SUPPLEMENTAL METHODS

All authors and the sponsor were involved in data gathering, analysis, review, interpretation, and writing. Funding was provided by the Intergroupe Francophone du Myélome and Celgene Corporation. This study was conducted in accordance with Declaration of Helsinki and International Conference 2, paragraphs 1-2 on Harmonization E6 requirements for Good Clinical Practice. Prior to initiation, this study was approved by the institutional review board of each site. All patients provided written informed consent prior to the performance of any study procedure. The full trial protocol is available with the primary study publication[1] (http://www.nejm.org/doi/suppl/10.1056/NEJMoa1402551/suppl_file/nejmoa1402551_protocol.pdf).

Patients

Patients were previously untreated with symptomatic, and measurable multiple myeloma (MM); aged ≥ 65 years or otherwise unable to receive stem cell transplant; and Eastern Cooperative Oncology Group performance status score between 0 and 2. Patients could not have had prior antimyeloma therapies except radiotherapy for bone healing/treating postfracture pain, bisphosphonates, or a short course of steroids; absolute neutrophil count (ANC) < 1000/μL; untransfused platelet count < 50,000/μL; aspartate aminotransferase or alanine aminotransferase > 3.0 × the upper limit of normal; or history of malignancies in the past 3 years other than MM except nonmelanoma skin cancer, carcinomas in situ of the cervix or breast, or incidental

findings of prostate cancer. Creatinine clearance (CrCl) level was not used as an exclusion factor, but patients requiring hemodialysis or peritoneal dialysis were not eligible for enrollment.

Dose adjustments

Lenalidomide starting dose was reduced to 10 mg daily for moderate renal impairment (RI; CrCl ≥ 30 to < 50 mL/min) or 15 mg every other day for severe RI (CrCl < 30 mL/min). Melphalan dose was reduced by 50% in patients with moderate or severe RI. Dexamethasone and thalidomide were reduced for patients aged > 75 years; melphalan was reduced for patients aged > 75 years or with low ANC or platelet count. Thromboprophylaxis with low-dose aspirin or other anticoagulation therapy was mandatory. Patients with a history of deep vein thrombosis or pulmonary embolism received low molecular weight heparin or warfarin for the first 4 months of the study.

During the treatment phase of the study, patients experiencing a dose-limiting toxicity had their dosing modified (interrupted and/or reduced) according to the protocol. Patients with initial lenalidomide or melphalan dose reductions for renal impairment who demonstrated improved renal function while on treatment could increase dose to the appropriate level at the next cycle. Patients discontinued treatment due to progressive disease or unacceptable toxicity.

International Myeloma Working Group criteria for renal response[2]

By this method, patients are classified at baseline by estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease Equation,[3] and response is assessed with best CrCl response. Patients with baseline eGFR < 50 mL/min/1.73 m^2 may achieve a complete renal response with a sustained improvement to near normal renal function (CrCl ≥ 60 mL/min), those with baseline eGFR < 30 mL/min/1.73 m^2 may achieve minimal renal response with some sustained improvement in renal function (CrCl ≥ 15 and ≤ 29 mL/min for patients with baseline eGFR < 15 mL/min/1.73 m^2; CrCl ≥ 30 and ≤ 59 mL/min for patients with baseline eGFR ≥ 15 and < 30 mL/min/1.73 m^2), and those with baseline eGFR < 15 mL/min/1.73 m^2 may achieve a partial renal response with a large but incomplete improvement in renal function (CrCl ≥ 30 and ≤ 59 mL/min).

Statistical analysis

Efficacy evaluations were performed on the intent-to-treat population comprising all patients randomized to treatment. The safety population comprised all patients who received ≥ 1 dose of study drug. Comparisons of time-to-event endpoints used a log rank test. Response rates were compared with exact test procedures for proportions.

When calculating the sample size for the primary analysis, a clinically relevant improvement for the primary comparison (median PFS for continuous lenalidomide plus low-dose dexamethasone vs melphalan, prednisone, and thalidomide) was considered to be 30 vs 24 months. To provide 80% power for detecting a hazard ratio (HR) of 0.80 using a two-sided log rank test with a significance level of 0.05 a sample size of 530

patients per treatment arm was selected. This analysis was planned when 950 events (progression or death) had occurred across all 3 treatment arms. Additionally an interim analysis of overall survival was also planned at this time using a step-down group sequential approach. The progression-free survival (PFS) analysis used the O'Brien-Fleming boundary and the overall survival analysis used the Pocock boundary.[4-6]

The event threshold for the primary analysis triggered a data cutoff of May 24, 2013. An unplanned updated analysis was performed at the request of regulatory authorities using a data cutoff of March 3, 2014. The results reported in this secondary analysis by renal function subgroup utilize the updated data set.

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Supplemental Table 1. Dosing information for lenalidomide (Rd continuous and Rd18 arms) or thalidomide (MPT arm)

Lenalidomide/ thalidomide	No RI CrCl ≥ 80 mL/min (n = 389)			Mild RI CrCl ≥ 50 to < 80 mL/min (n = 715)			Moderate RI CrCl ≥ 30 to < 50 mL/min (n = 372)			Severe RI CrCl < 30 mL/min (n = 147)		
	Rd Cont (n = 123)	Rd18 (n = 122)	MPT (n = 144)	Rd Cont (n = 240)	Rd18 (n = 252)	MPT (n = 222)	Rd Cont (n = 124)	Rd18 (n = 119)	MPT (n = 120)	Rd Cont (n = 45)	Rd 18 (n = 47)	MPT (n = 55)
Planned starting dose	25 mg daily	25 mg daily	200/100 mg daily[a]	25 mg daily	25 mg daily	200/100 mg daily[a]	10 mg daily	10 mg daily	200/100 mg daily[a]	15 mg every other day	15 mg every other day	200/100 mg daily[a]
Median average dose (range)	25 .0 (13.0-25.0)	25 .0 (16.7-25.0)	162.4 (54.0-200.0)	25 .0 (8.5-25.0)	25.0 (4.6-25.0)	120.4 (51.9-200.0)	10.0 (2.8-24.7)	10.0 (2.9-24.2)	100.0 (51.2-200.0)	15.0 (5.0-24.6)	15.0 (5.8-24.4)	100.0 (52.5-200.0)
Relative dose intensity, median (range)	0.9 (0.5-1.0)	1.0 (0.3-1.2)	0.8 (0.1-1.0)	0.9 (0.1-1.1)	0.9 (0.2-1.5)	0.8 (0.1-1.0)	1.0 (0.3-2.5)	1.0 (0.2-2.4)	0.8 (0.2-1.0)	0.7 (0.2-2.9)	1.0 (0.2-2.9)	0.8 (0.1-1.0)

[a] Thalidomide was reduced to 100 mg daily for patients aged > 75 y.

CrCl, creatinine clearance; MPT, melphalan, prednisone, and thalidomide; Rd, lenalidomide and low-dose dexamethasone; Rd18, Rd for 18 cycles; Tx, treatment.

Supplemental Figure 1.

Patient disposition flow diagram at the time of updated data cutoff (March 3, 2014). MPT, melphalan, prednisone, and thalidomide; Rd, lenalidomide and low-dose dexamethasone; Rd18, Rd for 18 cycles; RI, renal impairment.