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Management of Infusion-related Reactions Following Daratumumab Monotherapy in Patients With ≥3 Lines of Prior Therapy or Double Refractory Multiple Myeloma (MM): 54767414MMY2002 (SIRIUS)

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INTRODUCTION

- Treatment options for patients with multiple myeloma (MM) who are refractory to proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) are limited, and most patients die from refractory disease[1,2]
  - Median overall survival (OS) of these patients was estimated to be 9 months[3]
- Daratumumab (DARA) is an IgG1κ human monoclonal antibody that binds to CD38 and inhibits the growth of CD38-expressing tumor cells by inducing the following:
  - Direct apoptosis through Fc-mediated cross-linking[4]
  - Immune-mediated tumor cell lysis through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis[5,6]
  - Lysis of myeloid-derived suppressor cells and a subset of regulatory T cells that express CD38[7]
  - Increased $CD4^+$ and $CD8^+$ T-cell absolute counts and total lymphocyte percentages in both peripheral blood and bone marrow[7]
- DARA showed single-agent activity and a favorable safety profile in a phase 1/2 study of patients with relapsed or refractory MM[8]
  - DARA was associated with mild infusion-related reactions (IRRs); no dose-dependent adverse events (AEs) were reported
  - In Part 2 of the study, 71% of patients had IRRs of any grade, and 1% had a grade 3 IRR
- In the ongoing phase 2 SIRIUS study (MMY2002), DARA 16 mg/kg monotherapy demonstrated activity among patients with relapsed or refractory MM who had received ≥3 prior lines of therapy, including a PI and an IMiD, or who were double refractory to both a PI and an IMiD[8]
  - The overall response rate was 29% (95% confidence interval [CI], 21-39)
    - Forty-one patients achieved a partial response (PR) or better, including 18 PRs, 10 very good PRs, and 3 stringent complete responses
  - Median duration of response and time to response was 7.4 months (95% CI, 5.5-not estimable [NE]) and 1 month, respectively, with a median follow-up of 9.3 months
  - Median progression-free survival was 3.7 months (95% CI, 2.8-4.6)
  - After an updated median follow-up of 14.7 months, median OS was 17.5 months (95% CI, 13.7-NE)
- DARA 16 mg/kg also demonstrated a favorable safety profile in the SIRIUS study[9]
  - No febrile neutropenia or discontinuation due to DARA-related AEs was reported
  - Serious treatment-emergent AEs (TEAEs) were reported in 32 (30%) patients, and 24 (23%) had grade 3 or 4 serious TEAEs
  - 8 (7.5%) patients experienced serious TEAEs related to DARA
- This analysis examined the incidence and management of IRRs in the SIRIUS study in detail

METHODS

Eligibility Criteria

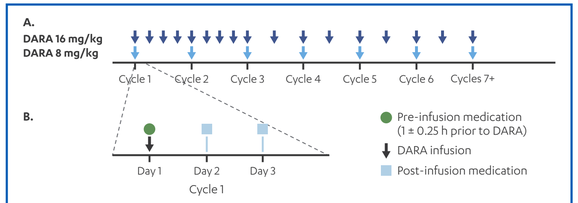
- Documented MM and evidence of disease progression on or within 60 days of the most recent prior treatment regimen
- Evidence of response to ≥1 prior treatment regimen
- Received ≥3 prior lines of therapy, including a PI and an IMiD, in any order during the course of treatment, or disease was double refractory to a PI and an IMiD
- Eastern Cooperative Oncology Group performance status of 0 to 2
- Excluded patients who received prior allogeneic stem cell transplantation; patients could not have received autologous stem cell transplantation within 12 weeks before the first treatment cycle
- Excluded nonsecretory MM based upon standard *M*-component criteria, unless the baseline serum free light chain level was elevated
- Did not receive a cumulative dose of corticosteroids more than the equivalent of ≥140 mg of prednisone within the 2-week period before the first treatment cycle

Study Design

- Open-label, 2-part, international, multicenter, phase 2 study
- In Part 1, patients were randomized 1:1 to receive DARA 16 mg/kg weekly for 8 weeks, then every 2 weeks for 16 weeks, and every 4 weeks thereafter, or DARA 8 mg/kg every 4 weeks (**Figure 1A**)
- Based on interim analysis, the recommended dose (16 mg/kg) and dose schedule were established and selected for further study in Part 2
- DARA infusion was initiated in 1,000 mL at 50 mL/h
  - In the absence of IRRs, rate increased to 200 mL/h at 50-mL/h intervals
  - Second and subsequent infusions (in 500 mL) began at 50 mL/h and 100 mL/h, respectively, and escalated to 200 mL/h

Assessment and Management of IRRs

- IRRs were reported by investigators
- Pre-infusion medication for the management of IRRs was administered 1 hour (±0.25 hours) prior to DARA infusion (**Figure 1B**), and consisted of the following:
  - Methylprednisolone 100 mg (or equivalent) for the first 2 infusions and 60 mg thereafter, administered intravenously
  - Paracetamol (acetaminophen) 650 mg to 1,000 mg
  - Diphenhydramine 25 mg to 50 mg (or equivalent antihistamine)
- Post-infusion medication consisting of a corticosteroid (20 mg methylprednisolone or equivalent) was given on the 2 consecutive days following DARA infusions (**Figure 1B**)
- Changes in cytokine levels between baseline and 4 hours after the first DARA infusion were measured to assess the correlation between cytokine levels and the onset of IRRs



DARA, daratumumab.

Figure 1. Dosing schedule of DARA and pre- and post-infusion medications in the SIRIUS study.

- Specific recommendations were provided to investigators for the management of grade 1 or 2 IRRs (**Table 1**) and grade ≥3 IRRs (**Table 2**)
  - Intravenous saline, antihistamine, oxygen, corticosteroids, and/or bronchodilators could be used per investigator discretion

Table 1. Recommendations for the Management of Grade 1 or 2 IRRs

IRR	Action
Grade 1 or 2	The infusion should be paused. When the patient's condition is stable, infusion may be restarted at the investigator's discretion Upon restart, the infusion rate should be half of that employed before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion
Grade 2 or higher event of laryngeal edema Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset	Patient must be withdrawn from treatment

IRR, infusion-related reaction.

Table 2. Recommendations for the Management of Grade ≥3 IRRs

IRR	Action
Grade 3 or higher	Infusion must be stopped and the patient must be observed carefully until resolution of the IRR
If the intensity of the IRR remains at grade 3 or 4 after 2 hours	Patient must be withdrawn from treatment
If the intensity of the IRR decreases to grade 1 or 2 within 2 hours	Infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that employed before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion
If the intensity of the IRR returns to grade 3 or 4 after restart of the infusion	The procedure described above may be repeated at the investigator's discretion
If the intensity of the IRR increases to grade 3 or 4 for a third time	Patient must be withdrawn from treatment

IRR, infusion-related reaction.

RESULTS

- Patients treated with DARA 16 mg/kg (n = 106) or 8 mg/kg (n = 18) were analyzed at 13.3 months after the last patient's first dose (clinical cut-off: June 30, 2015)
- All patients treated with DARA received pre-infusion medications consisting of analgesics, antihistamines, and corticosteroids
- All patients received post-infusion corticosteroids except for 3 patients in the 16-mg/kg group, none of whom reported IRRs
- For the 16-mg/kg group, 30 (28%) patients received additional steroids, beyond what was required by the protocol, during DARA treatment
  - The median total dose of steroid, over the course of the study, was equivalent to 240 mg of dexamethasone
    - A median dose of 9.5 mg/wk, 5.6 mg/wk, and 0.4 mg/wk was received prior to infusion, post-infusion, and concomitant with DARA, respectively, over the course of the study
    - Concomitant steroids were administered for AE (87%), medical history (10%), prophylaxis (7%), or other (7%) reasons
    - Median doses of steroid received per cycle were 85.7 mg/cycle, 37.5 mg/cycle, and 18.8 mg/cycle for Cycles 1 and 2, Cycles 3 to 6, and Cycles 7 and beyond, respectively
  - These doses are considered to be substantially lower than the therapeutic doses in earlier treatment lines; thus, DARA can be considered to have been used as a monotherapy in these dexamethasone-refractory patients
- The incidence of IRRs was 38% in the 16-mg/kg group and 44% in the 8-mg/kg group, and the most frequently reported IRRs are summarized in **Table 3**
  - Most IRRs were either grade 1 or 2 in severity
  - Grade 3 IRRs consisted of:
    - Bronchospasm (n = 2 at 16 mg/kg)
    - Dyspnea (n = 1 at 16 mg/kg)
    - Chills and cytokine release syndrome (both in 1 patient at 8 mg/kg)
    - Hypertension (n = 1 at 8 mg/kg)
  - No grade 4 IRRs were reported

Table 3. IRRs Reported in >2 Patients in Either Group

IRR, n (%)	16 mg/kg (n = 106) Any grade	8 mg/kg (n = 18) Any grade
Nasal congestion	13 (12.3)	1 (5.6)
Chills	6 (5.7)	5 (27.8)
Cough	6 (5.7)	3 (16.7)
Throat irritation	7 (6.6)	0
Dyspnea	6 (5.7)	1 (5.6)
Vomiting	6 (5.7)	1 (5.6)
Nausea	5 (4.7)	0
Bronchospasm	4 (3.8)	0
Pruritus	2 (1.9)	1 (5.6)
Wheezing	2 (1.9)	1 (5.6)

IRR, infusion-related reaction.

- Most IRRs occurred during the first infusion, and the median duration of infusion decreased with each cycle (**Table 4**)
  - Some patients had IRRs during >1 infusion

Table 4. Onset of IRRs and Duration of Infusions for Each Treatment Cycle

	16 mg/kg			8 mg/kg		
	1st infusion (n = 106)	2nd infusion (n = 104)	Subsequent infusions (n = 103)	1st infusion (n = 18)	2nd infusion (n = 16)	Subsequent infusions (n = 10)
Total number of patients with IRRs, n (%)[a]	38 (35.8)	2 (1.9)	3 (2.9)	8 (44.4)	2 (12.5)	0 (0.0)
Total number of IRRs[b]	77	3	3	22	4	0
Time to onset of IRRs, min						
Number of IRRs[c]	74	3	2	21	3	0
Median	90.0	93.0	53.5	130.0	92.0	–
Range	(1-470)	(93-93)	(38-69)	(13-514)	(90-107)	–
Duration of infusion, h						
Number of infusions	106	103	1,105	18	16	58
Median	7.0	4.2	3.4	7.0	4.1	3.5
Range	(1.5-14.3)	(2.7-8.5)	(1.1-6.7)	(5.3-23.5)	(2.4-8.8)	(2.8-6.2)

IRR, infusion-related reaction.
[a]It was possible for patients to have IRRs during >1 infusion.
[b]Some patients had >1 IRR during an infusion.
[c]IRRs with missing onset times were excluded.

- Treatment modifications, including infusion interruptions and infusion rate decreases, were implemented in most patients who experienced IRRs (**Table 5**)

Table 5. Treatment Modifications Due to DARA-related IRRs

Action taken during infusion, n (%)[a]	16 mg/kg (n = 106)	8 mg/kg (n = 18)
Infusion interrupted[b]	30 (28.3)	6 (33.3)
Infusion rate decreased	10 (9.4)	3 (16.7)
Infusion aborted	2 (1.9)	1 (5.6)

DARA, daratumumab; IRR, infusion-related reaction.
[a]Percentages were calculated using the number of patients in each group as the denominator.
[b]Includes per-protocol infusion rate reductions.

- Three patients were unable to finish an infusion due to an IRR but received subsequent DARA infusions
  - All remaining patients who experienced an IRR continued the infusion and received the full dose of DARA with supportive treatment
- No IRRs led to treatment discontinuation
- Cytokine changes (IL-6, TNFα, IFNγ, and IL-1β) from baseline to 4 hours after the first DARA infusion were variable, but did not correlate with IRRs

SUMMARY

- **At DARA 16 mg/kg, IRRs occurred most frequently during the first infusion (36%) and at low rates during the second (2%) and subsequent infusions (3%)**
  - **IRRs were predominantly grade 1 or 2 in severity, and did not recur at a higher grade with subsequent infusions**
- **No IRRs led to treatment discontinuation**
- **Early interventions allowed successful management of IRRs, and consisted of the following:**
  - **Interruption of infusion and/or a decrease in the rate of infusion**
  - **Administration of pre- and post-infusion medication**
- **Many IRRs occurred within the respiratory tract, including congestion, cough, throat irritation, dyspnea, and bronchospasm**
  - **These were easily controlled, recurred infrequently, and may be related to the normal physiologic function of CD38**

CONCLUSION

- **These results highlight the favorable safety profile and tolerability of DARA, with clinically manageable side effects, as a monotherapy**

REFERENCES

1. Kumar SK, et al. *Blood*. 2008;111(5):2516-2520.
2. Turesson I, et al. *J Clin Oncol*. 2010;28(5):830-834.
3. Kumar SK, et al. *Leukemia*. 2012;26(1):149-157.
4. Jansen JHJ, et al. *Blood*. 2012;120:2974.
5. de Weers M, et al. *J Immunol*. 2011;186(3):1840-1848.
6. Overdijk MB, et al. *MAbs*. 2015;7(2):311-321.
7. Krejcik J, et al. Presented at: 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL. Abstract 3037.
8. Lokhorst HM, et al. *N Engl J Med*. 2015;373(13)1207-1219.
9. Lonial S, et al. *Lancet*. 2015. In press.

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