

DARZALEX® (daratumumab)
**Compendia Communication – NCCN - Use of DARZALEX in Combination with
Lenalidomide and Dexamethasone December 2018**

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NCCN Guidelines® Panel: Multiple Myeloma

Dear NCCN,

On behalf of Janssen Biotech, Inc., I respectfully request that the NCCN Guidelines® - Multiple Myeloma Panel review the enclosed data regarding the use of DARZALEX® (daratumumab) in combination with lenalidomide and dexamethasone for the treatment of patients with newly diagnosed multiple myeloma who are transplant ineligible. We also request follow-up information on our previous submission in June 2018, regarding the use of DARZALEX in combination with carfilzomib and dexamethasone for the treatment of patients with relapsed/refractory multiple myeloma.

Specific Change Requested: Recommend the inclusion of DARZALEX® (daratumumab) in combination with lenalidomide and dexamethasone (D-Rd) for the treatment of patients with newly diagnosed multiple myeloma who are transplant ineligible with a Category 1 evidence level rating.

FDA Clearance: The FDA has approved DARZALEX® (daratumumab) for the treatment of multiple myeloma (1) in combination with bortezomib, melphalan and prednisone for patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant, (2) in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone in patients who have received at least one prior therapy, (3) in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI), and (4) as a monotherapy in patients who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.¹

Rationale: Combination therapy with lenalidomide and dexamethasone

MAIA (54767414MMY3008) Study

MAIA^{2, 3} is an international, phase 3, randomized, open-label, active-controlled, multicenter study in patients with newly diagnosed multiple myeloma not eligible for high dose chemotherapy and autologous stem cell transplantation (ASCT; N=737). Patients were randomized 1:1 to lenalidomide + dexamethasone (Rd; n=369) or daratumumab + Rd (D-Rd; n=368) and received 28-day cycles of:

- Daratumumab: 16 mg/kg intravenously (IV) every week in cycles 1-2, every 2 weeks in cycles 3-6, and every 4 weeks thereafter
- Lenalidomide: 25 mg orally (PO) daily on days 1-21
- Dexamethasone: 40 mg PO or IV weekly (patients >75 years of age or with a body mass index [BMI] <18.5 received 20 mg weekly)

Treatment was continued until disease progression in both arms of the study.

The primary endpoint was progression-free survival (PFS). Key secondary endpoints included overall response rate (ORR), minimal residual disease (MRD)-negativity rate at 10⁻⁵ sensitivity, and safety.

Facon et al³ presented results of a pre-specified interim analysis of this ongoing study at the annual meeting of the American Society of Hematology (ASH) in December 2018. The median follow-up was 28 months. Patients (52% male) ranged in age from 45-90 years (median 73 years; 44% ≥75 years), with key baseline characteristics being well-balanced between the groups.

The hazard ratio (HR) for the primary endpoint of PFS was 0.56 (96% confidence interval [CI], 0.43-0.73; $P < 0.0001$) indicating a 44% reduction in the risk of progression or death with D-Rd compared to the Rd comparator arm. Median PFS was 31.9 months for the Rd arm and was not reached for D-Rd. The ORR was 93% for D-Rd and 81% for Rd ($P < 0.0001$). The complete response (CR) or better rate was 48% for D-Rd compared to 25% for Rd ($P < 0.0001$). A very good partial response (VGPR) or better rate of 79% was reported for D-Rd compared to 53% for Rd ($P < 0.0001$). MRD-negativity at 10^{-5} was 3.4 times higher with D-Rd than with Rd (24% vs. 7%; $P < 0.0001$). With a median follow-up of 28.1 months, overall survival (OS) data are immature (HR 0.78; 95% CI, 0.56-1.1).

The most common (any grade, ≥20%) hematologic adverse events with D-Rd were neutropenia (57%) and anemia (35%). The most common (any grade, ≥20%) non-hematologic adverse events with D-Rd were diarrhea (57%), constipation (41%), fatigue (40%), peripheral edema (38%), back pain (34%), asthenia (32%), nausea (32%), and pneumonia (23%). Grade 3 or 4 pneumonia, neutropenia and lymphopenia were observed at higher rates (≥5% difference) in the D-Rd arm. The rate of infusion related reactions (IRRs) with D-Rd was 41% with grade 3 or 4 IRRs observed in 3% of the patients.

The following oral presentation is submitted with the Full Prescribing Information. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

- 1.) Facon T, Kumar S, Plesner T, et al. Phase 3 randomized study of daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in patients with newly diagnosed multiple myeloma (NDMM) ineligible for transplant (MAIA). Oral presentation presented at: 60th American Society of Hematology (ASH) Annual Meeting & Exposition; December 1-4, 2018; San Diego, CA.
- 2.) DARZALEX (daratumumab) [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.; https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-dc33e1e3-dde0-4c18-b1e3-a3a79c07d600.

Follow-up Regarding Our Previous MMY1001 (JNJ54767414MMY1001) Study Submission

In addition to the above submission, I am writing to follow-up on the status of our submission from June 7, 2018 regarding the use of DARZALEX[®] in combination with carfilzomib and dexamethasone for the treatment of patients with relapsed/refractory multiple myeloma.

Janssen Biotech shares NCCN's goal of having the most current and accurate information on treatment available in your monographs and database(s). Patient safety is paramount to Janssen, and we want to ensure that clinicians have access to the latest product information, so they can make the most informed prescribing decisions for patients.

I look forward to working with you as you consider the enclosed information. The information provided is not intended as an endorsement of any usage not contained in the Prescribing Information. For complete information, please refer to the full Prescribing Information, including the following sections: **INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS.**

If you require further information, please feel free to contact me via the Janssen Medical Information Center at 1-800-JANSSEN (1-800-526-7736).

Sincerely,

Darren Piscitelli, PharmD

Associate Director, Hematologic Malignancies Medical Information and Knowledge Integration
Janssen Scientific Affairs, LLC

REFERENCES

1. DARZALEX (daratumumab) [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.; https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-dc33e1e3-dde0-4c18-b1e3-a3a79c07d600.
2. Janssen Research & Development, LLC. Study comparing daratumumab, lenalidomide, and dexamethasone with lenalidomide and dexamethasone in participants with previously untreated multiple myeloma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2018 December 4]. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT02252172> NLM Identifier: NCT02252172.
3. Facon T, Kumar S, Plesner T, et al. Phase 3 randomized study of daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in patients with newly diagnosed multiple myeloma (NDMM) ineligible for transplant (MAIA). Oral presentation presented at: 60th American Society of Hematology (ASH) Annual Meeting & Exposition; December 1-4, 2018; San Diego, CA.