

DARZALEX® (daratumumab)
**NCCN Compendia Communication - Use of DARZALEX in Combination with
Cyclophosphamide, Bortezomib, and Dexamethasone May 2019**

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Date of request: May 9, 2019
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 cyclophosphamide, bortezomib, and dexamethasone for the treatment of patients with newly diagnosed and relapsed multiple myeloma.

Specific Change Requested: Recommend the inclusion of DARZALEX® (daratumumab) in combination with cyclophosphamide, bortezomib and dexamethasone (D-CyBorD) for the treatment of patients with newly diagnosed and relapsed multiple myeloma who are either transplant eligible or ineligible with a Category 2a 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 cyclophosphamide, bortezomib, and dexamethasone

LYRA (54767414MMY2012) Study^{2, 3}

LYRA is an ongoing, multicenter, single-arm, open-label, phase 2 US community study evaluating the safety and efficacy of daratumumab when administered in combination with cyclophosphamide + bortezomib + dexamethasone (CyBorD) for the treatment of multiple myeloma (MM) in patients who have not received previous therapy (newly diagnosed MM [NDMM]) or have relapsed after receiving 1 line of treatment (relapsed MM [RMM]).

During the induction phase (4-8 cycles), all patients were scheduled to receive:

- Daratumumab: 8 mg/kg intravenously (IV) on days 1 and 2 of cycle 1, then 16 mg/kg weekly in cycle 1 (starting on day 8) and cycle 2, then every 2 weeks in cycles 3-6; then every 4 weeks in cycles 7-8.
- Cyclophosphamide: 300 mg/m² orally (PO), all cycles: weekly on days 1, 8, 15, and 22.
- Bortezomib: 1.5 mg/m² subcutaneously (SC), all cycles: weekly on days 1, 8, and 15.
- Dexamethasone: 40 mg IV weekly on cycle 1; and 40 mg IV/PO weekly on cycles 2-8.

Eligible patients underwent autologous stem cell transplantation at the discretion of the investigator.

All patients received ≤12 daratumumab maintenance doses monthly.

The primary endpoint was very good partial response or better (≥VGPR) after 4 induction cycles. Key secondary endpoints included overall response rate (ORR), duration of response, progression-free survival (PFS), overall survival (OS), and safety/tolerability. The study enrolled a total of 101 patients (median age 64 years; 14.0% ≥75 years) of whom 87 had newly diagnosed MM and 14 had RMM. Primary and secondary efficacy variables were analyzed in those patients with measurable disease at baseline or

screening who received ≥ 1 post-baseline assessment (the response-evaluable population). The median follow-up time for NDMM and RMM patients was 7.9 and 8.8 months, respectively.

In response-evaluable NDMM patients (n=86), the primary endpoint of \geq VGPR was 44.2% (95% confidence interval [CI], 33.5%-55.3%) after 4 cycles of induction therapy which included 4 (4.7% [95% CI, 1.3%-11.5%]) patients who achieved a complete response (CR). At the end of induction, the ORR was 81.4% (95% CI, 71.6–89.0%), with 48 [55.8% (95% CI, 44.7–66.5%)] patients achieving VGPR + CR and 8 [9.3% (95% CI, 4.1–17.5%)] patients achieving CR. Patients with NDMM received a median (range) of 6.0 (2–8) treatment cycles during induction. Median duration of response was not reached. Median PFS was not reached among enrolled NDMM patients (n=87; 95% CI, not evaluable [NE]-NE) with a 12-month PFS rate of 87% (95% CI, 57.1%-96.6%). In response-evaluable RMM patients (n=14), the primary endpoint of \geq VGPR was 57.1% (95% CI, 28.9%-82.3%) after 4 cycles of induction therapy which included 2 (14.3% [95% CI, 1.8%-42.8%]) patients who achieved a CR. Median duration of response was 12.4 (95% CI, 3.7-12.4) months. Median PFS was 13.3 (95% CI, 6.8-13.3) months with a 12-month PFS rate of 66.2% (95% CI, 32.4%-86.0%).

The most frequent any-grade treatment-emergent adverse event (TEAE) in NDMM patients was fatigue (61.6%) and the most frequent grade 3/4 TEAE was neutropenia (11.6%). The most frequent any-grade TEAEs in RMM patients included fatigue, diarrhea, and upper respiratory tract infections (42.9% each) and the most frequent grade 3/4 TEAE was neutropenia (21.4%). Infusion reactions (IRs) were experienced by a total of 54.0% patients in the overall population and occurred in 49 (49.0%) patients on cycle 1 day 1 and in 4 (4.0%) patients on cycle 1 day 2. The most frequent IRs (>5%) reported were chills (13.0%), cough (9%), dyspnea (8.0%), pruritis (7.0%), and nausea (7.0%).

The following publication is submitted with the Full Prescribing Information. We would like to acknowledge the contributions of NCCN panel members who are potentially co-authors or co-contributors of this publication.

- 1.) Yimer H, Melear J, Faber E, et al. Daratumumab, bortezomib, cyclophosphamide, and dexamethasone in newly diagnosed and relapsed multiple myeloma: LYRA study [published online ahead of print March 3, 2019]. *Br J Haematol*. doi: 10.1111/bjh.15806.
- 2.) DARZALEX (daratumumab) [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.; https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-dc33e1e3-dde0-4c18-b1e3-a3a79c07d600.

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. Yimer H, Melear J, Faber E, et al. Daratumumab, bortezomib, cyclophosphamide, and dexamethasone in newly diagnosed and relapsed multiple myeloma: LYRA study [published online ahead of print March 3, 2019]. *Br J Haematol*. doi: 10.1111/bjh.15806.
3. Janssen Scientific Affairs, LLC. A study to evaluate Dara-CyBorD in previously untreated and relapsed subjects with multiple myeloma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2019 January 28]. Available from: <https://clinicaltrials.gov/ct2/show/study/NCT02951819> NLM Identifier: NCT02951819.