Continuous treatment with lenalidomide and low-dose dexamethasone in transplant-ineligible patients with newly diagnosed multiple myeloma in Asia: subanalysis of the FIRST trial

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Summary

The phase 3 FIRST (Frontline Investigation of REVLIMID + Dexamethasone Versus Standard Thalidomide) trial demonstrated that lenalidomide plus low-dose dexamethasone (Rd) until disease progression (Rd continuous) is an effective treatment option for transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM). Given genetic differences between Asian and Western populations, this subanalysis of the FIRST trial examined the safety and efficacy of Rd (given continuously or for 18 cycles [Rd18]) and MPT (melphalan, prednisone, thalidomide) in 114 Asian patients from Mainland China, South Korea and Taiwan. Efficacy and safety with Rd continuous in Asian patients were consistent with those in the overall study population. The overall response rates were 77·8% for Rd continuous, 57·5% for MPT and 65·8% for Rd18. The risk of progression or death was reduced by 39% with Rd continuous versus MPT and by 35% with Rd continuous versus Rd18. Rd continuous improved the 3-year survival rate compared with MPT (70·2% vs. 56·4%) and Rd18 (58·1%). Common grade 3/4 adverse events in the Rd continuous and MPT arms were neutropenia (25·0% vs. 43·6%), infection (19·4% vs. 28·2%) and anaemia (19·4% vs. 15·4%), respectively. Thromboembolic event rates were low, and no second primary malignancies were observed. Rd continuous is safe and effective in transplant-ineligible Asian patients with NDMM.

Keywords: lenalidomide, multiple myeloma, transplant-ineligible, newly diagnosed, Asia.

Multiple myeloma is the third most common haematological cancer and accounts for approximately 13% of all haematological cancers diagnosed worldwide (Palumbo & Anderson, 2011; Ferlay *et al*, 2013). The incidence of multiple myeloma in Asian countries is lower than that in Western countries, and this has been partly attributed to differences in genetics (Kang *et al*, 2008). However, several recent reports show that the incidence of multiple myeloma is increasing rapidly in several Asian countries (Huang *et al*, 2007; Lee *et al*, 2010). Environmental pollution and the Westernization of diets may be some factors contributing to this rise (Kim *et al*, 2014). Aging is also associated with an increased risk for multiple myeloma (Turesson *et al*, 2010) and, as in Western countries, life expectancy is increasing in several Asian countries (Huang *et al*, 2007; Kim *et al*, 2014). There is a need for effective and well-tolerated treatment regimens for multiple myeloma to help address the challenge of the rising incidence of this disease in Asia. Genetic differences across races can alter the pharmacokinetics and pharmacodynamics of drugs, which could potentially contribute to differences in drug response. Therefore, race is an important consideration when evaluating the efficacy and safety of a drug regimen (Yasuda *et al*, 2008; Ramamoorthy *et al*, 2015).

The standard of treatment for young patients with newly diagnosed multiple myeloma (NDMM) remains stem cell transplantation (SCT) (Attal *et al*, 2015; Mateos *et al*, 2015). For patients with NDMM who are SCT-ineligible, usually those who are older than 65–70 years, the introduction of immunomodulatory drugs and proteasome inhibitors has increased the number of efficacious therapy options (Palumbo *et al*, 2014; Mateos *et al*, 2015; Moreau *et al*, 2015). However, in Asia, approximately two-thirds of patients with multiple myeloma do not receive immunomodulatory agents, such as lenalidomide, or the proteasome inhibitor bortezomib in first-line treatment regimens, which may be due to resource and reimbursement limitations (Tan *et al*, 2013; Kim *et al*, 2014; Lu *et al*, 2014). Furthermore, although the median age of patients with multiple myeloma in Asia is lower than that of patients in the United States at 62 vs. 65 years, respectively, patients in Asia are less likely to undergo SCT (Kim *et al*, 2014; Gonsalves *et al*, 2015). This has been attributed to a lack of resources and/or infrastructure for SCT facilities (Kim *et al*, 2014).

Lenalidomide plus low-dose dexamethasone (Rd) is a recommended treatment option for patients with NDMM who are SCT-ineligible (Tan *et al*, 2013; Palumbo *et al*, 2014; Moreau *et al*, 2015; National Comprehensive Cancer Network, 2016). Data from this randomized, phase 3 FIRST (Frontline Investigation of REVLIMID + Dexamethasone *Versus* Standard Thalidomide) study demonstrated that Rd until disease progression (Rd continuous) is a safe and effective treatment option for this patient population (Benboubker *et al*, 2014). In this trial, Rd continuous reduced the risk of disease progression or death by 28% compared with MPT [hazard ratio (HR), 0·72 (95% CI, 0·61–0·85);

$P < 0.001$] and by 30% compared with the limited 18 cycles of Rd [Rd18; HR, 0·70 (95% CI, 0·60–0·82); $P < 0.001$] (Benboubker *et al*, 2014). In addition, Rd continuous reduced the risk of death by 22% compared with MPT [HR, 0·78 (95% CI, 0·64–0·96); $P = 0.02$] (Benboubker *et al*, 2014). This subanalysis of the FIRST study examines the safety and efficacy of Rd continuous for the treatment of specifically those SCT-ineligible patients with NDMM treated in Asia (Mainland China, South Korea, and Taiwan).

Methods

Study design

The FIRST study [MM-020/Intergroupe Francophone du Myélome (IFM) 07-01] was a multinational, open-label, randomized, phase 3 trial of Rd continuous *versus* Rd18 or 12 cycles of MPT in patients with NDMM who were SCT ineligible (Benboubker *et al*, 2014). The study was conducted at 246 treatment centres in 18 countries and included 3 countries in Asia: Mainland China, South Korea and Taiwan. Patients were randomly assigned 1:1:1 to receive 1 of 3 treatment arms using a validated interactive voice-response system and stratified by age (≤75 years vs. >75 years), International Staging System disease stage (I or II vs. III) and country. All sites received approval from their institutional review boards or ethics committees. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice.

Patients

Eligible patients had previously untreated, symptomatic multiple myeloma, were ≥65 years of age or <65 years of age and not candidates for SCT, and had an Eastern Cooperative Oncology Group performance score ≤2. Patients with any degree of renal impairment were included, except those requiring dialysis. Exclusion criteria were an absolute neutrophil count <1 × 10^9/l, an untransfused platelet count <50 × 10^9/l, a serum aspartate aminotransferase or alanine aminotransferase level >3 times the upper limit of normal, grade ≥2 peripheral neuropathy, or a history of malignancies other than multiple myeloma in the prior 3 years (excluding nonmelanoma skin cancer, carcinomas *in situ* of the cervix or breast, or incidental findings of prostate cancer). Written informed consent was provided by all patients.

Treatments

Patients in the Rd continuous and Rd18 groups received oral lenalidomide 25 mg/day on days 1–21 and oral dexamethasone 40 mg on days 1, 8, 15 and 22 in 28-day cycles until disease progression or for 72 weeks (18 cycles), respectively. Patients in the MPT group received oral melphalan 0·25 mg/

kg/day on days 1–4, oral prednisone 2 mg/kg per day on days 1–4, and thalidomide 200 mg/day in 42-day cycles for 72 weeks (12 cycles). Starting dose adjustments for dexamethasone and thalidomide were based on age, melphalan was based on age, absolute neutrophil count, platelet count and the level of renal function, and those for lenalidomide based on the level of renal function. All patients were required by protocol to receive thromboprophylaxis.

Assessments

The primary endpoint was progression-free survival (PFS). Key secondary endpoints included the overall response rate (ORR; defined as partial response or better), duration of response (DOR), overall survival (OS), time to second-line anti-myeloma therapy and safety. Progression and response were evaluated using the International Myeloma Working Group criteria (Durie et al, 2006) and reviewed by an independent response-adjudication committee. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (National Cancer Institute, 2006). Treatment-emergent AEs (TEAEs) were defined as AEs occurring or worsening on or after the first dose of any study drug, and within 28 days after receiving the last dose.

Statistical analysis

Efficacy analyses for this subpopulation included all randomized Asian patients in Asia. Safety analyses included Asian patients in Asia who received ≥1 dose of any study drug. All analyses, except OS, were conducted using a data cut-off of 24 May 2013, which was the date of the planned final PFS analysis. At the request of health regulatory authorities, an additional, previously unplanned, survival analysis was performed using an updated data cut-off of 3 March 2014. The unstratified log-rank test was used for comparisons of time-to-event endpoints. The Cox proportional-hazards model was used to estimate HRs and 95% CIs. Response data were compared between treatment arms using the Fisher exact test. For this subanalysis of the FIRST trial, no statistical significance was defined. Additional statistical detail is provided in the primary publication of the FIRST trial (Benboubker et al, 2014).

Results

Of 1623 total randomized patients, 114 NDMM patients in the Asian subpopulation were randomly assigned to receive Rd continuous ($n = 36$), Rd18 ($n = 38$) or MPT ($n = 40$). Forty-seven patients were enrolled in Mainland China, 56 patients in South Korea and 11 patients in Taiwan. Patient demographics and baseline characteristics were well balanced between the treatment arms, except for sex and severe renal insufficiency (creatinine clearance <30 ml/min; Table I). Rd continuous and Rd18 arms had an imbalance of more men than women patients. Severe renal impairment at baseline was more frequent in the Rd18 and MPT arms compared with the Rd continuous arm. The median age of the Asian subpopulation was lower than the overall study population (68·0 vs. 73·0 years, respectively; Table I). A slightly higher proportion of patients in Asia had advanced disease compared with the overall study

Table I. Baseline characteristics of the Asian subpopulation and intention-to-treat population.

Characteristic	Asian subpopulation ($n = 114$)			ITT population ($N = 1623$)		
	Rd continuous ($n = 36$)	Rd18 ($n = 38$)	MPT ($n = 40$)	Rd continuous ($n = 535$)	Rd18 ($n = 541$)	MPT ($n = 547$)
Median age (range), years	67·5 (44·0–83·0)	67·0 (43·0–80·0)	69·5 (51·0–86·0)	73·0 (44·0–91·0)	73·0 (40·0–89·0)	73·0 (51·0–92·0)
≥65 years, n (%)	23 (63·9)	26 (68·4)	30 (75·0)	504 (94·2)	507 (93·7)	520 (95·1)
Male, n (%)	23 (63·9)	23 (60·5)	20 (50·0)	294 (55·0)	273 (50·5)	287 (52·5)
ISS stage, n (%)						
I/II	21 (58·3)	20 (52·6)	22 (55·0)	319 (59·6)	322 (59·5)	323 (59·0)
III	15 (41·7)	18 (47·4)	18 (45·0)	216 (40·4)	219 (40·5)	224 (41·0)
CrCl, n (%)						
<30 ml/min	3 (8·3)	9 (23·7)	9 (22·5)	45 (8·4)	47 (8·7)	55 (10·1)
≥30–50 ml/min	3 (8·3)	9 (23·7)	5 (12·5)	126 (23·6)	120 (22·2)	126 (23·0)
≥50 ml/min	30 (83·3)	20 (52·6)	26 (65·0)	364 (68·0)	374 (69·1)	366 (66·9)
ECOG PS, n (%)						
0	4 (11·1)	7 (18·4)	5 (12·5)	155 (29·0)	163 (30·1)	156 (28·5)
1	22 (61·1)	20 (52·6)	24 (60·0)	257 (48·0)	263 (48·6)	275 (50·3)
2	10 (27·8)	11 (28·9)	11 (27·5)	119 (22·2)	113 (20·9)	111 (20·3)
≥3	0	0	0	2 (0·4)	2 (0·4)	2 (0·4)
Missing	0	0	0	2 (0·4)	0	3 (0·5)

CrCl, creatinine clearance; ECOG PS, Eastern Cooperative Oncology Group performance score; ISS, International Staging System; ITT, intention-to-treat; MPT, melphalan, prednisone, thalidomide; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.

population, as indicated by the rates of patients with International Staging System stage III disease (44·7% vs. 40·6%, respectively) and an Eastern Cooperative Oncology Group performance score of 2 (28·1% vs. 21·1), respectively; Table I). In addition, a greater proportion of patients in Asia had severe renal impairment compared with the overall study population (18·4% vs. 9·1%, respectively; Table I). In the intention-to-treat population, 762 patients were assessed for cytogenetics including 32 patients from Asia. Of the Asian patients with evaluable cytogenetics profiles, 21·9% (*n* = 7) had profiles associated with high-risk, defined as t(4;14), del 17p or t (14;16). Six patients (18·8%) had t(4;14), 2 patients (6·3%) had del 17p, and no patients had t(14;16). As of the 24 May 2013 data cut-off, one-third of the patients (*n* = 12) in the Rd continuous arm were treated for >2 years, with median treatment durations of 18·4, 11·0 and 11·1 months, respectively, with Rd continuous, Rd18 and MPT. An updated survival analysis conducted with a data cut-off of 3 March 2014 had a median follow-up of 38·1 months.

Efficacy

In this subpopulation, Rd continuous resulted in a PFS advantage compared with both MPT and Rd18 (Fig 1A). The median PFS was 21·1 months with Rd continuous *versus* 16·5 months with MPT and 17·4 months with Rd18. Rd continuous treatment reduced the risk of disease progression or death by 39% compared with MPT [HR, 0·61 (95% CI, 0·33–1·14)]. A similar reduction in the risk of progression or

death was observed for Rd continuous compared with Rd18 [35%; HR, 0·65 (95% CI, 0·35–1·20)]. The 2-year PFS rates were higher with Rd continuous *versus* MPT and Rd18 (48·0% vs. 24·9% and 35·6%, respectively).

At updated OS analysis, the risk of death with Rd continuous was reduced by 48% *versus* MPT [HR, 0·52 (95% CI, 0·24–1·13)] and by 36% *versus* Rd18 [HR, 0·64 (95% CI, 0·29–1·43); Fig 1B). In addition, Rd continuous improved the rate of 3-year survival *versus* MPT and Rd18 (70·2% vs. 56·4% and 58·1%).

Rd continuous led to a higher ORR than MPT and Rd18 (77·8%, 57·5% and 65·8%, respectively; Table II). Rd continuous more than doubled the rate of ≥ very good partial responses compared with MPT (52·8% and 22·5%, respectively). Rd continuous also prolonged the DOR compared with MPT and Rd18 (Table II). The median time to second-line anti-myeloma therapy was 24·1 months with Rd continuous, 23·3 months with MPT and 21·0 months with Rd18 (Table III).

Safety

The rate of grade 3/4 TEAEs was lower with Rd continuous than with MPT (66·7% and 87·2%, respectively; Table IV). Despite a longer duration of treatment in the Rd continuous arm, the rate of grade 3/4 TEAEs was similar with Rd continuous and Rd18. Rd continuous was associated with a lower rate of grade 3/4 infections than MPT or Rd18. No patients in either Rd arm experienced grade 3/4 deep vein
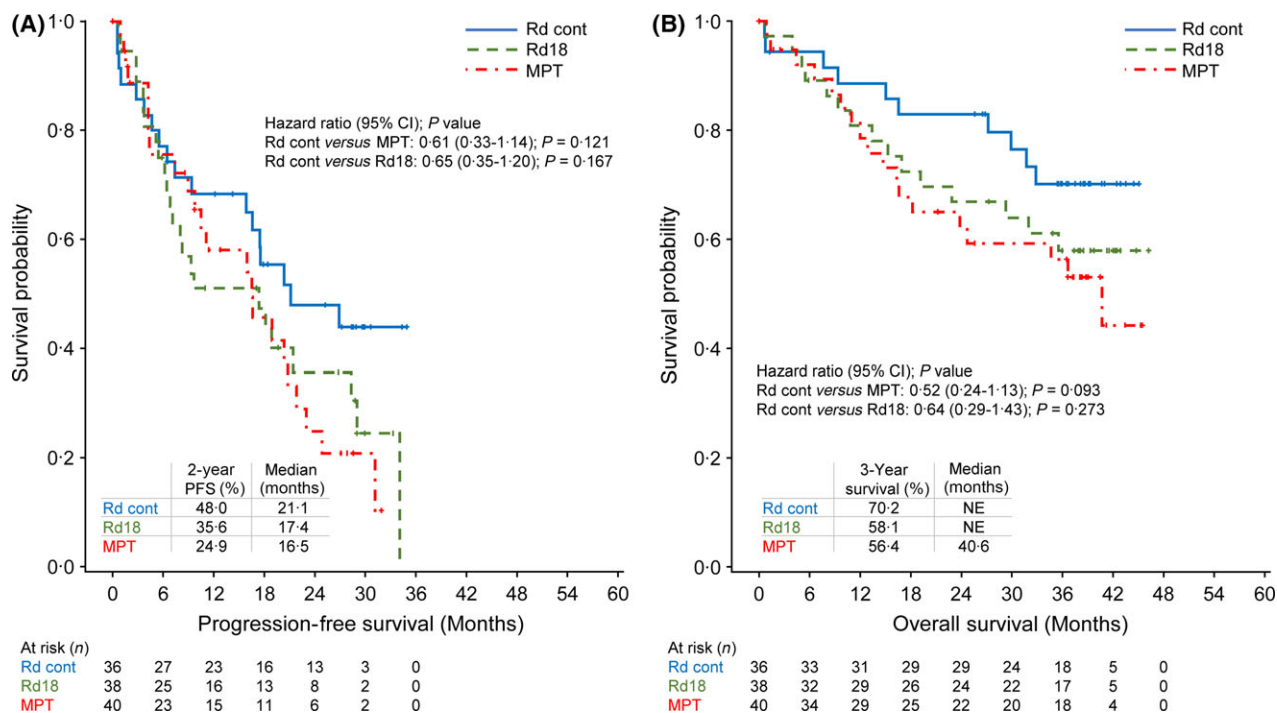

Fig 1. Progression-free survival and overall survival in the Asian subpopulation (A and B, respectively). NE, not estimable; MPT, melphalan, prednisone, thalidomide; Rd cont, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.

Table II. Response rates and duration of response (International Myeloma Working Group criteria; Durie *et al*, 2006) in the Asian subpopulation.

	Rd continuous (n = 36)	Rd18 (n = 38)	MPT (n = 40)
ORR (≥partial response), *n* (%)	28 (77·8)	25 (65·8)	23 (57·5)
Complete response	5 (13·9)	5 (13·2)	6 (15·0)
Very good partial response	14 (38·9)	11 (28·9)	3 (7·5)
Partial response	9 (25·0)	9 (23·7)	14 (35·0)
Stable disease, *n* (%)	3 (8·3)	11 (28·9)	10 (25·0)
Progressive disease, *n* (%)	2 (5·6)	1 (2·6)	1 (2·5)
Not evaluable, *n* (%)	3 (8·3)	1 (2·6)	6 (15·0)
Median DOR (95% CI), months*	NE (16·6-NE)	17·2 (5·5–32·2)	13·8 (7·6–22·8)
DOR HR (95% CI)			
Rd continuous *versus* MPT		0·43 (0·19–0·95)	
Rd continuous *versus* Rd18		0·53 (0·24–1·15)	
Rd18 *versus* MPT		0·83 (0·39–1·78)	

95% CI, 95% confidence interval; DOR, duration of response; HR, hazard ratio; MPT, melphalan, prednisone, thalidomide; NE, not estimable; ORR, overall response rate; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.

*For patients achieving ≥partial response.

Table III. Time to second-line antimyeloma treatment in the Asian subpopulation.

	Rd continuous (n = 36)	Rd18 (n = 38)	MPT (n = 40)
Median time to second-line AMT (95% CI), months	24·1 (18·6-NE)	21·0 (11·1-NE)	23·3 (11·9-34·7)
HR (95% CI)			
Rd continuous *versus* MPT		0·83 (0·44–1·55)	
Rd continuous *versus* Rd18		0·85 (0·46–1·61)	
Rd18 *versus* MPT		0·93 (0·50–1·73)	

95% CI, 95% confidence interval; AMT, anti-myeloma therapy; HR, hazard ratio; MPT, melphalan, prednisone, thalidomide; NE, not estimable; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles.

Table IV. Grade 3 or 4 treatment-emergent adverse events (safety population) of interest in the Asian subpopulation.

	Rd continuous (n = 36)	Rd18 (n = 38)	MPT (n = 39)
Grade 3/4 TEAE, *n* (%)	24 (66·7)	24 (63·2)	34 (87·2)
Haematological			
Neutropenia	9 (25·0)	13 (34·2)	17 (43·6)
Anaemia	7 (19·4)	2 (5·3)	6 (15·4)
Thrombocytopenia	5 (13·9)	2 (5·3)	2 (5·1)
Leucopenia	2 (5·6)	3 (7·9)	3 (7·7)
Nonhaematological			
Infection	7 (19·4)	12 (31·6)	11 (28·2)
Pneumonia	2 (5·6)	9 (23·7)	6 (15·4)
Hypokalaemia	4 (11·1)	2 (5·3)	2 (5·1)
Hyperglycaemia	4 (11·1)	3 (7·9)	1 (2·6)
Constipation	3 (8·3)	0	1 (2·6)
Peripheral sensory neuropathy	1 (2·8)	0	1 (2·6)
Cataract	1 (2·8)	1 (2·6)	0

MPT, melphalan, prednisone, thalidomide; Rd continuous, lenalidomide plus low-dose dexamethasone until disease progression; Rd18, lenalidomide plus low-dose dexamethasone for 18 cycles; TEAE, treatment-emergent adverse event.

thrombosis, compared to 1 patient in the MPT arm (2·6%). Rates of grade 3/4 pulmonary embolism were low and similar in patients receiving Rd continuous, MPT and Rd18 (2·8%, 2·6% and 2·6%, respectively). No second primary malignancies were reported among any of the treatment arms by the cut-off date of 24 May 2013.

Discussion

Rd continuous prolonged PFS and OS and improved ORR compared with MPT in the Asian subpopulation of the FIRST trial. PFS was prolonged by greater than 4 months with Rd continuous compared with MPT, and 2-year PFS with Rd continuous was nearly doubled compared with MPT. An OS benefit was also seen with Rd continuous, with an increase observed in 3-year survival compared with MPT. ORR was higher with Rd continuous *versus* MPT, largely due to a doubling of the rate of high-quality responses ≥ very good partial responses. Rd continuous also prolonged DOR compared with MPT and Rd18, suggesting that continuous treatment can suppress tumour growth and prolong patient remissions.

Efficacy results in the Asian subpopulation are consistent with those in the overall FIRST trial population. Median PFS was similarly extended by 4·3 months with Rd continuous compared with MPT in the overall trial population (Benboubker *et al*, 2014). ORR was also similar for patients receiving Rd continuous in the Asian subpopulation (77·8%) and the overall trial population (75·1%) (Benboubker *et al*, 2014). Interestingly, a greater relative reduction in the risk of death (48%) was observed with Rd continuous *versus* MPT in the Asian subpopulation than in the overall study population (25%). It is important to note that the population of Asian patients was small, so these data should be interpreted with caution.

The safety profile of Rd continuous in the Asian subpopulation was generally consistent with that in the overall trial population (Benboubker *et al*, 2014). Unlike the general study population, patients in Asia receiving Rd continuous had a higher rate of grade 3/4 thrombocytopenia compared with those receiving MPT (13·9% vs. 5·1%, respectively). A low rate of grade 3/4 thromboembolic events was observed across all treatment arms in the Asian subpopulation (3·5% in the Asian subpopulation *versus* 6·3% in the overall study population), a finding that is consistent with other studies in patients from Asia with multiple myeloma (Shyu *et al*, 2009). No second primary malignancies have been observed as of data cut-off in the Asian patient population.

The results presented here further support the improved patient outcomes with Rd, and as such, investigators have explored novel triplet regimens using the Rd backbone. In relapsed/refractory multiple myeloma, Rd has been the basis for new regimens in combination with the proteasome inhibitors carfilzomib (Stewart *et al*, 2015) and ixazomib (Moreau *et al*, 2016) and the monoclonal antibodies elotuzumab (Lonial *et al*, 2015) and daratumumab (Dimopoulos *et al*, 2016). In patients with NDMM, the addition of bortezomib to Rd (VRd) has improved clinical outcome in comparison with Rd alone (Durie *et al*, 2015). Results from ongoing studies with these novel treatment combinations in the frontline setting are eagerly awaited (ClinicalTrials.gov identifiers NCT01335399, NCT01668719 and NCT01850524).

In summary, given a more restricted access to SCT and the increasing incidence of multiple myeloma in Asian countries, the availability of Rd continuous treatment has the potential to greatly benefit patients with NDMM in Asia (Kim *et al*, 2014). The efficacy results for Rd continuous from this subanalysis of the FIRST trial show that treatment outcomes in the Asian subpopulation and the overall study population are similar and support the use of Rd until disease progression as the standard of care for Asian patients with NDMM who are SCT-ineligible.

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Author contributions

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