DARZALEX® (DARATUMUMAB) DOSAGE AND ADMINISTRATION – NINETY-MINUTE INFUSION

Thank you for your interest in DARZALEX® (daratumumab). The following information is provided because of your specific unsolicited request and is not intended to advocate the use of our product in any manner other than as described in the Product Monograph. Please refer to the DARZALEX® Product Monograph for full prescribing information, available at www.janssen.com/canada/products. For complete information, please consult the accompanying scientific summary.

RAPID INFUSION DOSING REGIMENS

Stakiw, et al. (2019) N=25

8 mg/kg in diluted volume of 500 mL

Cycle 1 Day 1
- Half dose (8 mg/kg) over 4 hours

Initial rate	Rate increments	Maximum rate
50 mL/hr	50 mL/hr	200 mL/hr

16 mg/kg in total volume of 500 mL

Cycle 1 Day 8 and subsequent doses
- 16 mg/kg over 90 minutes

Initial rate	Rate increments	Maximum rate
200 mL/hr	250 mL/hr	450 mL/hr

Set to deliver:
- 20% of the dose in the first 30 minutes
- 80% of the dose in the next 60 minutes

Gozzetti, et al. (2019) N=16

8 mg/kg in diluted volume of 500 mL

Cycle 1 Day 1
- Split 1st dose (8 mg/kg) over 4 hours

Initial rate	Maximum rate
50 mL/hr	200 mL/hr

Split 1st dose repeated on Cycle 1 Day 2

16 mg/kg in total volume of 500 mL (2nd dose) and 550 mL (3rd dose)

Cycle 1 Day 8 (2nd dose)
- 16 mg/kg over 4 hours

Initial rate	Maximum rate
50 mL/hr	200 mL/hr

Cycle 1 Day 15 (3rd dose)
- 16 mg/kg over 90 minutes

Initial rate 200 mL/hr — Set to deliver 20% of the dose in the first 30 minutes

Followed by 450 mL/hr — Set to deliver 80% of the dose in the next 60 minutes

Barr, et al. (2018) N=28

At least 2 prior standard-infusion rate daratumumab infusions were required for study inclusion

16 mg/kg in total volume of 550 mL*

Cycle 1 Day 15 (3rd dose)
- 16 mg/kg over 90 minutes

Initial rate 200 mL/hr — Set to deliver 20% of the dose in the first 30 minutes

Followed by 450 mL/hr — Set to deliver 80% of the dose in the next 60 minutes

Hamadeh, et al. (2018) N=100

Standard daratumumab infusion

16 mg/kg

Day 1 of a new cycle or Day 15 of Cycle 1 for naïve patients†
- 16 mg/kg over 90 minutes
- 20% of the dose administered in the first 30 minutes
- 80% of the dose administered in the next 60 minutes

In this comparative study, a separate cohort of patients were administered daratumumab according to standard practice.

Gordon, et al. (2019) N=168

Daratumumab infusions were categorized as rapid if:
- administered ≥5 days apart (to exclude split doses)
- ≥90% of the prescribed dose was received
- the duration was ≤110 minutes

The average of the first rapid infusion administration occurred around the 12th infusion and the average duration of infusion was 92.8 minutes with an SD of 8.8 minutes.

The percentage of patients who received daratumumab monotherapy was 34.5% and those who received DPd, DRd, or DVd were 31%, 14.3%, or 10.1%, respectively.

INFUSION RELATED REACTIONS

Stakiw, et al. (2019) N=25	Gozzetti, et al. (2019) N=16	Barr, et al. (2018) N=28	Hamadeh, et al. (2018) N=100	Gordon, et al. (2019) N=168
Eight patients (32%) experienced grade 1 or grade 2 IRRs on Cycle 1 Day 1 only. No grade ≥3 IRRs.	Split-first dose daratumumab IRRs were reported in 5 patients (31%). • All were grade 2 and occurred on Day 1. No serious adverse events were noted during rapid infusions. Grade 2 fever of unknown origin was reported in 4 patients (25%) and was treated with antibiotics.	Only one patient experienced an adverse event: hypertension (grade 2) during the 450 mL/hr rate.‡	During Day 1 of Cycle 1, 17 patients (32%) in the rapid infusion protocol cohort and 14 patients (30%) in the standard infusion cohort developed IRRs. Beyond Day 1 of Cycle 1, IRR rate was 1.9% in the rapid infusion protocol cohort and 4.3% in the standard infusion cohort (p=0.59).¶	Fifty-one of 142 patients (35.9%) in the safety population experienced ≥1 IRR, including rapid infusions and non-rapid infusions. The most common IRRs (≥10%) were nausea (11.3%) and chills (10.6%). Three patients (2.1%) experienced ≥1 IRR on first administration where rapid infusion may have been administered.

PRE- AND POST-INFUSION MEDICATIONS

Stakiw, et al. (2019) N=25	Gozzetti, et al. (2019) N=16	Barr, et al. (2018) N=28	Hamadeh, et al. (2018) N=100	Gordon, et al. (2019) N=168
• Montelukast • Cetirizine • Dexamethasone • Acetaminophen • Diphenhydramine	• Dexamethasone • Acetaminophen • Diphenhydramine • Salbutamol • Loratadine	• Dexamethasone • Acetaminophen • Diphenhydramine • Famotidine • Montelukast • Hydroxyzine	• Acetaminophen • Diphenhydramine • Dexamethasone • Montelukast	Information not available

* Includes the institution's standard estimated overfill.
† Patients were administered the rapid daratumumab infusion starting on either Day 1 of a new cycle if they had prior exposure to daratumumab, or if daratumumab naïve, on Day 15 of the first cycle.
‡ This patient had received 10 prior infusions at the standard rate. The infusion was paused, a diuretic was given and the infusion was resumed at a reduced rate of 200 mL/hr. Subsequently, the rate was increased again to the accelerated rate without further hypertension.
§ Including 30 minutes post-infusion.
¶ Beyond Day 1 of Cycle 1, IRR rate was 5.5% in the daratumumab treatment-naïve patients in the rapid infusion protocol cohort versus 4.3% in the standard infusion cohort (p=0.9).

The full capacity of the rate dial/wheel is 600 mL/hr.

Stakiw, et al. (2019): Initial safety results of a Canadian phase 2, multicentre, open-label study of 25 patients that evaluated accelerated daratumumab infusion regimen beginning after administration of an initial half-dose daratumumab (8 mg/kg) on Cycle 1 Day 1 (C1D1) over 4 hours with all subsequent doses (16 mg/kg) administered over 90 minutes in patients with RRMM. No grade ≥3 IRRs were reported. IRRs occurred in 32% of patients and all occurred on C1D1 and were grade 1 or 2. There were no grade ≥3 IRRs.[1]

Gozzetti, et al. (2019): Observational, prospective, single-centre study of 16 patients to assess safety and efficacy of a 90-minute daratumumab infusion beginning with the third dose in RRMM patients and in patients receiving daratumumab as consolidation therapy after induction treatment. During rapid infusions, no serious adverse events were noted. Response was noted in 13 patients with complete response (CR) reported in 5 patients.[2]

Barr, et al. (2018): Single-centre, open-label, prospective study of 28 patients receiving a 90-minute daratumumab infusion after the third dose to evaluate safety and tolerability of incidence of infusion related reactions (IRRs). No grade ≥3 infusion related reactions were reported.[3]

Hamadeh, et al. (2018): Retrospective analysis of 100 patients with relapsed/refractory multiple myeloma (RRMM) or amyloidosis to evaluate safety and tolerability of the 90-minute daratumumab infusion. Rate of infusion related reactions (IRRs) was not statistically significant for patients who received 90-minute rapid infusion vs. those who received standard infusion: 1.9% vs. 4.3% (p=0.59).[4]

Gordon, et al. (2019): A retrospective longitudinal cohort of 168 patients with MM who completed ≥1 daratumumab rapid infusion as part of their first daratumumab regimen in routine care. Most rapid infusions were administered for ≥3rd infusion. The average of the first rapid infusion administration occurred around the 12th infusion and the average duration of infusion was 92.8 minutes with an SD of 8.8 minutes. A total of 3 patients (2.1%) experienced ≥1 IRR on first administration where daratumumab rapid infusion may have been administered.[5]

For any questions, please contact Janssen Medical Information at:

1-800-567-3331 or 1-800-387-8781

http://www.janssenmedicalinformation.ca/

References: 1. Stakiw J, et al. Initial results of MCRN 009: Phase 2 study of an accelerated infusion rate of daratumumab in patients with relapsed/refractory multiple myeloma. Poster presented at: 17th International Myeloma Workshop (IMW); September 12–15, 2019; Boston, MA. **2.** Gozzetti A, et al. Long-term safety and efficacy of rapid infusion (90 minutes) of daratumumab IV in multiple myeloma patients. Poster presented at: 17th International Myeloma Workshop (IMW); September 12–15, 2019; Boston, MA. **3.** Barr H, et al. Ninety-minute daratumumab infusion is safe in multiple myeloma. *Leukemia* 2018; doi: 10.1038/s41375-018-0120-2. **4.** Hamadeh I, et al. Rapid infusion daratumumab is safe and well tolerated in clinical practice. Poster presented at: 60th American Society of Hematology (ASH) Annual Meeting & Exposition; December 1–4, 2018; San Diego, CA. **5.** Gordon L, et al. Real-World Utilization and Safety of Daratumumab Rapid Infusion Administered in a Community Setting: A Retrospective Observational Study. *Blood* 2019;134(Supplement_1): 5575.

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