



U.S. FDA Approves New DARZALEX® (daratumumab)-Based Combination Regimen for Patients with Relapsed/Refractory Multiple Myeloma

August 21, 2020

Approval broadens DARZALEX label to include fifth treatment option in the relapsed/refractory setting and represents the eighth approved indication for DARZALEX

HORSHAM, Pa., August 20, 2020 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today the U.S. Food and Drug Administration (FDA) approval of DARZALEX® (daratumumab) in combination with Kyprolis® (carfilzomib) and dexamethasone (DKd) for the treatment of adult patients with relapsed/refractory multiple myeloma who have received one to three previous lines of therapy. DARZALEX® has been approved in combination with two carfilzomib dosing regimens, 70 mg/m² once weekly and 56 mg/m² twice weekly, based on positive results from the Phase 3 CANDOR and Phase 1b EQUULEUS studies, representing the first-ever approval of an anti-CD38 with carfilzomib.

“The significant increase in progression-free survival (PFS) seen among patients receiving the DKd regimen supports the use of this new combination for patients with relapsed and refractory multiple myeloma. We continue to advance effective regimens for the most critical patients who have already relapsed,” said Saad Z. Usmani, M.D., Division Chief of Plasma Cell Disorders, Atrium Health’s Levine Cancer Institute, and principal investigator of the CANDOR study. “The DKd regimen fills an important gap in the treatment landscape, as many patients may relapse following an immunomodulatory drug-based therapy, such as lenalidomide-containing regimens, and therefore new therapeutic options are needed.”

The CANDOR study is the first Phase 3 randomized trial to compare DKd versus carfilzomib and dexamethasone (Kd) in patients with relapsed/refractory multiple myeloma. The study, which administered carfilzomib twice weekly, met its primary endpoint of PFS after a median follow-up of 16.9 months and 16.3 months for the DKd and Kd arms, respectively.¹ The median PFS had not been reached in the DKd arm and was 15.8 months in the Kd arm (Hazard Ratio=0.63; 95 percent confidence interval, 0.46- 0.85; P=0.0014), representing a 37 percent reduction in the risk of disease progression or death for patients treated with DKd versus Kd.¹ The inclusion of once-weekly dosing of carfilzomib as an approved DKd regimen was supported by positive results from the open-label, multi-cohort Phase 1b EQUULEUS trial, which evaluated DARZALEX® in combination with various treatment regimens.²

“With this most recent approval of the DKd regimen, patients with multiple myeloma now have the option to receive treatment with DARZALEX and carfilzomib as early as their first relapse, which is a critical time in their treatment journey,” said Craig Tendler, M.D., Vice President, Late Development and Global Medical Affairs, Janssen Research & Development, LLC. “With our deep disease focus and commitment to develop regimens which can help improve patient outcomes for patients with relapsed multiple myeloma, the CANDOR study further establishes another DARZALEX-containing regimen (DKd) which may provide benefit for this patient population.”

In CANDOR, the safety profile of DKd was generally consistent with the known safety profiles of DARZALEX® and Kd, and reflect a median treatment duration of 16.1 months for the DKd arm and 9.3 months for the Kd arm.¹ Serious adverse events (AEs) occurred in 56 percent and 46 percent of patients who received DKd and Kd, respectively.¹ The most frequent serious AE in the DKd arm, compared with the Kd arm, was pneumonia (14 percent vs 9 percent). Fatal AEs occurred in 10 percent of DKd patients and 5 percent of Kd patients, and the most frequent fatal AE was infection (5 percent vs 3 percent).

About the CANDOR Study¹

CANDOR is a randomized, open-label Phase 3 study of DARZALEX®, carfilzomib and dexamethasone (DKd) compared to carfilzomib and dexamethasone (Kd) alone. The study evaluated 466 relapsed or refractory patients with multiple myeloma who had received one to three prior lines of therapy from 102 global sites. Patients were treated until disease progression. The primary endpoint was PFS, and the key secondary endpoints were overall response rate, minimal residual disease and overall survival. PFS was defined as time from randomization until disease progression or death from any cause.

All patients received carfilzomib as a 30-minute intravenous (IV) infusion on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle (20 mg/m² on days 1 and 2 during cycle 1 and 56 mg/m² thereafter) and received 40 mg dexamethasone oral or IV weekly (20 mg/m² for patients aged >75 years). In the treatment arm, DARZALEX® 8 mg/kg was administered IV on days 1 and 2 of cycle 1 and 16 mg/kg IV once weekly for the remaining doses of the first two cycles, then every two weeks for four cycles (cycles 3 to 6), and every four weeks thereafter. Of the patients randomized in the study, 92 percent had received a prior proteasome inhibitor, 42 percent had received prior lenalidomide, and 33 percent were lenalidomide-refractory.¹

CANDOR is an Amgen-sponsored study and is co-funded by Janssen Research & Development, LLC. For more information about this trial, please visit www.clinicaltrials.gov under trial identification number NCT03158688.

About the EQUULEUS Study

EQUULEUS is an open-label, Phase 1b, multi-cohort trial which evaluated the safety, tolerability and dosing regimen of DARZALEX®, when administered in combination with various treatment regimens for the treatment of multiple myeloma. Among the regimens evaluated, the combination of DARZALEX®, carfilzomib and dexamethasone (DKd) was studied in 85 patients with relapsed/refractory multiple myeloma who had received at least one to three prior lines of therapy. Carfilzomib was evaluated using a once-weekly dosing regimen, with a starting dose of 20 mg/m², which was increased to 70 mg/m² on Cycle 1, Day 8 and onward.

About DARZALEX®

Janssen is committed to exploring the potential of DARZALEX® (daratumumab) for patients with multiple myeloma (MM) across the spectrum of the disease. DARZALEX® has been approved in eight indications, three of which are in the frontline setting, including newly diagnosed patients with MM

who are transplant eligible and ineligible.

In [August 2012](#), Janssen entered into an exclusive global license and development agreement with Genmab A/S to develop, manufacture, and commercialize DARZALEX®.³ DARZALEX® has become a backbone therapy in the treatment of multiple myeloma, having been used in the treatment of more than 143,000 patients worldwide and more than 68,000 patients in the U.S. alone since its U.S. FDA approval in 2015. DARZALEX® is the first CD38-directed antibody approved globally to treat MM.

CD38 is a surface protein that is present in high numbers on multiple myeloma cells, regardless of the stage of disease.⁴ DARZALEX® binds to CD38 and inhibits tumor cell growth causing myeloma cell death.⁵ DARZALEX® may also have an effect on normal cells.⁴ Data across seven Phase 3 clinical trials, in both the frontline and relapsed settings, have shown that DARZALEX®-based regimens resulted in significant improvement in progression-free survival and/or overall survival.^{5,6,7,8,9,10,11,12}

Please see full Prescribing Information at www.DARZALEX.com.

About Multiple Myeloma

Multiple myeloma is an incurable blood cancer that affects a type of white blood cell called plasma cells, which are found in the bone marrow.^{13,14} When damaged, these plasma cells rapidly spread and replace normal cells with tumors in the bone marrow. In 2020, it is estimated that more than 32,000 people will be diagnosed and close to 13,000 will die from the disease in the U.S.²⁴ While some patients with multiple myeloma have no symptoms, most patients are diagnosed due to symptoms, which can include bone fracture or pain, low red blood cell counts, tiredness, high calcium levels, kidney problems or infections.¹⁵

DARZALEX® IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

DARZALEX® is contraindicated in patients with a history of severe hypersensitivity (eg, anaphylactic reactions) to daratumumab or any of the components of the formulation.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

DARZALEX® can cause severe and/or serious infusion-related reactions including anaphylactic reactions. In clinical trials (monotherapy and combination: N=2066), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX®. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, laryngeal edema, and pulmonary edema. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting, and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, and hypotension.

When DARZALEX® dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range to 2.4; 6.9 months), upon re-initiation of DARZALEX®, the incidence of infusion-related reactions was 11% for the first infusion following ASCT. Infusion-related reactions occurring at re-initiation of DARZALEX® following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4: <1%) with those reported in previous studies at Week 2 or subsequent infusions. In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days, ie, 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt DARZALEX® infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX® therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX® infusions. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease.

Interference With Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive Indirect Antiglobulin Test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type is not impacted. Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX®. Type and screen patients prior to starting DARZALEX®.

Neutropenia and Thrombocytopenia

DARZALEX® may increase neutropenia and thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX® until recovery of neutrophils or for recovery of platelets.

Interference With Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX® can cause fetal harm when administered to a pregnant woman. DARZALEX® may cause depletion

of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX® and for 3 months after the last dose.

The combination of DARZALEX® with lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women, because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

ADVERSE REACTIONS

The most frequently reported adverse reactions (incidence $\geq 20\%$) were: upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia. The most common hematologic laboratory abnormalities ($\geq 40\%$) with DARZALEX® are: neutropenia, lymphopenia, thrombocytopenia, leukopenia, and anemia.

Please [click here](#) to see the full Prescribing Information.

About the Janssen Pharmaceutical Companies of Johnson & Johnson

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular & Metabolism, Immunology, Infectious Diseases & Vaccines, Neuroscience, Oncology, and Pulmonary Hypertension.

Learn more at www.janssen.com. Follow us at www.twitter.com/JanssenGlobal and www.twitter.com/JanssenUS. Janssen Research & Development, LLC and Janssen Biotech, Inc. are part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding DARZALEX®. The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Biotech, Inc. and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended December 29, 2019, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's most recently filed Quarterly Report on Form 10-Q, and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, <https://www.jnj.com> or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

#

¹ Saad Z. Usmani, MD et al. Carfilzomib, Dexamethasone, and Daratumumab Versus Carfilzomib and Dexamethasone for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma (RRMM): Primary Analysis Results from the Randomized, Open-label, Phase 3 Study CANDOR (NCT03158688). 2019 American Society of Hematology Annual Meeting. December 2019.

² Janssen Research & Development, LLC. A Study of JNJ-54767414 (HuMax CD38) (Anti-CD38 Monoclonal Antibody) in Combination With Backbone Treatments for the Treatment of Patients With Multiple Myeloma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2018 July 24]. Available at: <https://clinicaltrials.gov/ct2/show/NCT01998971> Identifier: NCT01998971

³ Janssen Biotech, Inc. "Janssen Biotech Announces Global License and Development Agreement for Investigational Anti-Cancer Agent Daratumumab." Issued August 30, 2012.

⁴ 2020 Fedele G et al. CD38 Ligation in Peripheral Blood Mononuclear Cells of Myeloma Patients Induces Release of Protumorigenic IL-6 and Impaired Secretion of IFN γ Cytokines and Proliferation. *Mediators Inflamm.* 2013;564687.

⁵ Janssen Research & Development, LLC. A Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Relapsed or Refractory Multiple Myeloma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2018 July 24]. Available at: <https://clinicaltrials.gov/ct2/show/NCT02076009?term=mmymy3003&rank=1> Identifier: NCT02136134.

⁶ Janssen Research & Development, LLC. Addition of Daratumumab to Combination of Bortezomib and Dexamethasone in Participants With Relapsed or Refractory Multiple Myeloma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2018 July 24]. Available at: <https://clinicaltrials.gov/ct2/show/NCT02136134?term=mmymy3004&rank=1> Identifier: NCT02076009.

⁷ Janssen Research & Development, LLC. A Study to Evaluate Daratumumab in Transplant Eligible Participants With Previously Untreated Multiple Myeloma (Cassiopeia). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2018 July 24]. Available at: <https://clinicaltrials.gov/ct2/show/NCT02541383?term=mmymy3006> Identifier: NCT02541383.

⁸ Janssen Research & Development, LLC. A Study of Combination of Daratumumab and Velcade (Bortezomib) Melphalan-Prednisone (DVMP) Compared to Velcade Melphalan-Prednisone (VMP) in Participants With Previously Untreated Multiple Myeloma In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2018 July 24]. Available at: <https://clinicaltrials.gov/ct2/show/NCT02195479?term=mmymy3007&rank=1> Identifier: NCT02195479.

⁹ Janssen Research & Development, LLC. Study Comparing Daratumumab, Lenalidomide, and Dexamethasone With Lenalidomide and Dexamethasone in Participants With Previously Untreated Multiple Myeloma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2018 July 24]. Available at: <https://clinicaltrials.gov/ct2/show/NCT02252172?term=mmymy3008&rank=1> Identifier: NCT02252172.

¹⁰ Janssen Research & Development, LLC. A Study of VELCADE (Bortezomib) Melphalan-Prednisone (VMP) Compared to Daratumumab in

Combination With VMP (D-VMP), in Participants With Previously Untreated Multiple Myeloma Who Are Ineligible for High-Dose Therapy (Asia Pacific Region). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2018 July 24]. Available at:

<https://clinicaltrials.gov/ct2/show/NCT03217812?term=MMY3011&rank=1> Identifier: NCT03217812.

¹¹ European Myeloma Network. Compare Progression Free Survival Btw Daratumumab/Pomalidomide/Dexamethasone vs Pomalidomide/Dexamethasone (EMN14). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2018 July 24] Available at: <https://clinicaltrials.gov/ct2/show/NCT03180736?term=MMY3013&rank=2> Identifier: NCT03180736

¹² Amgen. Study of Carfilzomib, Daratumumab and Dexamethasone for Patients With Relapsed and/or Refractory Multiple Myeloma. (CANDOR). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000-[cited 2018 July 24] Available at: <https://clinicaltrials.gov/ct2/show/NCT03158688?term=NCT03158688&rank=1> Identifier: NCT03158688.

¹³ Kumar, SK et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter international myeloma working group study. Leukemia. 2012 Jan; 26(1):149-57.

¹⁴ American Cancer Society. "What Is Multiple Myeloma?" Available at: <http://www.cancer.org/cancer/multiplemyeloma/detailedguide/multiple-myeloma-what-is-multiple-myeloma>. Accessed June 2019.

¹⁵ American Cancer Society. "Key Statistics About Multiple Myeloma." Available at: <https://www.cancer.org/cancer/multiple-myeloma/about/key-statistics.html>. Accessed January 2020.