P275

An Open-label, Multicenter, Phase 1b Study of Daratumumab in Combination With Pomalidomide-Dexamethasone and With Backbone Regimens in Patients With Multiple Myeloma

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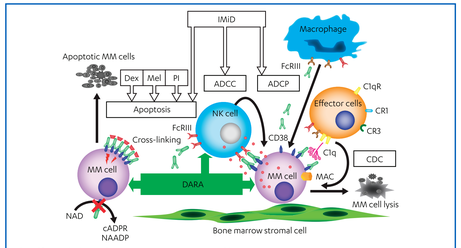
INTRODUCTION

- Despite the introduction of proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) into current treatment regimens, multiple myeloma (MM) remains an incurable disease[1,2]
  - The majority of patients will relapse, and outcomes are poor among patients with relapsed or refractory disease, particularly patients who are refractory to both PIs and IMiDs (double refractory)[3-6]
- CD38 is highly and ubiquitously expressed on myeloma cells, but is expressed at relatively low levels on normal lymphoid and myeloid cells, making it a logical target for antimyeloma therapy[7-9]
- Daratumumab (DARA) is a human IgG1κ monoclonal antibody that targets CD38-expressing tumor cells, inducing cell death through a number of different pathways[10,11] (**Figure 1**)
- DARA has shown promising antimyeloma activity and safety as a single agent[12] and in combination with lenalidomide and dexamethasone (RD)[13] in phase 1/2 studies of patients with relapsed or refractory MM



Adapted from Laubach JP, et al. *Expert Opin Investig Drugs*. 2004;23(4):445-452.

DARA, daratumumab; IMiD, immunomodulatory drug; MM, multiple myeloma; Dex, dexamethasone; Mel, melphalan; PI, proteasome inhibitor; ADCC, antibody-dependent cell-mediated toxicity; ADCP, antibody-dependent cell-mediated phagocytosis; NK, natural killer; CDC, complement-dependent cytotoxicity; MAC, membrane attack complex; NAD, nicotinamide adenine dinucleotide; cADPR, cyclic ADP-ribose; NAADP, nicotinic acid adenine dinucleotide phosphate.

Figure 1. Mechanism of action of DARA.

OBJECTIVE

- The primary objective was to evaluate the safety and tolerability of DARA in combination with pomalidomide plus dexamethasone (POM-D) or 3 backbone MM therapies: bortezomib plus dexamethasone (VD), bortezomib plus thalidomide and dexamethasone (VTD), and bortezomib plus melphalan and prednisone (VMP)

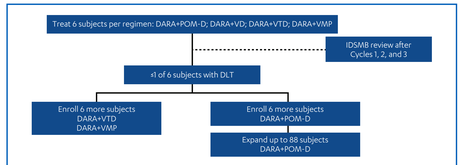
METHODS

Patients

- For the DARA+POM-D regimen, patients who had undergone prior treatment with ≥2 treatment lines of antimyeloma therapy, including ≥2 consecutive cycles of bortezomib and lenalidomide, and had refractory or relapsed and refractory (RR) MM were included
- For the DARA+VD and DARA+VTD regimens, newly diagnosed patients, regardless of eligibility for transplantation, were included
- For the DARA+VMP regimen, newly diagnosed patients who were not considered candidates for high-dose chemotherapy with stem cell transplantation were included

Study Design

- The study design is shown in **Figure 2**
- Safety review, including dose-limiting toxicities (DLTs), was conducted by an Independent Data Safety Monitoring Board (IDSMB)
- If a DLT was observed in ≤1 patient, that combination regimen was considered safe and well tolerated
- Clinical responses were also monitored by the IDSMB



DARA, daratumumab; POM-D, pomalidomide plus dexamethasone; VD, bortezomib plus dexamethasone; VTD, bortezomib plus thalidomide and dexamethasone; VMP, bortezomib plus melphalan and prednisone; IDSMB, Independent Data Safety Monitoring Board; DLT, dose-limiting toxicity.

Figure 2. Study design.

Treatment Schedule

- DARA+POM-D (28-day cycles): pomalidomide (4 mg once daily for 21 days) and dexamethasone (40 mg, or 20 mg for patients >75 years of age) weekly
  - DARA was given weekly for 2 cycles, then every other week for 4 cycles, and every 4 weeks for 7 cycles or until disease progression
- DARA+VD (21-day cycles): bortezomib (1.3 mg/m^2) twice weekly for 4 cycles, then weekly for 14 cycles, and dexamethasone (20 mg) 8 times per cycle for 4 cycles, then 4 times per cycle thereafter
  - DARA was given weekly for 2 cycles, then once every 3 weeks for 16 cycles or until transplantation
- DARA+VTD (21-day cycles): bortezomib (1.3 mg/m^2) twice weekly for 4 cycles, then weekly for 14 cycles, and thalidomide (100 mg/day) and dexamethasone (20 mg) 8 times per cycle for 4 cycles, then 4 times per cycle thereafter
  - DARA was given weekly for 2 cycles, then once every 3 weeks thereafter or until transplantation
- DARA+VMP (42-day cycles): bortezomib (1.3 mg/m^2) twice weekly for 1 cycle, then weekly for 8 cycles, and melphalan (9 mg/m^2)/prednisone (60 mg/m^2) on Days 1 through 4 of each cycle
  - DARA was given weekly for 1 cycle, then every 3 weeks for 8 cycles

Study Endpoints

- The primary endpoint was maximum tolerated dose of DARA when combined with backbone regimens
- Secondary endpoints included overall response rate (ORR), duration of response, and overall survival

RESULTS

Patients

- Patient disposition is summarized in **Table 1**
- Four patients discontinued the study
  - Three in the DARA+POM-D arm (one each due to physician's decision, progressive disease, and death following disease progression)
  - One in the DARA+VD arm (death due to neutropenic sepsis following autologous stem cell transplant)

Table 1. Patient Disposition

	DARA+POM-D (n = 24)	DARA+VD (n = 6)	DARA+VTD (n = 11)	DARA+VMP (n = 8)	Total (N = 49)
Patients discontinuing treatment, n (%)	5 (21)	2 (33)	6 (55)	0	13 (27)
Adverse event	1 (4)	0	0	0	1 (2)
Physician decision	1 (4)	0	0	0	1 (2)
Progressive disease	3 (13)	0	0	0	3 (6)
Autologous stem cell transplant	0	2 (33)	6 (55)	0	8 (16)
Patients discontinuing the study, n (%)	3 (13)	1 (17)	0	0	4 (8)
Death	1 (4)	1 (17)	0	0	2 (4)
Physician decision	1 (4)	0	0	0	1 (2)
Progressive disease	1 (4)	0	0	0	1 (2)

DARA, daratumumab; POM-D, pomalidomide plus dexamethasone; VD, bortezomib plus dexamethasone; VTD, bortezomib plus thalidomide and dexamethasone; VMP, bortezomib plus melphalan and prednisone.

- Baseline demographics are summarized in **Table 2**
- Among the patients in the DARA+POM-D arm
  - The median (range) number of prior therapies was 4 (2-9)
  - All patients had received prior treatment with PIs (bortezomib: 100%; carfilzomib: 38%), IMiDs (lenalidomide: 100%; thalidomide: 21%), and steroids (dexamethasone: 100%; prednisone 17%)
  - 92% were refractory to their last line of therapy
  - 75% were refractory to bortezomib, 38% to carfilzomib, 96% to lenalidomide, and 79% were refractory to both a PI and IMiD (double refractory)

Table 2. Patient Demographics

	DARA+POM-D (n = 24)	DARA+VD (n = 6)	DARA+VTD (n = 11)	DARA+VMP (n = 8)	Total (N = 49)
Median (range) age, y	62 (42-86)	73 (50-82)	60 (40-68)	72 (67-78)	64 (40-86)
Age category, n (%)					
18 to <65 years	15 (63)	2 (33)	9 (82)	0	26 (53)
65 to <75 years	7 (29)	1 (17)	2 (18)	6 (75)	16 (33)
≥75 years	2 (8)	3 (50)	0	2 (25)	7 (14)
Male, n (%)	13 (54)	2 (33)	6 (55)	4 (50)	25 (51)
Race, n (%)					
White	17 (71)	5 (83)	8 (80)	7 (88)	37 (77)
Black or African American	7 (29)	0	0	0	7 (15)
Not reported	0	1 (17)	2 (20)	1 (13)	4 (8)
Baseline ECOG score, n (%)					
0	5 (21)	2 (33)	7 (64)	5 (63)	19 (39)
1	17 (71)	3 (50)	3 (27)	3 (38)	26 (53)
2	2 (8)	1 (17)	1 (9)	0	4 (8)
>2	0	0	0	0	0

DARA, daratumumab; POM-D, pomalidomide plus dexamethasone; VD, bortezomib plus dexamethasone; VTD, bortezomib plus thalidomide and dexamethasone; VMP, bortezomib plus melphalan and prednisone.

Safety

- Median (range) durations of follow-up were: DARA+POM-D, 29 (1-286) days; DARA+VD, 193 (151-218) days; DARA+VTD, 164 (9-274) days; DARA+VMP, 267 (63-295) days
- The median (range) numbers of DARA infusions were: DARA+POM-D, 4 (1-20); DARA+VD, 13 (8-15); DARA+VTD, 8 (2-13); DARA+VMP, 16 (6-18)
- The most common adverse events (AEs) were hematologic toxicities and were likely related to POM-D or backbone therapies
- With the exception of infusion-related reactions (IRRs), the addition of DARA to POM-D or backbone therapies did not result in additional toxicity (**Table 3**)
- Across all treatment groups, IRRs occurred in 24 (49%) patients and were generally grade 1 or 2 (three grade 3 and no grade 4); most occurred within the first day of the first cycle
- Grade ≥3 AEs occurred in 22 (45%) patients overall; most commonly, neutropenia (25%), thrombocytopenia (10%), anemia (8%), and pneumonia (6%)
- Overall, 6 patients had serious AEs
  - There were 3 cases of pneumonia and 1 incidence each of soft-tissue infection, diarrhea, pre-renal failure, hyperviscosity syndrome, cardiac failure, mental status change, and indirect Coombs test interference
- One patient from the DARA+POM-D arm experienced an exacerbation of chronic angina pectoralis, which led to discontinuation of treatment so the patient could receive advanced cardiac care
- Two patients died on study: 1 patient in the DARA+POM-D arm died due to disease progression and the other patient (DARA+VD arm) died due to neutropenic sepsis following autologous stem cell transplant

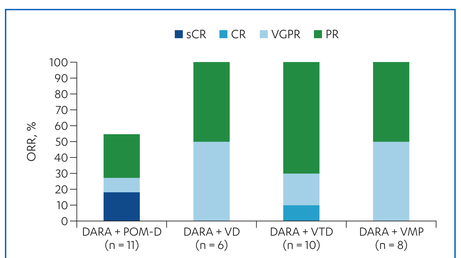
Table 3. Safety of DARA Combined With POM-D or Backbone Therapies

	DARA+POM-D (n = 24)	DARA+VD (n = 6)	DARA+VTD (n = 11)	DARA+VMP (n = 8)	Total (N = 49)
Any AE,* n (%)	21 (88)	6 (100)	10 (91)	8 (100)	45 (92)
Neutropenia	10 (42)	1 (17)	3 (27)	5 (63)	19 (39)
Constipation	3 (13)	3 (50)	9 (82)	2 (25)	17 (35)
Diarrhea	8 (33)	2 (33)	1 (9)	3 (38)	14 (29)
Peripheral sensory neuropathy	4 (17)	4 (67)	3 (27)	3 (38)	14 (29)
Thrombocytopenia	4 (17)	3 (50)	0	6 (75)	13 (27)
Nausea	8 (33)	3 (50)	0	1 (13)	12 (25)
Insomnia	6 (25)	2 (33)	3 (27)	0	11 (22)
Dizziness	5 (21)	1 (17)	4 (36)	0	10 (20)
Fatigue	10 (42)	0	0	0	10 (20)
Pyrexia	6 (25)	2 (33)	1 (9)	1 (13)	10 (20)
Asthenia	1 (4)	1 (17)	6 (55)	1 (13)	9 (18)
Chills	7 (29)	1 (17)	1 (9)	0	9 (18)
Peripheral edema	2 (8)	3 (50)	2 (18)	2 (25)	9 (18)
Anemia	5 (21)	0	2 (18)	1 (13)	8 (16)
Cough	5 (21)	2 (33)	0	0	7 (14)
Nasal congestion	7 (29)	0	0	0	7 (14)
Pruritus	5 (21)	1 (17)	1 (9)	0	7 (14)
Bone pain	3 (13)	0	2 (18)	1 (13)	6 (12)
Headache	2 (8)	2 (33)	1 (9)	1 (13)	6 (12)
Paresthesia	1 (4)	0	4 (36)	1 (13)	6 (12)
Upper respiratory tract infection	2 (8)	0	1 (9)	3 (38)	6 (12)
Back pain	1 (4)	0	3 (27)	1 (13)	5 (10)
Dysphea	1 (4)	1 (17)	1 (9)	2 (25)	5 (10)
Hepatic function, abnormal	2 (8)	1 (17)	2 (18)	0	5 (10)

DARA, daratumumab; POM-D, pomalidomide plus dexamethasone; VD, bortezomib plus dexamethasone; VTD, bortezomib plus thalidomide and dexamethasone; VMP, bortezomib plus melphalan and prednisone; AE, adverse event.
*Occurring in >10% of patients.

Efficacy

- High response rates were observed with all treatment combinations (**Figure 3**)
  - ORR was 54.5% in RR patients receiving DARA+POM-D
  - ORR was 100% in newly diagnosed patients receiving DARA+VD, DARA+VTD, or DARA+VMP



ORR, overall response rate; DARA, daratumumab; POM-D, pomalidomide plus dexamethasone; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; VD, bortezomib plus dexamethasone; VTD, bortezomib plus thalidomide and dexamethasone; VMP, bortezomib plus melphalan and prednisone.

Figure 3. ORR in patients treated with DARA combined with POM-D or backbone therapies.

- Median (range) time to first response
  - DARA+POM-D (n = 6): 31 (29-57) days
  - DARA+VD (n = 6): 23.5 (22-44) days
  - DARA+VTD (n = 10): 22 (21-43) days
  - DARA+VMP (n = 8): 22.5 (22-135) days
- Responses deepened over time in some patients (**Figure 4**)

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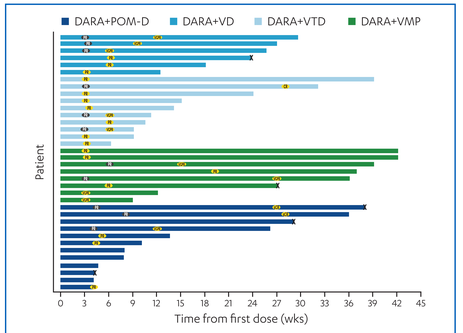
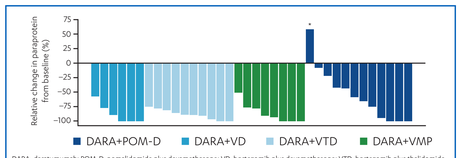


DARA, daratumumab; POM-D, pomalidomide plus dexamethasone; VD, bortezomib plus dexamethasone; VTD, bortezomib plus thalidomide and dexamethasone; VMP, bortezomib plus melphalan and prednisone; PR, partial response; VGPR, very good partial response; CR, complete response; sCR, stringent complete response.
Black ovals indicate first response and yellow ovals indicate best response; X indicates disease progression.

Figure 4. Best response and duration of response in patients treated with DARA combined with POM-D or backbone therapies.

- Responses were associated with reductions in paraprotein from baseline (**Figure 5**)



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*Urine M-protein.

Figure 5. Percent change in paraprotein from baseline in patients treated with DARA combined with POM-D or backbone therapies.

CONCLUSIONS

- **The addition of DARA to POM-D or other backbone therapies was well tolerated and, with the exception of DARA-related infusion reactions, did not result in additional toxicities**
- **High response rates were observed in all treatment arms, and many responses deepened over time**
- **Phase 3 randomized studies of DARA in combination with these backbone regimens are ongoing**
  - **Castor: DARA+VD versus VD in relapsed or refractory MM**
  - **Pollux: DARA+RD versus RD in relapsed or refractory MM**
  - **Cassiopeia: DARA+VTD versus VTD as induction therapy**
  - **Alcyone: DARA+VMP versus VMP in MM patients ineligible for transplant**
  - **Maia: DARA+RD versus RD in MM patients ineligible for transplant**

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