ORIGINAL ARTICLE

Lenalidomide and Dexamethasone in Transplant-Ineligible Patients with Myeloma

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ABSTRACT

BACKGROUND

The combination melphalan–prednisone–thalidomide (MPT) is considered a standard therapy for patients with myeloma who are ineligible for stem-cell transplantation. However, emerging data on the use of lenalidomide and low-dose dexamethasone warrant a prospective comparison of the two approaches.

METHODS

We randomly assigned 1623 patients to lenalidomide and dexamethasone in 28-day cycles until disease progression (535 patients), to the same combination for 72 weeks (18 cycles; 541 patients), or to MPT for 72 weeks (547 patients). The primary end point was progression-free survival with continuous lenalidomide–dexamethasone versus MPT.

RESULTS

The median progression-free survival was 25.5 months with continuous lenalidomide–dexamethasone, 20.7 months with 18 cycles of lenalidomide–dexamethasone, and 21.2 months with MPT (hazard ratio for the risk of progression or death, 0.72 for continuous lenalidomide–dexamethasone vs. MPT and 0.70 for continuous lenalidomide–dexamethasone vs. 18 cycles of lenalidomide–dexamethasone; P<0.001 for both comparisons). Continuous lenalidomide–dexamethasone was superior to MPT for all secondary efficacy end points, including overall survival (at the interim analysis). Overall survival at 4 years was 59% with continuous lenalidomide–dexamethasone, 56% with 18 cycles of lenalidomide–dexamethasone, and 51% with MPT. Grade 3 or 4 adverse events were somewhat less frequent with continuous lenalidomide–dexamethasone than with MPT (70% vs. 78%). As compared with MPT, continuous lenalidomide–dexamethasone was associated with fewer hematologic and neurologic toxic events, a moderate increase in infections, and fewer second primary hematologic cancers.

CONCLUSIONS

As compared with MPT, continuous lenalidomide–dexamethasone given until disease progression was associated with a significant improvement in progression-free survival, with an overall survival benefit at the interim analysis, among patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation. (Funded by Intergroupe, Francophone du Myélome and Celgene; FIRST ClinicalTrials.gov number, NCT00689936; European Union Drug Regulating Authorities Clinical Trials number, 2007-004823-39.)

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N Engl J Med 2014;371:906-17.
DOI: 10.1056/NEJMoa1402551

For patients with newly diagnosed multiple myeloma who are ineligible for autologous stem-cell transplantation, the standard therapy is melphalan and prednisone (MP) combined with either thalidomide (MPT) or bortezomib (VMP).[1-10] Lenalidomide (Revlimid, Celgene) is an immunomodulatory drug that, in combination with dexamethasone, is a standard treatment option for patients with multiple myeloma who have received at least one prior therapy as approved by the Food and Drug Administration and the European Medicines Agency.[7-13] In a randomized trial that included both younger and older patients with newly diagnosed multiple myeloma, lenalidomide plus low-dose dexamethasone was associated with fewer adverse events and a higher rate of overall survival at 1 year than lenalidomide plus high-dose dexamethasone (96% vs. 87%, P<0.001), making it an option for patients who are ineligible for stem-cell transplantation.[14] To our knowledge, there have been no reports of front-line use of lenalidomide–dexamethasone in a large, homogeneous cohort of elderly patients (≥65 years of age). In this phase 3 randomized trial, we compared the efficacy and safety of lenalidomide–dexamethasone, given until disease progression or for a fixed number of cycles, with MPT given for a fixed number of cycles in patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation.

Methods

Patients and Study Oversight

Eligible patients had previously untreated, symptomatic, and measurable multiple myeloma[15] and either were 65 years of age or older or were younger than 65 years of age and ineligible for stem-cell transplantation. Exclusion criteria were prior antimyeloma treatment (except for radiotherapy and treatment with bisphosphonates or a single course of glucocorticoids), an Eastern Cooperative Oncology Group performance-status score of more than 2 (on a scale from 0 to 5, with higher numbers indicating greater disability),[16] renal failure requiring dialysis, an absolute neutrophil count below 1000 cells per cubic millimeter, a platelet count (without transfusion) below 50,000 cells per cubic millimeter, a serum aspartate aminotransferase or alanine aminotransferase level that was more than three times the upper limit of the normal range, and peripheral neuropathy of grade 2 or higher. Patients had to be able and willing to undergo antithrombotic prophylaxis.

The study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonisation Guidelines for Good Clinical Practice. Before trial initiation, the protocol, informed-consent form, and other information for study participants were reviewed and approved by the institutional review board or independent ethics committee at each participating center. All the patients provided written informed consent.

The Frontline Investigation of Revlimid and Dexamethasone versus Standard Thalidomide (FIRST) study was designed by Intergroupe Francophone du Myélome (IFM study number, 2007-01/Multiple Myeloma 020) in collaboration with Celgene, which sponsored the trial. Employees of the sponsor assisted with the study design, data collection, data analysis, and writing of the manuscript in collaboration with the senior academic authors, who vouch for the accuracy and completeness of the data reported and the adherence of the study to the protocol. Agreements between the sponsor and authors were made to ensure data confidentiality. The first draft and the revised draft of the manuscript were developed by the last author. All the coauthors participated in the entire development of the manuscript and reviewed and approved it; together with the last author, they made the decision to submit the manuscript for publication. Assistance with the writing of the manuscript was funded by Celgene. All the authors had full access to the data and reviewed and approved the manuscript before submission. The protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org. More detailed information about study oversight and disclosure is provided in the Supplementary Appendix, available at NEJM.org.

Study Design and Treatment

The FIRST trial was an open-label, three-group, phase 3 randomized trial conducted at 246 treatment centers in 18 countries in Europe, North America, and the Asia–Pacific region. Enrollment occurred from August 2008 through March 2011. Using a validated interactive voice-response system, we randomly assigned patients in a 1:1:1 ratio to receive lenalidomide–dexamethasone in 28-day cycles until disease progression, lenalido-

mide–dexamethasone in 28-day cycles for 72 weeks (18 cycles), or MPT in 42-day cycles for 72 weeks (12 cycles). Patients were stratified according to age (≤75 years vs. >75 years), International Staging System disease stage (I or II vs. III, with higher stages indicating more severe disease) (Table S11 in the Supplementary Appendix), and country. In the two lenalidomide–dexamethasone groups, lenalidomide at a dose of 25 mg per day was given on days 1 to 21 of each 28-day cycle, and dexamethasone at a dose of 40 mg was given on days 1, 8, 15, and 22. In the MPT group, melphalan (at a dose of 0.25 mg per kilogram of body weight per day on days 1 to 4), prednisone (at a dose of 2 mg per kilogram per day on days 1 to 4), and thalidomide (at a dose of 200 mg per day) were administered in 42-day cycles. Dose adjustments are described in the Supplementary Appendix.

All patients received protocol-specified antithrombotic prophylaxis (see the Additional Methods section in the Supplementary Appendix). Bisphosphonates and other supportive therapies were allowed at the investigator's discretion. Detailed information on antithrombotic prophylaxis and supportive care is provided in the Supplementary Appendix.

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival with continuous lenalidomide–dexamethasone as compared with MPT. Secondary end points included overall survival, overall rate of response (partial response or better), time to response, duration of response, time to treatment failure, time to second-line antimyeloma therapy, health-related quality of life, and safety. Secondary comparisons (18 cycles of lenalidomide–dexamethasone vs. MPT, and continuous lenalidomide–dexamethasone vs. 18 cycles of lenalidomide–dexamethasone) were also performed for all end points. Exploratory analyses included time to disease progression and progression-free survival after the next line of treatment (progression-free survival 2) (Table S13 in the Supplementary Appendix).

Response was evaluated with the use of the International Uniform Response Criteria for Multiple Myeloma (Table S12 in the Supplementary Appendix)[17] after each treatment cycle and every 28 days during the follow-up phase. An independent response-adjudication committee reviewed the response data and the dates of progression. Health-related quality-of-life questionnaires (European Organisation for Research and Treatment of Cancer QLQ-C30,[18] QLQ-MY20,[19] and EQ-5D[20]) were collated (see the Supplementary Appendix). Adverse-event severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.[21] An independent data and safety monitoring committee monitored safety and efficacy data throughout the study.

STATISTICAL ANALYSIS

We estimated that 1590 patients (530 per treatment group) would need to be enrolled to provide the study with 80% power to detect a hazard ratio of 0.80 for disease progression or death (continuous lenalidomide–dexamethasone vs. MPT), using a two-sided log-rank test with a significance level of 0.05, including one interim analysis. The final analysis of progression-free survival was planned when at least 950 events of disease progression or death had occurred across all treatment groups. With a step-down group sequential approach, an interim analysis of overall survival was planned at the time of the final analysis of progression-free survival. The O'Brien–Fleming boundary was used for progression-free survival,[22,23] and the Pocock boundary was used for overall survival.[22,24]

RESULTS

PATIENTS AND TREATMENT

A total of 1623 patients were randomly assigned to continuous lenalidomide–dexamethasone (535 patients), 18 cycles of lenalidomide–dexamethasone (541), or MPT (547). The characteristics of the patients at baseline were well balanced among the treatment groups (Table 1). The median duration of treatment was 18.4 months with continuous lenalidomide–dexamethasone, 16.6 months with 18 cycles of lenalidomide–dexamethasone, and 15.4 months with MPT. A total of 39% of the patients assigned to continuous lenalidomide–dexamethasone received more than 2 years of study treatment. With a data cutoff of May 24, 2013, the median duration of follow-up among surviving patients was 37.0 months (range, 0 to 56.7). At the time of the analysis, 121 of 535 patients (23%) in the continuous lenalidomide–dexamethasone group were still receiving treatment (Fig. S1 in the Supplementary Appendix).

EFFICACY

The median progression-free survival was 25.5 months with continuous lenalidomide–dexamethasone, 20.7 months with 18 cycles of lenalidomide–dexamethasone, and 21.2 months with MPT. Continuous lenalidomide–dexamethasone was associated with a significant improvement in progression-free survival, as compared with MPT (hazard ratio for progression or death, 0.72; 95% confidence interval [CI], 0.61 to 0.85; P<0.001) (Fig. 1A). Continuous lenalidomide–dexamethasone also reduced the risk of progression or death, as compared with 18 cycles of lenalidomide–dexamethasone (hazard ratio, 0.70; 95% CI, 0.60 to 0.82; P<0.001) (Fig. 1A). The risk in the group that received 18 cycles of lenalidomide–dexamethasone was similar to that in the MPT group (hazard ratio, 1.03; 95% CI, 0.89 to 1.20; P=0.70).

At the time of the interim analysis of overall survival, 173 patients in the continuous lenalidomide–dexamethasone group, 192 in the group that received 18 cycles of lenalidomide–dexamethasone, and 209 in the MPT group had died. The overall survival rates at 3 years were 70% with continuous lenalidomide–dexamethasone, 66% with 18 cycles of lenalidomide–dexamethasone, and 62% with MPT; the overall survival rates at 4 years were 59%, 56%, and 51%, respectively. Although the difference in overall survival did not cross the prespecified superiority boundary (P<0.0096), continuous lenalidomide–dexamethasone reduced the risk of death, as compared with MPT (hazard ratio, 0.78; 95% CI, 0.64 to 0.96; P=0.02) (Fig. 1B).

The superiority of continuous lenalidomide–dexamethasone over MPT for both progression-free survival and overall survival was noted in most subgroups, including younger patients and patients older than 75 years of age. The benefit of continuous lenalidomide–dexamethasone was questionable in patients with poor prognostic features, such as a high-risk cytogenetic profile or a high level of lactate dehydrogenase (Fig. S2 and S3 in the Supplementary Appendix).

Response rates were higher with continuous lenalidomide–dexamethasone (75%) and with 18 cycles of lenalidomide–dexamethasone (73%) than with MPT (62%; P<0.001 for both comparisons) (Table 2). Rates of very good partial response (Table S12 in the Supplementary Appendix) or better were also higher with continuous lenalidomide–dexamethasone (44%) or 18 cycles of lenalidomide–dexamethasone (43%) than with MPT (28%), as were rates of complete response (15%, 14%, and 9%, respectively). Responses were more durable with continuous lenalidomide–dexamethasone than with 18 cycles of lenalidomide–dexamethasone or MPT (P<0.001 for both comparisons) (Fig. 1C), and the progression-free survival benefit associated with continuous lenalidomide–dexamethasone versus 18 cycles of lenalidomide–dexamethasone was more pronounced among patients who had a very good partial response or a complete response (Fig. S4 in the Supplementary Appendix). Time to disease progression and time to treatment failure also favored continuous lenalidomide–dexamethasone over MPT (Fig. S5 in the Supplementary Appendix).

Fewer patients received second-line therapy in the continuous lenalidomide–dexamethasone group (231 of 535 patients [43%]) than in the group that received 18 cycles of lenalidomide–dexamethasone (299 of 541 [55%]) or in the MPT group (309 of 547 [56%]) (Table S14 in the Supplementary Appendix). The time to second-line antimyeloma therapy was longer with continuous lenalidomide–dexamethasone (39.1 months) than with 18 cycles of lenalidomide–dexamethasone (28.5 months, P<0.001) or with MPT (26.7 months, P<0.001) (Fig. S5 in the Supplementary Appendix). The progression-free survival benefit observed with continuous lenalidomide–dexamethasone was maintained with the next line of therapy because the median progression-free survival 2 was longer with continuous lenalidomide–dexamethasone than with MPT (42.9 months vs. 36.3 months; hazard ratio for progression or death, 0.78; P=0.005) (Fig. S5 in the Supplementary Appendix). Clinically relevant health-related quality of life measurements generally improved in all the treatment groups (see the Supplementary Appendix).

SAFETY

The proportion of patients with one or more adverse events of grade 3 or 4 was 85% in the continuous lenalidomide–dexamethasone group, 80% in the group that received 18 cycles of lenalidomide–dexamethasone, and 89% in the MPT group (Table 3). The incidences of grade 3 or 4 neutropenia were lower with continuous lenalidomide–dexamethasone (28%) and with 18 cycles of lenalidomide–dexamethasone (26%) than

with MPT (45%); continuous lenalidomide–dexamethasone therapy did not appear to increase the rate of neutropenia. Febrile neutropenia was uncommon, occurring in 1% of patients treated with continuous lenalidomide–dexamethasone, in 3% of those treated with 18 cycles of lenalidomide–dexamethasone, and in 3% of those treated with MPT. The rates of grade 3 or 4 thrombocytopenia and anemia were similar across treatment groups.

Infection of grade 3 or 4 occurred in 29% of the patients who received continuous lenalidomide–dexamethasone, in 22% of those who received 18 cycles of lenalidomide–dexamethasone, and in 17% of those who received MPT. Most cases of infection in the continuous lena-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Continuous Lenalidomide–Dexamethasone (N=535)	Lenalidomide–Dexamethasone for 18 Cycles (N=541)	MPT (N=547)
Age			
Median — yr	73	73	73
Range — yr	44–91	40–89	51–92
≥65 yr — no. (%)	504 (94)	507 (94)	520 (95)
>75 yr — no. (%)	186 (35)	193 (36)	188 (34)
Sex — no. (%)			
Male	294 (55)	273 (50)	287 (52)
Female	241 (45)	268 (50)	260 (48)
Race or ethnic group — no. (%)†			
White	474 (89)	480 (89)	491 (90)
Asian	40 (7)	43 (8)	44 (8)
Black	9 (2)	6 (1)	5 (1)
Native Hawaiian or Pacific Islander	1 (<1)	0	1 (<1)
Other	6 (1)	11 (2)	3 (1)
Undisclosed	5 (1)	1 (<1)	3 (1)
ECOG performance-status score — no. (%)‡			
0	155 (29)	163 (30)	156 (29)
1	257 (48)	263 (49)	275 (50)
2	119 (22)	113 (21)	111 (20)
3	2 (<1)	2 (<1)	2 (<1)
Data not available	2 (<1)	0	3 (1)
International Staging System stage — no. (%)§			
I or II	319 (60)	322 (60)	323 (59)
III	216 (40)	219 (40)	224 (41)
Myeloma subtype — no. (%)			
IgA	138 (26)	142 (26)	123 (22)
IgD	4 (1)	7 (1)	4 (1)
IgG	334 (62)	331 (61)	350 (64)
IgM	3 (1)	1 (<1)	1 (<1)
IgA and IgG	7 (1)	6 (1)	8 (1)
IgA and IgM	0	0	1 (<1)
Light-chain only	46 (9)	54 (10)	57 (10)
Data not available	3 (1)	0	3 (1)

Table 1. (Continued.)

Characteristic	Continuous Lenalidomide–Dexamethasone (N=535)	Lenalidomide–Dexamethasone for 18 Cycles (N=541)	MPT (N=547)
Lactate dehydrogenase — no. (%)			
<200 U/liter	448 (84)	442 (82)	434 (79)
≥200 U/liter	86 (16)	99 (18)	112 (20)
Missing data	1 (<1)	0	1 (<1)
Creatinine clearance — no. (%)			
<30 ml/min	45 (8)	47 (9)	55 (10)
<60 ml/min	267 (50)	254 (47)	258 (47)
≥60 ml/min	268 (50)	287 (53)	289 (53)
History of bone lesions — no. (%)			
Present	380 (71)	382 (71)	394 (72)
Absent	154 (29)	158 (29)	153 (28)
Unknown	1 (<1)	1 (<1)	0
High-risk cytogenetic profile — no./total no. (%)¶	43/248 (17)	52/261 (20)	47/253 (19)

* There were no significant between-group differences at baseline. MPT denotes melphalan–prednisone–thalidomide.
† Race and ethnic group were self-reported.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher numbers indicating greater disability.[16] Six patients across the three study groups had worsening of their ECOG performance-status score from 2 to 3 during the screening period.
§ Higher stages indicate more severe disease.
¶ A high-risk cytogenetic profile was defined as translocations (4;14) or (14;16) or deletion 17p.

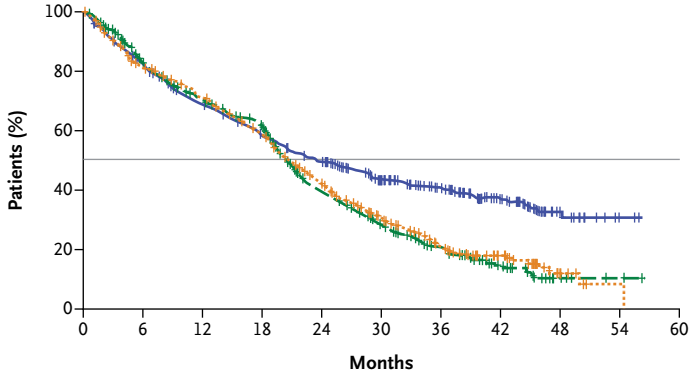
lidomide–dexamethasone group occurred in the absence of neutropenia (80%). The incidence of deep-vein thrombosis, pulmonary embolism, or both was 8% in the continuous lenalidomide–dexamethasone group, 6% in the group that received 18 cycles of lenalidomide–dexamethasone, and 5% in the MPT group. Cardiac events of grade 3 or 4 occurred in 12%, 7%, and 9% of the patients, respectively (see the Supplementary Appendix). Peripheral sensory neuropathy was reported in 1% or less of the patients treated with continuous lenalidomide–dexamethasone or 18 cycles of the therapy, as compared with 9% of those treated with MPT. Safety data according to age are presented in Table S15 in the Supplementary Appendix. In the continuous lenalidomide–dexamethasone group, most adverse events occurred within the first 18 months of therapy and decreased over time, with the exception of infection, which remained stable, and the development of cataracts, which increased with treatment beyond 18 months (Table S16 in the Supplementary Appendix).

Invasive second primary cancers were reported in 17 patients (3%) who received continuous lenalidomide–dexamethasone, in 30 (6%) who received 18 cycles of lenalidomide–dexamethasone, and in 27 (5%) who received MPT. Hematologic cancers (acute myeloid leukemia and the myelodysplastic syndrome) were more frequent with MPT (12 cases [in 2% of patients]) than with continuous lenalidomide–dexamethasone or 18 cycles of lenalidomide–dexamethasone (2 [<1%] in each group). Solid tumors were observed in 15 patients (3%) in the continuous lenalidomide–dexamethasone group, in 29 (5%) in the group that received 18 cycles of lenalidomide–dexamethasone, and in 15 (3%) in the MPT group (Tables S17 and S18 in the Supplementary Appendix).

DISCUSSION

This trial compared an alkylator-containing triplet regimen (MPT) with an alkylator-free doublet regimen (lenalidomide–dexamethasone) that was administered either until disease progression or for a limited period in patients with multiple myeloma who were ineligible for stem-cell transplantation. The study population was older and had

A Progression-free Survival



	Median Progression-free Survival (mo)
Continuous Ld (N=535)	25.5
Ld18 (N=541)	20.7
MPT (N=547)	21.2

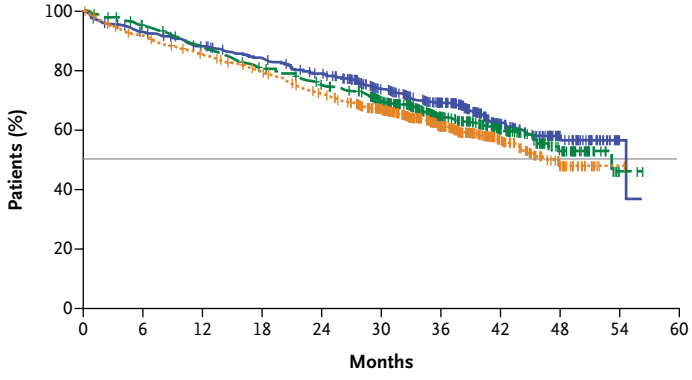
Hazard ratio:
Continuous Ld vs. MPT, 0.72; P<0.001

Continuous Ld vs. Ld18, 0.70; P<0.001

No. at Risk

Continuous Ld	535	400	319	265	218	168	105	55	19	2	0
Ld18	541	391	319	265	167	108	56	30	7	2	0
MPT	547	380	304	244	170	116	58	28	6	1	0

B Overall Survival



	4-Yr Overall Survival (%)
Continuous Ld (N=535)	59
Ld18 (N=541)	56
MPT (N=547)	51

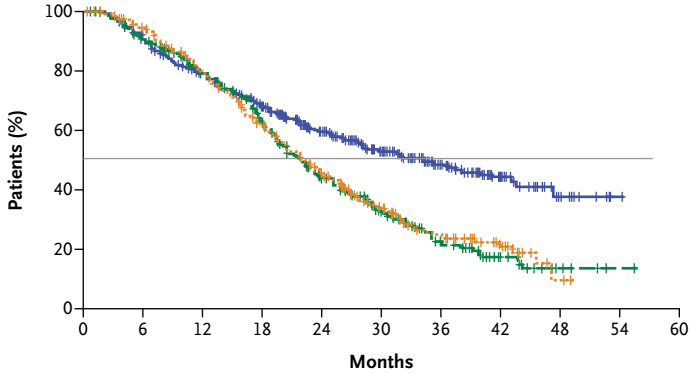
Hazard ratio:
Continuous Ld vs. MPT, 0.78; P=0.02

Continuous Ld vs. Ld18, 0.90; P=0.31

No. at Risk

Continuous Ld	535	488	457	433	403	338	224	121	43	5	0
Ld18	541	505	465	425	393	324	209	124	44	6	0
MPT	547	484	448	418	375	312	205	106	30	3	0

C Duration of Response



	Median Duration of Response (mo)
Continuous Ld (N=402)	35.0
Ld18 (N=397)	22.1
MPT (N=341)	22.3

Hazard ratio:
Continuous Ld vs. MPT, 0.63; P<0.001

Continuous Ld vs. Ld18, 0.60; P<0.001

No. at Risk

Continuous Ld	402	351	289	241	198	146	84	36	9	1	0
Ld18	397	338	286	214	145	92	40	19	5	1	0
MPT	341	297	239	179	123	75	35	14	2	0	—

Figure 1 (facing page). Kaplan–Meier Estimates of Progression-free Survival, Overall Survival, and Duration of Response.

Panel A shows the estimated median progression-free survival in the intention-to-treat population. Panel B shows the estimated overall survival in the intention-to-treat population. Panel C shows the estimated median duration of response in patients with a partial response or better. In all panels, the horizontal line indicates the median, and short vertical lines on each curve indicate patients with censored data. Ld denotes lenalidomide–dexamethasone, Ld18 18 cycles of lenalidomide–dexamethasone, and MPT melphalan–prednisone–thalidomide.

a poorer prognosis than otherwise similar patient populations in previous phase 3 trials.[1-3,25,26] The proportion of patients who were older than 75 years of age (35%) was 5 and 11 percentage points higher than that in the two trials of VMP and MP plus lenalidomide (MPR),[3,25] and more patients had International Staging System stage III disease (approximately 40%) than in previous trials of MPT and VMP (22% to 34%).[1-3,26]

We enrolled patients with severe renal impairment who did not require dialysis (9% of the study population had a creatinine clearance of <30 ml per minute). Our results indicate that continuous administration of lenalidomide–dexamethasone significantly reduced the risk of progression or death by 28% and the risk of death by 22%, as compared with MPT. Responses were 13% more frequent with continuous lenalidomide–dexamethasone than with MPT and were more durable. The progression-free survival benefit was maintained through further lines of therapy, as suggested by the time to second progression of disease or death, indicating that continuous lenalidomide–dexamethasone had no negative effect on second-line therapy or on the interim analysis of overall survival.

MPT is a standard treatment option for patients with newly diagnosed multiple myeloma who are ineligible for stem-cell transplantation.[1,2,7-9,27-31] A meta-analysis of data from six randomized trials showed that MPT improved progression-free and overall survival, as compared with MP.[5] VMP is another well-established standard of care. Initial results of the phase 3 VISTA (Velcade as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone) trial showed that VMP was superior to MP across all efficacy end points, including time to progression (24.0 vs. 16.6 months).[3] The final analysis of the VISTA trial confirmed the superiority of VMP over MP in terms of the median time to second-line therapy (30.7 vs. 20.5 months) and median overall survival (56.4 vs. 43.1 months).[4] Other studies have evaluated bortezomib as part of a four-drug induction regimen (bortezomib–melphalan–prednisone–thalidomide)[26] and as maintenance therapy.[26,32]

The rates of complete response in this trial were lower than previously reported with the VMP regimen,[3] but the rates of very good partial response or better were similar. In an analysis of several studies involving elderly patients, a correlation between complete response and more favorable clinical outcome was noted.[33] However, most of these studies involved fixed-duration chemotherapy, and whether this correlation applies to continuous therapy has not yet been established. In the current study, responses were more durable with continuous therapy.[7]

The benefit of continuous lenalidomide therapy in patients who are ineligible for stem-cell transplantation is supported by results from the phase 3 Multiple Myeloma 015 (MM-015) trial, which compared MPR followed by lenalidomide maintenance therapy with MPR or MP alone.[25] In that trial, MPR with lenalidomide maintenance therapy significantly improved progression-free survival, as compared with MPR or MP, but there was no significant benefit in overall survival.[25,34] The shapes of the progression-free survival curves from the MM-015 trial share some similarities with those generated in our study — namely, a distinct separation after the discontinuation of lenalidomide for the comparison of MPR plus lenalidomide maintenance therapy with MPR alone and for the comparison of continuous lenalidomide–dexamethasone with 18 cycles of lenalidomide–dexamethasone.

The safety profiles of MPT and continuous lenalidomide–dexamethasone in this trial were consistent with the known safety profiles of these regimens.[1,2,14] Both lenalidomide–dexamethasone groups had lower rates of hematologic toxic events than the MPT group, but the incidence of grade 3 or 4 infection was increased with continuous lenalidomide–dexamethasone as compared with 18 cycles of lenalidomide–dexamethasone or MPT (29% vs. 22% and 17%,

Table 2. Response Rates and Time to Response.

Variable	Continuous Lenalidomide–Dexamethasone (N=535)	Lenalidomide–Dexamethasone for 18 Cycles (N=541)	MPT (N=547)
Overall response — no. (%)	402 (75)*	397 (73)*	341 (62)
Complete response	81 (15)	77 (14)	51 (9)
Very good partial response	152 (28)	154 (28)	103 (19)
Partial response	169 (32)	166 (31)	187 (34)
Stable disease — no. (%)	101 (19)	111 (21)	145 (27)
Progressive disease — no. (%)	7 (1)	12 (2)	19 (3)
Response could not be evaluated — no. (%)	25 (5)	21 (4)	42 (8)
Median time to response — mo†	1.8‡	1.8‡	2.8

* P<0.001 by Fisher's exact test for the comparison with the MPT group.
† The median time to response was assessed in patients who had a partial response or better.
‡ P<0.001 by the Wilcoxon rank-sum test for the comparison with the MPT group.

respectively). Peripheral sensory neuropathy was more common with MPT than with lenalidomide–dexamethasone (administered continuously or for 18 cycles), as expected. The continuation of lenalidomide–dexamethasone beyond 72 weeks was associated with an increase of 5 percentage points in infection of any grade (an increase of 7 percentage points in grade 3 or 4 infection), an increase of 2 percentage points in thromboembolic events of grade 3 or 4, and an increase in the incidence of cataracts that was two times as high as the incidence observed during 72 weeks of therapy. It appears that long-term adverse events with continuous lenalidomide–dexamethasone are at least partly driven by glucocorticoids. This is a common finding in elderly patients with myeloma, suggesting the need to investigate alternative ways to deliver glucocorticoids, such as lower doses of dexamethasone or the use of prednisone. The discontinuation of dexamethasone after 18 months of therapy also warrants evaluation. The incidence of a second primary hematologic cancer was higher with MPT than with continuous lenalidomide–dexamethasone, which is consistent with reports suggesting that the increased risk of a second primary cancer among patients treated with lenalidomide may be related to prior or concurrent melphalan use.[25,35-38]

Regarding the two secondary comparisons (continuous lenalidomide–dexamethasone vs. 18 cycles of lenalidomide–dexamethasone, and 18 cycles of lenalidomide–dexamethasone vs. MPT), it is important to consider both efficacy and safety. Continuous lenalidomide–dexamethasone is a more effective regimen than 18 cycles of lenalidomide–dexamethasone: the continuous regimen was associated with a 30% reduction in the risk of progression or death as compared with 18 cycles of the therapy, with a longer duration of response and a longer time to progression. The median time to second-line antimyeloma therapy with continuous lenalidomide–dexamethasone was 39.1 months, as compared with 28.5 months for 18 cycles of lenalidomide–dexamethasone. This represents a clinically significant advantage, especially for elderly patients, in whom a response to rescue therapy at the time of first relapse may be difficult to achieve.

The final analysis of overall survival will further define the benefit of continuous lenalidomide–dexamethasone and provide more details regarding retreatment with a lenalidomide-based regimen in the patients who received 18 cycles of lenalidomide–dexamethasone as the primary treatment (followed by a treatment-free interval). The superior efficacy of continuous lenalidomide–dexamethasone over 18 cycles of lenalidomide–dexamethasone was achieved at the expense of a modest increase in toxicity. Regarding the comparison of 18 cycles of lenalidomide–dexamethasone with MPT, efficacy results were similar for progression-free survival, but overall survival was better with 18 cycles of lenalidomide–dexamethasone, suggesting that rescue at the time of relapse was more easily achieved in

Table 3. Grade 3 or 4 Adverse Events.

Event	Continuous Lenalidomide–Dexamethasone (N=532)	Lenalidomide–Dexamethasone for 18 Cycles (N=540)	MPT (N=541)
	number of patients with event (percent)		
Any grade 3 or 4 event*	453 (85)	433 (80)	480 (89)
Hematologic adverse event			
Neutropenia	148 (28)	143 (26)	243 (45)
Anemia	97 (18)	85 (16)	102 (19)
Thrombocytopenia	44 (8)	43 (8)	60 (11)
Lymphopenia	30 (6)	18 (3)	37 (7)
Leukopenia	24 (5)	30 (6)	53 (10)
Nonhematologic adverse event†			
Infection	154 (29)	118 (22)	93 (17)
Cardiac disorder	63 (12)	39 (7)	46 (9)
Pneumonia	43 (8)	45 (8)	31 (6)
Deep-vein thrombosis, pulmonary embolism, or both	42 (8)	30 (6)	29 (5)
Asthenia	41 (8)	33 (6)	32 (6)
Fatigue	39 (7)	46 (9)	31 (6)
Back pain	37 (7)	34 (6)	28 (5)
Hypokalemia	35 (7)	20 (4)	11 (2)
Hyperglycemia	28 (5)	23 (4)	9 (2)
Rash	33 (6)	28 (5)	28 (5)
Cataracts	31 (6)	14 (3)	3 (1)
Dyspnea	30 (6)	22 (4)	18 (3)
Constipation	12 (2)	10 (2)	29 (5)
Peripheral sensory neuropathy	6 (1)	2 (<1)	51 (9)

* The grade 3 or 4 adverse events listed here were those reported by the investigator in at least 5% of any study group in the safety population, which was defined as all the patients who underwent randomization and received at least one dose of the study treatment (lenalidomide, dexamethasone, melphalan, prednisone, or thalidomide).
† Diarrhea occurred in 21 patients (4%) in the continuous lenalidomide–dexamethasone group, in 18 (3%) in the group that received 18 cycles of lenalidomide–dexamethasone, and in 8 (1%) in the MPT group.

patients who received this regimen. The group that received 18 cycles of lenalidomide–dexamethasone also had fewer adverse events than the group that received MPT.

In conclusion, treatment with continuous lenalidomide–dexamethasone, an alkylator-free doublet oral regimen, significantly improved progression-free survival, as compared with the alkylator-based triplet regimen MPT among patients with newly diagnosed multiple myeloma who were ineligible for stem-cell transplantation. A survival benefit was also seen with continuous lenalidomide–dexamethasone in an interim analysis of overall survival. Although additional follow-up is needed to fully assess the survival benefit with continuous lenalidomide–dexamethasone versus 18 cycles of lenalidomide–dexamethasone, this trial provides substantial evidence that among patients with newly diagnosed multiple myeloma, those who are elderly or are ineligible for stem-cell transplantation may benefit from continuous therapy. The safety profile of continuous lenalidomide–dexamethasone was manageable, and the incidence of second primary cancers was low across treatment groups.

Supported by Intergroupe Francophone du Myélome and Celgene.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Adriana Stan, Ph.D., and Anna Georgieva, M.D., Ph.D., of Excerpta Medica for assistance in the preparation of an earlier version of the manuscript.

APPENDIX

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