TRANSLATING HEMATOLOGIC ONCOLOGY DISCOVERIES INTO PRACTICE

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DREAMM-7 Data Show Belamaf Triplet Is Superior to Daratumumab Triplet in Myeloma
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New Initiative Seeks to Jump-start Era of CMML Care

With expert opinions from:
Mrinal Patnaik, MBBS;
Eric Padron, MD; and more

MAIL TO:

ASSOCIATE EDITOR
KAMI MADDOCKS

Spring Forward in Initial Therapy for Mantle Cell Lymphoma

An official publication of

soho
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 newly diagnosed, transplant-ineligible multiple myeloma[1,2]

Are you considering DARZALEX® + Rd for these types of patients?

Helen, age 68

Younger patient

Samuel, age 78

Elderly patient with comorbidities

Luis, age 76

Patient with cytogenetic abnormalities

Hypothetical patient profiles.

MAIA, an open-label, randomized, active-controlled trial, compared treatment with DRd (n=368) to treatment with Rd (n=369) in patients with newly diagnosed multiple myeloma who were ineligible for autologous stem cell transplant. The baseline demographic and disease characteristics were similar between the 2 treatment groups. The median age was 73 years (range: 45-90 years). One percent (1%) of patients were <65 years, 20% were 65 to <70 years, 35% were 70 to <75 years, and 44% were ≥75 years of age. Thirty-four percent (34%) had an ECOG PS of 0, 50% had an ECOG PS of 1, and 17% had an ECOG PS of ≥2. Twenty-seven percent (27%) had International Staging System (ISS) Stage I, 43% had ISS Stage II, and 29% had ISS Stage III disease, including patients with high-risk cytogenetics. Eighty-six percent (86%) of patients had a standard-risk cytogenetic profile, and 14% had a high-risk cytogenetic profile.*[1,2]

After 28 months, median PFS was not reached with DRd vs 31.9 months with Rd alone (HR=0.56; 95% CI: 0.43, 0.73; *P*<0.0001).†[1]

After 64 months of follow-up, the median PFS was 61.9 months (95% CI: 54.8, NE) in the DRd arm vs 34.4 months (95% CI: 29.6, 39.2) with Rd alone.‡[1]

CI=confidence interval; DRd=DARZALEX® (D) + lenalidomide (R) + dexamethasone (d); ECOG PS=Eastern Cooperative Oncology Group Performance Status; HR=hazard ratio; NE=not estimable; PFS=progression-free survival; Rd=lenalidomide (R) + dexamethasone (d).

*Cytogenetic risk was based on fluorescence in situ hybridization (FISH) or karyotype analysis; patients who had a high-risk cytogenetic profile had at least one high-risk abnormality (del[17p], t[14;16], or t[4;14]).[2]

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

‡Median follow-up was 64 months.[1]

Discover efficacy and safety data for treating patients like these at darzalexhcp.com

Important Safety Information for DARZALEX® and DARZALEX *FASPRO*®

DARZALEX® AND DARZALEX *FASPRO*®: CONTRAINDICATIONS

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

DARZALEX®: Infusion-Related Reactions

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

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

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

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

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

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

DARZALEX *FASPRO*®: Hypersensitivity and Other Administration Reactions

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

Systemic Reactions

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

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

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

Full Indications and Important Safety Information continued on next page.

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

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

DARZALEX® and DARZALEX *FASPRO*®: Interference With Serological Testing

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

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

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

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

Based on the mechanism of action, DARZALEX® and DARZALEX *FASPRO*® can cause fetal harm when administered to a pregnant woman. DARZALEX® and DARZALEX *FASPRO*® may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX® or DARZALEX *FASPRO*® and for 3 months after the last dose.

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

DARZALEX®: ADVERSE REACTIONS

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

DARZALEX *FASPRO*®: ADVERSE REACTIONS

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

INDICATIONS

DARZALEX® (daratumumab) is indicated for the treatment of adult patients with multiple myeloma:

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

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

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

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

cp-248517v3

References: 1. DARZALEX® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Facon T, Kumar S, Plesner T, et al; the MAIA Trial Investigators. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med*. 2019;380(22):2104-2115.

Johnson&Johnson

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

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

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

INDICATIONS AND USAGE

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

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions

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

In clinical trials (monotherapy and combination: N=2,066), infusion-related reactions occurred in 37% of patients with the Week 1 (16 mg/kg) infusion, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction at Week 2 or subsequent infusions. The median time to onset was 1.5 hours (range: 0 to 73 hours). The incidence of infusion modification due to reactions was 36%. Median durations of 16 mg/kg infusions for the Week 1, Week 2, and subsequent infusions were approximately 7, 4, and 3 hours respectively. Nearly all reactions occurred during infusion or within 4 hours of completing DARZALEX. Prior to the introduction of post-infusion medication in clinical trials, infusion-related reactions occurred up to 48 hours after infusion.

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

When DARZALEX dosing was interrupted in the setting of ASCT (CASSIOPEIA) for a median of 3.75 months (range: 2.4 to 6.9 months), upon re-initiation of DARZALEX, the incidence of infusion-related reactions was 11% for the first infusion following ASCT. Infusion rate/dilution volume used upon re-initiation was that used for the last DARZALEX infusion prior to interruption for ASCT. Infusion-related reactions occurring at re-initiation of DARZALEX following ASCT were consistent in terms of symptoms and severity (Grade 3 or 4: <1%) with those reported in previous studies at Week 2 or subsequent infusions.

In EQUULEUS, patients receiving combination treatment (n=97) were administered the first 16 mg/kg dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2, respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 hours for Week 1-Day 1, 4.2 hours for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

Pre-medicate patients with antihistamines, antipyretics and corticosteroids. Frequently monitor patients during the entire infusion *[see Dosage and Administration (2.3) in Full Prescribing Information]*. Interrupt DARZALEX infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARZALEX therapy if an anaphylactic reaction or life-threatening (Grade 4) reaction occurs and institute appropriate emergency care. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion *[see Dosage and Administration (2.4) in Full Prescribing Information]*.

To reduce the risk of delayed infusion-related reactions, administer oral corticosteroids to all patients following DARZALEX infusions *[see Dosage and Administration (2.3) in Full Prescribing Information]*. Patients with a history of chronic obstructive pulmonary disease may require additional post-infusion medications to manage respiratory complications. Consider prescribing short- and long-acting bronchodilators and inhaled corticosteroids for patients with chronic obstructive pulmonary disease *[see Dosage and Administration (2.3) in Full Prescribing Information]*.

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

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum *[see References]*. The determination of a patient's ABO and Rh blood type are not impacted *[see Drug Interactions]*.

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX. Type and screen patients prior to starting DARZALEX *[see Dosage and Administration (2.1) in Full Prescribing Information]*.

Neutropenia

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

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX until recovery of neutrophils.

Thrombocytopenia

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

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Consider withholding DARZALEX until recovery of platelets.

Interference with Determination of Complete Response

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

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX can cause fetal harm when administered to a pregnant woman. DARZALEX may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX and for 3 months after the last dose *[see Use in Specific Populations]*.

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

The safety data described below reflects exposure to DARZALEX (16 mg/kg) in 2,459 patients with multiple myeloma including 2,303 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy. In this pooled safety population, the most common adverse reactions (≥20%) were upper respiratory infection, neutropenia, infusion-related reactions, thrombocytopenia, diarrhea, constipation, anemia, peripheral sensory neuropathy, fatigue, peripheral edema, nausea, cough, pyrexia, dyspnea, and asthenia.

Newly Diagnosed Multiple Myeloma Ineligible for Autologous Stem Cell Transplant

Combination Treatment with Lenalidomide and Dexamethasone (DRd)

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

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

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

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

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

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

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

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

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

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

[f] Dyspnea, Dyspnea exertional

[g] Cough, Productive cough

[h] Blood pressure increased, Hypertension

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

Table 2: Treatment-Emergent Hematology Laboratory Abnormalities in MAIA

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

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

Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide and Dexamethasone

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

Serious adverse reactions occurred in 49% of patients in the DRd arm compared with 42% in the Rd arm. Serious adverse reactions with at least a 2% greater incidence in the DRd arm compared to the Rd arm were pneumonia (DRd 12% vs Rd 10%), upper respiratory tract infection (DRd 7% vs Rd 4%), influenza and pyrexia (DRd 3% vs Rd 1% for each).

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

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

Adverse Reaction	DRd (N=283)			Rd (N=281)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Infections						
Upper respiratory tract infection[a]	65	6	< 1	51	4	0
General disorders and administration site conditions						
Infusion-related reactions[b]	48	5	0	0	0	0
Fatigue	35	6	< 1	28	2	0
Pyrexia	20	2	0	11	1	0

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

Adverse Reaction	DRd (N=283)			Rd (N=281)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal disorders						
Diarrhea	43	5	0	25	3	0
Nausea	24	1	0	14	0	0
Vomiting	17	1	0	5	1	0
Respiratory, thoracic and mediastinal disorders						
Cough[c]	30	0	0	15	0	0
Dyspnea[d]	21	3	< 1	12	1	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	26	1	0	19	2	0
Nervous system disorders						
Headache	13	0	0	7	0	0

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

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

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

[c] cough, productive cough, allergic cough

[d] dyspnea, dyspnea exertional

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

Table 4: Treatment-Emergent Hematology Laboratory Abnormalities in POLLUX

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

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

Herpes Zoster Virus Reactivation

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

Infections

Grade 3 or 4 infections were reported as follows:

- Relapsed/refractory patient studies: DVd: 21% vs. Vd: 19%; DRd: 28% vs. Rd: 23%; DPd: 28%; DKd[a]: 37%, Kd[a]: 29%; DKd[b]: 21%
  - [a] where carfilzomib 20/56 mg/m^2 was administered twice-weekly
  - [b] where carfilzomib 20/70 mg/m^2 was administered once-weekly
- Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%; DVTd: 22%; VTd: 20%.

Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. In active controlled studies, discontinuations from treatment due to infections occurred in 1-4% of patients.

Fatal infections (Grade 5) were reported as follows:

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

Fatal infections were generally infrequent and balanced between the DARZALEX containing regimens and active control arms. Fatal infections were primarily due to pneumonia and sepsis.

Hepatitis B Virus (HBV) Reactivation

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

Other Clinical Trials Experience

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

Nervous System disorders: Syncope

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other daratumumab products may be misleading.

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

Postmarketing Experience

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

Immune System disorders: Anaphylactic reaction, IRR (including deaths)
Gastrointestinal disorders: Pancreatitis
Infections: Cytomegalovirus, Listeriosis

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

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

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

Interference with Serum Protein Electrophoresis and Immunofixation Tests

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

DARZALEX® (daratumumab) injection

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

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

Data

Animal Data

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in regulating humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

Lactation

Risk Summary

There is no data on the presence of daratumumab in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX is administered with lenalidomide, pomalidomide, or thalidomide, advise women not to breastfeed during treatment with DARZALEX. Refer to lenalidomide, pomalidomide, or thalidomide prescribing information for additional information.

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

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

Pediatric Use

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

Geriatric Use

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

REFERENCES

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

PATIENT COUNSELING INFORMATION

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

Infusion-Related Reactions

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

Neutropenia

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

Thrombocytopenia

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

Interference with Laboratory Tests

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

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

Hepatitis B Virus (HBV) Reactivation

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

Embryo-Fetal Toxicity

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

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

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

Hereditary Fructose Intolerance (HFI)

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

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

For patent information: www.janssenpatents.com

 cp-264272v5

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use
Brief Summary of Full Prescribing Information

INDICATIONS AND USAGE

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

- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Hypersensitivity and Other Administration Reactions

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

Systemic Reactions

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

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

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

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

Local Reactions

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

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

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

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

Neutropenia

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

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX FASPRO until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO, higher rates of Grade 3-4 neutropenia were observed.

Thrombocytopenia

Daratumumab may increase thrombocytopenia induced by background therapy *[see Adverse Reactions].*

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Consider withholding DARZALEX FASPRO until recovery of platelets.

Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose *[see Use in Specific Populations].*

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

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum *[see References (15)].* The determination of a patient's ABO and Rh blood type are not impacted *[see Drug Interactions].*

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX FASPRO. Type and screen patients prior to starting DARZALEX FASPRO *[see Dosage and Administration (2.1) in Full Prescribing Information].*

Interference with Determination of Complete Response

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

Relapsed/Refractory Multiple Myeloma

In Combination with Lenalidomide and Dexamethasone

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Immunogenicity
As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other daratumumab products or other hyaluronidase products may be misleading.

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

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

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

Immune System: Anaphylactic reaction, Systemic administration reactions (including death)

Gastrointestinal: Pancreatitis

Infections: Cytomegalovirus, Listeriosis

DRUG INTERACTIONS

Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding *[see References]* or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies usingDTT-treated RBCs.

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

Interference with Serum Protein Electrophoresis and Immunofixation Tests

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

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

Clinical Considerations

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

Data

Animal Data
DARZALEX FASPRO for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

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

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

Lactation

Risk Summary

There is no data on the presence of daratumumab and hyaluronidase in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX FASPRO is administered with lenalidomide, thalidomide or pomalidomide, advise women not to breastfeed during treatment with DARZALEX FASPRO. Refer to lenalidomide, thalidomide or pomalidomide prescribing information for additional information.

Data

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

Females and Males of Reproductive Potential
DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations]*.

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

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

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

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

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

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

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

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

REFERENCES

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

PATIENT COUNSELING INFORMATION

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

Hypersensitivity and Other Administration Reactions

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

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

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

Neutropenia

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

Thrombocytopenia

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

Embryo-Fetal Toxicity

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

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

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

Interference with Laboratory Tests

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

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

Hepatitis B Virus (HBV) Reactivation

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

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

For patent information: www.janssenpatents.com

cp-264275v3

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New Initiative Seeks to Jump-start Era of CMML Care

Chronic myelomonocytic leukemia (CMML) has historically lingered in the penumbra of more prominent disorders such as myelodysplastic neoplasms and myeloproliferative neoplasms. However, a new collaborative effort between CMML researchers and The Leukemia & Lymphoma Society hopes to jump-start patient treatment and advance scientific understanding of this rare disease.

News

The HemOnc Pulse

Listen to new episodes of **"The HemOnc Pulse"** for all the latest news in hematologic oncology.

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Volume 3 | Number 2 | March/April 2024

PUBLISHER
MashupMedia
630 Madison Ave.
2nd Floor
Manalapan, NJ 07726

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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, 630 Madison Avenue, 2nd Floor, Manalapan, NJ 07726. Periodicals postage paid at Freehold, NJ, and additional mailing offices. POSTMASTER: Send address changes to Mashup Media, 630 Madison Avenue, 2nd Floor, Manalapan, NJ 07726. ©2024

Calendar

May 31–June 4
American Society of Clinical Oncology® Annual Meeting
Chicago, Illinois

June 13–16
European Hematology Association 2024 Hybrid Congress
Madrid, Spain

July 25–28
2024 Debates and Didactics in Hematology and Oncology Conference
Sea Island, Georgia

August 16–17
2024 Seattle Cellular Therapy Summit: Updates and Focus on Accessibility
Seattle, Washington

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

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

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

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

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

November 22
2024 SOHO Highlights: State of the Art and Next Questions
Virtual

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

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

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SEPTEMBER 4–7
2024 SOHO Annual Meeting
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Register now for the 2024 SOHO Annual Meeting

Associate Editor's Message

Spring Forward in Initial Therapy for Mantle Cell Lymphoma

Kami Maddocks, MD
Associate Editor

I have been heartened by the significant progress that has been made over the last decade in our approach to treating patients with mantle cell lymphoma (MCL). Once associated with an overall survival (OS) of only a few years, a patient diagnosed since 2000 now has an expected OS of more than 10 years.

The most significant advancement in the treatment approach to MCL came with the approval of Bruton's tyrosine kinase inhibitors (BTKis), the first-in-class covalent BTKi ibrutinib, followed by the second-generation BTKis acalabrutinib and zanubrutinib and, more recently, the first noncovalent BTKi, pirtobrutinib. This class of drugs provides an overall safe and effective oral therapy, with the majority of patients responding to treatment with manageable toxicity. Unfortunately, the cost can be less than desirable, which is an important topic for further discussion.

While almost all patients with MCL respond to treatment with BTKis, their disease will eventually become resistant to this approach. Arguably, the next biggest advancement in treating MCL was the approval of the autologous CD19-directed chimeric antigen receptor (CAR) T-cell product, brexucabtagene autoleucel. While highly active in patients with MCL, including in those with high-risk disease features that are known to be more resistant to standard approaches, this therapy comes with many challenges. The toxicities known to CAR-T therapies, namely cytokine release syndrome and immune effector cell-associated neurologic syndrome, occur with higher frequency in patients with MCL compared with other B-cell malignancies, along with a high rate of cytopenias and infection. Further, MCL is a disease that significantly impacts older adults, making this therapy challenging for the broad population of patients. Thankfully, alternative products with potentially less toxicity are on the horizon.

With all the advances in treating MCL in patients with relapsed or refractory disease, the best treatment approach for patients at the time of diagnosis remains unknown and, one could argue, very controversial. Historically, the approach to patients at diagnosis has been to consider treatment options based on patient age and co-morbidities. The use of autologous hemopoietic stem cell transplant (AHSCT) consolidation in younger patients has long been considered a standard approach in many countries, and yet recent data suggest that a minority of patients treated in the United States who are eligible for this approach receive AHSCT. The role of AHSCT has been questioned in recent trials conducted in both Europe and the United States.

Data from the TRIANGLE study presented at the 64th American Society of Hematology Annual Meeting & Exposition showed the addition of ibrutinib to standard intensive induction therapy and as maintenance improved outcomes over AHSCT alone. They also showed that AHSCT was not superior to ibrutinib without AHSCT, with toxicity favoring the elimination of AHSCT. These interesting results, not yet in publication, have led some practitioners to adopt the approach of BTKi maintenance in lieu of consolidation AHSCT for patients with MCL. Others believe there is still a clear role for AHSCT consolidation, while some await results of the ECOG4151 trial evaluating the role of using minimal residual disease (MRD) to determine which patients may benefit from AHSCT consolidation.

Several trials have evaluated advancing treatment in the older patient population at initial diagnosis. The standard approach for many of these patients has been the bendamustine-rituximab (BR) chemoimmunotherapy regimen, but building upon this backbone has been challenging due to toxicity and potentially the fact that BR can be a very effective therapy in this patient population. The addition of novel targeted therapies, including bortezomib, lenalidomide, and ibrutinib, to the BR regimen has fallen short of changing the standard approach due to either inability to improve efficacy or concerns about toxicity.

The million-dollar question for many is how we incorporate BTKis into the initial treatment approach for all patients with MCL and, taking it a step further, can we do so while eliminating chemotherapy. BTKis are very active in MCL and have already been incorporated into initial therapy in other B-cell malignancies where these agents are highly effective. Why are we not there yet in MCL? In addition to trials evaluating the use of these agents in combination with standard chemoimmunotherapy approaches, several trials have reported outcomes with BTKis in combination with CD20 monoclonal antibodies, CD20 monoclonal antibodies and lenalidomide, and CD20 monoclonal antibodies and BCL2 inhibitors. These combination trials have shown high overall response rates, high complete response rates, and even high rates of achieving undetectable MRD. However, they have been conducted in small patient populations, and we have yet to see randomized data in this setting. That said, there are ongoing studies looking at BTKi combinations versus chemoimmunotherapy that will address these questions.

While there is still no US Food and Drug Administration-approved indication in the United States for BTKis in the initial treatment approach for MCL, I have seen the recommendation to use BTKis in this setting make its way into the treatment guidelines, and many physicians recommend the treatment. It is my hope that the current ongoing trials will help us "spring forward" into a widespread chemotherapy-free approach to treating MCL in the very near future.

Kami Maddocks, MD, *is a Professor of Clinical Internal Medicine in the Division of Hematology at the Ohio State University in Columbus.*

Get to Know

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

Claire Harrison, MD

Dr. Harrison, Professor of Myeloproliferative Neoplasms (MPN) and Deputy Chief Medical Officer (Research, Data, and Analytics) of the Guy's and St. Thomas' NHS Foundation Trust in the United Kingdom, discusses her current clinical research, how she builds community with MPN Voice, and the nun who inspired her to pursue a career in medicine.

Where did you grow up, and what do you like about being a hematologist?

I'm British and was born in Wales, but I grew up in Yorkshire. My dad worked for a big, multinational company, and we moved to Africa when I was in my early teens. That's where some of my inspiration for science came from, because I was taught by the most amazing science teachers in a missionary school in Nairobi.

Hematology as a discipline is very scientific and diverse. You can be involved in the clinic, see your patient, take a blood or bone marrow sample, look at it down a microscope, and make a diagnosis. Nowadays, things are much more complex, but you can still be involved in the lab and the bedside.

I enjoy the ability to dive deep into a specialty and get involved in chronic disease management for my patients. I value that capability, as well as the opportunity for international collaboration and the development of new medicines.

Were there any mentors who shaped your career path?

This week, I was in touch with one of my teachers, Sister Pauline, from Nairobi. She was very dedicated and disciplined but also fair, honest, and highly supportive. As a young person, Sister Pauline inspired me to think about how I wanted to be as a person and, later, as a clinician. It was important for me to be able to write to her and say 40 years later, "Thank you, because my journey was inspired by what I learned from you and the amazing science in that small school."

Over time, many people have inspired and helped me on my journey, and I'm still in touch with a lot of them. I also get a lot of inspiration from my husband, who is a general physician and, of course, my children.

As someone who looks after patients with chronic disease, some of whom I have known for more than 20 years, this has been a privileged journey. It's really a partnership, and I've been involved in building those partnerships during my career, particularly through developing patient advocacy.

Most recently, we set up a collaboration with young patients across the globe and evaluate their outcomes with these diseases and lived experience of specific issues they face, some of which we presented at the American Society of Hematology (ASH) Annual Meeting & Exposition. We want to develop guidelines and involve patients in that process. We set up a patient support group that connects those who were younger than 25 at diagnosis. We can't fix everything, but we can connect patients in this population and ask them as a community to come to us with solutions.

> **"As a clinician, you get many important insights from your patients, but you also draw your strength, vision, and determination from them. This work has been incredibly valuable for me on a personal as well as professional level."**

Can you elaborate on the community-building efforts you are involved in?

When I started as a consultant 21 years ago, the internet existed, but only in a small way. Many patients were coming to our center because they didn't understand their condition. They'd never met anybody else with it. If you read about MPN in a medical textbook, it might say your average life expectancy is 18 months, which is inaccurate and highly concerning for patients. I started out with one of the nurses from our center and a group of patients, and working with the hospital charity, we set up an advocacy group. Somebody wrote the content for the website at their kitchen table one evening. We drew on expertise and the experiences of patients, and then gradually more clinicians and nurses became involved. We set up MPN Voice, which has a website in the United Kingdom and is linked through the National Health Service (NHS) IT system, and patients can find information there through NHS Choices. It also links internationally. There have been MPN Voice get-togethers in Hong Kong and Australia and many hits from around the world. Several thousand patients meet virtually or face-to-face via this community every year.

As a clinician, you get many important insights from your patients, but you also draw your strength, vision, and determination from them. This work has been incredibly valuable for me on a personal as well as professional level.

How did you become interested in MPN?

I met a patient who had an MPN when I was early in my hematology training, and I was struck by how little we knew and how complex the diagnosis was for her. She was quite advanced in her disease course. I went back to the center I trained in, which was University College London. At that time, thrombopoietin, which is the "platelet hormone," had just been discovered. I was talking to one of my mentors, who was a proper hematology professor. He said, "Oh, I'd like you to come and do research, and I would like you to think about doing it in myeloproliferative diseases, and particularly in essential thrombocythemia and looking at thrombopoietin."

It was a bit of a chance. I set up a specialist clinic and began to do research in the field, and I found it rewarding. After I finished my research, I went back to clinical practice and decided I didn't want to be primarily a laboratory-based academic. Instead, I wanted to be a clinical academic. This term has many definitions, but for me, it's somebody who is involved in research but still works substantially as a clinician. You can be doing some basic science, but it's very hard to do basic science as a clinician. My work involved multiple collaborations—collaborating in the discovery of mutations, being involved in targeted therapies such as Janus kinase (JAK) inhibitors, doing academic studies, increasingly integrating the voice of the patient and the community, and collaborating internationally.

Can you talk about your current research?
My current research responsibility includes looking after research and development for the hospital and the interface with the university and trying to increase our translational medicine footprint, which I find rewarding.

My own personal research is currently centered around the young people I mentioned earlier. We recently presented some data at ASH from this collaboration led by colleagues in Switzerland, France, the United Kingdom, and across the European Hematology Association, which showed the event rate for young people, in terms of risk of blood clotting and transformation of disease and death, can be altered using interferon.

Recently, I led a big, randomized study of JAK inhibitors in polycythemia vera. For the first time, we showed that a 50% reduction in the amount of JAK2 mutation translates into an overall survival benefit.

That study involved a massive team collaboration, including 38 hospitals in the United Kingdom and a university clinical trial center, 10 years of work, and lots of scientific input from people who know science much better than me. I see my role as a convener and facilitator.

We're also currently looking at the immune profiling effects of JAK inhibitors and how they can differ, and how we can predict responses for patients. We're potentially looking at immunological therapies. For the first time in my life, I'm venturing into first-in-human trials looking at CALR-directed therapies, which is interesting but also a bit terrifying.

What do you hope to see in the field over the next 10 years?
I think personalized medicine is a bit of a passé term, but I would like to see us move toward personalizing therapy for patients and knowing the therapy is going to have benefit because of the patient's mutational or immunological profile. I would like us to have therapies that deliver meaningful benefit for patients, by which I mean they live longer with less disease burden.

"We can't fix everything, but we can connect patients in this population and ask them as a community to come to us with solutions."

I'm not sure we need to focus so much on cure at all costs. Only around 5% of my patients would have a stem cell transplant. It's an incredibly risky procedure to undertake, but it's an important one for some patients. Fifty percent of patients will be cured at five years. A lot of patients miss out on that opportunity, and I would like to be able to deliver a therapy that we know should work based on the patient's profile, that will put their disease into a minimal disease state and allow them to live a better life without so many worries about disease. I would also like to do more collaboration and education, both for patients and clinicians. I've got lots of work to do yet.

What advice would you give to younger physicians or trainees in the field?
If you're going to do research, look carefully at the environment you are going into. Get to know your mentor and the people they work with. Don't just jump at a subject because someone offers it to you. It worked well for me, but it may not work for you.

Research can take many forms. Start looking at data, data analysis, and artificial intelligence. I think that's going to be a huge thing in the future. You don't just have to do wet lab; you can also do dry lab research. Take inspiration from people around you, and don't be afraid to reach out. I think people can be afraid to send an email to someone they don't know, but I'm often pleased to hear from people and would support them.

What hobbies or activities do you enjoy outside of work?
I'm a mom, so my kids are important to me. But they're not kids anymore—they're in their twenties. I love spending time with them, because it's great to have seen them grow up and be independent young men now. I am so proud of them both. I also love being outdoors. I like exercising. I have a dog, a black Labrador called Maya. We both enjoy long walks.

Claire Harrison, MD, *is a Professor of Myeloproliferative Neoplasms and Deputy Chief Medical Officer of the Guy's and St. Thomas' NHS Foundation Trust.*

Ojjaara (momelotinib)

200 mg • 150 mg • 100 mg tablets

OJJAARA is the **first & only** FDA-approved treatment indicated specifically for patients who have intermediate or high-risk myelofibrosis (MF) with anemia[1,2]

GET TO KNOW OJJAARA

OJJAARA was assessed in patients who have MF with anemia for the following endpoints[1]:

RATE OF TOTAL SYMPTOM SCORE REDUCTION

RATE OF SPLEEN VOLUME REDUCTION

RATE OF TRANSFUSION INDEPENDENCE

FDA=US Food and Drug Administration.

SEE THE SAFETY AND EFFICACY DATA FOR OJJAARA

INDICATION

OJJAARA is indicated for the treatment of intermediate or high-risk myelofibrosis (MF), including primary MF or secondary MF [post-polycythemia vera (PV) and post-essential thrombocythemia (ET)], in adults with anemia.

IMPORTANT SAFETY INFORMATION

Risk of Infections

- Serious (including fatal) infections (e.g., bacterial and viral, including COVID-19) occurred in 13% of patients treated with OJJAARA. Infections regardless of grade occurred in 38% of patients. Delay starting therapy until active infections have resolved. Monitor patients for signs and symptoms of infection and initiate appropriate treatment promptly.

Please see additional Important Safety Information on the following page with accompanying Brief Summary of the full Prescribing Information.

IMPORTANT SAFETY INFORMATION (cont'd)

Risk of Infections (cont'd)

Hepatitis B Reactivation

- Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine transaminase (ALT) or aspartate transaminase (AST), have been reported in patients with chronic hepatitis B virus (HBV) infection taking Janus Kinase (JAK) inhibitors, including OJJAARA. The effect of OJJAARA on viral replication in patients with chronic HBV infection is unknown. In patients with HBV infections, check hepatitis B serologies prior to starting OJJAARA. If HBsAg and/or anti-HBc antibody is positive, consider consultation with a hepatologist regarding monitoring for reactivation versus prophylactic hepatitis B therapy. Patients with chronic HBV infection who receive OJJAARA should have their chronic HBV infection treated and monitored according to clinical HBV guidelines.

Thrombocytopenia and Neutropenia

- New or worsening thrombocytopenia, with platelet count less than 50×10^9/L, was observed in 20% of patients treated with OJJAARA. Eight percent of patients had baseline platelet counts less than 50×10^9/L.
- Severe neutropenia, absolute neutrophil count (ANC) less than 0.5×10^9/L, was observed in 2% of patients treated with OJJAARA.
- Assess complete blood counts (CBC), including platelet and neutrophil counts, before initiating treatment and periodically during treatment as clinically indicated. Interrupt dosing or reduce the dose for thrombocytopenia or neutropenia.

Hepatotoxicity

- Two of the 993 patients with MF who received at least one dose of OJJAARA in clinical trials experienced reversible drug-induced liver injury. Overall, new or worsening elevations of ALT and AST (all grades) occurred in 23% and 24%, respectively, of patients treated with OJJAARA; Grade 3 and 4 transaminase elevations occurred in 1% and 0.5% of patients, respectively. New or worsening elevations of total bilirubin occurred in 16% of patients treated with OJJAARA. All total bilirubin elevations were Grades 1-2. The median time to onset of any grade transaminase elevation was 2 months, with 75% of cases occurring within 4 months.
- Delay starting therapy in patients presenting with uncontrolled acute and chronic liver disease until apparent causes have been investigated and treated as clinically indicated. When initiating OJJAARA, refer to dosing in patients with hepatic impairment.
- Monitor liver tests at baseline, every month for 6 months during treatment, then periodically as clinically indicated. If increases in ALT, AST or bilirubin related to treatment are suspected, modify OJJAARA dosage based upon Table 1 within the Prescribing Information.

Major Adverse Cardiovascular Events (MACE)

- Another JAK inhibitor increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke [compared with those treated with tumor necrosis factor (TNF) blockers] in patients with rheumatoid arthritis, a condition for which OJJAARA is not indicated.
- Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OJJAARA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Inform patients receiving OJJAARA of the symptoms of serious cardiovascular events and the steps to take if they occur.

Thrombosis

- Another JAK inhibitor increased the risk of thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis (compared with those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which OJJAARA is not indicated. Evaluate patients with symptoms of thrombosis and treat appropriately.

Malignancies

- Another JAK inhibitor increased the risk of lymphoma and other malignancies excluding nonmelanoma skin cancer (NMSC) (compared with those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which OJJAARA is not indicated. Current or past smokers were at increased risk.
- Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OJJAARA, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.

Adverse Reactions

- The most common adverse reactions (≥20% in either study) are thrombocytopenia, hemorrhage, bacterial infection, fatigue, dizziness, diarrhea, and nausea.

Organic Anion Transporting Polypeptide (OATP)1B1/B3 Inhibitors

- Momelotinib is an OATP1B1/B3 substrate. Concomitant use with an OATP1B1/B3 inhibitor increases momelotinib maximal concentrations (C_{max}) and area under the concentration-time curve (AUC), which may increase the risk of adverse reactions with OJJAARA. Monitor patients concomitantly receiving an OATP1B1/B3 inhibitor for adverse reactions and consider OJJAARA dose modifications.

Breast Cancer Resistance Protein (BCRP) Substrates

- Momelotinib is a BCRP inhibitor. OJJAARA may increase exposure of BCRP substrates, which may increase the risk of BCRP substrate adverse reactions. When administered concomitantly with OJJAARA, initiate rosuvastatin (BCRP substrate) at 5 mg and do not increase to more than 10 mg once daily. Dose adjustment of other BCRP substrates may also be needed. Follow approved product information recommendations for other BCRP substrates.

Pregnancy

- Available data in pregnant women are insufficient. OJJAARA should only be used during pregnancy if the expected benefits to the mother outweigh the potential risks to the fetus.

Lactation

- It is not known whether OJJAARA is excreted in human milk. Because of the potential for serious adverse reactions in a breastfed child, patients should not breastfeed during treatment with OJJAARA, and for at least 1 week after the last dose of OJJAARA.

Females and Males of Reproductive Potential

- Advise females of reproductive potential who are not pregnant to use highly effective contraception during therapy and for at least 1 week after the last dose of OJJAARA.

Hepatic Impairment

- Momelotinib exposure increased with severe hepatic impairment (Child-Pugh C). The recommended starting dose of OJJAARA in patients with severe hepatic impairment (Child-Pugh C) is 150 mg orally once daily. No dose modification is recommended for patients with mild hepatic impairment (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B).

Please see Brief Summary of full Prescribing Information on the following pages.

References: 1. OJJAARA (momelotinib). Prescribing Information. GSK; 2023. **2.** Chifotides HT, Bose P, Verstovsek S. Momelotinib: an emerging treatment for myelofibrosis patients with anemia. *J Hematol Oncol*. 2022;15(1):7. doi:10.1186/s13045-021-01157-4

MMLJRNA240001 February 2024
Produced in USA.

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION
OJJAARA (momelotinib) tablets, for oral use

The following is a brief summary only; see full prescribing information for complete product information available at www.OJJAARAhcp.com

1 INDICATIONS AND USAGE

OJJAARA is indicated for the treatment of intermediate or high-risk myelofibrosis (MF), including primary MF or secondary MF [post-polycythemia vera (PV) and post-essential thrombocythemia (ET)], in adults with anemia.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Infections

Serious (including fatal) infections (e.g., bacterial and viral, including COVID-19) occurred in 13% of patients treated with OJJAARA. Infections regardless of grade occurred in 38% of patients treated with OJJAARA *[see Adverse Reactions (6.1)]*. Delay starting therapy with OJJAARA until active infections have resolved. Monitor patients receiving OJJAARA for signs and symptoms of infection and initiate appropriate treatment promptly.

Hepatitis B Reactivation

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine transaminase (ALT) or aspartate transaminase (AST), have been reported in patients with chronic hepatitis B virus (HBV) infection taking Janus Kinase (JAK) inhibitors, including OJJAARA. The effect of OJJAARA on viral replication in patients with chronic HBV infection is unknown. In patients with HBV infections, check hepatitis B serologies prior to starting OJJAARA. If HBsAg and/or anti-HBc antibody is positive, consider consultation with a hepatologist regarding monitoring for reactivation versus prophylactic hepatitis B therapy. Patients with chronic HBV infection who receive OJJAARA should have their chronic HBV infection treated and monitored according to clinical HBV guidelines.

5.2 Thrombocytopenia and Neutropenia

OJJAARA can cause thrombocytopenia and neutropenia *[see Adverse Reactions (6.1)]*.

New or worsening thrombocytopenia, with platelet count less than 50×10^9/L, was observed in 20% of patients treated with OJJAARA. Eight percent of patients treated with OJJAARA had baseline platelet counts less than 50×10^9/L.

Severe neutropenia, absolute neutrophil count (ANC) less than 0.5×10^9/L, was observed in 2% of patients treated with OJJAARA.

Assess complete blood counts (CBC), including platelet and neutrophil counts, before initiating treatment and periodically during treatment as clinically indicated. Interrupt dosing or reduce the dose for thrombocytopenia or neutropenia *[see Dosage and Administration (2.4) of full prescribing information]*.

5.3 Hepatotoxicity

Two of the 993 patients with MF who received at least one dose of OJJAARA in clinical trials experienced reversible drug-induced liver injury. Overall, new or worsening elevations of ALT and AST (all grades) occurred in 23% and 24%, respectively, of patients treated with OJJAARA; Grade 3 and 4 transaminase elevations occurred in 1% and 0.5% of patients, respectively. New or worsening elevations of total bilirubin occurred in 16% of patients treated with OJJAARA. All total bilirubin elevations were Grades 1-2. The median time to onset of any grade transaminase elevation was 2 months, with 75% of cases occurring within 4 months.

Delay starting therapy in patients presenting with uncontrolled acute and chronic liver disease until apparent causes have been investigated and treated as clinically indicated. When initiating OJJAARA, refer to dosing in patients with hepatic impairment *[see Dosage and Administration (2.3) of full prescribing information]*.

Monitor liver tests at baseline, every month for 6 months during treatment, then periodically as clinically indicated. If increases in ALT, AST or bilirubin related to treatment are suspected, modify OJJAARA dosage based upon Table 1 *[see Dosage and Administration (2.4) of full prescribing information]*.

5.4 Major Adverse Cardiovascular Events (MACE)

Another JAK inhibitor increased the risk of MACE, including cardiovascular death, myocardial infarction, and stroke [compared with those treated with tumor necrosis factor (TNF) blockers] in patients with rheumatoid arthritis, a condition for which OJJAARA is not indicated.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OJJAARA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Inform patients receiving OJJAARA of the symptoms of serious cardiovascular events and the steps to take if they occur.

5.5 Thrombosis

Another JAK inhibitor increased the risk of thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis (compared with those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which OJJAARA is not indicated.

Evaluate patients with symptoms of thrombosis and treat appropriately.

5.6 Malignancies

Another JAK inhibitor increased the risk of lymphoma and other malignancies excluding nonmelanoma skin cancer (NMSC) (compared with those treated with TNF blockers) in patients with rheumatoid arthritis, a condition for which OJJAARA is not indicated. Current or past smokers were at increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OJJAARA, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy, and patients who are current or past smokers.

6 ADVERSE REACTIONS

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

- Risk of Infections and Hepatitis B Reactivation *[see Warnings and Precautions (5.1)]*
- Thrombocytopenia and Neutropenia *[see Warnings and Precautions (5.2)]*
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*
- Major Adverse Cardiovascular Events *[see Warnings and Precautions (5.4)]*
- Thrombosis *[see Warnings and Precautions (5.5)]*
- Malignancies *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

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

The safety of OJJAARA was evaluated in 215 patients in 2 clinical trials (MOMENTUM and SIMPLIFY-1 anemic subgroup [hemoglobin (Hb) <10 g/dL]) *[see Clinical Studies (14) of full prescribing information]*.

MOMENTUM

Patients in the MOMENTUM trial had been previously treated with a JAK inhibitor and were randomly assigned 2:1 to receive double-blind OJJAARA 200 mg orally once daily (n = 130) or danazol 300 mg orally twice daily (n = 65) for 24 weeks, after which they were eligible to receive open-label OJJAARA in an extended treatment phase. Among patients who received OJJAARA, 72% were exposed for 24 weeks or longer and 52% were exposed for 48 weeks or longer *[see Clinical Studies (14) of full prescribing information]*.

Serious adverse reactions occurred in 35% of patients who received OJJAARA during the randomized treatment period of the MOMENTUM trial; the most common serious adverse reactions (≥2%) included bacterial infection (8%), viral infection (5%), hemorrhage (4%), acute kidney injury (3%), pneumonia (3%), pyrexia (3%), thrombosis (3%), syncope (2%), thrombocytopenia (2%), and renal and urinary tract infection (2%). Fatal adverse reactions occurred in 12% of patients who received OJJAARA; the most common (≥2%) fatal adverse reaction was viral infection (5%).

Permanent discontinuation of OJJAARA due to an adverse reaction occurred in 18% of patients during the randomized treatment period of the MOMENTUM trial. Adverse reactions that resulted in permanent discontinuation (≥2%) included viral infection (2%) and thrombocytopenia (2%). Dosage reduction or treatment interruption due to an adverse reaction occurred in 34% of patients. Adverse reactions requiring dosage reduction and/or treatment interruption (≥2%) included thrombocytopenia (13%), bacterial infection (2%), diarrhea (2%), and neutropenia (2%).

Among the 130 patients treated with OJJAARA during the randomized treatment period of MOMENTUM, the most common adverse reactions (≥20%) were thrombocytopenia, diarrhea, hemorrhage, and fatigue (Table 1).

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ADVERSE REACTIONS (*cont'd*)

Clinical Trials Experience (*cont'd*)

Table 1: Adverse Reactions Occurring in ≥5% of Patients Receiving OJJAARA during Randomized Treatment in MOMENTUM

Adverse Reaction	OJJAARA n = 130		Danazol[a] n = 65	
	All Grades[b] %	Grade ≥3 %	All Grades %	Grade ≥3 %
Thrombocytopenia[c]	28	22	17	12
Diarrhea[c]	22	0	9	2
Hemorrhage[c]	22	2	18	8
Fatigue[c]	21	2	20	5
Nausea[c]	16	2	9	3
Bacterial infection[c,d]	15	8	18	8
Abdominal pain[c]	13	1	18	3
Viral infection[c,d]	12	5	3	0
Pruritus[c]	11	2	11	0
Elevated liver enzymes[c]	10	2	9	3
Pyrexia[c]	10	2	8	0
Cough[c]	8	0	5	0
Paresthesia[c]	8	1	2	0
Dizziness[c]	8	2	2	0
Vomiting[c]	8	1	0	0
Rash[c]	6	0	11	0
Renal and urinary tract infection[c,d]	6	2	11	5
Arrhythmia[c]	5	1	6	2
Neutropenia	5	5	3	3

[a]Study was not designed to evaluate meaningful comparisons of the incidence of adverse reactions across treatment groups.
[b]Adverse reactions graded using CTCAE v.5.
[c]Grouped term includes other related terms.
[d]Excludes opportunistic infections.

SIMPLIFY-1

Patients in the SIMPLIFY-1 trial were JAK inhibitor naïve and randomly assigned 1:1 to receive double-blind OJJAARA 200 mg orally once daily (n = 215) or ruxolitinib 5 to 20 mg orally twice daily (n = 217). Upon completion of the double-blind treatment phase, all patients were eligible to receive OJJAARA during the open-label phase. The safety of OJJAARA was evaluated in the population of patients with MF who were anemic at study entry. SIMPLIFY-1 enrolled 180 anemic patients who received OJJAARA (n = 85) or ruxolitinib (n = 95). Among these anemic patients who received OJJAARA, 78% were exposed for 24 weeks or longer and 61% were exposed for 48 weeks or longer [*see Clinical Studies (14) of full prescribing information*].

Serious adverse reactions occurred in 28% of the anemic patients who received OJJAARA during the randomized treatment period of the SIMPLIFY-1 trial; the most common serious adverse reactions (≥2%) included bacterial infection (7%), pneumonia (6%), heart failure (4%) arrhythmia (2%), and respiratory failure (2%). A fatal adverse reaction (bacterial infection) occurred in 1 patient who received OJJAARA.

Permanent discontinuation of OJJAARA due to an adverse reaction occurred in 19% of the anemic patients during the randomized treatment period of the SIMPLIFY-1 trial. Adverse reactions that resulted in permanent discontinuation of OJJAARA (≥2%) included bacterial infection (2%), dizziness (2%), fatigue (2%), hypotension (2%), and thrombocytopenia (2%). Dosage reductions or treatment interruptions of OJJAARA due to an adverse reaction occurred in 21% of patients. Adverse reactions requiring dosage reduction and/or treatment interruption (≥2%) were thrombocytopenia (8%), pneumonia (4%), bacterial infection (2%), abdominal pain (2%), elevated liver enzymes (2%), and hypotension (2%).

Among the 85 anemic patients treated with OJJAARA during the randomized treatment period of SIMPLIFY-1, the most common adverse reactions (≥20%) were dizziness, fatigue, bacterial infection, hemorrhage, thrombocytopenia, diarrhea, and nausea (Table 2).

Table 2: Adverse Reactions Occurring in ≥5% of Anemic Patients Receiving OJJAARA during Randomized Treatment in SIMPLIFY-1

Adverse Reactions	OJJAARA n = 85 Baseline Hb <10 g/dL		Ruxolitinib[a] n = 95 Baseline Hb <10 g/dL	
	All Grades[b] %	Grade ≥3 %	All Grades %	Grade ≥3 %
Dizziness[c]	24	1	15	2
Fatigue[c]	22	0	25	1
Bacterial infection[c,d]	21	8	12	2
Hemorrhage[c]	21	1	18	2
Thrombocytopenia[c]	21	11	34	6
Diarrhea[c]	20	1	20	1
Nausea[c]	20	0	3	1
Abdominal pain[c]	18	1	14	1
Cough[c]	14	0	11	0
Hypotension[c]	14	2	0	0
Pain in extremity	12	0	5	0
Pyrexia[c]	12	1	11	0
Rash[c]	12	0	3	0
Renal and urinary tract infection[c,d]	12	1	4	0
Elevated liver enzymes[c]	11	4	9	0
Headache[c]	11	0	16	0
Peripheral edema	11	0	8	0
Arrhythmia[c]	8	2	2	1
Paresthesia[c]	8	0	3	0
Pneumonia[c]	8	8	5	3
Vomiting[c]	8	0	5	0
Back pain	7	1	2	0
Viral infection[c,d]	6	0	13	2
Vitamin B1 deficiency	6	0	7	0

[a]Study was not designed to evaluate meaningful comparisons of the incidence of adverse reactions across treatment groups.
[b]Adverse reactions graded using CTCAE v.4.03.
[c]Grouped term includes other related terms.
[d]Excludes opportunistic infections.

Other Adverse Reactions

Clinically relevant adverse reactions occurring in <5% of anemic patients in the MOMENTUM and SIMPLIFY-1 studies include:
Eye Disorders: Blurred vision.
Infections and Infestations: Fungal infection (excludes opportunistic infections).
Nervous System Disorders: Neuralgia, peripheral neuropathy, peripheral motor neuropathy, polyneuropathy.
Vascular Disorders: Flushing.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on OJJAARA

Organic Anion Transporting Polypeptide (OATP)1B1/B3 Inhibitors

Momelotinib is an OATP1B1/B3 substrate. Concomitant use with an OATP1B1/B3 inhibitor increases momelotinib maximal concentrations (C_{max}) and area under the concentration-time curve (AUC) *[see Clinical Pharmacology (12.3) of full prescribing information]*, which may increase the risk of adverse reactions with OJJAARA. Monitor patients concomitantly receiving an OATP1B1/B3 inhibitor for adverse reactions and consider OJJAARA dose modifications *[see Dosage and Administration (2.4) of full prescribing information]*.

7.2 Effect of OJJAARA on Other Drugs

Breast Cancer Resistance Protein (BCRP) Substrates

Momelotinib is a BCRP inhibitor. OJJAARA may increase exposure of BCRP substrates, which may increase the risk of BCRP substrate adverse reactions [*see Clinical Pharmacology (12.3) of full prescribing information*]. When

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DRUG INTERACTIONS (*cont'd*)

Effect of OJJAARA on other Drugs (*cont'd*)

administered concomitantly with OJJAARA, initiate rosuvastatin (BCRP substrate) at 5 mg and do not increase to more than 10 mg once daily. Dose adjustment of other BCRP substrates may also be needed. Follow approved product information recommendations for other BCRP substrates.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data on the use of OJJAARA in pregnant women are insufficient to determine whether there is a drug-associated risk for major birth defects or miscarriage. Based on animal reproduction studies conducted in rats and rabbits, momelotinib may cause embryo-fetal toxicity at exposures lower than the expected exposure in patients receiving 200 mg once daily *(see Data)*. OJJAARA should only be used during pregnancy if the expected benefits to the mother outweigh the potential risks to the fetus.

The 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.

Data

Animal Data: In an embryofetal development study, pregnant rats received momelotinib 2, 6 or 12 mg/kg/day orally, during the period of organogenesis (Gestation Day 6 to 17). Embryo-fetal toxicity (embryonic death, soft tissue anomalies, skeletal variations, and lower mean fetal body weights) was observed at 12 mg/kg (in the presence of maternal toxicity). Skeletal variations were observed (in the absence of maternal toxicity) at 6 mg/kg/day at exposures 3.5 times the exposure at the recommended human dose of 200 mg daily based on combined momelotinib and M21 (a major human metabolite) AUC. No developmental toxicity was observed at 2 mg/kg/day at exposures equivalent to the recommended dose (based on combined momelotinib and M21 AUC).

In an embryofetal developmental study, pregnant rabbits received momelotinib at 7.5, 30 or 60 mg/kg/day orally during the period of organogenesis (Gestation Day 7 to 20). Momelotinib was associated with maternal toxicity at 60 mg/kg/day, which resulted in reduced mean fetal weight, delayed bone ossification, and an abortion at less than the exposure at the recommended dose (based on combined momelotinib and M21 AUC). No developmental toxicity was observed at lower doses tested in rabbits.

In a pre- and post-natal development study, pregnant rats received momelotinib 2, 6 or 12 mg/kg/day orally from organogenesis through lactation (Gestation Day 6 to lactation Day 20). Decreased pup body weights and embryo-lethality were observed in the dams administered 6 and 12 mg/kg/day. Pup survival was significantly reduced in the 12 mg/kg/day group from birth to Day 4 of lactation. Momelotinib exposure in dams at 12 mg/kg and 6 mg/kg were approximately 2 times the exposure at the recommended dose (based on combined momelotinib and M21 AUC). The exposure in dams at the No Observed Adverse Effect Level (NOAEL) dose of 2 mg/kg was less than the exposure at the recommended dose (based on combined momelotinib and M21 AUC).

8.2 Lactation

Risk Summary

There are no data on the presence of momelotinib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. It is not known whether OJJAARA is excreted in human milk. Momelotinib was present in rat pups following nursing from treated dams with adverse effects observed in the offspring. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the potential for serious adverse reactions in a breastfed child, patients should not breastfeed during treatment with OJJAARA, and for at least 1 week after the last dose of OJJAARA.

Data

Animal Data: In a pre- and postnatal development study, momelotinib was administered orally to rats during the lactation period; the drug was detected in plasma of nursing pups, which adversely affected pup survival.

8.3 Females and Males of Reproductive Potential

Contraception

Advise females of reproductive potential who are not pregnant to use highly effective contraception during therapy and for at least 1 week after the last dose of OJJAARA.

8.5 Geriatric Use

There were 275 patients aged 65 years and older in the clinical studies for MF *[see Clinical Studies (14) of full prescribing information]*. Of the total number of OJJAARA-treated patients in these studies, 163/216 (75%) were aged 65 years and older, and 63/216 (29%) were aged 75 years and older. No overall differences in safety or effectiveness of OJJAARA have been observed between patients aged 65 years and older and younger adult patients.

8.6 Hepatic Impairment

The recommended starting dose of OJJAARA in patients with severe hepatic impairment (Child-Pugh C) is 150 mg orally once daily *[see Dosage and Administration (2.3) of full prescribing information]*. No dose modification is recommended for patients with mild hepatic impairment (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B).

Momelotinib is extensively metabolized *[see Clinical Pharmacology (12.3) of full prescribing information]*. Momelotinib exposure increased with severe hepatic impairment (Child-Pugh C). No clinically significant changes in momelotinib exposure were observed in subjects with mild hepatic impairment (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B) *[see Clinical Pharmacology (12.3) of full prescribing information]*.

10 OVERDOSAGE

There is no known antidote for overdose with OJJAARA. If overdose is suspected, the patient should be monitored for signs or symptoms of adverse reactions or effects, and appropriate supportive treatment should be instituted immediately. Further management should be as clinically indicated. Hemodialysis is not expected to enhance the elimination of momelotinib.

17 PATIENT COUNSELING INFORMATION

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

Infections

Inform patients that OJJAARA can increase the risk of infections (including COVID-19) and instruct them to promptly report to their healthcare provider any signs and symptoms of infection *[see Warnings and Precautions (5.1)]*.

Thrombocytopenia and Neutropenia

Inform patients that OJJAARA can cause thrombocytopenia and neutropenia, and of the need to monitor complete blood count, including platelet and neutrophil counts, before and during treatment. Advise patients to observe for and report any bleeding to their healthcare provider *[see Warnings and Precautions (5.2)]*.

Hepatotoxicity

Inform patients that OJJAARA can cause hepatotoxicity, and of the need to monitor liver blood tests before and during treatment *[see Warnings and Precautions (5.3)]*.

Major Adverse Cardiovascular Events (MACE)

Advise patients that events of MACE including myocardial infarction, stroke, and cardiovascular death have been reported in clinical studies with another JAK inhibitor used to treat rheumatoid arthritis, a condition for which OJJAARA is not indicated. Advise patients, especially current or past smokers and patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events and to report them to their healthcare provider *[see Warnings and Precautions (5.4)]*.

Thrombosis

Advise patients that events of deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in clinical studies with another JAK-inhibitor used to treat rheumatoid arthritis, a condition for which OJJAARA is not indicated. Advise patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE *[see Warnings and Precautions (5.5)]*.

Malignancies

Advise patients, especially current or past smokers, that lymphoma and other malignancies (excluding non-melanoma skin cancers (NMSC)) have been reported in clinical studies with another JAK inhibitor used to treat rheumatoid arthritis, a condition for which OJJAARA is not indicated *[see Warnings and Precautions (5.6)]*.

Pregnancy

- Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their prescriber of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential who are not pregnant to use highly effective contraception during therapy and for 1 week after the last dose of OJJAARA *[see Use in Specific Populations (8.3)]*.

Lactation

Advise patients not to breastfeed during treatment with OJJAARA and for at least 1 week after the last dose of OJJAARA *[see Use in Specific Populations (8.2)]*.

GSK

GlaxoSmithKline
Durham, NC 27701

OJJ:1BRS 10/23

MMLJRNA240001 February 2024 Produced in USA.

In Focus

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

New Initiative Seeks to Jump-start Era of CMML Care

By Leah Sherwood

In Focus

Chronic myelomonocytic leukemia (CMML) has historically lingered in the penumbra of more prominent disorders such as myelodysplastic and myeloproliferative neoplasms (MDS/MPN). However, a new collaborative effort between CMML researchers and The Leukemia & Lymphoma Society (LLS) hopes to jump-start patient treatment and advance scientific understanding of this rare disease.

Central to this collaborative effort is a clinical trial network, an initiative currently in development, explained **Lee Greenberger, PhD,** the Chief Scientific Officer at LLS.

"The hope is to enroll patients into trials in an accelerated way," Dr. Greenberger said. "LLS could help recruit those patients because we have clinical trial support services and are building a clinical trial network for CMML patients."

With an estimated prevalence rate of four per 100,000 people per year,[1] CMML has been underrepresented both in clinical trials and drug development.[2]

"It definitely is a rare disease and a great unmet need because the disease over time has spent most of its life in the shadow of MDS or MPN," said **Mrinal Patnaik, MBBS,** a physician-scientist at the Mayo Clinic in Rochester, Minnesota. "The hope is that with LLS being involved, it will give us all the infrastructure, impetus, and support to continually evolve this into something more definitive than where it is now."

Additionally, strict criteria for trial inclusion often exclude patients with CMML from participating in the already limited studies available, Dr. Greenberger explained.

"These patients have to be placed in clinical trials," he said. "However, not all patients are going to want to—or be available to—participate in clinical trials, or even meet all the inclusion criteria."

Addressing this issue, **Guillermo Montalban-Bravo, MD,** an Assistant Professor at the University of Texas MD Anderson Cancer Center who is among the group of leading researchers contacted by LLS to help set up the network, pointed out only a handful of institutions, including his own, have CMML-specific studies.

"Right now, there are only a few major academic centers that focus on CMML in the United States or elsewhere," Dr. Montalban-Bravo said. "The initiative of LLS, in part, was to allow multiple institutions, or particularly smaller institutions, to more easily grant patients access to these CMML-specific trials."

The lack of CMML-specific trials also hinders the identification of effective treatments for these patients, explained Dr. Montalban-Bravo.

"It's going to be difficult to identify novel, effective drugs for these patients if we don't develop clinical trials that specifically address them," he said.

Becoming Its Own Entity

From a historical perspective, the current lack of CMML-specific clinical trials can be traced back to the difficulty in accurately diagnosing CMML in the first place. The lack of detailed genetic mutation data and the disease's overlapping features with MDS and MPN led it to be characterized as belonging to one group or the other depending on attributes such as the patient's bone marrow characteristics and disease behavior.[3]

"The real prevalence of the disease is not very well described," said **Douglas Tremblay, MD,** a hematologist at the Icahn School at Mount Sinai. "It's an inherently biologically diverse population of patients, and we frequently lump them together, but there's many different types of CMML. It also has been challenging to understand the optimal treatment for these patients because they're often lumped in with either MPN or MDS, and that makes it difficult to design therapeutic strategies for them."

Traditionally, CMML was grouped together with MDS when it presented with certain blood and bone marrow characteristics. Conversely, when CMML exhibited more proliferative traits, it was sometimes aligned more closely with myeloproliferative disorders, Dr. Tremblay explained.

> **"Rare diseases are not rare for the people affected by them. Just because it's a rare disease doesn't mean it shouldn't get support."** *—Mrinal Patnaik, MBBS*

"There's a lot of overlap between these diseases: patients with myelofibrosis may have monocytosis and patients with CMML may have bone marrow fibrosis, and so they may be classified as myelofibrosis but may actually have a disease more accurately characterized as CMML," he said.

As researchers began to discover CMML-specific mutations and disease markers, the World Health Organization (WHO) adapted its classification criteria, acknowledging CMML as a distinct disease entity. Since that time, and especially in the past decade, there has been fresh momentum in the international medical community to develop specific research in CMML and other MDS-MPN overlap syndromes, Dr. Montalban-Bravo said.

Recently, the WHO further adjusted its classification criteria for CMML, making them more inclusive and broadening the recognition of patients who may have previously been categorized as having MDS, according to Dr. Montalban-Bravo.

"This is a field that is ever-changing based on how the research moves forward and what we identify," he said. "Certainly, the scenario is very different today than it was 15 years ago in terms of recognition of and research in these specific entities, and then also the development of clinical trials and novel drugs and treatment for these patients."

Yet, this progress has not been without its setbacks. Dr. Patnaik expressed concern that valuable time has been lost because CMML was historically "lumped under MDS," and in particular because CMML response criteria were based on those used for MDS, which failed to fully encompass the intricacies of CMML.

The delay has had implications for treatment, as the only drugs approved by the US Food and Drug Administration (FDA) for CMML are azacitidine, which was approved in 2004, and decitabine,[4] including a fixed-dose oral combination of decitabine and cedazuridine approved in July 2020.[5-7]

"The [azacitidine] approval came off two studies, one in the United States and one in Europe, which were largely done for MDS. They had a handful of CMML patients enrolled, and all of them had dysplastic CMML," he explained. "It is a proper approval, but you can question whether it is valid for the myeloproliferative CMML variants where current data suggest that they are not really effective."

Dr. Patnaik also pointed out a more cautious approach in Europe, where azacitidine is only approved for myelodysplastic CMML when patients have an increased number of blasts, indicating that "the European counterpart of the FDA has been more restrictive than the US FDA in drug approvals for CMML."

The slow pace of the uncoupling of CMML from MDS has impeded the discovery of novel treatments and the establishment of CMML-specific clinical trials, he added.

"We have the response criteria, and we have the FDA's attention that this is a unique entity, but now we need to bring the therapies," Dr. Patnaik said. "The underlying problem is that there haven't been enough trials conducted. This has resulted in limited first-line options and no FDA/[European Medicines Agency]-approved second-line options for patients with CMML."

Advances Lag in CMML

While CMML is rare, it is not rarer than other blood cancers, according to **Eric Padron, MD,** who is the Scientific Director in the Division of Malignant Hematology at the Moffitt Cancer Center in Tampa, Florida.

"I certainly don't view it as more rare, complicated, or difficult to diagnose than any other blood cancer," he said. "So why aren't there advances in CMML like there are in the other blood cancers? It can't be just because of rarity."

Dr. Padron, who is part of the LLS initiative and has worked in CMML for the length of his career, believes that the slow pace of advancement in CMML might be tied to the lack of CMML-specific drug approvals by the FDA and other regulatory bodies.

A drug approval specific to CMML would catalyze a surge of interest in the hematology-oncology community, Dr. Padron believes. Currently, the absence of such an approval may lead some clinicians to view treatment as merely theoretical, particularly because patients with CMML have historically received the same protocols as those with MDS.

"When a drug approval happens, there's a rush of interest; diagnoses become better as people begin to care more," Dr. Padron said. "That's the whole premise behind the clinical trial network; in our view, getting a drug approved by the FDA for CMML specifically will lead to a lot of other downstream things to help take care of these patients."

Dr. Patnaik agreed that new drug approvals are essential and called on the research community to drive development by identifying mechanisms and targets.

"The onus lies on us to bring drugs to the FDA and

say, 'These are things that we think work.' It's up to us, the physician-scientist community, to find rationally derived therapeutic targets," Dr. Patnaik said.

Nonuniform Nature of CMML

Currently, allogeneic hematopoietic stem cell transplantation is the only curative treatment for these patients, but the treatment is associated with significant morbidity and mortality.[8,9] Other drugs, including the recombinant fusion protein luspatercept[10] and the Janus kinase inhibitor ruxolitinib[11] have been repurposed from MDS or MPN to treat CMML.

"There are patients who may not need intervention, and there are patients who should go to transplant relatively fast," Dr. Montalban-Bravo said. "There are patients who have a very benign disorder, where the disease is not defined by having any kind of high-risk features, but there are other patients in whom the disease is very aggressive, and it can behave as severely as AML."

CMML can progress to AML,[11] particularly in high-risk patients, where the progression to more aggressive leukemia is common, Dr. Tremblay noted.

"Many CMML patients also have a subtype of CMML-2 (a blast percentage of 10% to 19%), and while those patients are called CMML, they really have a disease that is biologically similar to AML," he said.

This progression of CMML to AML, especially in high-risk patients, sets a challenging backdrop for treatment. In response, Dr. Tremblay and colleagues presented a study on the efficacy of venetoclax with hypomethylating agents (HMAs) in CMML at the 65th American Society of Hematology Annual Meeting & Exposition, linking CMML treatment strategies to approaches validated in AML.[12]

Venetoclax is an approved therapy for AML and has been shown to improve survival in that disease and deliver an increase in response rates.[13]

"Because of that, there's been a little bit of creep into different related myeloid diseases, especially MDS, where there is now a phase III trial evaluating venetoclax plus azacitidine in MDS," Dr. Tremblay said, adding that "patients with CMML are really excluded from that phase III MDS experience."

The researchers reported in their study that even though higher response rates were reported, that didn't translate to survival.

"While HMA plus venetoclax in both CMML and CMML blast transformation induced higher response rates, it did not translate into survival differences," Dr. Tremblay said. "In the CMML population there was prolongation and improvement in leukemia-free survival. While there is activity in terms of response rates, it doesn't translate into survival."

While he thinks the results were disappointing in terms of prolonging survival, he noted another analysis part of the study looked promising for an HMA plus venetoclax combination in bridging patients.

"We also looked at a population of patients who were treated with an HMA first and then had venetoclax added on, and in those patients, in both CMML and CMML after blast transformation, about 25% of them were able to transition to transplant," he said, adding "I do still think there's probably a role for the combination in treating high-risk patients who are eligible for transplant."

No Funding

While there are phase I and II trials available at centers such as MD Anderson, Moffitt, and the Mayo Clinic, there are no phase III studies in CMML underway, mainly due to a lack of funding and the institutional scale that would be required.

"It is challenging to develop a phase III study without it being a large, multicenter, international, cooperative study," Dr. Montalban-Bravo said.

Dr. Tremblay singled out support from the pharmaceutical industry as the missing link in the transition to phase III.

"In order to do phase III trials in this disease, there has to be input and sponsorship from our pharmaceutical partners to really invest in this space because there is a huge unmet need," he said.

However, support from organizations like LLS and the demonstration of successful FDA approvals have the potential to alter the industry's perspective, according to Dr. Padron.

"When a drug approval happens, there's a rush of interest; diagnoses become better as people begin to care more." *—Eric Padron, MD*

"There's a misconception in the industry. They don't believe that the economics make sense for a phase III trial because the payoff isn't going to be high enough," he said. "But with LLS being behind this initiative and then showing, 'Hey, this is what happens when you get an FDA-approved drug,' I think it will change."

That shift in perception might already be taking place: the FDA has been increasingly raising awareness about CMML and the need for clinical trials in the disease, Dr. Padron explained.

"I think the industry's finally coming around to the notion that CMML is a huge unmet need," he said.

This is the moment for organizations and funding bodies to acknowledge the need to advance CMML research and for investigators to put their heads together to find solutions, Dr. Patnaik said.

"People like myself and Eric Padron have been fighting this battle for the last decade," he said. "Rare diseases are not rare for the people affected by them. Just because it's a rare disease doesn't mean it shouldn't get support."

***Leah Sherwood** is the Managing Editor of* Blood Cancers Today.

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Regulatory Actions

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

Ide-Cel for MM Moves Toward Approval in EU

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) gave a positive recommendation for the Marketing Authorization approval of idecabtagene vicleucel (ide-cel), a BCMA-targeted monoclonal antibody developed by Bristol Myers Squibb.

Ide-cel is designed to treat adult patients with relapsed or refractory multiple myeloma (MM) after at least two prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

"This positive CHMP opinion represents an important step toward bringing our potentially transformative, first-in-class, anti-BCMA [chimeric antigen receptor (CAR)] T-cell therapy, Abecma, to more patients earlier in the MM treatment paradigm to improve outcomes," said **Anne Kerber, MD,** the Senior Vice President and Head of Late Clinical Development at Bristol Myers Squibb.

Data supporting the approval of ide-cel include the pivotal, phase III KarMMa-3 study that compared ide-cel with conventional combination regimens in triple-class exposed adult patients who were refractory to their most recent therapy.

In KarMMa-3, ide-cel significantly improved progression-free survival (PFS) after a median follow-up of 30.9 months (range, 12.7-47.8 months), with a median PFS of 13.8 months versus 4.4 months with standard regimens (hazard ratio, 0.49; 95% CI, 0.38-0.63).

The recommendation for ide-cel will now be reviewed by the European Commission (EC) of the European Union (EU), which typically makes a decision approximately two months after a CHMP opinion is submitted.

Expanded Indications for Liso-Cel Under Review in United States, Japan

Lisocabtagene maraleucel (liso-cel), a CAR T-cell therapy, received two regulatory acceptances from the US Food and Drug Administration (FDA) and one from the Ministry of Health, Labour and Welfare (MHLW) of Japan, according to a press release from Bristol Myers Squibb.

The FDA accepted two additional supplemental Biologics License Applications (BLAs) that expand indications for liso-cel to include patients with relapsed or refractory follicular lymphoma (FL) and relapsed or refractory mantle cell lymphoma (MCL) after a previous Bruton's tyrosine kinase inhibitor (TKI). Both applications were granted priority review and assigned action dates in May 2024.

Japan's MHLW accepted a supplemental New Drug Application for liso-cel in the treatment of relapsed or refractory FL.

The applications are based on the TRANSCEND FL and TRANSCEND NHL 001 studies for FL and MCL, respectively. Both studies reported promising rates of complete response with liso-cel. No new safety signals were identified.

FDA Clears IND for OriCAR-017 in Relapsed or Refractory MM

The FDA has cleared an Investigational New Drug (IND) application for OriCAR-017 for the treatment of relapsed or refractory MM, according to a press release from the biotechnology company Oricell Therapeutics.

The IND allows clinical development to begin in the United States.

OriCAR-017 is a novel, GPRC5D-targeted, CAR T-cell therapy, which first gained approval from China's National Medical Products Administration in 2023 following results from the POLARIS study. The trial achieved a 100% overall response rate ORR, 80% stringent complete response, and 100% negative measurable residual disease (MRD) rate among 10 patients. OriCAR-017 was well tolerated, as there were no serious adverse events or treatment-related deaths.

FDA Approves Shorter Manufacturing Time for Axi-Cel

The FDA has approved a manufacturing process change for axicabtagene ciloleucel (axi-cel), according to a press release from the biotechnology company Kite, the manufacturer of the therapy.

This change will result in a shorter manufacturing time for axi-cel, with the median turnaround time expected to be reduced from 16 days to 14 days in the United States, the company reported. Median turnaround time is defined as the time from leukapheresis, in which a patient's T cells are collected, to product release. Manufacturing prepares each patient's cells for a customized, one-time therapy infusion.

Axi-cel is a CAR T-cell therapy that was first approved by the FDA in April 2022 for adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapsed within 12 months of first-line treatment. The approval was based on the results of the ZUMA-7 trial, in which axi-cel demonstrated a clinically meaningful and statistically significant improvement in event-free survival compared with the current standard of care.

Application for Linvoseltamab in Myeloma Accepted for Review in Europe

The Marketing Authorization Application for linvoseltamab has been submitted and is under review by the EMA, and a BLA was submitted to the FDA.

Linvoseltamab is a bispecific antibody against BCMA developed to treat adult patients with relapsed or refractory MM who progressed after at least three lines of therapy.

The linvoseltamab application includes data from the ongoing, pivotal phase I/II LINKER-MM1 trial. The primary endpoint is objective response rate, and secondary endpoints include duration of response, PFS, MRD, and overall survival (OS).

The trial enrolled 282 patients who received an initial step-up dosing regimen followed by a full dose. Patients who achieved a very good partial response or complete response could switch from linvoseltamab every two weeks to every four weeks after at least 24 weeks of treatment.

The follow-up phase III LINKER-MM3 trial is currently enrolling, and additional planned or ongoing trials include linvoseltamab in first-line therapy, high-risk smoldering MM, monoclonal gammopathy of undetermined significance, and in combination with a CD32×CD28 bispecific.

FDA Places Magrolimab Trials on Full Clinical Hold; AML ENHANCE-3 Trial Discontinued

The FDA placed all magrolimab studies in myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) on full clinical hold, including related expanded access programs.

Furthermore, Gilead Sciences, the manufacturer of magrolimab, announced that it is discontinuing the phase III ENHANCE-3 study of magrolimab in AML.

The company reported that these actions resulted from the recommendation of an independent Data Monitoring Committee, which reviewed top-line data from a planned interim analysis of OS in the ENHANCE-3 trial.

Gilead said that it "will not pursue further development of magrolimab in hematologic cancers" based on those results and data from the ENHANCE and ENHANCE-2 trials.

The company said it will be sharing a subanalyses of safety and efficacy data from the ENHANCE-3 trial with regulators.

"We are incredibly grateful to all the patients and investigators for their participation in the ENHANCE studies," said **Merdad Parsey, MD, PhD,** the Chief Medical Officer at Gilead, in a press release.

CHMP Issues Positive Opinion for Luspatercept in Anemia Due to MDS

CHMP of the EMA issued a positive opinion recommending that the EC approve luspatercept (Reblozyl) for the treatment of transfusion-dependent anemia due to MDS, according to a press release from Bristol Myers Squibb, the manufacturer of the drug.

If approved by the EC, adult patients with very low-, low-, and intermediate-risk MDS would be eligible to receive luspatercept to reduce transfusion requirements. This would be the fourth authorized indication for luspatercept in the EU.

The phase III COMMANDS trial compared luspatercept with epoetin alfa, an erythropoiesis-stimulating agent (ESA), in patients with low-risk MDS dependent on transfusions. Principal Investigator **Guillermo Garcia-Manero, MD,** of the University of Texas MD Anderson Cancer Center, noted that initial analyses from the trial had been presented at previous meetings before discussing the results of the final analysis.

"In general, luspatercept is superior to an ESA as a frontline drug for patients with low-risk MDS," Dr. Garcia-Manero summarized.

FDA Accepts BLA for Linvoseltamab in Relapsed or Refractory MM

The FDA has accepted for Priority Review a BLA for linvoseltamab for adult patients with relapsed or refractory MM that has progressed after at least three prior therapies, according to a press release from Regeneron Pharmaceuticals, the manufacturer of the drug.

The target action date for the FDA's decision is August 22, 2024. In early February 2024, the EMA accepted a Marketing Authorization Application for linvoseltamab for review.

The BLA is supported by data from the ongoing phase I/II LINKER-MM1 trial. The phase I dose-escalation portion of the trial assessed the safety, tolerability, and dose-limiting toxicities across nine dose levels of linvoseltamab, exploring either intravenous or subcutaneous administration regimens.

The phase II dose-expansion portion is currently assessing the safety and antitumor activity of linvoseltamab, with objective response rate as the primary endpoint.

A phase III confirmatory trial is currently enrolling.

Liso-Cel Approved by FDA for CLL, SLL

The FDA has approved liso-cel (Breyanzi®) for adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), according to a press release by Bristol Myers Squibb, the developer of the drug.

The approval follows the FDA's November 2023 statement on the potential risk of developing T-cell malignancies following CAR T-cell therapy. The FDA sent requests to drug manufacturers in January 2024 to update prescription labels with "Black Box" warnings on the six CAR-T therapies used to treat blood cancers.

Liso-cel was approved under accelerated approval based on response rate and duration of response data from the TRANSCEND CLL 004 trial. The phase I/II, open-label, single-arm study evaluated the safety and recommended dose of liso-cel in patients who have received at least two prior lines of therapy, including a Bruton's TKI and a B-cell lymphoma 2 inhibitor.

The complete response (CR) rate was 20% (95% CI, 11.1-31.8). Among those who achieved a CR, the median duration of response was not reached (NR; 95% CI, 15 months-NR) at the time of data cutoff. Among all responders, the median duration of response was 35.3 months (95% CI, 12.4-NR).

Those who achieved a CR also had an MRD-negativity rate of 100% in the blood (95% CI, 75.3-100) and 92.3% in the bone marrow (95% CI, 64-99.8).

Occurrences of cytokine release syndrome (CRS) and neurologic events (NEs) were mostly low grade. Of 89 patients, 83% experienced any grade CRS, and 46% experienced any grade NEs.

"CLL and SLL are currently considered incurable diseases with few treatment options in the relapsed setting that can confer complete responses, something that has historically been associated with improved long-term outcomes," said **Tanya Siddiqi, MD,** lead investigator of the TRANSCEND CLL 004 study and Associate Professor in the Division of Lymphoma at the City of Hope National Medical Center, in the press release.

FDA Approves Zanubrutinib Plus Obinutuzumab for Relapsed or Refractory Follicular Lymphoma

The FDA has granted accelerated approval to zanubrutinib (Brukinsa), a Bruton's TKI, when combined with obinutuzumab in the treatment of patients with relapsed or refractory FL after two or more systemic lines of therapy.

Approval for the therapy was supported by the ROSEWOOD study wherein 217 adult patients with a median of three lines of therapy (range, 2-11 lines) received obinutuzumab alone or in combination with oral zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity.

The study estimated an ORR of 69% (95% CI, 61-76) in the zanubrutinib group versus 46% (95% CI, 34-58) in the obinutuzumab group. At a median follow-up of 19.0 months, the median duration of response was not reached (95% CI, 25.3-not estimable) in the zanubrutinib group versus 14.0 months (95% CI, 9.2-25.1) in the obinutuzumab group. The estimated 18-month duration of response in the zanubrutinib group was 69% (95% CI, 58-78).

Common adverse reactions to zanubrutinib observed across studies included decreased neutrophil and platelet counts, upper respiratory tract infection, hemorrhage, and musculoskeletal pain. Serious adverse reactions were reported in 35% of patients treated in the zanubrutinib group.

FDA Approves Inotuzumab Ozogamicin in Pediatric B-Cell Precursor ALL

The FDA has approved inotuzumab ozogamicin (Besponsa) for pediatric patients one year and older with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukemia (ALL).

The efficacy of inotuzumab ozogamicin was assessed in a multicenter, single-arm, open-label study of 53 pediatric patients aged one year and older with relapsed or refractory CD22-positive B-cell precursor ALL. Two dose levels were evaluated: an initial dose of 1.4 mg/m^2/cycle in 12 patients and 1.8 mg/m^2/cycle in 41 patients, according to the FDA press release announcing the approval.

Among all patients, 22 out of 53 (42%; 95% CI, 28.1-55.9) achieved CR, with a median duration of CR of 8.2 months (95% CI, 2.6-not evaluable). The MRD negativity rate in patients with CR was 95.5% (95% CI, 77.2-99.9) based on flow cytometry and 86.4% (95% CI, 65.1-97.1) based on real-time quantitative polymerase chain reaction.

The most common adverse reactions were thrombocytopenia, pyrexia, anemia, vomiting, infection, hemorrhage, neutropenia, nausea, leukopenia, febrile neutropenia, increased transaminases, abdominal pain, and headache, according to the FDA.

Highlights From the **2024 TANDEM TRANSPLANTATION & CELLULAR THERAPY MEETINGS OF ASTCT® AND CIBMTR®**

What Is the Best Timing for CAR-T Treatment in Patients With LBCL?

Patients with large B-cell lymphoma (LBCL) who received chimeric antigen receptor (CAR) T-cell therapy earlier in treatment had lower occurrences of severe neutropenia, but overall treatment timing was not linked to survival outcomes, according to a retrospective analysis presented at the 2024 Tandem Transplantation & Cellular Therapy Meetings of ASTCT® and CIBMTR®.

"While earlier administration demonstrated a lower incidence of severe neutropenia, key efficacy metrics remained similar across early versus late introduction of CAR-T," wrote the researchers, led by **Magdalena Corona, MD,** of Memorial Sloan Kettering Cancer Center.

In the analysis, Dr. Corona and colleagues investigated the best CAR-T treatment timing in 368 patients from two medical centers who received CD19 CAR-T therapy. The timing of patient treatment was characterized as early indication (primary refractory disease or relapse occurring within 12 months after the initial line of treatment) or late indication (treatment administered after two lines of prior therapy).

Patients in the late indication group had higher levels of prelymphodepletion lymphodepletion (LDH) before lymphodepletion treatment ($P<.001$) and received 4-1BB-based CAR-T ($P=.008$). Patients in the early indication group tended to be older before receiving CAR-T treatment ($P=.021$) and more likely to have received systemic bridging therapy before CAR-T ($P=.034$).

No differences in overall or complete response rates were observed in either the early (median follow-up, 8.9 months) or late (median follow-up, 24.6 months) indication groups. The one-year progression-free survival (PFS) rates were 42% in the early indication group and 40% in the late indication group. The one-year overall survival (OS) rates were 86% and 66% for the early and the late indication groups, respectively.

A multivariable Cox regression analysis revealed certain patient characteristics were linked to reduced OS, including elevated prelymphodepletion LDH ($P<.0001$) and age ($P=.0007$). Lower PFS was also linked to higher prelymphodepletion LDH ($P<.0001$) and the use of tisagenlecleucel ($P<.0001$).

The researchers noted that comparable results were observed when the analysis was restricted to only those patients who were treated with axicabtagene ciloleucel.

The cumulative incidence of severe neutropenia (neutrophils $<0.5 \times 10^9$/L) within 30 days after infusion was higher in the late indication group, but the occurrence of severe thrombocytopenia (platelets <20,000/mm^3) and the rates of grade 2-4 cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome were the same across both groups.

Dr. Corona and colleagues noted that "additional follow-up is needed to determine whether the benefit of earlier exposure to CAR-T endures over time."

Reference

Corona M, de Abia AL, Sdayoor I, et al. Early versus late CAR-T therapy in large B-cell lymphoma: real-world outcomes. Abstract #500. Presented at the 2024 Tandem Transplantation & Cellular Therapy Meetings of ASTCT® and CIBMTR®; February 21-24, 2024; San Antonio, Texas.

Study Identifies Key Challenges, Needs Among CAR-T Therapies in MM

Cost, access, and aftercare following infusion were identified as the most prominent themes of pressing challenges and needs among CAR T-cell therapies for multiple myeloma (MM), according to a study presented at the 2024 Tandem Transplantation & Cellular Therapy Meetings of ASTCT® and CIBMTR®.

The study's goal was "to perform a comprehensive digital analysis to measure sentiment expression by different health care stakeholders and identify health information needs related to MM CAR-T therapies," according to the researchers, led by **Doris Hansen, MD,** of the Moffitt Cancer Center.

The study used public data from various online sources related to approved CAR-T therapies for MM. Those who self-identified as health care professionals based on their biography, social media name, or news article bylines, for example, were included in the stakeholder analysis.

Over the two-year study, CAR-T therapy was referenced most often in posts discussing efficacy, safety, and time to CRS. Of 471,500 MM posts, 47,909 were about CAR-T therapy, and 13,117 were specifically about ciltacabtagene autoleucel (Carvykti; 55%) or idecabtagene vicleucel (Abecma; 45%).

Among the overall population, the key themes of pressing challenges and needs included cost (60.5%), post-CAR-T infusion care (38.6%), access (37.5%), education (6.7%), and quality of life (6.4%). Among health care professionals, the significant key theme of pressing challenges and needs was post-CAR-T infusion care considerations (58.6%), such as extended hospital stays to manage immune-mediated toxicities.

Furthermore, ciltacabtagene autoleucel and idecabtagene vicleucel were mentioned similarly on topics related to diversity, equity, and inclusion. These topics included access to CAR-T therapies, diversity in clinical trials, geographic location implications, and racial disparities.

"Our findings highlight the importance of demystifying cost perceptions and implementing comprehensive post-CAR-T care protocols aligned with the concerns expressed in social media discussions for improvement in CAR-T therapies for [MM]," Dr. Hansen and colleagues concluded.

"This study offers valuable real-world insights that can inform clinical decision-making, enhance patient-centered care, and contribute to the development of strategies to overcome challenges associated with CAR-T therapies in [MM]."

Reference

Hansen D, Liu Y, Lu X, et al. Unveiling the digital landscape of CAR-T therapies in multiple myeloma using social media insights. Abstract #524. Presented at the 2024 Tandem Transplantation & Cellular Therapy Meetings of ASTCT® and CIBMTR®; February 21-24, 2024; San Antonio, Texas.

DREAMM-7 Data Show Belamaf Triplet Is Superior to Daratumumab Triplet in Myeloma

Among patients with relapsed or refractory multiple myeloma (MM), treatment with belantamab mafodotin (belamaf), bortezomib, and dexamethasone (BVd) significantly improved survival versus standard of care with daratumumab, bortezomib, and dexamethasone (DVd), based on results from the phase III DREAMM-7 trial.

The study, led by **María-Victoria Mateos, MD, PhD,** of the Hospital Universitario de Salamanca in Spain, enrolled 494 patients with relapsed or refractory MM and one or more prior lines of therapy to receive either BVd (n=243) or DVd (n=251).

The primary endpoint was progression-free survival (PFS) as assessed by an independent review committee. Secondary endpoints included overall survival (OS), duration of response (DOR), and overall response rate (ORR).

At a median follow-up of 28.2 months (range, 0.1-40.0 months), the median PFS was 36.6 months (95% CI, 28.4 to not reached) with BVd versus 13.4 months (95% CI, 11.1-17.5) with DVd (hazard ratio [HR], 0.41; 95% CI, 0.31-0.53; *P*<.00001). The authors noted the OS data were 29% mature, and median OS was not reached in either arm (HR, 0.57; 95% CI, 0.40-0.80; nominal *P*<.0005).

The ORR in the BVd group was 82.7% (95% CI, 77.4-87.3) compared with 71.3% (95% CI, 65.3-76.8) in the DVd group, and the median DOR was 35.6 months (95% CI, 30.5 to not reached) with BVd versus 17.8 months (95% CI, 13.8-23.6) for DVd.

One or more adverse events (AEs) were observed in all patients. Grade 3/4 treatment-related AEs were reported in 90% of BVd patients versus 67% of DVd patients, and serious AEs were reported in 50% of BVd patients versus 37% of DVd patients. Additionally, 79% of the BVd group had ocular AEs compared with 29% of the DVd group, though events were manageable, according to the authors.

"These results support BVd as a potential new [standard of care] in this setting," Dr. Mateos and colleagues wrote.

Reference

Mateos MV, Robak P, Hus M, et al. Results from the randomized phase III DREAMM-7 study of belantamab mafodotin (belamaf) + bortezomib, and dexamethasone (BVd) vs daratumumab, bortezomib, and dexamethasone (DVd) in relapsed/refractory multiple myeloma (RRMM). Abstract #439572. Presented at the ASCO® Plenary Series; February 6, 2024; Virtual. doi:10.1200/JCO.2024.42.36_suppl.439572

Adding Elotuzumab to Triplet Therapy Provides 'No Clinical Benefit' in Newly Diagnosed Myeloma

The addition of elotuzumab to lenalidomide, bortezomib, and dexamethasone (RVd) induction and consolidation therapy and lenalidomide maintenance therapy did not provide clinical benefit for transplant-eligible patients with newly diagnosed MM, according to results from the GMMG-HD6 trial.

The phase III, randomized trial was led by **Elias Mai, MD,** of the University Hospital Heidelberg in Germany, and published in *The Lancet Haematology*. The primary endpoint was PFS, while secondary endpoints included OS, rates of complete response after induction and consolidation therapy, time to progression, DOR, and quality-of-life assessment.

The authors noted that the results were "in line with observations from the ELOQUENT-1 and SWOG-1211 trials." They added that "the GMMG-HD6 trial complements the existing evidence on the use of elotuzumab" in this patient subgroup.

A total of 564 patients were randomly assigned to the following four treatment groups:

- In the RVd/R group, patients received RVd induction and consolidation followed by lenalidomide maintenance
- In the RVd/E-R group, patients received RVd induction, elotuzumab plus RVd consolidation, then elotuzumab plus lenalidomide maintenance therapy
- In the E-RVd/R group, patients received elotuzumab with RVd induction, RVd consolidation, then lenalidomide maintenance
- In the E-RVd/E-R group, patients received elotuzumab with RVd induction and consolidation, followed by elotuzumab plus lenalidomide maintenance

After a median follow-up of 49.8 months, there was no difference in PFS or OS between the four treatment groups. The three-year PFS rates were 69% (95% CI, 61-77) for RVd/R, 69% (95% CI, 61-76) for RVd/E-R, 66% (95% CI, 58-74) for E-RVd/R, and 67% (95% CI, 59-75) for E-RVd/E-R. The three-year OS rates were 89% (95% CI, 84-95) in the RVd/R group, 89% (95% CI, 84-94) in the RVd/E-R group, 93% (95% CI, 88-97) in the E-RVd/R group, and 90% (95% CI, 85-95) in the E-RVd/E-R group.

Furthermore, adding elotuzumab to induction, consolidation, or maintenance treatment did not result in improved time to progression or prolonged DOR compared with RVd/R alone.

Grade 3 or higher AEs occurred in 68 (48%) patients in the E-RVd/E-R group, 53 (39%) in the RVd/R group, 53 (38%) in the RVd/E-R group, and 50 (36%) in the E-RVd/R (36%) group.

Nine treatment-related deaths occurred during the study: two in the RVd/R group that were considered lenalidomide related; one in the RVd/E-R group that was considered lenalidomide and elotuzumab related; four in the E-RVd/R group; and two in the E-RVd/E-R group that were considered lenalidomide or elotuzumab related.

"The addition of elotuzumab to RVd induction or consolidation and lenalidomide maintenance in patients with transplant-eligible newly diagnosed [MM] did not provide clinical benefit," the authors wrote. "Elotuzumab-containing therapies might be reserved for patients with relapsed or refractory [MM]."

Funding was provided by Bristol Myers Squibb/Celgene and Chugai.

Reference

Mai EK, Goldschmidt H, Miah K, et al. Elotuzumab, lenalidomide, bortezomib, dexamethasone, and autologous haematopoietic stem-cell transplantation for newly diagnosed multiple myeloma (GMMG-HD6): results from a randomised, phase 3 trial. *Lancet Haematol*. 2024. doi:10.1016/S2352-3026(23)00366-6

Editor's Picks

In each issue of Blood Cancers Today, *our guest editors will take a closer look at a particular topic in hematologic malignancies. This month, Sangeetha Venugopal, MD, and Alexey Danilov, MD, PhD, highlight recent research in acute myeloid leukemia (AML) and chronic lymphocytic leukemia (CLL).*

ACUTE MYELOID LEUKEMIA

Triplet Therapy Achieves 'Encouraging Survival' in *FLT3*-Mutated AML

Azacitidine, venetoclax, and gilteritinib combination therapy achieved high complete remission (CR)/CR with incomplete count recovery (CRi) rates in patients with newly diagnosed *FLT3*-mutated AML, according to a recent study.

The phase I/II trial was led by **Nicholas Short, MD,** of the University of Texas MD Anderson Cancer Center, and published in the *Journal of Clinical Oncology.*

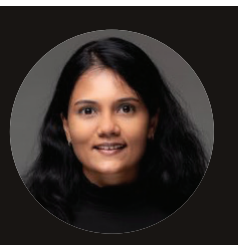
Dr. Short and colleagues evaluated the triplet therapy in 52 patients with either frontline (n=30) or relapsed or refractory (n=22) AML. Patients received the recommended phase II dose of gilteritinib 80 mg once a day in combination with azacitidine and venetoclax. The primary endpoints were the maximum tolerated dose of gilteritinib and the combined CR/CRi rate.

The CR/CRi rate was 96% for the frontline cohort compared with 27% for the relapsed or refractory cohort. Nine (41%) additional patients with relapsed or refractory AML achieved a morphologic leukemia-free state.

Within four cycles, 65% of patients achieved FLT3-internal tandem duplication measurable residual disease $<5 \times 10^{-5}$. Median relapse-free survival (RFS) and overall survival (OS) have not been reached after a median follow-up of 19.3 months. The 18-month RFS and OS rates are 71% and 72%, respectively.

The most common grade ≥3 nonhematologic adverse events included infection (62%) and febrile neutropenia (38%), and they occurred more frequently in the relapsed or refractory cohort.

Why I chose this research:



Sangeetha Venugopal, MD

"This phase I/II study was evaluated in two cohorts: newly diagnosed and relapsed or refractory FLT3*-mutated AML. In the frontline group, the CR/CRi rate was 96% and the median OS was not reached at a median follow-up of 19.3 months. In the relapsed or refractory cohort, the CR/CRi rate was 27% and the median OS was 5.8 months at a median follow-up of 30.7 months. In the VIALE-A study, the median OS in patients with* FLT3*-ITD mutation was 9.9 months. Given this background, azacitidine, venetoclax, and gilteritinib triplet therapy appears to have encouraging activity in patients with newly diagnosed* FLT3*-mutated AML, warranting further evaluation."*

Reference

Short NJ, Daver N, Dinardo CD, et al. Azacitidine, venetoclax, and gilteritinib in newly diagnosed and relapsed or refractory *FLT3*-mutated AML. *J Clin Oncol.* 2024. doi:10.1200/JCO.23.01911

CHRONIC LYMPHOCYTIC LEUKEMIA

Extended Follow-up Shows Sustained Benefits of Acalabrutinib-Based Therapy in CLL

Acalabrutinib with or without obinutuzumab had sustained safety and efficacy in patients with treatment-naïve CLL, including those with high-risk genetic features, over six years of follow-up in the ELEVATE-TN study.

Progression-free survival (PFS) was significantly longer with acalabrutinib plus obinutuzumab versus acalabrutinib monotherapy, and median OS was significantly longer with acalabrutinib plus obinutuzumab compared with obinutuzumab plus chlorambucil.

The data were presented by **Jeff Sharman, MD,** of Willamette Valley Cancer Institute and Research Center/US Oncology Research in Eugene, Oregon, at the 65th American Society of Hematology Annual Meeting & Exposition.

The study included 535 patients with CLL, of whom 179 received acalabrutinib monotherapy, 179 received acalabrutinib plus obinutuzumab, and 177 received obinutuzumab plus chlorambucil. The cohort had a median age of 70 years, 63% had unmutated immunoglobulin heavy chain variable region, and 14% had del(17p), mutated *TP53*, or both.

At the data cutoff of March 3, 2023, the median follow-up was 74.5 months (range, 0-89 months). Median PFS was 27.8 months with obinutuzumab plus chlorambucil and was not reached with acalabrutinib plus obinutuzumab (hazard ratio [HR], 0.14; $P<.0001$) or acalabrutinib alone (HR, 0.23; $P<.0001$). Acalabrutinib with obinutuzumab was superior to monotherapy (HR, 0.58; $P=.0229$).

The estimated PFS rates at 72 months were 78% with acalabrutinib plus obinutuzumab, 62% with acalabrutinib, and 17% with obinutuzumab plus chlorambucil. The respective estimated rates of 72-month OS were 68%, 72%, and 53%. Median OS was not reached in either the acalabrutinib combination or monotherapy groups versus 74.9 months in the obinutuzumab plus chlorambucil group.

Overall, acalabrutinib appeared to maintain safety and efficacy outcomes previously reported after 58.2 months in ELEVATE-TN patients with treatment-naïve CLL.

Why I chose this research:

Alexey Danilov, MD, PhD

"The six-year follow-up of the ELEVATE-TN randomized, clinical trial confirms improved PFS and OS with acalabrutinib-obinutuzumab compared with chlorambucil-obinutuzumab. PFS was also numerically higher in patients with CLL without del(17p) receiving acalabrutinib-obinutuzumab versus single-agent acalabrutinib."

Reference

Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib ± obinutuzumab vs obinutuzumab + chlorambucil in treatment-naive chronic lymphocytic leukemia: six-year follow-up of Elevate-TN. Abstract #636. Presented at the 65th American Society of Hematology Annual Meeting and Exposition; December 9-12, 2023; San Diego, California.

HemOnc Happenings

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

Erik Kimble, MD, Wins Underrepresented Minority Fellowship Award

Erik Kimble, MD

Dr. Kimble, a physician-scientist at the Fred Hutchinson Cancer Center (Fred Hutch) in Seattle, Washington, received the Underrepresented Minority Fellowship in Gene and Cell Therapy for Oncology from the American Society of Gene & Cell Therapy.

The award grants $100,000 to a postdoctoral or early-career oncology researcher from a racial or ethnic minority group underrepresented in the scientific workforce and who self-identifies as Black, Indigenous, and/or Latinx, according to the society's website. The award is supported by funding provided by Bristol Myers Squibb.

Dr. Kimble's area of focus is cellular immunotherapies for hematologic cancers, specifically acute myeloid leukemia (AML).

As a physician and research associate at Fred Hutch, his goal is to optimize the efficacy of chimeric antigen receptor (CAR) T-cell therapies in AML.

"I'm at a pivotal time in my career," said Dr. Kimble in a press release from Fred Hutch. "This is really big for me."

Dr. Kimble, who is half Mexican and half Black, attended medical school at Universidad de Guadalajara in Mexico and is a recent graduate of the University of Washington School of Medicine's Hematology-Oncology Fellowship Program.

Now, Dr. Kimble is investigating how CAR T cells interact with antigens and the mechanisms of resistance employed by leukemia cells to avoid annihilation.

CAR T cells are designed to bind to their target antigen and subsequently destroy the tumor cell, according to the press release. However, some cells may not have an antigen, which is one reason CAR T-cell therapy may not succeed.

To increase the effectiveness of CAR T cells against tumor cells with low-target antigen expression, Dr. Kimble's strategy consists of combining CAR T cells with drugs that modulate proteins in the cells that make them susceptible to TNF alpha, a protein produced by activated CAR T cells. Therefore, tumor cells that don't have an antigen targeted by CAR T cells can still be killed by them.

Robert Bradley, PhD, Director of the Translational Data Science Integrated Research Center at Fred Hutch and one of Dr. Kimble's mentors, reflected on Dr. Kimble's work.

Robert Bradley, PhD

"What's so interesting about Erik is that he is studying something that's not well understood, a recently described phenomenon that he played a role in articulating," said Dr. Bradley. "This award lets him pursue his research in a way that lets him go after what's most important, even if it's not the easiest research."

AACR Announces Newly Elected Class of Fellows

The American Association for Cancer Research (AACR) recently announced their newly elected 2024 class of fellows of the AACR Academy.

The AACR Academy recognizes and honors distinguished scientists whose contributions have propelled significant innovation and progress against cancer, according to a press release from the society. Those recognized for their work related to the field of hematologic oncology include the following:

- **Benjamin Ebert, MD, PhD**
- **Susan Galbraith, MBBChir, PhD**
- **Richard Gelber, PhD**
- **Margaret Goodell, PhD**
- **Miriam Merad, MD, PhD**

Benjamin Ebert, MD, PhD

Dr. Ebert serves as Professor of Medicine at Harvard Medical School, Chair of Medical Oncology at the Dana-Farber Cancer Institute, and Investigator at the Howard Hughes Medical Institute. He was nominated for his contributions to elucidating the mechanism of action of thalidomide analogs in multiple myeloma (MM), characterizing 5q deletions in myelodysplastic syndromes, defining the importance of age-related clonal hematopoiesis in carcinogenesis, and providing critical insights into targeted protein degradation as a therapeutic strategy.

Susan Galbraith, MBBChir, PhD

Richard Gelber, PhD

Dr. Galbraith, Executive Vice President of Oncology R&D at AstraZeneca, was nominated for her contributions to the development of several cancer medicines, including acalabrutinib for chronic lymphocytic leukemia.

Dr. Gelber, of the Dana-Farber Cancer Institute at Harvard Medical School, was nominated in part for his leadership of biostatistical collaborations on practice-changing clinical trials in pediatric leukemia, according to the AACR.

Margaret Goodell, PhD

At Baylor College of Medicine in Houston, Texas, Dr. Goodell serves as Professor and Chair of Molecular and Cellular Biology, the Vivian L. Smith Chair in Regenerative Medicine, and Director of the Stem Cells and Regenerative Medicine Center. She is recognized for her work surrounding hematopoietic stem cells (HSCs), specifically clarifying the role of interferons in coordinating hematopoietic regeneration from stem cells in response to stress and pathogens, discovering the critical role that methylation plays in HSC regeneration and expansion, and establishing DNMT3A as a master epigenetic regulator and tumor suppressor in the hematopoietic system.

Miriam Merad, MD, PhD

Dr. Merad serves as Chair of the Department of Immunology and Immunotherapy, Director of the Precision Immunology Institute at Mount Sinai School of Medicine, and Professor of Oncological Sciences, Medicine, and Hematology at the Icahn School of Medicine. She was honored for elucidating the roles of myeloid cells in inflammation and tumorigenesis, as well as contributing to the advancement of targeted therapies focused on myeloid cells in both cancer and inflammatory diseases.

Dr. Rajkumar Assumes Role of Chair, Board of Directors of International Myeloma Foundation

MM clinician and researcher **S. Vincent Rajkumar, MD,** assumed the role of Chairperson of the International Myeloma Foundation (IMF) Board of Directors, according to a press release from the organization.

S. Vincent Rajkumar, MD

Dr. Rajkumar currently serves as a Professor of Medicine at the Mayo Clinic; a Member of the National Cancer Institute Myeloma Steering Committee; Chair of the Myeloma Committee, ECOG-ACRIN Cancer Research Group; Editor-in-Chief of *Blood Cancer Journal*; and Associate Editor of *Leukemia* and the *European Journal of Haematology*.

He also served as principal investigator of several clinical trials in MM and has published more than 480 peer-reviewed papers in the field of myeloma and plasma cell disorders.

"I am honored to be selected for this important role," said Dr. Rajkumar in the press release. "My goal is to empower the superb team at the IMF to excel and to greatly enhance our global impact on research, advocacy, patient support, and physician education."

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

Send the details to editor@bloodcancerstoday.com.

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