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PRACTICAL, PEER-REVIEWED PERSPECTIVES

ONCOLOGY®

NOVEMBER 2023 | Vol 37 • No 11

BASAL CELL CARCINOMA: CASE STUDY

Exploring the Changing Diagnostic Criteria of Gorlin-Goltz Syndrome: A Case Report

CANCER INCIDENCE: INTERVIEW

Monique Gary, DO, MSc, FACS
Increase in Early-Onset Incidence May Be Driven by Breast/Gynecologic Cancers

Clinical Trial Awareness: CME
Overcoming Obstacles to Clinical Trial Recruitment and Retention
Laura S. Wood, MSN, RN, OCN

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1. Outside County Paid/Requested Mail Subscriptions stated on PS Form 3541.	15053	14591
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OUR BOARD MEMBERS HAVE BEEN BUSY! TAKE A LOOK TO SEE WHAT THEY HAVE BEEN UP TO.

Tanios S. Bekaii-Saab, MD
Gastrointestinal Tumor Chair
Bekaii-Saab was an author on the recently published paper "Tucatinib and Trastuzumab for Previously Treated Human Epidermal Growth Factor Receptor 2-Positive Metastatic Biliary Tract Cancer (SGNTUC-019): A Phase II Basket Study". Results found clinically significant antitumor activity for patients in the population above.

John Marshall, MD
Colorectal/Gastrointestinal Editorial Board Member
Marshall participated in the BellRinger bike ride through his institution, The Ruesch Center for the Cure of Gastrointestinal Cancers. He and his teammates rode to raise money for cancer research.

CALL FOR REVIEWERS AND PAPERS

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We are also seeking to expand coverage of original peer-reviewed research articles and are now encouraging authors to submit high-quality original manuscripts about clinical trials and investigations.

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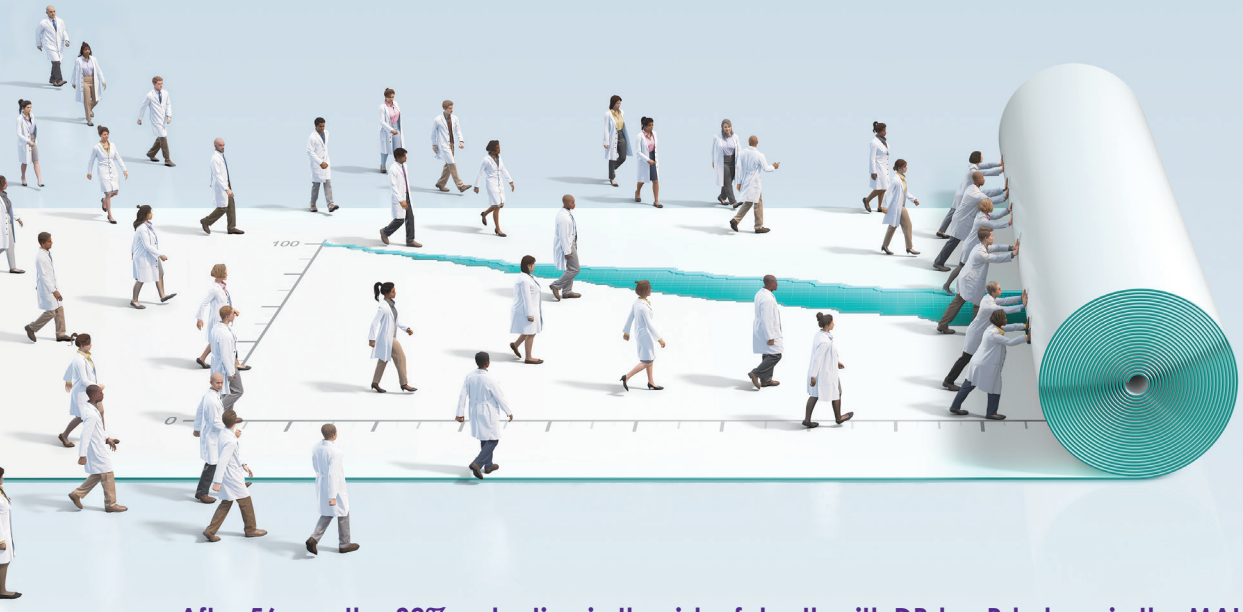
DARZALEX® (daratumumab)
injection for intravenous infusion
100 mg/5 mL, 400 mg/20 mL

DARZALEX *Faspro*® (daratumumab and hyaluronidase-fihj)
Injection for subcutaneous use | 1,800mg/30,000units

In the treatment of newly diagnosed, transplant-ineligible multiple myeloma[1]:

ADVANCE THE FRONTLINE MOMENTUM WITH DARZALEX® + Rd

Help your patients live longer than Rd alone with DRd, an established frontline treatment proven to significantly extend overall survival[1]



After 56 months: 32% reduction in the risk of death with DRd vs Rd alone in the MAIA trial
(HR=0.68; 95% CI: 0.53, 0.86; *P*=0.0013; mOS not reached in either arm).*[1]

*Median follow-up was 56 months in the DRd group (range: 53.0-60.1 months) and in the Rd group (range: 52.5-59.4 months)[1,2]

CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio; mOS=median overall survival; Rd=lenalidomide (R) + dexamethasone (d).

IMPORTANT SAFETY INFORMATION

DARZALEX® AND DARZALEX *FASPRO*®: CONTRAINDICATIONS

DARZALEX® and DARZALEX *FASPRO*® are contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase (for DARZALEX *FASPRO*®), or any of the components of the formulations.

DARZALEX®: Infusion-Related Reactions

DARZALEX® can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening, and fatal outcomes have been reported. 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, tachycardia, headache, laryngeal edema, pulmonary edema, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma.

Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting, and nausea. Less common signs and symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension, and blurred vision.

When DARZALEX® dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 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.

Please see Brief Summary of full Prescribing Information for DARZALEX® and DARZALEX *FASPRO*® on adjacent pages.

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

MAIA Study Design: A phase 3 global, randomized, open-label study, compared treatment with DARZALEX® (daratumumab) + Rd (n=368) to Rd (n=369) in adult patients with newly diagnosed, transplant-ineligible multiple myeloma.

Treatment was continued until disease progression or unacceptable toxicity. The primary efficacy endpoint was progression-free survival (PFS) and OS was a secondary endpoint.[1]

Powerful efficacy to start the treatment journey[1,3]

At follow-up of 28 months, **median progression-free survival (mPFS) was not reached** with DARZALEX® + Rd vs 31.9 months (95% CI, 28.9 to not reached) with Rd alone*

- **70.6% of patients had not progressed** with DRd vs 55.6% of patients in the Rd group (DRd: 95% CI, 65.0-75.4; Rd: 95% CI, 49.5-61.3)†

44% **reduction in the risk of disease progression or death** with DRd vs Rd alone (HR=0.56; 95% CI, 0.43-0.73; *P*<0.0001)

Efficacy results in long-term follow-up[1,4]

After 64 months of follow-up, the median PFS was 61.9 months (95% CI: 54.8, not evaluable) in the DRd arm and 34.4 months (95% CI: 29.6, 39.2) in the Rd arm

45% **reduction in the risk of disease progression or death** with DARZALEX® + Rd vs Rd alone (HR=0.55; 95% CI, 0.45-0.67)

Secondary endpoint of overall survival (OS)[1,2]
After 56 months of follow-up:

- 66% of patients were still alive with DRd vs 53% with Rd alone (DRd: 95% CI, 60.8-71.3; Rd: 95% CI, 47.2-58.6)†
- Median OS was not reached for either arm

32% **reduction in the risk of death** in patients treated in the DRd arm vs Rd alone (HR=0.68; 95% CI: 0.53, 0.86; *P*=0.0013)

Demonstrated safety profile
(median treatment duration of 25.3 months)[1]

- The most common adverse reactions (≥20%) for DRd were diarrhea, constipation, nausea, upper respiratory tract infection, bronchitis, pneumonia, infusion-related reactions, peripheral edema, fatigue, asthenia, pyrexia, back pain, muscle spasms, dyspnea, cough, peripheral sensory neuropathy, and decreased appetite
- Serious adverse reactions with a 2% greater incidence in the DRd arm compared with the Rd arm were pneumonia (DRd 15% vs Rd 8%), bronchitis (DRd 4% vs Rd 2%), and dehydration (DRd 2% vs Rd <1%)

Safety results in long-term follow-up
(median follow-up of 64.5 months)[4]

This information is not included in the current Prescribing Information and has not been evaluated by the FDA.

- Most frequent TEAEs for DRd occurring in ≥30% of patients were diarrhea, neutropenia, fatigue, constipation, peripheral edema, anemia, back pain, asthenia, nausea, bronchitis, cough, dyspnea, insomnia, weight decreased, peripheral sensory neuropathy, pneumonia, and muscle spasms‡
- Grade 3/4 infections were 43% for DRd vs 30% for Rd‡
- Grade 3/4 TEAEs occurring in ≥10% of patients were neutropenia (54% for DRd vs 37% for Rd), pneumonia (20% vs 11%), and anemia (17% vs 22%)‡

Treatment-emergent adverse events are reported as observed. These analyses have not been adjusted for multiple comparisons and no conclusions should be drawn.

CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); FDA=U.S. Food and Drug Administration; HR=hazard ratio; OS=overall survival; Rd=lenalidomide (R) + dexamethasone (d); TEAE=treatment-emergent adverse event.
*Range: 0.0-41.4 months.[1,3]
†Kaplan-Meier estimate.[3]
‡Safety analysis set. TEAEs are defined as any adverse event (AE) that occurs after the start of the first study treatment through 30 days after the last study treatment; or the day prior to start of subsequent antimyeloma therapy, whichever is earlier; or any AE that is considered related (very likely, probably, or possibly related) regardless of the start date of the event; or any AE that is present at baseline but worsens in toxicity grade or is subsequently considered drug related by the investigator.

See the rolled-out data.
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IMPORTANT SAFETY INFORMATION (CONTINUED)

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.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with DARZALEX® infusion. If ocular symptoms occur, interrupt DARZALEX® infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX®.

DARZALEX *FASPRO*® (daratumumab and hyaluronidase-fihj): Hypersensitivity and Other Administration Reactions

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX *FASPRO*®. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX *FASPRO*®.

Systemic Reactions

In a pooled safety population of 898 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=193) who received DARZALEX *FASPRO*® as monotherapy or in combination, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.2%, Grade 3: 1%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.3% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 140 systemic administration-related reactions that occurred in 77 patients, 121 (86%) occurred on the day of DARZALEX *FASPRO*® administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension, tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX *FASPRO*®. Consider administering corticosteroids and other medications after the administration of DARZALEX *FASPRO*® depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions.

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE▶

IMPORTANT SAFETY INFORMATION (CONTINUED)

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX *FASPRO*® and seek immediate ophthalmologic evaluation prior to restarting DARZALEX *FASPRO*®.

Local Reactions

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.7%. The most frequent (>1%) injection-site reaction was injection-site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX *FASPRO*®. Monitor for local reactions and consider symptomatic management.

DARZALEX® and DARZALEX *FASPRO*®: Neutropenia and Thrombocytopenia

DARZALEX® and DARZALEX *FASPRO*® 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® or DARZALEX *FASPRO*® until recovery of neutrophils or for recovery of platelets.

In lower body weight patients receiving DARZALEX *FASPRO*®, higher rates of Grade 3-4 neutropenia were observed.

DARZALEX® and DARZALEX *FASPRO*®: 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 administration. 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® and DARZALEX *FASPRO*®. Type and screen patients prior to starting DARZALEX® and DARZALEX *FASPRO*®.

DARZALEX® and DARZALEX *FASPRO*®: Interference With Determination of Complete Response

Daratumumab is a human immunoglobulin G (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.

DARZALEX® and DARZALEX *FASPRO*®: Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX® and DARZALEX *FASPRO*® can cause fetal harm when administered to a pregnant woman. DARZALEX® and DARZALEX *FASPRO*® 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® or DARZALEX *FASPRO*® and for 3 months after the last dose.

The combination of DARZALEX® or DARZALEX *FASPRO*® 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.

DARZALEX®: ADVERSE REACTIONS

The most frequently reported adverse reactions (incidence ≥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 (≥40%) with DARZALEX® are neutropenia, lymphopenia, thrombocytopenia, leukopenia, and anemia.

DARZALEX *FASPRO*®: ADVERSE REACTIONS

In multiple myeloma, the most common adverse reaction (≥20%) with DARZALEX *FASPRO*® monotherapy is upper respiratory tract infection. The most common adverse reactions with combination therapy (≥20% for any combination) include fatigue, nausea, diarrhea, dyspnea, insomnia, headache, pyrexia, cough, muscle spasms, back pain, vomiting, hypertension, upper respiratory tract infection, peripheral sensory neuropathy, constipation, pneumonia, and peripheral edema. The most common hematologic laboratory abnormalities (≥40%) with DARZALEX *FASPRO*® are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin.

INDICATIONS

DARZALEX® (daratumumab) 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 carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy
- In combination with pomalidomide and dexamethasone in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI)
- 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

DARZALEX *FASPRO*® (daratumumab and hyaluronidase-fihj) is indicated for the treatment of adult patients with multiple myeloma:

- In combination with bortezomib, melphalan, and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- 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, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- In combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor (PI)
- In combination with carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy
- In combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- 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

Please see Brief Summary of full Prescribing Information for DARZALEX® and DARZALEX *FASPRO*® on adjacent pages.

cp-248517v3

References: 1. DARZALEX® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Facon T, Kumar SK, Plesner T, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2021;22(11):1582-1596. doi:10.1016/s1470-2045(21)00466-6 **3.** Facon T, Kumar S, Plesner T, et al; the MAIA Trial Investigators. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med.* 2019;380(22):2104-2115. doi:10.1056/NEJMoa1817249 **4.** Kumar SK, Moreau P, Bahlis N, et al. Daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) alone in transplant-ineligible patients with newly diagnosed multiple myeloma (NDMM): updated analysis of the phase 3 MAIA study. Poster presented at: 64th American Society of Hematology (ASH) Annual Meeting & Exposition; December 10-13, 2022; New Orleans, LA.

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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.

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]*.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

DARZALEX can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening and fatal outcomes have been reported *[see Adverse Reactions]*.

In clinical trials (monotherapy and combination: N=2,066), 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). The incidence of infusion modification due to reactions was 36%. Median durations of 16 mg/kg infusions for the Week 1, Week 2, and subsequent infusions were approximately 7, 4, and 3 hours respectively. 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-related reactions occurred up to 48 hours after infusion.

Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, pulmonary edema, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common signs and symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension, and blurred vision *[see Adverse Reactions]*.

When DARZALEX dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX, the incidence of infusion-related reactions 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. 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 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-related 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 hours for Week 1-Day 1, 4.2 hours for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion *[see Dosage and Administration (2.3) in Full Prescribing Information]*. 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 (2.4) in Full Prescribing Information]*.

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX infusions *[see Dosage and Administration (2.3) 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 *[see Dosage and Administration (2.3) in Full Prescribing Information]*.

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with DARZALEX infusion. If ocular symptoms occur, interrupt DARZALEX infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX.

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

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. Consider withholding DARZALEX until recovery of neutrophils.

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. Consider withholding DARZALEX until 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 *[see Drug Interactions]*. 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 *[see Use in Specific Populations]*.

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

- Infusion-related 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 2,459 patients with multiple myeloma including 2,303 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy. In this pooled safety population, the most common adverse reactions (≥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.

Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant

Combination Treatment with Lenalidomide and Dexamethasone (DRd)

The safety of DARZALEX in combination with lenalidomide and dexamethasone was evaluated in MAIA *[see Clinical Studies (14.1) in Full Prescribing Information]*. Adverse reactions described in Table 1 reflect exposure to DARZALEX for a median treatment duration of 25.3 months (range: 0.1 to 40.44 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 21.3 months (range: 0.03 to 40.64 months) for lenalidomide-dexamethasone (Rd).

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)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
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
Infections						
Upper respiratory tract infection[a]	52	2	<1	36	2	<1
Bronchitis[b]	29	3	0	21	1	0
Pneumonia[c]	26	14	1	14	7	1
Urinary tract infection	18	2	0	10	2	0
General disorders and administration site conditions						
Infusion-related reactions[d]	41	2	<1	0	0	0
Peripheral edema[e]	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
Musculoskeletal and connective tissue disorders						
Back pain	34	3	<1	26	3	<1
Muscle spasms	29	1	0	22	1	0
Respiratory, thoracic and mediastinal disorders						
Dyspnea[f]	32	3	<1	20	1	0
Cough[g]	30	<1	0	18	0	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
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
Vascular disorders						
Hypertension[h]	13	6	<1	7	4	0

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

[a] 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

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

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

[d] Infusion-related reaction includes terms determined by investigators to be related to infusion

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

[f] Dyspnea, Dyspnea exertional

[g] Cough, Productive cough

[h] Blood pressure increased, Hypertension

DARZALEX® (daratumumab) injection

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)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Leukopenia	90	30	5	82	20	4
Neutropenia	91	39	17	77	28	11
Lymphopenia	84	41	11	75	36	6
Thrombocytopenia	67	6	3	58	7	4
Anemia	47	13	0	57	24	0

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

Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide and Dexamethasone

The safety of DARZALEX in combination with lenalidomide and dexamethasone was evaluated in POLLUX *[see Clinical Studies (14.2) in Full Prescribing Information]*. Adverse reactions described in Table 3 reflect exposure to DARZALEX for a median treatment duration of 13.1 months (range: 0 to 20.7 months) for daratumumab-lenalidomide-dexamethasone (DRd) and of 12.3 months (range: 0.2 to 20.1 months) for lenalidomide-dexamethasone (Rd).

Serious adverse reactions occurred in 49% of patients in the DRd arm compared with 42% in the Rd arm. 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 3: 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)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Infections						
Upper respiratory tract infection[a]	65	6	< 1	51	4	0
General disorders and administration site conditions						
Infusion-related reactions[b]	48	5	0	0	0	0
Fatigue	35	6	< 1	28	2	0
Pyrexia	20	2	0	11	1	0
Gastrointestinal disorders						
Diarrhea	43	5	0	25	3	0
Nausea	24	1	0	14	0	0
Vomiting	17	1	0	5	1	0
Respiratory, thoracic and mediastinal disorders						
Cough[c]	30	0	0	15	0	0
Dyspnea[d]	21	3	< 1	12	1	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	26	1	0	19	2	0
Nervous system disorders						
Headache	13	0	0	7	0	0

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

[a] 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

[b] Infusion-related reaction includes terms determined by investigators to be related to infusion

[c] cough, productive cough, allergic cough

[d] dyspnea, dyspnea exertional

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

Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

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

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

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

Grade 3 or 4 infections were reported as follows:

- Relapsed/refractory patient studies: DVd: 21% vs. Vd: 19%; DRd: 28% vs. Rd: 23%; DPd: 28%; DKd[a]: 37%, Kd[a]: 29%; DKd[b]: 21%
  - [a] where carfilzomib 20/56 mg/m^2 was administered twice-weekly
  - [b] where carfilzomib 20/70 mg/m^2 was administered once-weekly
- 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 active controlled studies, discontinuations from treatment due to infections occurred in 1-4% of patients.

Fatal infections (Grade 5) were reported as follows:

- Relapsed/refractory patient studies: DVd: 1%, Vd: 2%; DRd: 2%, Rd: 1%; DPd: 2%; DKd[a]: 5%, Kd[a]: 3%; DKd[b]: 0%
  - [a] where carfilzomib 20/56 mg/m^2 was administered twice-weekly
  - [b] where carfilzomib 20/70 mg/m^2 was administered once-weekly
- Newly diagnosed patient studies: D-VMP: 1%, VMP: 1%; DRd: 2%, Rd: 2%; DVTd: 0%, VTd: 0%.

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.

Other Clinical Trials Experience

The following adverse reactions have been reported following administration of daratumumab and hyaluronidase for subcutaneous injection:

Nervous System disorders: Syncope

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 in the studies described below with the incidence of antibodies in other studies or to other daratumumab products may be misleading.

In clinical trials of patients with multiple myeloma treated with DARZALEX as monotherapy or as combination therapies, 0.35% (6/1,713) of patients developed treatment-emergent anti-daratumumab antibodies. Of those, 4 patients tested positive for neutralizing antibodies.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of daratumumab. 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, IRR (including deaths)
Gastrointestinal disorders: Pancreatitis
Infections: Cytomegalovirus, Listeriosis

DARZALEX® (daratumumab) injection

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, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs 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

DARZALEX can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout animal models *(see Data)*. There are no available data on the use of DARZALEX in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

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% to 4% and 15% to 20%, respectively.

The combination of DARZALEX and lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women, because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Lenalidomide, pomalidomide, and thalidomide are only available through a REMS program. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

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 depletion of fetal CD38 positive immune cells 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. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in regulating humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

Lactation

Risk Summary

There is no data on the presence of daratumumab in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G 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. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX is administered with lenalidomide, pomalidomide, or thalidomide, advise women not to breastfeed during treatment with DARZALEX. Refer to lenalidomide, pomalidomide, or thalidomide prescribing information for additional information.

Females and Males of Reproductive Potential

DARZALEX can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*.

Pregnancy Testing

With the combination of DARZALEX with lenalidomide, pomalidomide, or thalidomide, refer to the lenalidomide, pomalidomide, or thalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX and for 3 months after the last dose. Additionally, refer to the lenalidomide, pomalidomide, or thalidomide labeling for additional recommendations for contraception.

Pediatric Use

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

Geriatric Use

Of the 2,459 patients who received DARZALEX at the recommended dose, 38% were 65 to 74 years of age, and 15% were 75 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. The incidence of serious adverse reactions was higher in older than in younger patients *[see Adverse Reactions]*. Among patients with relapsed and refractory multiple myeloma (n=1,213), the serious adverse reactions that occurred more frequently in patients 65 years and older were pneumonia and sepsis. Within the DKd group in CANDOR, fatal adverse reactions occurred in 14% of patients 65 years and older compared to 6% of patients less than 65 years. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n=710), the serious adverse reaction that occurred more frequently in patients 75 years and older was pneumonia.

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-Related Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion-related reactions: itchy, runny or blocked nose; fever, chills, nausea, vomiting, throat irritation, cough, headache, dizziness or lightheadedness, tachycardia, chest discomfort, wheezing, shortness of breath or difficulty breathing, itching, and blurred vision *[see Warnings and Precautions]*.

Neutropenia

Advise patients to contact their healthcare provider if they have a fever *[see Warnings and Precautions]*.

Thrombocytopenia

Advise patients to contact their healthcare provider if they notice signs of bruising or bleeding *[see Warnings and Precautions]*.

Interference with Laboratory Tests

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

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]*.

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]*.

Embryo-Fetal Toxicity

Advise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions, Use in Specific Populations]*.

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX and for 3 months after the last dose *[see Use in Specific Populations]*.

Advise patients that lenalidomide, pomalidomide, or thalidomide has the potential to cause fetal harm and has specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide, pomalidomide, and thalidomide are only available through a REMS program *[see Use in Specific Populations]*.

Hereditary Fructose Intolerance (HFI)

DARZALEX contains sorbitol. Advise patients with HFI of the risks related to sorbitol *[see Description (11) in Full Prescribing Information]*.

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044, USA
U.S. License Number 1864

For patent information: www.janssenpatents.com

cp-271933v4

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use

Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

DARZALEX FASPRO 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.

CONTRAINDICATIONS

DARZALEX FASPRO is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation *[see Warnings and Precautions* and *Adverse Reactions].*

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO. Fatal reactions have been reported with daratumumab-containing products, including DARZALEX FASPRO *[see Adverse Reactions].*

Systemic Reactions

In a pooled safety population of 898 patients with multiple myeloma (N=705) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 9% of patients experienced a systemic administration-related reaction (Grade 2: 3.2%, Grade 3: 1%). Systemic administration-related reactions occurred in 8% of patients with the first injection, 0.3% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 4 minutes to 3.5 days). Of the 140 systemic administration-related reactions that occurred in 77 patients, 121 (86%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions include hypoxia, dyspnea, hypertension, and tachycardia, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension, and blurred vision.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids *[see Dosage and Administration (2.5) in Full Prescribing Information].* Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions *[see Dosage and Administration (2.5) in Full Prescribing Information].*

Ocular adverse reactions, including acute myopia and narrowing of the anterior chamber angle due to ciliochoroidal effusions with potential for increased intraocular pressure or glaucoma, have occurred with daratumumab-containing products. If ocular symptoms occur, interrupt DARZALEX FASPRO and seek immediate ophthalmologic evaluation prior to restarting DARZALEX FASPRO.

Local Reactions

In this pooled safety population, injection-site reactions occurred in 8% of patients, including Grade 2 reactions in 0.7%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 6.5 days) after starting administration of DARZALEX FASPRO. Monitor for local reactions and consider symptomatic management.

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received DARZALEX FASPRO in combination with bortezomib, cyclophosphamide and dexamethasone *[see Adverse Reactions].* Serious cardiac disorders occurred in 16% and fatal cardiac disorders occurred in 10% of patients. Patients with NYHA Class IIIA or Mayo Stage IIIA disease may be at greater risk. Patients with NYHA Class IIIB or IV disease were not studied.

Monitor patients with cardiac involvement of light chain (AL) amyloidosis more frequently for cardiac adverse reactions and administer supportive care as appropriate.

Neutropenia

Daratumumab 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. Consider withholding DARZALEX FASPRO until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO, higher rates of Grade 3-4 neutropenia were observed.

Thrombocytopenia

Daratumumab 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. Consider withholding DARZALEX FASPRO until recovery of platelets.

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO 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 FASPRO and for 3 months after the last dose *[see Use in Specific Populations].*

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

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 administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum *[see References (15)].* 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 FASPRO. Type and screen patients prior to starting DARZALEX FASPRO *[see Dosage and Administration (2.1) in Full Prescribing Information].*

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 DARZALEX FASPRO-treated patients with IgG kappa myeloma protein.

ADVERSE REACTIONS

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

- Hypersensitivity and Other Administration Reactions *[see Warnings and Precautions].*
- Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis *[see Warnings and Precautions].*
- Neutropenia *[see Warnings and Precautions].*
- Thrombocytopenia *[see Warnings 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.

Relapsed/Refractory Multiple Myeloma

In Combination with Lenalidomide and Dexamethasone

The safety of DARZALEX FASPRO with lenalidomide and dexamethasone was evaluated in a single-arm cohort of PLEIADES *[see Clinical Studies (14.2) in Full Prescribing Information].* Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity (N=65) in combination with lenalidomide and dexamethasone. Among these patients, 92% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Serious adverse reactions occurred in 48% of patients who received DARZALEX FASPRO. Serious adverse reactions in >5% of patients included pneumonia, influenza and diarrhea. Fatal adverse reactions occurred in 3.1% of patients.

Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 11% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient were pneumonia and anemia.

Dosage interruptions due to an adverse reaction occurred in 63% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included neutropenia, pneumonia, upper respiratory tract infection, influenza, dyspnea, and blood creatinine increased.

The most common adverse reactions (≥20%) were fatigue, diarrhea, upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia, and dyspnea.

Table 1 summarizes the adverse reactions in patients who received DARZALEX FASPRO in PLEIADES.

Table 1: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

Adverse Reaction	DARZALEX FASPRO with Lenalidomide and Dexamethasone (N=65)	
	All Grades (%)	Grades ≥3 (%)
General disorders and administration site conditions		
Fatigue[a]	52	5#
Pyrexia	23	2#
Edema peripheral	18	3#
Gastrointestinal disorders		
Diarrhea	45	5#
Constipation	26	2#
Nausea	12	0
Vomiting	11	0
Infections		
Upper respiratory tract infection[b]	43	3#
Pneumonia[c]	23	17
Bronchitis[d]	14	2#
Urinary tract infection	11	0
Musculoskeletal and connective tissue disorders		
Muscle spasms	31	2#
Back pain	14	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea[e]	22	3
Cough[f]	14	0
Nervous system disorders		
Peripheral sensory neuropathy	17	2#
Psychiatric disorders		
Insomnia	17	5#
Metabolism and nutrition disorders		
Hyperglycemia	12	9#
Hypocalcemia	11	0

[a] Fatigue includes asthenia, and fatigue.
[b] Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection viral, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.
[c] Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia.
[d] Bronchitis includes bronchitis, and bronchitis viral.
[e] Dyspnea includes dyspnea, and dyspnea exertional.
[f] Cough includes cough, and productive cough.
[#] Only Grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with lenalidomide and dexamethasone included:

- **Musculoskeletal and connective tissue disorders:** arthralgia, musculoskeletal chest pain
- **Nervous system disorders:** dizziness, headache, paresthesia
- **Skin and subcutaneous tissue disorders:** rash, pruritus
- **Gastrointestinal disorders:** abdominal pain
- **Infections:** influenza, sepsis, herpes zoster
- **Metabolism and nutrition disorders:** decreased appetite
- **Cardiac disorders:** atrial fibrillation
- **General disorders and administration site conditions:** chills, infusion reaction, injection site reaction
- **Vascular disorders:** hypotension, hypertension

Table 2 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO in PLEIADES.

Table 2: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (DARZALEX FASPRO-Rd) in PLEIADES

Laboratory Abnormality	DARZALEX FASPRO with Lenalidomide and Dexamethasone[a]	
	All Grades (%)	Grades 3-4 (%)
Decreased leukocytes	94	34
Decreased lymphocytes	82	58
Decreased platelets	86	9
Decreased neutrophils	89	52
Decreased hemoglobin	45	8

[a] Denominator is based on the safety population treated with DARZALEX FASPRO-Rd (N=65).

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

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 in the studies described below with the incidence of antibodies in other studies or to other daratumumab products or other hyaluronidase products may be misleading.

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, less than 1% of 819 patients developed treatment-emergent anti-daratumumab antibodies.

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 7% of 812 patients developed treatment-emergent anti-rHuPH20 antibodies. The anti-rHuPH20 antibodies did not appear to affect daratumumab exposure. None of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies.

Postmarketing Experience

The following adverse reactions have been identified with post-approval use of daratumumab. 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: Anaphylactic reaction, Systemic administration reactions (including death)

Gastrointestinal: Pancreatitis

Infections: Cytomegalovirus, Listeriosis

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, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs 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 DARZALEX FASPRO-treated 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

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout animal models *(see Data)*. There are no available data on the use of DARZALEX FASPRO in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

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% to 4% and 15% to 20%, respectively.

The combination of DARZALEX FASPRO and lenalidomide, thalidomide or pomalidomide is contraindicated in pregnant women, because lenalidomide, thalidomide and pomalidomide may cause birth defects and death of the unborn child. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program. Refer to the lenalidomide, thalidomide or pomalidomide prescribing information on use during pregnancy.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX FASPRO may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to daratumumab *in utero* until a hematology evaluation is completed.

Data

Animal Data

DARZALEX FASPRO for subcutaneous injection contains daratumumab and hyaluronidase. 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. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously daily during organogenesis, which is 45 times higher than the human dose.

There were no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Lactation

Risk Summary

There is no data on the presence of daratumumab and hyaluronidase in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G 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. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX FASPRO is administered with lenalidomide, thalidomide or pomalidomide, advise women not to breastfeed during treatment with DARZALEX FASPRO. Refer to lenalidomide, thalidomide or pomalidomide prescribing information for additional information.

Data

Animal Data

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

Females and Males of Reproductive Potential

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*.

Pregnancy Testing

With the combination of DARZALEX FASPRO with lenalidomide, thalidomide or pomalidomide, refer to the lenalidomide, thalidomide or pomalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose. Additionally, refer to the lenalidomide, thalidomide or pomalidomide labeling for additional recommendations for contraception.

Pediatric Use

Safety and effectiveness of DARZALEX FASPRO in pediatric patients have not been established.

Geriatric Use

Of the 291 patients who received DARZALEX FASPRO as monotherapy for relapsed and refractory multiple myeloma, 37% were 65 to <75 years of age, and 19% were 75 years of age or older. No overall differences in effectiveness of DARZALEX FASPRO have been observed between patients ≥65 years of age and younger patients. Adverse reactions that occurred at a higher frequency (≥5% difference) in patients ≥65 years of age included upper respiratory tract infection, urinary tract infection, dizziness, cough, dyspnea, diarrhea, nausea, fatigue, and peripheral edema. Serious adverse reactions that occurred at a higher frequency (≥2% difference) in patients ≥65 years of age included pneumonia.

Of the 214 patients who received DARZALEX FASPRO as combination therapy with pomalidomide and dexamethasone or DARZALEX FASPRO as combination therapy with lenalidomide and low-dose dexamethasone for relapsed and refractory multiple myeloma, 43% were 65 to <75 years of age, and 18% were 75 years of age or older. No overall differences in effectiveness were observed between patients ≥65 years (n=131) and <65 years (n=85). Adverse reactions occurring at a higher frequency (≥5% difference) in patients ≥65 years of age included fatigue, pyrexia, peripheral edema, urinary tract infection, diarrhea, constipation, vomiting, dyspnea, cough, and hyperglycemia. Serious adverse reactions occurring at a higher frequency (≥2% difference) in patients ≥65 years of age included neutropenia, thrombocytopenia, diarrhea, anemia, COVID-19, ischemic colitis, deep vein thrombosis, general physical health deterioration, pulmonary embolism, and urinary tract infection.

Of the 193 patients who received DARZALEX FASPRO as part of a combination therapy for light chain (AL) amyloidosis, 35% were 65 to <75 years of age, and 10% were 75 years of age or older. Clinical studies of DARZALEX FASPRO as part of a combination therapy for patients with light chain (AL) amyloidosis did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs from that of younger patients. Adverse reactions that occurred at a higher frequency in patients ≥65 years of age were peripheral edema, asthenia, pneumonia and hypotension.

No clinically meaningful differences in the pharmacokinetics of daratumumab were observed in geriatric patients compared to younger adult patients *[see Clinical Pharmacology (12.3) 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).

Hypersensitivity and Other Administration Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of systemic administration-related reactions: itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing, and blurred vision *[see Warnings and Precautions]*.

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Advise patients to immediately contact their healthcare provider if they have signs or symptoms of cardiac adverse reactions *[see Warnings and Precautions]*.

Neutropenia

Advise patients to contact their healthcare provider if they have a fever *[see Warnings and Precautions]*.

Thrombocytopenia

Advise patients to contact their healthcare provider if they have bruising or bleeding *[see Warnings and Precautions]*.

Embryo-Fetal Toxicity

Advise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions, Use in Specific Populations]*.

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX FASPRO and for 3 months after the last dose *[see Use in Specific Populations]*.

Advise patients that lenalidomide, thalidomide and pomalidomide have the potential to cause fetal harm and have specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide, thalidomide and pomalidomide are only available through a REMS program *[see Use in Specific Populations]*.

Interference with Laboratory Tests

Advise patients to inform their healthcare provider, including personnel at blood transfusion centers, that they are taking DARZALEX FASPRO, in the event of a planned transfusion *[see Warnings and Precautions]*.

Advise patients that DARZALEX FASPRO 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]*.

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 FASPRO could cause hepatitis B virus to become active again *[see Adverse Reactions]*.

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044, USA
U.S. License Number 1864

For patent information: www.janssenpatents.com

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Chemotherapy Drug Shortages: It's Soluble

As the shortages of chemotherapy drugs continue to produce day-to-day treatment dilemmas and lead to enforced workarounds for clinicians—not to mention stir high anxiety in patients—we should reflect on how we got here. We should recall that periods of drug shortages have occurred for more than 20 years. We have survived these intermittent disruptions because they involved 1 or 2 drugs at most and have been of shorter duration. The current situation, however, is due to fundamental deficiencies in the chemotherapy drug supply.

These shortages are a result of a somewhat new dynamic brought on by market intermediates and reduced inspections abroad, partly due to the COVID-19 pandemic. In fact, it is difficult to understand a system in which generic drugs may cost pennies per gram and drugs under patent cost hundreds of dollars per gram (wholesale price). Isn't it reasonable that oncologists and patients would be willing to pay a moderate price of about $1 per gram for high-quality, reliable generic drugs? What happened to the United States (US) generic drug manufacturers that formerly and reliably supplied high-quality products that we could prescribe to our patients with confidence?

Like many manufactured items, the generic drug system is a victim of the same market forces that resulted in the loss of many industries in the US when manufacturing migrated to countries where it was less expensive to produce goods. Although it may have been a problem for some apparel and shoe manufacturers, many US brands have still managed to control quality with oversight so that product quality is not compromised.

In drug manufacturing, however, US generic manufacturers have been priced out of the industry and gone out of business due to the extremely low cost of drugs originating primarily in India or China. There was no economic incentive for US generic suppliers to manufacture abroad with adequate quality control. The drug system middlemen, pharmacy benefit managers, have relentlessly sought the cheapest sourcing for these drugs, believing that quality would be maintained by local oversight or FDA inspection. However, this is not the case, as we have seen. These companies are not inspected by the FDA in a process similar to US manufacturers, due to logistics of international oversight, lack of funding, and lack of inspectors. Of course, recent barriers related to the pandemic have exacerbated the inspection problem. When the FDA *did* inspect these manufacturers, the factories often were shut down for problems with the drug quality, with the subsequent collapse of the penny-drug supply.

How can we, consumer oncologists and pharmacists, make this system better? We need to demand somewhat more costly but high-quality generic drug products. How can we get the former US manufacturers of generic drugs to return to producing standard chemical drugs rather than just biosimilars? To do that, we, as consumers, need the right information. Regarding biosimilars, I have previously complained about the 4-letter suffixes on all new drugs that allow identification of manufacturers and tracking of interchangeability.

My complaint is based on the fact that all the biosimilar manufacturers are submitting thorough manufacturing data to the FDA, yet we have no data to help us choose between these branded biosimilars. This system would work well for our generic chemotherapy drugs, allowing manufacturers to be identified and their quality recognized. This supposes pharmacy departments, practices, and insurers would pay more for higher-quality generics. This must be coupled with more regular FDA inspections of generic drug manufacturers, which would receive FDA ratings or certification. The companies themselves would likely be willing to pay for the cost of more frequent inspections through a system such as the Prescription Drug User Fee Act. We do not need to subject ourselves and our patients to these shortages of critical agents. We just need to be willing to pay a little more and institute a system to identify high-quality manufacturers. ■

MEET OUR EXPERT

Monique Gary, DO, MSc, FACS
Breast surgeon and medical director at Grand View Health

Scan QR code to watch the full video series

Increase in Early-Onset Incidence May Be Driven by Breast/Gynecologic Cancers

"We should pay attention to the patient, and not just the patterns. Too often, young people are dismissed because they don't fit the typical mold of what cancer looks like. We have historically been taught that cancer is largely a disease of aging."

Patterns with increasing incidence of early-onset cancer are being primarily driven by patients around 30 years of age and women's cancers such as breast and gynecologic cancers, **Monique Gary, DO, MSc, FACS**, said in a conversation with CancerNetwork.

The increase may be attributed to risk factors often seen with sedentary lifestyles such as obesity, poor diet, and a lack of physical activity. Out of a total of 35,721 incidences of early-onset cancer that occurred in 2019, 12,649 were breast cancer, according to a study assessing patterns in cancer incidence in patients less than 50 years of age from 2010 to 2019. This was a higher incidence than for any other cancer during this period.

In addition to examining these patterns, Gary, a breast surgeon and medical director at Grand View Health, indicated that patients need to be considered at an individual level.

Q: What were some of the patterns in breast cancer incidence that were observed in this study?

The study looked at more than 500,000 individuals from 2010 to 2019. What they found was that the increase in cancer in younger individuals is being driven by cancers in women and adults in their 30s. When we say cancer in women, we particularly [mean] breast and gynecologic cancers like uterine cancers. There were 34,233 [women diagnosed with] early-onset cancers in 2010 and 35,721 in 2019; that increase was about 4.35%. While breast cancer showed the highest total among the early-onset [cases], it's an interesting juxtaposition because we're also noting that there's a decrease in overall cancer mortality. That's something that we need to look into a little bit further.

Q: What are some theories as to why these patterns might develop in these populations?

There are no definitive explanations that came out of this study. This was a study that was populationwide and designed to look at a cross-section of where we are and see where there might be some leads. There were some interesting associations with things like smoking, obesity, and physical activity. When you look at the number of gastrointestinal cancers, for example, that have increased, those are all going to be related to those risk factors [seen in] sedentary lifestyles. There are opportunities for us to do some interventions on that population's health and wellness because much of what we're seeing has a lot to do with what's been happening to us as a society.

What I mean by that is, when you look at even the rates of obesity, they're mirroring the rates of increase in cancer in young people. We know that younger people are struggling with their weight. Those increases are probably going to—at least we believe in the scientific

community—result in some increased cancer incidence and may be part of the phenomenon that we're experiencing.

Q: Where do you think that future research efforts need to be focused?

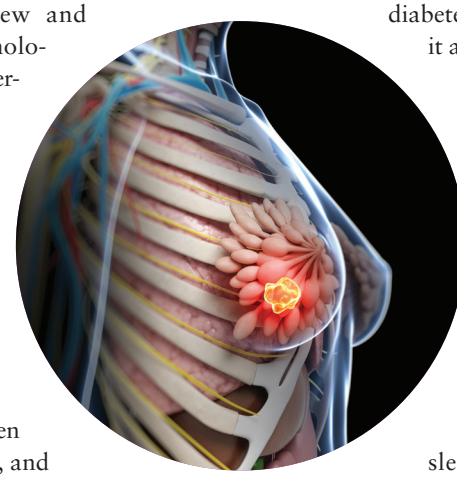
Our focus needs to be on teasing out the data that relate to marginalized and at-risk communities. Even though we see some changes in the incidence and changes in mortality, those individuals are at the highest risk of breast cancer. Women of color, Black women [specifically], have the highest mortality of any group. These types of studies did not necessarily include a large cross-section of women of color, [including] Hispanic women. We need to look into those data and see where those concomitant increases are.

We need to look at the screening guidelines, and this should be a huge clarion call for all those individuals who are involved in making guidelines because they continue to say there is insufficient evidence to recommend things such as supplemental screening for women with dense breasts and starting screening earlier for women of color—Black women, in particular. As we continue to say there's insufficient evidence, we have to then build upon this growing body of evidence. I would love to see us look to do things like more trial recruitment and enrollment of younger patients. We need to make sure that we think of their unique considerations. They may be working; they may have issues with child care; they may need supportive therapies like fertility preservation.

There are a whole host of things to think about, even down to supportive therapies like cold caps and preserving [patients'] hair follicles. There are so many things that you think about when you involve young people in this oncologic treatment journey, that we need to look at from the treatment lens but also from the research lens. Can we validate what we're seeing? What's happening in our Asian and Pacific Islander [patients]?

We [also] need to look at the screening technologies and make sure that they're appropriate for the age and incidence of people who are developing these cancers. Mammograms continue to be based on density. If we're finding cancers in younger and younger people, are we using the best tools for that?

Are there new and emerging technologies that could perhaps even support that? This gives us an opportunity as a scientific community to look to innovation and to be creative about how we look to screen younger people, and not just fall back on the same patterns of the retrospective studies that we have seen that are informing current practice. I have a saying: You can't walk forward while looking backward. We have to make sure that we are doing everything we can to be inclusive of these younger and higher-risk populations. As a scientific community, we're getting there.



Q: What should your colleagues take away from our conversation?

The only other thing I [want] to mention is that the one thing that these [themes] have in common is that this is teaching us about the need to focus on wellness. What I mean by that is, when you look at the associated or the potentially associated risk factors for why we're seeing this increase in cancers, things like a sedentary lifestyle, obesity, mental health, depression, anxiety, and stress are all preventable risk factors. There is a message of hope that I want people to take away from all of this; no matter which cancers we're looking at, we, as a global community, need to focus on those preventive best practices that promote wellness because the rising tide floats all boats. When we focus on the things that prevent inflammation in our body to decrease the rates of diabetes and heart disease, it also helps to decrease the risk of cancer and cancer recurrence. When we address our mental health, we typically will address other aspects of our physical health, our nutritional well-being, and even sleep. [These are all things] that people knew that they should do but [may not have understood how they] have such an impact on overall health. We're finding they do not just for chronic illnesses, but also for life-threatening illnesses like cancer. It's just so important for us to take that message home, which is that we need to focus on eating good food, getting good rest, making sure that we are doing practices to reduce our stress, and that we are moving our bodies. Those things are going to yield some dividends that hopefully reverse some of these very disturbing trends that we're seeing. ■

Reference

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Exploring the Changing Diagnostic Criteria of Gorlin–Goltz Syndrome: A Case Report

Sahith Kumar Shetty, BDS, MDS; Vidya G Doddawad, BDS, MDS; Shyam Sundar S, BDS, MDS; Shivananda S, BDS, MDS

ABSTRACT

Gorlin-Goltz syndrome, also known as Gorlin syndrome, basal cell nevus syndrome, and nevoid basal cell carcinoma syndrome, is an autosomal dominant genetic disorder. Its hallmark is an early onset of basal cell carcinoma. Additionally, the syndrome is characterized by a spectrum of distinct clinical attributes encompassing oral, skeletal, ophthalmic, neurological, and developmental aberrations. This condition arises due to anomalies in the Hedgehog signaling pathway, leading to constant pathway activity and uncontrolled growth of tumor cells. Early identification of the disorder through available diagnostic methods and clinical and radiological findings is crucial for accurate diagnosis, which subsequently leads to the formulation of an effective treatment regimen.

The purpose of this case report is to discuss the role of a dentist in early detection based on various author-prescribed criteria and the need for a multidisciplinary approach to the treatment of patients with this syndrome.

KEYWORDS

Nevoid basal cell carcinoma syndrome, basal cell nevus syndrome, Gorlin syndrome, basal cell carcinoma, odontogenic keratocyst, panoramic radiography

Introduction

Nevoid basal cell carcinoma syndrome (NBCCS), alternatively referred to as basal cell nevus syndrome or Gorlin-Goltz syndrome (GGS), was initially documented in the scientific literature in 1894 by Jarisch and White. They outlined the fundamental characteristics of this syndrome and designated it NBCCS. However, it was not until the middle of the 20th century that NBCCS gained acknowledgment as a distinct and separate medical entity.[1] In 1960, Robert James Gorlin and William Goltz identified the classical triad (consisting of multiple basal cell epitheliomas, keratocysts in the jawbones, and bifid ribs) that formed the diagnostic criteria for this syndrome.[2] The newly revised fifth edition of the World Health Organization's (WHO) classification for hereditary head and neck tumor syndromes reaffirms the consistent utilization of diagnostic criteria that have been in place for more than 10 years.[3] Although the existence of multiple odontogenic keratocysts (mOKCs) remains a significant criterion, there is still a lack of substantial evidence to determine the specifics of which individuals with multiple basal cell carcinomas should undergo dental screenings, including using panoramic radiographs to identify mOKCs associated with GGS.[4]

Gorlin-Goltz syndrome is a rare genetic condition inherited in an autosomal dominant manner. This disorder is marked by the presence of BCC, OKCs, and medulloblastomas, along with distinct features such as dyskeratotic palmar and plantar pitting, as well as a variety of skeletal and other developmental irregularities.[4] This study presents the cranial, facial, dermatological, dental, and skeletal expressions of GGS in a young adult. The diagnosis of GGS was established through an assessment of clinical symptoms, radiographic characteristics, and histopathological examinations.

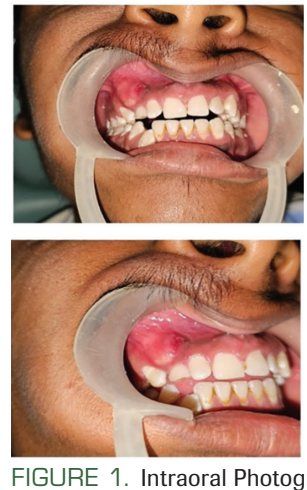

FIGURE 1. Intraoral Photograph Showing Solitary Palpable Swelling in the Back Close to the Midline

Case Presentation

A 21-year-old man presented at an outpatient JSS Dental Hospital in Mysore, India. His chief complaint was of swelling in his right upper jaw for 15 days. The patient's family history

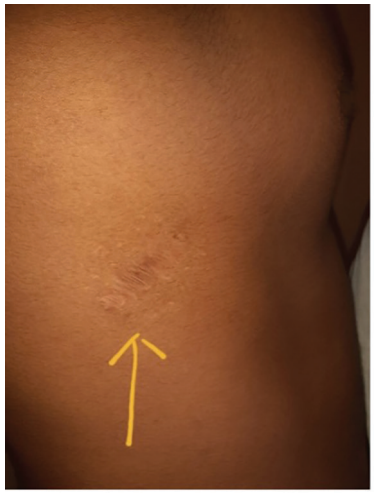

FIGURE 2. The Presence of Scar Markings of Basal Cell Carcinoma at the Upper Portion of the Trunk

FIGURE 3. Extraoral Photograph Showing Mild Frontal Bossing, Wide and Depressed Nasal Bridge, and Hypertelorism

and medical history were not significant. The swelling was 2 × 1 cm in dimension, nonpitting, and nontender (**Figure 1**). There was no lymphadenopathy, and no facial asymmetry was seen. He had a history of surgery at the back of his trunk due to a tumor that was diagnosed as BCC (**Figure 2**). On facial examination, mild frontal bossing, wide and depressed nasal bridge, and orbital hypertelorism were noted (**Figure 3**). Oral examination showed misaligned teeth with an open bite in the anterior region (**Figure 1**). Examination of the hands and palmar surface showed some brownish-black depression similar to palmar pitting (**Figure 4**).

An orthopantomogram revealed multiple radiolucent lesions in both upper and lower jawbones. A large radiolucency with a well-defined margin was seen on both sides of the posterior ramus of the mandible and was approximately 3.0 × 2.5 × 3.0 cm. A large radiolucent lesion with a well-defined margin was seen in the anterior maxilla with impacted maxillary right canine teeth. A smaller radiolucent lesion between the root apices of the mandibular right canine and lateral incisor was also noted (**Figure 5**). Posterior-anterior and lateral views of the skull radiograph showed calcification of falx cerebri and bridging of sella turcica (**Figure 6**). Chest radiographs showed no abnormality. The provisional diagnosis of GGS was made based on the presence of multiple cysts in the jaws and extra oral features.

Routine biochemical and hematological evaluations were carried out and showed normal parameters. An incisional biopsy of the cyst was sent for histopathological examination. On examination, the specimen demonstrated the presence of parakeratinized stratified squamous cell epithelium with corrugation that was 6 to 8 cell layers thick. The basal layer showed palisading nuclei and tombstone appearance. Epithelial connective tissue separation was seen. The underlying connective tissue showed odontogenic epithelial islands, blood vessels, and inflammatory cells. The lumen showed keratin flakes (**Figure 7**). All features were suggestive of odontogenic keratocyst or keratocystic odontogenic tumor (KCOT).

Under general anesthesia with all aseptic precautions, flaps were raised intraorally in all quadrants, one after the other. A surgical window was needed only in the third quadrant to reach the cyst. No vital structures were seen near the lesions. A surgical curette was used with saline irrigation for enucleating the cysts (**Figure 8**). The remnants of the cysts were removed using chemical cautery with Carnoy's solution (2.5%) for 3 minutes and irrigation with saline. The cysts were enucleated from all 4 quadrants, followed by extraction of impacted teeth. The enucleated tissues were sent for histopathological evaluation. All the lesions were diagnosed as odontogenic keratocysts.

The presence of 2 major signs (multiple odontogenic keratocysts and history of BCC) and 4 minor signs (calcification of falx cerebri, palmer pitting, bridging of sella turcica, and hypertelorism) confirmed that this patient had GGS. The patient is being followed up at 3-month intervals, and no recurrence of lesion has been noted.

Discussion

GGS is an autosomal dominant disorder. It is recognized by the occurrence of numerous BCCs and is accompanied by irregularities in the skeletal, ophthalmic, and neurological realms.[4] This condition affects various systems and presents a wide array of indications and effects, giving rise to irregularities in the skin,

FIGURE 4. Palmar Surface With Brownish-Black Depression Appearing as Palmar Pitting

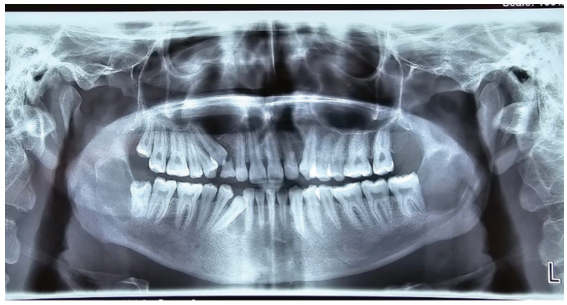

FIGURE 5. Orthopantomogram With Multiple Multilocular Radiolucent Lesions in the Maxilla and Mandible

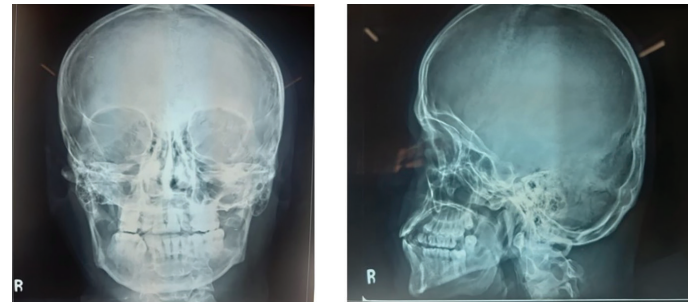

FIGURE 6. Radiograph of the Posterior-Anterior and Lateral View of the Skull With Calcification of Bilamellar Falx Cerebri

TABLE 1. **Jarisch and White's Explaination of the Essential Features of Gorlin-Goltz Syndrome[5]**

Cutaneous anomalies	Basal cell nevus, other benign dermal cysts and tumors, palmar pitting, palmar and plantar keratosis, dermal calcinosis
Dental and osseous anomalies	Multiple OKCs, mild mandibular prognathism, frontal and temporoparietal bossing, kyphoscoliosis or other vertebral defects, bifurcated ribs, spina bifida, brachymetacarpalism
Ophthalmic anomalies	Hypertelorism, wide nasal bridge, dystopia canthorum, congenital blindness, internal strabismus
Neurological anomalies	Mental retardation, dural calcification, bridging of sella, agenesis of the corpus callosum, congenital hydrocephalus, occurrence of medulloblastoma
Sexual anomalies	Hypogonadism, ovarian tumorlike fibrosarcoma.

OKC, odontogenic keratocyst.

TABLE 2. **Diagnostic Criteria for Nevoid Basal Cell Carcinoma Syndrome Given by Evan Anne and Adapted From Bree AF[1]**

Major criteria	Minor criteria
1. Basal cell carcinoma before age 20 years or excessive numbers of basal cell carcinomas out of proportion to prior sun exposure and skin type 2. Keratocystic odontogenic tumor before age 20 years 3. Palmar or plantar pitting 4. Lamellar calcification of the falx cerebri 5. Medulloblastoma, typically desmoplastic 6. First-degree relative with nevoid basal cell carcinoma syndrome	1. Rib abnormalities 2. Other specific skeletal malformations and radiologic changes (eg, vertebral anomalies, kyphoscoliosis, short fourth metacarpals, postaxial polydactyly) 3. Macrocephaly 4. Cleft lip or palate 5. Ovarian or cardiac fibroma 6. Lymphomesenteric cysts 7. Ocular abnormalities (eg, strabismus, hypertelorism, congenital cataracts, glaucoma, coloboma)
One major criterion with molecular confirmation	
Requirements for diagnosis included (1) 2 major diagnostic criteria and 2 minor diagnostic criteria, (2) 2 major diagnostic criteria and 2 minor diagnostic criteria.	

TABLE 3. **Diagnostic Criteria for Nevoid Basal Cell Carcinoma Syndrome Established by Rayner et al and Later Modified by Kimonis et al[5,7-9]**

Major criteria	Minor criteria
1. More than 1 basal cell carcinoma before age 20 years 2. Histologically proved OKCs 3. Three or more cutaneous palmar or plantar pitting 4. Bifid or fused or splayed ribs 5. First-degree relative with nevoid basal cell carcinoma syndrome	1. Macrocephaly 2. Orofacial congenital malformation such as cleft lip or palate, hypertelorism, frontal bossing, coarse facies 3. Other skeletal anomalies such as pectus deformities, Sprengel deformity, calcification of the falx cerebri 4. Radiologic abnormalities such as bridging of sella turcica, vertebral anomalies, modeling defects or flames, shaped radiolucencies of hand and feet 5. Medulloblastoma 6. Ovarian fibroma
Requirements for diagnosis included 2 major and 1 minor, or 1 major and 3 minor, diagnostic criteria.	

OKC, odontogenic keratocyst.

skeletal structure, craniofacial features, nervous system, oropharyngeal area, genitourinary system, and heart. The primary clinical characteristics of GGS demonstrate a triad of BCC, multiple KCOTs, and skeletal anomalies.[5]

NBCCS, a seldom-seen condition inherited through autosomal dominance, stands out due to its most prominent feature: the emergence of cutaneous BCCs starting at a young age, usually at puberty, although some instances occur during childhood. The estimated occurrence of this condition ranges from 1 in 57,000 to 1 in 256,000 individuals, affecting both men and women without any gender bias. Although this disorder affects various ethnicities, only a small proportion (5%) of cases involve African, American, or Asian individuals. Interestingly, the diagnosis of NBCCS often happens incidentally when extracutaneous signs such as OKCs are present, rather than through the observation of BCCs.[4,5] The male-to-female ratio is 1:0.62 for OKCs not associated with NBCCS and 1:1 for OKCs in NBCCS. That is, simple keratocysts are more common in males, but more females with NBCCS develop OKCs.[6] Similarly, the current case study presents a 21-year-old man exhibiting multiple OKCs that affected all 4 quadrants of the jaw.

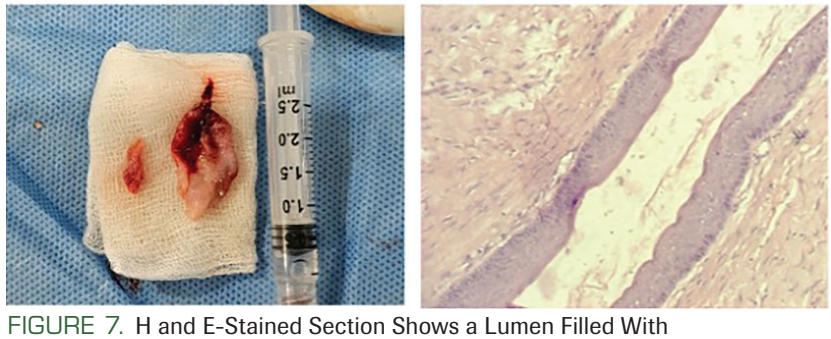

FIGURE 7. H and E-Stained Section Shows a Lumen Filled With Keratin Flakes and Cystic Capsule Lined by a Corrugated Epithelium Having 6 to 8 Layers of Thickness

FIGURE 8. Surgical Excision of the Lesion Under General Anesthesia

The underlying mechanisms of NBCCS are elucidated through molecular changes in components linked to genetic mutations in elements of the Hedgehog pathway. This encompasses the *PTCH1* gene, situated on chromosome 9q22.3, and the *SUFU* gene located on chromosome 10q24.3, which carries mutations that contribute to the disorder.[1-3] The Hedgehog pathway serves as a critical regulator of cellular growth and differentiation during developmental processes. Additionally, it governs interactions between epithelial and mesenchymal cells across various tissues in embryonic stages. Although this pathway is usually quiescent in adults, when disrupted it can lead to elevated production of crucial proteins involved in cell proliferation and the development of cancer.[5]

BCCs are frequently aggressive in

TABLE 4. **Diagnostic Criteria for Nevoid Basal Cell Carcinoma Syndrome After the Updated 5th Edition of the World Health Organization Classification of Head and Neck Tumors**[2,3]

Major criteria	Minor criteria
1. Basal cell carcinoma before age 20 years, or excessive numbers of basal cell carcinomas out of proportion to prior sun exposure and skin type 2. Odontogenic keratocyst before age 20 years 3. Three or more palmar or plantar pitting 4. Lamellar calcification of the falx cerebri 5. Medulloblastoma, typically desmoplastic 6. First-degree relative with nevoid basal cell carcinoma syndrome	1. Bifid, fused, or markedly splayed ribs 2. Other specific skeletal malformations and radiologic changes (eg, hemivertebrae, fusion, or elongation of the vertebral bodies such as kyphoscoliosis, Sprengel deformity, marked pectus deformity, short fourth metacarpals, postaxial polydactyly) 3. Macrocephaly 4. Cleft lip or palate (or any other congenital malformation of the craniofacial region; eg, frontal bossing, coarse face) 5. Ovarian or cardiac fibroma 6. Lymphomesenteric cysts 7. Ocular abnormalities (eg, strabismus, moderate or severe hypertelorism, congenital cataracts, glaucoma, coloboma).

Requirements for diagnosis included (1) 2 major diagnostic criteria and 1 minor diagnostic criterion, (2) 1 major and 3 minor diagnostic criteria, or (3) identification of a heterozygous germline *PTCH1* or *SUFU* pathogenic variant on molecular genetic testing.

a clinical context and are more prevalent in individuals with lighter pigmentation and higher exposure to UV light. Although they mainly develop on the face, they can also appear on the trunk and limbs. These carcinomas generally emerge from puberty to middle age, although instances have been documented as early as 2 years of age. Many patients (70%-80%) exhibit additional recognized clinical features, including KOTs, dyskeratotic palmar and plantar pitting, and rib and spine irregularities, with early calcification of the falx cerebri. In a significant portion of patients, facial characteristics such as frontal bossing, hypertelorism, macrocephaly, and cleft lip and/or palate are also observed. Uncommonly, patients are at risk of desmoplastic medulloblastoma during childhood, along with various other neoplasms such as ovarian and cardiac fibromas, mesenteric keratocysts, rhabdomyosarcomas, and meningiomas.[1,3]

OKCs are the primary oral lesion of this condition, arising approximately 3 times as often in the mandible as in the maxilla. They frequently appear near the crown of an unerupted tooth. More than 80% of these cysts are unilocular in nature, although multilocular occurrences are also possible. Multiple KCOTs are the most reliable signs of GGS, particularly during the initial 2 decades of life. Histologically, these lesions present a uniformly thick squamous epithelial lining, typically with 5 to 10 layers of cells, featuring parakeratosis and basal/parabasal cell palisading. They are often accompanied by satellite tumors. Epithelial lining is commonly notable for high Ki67 proliferation index, p53 immunopositivity in basal and suprabasal cell layers, and loss of heterozygosity at various loci.[3] In the current scenario, jaw cysts can present as multiple OKCs, possibly alongside impacted teeth, affecting all jaw quadrants. These cysts may exhibit unilocular or multilocular radiolucent characteristics. Clinical manifestations can include pain in the presence of swelling.

Early detection of the syndrome makes it possible to minimize the childhood and adult complications related to GGS. Furthermore, those who test negative for a known familial *PTCH1* mutation before or immediately after birth can be removed from the surveillance program in the neonatal period. Patients with a known *PTCH1* mutation should be informed about the possibility of early prenatal testing and termination of an affected fetus, and about the possibility of preimplantation genetic testing. All first-degree relatives of patients with a known mutation should be offered predictive molecular genetic testing.[5]

An echocardiogram can reveal cardiac fibromas. A neurological examination and measurement of head circumference are recommended every 6 months together with an annual MRI of the brain until age 7 years, after which a medulloblastoma is unlikely to appear. Dental screening with an orthopantomogram of the jaw is recommended from 4 to 8 years of age until 40 years to detect jaw cysts. A total skin examination should be performed at least annually starting during puberty but may need to be done more frequently if rapidly evolving skin lesions are present. Ovarian fibromas can be detected in the first and second decades by an ultrasound scan.[5]

Radiological examinations are pivotal for diagnosing GGS. Approximately 60% of patients exhibit distinctive dysmorphisms such as macrocephaly, protruding forehead, and facial milia. Skeletal irregularities can include fused or cuneiform vertebrae, hemivertebrae, and kyphoscoliosis, which may be evident. Additionally, facial dysmorphisms such as cleft lip/palate, macrocephaly, oral pathologies, and anomalies are commonly observed.[6]

Standard treatment strategies for odontogenic lesions that arise within the jawbones include as follows[4]:

- simple enucleation of the lesion;
- enucleation combined with

bone curettage, with or without the use of cytotoxic chemicals applied topically;
- complete resection in an en bloc manner, potentially followed by bone reconstruction;
- marsupialization procedure; and
- decompression of the lesion.

Given the often substantial tumor burden, individuals with NBCCS may undergo numerous excisions, leading to significant disfigurement. Besides surgical approaches, conventional therapies for localized disease involve applying agents such as 5-fluorouracil and imiquimod topically. Radiotherapy is not recommended for patients with NBCCS.[1]

The reported recurrence rate for OKC in the literature varies from 12% to 62.5%, influenced by factors such as duration, growth pattern, the inclusion of ortho- or parakeratinized epithelium lesions, and association with basal nevus syndrome. The possible reason for this wide range is likely the inadequate and incomplete removal of the primary lesion, although the exact cause remains uncertain.[2,4]

Postsurgery follow-up periods for OKC differ, with approximately 6 months for children and 1 year for adults. Recurrence observation spans 1 to 10 years, involving regular orthopantomography every 6 months for young patients and cone beam CT when doubts arise or anatomical structures need assessment. Follow-up for adult and older patients tends to be longer.[4]

Evolution of Early Diagnosis of GGS Based on the Criteria

Since 1894, numerous criteria have been proposed to diagnose GGS. Initially, Jarisch and White outlined essential features and termed it NBCCS (**Table 1**).[5] In 1960, Robert James Gorlin and William Goltz identified the classical triad (multiple basal cell epitheliomas, keratocysts in the jaws, and bifid ribs) that confirmed the syndrome's diagnosis. Evans et al originally defined the diagnostic criteria for NBCCS in 1993, later reviewed by Manfredi et al. In 2011, Bree et al suggested that for a GGS diagnosis, a minimum of 2 major and 2 minor, or 1 major and 3 minor criteria, must be met. He also suggested confirming the syndrome with molecular investigations (**Table 2**).[1] Rayner et al further refined the triad, asserting that for diagnosis, cysts should be present in combination with falx cerebri calcification or palmar/plantar pits.[9] Kimonis et al in 1997 adjusted this to require either 2 major or 1 major and 3 minor criteria for diagnosis (**Table 3**).[5,7-9] Presently, WHO recommends considering the diagnostic criteria for GGS if multiple basal cell carcinomas and/or OKCs occur before age 20 (**Table 4**).[2,3]

The current paper highlights the proposed diagnostic criteria for this syndrome and establishes the surveillance recommendations for these patients with the goal of early intervention to decrease morbidity and mortality because the syndrome may have potentially lethal complications in early childhood. A multispecialty health professional such as a dermatologist, neurologist, neurosurgeon, family physician, geneticist, or dentist needs to facilitate timely assessment through diagnostic criteria as well as laboratory evaluation.

Conclusion

GGS is a rare autosomal dominant disorder that involves multiple organ systems, including the skin, ophthalmic, cardiac, and jaws. Knowledge of the maxillofacial manifestations is important for early diagnosis of this syndrome so that optimal treatment can be given and progression to a threatening condition curbed. Early diagnosis requires early radiographic and clinical assessment. Multidisciplinary management of the disorder enhances life quality and symptom treatment.

Given the multisystem involvement of GGS, recognizing major and minor diagnostic criteria is vital. Clinicians identifying syndrome-associated morphological traits can prompt germline screening, aiding identification of at-risk individuals and genetic counseling. Genetic insights can guide therapy and surveillance approaches. ■

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AUTHORS' CONTRIBUTIONS

VGD: Concept, writing, and literature search for the manuscript
SS, SS: Review, data collection, and supervision of the manuscript
All authors read and approved the final manuscript.

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RAPID REPORTER

ONCOLOGY Reviews Key Presentations From the
2023 International Myeloma Society Annual Meeting

Daratumumab Combos Are Effective in NDMM Despite Relapses in Subgroups

Treatment with daratumumab (Darzalex) quadruplet regimens appears clinically effective in patients with newly diagnosed multiple myeloma (NDMM), although certain subsets of patients still experience early relapse.

The International Staging System (ISS) did not adequately predict outcomes in patients receiving daratumumab quadruplet therapy (P = .035), as well as revised ISS (R-ISS) staging (P = .00019). Additionally, although there appeared to be no differences in the rates of achieving minimal residual disease (MRD) negativity by the presence or absence of an IgH translocation, progression-free survival (PFS) was adverse in patients (P = .043). Similarly, there was no difference in MRD-negativity achievement concerning the gain of 1q, which also had an adverse impact on PFS (P = .00078).

When considering the deletion of any *TENT5C, RPL5, XBP1, IKZF1,* or *IKZF3* genes, investigators found no differences in MRD status among patients, although these deletions conferred a worse PFS (P = .042). Additionally, MRD negativity rates appeared to be similar regardless of APOBEC activity, although the presence of APOBEC activity correlated with worse PFS (P = .025). Regarding complex structural variant chromothripsis, investigators observed a trend toward significance, although there was no confirmation that would require prolonged follow-up.

The second-revision R-ISS (R2-ISS) staging, which accounts for a compounding effect of multiple genomic risk factors not included in R-ISS criteria, appeared to more accurately predict PFS (P = .0067). When adding 1 point for high APOBEC activity on top of R2-ISS disease, this defined a small cohort of patients with a median PFS of less than 18 months. In this population, the daratumumab-based quadruplets are failing.

A median follow-up of 1.4 years overall was observed. Additionally, the median follow-up was 4.4 years in the daratumumab plus carfilzomib (Kyprolis), lenalidomide (Revlimid), and dexamethasone (Dara-KRd) cohort and 1.0 year in the daratumumab plus bevacizumab (Velcade), lenalidomide, and dexamethasone (Dara-VRd) cohort. Overall, 50 patients experienced disease progression, including 26 who received Dara-KRd and 24 treated with Dara-VRd. There were no differences in PFS (P = .11) or overall survival (P = .73) between these treatment arms.

Concerning the genomic data set, fluorescence in situ hybridization testing was performed on 245 patients, SNP-array in 129, targeted sequencing with Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) Heme in 84, and whole genome sequencing in 57. Most patients had ISS stage I disease (n = 106) and R-ISS stage II disease (n = 134).

Ongoing research is focusing on 50 whole genome sequencing samples from patients treated with daratumumab quadruplet regimens.

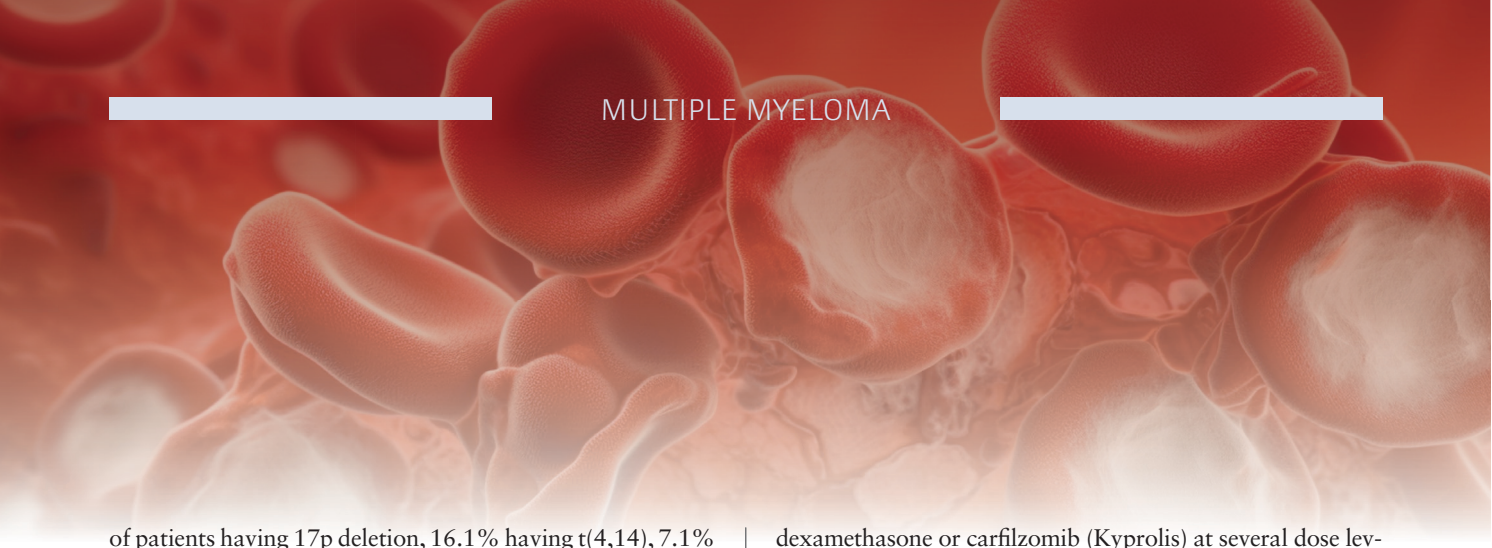
→ **For references and to read the full article, visit: cancernetwork.com/Daratumumab_IMS23**

Real-world Teclistamab Use Finds Comparable Efficacy With MajesTEC-1 in Multiple Myeloma

The use of teclistamab (Tecvayli) in a real-world study of patients with relapsed/refractory multiple myeloma showed comparable efficacy results with those of the phase 2 MajesTEC-1 trial (NCT03145181; NCT04557098).

The median progression-free survival (PFS) was 4.7 months, with a median follow-up of 69.5 days. For patients who had received prior B-cell maturation antigen (BCMA) directed therapy, the median PFS was 4.0 months compared with those who had not received prior therapy, in whom median PFS was 4.8 months (P = .48).

Investigators analyzed high-risk cytogenetics, with 26.8%



of patients having 17p deletion, 16.1% having t(4,14), 7.1% having t(14,16), and 39.3% having +1q21. Extramedullary disease was noted in 42.9% of patients, as well as central nervous system disease in 12.5%.

The overall response rate was 53.6%. If patients had not received prior BCMA treatment (n = 36), the rate was 58.3%; for those who did receive prior BCMA therapy (n = 20), it was 45%. In patients who received chimeric antigen receptor T-cell BCMA-directed therapy (n = 13), the rate was 30.8%; those who received prior BCMA antibody drug conjugate therapy (n = 13) had a response rate of 53.8%, and patients with extramedullary disease (n = 24) a rate of 37.5%. Those with high-risk cytogenetics also achieved fewer responses than those who did not have them.

Regarding safety, any-grade cytokine release syndrome (CRS) occurred in 51.8% of patients treated with teclistamab, with grade 3 or higher CRS occurring in 1.8%. The median time to onset of CRS was 5 days (range, 1-7), and the median duration of the adverse effect (AE) was 2 days. Any-grade neurotoxicity occurred in 1.8% of patients. To manage these AEs, tocilizumab (Actemra) was administered to 25% of patients with a median dose of 1, whereas 12.5% of patients received dexamethasone.

Infectious complications occurred in 57.1% of patients. A total of 48.4% of patients experienced grade 3/4 infectious complications; however, no deaths occurred. Infectious complications included upper respiratory infection (37%), pneumonia (19%), gastrointestinal issues (13%), skin and soft tissue (13%), and viremia, bacteremia, and genitourinary issues (6% each). The median onset of these AEs was 31.5 days; COVID-19 comprised 45.5% of the upper respiratory infections.

→ **For references and to read the full article, visit: cancernetwork.com/Teclistamab_IMS23**

Mezigdomide Combos Yield Encouraging Responses in R/R Multiple Myeloma

Treatment with mezigdomide demonstrated encouraging responses when combined with bortezomib (Velcade) and dexamethasone or carfilzomib (Kyprolis) at several dose levels in those with relapsed/refractory (R/R) multiple myeloma, according to data from the phase 1/2 CC-92480-MM-002 trial (NCT03989414).

Results showed that, in a dose-escalation cohort (cohort A), the triplet regimen elicited a 77.8% objective response rate (ORR) at the 0.3-mg mezigdomide dose (n = 9), which included a 22.2% stringent complete response (sCR) rate, a 22.2% very good partial response (VGPR) rate, and a 33.3% PR rate. One patient had stable disease (SD) and 1 patient had progressive disease (PD).

At the 0.6-mg dose of mezigdomide (n = 9), the ORR was 88.9%, and 1 person each had an sCR, a CR, and a VGPR; the PR rate was 55.6%. One patient had SD. At the 1-mg dose (n = 10), the ORR was 60.0% and 1 patient had an sCR; the VGPR rate was 30.0%, the PR rate was 20.0%, 1 patient had a molecular response (MR) and 3 patients (30.0%) had SD.

In a dose-expansion cohort of the combination treatment (cohort D), the ORR at the 0.6-mg dose (n = 11) was 90.9% and the sCR rate was 27.3%. The VGPR rate was 54.5%, the PR rate was 9.1%, and 1 patient had SD. At the 1.0-mg dose in this cohort (n = 38), the ORR was 84.2%, which included a 7.9% sCR rate, a 10.5% CR rate, a 44.7% VGPR rate, a 21.1% PR rate, and a 2.6% MR rate. The SD rate was 7.9%, the PD rate was 2.6%, and 1 patient was not evaluable.

Additional efficacy findings showed that, in cohort A, the median time to first response (TTFR) was 1.38 months, the median duration of response (DOR) was 10.9 months (95% CI, 8.8-32.8), and the follow-up time was 13.6 months (range, 3.2-44.7). In cohort D, the median TTFR was 0.89 months, the median DOR was not reached (NR; 95% CI, 12.1-NR), and the median follow-up time was 12.71 months (range, 1.5-26.1).

In the dose-escalation cohort (cohort C), in patients who received the 0.3-mg dose (n = 9), the ORR was 88.9%, which included a 22.2% CR rate, a 33.3% VGPR rate, a 33.3% PR rate, and an 11.1% MR rate. The ORR was also 88.9% with the 0.6-mg dose (n = 9); the sCR rate was 11.1%, the VGPR rate was 22.2%, and the PR rate was 55.6%. A total of 11.1% of patients had PD.

Finally, at the 1.0 mg-dose in cohort C (n = 9), the ORR with

mezigdomide and carfilzomib/dexamethasone was 77.8%, with 1 CR, a 33.3% VGPR rate, a 33.3% PR rate, and 1 MR. One patient had SD. The median TTFR was 0.95 months (range, 0.9-5.1), the median DOR was 12.3 months (95% CI, 6.4-NR), and the median follow-up time was 12.45 months (95% CI, 1.1-31.5).

→ **For references and to read the full article, visit: cancernetwork.com/Mezigdomide_IMS23**

Teclistamab Produces Responses in Pretreated R/R Multiple Myeloma

Treatment with teclistamab (Tecvayli) demonstrated responses in patients with relapsed/refractory (R/R) multiple myeloma, including those who previously received anti–B-cell maturation antigen (BCMA) therapy.

In the study, responses to teclistamab were observed, which were reduced compared with those of patients naïve to anti-BCMA therapies. However, positive outcomes were seen among patients treated with commercial teclistamab.

Investigators observed that patients with enriched cytotoxic effector memory cells had a higher likelihood of response than those who had an abundance of regulatory T cells and other CD4+ subsets, as these patients were less responsive. This may be due to the competition for space on the CD3 binding arm for patients who received teclistamab.

The majority of patients had BCMA expression of 90% or greater in the prior BCMA therapy group who were receiving teclistamab compared with those in the BCMA-naïve group (P = .17). When patients were stratified by whether they had a response to teclistamab per International Myeloma Working Group criteria, no differences were observed between patient populations (P =.56). Regardless of whether patients had responded to their prior anti-BCMA therapies, the same BCMA expression was maintained.

Given that BCMA expression was present in nearly all patients, investigators questioned why there was so much heterogeneity in response. They looked at clinical data sets and absolute lymphocyte count measured prior to day 1 of cycle 1 of teclistamab among patients who had response and noted that some patients with grade 3/4 lymphopenia responded to teclistamab.

→ **For references and to read the full article, visit: cancernetwork.com/Teclistamab_BCMA_IMS23**

CONTINUING MEDICAL EDUCATION (CME)

Overcoming Obstacles to Clinical Trial Recruitment and Retention

FACULTY
Laura S. Wood, MSN, RN, OCN

Renal Cancer Research Coordinator, Retired
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This activity was written by PER® editorial staff under faculty guidance and review. The Q&A portion of the activity was transcribed from a recorded interview with the faculty and edited by faculty and PER® editorial staff for clarity.

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LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:

- Describe the structural and institutional barriers to clinical trial enrollment.
- Identify available resources to encourage clinical trial participation among your patients.

RELEASE DATE: NOVEMBER 1, 2023
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Clinical trials, a cornerstone of drug development, link groundbreaking discoveries in cancer research with the general patient population. Enrolling adequate numbers of participants with characteristics that represent all patients with a particular cancer remains a daunting challenge.[1] As many as 20% of clinical trials fail due to insufficient enrollment.[2] Patient awareness of clinical trials is the first hurdle to clear, although financial and geographic constraints may also limit patients' involvement in this research. Stringent trial eligibility requirements may exclude up to 25% of patients attempting to enroll in a study.[3] Further, patient misperceptions of clinical trials may create reluctance to participate in research.[4] Despite the rarity of placebo-only use in oncology clinical trials, many patients fear receiving a placebo or substandard care. In this article, **Laura S. Wood, MSN, RN, OCN,** describes the obstacles to clinical trial recruitment, enrollment, and retention as well as opportunities to overcome these deterrents.

Q: What is involved in the clinical trial recruitment and enrollment process?

WOOD: Recruitment and enrollment are 2 very distinct processes.[5] Recruitment involves informing people about the clinical trial. Recruitment is done either by networking with colleagues—we have a lot of community physicians who have referred patients to us—or through the national organizations, such as the Oncology Nursing Society (ONS), the American Society of Clinical Oncology (ASCO), or the American Society of Hematology.[6-8] It can also involve radio, social media, or other internet sources to help patients identify available clinical trials.[9] Knowing which centers do clinical trials and which centers focus on specific diseases is certainly helpful.

The enrollment process, then, is what a patient goes through to determine whether or not they are appropriate and eligible for a clinical trial.[5] Clinical trials have very defined inclusion and exclusion criteria.[3] If the objective of this study is to look at how a drug, drug combination, or procedure works, who is the patient population who can meet that objective? What are the patient characteristics? There are typically 20 to 40 inclusion and exclusion criteria in a given protocol. We want to make sure that the potential benefits outweigh the potential risks. Early clinical trials and new drug clinical trials have laboratory parameters that are representative of the patient population.[5]

Q: Why is it important to have a representative or balanced patient population in trials?

WOOD: So much time, effort, and money go into developing new drugs and new drug combinations that drug companies want to be sure that the results are going to be generalizable.[10] So we are broad in our general clinical trials to be equitable for all individuals. We want to take all comers for whom the risk-benefit ratio is reasonable, recognizing that there is more that we do not know about the safety of a drug or drug combination than what we do know. That is why we are doing the clinical trial. Then there may be some smaller substudies that follow, looking at more specific patient populations, such as individuals who have poor kidney function or poor liver function, be it because of liver comorbidities or liver metastasis. The trials are looking, then, at extending the safety profile in a more high-risk patient population.

Q: What are the major barriers to clinical trial enrollment for patients in underrepresented populations?

WOOD: The biggest barrier is knowledge. The patient, the caregiver, and sometimes the local oncologist are not aware of the potential for clinical trials.[4] It is a specialized group of individuals who do clinical trials, and they are not always in your backyard.

One of the other significant barriers is location.[4] Patients may know about a clinical trial and may be ideal for the clinical trial, but can they get there? Is it feasible both location and transportation-wise? Is it feasible financially? Is it feasible logistically? Will the patient need a caregiver? Can the caregiver get time off from work? There is the Family Medical Leave Act (FMLA), but that is not always sufficient for the frequency of visits required to participate in clinical trials.

A lot of work has been done by the Clinical Trials Network, the Association of Community Cancer Centers (ACCC), and national organizations trying to make access easier.[11,12] Pharmaceutical companies may allow stipends to be provided to help with accessibility costs. Can laboratory testing be done at a local facility? Can certain parts of the clinical trial be done closer to home? Do you have to come to the main institution for everything, or can you go to one of our family health centers or one of our satellite locations that might be more feasible to you? I will always ask a patient, "Do you have a family member who lives in 1 of these 2 cities where this trial is being conducted that is probably closer to you or within your insurance network?"

There are a lot of nuances that the oncology team can help with. I would absolutely encourage patients to be referred for clinical trials and go with the premise that they are eligible and it is feasible until proven otherwise. There are a lot of resources out there. The whole research team—the oncologist, potentially a navigator, the research nurse, a social worker—can help with finding resources that might be available to minimize those barriers.[7]

Q: What are some options for patients who do not live near clinical trial sites?

WOOD: One of the things that I had to do for a patient was to find out where they could park their camper, because they basically did road trips. Every time they needed to come, they came in their camper, and they stayed in their camper. We just needed to find where on our campus was appropriate for them to park it.

We have long-term-stay hotels in our area that will work with us for patients with cancer needing extended stays due to clinical trial participation. They will discount the stay, because they know that patient will keep coming back, whether it is every 2 weeks, every 4 weeks, or every 8 weeks. There's that comfort level of continuity for the patient as well—knowing where they are going to be. They get to know the front desk staff, and it is another whole support group for them as they go through treatment. It is peace of mind, and it takes away a stressor for the patient and the caregiver. It's huge.

Q: In your experience, what are some key patient concerns when they are contemplating enrolling in a clinical trial?

WOOD: The key concerns are, "Is it feasible, and can I afford it?"[2] There are a lot of disease-specific groups, such as the Kidney Cancer Association (KCA), with members who can help look at what resources are available to address those concerns.[13] The institution's social worker, navigator, or research nurse also knows what resources may be available to help with the concerns of financial costs, time off work, filling out FMLA papers, and working with the co-pay assistance foundations to try to help cover the co-pay.[6]

One of the groups that I worked with extensively for clinical trial enrollment was the Lazarex Cancer Foundation.[14] It is a foundation that supports both pediatric and adult financial challenges with clinical trial participation. The foundation has a form for the clinical trial team to fill out, and they then identify needs with the patient and caregiver and see what financial resources, such as a gas card, are available to help them during the duration of their clinical trial participation.

Also, managers at the cancer center that is doing the clinical trial are going to develop a research budget to identify those things that are standard-of-care tests and procedures that are covered by insurance and those things that are not. The clinical trial sponsor will cover those as research-related costs.[15] So patients need to know which costs are their responsibility and which are covered by their insurance, as well as which tests and procedures are research related and covered by the clinical trial. This information is included in the informed consent for clinical trial participation.

Q: How would you counsel patients who are concerned that clinical trial participation will interfere with their work or family obligations?

WOOD: The technical term is shared decision-making, but most of that is listening.[5] What are the patient's goals? We have patients who refuse to participate in clinical trials, because they don't want any chance of extra costs to challenge the financial status of the family. That is their

> "Our role is to be the link in the chain between the community, the center doing the research, and ACCC, which is a nationwide network."
> Laura S. Wood, MSN, RN, OCN

right. I can try to support them, but the best support I can give them is to say, "I totally value what you are saying and what your goals are, and we are happy to continue with the standard plan." Clinical trials are not the ideal thing for everybody, and they are not even a potential consideration for some people. We need to respect that.

There are also some individuals who have a higher risk associated with participating from a safety perspective.[5] We need to know, are they able to take an oral medication? Can they keep track of it? Are they aware enough and able enough to communicate with us as frequently as needed about the potential adverse effects so we can identify and intervene early, or are they going to be at risk? In which case, it may be more appropriate for them to come into the clinic to get an infusion. Again, that is where that whole shared decision-making is important.

Q: How can patient navigators address the challenges facing clinical trial recruitment?

WOOD: The most important thing for any provider to do, especially a navigator or care coordinator, is to be aware of what the clinical trials are and what the time frames are.[16] They need to network with the research staff so that they are aware of frequency of visits, and they need to help facilitate the conversation between the patient and the research site. Perhaps the patient can do a virtual visit to go through the primary checklist and see if there are any red flags that can be identified before they pack a suitcase. The navigator can say, "Yes, it seems reasonable to pursue this," or "No, we are very sorry, but there's a red flag. You're not eligible. I recommend going back to your treating physician and resuming the discussion of local treatment options."

Q: What role can community oncologists and nurses play in supporting clinical trial enrollment and retention?

WOOD: Being a facilitator is the most important aspect. If you know a bit about the clinical trial and the patient already has some specific questions, you can make a quick phone call to the research site.[7] I get a lot of phone calls from community offices from oncology nurses saying, "Hey, we have a potential patient. Can we see if he is eligible or not? Walk me through what the frequency of visits are. What can we do by phone before we refer the patient over to you?"

It is also important to know what resources are available so you can find out the most pertinent information.[4] The ClinicalTrials.gov website can help facilitate awareness.[17] Look to your network and community, maybe the Leukemia & Lymphoma Society, etc.[18] There are a lot of different disease-specific groups that may cross-network with some of these other resources. Is there an organization that is geared toward your cancer, such as the KCA or the American Bladder Cancer Society? What groups are out there, and what are the reputable websites where you can get good, sound information and contact information, such as a phone number for you to be able to ask some of those questions? One of the resources that the KCA has, which I'm sure others do as well, is a clinical trial matching network through the KCA navigator.[13] The network can help patients identify available options for open clinical trials and help them navigate and understand what clinical trials are.

Patients and caregivers need to know what it means to participate in a clinical trial.[5] What are the terminologies? Is it randomized? Is it placebo controlled? Is the drug brand-new and early in clinical trial development? Giving patients information sheets from cancer.net or ASCO is an important step oncologists and nurses can take to help patients understand what clinical trials are. Our role is to be the link in the chain between the community, the center doing the research, and ACCC, which is a nationwide network.

Key References

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For references, visit
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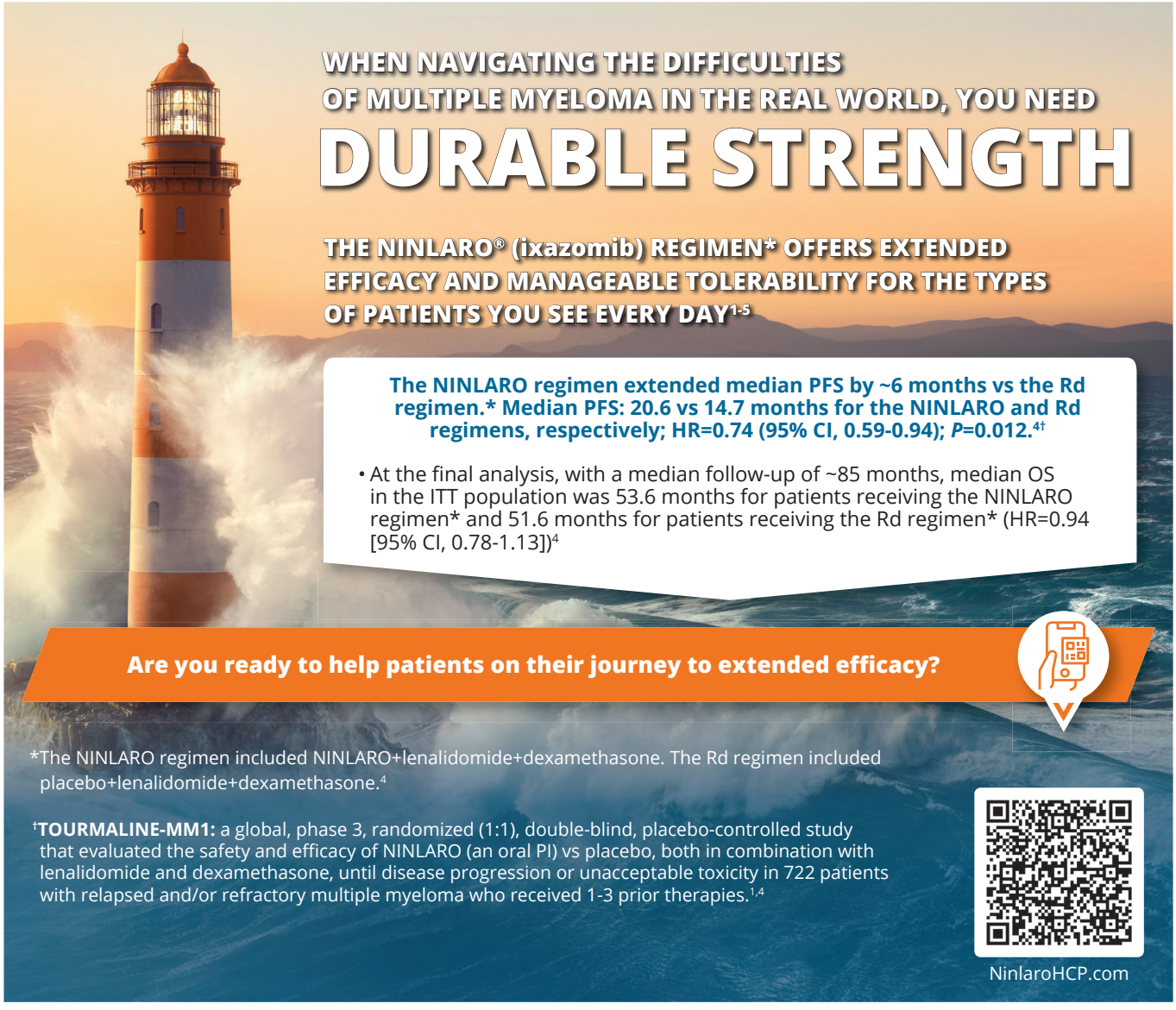

INDICATION AND USAGE

Indication: NINLARO is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Limitations of Use: NINLARO is not recommended for use in the maintenance setting or in newly diagnosed multiple myeloma in combination with lenalidomide and dexamethasone outside of controlled clinical trials.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Thrombocytopenia** has been reported with NINLARO. Platelet nadirs typically occurred between Days 14-21 of each 28-day cycle and recovered to baseline by the start of the next cycle. Grade 3 thrombocytopenia was reported in 17% of patients in the NINLARO regimen and Grade 4 thrombocytopenia was reported in 13% in the NINLARO regimen. During treatment, monitor platelet counts at least monthly, and consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines.
- **Gastrointestinal Toxicities,** including diarrhea, constipation, nausea and vomiting were reported with NINLARO and may occasionally require the use of antidiarrheal and antiemetic medications, and supportive

Please see additional Important Safety Information on the next page and accompanying Brief Summary.

NINLARO® (ixazomib) capsules
4mg | 3mg | 2.3mg

Proteasome inhibitor-based triplet regimens remain a cornerstone of treatment with optimal outcomes.[1,6]

How can you help patients on their journey to extended efficacy?

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

care. Diarrhea resulted in the discontinuation of one or more of the three drugs in 3% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Adjust dosing for Grade 3 or 4 symptoms.

- **Peripheral Neuropathy** was reported with NINLARO. The most commonly reported reaction was peripheral sensory neuropathy (24% and 17% in the NINLARO and placebo regimens, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (<1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 4% of patients in the NINLARO regimen and <1% of patients in the placebo regimen. During treatment, monitor patients for symptoms of neuropathy and consider adjusting dosing for new or worsening peripheral neuropathy.
- **Peripheral Edema** was reported with NINLARO. Evaluate for underlying causes and provide supportive care, as necessary. Adjust dosing of NINLARO for Grade 3 or 4 symptoms or dexamethasone per its prescribing information.
- **Cutaneous Reactions,** including a fatal case of Stevens-Johnson syndrome, were reported with NINLARO. If Stevens-Johnson syndrome occurs, discontinue NINLARO and manage as clinically indicated. Rash, most commonly maculo-papular and macular rash, was reported with NINLARO. Rash resulted in discontinuation of one or more of the three drugs in <1% of patients in both regimens. Manage rash with supportive care or with dose modification if Grade 2 or higher.
- **Thrombotic Microangiopathy** has been reported with NINLARO. Fatal cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/ hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received NINLARO. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop NINLARO and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting NINLARO. The safety of reinitiating NINLARO therapy in patients previously experiencing TTP/HUS is not known.
- **Hepatotoxicity** has been reported with NINLARO. Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in <1% of patients treated with NINLARO. Hepatotoxicity has been reported (10% in the NINLARO regimen and 9% in the placebo regimen). Monitor hepatic enzymes regularly and adjust dosing for Grade 3 or 4 symptoms.
- **Embryo-fetal Toxicity:** NINLARO can cause fetal harm. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days following the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the last dose.
- **Increased Mortality in Patients Treated with NINLARO in the Maintenance Setting:** In two prospective randomized clinical trials in multiple myeloma in the maintenance setting, treatment with NINLARO resulted in increased deaths. Treatment of patients with NINLARO for multiple myeloma in the maintenance setting is not recommended outside of controlled trials.

ADVERSE REACTIONS

The most common adverse reactions (≥ 20%) in the NINLARO regimen compared to placebo in combination with lenalidomide plus dexamethasone, respectively were thrombocytopenia (85%, 67%; pooled from adverse event and laboratory data), neutropenia (74%, 70%; pooled from adverse event and laboratory data), diarrhea (52%, 43%), constipation (35%, 28%), peripheral neuropathy (32%, 24%), nausea (32%, 23%), edema peripheral (27%, 21%), rash (27%, 16%), vomiting (26%, 13%), and bronchitis (22%, 17%). Serious adverse reactions reported in ≥ 2% of patients in the NINLARO regimen included diarrhea (3%), thrombocytopenia (2%), and bronchitis (2%).

DRUG INTERACTIONS: Avoid concomitant administration of NINLARO with strong CYP3A inducers.

USE IN SPECIFIC POPULATIONS

- **Lactation:** Advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.
- **Hepatic Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with moderate or severe hepatic impairment.
- **Renal Impairment:** Reduce the NINLARO starting dose to 3 mg in patients with severe renal impairment or end-stage renal disease requiring dialysis. NINLARO is not dialyzable.

Please see additional Important Safety Information on the previous page and accompanying Brief Summary.

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NINLARO® (ixazomib) capsules

4mg | 3mg | 2.3mg

NINLARO® (ixazomib) capsules 4mg | 3mg | 2.3mg

BRIEF SUMMARY OF PRESCRIBING INFORMATION
NINLARO (ixazomib) capsules, for oral use

1 INDICATIONS AND USAGE

NINLARO (ixazomib) is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.

Limitations of Use: NINLARO is not recommended for use in the maintenance setting or in newly diagnosed multiple myeloma in combination with lenalidomide and dexamethasone outside of controlled clinical trials.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombocytopenia: Thrombocytopenia has been reported with NINLARO with platelet nadirs typically occurring between Days 14-21 of each 28-day cycle and recovery to baseline by the start of the next cycle. Grade 3 thrombocytopenia was reported in 17% of patients in the NINLARO regimen and Grade 4 thrombocytopenia was reported in 13% in the NINLARO regimen. The rate of platelet transfusions was 10% in the NINLARO regimen and 7% in the placebo regimen. Monitor platelet counts at least monthly during treatment with NINLARO. Consider more frequent monitoring during the first three cycles. Manage thrombocytopenia with dose modifications and platelet transfusions as per standard medical guidelines.

5.2 Gastrointestinal Toxicities: Diarrhea, constipation, nausea, and vomiting have been reported with NINLARO, occasionally requiring use of antidiarrheal and antiemetic medications, and supportive care. Diarrhea was reported in 52% of patients in the NINLARO regimen and 43% in the placebo regimen, constipation in 35% and 28%, respectively, nausea in 32% and 23%, respectively, and vomiting in 26% and 13%, respectively. Diarrhea resulted in discontinuation of one or more of the three drugs in 3% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Adjust dosing for Grade 3 or 4 symptoms.

5.3 Peripheral Neuropathy: The majority of peripheral neuropathy adverse reactions were Grade 1 (18% in the NINLARO regimen and 16% in the placebo regimen) and Grade 2 (11% in the NINLARO regimen and 6% in the placebo regimen). Grade 3 adverse reactions of peripheral neuropathy were reported at 2% in both regimens. The most commonly reported reaction was peripheral sensory neuropathy (24% and 17% in the NINLARO and placebo regimen, respectively). Peripheral motor neuropathy was not commonly reported in either regimen (<1%). Peripheral neuropathy resulted in discontinuation of one or more of the three drugs in 4% of patients in the NINLARO regimen and <1% of patients in the placebo regimen. Patients should be monitored for symptoms of neuropathy. Patients experiencing new or worsening peripheral neuropathy may require dose modification.

5.4 Peripheral Edema: Peripheral edema was reported in 27% and 21% of patients in the NINLARO and placebo regimens, respectively. The majority of peripheral edema adverse reactions were Grade 1 (17% in the NINLARO regimen and 14% in the placebo regimen) and Grade 2 (7% in the NINLARO regimen and 6% in the placebo regimen). Grade 3 peripheral edema was reported in 2% and 1% of patients in the NINLARO and placebo regimens, respectively. Peripheral edema resulted in discontinuation of one or more of the three drugs in <1% of patients in both regimens. Evaluate for underlying causes and provide supportive care, as necessary. Adjust dosing of dexamethasone per its prescribing information or NINLARO for Grade 3 or 4 symptoms.

5.5 Cutaneous Reactions: Rash was reported in 27% of patients in the NINLARO regimen and 16% of patients in the placebo regimen. The majority of the rash adverse reactions were Grade 1 (15% in the NINLARO regimen and 9% in the placebo regimen) or Grade 2 (9% in the NINLARO regimen and 4% in the placebo regimen). Grade 3 rash was reported in 3% of patients in the NINLARO regimen and 2% of patients in the placebo regimen. Serious adverse reactions of rash were reported in <1% of patients in the NINLARO regimen. The most common type of rash reported in both regimens included maculo-papular and macular rash. Rash resulted in discontinuation of one or more of the three drugs in <1% of patients in both regimens. Manage rash with supportive care or with dose modification if Grade 2 or higher. Stevens-Johnson syndrome, including a fatal case, has been reported with NINLARO. If Stevens-Johnson syndrome occurs, discontinue NINLARO and manage as clinically indicated.

5.6 Thrombotic Microangiopathy: Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received NINLARO. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop NINLARO and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting NINLARO. The safety of reinitiating NINLARO therapy in patients previously experiencing TTP/HUS is not known.

5.7 Hepatotoxicity: Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in <1% of patients treated with NINLARO. Hepatotoxicity has been reported (10% in the NINLARO regimen and 9% in the placebo regimen). Monitor hepatic enzymes regularly and adjust dosing for Grade 3 or 4 symptoms.

5.8 Embryo-Fetal Toxicity: NINLARO can cause fetal harm when administered to a pregnant woman based on the mechanism of action and findings in animal studies. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days following the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the last dose.

5.9 Increased Mortality in Patients Treated with NINLARO in the Maintenance Setting: In two prospective randomized clinical trials in multiple myeloma in the maintenance setting, treatment with NINLARO resulted in increased deaths. Treatment of patients with NINLARO for multiple myeloma in the maintenance setting is not recommended outside of controlled trials.

6 ADVERSE REACTIONS

6.1 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 population from the randomized, double-blind, placebo-controlled clinical study included 720 patients with relapsed and/or refractory multiple myeloma, who received NINLARO in combination with lenalidomide and dexamethasone (NINLARO regimen; N=361) or placebo in combination with lenalidomide and dexamethasone (placebo regimen; N=359).

The most frequently reported adverse reactions (≥20% with a difference of ≥5% compared to placebo) in the NINLARO regimen were thrombocytopenia, neutropenia, diarrhea, constipation, peripheral neuropathy, nausea, peripheral edema, rash, vomiting, and bronchitis. Serious adverse reactions reported in ≥2% of patients in the NINLARO regimen included diarrhea (3%), thrombocytopenia (2%) and bronchitis (2%). One or more of the three drugs was permanently discontinued in 4% of patients reporting peripheral neuropathy, 3% of patients reporting diarrhea and 2% of patients reporting thrombocytopenia. Permanent discontinuation of NINLARO due to an adverse reaction occurred in 10% of patients.

Table 4 summarizes the non-hematologic adverse reactions occurring in at least 5% of patients with at least a 5% difference between the NINLARO regimen and the placebo regimen.

Table 4: Non-Hematologic Adverse Reactions Occurring in ≥5% of Patients with a ≥5% Difference Between the NINLARO Regimen and the Placebo Regimen (All Grades, Grade 3 and Grade 4)

	NINLARO + Lenalidomide and Dexamethasone N=361			Placebo + Lenalidomide and Dexamethasone N=359		
System Organ Class / Preferred Term	(%)			(%)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Gastrointestinal disorders						
Diarrhea	52	10	0	43	3	0
Constipation	35	<1	0	28	<1	0
Nausea	32	2	0	23	0	0
Vomiting	26	1	0	13	<1	0
Nervous system disorders						
Peripheral neuropathies†	32	2	0	24	2	0
Musculoskeletal and connective tissue disorders						
Back pain*	27	<1	0	24	3	0
Infections and infestations						
Upper respiratory tract infection*	27	1	0	23	1	0
Bronchitis	22	2	0	17	2	<1
Skin and subcutaneous tissue disorders						
Rash†	27	3	0	16	2	0
General disorders and administration site conditions						
Edema peripheral	27	2	0	21	1	0

Note: Adverse reactions included as preferred terms are based on MedDRA version 23.0.

*At the time of the final analysis, these adverse reactions no longer met the criterion for a ≥5% difference between the NINLARO regimen and the placebo regimen.

†Represents a pooling of preferred terms

(Continued on next page)

Brief Summary (cont'd)

Table 5 represents pooled information from adverse event and laboratory data.

Table 5: Thrombocytopenia and Neutropenia

	NINLARO + Lenalidomide and Dexamethasone N=361		Placebo + Lenalidomide and Dexamethasone N=359	
	(%)		(%)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Thrombocytopenia	85	30	67	14
Neutropenia	74	34	70	37

Herpes Zoster

Herpes zoster was reported in 6% of patients in the NINLARO regimen and 3% of patients in the placebo regimen. Antiviral prophylaxis was allowed at the healthcare provider's discretion. Patients treated in the NINLARO regimen who received antiviral prophylaxis had a lower incidence (1%) of herpes zoster infection compared to patients who did not receive prophylaxis (10%).

Eye Disorders

Eye disorders were reported with many different preferred terms but in aggregate, the frequency was 38% in patients in the NINLARO regimen. The most common adverse reactions of the eyes were cataract (15%), conjunctivitis (9%), blurred vision (7%), and dry eye (6%).

Other Clinical Trials Experience

The following serious adverse reactions have each been reported at a frequency of <1% in patients treated with NINLARO: acute febrile neutrophilic dermatosis (Sweet's syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, and thrombotic thrombocytopenic purpura.

7 DRUG INTERACTIONS

7.1 Strong CYP3A Inducers: Avoid concomitant administration of NINLARO with strong CYP3A inducers (such as rifampin, phenytoin, carbamazepine, and St. John's Wort).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Risk Summary: Based on its mechanism of action and data from animal reproduction studies, NINLARO can cause fetal harm when administered to a pregnant woman. There are no available data on NINLARO use in pregnant women to evaluate drug-associated risk. Ixazomib caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose. Advise pregnant women of the potential risk to a fetus. 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.

8.2 Lactation: Risk Summary: There are no data on the presence of ixazomib or its metabolites in human milk, the effects of the drug on the breast fed infant, or the effects of the drug on milk production. Because of the potential for serious adverse reactions from NINLARO in a breastfed infant, advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose.

8.3 Females and Males of Reproductive Potential: NINLARO can cause fetal harm when administered to pregnant women. Pregnancy Testing: Verify pregnancy status in females of reproductive potential prior to initiating NINLARO. Contraception: *Females:* Advise females of reproductive potential to use effective non-hormonal contraception during treatment with NINLARO and for 90 days after the last dose. Dexamethasone is known to be a weak to moderate inducer of CYP3A4 as well as other enzymes and transporters. Because NINLARO is administered with dexamethasone, the risk for reduced efficacy of contraceptives needs to be considered. *Males:* Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days after the last dose.

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

8.5 Geriatric Use: Of the total number of subjects in clinical studies of NINLARO, 55% were 65 and over, while 17% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment: In patients with moderate or severe hepatic impairment, the mean AUC increased by 20% when compared to patients with normal hepatic function. Reduce the starting dose of NINLARO in patients with moderate or severe hepatic impairment.

8.7 Renal Impairment: In patients with severe renal impairment or ESRD requiring dialysis, the mean AUC increased by 39% when compared to patients with normal renal function. Reduce the starting dose of NINLARO in patients with severe renal impairment or ESRD requiring dialysis. NINLARO is not dialyzable and therefore can be administered without regard to the timing of dialysis.

10 OVERDOSAGE: Overdosage, including fatal overdosage, has been reported in patients taking NINLARO. Manifestations of overdosage include adverse reactions reported at the recommended dosage. Serious adverse reactions reported with overdosage include severe nausea, vomiting, diarrhea, aspiration pneumonia, multiple organ failure and death. In the event of an overdosage, monitor for adverse reactions and provide appropriate supportive care. NINLARO is not dialyzable.

17 PATIENT COUNSELING INFORMATION

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

Dosing Instructions

- Instruct patients to take NINLARO exactly as prescribed.
- Advise patients to take NINLARO once a week on the same day and at approximately the same time for the first three weeks of a four week cycle. The importance of carefully following all dosage instructions should be discussed with patients starting treatment. Advise patients to take the recommended dosage as directed, because overdosage has led to deaths *[see Overdosage (10)]*.
- Advise patients to take NINLARO at least one hour before or at least two hours after food.
- Advise patients that NINLARO and dexamethasone should not be taken at the same time, because dexamethasone should be taken with food and NINLARO should not be taken with food.
- Advise patients to swallow the capsule whole with water. The capsule should not be crushed, chewed or opened.
- Advise patients that direct contact with the capsule contents should be avoided. In case of capsule breakage, avoid direct contact of capsule contents with the skin or eyes. If contact occurs with the skin, wash thoroughly with soap and water. If contact occurs with the eyes, flush thoroughly with water.
- If a patient misses a dose, advise them to take the missed dose as long as the next scheduled dose is ≥72 hours away. Advise patients not to take a missed dose if it is within 72 hours of their next scheduled dose.
- If a patient vomits after taking a dose, advise them not to repeat the dose but resume dosing at the time of the next scheduled dose.
- Advise patients to store capsules in original packaging, and not to remove the capsule from the packaging until just prior to taking NINLARO.

[see Dosage and Administration (2.1)]

Thrombocytopenia: Advise patients that they may experience low platelet counts (thrombocytopenia). Signs of thrombocytopenia may include bleeding and easy bruising. *[see Warnings and Precautions (5.1)]*.

Gastrointestinal Toxicities: Advise patients they may experience diarrhea, constipation, nausea and vomiting and to contact their healthcare providers if these adverse reactions persist. *[see Warnings and Precautions (5.2)]*.

Peripheral Neuropathy: Advise patients to contact their healthcare providers if they experience new or worsening symptoms of peripheral neuropathy such as tingling, numbness, pain, a burning feeling in the feet or hands, or weakness in the arms or legs. *[see Warnings and Precautions (5.3)]*.

Peripheral Edema: Advise patients to contact their healthcare providers if they experience unusual swelling of their extremities or weight gain due to swelling *[see Warnings and Precautions (5.4)]*.

Cutaneous Reactions: Advise patients to contact their healthcare providers immediately if they experience new or worsening rash *[see Warnings and Precautions (5.5)]*.

Thrombotic Microangiopathy: Advise patients to seek immediate medical attention if any signs or symptoms of thrombotic microangiopathy occur *[see Warnings and Precautions (5.6)]*.

Hepatotoxicity: Advise patients to contact their healthcare providers if they experience jaundice or right upper quadrant abdominal pain *[see Warnings and Precautions (5.7)]*.

Other Adverse Reactions: Advise patients to contact their healthcare providers if they experience signs and symptoms of acute febrile neutrophilic dermatosis (Sweet's syndrome), Stevens-Johnson syndrome, transverse myelitis, posterior reversible encephalopathy syndrome, tumor lysis syndrome, herpes zoster, cataracts, dry eyes, blurred vision, conjunctivitis and thrombotic thrombocytopenic purpura *[see Adverse Reactions (6.1)]*.

Embryo-Fetal Toxicity: Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [*see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the last dose. Advise women using hormonal contraceptives to also use a barrier method of contraception *[see Use in Specific Populations (8.1)]*. Advise males with female partners of reproductive potential to use effective contraception during treatment with NINLARO and for 90 days following the last dose *[see Use in Specific Populations (8.1)]*.

Lactation: Advise women not to breastfeed during treatment with NINLARO and for 90 days after the last dose *[see Use in Specific Populations (8.2)]*.

Concomitant Medications: Advise patients to speak with their healthcare providers about any other medication they are currently taking and before starting any new medications.

Please see full Prescribing Information for NINLARO at NINLAROhcp.com.

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