November 23, 2015

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Date of request: November 23, 2015
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 for inclusion of DARZALEX™ (daratumumab) for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and immunomodulatory agent. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Specific Change:

Recommend DARZALEX™ (daratumumab) 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 patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and immunomodulatory agent.

Rationale:

On May 1, 2013, Janssen announced that the U.S. Food and Drug Administration (FDA) granted a Breakthrough Therapy Designation for daratumumab as a monotherapy in the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and immunomodulatory agent.

GEN501 was a phase 1/2 dose-escalation (part 1) and dose-expansion (part 2) study primarily assessing the safety of daratumumab monotherapy in multiple myeloma (MM) who had relapsed after or were refractory to ≥2 prior lines of therapy. In part 1 of the study, patients received daratumumab 0.0005 to 24 mg/kg in 10 dose cohorts over an 8 week treatment period. In part 2 of the study, patients received daratumumab 8 mg/kg once weekly for 8 weeks, then twice monthly for 16 additional weeks or daratumumab 16 mg/kg as 1 infusion followed by a 3-week washout period, then once weekly for 7 weeks, twice monthly for 14 additional weeks, and monthly thereafter. The most commonly occurring adverse events (AEs, >25%) in part 2 of the study were fatigue, allergic rhinitis, pyrexia, diarrhea, upper respiratory tract infection, and dyspnea. Infusion-related reactions (IRRs) were observed in 71% of

patients across the daratumumab 8 mg/kg and 16 mg/kg cohorts in part 2 and were mostly grades 1 or 2 in severity. Patients who received daratumumab 16 mg/kg (n=42) had an overall response rate of 36% (95% confidence interval [CI] 22-52; confirmed complete response [CR] in 2 patients, very good partial response [VGPR] in 2 patients, and partial response (PR) in 11 patients). The median time to first response was 0.9 months (range 0.5-3.2) and the median duration of response was not reached. A total of 65% (95% CI 28-86) of responders remained in remission at 12 months.[1]

A phase 2 study is evaluating the efficacy and safety of daratumumab 16 mg/kg as monotherapy in patients with multiple myeloma (MM) who have received ≥3 prior lines of therapy or have disease refractory to both a proteasome inhibitor and an immunomodulatory drug. Patients were initially randomized 1:1 to receive daratumumab 8 mg/kg every 4 weeks (n=18); or daratumumab 16 mg/kg every week for 8 weeks, daratumumab 16 mg/kg every 2 weeks for 16 weeks, then daratumumab 16 mg/kg every 4 weeks thereafter (n=16). Response was evaluated and the daratumumab 16 mg/kg dose was established as the recommended dose for further evaluation. An additional 90 patients were enrolled in the daratumumab 16mg/kg group. The overall response rate was 29% (95% CI, 21%-39%). A stringent CR was achieved in 3% of patients (n=3;95% CI, 0.6%-8.0%), VGPR in 9% of patients (n=10), and partial response in 17% of patients (n=18). The median time to response among responders was 1 month and the median duration of response was 7.4 months (95% CI, 5.5-not estimable). Treatment-emergent adverse events that occurred in ≥20% of patients included fatigue, anemia, nausea, thrombocytopenia, neutropenia, back pain, and cough. Infusion-related reactions occurred in 43% of patients who received daratumumab 16 mg/kg.[2,3]

The following study publications are submitted with the Full Prescribing Information.[4] 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) Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. *N Engl J Med*. 2015;373(13)1207-1219.

2) Lonial S, Weiss B, Usmani S, et al. Phase 2 study of daratumumab (DARA) in patients with ≥3 lines of prior therapy or double refractory multiple myeloma: 54767414MMY2002 (Sirius) [oral presentation]. Presented at: The 2015 American Society of Clinical Oncology (ASCO) Annual Meeting; May 29-June 2, 2015; Chicago, IL.

3) Lonial S, Weiss B, Usmani S, et al. Phase II study of daratumumab (DARA) monotherapy in patients with ≥3 lines of prior therapy or double refractory multiple myeloma (MM): 54767414MMY2002 (Sirius). *J Clin Oncol*. 2015;33(15 Suppl). Abstract LBA8512.

4) DARZALEX™ (daratumumab) [package insert]. Horsham, PA: Janssen Biotech, Inc.

Sincerely,

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