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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 for inclusion of DARZALEX® (daratumumab) for use in combination therapy with lenalidomide and dexamethasone for the treatment of patients with relapsed/refractory multiple myeloma. In addition, please find enclosed the full publication of the CASTOR study that formed the basis for NCCN granting a category 1 recommendation for DARZALEX® in combination with bortezomib and dexamethasone as a preferred regimen for the treatment of patients with previously treated multiple myeloma.

Specific Changes:

1. Recommend DARZALEX® (daratumumab) for the treatment of patients with relapsed/refractory multiple myeloma with a category 1 evidence level rating for the following treatment option:
   - Combination therapy with lenalidomide and dexamethasone

2. Update CASTOR study citation in NCCN Multiple Myeloma Guidelines.

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. 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. DARZALEX® is not approved currently for use in combination therapy.

Rationale: Combination therapy with lenalidomide and dexamethasone

POLLUX (JNJ54767414MMY3003) study

In the phase 3, open-label, randomized, multicenter, active-controlled POLLUX study, the safety and efficacy of lenalidomide and dexamethasone (Rd) and DARZALEX® + Rd were assessed in patients with relapsed or refractory multiple myeloma. A total of 569 patients (DARZALEX® + Rd: 286 patients; Rd: 283 patients) were randomized 1:1 to receive 28-day cycles of Rd (lenalidomide 25 mg orally [PO] on days 1 through 21 of each cycle and dexamethasone 40 mg weekly) or DARZALEX® + Rd (lenalidomide 25 mg PO on days 1 through 21 of each cycle, dexamethasone 20 mg prior to each DARZALEX® infusion and 20 mg the day following each DARZALEX® infusion, plus DARZALEX® 16 mg/kg IV weekly for 8 weeks in

cycles 1 and 2, every 2 weeks for 16 weeks in cycles 3-6, and then every 4 weeks) until withdrawal of consent, disease progression, or unacceptable toxicity/death. After a median follow-up of 13.5 months, median progression free survival (PFS) was significantly improved in the DARZALEX® + Rd arm vs the Rd arm, showing a 63% reduction in the risk of disease progression or death for DARZALEX® + Rd vs Rd (not estimable vs estimated median of 18.4 months; hazard ratio [HR], 0.37; 95% confidence interval [CI], 0.27-0.52; P<0.001). DARZALEX® + Rd significantly delayed time to progression (TTP) vs Rd (not reached vs estimated median of 18.4 months; HR, 0.34; 95% CI, 0.23-0.48; P<0.001). Among patients who received prior lenalidomide treatment, there was a 58% reduction in the risk of disease progression or death for DARZALEX® + Rd vs Rd (HR, 0.42; 95% CI, 0.19-0.90). Among patients who did not receive prior lenalidomide treatment, there was a 64% reduction in the risk of disease progression/death for DARZALEX® + Rd vs Rd (HR, 0.36; 95% CI, 0.25-0.52). Among patients with responses that could be evaluated, the rates of ORR (93% vs 76%), VGPR or better (76% vs 44%), and CR or better (43% vs 19%) were significantly improved in the DARZALEX® + Rd arm vs. the Rd arm, respectively (all P<0.001). The median duration of response (DOR) was not reached in the DARZALEX® + Rd arm and was 17.4 months for the Rd arm. The most common (≥25%) adverse events (AEs) were neutropenia, diarrhea, fatigue, upper respiratory tract infection, anemia, constipation, cough, thrombocytopenia, and muscle spasm. Any grade infusion reactions (IRs) were reported in 49% of patients who received DARZALEX®. IRs were mostly grade 1 or 2 (grade 3 were observed in 5% of patients) and most (92%) occurred during the first infusion. No grade 4 IRRs were reported.[1]

In conclusion, we respectfully request that the NCCN Guidelines® - Multiple Myeloma Panel review the enclosed data for inclusion of DARZALEX® (daratumumab) for the treatment of patients with relapsed/refractory multiple myeloma with a category 1 evidence level rating for use in combination therapy with lenalidomide and dexamethasone. In addition, we ask that the citation for the CASTOR study[2] be updated in the NCCN Multiple Myeloma Guidelines to reflect the published manuscript which formed the basis for NCCN granting a category 1 recommendation for DARZALEX® in combination with bortezomib and dexamethasone in previously treated multiple myeloma. The following study publications are submitted with the Full Prescribing Information.[3] 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) Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375(14):1319-1331. doi: 10.1056/NEJMoa1607751
2) Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375(8):754-66. doi: 10.1056/NEJMoa1606038
3) DARZALEX (daratumumab) [package insert]. Horsham, PA: Janssen Biotech, Inc.

Sincerely,

Lisa Meadows Ambrose RPh, PharmD-c, BCOP
Medical Information