage was ≥ 30% |
| | If present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas |
| Stable disease | Not meeting the criteria for either complete response, very good partial response, partial response, or progressive disease |
| Progressive disease§ | Any one or more of the following: |
| | Increase of ≥ 25% from lowest response value in: |
| | Serum M-component (absolute increase must be ≥ 0.5 g/dL) and/or |
| | Urine M-component (absolute increase must be ≥ 200 mg per 24 hours) and/or |
| | Bone marrow plasma cell percentages (absolute % must be ≥ 10%) |
| | Only in patients without measurable serum and urine M protein levels: the increase in difference between involved and uninvolved FLC levels by ≥ 25% above the lowest response level provided the absolute increase is > 10 mg/dL |
| | Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in size of existing bone lesions or soft tissue plasmacytomas |
| | Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) attributed solely to the plasma cell proliferative disorder |

*Response criteria for all categories except stringent complete response (sCR) and complete response (CR) are applicable only to patients that have measurable disease defined by at least one of the following: serum (SPEP) ≥ 1 g/dL or urine (UPEP) ≥ 200 mg per 24 hours, or serum FLC assay involved free light chain level ≥ 10 mg/dL (≥ 100 mg/L) provided serum FLC ratio is abnormal (< 0.26 or > 1.65). With the exception of assessment of sCR or CR, patients with measurable disease restricted to SPEP need to be followed only by SPEP. Correspondingly, patients with measurable disease restricted to UPEP need to be followed only by UPEP. Patients with measurable disease in both SPEP and UPEP at study entry are required to meet response criteria in both UPEP and SPEP. FLC response criteria are only applicable to patients without measurable disease in the serum or urine.

†All response categories require two consecutive assessments made at any time before the institution of any new therapy, as well as no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments are not required to be confirmed by repeat testing.

§The investigation that qualified as progression should be repeated and verified on a subsequent occasion before the institution of any new therapy.

**TABLE A2.** American Society of Hematology/US Food and Drug Administration Panel Consensus[11]

| Category | Additional Response Criteria for Specific Disease Stages |
|---|---|
| Progression to active myeloma* | Evidence of progression on the basis of International Myeloma Working Group criteria for progressive disease in myeloma and any one or more of the following felt related to the underlying clonal plasma cell proliferative disorder† |
| | Development of new soft-tissue plasmacytomas or bone lesions |
| | Hypercalcemia (> 11 mg per 100 mL) |
| | Decrease in hemoglobin of ≥ 2 g per 100 mL |
| | Increase in serum creatinine by 2 mg per 100 mL |

*For use as progression end point in patients with monoclonal gammopathy of undetermined significance or smoldering multiple myeloma.
†Adapted from the definition of clinical relapse in the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma.[12]

**TABLE A3.** Treatment Duration

| Variable | Phase II Run In: Lenalidomide (n = 44) | Phase III Randomized Trial: Lenalidomide (n = 90) |
|---|---|---|
| Started treatment, No. (%) | 44 (100.0) | 88 (97.8) |
| Median treatment duration,* cycles (range) | 33.5 (1-99) | 23 (1-68) |
| On treatment, No. (% started) | 9 (20.4) | 43 (48.9) |
| Median treatment duration,* cycles (range) | 89 (73-99) | 36 (10-68) |
| Off treatment, No. (% started) | 35 (79.6) | 45 (51.1) |
| Median treatment duration,* cycles (range) | 15 (1-79) | 11 (1-38) |

*On the basis of the last cycle reported and not considering consecutive doses or dose modifications.

**TABLE A4.** Reason Off-Treatment

| Variable | Phase II Run In: Lenalidomide (n = 35) | Phase III Randomized Trial: Lenalidomide (n = 45) |
|---|---|---|
| Disease progression | 3 (8.6) | 7 (15.6) |
| Adverse events | 12 (34.3) | 18 (40.0) |
| Death | 2 (5.7) | 0 (0.0) |
| Patient withdrawal or refusal | 11 (31.4) | 11 (24.4) |
| Alternative therapy | 0 (0.0) | 2 (4.4) |
| MD decision | 0 (0.0) | 4 (8.9) |
| Other | 7 (20.0) | 3 (6.7) |

NOTE. Data are given as No. (%).

**TABLE A5.** Treatment Exposure

| Variable | Phase II Run In: Lenalidomide (n = 44) | | | | | | Phase III Randomized Trial: Lenalidomide (n = 88) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | % Started | Mean % Relative Dose Intensity | No. Reduced Dose | % On Treatment | Mean % Relative Dose Intensity | No. | % Started | Mean % Relative Dose Intensity | No. Reduced Dose | % On Treatment | Mean % Relative Dose Intensity |
| Year 1 | | | | | | | | | | | | |
| Cycle 12 | 29 | 65.9 | 71.0 | 15 | 51.7 | 44.0 | 61 | 69.3 | 55.0 | 49 | 80.3 | 43.9 |
| Year 2 | | | | | | | | | | | | |
| Cycle 24 | 24 | 54.5 | 69.6 | 12 | 50.0 | 39.1 | 44 | 50.0 | 54.8 | 33 | 75.0 | 39.7 |
| Year 3 | | | | | | | | | | | | |
| Cycle 36 | 20 | 45.5 | 57.4 | 13 | 65.0 | 34.4 | 24 | 27.3 | 51.8 | 18 | 75.0 | 35.8 |
| Year 4 | | | | | | | | | | | | |
| Cycle 48 | 18 | 40.9 | 63.7 | 10 | 55.6 | 34.7 | 14 | 15.9 | 51.4 | 10 | 71.4 | 32.0 |
| Year 5 | | | | | | | | | | | | |
| Cycle 60 | 12 | 27.3 | 58.3 | 8 | 66.7 | 37.5 | 7 | 8.0 | 45.7 | 5 | 71.4 | 24.0 |

**TABLE A6.** Basis of Progression

| Variable | Phase II Run In | Phase III Randomized Trial | | |
|---|---|---|---|---|
| | Lenalidomide (n = 6 PD cases) | Lenalidomide (n = 7 PD cases) | Observation (n = 21 PD cases) | Total (n = 28 PD cases) |
| Biochemical | | | | |
| Serum M | 6 (100.0) | 7 (100.0) | 18 (85.7) | 25 (89.3) |
| Urine M | 0 (0.0) | 0 (0.0) | 4 (19.0) | 4 (14.3) |
| Bone marrow plasma cell % | 0 (0.0) | 2 (28.6) | 6 (28.6) | 8 (28.6) |
| End organ | | | | |
| Hypercalcemia | 0 (0.0) | 0 (0.0) | 1 (4.8) | 1 (3.6) |
| Anemia | 2 (33.3) | 4 (57.1) | 8 (38.1) | 12 (42.9) |
| Renal failure | 0 (0.0) | 0 (0.0) | 3 (14.3) | 3 (10.7) |
| Bone lesion/soft-tissue plasmacytoma | 4 (66.7) | 3 (42.9) | 11 (52.4) | 14 (50.0) |

NOTE. Data are given as No. (%). Progression defined per protocol required biochemical and end organ failure. Within these categories, multiple bases of progression may be reported.

Abbreviation: PD, progressive disease.

**TABLE A7.** Second Primary Cancers Among Patients Starting Assigned Therapy

| | Phase II Run In | Phase III Randomized Trial | |
|---|---|---|---|
| **Variable** | **Lenalidomide (n = 44)** | **Lenalidomide (n = 88)** | **Observation (n = 86)** |
| Hematologic, No. (%) | | | |
| MDS | 1 (2.3) | 0 (0.0) | 0 (0.0) |
| ALL | 1 (2.3) | 0 (0.0) | 0 (0.0) |
| Hodgkin disease | 0 (0.0) | 1 (1.1) | 0 (0.0) |
| AML | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| NHL | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Subtotal heme | 2 (4.5) | 1 (1.1) | 0 (0.0) |
| Solid tumors | 1 (2.3) | 3 (3.4) | 2 (2.3) |
| Total invasive SPC | 3 (6.8) | 4 (4.5) | 2 (2.3) |
| Nonmelanoma skin* | 3 (6.8) | 6 (6.8) | 1 (1.2) |
| Total SPC | 6 (13.6) | 10 (11.4) | 3 (3.5) |
| Cumulative incidence, years† | 4 | 3 | 3 |
| Invasive SPC, % | 4.9 | 5.2 | 3.5 |
| Total SPC, % | 9.7 | 11.0 | 4.8 |
| Invasive SPC details, median (range)‡ | | | |
| Time to SPC, months | 46 (17-79) | 14 (11-28) | 19 (4-34) |
| Treatment duration, cycle | 48 (14-79) | 23 (3-52) | na |
| Age at reg, years | 54 (52-73) | 68 (61-71) | 69 (65-73) |

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; NHL, non-Hodgkin lymphoma; na, not applicable; SPC, second primary cancers.

*Only first instance of nonmelanoma skin was counted.

†Cumulative incidence estimates accounting for death as a competing risk.

‡Of invasive SPC lenalidomide cases: Mayo 2018 Risk High (n = 4), Intermediate (n = 1), and Low (n = 2).

**TABLE A8.** Cox Regression Estimates of Progression-Free Survival Within Prognostic Subgroups in Phase III

| | | Phase III Randomized Trial | | |
|---|---|---|---|---|
| **Prognostic Factor** | **Comparison** | **HR** | **95% CI** | ***P*** |
| MAYO 2008 risk stratification (3 levels) | High *v* intermediate | 1.76 | (0.77 to 4.02) | .181 |
| | High *v* low | 5.17 | (1.37 to 19.49) | .015 |
| MAYO 2018 risk stratification (3 levels) | High *v* intermediate | 1.56 | (0.71 to 3.45) | .270 |
| | High *v* low | 3.84 | (1.27 to 11.61) | .017 |
| Time from initial high-risk SMM diagnosis | $> 1$ y *v* $\leq 1$ y | 0.69 | (0.16 to 2.93) | .620 |
| ECOG PS | ECOG PS $> 0$ *v* ECOG PS $= 0$ | 1.17 | (0.54 to 2.53) | .697 |
| Age | Age $\geq 70$ y *v* age $< 70$ y | 2.08 | (1.00 to 4.34) | .050 |
| Sex | Female *v* male | 1.03 | (0.50 to 2.11) | .933 |
| Race | Black *v* white | 0.62 | (0.19 to 2.07) | .440 |
| IgA | IgA $> 1{,}530$ mg/dL *v* IgA $\leq 1{,}530$ mg/dL | 2.78 | (1.23 to 6.28) | .014 |

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IgA, immunoglobulin A; SMM, smoldering multiple myeloma.

**TABLE A9.** Descriptive Statistics for FACT-G Physical Plus Functional Quality-of-Life Score Over Time in Phase III

| | Phase III Randomized Trial | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Lenalidomide | | | | | | | Observation | | | | | | | |
| | Score | | | | Change Score From Baseline | | | Score | | | | Change Score From Baseline | | | |
| Time | No. | % St Trt | Mean | SD | No. | Mean | SD | No. | % St Obs | Mean | SD | No. | Mean | SD | Diff Mean Change Score | 95% CI |
| Baseline | 85 | 97 | 45.6 | 8.7 | na | na | na | 84 | 98 | 45.4 | 11.0 | na | na | na | na | na |
| Cycle 6 | 65 | 74 | 43.4 | 11.0 | 63 | −3.3 | 7.2 | 65 | 76 | 45.2 | 10.7 | 64 | 0.0 | 7.0 | −3.3 | (−5.8 to −0.8) |
| Cycle 12 | 57 | 65 | 44.8 | 8.4 | 54 | −1.4 | 5.2 | 55 | 64 | 45.4 | 10.2 | 53 | −0.2 | 6.8 | −1.2 | (−3.5 to 1.1) |
| Cycle 18 | 50 | 57 | 44.0 | 10.6 | 48 | −2.3 | 8.3 | 40 | 47 | 44.7 | 9.8 | 38 | −0.5 | 8.0 | −1.8 | (−5.3 to 1.7) |
| Cycle 24 | 38 | 43 | 45.0 | 8.6 | 36 | −1.7 | 4.2 | 27 | 31 | 43.0 | 8.4 | 25 | −1.6 | 9.8 | −0.1 | (−4.2 to 4.0) |
| Cycle 30 | 25 | 28 | 46.4 | 8.7 | 23 | −0.9 | 5.4 | 14 | 16 | 41.3 | 10.6 | 13 | 1.4 | 5.9 | −2.3 | (−6.2 to 1.6) |
| Cycle 36 | 23 | 26 | 45.6 | 9.0 | 22 | −1.5 | 5.7 | 12 | 14 | 44.3 | 6.9 | 12 | 2.1 | 8.0 | −3.6 | (−8.7 to 1.5) |
| Cycle 42 | 15 | 17 | 46.2 | 8.6 | 15 | −1.6 | 5.3 | 9 | 10 | 41.8 | 5.8 | 8 | −0.8 | 10.6 | −0.8 | (−8.6 to 7.0) |
| Cycle 48 | 13 | 15 | 42.8 | 8.8 | 13 | −3.7 | 6.6 | 5 | 6 | 43.0 | 6.8 | 5 | −4.3 | 7.1 | 0.6 | (−6.6 to 7.8) |

Abbreviations: FACT-G, Functional Assessment of Cancer Therapy-General; na, not applicable; SD, standard deviation; St Obs, started observation; St Trt, started treatment.