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

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INTRODUCTION

- CD38 is a type II transmembrane protein (45 kDa) that acts as a cell surface receptor and an ectoenzyme[1] (**Figure 1**)
- CD38 has several intracellular functions[1]
  - Regulates signaling, homing, and adhesion in close contact with BCR complex and CXCR4
  - Regulates activation and proliferation of human T lymphocytes
  - As an ectoenzyme, CD38 interacts with NAD^+ and $NADP^+$, which are converted to cyclic ADP-ribose (cADPR), ADPR, and NAADP, aiding intracellular Ca^{2+} mobilization
- CD38 is a rational therapeutic target for the treatment of myeloma
  - CD38 is highly and uniformly expressed on myeloma cells[2,3]
    - CD38 is present on $CD4^+$ cells, $CD8^+$ cells, NK cells, and B lymphocytes at relatively low levels[4]
    - Some CD38 expression is observed in tissues of nonhematopoietic origin[5]

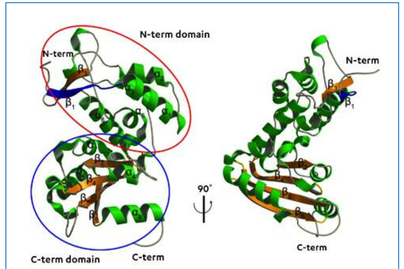

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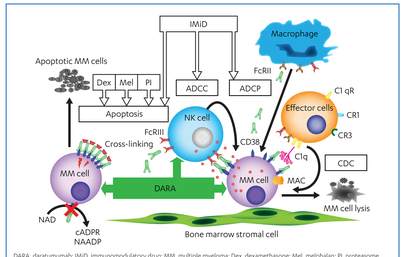
Figure 1. Ribbon representation of the CD38 extracellular domain.[6]

- Daratumumab (DARA) is a human IgG1κ monoclonal antibody that is in clinical development for the treatment of multiple myeloma (MM)
  - DARA binds to CD38 and elicits a signaling cascade and immune effector engagement that leads to the following[7,8]:
    - Complement-dependent cytotoxicity (CDC)
    - Antibody-dependent cell-mediated cytotoxicity (ADCC)
    - Antibody-dependent cell-mediated phagocytosis (ADCP)
    - Induction of apoptosis
    - Modulation of cellular enzymatic activities that are associated with calcium mobilization and signaling
  - These activities lead to the elimination of plasma cells from bone marrow in patients with MM (**Figure 2**)



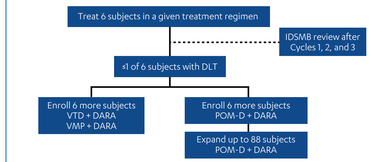
DARA, daratumumab; IMiD, immunomodulatory drug; MM, multiple myeloma; Dex, dexamethasone; Mel, melphalan; PI, proteasome inhibitor; ADCC, antibody-dependent cell-mediated toxicity; ADCP, antibody-dependent cell-mediated phagocytosis; NK, natural killer; CDC, complement-dependent cytotoxicity; MAC, membrane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

Figure 2. Mechanism of action of DARA.[9]

- Two open-label, phase 1/2 studies of DARA as a single-agent[10] or in combination with lenalidomide and dexamethasone[11] demonstrated promising efficacy and safety in relapsed or relapsed and refractory MM patients
- This ongoing, open-label, 4-arm, multicenter, phase 1b study (ClinicalTrials.gov Identifier: NCT01998971) examined DARA 16 mg/kg in combination with pomalidomide and dexamethasone (POM-D) in patients who received ≥2 prior therapies, or in combination with backbone treatments in patients with newly diagnosed MM
- The following were backbone treatments:
  - Bortezomib (subcutaneous) and dexamethasone (VD)
  - Bortezomib (subcutaneous), melphalan, and prednisone (VMP)
  - Bortezomib (subcutaneous), thalidomide, and dexamethasone (VTD)
- The primary objective of this study was to evaluate the safety, tolerability, and dosing of DARA in combination with POM-D and the backbone treatment regimens
- Major secondary objectives included assessment of clinical efficacy outcomes (complete and overall response rate [ORR]), and duration of and time to response

METHODS

- The study design is shown in **Figure 3**
  - Safety review, including dose-limiting toxicities (DLTs), was conducted by an Independent Data Safety Monitoring Board (IDSMB)
    - If DLT was observed in ≤1 patient, that combination regimen was considered safe and well tolerated
  - Clinical responses were also monitored by the IDSMB
- Patient eligibility
  - For the POM-D + DARA regimen, patients who had undergone prior treatment with ≥2 treatment lines of anti-myeloma therapy, including ≥2 consecutive cycles of bortezomib and lenalidomide, and had refractory or relapsed and refractory MM were included
  - For VD + DARA and VTD + DARA regimens, newly diagnosed patients, regardless of eligibility for transplantation, were included
  - For the VMP + DARA regimen, newly diagnosed patients who were not considered candidates for high-dose chemotherapy with stem cell transplantation were included



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

Figure 3. Study design.

- Treatment schedule
  - POM-D (28-day cycle): pomalidomide (4 mg once daily for 21 days)/ dexamethasone (40 mg) per week; dexamethasone 20 mg if aged >75 years
    - DARA was administered once weekly × 2 cycles, then once every 2 weeks × 4 cycles, then once every 4 weeks × 7 cycles or until disease progression
  - VD (21-day cycle): bortezomib (1.3 mg/m^2 twice weekly × 4 cycles, then once weekly × 14 cycles)/dexamethasone (20 mg) 8 times per cycle × 4 cycles, then 4 times per cycle
    - DARA was administered once weekly × 2 cycles, then once every 3 weeks × 16 cycles or until transplantation
  - VMP (42-day cycle): bortezomib (1.3 mg/m^2 twice weekly × 1 cycle, then once weekly × 8 cycles)/melphalan (9 mg/m^2)/prednisone (60 mg/m^2) Days 1 to 4 each cycle
    - DARA was administered once weekly × 1 cycle, then every 3 weeks × 8 cycles
  - VTD (21-day cycle): bortezomib (1.3 mg/m^2 twice weekly × 4 cycles, then once weekly × 14 cycles)/thalidomide (100 mg daily)/dexamethasone (20 mg) 8 times per cycle × 4 cycles, then 4 times per cycle
    - DARA was administered once weekly × 2 cycles, then once every 3 weeks × 16 cycles or until transplantation

RESULTS

- Demographic characteristics, exposure, and patient disposition are summarized in **Table 1**
  - Within the POM-D + DARA group, 2 patients were refractory to proteasome inhibitors (PIs); 1 patient was refractory to immunomodulatory drugs (IMiDs); 3 patients were refractory to both PI/IMiD; 1 patient relapsed, but was not refractory; 4 patients were refractory to the last line of prior therapy
- The cytogenetic profiles of patients are summarized in **Table 2**
- The addition of DARA 16 mg/kg to POM-D and the backbone treatments was well tolerated in all evaluable patients, and did not result in significant additional toxicity (**Table 3**)
- All infusion-related reactions were grade 1 or 2
- High response rates were observed in all combination treatments (**Figure 4**)
  - ORR of 50% was observed in relapsed patients receiving DARA 16 mg/kg in combination with POM-D
  - ORR of 100% was observed in newly diagnosed patients receiving DARA 16 mg/kg in combination with VD, VMP, or VTD

Table 1. Demographics, Exposure, and Disposition

	POM-D + DARA (n = 7)	VD + DARA (n = 6)	VMP + DARA (n = 6)	VTD + DARA (n = 6)
Median age (range), y	62 (45-85)	72.5 (50-82)	72 (67-75)	57 (40-61)
Sex				
Male	4	2	3	2
Female	3	4	3	4
Median # of DARA infusions (range)	11 (1-17)	9 (8-11)	12.5 (10-14)	8 (7-11)
Median # of cycles	4	5	4	4
Disposition	3 subjects discontinued study (1 due to physician decision after 1st dose; 2 due to PD)	1 subject electively taken off study for ASCT after Cycle 4	No discontinuations	5 subjects electively taken off study for ASCT after Cycle 4

POM-D, pomalidomide and dexamethasone; DARA, daratumumab; VD, bortezomib (subcutaneous) and dexamethasone; VMP, bortezomib (subcutaneous), melphalan, and prednisone; VTD, bortezomib (subcutaneous), thalidomide, and dexamethasone; PD, progressive disease; ASCT, autologous stem cell transplant.
All patients treated with DARA 16 mg/kg.

Table 2. Cytogenetic Profiles of Patients in the VD + DARA, VMP + DARA, and VTD + DARA Backbone Treatment Groups

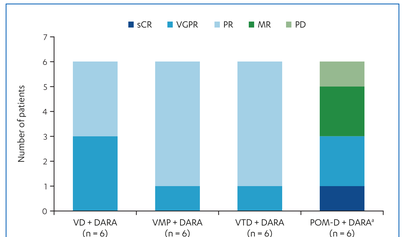
Patient	VD + DARA (n = 6)	VMP + DARA (n = 6)	VTD + DARA (n = 6)
1	Normal	FISH del17, AMP 1q	Unknown
2	T (14;16)	FISH AMP 1q	No high-risk features
3	Unknown	IgH translocation, otherwise normal	Normal
4	Normal	Normal FISH	T (4;14); FISH AMP 1q
5	Normal	T (14;16); FISH AMP 1q	Normal
6	Unknown	FISH AMP 1q	No high-risk features

VD, bortezomib (subcutaneous) and dexamethasone; DARA, daratumumab; VMP, bortezomib (subcutaneous), melphalan, and prednisone; VTD, bortezomib (subcutaneous), thalidomide, and dexamethasone; FISH, fluorescence in situ hybridization; AMP, amplification; T, translocation; IgH, immunoglobulin H.

Table 3. Safety of DARA 16 mg/kg in Combination With POM-D and Backbone Treatments

	POM-D + DARA (n = 7)	VD + DARA (n = 6)	VMP + DARA (n = 6)	VTD + DARA (n = 6)
Serious AEs, n				
Infectious pneumonia	1[c]	0	0	0
Pneumonia	0	1[b]	0	0
Soft tissue infection[a]	0	1[b]	0	0
Dehydration[a]	0	1[b]	0	0
Positive indirect Coombs assay	0	1[c]	0	0
Grade ≥3 AEs, n				
Neutropenia	5	1[b,c]	2[a]	1[b,c]
Anemia	2	1[b,c]	0	1[b,c]
Thrombocytopenia	1	0	1[c]	0
Leukopenia	1	0	0	0
Decreased lymphocyte count	1	0	0	0
Diarrhea	1	0	0	0
Flank pain	1	0	0	0
Peripheral sensory neuropathy	1	0	0	0
Hypokalemia	1	0	0	0
Pneumonia	1	0	0	0
Hip fracture	1	0	0	0
Rash	1	0	0	0
Eye hemorrhage	1	0	0	0

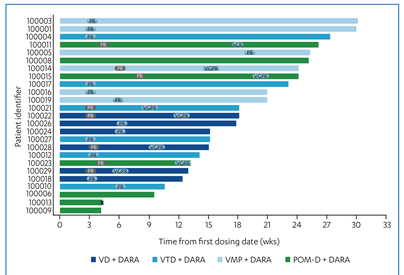
DARA, daratumumab; POM-D, pomalidomide and dexamethasone; VD, bortezomib (subcutaneous) and dexamethasone; VMP, bortezomib (subcutaneous), melphalan, and prednisone; VTD, bortezomib (subcutaneous), thalidomide, and dexamethasone; AE, adverse event.
[a]Not related to DARA.
[b]Same subject.
[c]Possibly or probably related to DARA.
[d]Reported pre-dose.
Each AE occurred in 1 subject unless otherwise noted.



DARA, daratumumab; POM-D, pomalidomide and dexamethasone; sCR, stringent complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; PD, progressive disease; VD, bortezomib (subcutaneous) and dexamethasone; VMP, bortezomib (subcutaneous), melphalan, and prednisone; VTD, bortezomib (subcutaneous), thalidomide, and dexamethasone.
[a]1 VGPR confirmed, 1 VGPR repeat assessment pending.

Figure 4. Response rates of patients treated with DARA 16 mg/kg in combination with POM-D and backbone treatments.

- Median (range) times to first response were the following:
  - POM-D + DARA (n = 3): 31 (29-57) days
  - VD + DARA (n = 6): 23.5 (22-44) days
  - VMP + DARA (n = 6): 32.5 (22-135) days
  - VTD + DARA (n = 6): 22 (22-43) days
- Duration of follow-up for all patients is shown in **Figure 5**



PR, partial response; sCR, stringent complete response; VGPR, very good partial response; **X**, disease progression; VD, bortezomib (subcutaneous) and dexamethasone; DARA, daratumumab; VTD, bortezomib (subcutaneous), thalidomide, and dexamethasone; VMP, bortezomib (subcutaneous), melphalan, and prednisone; POM-D, pomalidomide and dexamethasone.

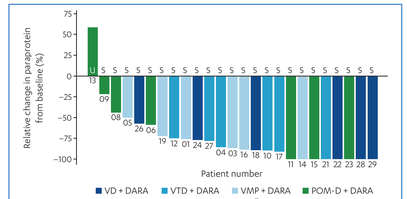
Figure 5. Swim lane of duration of follow-up and response.

- Almost all of the patients in each treatment group demonstrated decreases in paraprotein from baseline (**Figure 6**)
- Mobilization regimen and stem cell yield in transplant patients are summarized in **Table 4**

Table 4. Mobilization Regimen and Stem Cell Yield in Transplant Patients

Treatment	Mobilization regimen	Days of collection	Total stem cell yield (× 10^9/kg body weight)
VD + DARA	Cyclophosphamide	4	3.99
VTD + DARA	G-CSF and Plerixafor	2	6.67
VTD + DARA	G-CSF	2	7.76
VTD + DARA	Cyclophosphamide	3	5.14
VTD + DARA	Cyclophosphamide	1	11.44
VTD + DARA	G-CSF	1	2.5

VD, bortezomib (subcutaneous) and dexamethasone; DARA, daratumumab; VTD, bortezomib (subcutaneous), thalidomide, and dexamethasone; G-CSF, granulocyte colony-stimulating factor.



U, urine; S, serum; VD, bortezomib (subcutaneous) and dexamethasone; DARA, daratumumab; VTD, bortezomib (subcutaneous), thalidomide, and dexamethasone; VMP, bortezomib (subcutaneous), melphalan, and prednisone; POM-D, pomalidomide and dexamethasone

Figure 6. Percent change in paraprotein from baseline.

CONCLUSIONS

- **Addition of DARA 16 mg/kg to POM-D and backbone therapies was well tolerated in all evaluable patients, and did not result in significant additional toxicity**
- **DARA was associated with early response rates that deepened over time in combination with POM-D, VD, VMP, and VTD**
- **DARA does not appear to have a negative impact on stem cell mobilization**
- **Phase 3 studies are either ongoing or will be initiated shortly**
  - **VD (relapsed or refractory, MMY3004-CASTOR)**
  - **VMP (nontransplant eligible, MMY3007-ALCYONE)**
  - **VTD (induction, MMY3006/IFM-HOVON-CASSIOPEIA)**

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DISCLOSURES

Raymond Comenzo, MD: consultancy (Takeda Millenium and Prothena); membership on an entity's board of directors or advisory committees (Takeda Millenium and Janssen); research funding (Takeda Millenium, Prothena, Janssen, and Teva). Philippe Moreau, MD: honoraria (Janssen); membership on an entity's board of directors or advisory committees (Janssen). Maria-Victoria Mateos, MD, PhD: honoraria (Janssen); membership on an entity's board of directors or advisory committees (Janssen). Joan Bladé, MD: honoraria (Janssen and Celgene); research funding (Janssen and Celgene). Lotfi Benboubker, MD: none. Javier de la Rubia, MD, PhD: none. Thierry Facon, MD: membership on an entity's board of directors or advisory committees (Janssen). Joseph Fay, MD: honoraria (BMS). Xiang Qin, MS: employment (Janssen). Tara Masterson, MS: employment (Janssen). Jordan Schecter, MD: employment (Janssen). Tahamtan Ahmadi, MD, PhD: employment (Janssen). Jesus San-Miguel, MD, PhD: membership on an entity's board of directors or advisory committees (Takeda Millenium, Celgene, Novartis, Onyx, Janssen, BMS, and MSD).