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BEST PRACTICES

Multiple Myeloma: Daratumumab-Lenalidomide/Dexamethasone Combination - A New Treatment Option for Newly Diagnosed, Transplant-Ineligible Patients

Introduction

Multiple myeloma (MM) is a neoplastic disease characterized by the proliferation of abnormal bone marrow plasma cells and immunoglobulin or light chain overproduction that can lead to end-organ damage.[1] It is estimated that more than 32,000 individuals will be diagnosed with multiple myeloma in 2019, and nearly 13,000 deaths from multiple myeloma are expected to occur.[2] Multiple myeloma is the second-most common blood cancer.[3]

At the turn of the century, median survival of patients with multiple myeloma was only ~2.5 years.[1] Since then, improvements in overall medical care, including autologous stem cell transplant (ASCT) and the introduction of novel agents, have coincided with increased survival estimates for MM patients to between 5 and 7 years.[1] These novel agents include:

- Proteasome inhibitors—including bortezomib, carfilzomib, and ixazomib—which work to stop proteasomes in cells from breaking down proteins needed to control cell division[4]
- Immunomodulatory agents—including thalidomide, lenalidomide, and pomalidomide; their mechanism of action is not clearly understood[4]

Despite these advancements, long-term control of multiple myeloma remains challenging, as patients often relapse or become refractory to the treatments.

Daratumumab: An Important Treatment Option

Against this backdrop, researchers sought to fill a continuing need for new treatment options for relapsed and refractory individuals.[5] Daratumumab (DARZALEX®) emerged as one of these potential options. A key reason: the CD38 molecule, a target molecule of daratumumab, is expressed at a high level by myeloma cells.[5]

Mechanism of Action

Daratumumab is an immunoglobulin G1 kappa human monoclonal antibody that binds to CD38, a transmembrane glycoprotein that is expressed on the surface of hematopoietic cells, and is overexpressed on multiple myeloma cells.[6] Preclinical studies have shown daratumumab's mechanism of action produces both:

- Direct on-tumor activity
- Immunomodulatory actions[7]

Daratumumab may also affect normal cells.[7]

Daratumumab was first approved as a monotherapy for 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 an immunomodulatory agent. Daratumumab has since been approved for use in other combination treatments in multiple myeloma. Of note, the initial approval of the daratumumab/lenalidomide/dexamethasone combination (D-Rd) was based on results from the POLLUX trial, a Phase 3 randomized study that compared it with lenalidomide and dexamethasone (Rd) alone in patients with relapsed or refractory multiple myeloma.

Daratumumab for Patients Newly Diagnosed with MM: MAIA Trial

Based on the positive results seen with D-Rd in patients who have received at least one prior therapy, researchers evaluated the combination as a first-line treatment in newly diagnosed patients with multiple myeloma who are ineligible for autologous stem cell transplant.

Indication

DARZALEX® is a CD38-directed cytolytic antibody indicated for the treatment of adult patients with multiple myeloma:

- 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
- In combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- In combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- In combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor
- As monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent

Important Safety Information

CONTRAINDICATIONS

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

See additional Important Safety Information continued on next page and Brief Summary on adjacent pages.

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The results from the randomized Phase 3 MAIA trial were published in *The New England Journal of Medicine*, and the U.S. Food and Drug Administration approved D-Rd for newly diagnosed patients with multiple myeloma who are ineligible for transplant in June 2019.[9] Additionally, the National Comprehensive Cancer Network® (NCCN®) recommends D-Rd as a preferred primary therapy for non-transplant candidates with a category 1 therapy recommendation.[10]

MAIA comprised 737 individuals whose median age was 73.[9] It is important to note that more than 40% of the study population was aged 75 years and older.[9] Participants received either D-Rd (n=368) or Rd (n=369).[9] The D-Rd group received[9]:

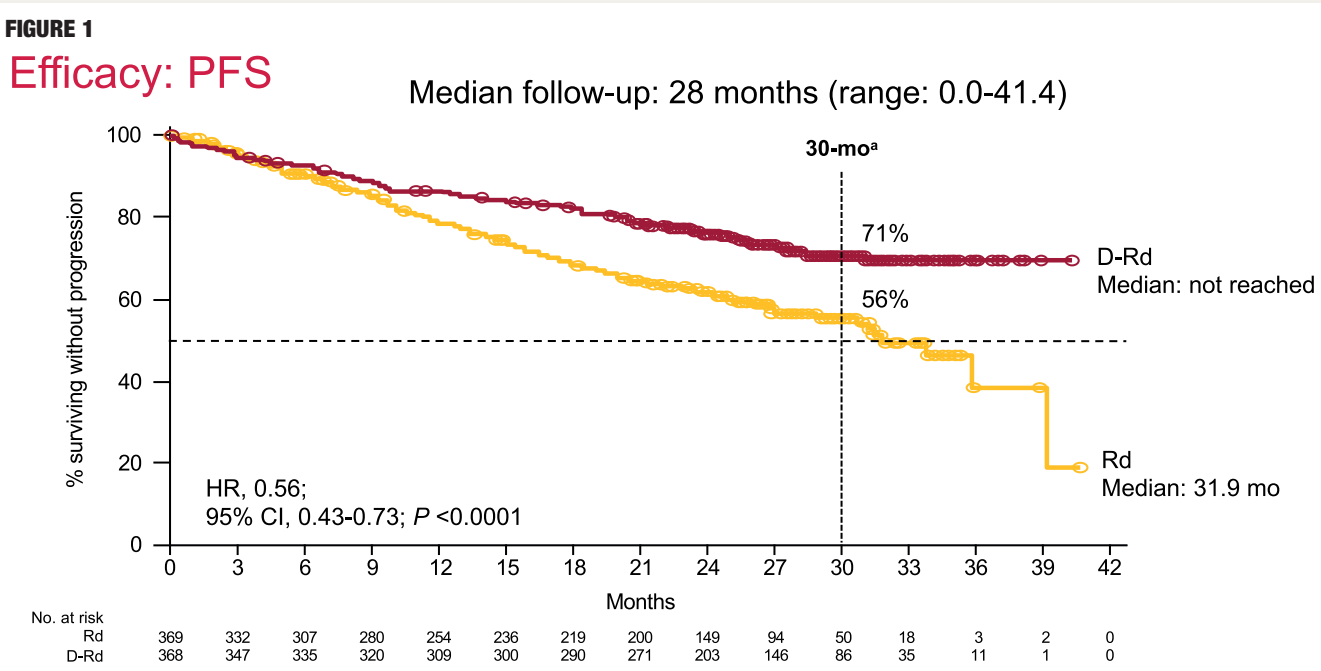
- 16 mg/kg of daratumumab intravenously (IV) once a week during the first two cycles, every two weeks for the next four cycles, and every four weeks thereafter until the disease progression
- Lenalidomide 25 mg orally on days 1 through 21 until disease progression
- Dexamethasone 40 mg orally or IV weekly until disease progression

The Rd contingent received just lenalidomide and dexamethasone at the same dosages and on the same regimens as the D-Rd cohort.[9] Investigators looked primarily at progression-free survival (PFS), as well as overall response rate (ORR) and the impact of minimal residual disease (MRD).[9]

Daratumumab + Rd's Efficacy in Newly Diagnosed MM

Superior Progression-Free Survival Compared with Rd Alone…

FIGURE 1



44% reduction in the risk of progression or death in patients receiving D-Rd

Abbreviations: D-Rd, daratumumab/lenalidomide/dexamethasone combination; Rd, lenalidomide and dexamethasone.
[a]Kaplan-Meier estimate.

At a median follow-up of 28 months, patients who received the D-Rd regimen experienced a 44% reduction in the risk of disease progression or death vs. Rd alone (hazard ratio [HR] 0.56; 95% confidence interval [CI], 0.43-0.73; $P<0.001$). Median PFS in the D-Rd group had not yet been reached at the time of the analysis vs. nearly 32 months in the Rd contingent.[9] See **Figure 1** for details.

Significantly Higher Overall Response Rate Seen for Daratumumab…

The D-Rd group also achieved a significantly higher overall response rate (93%) than the group that received Rd (81%).[9] Moreover, nearly half of the D-Rd patients attained a complete response (defined as no detectable disease in the blood or urine and <5% cancerous cells in the bone marrow), compared with just one-fourth of those receiving Rd (47.6% vs. 24.9%, respectively).[9] Additionally, 79% in the D-Rd cohort achieved a very good partial response (defined as a reduction of ≥90% of M protein in the blood and urine) vs. 53% of Rd patients.[9] See **Figure 2** for details.

…Along with Deep and Durable/ Higher MRD Negativity Rates

Importantly, deeper responses were observed in the form of higher rates of MRD negativity. Specifically, 24% of patients in the D-Rd group attained MRD-negativity compared with 7% of the Rd contingent.[9] This 3-fold higher MRD-negativity rate in individuals receiving D-Rd is a significant development. See **Figure 2** for details.

Adverse reactions reflect exposure to DARZALEX for a median treatment duration of 25.3 months (range: 0.1 to 40.44 months) for the D-Rd group and median treatment duration of

More than 40% of patients in the trial population were 75 years of age or older.

—Saad Z. Usmani, MD, FACP

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

Infusion Reactions – DARZALEX® can cause severe and/or serious infusion reactions, including anaphylactic reactions. In clinical trials, approximately half of all patients experienced an infusion reaction. Most infusion reactions occurred during the first infusion and were Grade 1-2. Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX®. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion. 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.

See additional Important Safety Information continued on next page and Brief Summary on adjacent pages.

21.3 months (range: 0.03 to 40.64 months) for the lenalidomide-dexamethasone (Rd) group in the Phase 3 active controlled MAIA study. The most frequent (≥20%) adverse reactions were infusion reactions, diarrhea, constipation, nausea, peripheral edema, fatigue, back pain, asthenia, pyrexia, upper respiratory tract infection, bronchitis, pneumonia, decreased appetite, muscle spasms, peripheral sensory neuropathy, dyspnea and cough.

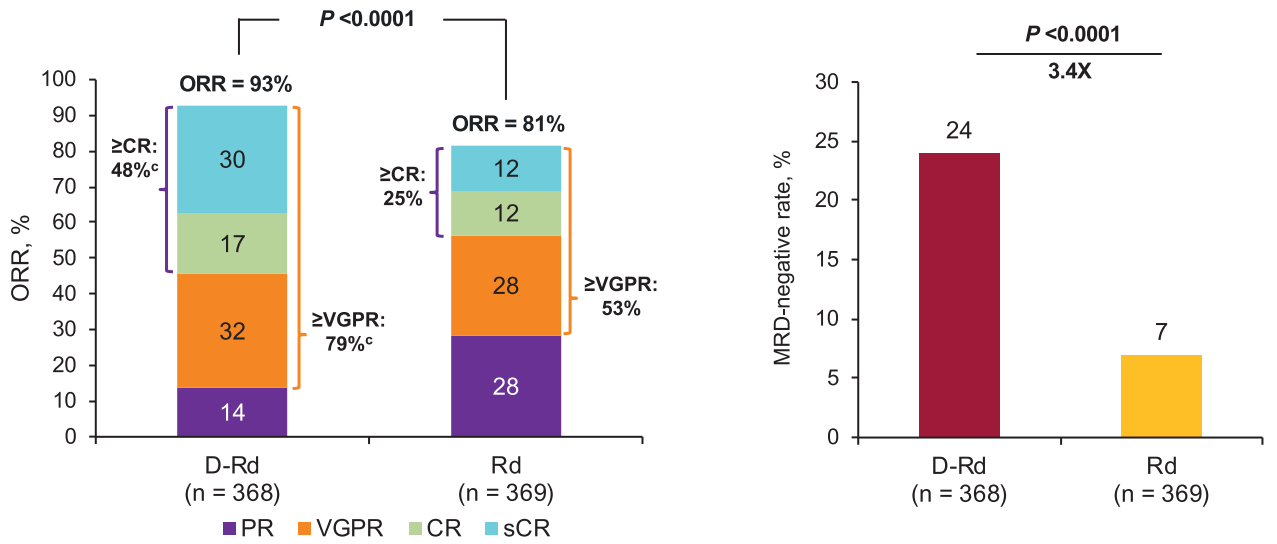
●●●

D-Rd is a new therapy approved by the FDA for newly diagnosed patients with MM who are not eligible for an autologous stem cell transplant.

—Saad Z. Usmani, MD, FACP

FIGURE 2

Efficacy: ORR[a] and MRD[b] (NGS; 10^{-5} Sensitivity Threshold)



Significantly higher ORR, ≥CR rate, ≥VGPR rate, and MRD-negative rate with D-Rd

Abbreviations: CR, complete response; D-Rd, daratumumab/lenalidomide/dexamethasone combination; MRD, minimal residual disease; NGS, next generation sequencing; ORR, objective response rate; PR, partial response; Rd, lenalidomide and dexamethasone; sCR, stringent complete response; VGPR, very good partial response..

[a]ITT population. [b]Assessed at time of confirmation of CR/sCR and, if confirmed, at 12, 18, 24, and 30 months after first dose. [c]*P* <0.0001. *P* values were calculated using the Cochran–Mantel–Haenszel chi-square test.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

Infusion Reactions (continued)
Pre-medicate patients with antihistamines, antipyretics, and corticosteroids. Frequently monitor patients during the entire infusion. Interrupt infusion for reactions of any severity and institute medical management as needed. Permanently discontinue 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 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 are 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/or thrombocytopenia induced by background therapy. Monitor complete blood cell counts periodically during treatment according to the manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. DARZALEX® dose delay may be required to allow recovery of neutrophils and/or platelets. No dose reduction of DARZALEX® is recommended. Consider supportive care with growth factors for neutropenia or transfusions for thrombocytopenia.

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.

Adverse Reactions – The most frequently reported adverse reactions (incidence ≥20%) were: infusion reactions, neutropenia, thrombocytopenia, fatigue, asthenia, nausea, diarrhea, constipation, decreased appetite, vomiting, muscle spasms, arthralgia, back pain, pyrexia, chills, dizziness, insomnia, cough, dyspnea, peripheral edema, peripheral sensory neuropathy, bronchitis, pneumonia, and upper respiratory tract infection.

See additional Important Safety Information continued on next page and Brief Summary on adjacent pages.

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Serious adverse reactions with a 2% greater incidence in the D-Rd arm compared to the Rd arm were pneumonia (D-Rd 15% vs. Rd 8%), bronchitis (D-Rd 4% vs. Rd 2%) and dehydration (D-Rd 2% vs. Rd <1%).[6]

Conclusion

The results of the MAIA trial offer hope to fill an unmet need for treatment options for patients newly diagnosed with multiple myeloma who are ineligible for autologous stem cell transplant. The findings support D-Rd as a new treatment option for such individuals.[7] When compared with lenalidomide/dexamethasone treatment alone, adding daratumumab to lenalidomide/dexamethasone[9]:

- Significantly reduced the risk of disease progression or death by 44% (at median follow-up of 28 months, 240 events of disease progression or death [26.4% in D-Rd arm and 38.8% in the Rd arm] had occurred)
- Induced significantly deeper responses, including a >3-fold higher MRD-negative rate (24% vs. 7%, respectively)
- Enabled nearly half of patients taking it to achieve a complete response (48% vs. 25%, respectively) or stringent complete response (30% vs. 12%, respectively).

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IMPORTANT SAFETY INFORMATION (continued)

Adverse Reactions (continued)

DARZALEX® in combination with lenalidomide and dexamethasone (DRd): The most frequent (≥20%) adverse reactions for newly diagnosed or relapsed/refractory patients were, respectively, infusion reactions (41%, 48%), diarrhea (57%, 43%), nausea (32%, 24%), fatigue (40%, 35%), pyrexia (23%, 20%), upper respiratory tract infection (52%, 65%), muscle spasms (29%, 26%), dyspnea (32%, 21%), and cough (30%, 30%). In newly diagnosed patients, constipation (41%), peripheral edema (41%), back pain (34%), asthenia (32%), bronchitis (29%), pneumonia (26%), peripheral sensory neuropathy (24%), and decreased appetite (22%) were also reported. In newly diagnosed patients, serious adverse reactions (≥2% compared to Rd) were pneumonia (15%), bronchitis (4%), and dehydration (2%), and treatment-emergent Grade 3-4 hematology laboratory abnormalities (≥20%) were neutropenia (56%), lymphopenia (52%), and leukopenia (35%). In relapsed/refractory patients, serious adverse reactions (≥2% compared to Rd) were pneumonia (12%), upper respiratory tract infection (7%), influenza (3%), and pyrexia (3%), and treatment-emergent Grade 3-4 hematology laboratory abnormalities (≥20%) were neutropenia (53%) and lymphopenia (52%).

DARZALEX® in combination with bortezomib, melphalan, and prednisone (DVMP): The most frequently reported adverse reactions (≥20%) were upper respiratory tract infection (48%), infusion reactions (28%), and peripheral edema (21%). Serious adverse reactions (≥2% compared to the VMP arm) were pneumonia (11%), upper respiratory tract infection (5%), and pulmonary edema (2%). Treatment-emergent Grade 3-4 hematology laboratory abnormalities (≥20%) were lymphopenia (58%), neutropenia (44%), and thrombocytopenia (38%).

DARZALEX® in combination with bortezomib and dexamethasone (DVd): The most frequently reported adverse reactions (≥20%) were peripheral sensory neuropathy (47%), infusion reactions (45%), upper respiratory tract infection (44%), diarrhea (32%), cough (27%), peripheral edema (22%), and dyspnea (21%). The overall incidence of serious adverse reactions was 42%. Serious adverse reactions (≥2% compared to Vd) were upper respiratory tract infection (5%), diarrhea (2%), and atrial fibrillation (2%). Treatment-emergent Grade 3-4 hematology laboratory abnormalities (≥20%) were lymphopenia (48%) and thrombocytopenia (47%).

DARZALEX® in combination with bortezomib, thalidomide, and dexamethasone (DVTd): The most frequent adverse reactions (≥20%) were infusion reactions (35%), nausea (30%), upper respiratory tract infection (27%), pyrexia (26%), and bronchitis (20%). Serious adverse reactions (≥2% compared to the VTd arm) were bronchitis (DVTd 2% vs VTd <1%) and pneumonia (DVTd 6% vs VTd 4%). Treatment-emergent Grade 3-4 hematology laboratory abnormalities (≥20%) were lymphopenia (59%), neutropenia (33%), and leukopenia (24%).

DARZALEX® in combination with pomalidomide and dexamethasone (DPd): The most frequent adverse reactions (>20%) were fatigue (50%), infusion reactions (50%), upper respiratory tract infection (50%), cough (43%), diarrhea (38%), constipation (33%), dyspnea (33%), nausea (30%), muscle spasms (26%), back pain (25%), pyrexia (25%), insomnia (23%), arthralgia (22%), dizziness (21%), and vomiting (21%). The overall incidence of serious adverse reactions was 49%. Serious adverse reactions reported in ≥5% of patients included pneumonia (7%). Treatment-emergent Grade 3-4 hematology laboratory abnormalities (≥20%) were neutropenia (82%), lymphopenia (71%), and anemia (30%).

DARZALEX® as monotherapy: The most frequently reported adverse reactions (≥20%) were infusion reactions (48%), fatigue (39%), nausea (27%), back pain (23%), pyrexia (21%), cough (21%), and upper respiratory tract infection (20%). The overall incidence of serious adverse reactions was 33%. The most frequent serious adverse reactions were pneumonia (6%), general physical health deterioration (3%), and pyrexia (3%). Treatment-emergent Grade 3-4 hematology laboratory abnormalities (≥20%) were lymphopenia (40%) and neutropenia (20%).

Please see the Brief Summary on the adjacent pages.

cp-60862v3

DARZALEX® (daratumumab) injection, for intravenous use
Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

DARZALEX is indicated for the treatment of adult patients with multiple myeloma:

- 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.
- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant.
- in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy.
- in combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.
- as monotherapy, in patients 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 an immunomodulatory agent.

CONTRAINDICATIONS

DARZALEX is contraindicated in patients with a history of severe hypersensitivity (e.g. anaphylactic reactions) to daratumumab or any of the components of the formulation *[see Warnings and Precautions and Adverse Reactions]*.

WARNINGS AND PRECAUTIONS

Infusion Reactions: DARZALEX can cause severe and/or serious infusion reactions including anaphylactic reactions. In clinical trials, approximately half of all patients experienced an infusion reaction. Most infusion reactions occurred during the first infusion and were Grade 1-2 *[see Adverse Reactions]*.

Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion.

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 *[see Adverse Reactions]*.

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 *[see Dosage and Administration (2.1) in Full Prescribing Information]*.

To reduce the risk of delayed infusion reactions, administer oral corticosteroids to all patients following DARZALEX infusions *[see Dosage and Administration (2.2) in Full Prescribing Information]*. 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 *[see References]*. The determination of a patient's ABO and Rh blood type are not impacted *[see Drug Interactions]*.

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: DARZALEX may increase neutropenia induced by background therapy *[see Adverse Reactions]*.

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. DARZALEX dose delay may be required to allow recovery of neutrophils. No dose reduction of DARZALEX is recommended. Consider supportive care with growth factors.

Thrombocytopenia: DARZALEX may increase thrombocytopenia induced by background therapy *[see Adverse Reactions]*.

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. DARZALEX dose delay may be required to allow recovery of platelets. No dose reduction of DARZALEX is recommended. Consider supportive care with transfusions.

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 *[see Drug Interactions]*. This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

ADVERSE REACTIONS

The following clinically significant adverse reactions are also described elsewhere in the labeling:

- Infusion reactions *[see Warning and Precautions]*.
- Neutropenia *[see Warning and Precautions]*.
- Thrombocytopenia *[see Warning and Precautions]*.

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflects exposure to DARZALEX (16 mg/kg) in 2,066 patients with multiple myeloma including 1,910 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy.

Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant

Combination Treatment with Lenalidomide and Dexamethasone (DRd)

Adverse reactions described in the table below reflect exposure to DARZALEX for a median treatment duration of 25.3 months (range: 0.1 to 40.44 months) for the daratumumab-lenalidomide-dexamethasone (DRd) group and median treatment duration of 21.3 months (range: 0.03 to 40.64 months) for the lenalidomide-dexamethasone group (Rd) in a Phase 3 active-controlled study MAIA. The most frequent (≥20%) adverse reactions were infusion reactions, diarrhea, constipation, nausea, peripheral edema, fatigue, back pain, asthenia, pyrexia, upper respiratory tract infection, bronchitis, pneumonia, decreased appetite, muscle spasms, peripheral sensory neuropathy, dyspnea and cough. Serious adverse reactions with a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%) and dehydration (DRd 2% vs Rd <1%).

Table 1: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in MAIA

Body System Adverse Reaction	DRd (N=364)			Rd (N=365)		
	Any Grade (%)	Grade 3 (%)	Grade 4 (%)	Any Grade (%)	Grade 3 (%)	Grade 4 (%)
Infusion reactions[a]	41	2	<1	0	0	0
Gastrointestinal disorders						
Diarrhea	57	7	0	46	4	0
Constipation	41	1	<1	36	<1	0
Nausea	32	1	0	23	1	0
Vomiting	17	1	0	12	<1	0
General disorders and administration site conditions						
Peripheral edema[b]	41	2	0	33	1	0
Fatigue	40	8	0	28	4	0
Asthenia	32	4	0	25	3	<1
Pyrexia	23	2	0	18	2	0
Chills	13	0	0	2	0	0
Infections and infestations						
Upper respiratory tract infection[c]	52	2	<1	36	2	<1
Bronchitis[d]	29	3	0	21	1	0
Pneumonia[e]	26	14	1	14	7	1
Urinary tract infection	18	2	0	10	2	0
Metabolism and nutrition disorders						
Decreased appetite	22	1	0	15	<1	<1
Hyperglycemia	14	6	1	8	3	1
Hypocalcemia	14	1	<1	9	1	1
Musculoskeletal and connective tissue disorders						
Back pain	34	3	<1	26	3	<1
Muscle spasms	29	1	0	22	1	0
Nervous system disorders						
Peripheral sensory neuropathy	24	1	0	15	0	0
Headache	19	1	0	11	0	0
Paresthesia	16	0	0	8	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnea[f]	32	3	<1	20	1	0
Cough[g]	30	<1	0	18	0	0
Vascular disorders						
Hypertension[h]	13	6	<1	7	4	0

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see section on Infusion Reactions below

[b] Generalized edema, Gravitational edema, Edema, Peripheral edema, Peripheral swelling

[c] Acute sinusitis, Bacterial rhinitis, Laryngitis, Metapneumovirus infection, Nasopharyngitis, Oropharyngeal candidiasis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinusitis, Tonsillitis, Tracheitis, Upper respiratory tract infection, Viral pharyngitis, Viral rhinitis, Viral upper respiratory tract infection

[d] Bronchiolitis, Bronchitis, Bronchitis viral, Respiratory syncytial virus bronchiolitis, Tracheobronchitis

[e] Atypical pneumonia, Bronchopulmonary aspergillosis, Lung infection, Pneumocystis jirovecii infection, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia aspiration, Pneumonia pneumococcal, Pneumonia viral, Pulmonary mycosis

[f] Dyspnea, Dyspnea exertional

[g] Cough, Productive cough

[h] Blood pressure increased, Hypertension

Laboratory abnormalities worsening during treatment from baseline listed in Table 2.

Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

	DRd (N=364) %			Rd (N=365) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Anemia	47	13	0	57	24	0
Thrombocytopenia	67	6	3	58	7	4
Leukopenia	90	30	5	82	20	4
Neutropenia	91	39	17	77	28	11
Lymphopenia	84	41	11	75	36	6

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

Combination Treatment with Bortezomib, Melphalan and Prednisone

Adverse reactions described in Table 3 reflect exposure to DARZALEX for a median treatment duration of 14.7 months (range: 0 to 25.8 months) for the daratumumab, bortezomib, melphalan and prednisone (D-VMP) group, and median treatment duration of 12 months (range: 0.1 to 14.9 months) for the VMP group in a Phase 3 active-controlled study ALCYONE. The most frequent adverse reactions (≥20% with at least 5% greater frequency in the D-VMP arm) were infusion reactions, upper respiratory tract infection and edema peripheral. Serious adverse reactions with at least a 2% greater incidence in the D-VMP arm compared to the VMP arm were pneumonia (D-VMP 11% vs VMP 4%), upper respiratory tract infection (D-VMP 5% vs VMP 1%), and pulmonary edema (D-VMP 2% vs VMP 0%).

Table 3: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the D-VMP Arm in ALCYONE

Body System Adverse Reaction	D-VMP (N=346)			VMP (N=354)		
	Any Grade (%)	Grade 3 (%)	Grade 4 (%)	Any Grade (%)	Grade 3 (%)	Grade 4 (%)
Infusion reactions[a]	28	4	1	0	0	0
General disorders and administration site conditions						
Edema peripheral[b]	21	1	< 1	14	1	0
Infections and infestations						
Upper respiratory tract infection[c]	48	5	0	28	3	0
Pneumonia[d]	16	12	< 1	6	5	< 1
Respiratory, thoracic and mediastinal disorders						
Cough[e]	16	< 1	0	8	< 1	0
Dyspnea[f]	13	2	1	5	1	0
Vascular disorders						
Hypertension[g]	10	4	< 1	3	2	0

Key: D=daratumumab, VMP=bortezomib-melphalan-prednisone

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see section on Infusion Reactions below.

[b] edema peripheral, generalized edema, peripheral swelling

[c] upper respiratory tract infection, bronchitis, bronchitis bacterial, epiglottitis, laryngitis, laryngitis bacterial, metapneumovirus infection, nasopharyngitis, oropharyngeal candidiasis, pharyngitis, pharyngitis streptococcal, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tonsillitis, tracheitis, tracheobronchitis, viral pharyngitis, viral rhinitis, viral upper respiratory tract infection.

[d] pneumonia, lung infection, pneumonia aspiration, pneumonia bacterial, pneumonia pneumococcal, pneumonia streptococcal, pneumonia viral, and pulmonary sepsis

[e] cough, productive cough

[f] dyspnea, dyspnea exertional

[g] hypertension, blood pressure increased

Laboratory abnormalities worsening during treatment from baseline listed in Table 4.

Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in ALCYONE

	D-VMP (N=346) %			VMP (N=354) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Anemia	47	18	0	50	21	0
Thrombocytopenia	88	27	11	88	26	16
Neutropenia	86	34	10	87	32	11
Lymphopenia	85	46	12	83	44	9

Key: D=daratumumab, VMP=bortezomib-melphalan-prednisone

Newly Diagnosed Multiple Myeloma Eligible for Autologous Stem Cell Transplant

Combination Treatment with Bortezomib, Thalidomide and Dexamethasone (DVTd)

Adverse reactions described in Table 5 reflect exposure to DARZALEX up to day 100 post-transplant in a Phase 3 active-controlled study CASSIOPEIA *[see Clinical Studies (14.1) in Full Prescribing Information]*. The median duration of induction/ASCT/consolidation treatment was 8.9 months (range: 7.0 to 12.0 months) for the DVTd group and 8.7 months (range: 6.4 to 11.5 months) for the VTd group. The most frequent adverse reactions (>20% with at least 5% greater frequency in the DVTd group) were infusion reactions, nausea, pyrexia, upper respiratory tract infection and bronchitis. Serious adverse reactions with a 2% greater incidence in the DVTd arm compared to the VTd arm were bronchitis (DVTd 2% vs VTd <1%) and pneumonia (DVTd 6% vs VTd 4%).

Table 5: Adverse Reactions Reported in ≥ 10% of Patients and With at Least a 5% Greater Frequency in the DVTd Arm in CASSIOPEIA

Body System Adverse Reaction	DVTd (N=536)			VTd (N=538)		
	Any Grade (%)	Grade 3 (%)	Grade 4 (%)	Any Grade (%)	Grade 3 (%)	Grade 4 (%)
Infusion reactions[a]	35	3	<1	0	0	0
Gastrointestinal disorders						
Nausea	30	4	0	24	2	<1
Vomiting	16	2	0	10	2	0
General disorders and administration site conditions						
Pyrexia	26	2	<1	21	2	0
Infections and infestations						
Upper respiratory tract infection[b]	27	1	0	17	1	0
Bronchitis[c]	20	1	0	13	1	0
Respiratory, thoracic and mediastinal disorders						
Cough[d]	17	0	0	9	0	0
Vascular disorders						
Hypertension	10	4	0	5	2	0

Key: D=daratumumab, VTd=bortezomib-thalidomide -dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see section on Infusion Reactions below

[b] Laryngitis, Laryngitis viral, Metapneumovirus infection, Nasopharyngitis, Oropharyngeal candidiasis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinusitis, Tonsillitis, Tracheitis, Upper respiratory tract infection, Viral pharyngitis, Viral rhinitis, Viral upper respiratory tract infection

[c] Bronchiolitis, Bronchitis, Bronchitis chronic, Respiratory syncytial virus bronchitis, Tracheobronchitis

[d] Cough, Productive cough

Note: Hematology laboratory related toxicities were excluded and reported separately in the table below

Table 6: Treatment-Emergent Hematology Laboratory Abnormalities in CASSIOPEIA

	DVTd (N=536) %			VTd (N=538) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Anemia	36	4	0	35	5	0
Thrombocytopenia	81	9	5	58	8	3
Leukopenia	82	14	10	57	6	9
Neutropenia	63	19	14	41	10	9
Lymphopenia	95	44	15	91	37	10

Key: D=daratumumab, VTd=bortezomib-thalidomide -dexamethasone.

Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide and Dexamethasone

Adverse reactions described in Table 7 reflect exposure to DARZALEX for a median treatment duration of 13.1 months (range: 0 to 20.7 months) for the daratumumab-lenalidomide-dexamethasone (DRd) group and median treatment duration of 12.3 months (range: 0.2 to 20.1 months) for the lenalidomide-dexamethasone (Rd) group in a Phase 3 active-controlled study POLLUX. The most frequent adverse reactions (≥20%) were infusion reactions, diarrhea, nausea, fatigue, pyrexia, upper respiratory tract infection, muscle spasms, cough and dyspnea. The overall incidence of serious adverse reactions was 49% for the DRd group compared with 42% for the Rd group. Serious adverse reactions with at least a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 12% vs Rd 10%), upper respiratory tract infection (DRd 7% vs Rd 4%), influenza and pyrexia (DRd 3% vs Rd 1% for each).

Adverse reactions resulted in discontinuations for 7% (n=19) of patients in the DRd arm versus 8% (n=22) in the Rd arm.

Table 7: Adverse Reactions Reported in ≥ 10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in POLLUX

Adverse Reaction	DRd (N=283) %			Rd (N=281) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Infusion reactions[a]	48	5	0	0	0	0
Gastrointestinal disorders						
Diarrhea	43	5	0	25	3	0
Nausea	24	1	0	14	0	0
Vomiting	17	1	0	5	1	0
General disorders and administration site conditions						
Fatigue	35	6	< 1	28	2	0
Pyrexia	20	2	0	11	1	0
Infections and infestations						
Upper respiratory tract infection[b]	65	6	< 1	51	4	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	26	1	0	19	2	0
Nervous system disorders						
Headache	13	0	0	7	0	0
Respiratory, thoracic and mediastinal disorders						
Cough[c]	30	0	0	15	0	0
Dyspnea[d]	21	3	< 1	12	1	0

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see section on Infusion Reactions below.

[b] upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection

[c] cough, productive cough, allergic cough

[d] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment from baseline listed in Table 8.

Table 8: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

	DRd (N=283) %			Rd (N=281) %		
	Any Grade	Grade 3	Grade 4	Any Grades	Grade 3	Grade 4
Anemia	52	13	0	57	19	0
Thrombocytopenia	73	7	6	67	10	5
Neutropenia	92	36	17	87	32	8
Lymphopenia	95	42	10	87	32	6

Key: D=Daratumumab, Rd=lenalidomide-dexamethasone.

Combination Treatment with Bortezomib and Dexamethasone

Adverse reactions described in Table 9 reflect exposure to DARZALEX for a median treatment duration of 6.5 months (range: 0 to 14.8 months) in the daratumumab-bortezomib-dexamethasone (DVd) group and median treatment duration of 5.2 months (range: 0.2 to 8.0 months) for the bortezomib-dexamethasone (Vd) group in a Phase 3 active-controlled study CASTOR. The most frequent adverse reactions (>20%) were infusion reactions, diarrhea, peripheral edema, upper respiratory tract infection, peripheral sensory neuropathy, cough and dyspnea. The overall incidence of serious adverse reactions was 42% for the DVd group compared with 34% for the Vd group. Serious adverse reactions with at least a 2% greater incidence in the DVd arm compared to the Vd arm were upper respiratory tract infection (DVd 5% vs Vd 2%), diarrhea and atrial fibrillation (DVd 2% vs Vd 0% for each).

Adverse reactions resulted in discontinuations for 7% (n=18) of patients in the DVd arm versus 9% (n=22) in the Vd arm.

Table 9: Adverse Reactions Reported in ≥10% of Patients and With at Least a 5% Greater Frequency in the DVd Arm CASTOR

Adverse Reaction	DVd (N=243) %			Vd (N=237) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Infusion reactions[a]	45	9	0	0	0	0
Gastrointestinal disorders						
Diarrhea	32	3	< 1	22	1	0
Vomiting	11	0	0	4	0	0
General disorders and administration site conditions						
Edema peripheral[b]	22	1	0	13	0	0
Pyrexia	16	1	0	11	1	0
Infections and infestations						
Upper respiratory tract infection[c]	44	6	0	30	3	< 1
Nervous system disorders						
Peripheral sensory neuropathy	47	5	0	38	6	< 1
Respiratory, thoracic and mediastinal disorders						
Cough[d]	27	0	0	14	0	0
Dyspnea[e]	21	4	0	11	1	0

Key: D=daratumumab, Vd=bortezomib-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see section on Infusion Reactions below.

[b] edema peripheral, edema, generalized edema, peripheral swelling

[c] upper respiratory tract infection, bronchitis, sinusitis, respiratory tract infection viral, rhinitis, pharyngitis, respiratory tract infection, metapneumovirus infection, tracheobronchitis, viral upper respiratory tract infection, laryngitis, respiratory syncytial virus infection, staphylococcal pharyngitis, tonsillitis, viral pharyngitis, acute sinusitis, nasopharyngitis, bronchiolitis, bronchitis viral, pharyngitis streptococcal, tracheitis, upper respiratory tract infection bacterial, bronchitis bacterial, epiglottitis, laryngitis viral, oropharyngeal candidiasis, respiratory moniliasis, viral rhinitis, acute tonsillitis, rhinovirus infection

[d] cough, productive cough, allergic cough

[e] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment are listed in Table 10.

Table 10: Treatment-Emergent Hematology Laboratory Abnormalities in CASTOR

	DVd (N=243) %			Vd (N=237) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Anemia	48	13	0	56	14	0
Thrombocytopenia	90	28	19	85	22	13
Neutropenia	58	12	3	40	5	< 1
Lymphopenia	89	41	7	81	24	3

Key: D=Daratumumab, Vd=bortezomib-dexamethasone.

Combination Treatment with Pomalidomide and Dexamethasone

Adverse reactions described in Table 11 reflect exposure to DARZALEX, pomalidomide and dexamethasone (DPd) for a median treatment duration of 6 months (range: 0.03 to 16.9 months) in EQUULEUS. The most frequent adverse reactions (>20%) were infusion reactions, diarrhea, constipation, nausea, vomiting, fatigue, pyrexia, upper respiratory tract infection, muscle spasms, back pain, arthralgia, dizziness, insomnia, cough and dyspnea. The overall incidence of serious adverse reactions was 49%. Serious adverse reactions reported in ≥5% patients included pneumonia (7%). Adverse reactions resulted in discontinuations for 13% of patients.

Table 11: Adverse Reactions With Incidence ≥10% Reported in EQUULEUS

Body System Adverse Reaction	DPd (N=103)		
	Any Grade (%)	Grade 3 (%)	Grade 4 (%)
Infusion reactions[a]	50	4	0
Gastrointestinal disorders			
Diarrhea	38	3	0
Constipation	33	0	0
Nausea	30	0	0
Vomiting	21	2	0
General disorders and administration site conditions			
Fatigue	50	10	0
Pyrexia	25	1	0
Chills	20	0	0
Edema peripheral[b]	17	4	0
Asthenia	15	0	0
Non-cardiac chest pain	15	0	0
Pain	11	0	0
Infections and infestations			
Upper respiratory tract infection[c]	50	4	1
Pneumonia[d]	15	8	2
Metabolism and nutrition disorders			
Hypokalemia	16	3	0
Hyperglycemia	13	5	1
Decreased appetite	11	0	0
Musculoskeletal and connective tissue disorders			
Muscle spasms	26	1	0
Back pain	25	6	0
Arthralgia	22	2	0
Pain in extremity	15	0	0
Bone pain	13	4	0
Musculoskeletal chest pain	13	2	0
Nervous system disorders			
Dizziness	21	2	0
Tremor	19	3	0
Headache	17	0	0
Psychiatric disorders			
Insomnia	23	2	0
Anxiety	13	0	0
Respiratory, thoracic and mediastinal disorders			
Cough[e]	43	1	0
Dyspnea[f]	33	6	1
Nasal congestion	16	0	0

Key: D=Daratumumab, Pd=pomalidomide-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see section on Infusion Reactions below.

[b] edema, edema peripheral, peripheral swelling.

[c] acute tonsillitis, bronchitis, laryngitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection

[d] lung infection, pneumonia, pneumonia aspiration

[e] cough, productive cough, allergic cough

[f] dyspnea, dyspnea exertional

Laboratory abnormalities worsening during treatment are listed in Table 12.

Table 12: Treatment-Emergent Hematology Laboratory Abnormalities in EQUULEUS

	DPd (N=103) %		
	Any Grade	Grade 3	Grade 4
Anemia	57	30	0
Thrombocytopenia	75	10	10
Neutropenia	95	36	46
Lymphopenia	94	45	26

Key: D=Daratumumab, Pd=pomalidomide-dexamethasone.

Monotherapy

The safety data reflect exposure to DARZALEX in 156 adult patients with relapsed and refractory multiple myeloma treated with DARZALEX at 16 mg/kg in three open-label, clinical trials. The median duration of exposure was 3.3 months (range: 0.03 to 20.04 months). Serious adverse reactions were reported in 51 (33%) patients. The most frequent serious adverse reactions were pneumonia (6%), general physical health deterioration (3%), and pyrexia (3%).

Adverse reactions resulted in treatment delay for 24 (15%) patients, most frequently for infections. Adverse reactions resulted in discontinuations for 6 (4%) patients.

Adverse reactions occurring in at least 10% of patients are presented in Table 13. Table 14 describes Grade 3–4 laboratory abnormalities reported at a rate of ≥10%.

Table 13: Adverse Reactions With Incidence ≥10% in Patients With Multiple Myeloma Treated With DARZALEX 16 mg/kg

	DARZALEX 16 mg/kg N=156		
	Incidence (%)		
Adverse Reaction	**Any Grade**	**Grade 3**	**Grade 4**
Infusion reaction[a]	48	3	0
General disorders and administration site conditions			
Fatigue	39	2	0
Pyrexia	21	1	0
Chills	10	0	0
Respiratory, thoracic and mediastinal disorders			
Cough	21	0	0
Nasal congestion	17	0	0
Dyspnea	15	1	0
Musculoskeletal and connective tissue disorders			
Back pain	23	2	0
Arthralgia	17	0	0
Pain in extremity	15	1	0
Musculoskeletal chest pain	12	1	0
Infections and infestations			
Upper respiratory tract infection	20	1	0
Nasopharyngitis	15	0	0
Pneumonia[b]	11	6	0
Gastrointestinal disorders			
Nausea	27	0	0
Diarrhea	16	1	0
Constipation	15	0	0
Vomiting	14	0	0
Metabolism and nutrition disorders			
Decreased appetite	15	1	0
Nervous system disorders			
Headache	12	1	0
Vascular disorders			
Hypertension	10	5	0

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see section on Infusion Reactions below.

[b] Pneumonia also includes the terms streptococcal pneumonia and lobar pneumonia.

Table 14: Treatment-Emergent Grade 3-4 Laboratory Abnormalities (≥10%)

	Daratumumab 16 mg/kg (N=156)		
	Any Grade (%)	**Grade 3 (%)**	**Grade 4 (%)**
Anemia	45	19	0
Thrombocytopenia	48	10	8
Neutropenia	60	17	3
Lymphopenia	72	30	10

Infusion Reactions: In clinical trials (monotherapy and combination treatments; N=2,066) the incidence of any grade infusion reactions was 37% with the first (16 mg/kg, Week 1) infusion of DARZALEX, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion reaction at Week 2 or subsequent infusions.

The median time to onset of a reaction was 1.5 hours (range: 0 to 72.8 hours). The incidence of infusion modification due to reactions was 36%. Median durations of 16 mg/kg infusions for the 1st week, 2nd week and subsequent infusions were approximately 7, 4, and 3 hours respectively.

Severe infusion reactions included bronchospasm, dyspnea, laryngeal edema, pulmonary edema, hypoxia, and hypertension. Other adverse infusion reactions included nasal congestion, cough, chills, throat irritation, vomiting and nausea.

When DARZALEX dosing was interrupted in the setting of ASCT (Study CASSIOPEIA) for a median of 3.75 months (range: 2.4; 6.9 months), upon re-initiation of DARZALEX the incidence of IRRs was 11% for the first infusion following ASCT. Infusion rate/dilution volume used upon re-initiation was that used for the last DARZALEX infusion prior to interruption for ASCT. IRRs 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 daratumumab combination treatment (n=97) were administered the first 16 mg/kg daratumumab dose at Week 1 split over two days i.e. 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 reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 h for Week 1-Day 1, 4.2 h for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

Herpes Zoster Virus Reactivation: Prophylaxis for Herpes Zoster Virus reactivation was recommended for patients in some clinical trials of DARZALEX. In monotherapy studies, herpes zoster was reported in 3% of patients. In the combination therapy studies, herpes zoster was reported in 2-5% of patients receiving DARZALEX.

Infections: In patients receiving DARZALEX combination therapy, Grade 3 or 4 infections were reported as follows:

Relapsed/refractory patient studies: DVd: 21%, Vd: 19%; DRd: 27%, Rd: 23%; DPd: 28%

Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%; DVTd: 22%; VTd 20%.

Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. In the active controlled studies, discontinuations from treatment due to infections (1-4%) and fatal infections were generally infrequent and balanced between the DARZALEX containing regimens and active control arms. Fatal infections were primarily due to pneumonia and sepsis.

Hepatitis B Virus (HBV) Reactivation: Hepatitis B virus reactivation has been reported in less than 1% of patients (including fatal cases) treated with DARZALEX in clinical trials.

Immunogenicity: As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to daratumumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading. In clinical trials of patients with multiple myeloma treated with DARZALEX as monotherapy or as combination therapies, none of the 111 evaluable monotherapy patients, and 2 of the 1,050 evaluable combination therapy patients, tested positive for anti-daratumumab antibodies. One patient administered DARZALEX as combination therapy, developed transient neutralizing antibodies against daratumumab. However, this assay has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab; therefore, the incidence of antibody development might not have been reliably determined.

Postmarketing Experience: The following adverse reactions have been identified during post-approval use of DARZALEX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System disorders: Anaphylactic reaction

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests: Interference with Indirect Antiglobulin Tests (Indirect Coombs Test): Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding *[see References]* or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, K-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests: Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: There are no human data to inform a risk with use of DARZALEX during pregnancy. Animal studies have not been conducted. However, there are clinical considerations *(see Clinical Considerations).* The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations: *Fetal/Neonatal Adverse Reactions:* Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX may cause fetal myeloid or lymphoid-cell depletion and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX *in utero* until a hematology evaluation is completed.

Data: *Animal Data:* Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. In cynomolgus monkeys exposed during pregnancy to other monoclonal antibodies that affect leukocyte populations, infant monkeys had a reversible reduction in leukocytes.

Lactation: Risk Summary: There is no information regarding the presence of daratumumab in human milk, the effects on the breastfed child, or the effects on milk production. Human IgG is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for DARZALEX and any potential adverse effects on the breast-fed child from DARZALEX or from the underlying maternal condition.

Females and Males of Reproductive Potential: Contraception: To avoid exposure to the fetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of DARZALEX treatment.

Pediatric Use: Safety and effectiveness of DARZALEX in pediatric patients have not been established.

Geriatric Use: Of the 2,066 patients that received DARZALEX at the recommended dose, 37% were 65 to 75 years of age, and 16% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients *[see Clinical Studies (14) in Full Prescribing Information].*

REFERENCES

1. Chapuy, CI, RT Nicholson, MD Aguad, et al., 2015, Resolving the daratumumab interference with blood compatibility testing, Transfusion, 55:1545-1554 (accessible at http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf).

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Infusion Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion reactions:

- itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing *[see Warnings and Precautions and Adverse Reactions]*.

Neutropenia

- Advise patients that if they have a fever, they should contact their healthcare professional *[see Warnings and Precautions and Adverse Reactions]*.

Thrombocytopenia

- Advise patients to inform their healthcare professional if they notice signs of bruising or bleeding *[see Warnings and Precautions and Adverse Reactions]*.

Interference with Laboratory Tests

Advise patients to inform healthcare providers including blood transfusion centers/personnel that they are taking DARZALEX, in the event of a planned transfusion *[see Warnings and Precautions and Drug Interactions]*.

Advise patients that DARZALEX can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response *[see Warnings and Precautions and Drug Interactions]*.

Hepatitis B Virus (HBV) Reactivation:

Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX could cause hepatitis B virus to become active again *[see Adverse Reactions]*.

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