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ADIS DRUG Q&A

Daratumumab in multiple myeloma: a guide to its use as monotherapy in the EU

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Abstract Daratumumab (Darzalex™) is a first-in-class, human immunoglobulin G1 kappa monoclonal antibody that targets the CD38 epitope that is highly expressed on the surface of multiple myeloma cells. In a key clinical trial, monotherapy with intravenous daratumumab in patients with relapsed and refractory multiple myeloma achieved an overall response in ≈30 % of patients. Across two clinical trials, response to daratumumab was rapid (≈1 month) and durable (median 7.6 months). Median overall survival was 20.1 months, and a clear overall survival benefit was evident in patients with stable disease or better. Daratumumab was generally well tolerated in clinical trials. Infusion-related reactions were common, particularly with the first infusion, but were manageable and did not lead to treatment discontinuation.

Adis evaluation of daratumumab monotherapy in patients with relapsed and refractory multiple myeloma
First targeted therapy for multiple myeloma
Induces an overall response in about 30 % of patients
Response is rapid and durable
Response improves with continued treatment in some patients
Survival benefit is conferred to patients with stable disease or better
Generally well tolerated
Infusion-related reactions are common with the first infusion, but are manageable

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What is the rationale for using daratumumab in multiple myeloma?

Multiple myeloma, a malignant neoplasm of plasma cells, is characterized by the uncontrolled production of monoclonal plasma cells in the bone marrow, followed by the production of non-functional intact immunoglobulins or immunoglobulin chains [1, 2]. Multiple myeloma accounts for ≈10–15 % of all haematological neoplasms and ≈1 % of all cancers worldwide [1, 2]. The incidence increases with age, with ≈98 % of patients being diagnosed during or after the fourth decade of life [1, 2]. Most patients present with bone pain, fatigue and anaemia, with other common findings including osteolytic skeletal lesions (80 % of patients), elevated serum creatinine levels (20 %) and hypercalcaemia (15 %) [1].

The survival of patients with multiple myeloma has improved over the past 15 years with the introduction of proteasome inhibitors (e.g. bortezomib) and immunomodulatory drugs (e.g. thalidomide and lenalidomide) [3, 4]. However, the disease remains incurable, and once patients relapse and become refractory to a proteasome inhibitor and an immunomodulatory agent, the prognosis is poor (median overall survival ≈8–9 months) [5, 6]. Therefore, new treatment strategies are needed, and one focus of research has been on targeted therapies [7].

Daratumumab is the first targeted therapy to become available for use in multiple myeloma. It is approved in several regions, including the USA [8] and EU [9]. This article focuses on its use as monotherapy in the EU.

How does daratumumab work?

Daratumumab (Darzalex™) is a first-in-class, human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that targets and binds to the CD38 epitope, which is highly expressed on the surface of myeloma cells, as well as to a lesser extent on other haematological cells and possibly non-haematological cells [9]. The drug binds to CD38 with high affinity where it causes on-tumour activity via several immune-mediated mechanisms, including complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, and antibody-dependent cell-mediated cytotoxicity, as well as inducing direct apoptosis via cross-linking [10–13] (Fig. 1).

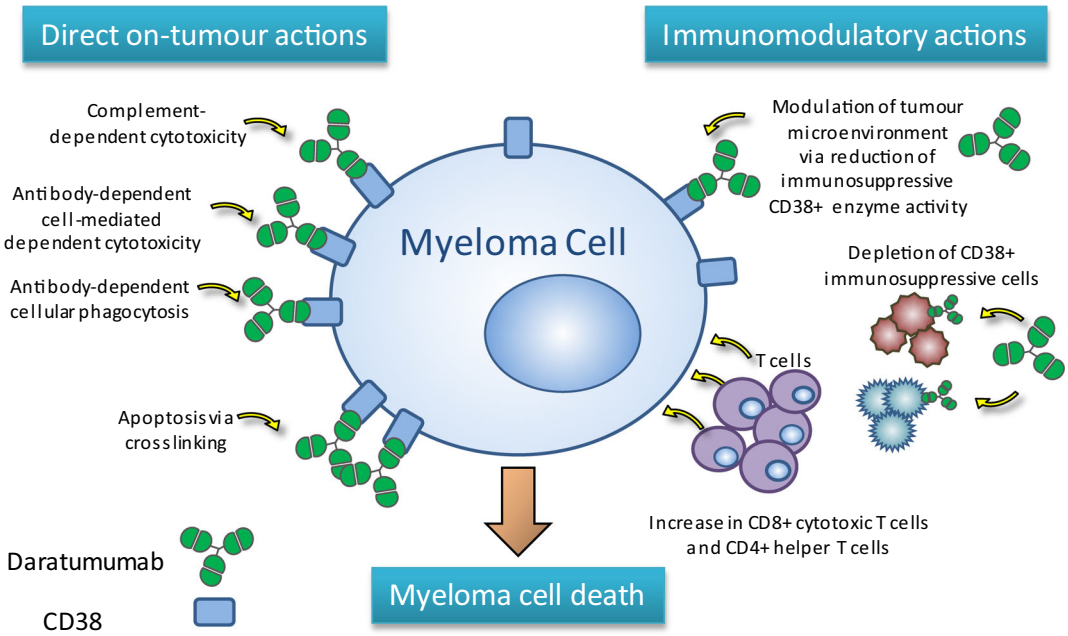
In addition, daratumumab works through immunomodulatory mechanisms, which are thought to adjust the immune response, including modulation of the tumour microenvironment, depletion of immunosuppressive cell populations and inducing an increase in cytotoxic and helper T cells [14] (Fig. 1). The direct on-tumour actions of daratumumab may provide rationale for the rapid response observed in some patients following treatment, and the immunomodulatory mechanisms may explain the sustained responses [12, 14]. Thus, daratumumab appears to provide a multifaceted approach to promoting myeloma cell death by combining the direct on-tumour activity of traditional antibody therapy with a systemic immunomodulatory role.

How should daratumumab monotherapy be used?

Daratumumab monotherapy via intravenous infusion is indicated for the treatment of adults with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy [9]. Table 1 provides a summary of the administration and use of daratumumab in the EU [9]. Consult local prescribing information for further details.

What is the clinical efficacy of daratumumab monotherapy?

The efficacy of intravenous daratumumab 16 mg/kg in the treatment of relapsed and refractory multiple myeloma was demonstrated in two open-label, multicentre trials (SIRIUS



When daratumumab binds to CD38 on the surface of myeloma cells, it can generate **direct on-tumour activity** through several immune-mediated mechanisms (complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity and antibody-dependent cellular phagocytosis), as well as direct apoptosis via cross-linking. Daratumumab also works through **immunomodulatory mechanisms**, which can adjust the immune response, including modulation of the tumor microenvironment, depletion of immunosuppressive cell populations and increases in cytotoxic and helper T cells. These direct on-tumor actions might explain the rapid responses observed, while the immunomodulatory mechanisms might explain the durable or sustained responses seen with daratumumab. By combining direct on-tumor actions of traditional antibody therapy with systemic modulation of the immune system, daratumumab provides a multifaceted approach.

Fig. 1 Mechanisms of action of daratumumab

Table 1 Prescribing summary of intravenous daratumumab (Darzalex™) in the treatment of multiple myeloma in the EU [9]

What is the approved indication for daratumumab?	
Monotherapy in adults with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy	
How is daratumumab available and how should it be stored?	
Availability	Single-dose vials containing daratumumab 100 mg/5 mL or 400 mg/20 mL (i.e. 20 mg/mL) concentrate for solution for IV infusion
Storage of vials before dilution	Refrigerate at 2–8 °C; protect from light; do not freeze or shake
Storage of infusion bag/container after dilution	Refrigerate at 2–8 °C for up to 24 h; protect from light; do not freeze
	Allow to come to room temperature and use immediately
What is the recommended dose and dosing schedule of daratumumab?	
Dose	16 mg/kg bodyweight
Dosing schedule	Weeks 1–8: weekly
	Weeks 9–24: every 2 weeks
	Week 25 onwards until disease progression: every 4 weeks
Adjustment of schedule if planned dose is missed	Administer missed dose as soon as possible
	Adjust the dosing schedule accordingly and maintain the recommended treatment interval
How should the solution be prepared for IV infusion?	
Prior to dilution	Based on the actual body weight of the patient, calculate the dose (mg), total volume (mL) of daratumumab solution required and the number of daratumumab vials needed
	Check that the daratumumab solution is colourless to pale yellow; do not use if opaque particles, discoloration or other foreign particles are present
	Of note, a central line for infusion is not required
Dilution of daratumumab (using aseptic technique)	Remove a volume of 0.9 % NaCl from the infusion bag/container that is equal to the required volume of daratumumab
	Withdraw the necessary amount of daratumumab solution and add to the infusion bag/container containing the appropriate dilution volume of 0.9 % NaCl (1000 mL for first infusion and 500 mL for subsequent infusions); discard any unused daratumumab left in vial
	Gently invert bag/container to mix (do not shake)
How should daratumumab be infused?	
First infusion	Dilution volume: 1000 mL
	Infusion rate: 50 mL/h for the first h, ↑ by 50 mL/h every h to a maximum of 200 mL/h
Second infusion	Dilution volume if first infusion well-tolerated (i.e. no IRR≥ Grade 1 during the first 3 h): 500 mL
	Dilution volume if the first infusion not well-tolerated: 1000 mL
	Infusion rate: 50 mL/h for the first h, ↑ by 50 mL/h every h to a maximum of 200 mL/h
Subsequent infusions	Dilution volume: 500 mL
	Infusion rate: 100 mL/h for the first h, ↑ by 50 mL/h every h to a maximum of 200 mL/h
	Escalate infusion rate only if the first two infusions were well tolerated (defined as no IRR ≥ Grade 1 during a final infusion rate of ≥100 mL/h)
Other comments	Do not infuse other agents in the same IV line
	Complete infusion within 15 h at room temperature (15–25 °C) and in room light
How should IRRs be managed?	
IRR of any grade/severity	Interrupt the infusion immediately and manage symptoms
Grade 1–2 (mild to moderate) IRR	Following resolution of symptoms: restart the infusion at no more than half the rate at which the reaction occurred
	No further reaction symptoms occur: resume escalation of infusion rate as appropriate
Grade 3 (severe) IRR	Following ↓ in symptom intensity to ≤ Grade 2: consider restarting the infusion at no more than half the rate at which the reaction occurred
	No further reaction symptoms occur: resume escalation of infusion rate in increments and at intervals as appropriate
	Second occurrence of Grade 3 IRR: interrupt treatment and repeat resumption procedures
	Third occurrence of Grade 3 IRR: permanently discontinue daratumumab
Grade 4 (life-threatening) IRR	Permanently discontinue daratumumab

Table 1 continued

What medications should be administered with daratumumab to ↓ the risk of IRRs?	
≈1 h prior to every infusion	IV CS (methylprednisolone 100 mg or equivalent dose of an intermediate- or long-acting CS; dose may be ↓ to methylprednisolone 60 mg following the second infusion)
	Oral antipyretic [paracetamol (acetaminophen) 650–1000 mg]
	Oral or IV antihistamine (diphenhydramine 25–50 mg or equivalent)
On each of the 2 days following all infusions (start day after infusion)	Oral CS (methylprednisolone 20 mg or equivalent)
Post-infusion in patients with a history of obstructive pulmonary disorder	Consider prescribing additional post-infusion medications, such as short and long-acting bronchodilators and inhaled CS, to manage respiratory complications
	Following the first 4 infusions, if the patient experiences no major IRRs, these inhaled post-infusion medications may be discontinued at the discretion of the physician
What medication should be administered with daratumumab to ↓ the risk of herpes zoster reactivation?	
Consider anti-viral prophylaxis for the prevention of herpes zoster virus reactivation	
What should be considered regarding pregnancy and lactation?	
Women of child-bearing potential	Use effective contraception during treatment and for 3 months following cessation of daratumumab
Pregnant women	No human or animal data on the risk of daratumumab during pregnancy; as IgG1 monoclonal antibodies cross the placenta after first trimester, daratumumab should not be used during pregnancy unless the benefit to the woman is considered to outweigh the potential risks to the fetus
	Patients who become pregnant while taking daratumumab: inform of potential risk to the fetus
Breast-feeding women	Not known if daratumumab is excreted in human or animal milk; maternal IgG is excreted in human milk, but does not enter the neonatal and infant circulations in substantial amounts
	Effect of daratumumab on newborns/infants is unknown; decide to discontinue breast feeding or daratumumab based on the benefits of breast feeding to the child and treatment for the woman
How should daratumumab be used in other special patient populations?	
Patients with renal impairment	Dosage adjustments are not required
Patients with hepatic impairment	Mild impairment: dosage adjustments are not required
	Moderate to severe impairment: use has not been studied
Elderly patients	Dosage adjustments are not required
Paediatric patients	Safety and effectiveness has not been established
What other special warnings/precautions pertain to its use?	
Interference with antiglobulin tests (Indirect Coombs test)	Daratumumab binds to CD38 on RBCs, thereby interfering with compatibility testing, including antibody screening and cross matching, for up to 6 months after the last daratumumab infusion; there is no impact on the determination of a patient's ABO and Rh blood type
	Type and screen patients before initiating treatment with daratumumab; phenotyping may be considered before starting daratumumab, as per local practice; daratumumab does not impact RBC genotyping, which may be performed at any time
	Mitigate daratumumab interference by treating reagent RBCs with dithiothreitol (to disrupt daratumumab binding) or other locally validated measures; as Kell blood group system is also sensitive to dithiothreitol, Kell-negative units should be supplied after ruling out or identifying alloantibodies using dithiothreitol-treated RBCs (or may consider phenotyping or genotyping)
	Inform blood banks that the patient has received daratumumab
	Emergency transfusion required: give non-cross-matched ABO/RhD-compatible RBCs, as per local blood bank practices
Interference with determination of complete response	Daratumumab may be detected on serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous M-protein; false positive results can affect the assessment of complete response and disease progression in some patients with IgG kappa myeloma protein
	Consider using other methods to evaluate the depth of response in patients with persistent very good partial response

CS corticosteroid, *IRR* infusion-related reaction, *IV* intravenous, *NaCl* sodium chloride, *RBCs* red blood cells, ↑ increase(d), ↓ decrease(d)

[15] and GEN501 [16]) and an updated pooled analysis of data from both trials [17]. In the phase 2 SIRIUS trial, eligible patients had been treated previously with ≥3 lines of therapy (including proteasome inhibitors and immunomodulatory drugs), or had disease that was double refractory to the most recently received proteasome inhibitor and immunomodulatory drug [15]. In the phase 1/2 GEN501 trial, eligible patients were refractory to ≥2 prior lines of therapy [16]. The primary endpoint in the SIRIUS trial was the overall response rate (ORR) as determined by

an independent review committee [15], whereas the GEN501 trial was primarily designed to evaluate safety [16]. Response evaluation was based on International Myeloma Working Group response criteria [18].

Patients enrolled in the daratumumab 16 mg/kg dosage arms of the SIRIUS (n = 106) [15] and GEN501 (n = 42) [16] trials had previously received a median of five and four lines of therapy, respectively, including bortezomib, carfilzomib, lenalidomide, pomalidomide and thalidomide. The proportion of patients who were refractory to both proteasome inhibitors and immunomodulatory drugs was 95 % in the SIRIUS trial and 64 % in the GEN501 trial. Autologous stem cell transplantation had been performed in 80 and 76 % of patients, respectively. In both trials, patients were premedicated with corticosteroids, paracetamol (acetaminophen) and antihistamines, and corticosteroids were given on each of the two days following each daratumumab infusion [15, 16]. The median time since initial diagnosis was 4.8 years in the SIRIUS trial [15] and 6 years in the GEN501 trial [16]. The median number of daratumumab cycles administered in the SIRIUS trial was 4.0 (range 1–16), and the median duration of first, second and subsequent infusions was 7.0, 4.2 and 3.4 h [15].

Monotherapy with daratumumab 16 mg/kg was effective in the treatment of relapsed or refractory multiple myeloma, with an ORR of 29.2 % in the SIRIUS trial [15] and 36.0 % in the GEN501 trial [16] (Table 2). Results of the pooled analysis demonstrated that almost one-third of patients achieved a response and >80% achieved stable disease or better with daratumumab [17] (Table 2).

Daratumumab was associated with a rapid response, with median times to first response of 1.0 [15] and 0.9 [16] months. Responses were observed across all prespecified subgroups irrespective of the number or types of previous therapy or the refractory status [15, 16]. For example, in the SIRIUS trial, 30 of 101 (29.7 %) patients who were refractory to both proteasome inhibitors and immunomodulatory drugs achieved a response [15].

In the updated pooled analysis, the median duration of response across both trials was 7.6 months [17]. Among 46 responders in both trials, the degree of response improved with continued treatment in 14 (22 %) patients. For example, among 10 patients who achieved an initial partial response, seven went on to achieve a very good partial response, one achieved a complete response and two achieved a stringent complete response [17].

After a median follow-up of 20.7 months in the updated pooled analysis, median progression-free survival for the combined overall patient population was 4.0 months and the overall 12-month progression-free survival rate was 21.6 % [17]. The median overall survival was 20.1 months, and a clear overall survival benefit with daratumumab was not restricted to patients with a partial response or better, but extended to those with stable disease or better. Among patients who achieved a minimal response or stable disease, the median overall survival was 18.5 months compared with 3.7 months in patients with progressive disease or who were not evaluable [17].

What is the tolerability profile of daratumumab monotherapy?

Intravenous daratumumab monotherapy was generally well tolerated in clinical trials in patients with relapsed and refractory multiple myeloma [15, 16]. Across both trials, only six (4.1 %) patients discontinued treatment as a result of adverse events [17]. The most frequent

Table 2 Efficacy of intravenous daratumumab 16 mg/kg in open-label trials in patients with relapsed and refractory multiple myeloma

Study (no. of pts)	Daratumumab regimen (16 mg/kg)	Results (% of pts) [95 % CI]			
		OR[a]	VGPR or better	CB[b]	SD or better
SIRIUS [15] phase 2 (106[c])	Once weekly for 8 weeks, once every 2 weeks for 16 weeks, then once every 4 weeks	29.2[d] [20.8–38.9]	12.3	34.0	77.3
GEN501 [16] phase 1/2 (42)	Once weekly for 8 weeks[e], twice monthly for 8 doses, then monthly up to 24 months	36.0 [22.0–52.0]	9.5	45.2	97.6
Pooled analysis [17] (148)		31.1 [23.7–39.2]	13.5	37.2	83.1

CB clinical benefit, *OR* overall response, *pts* patients, *SD* stable disease, *VGPR* very good partial response

[a] Pts who achieved a stringent complete response, complete response, VGPR or partial response

[b] Pts who achieved a stringent complete response, complete response, VGPR, partial response or minimal response

[c] Population who received ≥1 dose of daratumumab 16 mg/kg

[d] Primary endpoint

[e] After the first dose, a 3-week washout period was given in order to evaluate pharmacokinetics

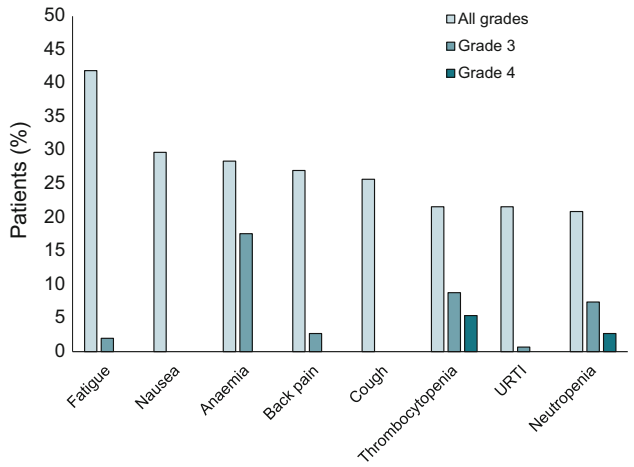


Fig. 2 Incidence and severity of most frequent (≥20 %) treatment-emergent adverse events associated with intravenous daratumumab 16 mg/kg monotherapy in 148 patients with relapsed and refractory multiple myeloma [17]. *URTI* upper respiratory tract infection

(occurring in ≥20 % of patients) treatment-emergent adverse events to occur across both trials are summarized in Fig. 2.

Infusion-related reactions occurred in 48 % of patients across both trials, but did not necessitate treatment discontinuation in any patients [17]. Among infusion-related reactions that occurred in ≥5 % of patients, respiratory conditions featured most commonly, including nasal congestion, cough, allergic rhinitis, throat irritation and dyspnoea [17]. Nausea and chills were the only nonrespiratory infusion-related reactions that occurred in ≥5 % of patients. Five infusion-related reactions with a severity of ≥Grade 3 occurred in four (2.7 %) patients (two patients with bronchospasm, and one patient each with dyspnoea, hypoxia and hypertension). Among patients who experienced an infusion-related reaction, most (95.8 %) occurred with the first infusion, and were substantially less common with the second (7.0 %) and subsequent (7.0 %) infusions (some patients experienced more than one infusion-related reaction) [17].

Patients experiencing infusion-related reactions were safely managed with pre- and post-infusion medications [17] (Table 1). Across both clinical trials, twelve (8.1 %) patients required treatment with granulocyte colony-stimulating factor [17]. Transfusions (199 in total) were administered in 46 (31.1 %) patients; 44 received red blood cells and 14 received platelets. As daratumumab binds to CD38 on the surface of red blood cells, there is a theoretical risk of haemolysis. However, no adverse events relating to haemolysis were reported in clinical trials [17].

The median time to an infusion-related reaction, based on a review of clinical trials reported in the European Medicines Agency's summary of product characteristics, was 1.5 (range 0.2–9.3) h [9].

What is the current clinical positioning of daratumumab?

Daratumumab monotherapy provides an option for the treatment of patients with relapsed and refractory multiple myeloma, irrespective of how many lines of previous treatment they had received or their refractory status. In clinical trials, a response was achieved by ≈30 % of patients. Patients who responded to daratumumab had a rapid (within ≈1 month) and durable (median 7.6 months) response, with some patients continuing to improve with continued treatment. Median overall survival was 20.1 months, and a clear overall survival benefit was evident in the 83 % of patients who achieved stable disease or better. Daratumumab was generally well tolerated and, although infusion-related reactions occurred during the first infusion in a substantial proportion of patients, they were manageable and did not lead to treatment discontinuation. Precautions should be followed to reduce the risk of infusion-related reactions and other potential adverse effects and drug–test interactions (Table 1).

Research is continuing into the use of daratumumab as part of combination therapy regimens. According to preliminary results from the randomized phase 3 CASTOR [19] and POLLUX [20] trials in patients with relapsed or refractory multiple myeloma, treatment with daratumumab + standard of care (bortezomib + dexamethasone in CASTOR [19], and lenalidomide + dexamethasone in POLLUX [20]) reduced the risk of disease progression or death by >60 % relative to treatment with standard of care alone.

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Compliance with ethical standards

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