TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

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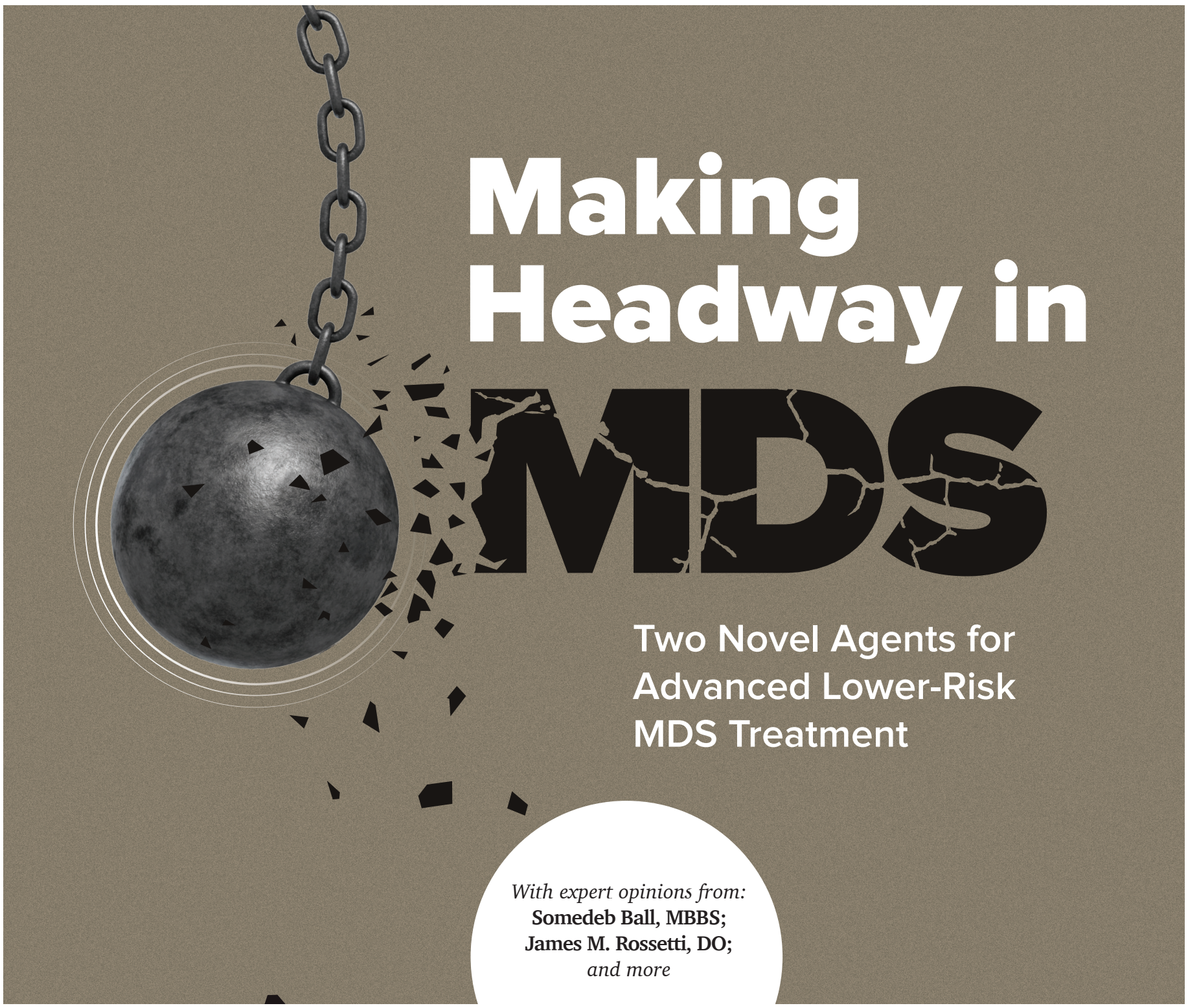

Making Headway in MDS

Two Novel Agents for Advanced Lower-Risk MDS Treatment

With expert opinions from:
Somedeb Ball, MBBS;
James M. Rossetti, DO;
and more

MAIL TO:

ASSOCIATE EDITOR
KAMI MADDOCKS, MD

Highlighting CAR-T Therapies in Lymphoma

An official publication of

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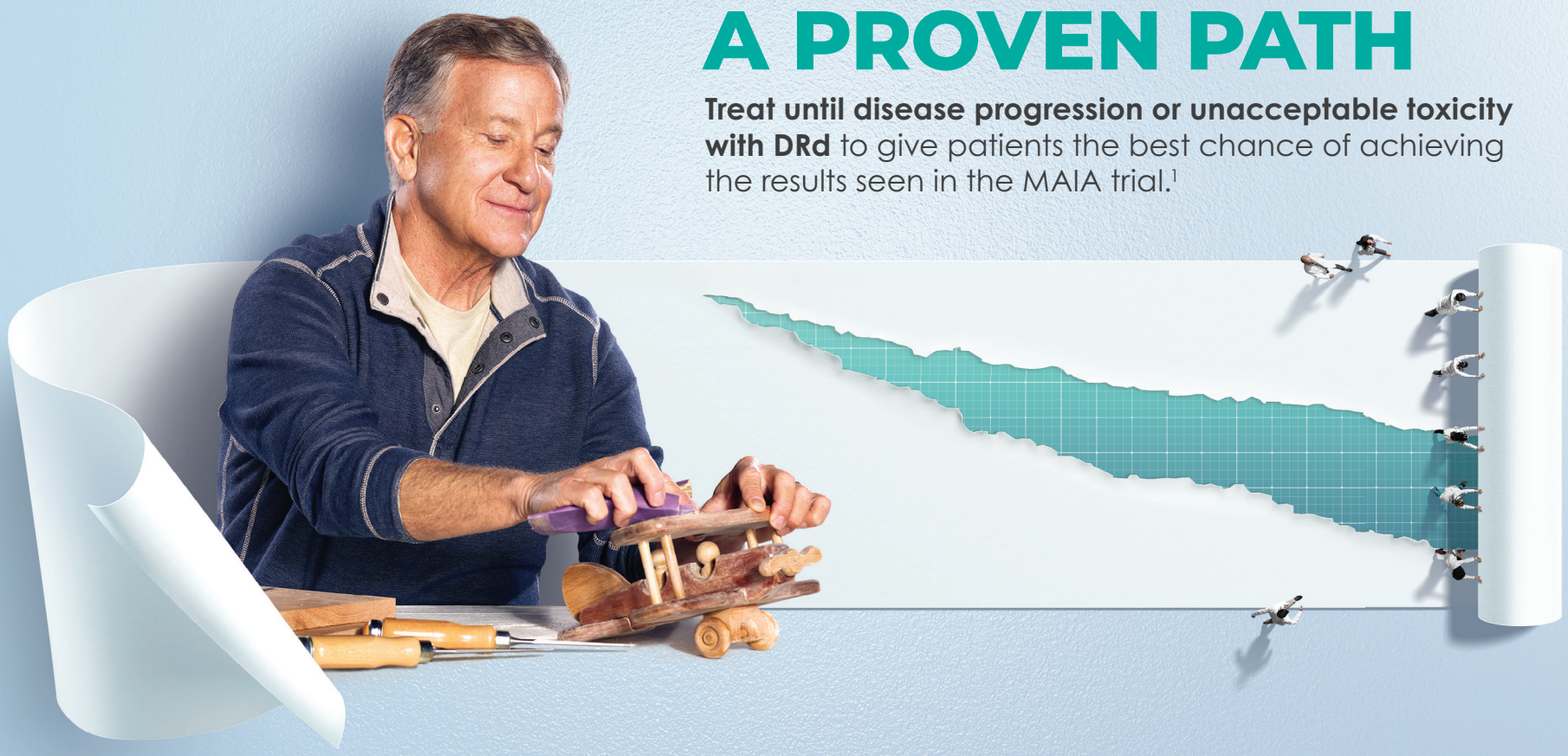
DARZALEX®
(daratumumab)
injection for intravenous infusion
100 mg/5 mL, 400 mg/20 mL

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

When treating newly diagnosed, transplant-ineligible multiple myeloma with DRd[1]:

KEEP PATIENTS ON A PROVEN PATH

Treat until disease progression or unacceptable toxicity with DRd to give patients the best chance of achieving the results seen in the MAIA trial.[1]



Scan the QR code or visit darzalexhcp.com for resources to help keep patients on track

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.

MAIA Trial Design: A phase 3 global, randomized, open-label study, compared treatment with DRd (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 PFS.[1,2]

Powerful efficacy to start the treatment journey[1,2]

At 28 months, mPFS was not reached with DRd vs 31.9 months with Rd.[1]

A 44% reduction in the risk of disease progression or death was seen at 30 months* in patients on DRd vs Rd alone (HR=0.56; 95% CI: 0.43, 0.73; *P*<0.0001)[1,2]

Efficacy results in long-term follow-up[1,3]

- After 64 months of follow-up, the mPFS was 61.9 months (95% CI: 54.8, NE) in the DRd arm and 34.4 months (95% CI: 29.6, 39.2) in the Rd arm (HR=0.55; 95% CI: 0.45, 0.67)

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

- The most frequent adverse reactions with DRd (≥20% and with at least a 5% greater frequency vs Rd) were infusion-related reactions, diarrhea, constipation, nausea, peripheral edema, fatigue, back pain, asthenia, pyrexia, upper respiratory tract infection, bronchitis, pneumonia, decreased appetite, muscle spasms, peripheral sensory neuropathy, dyspnea, and cough
- Serious adverse reactions with a 2% greater incidence in the DRd arm compared 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 treatment duration of 64.5 months)[†3]

TEAEs are reported as observed. These analyses are not in the Prescribing Information, have not been adjusted for multiple comparisons, and no conclusions should be drawn.

Most frequent TEAEs as observed (any grade reported in ≥30% of patients and/or Grade 3/4 reported in ≥20% of patients) in the DRd arm were diarrhea, neutropenia, fatigue, constipation, peripheral edema, back pain, asthenia, anemia, nausea, insomnia, bronchitis, cough, dyspnea, pneumonia, weight decreased, muscle spasms, and peripheral sensory neuropathy.

- Cumulative Grade 3/4 infection rates were 43% for DRd vs 30% for Rd
- Hematologic adverse events included in the follow-up analyses are investigator-reported TEAEs and not investigator-reported treatment-emergent laboratory abnormalities

Longer duration of response[1]

When treated until disease progression or unacceptable toxicity, **patients achieved longer duration of response with continuous DRd** vs continuous Rd.[1]

- **Among responders at 30 months,**[‡] 80.3% of patients in the DRd arm (n=342) were still in response (95% CI: 75.1, 84.5) vs 65.7% of patients in the Rd arm (n=300) (95% CI: 58.6, 71.8). Median duration of response was not reached with DRd vs 34.7 months (95% CI: 30.8, NE) for Rd alone[1,2]

This analysis is not included in the Prescribing Information, has not been adjusted for multiple comparisons, and no conclusions should be drawn.

- **Among responders after 60 months,**[‡] 62.1% of patients in the DRd arm (n=342) were still in response (95% CI: 56.3, 67.4) vs 39% of patients in the Rd arm (n=301) (95% CI: 32.5, 45.3)[4]

CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio; mPFS=median progression-free survival; NE=not estimable; PFS=progression-free survival; PR=partial response; Rd=lenalidomide (R) + dexamethasone (d); TEAE=treatment-emergent adverse event.

*Median follow-up was 28 months (range: 0.0–41.4 months).[1,2]

[†]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.

[‡]Responders were defined as patients who achieved a PR or better.[4]

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

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*®: 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*®.

Full Indications and Important Safety Information continue on next page.

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

Important Safety Information for DARZALEX® and DARZALEX *FASPRO*® (cont)

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.

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 the following pages.

cp-248517v3

References: 1. DARZALEX® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** 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. **3.** 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. **4.** Data on file. Janssen Biotech, Inc.

Johnson&Johnson

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

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

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

Table 3: Adverse Reactions Reported in ≥ 10% of Patients and With at Least a 5% Greater Frequency in the DRd Arm in POLLUX *(continued)*

Adverse Reaction	DRd (N=283)			Rd (N=281)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
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

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.

DARZALEX® (daratumumab) injection

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-264272v5

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).

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 usingDTT-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]*.

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

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]*.

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For patent information: www.janssenpatents.com

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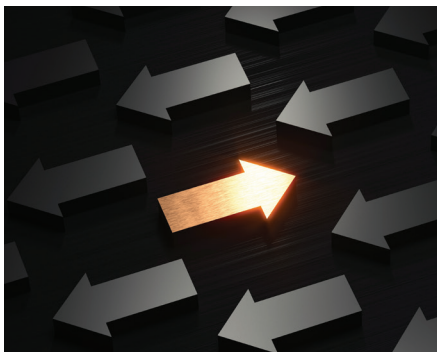

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About the Society of Hematologic Oncology

The Society of Hematologic Oncology was established as a nonprofit corporation in 2012 with aims to promote worldwide research, education, prevention, clinical studies, and optimal patient care in all aspects of hematologic malignancies and related disorders. The Society's global network supports and is supported by members from more than 110 countries, who are leading the vital efforts to further treatments for those afflicted by these diseases.

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Calendar

September 20–21, 2024
Inaugural CLL-Lymphoma EU Focus Meeting
Nové Město, Czechia

September 20–21, 2024
National Comprehensive Cancer Network Annual Congress: Hematologic Malignancies
New York, New York

September 21, 2024
Chicago Cellular Therapy in Hematology and Oncology: Expert Guidance for Clinical Practice
Deerfield, Illinois

September 25–28, 2024
21st International Myeloma Society Annual Meeting
Rio de Janeiro, Brazil

October 11–13, 2024
2024 Summit on Hematological Cancers
Nashville, Tennessee

October 24–25, 2024
16th International Congress on Myeloproliferative Neoplasms
Brooklyn, New York

October 24–27, 2024
9th Congress on Controversies in Stem Cell Transplantation and Cellular Therapies
Berlin, Germany

October 28–29, 2024
3rd European Congress on Hematology and Blood Disorders
Rome, Italy

November 6–10, 2024
Society for Immunotherapy of Cancer 39th Annual Meeting
Houston, Texas

November 22, 2024
2024 SOHO State of the Art Updates and Next Questions
Virtual

December 7–10, 2024
66th American Society of Hematology Annual Meeting & Exposition
San Diego, California

January 10–11, 2025
Highlights of ASH North America
New York, New York
Seattle, Washington

February 12–15, 2025
2025 Tandem Transplantation & Cellular Therapy Meetings of ASTCT® and CIBMTR®
Honolulu, Hawaii

February 27–March 2, 2025
29th Annual International Congress on Hematologic Malignancies®: Focus on Leukemias, Lymphomas, and Myeloma
Miami Beach, Florida

Get to Know

Learn more about the leaders, innovators, and educators in hematologic oncology

Amy DeZern, MD

Dr. DeZern, a Professor of Oncology and Medicine and recently appointed Vice-Chair of Hematologic Malignancies at the Johns Hopkins University School of Medicine, discusses how medicine has changed, particularly in diagnostics and genetics, and shares some advice for early-career clinicians.

What is your current appointment?
My primary appointment is at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. I conduct clinical research in bone marrow failure disorders, specifically aplastic anemia and myelodysplastic syndromes (MDS). My work involves novel therapeutics, as well as bone marrow transplantation for these diseases.

Where did you grow up, and when did you know you wanted to be a hematologist?
I'm originally from Texas. When I was 13, my mom was diagnosed with a rare form of cancer and had a fabulous doctor at the University of Texas MD Anderson Cancer Center. She participated in a clinical trial herself. From that point on, I really wanted to be a doctor.

Can you walk us down your career path? What was your first job?
My very first job was as a hostess at a Don Pablo's Mexican restaurant in Fort Worth, Texas, when I was 15. It was a fantastic job, actually! During college, I had several neat summer opportunities. I took part in the SMART (Science, Mathematics, and Research for Transformation) program through Baylor College of Medicine in Houston, Texas, and then I participated in a similar program at the University of Virginia after my sophomore year. My first true job as a physician was as an intern on the Osler medical service at Johns Hopkins Hospital.

When did you know you wanted to be a hematologist? Did you have any mentors who helped shape your career?
My interest has a lot to do with the type of patients I find interesting, as well as the training structure when I was a fellow. Hematology was part of the Department of Medicine at Johns Hopkins, whereas oncology is a separate and stand-alone department. At the time, the hematology fellowship was also freestanding and separate from the oncology fellowship, which was unusual and enticing. I had the opportunity to pursue either or both, and I chose to do both. I was particularly drawn to cases at the intersection of classical hematology and malignant disease.

Bone marrow failure, such as severe aplastic anemia, combines features of both high-acuity and noncancer conditions. It requires deep, intense, and timely patient relationships to gather data and make a therapeutic plan together, which I found rewarding, both in patient care and scientific investigation.

As for mentors, **Robert Brodsky, MD,** has been the most prominent. He was my mentor during fellowship and my early career as a faculty member. Even now, as a full professor, we collaborate and share patient cases.

"Medicine can be incredibly rewarding. It's about finding what interests you scientifically and clinically and merging those interests with a career that makes sense."

What are your thoughts on the recent advancements in anemia treatments and the approval of new therapies?
The population is aging, and MDS becomes more prevalent with age. We urgently need more drugs to treat MDS. Acute myeloid leukemia, which unfortunately develops from MDS in some patients, has several therapeutic options. However, MDS still lacks sufficient treatments. There are more in 2024, mainly for lower-risk disease, but we eagerly await further options in higher-risk disease.

How has medicine changed since you started your career?
Medicine has changed in many exciting ways, particularly in diagnostics and genetics. Turnaround time and access for patients, both financially and generally, have improved. However, there have been fewer ideal changes as well, such as the increase of required documentation and regulatory paperwork. Now, much more time is spent at the computer, which can detract from the patient experience. We need to try to minimize that impact.

What advancements do you hope to see for your patients in the next 10 years, particularly for rare blood disorders like paroxysmal nocturnal hemoglobinuria (PNH) and aplastic anemia and MDS?
It's interesting that for such a rare disease, there are quite a number of therapeutic options for PNH, with another one likely coming in 2024. Despite the availability of treatments, the cost of these drugs needs to decrease over the next decade. Access for those who are underinsured is also an ongoing issue.

In aplastic anemia, I anticipate more frequent use of transplants and less reliance on immunosuppressive therapy. However, immunosuppressive therapy will still be used thoughtfully when appropriate. As diagnostics improve, we will likely uncover a larger inherited component in aplastic anemia than previously known.

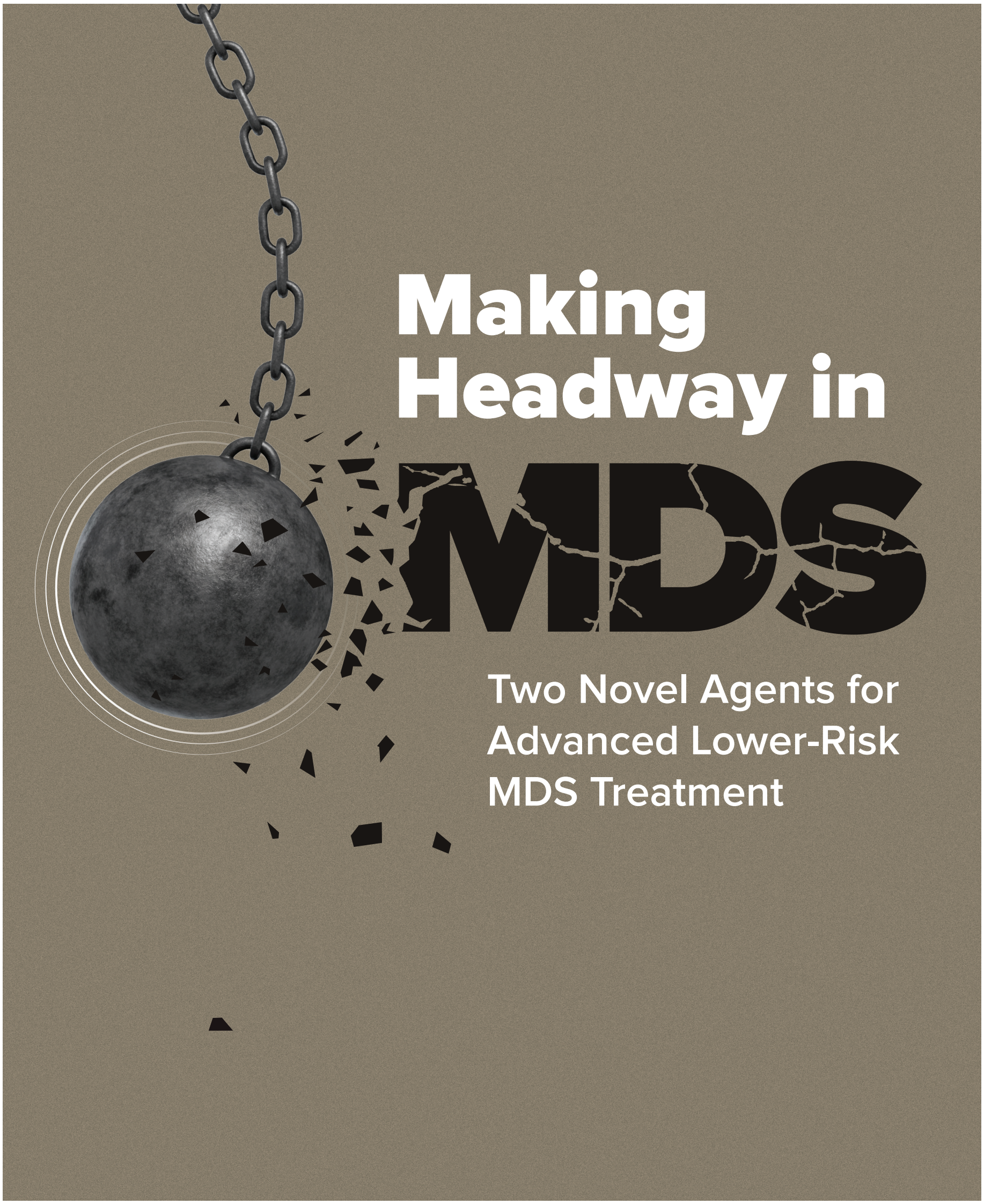
For MDS, I expect the development of more drugs and better transplant platforms to treat the disease. I think we may see patients treated earlier and later in the disease spectrum to extend time with a chronic disease.

Do you have any advice for early-career clinicians?
Medicine can be incredibly rewarding. It's about finding what interests you scientifically and clinically and merging those interests with a career that makes sense, whether in academics, the community, or even in policy-making or in the pharmaceutical industry. It's important to feel that you are contributing and that the career is giving something positive back to you.

What hobbies or activities do you enjoy in your free time?
I have four kids who are all actively involved in sports, and most of my hobbies involve taking them to their various activities. That is great fun. We also have a dog who I walk daily with my physician husband. It's an excellent time together.

In Focus

Blood Cancers Today *takes an in-depth look at hot topics in hematologic oncology*



Following FDA approval, luspatercept and imetelstat are propelling the MDS treatment landscape forward by improving transfusion dependence and anemia for many patients.

By Leah Lawrence

After a string of robust clinical trial data, patients with low-risk myelodysplastic syndromes (MDS) now have two newly approved treatment options: luspatercept and imetelstat. These novel agents have unique mechanisms of action that reflect a growing understanding of the biology of MDS, and they have the potential to improve outcomes and quality of life (QOL) for many patients.

"In the last one to two years, there has been an emergence of new agents that changed the treatment paradigm of low-risk MDS by focusing on improving anemia and transfusion dependence associated with this disease," said **Somedeb Ball, MBBS,** an Assistant Professor in the Division of Hematology and Oncology, Department of Medicine, at Vanderbilt University Medical Center. "We hope that by improving those aspects for patients, we can give them back some quality time of their life."

Blood Cancers Today recently spoke with several experts about low-risk MDS, the approvals of these new options, what they mean for patients, and which unmet needs remain.

MDS Burden

"Patients with low-risk MDS have a low risk of transformation to full blown acute myeloid leukemia, and risk of dying from the disease is not imminent," said Dr. Ball. "However, the burden of disease is still significant enough to have unfavorable effects on patient QOL and day-to-day activities."

According to Dr. Ball, the bulk of patients with low-risk MDS have low blood counts (cytopenias), which can cause fatigue, dizziness, and shortness of breath. Studies have shown that patients with MDS may report moderate or severe issues related to pain or discomfort, mobility, anxiety or depression, and usual activities.[1]

"Day-to-day things that patients were able to do before may not be as easy to do now with MDS," Dr. Ball elaborated.

Patients with cytopenias can also be at increased risk for infection and bleeding and may be in and out of the hospital for related complications, said **James M. Rossetti, DO,** a hematology specialist at the University of Pittsburgh Medical Center Hillman Cancer Center.

One small, single-center study from Europe found that in a group of patients diagnosed with MDS—two-thirds of whom were low risk—more than half developed infectious episodes, the majority of which were considered severe. For the patients who died, the main cause of death was infection.[2]

Many patients may also require red blood cell or platelet transfusions, sometimes as often as weekly, Dr. Rossetti said.

"These patients are frequently getting labs on a weekly basis and spending hours in a chair waiting for blood products to arrive and be transfused," according to Dr. Rossetti. On average, patients with MDS can spend as long as six hours at the infusion center to receive a transfusion.[3]

Although transfusions aim to relieve MDS symptoms, they are not without complications, Dr. Ball said. "With each bag of red blood cells, we infuse one month's worth of oral iron into the patient's body. This excess iron is hard to get rid of," he explained. "It goes to organs like the liver or the heart. In the long run, that can impact organ function in transfusion-dependent patients."

Until recently, the only treatments available to decrease transfusion needs and possibly improve survival for patients with low-risk MDS were the erythropoiesis-stimulating agents (ESAs) epoetin alfa and darbepoetin alfa, said **Srinivas K. Tantravahi, MBBS, MRCP,** an Associate Professor specializing in hematology and hematologic malignancies at the University of Utah's Huntsman Cancer Institute. ESAs mimic erythropoietin and stimulate the bone marrow to make red blood cells.

"[ESAs] particularly helped patients who had some degree of erythropoietin deficiency, or levels below 200," Dr. Tantravahi said. "However, only a fraction of patients respond to ESAs, and there was no other effective drug available until luspatercept."

New Options

Unlike ESAs, luspatercept is an erythroid maturation agent, explained **Amer Zeidan, MBBS, MHS,** Chief of Hematologic Malignancies and an Associate Professor of Internal Medicine at Yale School of Medicine. Luspatercept acts as a ligand trap, removing the ligands of the TGF-beta superfamily, a pathway that has been shown to be increasingly activated in anemic patients with lower-risk MDS. By interfering with the ligands of this pathway, luspatercept removes these erythropoiesis inhibitory signals, which in turn enables erythroid maturation and subsequent improvement in anemia.[4]

"Luspatercept restores maturation of red blood cells from their early progenitors so they don't die prematurely in the bone marrow," Dr. Zeidan said. "In other words, it reverses the process of ineffective erythropoiesis, which is a hallmark of lower-risk MDS and what causes anemia."

Luspatercept was first approved for anemia in patients with MDS with ring sideroblasts in whom prior ESAs have failed and who required two or more red blood cell units over eight weeks before study entry.[5] In 2023, the US Food and Drug Administration (FDA) expanded the approval of luspatercept to the first-line setting in patients with low-risk MDS who may require red blood cell transfusion, regardless of ring sideroblast status.[6]

This expanded indication was based on data from the phase III COMMANDS trial, which enrolled patients with anemia and previously untreated lower-risk MDS patients with or without ring sideroblasts. Patients were randomly assigned to receive either luspatercept or epoetin alfa.[7] Almost 60% of patients assigned to luspatercept achieved transfusion independence for at least 12 weeks and had an increase in hemoglobin of at least 1.5 g/dL, compared with only about one-third of patients assigned to ESAs.

Updated data presented in 2024 showed that more than 70.0% of patients assigned to luspatercept had achieved the primary endpoint of transfusion independence for at least 12 weeks compared with 43.1% of those assigned ESAs ($P<.0001$).[8]

"This was the first time we ever had a drug that beats ESAs in a head-to-head comparison in MDS," said Dr. Zeidan, who was an investigator on the COMMANDS trial. "It beat ESAs in a conclusive fashion in terms of rate of transfusion independence and durability of response."

The cumulative duration of all response episodes was almost three years (154.7 weeks) for luspatercept compared with less than two years (91.1 weeks) for ESAs ($P=.0016$).

"Administration of luspatercept is typically every three weeks, a less intense schedule than ESAs, which are given every one to two weeks," Dr. Tantravahi said. "The main side effect is mild local infusion reactions like itching and discomfort, and we don't see any hematologic toxicities like neutropenia or thrombocytopenia."

Imetelstat

In June 2024, the FDA approved imetelstat, an oligonucleotide telomerase inhibitor. This approval is for adults with low-risk MDS with transfusion-dependent anemia requiring four or more red blood cell units over eight weeks and who have not responded to or are ineligible for ESAs.[9]

"The greater the telomere length of a cell, the longer that cell lives. With each cell division we lose a portion of telomere, and its length is maintained by an enzyme called telomerase," Dr. Ball said. "In MDS, we see that diseased cells have higher telomerase activity than normal bone marrow cells."

Imetelstat inhibits the telomerase enzyme, thereby selectively targeting MDS cells in the bone marrow.

"What is cool about this mechanism of action is that you are allowing restoration of normal hematopoiesis, normal production of blood cells, by selectively killing bone marrow cells harboring MDS," Dr. Ball said.

Imetelstat was approved based on results from the phase III IMerge study, which randomly assigned 178 patients with low-risk MDS to receive either imetelstat or placebo. The primary endpoint of eight-week red blood cell transfusion independence was met in 40% of patients who received imetelstat, compared with 15% of patients who received placebo ($P=.0008$). Transfusion independence for at least 24 weeks was shown in 33% of patients assigned to imetelstat compared with 3% assigned to placebo ($P=.0001$).[10]

The median duration of transfusion independence

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In Focus

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was about one year with imetelstat compared with about 13 weeks with placebo.

Dr. Ball noted that there was no clear subgroup of patients that seemed to benefit more or less from imetelstat. However, data did seem to indicate that patients "who had eight-week transfusion independence were more likely to stay transfusion independent at 16 or 24 weeks." This is encouraging, Dr. Ball said, because it tells physicians within a relatively short period of time whether this agent will work for a patient.

"Importantly, [imetelstat] benefits were seen in both the ring sideroblast-positive and -negative setting," said Dr. Zeidan, who was an investigator and senior author of the pivotal IMerge trial.

Dr. Zeidan also pointed out that imetelstat can cause cytopenias, including neutropenia and thrombocytopenia. Patients have to be monitored closely, he said.

"Like luspatercept, imetelstat is also less cumbersome for patients," Dr. Rossetti added. "This is about a two-hour infusion given monthly."

Additionally, the median increase in hemoglobin during the longest transfusion-independent period was 3.50 g/dL with imetelstat, compared with 0.80 g/dL with placebo.

"Often, when a patient is given two units of blood, we see a transient increase of a couple grams," Dr. Rossetti said. "If we can push hemoglobin upward by three to four grams in a durable manner, we can significantly improve QOL."

Incorporating New Options

With these two new approvals, one important research area is how to sequence the available treatment options.

"For example, we know that luspatercept works after ESAs—at least with ring sideroblasts—but we don't have data about ESA use after luspatercept," Dr. Zeidan said. "Now that luspatercept has frontline approval, these data should accumulate quickly from real-world analyses and from COMMANDS follow-up."

Another important question is how imetelstat works after first-line luspatercept. In IMerge, only a small number of patients had previous treatment with luspatercept after ESA failure. Of these patients, 86% had a reduction in transfusion burden with imetelstat, but none achieved transfusion independence.[10]

"These are very small numbers to be able to draw any conclusion from, but what I see happening is that most patients are probably going to get luspatercept or ESA frontline. If they don't respond, they will then likely get imetelstat," Dr. Ball said. "In years to come, I will be interested to see real-world or retrospective studies about how one of these agents performs after exposure to the other."

Dr. Ball also pointed out that COMMANDS and IMerge had stringent endpoints to measure efficacy. For example, COMMANDS measured 12-week transfusion independence and IMerge measured eight-week transfusion independence.

"Many patients went on to have transfusion independence for even longer, and a lot of patients gained benefit from these agents even if that did not amount to the predefined standard set by the clinical trial," Dr. Ball said. "It is unlikely that the other 40% to 60% of patients who did not meet these strict trial endpoints had no benefit at all. For our patients in clinic, even a smaller reduction in transfusion burden may be meaningful."

Additionally, given these two agents' different mechanisms of action, Dr. Tantravahi wonders if they could be combined.

Questions Remain

Despite this progress, MDS remains incurable, and many unmet needs remain.

Among the research needs is determining whether the benefits of new agents translate into true QOL improvement and better survival.

"This is challenging to measure in MDS because of the need for long follow-up," Dr. Ball said. "These studies were not powered to measure it. I would be interested to know if the improvement these patients are experiencing on these drugs translates into an overall survival benefit."

The hope is that these newer agents can help transform MDS into a sort of "chronic condition" like diabetes or hypertension, where a patient cannot be cured but can live a long time while they remain on treatment with good QOL, Dr. Zeidan said.

"This is where we are headed, but eventually every patient will progress," Dr. Zeidan added.

While the QOL benefits and duration of response of these two agents are very good, "the unfortunate reality is that most patients will likely lose response to virtually any agent over time," Dr. Rossetti noted.

Obtaining extended durations of response is necessary for these patients, but experts believe it's also important to gain a better understanding of how to sequence these drugs to maintain the longest possible duration of transfusion independence.

Additional new agents are eagerly awaited, especially those that target genetic mutations or pathways specific to MDS. For example, in 2023, the FDA approved ivosidenib for patients with relapsed or refractory MDS with *IDH1* mutations.[11]

"*IDH1* mutations are fairly rare in the MDS space," Dr. Rossetti said. "Other more commonly occurring mutations have been identified but don't have targeted therapies available yet."

Agents with consistent activity against *TP53* mutations are also lacking, Dr. Rossetti mentioned.

However, the MDS field is moving forward to fill these treatment gaps. For example, the second-generation TGF-beta modulator KER-050 (elritercept) is being investigated in an ongoing phase II trial. Based on data presented at the European Hematology Association 2024 Hybrid Congress, more than 50% of patients were transfusion independent for at least eight weeks.[12]

"To my knowledge, this drug is principally being investigated in Europe, but a US trial has recently opened. It has the potential to fill some of the loopholes that luspatercept has," Dr. Ball said. "With this second-generation molecule, we are seeing responses in some additional subgroups, improved platelet counts, and improved red blood cells counts, which is very encouraging."

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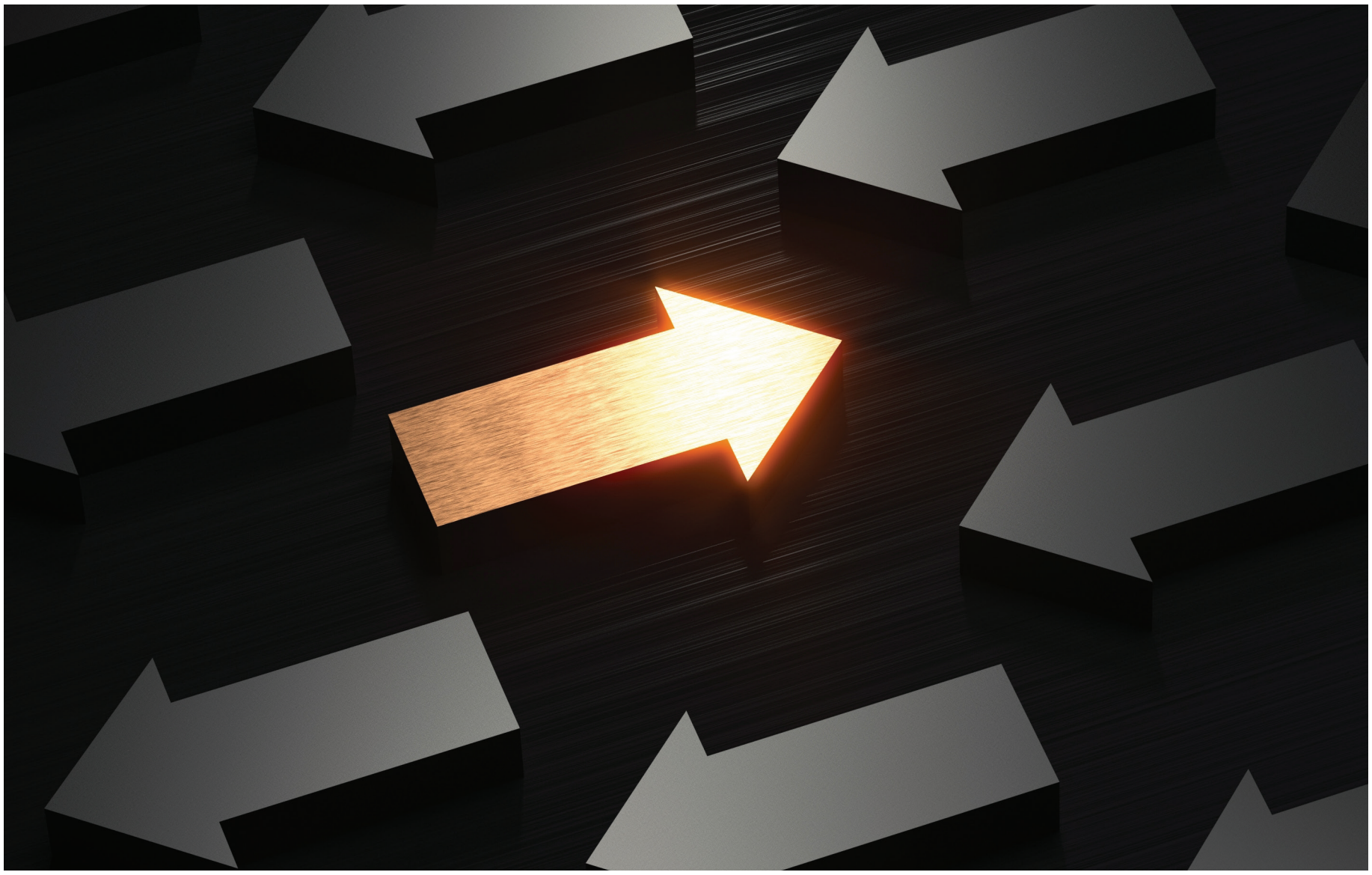

Out With the Old, in With the New: Shifting the Standard of Care in Myeloma

Bortezomib has become a staple in the multiple myeloma (MM) treatment landscape. The antineoplastic agent was first approved by the US Food and Drug Administration (FDA) in 2003,[1] and by the European Union in 2004,[2] based on results from the phase II SUMMIT trial. It even landed a spot on the World Health Organization's Model List of Essential Medicines in 2019, which lists "the most efficacious, safe, and cost-effective medicines for priority conditions."[3]

Due to its long-standing efficacy, **Rahul Banerjee, MD,** an Assistant Professor in the Clinical Research Division at the Fred Hutchinson Cancer Center in Seattle, Washington, described bortezomib as the "mainstay" of MM therapies, particularly in the newly diagnosed setting.

However, for 21 years, the standard of care (SOC) for bortezomib has remained largely the same: twice-weekly injections for two out of every three weeks or three out of every four weeks.

"That's just how the initial studies of this medication were done," Dr. Banerjee said. "Historically, clinical trials have been based on the model of the original chemotherapy studies from decades ago that were singularly focused on the idea of the maximum tolerated dose. The thought was always that bigger is better, and more often is better."

However, recent scientific literature reveals the benefits of decreasing the bortezomib dose. A 2020 trial led by **Joselle Cook, MBBS,** a hematology specialist at the Mayo Clinic in Rochester, Minnesota, investigated outcomes with different administration schedules of bortezomib in combination with lenalidomide and dexamethasone. The overall response rate was 73% with once-weekly administration versus 66% with twice-weekly, while the progression-free survival (PFS) was 36.2 months with once-weekly versus 38.9 months with twice-weekly.[4]

To understand perceptions of how bortezomib should be dosed, Dr. Banerjee and colleagues conducted a global online survey of 217 clinicians. Over 90% of respondents prefer once-weekly bortezomib for their patients due to comparable responses and less neuropathy.[5]

"A more accurate definition of SOC regimens involves how typical physicians in the field would approach a given situation," Dr. Banerjee and colleagues wrote.[5]

Now, myeloma experts are brainstorming strategies to shift the SOC and redesign clinical trials to match how they want to treat patients.

Once-Weekly Versus Twice-Weekly Bortezomib

A 2023 study co-led by **Fieke Hoff, MD, PhD,** a Resident Physician at the University of Texas (UT) Southwestern Medical Center, and Dr. Banerjee investigated bortezomib dosing patterns in the United States. Of 2,522 patients, 927 (36.8%) received twice-weekly bortezomib and 1,522 (63.2%) received once-weekly bortezomib. There were no significant associations between gender, International Staging System stage, practice setting, insurance category, or baseline creatinine.[6]

Replicating previous data, there were no

statistically significant differences in real-world PFS between the two cohorts (37.3 months with once-weekly vs 39.2 months with twice-weekly).[6]

"The main additional factor we wanted to study was neuropathy," said **Gurbakhash Kaur, MD,** an Assistant Professor in the Department of Internal Medicine at UT Southwestern Medical Center and senior author of the study. "We found that peripheral neuropathy incidence was 18.5% with once-weekly and 34.7% with twice-weekly bortezomib. That is one of my main factors in dosing this medication."

Similarly, a 2017 trial led by **Surbhi Sidana, MD,** an Assistant Professor at Stanford University School of Medicine, found that "lower neuropathy risk translated into longer treatment duration" when subcutaneous bortezomib was administered weekly.[7]

While improved safety and comparable efficacy are the main reasons clinicians are pushing for dose reductions, they also believe that convenience should be factored into the equation.

"It's much more convenient for patients who come from long distances to come to the clinic to get their therapy once a week versus twice a week," said **Thomas Martin, MD,** Clinical Research Director at the University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center.

In fact, some patients travel up to 300 miles for treatment at his center. "Sometimes, it's a two-day adventure," Dr. Martin continued. "They drive up the day before to get their therapy, then after therapy they drive home that whole next day. It's a full-time job, and it's very difficult."

Once-weekly visits to a treatment center are not only more convenient, but they also boost patient compliance. When given the option, patients will choose a treatment once every two weeks versus once a week, Dr. Martin explained.

In their 2023 published paper, Dr. Banerjee and colleagues reported that 93% of the clinicians they surveyed agreed that their patients preferred once-weekly bortezomib administration over twice-weekly.[5]

"Having someone come in once a week for an injection works just fine in terms of efficacy," Dr. Banerjee added.

A Modern Era of Myeloma Treatment

If once-weekly bortezomib is safer, more convenient, and just as efficacious as twice-weekly, then why is the SOC unchanged?

"You would think that the die has been cast, the game has been won, the world should be using once-weekly bortezomib. Unfortunately, that's not the case," Dr. Banerjee said.

In fact, about a third of patients are still receiving twice-weekly dosing. Dr. Banerjee believes this is because the oncologist either hasn't seen the data or doesn't know the dosing can be changed.

Fifty-nine percent of clinicians surveyed by Dr. Banerjee and colleagues were aware of at least one study showing comparable PFS with the two dosing cohorts, and 63% were aware of studies showing less neuropathy with once-weekly dosing.[5]

"I've had scenarios where physicians have come to me and said, 'I agree with you, but my pharmacist won't let me change it because it's not what's been studied in the trials.' Pharmacists are busy, and the chemotherapy order sets are typically copied and pasted from the trial and put into the chemotherapy plans," Dr. Banerjee explained.

However, Dr. Banerjee urged clinicians to act. "You are allowed to deviate from the historical trial to do what makes the most sense for the patient sitting in front of you," he said. "Once-weekly bortezomib is the way to do that."

Dr. Kaur provided additional insight into how clinicians make dosing decisions for their patients.

"When doctors are dosing, we look at references and clinical trial data. If the data aren't there, then it's less likely to be done that way," she said. "Many practices have pathways they use to select the regimens, and [clinicians] need to work with [their] pharmacy team to change the dosing of drugs."

While this offers a quick fix, once-weekly bortezomib is still firmly rooted as the SOC in MM.

"The most long-term solution is really to change our trials," Dr. Banerjee said. "The issue here is not physicians doing anything wrong, but that our trials are not matching how we actually want our patients to receive therapy."

Now that clinicians have figured out the what and the why of bortezomib dosing, they're stuck on the how. After all, redesigning clinical trials may be easier said than done.

"It's been frustrating," Dr. Banerjee admitted. "It's a systems issue. I'm not faulting community physicians at all, but a lot of our partners in industry are reluctant to move to once-weekly bortezomib. The FDA is seemingly not willing to budge on what is defined as the [SOC], because they haven't seen trials of once-weekly bortezomib. It's a circular logic. We're kind of stuck."

However, Dr. Banerjee has hope that his survey will drive change in the field without the need for a clinical trial. In fact, such a practice-changing feat has been achieved before. Without as much clinical trial data, subcutaneous bortezomib has been adopted as the SOC due to less neuropathy than intravenous bortezomib. This change is owed to a medical error in France, in which a patient accidentally received subcutaneous bortezomib, Dr. Martin explained.

"We're hoping to see the same with bortezomib dosing," Dr. Banerjee said. "There's no reason for clinical trials to keep getting stuck in this way of the past."

The Only Exceptions

When clinicians were asked if there are any instances in which patients should receive twice-weekly dosing, acute cast nephropathy shone through.[5]

"For patients who are having kidney failure because of the myeloma churning out these light chains, that is a very reasonable scenario in which to use twice-weekly bortezomib," Dr. Banerjee explained, "but only for that first cycle. As soon as the kidneys are improving, [patients] should move to once-weekly dosing."

There wasn't a large uptick of physicians who felt that twice-weekly bortezomib should be administered purely based on cytogenetic risk, he elaborated.

Twice-weekly dosing is also preferred when a patient has aggressive or high-risk disease. "They have hypercalcemia, a cord lesion, renal insufficiency, or some other reason, then we give twice-weekly bortezomib for the fastest response," Dr. Martin said.

In fact, researchers found that time to best response was shortest with twice-weekly administration (3.6 months) compared with once-weekly (3.9 months).[5]

However, Dr. Banerjee doesn't believe this outcome is advantageous in the larger picture.

"In the grand scheme of things, does two weeks really make a difference?" he asked.

The Future of Myeloma Treatment

While the percentage of patients receiving once-weekly dosing is increasing over time,[6] it's still not anywhere near the 100% clinicians want to achieve.

"We've come a long way in myeloma treatments," Dr. Kaur said. "While the treatment landscape changes every few months, I still think bortezomib will remain a part of myeloma treatment."

Clinicians are also trying to push for dose reductions of other drugs, namely carfilzomib and dexamethasone. There's even a #DownWithDex hashtag on X, formerly known as Twitter, which is advocating for clinical trials to reflect how the corticosteroid is being administered in practice. While most myeloma experts drop dexamethasone after a few cycles, many community physicians aren't aware that they are allowed to do so, according to Dr. Banerjee.

Despite the remaining obstacles in the myeloma treatment landscape, Dr. Kaur hopes her study serves as a reference that clinicians can use to advocate for the incorporation of once-weekly bortezomib.

"The more data that we have to show that the efficacy is the same and the neuropathy risk is lower, that can make a change," she concluded. "It will start a conversation at least."

***Melissa Badamo** is an Assistant Editor for* Blood Cancers Today.

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Highlights From the **2024 AMERICAN SOCIETY OF CLINICAL ONCOLOGY ANNUAL MEETING**

Luspatercept 'Preferred' Therapy in ESA-Naive Patients With Lower-Risk MDS-Associated Anemia

Luspatercept continued to show therapeutic benefit in transfusion-dependent, erythropoiesis-stimulating agent (ESA)–naive patients with very low-, low-, or intermediate-risk myelodysplastic syndromes (MDS), according to a study presented at the 2024 American Society of Clinical Oncology Annual Meeting.

Investigators, led by **Amer Zeidan, MBBS, MHS,** Associate Professor of Medicine at Yale Cancer Center, conducted the study in response to the lack of effective therapies that provide durable benefit in this group of patients.

Amer Zeidan, MBBS, MHS

In the study, authors reported clinically meaningful responses of luspatercept treatment from patients enrolled in the COMMANDS trial.

"Luspatercept provided clinically meaningful outcomes, supporting its use as the preferred [treatment] for ESA-naive patients with [lower-risk] MDS-associated anemia," Dr. Zeidan and colleagues wrote.

The open-label, randomized, controlled COMMANDS trial was conducted at 142 sites in 26 countries. It enrolled adults with MDS classified as very low, low, or intermediate risk per the Revised International Prognostic Scoring System. All patients were ESA-naive and required red blood cell (RBC) transfusions.

The new clinical benefit assessments reported in this study include the following:

- Achievement and duration of at least a 50% reduction in RBC units transfused over a period of at least 12 weeks (week 1-end of treatment)
- Transfusion burden during treatment (weeks 1-24)
- Time to first transfusion
- Achievement and cumulative duration of all separate episodes of RBC transfusion independence (RBC-TI) lasting at least 12 weeks
- Mean hemoglobin increase of at least 1.5 g/dL over weeks one through 24

As of March 31, 2023, the investigators found significant differences between the two treatment groups, including a reduction in RBC units transfused in the luspatercept group (83.0% of patients achieved at least a 50.0% reduction in RBC units transfused over a period of 12 weeks or more) versus the epoetin alfa group (66.9%), longer time to first transfusion (155 days vs 42 days), and a mean hemoglobin increase observed in luspatercept patients compared with epoetin alfa patients (74.2% vs 52.5%; $P<.0001$).

"Significantly greater proportions of luspatercept versus [epoetin alfa] patients achieved improvements in [hemoglobin] levels, reduction in [transfusion burden] and RBC units transfused, and had durable RBC-TI responses," according to the investigators.

Funding was provided by Celgene, a Bristol Myers Squibb company, in collaboration with Acceleron Pharma, Inc.

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Zeidan A, Platzbecker U, Giovanni Della Porta M. Clinical benefit of luspatercept treatment (tx) in transfusion-dependent (TD), erythropoiesis-stimulating agent (ESA)–naive patients (pts) with very low-, low- or intermediate-risk myelodysplastic syndromes (MDS) in the COMMANDS trial. Abstract #6565. Presented at the 2024 American Society of Clinical Oncology Annual Meeting; May 31-June 4, 2024; Chicago, Illinois.

Emavusertib Reduces Bone Marrow Blasts in Patients With *FLT3*-Mutated AML

The oral FLT3 inhibitor emavusertib is safe and effective in patients with pretreated acute myeloid leukemia (AML) with *FLT3* mutations, according to data from the TakeAim Leukemia trial.

Eric Winer, MD, of the Dana-Farber Cancer Institute, presented preliminary data from the ongoing, open-label, phase I/II trial at the 2024 American Society of Clinical Oncology Annual Meeting.

Eric Winer. MD

Of 11 patients who received emavusertib at the recommended phase II dose of 300 mg twice daily, eight patients had prior treatment with FLT3 inhibitors.

To evaluate the safety, clinical activity, and molecular characterization of emavusertib, Dr. Winer and colleagues performed next-generation sequencing of 68 genes in bone marrow or peripheral blood mononuclear cells at baseline and on treatment.

Patients who responded to treatment achieved a more than 90% bone marrow blast reduction compared with baseline, as well as decreased or undetectable FLT3 internal tandem duplication levels. Emavusertib also decreased the variant allele frequency of *RUNX1*, *NRAS*, and *TET2*, which were identified as common co-mutations in the patient population. Two (18%) patients experienced grade 3 or higher treatment-related adverse events (AEs).

"AML patients with *FLT3* [mutations] demonstrated increased bone marrow blast reductions ($P\leq.05$) on emavusertib treatment when compared [with] *FLT3* [wild-type] AML patients," wrote Dr. Winer and colleagues. "Mutational profiles are suggestive of the disease-modifying activity of emavusertib."

Funding for this study was provided by Curis, Inc.

Reference

Winer ES, Verma A, Groepper S, et al. Preliminary safety, efficacy and molecular characterization of emavusertib (CA-4948) in patients with relapsed/refractory (R/R) acute myeloid leukemia (AML) with *FLT3* mutation (FLT3m). Abstract #6539. Presented at the 2024 American Society of Clinical Oncology Annual Meeting; May 31-June 4, 2024; Chicago, Illinois.

Liso-Cel NCP Shows Safety, 'Clinical Benefit' in Patients With LBCL

Lisocabtagene maraleucel nonconforming product (liso-cel NCP) can benefit patients with relapsed or refractory large B-cell lymphoma (LBCL) without compromising safety, according to a study presented at the 2024 American Society of Clinical Oncology Annual Meeting.

The prospective, multicenter, expanded access protocol study was led by **Brian Till, MD,** of the Fred Hutchinson Cancer Center. A total of 167 patients intended to receive commercial liso-cel but received liso-cel NCP due to manufacturing outcomes.

Brian Till, MD

The study consisted of a pretreatment period to evaluate patients, a treatment period, and a post-treatment period. During the treatment period, patients were started at the first dose of lymphodepleting chemotherapy and continued through NCP administration at day 1. The median time from leukapheresis to NCP infusion was 50 days. During the post-treatment period, patients were followed up for a period of three months after NCP administration.

The primary endpoint was safety, and the secondary endpoint was efficacy as assessed by overall response rate (ORR) and complete response (CR) rate using the Lugano 2014 criteria. Duration of response, progression-free survival, and overall survival could not be estimated due to the three-month follow-up.

AEs included cytokine release syndrome (42%), prolonged cytopenia (40%), grade ≥3 infections (14%), neurological events (8%), immune effector cell-associated neurotoxicity (2%), infusion-related reactions (1%), and secondary primary malignancy (1%). Of 13 patient deaths, six occurred due to AEs, five occurred due to disease progression, and two occurred due to unknown reasons.

Of 118 efficacy-evaluable patients in the first three months, the ORR was 71% (95% CI, 62-79). Approximately half (53%) of patients achieved a CR (95% CI, 43-62), and 19% of patients achieved a partial response (95% CI, 12-27).

"These data add to current clinical experience with liso-cel, show that patients with [relapsed or refractory] LBCL can derive clinical benefit from receiving NCP without compromising safety, and provide important evidence to facilitate clinical decision-making," concluded Dr. Till and colleagues.

Funding for this study was provided by Juno Therapeutics.

Reference

Till BG, Jacobson CA, Palomba ML, et al. Patients (pts) with R/R large B-cell lymphoma (LBCL) treated with lisocabtagene maraleucel (liso-cel) nonconforming product (NCP) under the Expanded Access Protocol (EAP). Abstract #7026. Presented at the 2024 American Society of Clinical Oncology Annual Meeting; May 31-June 4, 2024; Chicago, Illinois.

Highlights From the **EUROPEAN HEMATOLOGY ASSOCIATION 2024 HYBRID CONGRESS**

Is Reduced-Duration Venetoclax in AML Effective?

A reduced venetoclax exposure of seven days showed outcomes comparable with the standard continual venetoclax exposure in older or unfit patients with newly diagnosed acute myeloid leukemia (AML), according to a retrospective analysis.

Data from the study were presented at the European Hematology Association 2024 Hybrid Congress by **Christophe Willekens, MD,** of Gustave Roussy in Villejuif, France.

Christophe Willekens, MD

The reduced venetoclax cohort included 82 patients from seven French centers treated with azacitidine plus venetoclax, both for seven days. The standard venetoclax cohort included 173 patients from one US center treated with venetoclax for 21 to 28 days plus decitabine for 10 days in 59% and either decitabine for five days or azacitidine for seven days in the remaining patients.

The authors stated the "7+7" and standard regimen cohorts had comparable baseline characteristics except for secondary AML (32% vs 18%), therapy-related AML (34% vs 22%), complex cytogenetics (22% vs 39%), *FLT3-ITD* mutations (13% vs 3%), and *RAS* mutations (9% vs 24%). They noted rates of *TP53*, *NPM1*, and *IDH1/2* mutations were similar.

Overall, the rates of complete remission (CR) plus CR with incomplete count recovery were 72% with the "7+7" regimen and 71% with the standard regimen (P=.089), and the rates of strictly CR were 57% and 55%, respectively (P=.72).

The median overall survival (OS) and two-year OS rate were 11.2 months and 28%, respectively, in the "7+7" group and 10.1 months and 33%, respectively, in the standard group (P=.93). The median event-free survival (EFS) and two-year EFS rate were 6.5 months and 25%, respectively, in the "7+7" group and 7.1 months and 26%, respectively, in the standard group.

Both groups had a median of one cycle until first response; "however, 42% of responders on '7+7' required more than one cycle for first response, whereas almost all responders (99%) on [standard venetoclax plus a hypomethylating agent (HMA)] had a first response after cycle one," Dr. Willekens stated.

Likewise, the median number of cycles to best response was two in the "7+7" group versus one in the standard group (P=.02).

In cycle one, the two regimens had similar rates of neutropenic fever and red blood cell transfusion requirements, although fewer patients in the "7+7" group required platelet transfusions (62%) versus the standard group (77%; P=.01).

Early mortality at four weeks was comparable at 2% in "7+7" patients and 6% in standard patients (P=.24), but eight-week mortality was lower in "7+7" patients at 6% versus 17% in standard patients (P=.02).

"Acknowledging the limitations of a retrospective comparison across multiple centers, we did not observe a signal for a difference in response rates or survival between shortened courses of venetoclax to seven days versus standard venetoclax-based HMA doublets," the authors summarized.

Reference

Willekens C, Bazinet A, Chraibi S, et al. Reduced venetoclax exposure to 7 days vs standard venetoclax exposure with hypomethylating agent in older/unfit patients with newly diagnosed acute myeloid leukemia: a retrospective comparison. Abstract #P590. Presented at the European Hematology Association 2024 Hybrid Congress; June 13-16, 2024; Madrid, Spain.

ESAs Before Transfusions Improve Outcomes Versus After Transfusions in MDS

Among patients with anemia related to lower-risk myelodysplastic syndromes (MDS), those who received erythropoiesis-stimulating agents (ESAs) after receiving red blood cell transfusions were older, had more comorbidities, and had worse survival versus those who received ESAs prior to transfusions, according to an analysis of real-world French patients.

Abdessamia Gandoul, MD

The data were presented by **Abdessamia Gandoul, MD,** of the Grenoble Alpes University Hospital in France, at the European Hematology Association 2024 Hybrid Congress in Madrid, Spain.

The retrospective analysis included 194 patients from 27 French hematology centers who had very low-, low-, or intermediate-risk MDS per the Revised International Prognostic Scoring System without 5q deletion and with hemoglobin under 10 g/dL.

Overall, 46.4% (n=90) of the patients received ESAs for anemia prior to red blood cell transfusion, while the remainder received ESAs after being transfused. The researchers reported 48% of all patients achieved an erythroid response, with a median duration of response of 16 months.

Patients in the transfusion-first group had a median age of 82 years compared with 78 years in the ESA-first group ($P<.005$). Additionally, 68.7% of patients in the transfusion-first group had a Charlson Comorbidity Index score greater than four compared with 44.4% in the ESA-first group ($P=.003$). Median hemoglobin levels at baseline were 8.3 g/dL in transfusion-first patients versus 9.2 g/dL in ESA-first patients ($P<.001$).

In the patients who received ESAs before transfusions, 68% eventually received transfusions due to lack of response to ESAs. The response rate to second-line treatments, including luspatercept, was 47%.

"This real-life analysis highlights a specific population in France receiving transfusions prior to ESA treatment," Dr. Gandoul summarized. "Those patients have more severe baseline characteristics, including older age [and] more comorbidities, and have poorer survival."

Reference

Gandoul A, Chermat F, Meunier M, et al. Real-life anemia treatment in low-risk myelodysplastic syndrome (MDS) patients: a retrospective multicenter study by the Groupe Francophone des Myélodysplasies (GFM) on 194 patients. Abstract #P778. Presented at the European Hematology Association 2024 Hybrid Congress; June 13-16, 2024; Madrid, Spain.

Oral Supplements Can Improve Vitamin C Deficiency in Myeloid Malignancies

Vitamin C deficiency in patients who have low-risk myeloid malignancies or precursor conditions can be improved with oral supplementation. This is according to phase II study findings presented at the European Hematology Association 2024 Hybrid Congress.

Stine Ulrik Mikkelsen, MD, PhD

The randomized, placebo-controlled EVI-2 study set out to explore use of oral vitamin C supplementation in management of myeloid malignancies and the precursor condition, clonal cytopenia of undetermined significance.

The study cohort was 109 patients with low-risk myeloid malignancies or precursor conditions, with 57% of this cohort having inadequate peripheral blood plasma vitamin C concentration at baseline. From this cohort, 54 patients received placebo, and 55 patients received oral vitamin C administered at 1,000 mg daily for 12 months. The placebo group had a median age of 75.0 years and was 78% male, and the vitamin C group had a median age of 72.3 years and was 65% male.

In the vitamin C group, the investigators observed a significant increase in median vitamin C plasma concentration of 45.85 µmol per liter at baseline to 81.90 µmol per liter at 12 months ($P<1\times10^{-7}$). The placebo group saw an increase from 43.75 µmol per liter at baseline to only 48.73 µmol per liter at 12 months ($P=.92$).

Serious adverse events occurred in 27% of the vitamin C group and 43% of the placebo group. There were 35 mortalities in the study, 11 of which were in the vitamin C group and 24 in the placebo group.

Multivariable analysis conducted in the study found the oral vitamin C supplements were statistically significantly associated with longer overall survival (OS) compared with placebo. Median OS was not reached in the vitamin C group and was 42.2 months in the placebo group (hazard ratio, 2.88; $P=.0025$).

"The significantly longer OS observed in the vitamin C group compared [with] the placebo group warrants further investigation in a sufficiently powered phase III study," the study investigators concluded.

Reference

Mikkelsen SU, Vallentin A, Nielsen A, et al. Vitamin C supplementation in patients with clonal cytopenia of undetermined significance or low-risk myeloid malignancies: results from EVI-2, a randomized, placebo-controlled phase 2 study. Abstract #LB3444. Presented at the European Hematology Association 2024 Hybrid Congress; June 13-16, 2024; Madrid, Spain.

Regulatory Actions

Recent therapy approvals, updates, and clinical trial results in the field of hematologic oncology

FDA Grants Second Approval to Epcoritamab for Follicular Lymphoma

The US Food and Drug Administration (FDA) granted second approval for epcoritamab (EPKINLY) for the treatment of patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of prior therapy, according to a press release from AbbVie, the manufacturer of the drug.

The T cell-engaging bispecific antibody was approved under the FDA's Accelerated Approval program based on results from the phase I/II EPCORE NHL-1 trial. Epcoritamab achieved an overall response rate (ORR) of 82%, a complete response rate (CRR) of 60%, and a partial response rate of 22%.

At a target dose of 48 mg, the most common adverse events included injection site reactions, cytokine release syndrome, COVID-19, fatigue, upper respiratory tract infection, musculoskeletal pain, rash, diarrhea, fever, cough, and headache.

Epcoritamab also received accelerated approval for relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in May 2023.

"Patients with relapsed or refractory [FL] face significant treatment challenges, and there is currently no clear standard-of-care treatment available across practice settings," said **Jeff Sharman, MD,** Disease Chair of Hematology Research at the Sarah Cannon Research Institute at Willamette Valley Cancer Institute, in the press release. "The responses observed in the [FL] cohort of the EPCORE NHL-1 clinical trial, as well as in patients with relapsed or refractory DLBCL from the trial, show the potential of [epcoritamab] to serve as an important treatment option for these patients."

Blinatumomab Receives FDA Approval in B-Cell ALL

The FDA has approved blinatumomab, a CD19-directed monoclonal antibody, in the treatment of CD19-positive, Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia (B-ALL), according to a release from Amgen.

Blinatumomab is now indicated for use in adult and pediatric patients aged one month or older with B-ALL in the consolidation phase of treatment, regardless of measurable residual disease (MRD) status.

The approval was predicated primarily on data from the phase III E1910 trial that showed blinatumomab added to multiphase consolidation chemotherapy achieved superior overall survival (OS) compared with chemotherapy alone.

"In the E1910 study, blinatumomab reduced risk of death and showed a remarkable improvement in [OS]," said **Selina Luger, MD,** an investigator on E1910 from the University of Pennsylvania's Perelman School of Medicine and Abramson Cancer Center. "This approval redefines the standard of care for patients with B-ALL and provides them with a more effective treatment option than standard chemotherapy alone."

This is the third FDA-approved indication for blinatumomab, adding to previous approvals for adult and pediatric patients one month or older with CD19-positive B-ALL in first or second complete remission with MRD greater than or equal to 0.1% or with relapsed or refractory CD19-positive B-ALL.

Gengluecel Receives Orphan Drug Designation for AML

The FDA has granted Orphan Drug Designation to IGNK001 (gengluecel) for the treatment of acute myeloid leukemia (AML).

IGNK001 is an investigational allogeneic natural killer cell therapy under development by Ingenium Therapeutics. This agent has already been approved by the Korean Ministry of Food and Drug Safety for phase II clinical trials.

The company is preparing to initiate clinical trials in the United States. These studies will include 80 patients and have an intended completion date of December 2027.

NMPA Accepts BLA for Tafasitamab Plus Lenalidomide in Relapsed or Refractory DLBCL

The China National Medical Products Administration (NMPA) has accepted a biologics license application (BLA) for tafasitamab in combination with lenalidomide to treat relapsed or refractory DLBCL in adults ineligible for autologous hematopoietic stem cell transplant (HSCT).

Tafasitamab is a humanized, Fc-modified monoclonal antibody that targets the CD19 antigen. InnoCare Pharma performs development and the exclusive commercialization of this immunotherapy agent in greater China.

In the United States, the combination of this agent with lenalidomide to treat relapsed or refractory DLBCL in adults ineligible for autologous HSCT has received accelerated approval by the FDA. The European Medicines Agency has granted conditional marketing authorization for the use of this doublet followed by tafasitamab monotherapy in this setting.

NMPA Approves Golidocitinib for Relapsed or Refractory PTCL

The NMPA in China has approved golidocitinib for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL) in adult patients.

Golidocitinib is an oral Janus kinase 1 selective inhibitor under development by Dizal Pharmaceutical.

The NMPA approval was based on results from the multinational JACKPOT8 Part B study. The study's researchers found that the efficacy and safety profile of golidocitinib monotherapy compared favorably against current treatments for relapsed or refractory PTCL.

In February 2022, the FDA granted golidocitinib Fast Track Designation for the treatment of relapsed or refractory PTCL in the United States.

Liso-Cel Receives Accelerated Approval for Relapsed or Refractory Follicular Lymphoma

The FDA has granted accelerated approval for lisocabtagene maraleucel (liso-cel), an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy developed by Bristol Myers Squibb under the name Breyanzi.

Liso-cel is now approved for the treatment of adult patients with relapsed or refractory FL after two or more prior lines of systemic therapy. Liso-cel has also been included in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for B-cell lymphomas with a category 2A recommendation for third-line and beyond therapy.

The FDA's decision was based on data from the phase II TRANSCEND FL study, in which liso-cel achieved an ORR of 95.7% (95% CI, 89.5-98.8) and a CRR of 73.4% (95% CI, 63.2-82.0), as confirmed by bone marrow biopsy. The median time to response after infusion was one month (range, 0.6-3.3 months), with 80.9% of responders maintaining a response at 12 months and 77.1% maintaining a response at 18 months.

"In the treatment of relapsed or refractory FL, patients often cycle through treatments, with typically shorter responses with each new line of therapy. Those who have experienced early disease progression have notably poor prognosis," said **Maria Lia Palomba, MD,** a lymphoma and CAR T-cell specialist at Memorial Sloan Kettering Cancer Center. "The FDA approval of liso-cel for patients with relapsed or refractory FL is an important advancement in addressing an ongoing unmet need in the FL treatment paradigm, providing patients with a new option that has shown remarkably high response rates and an established safety profile."

Editor's Picks

In each issue of Blood Cancers Today*, we will take a closer look at a particular topic in hematologic malignancies. This month, Associate Editor* ***Kami Maddocks, MD,*** *chose three articles highlighting chimeric antigen receptor (CAR) T-cell therapies in lymphoma.*

T-CELL LYMPHOMA

Kami Maddocks, MD
Associate Editor

Dr. Maddocks writes: There are now three autologous CD19-directed CAR therapies that have received accelerated approval in relapsed or refractory follicular lymphoma (FL) in the third-line setting. These agents are axicabtagene ciloleucel (axi-cel) based on the ZUMA-5 study, tisagenlecleucel based on the ELARA study, and lisocabtagene maraleucel (liso-cel; approved in May 2024) based on the TRANSCEND FL study. All of these CAR products had similar follow-up, and all showed this treatment produced very high overall response rates (ORRs) in patients with relapsed or refractory FL with high complete response rates (CRRs). While cross-trial comparisons cannot be made due to differences in the study designs and patient populations, there did seem to be differences in toxicity profiles, particularly in terms of higher-grade cytokine release syndrome (CRS) and neurologic toxicity.

Axi-Cel Produces Durable Response in Follicular Lymphoma, MZL

In results reported from the ZUMA-5 study, axi-cel produced sustained long-term responses in patients with FL and marginal zone lymphoma (MZL).

Axi-cel is an autologous, anti-CD19 CAR T-cell therapy. ZUMA-5 is a phase II, multicenter, single-arm study of axi-cel for use in relapsed or refractory indolent non-Hodgkin lymphoma (iNHL).

"After [three] years of follow-up in ZUMA-5, axi-cel demonstrated continued durable responses, with very few relapses beyond [two] years, and manageable safety in patients with [relapsed or refractory] iNHL," the investigators wrote regarding the long-term outcomes findings.

In a previously conducted primary analysis of 104 patients in the study over a median follow-up of 17.5 months, the treatment produced an ORR of 92% and a CRR of 74%.

Patients in the long-term outcomes analysis cohort had iNHL that was relapsed or refractory after at least two lines of therapy. They underwent leukapheresis and lymphodepleting chemotherapy, and then received axi-cel infusions.

The long-term ORR findings in this cohort were comparable with those in the primary analysis. For the 127 patients with FL in the cohort, ORR was 94% after a median follow-up of 41.7 months. For the cohort's 31 patients with MZL, ORR was 77% after a median follow-up of 31.8 months.

Why I chose this research:

"The ZUMA-5 trial evaluated axi-cel in relapsed or refractory indolent lymphomas and led to the first approved CAR T-cell product in FL. This trial evaluated patients with relapsed or refractory FL and MZL, resulting in very high response rates seen with axi-cel, including a 92% ORR with a 74% CRR in the entire patient population and a 94% ORR with a 79% CRR in patients with FL. CRS occurred in 78% of patients with FL, mostly grade 1-2 (72%), and neurologic events occurred in 56% of patients with FL, mostly grade 1-2 (41%). Responses were seen in patients with high-risk disease and were durable. The activity with this product was favorable overall to that reported with other approved agents in the third-line setting available for treating FL at the time."

The median progression-free survival (PFS) was 40.2 months for patients with FL but was not reached by patients with MZL. Neither set of patients reached median of overall survival.

The investigators found that any grade 3 or higher adverse events mainly occurred in recently treated patients. However, they did observe certain clinical factors correlating with less favorable remission outcomes.

"Elevated baseline total metabolic tumor volume and recent prior bendamustine use may affect durable remissions of patients with FL," the investigators wrote.

Reference

Neelapu SS, Chavez JC, Sehgal AR, et al. Three-year follow-up analysis of axicabtagene ciloleucel in relapsed/refractory indolent non-Hodgkin lymphoma (ZUMA-5). *Blood*. 2024;143(6):496-506. doi:10.1182/blood.2023021243

Liso-Cel Promising as Second-, Third-Line Follicular Lymphoma Therapy

The phase II TRANSCEND FL study found liso-cel to be an effective and safe treatment for relapsed or refractory FL. This finding was demonstrated even when it was used as second-line therapy in patients who have high-risk disease. These results were published in *Nature Medicine*.

"In this primary analysis, primary and key secondary endpoints were met, and similar efficacy was observed across lines of therapy," wrote lead author **Franck Morschhauser, MD, PhD,** of the Hospital Claude Huriez in Lille, France.

The study evaluated the use of liso-cel (autologous, CD19-directed CAR T-cell therapy) in patients with relapsed or refractory FL, including patients diagnosed with progressive disease within 24-months after treatment with anti-CD20 antibody and alkylator therapy within six months of FL diagnosis.

The total cohort included 130 patients with a median follow-up of 18.9 months after receiving liso-cel. In this cohort were 101 patients who received liso-cel as a third-line or later intervention, and they achieved an ORR of 97% and a CRR of 94%.

In the 23 patients from the total cohort who received liso-cel as second-line therapy, the ORR achieved was 96%, and all patients who responded to treatment achieved a complete response.

Regarding safety effects, 58% of the cohort experienced CRS, but only 1% of the cohort experienced grade 3 or higher CRS. Neurological events were experienced by 15% of the cohort, but only 2% of the cohort had events that were grade 3 or higher.

Reference

Morschhauser F, Dahiya S, Palomba ML, et al. Lisocabtagene maraleucel in follicular lymphoma: the phase 2 TRANSCEND FL study. *Nat Med.* 2024. doi:10.1038/s41591-024-02986-9. Published correction appears in *Nat Med.* 2024. doi:10.1038/s41591-024-03175-4

Why I chose this research:

"The TRANSCEND study evaluated liso-cel in patients with relapsed or refractory FL and included patients in the second line with high-risk disease features. In the third-line or later setting, where the other two products were studied or held approval, liso-cel resulted in a 97% ORR and a 94% CRR. CRS occurred in 58% of patients, with 1% grade 3 or higher, and neurologic events occurred in 15% of patients, with 2% grade 3 or higher. Responses with this product were also seen in high-risk disease and were durable. This trial reported the first population of FL patients receiving CAR-T in the second-line setting, which was in patients with high-risk FL."

Tisagenlecleucel Effective, Safe in Relapsed or Refractory Follicular Lymphoma

An interim analysis of the phase II ELARA trial found tisagenlecleucel to be effective and safe for the management of pretreated, relapsed or refractory FL. The analysis was recently published in *Nature Medicine*.

Tisagenlecleucel is an autologous CD19-directed CAR T-cell therapy. It has already been approved by the US Food and Drug Administration for use in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma and DLBCL that has developed from FL, and relapsed or refractory B-cell precursor acute lymphoblastic leukemia in patients aged up to 25 years.

The patient cohort in the multinational ELARA trial included 98 adults with relapsed or refractory FL, all of whom had already undergone at least two lines of treatment or experienced relapse after autologous stem cell transplant. The patients had undergone a median of four previous treatments, but a majority of the cohort was naïve to lenalidomide, lenalidomide plus rituximab, and phosphatidylinositol 3-kinase inhibitor therapies. Ninety-seven of the enrolled patients had received tisagenlecleucel as of March 2021, and they had a median treatment follow-up of 16.59 months.

The efficacy set of the trial comprised 94 patients. This cohort achieved a CRR of 69.1%, an ORR of 86.2%, and a PFS rate at 12 months of 67.0%. For the patients who achieved complete response, the analysis estimated a duration of response rate at nine months of 86.5% and a PFS rate at 12 months of 85.5%.

"Antitumor activity was seen independently of established risk factors for progression and across subgroups of patients," noted lead analysis author **Nathan H. Fowler, MD,** of the University of Texas MD Anderson Cancer Center. These factors included having advanced or bulky disease, a high Follicular Lymphoma International Prognostic Index score, progression of disease within 24 months, and disease refractory to more than two lines of therapy.

There were seven mortalities among the 97 patients who formed the safety set in the trial, but none were related to treatment. Within eight weeks of infusion there was a 48.5% CRS rate, but all of the occurrences were below grade 3. The set had a neurological event rate of 37.1%, with the rate specifically for events of grade 3 or higher calculated to be 3.0%. The rate of immune effector cell-associated neurotoxicity syndrome in the set was 4.1%, with the rate specifically for events of grade 3 or higher calculated to be 1.0%.

"Along with the possibility of outpatient treatment with tisagenlecleucel, the efficacy and safety data from the ELARA study in heavily pretreated patients with [relapsed or refractory] FL, including those with high-risk disease characteristics, are promising and will need to be evaluated for potential long-term benefits through studies with longer follow-up," Dr. Fowler said.

Why I chose this research:

"ELARA evaluated tisagenlecleucel for relapsed or refractory follicular lymphoma and led to the approval of this agent. The ORR with this product in FL was 86.2%, with a 69.1% CRR. CRS occurred in 48.5% of patients, all grade 1-2 and no grade 3 or higher. Neurologic events were reported in 37.1% of patients, with the majority being grade 1-2; 3.0% were grade 3 or higher. Responses with this product were seen in high-risk disease and were durable. This product appeared to have an improved safety profile, and the study showed proof of concept of outpatient administration."

Reference

Fowler NH, Dickinson M, Dreyling M, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. *Nat Med.* 2022;28(2):325-332. doi:10.1038/s41591-021-01622-0

HemOnc Happenings

Reporting on recent announcements, awards, and appointments in the hematology/oncology sphere

Satish Gopal, MD, MPH, Honored With Humanitarian Award at Annual Meeting

Dr. Gopal, Director of the Center for Global Health (CGH) at the National Cancer Institute (NCI), received the Humanitarian Award at the 2024 American Society of Clinical Oncology Annual Meeting for his research on lymphoma and HIV-associated malignancies in Africa.

Satish Gopal, MD, MPH

Since 2011, the Humanitarian Award has recognized oncologists who personify the society's mission and values through outstanding patient care, voluntary humanitarian endeavors, and exceptional service or leadership in the United States and abroad, according to the society's website. The award was presented during the annual meeting and included a $5,000 honorarium.

Dr. Gopal's research program, funded by the National Institutes of Health (NIH), addressed other common cancers in Africa, including cervical, breast, and esophageal cancers, according to the NCI. This endeavor pioneered some of the first published research to outline the molecular profiles of certain cancers, characterize lymphoproliferative disorders, incorporate patient-reported outcome measurements, and more.

In his current role as Director of the CGH, Dr. Gopal oversees the development of initiatives and collaborations with NCI and NIH partners, NCI-designated cancer centers, and other governmental and nongovernmental organizations to support cancer research in low- and middle-income countries.

He previously served as the Associate Chair for African International Sites for the NCI AIDS Malignancy Consortium, where he oversaw clinical trials in Africa, and has mentored more than 30 pre- and postdoctoral cancer researchers in the United States and Africa.

Remembering Nathan Berger, MD: Professor, Cancer Researcher, Mentor

Dr. Berger, Founding Director of the Case Comprehensive Cancer Center in Cleveland, Ohio, passed away on June 15, 2024, at the age of 83.

Nathan Berger, MD

Dr. Berger's 41-year history at Case Western Reserve University began in 1983, when he became Chief of the Department of Medicine's Division of Hematology Oncology and developed its first training program. He also served as dean from 1995 to 2002.

Most recently, he served as Director for Science Health and Society and Professor of Medicine, Oncology, Biochemistry, and Genetics and Genome Sciences at Case Western. His research at the Berger Lab included mouse model studies on energy balance, obesity, and cancer. Specifically, he looked at the effect of obesogenic diets on Barrett esophagus and esophageal adenocarcinoma.

Aside from his research endeavors, Dr. Berger also stepped into a mentoring role for students interested in pursuing medicine. In 2017, he created the Youth Enjoy Science program, which provides scientific educational opportunities for middle and high school students in the greater Cleveland area through funding from the NIH.

"Dr. Berger's [Youth Enjoy Science] summer program has profoundly impacted the education of students from our underrepresented community in cancer medicine," said **Gary Schwartz, MD,** current Director of the Case Comprehensive Cancer Center, in a statement. "It is just one part of his legacy as our first director."

In 2022, Dr. Berger received the university's Lifetime Achievement Award, which recognized his decades-long contributions to cancer care, research, and education.

"[Dr. Berger] had the greatest impact on medicine in Cleveland of anyone," **Stanton Gerson, MD,** Dean of the School of Medicine at Case Western, wrote in a statement.

Children's Hospital of Philadelphia, Sidra Medicine to Create First Pediatric Bone Marrow Transplant Program in Qatar

The Children's Hospital of Philadelphia (CHOP) has entered into a memorandum of understanding with Sidra Medicine, a specialty health care organization that provides hematology and oncology care for women, children, and young people, to establish the first pediatric bone marrow transplant (BMT) program in Qatar, according to a press release by CHOP.

Through this collaboration, CHOP's cellular therapy and transplant section will provide an education plan for Sidra Medicine's clinical staff and assess its readiness to begin treating pediatric patients.

Sidra Medicine's BMT program will treat patients with blood disorders and malignancies, such as sickle cell disease (SCD), thalassemia, leukemia, lymphoma, and solid tumors, as well as patients with primary immune deficiencies, metabolic diseases, and genetic and autoimmune disorders.

"It is truly a milestone to launch Qatar's first pediatric BMT program," **Ahmed Al Hammadi, MBCHB,** Acting Chief Medical Officer and Executive Chair of Pediatrics at Sidra Medicine, said in the press release. "We are delighted to partner with a world-class institution like CHOP to provide our patients with the most advanced and effective treatment options."

CHOP's BMT program has been treating pediatric patients since 1976.

"CHOP is dedicated to improving health outcomes for children across the world," **Ruth Frey,** Vice President of Global Strategy and Business Development at CHOP, said in the press release. "We are thrilled about this collaboration and the opportunity to offer CHOP's BMT expertise to support Sidra Medicine's launch of the first-ever pediatric BMT program in Qatar."

The collaboration will also explore clinical research initiatives in cell and gene therapies to treat SCD, beta thalassemia, and adrenoleukodystrophy. Experts at CHOP have previously developed two cell and gene therapies approved by the US Food and Drug Administration, exagamglogene autotemcel and lovotibeglogene autotemcel.

Nisha Unni, MD, Honored With Outstanding Teacher Award

Dr. Unni, an Associate Professor in the Department of Internal Medicine at the University of Texas (UT) Southwestern Medical Center, received the Eugene P. Frenkel, MD, Outstanding Teacher Award in the Hematology and Oncology Fellowship Program.

Nisha Unni, MD

Prior to joining the UT Southwestern faculty in 2013, Dr. Unni received her medical degree from the University of Kerala in India. She completed several fellowships in the United States, including a fellowship in transfusion medicine and blood banking at Yale University School of Medicine and a fellowship in hematology and oncology at Robert Wood Johnson Medical School. Specializing in breast cancer, she is also a member of UT Southwestern's Division of Hematology and Oncology, according to her faculty profile.

The award was created through a philanthropic gift from **Eugene P. Frenkel, MD,** a hematologist/oncologist and Professor of Internal Medicine at UT Southwestern from 1969 until his passing in 2019. Dr. Frenkel pioneered the medical center's Division of Hematology and Oncology and was known for his research on vitamin B12 metabolism and cancer, according to the institution's website.

Do you know of a clinician or researcher who has been the recipient of a recent award?

Send the details to editor@bloodcancerstoday.com.

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