Janssen Scientific Affairs, LLC

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December 20, 2019

Kristina Gregory RN, MSN, OCN
3025 Chemical Road
Plymouth Meeting, PA, USA 19462

Dear Ms. Gregory,

Please consider the following information.

Response(s):

- DARZALEX - NCCN Compendium Communication - Use in Combination with VMP - December 2019
- DARZALEX - NCCN Compendium Communication - Use in Combination with CyBorD - December 2019
- DARZALEX - NCCN Compendium Communication - Use in Combination with RVd - December 2019

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,

Cynthia Toso

Cynthia Toso, PharmD
Associate Director
Medical Information

Inquiry #:01596730

Enclosure(s)/Electronic Link(s):

- DARZALEX® (daratumumab) Prescribing Information at https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-dc33e1e3-dde0-4c18-b1e3-a3a79c07d600
- Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial.
- Daratumumab (DARA) maintenance therapy improves depth of response and results in durable progression-free survival (PFS) following DARA plus cyclophosphamide, bortezomib, and dexamethasone (CyBorD) induction therapy in multiple myeloma (MM): update of the LYRA study.
- Depth of response to daratumumab (DARA), lenalidomide, bortezomib, and dexamethasone (RVd) improves over time in patients (pts) with transplant-eligible newly diagnosed multiple myeloma (NDMM): GRIFFIN study update.
- DARZALEX Prescribing Information

Need Help? If you have any additional questions, please contact us via:

1-800-JANSSEN
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To report a possible adverse event or product quality complaint, please call the Medical Information Center immediately, at 1-800-JANSSEN (1-800-526-7736).

DARZALEX® (daratumumab)
NCCN Compendium Communication – Use in Combination with Bortezomib, Melphalan, and Prednisone - December 2019

December 19, 2019

Name: Cindy Toso, PharmD
Company/Organization: Janssen Biotech, Inc.
Address: 850 Ridgeview Drive Horsham, PA 19044
Phone: 215.325.4244
E-mail: ctoso@its.jnj.com
Date of request: December 19, 2019
NCCN Guidelines® Panel: Multiple Myeloma

Dear NCCN,

As a follow-up to our Janssen Biotech, Inc. submissions on 1/17/18, 2/16/18, and 5/9/18, we respectfully request the NCCN Guidelines® Multiple Myeloma Panel review the enclosed updated results from the phase 3 ALCYONE study evaluating daratumumab in combination with bortezomib, melphalan, and prednisone (VMP) for the treatment of patients with newly diagnosed (ND) multiple myeloma (MM) who are ineligible for high-dose chemotherapy with autologous stem cell transplantation (ASCT).

Specific Changes:
Request a change to the Guidelines to update the recommendation for daratumumab in combination with VMP to a category 1, preferred regimen for primary therapy for non-transplant patients (MYEL-F 2 of 3; Version 2.2020).

FDA Clearance: The FDA has approved DARZALEX® (daratumumab) for the treatment of adult patients with MM (1) in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy, (2) in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for ASCT, (3) in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant, (4) in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy, (5) in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI), and (6) as 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:

Updated efficacy and safety results from a prespecified interim overall survival analysis of the randomized, open-label phase 3 study (ALCYONE) of daratumumab in combination with VMP for the treatment of patients (n=706) with transplant-ineligible NDMM are submitted for your review.[2] These data are a follow-up to results for the primary endpoint of progression-free survival (PFS) described in the *New England Journal of Medicine*[3] publication that was included with our submission on 1/17/18.

After a median follow-up of 40.1 months, the hazard ratio (HR) for death in the daratumumab + VMP group vs the VMP group was 0.60 (95% confidence interval [CI] 0.46-0.80; *P*=0.0003). The primary endpoint of PFS remained significantly improved for the daratumumab + VMP group (HR 0.42 [95% CI 0.34-0.51]; *P*<0.0001). The most frequent adverse events (≥10%) during maintenance daratumumab monotherapy in patients in the daratumumab +VMP group were respiratory infections, cough, and diarrhea. Grade 3-4 adverse events (≥1%) during maintenance daratumumab monotherapy included anemia, neutropenia, thrombocytopenia, upper respiratory tract infection, bronchitis, urinary tract infection, back pain, pneumonia, and hypertension.[2]

The following publication is submitted with the Full Prescribing Information.

Mateos MV, Cavo M, Blade J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. [published online ahead of print December 9, 2019]. *Lancet*. doi:10.1016/S0140-6736(19)32956-3.

Sincerely,

Cindy Toso, PharmD
Associate Director, Payer & Health Systems, Medical Information & 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. Mateos MV, Cavo M, Blade J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. [published online ahead of print December 9, 2019]. *Lancet*. doi:10.1016/S0140-6736(19)32956-3.
3. Mateos M, et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. *N Engl J Med*. 2018;378(6):518-528.

DARZALEX® (daratumumab)
NCCN Compendium Communication – Use in Combination with Cyclophosphamide, Bortezomib, and Dexamethasone - December 2019

December 19, 2019

Name: Cindy Toso, PharmD
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Date of request: December 19, 2019
NCCN Guidelines® Panel: Multiple Myeloma

Dear NCCN,

As a follow-up to our Janssen Biotech, Inc. submission on April 30, 2019, we respectfully request the NCCN Guidelines® Multiple Myeloma Panel review the enclosed updated results from the ongoing phase 2 LYRA study evaluating daratumumab in combination with cyclophosphamide, bortezomib, and dexamethasone (CyBorD) for the treatment of newly diagnosed (ND) and relapsed multiple myeloma (MM) presented at the 2019 American Society of Hematology (ASH) Annual Meeting.

Specific Changes:
Request an update to the Guidelines to include daratumumab in combination with CyBorD for primary therapy of transplant candidates (MYEL-F 1 of 3; Version 2.2020) and non-transplant candidates (MYEL-F 2 of 3; Version 2.2020) with Category 2a evidence level ratings.

FDA Clearance: The FDA has approved DARZALEX® (daratumumab) for the treatment of adult patients with MM (1) in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy, (2) in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant (ASCT), (3) in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant, (4) in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy, (5) in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI), and (6) as 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:

Updated results from the ongoing, single-arm, open-label phase 2 US community study (LYRA; MMY2012) of daratumumab in combination with CyBorD for the treatment of MM in transplant-eligible or ineligible patients who have not received previous therapy (NDMM) are submitted for your review.[2] These data are a follow-up to preliminary study results described in the *British Journal of Haematology*[3] publication that was included with our submission on April 30, 2019.

Treatment consisted of 4-8 induction cycles of daratumumab plus CyBorD followed by ASCT in eligible patients. All patients received maintenance therapy with daratumumab for ≥12 cycles. By the completion of therapy, overall response rate, ≥very good partial response and ≥complete response rates were 97%, 82% and 49%, respectively, in NDMM patients

who underwent ASCT and 83%, 70% and 30%, respectively, in NDMM patients who did not receive ASCT. After a median follow-up of 25.8 months, the 24-month progression-free survival (PFS) rate was 72.6% in non-transplant NDMM patients and 89.0% in NDMM patients who underwent ASCT. Common treatment-emergent adverse events (TEAEs) (≥25%) included fatigue, nausea, cough, diarrhea, upper respiratory tract infection, back pain, vomiting, insomnia, dyspnea, constipation, and headache. The most common grade 3/4 TEAE (≥10%) was neutropenia (14%). Any grade infusion-related reactions (IRRs) occurred in 56% of patients; the most common (>5%) IRRs included chills, cough, dyspnea, nausea, pruritus, flushing, and nasal congestion. Grade 3/4 IRRs occurred in 4% of patients.

The following oral presentation is submitted with the Full Prescribing Information. We would like to acknowledge the contributions of NCCN Panel members who are co-authors or co-contributors to this study.

Rifkin RM, Melear J, Faber E, et al. Daratumumab (DARA) maintenance therapy improves depth of response and results in durable progression-free survival (PFS) following DARA plus cyclophosphamide, bortezomib, and dexamethasone (CyBorD) induction therapy in multiple myeloma (MM): update of the LYRA study. Oral presentation presented at: 61st American Society of Hematology (ASH) Annual Meeting; December 7-10, 2019; Orlando, FL.

Sincerely,

Cindy Toso, PharmD
Associate Director, Payer & Health Systems, Medical Information & 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. Rifkin RM, Melear J, Faber E, et al. Daratumumab (DARA) maintenance therapy improves depth of response and results in durable progression-free survival (PFS) following DARA plus cyclophosphamide, bortezomib, and dexamethasone (CyBorD) induction therapy in multiple myeloma (MM): update of the LYRA study. Oral presentation presented at: 61st American Society of Hematology (ASH) Annual Meeting & Exposition; December 7-10, 2019; Orlando, FL.
3. Yimer H, Melear J, Faber E, et al. Daratumumab, bortezomib, cyclophosphamide and dexamethasone in newly diagnosed and relapsed multiple myeloma: LYRA study. *Br J Haematol*. 2019;185:492-502.

DARZALEX® (daratumumab)
NCCN Compendium Communication – Use in Combination with Lenalidomide, Bortezomib, and Dexamethasone - December 2019

December 19, 2019

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Date of request: December 19, 2019
NCCN Guidelines® Panel: Multiple Myeloma

Dear NCCN,

As a follow-up to our Janssen Biotech, Inc. submission on September 24, 2019, we respectfully request the NCCN Guidelines® Multiple Myeloma Panel review the enclosed updated results from the ongoing phase 2 GRIFFIN study of daratumumab in combination with lenalidomide, bortezomib, and dexamethasone (RVd) for the treatment of transplant-eligible newly diagnosed (ND) multiple myeloma (MM) patients which were presented at the 2019 American Society of Hematology Annual Meeting.

Specific Changes:
Request an update to the Guidelines to include daratumumab in combination with RVd for primary therapy of transplant candidates (MYEL-F 1 of 3; Version 2.2020) with a Category 2a evidence level rating.

FDA Clearance: The FDA has approved DARZALEX® for the treatment of adult patients with MM (1) in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy, (2) in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant (ASCT), (3) in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant, (4) in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy, (5) in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI), and (6) as 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:

Updated results from the ongoing phase 2, randomized, open-label study (GRIFFIN; MMY2004) of daratumumab + RVd (D-RVd) in patients with NDMM eligible for high-dose therapy and ASCT are submitted for your review.[2] These data are a follow-up to preliminary study results presented at the 17th International Myeloma Workshop[3] that was included with our submission on September 24th, 2019.

Patients (n=207) were randomized 1:1 to an induction phase (D-RVd or RVd [cycles 1-4]), followed by ASCT, followed by a consolidation phase (D-RVd or RVd [cycles 5-6]), followed by a maintenance phase (D-Rd or Rd [cycles 7-32]).[4] After a median follow-up of 22.1 months, D-RVd achieved higher rates of stringent complete response (sCR) (62.6% vs 45.4%; odds ratio [OR], 1.98; 95% confidence interval [CI], 1.12-3.49; 2-sided *P*=0.0177) and ≥CR (79.8% vs 60.8%, OR, 2.53; 95% CI, 1.33-4.81; 2-sided *P*=0.0045) compared with RVd. Minimal residual disease (10^{-5}) negativity in the intent-to-treat population was 51.0% with D-RVd vs 20.4% with RVd (*P*<0.0001). The 24-month progression-free survival rate was 95.8% for D-RVd vs 89.8% for RVd. Grade 3-4 treatment-emergent adverse events (≥10%) with D-RVd vs RVd included neutropenia (41% vs 22%), thrombocytopenia (16% vs 9%), leukopenia (16% vs 7%), and lymphopenia (23% vs 22%).

The following oral presentation is submitted with the Full Prescribing Information. We would like to acknowledge the contributions of NCCN Panel members who are co-authors or co-contributors to this study.

Voorhees PM, Kaufman J, Laubach JP, et al. Depth of response to daratumumab (DARA), lenalidomide, bortezomib, and dexamethasone (RVd) improves over time in patients (pts) with transplant-eligible newly diagnosed multiple myeloma (NDMM): GRIFFIN study update. Oral presentation presented at: 61st American Society of Hematology (ASH) Annual Meeting; December 7-10, 2019; Orlando, FL.

Sincerely,

Cindy Toso, PharmD
Associate Director, Payer & Health Systems, Medical Information & 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. Voorhees PM, Kaufman JL, Laubach J, et al. Depth of response to daratumumab (DARA), lenalidomide, bortezomib, and dexamethasone (RVd) improves over time in patients (pts) with transplant-eligible newly diagnosed multiple myeloma (NDMM): GRIFFIN study update. Oral presentation presented at: 61st American Society of Hematology (ASH) Annual Meeting & Exposition; December 7-10, 2019; Orlando, FL.
3. Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab + lenalidomide, bortezomib & dexamethasone improves depth of response in transplant-eligible newly diagnosed multiple myeloma: GRIFFIN. Oral presentation presented at: 17th International Myeloma Workshop (IMW); September 12-15, 2019; Boston, MA.
4. Voorhees P, Costa LJ, Reeves B, et al. Interim safety analysis of a phase 2 randomized study of daratumumab (Dara), lenalidomide (R), bortezomib (V), and dexamethasone (d; Dara-RVd). vs. RVd in patients (pts) with newly diagnosed multiple myeloma (MM) eligible for high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) (GRIFFIN). Poster presented at: The Annual Meeting of the American Society of Hematology (ASH); December 9-12, 2017; Atlanta, GA.