DARZALEX® (daratumumab)
Compendia Communication – NCCN - Use of DARZALEX in Combination with Carfilzomib and Dexamethasone June 2018

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NCCN Guidelines® Panel: Multiple Myeloma

Dear NCCN,

On behalf of Janssen Biotech, Inc., I respectfully request the NCCN Guidelines® - Multiple Myeloma Panel review the enclosed data regarding the use of DARZALEX® (daratumumab) 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 carfilzomib and dexamethasone (D-Kd) for the treatment of patients with relapsed/refractory multiple myeloma 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 carfilzomib and dexamethasone

MMY1001 (JNJ54767414MMY1001) Study

MMY1001[2, 3] is a phase 1b, open-label, non-randomized, multicenter study in patients with relapsed or refractory multiple myeloma. The study includes a D-Kd treatment arm (N=85). Patients received 28-day cycles of:

- Daratumumab: 16 mg/kg IV every week on cycles 1-2, every 2 weeks on cycles 3-6, and every 4 weeks thereafter
  - Ten patients received a standard first daratumumab dose (16 mg/kg) on cycle 1 day 1
  - Per protocol, the remaining patients received the first dose of daratumumab split over 2 days (8 mg/kg days 1-2 of cycle 1)
- Carfilzomib: 20 mg/m^2 on cycle 1 day 1 escalated to 70 mg/m^2 on cycle 1 day 8 if deemed tolerable (administered weekly on days 1, 8, and 15 of each cycle)
- Dexamethasone: 40 mg/week (≤75 years of age) or 20 mg/week (>75 years of age)

Lonial et al presented results of this study at the annual ASH meeting in December 2017. Chari et al presented updates at the 2018 annual ASCO meeting, including a subgroup analysis of lenalidomide-refractory patients (n=51). The median (range) follow-up was 12.0 months (0.5-23.2) in the overall population and similar for lenalidomide-refractory patients. Eighty-three (98%) patients were escalated to carfilzomib 70 mg/m^2.

The most common (any grade, ≥20%) hematologic adverse events were thrombocytopenia (67%), anemia (47%), neutropenia (29%), and lymphopenia (25%). The most common (any grade, ≥20%) non-hematologic adverse events were nausea (40%), upper respiratory tract infection (39%), asthenia (38%), vomiting (37%), dyspnea (34%), pyrexia (33%), insomnia (31%), diarrhea (31%), hypertension (25%), cough (25%), headache (22%), and back pain (22%). A similar safety profile was observed in lenalidomide-refractory patients. No notable change in median left ventricular ejection fraction was observed from baseline over time and cardiac adverse events were manageable. Five (50%) patients who received a single first infusion had an infusion related reaction. In patients who received a split first infusion, infusion related reactions occurred in 27 (36%) patients on cycle 1 day 1 and 3 (4%) patients on cycle 1 day 2. Single and split first infusions exhibited similar pharmacokinetic profiles.

At median follow-up of 12 months, the overall response rate for all-treated patients (n=82) was 84%. Minimal residual disease (MRD) was evaluated in 11 all-treated patients with CR/sCR, of which 4 tested MRD-negative at a 10^{-5} sensitivity threshold. Five lenalidomide-refractory patients were evaluated and 1 tested MRD-negative (10^{-5} sensitivity). In the overall treatment population, the median progression-free survival (PFS) was not reached. In lenalidomide refractory patients the median PFS was 14.1 (95% CI, 12.0-not estimable) months. The 12-month PFS rates were 71% and 62%, respectively. The median overall survival was not estimable in the overall treatment population and was 21.1 (95% CI, 18.8-not estimable) months in lenalidomide-refractory patients.

The following study publications are 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.) Lonial S, San-Miguel J, Martinez-Lopez J, et al. Daratumumab in combination with carfilzomib and dexamethasone in patients (pts) with relapsed multiple myeloma (MMY1001): an open-label, phase 1b study. Poster presented at: The Annual Meeting of the American Society of Hematology (ASH); December 9-12, 2017; Atlanta, GA.; http://files.shareholder.com/downloads/AMDA-KPIBN/6298629625x0x966328/9EE7DA5C-03A7-447D-B9F9-C368EABDA901/Lonial_MMY1001.pdf

2.) Chari A, Martinez-Lopez J, Mateos MV, et al. Daratumumab in combination with carfilzomib and dexamethasone (D-Kd) in lenalidomide-refractory patients with relapsed multiple myeloma: subgroup analysis of MMY1001. Presented at: The Annual Meeting of the American Society of Clinical Oncology (ASCO); June 1-5, 2018; Chicago, IL.; http://files.shareholder.com/downloads/AMDA-KPIBN/6250362498x0x981216/FC8F5CE2-0DD7-45D8-AD3F-BBF80249FD85/JJD63617_MMY1001_D-Kd_ASCO_oral_31May_FINAL_2_.pdf

3.) DARZALEX (daratumumab) [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.; https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-dc33e1e3-dde0-4c18-b1e3-a3a79c07d600.

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, Oncology 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. Lonial S, San-Miguel J, Martinez-Lopez J, et al. Daratumumab in combination with carfilzomib and dexamethasone in patients (pts) with relapsed mutliple myeloma (MMY1001): an open-label, phase 1b study. Poster presented at: The Annual Meeting of the American Society of Hematology (ASH); December 9-12, 2017; Atlanta, GA.

3. Chari A, Martinez-Lopez J, Mateos MV, et al. Daratumumab in combination with carfilzomib and dexamethasone (D-Kd) in lenalidomide-refractory patients with relapsed multiple myeloma: subgroup analysis of MMY1001. Presented at: The Annual Meeting of the merican Society of Clinical Oncology (ASCO); June 1-5, 2018; Chicago, IL.