PF583

Impact of Baseline Renal Function on Efficacy and Safety of Daratumumab Plus Bortezomib-Melphalan-Prednisone (VMP) in Newly Diagnosed Multiple Myeloma Patients Ineligible for Transplantation (ALCYONE)

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INTRODUCTION

- In patients with multiple myeloma, renal impairment is common and can negatively impact outcomes[1]
- Outside of the United States, bortezomib, melphalan, and prednisone (VMP) is a standard of care for transplant-ineligible patients with NDMM based on the VISTA,[2,3] PETHEMA/GEM2005MAS65,[4] and GIMEMA[5] studies
- Daratumumab is a human IgG1κ monoclonal antibody targeting CD38 with a direct on-tumor and immunomodulatory mechanism of action[6]
- Daratumumab is approved in many countries as a monotherapy for heavily pretreated patients with relapsed or refractory multiple myeloma (RRMM) and in combination with standard-of-care regimens in patients with RRMM who have received ≥1 prior therapy[7]
- In patients with NDMM who were ineligible for ASCT, daratumumab plus VMP (D-VMP) prolonged progression-free survival (PFS) compared with VMP and was well tolerated in the phase 3 ALCYONE study (NCT02195479)[8]
  - Based on these findings, D-VMP has recently been approved in the United States and Brazil for NDMM patients ineligible for ASCT[9]
- We report the efficacy and safety data of NDMM patients with moderate renal impairment (creatinine clearance [CrCl] ≤60 mL/min) and without moderate renal impairment (CrCl >60 mL/min) at baseline in ALCYONE

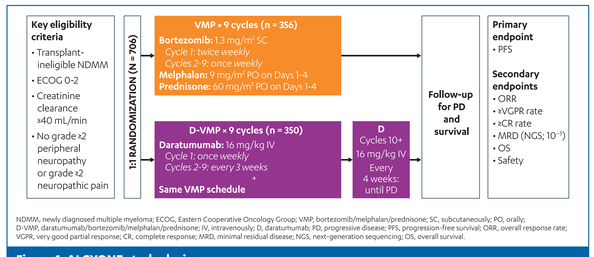
METHODS

Patients

- Eligible patients had NDMM and were ≥65 years of age or otherwise ineligible for high-dose chemotherapy and ASCT
- Patients were excluded for the following:
  - Hemoglobin <7.5 g/dL
  - Neutrophils <1.0 × 10^9/L
  - Platelets <70 × 10^9/L
  - Aspartate aminotransferase and alanine aminotransferase >2.5 times the upper limit of normal
  - Creatinine clearance <40 mL/min
  - Primary amyloidosis, monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, or Waldenström's macroglobulinemia
  - Previous systemic therapy or stem cell transplantation
  - Grade ≥2 peripheral neuropathy or grade ≥2 neuropathic pain

Study Design and Treatment

- ALCYONE is a randomized phase 3 study of D-VMP versus VMP in transplant-ineligible patients with NDMM (**Figure 1**)
- All patients received up to nine 6-week cycles of VMP (bortezomib 1.3 mg/m^2 subcutaneously on Days 1, 4, 8, 11, 22, 25, 29, and 32 of Cycle 1 and Days 1, 8, 22, and 29 of Cycles 2-9; melphalan 9 mg/m^2 orally and prednisone 60 mg/m^2 orally on Days 1-4 of each cycle)
  - Cycles 1-9: 6-week cycles
- Patients in the D-VMP group also received daratumumab 16 mg/kg intravenously every week in Cycle 1, every 3 weeks in Cycles 2-9, and every 4 weeks in Cycles 10+ (post VMP-treatment phase) until disease progression
  - Cycles 10+: 4-week cycles
- Stratification factors were International Staging System (I vs II vs III), region (Europe vs other), and age (<75 vs ≥75 years)



NDMM, newly diagnosed multiple myeloma; ECOG, Eastern Cooperative Oncology Group; VMP, bortezomib/melphalan/prednisone; SC, subcutaneously; PO, orally; D-VMP, daratumumab/bortezomib/melphalan/prednisone; IV, intravenously; D, daratumumab; PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; VGPR, very good partial response; CR, complete response; MRD, minimal residual disease; NGS, next-generation sequencing; OS, overall survival.

Figure 1. ALCYONE study design.

Statistical Analyses and Assessments

- PFS, overall response rate (ORR), rate of very good partial response or better, rate of complete response (CR) or better, and minimal residual disease (MRD)–negativity rate were sequentially tested
  - Time to event variables were evaluated using the Kaplan-Meier method
  - Response rates were assessed with a stratified Cochran-Mantel-Haenszel test
- A total of 360 PFS events was estimated to provide 85% power to detect an 8-month PFS improvement over a 21-month median PFS for VMP; interim analysis was planned for when 216 events of disease progression or death occurred (60% of planned events)
- MRD-negativity rate (10^{-5} sensitivity threshold) was evaluated in the intent-to-treat (ITT) population using clonoSEQ® assay V2.0 (Adaptive Biotechnologies, Seattle, WA, USA)

RESULTS

Patients and Treatments

- The median duration of follow-up was 16.5 months
- Among the 706 patients enrolled in the study (350 D-VMP; 356 VMP), 295 had baseline CrCl ≤60 mL/min, and 411 had baseline CrCl >60 mL/min (**Table 1**)
- The median duration of study treatment was 15.3 months for D-VMP versus 12.0 months for VMP among patients with baseline CrCl ≤60 mL/min, and 14.5 months for D-VMP versus 12.0 months for VMP among patients with CrCl >60 mL/min
- The median cumulative dose of bortezomib was 45.7 mg/m^2 and 41.2 mg/m^2 with D-VMP and VMP, respectively, for patients with baseline CrCl ≤60 mL/min, and 48.1 mg/m^2 and 42.7 mg/m^2 with D-VMP and VMP, respectively, for patients with CrCl >60 mL/min
- By the end of Cycle 9, more VMP-treated patients discontinued treatment compared with D-VMP–treated patients in both the CrCl ≤60 mL/min subgroup (41% vs 18%) and the CrCl >60 mL/min subgroup (28% vs 21%)
  - By the end of Cycle 9, more VMP-treated patients discontinued treatment due to progressive disease compared with D-VMP–treated patients in both the CrCl ≤60 mL/min subgroup (15% vs 4%) and the CrCl >60 mL/min subgroup (12% vs 9%)
  - By the end of Cycle 9, more VMP-treated patients discontinued treatment due to adverse events (AEs) compared with D-VMP–treated patients in both the CrCl ≤60 mL/min subgroup (12% vs 6%) and the CrCl >60 mL/min subgroup (8% vs 4%)

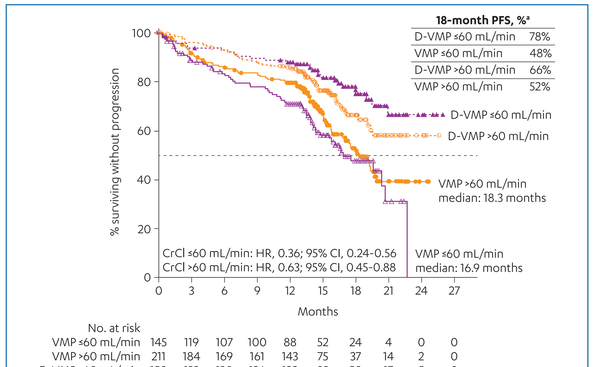
Table 1. Demographics and Baseline Characteristics of the ITT Population by Baseline Renal Function Subgroup (N = 706)

	Baseline CrCl ≤60 mL/min		Baseline CrCl >60 mL/min	
Characteristic	D-VMP (n = 150)	VMP (n = 145)	D-VMP (n = 200)	VMP (n = 211)
Age				
Median (range), y	74 (52-93)	74 (59-91)	70 (40-85)	70 (50-82)
Male, %	39	37	51	54
ECOG status,[a] %				
0	24	20	21	33
1	45	55	58	45
2	31	26	22	22
ISS stage,[b] %				
I	9	8	28	27
II	33	39	45	49
III	57	54	28	24
Cytogenetic profile[c]				
N	127	124	187	178
Standard risk, %	83	86	83	84
High risk, %	17	14	17	16

ITT, intent-to-treat; CrCl, creatinine clearance; D-VMP, daratumumab/bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System.
[a]ECOG performance status is scored on a scale from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability.
[b]Based on the combination of serum β_2-microglobulin and albumin.
[c]Based on fluorescence in situ hybridization/karyotype testing performed at local sites; t(4;14), t(14;16), and del17p were classified as high risk.

Efficacy

- In the ITT population, D-VMP reduced the risk of disease progression or death by 50% (median PFS: D-VMP, not reached vs VMP, 18.1 months; hazard ratio [HR], 0.50; 95% confidence interval [CI], 0.38-0.65; *P* <0.0001)[a]
- Median PFS was prolonged for D-VMP versus VMP in both baseline CrCl subgroups (**Figure 2**)
  - CrCl ≤60 mL/min: not reached with D-VMP versus 16.9 months with VMP (HR, 0.36; 95% CI, 0.24-0.56)
  - CrCl >60 mL/min: not reached with D-VMP versus 18.3 months with VMP (HR, 0.63; 95% CI, 0.45-0.88)
- Patients receiving D-VMP demonstrated higher ORRs and rates of CR or better versus those receiving VMP in both renal function subgroups (**Table 2**)
- For D-VMP versus VMP, median time to first response across renal function subgroups was consistent with the ITT population (**Table 2**)
- Median time to CR or better was nominally shorter with D-VMP versus VMP for the CrCl ≤60 mL/min subgroup only (**Table 2**)
- The MRD-negativity rate (10^{-5} sensitivity threshold) was increased with D-VMP versus VMP in patients with baseline CrCl ≤60 mL/min (25% vs 8%; *P* <0.0001) and >60 mL/min (20% vs 5%; *P* <0.0001), consistent with the ITT population (22% vs 6%; *P* <0.0001; **Figure 3**)



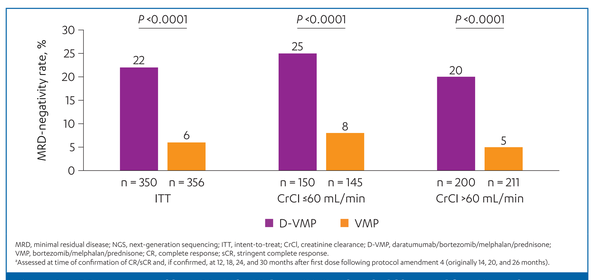
PFS, progression-free survival; D-VMP, daratumumab/bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; CrCl, creatinine clearance; HR, hazard ratio; CI, confidence interval.
[a]Kaplan-Meier estimate.

Figure 2. PFS by baseline renal function subgroup.

Table 2. Response Rates and Characteristics by Renal Function Subgroup

	ITT		Baseline CrCl ≤60 mL/min		Baseline CrCl >60 mL/min	
Response characteristic	D-VMP (n = 350)	VMP (n = 356)	D-VMP (n = 150)	VMP (n = 145)	D-VMP (n = 200)	VMP (n = 211)
ORR, %	90.9	73.9	89.3	73.1	92.0	74.4
≥CR, %	42.6	24.4	42.7	24.1	42.5	24.6
sCR,%	18.0	7.0	19.3	9.0	17.0	5.7
≥VGPR, %	71.1	49.7	74.7	49.0	68.5	50.2
Median (range) time to first response,[a] months	0.79 (0.4-15.5)	0.82 (0.7-12.6)	0.79 (0.5-15.3)	0.84 (0.7-12.6)	0.80 (0.4-15.5)	0.82 (0.7-10.0)
Median (range) time to CR or better,[a] months	8.31 (1.9-21.0)	7.46 (0.7-20.5)	6.93 (1.9-21.0)	7.46 (2.8-14.4)	9.00 (2.3-18.3)	7.67 (0.7-20.5)

ITT, intent-to-treat; CrCl, creatinine clearance; CrCl, creatinine clearance; D-VMP, daratumumab/bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; ORR, overall response rate; CR, complete response; sCR, stringent complete response; VGPR, very good partial response; PR, partial response; MM, multiple myeloma.
[a]Response of PR or better in the response-evaluable population (ie, subjects who have a confirmed diagnosis of MM and measurable disease at baseline, and must have received ≥1 component of study treatment and have adequate post-baseline disease assessments).



MRD, minimal residual disease; NGS, next-generation sequencing; ITT, intent-to-treat; CrCl, creatinine clearance; D-VMP, daratumumab/bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; CR, complete response; sCR, stringent complete response.
[a]Assessed at time of confirmation of CR/sCR and, if confirmed, at 12, 18, 24, and 30 months after first dose following protocol amendment 4 (originally 14, 20, and 26 months).

Figure 3. MRD[a] as assessed by NGS at the 10^{-5} sensitivity threshold by renal function subgroup.

Safety

- Incidences of the most common all-grade (≥25%) treatment-emergent AEs (TEAEs), along with TEAEs of interest (peripheral sensory neuropathy and infections), are summarized in **Table 3**
  - For both renal function subgroups, TEAE rates were generally consistent with those of the overall population
- Overall rates of grade 3/4 TEAEs in the overall population were 78% for D-VMP and 77% for VMP (**Table 4**)
  - Grade 3/4 TEAEs were reported in 81% and 82% of patients with baseline CrCl ≤60 mL/min receiving D-VMP and VMP, respectively, and in 75% and 74% of patients with baseline CrCl >60 mL/min receiving D-VMP and VMP, respectively
- Incidences of the most common grade 3/4 (≥10%) TEAEs, along with TEAEs of interest (peripheral sensory neuropathy and infections), are summarized in **Table 4**
  - For both renal function subgroups, TEAE rates were generally consistent with those of the overall population
- In the D-VMP arm, infusion-related reactions were observed in 27% (5% grade 3/4) of patients with baseline CrCl ≤60 mL/min and 29% (5% grade 3/4) of patients with CrCl >60 mL/min; most occurred during the first infusion
- In the CrCl ≤60 mL/min subgroup, second primary malignancies (SPMs) were observed in 4 D-VMP–treated patients versus 4 VMP-treated patients; in the CrCl >60 mL/min subgroup, SPMs were observed in 4 D-VMP–treated patients versus 5 VMP-treated patients

Table 3. Most Common (≥25%) All-grade TEAEs and Incidences of Peripheral Sensory Neuropathy and Infections

	Overall population[a]		Baseline CrCl ≤60 mL/min[a]		Baseline CrCl >60 mL/min[a]	
All-grade TEAEs	D-VMP (n = 346)	VMP (n = 354)	D-VMP (n = 146)	VMP (n = 144)	D-VMP (n = 200)	VMP (n = 210)
Most common (≥25%) TEAEs, %						
Neutropenia	50	53	58	55	44	51
Thrombocytopenia	49	54	54	58	45	51
Anemia	28	38	32	47	26	31
URTI	26	14	25	17	27	12
Diarrhea	24	25	27	31	21	21
Pyrexia	23	21	27	18	20	23
Peripheral sensory neuropathy, %	28	34	28	35	29	33
Infections,[b] %	67	48	71	49	64	47

TEAE, treatment-emergent adverse event; CrCl, creatinine clearance; D-VMP, daratumumab/bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; URTI, upper respiratory tract infection; MedDRA, *Medical Dictionary for Regulatory Activities*.
[a]Includes all patients who received ≥1 dose of study treatment.
[b]MedDRA system organ class.

Table 4. Most Common (≥10%) Grade 3/4 TEAEs and Incidences of Peripheral Sensory Neuropathy and Infections

	Overall population[a]		Baseline CrCl ≤60 mL/min[a]		Baseline CrCl >60 mL/min[a]	
Grade 3/4 TEAEs	D-VMP (n = 346)	VMP (n = 354)	D-VMP (n = 102)	VMP (n = 106)	D-VMP (n = 244)	VMP (n = 248)
Patients with grade 3/4 TEAEs, %	78	77	81	82	75	74
Most common (≥10%) TEAEs, %						
Neutropenia	40	39	47	38	35	39
Thrombocytopenia	34	38	43	42	28	34
Anemia	16	20	21	29	12	13
Pneumonia	11	4	15	6	9	2
Peripheral sensory neuropathy, %	1	4	2	4	1	4
Infections,[b] %	23	15	26	17	21	13

TEAE, treatment-emergent adverse event; CrCl, creatinine clearance; D-VMP, daratumumab/bortezomib/melphalan/prednisone; VMP, bortezomib/melphalan/prednisone; *MedDRA, Medical Dictionary for Regulatory Activities*.
[a]Includes all patients who received ≥1 dose of study treatment.
[b]MedDRA system organ class.

CONCLUSIONS

- **The superior efficacy of D-VMP over VMP in patients with baseline CrCl ≤60 mL/min was consistent with that previously seen in the overall population**
  - **Moderate renal impairment had no negative impact on efficacy of D-VMP**
  - **D-VMP induced deeper responses (2-fold increase in stringent CR rates) and high rates of MRD negativity (±3-fold higher) at the 10^{-5} sensitivity threshold**
- **D-VMP demonstrated acceptable tolerability regardless of baseline renal function**
  - **No new safety signals were observed in either renal function subgroup**
  - **Grade 3/4 infection rates were consistent with the overall population**
  - **Grade 3/4 peripheral sensory neuropathy rates remained low with D-VMP across renal function subgroups**
- **D-VMP was efficacious and well tolerated in patients with NDMM and baseline CrCl ≤60 mL/min**

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DISCLOSURES

MCavo received honoraria from, consulted for, and served on speakers bureaus for Celgene, Amgen, BMS, Takeda, and Janssen; and received travel expenses from Janssen and Celgene. MAD consulted for and received honoraria from Celgene, Janssen, Takeda, and Amgen. JS-M consulted for Amgen, BMS, Celgene, Janssen, MSD, Novartis, Takeda, Sanofi, and Roche. AJ received honoraria from AbbVie, Amgen, BMS, Celgene, Janssen, Karyopharm, Sanofi, SkylineDx, and Takeda; and consulted for AbbVie, Amgen, BMS, Celgene, Janssen, Karyopharm, SkylineDx, and Takeda. KS received honoraria from Celgene, Takeda, and Janssen; and consulted for Takeda. MCook received honoraria from Celgene, Janssen, and Amgen; consulted for Celgene, Janssen, Chugai, and Takeda; received research funding from Celgene; and received travel expenses from Amgen, Janssen, and Takeda. MB received honoraria from Sanofi, Celgene, Amgen, Janssen, Novartis, AbbVie, and BMS; and received research funding from Celgene, Janssen, Amgen, BMS, Novartis, Sanofi, and Mundipharma. PJH received honoraria from Amgen; consulted for Amgen, BMS, Celgene, Novartis, Janssen, and Takeda; received research funding from Amgen, Celgene, Novartis, Janssen, Sanofi, and AbbVie; and received travel expenses from Celgene. SK received honoraria from and consulted for Amgen, BMS, Celgene, and Janssen; and received travel expenses from Celgene and Novartis. CD received honoraria from, consulted for, and served on a speakers bureau for Janssen. TM consulted for Takeda, Novartis, and BMS. JB received honoraria from Janssen, Celgene, Amgen, and Takeda; received research funding from Janssen and Celgene; and received travel expenses from Janssen, Celgene, Amgen, and Takeda. JW, SW, WD, and MQ are employees of Janssen. M-VM received honoraria from and consulted for Celgene, Janssen, Takeda, and Amgen. S-SY, LP, and AC have nothing to disclose.

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