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ORIGINAL REPORT

Community-Based Phase IIIB Trial of Three UPFRONT Bortezomib-Based Myeloma Regimens

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ABSTRACT

Purpose
The US community-based, phase IIIB UPFRONT trial was designed to compare three frontline bortezomib-based regimens in transplantation-ineligible patients with myeloma.

Patients and Methods
Patients (N = 502) were randomly assigned 1:1:1 to 24 weeks (eight 21-day cycles) of induction with bortezomib-dexamethasone (VD; n = 168; intravenous bortezomib 1.3 mg/m^2, days 1, 4, 8, and 11 plus oral dexamethasone 20 mg, days 1, 2, 4, 5, 8, 9, 11, and 12 [cycles 1 to 4], or 1, 2, 4, and 5 [cycles 5 to 8]), bortezomib-thalidomide-dexamethasone (VTD; n = 167; bortezomib and dexamethasone as before plus oral thalidomide 100 mg, days 1 to 21), or bortezomib-melphalan-prednisone (VMP; n = 167; bortezomib as before plus oral melphalan 9 mg/m^2 and oral prednisone 60 mg/m^2, days 1 to 4, every other cycle), followed by 25 weeks (five 35-day cycles) of bortezomib maintenance (1.6 mg/m^2, days 1, 8, 15, and 22). The primary end point was progression-free survival.

Results
After 42.7 months' median follow-up, median progression-free survival with VD, VTD, and VMP was 14.7, 15.4, and 17.3 months, respectively; median overall survival was 49.8, 51.5, and 53.1 months, with no significant differences among treatments for either end point (global $P = .46$ and $P = .79$, respectively, Wald test). Overall response rates were 73% (VD), 80% (VTD), and 70% (VMP). Adverse events were more common with VTD than VD or VMP. Bortezomib maintenance was feasible without producing cumulative toxicity.

Conclusion
Although all bortezomib-containing regimens produced good outcomes, VTD and VMP did not appear to offer an advantage over VD in transplantation-ineligible patients with myeloma treated in US community practice.

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INTRODUCTION

The introduction of agents including thalidomide, lenalidomide, and bortezomib has contributed to improved long-term survival for patients with multiple myeloma (MM).[1-3] Bortezomib forms the basis of preferred regimens in the frontline, stem-cell transplantation–eligible setting,[4] where combinations such as bortezomib-dexamethasone (VD)[5] and bortezomib-thalidomide-dexamethasone (VTD)[6] have demonstrated efficacy. Historically, patients ineligible for transplantation because of older age, frailty, or comorbidities[7-9] were treated with melphalan-prednisone (MP).[10] However, MP has been superseded by modern regimens such as bortezomib-melphalan-prednisone (VMP), which demonstrated superior efficacy, including significantly prolonged overall survival (OS), versus MP.[11,12] Optimal therapy for transplantation-ineligible patients remains to be determined.

Phase III trials of novel agent-based regimens have generally been large, international studies enrolling patients predominantly in academic, tertiary-care centers. However, because most oncology patients (approximately 85% in the United States) undergo treatment in community practice,[13] understanding how to obtain the best outcomes for patients with MM in this setting is paramount. To investigate optimal combination partners for bortezomib in the context of the standard of care, VMP, the randomized, phase IIIB UPFRONT trial (NCT00507416) compared tailored frontline VD,

VTD, and VMP therapy for transplantation-ineligible patients with MM in US community practice.

PATIENTS AND METHODS

Patients

Patients with newly diagnosed, symptomatic, measurable MM requiring systemic therapy, and who were ineligible for stem-cell transplantation because of age (≥ 65 years), comorbidities, or personal preference, were eligible (the online-only Data Supplement provides detailed inclusion/exclusion criteria). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Ethics committees at each study site reviewed and approved the protocol. Patients provided written informed consent.

Study Design

This randomized, open-label study recruited patients at 159 US centers between June 26, 2007, and March 31, 2010. Study closure and data cut for final analysis was March 31, 2013.

Randomization

Patients were assigned to treatment using an interactive voice response system on the basis of a computer-generated randomization schedule prepared by the sponsor. A central randomization system with permuted blocks was used. No stratification was used.

Treatment

Patients were randomly assigned 1:1:1 to receive 24 weeks (eight 21-day cycles) of VD, VTD, or VMP induction (VD: intravenous bortezomib 1.3 mg/m^2, days 1, 4, 8, and 11 plus oral dexamethasone 20 mg, days 1, 2, 4, 5, 8, 9, 11, and 12 [cycles 1 to 4], or days 1, 2, 4, and 5 [cycles 5 to 8]; VTD: bortezomib and dexamethasone as before plus oral thalidomide 100 mg, days 1 to 21; VMP: bortezomib as before plus oral melphalan 9 mg/m^2 and oral prednisone 60 mg/m^2, both days 1 to 4, every other cycle), followed by 25 weeks (five 35-day cycles) of maintenance with single-agent intravenous bortezomib 1.6 mg/m^2, days 1, 8, 15, and 22.

Concomitant treatments/prophylactic medications are listed in the Data Supplement. Dose reductions/delays were per prespecified dose-modification guidelines for peripheral neuropathy (PN) and hematologic/nonhematologic toxicities.

End Points and Assessments

The overall objective was to define the optimal regimen (VD, VTD, or VMP). The primary end point was progression-free survival (PFS; time from randomization to date of progression, relapse, or death, whichever came first). Patients without events were censored at the date of last response assessment. Prespecified secondary end points were as follows: overall response rate (ORR; partial response [PR] or better); complete response (CR) rate; CR plus very good PR (CR + VGPR) rate; duration of response; time to alternate anti-MM therapy; OS; safety, including rates of grade ≥ 3 adverse events (AEs), serious AEs, and PN; and patient-reported quality of life (QoL).

Response was investigator assessed per International Myeloma Working Group criteria,[14] in addition incorporating the near-CR category[15] (Data Supplement). Best confirmed response was determined in response-evaluable patients with at least two postbaseline assessments. For M-protein assessments, serum and 24-hour urine samples were collected at baseline (day 1, cycle 1), predosing on day 1 of cycles 3, 5, 7, 9, 11, and 13, and every 12 weeks until disease progression, and analyzed at a central laboratory. After maintenance, patients completed an end-of-treatment visit and were assessed every 12 weeks until progression and every 12 weeks thereafter for survival and subsequent anti-MM therapy until study closure.

AEs were assessed per the National Cancer Institute's Common Terminology Criteria for Adverse Events v3.0. QoL was recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) via a handheld personal data instrument before dosing at baseline (day 1, cycle 1), on day 1 of every odd-numbered cycle, at the end-of-treatment visit, and every 12 weeks thereafter until progression.

Statistical Analysis

A protocol-specified interim analysis of efficacy (on the basis of response rates) and safety was planned after the first 70 patients in each arm had completed at least four cycles or discontinued earlier, to determine which of the three arms was inferior and would cease enrolling. The original sample size was based on a two-sided test (α = .10) with 80% power to detect 40% improvement in median PFS (20 to 28 months), assuming an inferior arm would be dropped after the first interim analysis. To detect this improvement, 219 progression/death events were needed. Approximately 500 patients were to be enrolled.

At the first interim analysis, the independent data monitoring committee recommended enrollment to continue in all three arms because no arm was inferior, and that a second interim analysis be conducted after 300 patients (100 per arm) had completed at least eight cycles or discontinued earlier. At the second interim analysis, the independent data monitoring committee recommended enrollment to continue with three arms. A protocol amendment extended study duration from 2 to 3 years, to provide 219 events in any two arms, or 329 total events.

Intent-to-treat, safety, and response-evaluable populations are defined in the Data Supplement. Kaplan-Meier method was used for time-to-event analyses; global differences among arms were based on the Wald test. Potential prognostic factors for PFS (age, sex, race, International Staging System [ISS] stage, myeloma type, Charlson comorbidity index, and Karnofsky performance status [KPS]) were analyzed using Cox regression modeling. Reasons for patient censoring in PFS analysis are summarized in the Data Supplement. The χ^2 test was used for response rate comparisons.

EORTC QLQ-C30 scores were collected within 1 year of randomization, regardless of discontinuation. For patients dying within 1 year, missing assessments were assigned the worst possible score. A linear mixed model was used to assess changes from baseline in scores within and between arms. Sensitivity analyses, incorporating post-treatment data or last observation carried forward, were performed to investigate the impact of missing scores.

RESULTS

Patients

In total, 502 patients were randomly assigned (168 VD, 167 VTD, and 167 VMP); 486 (97%) received at least one dose and were safety evaluable. Four hundred seventy-four (94%) of the patients were enrolled at community-based practices and 28 (6%) at large hospitals/academic institutions (median, 2 patients per center [range, 1 to 21]). Figure 1 summarizes patient disposition.

Baseline characteristics were generally well balanced across arms (Table 1). Median age was 73 years (interquartile range [IQR], 67 to 78 years); 210 (42%) of the patients were aged ≥ 75 years, and 90 (18%) of the patients were aged ≥ 80 years. Of patients, 73% (343 of 467) had ISS stage II/III myeloma and 48% (235 of 489) had comorbidities (19% [91 of 489] Charlson comorbidity index ≥ 2), including diabetes mellitus (21% [104 of 489]), renal disease (15% [74 of 489]), and chronic pulmonary disease (8% [38 of 489]; Data Supplement).

Patients received a median of 7 (IQR, 4 to 13) cycles overall (VD, 8 [IQR, 4 to 13]; VTD, 6 [IQR, 3 to 13]; VMP, 7 [IQR, 4 to 13]; Data Supplement). Of patients, 50% (82 of 165), 38% (60 of 158), and 42% (69 of 163), respectively, received bortezomib maintenance. Mean bortezomib dose intensity for VD, VTD, and VMP was 72%, 63%, and 68%, respectively, during induction, and 75%, 81%, and 87%, respectively, during maintenance. Of patients, 31% (149 of 486) received the

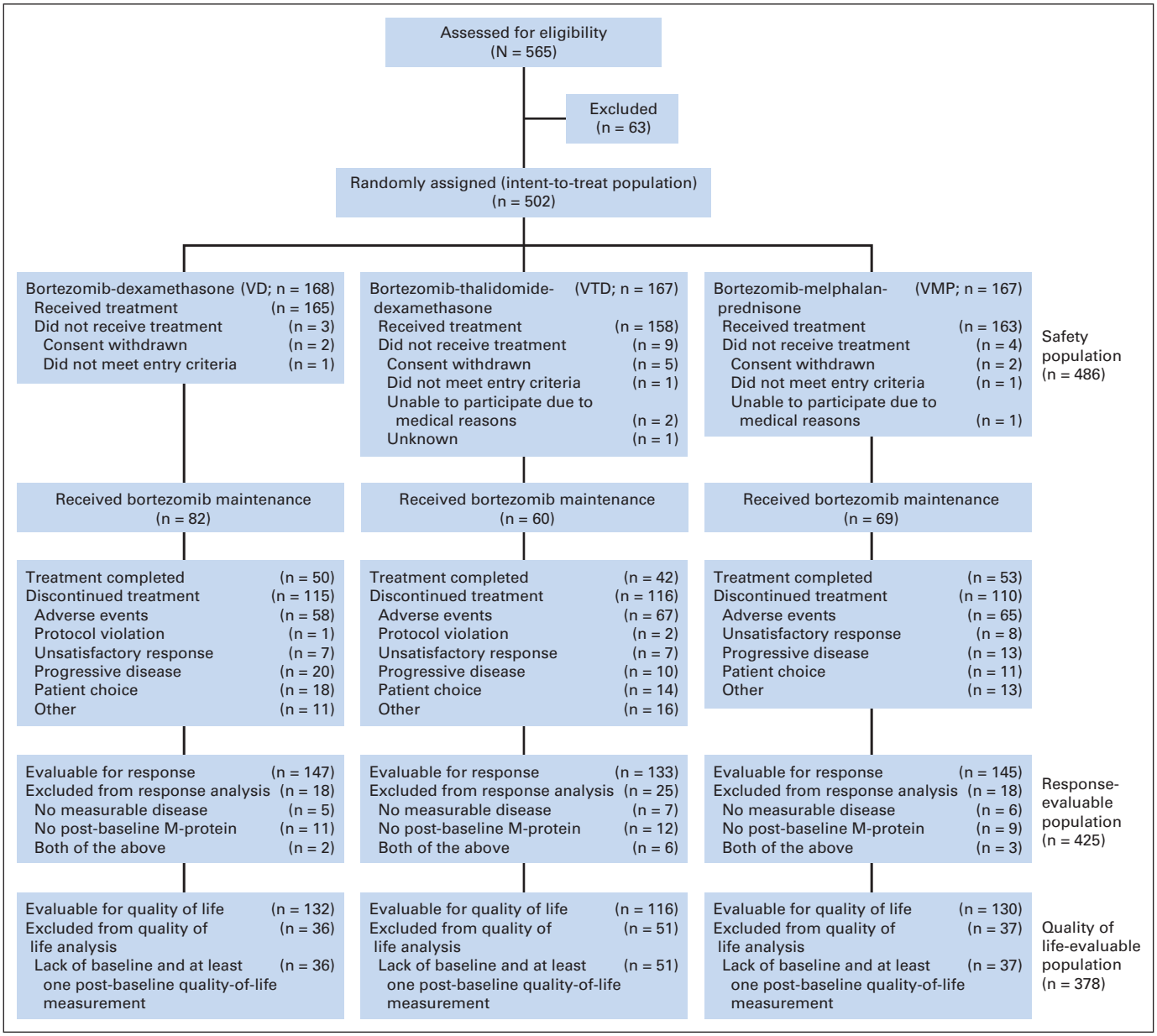

Fig 1. CONSORT diagram. VD, bortezomib-dexamethasone; VMP, bortezomib-melphalan-prednisone; VTD, bortezomib-thalidomide-dexamethasone.

maximum 13 cycles (VD, 32% [53 of 165]; VTD, 27% [43 of 158]; VMP, 33% [53 of 163]). Supportive therapies and thromboembolic prophylaxis are summarized in the Data Supplement. Of patients, 33% (158 of 486) received antivirals and 59% (285 of 486) received anticoagulants during the study.

Efficacy

After 42.7 months' median follow-up (IQR, 26.3 to 52.8 months) from randomization (VD, 44.3 months [IQR, 24.7 to 53.3 months]; VTD, 41.3 months [IQR, 21.1 to 49.1 months]; VMP, 43.4 months [IQR, 35.2 to 54.3 months]), median (95% CI) PFS for VD, VTD, and VMP was 14.7 (12.0 to 18.6), 15.4 (12.6 to 24.2), and 17.3 (14.8 to 20.3) months, respectively (Fig 2A), with no significant difference among arms (global $P = .46$). In multivariable Cox regression analysis, ISS stage I and KPS $\geq$ 90% were associated with longer PFS.

Best confirmed ORRs over 13 cycles were 73% (VD, 107 of 147), 80% (VTD, 106 of 133), and 70% (VMP, 101 of 145), including CR rates of 3% (5 of 147), 4% (5 of 133), and 4% (6 of 145), respectively (Table 2). CR + VGPR rates were 37% (54 of 147), 51% (68 of 133), and 41% (59 of 145), respectively ($P = .0153$ for the VTD *v* VD comparison), including near-CR rates of 27% (39 of 147), 36% (48 of 133), and 28% (41 of 145), respectively. First response was achieved by end of cycle 2 in 84% (263 of 314) of patients (VD, 87% [93 of 107]; VTD, 91% [96 of 106]; VMP, 73% [74 of 101]). Among 166 patients with best response of PR or better during induction, 148 (89%) continued to respond during maintenance, with improved response depth in 28 (11 to CR; Data Supplement).

Median (95% CI) duration of response was 18.3 (14.3 to 24.2; VD), 22.4 (12.7 to 29.1; VTD), and 19.8 (16.4 to 23.3; VMP) months, with no significant difference among arms (global $P = .81$); median

Table 1. Patient Demographics and Baseline Characteristics (intent-to-treat population)

Demographic or Characteristic	VD (n = 168)	VTD (n = 167)	VMP (n = 167)
Age, years			
Median (IQR)	74.5 (67.0-79.0)	73.0 (66.0-77.0)	72.0 (68.0-77.0)
Age subgroup, No. (%)			
≥ 75	84 (50)	64 (38)	62 (37)
≥ 80	40 (24)	27 (16)	23 (14)
Male, No. (%)	101 (60)	70 (42)	90 (54)
Race,* No. (%)			
White	131 (78)	124 (74)	118 (71)
Black	23 (14)	31 (19)	29 (17)
Asian	2 (1)	1 (< 1)	0
Other†	10 (6)	11 (7)	19 (11)
Not reported	2 (1)	0	1 (< 1)
Charlson comorbidity index, No. (%)‡			
0	88 (53)	94 (59)	89 (54)
1	39 (24)	41 (26)	47 (28)
≥ 2	38 (23)	24 (15)	29 (18)
Myeloma type, No. (%)‡			
IgG	101 (62)	89 (58)	100 (62)
IgA	41 (25)	43 (28)	40 (25)
IgD	0	1 (< 1)	0
IgM	0	1 (< 1)	1 (< 1)
Light chain	21 (13)	20 (13)	18 (11)
Biclonal	1 (< 1)	0	2 (1)
ISS disease stage, No. (%)‡			
I	33 (22)	50 (33)	41 (25)
II	70 (46)	53 (35)	63 (39)
III	50 (33)	49 (32)	58 (36)
Karnofsky performance status < 70%, No. (%)‡	18 (11)	13 (8)	19 (12)
Serum albumin level, g/dL			
Median (IQR)	3.5 (3.1-4.0)	3.7 (3.3-3.9)	3.5 (3.1-3.8)
Subgroup, No. (%)‡			
< 3.5	75 (45)	56 (35)	78 (48)
≥ 3.5	90 (55)	103 (65)	86 (52)
Serum β_2-microglobulin level, mg/L			
Median (IQR)	4.5 (3.1-6.2)	3.9 (2.8-6.2)	4.1 (3.0-6.6)
Subgroup, No. (%)‡			
< 2.5	20 (13)	27 (18)	24 (15)
2.5 to 5.5	84 (55)	76 (50)	80 (49)
> 5.5	49 (32)	49 (32)	58 (36)
Serum creatinine level, mg/dL			
Median (IQR)	1.1 (0.9-1.4)	1.0 (0.8-1.4)	1.0 (0.8-1.3)

Abbreviations: Ig, immunoglobulin; IQR, interquartile range; ISS, International Staging System; VD, bortezomib-dexamethasone; VMP, bortezomib-melphalan-prednisone; VTD, bortezomib-thalidomide-dexamethasone.
*Race was self-reported.
†Other includes native Hawaiian or other Pacific Islander, American Indian, or Alaskan Native.
‡Calculated in patients with available data and may not equal 100% because of rounding.

time to alternate anti-MM therapy was 19.7 (16.0 to 27.8), 24.5 (16.6 to 27.6), and 19.0 (15.2 to 23.1) months, respectively (global $P = .67$). Of patients, 53% (89 of 168), 49% (82 of 167), and 56% (94 of 167), respectively, had received subsequent therapy; 57% (51 of 89), 48% (39 of 82), and 50% (47 of 94), respectively, of patients received immunomodulatory drugs as first alternative treatment (Data Supplement). Of patients, 22% (110 of 502) received subsequent therapy without documented progression. Median (95% CI) time to third-line therapy was 30.9 (26.5 to 36.5; VD), 38.5 (29.7 to 48.9; VTD), and 36.3 (29.7 to 41.9; VMP) months (global $P = .56$; Data Supplement).

At the final analysis, 40% (68 of 168; VD), 37% (62 of 167; VTD), and 40% (66 of 167; VMP) of patients had died. Median (95% CI) OS was 49.8 (35.7 to not estimable [NE]), 51.5 (38.5 to NE), and 53.1 (41.1 to NE) months, respectively (Fig 2B), with no significant difference among arms (global $P = .79$).

Safety

PN was the most common AE (52% [255 of 486] across arms: VD, 50% [83 of 165]; VTD, 60% [95 of 158]; VMP, 47% [77 of 163]; Table 3). Grade ≥ 2 PN was reported in 35% (58 of 165), 47% (75 of 158), and 35% (57 of 163) of patients, respectively. Rates of grade ≥ 3 infections were 21% (35 of 165), 16% (25 of 158), and 18% (29 of 163), and grade ≥ 3 sepsis was reported in 3% (5 of 165), 3% (5 of 158), and 2% (3 of 163) of patients, respectively. Rates of grade ≥ 3 deep-vein

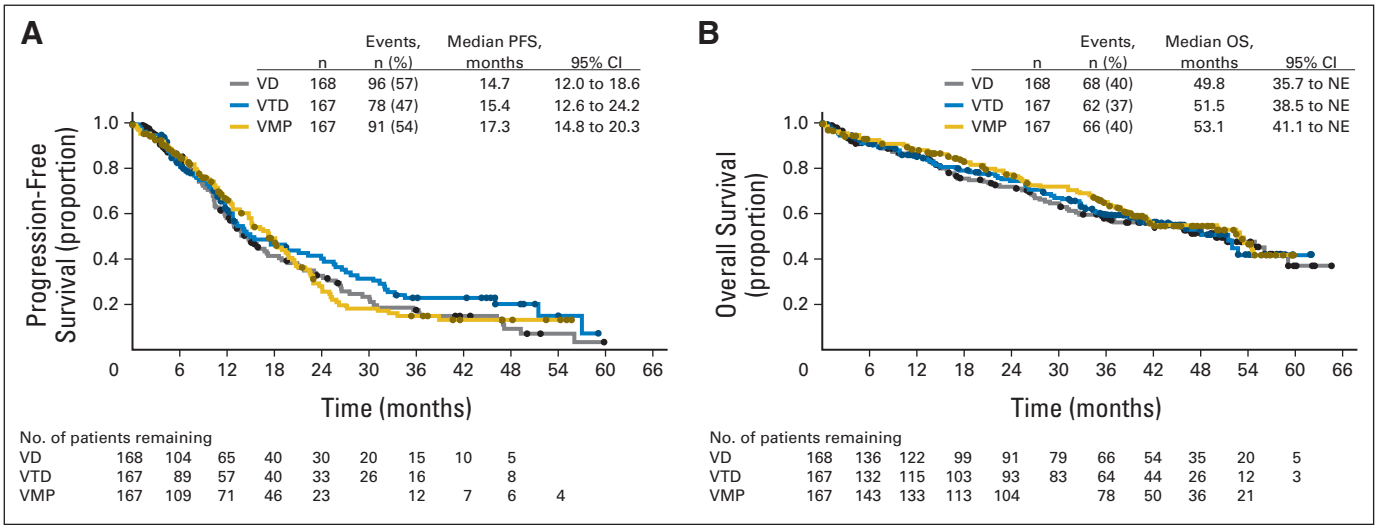

Fig 2. Kaplan-Meier analysis of (A) progression-free survival (PFS) and (B) overall survival (OS) in the intent-to-treat population. NE, not estimable; VD, bortezomib-dexamethasone; VMP, bortezomib-melphalan-prednisone; VTD, bortezomib-thalidomide-dexamethasone.

thrombosis and pulmonary embolism were low (< 5% all arms). Individual grade ≥ 4 AEs were infrequent; however, grade ≥ 4 thrombocytopenia rates appeared higher with VMP (VD, 1% [2 of 165]; VTD, 1% [2 of 158]; VMP, 7% [11 of 163]).

Safety profiles for VD, VTD, and VMP during induction and maintenance are summarized in the Data Supplement. Bortezomib maintenance produced limited additional toxicity compared with induction. New-onset grade ≥ 3 PN rates were low during maintenance (VD, 6% [5 of 82]; VTD, 7% [4 of 60]; VMP, 3% [2 of 69]).

Rates of AEs and discontinuations because of AEs appeared higher with VTD than with VD or VMP. Of patients, 29% (48 of 165; VD), 38% (60 of 158; VTD), and 34% (55 of 163; VMP) discontinued because of AEs, which were treatment related in 22% (37 of 165), 26% (41 of 158), and 28% (45 of 163) of patients, respectively. PN was the most common reason for discontinuation, occurring in 13% (22 of 165; VD), 16% (26 of 158; VTD), and 18% (29 of 163; VMP) of patients. Of patients, 7% (11 of 165), 6% (10 of 158), and (4% seven of 163) died within 30 days of the last dose of study drug, respectively; deaths in one patient in each arm were deemed treatment related by investigators (natural causes, pneumonia, and cardiac arrest, respectively). One second primary malignancy was reported (VMP: unknown origin, metastases to lung/liver).

QoL

EORTC QLQ-C30 assessments were available at baseline and one or more postbaseline time points in 79% (132 of 168; VD), 69% (116 of 167; VTD), and 78% (130 of 167; VMP) of patients. In all arms, there was a transitory decrease in mean global health status scores during induction, followed by a trend for improvement/stabilization thereafter (Fig 3A and 3B). Sensitivity analyses confirmed the primary findings (Data Supplement). In all arms, there was a trend for worsening functioning and symptoms during induction (particularly VTD), followed by improvement/stabilization during maintenance,

Table 2. Best Confirmed Response Rates During Induction (cycles 1-8) and During the Entire Treatment Period (cycles 1-13)

	VD (n = 147)		VTD (n = 133)		VMP (n = 145)	
Variable	Cycles 1-8	Cycles 1-13	Cycles 1-8	Cycles 1-13	Cycles 1-8	Cycles 1-13
Response rate, No. (%)						
ORR (≥ PR)	104 (71)	107 (73)	105 (79)	106 (80)	98 (68)	101 (70)
CR + VGPR*	49 (33)	54 (37)†	65 (49)	68 (51)†	53 (37)	59 (41)
CR	2 (1)	5 (3)	1 (< 1)	5 (4)	4 (3)	6 (4)
nCR	36 (24)	39 (27)	49 (37)	48 (36)	39 (27)	41 (28)
PR	55 (37)	53 (36)	40 (30)	38 (29)	45 (31)	42 (29)
SD, No. (%)	24 (16)	21 (14)	4 (3)	3 (2)	25 (17)	22 (15)
PD, No. (%)	3 (2)	3 (2)	1 (< 1)	1 (< 1)	5 (3)	5 (3)
NE, No. (%)	16 (11)	16 (11)	23 (17)	23 (17)	17 (12)	17 (12)

NOTE. Response rates in patients who received at least one dose of study drug, had measurable disease at baseline, and had at least two postbaseline M-protein measurements.
Abbreviations: CR, complete response; nCR, near-CR; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VD, bortezomib-dexamethasone; VGPR, very good PR; VMP, bortezomib-melphalan-prednisone; VTD, bortezomib-thalidomide-dexamethasone.
*Includes the nCR category.
†P = .0153 for the comparison between VD and VTD.

Table 3. Adverse Events (safety population)

Events, No. (%)	VD (n = 165)			VTD (n = 158)			VMP (n = 163)		
	Any Grade	Grade ≥ 3	Grade ≥ 4	Any Grade	Grade ≥ 3	Grade ≥ 4	Any Grade	Grade ≥ 3	Grade ≥ 4
Any AE	150 (91)	129 (78)	31 (19)	153 (97)	138 (87)	43 (27)	151 (93)	135 (83)	36 (22)
Hematologic events									
Anemia	13 (8)	3 (2)	1 (< 1)	17 (11)	10 (6)	0	18 (11)	12 (7)	2 (1)
Neutropenia	3 (2)	3 (2)	0	6 (4)	4 (3)	1 (< 1)	38 (23)	31 (19)	5 (3)
Thrombocytopenia	7 (4)	4 (2)	2 (1)	10 (6)	6 (4)	2 (1)	30 (18)	24 (15)	11 (7)
GI tract events									
Diarrhea	23 (14)	18 (11)	1 (< 1)	18 (11)	8 (5)	0	29 (18)	16 (10)	0
Constipation	21 (13)	9 (5)	0	19 (12)	3 (2)	1 (< 1)	10 (6)	3 (2)	0
Nausea	10 (6)	2 (1)	0	12 (8)	4 (3)	0	18 (11)	6 (4)	0
Infections									
Pneumonia	20 (12)	17 (10)	1 (< 1)	12 (8)	10 (6)	1 (< 1)	10 (6)	10 (6)	3 (2)
Herpes zoster	18 (11)	5 (3)	0	9 (6)	4 (3)	0	10 (6)	5 (3)	0
Nervous system disorders									
Peripheral neuropathy*	83 (50)	37 (22)	3 (2)	95 (60)	43 (27)	3 (2)	77 (47)	32 (20)	2 (1)
Dizziness	7 (4)	1 (< 1)	0	18 (11)	13 (8)	0	5 (3)	1 (< 1)	0
Other conditions									
Fatigue	29 (18)	18 (11)	0	33 (21)	19 (12)	0	25 (15)	13 (8)	0
Edema peripheral	16 (10)	3 (2)	0	35 (22)	10 (6)	0	11 (7)	1 (< 1)	0
Back pain	18 (11)	13 (8)	0	11 (7)	7 (4)	1 (< 1)	14 (9)	7 (4)	1 (< 1)
Dehydration	12 (7)	9 (5)	1 (< 1)	12 (8)	8 (5)	1 (< 1)	17 (10)	8 (5)	0
Deep-vein thrombosis	9 (5)	7 (4)	0	6 (4)	5 (3)	1 (< 1)	3 (2)	2 (1)	0
Pulmonary embolism	5 (3)	4 (2)	4 (2)	5 (3)	5 (3)	4 (3)	1 (< 1)	1 (< 1)	1 (< 1)

NOTE. The safety population (n = 486) included all patients who received at least one dose of any study drug. Any-grade AEs listed occurred in ≥ 10% of patients in any arm during the treatment period; corresponding rates of grade ≥ 3 AEs and grade ≥ 4 AEs are shown. Other AEs of clinical relevance (deep-vein thrombosis and pulmonary embolism) are also listed. Patients could have more than one AE. Per protocol, all grades of peripheral neuropathy and skeletal events, grade 3/4 AEs, and all serious AEs were recorded on the electronic case report form from the first dose of study drug through 30 days after the last dose of study drug. There may have been grade 1 or grade 2 events that were not required to be collected.

Abbreviations: AE, adverse event; VD, bortezomib-dexamethasone; VMP, bortezomib-melphalan-prednisone; VTD, bortezomib-thalidomide-dexamethasone.

*Peripheral neuropathy includes neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, neuralgic amyotrophy, and peripheral sensorimotor neuropathy.

except for cognitive functioning, nausea and vomiting, and diarrhea (Fig 3C).

DISCUSSION

UPFRONT is, to our knowledge, the first randomized study of multiple bortezomib-based regimens in transplantation-ineligible patients with MM, and to our knowledge the first investigating VD and VTD in this patient population. UPFRONT demonstrates the feasibility of conducting large, randomized oncology trials in community practice, providing real-world data on frontline therapy in elderly patients, augmenting registration trials such as VISTA.[11] The UPFRONT population reflects the patient diversity seen in everyday practice; proportions of nonwhite and very elderly (≥ 75 years) patients were higher in UPFRONT than in VISTA,[11] and contrary to many trials,[8,15a] patients with comorbidities were enrolled. Patient-reported QoL was also assessed, which is particularly relevant for these typically frail patients. Attempts were made to tailor the regimens toward steroid reductions and lower dose intensity in the latter half of induction, and replace continued therapy with single-agent bortezomib administered once per week for 4 weeks in 5-week cycles.

At the first interim analysis, the initial hypothesis that the efficacy of VD would be inferior to that of VTD and VMP was not confirmed, highlighting a less-than-expected difference between doublet and triplet therapy. All three regimens exhibited substantial activity, with ORRs of up to 80%, and CR + VGPR rates of up to 51%. The ORR with VMP in this study was similar to that reported in VISTA.[11] Despite higher CR + VGPR rates with VTD versus VD over 13 cycles, this did not translate into prolonged PFS, possibly explained by the additional burden of toxicity observed with VTD (highest rates of any-grade AEs, grade ≥ 3 AEs, serious AEs, discontinuations because of AEs, and fewest treatment cycles received). The shorter-than-expected PFS observed across arms (median, 14.7 to 17.3 months) may be a result, in part, of the high proportion of patients discontinuing treatment before completing the planned 13 cycles; only 30% of patients received the maximum 13 cycles, and only 40% received bortezomib maintenance, highlighting the difficulty in delivering a full dosage to elderly, transplantation-ineligible patients with MM. Notably, approximately one fifth of patients received subsequent therapy without documented progression, primarily because of toxicity-related discontinuation of treatment, which likely affected the PFS results. PFS with VMP appeared shorter than in previous studies of elderly, transplantation-ineligible patients,[11,16] which may reflect modification of VMP in this study (reduced melphalan dose) or differences between patient populations, as well as the less healthy nature of patients in the community versus academic clinical trial setting. ISS stage I disease and KPS ≥ 90% were associated with improved PFS, consistent with previous reports indicating the prognostic importance of these factors.[17,18] OS was similar among arms, with approximately

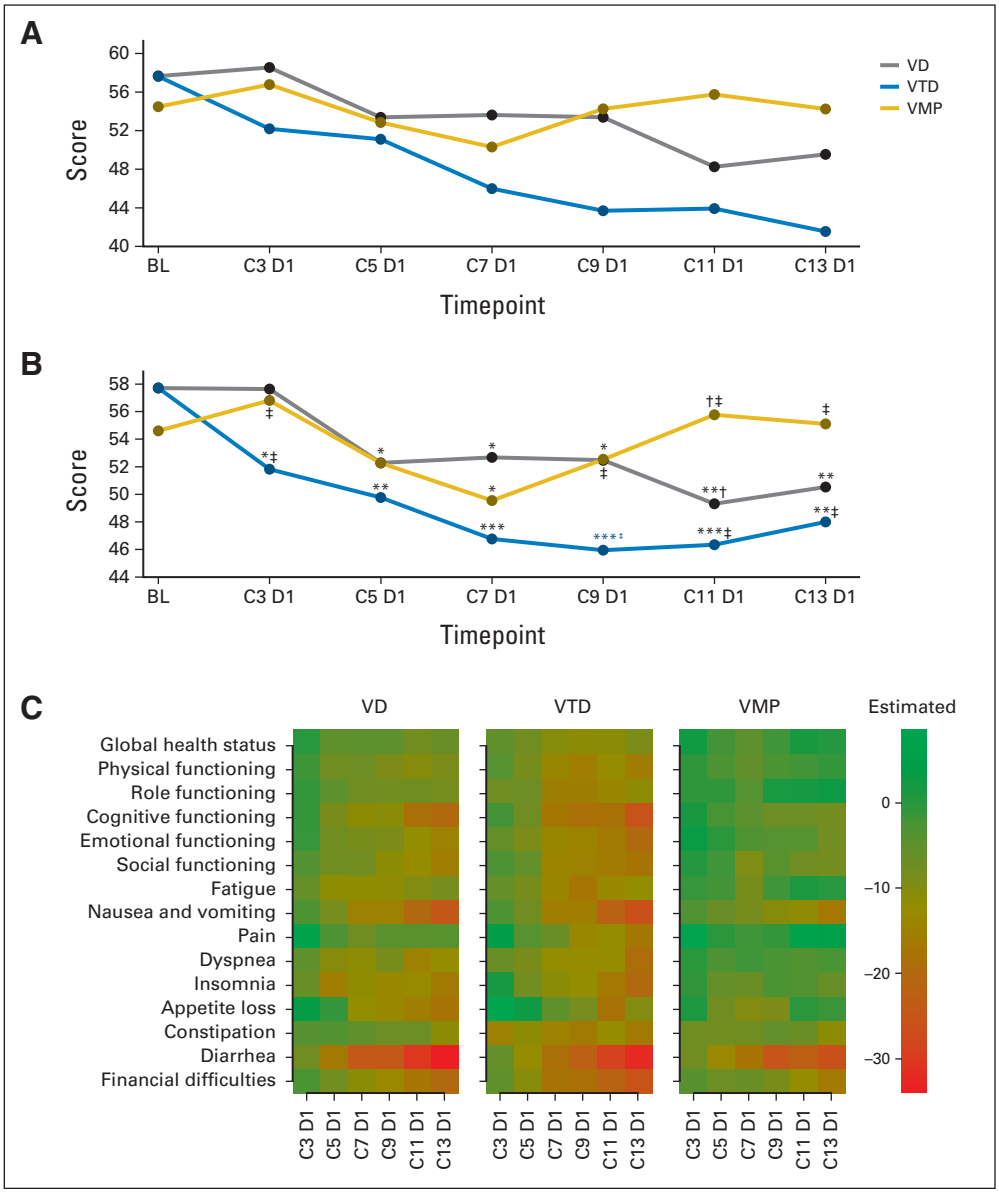

Fig 3. Assessment of patient-reported quality of life using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). (A and B) Mean global health status score by treatment arm: (A) observed data; (B) linear mixed-model mean estimates. (*) $P < .05$, (**) $P < .01$, and (***) $P < .001$, indicating a statistically significant decrease from baseline (BL) in mean global health status score; (†) $P < .05$ for bortezomib-dexamethasone (VD) versus bortezomib-melphalan-prednisone (VMP) at cycle (C) 11 day (D) 1; (‡) $P < .05$ for bortezomib-thalidomide-dexamethaxone (VTD) versus VMP at C3 D1, C9 D1, C13 D1; $P < .01$ at C11 D1. (C) Change from baseline in EORTC QLQ-C30 global health status and individual functioning and symptom scores over the course of treatment (linear mixed model mean estimates); positive (green) changes represent improvements in scores, and negative (red) changes represent worsening scores.

half of patients in each arm having received subsequent anti-MM therapy at the final analysis. Our results indicate that the type and number of agent(s) included in combination therapy for elderly persons are important, and offer caution to the current trend of incorporating three, or even four, agents into anti-MM regimens to boost efficacy[19] without confirmatory randomized studies.

Safety profiles were consistent with known toxicities for the component drugs.[5,6,11,20] PN was the most common AE overall leading to discontinuation. VTD exhibited the highest toxicity rates. Given that bortezomib was administered twice per week for 2 weeks in 3-week cycles, intravenous bortezomib was used for the first part of induction in UPFRONT, less intensive bortezomib dosing[16] and/or subcutaneous bortezomib[21] may be beneficial for reducing the toxicities (particularly the high rates of PN) associated with these regimens while maintaining efficacy, an important consideration in elderly persons.[22] The importance of less toxic treatment approaches for elderly patients with MM has been highlighted in a recent meta-analysis of randomized trials.[23]

UPFRONT is the first study to evaluate single-agent bortezomib administered once per week for 4 weeks in 5-week cycles as maintenance after VD, VTD, or VMP, in elderly, transplantation-ineligible patients. Bortezomib maintenance produced limited additional toxicity compared with induction, while sustaining responses achieved during induction in 89% of patients. The benefit of extended bortezomib may account, in part, for the similar PFS among arms; the lower toxicity and discontinuation rates, and greater number of completed cycles, with VD versus VTD and VMP might counteract a possible efficacy deficit with VD because of lack of a third agent. A role for proteasome inhibition in extended therapy has been suggested in previous studies of frontline bortezomib-based maintenance,[16,24,25] and extended treatment with alternative regimens has also shown benefit in MM.[26] A recent analysis of VMP data from VISTA suggests

that higher cumulative bortezomib dose, reflecting prolonged treatment duration and/or dose intensity, is associated with superior OS,[27] further substantiating the impact of bortezomib dose and duration on outcomes.

QoL analyses showed a common trend for decreasing global health status score during induction (particularly with VTD), followed by a trend for stabilizing/improving scores during maintenance. This may reflect the onset of treatment-associated toxicities during induction, followed by the positive impact of achieving/maintaining a response, and the limited toxicity associated with bortezomib maintenance. The transitory treatment-associated decrease in QoL is consistent with other studies.[28]

We propose that the efficacy benefits of treatment are accompanied by increased toxicity and decrements in QoL, and that final outcome for patients is a sum of these effects. Patients should be monitored carefully for treatment-related toxicities, with appropriate dose reduction to prolong therapy and maximize QoL and survival outcomes.

In conclusion, all three bortezomib-based regimens showed substantial activity in this patient population, albeit with higher than anticipated toxicity. This study confirms the importance of extended proteasome inhibition in anti-MM treatment irrespective of setting or number/type of additional drugs received. VD may be as effective as VTD or VMP when drug exposure and treatment-related toxicities are taken into consideration. Since UPFRONT, additional bortezomib-based regimens, including bortezomib-cyclophosphamide-dexamethasone[29,30] and bortezomib-lenalidomide-dexamethasone,[29,31] have shown promising activity in transplantation-eligible patients. Their evaluation in the nontransplantation setting may be warranted in light of recent results with non–bortezomib-based regimens, including lenalidomide-dexamethasone.[26] Furthermore, combination regimens incorporating second-generation proteasome inhibitors, such as oral ixazomib, might offer the potential for prolonged therapy in elderly, transplantation-ineligible patients with MM.[32,33]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Community-Based Phase IIIB Trial of Three UPFRONT Bortezomib-Based Myeloma Regimens

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Appendix

List of All UPFRONT Study Investigators

In total, 275 UPFRONT study sites were set up; only 159 of these sites enrolled patients. In addition to the authors, the following investigators (listed in alphabetical order) enrolled patients onto the study (all in the United States): R. Abou-Jawde (St. Joseph, MO), H. Adler (Boca Raton, FL), B. Akhund (Huntingdon Station, NY), B. Alasad (Oklahoma City, OK), A. Al-Janadi (Lansing, MI), G. Al-Jazayrly (Glendale, CA), E. Aly (Indianapolis, IN), R. Anderson (Waco, TX), T. Anderson (Bedford, TX), E. Arrowsmith (Chattanooga, TN), I. Arshad (West Bend, WI), M. Auerbach (Baltimore, MD), K. Ayrons (Gastonia, NC), S. Baidas (Orlando, FL), B. Baltz (Little Rock, AZ), F. Barhamand (Naperville, IL), N. Belman (Bethlehem, PA), Z. Bernstein (Buffalo, NY), W. Berry (Raleigh, NC), B. Bhaskar (Orange, CA), R. Boccia (Bethesda, MD), T. Boyd (Yakima, WA), F. Brescia (Mt. Pleasant, SC), D. Brooks (Tucson, AZ), D. Bruno (Hastings, NE), G. Buchanan (Eugene, OR), P. Byeff (Southington, CT), J. Cantrell (Birmingham, AL), T. Cartwright (Ocala, FL), R. Catchatourian (Chicago, IL), C. Chay (Asheville, NC), B. Chinnasami (High Point, NC), J. Choksi (Burlington, NC), N. Chowhan (New Albany, IN), C. Cole (La Crosse, WI), M. Conde (Livingston, NJ), J. Congdon (Everett, WA), B. Cooper (Cleveland, OH), S. Cross (Norfolk, VA), J. Cuevas (Chesterfield, MO), R. Decker (Beverly Hills, CA), T. Dobbs (Knoxville, TN), L. Drinkard (Grapevine, TX), R. Droder (Tyler, TX), J. Fain (Austin, TX), J. Fetten (Rochester, NY), S. Fleischauer (Arlington, TX), M.R. Flores (Orlando, FL), P. Flynn (Minneapolis, MN), G. Fonseca (Lecanto, FL), D. Friedman (Bronx, NY), M. Garrison (Wenatchee, WA), H. Ghazal (Hazard, KY), M. Ghraowi (Corpus Christie, TX), D. Gravenor (Memphis, TN), L. Gressot (Sugar Land, TX), H. Gross (Dayton, OH), K. Guter (Great Falls, MT), T. Guthrie Jr (Jacksonville, FL), G. Guzley (San Antonio, TX), S. Hager (Fresno, CA), W. Hanna (Knoxville, TN), V. Hansen (Ogden, UT), W. Harker (Salt Lake City, UT), H. Hassoun (New York, NY), B. Hellerstedt (Round Rock, TX), R. Hermann (Marietta, GA), D. Hill (Casa Grande, AZ), R. Hirsch (Hollywood, FL), K. Hubbard (Kansas City, MO), M. Hyzinski (Scranton, PA), E. Ibrahim (Highland, CA), P. Jacquin (Cookeville, TN), N. Janakiraman (Detroit, MI), H. Jhangiani (Corona and Fountain Valley, CA), C. Jones (Germantown, TN), S. Kahanic (Sioux City, IA), S. Kambhampati (Kansas City, MO), K. Karamlou (Beaverton, OR), A. Kashyap (Westlake Village, CA), H. Kaya (Spokane, WA), W. Khan (Lake City, FL), L. Klein (Niles, IL), K. Kolibaba (Vancouver, WA), M. Kosmo (Escondido, WA), R. Koya (Longview, TX), J. Letzer (Kalamazoo, MI), R. Levine (Titusville, FL), L. Lewkow (Richmond, VA), K. LoRusso (Santa Fe, NM), J. Mace (St. Petersburg, FL), W. MacLaughlin (Chesapeake, VA), J. Maher (Cincinatti, OH), Y. Manalo (Corpus Christie, TX), R. Manges (Indianapolis, TN), K. McCaul (Sioux Falls, SD), R. McIntyre (Oxnard, CA), S. McKenny (Beaumont, TX), M. McKenzie (Woodhaven, MI), A. MeInyk Jr (Abilene, TX), E. Middleman (Duncanville, TX), C. Miller (Baltimore, MD), R. Moss (Fountain Valley, CA), T. Nazir (Fayetteville, NC), M. Neubauer (Overland Park, KS), P. Nivatpumin (Baltimore, MD), J. O'Donnell (White River Junction, VT), D. Oldham (Lynchburg, VA), M. Olsen (Tulsa, OK), T. O'Rourke (Grand Rapids, MI), R. Page (Fort Worth, TX), N. Parikh (Henderson, NV), D. Patel-Donnelly (Fairfax, VA), S. Prakash (Paris, TX), D. Prow (Ames, IA), V. Rajagopalan (Langhorne, PA), F. Rana (Jacksonville, FL), R. Rao (Brooksville, FL), V. Rao (Bismarck, ND), A. Raptis (Pittsburgh, PA), P. Reddy (Wichita, KS), R. Redner (Pittsburgh, PA), E. Reyes (Riverside, CA), R. Rice (Westminster, MD), D. Richards (Tyler, TX), P. Richards (Salem, VA), M. Saltzman (Aventura, FL), V. Sanchorawala (Boston, MA), S. Sarwar (Columbus, OH), F. Schnell (Macon, GA), S. Selonick (Annapolis, MD), C. Shull (Idaho Falls, ID), K. Sivarajan (Joliet, IL), R. Smith (Quincy, IL), J. Sprague (Burlington, VT), P. Srivatana (Sayre, PA), L. Steinbrenner (Buffalo, NY), R. Stuart (Charleston, SC), M. Taylor (Savannah, GA), H. Terebelo (Southfield, MI), D. Testori (Wilmington, NC), G. Tillinghast (Newport News, VA), M. Venigalla (Lakeland, FL), N. Vogelzang (Las Vegas, NV), F. Volterra (Bronx, NY), T. Walters (Boise, ID), R. Weiner (Lake Success, NY), M. Wertheim (Port St. Lucie, FL), G. Wright (New Port Richey, FL), K.-Y. Yeung (Clinton, MD), and T. Zimmerman (Chicago, IL).