From:	Meadows, Lisa [COBIUS]
To:	Submissions
Subject:	Submission Request
Date:	Friday, July 08, 2016 8:15:43 AM
Attachments:	image001.png 1. Plesner 2015 GEN503 Oral Presentation.pdf 2. Dimopoulos 2016 POLLUX Oral Presentation.pdf 3. Dimopoulos 2016 POLLUX Abstract.pdf 4. Palumbo 2016 CASTOR Oral Presentation.pdf 5. Palumbo 2016 CASTOR Abstract.pdf 6. DARZALEX USPI Rev 6-2016.pdf

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July 7, 2016

Name: Lisa Meadows Ambrose, RPh, PharmD-c, BCOP
Company/Organization: Janssen Biotech, Inc.
Address: 850 Ridgeview Drive Horsham, PA 19044
Phone: 804.539.7417
E-mail: LMeadows@its.jnj.com
Date of request: June 7, 2016
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 relapsed/refractory multiple myeloma.

Specific Change:

Recommend DARZALEX® (daratumumab) for the treatment of patients with relapsed/refractory multiple myeloma with a category 1 evidence level rating for the following treatment options:

- Combination therapy with lenalidomide and dexamethasone
- Combination therapy with bortezomib and dexamethasone

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

GEN503 was a phase 1/2 dose escalation (part 1) and dose expansion (part 2) study which evaluated the safety and efficacy of DARZALEX® + lenalidomide and dexamethasone (Rd) in patients with

relapsed or refractory multiple myeloma. In part 1, patients received (in 28-day cycles) DARZALEX® 2-16 mg/kg weekly for months 1-2, every 2 weeks for months 3-6, and every 4 weeks thereafter, lenalidomide 25 mg on days 1-21, and dexamethasone 40 mg once weekly. In part 2, patients received (in 28-day cycles) DARZALEX® 16 mg/kg weekly for months 1-2, every 2 weeks for months 3-6, and every 4 weeks thereafter, lenalidomide 25 mg on days 1-21, and dexamethasone 40 mg once weekly. The primary endpoint was the incidence of adverse events (AEs). Key secondary endpoints included rate of response, pharmacokinetics, time to progression (TTP), duration of response (DOR), and progression-free survival (PFS). The overall response rate (ORR) was 81% (26/32 patients; 95% confidence interval [CI], 63.6%-92.8%). The most frequent (>20%) treatment-emergent adverse events were neutropenia, cough, diarrhea, muscle spasms, fatigue, pyrexia, thrombocytopenia, hypertension, nausea, anemia, peripheral edema, upper respiratory tract infection, and peripheral sensory neuropathy. A total of 56% of patients experienced infusion-related reactions (IRRs).[1]

POLLUX (JNJ54767414MMY3003) is an ongoing, phase 3, randomized, open-label, active-controlled, multicenter study evaluating the safety and efficacy of lenalidomide and dexamethasone (Rd) and DARZALEX® + Rd in patients with relapsed or refractory MM. The trial has enrolled a total of 569 patients from about 145 sites in 18 countries, including the United States. Patients were randomized 1:1, receiving 28-day cycles of the following: (1) Rd: lenalidomide 25 mg orally on days 1 through 21; dexamethasone 40 mg weekly (or 20 mg weekly for patients >75 years old or with a body mass index <18.5), or (2) DARZALEX® + Rd: lenalidomide and dexamethasone, as above, plus DARZALEX® 16 mg/kg intravenously weekly in cycles 1 and 2, every 2 weeks in cycles 3 through 6, and once (on day 1) in cycle 7 onwards. The primary endpoint is PFS. Key secondary endpoints included TTP, ORR, rate of very good partial response (VGPR) or better, time to complete response (CR) or partial response (PR), overall survival (OS), DOR, and percentage of patients with minimal residual disease (MRD). In an analysis of 569 randomized patients, the combination of DARZALEX®+ Rd significantly improved median PFS, delayed TTP, increased ORR, increased rates of VGPR or better, and increased rates of CR or better vs Rd (all P<0.001). The most common (≥25%) adverse events (AEs) were neutropenia, diarrhea, fatigue, upper respiratory tract infection, anemia, constipation, cough, thrombocytopenia, and muscle spasm. Infusion-related reactions occurred in 48% of patients who received DARZALEX®, were mostly grade 1 or 2 (grade 3/4, 5%/0%)[2,3]

Rationale: Combination therapy with bortezomib and dexamethasone

CASTOR (JNJ54767414MMY3004) is an ongoing, phase 3, open-label, randomized, multicenter, active-controlled study evaluating the safety and efficacy of bortezomib and dexamethasone (Vd) and DARZALEX® + Vd in patients with relapsed or refractory multiple myeloma. The trial has enrolled a total of 498 patients from about 108 sites in 15 countries, including the United States. Patients were randomized 1:1, receiving the following: (1) Vd: bortezomib 1.3 mg/m2 subcutaneously on days 1, 4, 8, and 11 of each 21-day cycle for 8 cycles; dexamethasone 20 mg orally on days 1, 2, 4, 5, 8, 9, 11, and 12 of the 8 cycles (2) DARZALEX® + Vd: bortezomib and dexamethasone as above, plus DARZALEX® 16 mg/kg intravenously weekly for the first 3 cycles, on day 1 of cycles 4-8, and every 4 weeks thereafter. The primary endpoint is PFS. Secondary endpoints included TTP, percentage of patients with overall response, DOR, time to response, percentage of patients with VGPR or better, percentage of patients

with minimal residual disease (MRD), and percentage of patients with OS. The combination of DARZALEX® + Vd vs Vd has significantly improved median PFS, median TTP, increased ORR, and increased rates of VGPR or better (all P<0.0001). The most common (≥20%) treatment-emergent adverse events have included thrombocytopenia, peripheral sensory neuropathy, diarrhea, anemia, upper respiratory tract infection, cough, fatigue, and constipation. Infusion-related reactions occurred in 45% of patients who received DARZALEX® (grade 3/4, 9%/0%).[4,5]

In conclusion, we respectfully request 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 the following treatment options: (1) combination therapy with lenalidomide and dexamethasone (2) combination therapy with bortezomib and dexamethasone. The following study publications are submitted with the Full Prescribing Information.[6] 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) Plesner T, Arkenau HT, Gimsing P, et al. Daratumumab in combination with lenalidomide and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: updated results of a phase 1/2 study (GEN503) [oral presentation]. Presented at: The 57th American Society of Hematology (ASH) Annual Meeting & Exposition; December 5-8, 2015; Orlando, FL.

2) Dimopoulos MA, Oriol A, Nahi H, et al. An open-label, randomized, phase 3 study of daratumumab, lenalidomide, and dexamethasone (DRd) versus lenalidomide and dexamethasone (Rd) in relapsed or refractory multiple myeloma (RRMM): POLLUX [oral presentation]. Presented at: EHA 2016 - The 21st European Hematology Association Congress; June 9-12, 2016; Copenhagen, Denmark.

3) Dimopoulos MA, Oriol A, Nahi H, et al. An open-label, randomized phase 3 study of daratumumab, lenalidomide, and dexamethasone (DRd) versus lenalidomide and dexamethasone (Rd) in relapsed or refractory multiple myeloma (RRMM): POLLUX [abstract]. Presented at: EHA 2016 - The 21st European Hematology Association Congress; June 9-12, 2016; Copenhagen, Denmark. Abstract LB2238.

4) Palumbo A, Chanan-Khan A, Weisel K, et al. Phase 3 randomized controlled study of daratumumab, bortezomib and dexamethasone (DVd) vs bortezomib and dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma (RRMM): CASTOR [oral presentation]. Presented at: The 2016 American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2016; Chicago, IL.

5) Palumbo A, Chanan-Khan A, Weisel K, et al. Phase 3 randomized controlled study of daratumumab, bortezomib and dexamethasone (DVd) vs bortezomib and dexamethasone (Vd) in patients (pts) with relapsed or refractory multiple myeloma (RRMM): CASTOR study. J Clin Oncol. 2016; 34(15 suppl): abstract LBA4.

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

Sincerely,

Lisa Meadows Ambrose RPh, PharmD-c, BCOP

Janssen Scientific Affairs, LLC
Office Phone: 804.562.6418
Mobile: 804.539.7417
LMeadows@its.jnj.com

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