TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

Prognostic Tools Need Updates to Recognize High-Risk Features in Lower-Risk MDS **p. 20**

More Intrathecal Chemotherapy Significantly Reduces CNS Relapse Risk in Ph+ ALL **p. 24**

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March/April 2023

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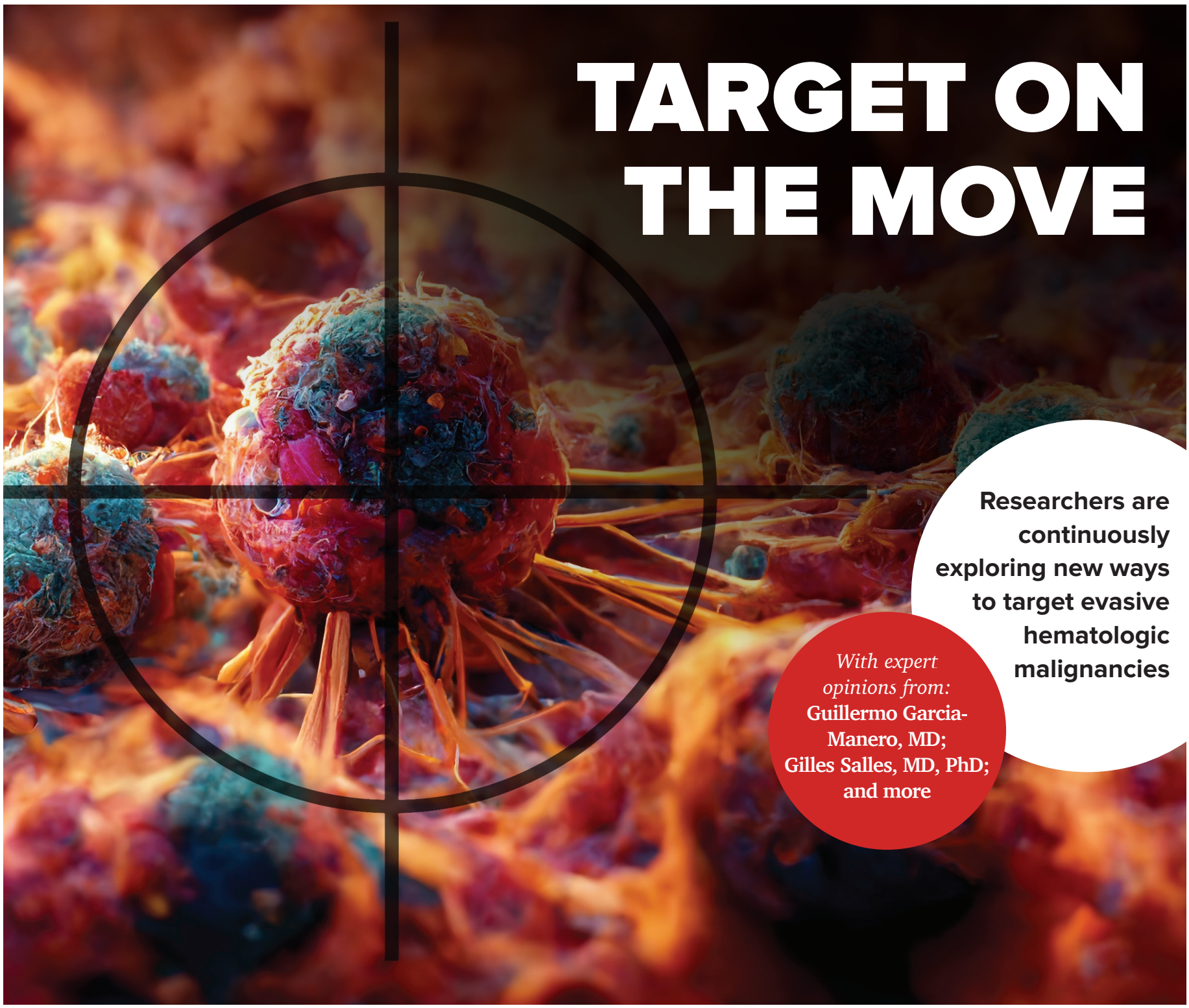
News from the 2023 EHA-EBMT 5th European CAR T-Cell Meeting **p. 26**



TARGET ON THE MOVE

Researchers are continuously exploring new ways to target evasive hematologic malignancies

With expert opinions from: **Guillermo Garcia-Manero, MD; Gilles Salles, MD, PhD; and more**

MAIL TO:

ASSOCIATE EDITOR THOMAS MARTIN, MD:

2023 Is the Year We Combat Burnout

An official publication of

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society of hematologic oncology

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

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

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

ADVANCE THE FRONTLINE MOMENTUM WITH DARZALEX® + Rd

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

At ~5 years: 32% reduction in the risk of death with DRd vs Rd alone in the MAIA trial
(HR=0.68; 95% CI: 0.53, 0.86; *P*=0.0013; mOS not reached in either arm).[1]*

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

DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); mOS=median overall survival; Rd=lenalidomide (R) + dexamethasone (d).

IMPORTANT SAFETY INFORMATION

DARZALEX® AND DARZALEX *FASPRO*®: CONTRAINDICATIONS

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

DARZALEX®: Infusion-Related Reactions

DARZALEX® can cause severe and/or serious infusion-related reactions including anaphylactic reactions. These reactions can be life-threatening, and fatal outcomes have been reported. In clinical trials (monotherapy and combination: N=2066), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX®. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, hypertension, tachycardia, headache, laryngeal edema, pulmonary edema, and ocular adverse reactions, including choroidal effusion, acute myopia, and acute angle closure glaucoma.

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

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.

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

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

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

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

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

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

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

Efficacy results in long-term follow-up

After 64 months of follow-up, the median PFS was 61.9 months (95% CI: 54.8, not evaluable) in the DRd arm and 34.4 months (95% CI: 29.6, 39.2) in the Rd arm[1]

45% **reduction in the risk of disease progression or death** with DARZALEX® + Rd vs Rd alone (HR=0.55; 95% CI, 0.45-0.67)[4]

Secondary endpoint of overall survival (OS)[1,2]
At ~5 years (56 months) of follow-up:

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

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

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

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

Safety results in long-term follow-up
(median treatment duration of 47.5 months)[2]

At median ~5 years of follow-up:

- Most frequent TEAEs§ for DRd ≥30% were diarrhea, neutropenia, fatigue, constipation, peripheral edema, anemia, back pain, asthenia, nausea, bronchitis, cough, dyspnea, insomnia, weight decreased, peripheral sensory neuropathy, pneumonia, and muscle spasms
- Grade 3/4 infections were 41% for DRd vs 29% for Rd
- Grade 3/4 TEAEs ≥10% were neutropenia (54% for DRd vs 37% for Rd), pneumonia (19% vs 11%), anemia (17% vs 22%), lymphopenia (16% vs 11%), hypokalemia (13% vs 10%), leukopenia (12% vs 6%), and cataract (11% vs 11%)

These analyses are not included in the current Prescribing Information.

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

CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); HR=hazard ratio; IRR=injection-related reaction; OS=overall survival; Rd=lenalidomide (R) + dexamethasone (d); TEAE=treatment-emergent adverse event.
*Range: 0.0-41.4 months.[3]
†Kaplan-Meier estimate.
‡Range: 0.03-69.52 months.[2]
§TEAEs are defined as any adverse event (AE) that occurs after 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 drug related (very likely, probably, or possibly related) regardless of the start date of the event; or any AE that is present at baseline but worsens in toxicity grade or is subsequently considered drug related by the investigator.

See the rolled out data.
Visit darzalexhcp.com

IMPORTANT SAFETY INFORMATION (CONTINUED)

For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion.

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

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

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

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

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

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

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen, and corticosteroids. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX *FASPRO*®.

IMPORTANT SAFETY INFORMATION CONTINUES ON NEXT PAGE ▶

IMPORTANT SAFETY INFORMATION (CONTINUED)

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 adjacent pages.

cp-248517v3

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

04/23 cp-334894v3

Janssen Oncology
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

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
U.S. License Number 1864

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

	DARZALEX FASPRO with Lenalidomide and Dexamethasone (N=65)	
Adverse Reaction	**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

	DARZALEX FASPRO with Lenalidomide and Dexamethasone[a]	
Laboratory Abnormality	**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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Calendar

May 3–6
17th International Congress on Myelodysplastic Syndromes
Marseille Chanot Convention Center
Marseille, France

May 10–13
American Society of Pediatric Hematology/Oncology Conference
Fort Worth Convention Center
Fort Worth, Texas

May 12–13
Turkish Society of Hematology 9th International Congress on Leukemia, Lymphoma, Myeloma
Virtual event

June 2–6
American Society of Clinical Oncology Annual Meeting
McCormick Place
Chicago, Illinois

June 8–11
European Hematology Association Hybrid Congress
Messe Frankfurt
Frankfurt, Germany

June 13–17
17th International Conference on Malignant Lymphoma
Palazzo dei Congressi
Lugano, Switzerland

July 27–29
32nd Annual Mayo Clinic Hematology/Oncology Reviews 2023
The Ritz-Carlton Amelia Island
Amelia Island, Florida

September 22–23
National Comprehensive Cancer Network 2023 Annual Congress: Hematologic Malignancies
Hilton San Francisco Union Square
San Francisco, California

September 27–30
20th Annual International Myeloma Society Meeting and Exposition
Megaron Athens International Conference Centre
Athens, Greece

October 6–9
20th International Workshop on Chronic Lymphocytic Leukemia
Hynes Convention Center
Boston, Massachusetts

October 18–21
Lymphoma, Leukemia, and Myeloma Society Congress
Sheraton New York Times Square Hotel
New York City, New York

October 20–24
European Society of Medical Oncology Congress
IFEMA Madrid
Madrid, Spain

November 1–5
38th Society for Immunotherapy of Cancer Annual Meeting
San Diego Convention Center
San Diego, California

MARK YOUR CALENDARS
SEPTEMBER 6–9
2023 SOHO Annual Meeting
George R. Brown Convention Center
Houston, Texas

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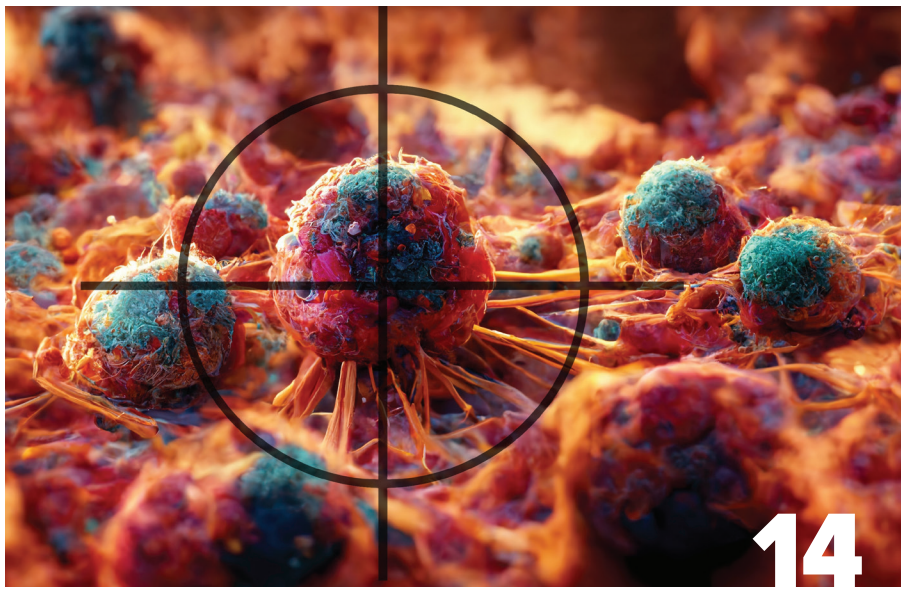

Target on the Move

Researchers are continuously exploring new ways to target evasive hematologic malignancies

The eventual acquired resistance to precision therapies in hematologic oncology sets off a race for researchers and clinicians to discover novel targets in evasive hematologic malignancies.

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Volume 2 | Number 3 | March/April 2023

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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.

Blood Cancers Today is published monthly by Mashup Media, 670 Madison Avenue, 2nd Floor, Manalapan, NJ 07726. Periodicals postage paid at Freehold, NJ, and additional mailing offices. POSTMASTER: Send address changes to Mashup Media, 670 Madison Avenue, 2nd Floor, Manalapan, NJ 07726. ©2023

Is anemia weighing your patients down?

IN MDS, TRANSFUSION DEPENDENCE COINCIDES WITH LOWER OVERALL SURVIVAL[1]

94%
(n=515)

of patients with MDS receive red blood cell transfusions for treatment of anemia[2*]

59%
LOWER RISK OF DEATH

Patients who are transfusion-independent are associated with a 59% decreased risk of death than those who are transfusion-dependent[3†]

Explore more data at www.ThinkOutsideTheBag.com

MDS=myelodysplastic syndromes.
*Per SEER registry data for patients with MDS from 2001 to 2007.[2]
†According to a meta-analysis of 89 publications on the association between overall survival and transfusion independence in patients with MDS.[3]

References: 1. Kaka S, Jahangirnia A, Beauregard N, Davis A, Tinmouth A, Chin-Yee N. Red blood cell transfusion in myelodysplastic syndromes: a systematic review. *Transfus Med*. 2022;32(1):3-23. **2.** Ramsey SD, McCune JS, Blough DK, et al. Patterns of blood product use among patients with myelodysplastic syndrome. *Vox Sang*. 2014;102(4):331-337. **3.** Harnan S, Ren S, Gomersall T, et al. Association between transfusion status and overall survival in patients with myelodysplastic syndromes: a systematic literature review and meta-analysis. *Acta Haematol*. 2016;136(1):23-42.

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Associate Editor's Message

2023 Is the Year We Combat Burnout

Thomas Martin, MD
University of California, San Francisco

I find the practice of hematologic oncology to be one of the most gratifying professions. Amazing breakthroughs and discoveries happen regularly, and a significant number of our patients are living longer and with a better quality of life. The tools we have today advanced dramatically over the past three decades, and I'm optimistic that the next decade will bring even greater heights.

Despite these advances, there are many challenges in our profession, and physician burnout is an ever-increasing problem in oncology.

As the term suggests, burnout is an occupational-related syndrome characterized by physical and emotional exhaustion, feeling overwhelmed, having a low sense of professional esteem or accomplishment, and depersonalization in interactions with others. There are multiple factors related to hematologic oncology that increase our susceptibility to the development of burnout.

First and foremost is the daily exposure to life-and-death decisions and the helplessness we experience when treating some of our most advanced and highest-risk patients with cancer. We often develop tight bonds with patients and their families, and many of these relationships end, unfortunately, much too early. We were aware of these challenges when we selected the field of hematologic oncology, but perhaps with today's advances, we can better serve some of our patients.

Several new challenges in the field are likely to lead to burnout, including the demands of maintaining the electronic medical record, increased administrative burden, and more attention being paid to relative value units as a measure of our productivity. The pandemic brought us the "benefit" of working from home, yet we now spend more time doing job-related work—at home. The boundaries between work and our personal lives are less apparent.

We are spending much more time answering questions and comments from staff and patients within the electronic health record. The inbox has led to new frustrations, including mandates on how quickly we respond to messages and fewer days we are able to log out. These obligations are a major contributor to burnout and job dissatisfaction. How can we reverse the current trend?

I wish I could provide the universal solution, but these are challenging issues. It's likely solutions are best developed locally. Some strategies include having team-building retreats and off-site meetings where issues can be discussed openly. Some individuals look to spiritual support or find support within their community. There is not a one-size-fits-all solution, and everyone should contribute and be heard. The more everyone participates in the solution, the better the outcome.

We will all experience burnout at some point, and we all need to seek more personalized ways to cope. Exercise is a common way to decompress. I personally decompress in Tahoe by engaging in my favorite activity—downhill skiing. There is no better way to relax than to be with my kids in nature, and with limited cell service!

Many hobbies, like reading a novel or watching a movie, can bring similar joy. Whatever activity you choose, make sure you make time for yourself. Most of my faculty have maxed out their accrued vacation time, and I encourage them to take vacation! Recognizing one's own stress level and asking for help is also important. We should try to check in with one another, and there is always professional help if needed.

One of my favorite activities that we have incorporated at the University of California, San Francisco (UCSF) within the Hematology, Blood and Marrow Transplant, and Cellular Therapy Program is a yearly Remembrance Ceremony. All in the program are invited to attend. During the ceremony, which is performed by one of our spiritual leaders at UCSF, we read the names of the patients who lost their battle with cancer over the past year. After the names are read, everyone has the opportunity to share a story, perhaps a patient experience that touched them, or some way that our collective energy helped a patient or a family. I encourage you all to consider implementing something like this ceremony in your local practice.

Overall, I hope that everyone participates in solutions and develops their own strategies to fight the escalating battle with burnout. Please feel free to send me your comments at *editor@bloodcancerstoday.com*, and I hope you will share your success stories.

Wishing everyone a productive and less stressful 2023.

Thomas Martin, MD, *is the Clinical Research Director of Hematologic Malignancies at the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center.*

Get to Know

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

Noopur Raje, MD

Dr. Raje, a Professor of Medicine at Harvard Medical School and Director of the Multiple Myeloma Program at Massachusetts General Hospital, reflects on the mentors who shaped her career, seeing myeloma treatments go from the bench to the bedside, and the importance of understanding personal priorities during a career in academic medicine.

Where did you grow up, and when did you know that you wanted to be a physician?

I grew up and trained in medicine in India. No one else in my family is a physician. I think the left brain and the right brain dominance is very different among us. All my siblings are more in the art and architecture world, and I didn't have parents who were in the medical field.

I always thought I wanted to be a doctor, and I'm not sure why. I just pushed on and did medicine. When did I want to become an oncologist? That happened a lot later. Once I did medicine—which was something that I started on a whim—it became ingrained, and I couldn't think of doing anything else. My alternative plan, to be honest, was if I didn't get into medical school, I was going to go into catering, because I love it. I'm a bad cook, I will tell you that, but that was my alternative plan. Thankfully, it didn't go down that way.

That's how I started off in medicine. In terms of oncology—once I did medicine, I loved internal medicine; I loved the complexity of internal medicine. I wanted to specialize, but I did not want to specialize in one kind of organ. I didn't want to do cardiology or gastrointestinal specialization. Oncology gives you the opportunity to study all systems. A lot of what we do is internal medicine, which was special to me. I think that's why I ended up doing oncology.

Were there any particular mentors who shaped your path in medicine?

I had a lot of mentors along the way. I think my biggest influence outside of the academic world was my father, who really believed in me and pushed me. He allowed all of us to do what we wanted to do and gave us every opportunity to pursue our interests. I wouldn't have gone into medicine without my father pushing me down that road. It was not because he wanted me to do it, it was because he knew that I wanted it. I think that was special.

Along the way, I've had many, many mentors, and I am so grateful for that. It's not always easy to find mentors, but my mentors have been incredibly supportive. They've not just been mentors; they've also been sponsors. They've helped me, they've guided me when I needed it, and they've allowed me to grow.

It started off very early back in India when I began doing medical oncology. My first mentor was Dr. Suresh Advani. I'm still in touch with him and keep him posted on where I am in life, because he has been such a big influence on me. Dr. Ken Anderson has also been an incredibly big part of my career. He's really shaped how I think about research in multiple myeloma (MM), even clinical work and translational work. He has been pretty special; he has helped guide me along in my career. I have many other mentors within the myeloma world and outside of the myeloma world as well. It's always nice to get mentors in the myeloma world, like Dr. Sundar Jagannath who's been incredible. He is one of the most giving individuals in terms of advice and knowledge. He is extremely supportive.

"I think it's important for any young faculty member to really know what it is that they want to do, and then pace themselves."

People like Dr. Nikhil C. Munshi have been fantastic in helping me along my journey. Outside of that, folks within my institution, leaders within my institution have always been exceedingly supportive. That's been incredibly helpful. Having these mentors from within my specialty, as well as outside my specialty, has helped me see things more clearly and has helped ground me.

I also want to mention Dr. David Roodman, who really influenced why I ended up doing the research path that I did. He's been influential in me taking on bone disease, which I never would have thought of doing without him pushing me on.

How have you seen research and treatment for MM evolve over your career?

I live in Boston. I feel very spoiled. I tell my children they are very spoiled—I'm going to use the sports analogy here—because in Boston we've seen too many championships as my kids have grown up.

I honestly feel like a kid in a candy store. When I started out here, all the drugs that we have right now were drugs that I knew by numbers. Bortezomib, for example, was PS-341. I was pipetting it in Dr. Anderson's lab. I never once thought that it was going to be used in patients. For us to be able to see within our lifetime the drugs that we worked with in the lab make a difference to patients has been the most empowering experience. That's part of the reason why I keep doing what I do.

There's a lot more work to do, but for me to be able to see the kind of drug development and the approvals for our patients over the last 15 to 20 years has been incredible. Being involved in all the drug approvals and all the changes in the treatment of MM has been very special.

What do you think are some of the major unanswered questions and challenges that remain in the field of MM?

The good news is we have lots of drugs, and we are doing better every year. Even through the pandemic, we had lots of drugs approved, including novel drugs like immunotherapies. And yet, I think our goal now is to cure myeloma.

The challenge is to transform this disease—which has already transformed into a chronic disease—to a curative platform. I think we're already maybe halfway there; we are probably already curing about 50% of people. There is an unmet need in the subset of high-risk and ultra high-risk patients we do not completely understand. It may not be all about the genetics of the myeloma, but it may be about what surrounds the myeloma tumor cells in the tumor microenvironment, which is of special interest to me in my research.

I think [looking at this] in an in-depth way and then targeting it specifically is what's ultimately going to make a difference. That's where I think the need is. That's where I think we are all moving toward. The good news is we have the tools to try and ask all these questions.

Continued on page 13

Focus on Clinical Research Nursing in Myeloma

Blood Cancers Today *spotlights different specialties within the hematologic oncology discipline.*

Molly Stoddart, RN, BSN

Stoddart is a clinical research nurse on the multiple myeloma (MM) team at the Winship Cancer Institute at Emory University in Atlanta, Georgia. Stoddart works with *Blood Cancers Today* Editor-in-Chief Sagar Lonial, MD, FACP, and is responsible for managing his patients who are enrolled in clinical trials.

How did you become a clinical research nurse?
I graduated from Emory's School of Nursing in 2011, and I've been a nurse for 12 years. My background is in orthopedics, and I worked at the Hospital for Special Surgery when I lived in New York. I was there for almost 10 years doing inpatient orthopedics. When I moved back to Atlanta, I returned to Emory and worked in outpatient orthopedics, but I was looking for something different. I connected with a nursing school friend for this job I am in now. When I went to the interview, I knew it was for clinical trials, but I didn't know the details. During the interview, they told me the position was for the MM team. I said, "Wow, that really is interesting because my grandmother was a patient with MM here on clinical trials for 16 years." She passed in 2015, but Dr. Lonial remembered her. I feel like the job was not a coincidence, so I switched specialties, and I've been so happy here.

How many clinical trials are you responsible for currently? Walk us through your week.
I'm currently working on six phase I clinical trials. I have, on average, eight to 10 patient visits per week, and I structure my week around those visits. The patients are scheduled based on the trial's requirements, so whether they come weekly or biweekly, that's up to the study's protocol. We have a dedicated unit where the patients go for phase I trials at Emory.

I make sure that all the research duties are organized, that the patient treatment plan is accurate, and that any research labs that need to be drawn are there for the nurses. I visit with patients to see if anything new is going on and to find out how they're doing. Then I work with the providers and the nurse practitioners in the clinic on any issues and to make sure we're good to proceed with treatment for that day.

I'm able to build a personal relationship with my patients in a way that I never was able to in my previous jobs because you don't see them over an extended period as an inpatient nurse. There's also a lot of behind-the-scenes research tasks to do related to data, compiling information, and screening new patients for trials.

"[A clinical trial] can be a big commitment for the patient. You want them to buy in and be active participants."

How do you build a relationship of trust with patients? What kind of challenges and barriers do you face in your role?
For the first part of the question, I would say these patients come to us for clinical trials in a very vulnerable state. All the standard-of-care or on-the-market treatments have failed or are not available to these patients for some reason. It's an interesting place of giving hope but also not [offering] a guarantee. Nothing in medicine is a guarantee, but [that's true for] clinical trials especially. It's a unique position, but then I get to see these patients every week and guide them through this process. I talk to them in between visits most weeks. I know what's going on in their lives; I know about their kids, about their grandkids, their cats, and vacations they're taking, so it is a more personal nursing relationship. Whereas before, when I worked in hospitals, people were in and out and that's it. You never saw them after.

As far as barriers, time is always a barrier. Not to providing care, but just to being able to get everything done. These are complicated protocols. The learning curve was steep when I started this job, in terms of learning both MM and then learning research, starting with the basics of how to read a protocol and building from there. The other barrier is more of an emotional barrier for me personally. You can't magically fix patients, unfortunately. It's emotional when patients' disease progresses no matter the circumstance.

How do you help ease patients' apprehensions about enrolling in clinical trials?
The way it works here at Emory is the physicians identify a patient who they think would be a good candidate for a trial, and then I look through their chart and make sure that they are eligible. Then I'll meet them in the clinic with the physician, and we'll go over the consent form, which has all the basic information about the trial. I also send it to them ahead of time so they can read it alone, or with their family, or whoever else might be helping them decide. [Some patients] will absolutely come in with tons of questions, but some people don't. Some people are like, "This is what Dr. Lonial suggested, so let's do it," and some people are hesitant.

There's a lot of hesitancy among patients that I had not encountered before this job. Patients have told me, "I don't want to be a guinea pig." Reassuring them that everyone here has their best interests at heart and using the data and research that is available for those drugs is important. I believe a lot of it comes down to their trust in the medical system, our physicians, and Emory. Most patients have a very long-standing relationship with the Winship Cancer Institute by the time they get to clinical trials, and they do have that trust.

I like it when patients have questions. It means that they are interested in their care, that they read the consent form that we sent them, and are an active participant in making their decisions. I think that's important for a clinical trial because it's not easy, necessarily, for the patients. It might not necessarily require more appointments but longer appointments. They have surveys, blood draws, sometimes imaging tests on a frequent basis. There isn't much flexibility for the patients because we're bound by the requirements of the protocol. It can be a big commitment for the patient. You want them to buy in and be active participants.

Your position has a steep learning curve. How do you stay current in your skills?
I immediately did a deep dive into myeloma when I onboarded. I certainly wouldn't say that I know everything there is to know about myeloma, but between reading and studying, and I have learned a lot. Our physicians and team members are wonderful educators. Dr. Lonial is a phenomenal educator and resource. I've gone to him many times with questions related to patients.

Our team does a great job of this by sending out current publications, doing grand rounds in our

weekly meetings, and keeping us up to date on anything that might impact patient care. A lot of our studies are novel in the myeloma world. One of our drugs, teclistamab, was approved by the US Food and Drug Administration (FDA) recently, which was phenomenal.

What is one thing that other people would be surprised to learn about in your profession?
I think people would be surprised by the variety of skills I use daily in this job.

What is something that you would like clinicians to know?
The clinicians put a lot of trust in us (and the nurse practitioners) in the phase I clinic to manage the day-to-day care of their patients. They trust me to tell them if there's anything that they need to know regarding our trial participants. I would love for the clinicians to know that I as a research nurse care so much about our patients and their outcomes. It's an interesting relationship because I feel like we work closely with them, but I see them weekly, not daily.

Can you describe what it is like working at an institution like Emory, where these emerging therapies are front and center?
It is personally rewarding. Dr. Lonial always tells us that Emory has been a part of many FDA-approved myeloma drug trials over the years. I think that's incredible. For me personally, I think about how my grandmother was on clinical trials here and how that gave her so much more life than she would've had somewhere else. It's amazing to be able to help be a part of that with the patients I work with now.

Burnout is notorious in the nursing profession. How do you stave off burnout and leave work at work, especially while caring for patients?
I think preventing and dealing with burnout are skills that nursing school should teach instead of having to pick it up on your own and figure out what does or doesn't work. As I've gotten older, I have gotten better at compartmentalizing. I find myself thinking about my patients (and about work) even when I'm not actively working—it's always there in the back of my mind, even on the weekends. I work hard while I'm at work, but I also have a family, and my time with them outside of work is just as important to me. My weekends are sacred, and I really do my best to be present. I have two young children, a two-year-old and a four-year-old, and my husband and I make a conscious effort to keep work out of our family time as much as possible, so that we can recharge, relax, and combat those feelings of burnout. I also try to dedicate just a few minutes to myself every day, like escaping into a fiction book.

Molly Stoddart, RN, BSN, *is a clinical research nurse on the MM team at the Winship Cancer Institute at Emory University.*

Dr. Raje from page 11

What are you most proud of in your career so far?
I've enjoyed doing what I've done and being able to have a fantastic family. I can't overstate how grateful I am for having an amazing husband and two incredible children. It's hard when both partners are working. My husband is a physician, so both of us were working and bringing up kids. And I feel very blessed and very fortunate. But it really doesn't happen without compromises on both ends, understanding on both ends, and working in partnership so each of us has an opportunity to grow.

I think top-most on my list, even beyond career, is my family. I'm really proud of my absolutely amazing children who—despite both me and my husband being as busy as we've been—have done an incredible job. I have a daughter in medical school right now. I have a son who is doing incredible work. I feel fortunate.

It does take a lot of commitment. It was a village that helped me through all the training and research years, and a very supportive partner. I'm incredibly grateful. In terms of my proudest moments, the things in my life I am proudest of are my kids. And then next, in my career, it's not so much the pride, I just feel so fortunate. I truly feel humbled by being able to take care of our patients, because taking care of my patients is what drives my research and having that relationship with my patients has been so special.

A lot of times people will say, "Why do you do clinic and research?" and "How can you do both?" I think each of those experiences helps ground me and helps me know why I am doing what I'm doing when I see my patients. The relationship I have with my patients is that they're like my extended family. I love what I'm doing for that reason. It pushes me. They are so incredible in terms of what they are willing to do for us. We just have to come up with the best that we can for them. That really is the driving force for what we do.

I feel fortunate that we've been able to get a lot of these drugs approved, and I feel tremendously grateful that I've been a small part of this. All that, to me, has been a blessing. It was a team effort. It was the opportunity of being at the right place at the right time. Being able to see this through is something that has been an amazing experience.

What inspiration or recommendations would you give to younger physicians or trainees in the field?
I think there are so many pressures in life right now for young physicians, with the burden of care of patients, what we have to do with new systems in place, and so forth. I think it's important for any young faculty member to really know what it is that they want to do, and then pace themselves. It takes many years to get from point A to point B. It does require a lot of hard work, and everybody is willing and able to do that. But give yourself time. Give yourself the space to know that you're going to fail at times. There are many times that you will make many wrong decisions, but those decisions allow you to make other decisions, which hopefully will work out. Don't be afraid to fail, because [failure] opens a new avenue. That's the way I look at it. Learn from those past experiences. Have a strong network of people that you can rely on. Identify mentors. In my case, having mentors inside and outside of my institution, inside and outside of my specialty, was really important.

Invest in what's important. To me, my family is incredibly important, they are the backbone of what I'm able to do. Know how to prioritize things. When your kids need you, be there for them. It's okay if your one paper goes in a month later, it's not going to be the end of the world.

I really think knowing what it is that you want in life, giving yourself time—it's never a three-year timeframe, it's a little bit longer than that in academic medicine—is important. As long as you're willing to allow for that, you're going to be okay. Know that you may not do all the things that you set out to do, but even if you do half of those, that's pretty good. Don't be too hard on yourself either.

"For us to be able to see within our lifetime the drugs that we worked with in the lab make a difference to patients has been the most empowering experience."

What do you like to do outside of work?
As I mentioned, I would've gone to culinary school. Exercise is something I do, but what I love is food. I love binging on the Food Network shows. I'm not a great cook, but I love learning. I love experimenting. Cooking is sort of therapeutic. I love trying things. I also work out—running, biking—in my spare time.

Noopur Raje, MD, *is a Professor of Medicine at Harvard Medical School and Director of the Multiple Myeloma Program at Massachusetts General Hospital.*

In Focus

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

Researchers are continuously exploring new ways to target evasive hematologic malignancies.

The goal of modern cancer treatment is to provide targeted and personalized care. For more than 20 years, precision therapies have revolutionized the treatment of many cancer types, including hematologic malignancies. The targets have varied over the years—growth signal inhibitors, angiogenesis inhibitors, cell cycle inhibitors—and so have their success.

The gold standard for targeted treatments has long been the tyrosine kinase inhibitors developed to target BCR-ABL that changed the disease course of patients with chronic myeloid leukemia. Unfortunately, some other targeted therapies have been less effective and less successful. For example, the BCMA-targeting antibody-drug conjugate belantamab mafodotin-blmf, which was granted accelerated approval for relapsed or refractory multiple myeloma (MM), was withdrawn from the US market in late 2022 after disappointing results of a confirmatory trial.[1]

Although many of these targeted therapies have improved tumor responses, progression-free survival, and sometimes overall survival for patients, few, if any, are curative. The eventual acquired resistance to these precision therapies means that one thing has remained constant: the need for novel targets.

Blood Cancers Today recently spoke with several researchers and clinicians about novel targets being investigated in several types of hematologic malignancies.

GPRC5D

Despite the withdrawal of the BCMA-targeting antibody-drug conjugate, other therapies targeting BCMA, which is highly expressed in mature B-lymphocytes and plasma cells, have been more successful in the treatment of MM, including two chimeric antigen receptor (CAR) T-cell therapies (ciltacabtagene autoleucel and idecabtagene vicleucel) and a T-cell engager (teclistamab).[2,3]

BCMA-directed CAR T cells have shown deep responses in some patients with advanced MM, but most patients are likely to eventually relapse. One of the targets being explored for patients with relapsed or recurrent disease, or those who have progressed after BCMA-targeting therapies, is orphan G protein-coupled receptor, class C, group 5, member D (GPRC5D).

In 2019, **Eric L. Smith, MD, PhD,** of the Memorial Sloan Kettering Cancer Center, and colleagues published a paper detailing that the GPRC5D protein, which is normally expressed in the hair follicle, was expressed in MM cells independently of BCMA. Experiments in mouse models showed that

targeting GPRC5D eradicated MM and led to long-term survival.[4]

"We don't know a lot about its activity or the mechanism of how it helps myeloma cells survive," said **Saad Z. Usmani, MD, MBA, FACP,** Chief of the Myeloma Service at the Memorial Sloan Kettering Cancer Center. "What we do know it that it is highly expressed on myeloma cells and more preferentially expressed in plasma cells compared to other cell types."

Drs. Smith and Usmani were both part of a team of researchers who published results of a first-in-human, phase I, dose-escalation study looking at GPRC5D-targeted CAR T-cell therapy in patients with heavily pretreated MM, including some with prior BCMA CAR T-cell therapy.[5]

The study looked at four different dose levels: 25×10^6, 50×10^6, 150×10^6, and 450×10^6 total CAR T cells. The maximum tolerated dose was identified at 150×10^6.

"It is important to note that the overall response rate (ORR) for the entire cohort was 71%, which included a majority of patients who had prior BCMA treatment," Dr. Usmani said. "Seven of the nine patients with prior BCMA treatment responded."

Data indicated that the therapy was safe. Cytokine release syndrome (CRS) was mostly grade 1 or 2, with one patient experiencing grade 4 CRS and neurotoxicity.

Targeting GPRC5D is also being explored in the form of a bispecific T-cell engager antibody that targets both GPRC5D and CD3. The drug, talquetamab, was granted US Food and Drug Administration (FDA) Breakthrough Therapy Designation in June 2022.[6]

In December 2022, results of a phase I study of talquetamab as treatment for patients with heavily pretreated relapsed or refractory MM were published in the *New England Journal of Medicine*.[7] Patients received talquetamab either intravenously weekly or every other week or subcutaneously weekly, every other week, or monthly, with two subcutaneous doses recommended for phase II study (405 µg/kg weekly and 800 µg/kg every other week).

At follow-up, patients treated with 405 µg/kg weekly had a response rate of 70%; patients treated with 800 µg/kg every other week had a response rate of 64%. Median durations of response were 10.2 and 7.8 months, respectively, for the two doses.

Dr. Usmani noted that the GPRC5D bispecific antibody did have a different safety profile compared with the CAR T-cell therapy.

In addition to mostly grade 1 or 2 CRS, skin-related events occurred in 67% and 70% of patients at the two dose levels, respectively, and dysgeusia occurred in 63% and 57%. One dose-limiting grade 3 rash was also reported at the higher dose. Bispecific antibodies, in general, are also associated with increased infection risk, Dr. Usmani noted.

"The advantage of CAR T-cell therapy is that you give a single dose and let the patients recover," Dr. Usmani said. "There is not any consolidation or maintenance treatment."

In contrast, talquetamab is given on a regular basis.

"The skin- and nail-related changes are a quality-of-life concern, of course," Dr. Usmani said. "Right now, the strategy with bispecifics is to focus on giving less treatment to mitigate these side effects. We want to see if patients get a good response if you can back off treatment frequency."

There are also other GPRC5D bispecific antibodies in development, like RG6234 (Regeneron), which also showed response rates of approximately 70%.[8] In addition, researchers are looking into the feasibility and efficacy of a CAR T-cell therapy simultaneously targeting BCMA and GPRC5D.

If these GPRC5D-targeting therapies prove effective and gain regulatory approval, the next step will be to determine the appropriate sequencing of these drugs.

"The therapies we have for MDS are, at best, very limited. We need new, effective therapies." *—Guillermo Garcia-Manero, MD*

IRAK4

Another area of hematologic malignancies in need of new targets is myelodysplastic syndromes (MDS). Although many patients diagnosed with MDS will have lower-risk disease, those with higher-risk disease need effective strategies. Right now, most patients who undergo first-line treatment for MDS will eventually experience relapse or resistance, according to **Guillermo Garcia-Manero, MD,** Chief of the Section of MDS in the Department of Leukemia at the University of Texas MD Anderson Cancer Center.

"The therapies we have for MDS are, at best, very limited," Dr. Garcia-Manero said. "We need new, effective therapies."

Molecular diagnostics have helped researchers to identify several gene mutations in MDS, including genes responsible for epigenetic regulation, RNA splicing, DNA damage response, transcriptional regulation, and signal transduction.[9] A recent area of interest involves the role of interleukin (IL) 1 receptor-associated kinases (IRAKs), which are involved in multiple inflammatory pathways implicated in hematologic malignancies.

"Over the last decade or so, there has been an effort to understand the molecular pathogenesis of MDS," Dr. Garcia-Manero said. "A number of investigators, including our group, discovered that a pathway that we refer to as innate immunity signaling is overexpressed in a large fraction of patients, particularly those with lower-risk disease."

Dr. Garcia-Manero said this signaling starts with activation of certain receptors, like toll-like receptors, which leads to activation of the NF-κB pathway. Overactivity of the NF-κB signaling pathway is implicated in the development of both MDS and acute myeloid leukemia (AML).

These and related discoveries have spurred interest in targeting IRAKs.

"The idea is that if you block this IRAK4, for instance, you may dampen signaling via NF-κB and decrease production of inhibitory cytokines such as IL-1 and IL-6 and potentially restore hematopoiesis," Dr. Garcia-Manero said.

There are a few compounds targeting IRAK4 currently under investigation. These drugs may have activity in both lower- and higher-risk disease.

In 2022, Dr. Garcia-Manero presented data at the European Hematology Association Annual Meeting on emavusertib (CA-4948; Curis), which is a novel inhibitor of both IRAK4 and *FLT3*. The open-label, phase I/IIa trial established a phase II dose of the drug (300 mg twice daily) and showed efficacy in the group of patients with heavily pretreated AML and high-risk MDS. In the five patients with AML, 40% achieved complete response (CR) or CR with incomplete hematologic recovery. In the seven patients with high-risk MDS, 57% reached bone marrow CR.[10]

German researchers are also investigating the use of emavusertib for the treatment of anemia in patients with very low-, low-, or intermediate-risk MDS.[11]

In December 2022, Rigel Pharmaceuticals announced it was launching a phase Ib study of its dual IRAK1/4 inhibitor R289 in patients with lower-risk refractory or resistant MDS.[12]

One concern with targeting IRAK4, Dr. Garcia-Manero said, is that innate immunity is part of our natural defense mechanism used to defend against infection.

"One potential problem with targeting that pathway is that you also inhibit the physiological mechanisms of defense and patients are more prone to infection," he said, adding that the issue is more theoretical and has not yet been seen in trials of other drugs that disturb this pathway.

"There is quite a bit of interest in these agents, but we need to figure out the proper dose and schedule in higher-risk disease and eventually in low-risk disease," Dr. Garcia-Manero said. "A next step would also be to find a subset of patients who are vulnerable to this type of drug." Data from several groups have suggested that leukemias with splicing mutations may be vulnerable to this kind of intervention.

Dr. Garcia-Manero also mentioned that the innate immunity signaling pathway is quite redundant, with many receptors that could trigger activation.

"In my mind, there will be a need for some type of combination treatment to make these compounds more effective," he said.

EZH2

Another novel target that may have some interaction with the immune system is EZH2, an enzymatic catalytic subunit of polycomb repressive complex 2 (PRC2). PRC2 controls the organization of chromatin

in many cells, including in germinal center B cells where follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) originate, according to **Gilles Salles, MD, PhD,** Chief of the Lymphoma Service at the Memorial Sloan Kettering Cancer Center.

"EZH2 was one of the first genes found to be mutated in FL and some DLBCL more than 10 years ago," Dr. Salles said. "Interestingly, these mutations, which are present in up to 20% of FL, are activating mutations that lead to overexpression of the protein, and experimental data suggest that this contributes to the malignant process."

Early data indicated that inhibiting EZH2, whether it is mutated or unmutated, would be a reasonable target in patients with FL.

"Based on this target identification, it was tempting to try to develop an inhibitor of EZH2, and tazemetostat was the first oral inhibitor developed and tested in patients with B-cell lymphoma," Dr. Salles said.

In 2020, tazemetostat was granted FDA accelerated approval based on data out of two open-label, single-arm cohorts.[13] Eligible patients were treated with tazemetostat 800 mg twice daily for 28-day cycles. Among patients with FL with *EZH2* mutations, the objective response rate was 69%; among those with EZH2 wild-type disease, it was 35%.[14]

"The duration of the response of both cohorts, with and without the mutations, was found to be about one year," said Dr. Salles, who was a researcher on the study. "Based on these data, the drug was approved by the FDA with two distinct indications."

In patients with the *EZH2* mutation, tazemetostat should be used as a third-line therapy in patients who have failed at least two lines of therapy and in patients without characterization with relapsed or refractory FL who have no other alternative treatment options, noted Dr. Salles.

Given that the drug is an oral agent and was well-tolerated, Dr. Salles said that he considers it a "useful tool, but not a magical tool."

According to Dr. Salles, EZH2 inhibition also leads to the expression of a couple of molecules on the surface of the B cell that may participate with immune interaction with T cells. Because of this interaction, researchers are curious to try combining tazemetostat with some immunotherapy regimens.

In December 2022, Dr. Salles presented the results of the phase Ib SYMPHONY-1 trial that tested tazemetostat in combination with lenalidomide and rituximab (R^2) in patients with relapsed or refractory FL.[15] The ORR among evaluable patients was 97.6%, with a little more than half (51.2%) achieving CR and a little less than half (46.3%) achieving partial response.

"The results appear to be very promising and may be superior to those we observed when using R^2 alone," Dr. Salles said, adding that the populations are not comparable.

The tolerability of the combination was satisfactory, he said, with side effects similar to those seen with R^2.

"It really acts on an interesting pathway given that it affects the intimate molecular level of FL biology but also has some more broad immune effects," Dr. Salles said. "I will, however, add a word of caution about targeting epigenetics. The potential long-term effects of this modification of epigenetic machinery on other cell types, including hematopoietic stem cells, are unknown, and we need to continue to follow patients exposed to molecules of this family."

"PLK4 is interesting in that its function does not have a redundancy, whereas other PLKs can have redundancy. That means that as a target, if you hit it, there is not a compensatory mechanism that can take over." *—Gautam Borthakur, MD*

PLK4

Another potential drug class was developed with potential synergizy with immunotherapy, according to **Gautam Borthakur, MD,** a Professor in the Department of Leukemia at the University of Texas MD Anderson Cancer Center.

PLK4 is a novel target of interest in the management of leukemia. PLK4—or polo-like kinase 4—is a member of the polo-like kinase family of serine/threonine kinases, which are linked to cell cycle regulation. PLK4 is linked specifically with the regulation of centriole duplication during cell division and has been shown to be overexpressed in a number of human cancers.[16] In addition, its expression has been linked with poor outcomes, Dr. Borthakur noted.

"PLK4 is interesting in that its function does not have a redundancy, whereas other PLKs can have redundancy," Dr. Borthakur said. "That means that as a target, if you hit it, there is not a compensatory mechanism that can take over."

According to Dr. Borthakur, there is a substantial unmet need for new options in patients with high-risk AML.

"Despite the introduction of venetoclax, and the improved outcomes seen with the drug, there is still a large percentage of patients whose responses don't last," he said.

In 2020, researchers from Toronto published an abstract with preliminary results of a phase I study of an oral PLK4 inhibitor—CFI-400945—tested in patients with AML and high-risk MDS.[17]

"In this investigator-initiated study, responses were seen in patients with high-risk AML with complex cytogenetics, supporting the idea that maybe PLK4 inhibition would be effective in patients with *p53* mutations or other complex cytogenetics," Dr. Borthakur said.

Late last year, a poster presentation included preliminary results of the dose optimization of the TWT-202 trial of CFI-400945 in advanced leukemias.[18]

It is still too early to tell what patient populations might benefit most from a PLK4 inhibitor, Dr. Borthakur said. At the end of the day, it must still be determined if this type of drug is best delivered as a single agent or in combination with other agents. For example, there is interest in combining a PLK4 inhibitor with hypomethylating agents to see if that would enhance activity in patients with high-risk AML.

One of the biggest remaining questions, according to Dr. Borthakur, is what toxicities will be seen with drugs targeting PLK4.

"There are cells in our body that are mitotically active, particularly those in the gut and normal cells in the bone marrow, so there is a question about toxicities," he said. "This is also an area where research into combinations would help. We may not need to push a single agent to the maximum-tolerated dose if we use a multipronged strategy to hit similar targets."

Leah Lawrence is a freelance health writer and editor based in Delaware.

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Legislative Update

Blood Cancers Today *reports on legislative actions affecting patients with hematologic malignancies*

California Legislation Takes Aim at Disparities in Access to Cancer Care

A new California law promises access to high-quality cancer care for underserved communities. Although much work still needs to be done, advocates of the bill hope it will bring much-needed change to patient care for complex cancers—including hematologic malignancies.

Signed into law by California Gov. Gavin Newsom in September 2022, the California Cancer Care Equity Act (SB 987) went into effect in January 2023. It addresses the issue of access disparity for patients enrolled in Medi-Cal, the state's Medicaid program, who have been diagnosed with complex cancers. The bill seeks to improve access to patient care, outcomes (survival), and experience by enhancing referrals to designated specialty centers.

Similar legislation has been passed in New York and is being considered in other states. In this legislative update, *Blood Cancers Today* explores the background and implications of this groundbreaking law and interviews some of the advocates and medical professionals involved in developing it.

Disparities in Access to Health Care

Approximately 84 million people in the United States are enrolled in a state Medicaid program, which serves children, low-income individuals and families, and individuals with disabilities.[1] For many enrollees, the Medicaid program is their only source of long-term health coverage, with the majority lacking access to other affordable health insurance.[2]

What happens when patients who are enrolled in Medicaid are diagnosed with a complex cancer such as multiple myeloma (MM)? In theory, the patient would work with a team of health care professionals to develop a treatment plan and receive supportive care.

In practice, however, these patients face a daunting array of challenges, including limited access to care and support services, affordability of treatment, limited health coverage, and difficulty navigating the system to find providers and get treatment authorizations. Lacking financial resources, they may be unable to afford transportation (especially in rural areas), child care, and other daily living needs, making it difficult for them to attend appointments and follow through with treatment plans.

Joseph Alvarnas, MD, a hematologist-oncologist and Vice President of Government Affairs at the City of Hope, explained that certain barriers to care are universal.

"If you look at barriers created by social determinants of health—having gas money, issues of health literacy, poverty, geographic distance from centers with appropriate expertise—I think those kinds of issues are found throughout the country," he said.

Even in California, known for progressive health care policies and its aggressive implementation of the Affordable Care Act and expansion of Medi-Cal, patients in underserved populations still face significant hurdles to care.

An unintended consequence of the state's expansion of universal health care coverage was the

creation of narrow provider networks that were not equipped to handle complex cancer cases. Patients and families found themselves facing numerous barriers and battles just to access the care they needed, Dr. Alvarnas explained.

"What we found was that you could have coverage but not actually have access to care," said Dr. Alvarnas. "The challenge was that as Medi-Cal expanded, one of the things that it used as a means of controlling costs was the managed care model. Those [models] weren't designed with cancer in mind, and one of the unintended consequences is that, in fact, you create networks that may have no one with particular expertise in leukemia, or in very advanced and refractory cancers, or in genomics."

California Cancer Patients Bill of Rights

The origin of SB 987 lies in the California Cancer Patients Bill of Rights, which was passed in 2021. Sponsors of the bill called it "a first of its kind in the nation."[3] The bill enumerated six core patient rights, including access to cutting-edge treatments and clinical trials and the right to contract with top cancer centers.[4]

Although both houses of the California State Legislature unanimously approved the Cancer Patients Bill of Rights resolution in 2021, it carried no force of law.

"If you look at barriers created by social determinants of health—having gas money, issues of health literacy, poverty, geographic distance from centers with appropriate expertise—I think those kinds of issues are found throughout the country." *—Joseph Alvarnas, MD*

SB 987: California Cancer Care Equity Act

At the heart of SB 987 is the issue of disparities in cancer outcomes in cases of complex diagnoses, which include hematologic malignancies such as acute leukemia, non-Hodgkin lymphoma, or MM for communities of color and low-income populations. The bill ensures that underserved communities in California have access to the care they need, regardless of whether the cancer is newly diagnosed, relapsed, or refractory.

"SB 987 was conceived to figure out a way in which those core principles could translate into meaningful, actionable change for the most vulnerable members of our society," Dr. Alvarnas said.

Prior to the passage of SB 987, patients on Medi-Cal had no access to high-quality care, according to **Ernie Davis,** Regional Director of Government Affairs at the Leukemia & Lymphoma Society (LLS).

"Blood cancers are very complex cancers, and access to high-quality cancer care, if you are an individual on Medi-Cal prior to the passage of this legislation, did not exist," Davis said.

One in three Californians is enrolled in Medi-Cal, and Davis estimates that 70% of those enrollees are minorities.

"When you're talking about the dynamics of Medi-Cal, you're talking about public health coverage that covers one in three Californians, which is huge, and it's also the primary insurance provider for individuals between the ages of zero to 18 years."

Davis hopes that the bill will give access to high-quality cancer care to those who were previously lacking it. A large part of making care more accessible to these patients is referrals, a crucial provision of SB 987.

The bill asks medical plans caring for low-income patients to make a good-faith effort to contract with at least one designated specialty center such as a US National Cancer Institute (NCI)-designated Comprehensive Cancer Center or a qualifying academic cancer center. It also requires Medi-Cal managed care plans to notify all enrollees when they are diagnosed with cancer of their right to request a referral to a specialized cancer center. Davis said that LLS is able to help patients with this process.

"Our hope is [that] through the LLS network, folks can call in and ask for advice when they get a blood cancer diagnosis," said Davis, adding that when patients from California contact the LLS network, they'll be directed to the legislation to make those patients aware that they now have access—and the right to request a referral—to a specialized cancer center in California if they're a Medi-Cal recipient.

Although the bill has been passed, Davis estimates that implementation will take six months to a year, as there are administrative and back-end processes that need to be completed.

LLS helped pass similar legislation in New York, and Davis became involved with the California bill after working on the New York bill. The organization is planning for similar legislation in other states but is still assessing which states would be a good fit.

The Road Ahead

"This bill is important, but its impact on the state of California is still uncertain," said **Thomas Martin, MD,** Associate Editor of *Blood Cancers Today* and Clinical Research Director of Hematologic Malignancies at the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center. "The bill aims to increase access to health care for managed Medi-Cal patients who may not have the greatest access to care. It's important to provide care to all patients, regardless of where they live or their socioeconomic background."

Dr. Martin explained the need for the bill to provide resources and financial support to ensure that these services are available to patients in all areas of California, not just the big cities.

"I think it's a good bill to enhance diversity in care for these patients, but how it will actually work is a challenge," he said. "There are questions about where patients would be referred and how they would get there, especially for those who live a long distance from an NCI-designated center. We need to make sure that treatments, including clinical trials, are available to all patients, including those on Medi-Cal plans. But we also need to have resources to help patients get there, as they have to come back recurrent times, and that can be financially challenging."

SB 987 is still a first step—if only a small step—in the right direction, according to Dr. Alvarnas.

"SB 987, I think, is a win, but it's an incremental win. It's the first step. I expect us to do a lot more work to move this forward—a lot more work," he said.

Leah Sherwood is the Managing Editor of Blood Cancers Today.

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Prognostic Tools Need Updates to Recognize High-Risk Features in Lower-Risk MDS

Take-aways:
- Current prognostic scoring systems for MDS, such as the IPSS-R, may classify certain cases as lower-risk MDS, despite the presence of high-risk features.
- Lower-risk MDS with high-risk features may require a different treatment approach, making it critical to optimize prognostic tools that allow clinicians to balance the risk of therapy with the risk of the disease.
- Current prognostic scoring systems for MDS could be improved by incorporating relevant clinical features, molecular data, etiological information, and other factors that impact risk.

Low-risk myelodysplastic syndromes (MDS) can have high-risk features, but current prognostic scoring systems for MDS may not capture key variables that impact risk and treatment outcomes in patients with lower-risk MDS, according to a recent perspective published in the *Expert Review of Hematology*.

Amy E. DeZern, MD, MHS, and **William Brian Dalton, MD, PhD,** both of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University School of Medicine, reviewed the literature on diagnostics, prognostics, therapeutics, and outcomes in patients with MDS because accurate prognostication is "especially important" in MDS, a heterogenous condition with varied survival.

MDS is "distinct from other cancers," as diseased cells in MDS "still serve a productive role for patients, however feebly." That means MDS therapies must contend with potential "on-target effects of eliminating the mutant blood system," Drs. DeZern and Dalton said in the review article.

"Thus, the limited but available treatments in MDS must be carefully timed along the disease trajectory so that their potential benefits to both quantity and quality of life outweigh their potential risks," they wrote. "Given this, precise disease prognostication is imperative."

Current MDS Prognostic Scoring Systems: Advantages and Limitations

It is critical to identify high-risk features in patients who have otherwise lower-risk MDS, as management of lower-risk disease is "generally conservative," and "underestimating the risk of progression may miss the optimal time to initiate more aggressive treatments," the review's authors wrote.

Several MDS prognostic scoring systems are available, including the World Health Organization classification-based Prognostic Scoring System (WPSS), the MD Anderson Risk Model Score (MDAS), the MDS Lower-Risk Prognostic Scoring System, and the revised International Prognostic Scoring System (IPSS-R).

The IPSS-R, which has been the "most widely adopted risk stratification system," has advantages, including updated cytogenetic risk groups, validation in multiple independent groups, validation in treated patients, and "evidence that it directly outperforms other scoring systems in some populations," according to the review's authors.

However, the IPSS-R has "limitations in prognostic power," particularly in patients with lower-risk disease, Drs. DeZern and Dalton wrote. For example, 7% of patients classified as lower risk by the IPSS-R were classified as high risk by the WPSS system, and 29% of patients classified as lower risk by IPSS-R were classified as high risk by the MDAS system.

Each system has its relative advantages and limitations, but the current systems "may fail to capture important prognostic information at the individual level due to the lack of incorporation of salient clinical features, molecular data, and dynamic changes in risk over time," Drs. DeZern and Dalton said.

Specific Clinical Features Elevate MDS Risk

Certain clinical features may elevate the risk of lower-risk MDS, particularly red blood cell transfusion dependence, which independently predicts poor prognosis and adds prognostic value to the IPSS-R. Higher-grade bone marrow fibrosis can also "signal poorer outcomes in lower-risk MDS," according to the review. See **TABLE 1** for a list of clinical features that can elevate the risk of lower-risk MDS.

TABLE 1. Clinical Features That Can Elevate the Risk of Lower-Risk MDS

- Red blood cell transfusion dependence
- Higher-grade bone marrow fibrosis
- Platelet change velocity
- High ferritin
- High lactate dehydrogenase
- Poor performance status
- Presence of peripheral blood blasts
- Higher frailty indices
- Patient age
- Lack of response to therapies such as erythropoiesis-stimulating agents, lenalidomide, and hypomethylating agents

Mutation Quantity, Type, and Context Can Shape MDS Risk Level

Most patients with MDS have mutations, and "clear examples of their independent prognostic utility have been well-documented," Drs. DeZern and Dalton wrote. Despite this evidence, the "most notable deficiency" of all the validated scoring systems is the "lack of incorporation of gene mutations gleaned from next-generation sequencing."

The quantity and type of mutations can both play a role in shaping risk.

For example, the total number of driver mutations is negatively correlated with leukemia-free survival in patients with MDS, and the quantity of mutations has independent prognostic value for IPSS categories. Furthermore, an increasing number of mutations negatively correlates with leukemia-free survival and overall survival.

"Thus, IPSS-R lower-risk patients with [an] elevated driver mutation number, especially those with three or more, are generally accepted as higher-risk and deserving of more proactive therapy," Drs. DeZern and Dalton wrote.

Specific gene mutations are also associated with varying risk levels, with multiple studies showing mutations in certain genes can have prognostic value. For example, mutations in *ASXL1, EZH2, RUNX1,* and *TP53* were "most consistently identified as predictive of negative outcomes," Drs. DeZern and Dalton said.

Wild-type *SF3B1* is associated with negative outcomes in patients with MDS, while mutations in *SF3B1*—which are present in more than 80% of cases of MDS with ring sideroblasts—are independent predictors of "more favorable outcomes," according to the review's authors.

However, there are "important exceptions that warrant consideration in risk assessment," they wrote, as the impact of the mutation may be dependent on context. For example, *SF3B1* mutations are associated with poorer survival in patients with complex cytogenetics and in patients with isolated del(5q).

In the case of *TP53* mutations, patient risk can vary with the allelic state of *TP53*. Patients with more than one *TP53* mutation, chromosome 17 monosomy or 17p deletion, and high total *TP53* variant allele frequency are considered high-risk patients. However, patients who have one *TP53* mutation, a lack of chromosome 17 abnormalities, lower variant allele frequency, and more co-mutations in other genes are considered average-risk patients.

According to Drs. DeZern and Dalton, "the clinical implications of these findings are clear: The allelic state of *TP53* should be incorporated into the risk stratification" of patients with MDS.

MDS Etiology Can Impact Risk

While the IPSS-R does not "incorporate the underlying etiology" of MDS, there is "evidence that the cause(s) of a patient's MDS may be relevant to their prognosis independently of other established risk factors," the review's authors wrote.

For example, the IPSS-R has "less precision in prognosis" when applied to patients with therapy-related MDS, as those patients "generally have poorer outcomes" than patients with non-therapy-related MDS in the same IPSS-R risk group, according to Drs. DeZern and Dalton.

"Current evidence indicates that, in general, IPSS-R low-risk [therapy-related] MDS will likely be higher risk," they wrote, noting further research is needed to determine the role of factors such as high-risk mutations, comorbidities, and sequalae of previous therapies in therapy-related MDS.

A germline predisposition to MDS, which can occur as part of a syndrome or an isolated myeloid disease, could also impact a patient's prognosis. For example, in syndromic cases, which are "likely presenting earlier and with more IPSS-R low-risk disease due to increased surveillance," there may be a reason to believe they are higher-risk due to the "potential lead-time bias," Drs. DeZern and Dalton wrote.

Additional reasons there may be a higher risk in patients who are otherwise low risk but have a germline predisposition to MDS include "idiosyncratic pathologic and genetic features not captured by standard assays or scoring systems; tendency to develop additional, independent myeloid malignancies; syndromic comorbidities; increased disease-related toxicities from therapies; and the simple observation of poor MDS outcomes in relevant patient series."

Therapeutic Considerations in Lower-Risk MDS with High-Risk Features

While standard treatments for lower-risk MDS are still currently used "regardless of higher-risk features," Drs. DeZern and Dalton "emphasize the frequent need for reassessment if responses to treatment are not positive."

Hypomethylating agents and lenalidomide are not approved for lower-risk MDS in many countries, but those therapies are "considerations in disease that has upstaged or has the adverse molecular features noted," they wrote. "For example, patients with multilineage dysplasia, pancytopenia, or greater than three mutations are often treated much earlier with [hypomethylating agents], regardless of IPSS-R lower scores."

Transplantation may even be an option for certain patients with lower-risk MDS who have high-risk features.

"Historically, [bone marrow transplant] has been reserved for patients with higher-risk MDS, given its potential curative benefit is offset by the morbidity and mortality that can result from the procedure," the review's authors wrote. "Nonetheless, efforts have been made to weigh the toxicities of this intervention in [lower-risk] MDS, and many [lower-risk] patients are offered [bone marrow transplant], especially those with higher-risk molecular features such as *RUNX1*, *TP53*, or *ASXL1*."

The Future of MDS Prognostic Scoring Systems

Drs. DeZern and Dalton emphasized the need for new prognostic scoring systems that incorporate parameters on additional clinical features, molecular data, etiological information, and other variables discussed in the review. See **TABLE 2** for an overview of features that can elevate the risk of lower-risk MDS.

TABLE 2. Higher-Risk Features in MDS Otherwise Considered Lower-Risk by the IPSS-R

Features	Exceptions
High number of mutations	Multi-hit *TP53* has few co-mutations but is high risk.
ASXL1 mutation	N/A
EZH2 mutation	N/A
RUNX1 mutation	N/A
TP53	Monoallelic *TP53* is average risk.
Wild-type *SF3B1*	• Co-mutation with *ASXL1, RUNX1, EZH2* is higher risk. • Co-occurrence with complex cytogenetics or isolated del(5q) is higher risk. • One specific *SF3B1* mutation is higher risk.
Therapy-related MDS	"Therapy-coincident" MDS may be average risk.
Germline predisposition to MDS	N/A
Red blood cell transfusion dependence	N/A
High-grade bone marrow fibrosis	N/A
Relative platelet drop	N/A

They referenced two approaches that were published in the *Journal of Clinical Oncology* in 2021, one of which modeled clinical and genomic variables, including mutations, to generate a personalized prognostic assessment. The second approach used clinical and mutational data to develop a personalized prediction model. Both approaches "outperformed" the IPSS-R in independent datasets, and "both groups intend to make their personalized prediction tools available online for application to individual MDS patients," Drs. DeZern and Dalton wrote.

A large multi-institutional group has proposed a Molecular IPSS (IPSS-M) based on an analysis of clinical, cytogenetic, and mutational features from nearly 3,000 patients. This system changes stratification from the IPSS-R classification in nearly half of patients, including 6% of patients who were classified as very low/low-risk by IPSS-R and were reclassified as very high/high-risk by the IPSS-M.

"Implementation of these tools should launch a new era of molecular prognostication of low-risk MDS," Drs. DeZern and Dalton wrote.

The authors also noted that there are "several areas where the precision of MDS prognosis can likely be further refined." These areas include:

- Considering the prognostic value of individual variants of mutated genes
- Investigating the impact of mutation variant allele frequency on prognosis
- Understanding how less frequent mutations and cytogenetic abnormalities contribute to prognosis
- Evaluating prognostic context dependence on various combinations of genetic and clinical features

"Finally, there will likely be new disease parameters that bear on MDS prognosis in ways that we do not even incorporate clinically at present," Drs. DeZern and Dalton wrote. "These include variables like DNA methylation, gene expression, RNA splicing, and measures of the 'immunome,' among others. With the tools available to us now, the field of MDS prognostication in the next 50 years promises to be even more exciting than the last."

Experts Provide Opinion on Prognostic Scoring System Needs in Lower-Risk MDS

With the heterogeneity of lower-risk MDS and the need for accurate risk stratification to balance the risks and benefits of treatment, it is critical to develop and refine prognostic tools.

"Currently available prognostic scoring systems aid in risk stratification but do not capture all important variables, and they are also insufficient for prediction of response to therapy," Drs. DeZern and Dalton wrote.

They believe the "goal is a proactive approach" in all lower-risk patients that will "extend quantity of life with quality through use of all available treatments." Lower-risk MDS "requires an optimized understanding of a patient's risk, as the risk of therapy must not exceed the risk of the disease in its current form."

While treatment can vary—from observation and supportive treatments to active chemotherapy and allogeneic hematopoietic stem transplantation—based on the severity of the disease, these approaches may not be applicable to every case, Drs. DeZern and Dalton wrote.

It's critical to understand the biology and natural history of the disease, as that information can help predict the likelihood of an adverse outcome and determine the appropriate intervention.

"In the future, incorporation of molecular profiling in diagnosis, prognosis, and formal classification/prognostication schemes will be paramount to help establish initiation of therapeutic interventions to alter the natural history of these syndromes," the review's authors said.

Integrating clinical data with diagnostic genome profiling can "then provide prognostic predictions that are tailored to individual patients and their dynamic course with a myeloid disorder," they wrote.

"A key corollary to this personalized prognostic approach over the coming five years must be an active and growing portfolio of standard and investigational therapeutics to empower the clinician to intervene," Drs. Dalton and DeZern concluded. "We cannot improve outcomes for patients through diagnostics alone; we require active, nontoxic interventions to alter the natural history of their MDS—from higher- to lower-risk disease."

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Spotlight on The HemOnc Pulse

Chadi Nabhan, MD, MBA, FACP, a hematologist and medical oncologist and host of The HemOnc Pulse, a podcast brought to you by Blood Cancers Today *and the Society of Hematologic Oncology, covers the latest news in hematologic oncology with leaders in the field.*

Which CLL Abstracts From ASH 2022 Can't Be Ignored?

On a recent episode of The HemOnc Pulse, **Elizabeth Brem, MD,** a Clinical Associate Professor of Medicine at the University of California in Irvine, discussed the latest updates in chronic lymphocytic leukemia (CLL). Dr. Brem shared her insights on newly diagnosed patients with CLL and the most relevant abstracts presented at the 64th American Society of Hematology Annual Meeting and Exposition in New Orleans, Louisiana.

Dr. Brem emphasized the importance of combination therapies and time-limited treatments in CLL management and mentioned that several abstracts presented at the conference focused on minimal residual disease (MRD)-driven endpoints and higher-risk subgroups. The podcast episode provided a comprehensive overview of the progress made in CLL research and clinical care over the past decade, including the shift from chemotherapy to a better understanding of the molecular pathophysiology of the disease.

Elizabeth Brem, MD

Chadi Nabhan, MD, MBA, FACP

According to Dr. Brem, in general, chemotherapy is no longer recommended for frontline treatment of CLL. Regarding specific studies, Dr. Brem highlighted the ALPINE trial for single-agent Bruton's tyrosine kinase (BTK) therapy, a phase III randomized study of zanubrutinib versus ibrutinib. The study focused on a relapsed or refractory population and demonstrated improved safety and efficacy of zanubrutinib compared with ibrutinib.

"It's going to be really hard to start too many new patients on ibrutinib now knowing what we know about safety and efficacy," Dr. Brem said.

In terms of BTK inhibitors, Dr. Brem explained that she reaches for acalabrutinib in her practice, regardless of whether the patient is new or relapsed or refractory. She also is no longer treating patients with CLL in the frontline with chemotherapy.

Drs. Nabhan and Brem discussed how acalabrutinib may be a more effective treatment option than ibrutinib. While some patients may still receive chemotherapy treatments like bendamustine and rituximab or fludarabine, cyclophosphamide, and rituximab, acalabrutinib is the preferred option for many.

However, there is concern about the toxicities of acalabrutinib versus ibrutinib, particularly when it comes to cardiotoxicity. Dr. Brem cited a study that found a higher rate of atrial fibrillation (AF) in patients taking acalabrutinib compared with ibrutinib, but she also noted that the overall rates of AF for both drugs were still relatively low.

Dr. Nabhan asked how hematologists are managing patients who develop AF while taking these drugs. Dr. Brem said she typically manages anticoagulation and can rate control patients, but may seek help from a cardiologist if cardioversion is necessary.

The conversation then shifted to new research on Richter's transformation (RT), which occurs when CLL turns into diffuse large B-cell lymphoma. Dr. Brem highlighted a study that looked at a combination therapy of ibrutinib and venetoclax for patients with RT. The study found that this treatment option had a high response rate and was well-tolerated by patients.

Dr. Brem also emphasized the importance of monitoring MRD in patients with CLL, as it may provide information on when to stop therapy. She presents her patients with the available options and offers both indefinite and time-limited therapies. Dr. Brem noted that she prefers time-limited therapies for patients with longer life expectancies, as they allow those patients to have several years without being on any therapy.

"I [find] myself really biased toward the time-limited therapies, just thinking about how it'd be nice for this particular person to have several years of their life without being on any therapy. I'm finding it's sometimes the patients who I think have a shorter overall life expectancy where I'm biased, maybe a little bit, toward the more indefinite therapies. I'm thinking that maybe it's not going to be as much of a burden for them to take something for a few years," she said.

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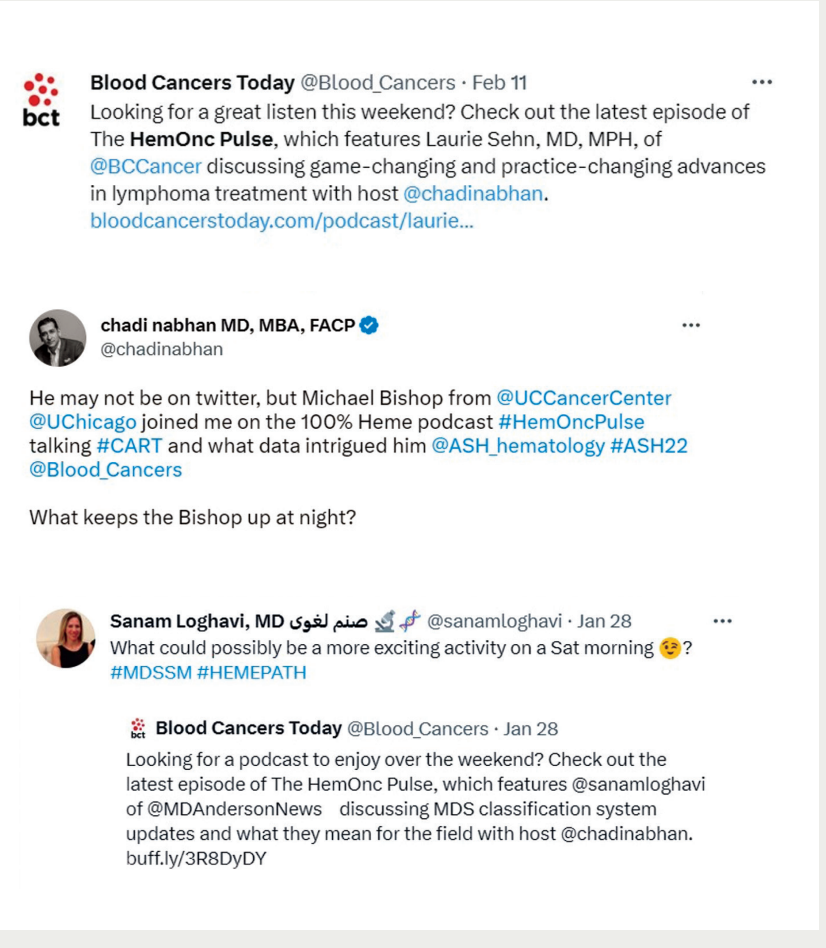


Regulatory Actions

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

FDA Grants Priority Review to Elranatamab for Relapsed or Refractory Multiple Myeloma

The US Food and Drug Administration (FDA) has granted priority review to the Biologics License Application (BLA) for elranatamab for the treatment of patients with relapsed or refractory multiple myeloma (MM).

The new FDA decision follows its granting of the Breakthrough Therapy Designation to elranatamab in November 2022 and its Orphan Drug Designation for the treatment of MM.

The BLA for elranatamab, an investigational, BCMA CD3-targeted, bispecific antibody, is primarily based on data from cohort A (BCMA-naïve; n=123) of MagnetisMM-3, an ongoing, open-label, multicenter, single-arm, phase II study designed to evaluate the safety and efficacy of elranatamab monotherapy in patients with relapsed or refractory MM. The data were presented at the 64th American Society of Hematology (ASH) Annual Meeting and Exposition in December 2022.

Patients enrolled in MagnetisMM-3 represent a heavily pretreated population and previously received at least three classes of therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

With a median follow-up of 10.4 months, patients who received elranatamab as their first BCMA-targeted therapy achieved an objective response rate of 61%, with an 84% probability of maintaining the response at nine months.

The MagnetisMM-3 results also suggest elranatamab has a manageable safety profile. The two-step-up priming dose regimen (12/32 mg) helped mitigate the rate and severity of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) among the 119 patients in cohort A who were treated with this priming regimen. All cases of CRS were grade 1 or 2 and the majority occurred after the first (43% of patients) or second (24% of patients) dose, with only 6% of patients experiencing CRS after the third dose and fewer than 1% experiencing CRS after the fourth dose. Observed cases of ICANS (3%) were neither common nor severe (grade 1/2 only were reported). No fatal neurotoxicity events were observed.

Elranatamab is designed to bind to BCMA and CD3 receptors found on the surface of T cells, bridging them together and activating the T cells to kill the myeloma cells.

Source: Pfizer, February 2023

AB-101/Rituximab Combination Granted Fast Track Status

The FDA has granted Fast Track Designation to AB-101 in combination with the anti-CD20 monoclonal antibody rituximab for the treatment of relapsed or refractory B-cell non-Hodgkin lymphoma (NHL), including in patients who have failed prior chimeric antigen receptor (CAR)-T treatment.

AB-101 is an allogeneic, cryopreserved, ADCC-enhancing, natural killer-cell therapy candidate derived from umbilical cord blood for use in combination with monoclonal antibodies or innate cell engagers in the outpatient setting.

AB-101 is currently undergoing a phase I/II, multicenter clinical trial at multiple clinical sites across the United States to assess its safety and clinical activity alone and in combination with rituximab in patients with relapsed or refractory B-cell NHL who have progressed beyond two or more prior lines of therapy, including CAR-T therapy. In the trial, AB-101 is administered weekly in the outpatient setting over one-month cycles with up to four cycles to assess therapeutic efficacy and durability.

The developer of AB-101, Artiva Biotherapeutics, is also collaborating with the biotech company Affimed N.V. to develop a combination therapy comprising AB-101 and the innate cell engager AFM13 for the treatment of patients with relapsed or refractory CD30-positive lymphomas, according to the company.

Source: Artiva Biotherapeutics, February 2023

FDA Approves IND for EP0042

The FDA has approved an Investigational New Drug (IND) application for EP0042, a dual *FLT3* and aurora kinase inhibitor. The therapy is being developed as a new potential treatment to overcome acquired resistance to *FLT3* inhibitors in patients with acute myeloid leukemia (AML).

This approval will allow Ellipses, the manufacturer of the drug, to expand its ongoing, first-in-human, phase I/II clinical trial, which is currently in its dose-ranging phase. Once a recommended phase II dose is confirmed, Ellipses will continue to evaluate EP0042 as a monotherapy and explore EP0042 in combination with established standard treatments.

Preliminary data shared from this ongoing study at the 64th ASH Annual Meeting and Exposition showed that EP0042 had acceptable safety and tolerability, with evidence of prolonged disease control in a number of heavily pretreated patients.

Source: Ellipses, February 2023

Patient Death Leads to Voluntary Pause of MGTA-117 Trial for AML, MDS

A participant's death led to a voluntary pause of the phase I/II dose-escalation trial evaluating MGTA-117 in patients with relapsed or refractory AML and myelodysplastic syndromes (MDS). The announcement was made by the manufacturer of MGTA-117, Magenta Therapeutics, in a company press release.

The death, which occurred in the participant who most recently received the cohort three dose of 0.08 mg/kg, was "deemed to be possibly related to MGTA-117," according to the company. The participant experienced grade 5 respiratory and cardiac arrest that resulted in death.

The company announced in late December 2022 that it stopped dosing participants at the cohort four dosing level of 0.13 mg/kg and planned to dose additional participants at the cohort three dosing level, as dose-limiting toxicities occurred in two of the three participants who received the cohort four dose. At that time, it planned to continue enrollment at the cohort three dose level "in accordance with the clinical trial protocol and following the recommendation of the trial's safety Cohort Review Committee," Magenta Therapeutics officials said in a news release.

MGTA-117, an anti-CD117 antibody conjugated to an amanitin payload, is designed to deplete CD117-expressing cells in the blood and/or bone marrow before a patient undergoes hematopoietic stem cell transplantation (HSCT) or receives an ex vivo gene therapy product.

The known information about the death has been reported to the FDA as a Suspected Unexpected Serious Adverse Reaction.

Source: Magenta Therapeutics, January 2023

Lisocabtagene Maraleucel Receives Positive CHMP Opinion

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency has recommended approval of the CAR T-cell therapy lisocabtagene maraleucel for the treatment of adult patients with diffuse large B-cell lymphoma (LBCL), high grade B-cell lymphoma, primary mediastinal LBCL, and follicular lymphoma grade 3b, who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy.

The CHMP adopted a positive opinion based on results from the phase III TRANSFORM study evaluating the CAR-T as a second-line treatment in adults with relapsed or refractory LBCL compared with the standard of care, consisting of salvage chemotherapy followed by high-dose chemotherapy plus HSCT.

Source: Bristol Myers Squibb, March 2023

Knowledge Hubs

In each issue of Blood Cancers Today, *we will take a closer look at a particular topic in hematologic malignancies. This month,* Blood Cancers Today *Associate Editors Elias Jabbour, MD; Thomas Martin, MD; and Laurie H. Sehn, MD, MPH, highlight news in hematologic oncology. Visit* BloodCancersToday.com *to view all of our Knowledge Hubs and stay up to date on the latest news in each area of hematologic oncology.*

ALL

More Intrathecal Chemotherapy Significantly Reduces CNS Relapse Risk in Ph+ ALL

Intrathecal chemotherapy is "essential" to prevent central nervous system (CNS) relapse in patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL), but the effectiveness of the prophylaxis depends upon how many times it is administered, according to recent research.

Shilpa Paul, PharmD, BCOP, of the University of Texas MD Anderson Cancer Center, and colleagues published their findings in correspondence to the *American Journal of Hematology*.

They conducted the research because treatment protocols with hyper-fractionated cyclophosphamide, dexamethasone, vincristine, and doxorubicin alternating with high-dose methotrexate and cytarabine (hyper-CVAD) plus a *BCR-ABL1* tyrosine kinase inhibitor (TKI) for adults with Ph+ ALL were amended in 2012 to increase the number of prophylactic intrathecal chemotherapy doses from eight to 12.

Dr. Paul and colleagues compared the rate of CNS relapse in 150 consecutive adult patients with Ph+ ALL who received intrathecal chemotherapy eight or 12 times with hyper-CVAD with or without rituximab with imatinib, dasatinib, or ponatinib between July 2001 and January 2019.

They excluded patients who had CNS disease at diagnosis. Intrathecal chemotherapy "consisted mainly" of methotrexate 12 mg alternating with cytarabine 100 mg given via lumbar puncture during each cycle for up to six cycles, according to Dr. Paul and colleagues.

Most patients (71%) received eight or fewer doses of intrathecal chemotherapy, while 29% received more than eight doses. Significantly higher proportions of patients who received more than eight doses underwent therapy with rituximab or ponatinib than patients who received eight or fewer doses. Other than those differences, patient characteristics were "similar between groups," Dr. Paul and colleagues said.

Both groups had a 100% complete remission rate in response to frontline therapy, but patients who received more than eight doses of intrathecal chemotherapy had a higher three-month complete molecular remission rate (70%) than patients who received eight or fewer doses (53%; $P=.08$).

The median follow-up time was 125.8 months for patients who received more than eight doses of intrathecal chemotherapy and 76.9 months for patients who received eight or fewer doses.

CNS relapse occurred in 11 patients, all of whom received eight or fewer doses, with a CNS relapse incidence of 10% in the group who received eight or fewer doses and 0% in patients who received more than eight doses ($P=.023$).

The three-year CNS relapse-free survival (RFS) rate was 92% in the group receiving eight or fewer doses and 100% in the group receiving more than eight doses ($P=.06$). The six-year RFS rate was 91% in the group receiving eight or fewer doses and 100% in those receiving more than eight doses ($P=.04$).

CNS relapses occurred after a median of 17 months. The researchers detected *BCR-ABL1* transcript in the peripheral blood or bone marrow of all patients who experienced a CNS relapse. In four of the 11 (36%) patients, CNS relapse co-occurred with systemic relapse, with one patient experiencing systemic relapse after an isolated CNS relapse. Of the 11 patients who relapsed, 45% underwent allogeneic hematopoietic stem cell transplantation (HSCT) during their treatment course, with allogeneic HSCT preceding CNS relapse in one case.

"Treatment of CNS relapse varied from systemic chemotherapy to craniospinal irradiation, but all continued TKI with [intrathecal chemotherapy], consisting of cytarabine alternating with methotrexate, with hydrocortisone, or combination given twice weekly until CNS clearance," said Dr. Paul and colleagues.

All patients achieved CNS clearance, with 36% experiencing subsequent CNS relapses. The median survival from time of first CNS relapse was 14.7 months (95% CI, 8.6-20.8). At the time of data cutoff, only one patient remained alive after CNS relapse, the researchers reported.

Of the 10 patients who died after CNS relapse, five died due to infectious complications, one died from intracranial hemorrhage, two died from cardiac arrest, and two died from progressive leukemia.

"In conclusion, [intrathecal chemotherapy] is essential in preventing CNS disease in Ph+ ALL, and effectiveness depends on the total number of [times that intrathecal chemotherapy is] administered," Dr. Paul and colleagues wrote. "Our study shows that 12 [intrathecal chemotherapy doses] should be administered with [hyper]-CVAD plus a *BCR-ABL1* TKI to reduce the risk of CNS relapse."

Why I picked this article:

Elias Jabbour, MD

"Intrathecal chemotherapy (ITC) is essential in preventing CNS disease in Ph+ ALL, and its effectiveness depends on the total number of ITCs administered. At least 12 ITCs should be administered to reduce the risk of CNS relapse."

Reference

Paul S, Kantarjian H, Sasaki K, et al. Intrathecal prophylaxis with 12 versus 8 administrations reduces the incidence of central nervous system relapse in patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukemia. *Am J Hematol.* 2023;98(1):E11-E14. doi:10.1002/ajh.26622

MCL

Zilovertamab Plus Ibrutinib 'Well-Tolerated' in Patients with Relapsed or Refractory MCL

A phase I/II study of the humanized monoclonal antibody zilovertamab and ibrutinib in relapsed or refractory mantle cell lymphoma (MCL) showed that the combination was well-tolerated and had a similar safety profile when compared with ibrutinib alone.

The retrospective study, led by **Hun Ju Lee, MD,** of the Department of Lymphoma and Myeloma at the University of Texas MD Anderson Cancer Center, also investigated the combination in patients with chronic lymphocytic leukemia (CLL) and in those patients with CLL plus *p53* mutations.

The results of the trial were presented during the 64th American Society of Hematology Annual Meeting and Exposition in New Orleans, Louisiana, in December 2022.

The trial enrolled patients with relapsed or refractory MCL who received one or more prior lines of therapy or with treatment-naïve or relapsed or refractory CLL who received one or more prior lines of therapy. The study had

three parts: a dose-escalation portion, a dose-expansion portion, and a 2:1 randomization in only the CLL group to receive zilovertamab and ibrutinib versus ibrutinib alone.

In patients with relapsed or refractory MCL, the objective response rate was 85.2%, which included 40.7% complete response (CR) and 44.4% partial response, with a median duration of response of 34.1 months (95% CI, 13.67-not estimated [NE]). The CR rate was 29.6%, 37.0%, and 40.7% at six, 12, and 26 months, respectively. The median progression-free survival (PFS) was 35.9 months (95% CI, 17.3-NE).

With respect to grade ≥3 neutropenia in patients with relapsed or refractory MCL, the rate observed with the combination of zilovertamab and ibrutinib was 9.1%, lower than the 29.0% previously reported for ibrutinib alone.

"In this study, [zilovertamab plus ibrutinib] is well-tolerated, with a safety profile that is very similar compared with [ibrutinib] alone," said Dr. Lee and colleagues.

The most frequent (≥30%) treatment-emergent adverse events, regardless of causality, for all patients (MCL and CLL) treated with the combination therapy (n=85) were fatigue (42.4%), contusion (36.5%), and diarrhea (37.6%).

The median PFS was not reached for all patients with CLL at a median follow-up of 32.9 months. However, for patients with CLL and *p53* alterations, overall efficacy of the combination of zilovertamab and ibrutinib was very promising, with a PFS at 30 months of 100% compared with a historic locoregional PFS of around 55% for ibrutinib monotherapy.

Why I picked this article:
"Zilovertamab is a novel, humanized monoclonal antibody targeting ROR1, a new epitope. In this phase I/II trial, it was combined with a Bruton's tyrosine kinase inhibitor and showed promising efficacy, with a high ORR of 85.4% and a high CR rate of 40.7% in the MCL subgroup. This looks highly favorable compared with historical results with ibrutinib alone. While this is early data, further evaluation of this novel targeted agent appears warranted."

Laurie H. Sehn, MD, MPH

"For [patients with CLL] with *p53* alterations, overall efficacy with zilovertamab and ibrutinib is also very promising," the investigators wrote.

The trial began enrolling patients with relapsed or refractory marginal zone lymphoma who received one or more prior anti-CD20-based treatments in June 2022.

Reference

Lee HJ, Choi MY, Siddiqi T, et al. Phase 1/2 study of zilovertamab and ibrutinib in mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), or marginal zone lymphoma (MZL). Abstract #232. Presented at the 64th ASH Annual Meeting and Exposition; December 10-13, 2022; New Orleans, Louisiana.

MYELOMA

New MRD Test for Peripheral Blood Has 'Unprecedented Sensitivity' in MM

A new method to detect minimal residual disease (MRD) in peripheral blood had an "unprecedented sensitivity" level of 10^{-8} in samples from patients with MM, according to a recent study.

Laura Notarfranchi, MD, of the University of Parma in Italy, and colleagues conducted the research because assessing MRD in bone marrow with NGF or next-generation sequencing processes "precludes periodic evaluations because of its invasiveness" and MRD assessment in peripheral blood "could overcome this limitation."

However, the clinical value of peripheral blood MRD assessment is "not established," Dr. Notarfranchi and colleagues wrote. The negative predictive value when compared to bone marrow is less than 70%, as the tumor burden in peripheral blood is much lower than in bone marrow, which requires methods that can detect MRD below 10^{-6} to improve concordance.

They evaluated MRD in 138 patients with MM by using NGF on peripheral blood samples from the second year of maintenance therapy, when patients stopped treatment if they were MRD negative in bone marrow, or continued therapy for three more years if they were MRD positive at that time.

They found 15 (12%) patients were MRD positive, with a median PFS of 22 months since MRD testing, which was significantly inferior to the median PFS of patients who had undetectable MRD in peripheral blood samples. The two-year PFS rate was also significantly lower in patients with detectable MRD (50%) than in those with undetectable MRD (98%; $P<.0001$) in peripheral blood samples.

However, of the 123 patients with undetectable MRD in peripheral blood samples, 27% had persistent MRD in bone marrow. Those patients had significantly lower two-year PFS rates (62%) than patients who had undetectable MRD in peripheral blood and bone marrow (100%; $P<.0001$).

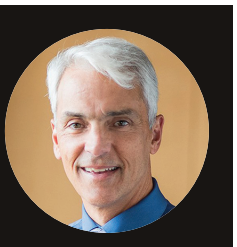
In the second part of the study, the investigators developed an optimized BloodFlow protocol after comparing lysing methods and MicroBeads combinations for "optimal enrichment" of circulating plasma cells. Initial testing in peripheral blood samples from healthy people showed, on average, an 82-fold increment in the number of circulating normal plasma cells with BloodFlow compared to NGF. They also performed dilution experiments in MM cell lines and found they could detect to 1×10^{-7} tumor cells.

Dr. Notarfranchi and colleagues magnetically labeled samples of peripheral blood that were approximately 50 mL and processed them with MACS® columns. They also analyzed 100 μL aliquots enriched with circulating plasma cells using EuroFlow NGF to examine the concordance between MRD assessment with BloodFlow and NGF.

The researchers compared BloodFlow with NGF in 353 peripheral blood samples that they collected in different treatment scenarios. BloodFlow detected MRD in 9% of samples, with 58% of those samples showing MRD negativity on NGF. All cases of MRD negativity according to BloodFlow were also MRD negative by NGF. The lowest MRD level was 6×10^{-8}.

They subsequently compared the performance of BloodFlow with NGF in 199 paired samples from peripheral blood and bone marrow of patients with MM. Concordance occurred in 69% of double-negative samples and in 9.5% of double-positive samples. MRD was detected in bone marrow but not in peripheral blood in 20.5% of paired samples, while 1% were negative in bone marrow but positive in peripheral blood. BloodFlow had a negative predictive value of 77% compared with NGF in bone marrow.

Why I picked this article:
"The Pavia lab utilized a novel magnetic bead separation system with next-generation flow (NGF) cytometry to identify circulating multiple myeloma (MM) cells in peripheral blood. They report this method has the potential to be a much more sensitive way to detect circulating plasma cells and investigated the use of this novel technology in patients receiving therapy for MM. This truly would be an amazing invention, and I look forward to more data."



Thomas Martin, MD

"MRD assessment during induction and intensification was the feature more frequently associated with a false-negative result using BloodFlow," the study's authors wrote, noting that reduced peripheral blood cellularity and MRD levels $<10^{-5}$ in bone marrow were also associated with a false-negative result using BloodFlow.

"These results suggest the possibility of periodic and ultra-sensitive MRD assessment in [peripheral blood] during maintenance/observation," they concluded.

Reference

Notarfranchi L, Zherniakova A, Lasa M, et al. Ultra-sensitive assessment of measurable residual disease (MRD) in peripheral blood (PB) of multiple myeloma (MM) patients using Bloodflow. Abstract #865. Presented at the 64th ASH Annual Meeting and Exposition; December 10-13, 2022; New Orleans, Louisiana.

Meeting News

Blood Cancers Today *reports from recent major medical meetings, including the 2023 European Hematology Association-European Society for Blood and Marrow Transplantation (EHA-EBMT) 5th European CAR T-Cell Meeting and the American Association for Cancer Research (AACR) Special Conference: Acute Myeloid Leukemia and Myelodysplastic Syndrome.*

Highlights from the **2023 EHA-EBMT Meeting**

CAR T Cell Outperforms Standard Regimens in KarMMa-3 Trial

Idecabtagene vicleucel led to "deeper and more durable responses" than standard regimens in patients with triple-class-exposed relapsed or refractory multiple myeloma (MM), according to results from the phase III KarMMa-3 trial.

Paula Rodríguez-Otero, MD, PhD, of the Clínica Universidad de Navarra in Pamplona, Spain, and colleagues conducted the research because survival outcomes are poor in patients with triple-class-exposed relapsed or refractory MM, and treatment options are limited as patients become triple-class-exposed in earlier lines of therapy.

"In the absence of an established standard of care for [triple-class-exposed relapsed or refractory MM], therapies with new mechanisms of action are needed," Dr. Rodríguez-Otero and colleagues wrote, noting that idecabtagene vicleucel, a BCMA-directed chimeric antigen receptor (CAR) T-cell therapy has "demonstrated deep, durable responses" in this population.

The international, open-label, phase III trial enrolled 386 patients with relapsed or refractory MM who received two to four prior regimens, including an immunomodulatory agent, proteasome inhibitor, and daratumumab, and who were refractory to the last regimen.

Dr. Rodríguez-Otero and colleagues randomized patients 2:1 to receive idecabtagene vicleucel (n=254) or a standard regimen selected by the investigator based on prior regimens (n=132). Of the 254 patients randomized to the idecabtagene vicleucel group, 225 underwent treatment, while 126 of the 132 patients randomized to the standard regimen underwent treatment. Baseline characteristics such as median age, median time since diagnosis, median number of prior therapies, high-risk cytogenetics, triple-class refractoriness, and daratumumab refractoriness "were generally balanced between arms," the study's investigators said.

Patients underwent lymphodepletion with fludarabine and cyclophosphamide and optional bridging therapy before receiving an idecabtagene vicleucel infusion. The target dose was 150 to 450×10^6 CAR-positive T cells (median dose, 445×10^6 CAR-positive T cells). Patients who received standard regimens continued therapy until disease progression, unacceptable toxicity, or consent withdrawal. The primary endpoint was progression-free survival (PFS) as assessed by an independent response committee. The median follow-up from randomization to data cutoff was 18.6 months.

Patients who received idecabtagene vicleucel had a median PFS of 13.3 months, a significant improvement over the median PFS of 4.4 months in patients who received standard regimens ($P<.0001$). The overall response rate (ORR) was 71% in patients receiving idecabtagene vicleucel and 42% in patients receiving standard regimens ($P<.0001$).

"[The] PFS and ORR benefit of [idecabtagene vicleucel] was consistent across subgroups, including patients with high-risk features," Dr. Rodríguez-Otero and colleagues wrote, noting that overall survival (OS) "was immature at data cutoff."

Grade 3 to 4 adverse events occurred in 93% of patients who received idecabtagene vicleucel and in 75% of those who received a standard regimen. Grade 5 adverse events occurred in 14% of patients who received idecabtagene vicleucel and in 6% of those who received a standard regimen, while grade 5 treatment-related adverse events occurred in 3% and 1%, respectively. Grade 3 to 4 infections occurred in 24% of patients receiving idecabtagene vicleucel and in 18% of those receiving a standard regimen.

Nearly all patients (88%) receiving idecabtagene vicleucel experienced cytokine release syndrome of any grade. A grade 3 or 4 cytokine release event occurred in 4% of patients, and a grade 5 event occurred in 1%. Investigator-identified neurotoxicity occurred in 15% of patients, with 3% experiencing a grade 3 or 4 neurotoxicity event.

"[Idecabtagene vicleucel] treatment resulted in a significant improvement in PFS and ORR, with deeper and more durable responses than standard regimens. [The benefit of idecabtagene vicleucel] was consistent across difficult-to-treat subgroups," Dr. Rodríguez-Otero and colleagues concluded. "The toxicity profile of [idecabtagene vicleucel] was consistent with previous studies. These results support use of [idecabtagene vicleucel] in [triple-class-exposed relapsed or refractory MM], a population with poor survival outcomes."

Reference

Rodríguez-Otero P, Ailawadhi S, Arnulf B, et al. Idecabtagene vicleucel (ide-cel; bb2121) versus standard regimens in triple-class–exposed (TCE) relapsed and refractory multiple myeloma (RRMM): phase 3 randomized controlled trial (RCT) KarMMa-3. Presented at the EHA-EBMT 5th European CAR T-Cell Meeting; February 9-11, 2023; Rotterdam, the Netherlands.

Pembrolizumab Demonstrates Good Safety After CAR-T in DLBCL

A new study supports the safety of the anti-programmed cell death 1 protein (PD-1) immune checkpoint inhibitor pembrolizumab administered as salvage therapy after CD19-directed CAR T-cell therapy in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

Since only approximately 30% to 40% of relapsed or refractory DLBCL patients achieve durable remission, many patients will require subsequent treatments, the researchers noted, which is why pembrolizumab is sometimes administered in the hope that it will reverse T-cell exhaustion following CAR T-cell therapy.

The study, led by **Ana África Martín López,** of the Hospital Universitario de Salamanca in Spain, covered 59 patients with relapsed or refractory DLBCL treated with commercial CAR T-cell therapy at the Hospital Universitario de Salamanca between May 2019 and December 2022. Of those patients, 61% (n=36/59) was treated with axicabtagene ciloleucel and 39% (n=23/59) with tisagenlecleucel.

Among the 59 patients treated with commercial CAR T-cell therapy, 31 (52.5%) experienced relapse or disease progression after the CAR-T treatment. Of the 31 relapsed or progressed patients, 17 were treated with pembrolizumab as salvage therapy at a dose of 200 mg intravenously every three weeks.

The median time from CAR T-cell infusion to the first pembrolizumab treatment was 42 days (range, 16-211 days), and the median number of doses administered was two (range, 1-22 doses).

The results showed that pembrolizumab was well tolerated, with the only treatment-related adverse events being grade 2 immune effector cell-associated neurotoxicity syndrome (ICANS; n=1), neutropenia (n=7; 41.2%), and arthritis (n=1). The patient who developed ICANS after pembrolizumab received it only 16 days after infusion due to the rapid progression of the disease.

The best ORR after pembrolizumab was 23.5% (n=4), and all four of these

patients achieved complete response (CR; 23.5%).

"PD-1 blockade with pembrolizumab after CD19-directed CAR T-cell therapy appears to be safe," the researchers concluded. "Although some patients with [relapsed or refractory] DLBCL who experienced disease relapse or progression after CAR-T may achieve clinical responses, it would be of interest to identify predictors of response together with developing more effective salvage therapy options."

Reference

Martín López AA, Pérez López E, Cabero Martínez A, et al. Pembrolizumab after CAR T-cell therapy: a single center experience. Presented at the EHA-EBMT 5th European CAR T-Cell Meeting; February 9-11, 2023; Rotterdam, the Netherlands.

Tisagenlecleucel Shows 'Durable Efficacy and Favorable Safety' in Phase II ELARA Trial

Tisagenlecleucel, a CD19-directed CAR T-cell therapy, demonstrated "durable efficacy and favorable safety" in patients with relapsed or refractory follicular lymphoma (FL), according to long-term data from the phase II ELARA trial.

Tisagenlecleucel previously demonstrated "high response rates and an excellent safety profile" in the phase II ELARA trial, according to the investigators, who presented long-term data on safety and response duration at the meeting, as well as findings from exploratory analyses.

The study, presented by **Catherine Thieblemont, MD, PhD,** of Hôpital Saint-Louis in France, and colleagues, included 94 eligible patients with relapsed or refractory FL grade 1 to 3a. All received at least two prior lines of therapy, including an anti-CD20 antibody and alkylating agent, or relapsed after autologous hematopoietic stem cell transplantation (HSCT). The investigators permitted bridging chemotherapy. Patients received lymphodepleting chemotherapy, followed by a tisagenlecleucel dose of 0.6 to 6×10^8 CAR+ viable T cells.

Dr. Thieblemont and colleagues assessed the correlation between baseline clinical factors, the tumor microenvironment, blood soluble factors, and circulating cells with clinical response and PFS.

The CR rate was 68% at a median follow-up of 28.9 months, with an ORR of 86.2%. The medians of PFS, duration of response, time to next treatment, and OS were not reached. The estimated 24-month post-infusion PFS rate was 57.4%, while the estimated 24-month OS rate was 87.7%.

At data cutoff, 61.7% of patients who responded had ongoing responses, while 73.4% of patients with a best overall response of CR had ongoing responses.

Dr. Thieblemont and colleagues reported "high rates of durable responses" in most patients who were in high-risk disease subgroups, including patients with elevated baseline tumor burden or progression of disease within two years, "who typically have poor prognosis with non-CAR-T therapies."

Lower baseline serum interleukin 10 (IL-10) and TNF-α levels were significantly correlated with lower tumor volume and prolonged PFS (both $P<.001$) in exploratory analyses. Favorable baseline tumor microenvironment was significantly associated with longer duration of response (not reached vs 12 months; $P=.0086$) and PFS (median PFS, not reached vs 5.9 months; $P=.0017$).

"Exploratory biomarker analyses suggest that favorable [tumor microenvironment] and decreased inflammatory status were associated with improved clinical outcomes," Dr. Thieblemont and colleagues wrote.

The investigators observed persistence of the CAR transgene for up to 925 days, noting "favorable responses" occurred in patients who had progression of disease within two years, "despite lower median in vivo expansion relative" to patients who did not have progression of disease within two years.

Nearly one-quarter (24%) of patients received at least one subsequent therapy after the CAR-T infusion, including four patients who received allogeneic HSCT.

The investigators reported no new safety signals. Neurological events occurred in 12.4% of patients, including in one patient with probable progressive multifocal leukoencephalopathy who had prior grade 4 ICANS.

A total of 13 deaths occurred in the ELARA trial, including three new deaths that occurred during the longer-term follow-up period, but none of the new deaths were related to treatment, according to Dr. Thieblemont and colleagues.

"Long-term data (>2 years) from following treatment with tisagenlecleucel in the ELARA trial demonstrates durable efficacy and favorable safety in patients with [relapsed or refractory FL]; median [duration of response], PFS, [time to next treatment], and OS were not reached," Dr. Thieblemont and colleagues concluded. "Most patients with high-risk disease characteristics (e.g., [progression of disease within two years], high tumor burden) also benefitted, with a continued favorable safety profile."

Reference

Dreyling M, Dickinson M, Martinez-Lopez J, et al. Long-term clinical outcomes and correlative efficacy analyses in patients with relapsed/refractory follicular lymphoma (r/r FL) treated with tisagenlecleucel in the ELARA trial. Presented at the EHA-EBMT 5th European CAR-T cell Meeting; February 9-11, 2023; Rotterdam, the Netherlands.

Study Validates Presence of Immunotherapeutic Targets for Myeloma

A new study verified the presence of three different surface antigens on MM cells. The research demonstrated an emerging target for the development of novel CAR T-cell immunotherapies.

The three different surface antigens presented in the study included the following: (1) BCMA, which is the main antigen targeted by currently available CAR-T treatments; (2) Fc receptor-like 5 (FCRL5), which has also been used as a target of antibody-drug conjugates for the treatment of MM; and (3) endothelin receptor B (ETRB), a novel tumor-specific antigen that represents a new tumoral target that may lead to development of new CAR-T immunotherapies.

The researchers quantified BCMA in seven MM cell lines using the Becton Dickinson Quantibrite Beads-PE kit, with the MM cell line OPM-2 used as a negative control. As a positive control, MM cell lines were incubated with a γ-secretase inhibitor to prevent natural cleavage of BCMA on the cell surface, which resulted in higher cell surface BCMA expression in the tested cell lines.

The presence of FCRL5 was also validated on 20 MM patient bone marrow samples with almost 100% expression frequency.

Finally, the researchers performed a proteomic analysis on six different MM cell lines to uncover ETRB, a novel tumor-specific antigen that represents a new tumoral target. ETRB was successfully validated on three MM patients' bone marrow samples using flow cytometry. The gating strategy for ETRB validation involved isolation of the patient plasmocytes (CD38 and CD56 double-positive) followed by selection of ETRB-positive patient tumoral plasmocytes in comparison with the immunoglobulin control.

"In conclusion, this data validates that BCMA, ETRB, and FCRL5 are localized to the tumoral plasmocytes' cell surface," the authors wrote, noting that ETRB could emerge as a target for the development of new CAR-T immunotherapies.

Reference

Jassin M, Köse MC, Marcion G, et al. Evaluation of new immunotherapeutic targets for multiple myeloma. Presented at the EHA-EBMT 5th European CAR T-Cell Meeting; February 9-11, 2023; Rotterdam, the Netherlands.

Highlights from the **AACR SPECIAL CONFERENCE**

Bexmarilimab Has 'Therapeutic Potential' for Myeloid Malignancies

Results of a recent study "validate the therapeutic potential" of bexmarilimab, a Clever-1-targeting antibody under evaluation in clinical trials as part of a combination treatment for myeloid malignancies.

Arno Ylitalo, a doctoral student at the University of Turku in Finland, and senior author **Mika Kontro, MD, PhD,** of the University of Helsinki, presented the study's results during the AACR Special Conference: Acute Myeloid Leukemia and Myelodysplastic Syndrome.

Clever-1—also known as Stabilin-1—is expressed by monocytes and immunosuppression macrophages. Bexmarilimab "demonstrates many immunomodulatory effects, along with promising antitumor activity against solid tumors in patients with multiple lines of previous treatment," according to the study's authors.

The researchers profiled Clever-1 expression in acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). They also tested the potential of bexmarilimab—alone and in combination with azacitidine and venetoclax—as a growth inhibitor and immunomodulator.

The study's investigators used AML cell lines (n=11) and frozen mononuclear cells extracted from bone marrow aspirates of patients with AML (n=42) and very high-risk MDS (n=4). They treated the samples with bexmarilimab alone or in combination with azacitidine and venetoclax for 48 hours.

They confirmed the Clever-1 protein was expressed in AML cell lines and showed bexmarilimab induced metabolic and growth inhibition of KG1 blasts, which have high Clever-1 levels.

In patients with AML, those with French, American, and British (FAB) classification subtype M4/M5 had the highest levels of Clever-1, along with patients classified as FAB subtype M2, "with consequent rapid release," the authors wrote.

Clever-1 expression was negatively correlated with the expression of the human leukocyte antigen (HLA)-DR isotype. Clever-1 expression was also negatively correlated with bone marrow T-cell frequency, which is "in line with the immunosuppressed state associated with high Clever-1," they wrote.

Ex vivo treatment with bexmarilimab in primary AML bone marrow cells led to a "notable increase" of fivefold to tenfold in monocyte HLA-DR in samples with low basal HLA-DR and high Clever-1. Adding azacitidine to bexmarilimab augmented HLA-DR induction by 20% to 110%.

"These results validate the therapeutic potential of bexmarilimab in myeloid malignancies," the authors concluded. "The safety, tolerability, and preliminary efficacy of bexmarilimab is now [being] further investigated in combination with venetoclax and/or azacitidine in a phase I/II clinical trial, BEXMAB."

Reference

Ylitalo A, Aakko S, Kuusanmäki H, et al. Ex vivo immune activation with the macrophage-targeting immunotherapy, anti-Clever-1 antibody bexmarilimab, in acute myeloid leukemia and myelodysplastic syndrome. Abstract #14. Presented at the AACR Special Conference: Acute Myeloid Leukemia and Myelodysplastic Syndrome; January 23-25, 2023; Austin, Texas.

Targeting ERK1/2 Can Overcome Venetoclax Resistance in AML

Data from a recent preclinical study "support combining ERK1/2 and BCL2 inhibitors" in the treatment of AML, according to investigators.

Priyanka Sharma, MD, of the University of Texas MD Anderson Cancer Center, and colleagues conducted the research because activation of the RAS/RAF/ERK pathway is linked with primary or secondary resistance to the BCL2 inhibitor venetoclax in AML, but the "role of RAS-driven mitochondrial dynamics in AML is unclear."

"Inhibiting ERK1/2 may, therefore, shed light on AML cells' dependence on RAS-driven mitochondrial dynamics and metabolism," the researchers wrote.

They assessed the antileukemic efficacy of concomitantly inhibiting BCL2 and ERK1/2 in preclinical models of venetoclax resistance. They also "further investigated the role of ERK1/2/Drp1-dependent mitochondrial fission in mediating resistance to venetoclax through altered metabolism."

The researchers inhibited ERK1/2 by using compound 27, which inhibits the phosphorylating activity of ERK1/2 and the phosphorylation of ERK1/2. Compound 27 sensitized intrinsically resistant and *NRAS*-mutant OCI-AML3 cells to venetoclax (combination index, 0.008). The study's authors also confirmed the combination's synergy in OCI-AML2 cells with acquired venetoclax resistance, showing a 75% apoptosis rate compared with a 22% apoptosis rate with venetoclax (combination index, 0.6).

The combination also eliminated bulk and CD34-positive/CD38-negative leukemia-initiating cells in primary AML samples (combination index, 0.03-0.23). A colony formation assay and cytometry by time of flight using *NRAS*-mutant, patient-derived xenografts showed "impaired clonogenic potential" (P=.0002) and decreased expression of cMyc and CD44 in leukemia-initiating cells in response to ERK1/2 inhibition and combination treatment, "suggesting [an] impact on stemness," the investigators wrote.

They also tested the ERK1/2 inhibitor ASTX029 alone and in combination with venetoclax, finding it "reduced leukemia burden" in vivo and extended survival (P<.05).

ERK1/2 inhibition decreased levels of Drp1 with serine 616 phosphorylation, increased mitochondrial length, and increased mitochondrial reactive oxygen species, "suggesting impaired mitochondrial fission," they wrote.

The combination treatment in OCI-AML3 cells led to downregulation of Drp1 mRNA and decreased phosphorylation of Drp1 at serine 616. Overexpression of phospho-mimetic in OCI-AML3 cells decreased apoptosis and "reversed synergy between ERK1/2 and BCL2 inhibition as compared to wild-type and [phosphorylation]-null Drp1," according to Dr. Sharma and colleagues.

"Of note, overexpression of Drp1-phospho-mimetic led to decreased mitochondrial length, suggesting enhanced fission with a distinct metabolic phenotype, including reduced basal respiration, significantly decreased maximal oxygen consumption rate, [adenosine triphosphate] production, and [reactive oxygen species] production," the authors wrote. "Moreover, combination treatment failed to significantly induce [reactive oxygen species] production in cells expressing phospho-mimetic Drp1 as opposed to those expressing [phosphorylation]-null or wild-type Drp1."

"These data support combining ERK1/2 and BCL2 inhibitors in the treatment of AML and warrant further clinical investigation," they concluded.

Reference

Sharma P, Ostermann L, Piya S, et al. Targeting ERK1/2 overcomes resistance to venetoclax by altering Drp1-dependent mitochondrial fission and metabolism in AML. Abstract #43. Presented at the AACR Special Conference: Acute Myeloid Leukemia and Myelodysplastic Syndrome; January 23-25, 2023; Austin, Texas.

HemOnc Happenings

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

ASH Names 2023 Scholar Award Recipients

Urvi A. Shah, MD, a hematologic oncologist at the Memorial Sloan Kettering Cancer Center, has been named a recipient of the American Society of Hematology (ASH) 2023 Scholar Award.

"One of ASH's most prestigious research award programs, the ASH Scholar Awards support early-career investigators dedicated to careers in hematology research as they transition from training programs to careers as independent investigators," officials said in an announcement.

Urvi A. Shah, MD

Each Scholar Award provides $100,000 for the Fellow level, $125,000 for the Fellow to Faculty Scholars level, or $150,000 for the Junior Faculty level. The program funds hematologists in the United States and Canada who conduct basic, translational, and clinical research that furthers the understanding and treatment of blood disorders.

Source: Memorial Sloan Kettering Cancer Center press release, February 2023

AACR Announces Recipient of 2023 Award for Lifetime Achievement in Cancer Research

Carl H. June, MD, a Fellow of the American Association for Cancer Research (AACR) Academy, received the 2023 AACR Award for Lifetime Achievement in Cancer Research during the AACR Annual Meeting in April.

Dr. June, who has made "seminal contributions" to chimeric antigen receptor (CAR) T-cell therapy for blood cancers, is the Richard W. Vague Professor in Immunotherapy, Director of the Center for Cellular Immunotherapies, and Director of the Parker Institute for Cancer Immunotherapy in the Perelman School of Medicine at the University of Pennsylvania, AACR officials said in a news release about the award.

Carl H. June, MD

The AACR Award for Lifetime Achievement in Cancer Research was established to honor an individual who has made significant fundamental contributions to cancer research, either through a single scientific discovery or a body of work.

"He is recognized for his groundbreaking work in developing the first gene-edited cell therapy for cancer and for demonstrating that adoptive T-cell therapy can induce remission and, in some cases, cure patients with advanced cancer," AACR officials said in the release. "Following his early report of synthetic T-cell activation nearly 30 years ago, Dr. June successfully developed a method of producing [CAR] T cells to treat refractory and relapsed leukemia. This technology, which involves the genetic reengineering of a patient's T cells to combat their disease, is the first gene transfer therapy technique that has demonstrated sustained success in cancer patients and has shown tremendous promise for the treatment of hematologic malignancies."

Dr. June has been a member of the AACR since 2000, served as a member of the AACR Board of Directors from 2018 to 2021, and was elected as a Fellow of the AACR Academy in 2017. In 2015, Dr. June received the AACR-Cancer Research Institute Lloyd J. Old Award in Cancer Immunology.

"Dr. June is a trailblazer in the field of cancer immunotherapy whose scientific expertise and vision for the field have been crucial to pivotal scientific discoveries that have improved and saved many lives from cancer," AACR Chief Executive Officer **Margaret Foti, MD, PhD,** said in the release. "His work has transformed the treatment of hematologic malignancies and holds great promise for many other types of cancer."

Dr. June is an elected fellow of the American Academy of Arts and Sciences (2014) and an elected member of the National Academy of Medicine (2012) and the National Academy of Sciences (2020).

Source: AACR press release, February 2023

American Society for Clinical Investigation Elects New Member

Supriya Mohile, MD, MS, who has an "international reputation for advancing the field of geriatric oncology," has been elected to the American Society for Clinical Investigation (ASCI), one of the oldest medical honor societies, according to a news release from the University of Rochester Medical Center.

Supriya Mohile, MD, MS

Dr. Mohile, who was recently awarded tenure at the University of Rochester Medical Center, is the Philip and Marilyn Wehrheim Professor in the Division of Hematology/Oncology. She is co-leader of the Cancer Prevention and Control research program at the Wilmot Cancer Institute, Vice-Chair for Academic Affairs in the Department of Medicine at the University of Rochester Medical Center, and Editor-in-Chief of the *Journal of Geriatric Oncology*.

ASCI receives hundreds of nominations each year and chooses fewer than 100 physician-scientists for membership, all of whom are under the age of 50, with "outstanding scholarly achievement," officials said in a news release from the University of Rochester Medical Center.

Dr. Mohile's "trailblazing efforts in geriatric oncology began several years ago, as she pursued the need for more data about the oldest cancer patients, who comprise the majority of cases but had been historically ineligible for clinical studies," officials said in the release. "Because of that, there was little understanding of their unique needs upon a cancer diagnosis. At Wilmot, she established a geriatric oncology research group and also founded one of the nation's few geriatric oncology clinics as a model for caring for adults 70 years and older."

Furthermore, Dr. Mohile and a group of colleagues at the Cancer and Aging Research Group "led a transformational shift in cancer care toward properly assessing an older patient's overall health and support systems," according to the news release. In 2021, she was the lead author on the nation's first-ever, evidence-based, geriatric oncology guidelines for doctors, promoting the benefits of a geriatric assessment.

She has made "her mark in this area at the University of Rochester Medical Center and Wilmot Cancer Institute by serving in many leadership positions while juggling patient care and groundbreaking research activities," officials said in the release.

Source: University of Rochester Medical Center press release, February 2023

ASH Appoints Stewardship and Systems-Based Hematology Subcommittee Member

Rekha Parameswaran, MD, a hematologic oncologist at Memorial Sloan Kettering Cancer Center, was appointed to the ASH Stewardship and Systems-Based Hematology Subcommittee. Members of the Subcommittee on Stewardship and Systems-Based Hematology serve staggered two-year renewable terms. Members of the subcommittee are required to participate in email discussions, regularly scheduled conference calls, and meet in person as deemed necessary. Individual projects are overseen by working groups comprised of a subset of members of the subcommittee.

Rekha Parameswaran, MD

Source: Memorial Sloan Kettering Cancer Center press release, February 2023

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HISTORY OF THE SOCIETY OF HEMATOLOGIC ONCOLOGY

Over the course of the last decade, it has been recognized by hematologists and hematologist oncologists that the amount of research and interest in the field of hematologic oncology has increased to the point that the exchange of information could not be accomplished at the other major scientific societies. It was clear that this specialized group needed an opportunity to focus on these malignancies, and to have a meeting where outstanding leaders, innovators and budding young investigators, could interact to stimulate progress in this important field. In 2012, the decision was made to form a new society, the **Society of Hematologic Oncology** (SOHO), which would sponsor an annual meeting to bring together leading investigators and practitioners in the field.

Today, SOHO is a non-profit association committed to promoting worldwide research, education, prevention, clinical studies and optimal patient care in all aspects of hematologic malignancies and related disorders.

GLOBAL REACH

SOHO represents physicians and other health care professionals from all corners of the world. The SOHO global network supports and is supported by nearly 6,000 members from 122 countries, who are leading vital efforts to further treatments for patients with hematologic malignancies. The society is an organization that focuses on learning and educational excellence, and promotes diversity and inclusion.