Ferrata Storti Foundation

Haematologica 2020
Volume 105(2):468-477

Daratumumab-based regimens are highly effective and well tolerated in relapsed or refractory multiple myeloma regardless of patient age: subgroup analysis of the phase 3 CASTOR and POLLUX studies

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ABSTRACT

The phase 3 POLLUX and CASTOR studies demonstrated superior benefit of daratumumab plus lenalidomide/dexamethasone or bortezomib/dexamethasone in relapsed/refractory multiple myeloma. Efficacy and safety of daratumumab was analyzed according to age groups of 65 to 74 years and ≥75 years. Patients received ≥1 prior line of therapy. In POLLUX, patients received lenalidomide/dexamethasone ± daratumumab (16 mg/kg weekly, cycles 1-2; every two weeks, cycles 3-6; monthly until progression). In CASTOR, patients received eight cycles of bortezomib/dexamethasone ± daratumumab (16 mg/kg weekly, cycles 1-3; every three weeks, cycles 4-8; monthly until progression). Patients aged >75 years received dexamethasone 20 mg weekly. For patients aged ≥75 years in POLLUX (median follow-up: 25.4 months), daratumumab/lenalidomide/dexamethasone prolonged progression-free survival *versus* lenalidomide/dexamethasone (median: 28.9 *versus* 11.4 months; hazard ratio, 0.27; 95% confidence interval, 0.10-0.69; *P*=0.0042) and increased overall response rate (93.1% *versus* 76.5%; *P*=0.0740). Neutropenia was the most common grade 3/4 treatment-emergent adverse event (daratumumab: 44.8%; control: 31.4%). Infusion-related reactions occurred in 12 (41.4%) patients. For patients aged ≥75 years in CASTOR (median follow-up: 19.4 months), daratumumab/bortezomib/dexamethasone prolonged progression-free survival versus bortezomib/dexamethasone (median: 17.9 *versus* 8.1 months; hazard ratio, 0.26; 95% confidence interval, 0.10-0.65; *P*=0.0022) and increased overall response rate (95.0% *versus* 78.8%; *P*=0.1134). Thrombocytopenia was the most common grade 3/4 treatment-emergent adverse event (daratumumab: 45.0%; control: 37.1%). Infusion-related reactions occurred in 13 (65.0%) patients. Similar findings were reported for patients aged 65 to 74 years in both studies. Taken together, this subgroup analysis of efficacy and safety of daratumumab was largely consistent with the overall populations.

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Received: January 23, 2019.

Accepted: June 20, 2019.

Pre-published: June 20, 2019.

doi:10.3324/haematol.2019.217448

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: www.haematologica.org/content/105/2/468

Introduction

Multiple myeloma (MM) is a disease of the elderly, which is evidenced by an increasing incidence with advancing age and a median onset age of 69 years.[1,2] Treatment regimens including proteasome inhibitors and immunomodulatory drugs have significantly improved survival for patients with MM;[3] however, survival benefits are less pronounced in patients aged >60 years.[4] Among patients with MM, median survival times were shown to decrease steadily over each decade from age <50 years (5.2 years) to age ≥80 years (2.6 years).[5] Aging is associated with organ dysfunction, reduced functional status, poor resilience to physiologic stressors, an increased burden of comorbidities, and an increased risk of frailty, which affects the ability of elderly patients to tolerate MM treatment regimens.[6] Furthermore, higher age correlates with more advanced International Staging System (ISS) stage.[5] Based on the challenges of treating MM in elderly patients, a need exists for effective treatment regimens that exhibit a favorable benefit/risk profile in this age group.

Daratumumab is a human immunoglobulin G1 (IgG1κ) monoclonal antibody targeting CD38 with a direct on-tumor[7-10] and immunomodulatory[11-13] mechanism of action. Tumor cell death is induced by daratumumab via several CD38 immune-mediated actions, including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, apoptosis, and modulation of CD38 enzymatic activity.[7-10] Daratumumab exhibits immunomodulatory effects through reduction of $CD38^+$ immunosuppressive cellular populations, including myeloid-derived suppressor cells, regulatory B cells and regulatory T cells; induction of helper and cytotoxic T-cell expansion; increased T-cell clonality, and production of interferon in response to viral peptides.[11]

In two randomized, open-label, active-controlled, phase 3 studies (POLLUX and CASTOR), daratumumab in combination with standard-of-care regimens (lenalidomide and dexamethasone [RD] or bortezomib and dexamethasone [VD]) demonstrated superior clinical benefit compared with Rd or Vd alone in patients with MM who had received ≥1 prior line of therapy. In POLLUX, daratumumab in combination with Rd (D-Rd) reduced the risk of disease progression or death by 63% compared with Rd after a median follow-up of 13.5 months.[14] Similarly, in CASTOR, the risk of the progression or death was reduced by 61% with daratumumab in combination with Vd (D-Vd) *versus* Vd after a median follow-up of 7.4 months.[15] Findings from these pivotal studies led to the approval of daratumumab in combination with Rd or Vd in many countries for the treatment of patients with MM who received ≥1 prior line of therapy.[16] This analysis reports the efficacy and safety of daratumumab in patients aged 65 to 74 years or ≥75 years from POLLUX and CASTOR after further median follow-up of 25.4 and 19.4 months, respectively.

Methods

Study design and patients

POLLUX and CASTOR were multicenter, randomized, open-label, active-controlled, phase 3 studies of patients with relapsed or refractory MM (RRMM). Trials were approved by an institutional review board or independent ethics committee at each site. Study protocols were conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. Detailed study designs were published previously.[14,15] Briefly, patients received ≥1 prior line of therapy, had at least a partial response to ≥1 prior therapy, and had documented progressive disease, according to the International Myeloma Working Group (IMWG) criteria.[14,15,17,18] Patients refractory or intolerant to lenalidomide were excluded from POLLUX. Patients refractory or intolerant to bortezomib, or refractory to another proteasome inhibitor were excluded from CASTOR.

Procedures

Patients were randomized 1:1 to D-Rd or Rd in POLLUX and D-Vd or Vd in CASTOR.[14,15] Stratification was described previously and did not include age.[14,15] In POLLUX, all patients received 28-day cycles of lenalidomide (25 mg orally [PO] on days 1-21 of each cycle) and dexamethasone (40 mg PO weekly in patients aged ≤75 years; 20 mg PO weekly in patients aged >75 years) with or without daratumumab (16 mg/kg intravenously [IV] weekly during cycles 1 and 2, every 2 weeks during cycles 3-6, and every 4 weeks thereafter until disease progression, unacceptable toxicity, or withdrawal of consent). Patients in the D-Rd group received a split dose of dexamethasone during daratumumab dosing weeks (20 mg before infusion; 20 mg the following day). Patients aged >75 years received the entire 20-mg dose prior to infusion.

In CASTOR, patients received eight, 21-day cycles of bortezomib (1.3 mg/m^2 subcutaneously (SC) on days 1, 4, 8, and 11) and dexamethasone (20 mg PO or IV on days 1, 2, 4, 5, 8, 9, 11, and 12; for a total dose of 160 mg/cycle during cycles 1-8) with or without daratumumab (16 mg/kg IV weekly in cycles 1-3, every three weeks during cycles 4-8, and every four weeks thereafter until withdrawal of consent, disease progression, or unacceptable toxicity). In patients aged >75 years, dexamethasone could be reduced to 20 mg weekly. In both studies, daratumumab-treated patients received pre- and post-infusion medications to prevent the onset of infusion-related reactions (IRR).[14,15]

Outcomes and statistical analyses

Frailty score was not assessed as these studies were initiated before this metric was adopted.[19] The safety analysis set included all patients who received ≥1 administration of study treatment. Efficacy was assessed by progression-free survival (PFS) and response rates,[14,15] which were based on the intent-to-treat (ITT) and response-evaluable populations, respectively. A stratified log-rank test compared PFS between groups. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated using a stratified Cox regression model, with treatment as the sole explanatory variable. Distributions were estimated using the Kaplan-Meier method. A stratified Cochran-Mantel-Haenszel chi-square test measured treatment differences in overall response rate (ORR) and rates of very good partial response (VGPR) or better and complete response (CR) or better.

Results

At the clinical cut-off date of March 7, 2017, the median (range) duration of follow-up was 25.4 (0-32.7) months for POLLUX. Of the 569 patients enrolled, 29/286 (D-Rd) and 35/283 (Rd) were aged ≥75 years, and 124/286 (D-Rd) and 108/283 (Rd) were aged 65 to 74 years. The clinical cut-off date for CASTOR was January 11, 2017, conferring a

Table 1. Baseline and demographic characteristics.

Characteristic: POLLUX	65-74 years D-Rd (n=124)	65-74 years Rd (n=108)	≥75 years D-Rd (n=29)	≥75 years Rd (n=35)
Age (years)				
Median (range)	69.0 (65-74)	69.0 (65-74)	77.0 (75-89)	78.0 (75-87)
Sex, n (%)				
Male	83 (66.9)	62 (57.4)	14 (48.3)	21 (60.0)
Female	41 (33.1)	46 (42.6)	15 (51.7)	14 (40.0)
Race, n (%)[a]				
White	95 (76.6)	72 (66.7)	19 (65.5)	21 (60.0)
Asian	18 (14.5)	19 (17.6)	6 (20.7)	4 (11.4)
Black or African American	2 (1.6)	3 (2.8)	1 (3.4)	2 (5.7)
Unknown	0	1 (0.9)	1 (3.4)	0
Not reported	9 (7.3)	13 (12.0)	2 (6.9)	8 (22.9)
Baseline ECOG score, n (%)				
0	60 (48.4)	54 (50.0)	10 (34.5)	11 (31.4)
1	60 (48.4)	46 (42.6)	15 (51.7)	21 (60.0)
2	4 (3.2)	8 (7.4)	4 (13.8)	3 (8.6)
ISS staging, n (%)[b]				
I	51 (41.1)	57 (52.8)	10 (34.5)	12 (34.3)
II	42 (33.9)	31 (28.7)	13 (44.8)	11 (31.4)
III	31 (25.0)	20 (18.5)	6 (20.7)	12 (34.3)
Time from diagnosis, years				
Median (range)	3.8 (0.4-22.5)	3.6 (0.4-18.3)	2.6 (0.8-27.0)	4.0 (0.8-14.6)
Prior lines of therapy, n (%)				
1	62 (50.0)	59 (54.6)	17 (58.6)	16 (45.7)
2	36 (29.0)	31 (28.7)	7 (24.1)	8 (22.9)
3	19 (15.3)	11 (10.2)	3 (10.3)	10 (28.6)
>3	7 (5.6)	7 (6.5)	2 (6.9)	1 (2.9)
Cytogenetic profile, n (%)[c]				
N	67	57	13	16
Standard	56 (83.6)	44 (77.2)	10 (76.9)	12 (75.0)
High	11 (16.4)	13 (22.8)	3 (23.1)	4 (25.0)

Characteristic: CASTOR	D-Vd (n=96)	Vd (n=87)	D-Vd (n=23)	Vd (n=35)
Age (years)				
Median (range)	69.0 (65-74)	69.0 (65-74)	78.0 (75-88)	78.0 (75-85)
Gender, n (%)				
Male	53 (55.2)	53 (60.9)	13 (56.5)	20 (57.1)
Female	43 (44.8)	34 (39.1)	10 (43.5)	15 (42.9)
Race, n (%)[a]				
White	83 (86.5)	81 (93.1)	22 (95.7)	29 (82.9)
Black or African American	6 (6.3)	1 (1.1)	0	1 (2.9)
Asian	4 (4.2)	2 (2.3)	0	2 (5.7)
American Indian or Alaska Native	1 (1.0)	0	0	0
Other	2 (2.1)	0	1 (4.3)	0
Unknown	0	0	0	1 (2.9)
Not reported	0	3 (3.4)	0	2 (5.7)
Baseline ECOG score, n (%)				
0	39 (40.6)	38 (43.7)	6 (26.1)	16 (45.7)
1	51 (53.1)	39 (44.8)	17 (73.9)	17 (48.6)
2	6 (6.3)	10 (11.5)	0	2 (5.7)

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ISS staging, n (%)[b]				
I	34 (35.4)	33 (37.9)	6 (26.1)	13 (37.1)
II	37 (38.5)	32 (36.8)	7 (30.4)	13 (37.1)
III	25 (26.0)	22 (25.3)	10 (43.5)	9 (25.7)
Time from diagnosis, years				
Median (range)	4.0 (0.7-20.7)	3.9 (0.9-17.2)	4.6 (1.0-14.7)	3.6 (1.2-18.6)
Prior lines of therapy, n (%)				
1	47 (49.0)	38 (43.7)	8 (34.8)	17 (48.6)
2	29 (30.2)	23 (26.4)	8 (34.8)	13 (37.1)
3	15 (15.6)	15 (17.2)	3 (13.0)	2 (5.7)
>3	5 (5.2)	11 (12.6)	4 (17.4)	3 (8.6)
Cytogenetic profile[c], n (%)				
N	72	71	11	28
Standard	60 (83.3)	53 (74.6)	9 (81.8)	22 (78.6)
High	12 (16.7)	18 (25.4)	2 (18.2)	6 (21.4)

D-Rd: daratumumab/lenalidomide/dexamethasone; Rd: lenalidomide/dexamethasone; ECOG: Eastern Cooperative Oncology Group; daratumumab/bortezomib/dexamethasone;Vd: bortezomib/dexamethasone. [a]Percentages may not add up to 100% due to rounding. [b]ISS staging is derived based on the combination of serum β2-microglobulin and albumin. [c]Cytogenetic risk determined by next-generation sequencing.

median (range) duration of follow-up of 19.4 (0-27.7) months. Of the 498 patients enrolled in CASTOR, 23/251 (D-Vd) and 35/247 (Vd) were aged ≥75 years, and 96/251 (D-Vd) and 87/247 (Vd) were aged 65 to 74 years. In both studies, demographic and baseline clinical characteristics were well balanced between treatment groups (Table 1). In POLLUX, among patients aged ≥75 years, 3/13 (23.1%) patients in the D-Rd group and 4/16 (25.0%) patients in the Rd group had high-risk cytogenetic abnormalities. Similarly, among patients aged ≥75 years in CASTOR, 2/11 (18.2%) patients in the D-Vd group and 6/28 (21.4%) patients in the Vd group had high cytogenetic risk. Among patients aged 65 to 74 years in POLLUX, 11 (16.4%) patients in the D-Rd group and 13 (22.8%) of patients in the Rd group had high cytogenetic risk abnormalities. Similarly, among patients aged 65 to 74 years in CASTOR, 12 (16.7%) patients in the D-Vd group and 18 (25.4%) patients in the Vd group had high cytogenetic risk.

The dispositions of patients according to age from POLLUX and CASTOR are summarized in Figure 1. In POLLUX, nine (31.0%) patients aged ≥75 years who were treated with D-Rd and 24 (68.6%) patients who were treated with Rd discontinued treatment. In CASTOR, 11 (55.0%) patients aged ≥75 years who received D-Vd and 15 (42.9%) patients who were treated with Vd discontinued treatment. Among patients aged ≥75 years who were randomized to D-Vd, 3 (13.0%) did not receive treatment. Similar findings were observed in the patients aged 65 to 74 years: in POLLUX, 51 (41.5%) patients who were treated with D-Rd and 76 (70.4%) patients who received Rd discontinued treatment, and in CASTOR, 56 (59.6%) patients who were treated with D-Vd and 44 (51.2%) patients who received Vd discontinued treatment.

In POLLUX, the median dose intensity of lenalidomide was generally lower in both treatment arms for patients aged ≥75 years (D-Rd, 210.00 mg/cycle; Rd, 305.00 mg/cycle) compared with patients aged 65 to 74 years (D-Rd, 333.93 mg/cycle; Rd, 420.00 mg/cycle). In CASTOR, the median dose intensity of bortezomib was similar among patients aged ≥75 years (D-Vd, 4.06 mg/m^2/cycle; Vd, 4.37 mg/m^2/cycle) and 65 to 74 years (D-Vd, 4.56 mg/m^2/cycle; Vd, 4.70 mg/m^2/cycle).

In POLLUX, in the ITT population, the clinical benefit of D-Rd over Rd was maintained after a median follow-up of 25.4 months (Figure 2). PFS was significantly prolonged with D-Rd *versus* Rd in the ITT population (median: not reached *versus* 17.5 months; HR, 0.41; 95% CI, 0.31-0.53; *P*<0.0001; Figure 2A),[20] with 18-month PFS rates of 75.3% and 48.5%, respectively. Similarly, PFS was significantly prolonged with D-Rd compared with Rd in patients aged ≥75 years (median: 28.9 *versus* 11.4 months; HR, 0.27; 95% CI, 0.10-0.69; *P*=0.0042; Figure 2A), with 18-month PFS rates of 86.2% *versus* 36.9%, respectively. PFS was also significantly prolonged with D-Rd *versus* Rd in patients aged 65 to 74 years (median: not reached *versus* 17.1 months; HR, 0.40; 95% CI, 0.27-0.60; *P*<0.0001; Figure 2B), with 18-month PFS rates of 72.0% and 48.7%, respectively. At the time of the clinical cut-off, overall survival (OS) data were immature. Survival follow-up for POLLUX will continue until 330 deaths are observed in the ITT population.

In CASTOR, in the ITT population, the clinical benefit of D-Vd over Vd was maintained after a median follow-up of 19.4 months (Figure 2). PFS was significantly prolonged with D-Vd *versus* Vd in the ITT population (median: 16.7 *versus* 7.1 months; HR, 0.31; 95% CI, 0.24-0.39; *P*<0.0001; Figure 2C), with 18-month PFS rates of 48.0% *versus* 7.9%, respectively.[21] Similarly, PFS was significantly prolonged with D-Vd compared with Vd in patients aged ≥75 years (median: 17.9 versus 8.1 months; HR, 0.26; 95% CI, 0.10-0.65; *P*=0.0022; Figure 2C), with 18-month PFS rates of 45.8% *versus* 0%, respectively. PFS was also significantly prolonged for D-Vd *versus* Vd in patients aged 65 to 74 years (median: 18.9 *versus* 6.1 months; HR, 0.25; 95% CI, 0.16-0.40; *P*<0.0001; Figure 2D). Follow-up for OS in CASTOR will continue until 320 deaths are reported in the ITT population, per protocol.

In POLLUX, among patients aged ≥75 years, higher ORR were observed with D-Rd *versus* Rd (93.1% *versus* 76.5%; *P*=0.0740), with significantly higher rates of VGPR

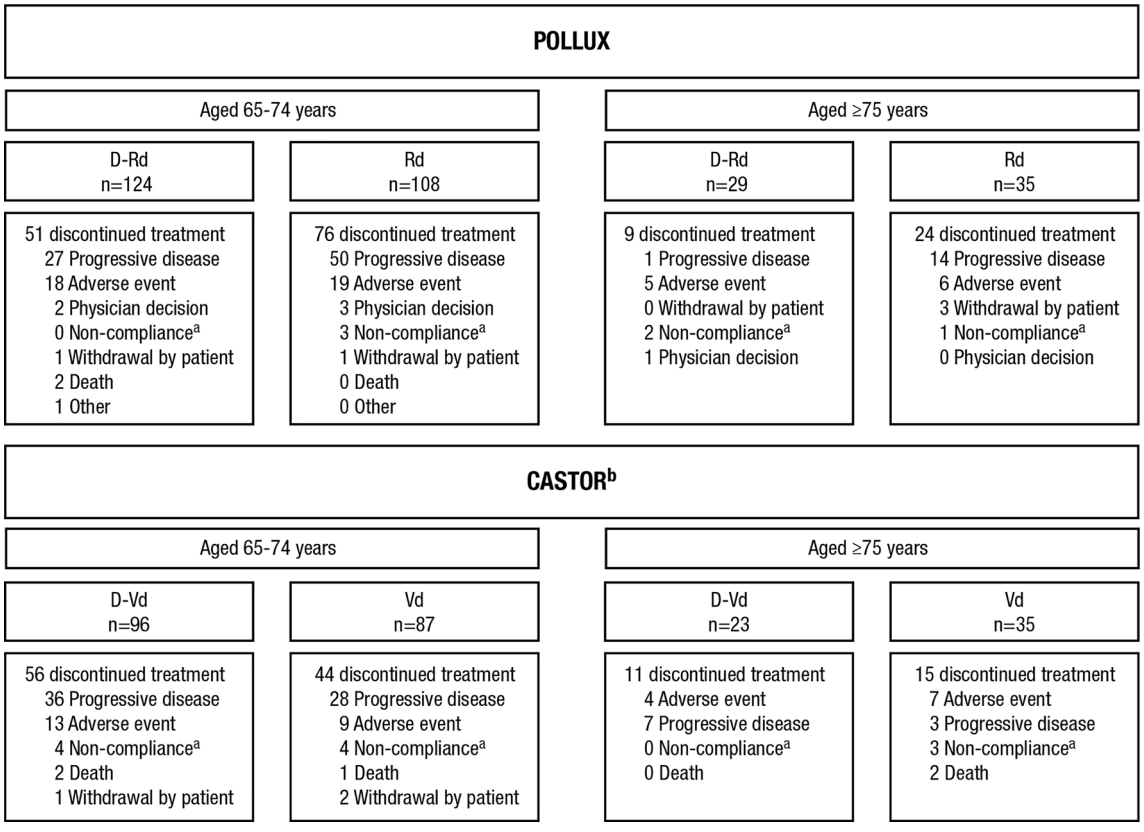

Figure 1. Disposition of patients aged 65 to 74 years and ≥75 years based on the intent-to-treat population of (A) POLLUX and (B) CASTOR. D-Rd: daratumumab/lenalidomide/dexamethasone; Rd: lenalidomide/dexamethasone; D-Vd: daratumumab/bortezomib/dexamethasone; Vd, bortezomib/dexamethasone. [a]Based on reason 'patient refused to further study treatment'. [b]All patients were to receive eight cycles of bortezomib and dexamethasone. After cycle 8, patients receiving only bortezomib and dexamethasone were entered into an observation phase, while patients in the daratumumab group continued to receive daratumumab monotherapy every 4 weeks. All patients had discontinued or completed eight cycles of bortezomib and dexamethasone by the interim analysis.[15]

or better (75.9% *versus* 41.2%; *P*=0.0059) and CR or better (55.2% *versus* 8.8%; *P*<0.0001), respectively (Table 2). Similar findings were observed in patients aged 65 to 74 years (ORR: 92.6% *versus* 80.2%; *P*=0.0057; VGPR or better: 76.2% *versus* 49.1%; *P*<0.0001; CR or better: 50.0% *versus* 22.6%; *P*<0.0001). In both age groups, deeper responses with D-Rd *versus* Rd translated to a significantly higher proportion of patients with minimal residual disease (MRD)-negative status at a sensitivity threshold of 10^{-5} (Table 2). Among patients aged ≥75 years, the rates of MRD negativity were 27.6% *versus* 5.7% (*P*=0.014464), and in patients aged 65 to 74, the rates were 23.4% *versus* 8.3% (*P*=0.001520).

In patients who received one prior line of therapy, a higher proportion of patients who received D-Rd achieved MRD negativity at a sensitivity threshold of 10^{-5} (*Online Supplementary Table S1*). Among patients aged ≥75 years, the rates of MRD negativity were 23.5% *versus* 12.5% (*P*=0.407414), and in patients aged 65 to 74 years, the rates were 24.2% *versus* 8.5% (*P*=0.017519).

In CASTOR, among patients aged ≥75 years, higher ORR were observed with D-Vd *versus* Vd (95.0% *versus* 78.8%; *P*=0.1134), including higher rates of VGPR or better (70.0% *versus* 18.2%; *P*=0.0002) and CR or better (25.0% *versus* 3.0%; *P*=0.0154), respectively (Table 2). Similar findings were observed for patients aged 65 to 74 years (ORR: 82.8% *versus* 62.4%; *P*=0.0022; VGPR or better: 64.5% *versus* 27.1%; *P*<0.0001; CR or better: 33.3% *versus* 10.6%; *P*=0.0003). The rates of MRD-negative status (10^{-5} sensitivity) were significantly higher with D-Vd *versus* Vd among patients aged 65 to 74 years (15.6% *versus* 2.3%; *P*=0.000959; Table 2). One (4.3%) patient treated with D-Vd in the subgroup of patients aged ≥75 years achieved MRD-negative status (10^{-5} sensitivity) compared with no patients in the Vd treatment group. Rates of MRD negativity at sensitivity thresholds of 10^{-4} and 10^{-6} are presented for both POLLUX and CASTOR in the *Online Supplementary Table S2*.

In patients who received one prior line of therapy, a higher proportion of patients who received D-Vd achieved MRD negativity at a sensitivity threshold of 10^{-5} (*Online Supplementary Table S1*). Among patients aged ≥75 years, the rates of MRD negativity were 12.5% *versus* 0% (*P*=0.123775), and in patients aged 65 to 74, the rates were 19.1% *versus* 2.6% (*P*=0.011285).

In POLLUX and CASTOR, all patients aged ≥75 years reported at least 1 treatment-emergent adverse event (TEAE; Table 3). In POLLUX, among patients aged ≥75 years, grade 3/4 TEAE occurred in 25 (86.2%) and 27 (77.1%) patients in the D-Rd and Rd treatment groups, respectively (Table 3). Neutropenia was the most common grade 3/4 TEAE among patients aged ≥75 years (D-Rd: 44.8%; Rd: 31.4%) and among patients aged 65 to 74 years (D-Rd: 55.3%; Rd: 39.8%). Higher rates of pneumonia were observed with daratumumab in both age groups. In CASTOR, among patients aged ≥75 years, grade 3/4

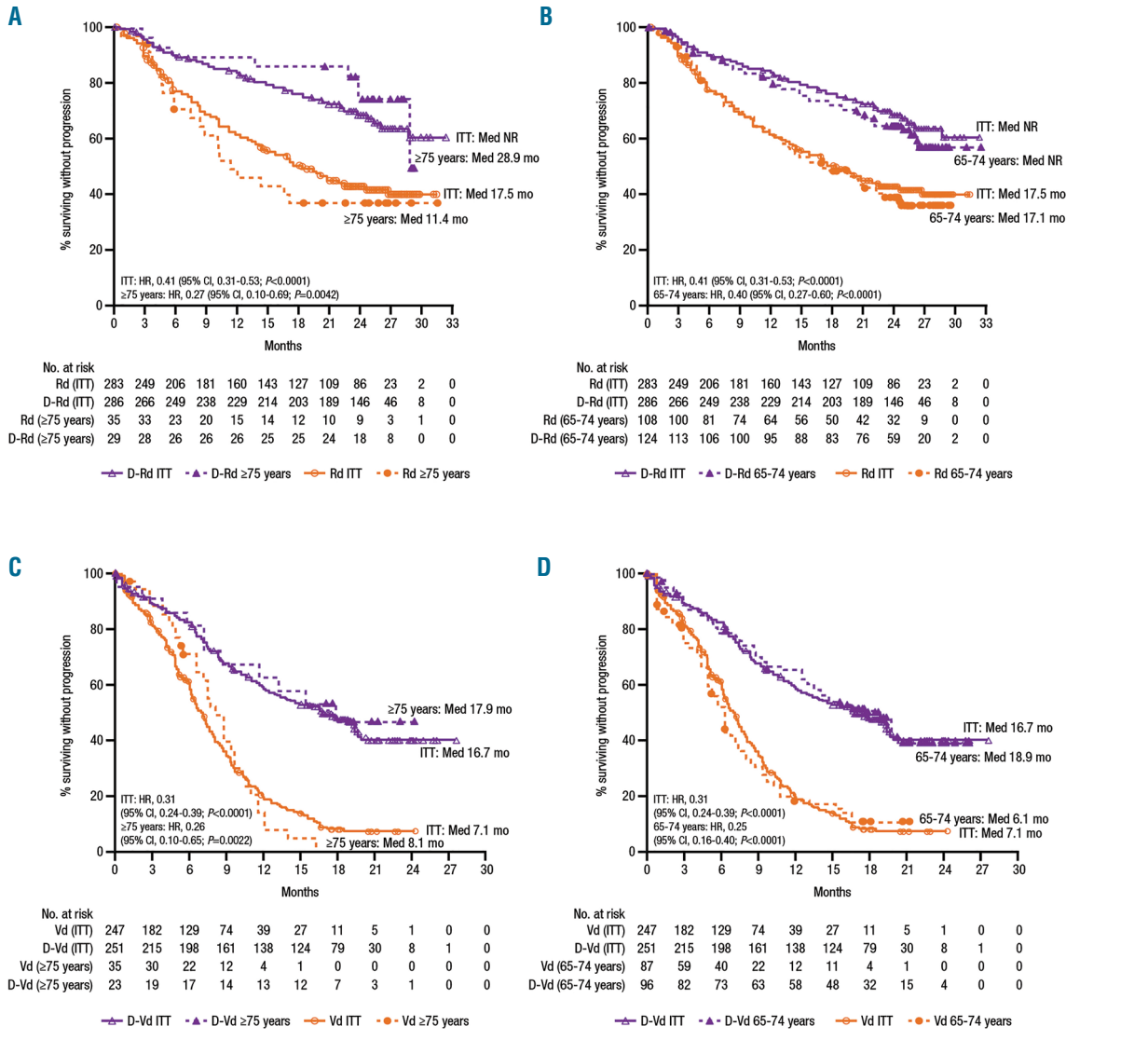

Figure 2. PFS of patients aged 65 to 74 years and ≥75 years in POLLUX and CASTOR. PFS in the ITT populations compared with patients aged ≥75 years (A) and 65 to 74 years (B) in POLLUX and with patients aged ≥75 years (C) and 65 to 74 years (D) in CASTOR. PFS is based on Kaplan-Meier estimates. PFS: progression-free survival; ITT: intent-to-treat; Med: median; NR: not reached; HR: hazard ratio; CI: confidence interval; Rd: lenalidomide/dexamethasone; D-Rd: daratumumab/lenalidomide/dexamethasone; Vd: bortezomib/dexamethasone; D-Vd: daratumumab/bortezomib/dexamethasone.

TEAE were reported in 18 (90.0%) and 26 (74.3%) patients in the D-Vd and Vd treatment groups, respectively (Table 3). Thrombocytopenia was the most common grade 3/4 TEAE in both treatment groups among patients aged ≥75 years (D-Vd: 45.0%; Vd: 37.1%) and in patients aged 65 to 74 years (D-Vd: 52.1%; Vd: 32.6%).

In POLLUX, IRR of any grade were reported in 12 (41.4%) patients aged ≥75 years and 57 (46.3%) patients aged 65 to 74 years (Table 4). The most common IRR in both age groups was dyspnea (≥75 years: 13.8%; 65-74 years: 10.6%). The majority of IRR were mild, with grade 3/4 IRR occurring in four (13.8%) patients aged ≥75 years and six (4.9%) patients aged 65 to 74 years. Among patients aged ≥75 years, all IRR occurred with the first infusion, with the exception of one IRR that occurred in a subsequent infusion. Among patients aged 65 to 74 years, two (1.6%) patients reported an IRR in the second infusion, and seven (5.9%) patients reported an IRR in subsequent infusions. In CASTOR, 13 (65.0%) patients aged ≥75 years and 43 (45.7%) patients aged 65 to 74 years reported an IRR of any grade (Table 4). IRR were generally mild, with grade 3/4 IRR occurring in 2 (10.0%) and 8 (8.5%) patients aged ≥75 and 65 to 74 years, respectively. Among patients aged ≥75 years, no IRR in the second or subsequent infusions were reported; only one patient (aged 65-74 years) had an IRR in the second infusion. In both studies, IRR were manageable and did not result in treatment discontinuations in these populations.

Discussion

MM is a disease of the elderly, and patients are a heterogeneous population with the potential for various comorbidities, reduced functional status, and increased risk of frailty.[6] Approximately 35% to 40% of patients with MM

are aged >75 years, but conversely this age group is underrepresented in clinical studies.[22] To determine if treatment strategies are safe and effective for elderly patients with MM, subgroup analyses of clinical trial data are needed. In the current sub-analysis of POLLUX and CASTOR, the efficacy and safety of daratumumab in combination with standard-of-care regimens were evaluated in patients aged ≥75 years and 65 to 74 years.

Efficacy results were consistent with those observed in the overall study populations, showing significantly prolonged PFS for patients aged ≥75 years and 65 to 74 years. In both studies, ORR were significantly higher with daratumumab *versus* standard-of-care treatment in patients aged 65 to 74 years and numerically higher in patients aged ≥75 years, with significantly higher rates of CR or better and VGPR or better in both age categories. While responses were considerably deeper among patients treated with daratumumab, the lack of statistical significance observed with ORR between groups may be due in part to the small number of patients aged ≥75 years in POLLUX (D-Rd, n=29; Rd, n=35) and CASTOR (D-Vd, n=23; Vd, n=35). Consistent with the overall study populations, deeper responses with daratumumab translated to a higher proportion of patients who achieved MRD-negative status. In both studies, safety analyses identified that the rates of common grade 3/4 hematologic TEAE were similar to those of the overall study populations.[14,15] Importantly, IRR were manageable and did not result in treatment discontinuations. While the incidence of grade 3/4 IRR was numerically higher for patients aged ≥75 years *versus* patients aged 65-74 years (13.8% *versus* 4.9%) and what was reported for the primary analysis of POLLUX (grade 3 IRR; 5.3%),[14] a larger sample size is needed to appropriately determine if this age group is more susceptible to experiencing an IRR.

There are limited clinical trial data focused on elderly

Table 2. Summary of response rates and MRD (10^{-5} sensitivity threshold) among patients aged 65 to 74 years and ≥75 years in POLLUX and CASTOR.

	POLLUX								
	ITT			65-74 years			≥75 years		
Response rate[a], n (%)[a]	D-Rd (n=281)	Rd (n=276)	*P*	D-Rd (n=122)	Rd (n=106)	*P*	D-Rd (n=29)	Rd (n=34)	*P*
ORR	261 (92.9)	211 (76.4)	<0.0001	113 (92.6)	85 (80.2)	0.0057	27 (93.1)	26 (76.5)	0.0740
≥CR	144 (51.2)	58 (21.0)	<0.0001	61 (50.0)	24 (22.6)	<0.0001	16 (55.2)	3 (8.8)	<0.0001
sCR	73 (26.0)	24 (8.7)		31 (25.4)	10 (9.4)		10 (34.5)	1 (2.9)	
CR	71 (25.3)	34 (12.3)		30 (24.6)	14 (13.2)		6 (20.7)	2 (5.9)	
≥VGPR	221 (78.6)	132 (47.8)	<0.0001	93 (76.2)	52 (49.1)	<0.0001	22 (75.9)	14 (41.2)	0.0059
VGPR	77 (27.4)	74 (26.8)		32 (26.2)	28 (26.4)		6 (20.7)	11 (32.4)	
PR	40 (14.2)	79 (28.6)		20 (16.4)	33 (31.1)		5 (17.2)	12 (35.3)	
MR	5 (1.8)	26 (9.4)		1 (0.8)	9 (8.5)		0	5 (14.7)	
SD	13 (4.6)	33 (12.0)		7 (5.7)	11 (10.4)		2 (6.9)	3 (8.8)	
PD	0	4 (1.4)		0	1 (0.9)		0	0	
NE	2 (0.7)	2 (0.7)		1 (0.8)	0		0	0	
MRD[b] (10^{-5} sensitivity threshold)									
Patients evaluated, n	286	283		124	108		29	35	
MRD negative, n (%)	75 (26.2)	18 (6.4)	<0.000001	29 (23.4)	9 (8.3)	0.001520	8 (27.6)	2 (5.7)	0.014464
	CASTOR								
	ITT			65-74 years			≥75 years		
Response rate[a], n (%)	D-Vd (n=240)	Vd (n=234)	*P*	D-Vd (n=93)	Vd (n=85)	P	D-Vd (n=20)	Vd (n=33)	*P*
ORR	201 (83.8)	148 (63.2)	<0.0001	77 (82.8)	53 (62.4)	0.0022	19 (95.0)	26 (78.8)	0.1134
≥CR	69 (28.8)	23 (9.8)	<0.0001	31 (33.3)	9 (10.6)	0.0003	5 (25.0)	1 (3.0)	0.0154
sCR	21 (8.8)	6 (2.6)		12 (12.9)	2 (2.4)		2 (10.0)	0	
CR	48 (20.0)	17 (7.3)		19 (20.4)	7 (8.2)		3 (15.0)	1 (3.0)	
≥VGPR	149 (62.1)	68 (29.1)	<0.0001	60 (64.5)	23 (27.1)	<0.0001	14 (70.0)	6 (18.2)	0.0002
VGPR	80 (33.3)	45 (19.2)		29 (31.2)	14 (16.5)		9 (45.0)	5 (15.2)	
PR	52 (21.7)	80 (34.2)		17 (18.3)	30 (35.3)		5 (25.0)	20 (60.6)	
MR	9 (3.8)	20 (8.5)		2 (2.2)	4 (4.7)		0	4 (12.1)	
SD	23 (9.6)	47 (20.1)		13 (14.0)	18 (21.2)		1 (5.0)	3 (9.1)	
PD	5 (2.1)	16 (6.8)		0	10 (11.8)		0	0	
NE	2 (0.8)	3 (1.3)		1 (1.1)	0		0	0	
MRD[b] (10^{-5} sensitivity threshold)									
Patients evaluated, n	251	247		96	87		23	35	
MRD negative, n (%)	29 (11.6)	6 (2.4)	0.000034	15 (15.6)	2 (2.3)	0.000959	1 (4.3)	0	0.170712

MRD: minimal residual disease; ITT: intent-to-treat; D-Rd: daratumumab/lenalidomide/dexamethasone; Rd: lenalidomide/dexamethasone; ORR: overall response rate; CR: complete response; sCR: stringent complete response; VGPR: very good partial response; PR: partial response; MR: minimal response; SD: stable disease; PD: progressive disease; NE: not evaluated; ; D-Vd: daratumumab/bortezomib/dexamethasone; Vd: bortezomib/dexamethasone. [a]Response-evaluable population. [b]Based on the ITT analysis set.

patients with RRMM, a population that is likely to exhibit tolerability and safety concerns with treatment.[6,23] A retrospective, observational study was conducted to assess the efficacy and toxicity of bortezomib-based regimens used in combination with dexamethasone as salvage therapy for elderly patients with RRMM.[23] Patients (n=81) who were aged 65 to 89 years (median, 73 years) and received a median of two prior lines of therapy (range 1-3) were included. A median of six cycles (range 1-11) of Vd were administered, and after a median follow-up of 24 months, the median PFS and OS were 8.7 and 22 months, respectively. Partial response or better was achieved in 65.4% of

Table 3. Most common TEAE among patients aged 65 to 74 years and ≥75 years in POLLUX and CASTOR.

TEAE: POLLUX[a]	65-74 years				≥75 years			
	Any grade (>25%)		Grade 3/4 (>10%)		Any grade (>25%)		Grade 3/4 (>10%)	
	D-Rd (n=123)	Rd (n=108)	D-Rd (n=123)	Rd (n=108)	D-Rd (n=29)	Rd (n=35)	D-Rd (n=29)	Rd (n=35)
Patients with TEAE, n (%)	122 (99.2)	104 (96.3)	113 (91.9)	89 (82.4)	29 (100.0)	35 (100.0)	25 (86.2)	27 (77.1)
Hematologic TEAE, n (%)								
Neutropenia	77 (62.6)	49 (45.4)	68 (55.3)	43 (39.8)	14 (48.3)	14 (40.0)	13 (44.8)	11 (31.4)
Anemia	52 (42.3)	47 (43.5)	23 (18.7)	24 (22.2)	12 (41.4)	13 (37.1)	3 (10.3)	7 (20.0)
Thrombocytopenia	37 (30.1)	37 (34.3)	19 (15.4)	16 (14.8)	10 (34.5)	9 (25.7)	3 (10.3)	5 (14.3)
Nonhematologic TEAE, n (%)								
Diarrhea	61 (49.6)	37 (34.3)	8 (6.5)	1 (0.9)	11 (37.9)	12 (34.3)	0	2 (5.7)
Fatigue	43 (35.0)	38 (35.2)	5 (4.1)	6 (5.6)	10 (34.5)	13 (37.1)	1 (3.4)	1 (2.9)
Nasopharyngitis	41 (33.3)	25 (23.1)	0	0	4 (13.8)	5 (14.3)	0	0
Upper respiratory tract infection	40 (32.5)	26 (24.1)	2 (1.6)	2 (1.9)	11 (37.9)	9 (25.7)	1 (3.4)	0
Constipation	39 (31.7)	30 (27.8)	2 (1.6)	0	7 (24.1)	12 (34.3)	0	1 (2.9)
Nausea	34 (27.6)	17 (15.7)	1 (0.8)	1 (0.9)	7 (24.1)	9 (25.7)	0	0
Muscle spasms	33 (26.8)	19 (17.6)	1 (0.8)	2 (1.9)	8 (27.6)	6 (17.1)	0	0
Cough	32 (26.0)	16 (14.8)	0	0	6 (20.7)	6 (17.1)	1 (3.4)	0
Dyspnea	31 (25.2)	11 (10.2)	7 (5.7)	0	7 (24.1)	11 (31.4)	3 (10.3)	0
Pneumonia	29 (23.6)	14 (13.0)	19 (15.4)	7 (6.5)	9 (31.0)	6 (17.1)	5 (17.2)	4 (11.4)
Peripheral edema	29 (23.6)	17 (15.7)	1 (0.8)	0	8 (27.6)	15 (42.9)	0	2 (5.7)
Asthenia	22 (17.9)	19 (17.6)	5 (4.1)	3 (2.8)	4 (13.8)	10 (28.6)	1 (3.4)	2 (5.7)
Back pain	21 (17.1)	20 (18.5)	1 (0.8)	3 (2.8)	8 (27.6)	7 (20.0)	2 (6.9)	1 (2.9)
Hypokalaemia	16 (13.0)	12 (11.1)	5 (4.1)	5 (4.6)	7 (24.1)	4 (11.4)	4 (13.8)	1 (2.9)
Pulmonary embolism	5 (4.1)	3 (2.8)	4 (3.3)	2 (1.9)	1 (3.4)	4 (11.4)	1 (3.4)	4 (11.4)

TEAE: CASTOR[a]	65-74 years				≥75 years			
	Any grade (>25%)		Grade 3/4 (>10%)		Any grade (>25%)		Grade 3/4 (>10%)	
	D-Vd (n=94)	Vd (n=86)	D-Vd (n=94)	Vd (n=86)	D-Vd (n=20)	Vd (n=35)	D-Vd (n=20)	Vd (n=35)
Patients with TEAE, n (%)	93 (98.9)	82 (95.3)	77 (81.9)	60 (69.8)	20 (100.0)	35 (100.0)	18 (90.0)	26 (74.3)
Hematologic TEAE, n (%)								
Thrombocytopenia	60 (63.8)	36 (41.9)	49 (52.1)	28 (32.6)	14 (70.0)	22 (62.9)	9 (45.0)	13 (37.1)
Anemia	29 (30.9)	31 (36.0)	14 (14.9)	15 (17.4)	5 (25.0)	15 (42.9)	2 (10.0)	4 (11.4)
Neutropenia	19 (20.2)	6 (7.0)	15 (16.0)	3 (3.5)	1 (5.0)	2 (5.7)	0	1 (2.9)
Lymphopenia	14 (14.9)	5 (5.8)	12 (12.8)	5 (5.8)	1 (5.0)	0	1 (5.0)	0
Nonhematologic TEAE, n (%)								
Peripheral sensory neuropathy	49 (52.1)	30 (34.9)	3 (3.2)	9 (10.5)	13 (65.0)	17 (48.6)	2 (10.0)	2 (5.7)
Diarrhea	38 (40.4)	13 (15.1)	2 (2.1)	1 (1.2)	11 (55.0)	13 (37.1)	2 (10.0)	0
Upper respiratory tract infection	30 (31.9)	13 (15.1)	2 (2.1)	0	5 (25.0)	7 (20.0)	0	0
Cough	29 (30.9)	13 (15.1)	0	0	10 (50.0)	5 (14.3)	0	0
Fatigue	23 (24.5)	15 (17.4)	6 (6.4)	1 (1.2)	7 (35.0)	14 (40.0)	3 (15.0)	4 (11.4)
Peripheral edema	23 (24.5)	11 (12.8)	1 (1.1)	0	8 (40.0)	4 (11.4)	0	0
Constipation	22 (23.4)	14 (16.3)	0	2 (2.3)	4 (20.0)	12 (34.3)	0	0
Pneumonia	16 (17.0)	9 (10.5)	12 (12.8)	6 (7.0)	5 (25.0)	6 (17.1)	3 (15.0)	6 (17.1)
Bronchitis	14 (14.9)	8 (9.3)	3 (3.2)	3 (3.5)	6 (30.0)	2 (5.7)	2 (10.0)	0
Dizziness	9 (9.6)	9 (10.5)	0	0	5 (25.0)	11 (31.4)	0	0
Bone pain	7 (7.4)	8 (9.3)	2 (2.1)	2 (2.3)	7 (35.0)	2 (5.7)	1 (5.0)	1 (2.9)

TEAE: treatment-emergent adverse event; D-Rd: daratumumab/lenalidomide/dexamethasone; Rd: lenalidomide/dexamethasone; D-Vd: daratumumab/bortezomib/dexamethasone; Vd: bortezomib/dexamethasone. [a]The safety analysis set included all patients who received ≥1 administration of study treatment.

Table 4. Most common IRR among patients aged 65-74 years and ≥75 years in POLLUX and CASTOR.

	65-74 years		≥75 years	
	D-Rd (n=123)		D-Rd (n=29)	
TEAE (>5%): POLLUX[a]	Any grade	Grade 3/4	Any grade	Grade 3/4
Patients with IRR, n (%)	57 (46.3)	6 (4.9)	12 (41.4)	4 (13.8)
Dyspnea	13 (10.6)	1 (0.8)	4 (13.8)	1 (3.4)
Chills	8 (6.5)	0	3 (10.3)	1 (3.4)
Feeling cold	2 (1.6)	0	2 (6.9)	1 (3.4)
Wheezing	3 (2.4)	1 (0.8)	2 (6.9)	1 (3.4)
Vomiting	8 (6.5)	1 (0.8)	2 (6.9)	0
Bronchospasm	7 (5.7)	0	0	0
Cough	7 (5.7)	0	0	0
Nausea	7 (5.7)	0	0	0
	65-74 years		≥75 years	
	D-Vd (n=94)		D-Vd (n=20)	
TEAE (>5%): CASTOR[a]	Any grade	Grade 3/4	Any grade	Grade 3/4
Patients with IRR, n (%)	43 (45.7)	8 (8.5)	13 (65.0)	2 (10.0)
Bronchospasm	11 (11.7)	1 (1.1)	4 (20.0)	1 (5.0)
Throat irritation	2 (2.1)	0	4 (20.0)	0
Dyspnea	10 (10.6)	4 (4.3)	3 (15.0)	0
Cough	8 (8.5)	0	3 (15.0)	0
Nausea	6 (6.4)	0	0	0
Hypertension	6 (6.4)	5 (5.3)	0	0
Chills	3 (3.2)	0	2 (10.0)	0

IRR: infusion-related reaction; D-Rd: daratumumab/lenalidomide/dexamethasone; Rd: lenalidomide/dexamethasone; D-Vd: daratumumab/bortezomib/dexamethasone; Vd: bortezomib/dexamethasone. [a]The safety analysis set included all patients who received ≥1 administration of study treatment.

patients, including 11% CR and 12.5% VGPR. The most common adverse events included peripheral neuropathy (47% of patients), gastrointestinal symptoms (22.2%), thrombocytopenia (11.1%), and anemia (7.4%). Overall, these results are comparable with studies of Vd in younger patients.[23]

Sub-analyses of the phase 3 ASPIRE and ENDEAVOR studies demonstrated a benefit for carfilzomib in elderly patients with MM. The ASPIRE study of carfilzomib, lenalidomide, and dexamethasone (KRd) *versus* Rd demonstrated prolonged PFS with KRd in patients with relapsed multiple myeloma aged ≥70 years (median: 23.8 *versus* 16.0 months; HR, 0.75, 95% CI, 0.53-1.08) and an improved ORR (90.3% *versus* 66.1%, respectively).[24] While cardiovascular events occurred more frequently in the elderly population compared with patients aged <70 years, KRd demonstrated a favorable benefit-risk profile in elderly patients.[25] The ENDEAVOR study of carfilzomib and dexamethasone (Kd) *versus* Vd demonstrated prolonged PFS with Kd in patients with RRMM who received 1 to 3 prior lines of therapy and were aged 65 to 74 years (median: 15.6 *versus* 9.5 months; HR, 0.528, 95% CI, 0.382-0.728) or ≥75 years (median: 18.7 *versus* 8.9 months; HR, 0.383; 95% CI, 0.227-0.647).[26] While hypertension was the most common grade ≥3 TEAE in patients aged 65 to 74 years and ≥75 years who received Kd, the safety results were similar to the overall population in ENDEAVOR.

Due to the nature of drug development, clinical trials and regulatory approvals usually proceed with patients with more advanced disease. Ideally, moving these regimens into front-line treatment may provide the best opportunity for patients to mount prolonged responses and delay relapse. Newly diagnosed elderly patients are usually excluded from receiving stem cell transplants due to their age. The VISTA phase 3 study of bortezomib, melphalan, and prednisone (VMP) established this regimen as a standard of care in transplant-ineligible newly diagnosed MM patients.[27] Of interest is whether the benefit of daratumumab-based regimens in RRMM could be extended to these patients. In the phase 3 ALCYONE study, daratumumab in combination with VMP reduced the risk of disease progression or death by 50% compared with VMP alone (HR, 0.50; 95% CI, 0.38-0.65).[28] Over 90% of patients were aged ≥65 years, and 30% were aged ≥75 years. In a prespecified subgroup analysis, the HR for the primary endpoint of PFS were similar for patients aged ≥75 years (0.53) and <75 years (0.49). The addition of daratumumab to VMP produced no new safety signals except for a higher rate of infections that resolved with few discontinuations.[28] Furthermore, Rd is also a standard treatment regimen for patients with transplant-ineligible newly diagnosed MM. Recently, in the phase 3 MAIA study, D-Rd significantly reduced the risk of disease progression or death and nearly doubled the rate of CR or better.[29] MAIA enrolled patients aged ≥65 years, 44% of whom were aged ≥75 years.[29]

MM is a disease of the elderly with 35 to 40% of patients aged ≥75 years at diagnosis.[22] One of the limitations of the current analysis is that the subgroup of patients aged ≥75 years in POLLUX and CASTOR was relatively small (<15% of the overall study population was ≥75 years of age). Comorbidities and other ailments, including frailty, that are often associated with elderly patients may have compro-

mised eligibility for the study, and it is recognized that this is a limitation of many MM studies.[30] However, differences in efficacy were still observed between the treatment groups. An additional limitation is that the study did not assess frailty. The IMWG frailty score system which is based on age, comorbidities, and functional status, can be used to predict survival and toxicity, making it a useful metric for determining feasibility of a treatment regimen and for clinical trial design.[19] This metric was adopted after these studies were initiated.

In conclusion, the safety and efficacy of daratumumab in combination with Rd or Vd does not appear to be negatively impacted by age in patients studied in POLLUX and CASTOR, and is consistent with the overall study populations. This subgroup analysis supports the addition of daratumumab to standard-of-care regimens in patients with RRMM, regardless of age.

Acknowledgments

The authors thank the patients who participated in this study, the staff members at the study sites, the data and safety monitoring committee, and staff members who were involved in data collection and analyses.

Funding

These studies (ClinicalTrials.gov Identifiers: NCT02076009 and NCT02136134) were sponsored by Janssen Research & Development, LLC. The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.Editorial and medical writing support were provided by Kristin Runkle, PhD, of MedErgy, and were funded by Janssen Global Services, LLC.

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