Impact of maintenance therapy on subsequent treatment in patients with newly diagnosed multiple myeloma: use of "progression-free survival 2" as a clinical trial end-point

Maintenance therapy has generally been shown to improve outcomes in newly diagnosed multiple myeloma (NDMM).[1-8] Increases in progression-free survival (PFS) and overall survival (OS) have been demonstrated in some trials of maintenance therapy,[4-6] but others have reported improved PFS with no corresponding improvement in OS.[1-3] The lack of OS benefit may be due to crossover and insufficient follow-up, as well as the fact that these trials were not powered to detect differences in OS between treatment groups. Theoretically, an experimental treatment may negatively affect OS (despite improving PFS) by increasing long-term toxicity or altering the tumor population or microenvironment to induce drug resistance or evolution of an aggressive clone.[9-11] To account for these possibilities, the European Medicines Agency (EMA) has recently recommended using "progression-free survival 2" (PFS2) as a clinical end-point to evaluate the efficacy of maintenance therapy in hematology/oncology trials.[10] To rule out possible negative effects of treatment on the efficacy of next-line therapy, PFS2 in the experimental arm should be sufficiently superior to that in the control arm.[10] In this article, we explore the concept of PFS2 and apply it to a trial in NDMM patients to determine whether lenalidomide maintenance therapy influenced the efficacy of subsequent treatment.

The design of this multicenter, double-blind, placebo-controlled, phase III MM-015 trial has been published previously.[1] In brief, 459 transplant-ineligible NDMM patients aged ≥65 years were randomized (1:1:1) to: melphalan, prednisone, lenalidomide (MPR) followed by lenalidomide maintenance (MPR-R) (nine 4-week cycles); MPR (nine 4-week cycles followed by placebo maintenance therapy); or melphalan and prednisone (MP) (nine 4-week cycles followed by placebo maintenance therapy). Maintenance therapy continued until disease progression or unacceptable toxicity. Patients who progressed could either enroll in an open-label extension phase to receive lenalidomide with or without dexamethasone, or be offered any other second-line therapy during the follow-up phase of the protocol. All patients were followed for survival and subsequent therapy for ≥5 years from randomization or until death.

At a median follow-up of 30 months, median PFS was significantly longer with MPR-R (31 months) than MPR (14 months; $P<0.001$) or MP (13 months; $P<0.001$), indicating that lenalidomide maintenance led to a substantial delay in disease progression of approximately 18 months.[1] However, the 3-year OS rates were similar among the treatment groups (70% in patients treated with MPR-R, 62% with MPR, and 66% with MP).[1]

The MM-015 trial was completed before the EMA's proposal in December 2012 to include PFS2 as a clinical end-point in trials of maintenance therapy.[10] Thus, PFS2 was not part of the original MM-015 study design, but was added as an exploratory, *post hoc* assessment. For this analysis, as per the EMA definition, PFS2 was calculated in the intent-to-treat population as the time from randomization to the date of disease progression or death from any cause after second-line therapy.[10] Because the date of disease progression after second-line therapy was not collected prospectively, the starting date of third-line therapy was used as a proxy to PFS2, as recommended by the EMA.[10]

Comparisons between treatment groups were made using a proportional hazards model. *P*-values were based on an unstratified log-rank test of Kaplan-Meier curves between treatment groups. The data cut off for this analysis was April 30, 2013, and the median follow-up was 62 months.

Of the 152 patients assigned to MPR-R (data cut off April 30, 2013), 85 started second-line therapy, 5 died before second-line therapy was initiated, and 62 had no disease progression. In the MPR group (n=153), 120 received second-line therapy, 8 died before receiving second-line therapy, and 25 had no disease progression. Of the 154 patients assigned to MP, 129 started second-line therapy, 5 died before second-line therapy was initiated, and 20 had no disease progression. Thus, fewer patients in the MPR-R group received second-line therapy (56%; 85 out of 152) than in the MPR (78%; 120 out of 153) and MP (84%; 129 out of 154) groups.

Approximately half of the patients who received second-line therapy had International Staging System stage III disease (Table 1). Adverse cytogenetic features were slightly more common in the MPR-R and MPR groups (32% and 35%, respectively) than in the MP group (26%).

Patients originally assigned to MPR-R were more likely to receive a bortezomib-based regimen as second-line therapy (49%) than those originally assigned to MP (21%),

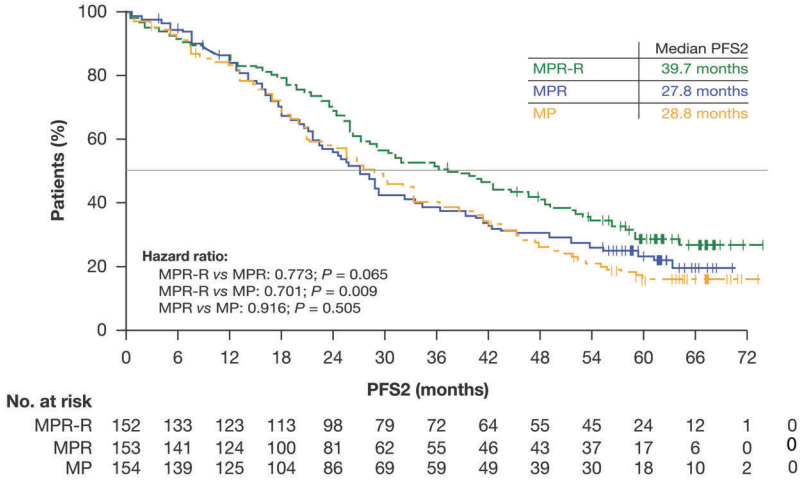

Figure 1. Median PFS2 for each treatment group. MP: melphalan and prednisone; MPR: melphalan, prednisone, lenalidomide; MPR-R: MPR followed by lenalidomide maintenance; PFS2: progression-free survival 2.

whereas lenalidomide-based therapy was more commonly chosen for patients originally assigned to MP (72%) or MPR (58%) than for those who received MPR-R (28%) (Table 2).

Median PFS2 was 39.7 months in the MPR-R group, 27.8 months in the MPR group, and 28.8 months in the MP group (Figure 1). MPR-R was associated with a significant (30%) reduction in PFS2 events compared with MP (hazard ratio [HR] 0.701; 95% confidence interval [CI] 0.536-0.916; *P*=0.009) and a non-significant (23%) reduction in PFS2 events compared with MPR (HR 0.773; 95% CI 0.588-1.017; *P*=0.065). There was no statistical difference between MPR and MP in terms of PFS2 (HR 0.916; 95% CI 0.707-1.187; *P*=0.505).

The present results confirm that adding lenalidomide therapy to MP provided a clinically meaningful progression-free interval that was nearly 1 year longer than that achieved with MP, even when accounting for second-line therapy and the different types of subsequent regimens used. Furthermore, the fact that PFS2 was significantly longer with MPR-R than MP, despite the high number of patients in the MP arm who received lenalidomide as second-line therapy (72%), supports the incorporation of lenalidomide in the first-line setting rather than waiting until relapse. Median PFS2 in the MPR group was similar to that in the MP group, which indirectly suggests an important contribution of maintenance therapy. Although there was a trend toward improved PFS2 with MPR-R (39.7 months) compared with MPR (27.8 months), the difference between groups did not reach statistical significance (*P*=0.065). It was also noteworthy that 58% of MPR patients received lenalidomide in second-line treatment. Future prospectively designed studies should further assess the impact of continuous lenalidomide therapy versus sequential intermittent treatment. Altogether, these findings indicate that continuous lenalidomide-based therapy is unlikely to induce greater resistance at the time of relapse, and it appears to have no impact on the efficacy of second-line therapy that would have negatively affected OS.

It is important to note that PFS2 differs from "2nd PFS", which is the PFS associated with next-line treatment (the interval between relapse/start of next-line treatment and second disease progression or death from any cause). PFS2 includes the intent-to-treat population, whereas 2nd PFS is limited to the subset of patients who have relapsed and received next-line therapy and are, therefore, likely to have more aggressive disease. Thus, PFS2 provides a more comprehensive and unbiased picture of clinical outcomes from the time of randomization through next-line therapy.

For optimal results, PFS2 should be included as a pre-specified clinical trial end-point, and the use of next-line therapy should be specified in the protocol to ensure uniform care in relapsing patients. This study was designed several years before the EMA defined PFS2, and thus we could only explore this concept in a retrospective analysis. A similar *post hoc* approach has been used in other trials of maintenance therapy in transplant-ineligible NDMM patients.[12,13] Palumbo *et al.*[13] pooled data from two phase III trials comparing continuous therapy with fixed-duration therapy and found that median PFS2 was significantly longer with continuous therapy (63 *vs.* 47 months; HR 0.69; *P*=0.0001). In an exploratory analysis of the largest prospective randomized trial conducted in NDMM patients (FIRST trial), Benboubker *et al.*[12] similarly reported a significant improvement in median PFS2 with continuous lenalidomide and dexamethasone therapy compared with a fixed-duration regimen of melphalan, prednisone, thalidomide (42.9 *vs.* 36.3 months; HR 0.78; *P*=0.005).

The current analysis has other limitations. The decision to administer, and the type of second-line therapy was left to the discretion of the individual investigator and was not regulated by the study protocol. As such, there was an imbalance among the treatment arms in terms of the types of therapy administered. It should also be noted that PFS2 analysis does not account for the impact of subsequent therapies given after second-line therapy. This may be particularly relevant in myeloma as new therapies such as carfilzomib and pomalidomide continue to provide additional therapeutic options for patients with relapsed/refractory disease.[14,15] In MM-015, effective post-second-line therapy may have contributed to the generally excellent, but similar, OS in each treatment group. It should be noted that the MM-015 trial was neither designed nor powered to evaluate OS, and crossover was encouraged by providing the option to all patients to participate in an open-label

Table 1. Baseline characteristics of patients who received second-line therapy.

	MPR-R (N=85)	MPR (N=120)	MP (N=129)
Age, median (range), years	71 (65-84)	71 (65-86)	71 (65-83)
Age >75 years	17 (20)	23 (19)	28 (22)
Male	38 (45)	64 (53)	62 (48)
ISS stage III	42 (49)	59 (49)	62 (48)
β_2-microglobulin ≤5.5 mg/L	44 (52)	61 (51)	78 (61)
Hypercalcemia[a]	6 (7)	6 (5)	7 (5)
Creatinine clearance <60 mL/min	39 (46)	48 (40)	60 (47)
Anemia[b]	28 (33)	49 (41)	42 (33)
Lytic bone lesions	63 (74)	91 (76)	90 (70)
Cytogenetic abnormalities			
Normal	1 (1)	4 (3)	2 (2)
Favorable hyperdiploidy	8 (9)	13 (11)	11 (9)
Adverse	27 (32)	42 (35)	34 (26)
Deletion 13q	24 (28)	40 (33)	33 (26)
Translocation (4;14)	5 (6)	1 (1)	3 (2)
Translocation (14;16)	0	0	0
Deletion 17p	5 (6)	5 (4)	6 (5)
Not evaluable	33 (39)	47 (39)	49 (38)
Missing	16 (19)	14 (12)	33 (26)

Values are n (%) unless stated otherwise. [a]Serum calcium >11.5 mg/L or above upper limit of normal. [b]Hemoglobin <10 g/dL, or 2 g/dL below lower limit of normal. ISS: International Staging System; MP: melphalan and prednisone; MPR: melphalan, prednisone, lenalidomide; MPR-R: MPR followed by lenalidomide maintenance.

Table 2. Type of second-line therapy received.[a]

	MPR-R (N=85)	MPR (N=120)	MP (N=129)	Total (N=334)
Lenalidomide	24 (28)	69 (58)	93 (72)	186 (56)
Bortezomib	42 (49)	33 (28)	27 (21)	102 (31)
Thalidomide	11 (13)	9 (8)	6 (5)	26 (8)
Glucocorticoid	47 (55)	51 (43)	40 (31)	138 (41)
Other[b]	34 (40)	24 (20)	23 (18)	81 (24)

All values n (%). [a]Patients may have received >1 drug as second-line therapy. [b]Other therapy includes antineoplastic agents, bendamustine, carmustine, cyclophosphamide, doxorubicin, epirubicin, etoposide, etoposide phosphate, fotemustine, investigational drug, melphalan, monoclonal antibodies, other antineoplastic agents, vincristine, and vincristine sulfate. MP: melphalan and prednisone; MPR: melphalan, prednisone, lenalidomide; MPR-R: MPR followed by lenalidomide maintenance.

extension phase of lenalidomide therapy at relapse.

In summary, PFS2 provides insights into the effects of maintenance treatment on the efficacy of next-line therapy and should be incorporated into future trials in NDMM patients. In the MM-015 trial, median PFS2 was markedly longer in the MPR-R group than in the MP group, indicating that continuous lenalidomide-based therapy provided better disease control and had no negative effect on the efficacy of second-line therapy. Given the well-established and manageable safety profile of lenalidomide in the maintenance setting,[1,12] continuous lenalidomide-based therapy is a safe and effective treatment option for transplant-ineligible patients with NDMM.

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