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# Daratumumab

Updated: May 25, 2017.

# OVERVIEW

## Introduction

Daratumumab is a human monoclonal antibody to CD38 which is used in combination with other antineoplastic agents in the therapy of multiple myeloma. Daratumumab has been implicated in instances of transient, mild-to-moderate serum enzyme elevations, but has not been linked to cases of clinically apparent liver injury with jaundice.

## Background

Daratumumab (dar" a toom' ue mab) is human IgG1 monoclonal antibody to CD38, which is a transmembrane glycoprotein that is frequently overexpressed on cancer cells including multiple myeloma cells. The monoclonal antibody binds to the CD38 molecule and triggers cell apoptosis, probably as a result of antibody mediated cytotoxicity. Daratumumab has been evaluated in heavily pretreated patients with refractory multiple myeloma and shown overall response rates of higher than expected. Daratumumab was given accelerated approval in the United States in 2015 for use in multiple myeloma. Current indications are as therapy of patients with refractory multiple myeloma in combination with lenalidomide (or bortezomib) and dexamethasone or as monotherapy in patients who have failed at least three previous regimens. Daratumumab is available as a solution for intravenous infusion in single use vials of 100 mg in 5 mL or 400 mg in 20 mL (20 mg/mL). The recommended dose is 16 mg/kg intravenously every week for 8 to 9 weeks, and then every 2, 3 or 4 weeks based upon indications and other agents being used. Premedication with methylprednisolone is recommended. Side effects are common and can include infusion reactions, bone marrow suppression, fatigue, nausea and vomiting, diarrhea, muscle spasms, back pain, fever, cough, dyspnea, peripheral edema, peripheral neuropathy and upper respiratory infection. Rare, but potentially serious side effects include severe infusion reactions, neutropenia, thrombocytopenia and interference with cross matching and red blood cell antibody screening.

## Hepatotoxicity

In summary analyses of the registration trials of daratumumab for multiple myeloma, 15% of patients developed elevations in ALT during therapy, 13% alkaline phosphatase and 7% bilirubin. The abnormalities were generally mild-to-moderate, transient and asymptomatic. ALT elevations above 5 times the upper limit of normal occurred in less than 1% of patients. In these studies, daratumumab was given with lenalidomide and dexamethasone, and similar rates of liver enzyme elevations occurred with those agents alone without the monoclonal antibody. There were no instances of clinically apparent liver injury with jaundice attributable to daratumumab in these trials and no patient stopped therapy because of hepatic adverse events. Since its approval

and more general use, there have been no published reports of clinically apparent liver injury due to daratumumab, and its product label does not list hepatotoxicity as an adverse event.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

### Mechanism of Injury

The mechanism by which daratumumab might cause liver injury is not known. There is no evidence that CD38 is expressed on hepatocytes. Like other monoclonal antibodies, daratumumab is unlikely to have intrinsic hepatotoxicity, is metabolized to smaller peptides or amino acids by many cells, and does not affect the hepatic drug metabolizing enzymes or transporting molecules.

### Outcome and Management

The liver injury attributed to daratumumab has invariably been self-limited and not associated with symptoms or jaundice. There is no information on possible cross sensitivity to the injury among different monoclonal antibodies or therapies directed at epidermal growth factor receptors.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies

## PRODUCT INFORMATION

**REPRESENTATIVE TRADE NAMES**

Daratumumab – Darzalex®

**DRUG CLASS**

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

## CHEMICAL FORMULA AND STRUCTURE

| DRUG | CAS REGISTRY NO | MOLECULAR FORMULA | STRUCTURE |
|---|---|---|---|
| Daratumumab | 945721-28-8 | Monoclonal Antibody | Not Available |

## ANNOTATED BIBLIOGRAPHY

References updated: 25 May 2017

Zimmerman HJ. Hepatotoxic effects of oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 673-708.

*(Expert review of hepatotoxicity published in 1999, well before the availability of most monoclonal antibody therapies).*

Reuben A. Hepatotoxicity of immunosuppressive drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2011, pp. 569-91.

*(Review of hepatotoxicity of immunosuppressive drugs; mentions that "the biological immunosuppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists").*

Chabner BA, Barnes J, Neal J, Olson E, Mujagiv H, Sequist L, Wilson W, et al. Targeted therapies: tyrosine kinase inhibitors, monoclonal antibodies, and cytokines. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-53.

*(Textbook of pharmacology and therapeutics).*

Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, Minnema MC, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. N Engl J Med 2015; 373: 1207-19. PubMed PMID: 26308596.

*(Among 72 patients with refractory multiple myeloma treated with daratumumab [8 vs 16 mg/kg] for up to 24 months, the overall response rate was 25%, and side effects were frequent, with serious adverse events in 40% vs 33%; no mention of ALT elevations or hepatotoxicity).*

Usmani SZ, Weiss BM, Plesner T, Bahlis NJ, Belch A, Lonial S, Lokhorst HM, et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma. Blood 2016; 128: 37-44. PubMed PMID: 27216216.

*(Among 148 patients with refractory multiple myeloma treated with daratumumab, the overall response rate was 31% and adverse events included fatigue [42%], nausea [30%], anemia [28%], back pain [27%], cough [26%], thrombocytopenia [22%] and neutropenia [21%]; no mention of ALT elevations or hepatotoxicity).*

Plesner T, Arkenau HT, Gimsing P, Krejcik J, Lemech C, Minnema MC, Lassen U, et al. Phase 1/2 study of daratumumab, lenalidomide, and dexamethasone for relapsed multiple myeloma. Blood 2016; 128 (14): 1821-8. PubMed PMID: 27531679.

*(Phase 1 studies of daratumumab identified no dose limiting toxicities, and phase 2 studies showed that common side effects included neutropenia, thrombocytopenia, cough, diarrhea and fatigue; ALT elevations above 5 times ULN occurred in 1 patient who was also taking lenalidomide and the abnormalities resolved with its dose adjustment).*

Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, Rabin N, et al.; POLLUX Investigators. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016; 375: 1319-31. PubMed PMID: 27705267.

*(Among 569 patients with previously treated multiple myeloma treated with lenalidomide and dexamethasone, progression-free survival was prolonged by addition of daratumumab [83% vs 60% at one year], while side effects were more common and included neutropenia, diarrhea, upper respiratory infection and cough; no mention of ALT elevations or hepatotoxicity).*

Palumbo A, Chanan-Khan A, Weisel K, Nooka AK, Masszi T, Beksac M, Spicka I, et al.; CASTOR Investigators. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med 2016; 375: 754-66. PubMed PMID: 27557302.

*(Among 498 patients with relapsed or refractory multiple myeloma treated with bortezomib and dexamethasone, progression-free survival was increased by the addition of daratumumab [61% vs 27%], and side effects were also greater including thrombocytopenia, neutropenia, peripheral neuropathy, diarrhea, cough and dyspnea; no mention of ALT elevations or hepatotoxicity).*

Lonial S, Weiss BM, Usmani SZ, Singhal S, Chari A, Bahlis NJ, Belch A, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Lancet 2016; 387 (10027): 1551-60. PubMed PMID: 26778538.

*(Among 106 patients with refractory multiple myeloma treated with daratumumab, the overall response rate was 29% and adverse events included neutropenia, diarrhea, fatigue, nausea, anemia, thrombocytopenia, back pain and cough; no mention of ALT elevations or hepatotoxicity).*

Rajkumar SV. Daratumumab in multiple myeloma. Lancet 2016; 387 (10027): 1490-2. PubMed PMID: 26778537.

*(Editorial in response to Lonial [2016] pointing out the improving results of chemotherapy of multiple myeloma, particularly with using combinations of 2 or 3 agents).*

Three new drugs for multiple myeloma. Med Lett Drugs Ther 2016; 58 (1495): e70-1. PubMed PMID: 27192621.

*(Concise review of three agents that had been recently approved for use in multiple myeloma including daratumumab; no mention of ALT elevations or hepatotoxicity).*

Brioli A, Mügge LO, Hochhaus A, Von Lilienfeld-Toal M. Safety issues and management of toxicities associated with new treatments for multiple myeloma. Expert Rev Hematol 2017; 10: 193-205. PubMed PMID: 28116920.

*(Review of adverse events from new treatments of multiple myeloma and their management; does not specifically discuss hepatotoxicity).*

Kapoor P, Rajkumar SV. Multiple myeloma in 2016: Fresh perspectives on treatment and moments of clarity. Nat Rev Clin Oncol 2017; 14: 73-4. PubMed PMID: 28071678.

*(Review of new agents for therapy of multiple myeloma, focusing upon the advantages of triple therapy).*