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Real-world Data on the Use of Subcutaneous Daratumumab Plus Bortezomib, Thalidomide, and Dexamethasone in Transplant-eligible Patients With Newly Diagnosed Multiple Myeloma

Vania Hungria[1], Fernanda Lemos Moura[2], Paulo Soares[3], Juliana Souza Lima[4], Lisa Aquaroni Ricci[5], Fabio Moore Nucci[6], Eduardo Flávio Oliveira Ribeiro[7], Edvan de Queiroz Crusoe[8], Marinus de Moraes Lima[9], Roberto Jose Pessoa de Magalhães Filho[10], Celso Arrais-Rodrigues[11], Amitabha Bhaumik[12], Trilok Parekh[13], Fredrik Borgsten[13], Robin Carson[14], Damila C Trufelli[15], Abel Costa Neto[16]

[1]Clinica São Germano, São Paulo, SP, Brazil; [2]Fundação Antonio Prudente - AC Camargo Cancer Center, São Paulo, SP, Brazil; [3]Instituto D'Or de Pesquisa e Ensino, Brasilia, Distrito Federal, Brazil; [4]Instituto de Hematologia e Oncologia Curitiba, Curitiba, PR, Brazil; [5]Instituto de Oncologia de Sorocaba, Sorocaba, SP, Brazil; [6]Instituto D'Or de Pesquisa e Ensino, Rio de Janeiro, RJ, Brazil; [7]Hospital Santa Lúcia, Brasilia, Distrito Federal, Brazil; [8]Instituto D'OR de Pesquisa e Ensino, Hospital São Rafael, Salvador, BA, Brazil; [9]Instituto D'Or de Pesquisa e Ensino, Recife, PE, Brazil; [10]Complexo Hospitalar de Niterói, Niterói, RJ, Brazil; [11]Hospital Nove de Julho (DASA), São Paulo, SP, Brazil; [12]Janssen Research & Development, LLC, Titusville, NJ, USA; [13]Janssen Research & Development, LLC, Raritan, NJ, USA; [14]Janssen Research & Development, LLC, Spring House, PA, USA; [15]Janssen-Cilag Farmacêutica Ltda., São Paulo, SP, Brazil; [16]Instituto D'Or de Pesquisa e Ensino, São Paulo, SP, Brazil

Key Takeaway

These findings from a real-world clinical practice setting in Brazil provide additional evidence to support the frontline use of DARA SC plus VTd in transplant-eligible patients with NDMM

Conclusions

Notably, patients receiving D-VTd achieved deep responses, permitting the majority of patients to successfully undergo ASCT

The safety profile of DARA SC plus VTd in real-world practice was consistent with the established profile of DARA IV plus VTd, with no new safety concerns observed

A lower frequency of IRRs was observed with DARA SC than was reported in prior DARA IV–based clinical trials, highlighting the positive impact of SC administration on patient burden

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Poster

https://www.congresshub.com/Oncology/IMS2024/Daratumumab/Hungria

Acknowledgments

The authors would like to thank the patients who participated in this study and their families, the staff members at the study sites who cared for them, and the representatives of the sponsor who were involved in data collection and analyses. This study was supported by Janssen Research & Development, LLC. Medical writing and editorial support were provided by Jessica A Weaver, PhD, of Lumanity Communications Inc., and were funded by Janssen Research & Development, LLC.

Disclosure

VH received honoraria from AbbVie, Amgen, Bristol Myers Squibb, GSK, Janssen, Pfizer, Regeneron, Sanofi, and Takeda.

Introduction

- Daratumumab (DARA), a human IgGκ monoclonal antibody that targets CD38 with direct on-tumor[1-4] and immunomodulatory[5-7] mechanisms of action, demonstrates greater cytotoxicity toward multiple myeloma (MM) cells ex vivo compared with analogs of other CD38 antibodies[8]
  - DARA has consistently demonstrated clinical efficacy in combination regimens as frontline therapy in pivotal clinical trials[9-13] and is approved in a number of countries in combination with standard-of-care regimens for patients with newly diagnosed MM (NDMM)
  - DARA has been used to treat >548,000 patients worldwide[14]
- In the phase 3 CASSIOPEIA study, the addition of intravenous DARA (DARA IV) to bortezomib, thalidomide, and dexamethasone (VTd) demonstrated improved progression-free survival and deeper clinical response compared to VTd alone in transplant-eligible patients with NDMM[13]
- Despite its favorable clinical benefits, DARA IV is associated with infusion-/injection-related reactions (IRRs)[15]; this has led to the development of a subcutaneous (SC) formulation of DARA (DARA SC)
  - In the phase 3 COLUMBA study, DARA SC was noninferior to DARA IV as monotherapy and found to have comparable efficacy and safety and reduced rates of IRRs[16]
  - DARA SC also demonstrated favorable efficacy and infrequent IRRs in combination with several standard-of-care regimens in the phase 2 PLEIADES study[17]
- While clinical trials utilize controlled conditions with strict protocols, extensive monitoring, and well-defined endpoints, they often do not account for diversity, patient population nuances, medical adherence, comorbidities, concurrent medication use, and health care system variabilities; therefore, real-world studies, which consider these challenges, offer a more comprehensive understanding of treatment outcomes in the context of routine clinical practice, allowing for the generalizability of results to real-life scenarios
- Here, we report a real-world analysis of the effectiveness and safety of DARA SC in combination with VTd (hereafter denoted as D-VTd) in transplant-eligible patients with NDMM in Brazil

Methods

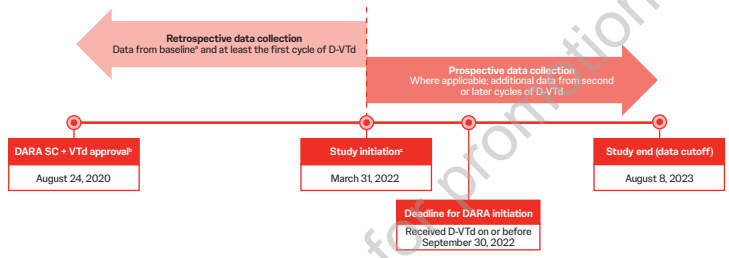
Study design and patients

- MMY4046 was a noninterventional, multicenter, observational, post-authorization safety study that took place across multiple hematology-focused, specialized and community private centers in Brazil
- The primary objective of this study was to determine the clinical outcomes and safety of D-VTd in routine clinical practice
- The study enrolled treatment-naive patients with NDMM who were eligible for autologous stem cell transplant (ASCT) at the start of D-VTd and completed ≥1 cycle of D-VTd per local practice by September 30, 2022
- Patients who had contraindications for D-VTd, planned to change treatment, received investigational drugs within 60 days of study initiation/first data point collection, or were currently enrolled in an interventional study were excluded

Data collection

- Data were collected retrospectively from the initiation of D-VTd therapy (baseline) to study inclusion using patient medical records (**Figure 1**)
- Where applicable, data were collected prospectively from the study inclusion visit to 30 days post-consolidation via electronic case report forms
- Data collected and reported here include:
  - Patient and disease characteristics at baseline
  - D-VTd treatment exposure
  - Response (very good partial response or better [≥VGPR] and overall response rate [ORR; defined as partial response or better]) per physician's assessment (post-induction, post-ASCT, and post-consolidation) according to the International Myeloma Working Group (IMWG) response criteria[18]
  - Stem cell mobilization and ASCT outcomes, including the number of CD34+ cells collected and rate of successful ASCT
  - Safety and tolerability, including the incidence of treatment-emergent adverse events (TEAEs; severity assessed per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4), particularly neutropenia and infections, and treatment discontinuations

Figure 1: Study design



D-VTd, subcutaneous daratumumab plus bortezomib/thalidomide/dexamethasone; DARA SC, subcutaneous daratumumab; VTd, bortezomib/thalidomide/dexamethasone.
[a]Baseline was defined as the start of D-VTd therapy.
[b]Approval in Brazil.
[c]Patients must have provided informed consent prior to study initiation.

Results

Patients

- As of the data cutoff date (August 8, 2023), 51 patients were enrolled, 49 of whom were included in the safety analysis population
- At baseline, the median age was 58 years and the median time since initial MM diagnosis was 0.7 months (**Table 1**)
- Most patients had an Eastern Cooperative Oncology Group performance status score of 0 (74.4%) and, as a group, were representative of various myeloma types and International Staging System disease stages at diagnosis

Table 1: Baseline patient and disease characteristics in the safety analysis population[a]

	D-VTd (N = 49)
Age, median (range), years	58 (38-73)
Male, n (%)	24 (49.0)
Ethnicity, n (%)	
Hispanic or Latino	47 (95.9)
Not Hispanic or Latino	0
Unknown/not reported	2 (4.1)
Race, n (%)	
White	36 (73.5)
Black	8 (16.3)
Asian	1 (2.0)
Unknown	4 (8.2)
ECOG PS score, n (%)	
n	39
0	29 (74.4)
1	6 (15.4)
≥2	4 (10.3)
Time since initial MM diagnosis,[b] median (range), months	0.7 (0-48.2)
Type of MM, n (%)	
n	43
IgA	15 (34.9)
IgG	13 (30.2)
Other[c]	15 (34.9)
ISS disease stage at diagnosis, n (%)	
I	18 (36.7)
II	14 (28.6)
III	15 (30.6)
Missing	2 (4.1)

D-VTd, subcutaneous daratumumab plus bortezomib/thalidomide/dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; MM, multiple myeloma; ISS, International Staging System.
[a]Safety analysis population was defined as all patients who had ≥1 dose of D-VTd.
[b]Time since initial MM diagnosis was based on data from 45 patients.
[c]Inclusive of IgM (n = 1), IgD (n = 1), light chain (n = 7), biclonal (n = 4), and nonsecretory (n = 2) types.

Treatment exposure

- The median treatment duration was 8.9 months, with most patients receiving ≥4 induction cycles (n = 47 [95.9%]) and 2 consolidation cycles (n = 33 [67.3%]; **Table 2**)
- Cycle delays were reported in 16 (32.7%) patients, including 7 (14.3%) patients with delays due to adverse events
- Dose adjustments for bortezomib, thalidomide, and dexamethasone occurred in 10 (20.4%), 5 (10.2%), and 12 (24.5%) patients, respectively, but were not permitted for DARA SC
- Dose interruptions occurred in 1 (2.0%) patient each for DARA SC, bortezomib, and dexamethasone and in 11 (22.4%) patients for thalidomide

Table 2: Summary of treatment exposure in the safety analysis population[a]

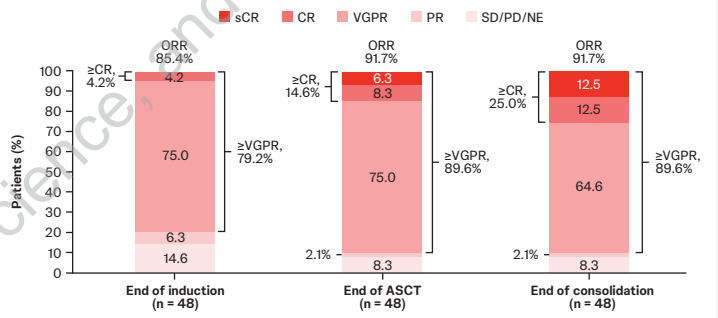
	D-VTd (N = 49)
Overall treatment duration,[b] months	
Median (range)	8.9 (1.0-15.7)
Induction[c]	
n	49
Median (range)	3.8 (1.0-11.0)
ASCT[d]	
n	44
Median (range)	2.6 (0.5-6.2)
Consolidation[e]	
n	37
Median (range)	1.8 (0.3-2.4)
No. of treatment cycles	
Induction	
n	49
Median (range)	4 (1-6)
Consolidation	
n	37
Median (range)	2 (1-2)

D-VTd, subcutaneous daratumumab plus bortezomib/thalidomide/dexamethasone; ASCT, autologous stem cell transplant.
[a]Safety analysis population was defined as all patients who had ≥1 dose of D-VTd.
[b]Across all treatment phases (induction/ASCT/consolidation).
[c]From the day of the first induction dose to the apheresis date −1.
[d]Period between the apheresis date and the beginning of consolidation.
[e]From the day of the first consolidation dose to the day of the last consolidation dose.

Response rates

- By the end of induction, the ORR was 85.4%, 79.2% of patients had achieved ≥VGPR, and 4.2% of patients had achieved complete response or better (≥CR; **Figure 2**)
- By the end of consolidation, response rates had improved to 91.7% for ORR, 89.6% for ≥VGPR, and 25.0% for ≥CR

Figure 2: Response rates categorized by the end of each D-VTd treatment phase in the response-evaluable population[a]



D-VTd, subcutaneous daratumumab plus bortezomib/thalidomide/dexamethasone; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, overall response rate; ASCT, autologous stem cell transplant.
[a]Percentages were calculated based on the response-evaluable population, defined as all patients who had ≥1 dose of D-VTd and ≥1 response assessment by the participating physician.

Stem cell mobilization and transplant outcomes

- Overall, 45 (91.8%) patients underwent stem cell mobilization (**Table 3**), with plerixafor given to 20 (40.8%) patients
  - Of the 4 patients who did not undergo stem cell mobilization, 2 had progressive disease, 1 refused ASCT, and 1 switched from thalidomide to lenalidomide therapy
  - Stem cell yields were sufficient to allow patients to undergo ASCT
- A total of 44 (89.8%) patients underwent ASCT; of these, 43 (97.7%) successfully completed ASCT and 1 died due to post-ASCT septic shock

Table 3: Stem cell mobilization and transplant outcomes in the safety analysis population[a]

	D-VTd (N = 49)
Stem cell mobilization performed, n (%)	45 (91.8)
CD34+ stem cell yield[b]	
n	37
Median (range), ×10⁶/kg	5.7 (2.3-15.0)
ASCT performed, n (%)	44 (89.8)
CD34+ stem cells transplanted	
n	41
Median (range), ×10⁶/kg	4.4 (2.3-11.1)
Successful ASCT, n/N (%)	43/44 (97.7)

D-VTd, subcutaneous daratumumab plus bortezomib/thalidomide/dexamethasone; ASCT, autologous stem cell transplant.
[a]Safety analysis population was defined as all patients who had ≥1 dose of D-VTd.
[b]CD34+ stem cells collected in total.

Safety and tolerability

- Overall, D-VTd was well tolerated, with no new safety concerns observed in real-world practice
- Among the safety population, 89.8% of patients experienced TEAEs of any grade, 49.0% experienced grade 3/4 TEAEs, and 28.6% experienced serious TEAEs; the most common events are shown in **Table 4**
  - Grade 3/4 neutropenia/febrile neutropenia occurred in 16 (32.7%) patients, while serious events occurred in 2 (4.1%) patients (both were febrile neutropenia)
  - Grade 3/4 infections occurred in 9 (18.4%) patients; serious infections occurred in 10 (20.4%) patients, the most common being COVID-19 (10.2%) and pneumonia (4.1%)
- IRRs were reported in 3 (6.1%) patients, all of which occurred during induction, were of grade 1 or 2 severity, and were considered related to DARA SC by the investigators
- As of the cutoff date, 1 patient had discontinued thalidomide treatment due to a grade 1 TEAE of lower limb paresthesia; no patient had discontinued DARA SC due to a TEAE
- One patient died due to post-ASCT septic shock, which occurred 32 days after the last D-VTd dose; no deaths due to TEAEs were reported

Table 4: Safety summary in the safety analysis population[a]

	D-VTd (N = 49)
Any grade TEAEs, n (%)	44 (89.8)
Treatment-related any grade TEAE[b]	35 (71.4)
Most common any grade TEAEs[c]	
Neutropenia	26 (53.1)
Peripheral neuropathy[d]	20 (40.8)
Febrile neutropenia	14 (28.6)
COVID-19 infection	11 (22.4)
Constipation	6 (12.2)
Sinusitis	5 (10.2)
Upper respiratory tract infection	5 (10.2)
Grade 3/4 TEAEs, n (%)	24 (49.0)
Treatment-related grade 3/4 TEAE[b]	9 (18.4)
Most common grade 3/4 TEAEs[e]	
Febrile neutropenia	9 (18.4)
Neutropenia	8 (16.3)
COVID-19 infection	4 (8.2)
Neutropenic colitis	2 (4.1)
Peripheral neuropathy[d]	2 (4.1)
Pneumonia	2 (4.1)
Serious TEAEs, n (%)	14 (28.6)
Treatment-related serious TEAE[b]	5 (10.2)
Most common serious TEAEs[e]	
COVID-19 infection	5 (10.2)
Pneumonia	2 (4.1)
Febrile neutropenia	2 (4.1)
TEAEs resulting in study discontinuation, n (%)	1 (2.0)
Deaths due to a TEAE, n	0

D-VTd, subcutaneous daratumumab plus bortezomib/thalidomide/dexamethasone; TEAE, treatment-emergent adverse event; DARA SC, subcutaneous daratumumab.
[a]Safety analysis population was defined as all patients who had ≥1 dose of D-VTd.
[b]Relationship to study agent was assessed by the investigator. Includes TEAEs that were very likely, probably, or possibly related to ≥1 of the 4 study treatments: DARA SC, bortezomib, thalidomide, or dexamethasone.
[c]TEAEs reported in ≥10% of patients.
[d]Neuropathy-related TEAEs included peripheral neuropathy, peripheral sensory neuropathy, peripheral motor neuropathy, and paresthesia.
[e]Grade 3/4 TEAEs and serious TEAEs reported in ≥2 patients.

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Multiple Myeloma

Presented by V Hungria at the 21st International Myeloma Society (IMS) Annual Meeting; September 25-28, 2024; Rio de Janeiro, Brazil